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Revascularization grading in endovascular acute ischemic stroke therapy

O.O. Zaidat, MD, MS
M.A. Lazzaro, MD
D.S. Liebeskind, MD
N. Janjua, MD
L. Wechsler, MD
R.G. Nogueira, MD
R.C. Edgell, MD
J.S. Kalia, MD
A. Badruddin, MD
J. English, MD
D. Yavagal, MD
J.F. Kirmani, MD
A.V. Alexandrov, MD
P. Khatri, MD

Correspondence & reprint requests to Dr. Zaidat: szaidat@mcw.edu

ABSTRACT

Background: Recanalization and angiographic reperfusion are key elements to successful endovascular and interventional acute ischemic stroke (AIS) therapy. Intravenous recombinant tissue plasminogen activator (rt-PA), the only established revascularization therapy approved by the US Food & Drug Administration for AIS, may be less effective for large artery occlusion. Thus, there is enthusiasm for endovascular revascularization therapies, which likely provide higher recanalization rates, and trials are ongoing to determine clinical efficacy and compare various methods. It is anticipated that clinical efficacy will be well correlated with revascularization of viable tissue in a timely manner.

Method: Reporting, interpretation, and comparison of the various revascularization grading methods require agreement on measurement criteria, reproducibility, ease of use, and correlation with clinical outcome. These parameters were reviewed by performing a Medline literature search from 1965 to 2011. This review critically evaluates current revascularization grading systems.

Results and Conclusion: The most commonly used revascularization grading methods in AIS interventional therapy trials are the thrombolysis in cerebral ischemia (TICI, pronounced “tissy”) and thrombolysis in myocardial ischemia (TIMI) scores. Until further technical and imaging advances can incorporate real-time reliable perfusion studies in the angio-suite to delineate regional perfusion more accurately, the TICI grading system is the best defined and most widely used scheme. Other grading systems may be used for research and correlation purposes. A new scale that combines primary site occlusion, lesion location, and perfusion should be explored in the future. *Neurology*® 2012;79 (Suppl 1):S110-S116

GLOSSARY

AIS = acute ischemic stroke; **AOL** = arterial occlusive lesion; **ASITN/SIR** = American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; **DSA** = digital subtraction angiography; **ERT** = endovascular revascularization therapy; **MCA** = middle cerebral artery; **rt-PA** = recombinant tissue plasminogen activator; **SVIN** = Society of Vascular & Interventional Neurology; **TIBI** = thrombolysis in brain ischemia; **TICI** = thrombolysis in cerebral ischemia; **TIMI** = thrombolysis in myocardial ischemia.

Rapid and safe revascularization leading to good clinical outcome is the goal of acute ischemic stroke (AIS) therapy. Despite extensive investigation, only one therapy has demonstrated efficacy with randomized controlled trial: thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA).¹ The efficacy of rt-PA as an emergency treatment for AIS was demonstrated in 1995, which marked a milestone in stroke care.¹ Limitations to systemic rt-PA use have led to enthusiasm for alternative methods of revascularization therapy. Endovascular revascularization therapy (ERT) in AIS employs methods including intra-arterial thrombolysis, thromboaspiration, sonothrombolysis, and mechanical thrombectomy. A favorable clinical outcome is the ultimate goal of ERT, and revascularization has been shown to be associated with good clinical outcome in stroke studies.²

From the Departments of Neurology (O.O.Z., M.A.L.), Neurosurgery (O.O.Z.), and Radiology (O.O.Z.), Medical College of Wisconsin/Froedtert Hospital, Milwaukee; UCLA Stroke Center (D.S.L.), Los Angeles, CA; Department of Neurology, Asia Pacific Comprehensive Stroke Institute (N.J.), Pahoia, HI; Department of Neurology, University of Pittsburgh Medical Center (L.W.), PA; Emory University (R.G.N.), Atlanta, GA; St. Louis University (R.C.E.), St. Louis, MO; University of Illinois at Chicago/Provena St. Joseph Hospital (A.B. [Daniel M. Soref Clinical Neuroscience Fellow]), Chicago; Department of Neurology, University of California San Francisco (J.E.), San Francisco; University of Miami (D.Y.), Miami, FL; JFK Neuroscience Center (J.F.K.), Edison, NJ; Comprehensive Stroke Center, University of Alabama Hospital (A.V.A.), Birmingham; and University of Cincinnati (P.K.), Cincinnati, OH.

