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Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke:

A Consensus Statement

Osama O. Zaidat, MD, **Albert J. Yoo, MD**, **Pooja Khatri, MD**, **Thomas A. Tomsick, MD**, **Rüdiger von Kummer, MD**, **Jeffrey L. Saver, MD**, **Michael P. Marks, MD**, **Shyam Prabhakaran, MD**, **David F. Kallmes, MD**, **Brian-Fred M. Fitzsimmons, MD**, **J. Mocco, MD**, **Joanna M. Wardlaw, MD**, **Stanley L. Barnwell, MD**, **Tudor G. Jovin, MD**, **Italo Linfante, MD**, **Adnan H. Siddiqui, MD**, **Michael J. Alexander, MD**, **Joshua A. Hirsch, MD**, **Max Wintermark, MD**, **Gregory Albers, MD**, **Henry H. Woo, MD**, **Donald V. Heck, MD**, **Michael Lev, MD**, **Richard Aviv, MD**, **Werner Hacke, MD**, **Steven Warach, MD**, **Joseph Broderick, MD**, **Colin P. Derdeyn, MD**, **Anthony Furlan, MD**, **Raul G. Nogueira, MD**, **Dileep R. Yavagal, MD**, **Mayank Goyal, MD**, **Andrew M. Demchuk, MD**, **Martin Bendszus, MD**, **David S. Liebeskind, MD**, and **for the Cerebral Angiographic Revascularization, Grading (CARG) Collaborators, STIR Revascularization working group, and STIR Thrombolysis in, Cerebral Infarction (TICI) Task Force**

Department of Neurology, Medical College of Wisconsin, Milwaukee, WI (O.O.Z., B.-F.M.F.); Department of Radiology, Harvard Medical Center, Boston, MA (A.J.Y., J.A.H., M.L.); Department of Neurology (P.K., J.B.), Department of Radiology (T.A.T.), University of Cincinnati, Cincinnati, OH; Department of Radiology, Technical University Dresden, Dresden, Germany (R.v.K.); Department of Neurology, University of Los Angeles, Los Angeles, CA (J.L.S., D.S.L.); Department of Radiology (M.P.M.), Department of Neurology (G.A.), Stanford University, San Francisco, CA; Department of Neurology, Northwestern University, Chicago, IL (S.P.); Department of Radiology, Mayo Clinic, Rochester, MN (D.F.K.); Department of Neurosurgery, Vanderbilt University, Nashville, TN (J.M.); Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, United Kingdom (J.M.W.); Department of Neurosurgery, Oregon State University, Portland, OR (S.L.B.); Department of Neurology, University of Pittsburgh, Pittsburgh, PA (T.G.J.); Baptist Vascular Center, Miami, FL (I.L.); Department of Neurosurgery, University of Buffalo, Buffalo, NY (A.H.S); Department of Neurosurgery, Mount Sinai Medical Center, Los Angeles, CA (M.J.A.); Department of Radiology, University of Virginia, Charlottesville, VA (M.W.); Department Neurosurgery, Stony Brook University, East Setauket, NY (H.H.W.); Department of Radiology, Forsyth Medical Center, Kernersville, NC (D.V.H.); Department of Medical Imaging,

Correspondence to Osama O. Zaidat, MD, MS, Department of Neurology, Neurosurgery, and Radiology, Froedtert Hospital and Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI. szaidat@mcw.edu.
A list of all STAIR Participant Endorsees is given in the Appendix.

University of Toronto, Toronto, ON, Canada (R.A.); Department of Neurology (W.H.), Department of Neuroradiology (M.B.), University of Heidelberg, Heidelberg, Germany; Department of Neurology, University Medical Center, Brackenbridge, Bethesda, MD (S.W.); Department of Radiology, Washington University, St Louis, MO (C.P.D.); Department of Neurology, Case Western University, Cleveland, OH (A.F.); Department of Neurology, Emory University, Atlanta, GA (R.G.N.); Department of Neurology, Miami University, Miami, FL (D.R.Y.); and Department of Radiology (M.G.), Department of Neurology (A.M.D.), University of Calgary, Calgary, AB, Canada.

Keywords

Intra-arterial therapy (IAT) for acute ischemic stroke (AIS) has dramatically evolved during the past decade to include aspiration and stent-retriever devices. Recent randomized controlled trials have demonstrated the superior revascularization efficacy of stent-retrievers compared with the first-generation Merci device.[1,2] Additionally, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and the Interventional Management of Stroke (IMS) III trials have confirmed the importance of early revascularization for achieving better clinical outcome.[3–5] Despite these data, the current heterogeneity in cerebral angiographic revascularization grading (CARG) poses a major obstacle to further advances in stroke therapy. To date, several CARG scales have been used to measure the success of IAT.[6–14] Even when the same scale is used in different studies, it is applied using varying operational criteria, which further confounds the interpretation of this key metric.[10] The lack of a uniform grading approach limits comparison of revascularization rates across clinical trials and hinders the translation of promising, early phase angiographic results into proven, clinically effective treatments.[6–14] For these reasons, it is critical that CARG scales be standardized and end points for successful revascularization be refined.[6] This will lead to a greater understanding of the aspects of revascularization that are strongly predictive of clinical response.

The optimal grading scale must demonstrate (1) a strong correlation with clinical outcome, (2) simplicity and feasibility of scale interpretation while ensuring characterization of relevant angiographic findings, and (3) high inter-rater reproducibility.

To address these issues, a multidisciplinary panel of neurointerventionalists, neuroradiologists, and stroke neurologists with extensive experience in neuroimaging and IAT, convened at the "Consensus Meeting on Revascularization Grading Following Endovascular Therapy" with the goal of establishing consensus recommendations for the standardization of revascularization grading in AIS clinical studies. Presented here are the recommendations of the panel.

Methods

A hybrid approach based on established processes described by Glaser[15] and by the National Institutes of Health (http://prevention.nih.gov/cdp/about.aspx)[16] was used to structure the conference and consensus statement. Before the meeting, a comprehensive literature review was performed, and relevant documents were distributed to each participant. Twelve expert panelists attended the full-day roundtable meeting held in Chicago, IL, on January 7, 2012. The panel comprised a multidisciplinary group of noninvasive stroke neurologists and neurointerventionalists with neuroradiology, neurosurgery, and neurology backgrounds.

Panelists presented their views on CARG after IAT using case illustrations, followed by an open discussion. A preselected set of angiograms from IAT-treated patients with AIS was reviewed at the beginning of the meeting and again at the end of the day to identify key points for discussion. After the meeting, draft proposals were presented for voting via an online survey to arrive at consensus recommendations. The final consensus document was based on a systematic literature review, the roundtable discussion, and the postmeeting survey results.

The consensus recommendations were presented to the revascularization grading task force assembled at the Stroke Imaging Repository (STIR) Consortium/Stroke Treatment Academic Industry Roundtable (STAIR) meetings in March 2013, and their feedback was incorporated into the final draft. The article was distributed to 68 national and international experts for further comments or suggestions. The final copy was endorsed by stakeholder Cerebrovascular Coalition societies.

Results

The consensus recommendations are classified into the following 4 key areas: (1) CARG, (2) anatomic and collateral considerations, (3) additional grading considerations, and (4) technical considerations and documentation.

Cerebral Angiographic Revascularization Grading

Effective Revascularization: Recanalization Versus Reperfusion—Issue: Recanalization and reperfusion are often interchanged in CARG scales. Recanalization and reperfusion scales lack clear definitions.

Revascularization encompasses all treatment-related improvements in blood flow, including local recanalization of the arterial occlusion and reperfusion of the downstream territory. Although these end points are closely related, recanalization and reperfusion are different. Recanalization is required for antegrade tissue reperfusion, but recanalization may not necessarily lead to reperfusion in regions where distal emboli or established infarctions are present. Because of their intimate relationship, both measures have been shown to predict improved clinical outcomes after IAT.[17–28] Of the 2 parameters, reperfusion is more strongly associated with tissue and clinical outcomes because of its measurement of tissue-level effects.[18,28] Therefore, reperfusion is the best marker of effective revascularization. However, recanalization is an important metric of the treatment effect on the target lesion.

