Effect of endovascular reperfusion in relation to site of arterial occlusion

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ABSTRACT

Objective: To assess whether the association between reperfusion and improved clinical outcomes after stroke differs depending on the site of the arterial occlusive lesion (AOL).

Methods: We pooled data from Solitaire With the Intention for Thrombectomy (SWIFT), Solitaire FR Thrombectomy for Acute Revascularisation (STAR), Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 (DEFUSE 2), and Interventional Management of Stroke Trial (IMS III) to compare the strength of the associations between reperfusion and clinical outcomes in patients with internal carotid artery (ICA), proximal middle cerebral artery (MCA) (M1), and distal MCA (M2/3/4) occlusions.

Results: Among 710 included patients, the site of the AOL was the ICA in 161, the proximal MCA in 389, and the distal MCA in 160 patients (M2 = 131, M3 = 23, and M4 = 6). Reperfusion was associated with an increase in the rate of good functional outcome (modified Rankin Scale [mRS] score 0–2) in patients with ICA (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.7–7.2) and proximal MCA occlusions (OR 6.2, 95% CI 3.8–10.2), but not in patients with distal MCA occlusions (OR 1.4, 95% CI 0.8–2.6). Among patients with M2 occlusions, a subset of the distal MCA cohort, reperfusion was associated with excellent functional outcome (mRS 0–1; OR 2.2, 95% CI 1.0–4.7).

Conclusions: The association between endovascular reperfusion and better clinical outcomes is more profound in patients with ICA and proximal MCA occlusions compared to patients with distal MCA occlusions. Because there are limited data from randomized controlled trials on the effect of endovascular therapy in patients with distal MCA occlusions, these results underscore the need for inclusion of this subgroup in future endovascular therapy trials. *Neurology*® 2016;86:762–770

GLOSSARY

AOL = arterial occlusive lesion; **CI** = confidence interval; **DEFUSE 2** = Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2; **ICA** = internal carotid artery; **IMS III** = Interventional Management of Stroke Trial; **M1** = proximal middle cerebral artery; **M2/3/4** = distal middle cerebral artery; **MCA** = middle cerebral artery; **MERCI** = Mechanical Embolus Removal in Cerebral Ischemia; **MR** = magnetic resonance; **mRS** = modified Rankin Scale; **mTICI** = modified Thrombolysis in Cerebral Infarction; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **sICH** = symptomatic intracranial hemorrhage; **STAR** = Solitaire FR Thrombectomy for Acute Revascularisation; **SWIFT** = Solitaire With the Intention for Thrombectomy; **tPA** = tissue plasminogen activator.

Reperfusion is associated with improved outcomes in acute ischemic stroke,[1] but it is not known if the response to endovascular reperfusion differs depending on the site of the arterial occlusive lesion (AOL). A modifying role of the site of AOL on the clinical effect of reperfusion could potentially impact clinical trial design in terms of patient selection criteria and sample size calculations. The results of prior studies that have examined the effect of the site of the arterial

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occlusion (internal carotid artery [ICA] vs proximal middle cerebral artery [MCA]) on the association between endovascular reperfusion and clinical outcome have been inconclusive.[2–5] Some studies suggest that there may be less benefit from reperfusion in patients with ICA occlusions.[2,4,5] In a pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi-MERCI studies, ICA occlusion was associated with an approximate 2-fold increased chance of mortality after adjusting for reperfusion, baseline NIH Stroke Scale (NIHSS) score, and age.[4] Second, a large ($n > 600$) prospective study showed that patients with proximal occlusions had worse clinical outcomes despite higher reperfusion rates compared to patients with more peripheral occlusions.[2] Third, in a systematic review of endovascular therapy, patients with ICA occlusions had worse outcomes compared to patients with more peripheral occlusions.[5] The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 (DEFUSE 2), a prospective cohort of ischemic stroke patients who underwent a baseline MRI scan before endovascular therapy, also showed worse outcomes in patients with ICA occlusions, but this association was driven by a high rate of poor outcomes in patients with ICA occlusions who did not reperfuse. An assessment of the response to reperfusion suggested that patients with ICA occlusions benefitted more from reperfusion than patients with MCA occlusions.[3]