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Several nonrandomized trials have evaluated the safety and efficacy of various endovascular approaches, but interpreting and comparing their results is challenging because of heterogeneous trial designs. In particular, a uniform revascularization grading system is lacking. Furthermore, ischemia in acute stroke is extremely complex and perhaps warrants distinction of primary ischemia resulting from a vessel occlusion vs secondary ischemia characterized by collateral blood flow and cerebral oxygen supply that is dependent on other parameters, including arterial blood pressure and arterial oxygen content.³ We review the literature on available methods for measuring cerebrovascular revascularization and emphasize the need for consensus on reporting standards for revascularization. Although revascularization would seem to be only one of the factors important in salvaging tissue at risk, it appears to play a considerable role. In selected patients with AIS, successful recanalization of the thrombotic occlusion is a strong predictor of lower 3-month mortality and favorable functional outcomes.^{2,4,5} Furthermore, successful recanalization has been reported as the main predictor of good outcome among patients treated with mechanical thrombectomy.⁶ In addition, time to revascularization is an independent predictor of good outcome in select patients with AIS.⁷ Although these findings fuel a growing interest in thrombectomy, rigorous clinical trials are needed to better understand the role of endovascular revascularization for optimizing clinical outcomes. This underscores the importance of defining, scoring, and reporting revascularization in AIS studies.^{8,9}

REVASCULARIZATION, REPERFUSION, AND RECANALIZATION Revascularization is variably defined in AIS studies as recanalization, which represents restoration of vessel patency at the site of occlusion; angiographic reperfusion, which includes contrast opacification of the distal arterial territory; and a combination of these definitions. The combination of recanalization and reperfusion is the more comprehensive and perhaps most clinically relevant descriptor of revascularization. Recanalization and reperfusion can occur independently of each other, but typically they have considerable overlap. Recanalization does not guarantee angiographic or tissue reperfusion, as the no-reflow phenomenon may pre-

clude perfusion of target tissue because of distal branch occlusions, despite restoration of proximal vessel patency. Reperfusion refers to antegrade perfusion of patent microvasculature supplying the target tissue after recanalization. It is important to note that distal territory may also receive perfusion in a retrograde flow pattern from collateral supply; therefore, angiographic reperfusion distinctly involves perfusion of distal territory in an antegrade manner following recanalization. The collateral supply, providing retrograde filling, is an additional important element of revascularization that has received limited attention in clinical trial reporting.

Recanalization scoring seems to be intuitive, requiring grading of the vessel patency or, in other words, residual clot burden. Reperfusion, on the other hand, involves a more intricate set of parameters including distinguishing antegrade perfusion, quantifying the extent of the vascular bed that is reperfused, and assessing the perfusion time. Collateral supply is also challenging to characterize, in part because of poorly defined parameters for grading and individual variability in the Circle of Willis evaluation amid the endovascular intervention. Agreement on the definition of revascularization is essential for reporting, reproducibility, and comparative interpretation of ERT studies. An optimal grading system would take into consideration all of the latter criteria (table 1).

ANGIOGRAPHIC GRADING SYSTEMS Endovascular revascularization therapy involves digital subtraction angiography (DSA), which offers characterization of blood flow in AIS. Angiography allows evaluation of the occlusion site, potentially the length of the vessel harboring the clot, extent of collateral supply, as well as postintervention characterization of vessel patency, rate of blood flow, reperfusion territory, distal occlusion/embolization, and early venous shunting. Features poorly represented by less-invasive imaging, including spatial and temporal resolution and retrograde flow characterization, are permitted with catheter angiography. These factors are measured to

Table 1 Criteria for an optimal revascularization scale

- Takes into account both recanalization and reperfusion
- Takes into account cerebral collateral circulations
- Reproducibility: intra- and inter-rater reliability
- Ease of use and application in daily practice, not trials-only scale
- Comparable results across clinical trials
- Prognostic significance and correlation with clinical outcome

varying degrees in the available angiographic grading scales. Several grading systems have been proposed to characterize angiographic findings in cerebral ischemia. Each scheme shows variable emphasis on the different angiographic aspects that include arterial occlusion, perfusion, lesion location, and collateral flow (table 2). Several of the grading systems have also been shown to be associated with clinical outcome.

