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eTICI reperfusion: defining success in endovascular stroke therapy

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► **To cite this version:**

David Liebeskind, Serge Bracard, Francis Guillemin, Reza Jahan, Tudor Jovin, et al.. eTICI reperfusion: defining success in endovascular stroke therapy. *Journal of Neurointerventional Surgery*, 2019, 11 (5), pp.433-438. 10.1136/neurintsurg-2018-014127 . inserm-02444433

HAL Id: inserm-02444433

<https://inserm.hal.science/inserm-02444433v1>

Submitted on 25 Sep 2024

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Liebekind, D. S. et al. (2018) eTICI reperfusion: defining success in endovascular stroke therapy. *Journal of NeuroInterventional Surgery*, (doi:10.1136/neurintsurg-2018-014127).

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Deposited on: 23 August 2018

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Abstract

Background

Revascularization after endovascular therapy for acute ischemic stroke is measured by TICI, yet variability exists in scale definitions. We examined the degree of reperfusion with the expanded TICI (eTICI) scale and association with outcomes in the HERMES collaboration of recent endovascular trials.

Methods

The HERMES Imaging Core, blind to all other data, evaluated angiography after endovascular therapy in HERMES. A battery of TICI scores (mTICI, TICI, TICI2C) was used to define reperfusion of the initial target occlusion defined by noninvasive imaging and conventional angiography.

Results

Angiography of 801 subjects was available, including 797 defined by non-invasive imaging (154 ICA, 583 M1, 60 M2) and 748 by conventional angiography (195 ICA, 459 M1, 94 M2). Among 729 subjects in whom reperfusion grade could be established, using eTICI (3=100%, 2C=90-99%, 2b67=67-89%, 2b50=50-66%) of the conventional angiography target occlusion, there were 63 eTICI 3 (9%), 166 eTICI 2c (23%), 218 eTICI 2b67 (30%), 103 eTICI 2b50 (14%), 100 eTICI 2a (14%), 19 eTICI 1 (3%) and 60 eTICI 0 (8%). mRS shift analyses from baseline to 90 days revealed increasing TICI grades were linked with better outcomes, with significant distinctions between TICI 0/1 vs 2a ($p=0.028$), 2a vs 2b50 ($p=0.017$) and 2b50 vs 2b67 ($p=0.014$).

Conclusions

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3 The benefit of endovascular therapy in HERMES was strongly associated with increasing
4
5 degrees of reperfusion defined by eTICI. The eTICI metric identified meaningful distinctions in
6
7 clinical outcomes and may be used in future studies and routine practice.
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13 **Key Words**

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16 Stroke, reperfusion, ischemia, angiography, endovascular therapy
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3 Endovascular therapy is a highly effective treatment for acute ischemic stroke caused by
4 large artery occlusion in the anterior cerebral circulation, significantly increasing the likelihood
5 of recovery to independence.¹ Reperfusion of the ischemic territory downstream from an arterial
6 occlusion is the therapeutic mechanism responsible for benefit. The extent of reperfusion,
7 however, may vary across individual cases depending on numerous factors, including the degree
8 of collateral circulation.²⁻⁵ Most commonly, reperfusion is evaluated on angiography performed
9 immediately after recanalization or when reopening of the arterial occlusion is achieved.

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19 Several iterations of the Thrombolysis In Cerebral Infarction (TICI) score, adapted from
20 the TIMI coronary circulation scoring system to the cerebral circulation have been used to
21 quantify reperfusion.⁶ Successive refinements of the original TICI scale were implemented to
22 enhance standardization for different sites of arterial occlusion and to optimally discern subtle
23 distinctions in the amount of blood flow restored after thrombectomy. Multiple studies have
24 examined the inter-rater reliability of TICI grades and future such analyses are warranted.
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Several iterations of the Thrombolysis In Cerebral Infarction (TICI) score, adapted from the TIMI coronary circulation scoring system to the cerebral circulation have been used to quantify reperfusion.⁶ Successive refinements of the original TICI scale were implemented to enhance standardization for different sites of arterial occlusion and to optimally discern subtle distinctions in the amount of blood flow restored after thrombectomy. Multiple studies have examined the inter-rater reliability of TICI grades and future such analyses are warranted. Variability exists, however, in definitions, nomenclature, use and reporting. Consensus recommendations for angiographic revascularization standards developed in 2013 defined successful reperfusion by a modified TICI (mTICI) score signifying filling of 50% or more of the downstream territory.⁷