Future studies are needed to assess whether recanalization imparts additional prognostic information in combination with reperfusion.

Reperfusion Scales—On digital subtraction angiography (DSA) in normal patients, tissue-level perfusion is evidenced by a capillary blush. After IAT, reperfusion is operationally defined as the antegrade (ie, not by pial collaterals) restoration of a capillary blush. As such, reperfusion scales account for distal emboli and would identify treatment modalities that achieve revascularization without clot fragmentation and distal embolization (DE).

<u>**Thrombolysis in Myocardial Infarction Scale:**</u> Originally constructed to measure myocardial reperfusion, the Thrombolysis in Myocardial Infarction (TIMI) scale has been widely adopted for use in the cerebral circulation (Table 1).[29–36] However, variable permutations of TIMI have been used in previous IAT studies, most of which measure recanalization.[1,32–36] In the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials,[33,34] treatment success required recanalization of all treatable vessels. For internal carotid artery (ICA) terminus occlusions, this translated to recanalization of the ICA, M1, and all M2 segments. The investigators stated that "the status of arterial branches distal to the treatable vessel was not considered when ascribing the TIMI scale."[33] The general uncertainty on how to grade TIMI was demonstrated in a recent study of 48 patients with AIS treated with IAT, where the inter-rater reliability was poor using the modified TIMI grading scale (κ=0.4).[37] Similarly, there was wide discordance between the site and core laboratory TIMI scale readings in the Solitaire with Intention for Thrombectomy (SWIFT) trial (14.8% and 19.1% difference in the Solitaire FR and Merci arms, respectively).[1] Nevertheless, TIMI has been predictive of clinical outcome across studies; reflecting the strong correlation of recanalization and reperfusion.[12,19–21,24,27]

The original TIMI scheme has 2 issues that limit its use in the cerebral vasculature. First, the major criterion for grading myocardial reperfusion is the rate of contrast clearance from the distal tissue bed. However, in the carotid circulation, Mori et al[38] found that if there is tissue-level reperfusion, flow delay is an infrequent occurrence; the return of a parenchymal contrast blush is a sign of sufficient flow. The second issue is that the extent of reperfusion is not considered in the TIMI criteria. This is critical in cerebral ischemia because final infarct volume is the single best predictor of outcome after IAT,[39–41] and greater degrees of reperfusion are associated with higher rates of good outcome.[3,12,18,25,26]

<u>**Thrombolysis in Cerebral Infarction Scale:**</u> The Thrombolysis in Cerebral Infarction (TICI) scale was originally proposed in a position statement that attempted to standardize clinical trial design and reporting for IAT.[14,32] The TICI scale specifically addresses the extent of tissue reperfusion, as represented by the capillary blush on DSA.[14] TICI is graded by visually estimating how much of the initial antegrade capillary blush defect (or target downstream territory [TDT]; see Target Downstream Territory section; denominator) is reperfused (numerator). The TICI scale distinguishes no perfusion (TICI grade 0; Figure 1), minimal flow past the occlusion but no perfusion (grade 1; Figure 2), minor partial reperfusion (grades 2a; Figures 3 and 4), major partial reperfusion (2b; Figure 1), and complete reperfusion without any flow defects (grade 3; Figures 2 and 5; Table 2). Two

variations of the TICI scale exist on the threshold for major partial reperfusion. The original TICI system defined TICI 2b as restoration of more than two thirds of the TDT.[14] This is in contrast to the subsequent modification (modified treatment in cerebral ischemia [mTICI]) introduced by the IMS investigators, which uses a threshold of more than half of the TDT.[18,42,43] There is indirect evidence of better inter-rater variability using the original TICI scale than TIMI. The discordance was higher between site and core laboratory readers in the SWIFT (using TIMI) versus TREVO2 (using original TICI) trials (≈15% versus 1% in the stent-retriever arms, respectively).[1,2] The advantage of mTICI is its simplicity (ease of visually estimating 1/2 versus 2/3 reperfusion), and previous work has demonstrated excellent inter-rater agreement for distinguishing <50% versus 50% reperfusion of the downstream territory.[21] Moreover, mTICI has proven value for predicting clinical outcome.[18,23,25,26,44] In a comparative study of TIMI and mTICI, the c-statistic for predicting 90-day good outcome (mRS 0–2) was significantly higher for mTICI versus TIMI (0.74 versus 0.68; $P<0.0001$).[25]

Recanalization Scales—Recanalization measures the direct action of the therapeutic intervention on the target arterial lesion (TAL). Although it neglects downstream effects within the ischemic bed, it may provide additional prognostic information, particularly in the setting of incomplete vessel patency where there may be an increased risk of reocclusion or DE.

<u>Arterial Occlusive Lesion Scale:</u> The only grading scale explicitly intended to measure the degree of recanalization at the TAL is the Arterial Occlusive Lesion (AOL) scale, which was proposed by the IMS investigators (Table 3).[5,12,18,42,43] AOL describes arterial patency at the site of occlusion based on the degree of luminal opening (none, partial, or complete) with further qualification based simply on the presence (grades 2 or 3) or absence (grades 0 or 1) of any downstream flow.[11,18]

Reflecting the strong relationship between recanalization and reperfusion, AOL and mTICI showed good agreement (κ=0.66), with no difference in their ability to predict clinical outcome (61% versus 71% for AOL 2–3 and mTICI 2a-3, respectively; P=0.9) in 96 angiograms from IAT cases.[23] Similarly, AOL and TIMI scales showed modest agreement (κ=0.30) with no difference in their ability to predict clinical outcome (49% versus 54% in AOL 2–3 and TIMI 2–3, respectively; P=0.13) in 61 angiograms from IMS I trial.[12] However, as previously noted, both mTICI 2a-3 and 2b-3 were demonstrated to be superior to AOL 2 to 3 for predicting 90-day functional independence in the combined IMS II data set, supporting the preeminent role of tissue reperfusion in shaping clinical outcome.[18] Nevertheless, recanalization grading is important and is likely to contribute further prognostic information to reperfusion alone.

Although easy to use, there are 3 main issues with the AOL grading system. First, in IMS II and III, AOL scoring was applied only to the TAL.[5,18] For example, recanalization of a carotid terminus occlusion yielded AOL 3, but mTICI 0, if the middle cerebral artery (MCA) remained occluded. The alternative approach is to use the entire clot span for grading recanalization, which raises a second issue; the distal extent of clot is frequently unknown, particularly when it extends into several branches. For example, if a clot within

the MCA M1 segment extends into both proximal M2 segments, is the TAL within the M1 only, or the M1 and both M2 segments? In the former case, opening the M1 and one of the M2 branches only would yield an AOL 3; in the latter case, the same result would yield an AOL 2. The third issue relates to the difficulty in distinguishing between AOL 2 (partial recanalization) versus possible underlying stenosis, or device-related vasospasm. Despite these shortcomings, AOL is the only scale that specifically addresses device efficiency at the TAL.

Other CARG Scales—In addition to the commonly used revascularization grading schemes, other scales have been proposed. The Qureshi scale rates both occlusion site and collaterals; however, its major disadvantages are scale complexity and incorporation of disparate elements of stroke physiology. These issues make it difficult to distinguish treatment-related gains from baseline anatomic and collateral status, and also complicate statistical analysis.[45] Similarly, an additional attempt to develop specific comprehensive scale, recanalization in brain ischemic (RBI), did not yield wide adaptation.[46] Another reperfusion grading system, the Mori scale, considers the proximal arterial occlusive lesion and distal perfusion, but has been infrequently used in AIS studies.[38]

Consensus Revascularization Scales—Issue: What CARG scale should be recommended?

There was consensus agreement that proposing a novel CARG system with completely new scale definitions would add further confusion to the field, given the multiple grading schemes already established. The panelists strongly supported the recommendation of adopting a single CARG system for perfusion and one for recanalization with consistent operational definitions across AIS trials.

