Successful reperfusion in relation to the number of passes

MR CLEAN Registry Investigators; Bruggeman, Agnetha A E; Kappelhof, Manon; den Hartog, Sanne J; Burke, James F; Berkhemer, Olvert A; van Es, Adriaan C G M; van Zwam, Wim H; Dippel, Diederik W J; Coutinho, Jonathan M

Published in:
Journal of Neurointerventional Surgery

DOI:
10.1136/neurintsurg-2021-018465

Original research

Successful reperfusion in relation to the number of passes: comparing outcomes of first pass expanded Treatment In Cerebral Ischemia (eTICI) 2B with multiple-pass eTICI 3

Agnetha A E Bruggeman ,[1] Manon Kappelhof,[1,2] Sanne J den Hartog ,[3,4,5] James F Burke,[6] Olvert A Berkhemer,[1,4,5] Adriaan C G M van Es,[7] Wim H van Zwam ,[8] Diederik W J Dippel ,[3] Jonathan M Coutinho,[9] Henk A Marquering,[1,2] Charles B L M Majoie,[1] Bart J Emmer,[1] MR CLEAN Registry investigators

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2021-018465).

For numbered affiliations see end of article.

Correspondence to
Dr Bart J Emmer, Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; b.j.emmer@amsterdamumc.nl

Received 18 November 2021
Accepted 13 January 2022
Published Online First 27 January 2022

To cite: Bruggeman AAE, Kappelhof M, den Hartog SJ, *et al*. *J NeuroIntervent Surg* 2023;**15**:120–126.

ABSTRACT

Background Higher expanded Treatment In Cerebral Ischemia (eTICI) reperfusion scores after endovascular treatment (EVT) are associated with better outcomes. However, the influence of the number of passes on this association is unclear. We aimed to compare outcomes of single-pass good reperfusion (eTICI 2B) with multiple-pass excellent/complete reperfusion (eTICI 2C/3) in daily clinical practice.

Methods We compared outcomes of patients in the MR CLEAN Registry with good reperfusion (eTICI 2B) in a single pass to those with excellent/complete reperfusion (eTICI 2C/3) in multiple passes. Regression models were used to investigate the association of single-pass eTICI 2B versus multiple-pass eTICI 2C/3 reperfusion with 90-day functional outcome (modified Rankin Scale (mRS)), functional independence (mRS 0–2), per-procedural complications and safety outcomes.

Results We included 699 patients: 178 patients with single-pass eTICI 2B, and 242 and 279 patients with eTICI 2C/3 after 2 and ≥3 passes, respectively. Patients with eTICI 2C/3 after 2 or ≥3 passes did not achieve significantly better functional outcomes compared with patients with single-pass eTICI 2B (adjusted common OR (acOR) 1.06, 95% CI 0.75 to 1.50 and acOR 0.88, 95% CI 0.74 to 1.05 for 90-day mRS, and adjusted OR (aOR) 1.24, 95% CI 0.78 to 1.97 and aOR 0.79, 95% CI 0.52 to 1.22 for functional independence).

Conclusions Our results did not show better outcomes for patients who achieved eTICI 2C/3 in multiple, that is, two or more, passes when compared with patients with single-pass eTICI 2B. However, this concerns observational data. Further research is necessary to investigate the per-pass effect in relation to reperfusion and functional outcome.

INTRODUCTION

The procedural goal of endovascular treatment (EVT) for acute ischemic stroke is to remove the causative thrombus and achieve successful reperfusion of the ischemic brain tissue as fast as possible.[1] EVT is considered successful if >50% of the area distal from the original thrombus is reperfused, scored as an extended Thrombolysis in Cerebral Ischemia (eTICI) ≥2B (good reperfusion).[2 3] A further improved reperfusion grade to eTICI 2C (indicating excellent, 99% reperfusion) or 3 (indicating complete, 100% reperfusion) is associated with a further improved functional outcome.[4 5]

However, additional EVT device passes have been associated with worse functional outcomes.[1 6–12] As such, too many additional attempts could ultimately outweigh the benefit of an improved reperfusion grade. Previous studies have indeed found that the positive effect on functional outcome of reaching excellent/complete reperfusion over good reperfusion diminishes with an increasing number of passes and prolonged procedure time.[6 13] Greater infarct volumes, increased clot fragmentation with distal embolization, and accumulated endothelial damage after multiple passes are possible explanations for this negative association between increasing number of passes and functional outcome.[13–16]

The question arises whether during EVT, additional passes to achieve eTICI 2C/3 should be undertaken when eTICI 2B has been achieved after one pass. Although it is known that more attempts lead to worse outcomes,[1 6–12] it is unknown whether an optimal or maximum number of attempts can be defined when trying to achieve the highest possible reperfusion grade if sufficient reperfusion has already been achieved during the procedure. This question hinges on when the disadvantages associated with additional passes begin to outweigh the expected benefit of improved tissue reperfusion.

Therefore, we aimed to explore the relation between number of passes, final reperfusion score and functional outcome. To this end, we compared functional outcomes of single-pass good reperfusion (eTICI 2B) with multiple-pass excellent/complete reperfusion (eTICI 2C/3) in a large dataset of patients treated with EVT in daily clinical practice.

METHODS

Patient selection

Patients included in this study were recruited from the MR CLEAN Registry: a prospective, observational multicenter registry that collected data of patients treated with EVT for acute ischemic stroke due to intracranial large vessel occlusion in 17 intervention hospitals in the Netherlands, since the completion of the MR CLEAN trial in March 2014.[17] The central medical ethics committee of the Erasmus MC gave permission to carry out the study as a registry (MEC-2014–235).[17] With this approval it was approved by the research board of each participating center. At UMC Utrecht, approval to participate in the study was obtained from their own research board and ethics committee. Source data of this study will not be available due to privacy regulations, but analytic methods, study materials and scripts of the statistical analysis are available on reasonable request.

The current study reports on patients treated between March 14, 2014 and November 1, 2017. All patients without contraindications received 0.9 mg/kg intravenous alteplase before EVT. We used the following inclusion criteria: intracranial proximal occlusion in the anterior circulation (internal carotid artery (ICA), M1 or M2 segments of the middle cerebral artery), age ≥18 years, onset to groin <6.5 hours, and treatment performed in a MR CLEAN trial center. We excluded patients who did not receive mechanical thrombectomy due to access problems or patients with reperfusion on the first intracranial digital subtraction angiography (DSA) run.

Imaging analyses

All patients underwent the standard acute ischemic stroke imaging protocol at baseline, as advised by the Dutch guidelines, including non-contrast computed tomography (NCCT) and CT angiography (CTA). The following imaging characteristics were evaluated by the MR CLEAN Registry imaging core lab, whose members were blinded to all clinical data except for occlusion side [17]: Alberta Stroke Program Early CT Score (ASPECTS) on baseline NCCT, clot burden score, 4-grade collateral score, presence of cervical carotid lesions, and location of the occlusion on baseline CTA. Reperfusion status, occurrence of per-procedural embolization to a new territory (ENT) and vessel perforation were evaluated by the imaging core lab on DSA imaging.

Post-treatment reperfusion status was evaluated according to the eTICI score.[18] Complete post-intervention DSA imaging including anteroposterior and lateral views were mandatory in order to evaluate successful reperfusion (eTICI ≥2B). Good reperfusion was defined as eTICI 2B (≥50% reperfusion), excellent reperfusion as eTICI 2C (99% reperfusion), and complete reperfusion as eTICI 3 (100% reperfusion). We only included the patients who achieved eTICI 2B in a single pass and patients who achieved eTICI 2C/3 after multiple passes according to the core lab assessment. In the MR CLEAN Registry, only post-treatment reperfusion score was recorded and per pass information was not available.

EVT procedure

EVT consisted of arterial catheterization with a microcatheter to the intracranial occlusion location, followed by stent retrieval, aspiration thrombectomy, or a combined approach, with or without additional intra-arterial thrombolytics. Patients treated with a combined approach were included in the first-line stent retriever group. The exact method of EVT and material choice were left to the discretion of the treating neurointerventionalist.