Reperfusion of the ischemic territory downstream from an arterial occlusion in stroke is distinct from recanalization, defined as restoring patency in the occluded arterial segment.^{8,9} Reperfusion specifically refers to re-establishing blood flow via normal arterial routes, in contrast to indirect collateral perfusion. The extent of reperfusion is quantified by the percentage of the downstream territory and is therefore dependent on defining the specific site of initial arterial occlusion. Such measurement of reperfusion is most often conducted on biplane

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3 angiography where the three-dimensional nature of the arterial territory must be inferred.
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5 Grading the extent of reperfusion or assigning a TICI score is typically conducted by the local
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7 operator or treating physician at the end of the procedure. Achieving a favorable TICI grade is
8
9 considered a quality metric for endovascular stroke therapy. Rating is influenced by local rater
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11 experience and central core-lab adjudication is commonly more conservative compared to local
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13 ratings. Since the original description of TICI 15 years ago, several intermediate grades of
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15 reperfusion have been introduced. The entire range of grade 2 TICI reperfusion, extending from
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17 a minimum of any distal branch filling to almost complete downstream perfusion, has been
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19 subdivided and confusingly labeled with inconsistent terminology.
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24 Availability of data from reperfusion trials now allows critical review of TICI reperfusion
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26 grade definitions. Standardization of TICI grading is essential for clinical practice and for future
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28 trials. We examined the relationship of reperfusion grades and clinical outcomes using individual
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30 patient data in the Highly Effective Reperfusion Evaluation in Multiple Endovascular Stroke
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32 (HERMES) trials that comprise the majority of randomized, controlled trials undertaken with
33
34 modern endovascular treatments.¹⁰ Data were systematically analyzed by an experienced core lab
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36 to delineate TICI reperfusion and substantiate prior scale distinctions with the associated clinical
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38 outcomes after stroke treatment.
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44 **Methods**

45 *Study Design*

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49 HERMES included 7 distinct endovascular therapy trials that established the efficacy of
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51 mechanical thrombectomy for acute ischemic stroke. Detailed methodology of each trial has
52
53 been previously reported.¹¹⁻¹³ Ethics approval was obtained from the local institutional review
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3 board and written informed consent was obtained from patients. In HERMES, the entire imaging
4 and angiography datasets of the 7 participating trials were centrally pooled in the Neurovascular
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6 and angiography datasets of the 7 participating trials were centrally pooled in the Neurovascular
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8 Imaging Research Core. Anonymized images of each enrolled subject were indexed and
9
10 relabeled by a randomly assigned HERMES subject identification number to mask any possible
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12 association with the original randomized controlled trial. In each of the original trials, only the
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14 subjects randomized to endovascular therapy underwent angiography. As a result, the HERMES
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16 angiography dataset reflects solely those subjects assigned to endovascular therapy.
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21 *Angiography Core Laboratory Evaluation*

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24 The HERMES angiography dataset was analyzed by an independent core laboratory with
25
26 extensive experience in adjudication of imaging and angiography from numerous multicenter
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28 stroke trials and registries. The angiography images were provided to the core lab without any
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30 additional information other than the site of the initial target occlusion determined by
31
32 noninvasive imaging in the original trial. As technical differences in imaging technique, or
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34 dynamic changes in occlusion due to recanalization or distal thrombus migration may occur
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36 between baseline noninvasive imaging and conventional angiography, reperfusion was graded
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38 based on location of the conventional angiography procedure start.
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42 The HERMES angiography core lab performed a quality assessment of the angiography
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44 data, denoting availability, adequacy and limiting factors associated with each subject's data. As
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46 TICI reperfusion in the downstream territory is critically contingent on the specific location of
47
48 the arterial occlusion, it was imperative that a diagnostic run or contrast injection of the
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50 occlusion was available at the procedure start to determine the conventional angiography target
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52 occlusion location. Similarly, a final run or diagnostic injection of the same arterial territory was
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3 required to determine TIC1 reperfusion. In addition, the angiography core lab noted when limited
4 data were available, such as the lack of biplane angiography or failure to acquire adequate runs
5 that precluded evaluation of reperfusion. A battery of various TIC1 scores in this study
6
7 population (Table 1) was used to define reperfusion of the initial target occlusion on noninvasive
8
9 imaging and conventional angiography. This 7-point compilation of TIC1 grades, termed the
10
11 expanded TIC1 or eTIC1, reflects all previously reported thresholds used to define reperfusion
12
13 after endovascular stroke therapy. In brief, eTIC1 grade 0 is equivalent to no reperfusion or 0%
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15 filling of the downstream territory; eTIC1 1 reflects thrombus reduction without any reperfusion
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17 of distal arteries; eTIC1 2a is reperfusion in less than half or 1-49% of the territory; eTIC1 2b50 is
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19 50-66% reperfusion, exceeding the modified TIC1 (mTIC1) 2B threshold but below the original
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21 TIC1 2B cutpoint; eTIC1 2b67 is 67-89% reperfusion, exceeding TIC1 but below TIC1 2C; eTIC1
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23 2c is equivalent to TIC1 2C or 90-99% reperfusion; and eTIC1 3 is complete or 100%
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25 reperfusion, tantamount to TIC1 3. Multiple studies have already examined the inter-rater
26
27 reliability of all the components of the eTIC1.^{14, 15} In order to define the inter-rater reliability of
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29 the distinction between eTIC1 2b50 (50-66% reperfusion, mTIC1 2B) and eTIC1 2b67 (67-89%
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31 reperfusion, TIC1 2B), a cohort of 52 subjects was rated independently by 2 readers.