From the most commonly used scales, the panel recommended mTICI as the primary reperfusion scale because it was specifically designed for the cerebral circulation, has good inter-rater reliability, and strongly predicts clinical outcome.[18,23,25,26] Furthermore, the consensus was to maintain the acronym mTICI, which now stands for modified treatment in cerebral ischemia (previously modified thrombolysis in cerebral ischemia), to more accurately reflect current IAT practice.

For assessing recanalization, the AOL scale is preferred because of its ease of use and precise assessment of device efficacy at the occlusion. The AOL scale can be used at different locations.

Because mTICI and AOL assess different dimensions of revascularization, (reperfusion and recanalization, respectively), it is optimal to obtain and report both measures.

Recommendations:

- The angiographic criterion for tissue reperfusion is restoration of capillary-level opacification, which is achieved in an antegrade fashion (ie, across the occlusive lesion).

- For primary measures of procedural success, reperfusion scales should be used.

- The mTICI scale should be used as the standard reperfusion grading scale.

- mTICI should stand for modified treatment in cerebral ischemia.

- Recanalization should be measured using the AOL scale.

Defining TICI Grades and the Target Angiographic End Point—Issue: Consistent thresholds for TICI grades are lacking. The target angiographic end point is variable and not well defined in stroke studies.

Clear operational definitions for TICI grades 3 and 2 have not been standardized. These variations may have different clinical implications and limit comparisons between device studies. For mTICI 3, there is no clear consensus on whether it should represent complete versus near complete antegrade reperfusion. Although complete reperfusion is associated with the best outcomes,[5,25] the benefits and risks of attempting to achieve full reperfusion are not yet fully understood. However, the requirement for complete reperfusion may potentially increase the reliability of mTICI 3 grading between readers and help to distinguish mTICI 2b from mTICI 3. Hence, the consensus was to define mTICI 3 as complete antegrade reperfusion, without any distal branch occlusion or stagnation.

As previously noted, TICI 2b has been dichotomized into 2 main variations: (1) more than half (mTICI) and (2) more than two thirds (original TICI) reperfusion. In available studies, good interobserver agreement was demonstrated using either threshold.[25,26] Given the current reliability data, and potential simplicity of the one half threshold, the panel recommended that TICI 2b should be defined as more than half but less than full antegrade reperfusion of the TDT.

In IAT studies, procedural success had been variably defined using different target angiographic end points. The most frequent definition of IAT angiographic success has been TIMI 2 to 3 or TICI 2a–3 reperfusion grades.[1–5,32–36] Several studies have shown that mTICI 2b yields significantly better outcomes than minor reperfusion.[18,25,26,44] Data from IMS II revealed a trend favoring mTICI 2b for predicting outcome versus mTICI 2a (P=0.08).[18] Furthermore, mTICI 2b-3 was demonstrated as the optimal threshold for predicting good outcome in 313 AIS undergoing IAT (sensitivity 78%, specificity 65%) versus mTICI 2a-3.[25] In core laboratory adjudicated results from the IMS III trial, mTICI 3 and 2b grades were associated with 80% and 46.3% good clinical outcome (90-day mRS 2), respectively, versus 19.4% for mTICI 2a.[5] Given that mTICI 2b-3 reperfusion seems to have a higher accuracy for discriminating a good functional outcome than mTICI 2a-3,[18,25,26] its use as the target angiographic end points is recommended until further data are available.

Recommendations:

- mTICI 3 should be defined as complete antegrade reperfusion of the TDT, with absence of visualized occlusion in all distal branches.

- mTICI 2b should be defined as more than half, but less than complete antegrade reperfusion of the TDT.

- The target angiographic end point for technical success should be defined as mTICI 2b or higher.

Adjusting the mTICI Grading Scale—Issue: Arterial occlusion locations and new embolization may be associated with different clinical outcomes that may not be accounted for in the mTICI score.

Different vessel occlusions are associated with different clinical outcomes; for example, distal ICA and basilar artery occlusions are associated with worse clinical outcome when compared with other locations.[47–51] Given how the occlusion location influences outcome, should an adjustment to the mTICI scale be implemented based on the occlusion site? One scale attempted to incorporate the site of occlusion into the revascularization grade; however, this modification made the scale more complex and prohibitive.[45,46]

The panel decided against adjusting or imposing a negative mTICI score based on location. Instead, the recommendation was to define the location of the vessel occlusion clearly to allow pooling of similar location data within and across trials. To improve mTICI correlation with clinical outcome, studies should report subgroup analyses by the level of occlusion, or alternatively studies should enroll patients with homogeneous clot location, such as the Prolyse in Acute Cerebral Thromboembolism (PROACT) in MCA, MCA Embolism Local Fibrinolytic Intervention (MELT), and the Basilar Artery International Cooperation Study (BASICS) trials.[32,50,52]

Similarly, embolization into new territory (ENT) should be captured separately without adjustment of the mTICI scale. It is recognized that the mTICI scale will incorporate information on distal emboli. New embolization is discussed in more detail below (see ENT and DE in the Target Downstream Territory section).

Recommendations:

- mTICI grading should not be modified based on the level of vessel occlusion or new embolization.

- mTICI grading should be reported by level of occlusion for comparison of treatment arms within studies and to allow comparison across studies.

Anatomic and Collateral Considerations

Once all arterial stenoses and occlusions (eg, single or multiple emboli, tandem lesions) and baseline anatomic variants (eg, hypoplastic A1 segment or posterior communicating artery) have been identified and documented, the TAL can be designated.

Target Arterial Lesion—Issue: The terminology used to describe the TAL is not well defined.

Anatomic definitions of TAL, or the primary focus of intraarterial treatment, at baseline angiography have varied across the literature. The consensus recommendation was to designate the proximal-most intracranial occlusive lesion as the TAL. Therefore, in cases of multiple intracranial emboli (eg, distal anterior cerebral artery [ACA] and MCA emboli), the

most proximal one will be considered the TAL. Alternatively, in the setting of tandem extracranial-intracranial occlusions (eg, cervical ICA plus proximal MCA occlusions), the intracranial lesion will be considered the TAL. The only exception to this definition would be in cases where there is no intracranial occlusion; in this case, the extracranial lesion is the TAL. In addition to specifying the location of the most proximal intracranial lesion, a more granular descriptive terminology should be used, whenever possible, to allow for subsequent detailed and supraordinate analyses.

Recommendation:

- The TAL is the most proximal treated intracranial occlusive lesion.

Intracranial ICA Occlusion Nomenclature: Issue: Intracranial ICA clot topography has been largely neglected in stroke studies.

The intracranial carotid occlusion may have variable outcomes depending on the extent of the clot.[47–49] Such lesions are often grouped under the term carotid T, but this designation implies a particular shape of the occlusion, namely contiguous clot extending from the distal ICA into both A1 and M1 arteries. However, a distinction should be made from other configurations, such as L when it extends only to the M1 segment, or even as I where there is flow across the circle of Willis into both the A1 and M1 segments (ie, clot is isolated to the distal ICA only). This distinction may be made from injecting the contralateral ICA or from pretreatment computed tomography (CT) angiography (CTA) or MR angiography when available.

Recommendation:

- Intracranial carotid occlusions should be documented based on the best available data: carotid T if terminal ICA, origin of M1, and origin of A1 are all occluded; carotid L if only both terminal ICA and the M1 origin are occluded; isolated intracranial ICA if only the intracranial ICA is occluded.

MCA Occlusion Nomenclature: Issue: Description of MCA clot location varies across studies.

Anatomic variations have made MCA clot location nomenclature challenging. The panel supports the definition of the M1 segment as the first portion of the MCA up to the major bifurcation. Occlusion of the proximal M1 segment should be assigned when it involves the proximal half of the M1 segment or when no lenticulostriate vessels are visualized. Distal M1 occlusions involve the distal half of the M1 segment or spare the lenticulostriate perforators.