Outcome assessment

Primary outcome was the ordinal modified Rankin Scale (mRS), a 7-point scale ranging from 0 (no symptoms) to 6 (death).[19 20] The mRS score was assessed at 90 days after stroke by local investigators as part of usual care. Secondary outcomes were functional independence (mRS 0–2), 24 hour National Institutes of Health Stroke Scale (NIHSS) and ΔNIHSS (median improvement between baseline NIHSS and 24–48 hour NIHSS); 24 hour NIHSS and ΔNIHSS were reported as descriptive outcome measures. Patients who had died before NIHSS assessment, 24–48 hours after treatment, received the maximum NIHSS score of 42.

Safety outcomes were 90-day mortality, stroke progression (defined as a worsening of stroke symptoms of ≥4 points on the NIHSS not due to hemorrhage), new ischemic stroke (defined as new stroke outside the previous ischemic territory resulting in neurological deterioration or death), and symptomatic intracranial hemorrhage. An adverse events committee consisting of two vascular neurologists and one neuroradiologist evaluated the safety variables based on discharge letters and follow-up imaging. According to the Heidelberg criteria, intracranial hemorrhage was considered symptomatic if the patient died or deteriorated neurologically (increase of ≥4 points on the NIHSS), and the hemorrhage was related to the deterioration.[21]

Statistical analysis

Continuous data are displayed as medians and IQRs. Categorical data are displayed as frequencies and percentages. For our primary analyses, we compared baseline, treatment and outcome variables in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in two, or three or more passes as adjudicated by the imaging core lab. Group comparisons were made using the Pearson χ^2 test for trend and Kruskal-Wallis test appropriate to the type of data.

We used ordinal logistic regression to evaluate the association between good reperfusion in a single pass versus excellent/complete reperfusion in multiple passes and ordinal 90-day mRS score, resulting in an unadjusted and adjusted common odds ratio (cOR and acOR) for a one-step shift towards a better functional outcome with 95% confidence interval (95% CI). We used binary logistic regression to assess the association between good reperfusion in a single pass versus excellent/complete reperfusion in multiple passes for dichotomous outcomes, resulting in unadjusted and adjusted ORs (OR, aOR) with 95% CI. Based on baseline imbalances and prespecified prognostic factors, we adjusted for age, sex, time from onset to groin puncture, administration of intravenous alteplase, baseline NIHSS, and occlusion location in multivariable regression models. To assess the effect of longer procedure times in patients with multiple passes we performed an additional analysis where we added onset to reperfusion time to the multivariable regression model instead of time from onset to groin puncture.

For the regression analyses only, missing data were imputed using multiple imputation based on relevant covariates and outcomes.[22] Since reperfusion can only be reliably assessed when biplane DSA imaging is available,[23] reperfusion scores of eTICI 2A or higher assessed in a single direction (anteroposterior or lateral only) were recoded as missing and imputed for regression analyses. Conventional levels of α were used. All statistical analyses were performed with SPSS Statistics 26.0.

Table 1 Baseline and treatment characteristics in patients with single-pass good reperfusion (eTICI 2B) compared with excellent/complete reperfusion (eTICI 2C/3) in multiple passes

Baseline characteristics	eTICI 2B in 1 pass (n=178)	eTICI 2C/3 in 2 passes (n=242)	eTICI 2C/3 in ≥3 passes (n=279)
Age – median, IQR, total n	73 (61–82), 178	71 (61–79), 242	71 (62–78), 279
Male – n/total n (%)	90/178 (51)	141/242 (58)	148/279 (53)
Baseline NIHSS – median (IQR), total n	15 (12–19),175	16 (11–20), 240	17 (13–20), 277*
Imaging characteristics			
Occlusion location on CTA – n/total n (%)			
ICA	33/171 (19)	63/234 (27)	94/270 (35)*
M1	114/171 (67)	144/234 (62)	148/270 (55)
M2	24/171 (14)	27/234 (12)	28/270 (10)
Clot burden score – median (IQR), total n	6 (5–8), 141	6 (4–8), 194	6 (4–7), 226
ASPECTS – median (IQR), total n	9 (7–10), 170	9 (7–10), 236	9 (8–10), 271
Collaterals – n/total n (%)			
0. 0% filling of the occluded territory	5/168 (3)	10/229 (4)	19/265 (7)*
1. >0% and ≤50% filling of the occluded territory	58/168 (35)	80/229 (35)	95/265 (36)
2. >50% and <100% filling of the occluded territory	69/168 (41)	94/229 (41)	114/265 (43)
3. 100% filling of the occluded territory	36/168 (21)	45/229 (20)	37/265 (14)
Ipsilateral atherosclerotic carotid artery stenosis >50% – n/total n (%)	20/162 (12)	15/212 (7)	20/252 (8)
Intravenous alteplase treatment – n/total n (%)	133/178 (75)	179/242 (74)	209/277 (75)
Treatment variables			
Onset to groin time in min – median (IQR), total n	195 (145–246), 177	181 (140–237), 242	190 (155–246), 278
Onset to reperfusion time – median (IQR), total n†	236 (186–291), 175	235 (187–291), 241	262 (208–322), 277*
Procedure duration, min – median (IQR), total n	43 (34–55), 171	55 (42–70), 229	77 (63–100), 265*
First-line EVT approach – n/total n (%)			
Stent retriever	119/175 (68)	170/232 (73)	193/272 (71)
Aspiration device	56/175 (32)	62/232 (27)	79/272 (29)

Categorical variables are presented as n/N and percentage. Continuous variables are presented as median (IQR), total number.
*Significant at p<0.05.
†Or last contrast bolus.
ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; DSA, digital subtraction angiography; eTICI, expanded Thrombolysis In Cerebral Infarction; EVT, endovascular treatment; ICA, internal carotid artery; M1/M2, M1 and M2 segments of the middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

Sensitivity analysis

A previously performed study demonstrated that interventionalists tend to score higher reperfusion grades (for their own procedures) than core lab members (blinded to all clinical details).[24] In order to evaluate the effect of this difference on outcomes, we additionally performed regression analyses when post-treatment reperfusion score was assessed by the local interventionalist instead of the core lab as a sensitivity analysis. Additionally, we performed sensitivity analysis for our primary and secondary outcomes in patients with M1 occlusions only.

RESULTS

Baseline and treatment characteristics

In total, 1520/2123 (72%) of the patients achieved successful reperfusion (eTICI ≥2B) as adjudicated by the core lab (online supplemental figure lI). We included 699/1520 patients: 178 patients with single-pass eTICI 2B were compared with patients with excellent/complete reperfusion (eTICI 2C/3) in two and three or more passes (n=242 and n=279, respectively) (table 1 and online supplemental table I). In patients with single-pass eTICI 2B, baseline NIHSS was significantly lower than in patients with multiple-pass eTICI 2C/3 (p=0.02). ICA occlusions were less often present in the single-pass eTICI 2B group (p=0.003). A collateral score of 3 (100% filling of the occluded territory) was most often seen in patients with single-pass eTICI 2B and patients with eTICI 2C/3 after two passes (p=0.03). Procedure duration was significantly shorter in patients with single-pass eTICI 2B compared with patients with multiple-pass eTICI 2C/3 (p<0.001). Similarly, onset to reperfusion time was significantly shorter in patients with single-pass eTICI 2B compared with patients with eTICI 2C/3 in three or more passes: median 236 min (IQR 186–291) for patients with single-pass eTICI 2B versus median 262 min (IQR 208–322) for patients with eTICI 2C/3 in three or more passes (p<0.001). A stent retriever was most often used during the first pass in all groups of patients: 119/175 (68%) in patients with eTICI 2B in a single pass, 170/232 (73%) in patients with eTICI 2C/3 in two passes, and 193/272 (71%) in patients with eTICI 2C/3 after three or more passes (table 1).

Primary outcome

Multiple-pass eTICI 2C/3 compared with patients with single-pass eTICI 2B was not significantly associated with better 90-day mRS scores (acOR 1.06, 95% CI 0.75 to 1.50 for 2 passes, and acOR 0.88, 95% CI 0.74 to 1.05 for ≥3 passes) (table 2, figure 1). When adding onset to reperfusion time to the adjustments, instead of onset to groin puncture time, similar results were seen.

