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TIMI, TIBI, TICI: I Came, I Saw, I Got Confused

Reports continue to appear regarding intravascular treatment paradigms that restore blood flow to occluded intracranial cerebral blood vessels.¹⁻⁴ Flow restoration is the only therapy proved of benefit, and it is indeed important to monitor and share results of therapeutic efforts. Clinical studies, case series, and reviews continue to be conducted and published with different, or unclear methods of assessment of flow restoration. This variability in reporting methods of flow-restoration evaluation render comparison of 1 study with others difficult, if not impossible. The problem of variability in reporting methods can be divided into problems with 1) terminology and definition, 2) convention, and 3) application. Having contributed to some of the confusion myself, I will comment on the variability in reporting methods in the context of these problems, likely raising more questions than answering them.

Terminology and Definition. Arteriographic demonstration of flow restoration or revascularization, in reality, has 2 components: recanalization of the original or primary arterial occlusive lesion (AOL) and reperfusion past the occlusion and into the distal arterial bed and terminal branches with tissue staining. Complete recanalization of the primary occlusion may have variable distal patency and perfusion/reperfusion. Complete proximal recanalization with limited distal perfusion may be associated with a greater central hemorrhage risk into areas supplied by injured penetrating arteries subjected to altered pulse pressures. Conversely, recanalization may be incomplete, sometimes with complete distal patency and perfusion, though at a reduced flow rate difficult to quantitate angiographically. Variable distal patency and perfusion may be due to pre-existing emboli or emboli released by the recanalization procedure itself. Incomplete recanalization may lead to reocclusion, with clinical deterioration.^{5,6} Recanalization does not equal reperfusion, though total reperfusion does not occur without some recanalization. Varying degrees of reperfusion occur via collateral sources and may be very effective in certain patients.

Mori et al⁷ first described a system that assessed both recanalization and perfusion following intravenous administration of recombinant tissue plasminogen activator (rtPA). Zeumer et al⁸ described complete, partial, or no recanalization but did not clarify the magnitude of perfusion achieved, with no specific reference to flow in distal branches. Others have followed Mori et al and Zeumer et al in their descriptions, with variations on the themes. The Thrombolysis in Myocardial Infarction (TIMI) score described distal flow perfusion and revascularization before and following therapy and became a standard for reporting cardiac reperfusion procedure efficacy.⁹ It was applied to intracranial thrombolysis, though the TIMI score does not specifically describe both the recanalization effect and the distal perfusion effect simultaneously. Various authors have reported TIMI recanalization or TIMI perfusion scores, without fully describing the features of each

grade and ignoring the issues of AOL recanalization versus distal perfusion. The Prolyse in Acute Cerebral Thromboembolism (PROACT II) protocol called for application of the TIMI perfusion method of assessment, but then the final core laboratory analysis reported patency of the middle cerebral artery (MCA) M1 and M2 branches.¹⁰ In the EKOS MicroLysUS feasibility trial of sonography-catheter-assisted thrombolysis, a TIMI flow score was ascribed by operators (ie, no core laboratory) to the recanalization of each occluded vessel and to each successive occluded vessel, without specific description of distal perfusion.¹¹ Subsequent to PROACT II, Higashida et al¹² made an attempt to standardize reporting of flow restoration and described a thrombolysis in cerebral infarction (TICI) score. Published in 2003, it has been included as a tool in only a few case series¹³ but will be used in a number of prospective trials currently being planned or underway.

A thrombolysis in brain ischemia (TIBI) score has been derived for a transcranial sonography description of intracranial flow at the occlusion site¹⁴ on the basis of flow-velocity signal intensity. TIMI scores are even being applied to MR angiography studies, in which local flow signal intensity is imperfectly depicted and distal flow is not well evaluated.¹⁵ If a perfusion CT or perfusion MR imaging now assesses contrast perfusion to the capillary level, further room for imprecision and confusion exists. When it comes to gold standard arteriographic analysis, how can we evaluate therapies and compare revascularization scores among different studies and therapies when the authors have not guaranteed that they are reporting results similar to those of other reports or to the reader's own particular frame of reference? Certainly within their own study, when determined by a core laboratory, they are presumably giving us apples and apples, but when it comes to comparison between studies, we may be dealing with apples and oranges.