Detailed description of any anatomic variant must be reported, including duplicated M1 segments, dominant anterior temporal artery (ATA) branches, and A1 segment variations (ie, aplastic, hypoplastic, normal caliber).

Recommendations:

- MCA clot location should be clearly and precisely described.

- The M1 segment should be defined as the first portion of the MCA up to the major bifurcation.

- M1 clot location should be further localized as proximal (ie, involving the proximal half of the M1 or occluding the lenticulostriate vessels) or distal (ie, involving the distal half of the M1 segment or sparing the lenticulostriate vessels).

- Anatomic variations should be described (eg, duplicate M1 segment, dominant anterior temporal artery, A1 anatomy).

Target Downstream Territory—Issue: Criteria for determining the TDT are not well defined.

The TDT is the region of the brain that was previously supplied in an antegrade fashion, but attributable to the target lesion, now has absent capillary-level opacification or capillary opacification, which is achieved via pial collaterals. Territory receiving retrograde collateral perfusion should be considered as part of the TDT. The full extent of this territory serves as the denominator in calculating the percentage of tissue reperfusion. This definition is particularly important for ICA or vertebrobasilar occlusion. For instance, in an intracranial ICA occlusion, the TDT comprises both ipsilateral ACA and MCA territories in cases with no evidence of ipsilateral ACA filling from contralateral carotid injection (or equivalent data from CTA or MR angiography). In many cases of intracranial ICA occlusion, there is antegrade filling of the ipsilateral ACA territory over the anterior communicating artery such that the TDT is the MCA territory only. In cases of vertebrobasilar occlusion, the TDT is the territory of the basilar artery, superior cerebellar arteries, and bilateral posterior cerebral arteries territories, unless imaging data from CTA, MR angiography, or DSA demonstrate the distal extent of the clot or anterior circulation supplying the posterior cerebral arteries (fetal origin).

Recommendations:

- The TDT is the brain region that lacks antegrade capillary staining secondary to the target occlusion. Capillary opacification that is achieved via pial collaterals should be considered part of the TDT.

- In intracranial ICA occlusion, the TDT should include both ACA and MCA territories.

- In vertebrobasilar occlusion, the TDT should be basilar artery branches above the level of occlusion and both posterior cerebral arteries.

- If evidence from other baseline imaging data shows a different pattern than expected above, adjustment to the TDT must be made (eg, in most ICA occlusions, the TDT will be the MCA territory attributable to anterior communicating artery supply to the ipsilateral ACA territory).

Cerebral Collateral Flow Grading—Issue: No consensus or consistency exists in obtaining and grading collateral circulation data during IAT.

The pial collateral circulation predicts the response to IAT revascularization and clinical outcomes in AIS cases.[53–58] Collateral maintenance may prolong the time window for revascularization, and failure may hasten ischemia and lead to futile revascularization.[53] Collateral grading has been reported using several scales.[59] The American Society of Interventional and Therapeutic Neuroradiology (ASITN) collateral grading (ACG) system is the most commonly used scale, and assigns scores based on the extent and rate of retrograde collateral flow to the TDT. Score ranges between 0 (no collaterals) and 4 (complete and rapid collateral perfusion to the ischemic bed; Table 4). Higher ACG score has been associated with a higher rate of successful revascularization after IAT.[54] The same group reported the highest rates of infarct growth on day 3 to 5 brain MRI in those with no recanalization and poor ACG score at baseline.[55]

In addition to the ACG scale, the pial collateral scale has been described by Christoforidis et al.[56] The pial collateral scale grade measures the proximal-most extent of retrograde vessel filling from pial collaterals, with the best grade defined as retrograde filling of the occluded segment up to the distal extent of the clot. The authors demonstrated smaller final infarct volumes and better discharge mRS scores in those with a better collateral grade.

Recently, a third collateral scale has been described in a study of 26 IAT-treated patients with ICA or MCA occlusion. In the Capillary Index Score,[57] the TDT is divided into 3 equal parts, and each part is given a score of 1 if normal capillary blush is present, or 0 if absent. The individual scores are summated to yield a total Capillary Index Score between 0 and 3. A high Capillary Index Score scale was associated with better outcome and recanalization in that study.

Collateral scales have been shown to predict revascularization and clinical and tissue outcome after IAT. The panel recommends that the ASITN collateral grading scale should be used for cerebral collateral flow grading when angiographic data are available and adequate. However, performing a complete diagnostic angiogram for collateral assessment poses a delay to treatment. In cases where this information cannot be obtained quickly (eg, because of difficult vessel catheterization), collaterals may be imputed from noninvasive imaging modalities, such as CTA and CT/ MR perfusion.[58]

Recommendations:

- Cerebral collateral flow grading on DSA should be performed using the ASITN grading scale.

- When DSA data are not available, noninvasive imaging should be used to evaluate the collateral circulation before IAT.

Additional Considerations

ENT and DE Into the Target Downstream Territory—Issue: Criteria for new embolization (into the target or new territories) are not well defined, and these data are not routinely recorded.

The panel supports the definition of ENT as any treatment-related embolus outside of the TDT. The consensus definition of DE is any treatment-related embolus within the TDT. Therefore, in a terminal ICA occlusion, a treatment-related ACA embolus would represent an ENT if the ipsilateral ACA was patent and received antegrade flow from the contralateral ICA at baseline. The same embolus would represent a DE if no such ACA flow was seen at baseline (eg, isolated hemisphere).

ENT during IAT was reported in 3.8% of the MERCI trial cohort, 1.5% in a retrospective study of the Solitaire device, and in 1.7% of treated MCA occlusions in the pooled IMS I and II data.[60–62] ENT after treatment of ICA terminus occlusions has been shown to be associated with poor clinical outcome in the pooled IMS I and II analyses.[62] Similarly, in IMS III, ENT was found in 14% (28/200) of M1 and ICA occlusions after IAT, and was associated with poor clinical outcome (mRS 2 in 17.9% versus 30.2% in those without ENT).[63]

Downstream DE has been reported in ≈7% to 16% of IAT cases, and has not been independently associated with worse outcome in these studies.[61,63–65] However, this may be attributable to the lack of a clear definition of DE, or may be more likely because of the fact that DE is accounted for by the mTICI scale. The panel recognizes that accurate documentation of DE is difficult because it requires knowledge of whether distal emboli were present in the TDT before treatment. To obtain this information would require microcatheter selection of branches distal to the clot with subsequent contrast injection, which would add a time delay to treatment, as well as the potential increased risk of hemorrhage from microcatheter injections. Alternatively, close inspection of pretreatment CTA would be necessary for identifying such occlusions, although this may not be reliable. Given these challenges and the fact that treatment-related DE is incorporated into the final mTICI grade, separate documentation of DE is of uncertain value.

Given the potential deleterious effect of ENT, the panel recommends that any occurrence of ENT be documented. In ICA terminus occlusions, any new post-treatment ACA occlusion is considered DE unless there was normal ACA flow at baseline, then it would be considered ENT. Similar definitions can be applied to the vertebrobasilar occlusion, where any downstream occlusion distal to the TAL is considered DE unless complete angiogram or pre-IAT noninvasive imaging demonstrated patency of these distal branches.

Recommendations:

- ENT denotes treatment-related embolization to territories outside of the TDT (eg, ACA embolization during MCA occlusion treatment).

- DE is defined as any treatment-related embolization into the TDT.

- Occurrences of ENT after IAT should be reported.

Venous Shunting—Issue: Few studies have documented venous shunting or correlated this finding with outcome.

The presence of unexpected findings such as early venous shunting (Figures 2 and Figure 5) or a prominent capillary phase blush should be noted, as they may provide information about not just reperfusion, but tissue infarction, impaired autoregulation, and risk for hemorrhagic transformation.[66,67]

Recommendation:

- Early venous shunting during IAT should be reported.

Technical Considerations and Documentation

Procedural Time Metrics—Issue: Recording of important time milestones and procedural events is not standardized; consensus on terminology is currently lacking.