Secondary outcomes

Functional independence rates 90 days after EVT were comparable between patients with multiple-pass eTICI 2C/3 and

Table 2 Ordinal and binary logistic regression to compare outcomes in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes (reference category: single-pass eTICI 2B)

	Single pass eTICI 2B vs eTICI 2C/3 in 2 passes	Single pass eTICI 2B vs eTICI 2C/3 in ≥3 passes
Primary outcome		
mRS at 90 days		
cOR (95% CI)	1.08 (0.77 to 1.49)	0.90 (0.77 to 1.04)
acOR (95% CI)†	1.06 (0.75 to 1.50)	0.88 (0.74 to 1.05)
acOR (95% CI)‡	1.09 (0.77 to 1.54)	0.92 (0.78 to 1.10)
Secondary outcomes		
mRS 0–2 at 90 days		
OR (95% CI)	1.18 (0.80 to 1.73)	0.82 (0.58 to 1.16)
aOR (95% CI) †	1.24 (0.78 to 1.97)	0.79 (0.52 to 1.22)
aOR (95% CI)‡	1.27 (0.80 to 2.02)	0.86 (0.57 to 1.31)

*P<0.05.
†Adjustments: age, sex, time from onset to groin, administration of intravenous alteplase, baseline NIHSS and occlusion location.
‡Adjustments: age, sex, time from onset to reperfusion, administration of intravenous alteplase, baseline NIHSS and occlusion location.
(a)cOR, (adjusted) common odds ratio; (a)OR, (adjusted) odds ratio; eTICI, expanded Thrombolysis In Cerebral Infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

single-pass eTICI 2B (aOR 1.24, 95% CI 0.78 to 1.97 for 2 passes, and aOR 0.79, 95% CI 0.52 to 1.22 for ≥3 passes) (table 2, figure 1). Similar ORs were seen when adding onset to reperfusion time to the adjustments, instead of onset to groin time.

Post-treatment NIHSS

Twenty-four hour NIHSS was significantly worse in patients with multiple-pass eTICI 2C/3 compared with patients with single-pass eTICI 2B (p<0.001; table 3). Median ΔNIHSS was not significantly different between the groups. However, a decline in ΔNIHSS was seen with more passes needed to achieve eTICI 2C/3 (online supplemental figure II).

Per-procedural complications

The occurrence of ENT was similar between patients with eTICI 2B in a single pass compared with eTICI 2C/3 in three or more passes (aOR 0.91, 95% CI 0.35 to 2.38 for 2 passes, and aOR 1.02, 95% CI 0.42 to 2.47 for ≥3 passes) (table 3 and online supplemental table II). Vessel perforation most often occurred in patients with eTICI 2C/3 after ≥3 passes (p=0.07).

Safety outcomes

Mortality rates were comparable between multiple-pass eTICI 2C/3 and single-pass eTICI 2B (aOR 1.23, 95% CI 0.73 to 2.07 for 2 passes, and aOR 1.58, 95% CI 0.95 to 2.61 for ≥3 passes) (table 3 and online supplemental table II, figure 1). No significant differences were found between the groups for the occurrence of stroke progression (aOR 0.84, 95% CI 0.38 to 1.83 for 2 passes, and aOR 1.35, 95% CI 0.65 to 2.79 for ≥3 passes), new ischemic stroke (aOR 1.24, 95% CI 0.26 to 5.81 for 2 passes, and aOR 0.64, 95% CI 0.10 to 3.99 for ≥3 passes), and symptomatic intracranial hemorrhage (aOR 1.53, 95% CI 0.63 to 3.71 for 2 passes, and aOR 0.95, 95% CI 0.39 to 2.30 for ≥3 passes) (table 3 and online supplemental table II).

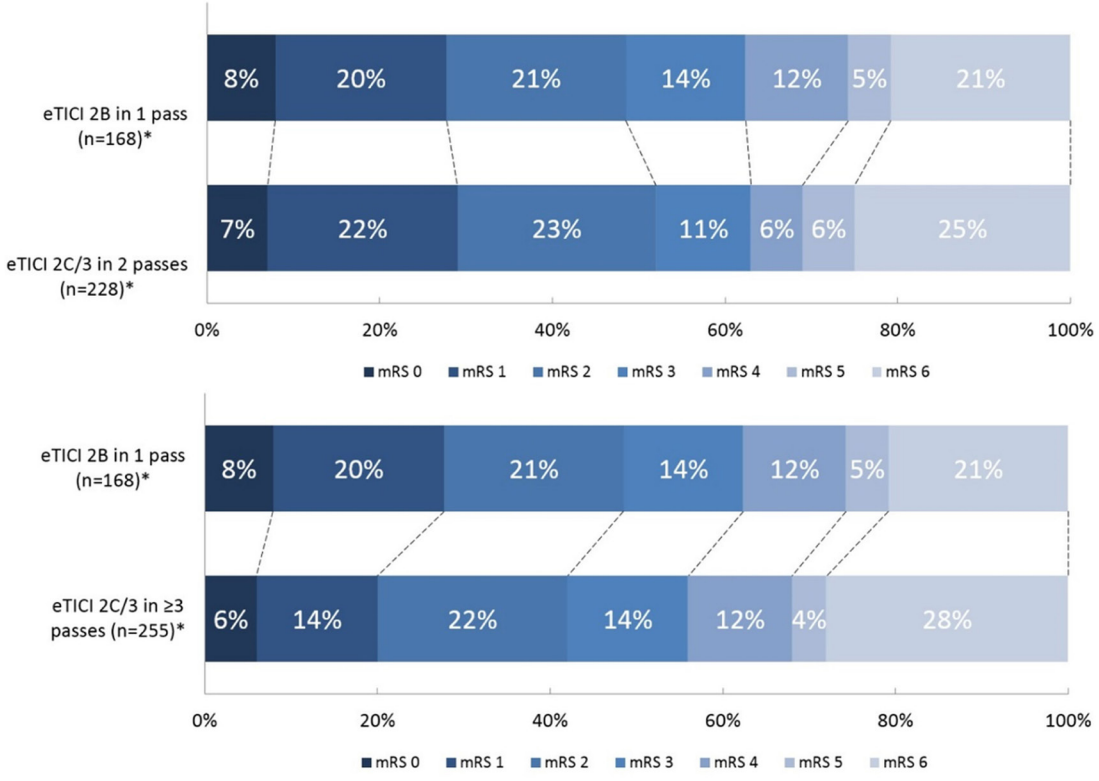


Figure 1 Ninety-day modified Rankin Scale score (mRS) in patients with single-pass eTICI 2B compared with patients with eTICI 2C/3 in multiple passes. *Number of patients with available mRS scores. eTICI, expanded Thrombolysis In Cerebral Infarction.

Table 3 Clinical outcomes, per-procedural complications and safety outcomes in patients with single-pass good reperfusion (eTICI 2B) compared with patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes

	eTICI 2B in 1 pass (n=178)	eTICI 2C/3 in 2 passes (n=242)	eTICI 2C/3 in ≥3 passes (n=279)
Outcomes – median (IQR), total n			
NIHSS at 24 hours	7 (3–15), 168	8 (3–15), 226	11 (5–17), 260*
Δ NIHSS	6 (1–9), 167	6 (2–12), 225	5 (1–10), 260
Per-procedural complications on DSA – n/total n (%)			
ENT	6/163 (4)	11/226 (5)	14/264 (5)
Vessel perforation	0/163 (0)	0/222 (0)	3/263 (1)
Safety outcomes – n/total n (%)			
Stroke progression	11/178 (6)	14/242 (6)	27/279 (10)
New ischemic stroke	3/178 (2)	4/242 (2)	3/279 (1)
Symptomatic intracranial hemorrhage	8/178 (5)	17/242 (7)	10/279 (4)
Mortality	35/168 (21)	57/228 (25)	71/255 (28)

Categorical variables are presented as n/N and percentage. Continuous variables are presented as median (IQR), total number.
ΔNIHSS: median difference between baseline NIHSS and NIHSS after 24–48 hours.
*Significant at p<0.05.
DSA, digital subtraction angiography; ENT, embolization to a new territory; NIHSS, National Institutes of Health Stroke Scale.

