2B, 2C, or 3

What Should Be the Angiographic Target for Endovascular Treatment in Ischemic Stroke?

Natalie E. LeCouffe, MD; Manon Kappelhof, MD; Kilian M. Treurniet, MD; Hester F. Lingsma, PhD; Guang Zhang, MD; Ido R. van den Wijngaard, MD, PhD; Adriaan C.G.M. van Es, MD, PhD; Bart J. Emmer, MD, PhD; Charles B.L.M. Majoie, MD, PhD; Yvo B.W.E.M. Roos, MD, PhD; Jonathan M. Coutinho, MD, PhD; on behalf of the MR CLEAN Registry Investigators*

Background and Purpose—A score of ≥2B on the modified Thrombolysis in Cerebral Infarction scale is generally regarded as successful reperfusion after endovascular treatment for ischemic stroke. The extended Thrombolysis in Cerebral Infarction (eTICI) includes a 2C grade, which indicates near-perfect reperfusion. We investigated how well the respective eTICI scores of 2B, 2C, and 3 correlate with clinical outcome after endovascular treatment.

Methods—We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry, a prospective, nationwide registry of endovascular treatment in the Netherlands. We included patients with a proximal intracranial occlusion of the anterior circulation for whom final antero-posterior and lateral digital subtraction angiography imaging was available. Our primary outcome was the distribution on the modified Rankin Scale at 90 days per eTICI grade. We performed (ordinal) logistic regression analyses, using eTICI 2B as reference group, and adjusted for potential confounders.

Results—In total, 2807/3637 (77%) patients met the inclusion criteria. Of these, 17% achieved reperfusion grade eTICI 0 to 1, 14% eTICI 2A, 25% eTICI 2B, 12% eTICI 2C, and 32% eTICI 3. Groups differed in terms of age (P<0.001) and occlusion location (P<0.01). Procedure times decreased with increasing reperfusion grades. We found a positive association between reperfusion grade and functional outcome, which continued to increase after eTICI 2B (adjusted common odds ratio, 1.22 [95% CI, 0.96–1.57] for eTICI 2C versus 2B; adjusted common odds ratio, 1.33 [95% CI, 1.09–1.62] for eTICI 3 versus 2B).

Conclusions—Our results indicate a continuous relationship between reperfusion grade and functional outcome, with eTICI 3 leading to the best outcomes. Although this implies that interventionists should aim for the highest possible reperfusion grade, further research on the optimal strategy is necessary. **(*Stroke*. 2020;51:1790-1796. DOI: 10.1161/STROKEAHA.119.028891.)**

Key Words: cerebral infarction ■ digital subtraction angiography ■ goals ■ reperfusion ■ thrombectomy

The current American Heart Association guidelines recommend a score of 2B or more on the modified Thrombolysis in Cerebral Infarction (mTICI) scale as the angiographic goal of endovascular treatment (EVT) for acute ischemic stroke of the anterior circulation.[1] The most recent European Stroke Organisation—European Society for Minimally Invasive Neurological Therapy guidelines also define successful reperfusion as a TICI score of 2B or 3, although expert opinion states that interventionists should aim for TICI grade 3 reperfusion.[2] The mTICI 2B/3 target is based on the threshold used in the thrombectomy trials that established EVT as standard care.[3] However, already in 2005, an additional 2C grade was introduced to the TICI scale, to identify those cases with near-perfect angiographic results.[4] This addition was later termed the extended TICI (eTICI) scale, with eTICI 2C defined as near-complete perfusion except for slow flow in a few distal

Received December 31, 2019; final revision received March 21, 2020; accepted April 14, 2020.

From the Department of Neurology (N.E.L., Y.B.W.E.M.R., J.M.C.) and Department of Radiology and Nuclear Medicine (M.K., K.M.T., B.J.E., C.B.L.M.M.), Amsterdam UMC, University of Amsterdam, the Netherlands; Department of Public Health, Center for Medical Decision Making, Erasmus MC University Medical Center Rotterdam, the Netherlands (H.F.L.); Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, China (G.Z.); Department of Neurology, Haaglanden Medical Center, the Hague, the Netherlands (I.R.v.d.W.); and Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands (A.C.G.M.v.E.).

*A complete list of the MR CLEAN Registry Investigators can be found in the Data Supplement.

Presented in part at the European Stroke Organisation Conference, Milan, Italy, May 22–24, 2019.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.028891.

Correspondence to Jonathan M. Coutinho, MD, PhD, Department of Neurology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1100 DD Amsterdam, the Netherlands. Email j.coutinho@amsterdamumc.nl

cortical vessels or presence of small distal cortical emboli, a category which is now widely implemented.[5]

Patients with eTICI 2C, generally scored as 90% to 99% reperfusion of the target downstream territory on digital subtraction angiography (DSA),[6] show more angiographic similarities to mTICI 3 patients (ie, patients with 100% reperfusion) than to mTICI 2B patients (patients with 50%–89% reperfusion). From this observation, one would expect that patients with eTICI 2C have a clinical outcome that more closely resembles that of patients with eTICI 3 than that of patients with eTICI 2B. A few studies have previously investigated the relation between various eTICI scores and clinical outcome.[6–10] The results of these studies varied, which may be due to variations in definitions and the fact that some studies had a small sample size.[7–10] Moreover, some studies used clinical trial data,[6] which may not reflect daily clinical practice.