32 33 34 35 36 37 38 39 40 41 42 *Statistical Analyses*

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44 Descriptive methods were used to characterize baseline angiographic features, including
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46 distributions across categories. For each HERMES subject, the blinded evaluation of the
47
48 conventional angiography target occlusion location was noted and compared with the initial
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50 target occlusion location for each case. Inter-rater reliability was analyzed using a correlation
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52 coefficient and Cohen's kappa statistic. The distribution of eTIC1 scores for the conventional
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3 angiography target occlusion was described and analyzed with respect to the key stroke outcome
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5 variable of the modified Rankin score (mRS) at 90 days. Graphical analyses were also used to
6
7 describe the distribution of mRS at day 90 stroke clinical outcomes for each eTICI grade. mRS
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9 distribution analyses at day 90 were used to compare clinical outcomes between neighboring
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11 eTICI thresholds, with statistical comparisons by Wilcoxon's rank-sum test for nonparametric
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13 analysis. Finally, receiver operating characteristic (ROC) curves were constructed to illustrate
14
15 the discriminative value of various TICI classification schemes on the mRS outcomes. The ROC
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17 results were described by the area under the curve (AUC) statistic and associated p-values
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19 computed by the method of DeLong. For all analyses, a two-tailed p-value less than 0.05 was
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21 considered statistically significant, without adjustment for multiple testing. Analyses were
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23 performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.2 (R
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25 Foundation for Statistical Computing, Vienna, Austria).
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Results

Arterial Occlusions

Angiography was available in a total of 801 subjects in HERMES, reflecting 801/871 (92%) of patients assigned to the endovascular treatment arms of the 7 participating trials. The target occlusion on non-invasive imaging was located at the ICA in 154 (19%), proximal MCA or M1 in 583 (73%) and M2 arterial segment in 50 (6%), and on conventional angiography at the ICA in 195 (24%), proximal MCA or M1 in 459 (57%) and M2 arterial segment in 94 (12%).

Extent of Reperfusion on eTICI

The extent of reperfusion was distributed across the entire range of the eTICI scale, including the spectrum from absolutely no reperfusion to complete restoration of flow in the territory downstream of the conventional angiography target occlusion. Among the 801 subjects noted above, reperfusion grade could not be established due to imaging limitations in 72, giving 729 evaluable eTICI scores. No reperfusion or eTICI 0 was noted in 60 (8%) and only reduction in thrombus without filling of distal arterial branches or eTICI 1 in 19 (3%). Reperfusion in less than half the territory or eTICI 2a was noted in 100 (14%). Reperfusion in 50-66% of the territory or eTICI 2b50, equivalent to mTICI 2B yet less than TICl 2B, was noted in 103 (14%). Restoration of flow in 67-89% of the territory or eTICI 2b67, above the TICl 2B threshold yet less than TICl2C, occurred in 218 (30%). Extensive reperfusion between 90-99%, or eTICI 2c equivalent to TICl 2C, was noted in 166 (23%). Finally, complete or full reperfusion of eTICI 3, equivalent to TICl 3, was found in only 63 (9%).