Sensitivity analyses

When reperfusion status was assessed by the interventionalist during EVT, 1703/2097 (81%) of the patients achieved successful reperfusion (online supplemental figure III). For the sensitivity analysis we included 714/1703 patients: 191 patients with single-pass eTICI 2B and 523 patients with multiple-pass eTICI 2C/3. Similar to our main analysis, no significant differences in outcomes were seen between patients with multiple-pass eTICI 2C/3 and patients with single-pass eTICI 2B (online supplemental table III, online supplemental figure IV).

Results from our sensitivity analysis in patients with M1 occlusions (n=406) were similar to our main analysis (online supplemental table IV and V). Multiple-pass eTICI 2C/3 compared with patients with single-pass eTICI 2B was not significantly associated with better 90-day mRS scores (acOR 0.91, 95% CI 0.58 to 1.42 for 2 passes, and acOR 0.87, 95% CI 0.68 to 1.12 for ≥3 passes). No significant differences were seen in 24 hour NIHSS between the groups, and median Δ NIHSS was 6 in all groups.

DISCUSSION

In this study, we compared functional outcomes of patients with single-pass eTICI 2B and multiple-pass eTICI 2C/3 in order to explore the relation between number of passes, final reperfusion score and functional outcome. We did not find significantly better functional outcomes when excellent/complete reperfusion was achieved in multiple passes compared with good reperfusion in a single pass.

Excellent and complete reperfusion (eTICI 2C and 3) are associated with better functional outcomes (90-day mRS) than good reperfusion (eTICI 2B).[4 5] In general, increasing the number of passes and increasing the treatment time to achieve successful reperfusion were shown to lead to worse functional outcome.[1 6–12] This trend to worse functional outcome was also seen when excellent or complete reperfusion (eTICI 2C/3) was reached.[6 13] However, in patients with complete reperfusion a decline in the odds of post-stroke functional independence was only seen if more than three passes were necessary to achieve this result, while in patients with a final eTICI score of 2B this decline had already occurred if more than two passes were necessary.[6] Prolonged procedure time, greater infarct volumes, increased clot fragmentation with distal embolization, and accumulated endothelial damage after multiple passes are possible explanations for this negative effect of an increasing number of passes on functional outcome.[13–16]

While a previously performed MR CLEAN Registry sub-study focused on the effect of the number of passes on functional outcome and found that first-pass reperfusion was associated with favorable functional outcome,[25] we went one step further and compared single pass good reperfusion with multiple pass excellent/complete reperfusion. In line with a previous descriptive analysis,[6] we found that if three or more passes were necessary to achieve excellent/complete reperfusion, functional outcome was not better compared with good reperfusion in a single pass. There might be several explanations for this finding. First, we found a non-significant shift towards a higher occurrence of per-procedural complications (vessel perforation and ENT) in patients with multiple-pass eTICI 2C/3 compared with single-pass eTICI 2B. This finding was probably not significant because of low statistical power. Furthermore, we cannot rule out the possibility that clot fragmentation and, more specifically, microembolic shower more often occurred in patients with multiple pass excellent/complete reperfusion and negatively affected clinical outcome. An in vitro study demonstrated that the number of passes is one of the most important determinants of embolic shower and that most of these emboli were microemboli <20 µm, which cannot be seen on DSA or post-intervention MRI but might worsen clinical outcome.[15 26] Another explanation for the diminished benefit of achieving excellent/complete reperfusion with three or more passes over single-pass eTICI 2B might be the non-significant trend towards a higher occurrence of stroke progression in patients with excellent/complete reperfusion after three or more passes, which is probably caused by the longer procedure and onset to reperfusion times. This explanation is supported by a smaller non-significant shift towards worse functional outcome in patients who achieved eTICI 2C/3 after three or more passes compared with patients with single-pass eTICI 2B when we adjusted for onset to reperfusion time instead of onset to groin puncture time.

There are limitations to our study. First, since we did not have information on the reperfusion grade achieved after each individual pass, we were not able to give the true value of additional passes because the patients with eTICI 2C/3 after multiple passes did not necessarily have a first-pass eTICI 2B.

Without the per pass reperfusion score, we were not able to define a certain number of passes that are justified to undertake after good reperfusion has been achieved successfully to achieve excellent or complete reperfusion. However, we demonstrated that the advantage of an eTICI 2C/3 diminishes with an increasing number of passes. Therefore, eTICI 2C/3 is not always better than eTICI 2B. Second, occlusion location on CTA was different between the groups. Patients with eTICI 2C/3 after three or more passes more often had an ICA occlusion at baseline. Baseline NIHSS was also highest in this group of patients. While we adjusted for both baseline NIHSS and occlusion location, residual confounding might be present. However, a sensitivity analysis in patients with M1 occlusions only showed similar results to our main analysis. Third, timing to stop EVT was at the interventionalist's discretion. Ideally, randomization after single pass good reperfusion between continuing to achieve excellent or complete reperfusion and stopping would provide information on the best procedural strategy. Fourth, we chose to use core lab assessment of post-treatment reperfusion score instead of assessment by the interventionalist in our primary analyses. One could argue that for this specific research question, it would be better to use the interventionalist's reperfusion scores since the interventionalist will decide whether to continue or stop the procedure. However, a previously performed study demonstrated that interventionalists tend to score higher reperfusion grades (for their own procedures) than core lab members (blinded to all clinical details).[24] While this did not significantly affect clinical outcome,[24] we think that in our study the use of core lab reperfusion assessment leads to a more conservative and objective comparison of the different groups of patients. This is further supported by the supplemental analyses performed in this study using the interventionalist's reperfusion scores which demonstrated similar outcomes between patients with single pass good reperfusion and multiple-pass excellent/complete reperfusion. Finally, we did not distinguish between eTICI 2B50 (50–66% reperfusion) and 2B67 (67–89% reperfusion) as the 7-point eTICI scale was not yet validated at the time of the core lab assessment of post-treatment reperfusion scores. As such, those data were unfortunately not collected. eTICI 2B covers a broad range of reperfusion results (50–90%) and previous research has shown that a 7-point eTICI scale allows for a more accurate outcome prediction.[27] So, it is important to acknowledge that a patient with TICI 2B50 after one attempt might very well benefit from further recanalization.

CONCLUSIONS

Our results did not show better outcomes for patients who achieved eTICI 2C/3 in multiple, that is, two or more, passes when compared with patients with single-pass eTICI 2B. However, this concerns observational data. Further research is necessary to investigate the per-pass effect in relation to reperfusion and functional outcome.

Author affiliations
[1]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
[2]Biomedical Engineering and Physics, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
[3]Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands
[4]Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
[5]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands
[6]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA
[7]Department of Radiology and Nuclear Medicine, Leiden University Medical Center, Leiden, The Netherlands
[8]Department of Radiology and Nuclear Medicine, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands
[9]Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