Convention. In PROACT II, the arteries evaluated were homogeneous: MCA M1 trunks and M2 divisions. Thus, a scoring scale could be more easily applied. However, there is no convention for describing revascularization of internal carotid artery (ICA) T occlusion or basilar artery occlusion by using the TIMI method. Cases of basilar artery revascularization may be reported as TIMI 3 if the basilar artery completely recanalizes, with superior cerebellar or posterior cerebral artery emboli commonly evident. The Multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial reported revascularization results for ICA T occlusions, operationally defining TIMI flow through eligible MCA M2 vessels, but with no convention for assessing anterior cerebral artery (ACA) flow, which may be the primary determinant of outcome with T occlusion based on preserved collateral flow.¹⁶

Could it be that it does not matter if reports have used different grading systems or different definitions, terminology, conventions, and application within the same system? Could broad similarities between different scoring applications render narrow differences inconsequential? We sought to answer these questions by reviewing the Interventional Management of Stroke (IMS I) case series of 62 subjects treated with reduced-dose intravenous rtPA, followed by intra-arterial rtPA, and we ascribed TIMI reperfusion scores once again and also applied a new AOL recanalization score, which focused specifically on recanalization patency of the

AOL recanalization and TIMI reperfusion scoring system from IMS I review (after Khatri¹⁸)

Score	AOL Recanalization	Score	TIMI Reperfusion
0	No recanalization of the primary occlusive lesion	0	No perfusion
I	Incomplete or partial recanalization of the primary occlusive lesion with no distal flow	1	Perfusion past the initial occlusion, but no distal branch filling
II	Incomplete or partial recanalization of the primary occlusive lesion with any distal flow	2	Perfusion with incomplete or slow distal branch filling
III	Complete recanalization of the primary occlusion with any distal flow	3	Full perfusion with filling of all distal branches, including M 3, 4

AOL indicates arterial occlusive lesion; TIMI, Thrombolysis in Myocardial Infarction.

primary occluded vessel, without attention to the next branch or distal vessels (Table). The need to perform this analysis arose when we began IMS II and realized that we had a disconnect between the TIMI conventions in IMS I and in the EKOS feasibility study definition (again, where each vessel was ascribed a recanalization score), and we had to find a way to understand, and hopefully resolve, the potential discrepancy.¹⁷

In IMS I, TIMI recanalization was reported by a core laboratory, but the scoring system actually focused on proximal and distal perfusion, similar to a modified TICI system (mentioned previously), in which a TIMI 3 arteriogram was a study with normal or near-normal findings, with perfusion to distal cortical vessels and brain staining throughout and a TIMI 2 score implying near-normal perfusion throughout and at least 1 M2 division, similar to the operational application in PROACT II (W. Dillon, personal communication, 2005).¹⁷ The IMS I review determined that a TIMI 2–3 perfusion score predicted better functional (modified Rankin Scale, 0–2) outcome compared with TIMI 0–1 ($P = .02$). Of interest, an AOL recanalization score of 2–3 also predicted functional outcome, but less significantly ($P = .05$).¹⁸ This finding implies that the AOL recanalization score ultimately largely predicts distal perfusion, suggesting that either distal emboli may not occur sufficiently commonly or that they may not matter greatly, or both. So, insofar as there was little difference in outcomes by using the 2 scoring systems, perhaps much of this previous discussion of reporting comparability is moot—merely a tempest in a teapot: all past TIMI data, whether reporting based on reperfusion, recanalization, or some amalgamation, are generally legitimate and broadly comparable.

This seems to be the case with the IMS paradigm, but we still have not demonstrated that treatment methods other than the IMS paradigm are comparable. Inattention to distal emboli ignored in the AOL score may be mitigated by the thrombolytic effect of intravenous and intra-arterial thrombolytic drugs on distal emboli. Thrombolytic therapy applied at later times in different paradigms may be associated with larger primary infarct, with distal emboli possibly having a more deleterious distal effect, while amplifying any deleterious effect on collateral flow. Clot-removal devices, which have an emphasis on rapid revascularization of the primary AOL, may lead to new or distal emboli that may be significant in reducing collateral flow without the benefit of ongoing thrombolytic activity. Therapies that partially recanalize the AOL may be more subject to reocclusion. Other adjunctive therapy (eg, antiplatelet agents) may be needed to prevent reocclusion under certain conditions. There should be a way to convert the

potential impact of different treatment paradigms into a shorthand description of the revascularization result.