The distinctions between individual eTICI grades and the resultant discriminant ability of these perfusion categories was critically dependent on the availability of adequate angiographic

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3 views. Diagnostic confidence or potential limitations in the separation of eTICI categories was
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5 documented in 25/729 (3%) of subjects. The most common difficulty (n=12) occurred at the
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7 intermediate eTICI grades that demarcated eTICI 2b50 from eTICI 2b67, demarcating
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9 reperfusion thresholds around the 67% level (Figure 1). Interestingly, the subtle distinction of
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11 eTICI 2c and 3, discriminating the TICI 2C (90-99%) category from full or TICI 3 (100%)
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13 categories (Figure 2) occurred in only 8/729 (1%) with difficulties between 2b67 and 2c in the
14
15 remaining 5 cases. Within the eTICI 2c or TICI 2C category, overt distal emboli manifest as
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17 vessel cutoffs or menisci were visualized in 67/166 (40%).
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21 Inter-rater reliability for the distinction between eTICI 2b50 and 2b67 (mTICI 2B versus
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23 TICI 2B) revealed an agreement of 92% (48/52), with a Cohen's kappa statistic of $k=0.83$,
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25 $p<0.001$.
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30 31 *Relationship of eTICI Reperfusion and Clinical Outcomes*

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33 More extensive eTICI reperfusion was associated with better outcomes. Graphical
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35 depictions of this relationship for subsets of ICA and M1 MCA occlusions are illustrated in
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37 Figure 3. There was an unequivocal, graded pattern of increased proportion of subjects with no
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39 or minimal disability (mRS 0-1) hierarchically linked with higher eTICI grades. Similarly, the
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41 proportion of severe disability or death (mRS 5-6) was less with higher eTICI grades.
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43 Interestingly, even intermediate levels of disability (mRS 2-4) exhibited a clear relationship of
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45 decreasing disability with more extensive reperfusion. It should be noted, however, that across
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47 almost all eTICI reperfusion grades, there was still a broad distribution of mRS day 90 clinical
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49 outcomes.
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3 Direct comparison of the distribution in clinical outcomes of individual, neighboring
4 eTICI grades revealed specific differences between reperfusion categories (Table 2). The
5 relatively small number of subjects with extremely limited (eTICI 0-1) or complete (eTICI 3)
6 reperfusion may have limited such distinctions between eTICI categories at the extreme ends of
7 the scale, whereas differences between intermediate categories of reperfusion were more
8 apparent. The distribution of clinical outcomes was clearly different between eTICI grades 0/1
9 versus 2a, 2a versus 2b50, and 2b50 versus 2b67 that demarcate the extent of reperfusion at any
10 versus none, 50%, and the 67% thresholds, respectively.
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21 Multivariable modeling of mRS shift on eTICI with covariate adjustment demonstrates
22 that eTICI is an independent predictor of outcome in the presence of covariate adjustment, and
23 more importantly, that adjacent categories 2a/2b50/2b67 are important distinctions (Table 3).
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28 ROC curve analyses (Figure 4) showed similar performance of TICI (AUC 0.657), TICI
29 2C (AUC 0.661) and eTICI (AUC 0.664) in discriminating better clinical outcomes. All three of
30 these were statistically superior to the mTICI AUC (0.634) ($p=0.013$ for eTICI vs mTICI in
31 particular).
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40 **Discussion**