Collaborators MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry Investigators: Diederik WJ Dippel; Aad van der Lugt; Charles BLM Majoie; Yvo BWEM Roos; Robert J van Oostenbrugge; Wim H van Zwam; Jelis Boiten; Jan Albert Vos;, Ivo GH Jansen; Maxim JHL Mulder; Robert- Jan B Goldhoorn; Kars CJ Compagne; Manon Kappelhof; Josje Brouwer; Sanne J den Hartog; Wouter H Hinsenveld; Bob Roozenbeek; Adriaan CGM van Es; Bart J Emmer; Jonathan M Coutinho; Wouter J Schonewille; Marieke JH Wermer; Marianne AA van Walderveen; Julie Staals; Jeannette Hofmeijer; Jasper M Martens; Geert J Lycklama à Nijeholt; Sebastiaan F de Bruijn; Lukas C van Dijk; H Bart van der Worp; Rob H Lo; Ewoud J van Dijk; Hieronymus D Boogaarts; J de Vries; Paul LM de Kort; Julia van Tuijl ; Jo P Peluso; Puck Fransen; Jan SP van den Berg; Boudewijn AAM van Hasselt; Leo AM Aerden; René J Dallinga; Maarten Uyttenboogaart; Omid Eschgi; Reinoud PH Bokkers; Tobien HCML Schreuder; Roel JJ Heijboer; Koos Keizer; Lonneke SF Yo; Heleen M den Hertog; Tomas Bulut; Paul JAM Brouwers; Marianne AA van Walderveen; Marieke ES Sprengers; Sjoerd FM Jenniskens; René van den Berg; Albert J Yoo; Ludo FM Beenen; Alida A Postma; Stefan D Roosendaal; Bas FW van der Kallen; Ido R van den Wijngaard; Lonneke SF Yo; Joost Bot, Pieter-Jan van Doormaal; Anton Meijer; Elyas Ghariq; Reinoud PH Bokkers; Marc P van Proosdij; G Menno Krietemeijer; Jo P Peluso; Hieronymus D Boogaarts; Rob Lo; Wouter Dinkelaar; Auke PA Appelman; Bas Hammer; Sjoert Pegge; Anouk van der Hoorn; Saman Vinke; H Zwenneke Flach; Hester F Lingsma; Naziha el Ghannouti; Martin Sterrenberg; Wilma Pellikaan; Rita Sprengers; Marjan Elfrink; Michelle Simons; Marjolein Vossers; Joke de Meris; Tamara Vermeulen; Annet Geerlings; Gina van Vemde; Tiny Simons; Gert Messchendorp; Nynke Nicolaij; Hester Bongenaar; Karin Bodde; Sandra Kleijn; Jasmijn Lodico; Hanneke Droste; Maureen Wollaert; Sabrina Verheesen; D Jeurrissen; Erna Bos; Yvonne Drabbe; Michelle Sandiman; Nicoline Aaldering; Berber Zweedijk; Jocova Vervoort; Eva Ponjee; Sharon Romviel; Karin Kanselaar; Denn Barning; Esmee Venema; Vicky Chalos; Ralph R Geuskens; Tim van Straaten; Saliha Ergezen; Roger RM Harmsma; Daan Muijres; Anouk de Jong; Olvert A Berkhemer; Anna MM Boers; J Huguet; PFC Groot; Marieke A Mens; Katinka R van Kranendonk; Kilian M Treurniet; Manon L Tolhuisen; Heitor Alves; Annick J Weterings; Eleonora LF Kirkels; Eva JHF Voogd; Lieve M Schupp; Sabine L Collette; Adrien ED Groot; Natalie E LeCouffe; Praneeta R Konduri; Haryadi Prasetya; Nerea Arrarte-Terreros; Lucas A Ramos.

Contributors AAEB and BJE developed the study. AAEB performed the data analysis, wrote the manuscript and is responsible for the overall content of the manuscript as the guarantor. BJE contributed to the study design. MK and SJdH helped with data acquisition and interpretation. JFB, OAB, ACGvE, WvZ, DWJD, JMC, CBLM and BJE contributed to the clinical assessment of the data. JMC, HAM, CBLM and BJE contributed to the research development and project supervision. All authors provided feedback and contributed to the final version of the manuscript.

Funding The MR CLEAN Registry was partly funded by the TWIN Foundation, Erasmus MC University Medical Center, Maastricht University Medical Center, and Amsterdam UMC.

Competing interests Amsterdam UMC received funds from Stryker for consultation by CBLM. Unrelated to this study, Amsterdam UMC received grants from the Netherlands Organization for Health Research and Development, Health Holland Top Sector LSH and Nicolab B.V. Erasmus University Medical Center received funds from Stryker, Siemens Healthineers, GE Healthcare and Bracco Imaging for consultation by DWJD. Maastricht University Medical Center received funds from Stryker, Cerenovus, Nicolab B.V. and Philips for consultation by WvZ. JMC reports a grant from Medtronic, all fees paid to institution. HAM is co-founder and shareholder of Nicolab B.V. Dr Charles BLM Majoie reports grants from the TWIN Foundation, CVON/Dutch Heart Foundation, European Commission, Health Evaluation Netherlands, and Stryker, all paid to the institution. CBLM is minor shareholder of Nicolab B.V. Dr Bart J Emmer reports a TKI-Private PPP Grant from the Dutch Ministry of Economics. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Source data of this study will not be available due to privacy regulations, but analytic

methods, study materials and scripts of the statistical analysis are available upon reasonable request.

ORCID iDs
Agnetha A E Bruggeman http://orcid.org/0000-0002-6873-2545
Sanne J den Hartog http://orcid.org/0000-0002-1650-951X
Wim H van Zwam http://orcid.org/0000-0003-1631-7056
Diederik W J Dippel http://orcid.org/0000-0002-9234-3515

REFERENCES

1 Zaidat OO, Castonguay AC, Linfante I, *et al*. First pass effect: a new measure for stroke thrombectomy devices. *Stroke* 2018;49:660–6.
2 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
3 Zaidat OO, Yoo AJ, Khatri P, *et al*. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650–63.
4 Kaesmacher J, Dobrocky T, Heldner MR, *et al*. Systematic review and meta-analysis on outcome differences among patients with TICI2b versus TICI3 reperfusions: success revisited. *J Neurol Neurosurg Psychiatry* 2018;89:910–7.
5 LeCouffe NE, Kappelhof M, Treurniet KM, *et al*. 2B, 2C, or 3: what should be the angiographic target for endovascular treatment in ischemic stroke? *Stroke* 2020;51:1790–6.
6 Garcia-Tornel A, Requena M, Rubiera M. When to stop detrimental effect of device passes in acute ischemic stroke secondary to large vessel occlusion. *Stroke* 2019;50:1781–8.
7 Flottmann F, Leischner H, Broocks G, *et al*. Recanalization rate per retrieval attempt in mechanical thrombectomy for acute ischemic stroke. *Stroke* 2018;49:2523–5.
8 Seker F, Pfaff J, Wolf M, *et al*. Correlation of thrombectomy maneuver count with recanalization success and clinical outcome in patients with ischemic stroke. *AJNR Am J Neuroradiol* 2017;38:1368–71.
9 Baek J-H, Kim BM, Heo JH, *et al*. Number of stent retriever passes associated with futile recanalization in acute stroke. *Stroke* 2018;49:2088–95.
10 Nikoubashman O, Dekeyzer S, Riabikin A, *et al*. True first-pass effect. *Stroke* 2019;50:2140–6.
11 Kharouba R, Gavriliuc P, Yaghmour NE, *et al*. Number of stentriever passes and outcome after thrombectomy in stroke. *J Neuroradiol* 2019;46:327–30.
12 den Hartog SJ, Roozenbeek B, Boodt N, *et al*. Effect of first pass reperfusion on outcome in patients with posterior circulation ischemic stroke. *J Neurointerv Surg* 2021. doi:10.1136/neurintsurg-2021-017507. [Epub ahead of print: 04 May 2021].
13 Kitano T, Todo K, Yoshimura S, *et al*. Futile complete recanalization: patients characteristics and its time course. *Sci Rep* 2020;10:4973.
14 Arai D, Ishii A, Chihara H, *et al*. Histological examination of vascular damage caused by stent retriever thrombectomy devices. *J Neurointerv Surg* 2016;8:992–5.
15 Chueh J-Y, Puri AS, Wakhloo AK, *et al*. Risk of distal embolization with stent retriever thrombectomy and adapt. *J Neurointerv Surg* 2016;8:197–202.
16 Ben Hassen W, Touloupas C, Benzakoun J, *et al*. Impact of repeated clot retrieval attempts on infarct growth and outcome after ischemic stroke. *Neurology* 2021;97:e444–53.
17 Jansen IGH, Mulder MJHL, Goldhoorn R-JB, *et al*. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ* 2018;360:k949.
18 Liebeskind DS, Bracard S, Guillemin F, *et al*. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg* 2019;11:433–8.
19 Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007;38:1091–6.
20 van Swieten JC, Koudstaal PJ, Visser MC, *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7.
21 von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
22 Donders ART, van der Heijden GJMG, Stijnen T, *et al*. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006;59:1087–91.
23 Gerber JC, Miaux YJ, von Kummer R. Scoring flow restoration in cerebral angiograms after endovascular revascularization in acute ischemic stroke patients. *Neuroradiology* 2015;57:227–40.
24 Zhang G, Treurniet KM, Jansen IGH, *et al*. Operator versus core lab adjudication of reperfusion after endovascular treatment of acute ischemic stroke. *Stroke* 2018;49:2376–82.
25 den Hartog SJ, Zaidat O, Roozenbeek B, *et al*. Effect of first-pass reperfusion on outcome after endovascular treatment for ischemic stroke. *J Am Heart Assoc* 2021;10:e019988.
26 Shih AY, Blinder P, Tsai PS, *et al*. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci* 2013;16:55–63.
27 Behme D, Tsogkas I, Colla R, *et al*. Validation of the extended thrombolysis in cerebral infarction score in a real world cohort. *PLoS One* 2019;14:e0210334.