Thrombolysis in Myocardial Infarction score. The Thrombolysis in Myocardial Infarction (TIMI) Study Group devised the first angiographic score for reperfusion in acute myocardial infarction.^{10,11} This is a simple angiographic score that has been used in numerous major cardiovascular trials of thrombolytic agents, balloon angioplasty, and stent placement. The TIMI score is graded from 0 to 3 according to angiographic demonstration of blood flow (table 2). The TIMI flow grading system has been useful in predicting outcome for cardiac patients.¹² In AIS trials, TIMI has been applied in a variable manner and with variable operating definitions to assess recanalization, angiographic reperfusion, or both.¹³ Some applications of the TIMI scale that have been associated with clinical functional outcomes have been demonstrated in studies of intra-arterial thrombolysis for AIS.^{13,14} The variability in the operating manual/grading definition of the TIMI scoring system is the main disadvantage of its use across clinical trials; however, its biggest advantage is its simplicity and familiarity to many stroke neurologists and neurointerventionalists.

Mori reperfusion scale. In 1992, Mori et al.¹⁵ published a report of intracarotid urokinase injection for acute middle cerebral artery (MCA) occlusion in 22 patients. In the manuscript, the authors described a novel grading scale for reporting cerebral angiographic reperfusion. The Mori scale ranges from 0 to 4, representing no reperfusion to complete reperfusion (table 2). Whereas the TIMI score of 2 represents partial recanalization, the Mori scale subdivides this into Mori grades 2 and 3, based on reperfusion of the distal arterial territory. Mori grade 2 represents less than 50% distal flow, and grade 3 represents greater than 50% distal flow. Subsequent evaluation of the Mori grading system demonstrated association with clinical outcome and suggested that the expanded distinction of reperfusion categories may improve outcome prediction.¹⁴

Qureshi scale. A new classification scheme proposed by Qureshi¹⁶ in 2002 is different from other grading schemes in several ways. This scale includes 6 grades that range from 0 to 5, classifying no occlusion (0) to large-vessel occlusion of the internal carotid artery or basilar artery with no collaterals; thus, higher grades indicate worse angiographic outcomes than lower

grades. This scale also is based on the site of arterial occlusion and the presence of collateral pathways. The grading increases in severity according to the size and location of occlusions, starting from smaller-vessel occlusions (M3, A2, BA branches) to the intermediate-sized M1 segment, to large arteries (internal carotid artery, basilar artery). This scale's strength is in its design to incorporate clinical severity by considering the size of the occluded vessel's vascular territory. However, its complexity may preclude its routine use.

Thrombolysis in Cerebral Infarction scale. With the growth of AIS studies, standards for design and reporting were proposed in 2003 by Higashida et al., including recommendation of the Thrombolysis in Cerebral Infarction (TICI) scale.¹⁷ This scale is a modified version of the TIMI scale that provides a subcategorization of the second perfusion score into grades 2A and 2B (table 2). Additionally, the authors also provided explicit definitions for designating each grade that are directly relevant to cerebral vasculature. The TICI grading approach uses contrast filling and clearance time to further stratify the wide range of partial reperfusion that exists between the TIMI grades 1 (minimal reperfusion) and 3 (complete reperfusion). Thus, as with the Mori scale, the TICI scale creates further categories of partial reperfusion, and study of the Mori scale suggests that this is likely to be clinically relevant.¹⁴ The TICI scale is being used to grade revascularization in the recently stopped IMS-III trial; these results may offer further evaluation of this grading scale.

Arterial Occlusive Lesion score. The Arterial Occlusive Lesion (AOL) scoring system was introduced in the IMS I pilot trial to evaluate recanalization directly.¹³ It focuses solely on the clot burden at the original arterial occlusive site. The AOL system assigns a score from 0 to 3, which represents the range from no recanalization to complete recanalization with any distal flow (table 2). This method was compared with TIMI reperfusion scoring in the IMS I trial to determine the relationship between recanalization and reperfusion; there was no statistical difference between the two methods of prediction of clinical outcome ($p = 0.11$), although numerically TIMI reperfusion had a higher association.¹³ The agreement between the 2 scales was modest (inter-scales AOL to TIMI κ is 0.30; confidence interval, 0.16 to 0.44).¹³ This analysis suggested that recanalization is related to reperfusion, and both may be important in overall clinical outcomes. The AOL score will also be reported in the IMS-III trial results.