As noted, in facilitating distal perfusion, treatment paradigms may have different potentials to cause and/or resolve pre-existing or new distal emboli, and these potentials might be described in an appropriate angiographic perfusion scoring method. Such distal emboli are difficult to prove in the MCA distribution. Some operators suggest that injections beyond the occlusion allow this assessment, but flow in the opacified vessels is seldom completely depicted, is frequently slow and incomplete, and is affected by retrograde collateral flow. Intrathrombus or distal microcatheter contrast injection to demonstrate the distal vasculature may actually be harmful.¹⁹

Even with intra-arterial thrombolysis, a clot in the proximal MCA may be fragmented, with an embolus entering a previously uninvolved ACA. ACA emboli may decrease collateral flow to the MCA distribution and enlarge the watershed infarct in the setting of incomplete reperfusion. This may occur more with 1 treatment method than with another. Such emboli have been largely ignored in the revascularization literature, but we have been looking at them in the IMS studies, as well as in a local registry. New ACA emboli are uncommon with MCA occlusion; 1 has occurred with treatment of 48 MCA M1-M2 occlusions in IMS I and II. With ICA T occlusion, new emboli may also be introduced into the ACA distribution that might not otherwise have occurred. We assume an A1 occlusion with ICA T occlusion, but that does not mean more distal ACA emboli need occur. In fact, our IMS I-II data suggest that 15% of ICA T occlusions have distal ACA A2–A4 occlusions on pretreatment angiography, and 15% will have new distal emboli following treatment. EKOS ultrasound microcatheter (EKOS, Bothell, Wash) use led to fewer new ACA emboli, again suggesting different paradigms might have different results.

In addition to this question of local recanalization versus global reperfusion, it would be important to interrogate for an incomplete or even rudimentary treatment effect: has any recanalization occurred in the time interval that might indicate a positive device or drug effect? We have tested the TIMI and AOL scores again in the recently completed IMS II study, in which the EKOS MicroLysUS sonography catheter was again studied for ultrasound-assisted thrombolysis. Statistically significant differences in AOL recanalization, though not TICI perfusion, were determined. The TICI and AOL scores will be used in the IMS III trial, in which both rtPA and selected revascularization devices may be used.

Application. Study center reporting in the IMS II trial included operator reporting of TIMI scores, allowing compari-

son of operator reporting with core laboratory reporting. Review demonstrated a 41% discrepancy rate in 51 subjects, in which discrepancies typically involved over-rating the TIMI score by the clinical site—or underrating by the core laboratory (N. Zumberge, personal communication, 2005). This reminds us that application of scoring systems and interobserver variability in ascribing revascularization scores have, to our knowledge, never been reported and emphasizes that definitions and terminology must be clear and application of the system must be universal and reproducible. Until that time, this discrepancy rate implies that appropriate scores using meaningful systems should be assigned by a core laboratory to decrease interobserver variances and diminish the effect of potential operator/investigator enthusiasm and bias on results.

There is a great deal yet to learn about revascularization effects and clinical outcomes. Different treatment paradigms will offer different advantages and disadvantages regarding primary recanalization and distal reperfusion, and these may be clinically significant. New devices offer new challenges in revascularization assessment. Does a wide-cell self-expanding stent have the same incidence of incomplete local recanalization (which might be attributed to clot beneath the stent) compared with a narrow-cell balloon-expandable one and perhaps a higher reocclusion risk?^{20,21} Will prevention of this stent occlusion require dangerous antiplatelet agent regimens? Are local striate arteries that are patent before revascularization also patent following it? Do more new distal emboli occur with 1 treatment option or another, affecting distal perfusion rates, and are these rates equal to, or better than, other treatment methods? Finally, what is the final sum effect of these (and other) occurrences, as reflected in clinical outcomes? The answer to this question, after all, is the most important end point of a therapy.

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