Supplemental materials

Table of contents

Supplemental Table I: Medical history and pre-stroke mRS in patients with single-pass good reperfusion (eTICI 2B) compared with excellent/complete reperfusion (eTICI 2C/3) in multiple passes

Baseline characteristics	**eTICI 2B in 1 pass (n=178)**	**eTICI 2C/3 in 2 passes (n=242)**	**eTICI 2C/3 in ≥3 passes (n=279)**
Medical History - n/total n (%)			
Stroke	30/177 (17)	34/241 (14)	44/276 (16)
Myocardial infarction	28/176 (16)	36/239 (15)	38/273 (14)
Diabetes	23/174 (13)	52/242 (22)	37/276 (13)
Hypertension	97/172 (56)	126/239 (53)	140/270 (52)
Atrial fibrillation	46/174 (26)	56/241 (23)	71/276 (26)
Hypercholesterolemia	51/170 (30)	66/235 (28)	77/267 (29)
Current smoker	49/142 (35)	48/179 (27)	50/205 (24)
Anticoagulation (vitamin K antagonists)	24/176 (14)	33/240 (14)	36/279 (13)
Direct oral anticoagulants	11/176 (6)	4/241 (2)	8/279 (3)
Prestroke mRS - n/total n (%)			
0-2	152/174 (87)	222/239 (93)	244/274 (89)
≥3	22/174 (13)	17/239 (7)	30/274 (11)

Categorical variables are presented as n/N and percentage. mRS: modified Rankin Scale; eTICI: expanded Trombolysis In Cerebral Infarction; *significant at $p<0.05$.

Supplemental Table II: Regression analyses to compare per-procedural complications and safety outcomes in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes. (Reference category: single-pass eTICI 2B)

	Single pass eTICI 2B vs eTICI 2C/3 in 2 passes	**Single pass eTICI 2B vs eTICI 2C/3 in ≥3 passes**
Per-procedural complications		
ENT		
OR (95% CI)	1.01 (0.39-2.61)	1.12 (0.47-2.66)
aOR (95% CI) †	0.91 (0.35-2.38)	1.02 (0.42-2.47)
aOR (95% CI) ‡	0.90 (0.35-2.34)	1.00 (0.42-2.42)
Safety outcomes		
Mortality at 90 days		
OR (95% CI)	1.13 (0.73-1.75)	1.35 (0.89-2.04)
aOR (95% CI) †	1.23 (0.73-2.07)	1.58 (0.95-2.61)
aOR (95% CI ‡	1.20 (0.71-2.03)	1.45 (0.87-2.41)
Stroke progression		
OR (95% CI)	0.88 (0.41-1.91)	1.35 (0.67-2.74)
aOR (95% CI) †	0.84 (0.38-1.83)	1.35 (0.65-2.79)
aOR (95% CI) ‡	0.83 (0.38-1.82)	1.32 (0.64-2.74)
New ischemic stroke		
OR (95% CI)	1.28 (0.28-5.73)	0.80 (0.16-4.03)
aOR (95% CI) †	1.24 (0.26-5.81)	0.64 (0.10-3.99)
aOR (95% CI) ‡	1.37 (0.29-6.48)	0.66 (0.11-3.96)
Symptomatic intracranial hemorrhage		
OR (95% CI)	1.50 (0.63-3.56)	1.01 (0.42-2.42)
aOR (95% CI) †	1.53 (0.63-3.71)	0.95 (0.39-2.30)
aOR (95% CI) ‡	1.51 (0.62-3.64)	0.89 (0.37-2.19)

* $p<0.05$. † adjustments: age, sex, time from onset to groin, administration of intravenous alteplase, baseline National Institutes of Health Stroke Scale (NIHSS) and occlusion location. ‡ adjustments: age, sex, time from onset to reperfusion, administration of intravenous alteplase, baseline NIHSS and occlusion location eTICI: expanded Thrombolysis In Cerebral

Infarction; mRS: modified Rankin Scale; (a)cOR: (adjusted) common odds ratio; aOR: (adjusted) odds ratio; ENT: Embolization to a new territory

Supplemental Table III. Ordinal and binary logistic regression to compare outcomes in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes as assessed by the interventionist during the procedure (Reference category: single-pass eTICI 2B)

	Single pass eTICI 2B vs eTICI 2C/3 in 2 passes	**Single pass eTICI 2B vs eTICI 2C/3 in ≥3 passes**
Primary outcome		
mRS at 90 days		
cOR (95% CI)	0.89 (0.64-1.25)	0.85 (0.68-1.06)
acOR (95% CI)†	1.01 (0.73-1.39)	0.91 (0.72-1.16)
acOR (95% CI)‡	1.04 (0.74-1.44)	0.96 (0.76-1.22)
Secondary outcomes		
mRS 0-2 at 90 days		
OR (95% CI)	1.00 (0.68-1.46)	0.76 (0.49-1.20)
aOR (95% CI) †	1.24 (0.80-1.92)	0.89 (0.53-1.49)
aOR (95% CI) ‡	1.30 (0.83-2.02)	1.01 (0.61-1.69)
Per-procedural complications		
ENT		
OR (95% CI)	0.92 (0.34-2.47)	0.71 (0.30-1.68)
aOR (95% CI) †	0.82 (0.29-2.29)	0.61 (0.25-1.47)
aOR (95% CI) ‡	0.80 (0.29-2.23)	0.59 (0.24-1.47)
Safety outcomes		
Mortality at 90 days		
OR (95% CI)	1.14 (0.71-1.85)	1.53 (0.96-2.45)
aOR (95% CI) †	1.02 (0.59-1.76)	1.47 (0.86-2.49)
aOR (95% CI) ‡	1.00 (0.58-1.73)	1.37 (0.82-2.30)
Stroke progression		
OR (95% CI)	1.30 (0.53-3.23)	2.19 (0.99-4.82)
aOR (95% CI) †	1.26 (0.51-3.11)	1.99 (0.89-4.42)
aOR (95% CI) ‡	1.25 (0.50-3.08)	1.89 (0.85-4.22)

New ischemic stroke		
OR (95% CI)	0.44 (0.10-1.87)	0.42 (0.12-1.45)
aOR (95% CI) †	0.47 (0.11-2.04)	0.42 (0.12-1.52)
aOR (95% CI) ‡	0.47 (0.11-2.06)	0.41 (0.11-1.53)
Symptomatic intracranial hemorrhage		
OR (95% CI)	2.03 (0.86-4.81)	1.44 (0.53-3.88)
aOR (95% CI) †	2.01 (0.84-4.83)	1.33 (0.49-3.65)
aOR (95% CI) ‡	1.99 (0.83-4.78)	1.31 (0.48-3.54)

* p<0.05. † adjustments: age, sex, time from onset to groin, administration of intravenous alteplase, baseline National Institutes of Health Stroke Scale (NIHSS) and occlusion location. ‡adjustments: age, sex, time from onset to reperfusion, administration of intravenous alteplase, baseline NIHSS and occlusion location. eTICI: expanded Thrombolysis In Cerebral Infarction; mRS: modified Rankin Scale; (a)cOR: (adjusted) common odds ratio; aOR: (adjusted) odds ratio; ENT: Embolization to a new territory.