Extent of collateral supply. Collateral supply has an important role in sustaining the threatened vascular

Table 2 Current grading systems for vessel revascularization on cerebral arteriography^a

Grade	TIMI	TICI and modified TICI	Mori	AOL
0	No recanalization	No perfusion and no antegrade flow beyond the point of occlusion	No reperfusion	No recanalization of the primary AOL
1	Minimal recanalization	Penetration with minimal perfusion; the contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run	Minimal reperfusion	Complete or partial recanalization of the primary occlusive lesion with no distal flow
2	Partial recanalization	Partial perfusion; the contrast material passes the obstruction and opacifies the arterial bed distally. However, the rate of entry of contrast into the vessel distal to the obstruction or its clearance rate from the distal bed is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.	Reperfusion of <50% of the territory of the occluded artery	Incomplete or partial recanalization of the primary occlusive lesion with any distal flow
		2A: Only partial filling (<2/3, modified <50%) of the vascular territory is visualized		
		2B: Complete (or >50% modified) filling of the expected vascular territory is visualized, but the filling is slower than normal		
3	Complete recanalization	Complete perfusion	Reperfusion of >50% of the occluded artery territory	Complete recanalization of AOL with any distal flow
4	No grade 4	No grade 4	Complete reperfusion	No grade 4
5	No grade 5	No grade 5	No grade 5	No grade 5
Grade	TICI Grading Scale		Qureshi Grading Scale	ASITN/SIR Collateral Flow Grading Scale
0		Absent: absent flow	No occlusion	No collaterals visible to the ischemic site
1		Minimal: systolic spikes of variable velocity and duration and absent diastolic flow	MCA occlusion (M3 Segment) or ACA occlusion (A2 or distal segments) or one basilar or vertebral branch occlusion	Slow collaterals to the periphery of the ischemic site, with persistence of some of the defect
2		Blunted: flattened systolic flow with positive EDV and pulsatility	MCA occlusion (M2 Segment) or ACA occlusion (A1 or distal segments) or two basilar or vertebral branch occlusions	Rapid collaterals to the periphery of ischemic site, with persistence of some of the defect, and to only a portion of the ischemic territory
3		Dampened: normal systolic flow and positive and EDV pulsatility but with decreased MFV (by >30%)	MCA occlusion (M1 Segment)	Collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
			3A: lenticulostriate arteries are spared and/or leptomeningeal collaterals visualized	
			3B: lenticulostriate arteries and leptomeningeal collateral supply is not visualized	
4		Stenotic: MFV of >80% and velocity difference of >30%	ICA occlusion (collaterals present) or BA occlusion (partial filling direct or via collaterals)	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion
5		Normal: <30% MFV difference vs control	Complete occlusion of the ICA or BA with no collateral filling	No grade 5

Abbreviations: ACA = anterior cerebral artery; AOL = arterial occlusion lesion; ASITN/SIR = American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; BA = basilar artery; EDV = end diastolic velocity; ICA = internal carotid artery; MCA = middle cerebral artery; MFV = mean flow velocity; TICI = thrombolysis in cerebral infarction; TIMI = thrombolysis in myocardial infarction.

^a Classification by Mori et al.¹⁵

territory and is a predictor of recanalization after ERT.¹⁸ The interrelationship between revascularization and the extent of collateral supply is likely to be important, but it is not as well studied.

American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading Scale. In addition to proposing the TICI scale for stroke trial design and report-

ing standards, Higashida et al. described the importance of collateral flow and proposed an adjunctive Collateral Flow Grading System. This scale grades collateral supply from 0 to 4, characterizing collateral flow from absent to complete and rapid (table 2). This collateral scale has been shown to predict infarct growth,¹⁹ and a more recent study found that baseline collateral scores predict recanalization success.¹⁸

Table 3 Advantages and limitations of different revascularization scales in ischemic stroke