Given the negative impact of time delays on clinical outcome after IAT, documentation of time variables is important.[68] The key management milestone's times must be documented in all studies, including the time of patient arrival in the suite, groin puncture, first access of the target clot by the microcatheter, and procedure end.[69–71] Time to first achievement of revascularization should be carefully defined (see below) and documented. If functional flow is not established during the case, time to the end of the procedure, defined as the time to the final angiogram, should be recorded (Table 5 showing suggested time intervals).

When performing clinical studies, additional procedural steps should be documented in a manner that matches the published protocols. In PROACT-II and the IMS trials, drug delivery or device use was followed by intermittent DSA to assess interval revascularization results (eg, hourly in PROACT-II and every 15 minutes in the IMS III trial or after each device pass).[5,32] It is imperative to define the main study treatment and subsequent rescue phases to allow investigators and treating physicians to scale revascularization separately for the investigational intervention alone and for the entire procedure.

Recommendation:

- Suggested Stroke Intervention Times Intervals are onset to door, door to imaging, imaging (noncontrast head CT scan) to room entry, room entry to puncture, puncture to clot, clot to substantial reperfusion, and clot to end of procedure.

Therapeutic Intervention Details—Issue: Device or thrombolytic delivery documentation is not consistent.

It is important to describe exactly what was done from a therapeutic standpoint. For intra-arterial drug delivery, it is important to define the site of arterial injection, including the vessel injected and the position of the catheter tip relative to the target thrombus (proximal to the clot, intraclot, or distal to the clot). The amount and duration of drug delivery must be denoted. When devices are placed, the deployment location and time, and adjuvant approaches, should be detailed. Individual device pulls should be reported as discrete steps. Adjunctive medications, such as vasodilator infusion, are important to document because they may affect ultimate revascularization results. Such treatments may be used to relieve or prevent vasospasm, or to enhance the retrieval process.[72,73]

Recommendation:

- Therapeutic intervention steps need to be reported in a standardized format and documented with proper imaging acquisition.

Angiography Imaging Techniques—Issue: Inconsistent image acquisition may hinder assessment of revascularization.

Obtaining adequate images during acquisition of cerebral angiography for endovascular AIS therapy and the subsequent filming and annotation of such data are critical (Table 6). Such information is imperative for comprehensive revascularization grading. Angiography should be performed as DSA and according to the following specifications at baseline, at key intervals, and at the termination of the procedure. Both true anteroposterior (slightly cranial because transfacial more likely not to be true anteroposterior and lead to superior orbital edge bony contamination of M1 segment) and lateral projections centered on the target cerebral artery distribution including the distal branches (unmagnified) should be acquired. It should span the vertex superiorly and the inferior orbit inferiorly on anteroposterior projection and the frontal bone anteriorly and occipital bone posteriorly on lateral projection aligning the ear canals. Subsequent oblique views should be acquired as needed to allow clear documentation of the location, extent, and vessel caliber at the occlusion site, as well as to demonstrate the extent of collaterals. In addition to selective injections proximal to the target lesion, suggested additional runs to evaluate collateral circulation depending on the target vessel lesion location may be obtained.

At a minimum of the initial and final angiographic runs, image acquisition should be performed to the terminal venous phase, until all contrast is cleared through.

When a device is used, a still image of the aspiration device, stent-retriever, balloon, stent, or other device should be captured each time the device is deployed with proper annotation. All microcatheter injections should also be captured, and all procedural steps should be imaged (pre- and postintervention), including all passes, aspiration devices change, intra-arterial thrombolytic or antiplatelet infusion, balloon inflations, stent placement, and other mechanical device intervention.

Once images are acquired, the full set of angiography sequences from the start of the procedure to images of the femoral artery should be stored together under 1 file. These time sequences on each of the angiographic images provide important data used to verify integrity of the angiography data set. The entire data set from each procedure should ideally be archived in DICOM file type format, reflecting the nature of original image acquisition. Proper documentation of the angiographic procedure, including both diagnostic and therapeutic aspects, should always be maintained.

Recommendations:

- Baseline and final biplane images must be inclusive of all TDT, obtained throughout the venous phase, and used for interpretation of reperfusion scale.

- Oblique images should be obtained to identify the site and extent of the clot as needed, capturing still images of each device used during the intervention.

Future Directions and Conclusion

Future Collaborative Research

The pace of research and development for IAT has accelerated in recent years. There has been a remarkable evolution of technologies, procedural refinements, and systematic studies and trials that have yielded a wealth of angiographic information. The pathophysiology of ischemic stroke and the impact of endovascular interventions can be readily ascertained from these data sets, in both routine clinical practice and the research realm. Ongoing collaborations should address the following key areas for further study:

1. Future revascularization consensus meetings should be convened on a regular basis for refinement of these grading scales because endovascular therapies evolve and more data become available.

2. The reliability and clinical predictive value of CARG scales need to be further established in future prospective randomized, blinded trials.

3. Different TICI thresholds (eg, TICI 2c defined as >90% but less than TICI 3 or near complete reperfusion) should be tested against the standard mTICI thresholds for improving outcome prediction.

4. Future studies must clarify the optimal definition of the TDT for each level of vessel occlusion. This will have important consequences for revascularization grading and for documentation of DE and ENT.

5. Prospective blinded collateral grading data are needed concerning the reliability and clinical predictive values.

6. Incorporation of a time metric (eg, time from groin puncture to reperfusion) into the mTICI scale may further improve outcome prediction.

7. Online training modules for revascularization grading should be developed, in a similar fashion to training modules for stroke severity grading.

Conclusions

These definitions for the pathophysiology, procedural details, therapeutic interventions, and revascularization results are not perfect at present, yet use of standard methodology will allow for common terminology to describe what takes place in the setting of ischemic stroke studies and multicenter trials. Interpretation of any subsequent publication is critically dependent on the use of such definitions. A summary of the key consensus recommendations is provided in Table 7.