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42 Our study demonstrates that grades of better reperfusion are incrementally associated
43 with better clinical outcomes. This study is novel as HERMES is a large and ideal dataset to
44 examine TICI grading as it relates to clinical outcomes, pooling many of the large, landmark
45 trials in endovascular therapy. The use of all previously described TICI variants demonstrates the
46 utility of using an expanded or eTICI scale that encompasses these prior scale definitions. We
47 also demonstrated that these eTICI grades are linked with subsequent clinical outcomes after
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3 stroke therapy, providing a cogent rationale for future adoption and largescale use of eTICI.
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5 However, while more extensive reperfusion is associated with better clinical outcomes, a wide
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7 range of outcomes was evident even at the extremes of poor and full reperfusion, indicating that
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9 additional factors remain important determinants of outcome. Previous reports have
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11 demonstrated better outcomes with more extensive reperfusion, yet application of all TICI grades
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13 and their relative impact on outcomes from HERMES provides important data for the
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15 literature.^{16, 17}
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19 We confirmed a predominance of M1 occlusions with considerably fewer ICA or M2
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21 occlusions, as reported in individual trials and in previous pooled analyses. We noted that the
22
23 target occlusion defined on conventional angiography at procedure start differed from that on
24
25 baseline noninvasive imaging. This may result from interval recanalization or thrombus
26
27 migration, or alternatively be ascribed to technical differences in acquisition of non-invasive
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29 versus invasive imaging techniques. Based on the conventional angiography target occlusion site
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31 determined by our HERMES core lab, we corroborate the reperfusion rates reported in the
32
33 original trial reports, exhibiting substantial predominance of flow restoration to much of the
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35 ischemic territory. Importantly, however, the proportion of complete or full reperfusion was
36
37 substantially less than originally described. There were key distinctions in reperfusion categories
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39 when specific thresholds were used to subdivide the ischemic territory. Established consensus
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41 recommendations for angiographic standards in endovascular therapy have defined successful
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43 reperfusion as exceeding 50% of the territory.⁷ We have demonstrated, however, that within the
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45 >50% reperfusion category, a considerable number of cases fell into previously-defined finer
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47 subdivisions of 50-66%, 67-89% and 90-99%, and that these refinements identify meaningful
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49 differences in clinical outcomes.
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3 Our use of all previously defined TICI categories, redefined as eTICI grades,
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5 demonstrated that such categories identify gradation of outcomes associated with the extent of
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7 reperfusion. Comparison of adjacent or ordinal reperfusion grades on the eTICI scale showed
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9 that clinical outcomes vary between each grade, with more pronounced differences within
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11 intermediate eTICI categories. Prior studies have provided preliminary evidence that, compared
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13 with less granular TICI scales, the more fine-grained TICI scales have added prognostic value
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15 and clinical utility.¹⁸⁻²² The prior studies have been relatively small and with limited geographic
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17 scope, limiting their precision and generalizability. We therefore undertook the current study to
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19 validate and quantify the superiority of the eTICI in the large, multinational HERMES data set.
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21 We have extended previous reports concerning inter-rater reliability of eTICI cutpoints by
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23 demonstrating excellent reliability for distinguishing eTICI 2b50 and 2b67 (mTICI 2B versus
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25 TICI 2B).^{14, 15} This distinction between eTICI 2b50 and 2b67 may be difficult to discern, unlike
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27 or more so than other category distinctions (e.g. 2a v. 2b50; 2b67 v. 2c; 2c v. 3). Furthermore,
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29 these other category distinctions have been addressed in prior publications, hence it was
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31 important to demonstrate inter-rater reliability in this subset. Our results also indicate that this
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33 eTICI category distinction is the most significant as it relates to different subsequent clinical
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35 outcomes.
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42 Although this analysis establishes that the 7-point eTICI scale predicts increasingly better
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44 clinical outcomes, it is important to note that even at the extreme ends of the scale a wide
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46 distribution of outcomes may be evident. For example, not all subjects with eTICI 0/1
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48 reperfusion have poor clinical outcomes and conversely, there are subsets of patients with eTICI
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50 2c or 3 reperfusion with outcomes of severe disability or death. Such examples suggest that
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52 angiographic outcomes alone have limited utility for clinical outcome prediction. The AUC
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3 values for predicting good clinical outcomes were higher for eTICI 2b67 or 2c (>66% or >90%,
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5 respectively) compared with eTICI 3 (>50%), yet such AUC values of 0.66 are relatively
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7 modest, at best. Factors beyond reperfusion, including the underlying pathophysiology such as
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9 extent of established tissue injury, or collateral circulation, clinical variables, or subsequent
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11 events, such as recurrent stroke or hemorrhage, likely influence clinical outcomes. It also
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13 remains unclear whether the cause of limited reperfusion, due to distal emboli or increased
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15 downstream resistance, have different impact in clinical outcomes, even when reperfusion is
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17 almost complete as in eTICI 2c or TICI 2C flow.
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22 Limitations of our systematic angiographic evaluation in HERMES include the
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24 availability of adequate images, already restricted to subjects in the endovascular arm of these
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26 randomized, controlled trials. There are numerous aspects of angiography that we may not have
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28 been able to elucidate in this overall or primary paper on eTICI reperfusion in HERMES. Many
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30 of such limitations and data considerations have been addressed in the vast experience of the
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32 IMS I-III trials.^{4, 23-25} Evaluation of reperfusion may have been limited by incomplete depiction
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34 of the conventional angiography target occlusion or final diagnostic runs with biplane
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36 angiography. Aside from potentially missing data, variations in technique or local practice may
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38 have precluded adequate visualization of key angiography data. The degree of reperfusion and
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40 clinical outcomes may vary by location of occlusion site and availability of data may be limited
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42 even for ICA versus M1 MCA occlusions (Figure 3). For ICA occlusions, the role of the
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44 ipsilateral ACA and collateral flow may be handled differently with respect to subsequent
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46 reperfusion grading.^{24, 25} In our analyses, most of the ICA occlusions did not have any pre-
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48 treatment DSA information on collaterals. As a result, we defined eTICI for ICA lesions without
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50 accounting for potential collateral flow – we scored all based on the ICA lesion being
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3 responsible for the ipsilateral ACA and MCA territories. It is agreed that this scenario could be
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5 further addressed by a new scoring system in the future. We did not account for the time required
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7 to achieve final eTICI reperfusion or consider local factors that may have influenced the duration
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9 of the procedure.²⁶ Such challenges in blinded readings may not capture subtle aspects apparent
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11 at the time of intervention. Importantly, it remains unclear how the angiography was used in real-
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13 time to decide how far to continue with revascularization. The endpoints of successful
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15 reperfusion or the need to continue may have varied widely from operator to operator.
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17 Furthermore, lack of additional clinical demographics and medical history (e.g. atrial fibrillation,
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19 atherosclerosis, other risk factors) beyond those noted in the multivariable model in Table 3 limit
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21 our analyses. In addition, wider application of any rating scale requires ongoing examination.
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26 In sum, the benefit of endovascular therapy in HERMES was strongly associated with
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28 increasing degrees of eTICI reperfusion. The eTICI scale reveals important distinctions in the
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30 degree of reperfusion with respect to clinical outcomes, underscoring the need to implement
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32 standard methodology for reporting of angiography in stroke treatment in trials and routine
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34 practice. eTICI provides granularity in distinguishing the extent of reperfusion that is clinically
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36 meaningful. Defining successful reperfusion should be linked with good clinical outcomes,
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38 making it unlikely that a single threshold of eTICI reperfusion will work in all cases. Our
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40 analyses suggest that if a dichotomous threshold were to be used for the definition of successful
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42 reperfusion, then eTICI 2b67, equivalent to TICI 2B, is optimal.
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Figure Legend