Scale	Advantages	Limitations
Thrombolysis in myocardial ischemia (TIMI)	Simple, frequently used	Not accurate for collateral and reperfusion Does not account for eloquency/occlusion site
Thrombolysis in cerebral ischemia (TICI)	Simple, frequently used, reperfusion adjustment	Better reperfusion adjustment but still not precise Does not account for eloquency/occlusion site
Arterial occlusion lesion (AOL)	Simplest, high interobserver reliability	No reperfusion
Mori reperfusion	Simple, reperfusion adjustment	Better reperfusion adjustment but still not precise Does not account for eloquency/occlusion site
Qureshi	Accounts for occlusion site	Complex Not precise for reperfusion
ASITN/SIR collateral flow grading	Collateral grading	No recanalization No reperfusion

Christoforidis pial collateral scale. Christoforidis et al.²⁰ described a pial collateral grading scale for proximal MCA occlusions. The scale ranges from 1 to 5, indicating very good to very poor collaterals. This scale was used in angiograms for a series of patients with AIS and demonstrated lower infarct volume and discharge modified Rankin scale score for those patients with better pial collateral scores.

The Matas test. Wang et al.²¹ first reported on a provocative test of temporary large vessel occlusion to evaluate the adequacy of collateral circulation. This evolved to include clinical assessment, nuclear brain imaging to assess the first-pass effect of an isotope injected during the occlusion and, more recently, estimating the difference in contrast transit time by

injecting the contralateral vessel with poor collateral, indicated by a delay of more than 2 seconds.

Thrombolysis in brain ischemia scale. Application to noninvasive imaging of the optimal scale would provide wider application to AIS trials, beyond endovascular therapy, or provide application for reocclusion monitoring following interventional therapy. The thrombolysis in brain ischemia (TIBI) scale correlates with initial stroke severity and clinical improvement post-thrombolysis and is now in use in AIS clinical trials of sonothrombolysis.^{22,23} The TIBI scale is composed of 5 points; 0 indicates absence of flow signals, and 5 indicates a less than 30% difference from control in the mean blood flow velocity (table 2).

COMMENT Applying a simple grading scale to a complex disease is challenging. There are numerous difficulties encountered in revascularization grading of arterial occlusions. Ischemic stroke is a complex and heterogeneous disease that includes varying sizes of arterial occlusions (from proximal to distal), with varying territories in individual patients, varying baseline neuroanatomy of collateral supply, and varying functional collateralization. Furthermore, the specific tissue “eloquence” of the affected vascular territory will dramatically affect clinical outcomes. Less attention has been given to the role of cerebral collateral circulation in revascularization studies. The presence of collateral circulation may have a considerable prognostic role. Collateral grading is often challenging because of the need for very complex characterizations to eliminate subjectivity. Performing angiography of the neighboring vascular territory is necessary to describe this collateral flow. Finally,

Table 4 Revascularization scale use in selected endovascular acute ischemic stroke clinical studies

Trial	Sample size/no. of centers	Primary reperfusion scale
MERCI Pilot ²⁵	28/7	TIMI
MERCI Trial ²⁶	141/25	TIMI
PROACT Trial ²⁷	40/37	TIMI
PROACT II Trial ²⁸	180/54	TIMI
IMS I ¹³	80/17	TICI
IMS II ²⁹	72/13	TICI
IMS III ³⁰	900/60 (planned)	AOL, TICI
Penumbra ³¹	30/6	TIMI
Penumbra Pivotal Stroke Trial ³²	125/24	TIMI
Qureshi et al. study ¹⁶	15/1	Qureshi

angiographic observation of early venous shunting in intra-arterial reperfusion therapy is predictive of hemorrhage, which is not accounted for in the current scales.²⁴

Many unanswered questions remain about current grading systems, including their inter-rater reliability, their individual and relative prognostic value for clinical outcomes, and their association with each other.

Grading scales that measure recanalization or angiographic reperfusion are likely to be comparable in predictive ability; however, they should not be used interchangeably, because they measure properties of arterial revascularization that are potentially exclusive of each other. Different therapies may affect recanalization and reperfusion differently, and therefore consistent use of the same grading scale may be necessary. For example, the reperfusion grade, as opposed to the recanalization grade measured by the AOL scale, may be less important when using thrombolytics that could lyse small distal emboli. Angiographic reperfusion may be more relevant for mechanical thrombectomy without systemic thrombolysis, in which case small distal emboli may be more likely to persist.

Comparison between the AIS revascularization scales discussed above, with pros and cons, is shown in table 3. The TICI and TIMI are the scales most commonly used in AIS trials; table 4 outlines the various revascularization scales used in selected AIS studies. Future gathering of expert opinion and consensus on revascularization grading are needed, along with more data on inter-rater/intra-rater and scale agreement.