Supplemental Table IV. Regression analyses to compare outcomes in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes; in patients with M1 occlusions only**.** (Reference category: single-pass eTICI 2B)

	Single pass eTICI 2B vs eTICI 2C/3 in 2 passes	**Single pass eTICI 2B vs eTICI 2C/3 in ≥3 passes**
Primary outcome		
mRS at 90 days		
cOR (95% CI)	0.98 (0.64-1.49)	0.88 (0.71-1.09)
acOR (95% CI) †	0.91 (0.58-1.42)	0.87 (0.68-1.12)
acOR (95% CI) ‡	0.92 (0.59-1.43)	0.91 (0.70-1.17)
Secondary outcomes		
mRS 0-2 at 90 days		
OR (95% CI)	1.04 (0.65-1.67)	0.80 (0.49-1.31)
aOR (95% CI) †	0.99 (0.52-1.88)	0.74 (0.36-1.49)
aOR (95% CI) ‡	1.00 (0.52-1.91)	0.78 (0.39-1.58)

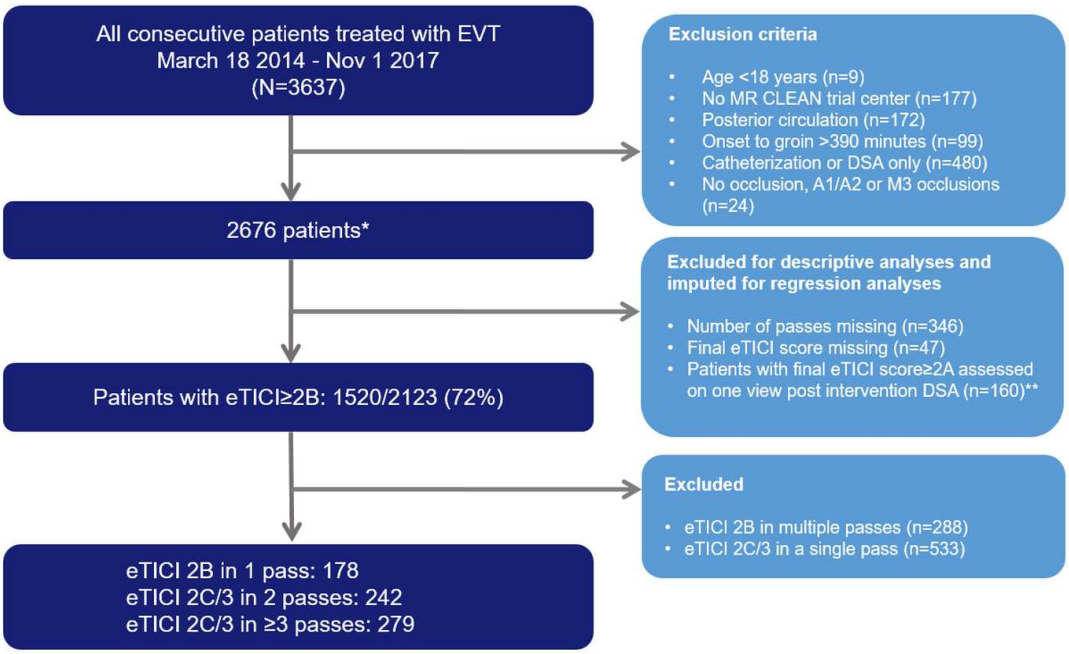
* p<0.05. † adjustments: age, sex, time from onset to groin, administration of intravenous alteplase, baseline National Institutes of Health Stroke Scale (NIHSS) and occlusion location.

‡ adjustments: age, sex, time from onset to reperfusion, administration of intravenous alteplase, baseline NIHSS;. eTICI: expanded Thrombolysis In Cerebral Infarction; mRS: modified Rankin Scale; (a)cOR: (adjusted) common odds ratio; aOR: (adjusted) odds ratio.

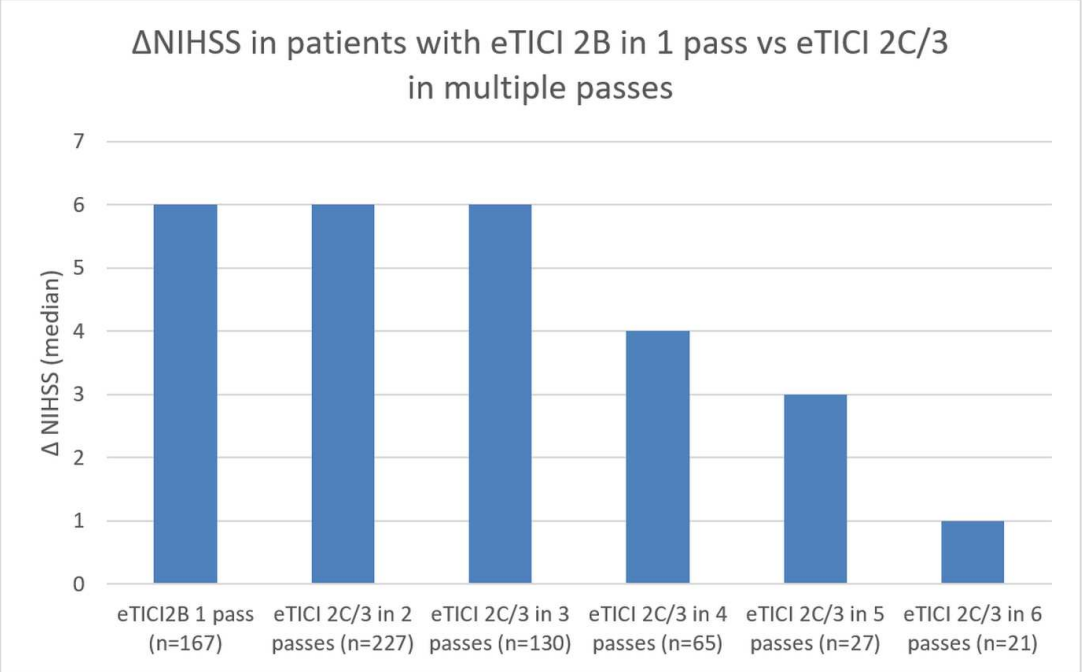
Supplemental Table V. 24-hour NIHSS and Δ NIHSS in patients with single-pass good reperfusion (eTICI 2B) and patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes; in patients with M1 occlusions only

	eTICI 2B in 1 pass (n=114)	**eTICI 2C/3 in 2 passes (n=144)**	**eTICI 2C/3 in ≥3 passes (n=148)**
Outcomes - median (IQR), total n			
NIHSS at 24 hours	7 (2-14), 107	7 (3-15), 136	11 (4-16), 135
Δ NIHSS	6 (2-10), 106	6 (2-11), 136	6 (2-10), 135

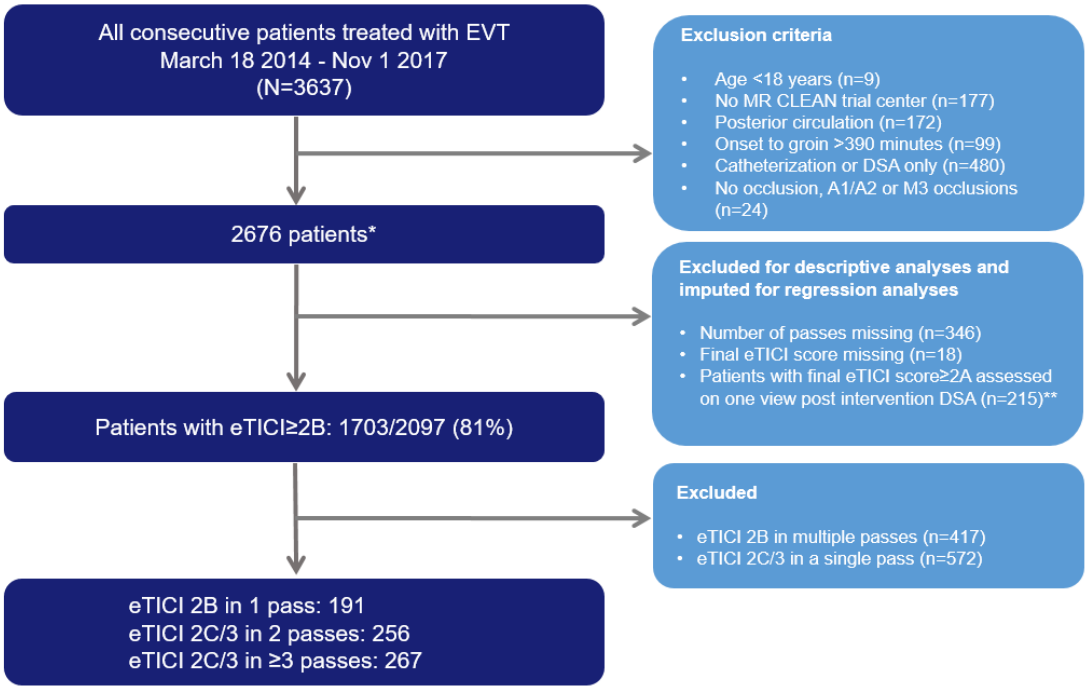
Continuous variables are presented as median (IQR), total number. NIHSS: National Institutes of Health Stroke Scale; Δ NIHSS: median difference between baseline NIHSS and 24-hour NIHSS. *significant at p<0.05.