We aimed to investigate the association between clinical outcome and scores on the eTICI scale, specifically focusing on scores 2B, 2C, and 3, using data of a nationwide cohort representing daily clinical practice.[11]

Methods

Data will not be made available to other researchers, as no patient approval was obtained for sharing coded data. However, syntax and output files of statistical analyses may be made available via secured download link on request to the corresponding author.

Design and Study Population

We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry part 1 and 2, a prospective, nationwide registry of consecutive patients undergoing EVT in the Netherlands who were treated between March 2014 and November 2017.[11,12] We included adult patients with a large vessel occlusion of the anterior circulation (internal carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], or anterior cerebral artery [A1/A2]) confirmed on CT angiography, who had both antero-posterior and lateral DSA runs postreperfusion, as reperfusion grade can only be reliably assessed with 2 planes.[13] All patients received intravenous recombinant tissue-type plasminogen activator (IV r-tPA; 0.9 mg/kg alteplase over 1 hour with 10% initial bolus) unless contraindicated, according to national guidelines.[14]

An imaging core laboratory adjudicated all patient imaging. The members of the core lab were blinded to all clinical data except for symptom side. Reperfusion grade was measured according to the eTICI scale on final DSA, as compared with initial DSA. In case the initial angiographic run did not show a target occlusion anymore, a minimum eTICI score of 2B was assigned. For patients in whom the target occlusion was not accessible, for example, due to elongation of the carotid artery or aortic arch, treatment was considered unsuccessful and these patients were assigned reperfusion grade eTICI 0. Safety outcome measures were scored by a complication committee whose members were blinded to treatment center. A central medical ethics committee granted permission to perform the study as a registry.

Outcome Measures

We compared functional outcome at 90 days as measured by the distribution on the modified Rankin Scale (mRS) across the eTICI categories. Patients with eTICI 0 or eTICI 1 were collapsed into a single category. Other outcome measures were functional independence at 90 days (mRS 0–2); all-cause mortality at 90 days; and symptomatic intracranial hemorrhage (sICH). Intracranial hemorrhage was considered symptomatic if patients died or deteriorated neurologically (a decline of at least 4 points on the National Institutes of Health Stroke Scale), and the hemorrhage was related to the clinical deterioration (according to the Heidelberg Bleeding Classification[15]).

Statistical Analysis

Baseline and treatment characteristics were analyzed using standard statistics. We estimated the odds ratio (OR) for a shift towards better functional outcome using ordinal logistic regression analysis for each reperfusion grade, using the eTICI 2B patient group as the reference group. Similarly, we estimated the OR for functional independence at 90 days, mortality at 90 days, and sICH for each reperfusion grade as compared with eTICI 2B patients with logistic regression analyses. We further performed a shift analysis to estimate the common OR for a better functional outcome for every step increase on the eTICI scale. In a sensitivity analysis, we estimated the common OR for better functional outcome for every step increase on the eTICI scale, after excluding patients with eTICI 2B or better on initial angiography. In this subgroup, we also compared functional outcome between patients with eTICI 2C and those with eTICI 2B, and between patients with eTICI 3 and eTICI 2B.

For mRS at 90 days, functional independence, and mortality at 90 days, we adjusted for age, baseline National Institutes of Health Stroke Scale score, collateral status,[16] IV r-tPA before EVT, systolic blood pressure at baseline, time of symptom onset to groin puncture, occlusion location and use of general anesthesia. For sICH, we adjusted for baseline National Institutes of Health Stroke Scale score, collateral status, IV r-tPA before EVT, systolic blood pressure at baseline, and time of symptom onset to groin puncture.

To further assess whether outcomes were significantly better in patients with eTICI 3 than in patients with eTICI 2C, we compared a model with eTICI 2C and eTICI 3 combined, to a model with eTICI 3 as a separate category based on the likelihood ratio test. Lastly, we assessed the reperfusion grades as scored by local operating physicians (who applied the mTICI scale) versus those scored by the core laboratory (who applied the eTICI scale) for descriptive purposes, although we could not make a formal comparison due to differences in grading scales.

Adjusted (common) ORs (a[c]ORs) are reported with 95% CI, and all *P* values are 2-sided. Multiple imputation was performed for missing data based on relevant covariates and outcome. Statistical analyses were performed with IBM Statistics for Windows, Version 25.0 and graphics were made using the computing environment R (R Development Core Team, 2013).