Acknowledgments

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Appendix

Listing of STAIR Participant Endorsees

1. Erkan Akyuz

2. Andrei V. Alexandrov

3. Jean-Claude Baron

4. Johannes Boltze

5. Arani Bose

6. Robert Croop

7. Christopher D. d'Esterre

8. Jens Fiehler

9. Brian Frake

10. Philip B.Gorelick

11. David C. Hess

12. Michael D. Hill

13. William Holt

14. Reza Jahan

15. Kennedy R. Lees

16. Richard Leigh

17. Weili Lin

18. Marie Luby

19. Patrick Lyden

20. Jose Merino

21. Keith W.Muir

22. Mark W. Parsons

23. Howard Rowley

24. Sean I. Savitz

25. Richard D. Scheyer

26. Larry Wechsler

27. Ona Wu

28. Hui Jing Yu

29. Vallabh Janardhan

30. Edgard Pereira

31. Rishi Gupta

32. Syed I Hussain

33. Thanh Nguyen

34. Alicia Castonguay

35. Mohammad Issa
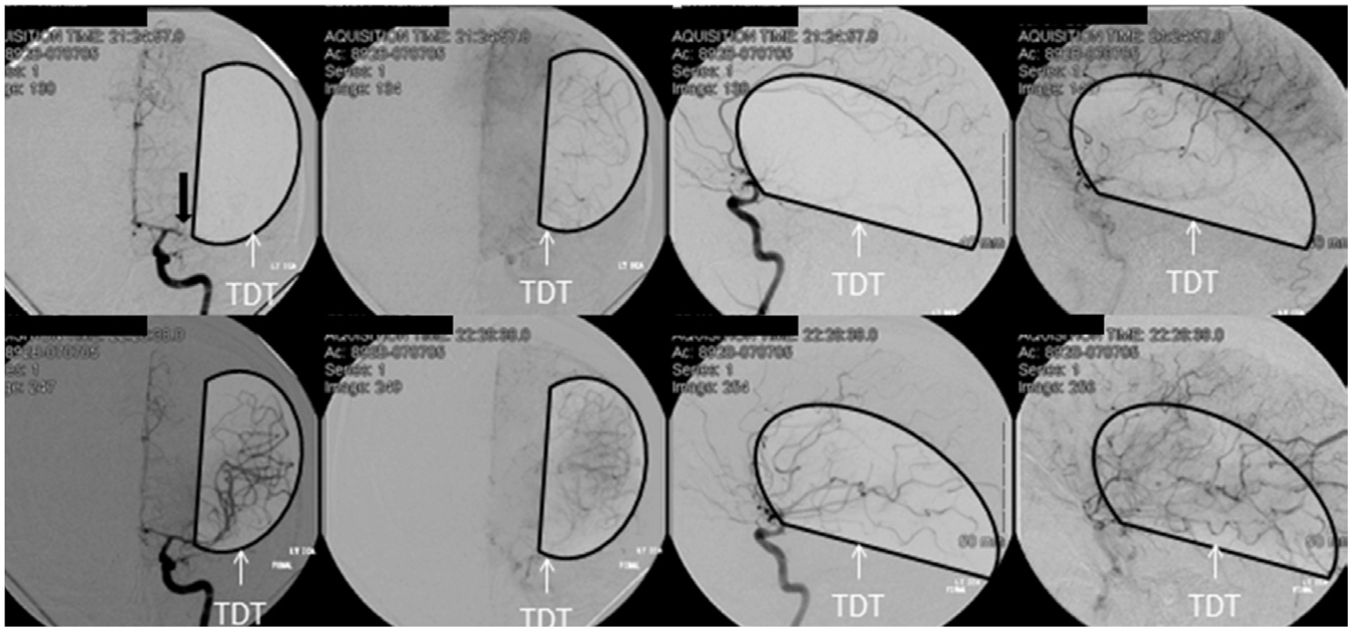
Figure 1.
Example of thrombolysis in cerebral infarction (TICI) 0 and TICI 2b. **Top**, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2b after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).
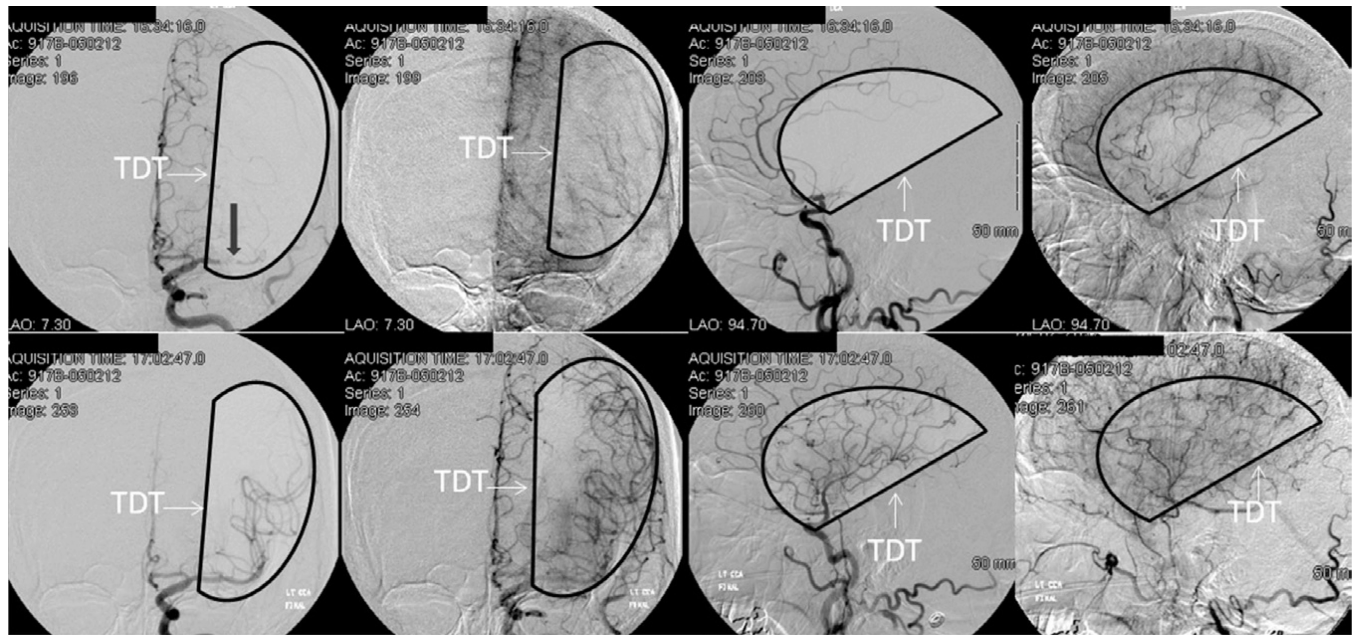
Figure 2.
Example of thrombolysis in cerebral infarction (TICI) 1 and TICI 3. **Top**, Anteroposterior **(left)** and lateral **(right)** in an early arterial and late capillary phases depicting TICI 1 at baseline. **Bottom**, Same phases depicting TICI 3 after intraarterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL). Ischemic arteriovenous shunting is noted with opacification of straight sinus (**right bottom** corner).
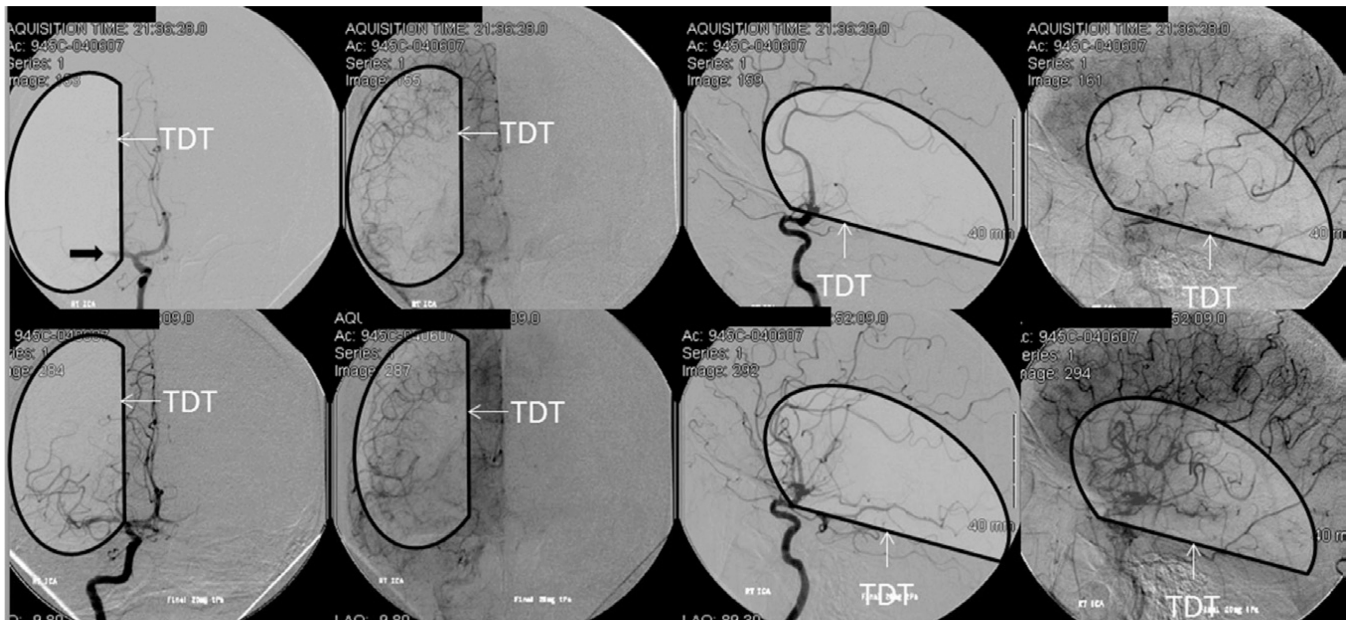
Figure 3.