Figure 1. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2b50=50-66% versus (B) eTICI 2b67 = 67-89%.

Figure 2. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2c=90-99% versus (B) eTICI 3 = 100%.

Figure 3. Graphical depiction of mRS outcomes at 90 days based on eTICI grades for ICA occlusions (above) and M1 MCA occlusions (below).

Figure 4. ROC curves showing the predictive ability of various TICI grades with respect to clinical outcomes, using (A) mRS (0-1) and (B) mRS (0-2).

Table 1. Study population

Characteristic	Mean \pm SD (N) Median (IQR) or % (n/N)
Age (years)	65.4 \pm 13.5 (729) [67.0] (56.8, 76.0)
Female sex	47.5% (346/729)
NIHSS at baseline	17.1 \pm 4.8 (725) [17.0] (14.0, 20.0)
ASPECTS at baseline	7.6 \pm 1.8 (722) [8.0] (7.0, 9.0)
Collateral grade	
0	0.9% (5/562)
1	13.7% (77/562)
2	44.3% (249/562)
3	41.1% (231/562)
tPA delivered	85.7% (625/729)
Onset to randomization (min)	205.7 \pm 96.9 (728) [184.5] (140.5, 246.3)
Onset to arterial puncture (min)	252.6 \pm 96.8 (685) [240.0] (185.0, 300.0)
eTICI category post-procedure	
0	8.2% (60/729)
1	2.6% (19/729)
2a (0-49%)	13.7% (100/729)
2b50 (50-66%)	14.1% (103/729)
2b67 (67-89%)	29.9% (218/729)
2c	22.8% (166/729)
3	8.6% (63/729)

Table 2. Distinctions between eTICI categories with respect to clinical outcomes for all cases

eTICI	mRS 0 % (n/N)	mRS 1 % (n/N)	mRS 2 % (n/N)	mRS 3 % (n/N)	mRS 4 % (n/N)	mRS 5 % (n/N)	mRS 6 % (n/N)
0	0.0% (0/59)	3.4% (2/59)	18.6% (11/59)	5.1% (3/59)	33.9% (20/59)	6.8% (4/59)	32.2% (19/59)
1	0.0% (0/19)	5.3% (1/19)	15.8% (3/19)	10.5% (2/19)	21.1% (4/19)	5.3% (1/19)	42.1% (8/19)
2a (0-49%)	10.0% (10/100)	6.0% (6/100)	13.0% (13/100)	14.0% (14/100)	25.0% (25/100)	10.0% (10/100)	22.0% (22/100)
2b50 (50-66%)	4.9% (5/103)	16.5% (17/103)	25.2% (26/103)	14.6% (15/103)	18.4% (19/103)	7.8% (8/103)	12.6% (13/103)
2b67 (67-89%)	13.3% (29/218)	21.1% (46/218)	17.9% (39/218)	23.4% (51/218)	10.1% (22/218)	5.0% (11/218)	9.2% (20/218)
2c	14.5% (24/165)	22.4% (37/165)	20.0% (33/165)	17.0% (28/165)	12.1% (20/165)	4.8% (8/165)	9.1% (15/165)
3	12.7% (8/63)	36.5% (23/63)	19.0% (12/63)	9.5% (6/63)	11.1% (7/63)	4.8% (3/63)	6.3% (4/63)