Results

In total, 3637 patients were included in the MR CLEAN Registry. We excluded 830 patients (23%), mostly because they did not meet imaging criteria (Figure 1). Of the remaining 2807 patients, 470 (17%) achieved reperfusion grade eTICI 0 to 1, 404 (14%) eTICI 2A, 700 (25%) eTICI 2B, 340 (12%) eTICI 2C, and 893 (32%) eTICI 3.

Baseline characteristics per eTICI grade are reported in the Table. Median age tended to decrease with increasing reperfusion grade (ranging from 75 years to 71 years, $P<0.001$). Onset to groin times were slightly shorter in patients with higher reperfusion grades (ranging from 203 minutes to 190 minutes, $P=0.16$). The distribution of occlusion location on baseline computed tomography angiography differed per eTICI grade ($P<0.01$). Patients with eTICI 2C more often underwent general anesthesia compared with other groups (eTICI 0–1 22%; eTICI 2A 21%; eTICI 2B 26%; eTICI 2C 37%; eTICI 3 29%; $P<0.001$). Rates of IV rtPA before EVT did not differ between groups. There was a clear decline in duration of procedure as reperfusion grade increased, ranging

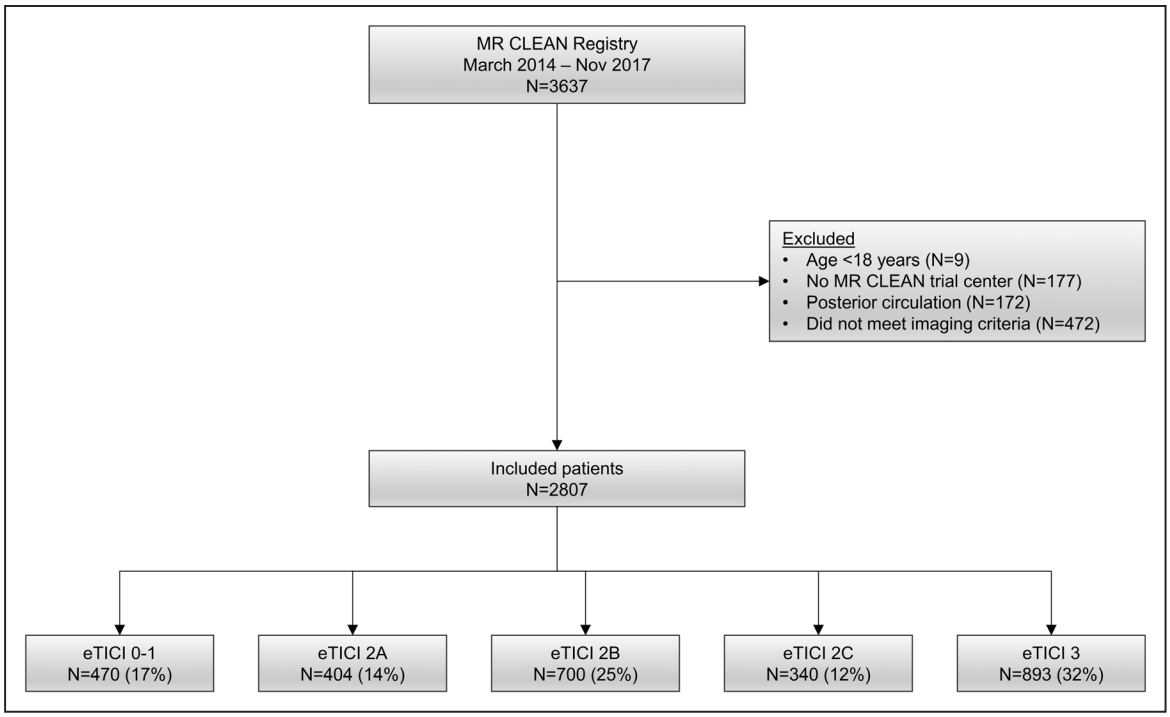

Figure 1. Flowchart of patient selection. eTICI indicates extended Thrombolysis in Cerebral Infarction; and MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands.

from median 68 minutes for eTICI 0 to 1 patients to 45 minutes for eTICI 3 patients (P<0.001).

There was an overall positive association between reperfusion grade and functional outcome at 90 days (acOR for a shift on the mRS per step on the eTICI scale 1.34 [95% CI, 1.28–1.41], Figure 2). When compared with patients with eTICI 2B, patients with eTICI 2C had higher odds for better functional outcome, although this difference did not reach statistical significance (acOR, 1.22 [95% CI, 0.96–1.57]; Figure 3A). Patients with eTICI 3 did have a statistically significant better functional outcome compared with those with eTICI 2B (acOR, 1.33 [95% CI, 1.09–1.62]). We found a similar trend for functional independence (Figure 3B), as well as a decrease in risk of mortality and sICH with increasing reperfusion grades (Figure 3C and 3D).