Example of thrombolysis in cerebral infarction (TICI) 0 and TICI 2a (compared with TICI 2b and 3 above). **Top**, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2a after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).
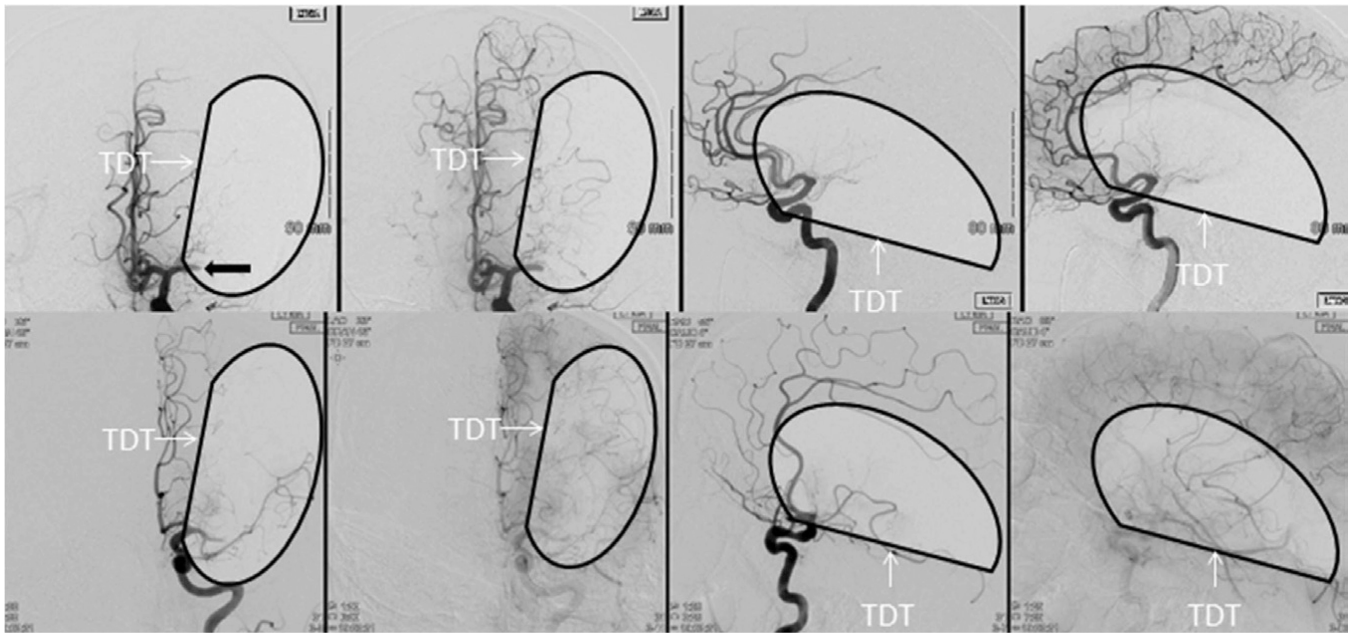
Figure 4.
Example of thrombolysis in cerebral infarction (TICI) 0 and TICI 2a (compare with TICI 3 and 2b above). **Top**, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and late capillary phases depicting TICI 0 at baseline. **Bottom**, Same phases depicting TICI 2a after intra-arterial therapy. Black arrow indicating the target arterial lesion (TAL): middle cerebral artery/M1 horizontal segment occlusion (TAL) distal to the lenticulostriate (LS). Black half circles approximate the target downstream territory (TDT; the presumed area supplied by the TAL).
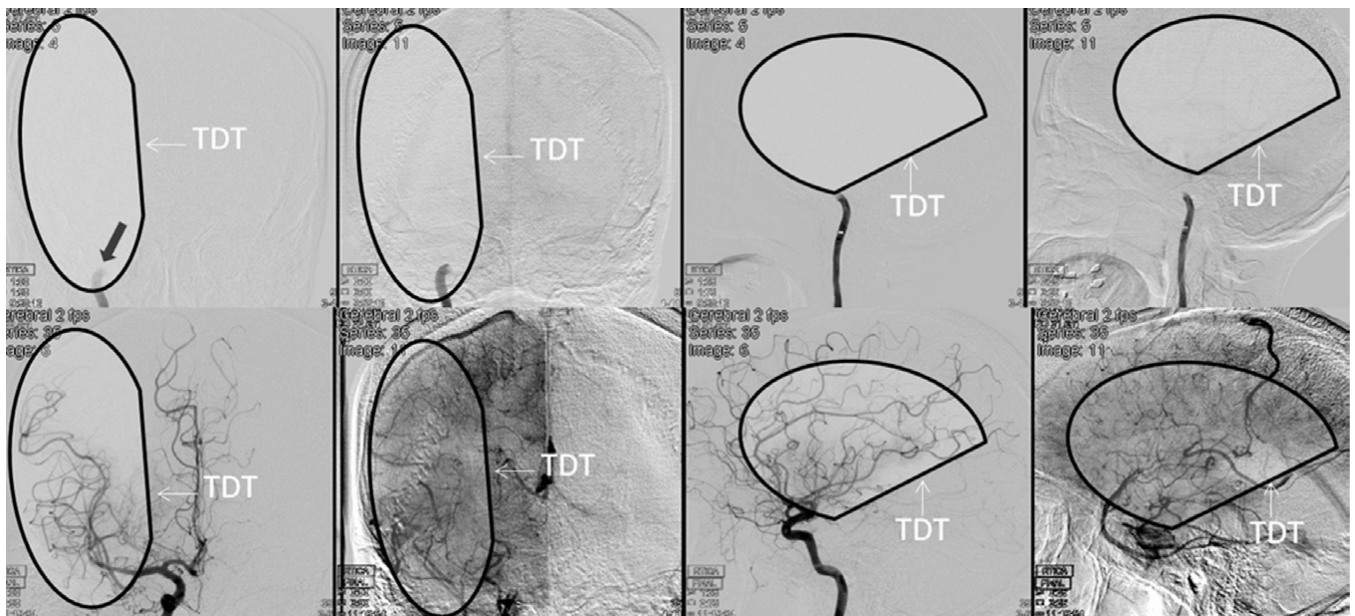
Figure 5.
Example of downstream territory (TDT) for an ICA occlusion with pre–intra-arterial therapy
(IAT) data from CT angiogram showing cross-filling from the contralateral anterior cerebral
artery. **Top**, Anteroposterior (first 2 boxes) and lateral (last 2 boxes) in an early arterial and
late capillary phases depicting thrombolysis in cerebral infarction (TICI) 0 at baseline.
Bottom, Same phases depicting TICI 3 after IAT. Black arrow indicating the target arterial
lesion (TAL): Distal ICA proximal to the ophthalmic artery. Black half circles approximate
the target downstream territory (TDT; the presumed area supplied by the TAL). Early
ischemic arteriovenous shunting is noted in the right lower corner.