Table 3. Multivariable model of eTICI categories and clinical outcomes

Multivariable model: Ordinal logistic regression, outcome mRS (shift)

Predictor	Common odds ratio	LCL	UCL	p-value
Age (per year)	0.96	0.95	0.97	<0.001
NIHSS at baseline (per point)	0.92	0.89	0.95	<0.001
Male gender (vs female)	1.16	0.89	1.52	0.270
ASPECTS (per point)	1.20	1.11	1.30	<0.001
Onset to randomization (per 60 min)	0.89	0.82	0.98	0.017
Occlusion location				
ICA (reference level)	1.00	NA	NA	NA
MCA	1.36	0.99	1.87	0.056
tPA administered (vs no tPA)	1.02	0.66	1.56	0.938
eTICI grade				
0 (reference level)	1.00	NA	NA	NA
1	0.91	0.35	2.38	0.843
2a	1.43	0.78	2.64	0.251
2b50	2.44	1.34	4.43	0.003
2b67	5.11	2.93	8.91	<0.001
2c	5.19	2.93	9.21	<0.001
3	7.33	3.72	14.44	<0.001

eTICI level adjacency comparisons by above adjusted multivariable analysis, outcome mRS (shift)

Adjacency	Common odds ratio	LCL	UCL	p-value
2a vs 0/1	1.47	0.84	2.57	0.181
2b50 vs 2a	1.71	1.02	2.85	0.041
2b67 vs 2b50	2.10	1.36	3.22	0.001
2c vs 2b67	1.02	0.70	1.46	0.934
3 vs 2c	1.41	0.83	2.40	0.205

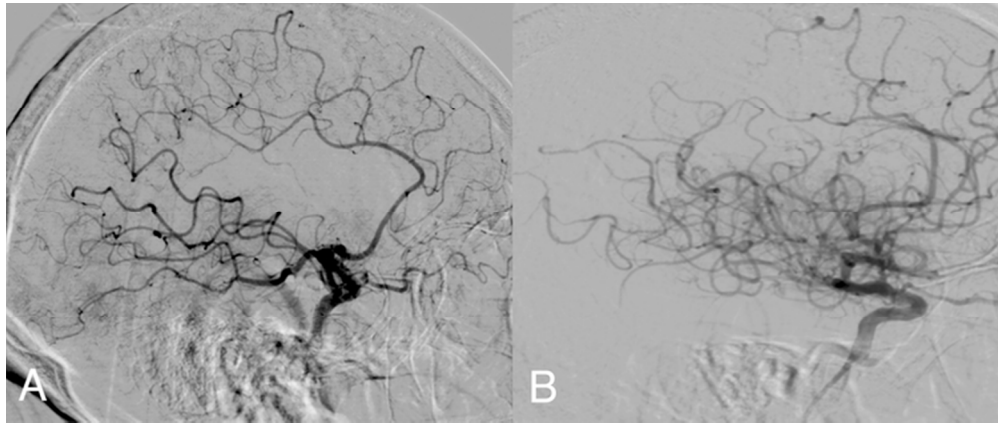


Figure 1. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2b50=50-66% versus (B) eTICI 2b67 = 67-89%.