In a sensitivity analysis excluding patients with eTICI 2B or better on initial angiography, the positive association between reperfusion grade and functional outcome at 90 days remained significant (acOR, 1.28 [95% CI, 1.22–1.33]; Figure I in the Data Supplement). Moreover, patients with eTICI 2C had a statistically significantly better functional outcome than those with eTICI 2B (acOR, 1.40 [95% CI, 1.10–1.78]), as did patients with eTICI 3 (acOR, 1.55 [95% CI, 1.26–1.91]).

However, when comparing a model with eTICI 2C and eTICI 3 scores combined, to a model with eTICI 3 as a separate category, a likelihood test showed that the model fit with eTICI 3 as a separate category was not significantly better than the model fit with eTICI 2C and eTICI 3 combined (P=0.47).

Lastly, local operating physicians appeared to more often assign a score of mTICI 3 than core laboratory observers assigned eTICI 3 (46.9% versus 31.8%, respectively; Table I in the Data Supplement).

Discussion

We found that increasing scores on the eTICI scale are associated with better clinical outcomes after EVT in patients with stroke. Given the angiographic proximity of eTICI 2C and 3, we had expected that outcomes for patients with these scores would closely resemble each other. However, our results do not seem to substantiate this hypothesis. All outcomes appear to gradually improve per eTICI score, with eTICI 3 patients having the best outcomes. This suggests that, contrary to guideline recommendations,[1] interventionists should not settle for eTICI 2B, a notion which is supported by expert opinion.[2] However, it remains unclear whether extending the procedure with additional thrombectomy attempts safely leads to higher reperfusion grades.

Previous studies did find that patients with eTICI 2C had outcomes closely resembling those of eTICI 3 patients.[7,8,10] However, the statistical power of these studies may have been too small to detect a true difference between eTICI 2C and eTICI 3 patients, and only one study employed an independent core laboratory to evaluate imaging.[8] It is thus conceivable that some patients were incorrectly scored as eTICI 3, when they really still had a few distal emboli, leading to distortion of groups.[17] Other, older studies observed a clear threshold of mTICI 2B as the best predictor for functional independence at 90 days,[18,19] but this might be explained by the fact that these older studies did not include a separate 2C category. A recent meta-analysis[6] also found an incremental association between eTICI score and clinical outcome, as we did. However, these results were based on data from clinical trials, which likely represent a biased patient group with favorable clinical and imaging characteristics. Moreover, in a sensitivity analysis in our study excluding patients with eTICI 2B or better on initial

Table. Baseline Characteristics of Patients per eTICI Category

Characteristic	eTICI 0–1 (n=470)	eTICI 2A (n=404)	eTICI 2B (n=700)	eTICI 2C (n=340)	eTICI 3 (n=893)	*P* Value
Clinical data						
Age	75 (65–83)	72 (61–81)	71 (60–80)	71 (60–79)	71 (61–80)	<0.001
Men	240/470 (51)	208/404 (52)	356/700 (51)	185/340 (54)	472/883 (53)	0.80
Transferred from primary stroke center	262/470 (56)	214/404 (53)	376/700 (54)	175/340 (52)	514/892 (58)	0.25
Time symptom onset to groin puncture*	200 (150–272)	203 (150–263)	200 (150–260)	195 (148–260)	190 (150–245)	0.16
NIHSS†	16 (11–19)	16 (12–20)	15 (10–19)	16 (11–20)	16 (11–20)	0.02
SBP, mm Hg‡	150 (135–166)	152 (133–170)	148 (130–166)	150 (133–167)	146 (130–162)	<0.01
DBP, mm Hg§	84 (75–94)	83 (72–91)	82 (70–91)	80 (73–93)	80 (70–90)	<0.01
Medical history						
Atrial fibrillation	135/462 (29)	101/400 (25)	139/690 (20)	89/337 (26)	199/880 (23)	<0.01
Diabetes mellitus	80/465 (17)	65/402 (16)	101/693 (15)	64/339 (19)	151/888 (17)	0.46
Hypertension	242/459 (53)	211/397 (53)	345/679 (51)	175/336 (52)	462/876 (53)	0.94
Ischemic stroke	83/466 (18)	70/402 (17)	114/693 (17)	59/340 (17)	139/885 (16)	0.86
Prestroke mRS 0–1	358/457 (78)	312/395 (79)	546/681 (80)	274/333 (82)	722/875 (83)	0.30
Use of oral anticoagulation	99/467 (21)	59/401 (15)	90/692 (13)	57/340 (17)	139/886 (16)	<0.01
Antiplatelet use	141/466 (30)	125/398 (31)	203/686 (30)	114/339 (34)	289/882 (33)	0.58
Imaging and treatment characteristics						
ASPECTS‖	9 (8–10)	9 (7–10)	9 (7–10)	9 (8–10)	9 (8–10)	0.20
Clot burden score¶	6 (4–8)	6 (4–8)	6 (4–8)	6 (4–8)	6 (4–8)	0.11
Collateral status						0.61
Absent collaterals	26/430 (6)	29/387 (8)	38/653 (6)	21/320 (7)	42/846 (5)	
Poor collaterals	158/430 (37)	132/387 (34)	236/653 (36)	120/320 (38)	297/846 (35)	
Moderate collaterals	167/430 (39)	144/387 (37)	260/653 (40)	130/320 (41)	328/846 (39)	
Good collaterals	79/430 (18)	82/387 (21)	119/653 (18)	49/320 (15)	179/846 (21)	
Occlusion location on CTA						<0.01
ICA	30/438 (7)	27/393 (7)	30/670 (5)	15/327 (5)	35/873 (4)	
ICA-T	96/438 (22)	89/393 (23)	129/670 (19)	75/327 (23)	172/873 (20)	
Proximal M1	98/438 (22)	78/393 (20)	157/670 (23)	99/327 (30)	233/873 (27)	
Distal M1	131/438 (30)	144/393 (37)	235/670 (35)	100/327 (31)	309/873 (35)	
M2	78/438 (18)	53/393 (14)	112/670 (17)	38/327 (12)	112/873 (13)	
Other (M3/anterior)	5/438 (1)	2/393 (1)	7/670 (1)	0/327 (0)	12/873 (1)	
Location of stroke in left hemisphere	251/469 (54)	201/404 (50)	382/700 (55)	183/340 (54)	468/893 (52)	0.48
IV rtPA	344/468 (74)	300/402 (75)	535/697 (77)	246/339 (73)	676/889 (76)	0.51
General anesthesia	95/424 (22)	81/387 (21)	172/652 (26)	119/322 (37)	249/862 (29)	<0.001
Procedure time#	68 (45–94)	75 (55–105)	54 (35–75)	56 (40–78)	46 (33–70)	<0.001
Onset-to-last-contrast-bolus time**	273 (209–337)	273 (222–337)	250 (198–311)	248 (192–320)	237 (189–298)	<0.001
Total number of passes††	0 (0–3)	2 (1–4)	1 (1–3)	2 (1–3)	1 (1–2)	<0.001
Intra-arterial thrombolytics (alteplase/urokinase)	9/470 (2)	16/404 (4)	14/700 (2)	7/340 (2)	14/893 (2)	0.09
Intraarterial nimodipine	19/470 (4)	35/404 (9)	57/700 (8)	21/340 (6)	64/893 (7)	0.04