AUTHOR CONTRIBUTIONS

Dr. Zaidat: drafting/revising the manuscript, study concept or design, study supervision. Dr. Lazzaro: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Liebeskind: drafting/revising the manuscript, acquisition of data. Dr. Janjua: drafting/revising the manuscript, study concept or design. Dr. Wechsler: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data. Dr. Nogueira: study concept or design, analysis or interpretation of data. Dr. Edgell: drafting/revising the manuscript, analysis or interpretation of data. Dr. Kalia: drafting/revising the manuscript. Dr. Badruddin: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. English: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis, study supervision, obtaining funding. Dr. Yavagal: drafting/revising the manuscript. Dr. Kirmani: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Alexandrov: drafting/revising the manuscript, acquisition of data. Dr. Khatri: study concept or design, study supervision.

DISCLOSURE

Dr. Zaidat serves on the scientific advisory board for Talecris; served on the adjudication committee for Stryker; received speaker honoraria from Stryker; served on the editorial board of *Frontiers in Neurology* (Endovascular & Interventional Neurology Section); serves as Editor of *The Journal*

of *Neurointerventional Surgery*; serves as Associate Editor and is a member of the Editorial Board of *Journal of Stroke & Cerebrovascular Diseases*; served as a consultant for Stryker Neurovascular, Codman Neurovascular, Microvention Inc; and has received research support from Society of Vascular & Interventional Neurology (SVIN) for this educational activity. Dr. Lazzaro reports no disclosures. Dr. Liebeskind served as a consultant for Concentric Medical and CoAxia and receives research support from NIH. Dr. Janjua serves on the scientific advisory board for Lundbeck/DSMB and Neurointerventions; receives research support from NIH/NINDS; and holds stock or stock options or Board of Directors Compensation for Neurointerventions. Dr. Wechsler reports no disclosure. Dr. Nogueira serves as a consultant for Concentric and CoAxia. Dr. Edgell serves as a member of the data safety monitoring board for the Medtronic INPACT SFT clinical trial and Medtronic ACTIVE clinical trial; serves as a member of the Clinical Events Committee, Concentric TREVO-2 clinical trial; and serves as an editorial board member for *The Neurohospitalist*. Dr. Kalia has received funding for travel or speaker honoraria from Penumbra Inc. for consultation and speaking over the past 2 years; serves as Associate Editor for *Frontiers in Endovascular Neurology*; served as a consultant to Penumbra Inc, Codman Neurovascular, Micrus Inc, Genentech, and Boston Scientific; received research support from the Florida Biomedical New Investigator Award; and received an intramural grant. Dr. Badruddin received funding for travel and speaker honoraria for the SVIN conference and to attend the SVIN roundtable summit. Dr. English served on the scientific advisory boards for Concentric Medical Inc.; served as a medical advisory board member of Co-Axial Inc. and eV 3 Inc.; served as an Associate Editor for *Journal of Neuroimaging*; was employed by Concentric Medical Inc. in 2008–2009, Co-Axial Inc. in 2008, and eV 3 Inc. in 2008; and has acted as an expert witness. Dr. Yavagal received an honorarium from Penumbra Inc. for consultation and speaking; serves as an Associate Editor for *Frontiers in Endovascular Neurology*; and serves as a consultant to Penumbra Inc., Codman Neurovascular, Micrus Inc., Genentech, and Boston Scientific. Dr. Kirmani served on the advisory board for Otsuka Pharmaceuticals; served as an Associate Editor for *Frontiers in Clinical Trials in Neurology*; received publishing royalties from Taylor and Francis Group for *The Stroke Center Handbook*; receives research support from Penumbra, Inc., and Genentech, Inc.; received research support from NIH/NINDS; and has served as expert witness for stroke cases. Dr. Alexandrov serves as an Associate Editor for *Frontiers of Interventional Neurology*. Dr. Khatri is on the Executive Committee of the IMS III Trial; is the Neurology PI of the Penumbra THERAPY Trial; has received research support from Genentech, Inc., for survey implementation; and served on the editorial boards of *Frontiers in Endovascular and Interventional Neurology*. **Go to Neurology.org for full disclosures.**

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O.O. Zaidat, M.A. Lazzaro, D.S. Liebeskind, et al.

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