Table 1

Thrombolysis in Myocardial Ischemia Scale

TIMI Grades	Definitions
Grade 0	Absence of any antegrade flow beyond the target occlusion (no perfusion)
Grade 1	Any faint antegrade flow beyond the target occlusion, with incomplete filling of the distal branches (penetration without perfusion)
Grade 2	Delayed or sluggish antegrade flow with complete filling of the distal M2 branches flow (partial perfusion)
Grade 3	Normal flow that fills all distal branches, including M3 and M4 (complete perfusion)

TIMI indicates thrombolysis in myocardial ischemia.

Table 2

Modified Treatment in Cerebral Ischemia Scale

mTICI Grades	Definitions
Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
Grade 2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

MCA indicates middle cerebral artery; and mTICI, Modified Treatment in Cerebral Ischemia Scale.

Table 3

Arterial Occlusive Lesion Scale

AOL Grades	Definitions
Grade 0	Complete occlusion of the target artery
Grade 1	Incomplete occlusion or partial local recanalization at the target artery with no distal flow
Grade 2	Incomplete occlusion or partial local recanalization at the target artery with any distal flow
Grade 3	Complete recanalization and restoration of the target artery with any distal flow

AOL indicates arterial occlusive lesion.

Table 4

American Society of Interventional and Therapeutic Neuroradiology Collateral Grading System

ACG Grades	Definitions
Grade 0	No collaterals visible to the ischemic site
Grade 1	Slow collaterals to the periphery of the ischemic site, with persistence of some of the defect
Grade 2	Rapid collaterals to the periphery of the ischemic site, with persistence of the defect, and only to a portion of the ischemic territory
Grade 3	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
Grade 4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion
N/A	Not applicable based on the territory or injections available

ACG indicates the American Society of Interventional and Therapeutic Neuroradiology collateral grading.

Table 5

Suggested Stroke Intervention Time Intervals

Time Interval Variables	Definitions
Onset to door (Off))[*]	Time from last known well to Emergency Department registration
Door to imaging (DtI)[*]	Time from ED arrival to start of noncontrast CT head imaging used for treatment selection
Imaging to endovascular team activation	Time from start of noncontrast CT head to activation (contacting) the endovascular team
Endovascular team activation to arrival to angiosuite (ATAtAA)	
Imaging to angiosuite (ItA)	Time from start of noncontrast CT head imaging to angiosuite room entry
Angiosuite entry to puncture (AtP)[*]	Time from room entry to arterial puncture
Puncture to baseline angiogram (PtBA)	Puncture to placing the main catheter/sheath in the base vessel (carotid or vertebral)
Puncture to clot (PtC)	Time from arterial puncture to first access of the clot by microcatheter
Clot to TICI 2a perfusion (CtP)	Time from first access of the clot by microcatheter to first achievement of persistent TICI 2a or better reperfusion
Clot to substantial perfusion (CtSP)[*]	Time from first access of the clot by microcatheter to first achievement of persistent TICI 2b or better reperfusion
Clot to end of procedure (CtE)[*]	Time from first access of the clot by microcatheter to final angiogram

SITI indicates stroke interventional time intervals; and TICI, thrombolysis in cerebral infarction.

[*] Strong consideration.

Table 6

Imaging Acquisitions

Images	Instructions	Comments
Baseline angiogram	Acquired in biplane frontal and lateral projections and filmed throughout the arterial and venous phases	
Intermittent biplane angiograms	Every 15 min or after each device pass Acquired in biplane frontal and lateral projections and filmed	Some studies have suggested that additional intraprocedural contrast injections may increase hemorrhage risk
Superselective microcatheter angiograms	Acquired in biplane frontal and lateral projections, with injections beyond the target occlusion	Some studies have suggested that additional microcatheter contrast injections may increase hemorrhage risk
Final angiogram	Acquired final biplane angiogram at the same angles and magnification of the baseline angiogram inclusive of the target ischemic territory	
Angiographic image annotation	Annotation of each angiogram critical for each imaging obtained.	For example: Side and vessel name, baseline angiogram, baseline microcatheter angiogram before first pass, after first pass angiogram, angiogram after XX mg of thrombolytic.. .etc.
Filming rate	Angiographic acquisition at filming rate adequate for assessment of all angiographic phases	
Still images	Still images should be obtained when any device is deployed with annotation indicating the name of the device and the order of the deployment	

Table 7

Summary of Panel Recommendations

Consensus Issues	Recommendations	Considerations
Cerebral angiographic revascularization grading (CARG)	• Revascularization scales should measure recanalization and reperfusion separately • mTICI should be used as the standard reperfusion grading scale • mTICI should stand for modified treatment in cerebral ischemia (mTICI) instead of thrombolysis • Arterial occlusive lesion (AOL) should be used to measure recanalization	• The panelists strongly recommended adopting a single CARG scale for reperfusion and another for recanalization with consistent definitions across studies • Because mTICI and AOL assess different revascularization aspects, it is optimal to obtain and report both measures
Definition of mTICI grades	• mTICI 2b should be defined as more than half, but less than complete, antegrade reperfusion of the target downstream territory (TDT) • mTICI 3 should be defined as complete antegrade reperfusion of the TDT, with absence of visualized occlusion in all distal branches	• The recommended definition of mTICI 2b seems to have good inter-rater reliability and is highly predictive of clinical outcome
Target angiographic end point	• Target angiographic end point for assigning technical success should be mTICI 2b or higher	• mTICI 2b reperfusion seems to have higher specificity and sensitivity in discriminating between poor and good clinical outcome than mTICI 2a
Target arterial lesion (TAL)	• TAL is the most proximal treated intracranial occlusive lesion	• Identification of the TAL is important for describing and systematically evaluating procedural technical efficacy
Intracranial ICA occlusion evaluation	• Carotid terminus occlusion extent must be documented based on the best available data: • Carotid T if terminal ICA, M1, and A1 are occluded • Carotid L if both terminal ICA and M1 are occluded (sparing of A1) • Carotid I if only terminal ICA occluded (sparing of M1 and A1)	• Both functional and anatomic considerations should be taken into account when reporting ICA occlusions
MCA segment clot location	• The M1 segment should be taken as the first portion of the MCA until the major bifurcation • Clot location in the M1 should be further localized as proximal or distal based on which half of the M1 segment is involved or whether the lenticulostriates are involved (proximal) or spared (distal) • Normal anatomic variations should be described (eg, duplicated M1, dominant anterior temporal branch, or aplastic, hypoplastic or normal caliber A1)	• The prognosis of M1 occlusion in the setting of a duplicated horizontal segment, dominant temporal artery, or aplastic A1 may be different
Target downstream territory (TDT)	• TDT is the brain region that lacks antegrade capillary staining secondary to the target lesion	• Territory receiving retrograde collateral perfusion should be considered as part of the TDT

Consensus Issues	Recommendations	Considerations
	• In ICA occlusion, the TDT should be both ACA and MCA	• The full extent of this territory serves as the denominator in calculating the percentage of tissue reperfusion
	• In VB occlusion, the TDT should be BA, both superior and posterior cerebral arteries	
	• If evidence from other baseline imaging data shows a different pattern than expected above, adjustment to the TDT must be made	
Cerebral collateral flow grading (CCFG)	• For DSA data, CCFG must be assessed using the ASITN grading scale	
	• In the absence of DSA collateral information, noninvasive imaging data should be evaluated	
Embolization into new territory (ENT) and distal embolization (DE) into the TDT	• ENT denotes treatment-related embolization into areas outside the TDT	• Given the potential deleterious effect of ENT and unknown prognosis of DE, it is important to define and document their occurrence
	• DE is defined as any treatment-related embolization into the TDT	
	• ENT after IAT should be reported	
	• DE is difficult to accurately characterize (ie, requires knowledge of baseline emboli in the TDT), and is accounted for in the mTICI grade	
Venous shunting	• Early venous shunting during IAT should be recorded	
Procedural time metrics	• The following Stroke Interventional Time Intervals should be documented: onset to door, door to imaging, door to needle (IV thrombolysis), picture to puncture and puncture to revascularization/ end of the procedure	• When performing clinical studies, additional procedural steps should be documented in a manner that matches the published protocols
Therapeutic intervention details	• Therapeutic intervention steps need to be reported in a standardized format and documented with proper imaging acquisition	
Angiography imaging techniques	• Baseline and final biplane images must be obtained	• Digital subtraction angiography should be performed at baseline, at key intervals, and at the end of the procedure in biplane projection and performed in the venous phase
	• Oblique images should be obtained to identify the site and extent of the clot	
	• Filming at adequate rate for assessment of all angiographic phases	
	• Filming throughout the angiographic phases into the venous phase	• Archiving of at least every other frame is necessary for adequate documentation
	• Capturing still images of each device used during the intervention	

ACA indicates distal anterior cerebral artery; ASITN, American Society of Interventional and Therapeutic Neuroradiology; BA, basilar artery; DSA, digital subtraction angiography; IAT, intra-arterial therapy; ICA, internal carotid artery; MCA, middle cerebral artery; and VB, vertebrobasilar.