Percentages may not total 100 due to rounding. All continuous measures are reported as median (interquartile range). Proportions are reported as n/N (%). ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DBP, diastolic blood pressure; eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; M3, middle cerebral artery segment 3; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

Missing: *13; †48; ‡78; §85; ‖92; ¶670; #247; **181; ††308.

angiography, the overall association between increasing reperfusion grade and better functional outcome remained statistically significant. Therefore, our results add to current literature as they further support this association in a cohort reflecting daily clinical practice, whilst applying the eTICI scale.

There are several potential explanations why patients with eTICI 2C do not follow a similar clinical course to that of patients with eTICI 3. First, it could indicate that eTICI 2C actually heralds irreversible tissue damage due to impaired microvascular reperfusion despite recanalization of

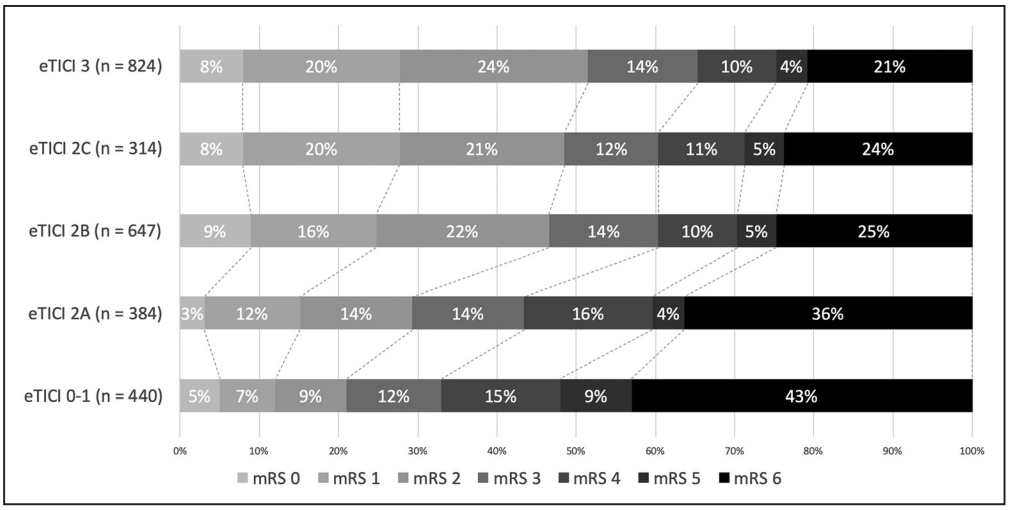

Figure 2. Distribution of modified Rankin Scale (mRS) per extended Thrombolysis in Cerebral Infarction (eTICI) grade. Functional outcome per reperfusion grade was scored on the mRS score: a 7-point scale ranging from 0 (no disability) to 6 (death). Percentages may not total 100 due to rounding. Shift analysis showed an increase in odds for a better functional outcome for increasing reperfusion grade (common odds ratio [OR], 1.31 [95% CI, 1.26–1.37]; adjusted common OR, 1.34 [95% CI, 1.28–1.41]).