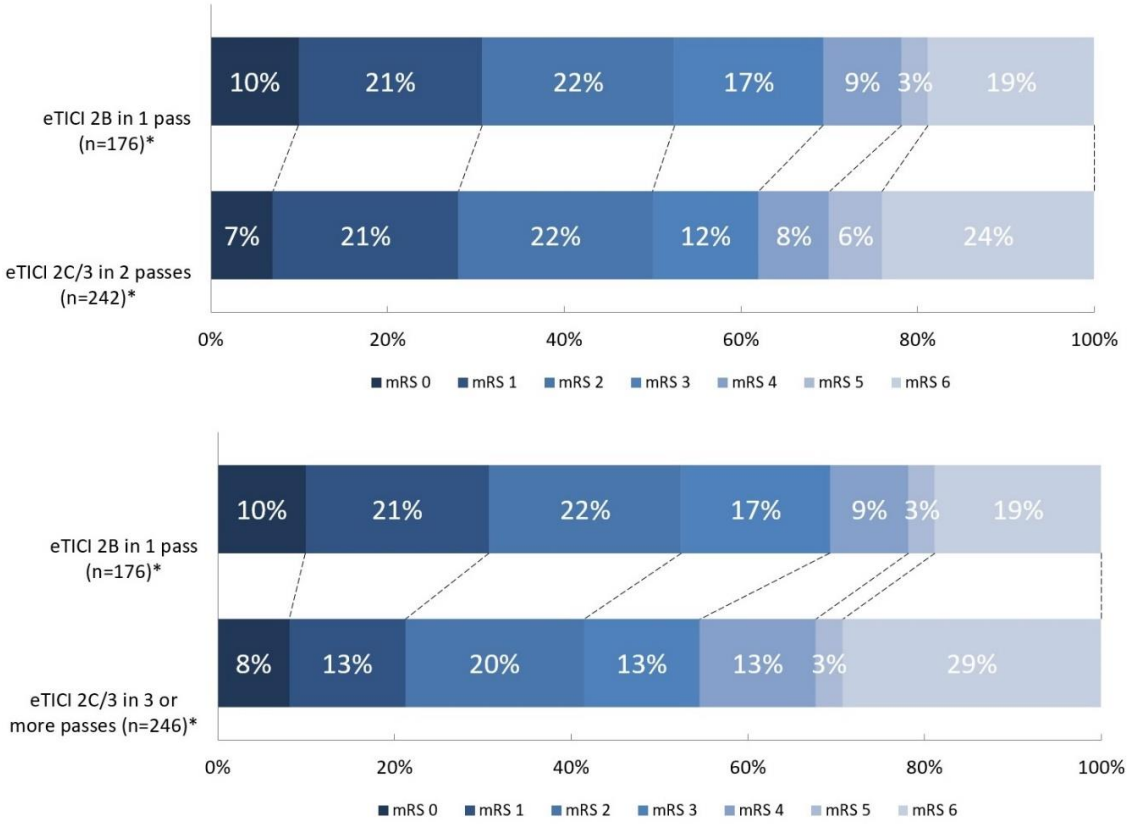
Supplemental Figure I. Flowchart of the patient selection procedure. eTICI: extended Thrombolysis in Cerebral Infarction (eTICI) score; DSA: digital subtraction angiography. * We performed multiple imputation on the dataset of 2676 patients. In this multiple imputed dataset outcomes of patients with good reperfusion (eTICI 2B) in a single pass were compared with outcomes of patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes; ** Patients with a final eTICI score of ≥2A assessed on one view post intervention DSA were recoded as missing and imputed.



Supplemental Figure II. Δ NIHSS (median improvement between baseline and 24 hour-National Institutes of Health Stroke Scale (NIHSS) score) in patients with single-pass eTICI 2B compared with patients with multiple-pass eTICI 2C/3.



Supplemental Figure III. Flowchart of the patient selection procedure in patients in whom post treatment reperfusion was assessed by the interventionist. eTICI: extended Thrombolysis in Cerebral Infarction (eTICI) score as assessed by the interventionist; DSA: digital subtraction angiography. * We performed multiple imputation on the dataset of 2676 patients. In this multiple imputed dataset outcomes of patients with good reperfusion (eTICI 2B) in a single pass were compared with outcomes of patients with excellent/complete reperfusion (eTICI 2C/3) in multiple passes; ** Patients with a final eTICI score of ≥2A assessed on one view post intervention DSA were recoded as missing and imputed.



Supplemental Figure IV: Ninety-day modified Rankin Scale score (mRS) in patients with single-pass eTICI 2B compared with patients with eTICI 2C/3 in multiple passes as assessed by the interventionist during the procedure. *Number of patients with available mRS scores.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Olvert Berkhemer

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Agnetha Bruggeman

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: James Burke

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Jonathan Coutinho

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ **None**	
		Medtronic grant	all fees paid to my employer
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/18/2021

Your Name: Diederik Dippel

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ None	
		Stryker®	Unrestricted grant paid to institution (Erasmus University Medical Center)
		Penumbra	Unrestricted grant paid to institution (Erasmus University Medical Center)
		Medtronic	Unrestricted grant paid to institution (Erasmus University Medical Center)
		Cerenovus	Unrestricted grant paid to institution (Erasmus University Medical Center)
		Dutch Heart foundation	Grant, paid to institution (Erasmus University Medical Center)
		Brain foundation Netherlands	Grant, paid to institution (Erasmus University Medical Center)
		The Netherlands Organization for Health Research and development	Grant, paid to institution (Erasmus University Medical Center)
		Health Holland Top Sector Life Sciences & Health	Grant, paid to institution (Erasmus University Medical Center)
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board,	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	society, committee or advocacy group, paid or unpaid		
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Bart Emmer

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		TKI-Private PPP Grant	Dutch Ministry of Economics
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Sanne den Hartog

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/17/2021

Your Name: Manon Kappelhof

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Charles Majoie

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ **None**	
		Stryker®	Paid to institution (Amsterdam UMC)
		CVON/Dutch Heart Foundation	Paid to institution (Amsterdam UMC)
		Twin Foundation	Paid to institution (Amsterdam UMC)
		European Commission	Paid to institution (Amsterdam UMC)
		Health evaluation Netherlands	Paid to institution (Amsterdam UMC)
		Minor shareholder of Nico-Lab (a company focusing at AI use in neuroradiology)	Personal disclosure
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Henk Marquering

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ **None**	
		Co-founder and shareholder of Nico-Lab (a company focusing at AI use in neuroradiology)	Personal disclosure
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Adriaan van Es

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 11/16/2021

Your Name: Wim van Zwam

Manuscript Title: Successful Reperfusion in Relation to the Number of Passes: Comparing outcomes of first pass eTICI 2B with multiple-pass eTICI 3

Manuscript Number (if known): 2021-018465

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☐ **None**	
		Philips	Maastricht University Medical Center
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Stryker®	Maastricht University Medical Center
		Cerenovus®	Maastricht University Medical Center
		NicoLab	Maastricht University Medical Center
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.