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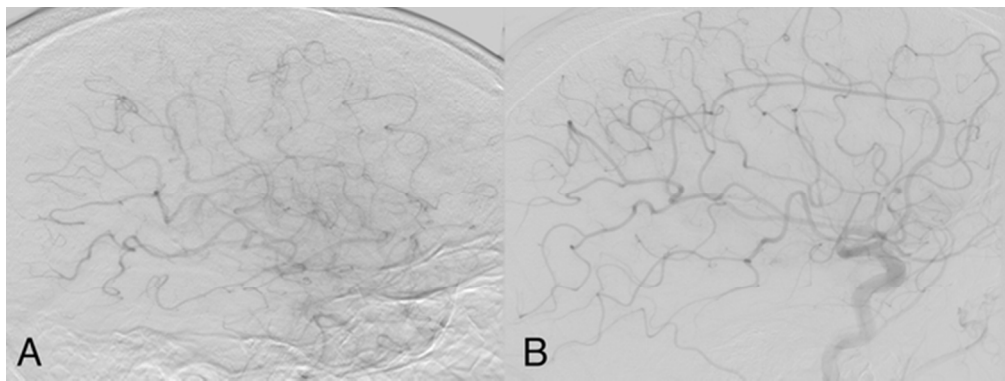
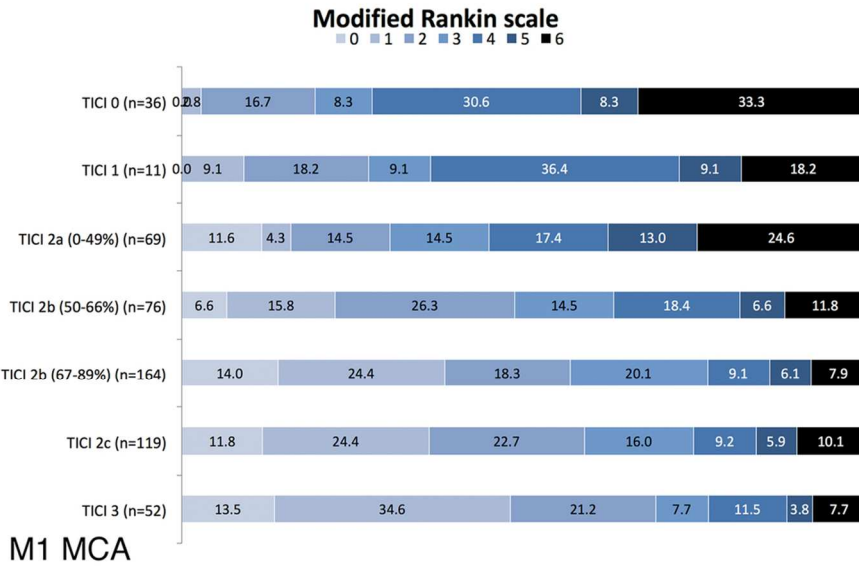
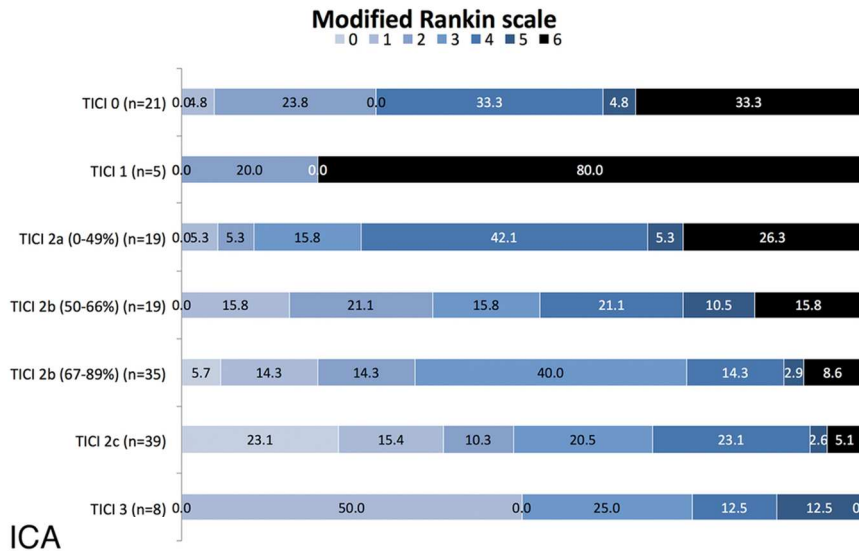


Figure 2. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2c=90-99% versus (B) eTICI 3 = 100%.

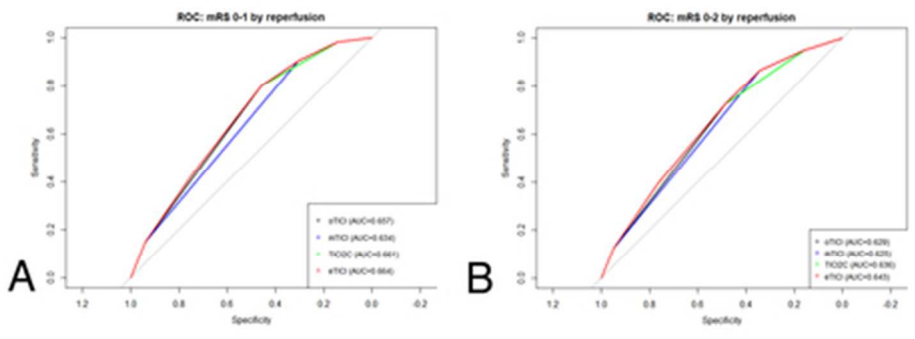
56x21mm (300 x 300 DPI)



Graphical depiction of mRS outcomes at 90 days based on eTICI grades for ICA occlusions (above) and M1 MCA occlusions (below).

96x122mm (300 x 300 DPI)

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ROC curves showing the predictive ability of various TICI grades with respect to clinical outcomes, using (A) mRS (0-1) and (B) mRS (0-2).

40x14mm (300 x 300 DPI)