the occluded vessel, as opposed to it signaling a near-perfect angiographic result.[20] Ongoing randomized clinical trials such as the MR CLEAN-MED trial (ISRCTN76741621) will provide insight on the effect of periprocedural intravenously applied acetylsalicylic acid combined with or without low dose unfractionated heparin on improving microvascular reperfusion. Similarly, although the proportion of patients who received IVT before EVT in our study was comparable across all reperfusion grades, ongoing trials such as the MR CLEAN-NO IV (ISRCTN80619088), SWIFT-DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke; NCT03192332), DIRECT-MT (Direct Intra-Arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: A Multicenter Randomized Clinical Trial; NCT03469206), and DIRECT-SAFE (A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval; NCT03494920) will provide additional evidence to whether IVT contributes to higher reperfusion grades or more often successful first attempts[21] and, therefore, possibly better functional outcome. Another potential explanation could be related to the high proportion of eTICI 2C patients that were treated under general anesthesia, compared with other groups (37% versus 21%–29%). Although this may indicate that interventionists achieve better angiographic outcomes in patients who lie completely still, the use of general anesthesia could also have negatively impacted functional outcome of patients.[22]

Conversely, an additional analysis comparing a model with eTICI 2C and eTICI 3 combined, to a model with eTICI 3 as a separate category showed that the model with eTICI 3 as a separate category did not have a statistically significantly better fit than the model with eTICI 2C and 3 combined as one category. This might imply that eTICI 2C is not that different from eTICI 3, and that subtle radiological subdivisions of reperfusion scores are not necessarily clinically relevant. However, more likely this analysis is underpowered, as the distribution of the mRS scores shows a clear improvement per increasing eTICI score. Lastly, patients with eTICI 3 had shorter procedure times and a low number of passes compared with other reperfusion grades, most likely indicating procedures under ideal circumstances. Should the procedure become more complicated (and consequently longer), for example, due to a difficult anatomy of the carotid arteries or differences in thrombus characteristics and location, perhaps it also becomes more difficult to achieve higher reperfusion grades.

Several limitations of our study warrant comment. First, while the data suggest that achieving better angiographic outcomes beyond eTICI 2B is associated with better outcomes, we were not able to compare patients with eTICI 2B to patients who initially had eTICI 2B and in which the interventionist continued to attempt to improve reperfusion. However, the fact that the risk of sICH appeared to decrease as reperfusion grade increased, suggests that reperfusion injury is not an issue with increasing reperfusion grade. Conversely, our results showed only a small absolute difference between eTICI 2B and eTICI 3 patients, despite being statistically significantly different. Although eTICI 3 produces superior results, only a clinical trial in which patients are randomized between ending EVT at eTICI 2B and continuation of EVT to improve beyond eTICI 2B can definitively answer whether the benefits of pursuing higher reperfusion grades after 2B outweigh the risks.

A second limitation is that not all patients in the MR CLEAN Registry had antero-posterior and lateral views on DSA imaging, thereby not meeting our inclusion criteria and possibly introducing unmeasured confounding in our patient selection. However, since eTICI grades cannot be reliably estimated on a single plane image,[13] we felt that excluding these patients would lead to the lowest risk of

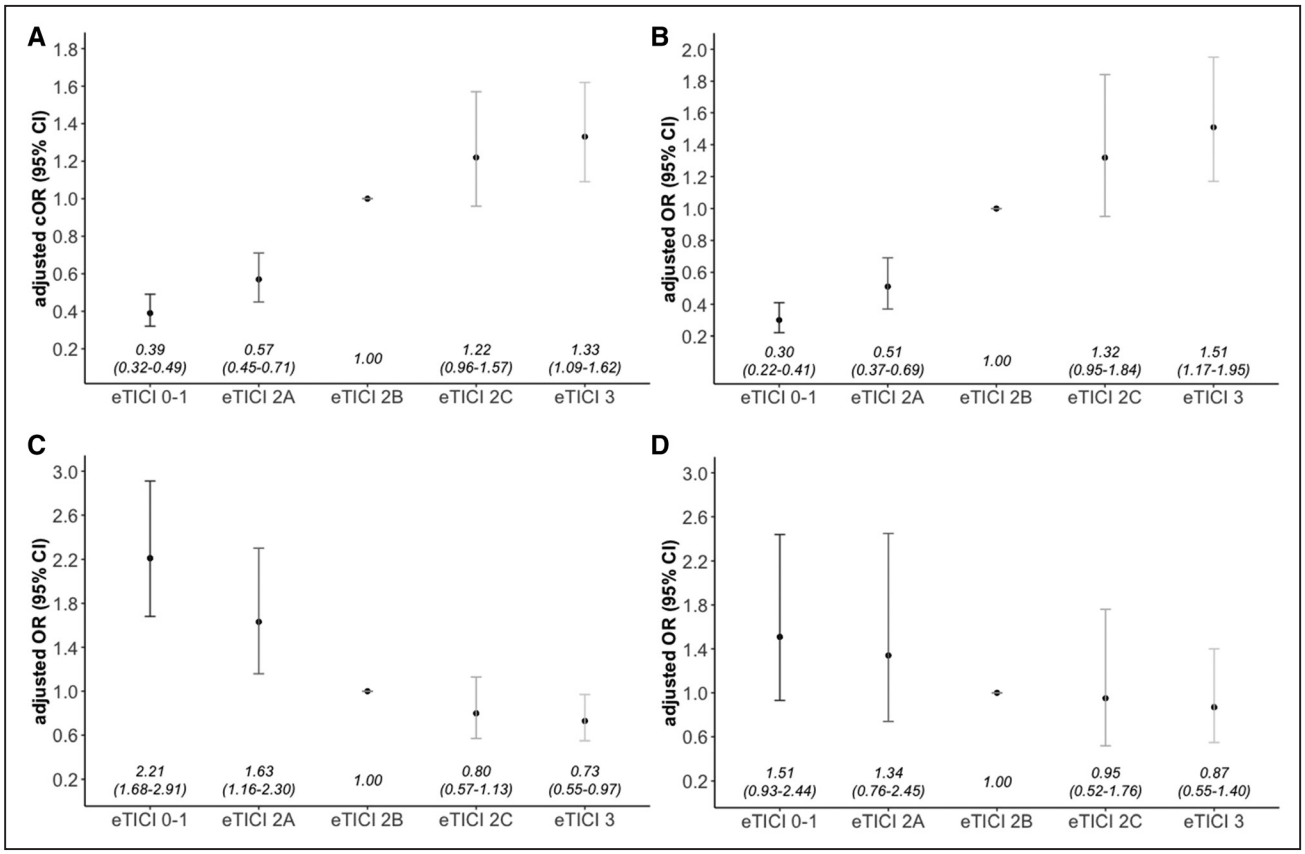

Figure 3. Outcomes per extended Thrombolysis in Cerebral Infarction (eTICI) grade for better functional outcome on the modified Rankin Scale (mRS; **A**), functional independence (mRS 0–2; **B**), mortality (**C**), and symptomatic intracranial hemorrhage (sICH; **D**), per reperfusion grade. Adjusted (common) odds ratios (ORs) with 95% CIs are reported per reperfusion grade. In all analyses, eTICI 2B is used as reference category; sICH: according to the Heidelberg criteria.[15]

bias. Third, we may have overestimated the proportion of patients with eTICI 0 to 1, as we assigned eTICI 0 to those patients in whom intracranial access was not achieved. This may have led to an overall pessimistic assessment of our imaging outcomes. Fourth, a recent study by Liebeskind et al[6] further subdivided the 2B category into 2b50 (50%–66% reperfusion) and 2b67 (67%–89% reperfusion) and observed clinically meaningful differences between both outcomes. It would have been interesting to analyze these categories in our data set, but unfortunately this subdivided 2B category was not measured by the core laboratory. Lastly, operators may overestimate reperfusion grade compared with core laboratory observers.[17] Although we could not make a formal comparison between local readers and the core laboratory due to differences in grading scales, overestimation of the eTICI score by local readers also seems to have happened in our study (Table I in the Data Supplement). Such a discrepancy might affect the external validity of our study, as in routine practice, the local operator decides whether or not to continue the procedure and, therefore, pursue a higher reperfusion grade.

In conclusion, we found that increasing scores on the eTICI scale are associated with better clinical outcome in stroke patients who underwent EVT. This suggests that interventionists should not settle for eTICI 2B as angiographic target end point, but rather for the highest possible reperfusion grade. Ongoing randomized clinical trials will provide additional insight on how to improve reperfusion for patients with EVT .

Sources of Funding

This study was funded and carried out by the Erasmus University Medical Centre, the Amsterdam UMC, location AMC, and the Maastricht University Medical Centre. The study was additionally funded by the Applied Scientific Institute for Neuromodulation (Toegepast Wetenschappelijk Instituut voor Neuromodulatie), which played no role in trial design and patient enrollment, nor in data collection, analysis, or writing of the manuscript.

Disclosures

Dr LeCouffe, Dr Treurniet, Dr Kappelhof, Dr Emmer and Dr Coutinho are research coordinators for the MR CLEAN-NO IV trial (ISRCTN80619088). Dr Roos and Dr Majoie are principal investigators of the MR CLEAN-NO IV trial. Dr Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation and Stryker, outside the submitted work (paid to institution). In addition, Dr Majoie is shareholder of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Dr Roos reports stockholdings from Nico.lab outside the submitted work. Dr Coutinho reports grants from Medtronic and Boehringer outside the submitted work, which were paid to his institute. Dr Lingsma, Dr Zhang, Dr van den Wijngaard and Dr van Es report no disclosures.

References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
2. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European Stroke Organisation (ESO) - guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;0:1–30.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
4. Noser EA, Shaltoni HM, Hall CE, Alexandrov AV, Garami Z, Cacayorin ED, et al. Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? *Stroke*. 2005;36:292–296. doi: 10.1161/01.STR.0000152331.93770.18
5. Goyal M, Fargen KM, Turk AS, Mocco J, Liebeskind DS, Frei D, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg*. 2014;6:83–86. doi: 10.1136/neurintsurg-2013-010665
6. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CB, et al. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg* 2019;11:433–438. doi: 10.1136/neurintsurg-2018-014127
7. Naragum V, Jindal G, Miller T, Kole M, Shivashankar R, Merino JG, et al. Functional independence after stroke thrombectomy using thrombolysis in cerebral infarction grade 2c: a new aim of successful revascularization. *World Neurosurg*. 2018;119:e928–e933. doi: 10.1016/j.wneu.2018.08.006
8. Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, et al; ASTER Trial Investigators. Modified thrombolysis in cerebral infarction 2C/Thrombolysis in cerebral infarction 3 reperfusion should be the aim of mechanical thrombectomy: insights from the ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization). *Stroke*. 2018;49:1189–1196. doi: 10.1161/STROKEAHA.118.020700
9. Dekker L, Geraedts VJ, Hund H, Cannegieter SC, Nogueira RG, Goyal M, et al. Importance of reperfusion status after intra-arterial thrombectomy for prediction of outcome in anterior circulation large vessel stroke. *Interv Neurol*. 2018;7:137–147. doi: 10.1159/000486246
10. Tung EL, McTaggart RA, Baird GL, Yaghi S, Hemendinger M, Dibiasio EL, et al. Rethinking thrombolysis in cerebral infarction 2b: which thrombolysis in cerebral infarction scales best define near complete recanalization in the modern thrombectomy era? *Stroke.* 2017;48:2488–2493. doi: 10.1161/STROKEAHA.117.017182
11. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949
12. Compagne KCJ, Kappelhof M, Hinsenveld WH, Brouwer J, Goldhoorn RB, Uyttenboogaart M, et al, on behalf of the MR CLEAN Registry Investigators. E-Poster Discussions. *Eur Stroke J*. 2019;4:96–149.
13. Gerber JC, Miaux YJ, von Kummer R. Scoring flow restoration in cerebral angiograms after endovascular revascularization in acute ischemic stroke patients. *Neuroradiology*. 2015;57:227–240. doi: 10.1007/s00234-014-1460-x
14. Dippel DWJ, van der Worp HB, Hofmeijer J, van den Berg-Vos RM, van Dijk EJ, Geurts M, et al. Richtlijn herseninfarct/-bloeding. The Netherlands: 2018. Available at: https://richtlijnendatabase.nl/richtlijn/herseninfarct_en_hersenbloeding/startpagina_herseninfarct_-bloeding.html. Accessed August 30, 2018.
15. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981–2986. doi: 10.1161/STROKEAHA.115.010049
16. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525–531. doi: 10.3174/ajnr.A1408
17. Zhang G, Treurniet KM, Jansen IGH, Emmer BJ, van den Berg R, Marquering HA, et al; MR CLEAN Registry Investigators. Operator versus core lab adjudication of reperfusion after endovascular treatment of acute ischemic stroke. *Stroke*. 2018;49:2376–2382. doi: 10.1161/STROKEAHA.118.022031
18. Yoo AJ, Simonsen CZ, Prabhakaran S, Chaudhry ZA, Issa MA, Fugate JE, et al; Cerebral Angiographic Revascularization Grading Collaborators. Refining angiographic biomarkers of revascularization: improving outcome prediction after intra-arterial therapy. *Stroke*. 2013;44:2509–2512. doi: 10.1161/STROKEAHA.113.001990
19. Marks MP, Lansberg MG, Mlynash M, Kemp S, McTaggart R, Zaharchuk G, et al; DEFUSE 2 Investigators. Correlation of AOL recanalization, TIMI reperfusion and TICI reperfusion with infarct growth and clinical outcome. *J Neurointerv Surg*. 2014;6:724–728. doi: 10.1136/neurintsurg-2013-010973
20. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009;15:1031–1037. doi: 10.1038/nm.2022
21. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, et al. First pass effect: a new measure for stroke thrombectomy devices. *Stroke*. 2018;49:660–666. doi: 10.1161/STROKEAHA.117.020315
22. Campbell BCV, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, et al; HERMES collaborators. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. *Lancet Neurol*. 2018;17:47–53. doi: 10.1016/S1474-4422(17)30407-6