In this study, we used pooled individual patient data from 4 large endovascular trials to investigate whether the effect of endovascular reperfusion on clinical outcomes differs depending on the site of the AOL. This pooled data analysis provides us with sufficient power to compare the response to endovascular reperfusion between patients with ICA, proximal MCA (M1), and more distal MCA (M2/3/4) occlusions.

METHODS

Study design and procedures. Criteria for inclusion in this pooled analysis were as follows: prospective clinical studies with more than 100 endovascularly treated patients, blinded outcome assessment, and determination of AOL and reperfusion status on angiography by core laboratory reading. A PubMed search identified 8 studies that fulfilled these criteria.[2,4,6–12] Corresponding authors from all studies were contacted with a request for participation and 4 agreed: Interventional Management of Stroke Trial (IMS III), Solitaire With the Intention for Thrombectomy (SWIFT), Solitaire FR Thrombectomy for Acute Revascularisation (STAR), and DEFUSE 2. The full methodology of the 4 studies has been described previously.[8–11] In brief, SWIFT was a randomized trial comparing the efficacy and safety of Solitaire with the MERCI Retrieval System.[10] STAR was a prospective single-arm study of patients who received the Solitaire retrievable stent device.[12] DEFUSE 2 was a prospective cohort of ischemic stroke patients who underwent a baseline MRI scan before endovascular therapy.[8] From IMS III, a randomized trial assigning patients to IV thrombolysis alone vs IV thrombolysis with additional endovascular treatment, only patients who underwent endovascular therapy and had evidence of a large artery occlusion on angiography were included.[11] Patients with extensive early infarct signs on the baseline CT or magnetic resonance (MR) scan (CT showing hypodensity or MR showing hyperintensity involving greater than 1/3 of the MCA territory) were excluded from the IMS III, STAR, and SWIFT studies, to limit the rate of futile reperfusion.[13] Similarly, patients with extensive early infarct signs on baseline MRI or CT were generally not offered endovascular treatment at the DEFUSE 2 study sites and were thus excluded from enrollment.

Baseline stroke severity was assessed with the NIHSS by a certified investigator. Functional outcome was assessed at day 90 with the modified Rankin Scale (mRS). Good functional outcome was defined as an mRS score of 0–2 and excellent functional outcome as mRS 0–1. Clinical endpoints at 90 days were assessed by investigators masked to the patients' baseline clinical and radiographic data. For each study, blinded investigators at core imaging laboratories reviewed cerebral angiography studies and were masked to clinical data. Angiograms were evaluated for reperfusion status by using the modified Thrombolysis in Cerebral Infarction (mTICI) rating scale.[11] Symptomatic intracranial hemorrhage (sICH) in the present study was defined as originally reported in each study. In DEFUSE 2, this was defined according to the definition in the Safe Implementation of Thrombolysis in Stroke Monitoring Study 2 (SITS MOST).[14] SWIFT defined sICH as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with a worsening of the NIHSS score by 4 or more within 24 hours. In STAR, sICH was scored according to the European Cooperative Acute Stroke Study trial definition.[12] The definition in IMS III was an intracranial hemorrhage temporally related to a decline in neurologic status in the judgment of the clinical investigator.[11]

Standard protocol approvals, registrations, and patient consents. Approval for the study was obtained from local institutional review boards. Written informed consent was provided by all patients or a legally authorized representative. Included studies in this analysis have been registered previously: DEFUSE 2 NCT01327989, IMS III NCT00359424, STAR NCT01327989, and SWIFT NCT01054560.

Statistical analysis. In the primary analysis, final mTICI scores were dichotomized and defined as substantial reperfusion (mTICI 2B–3) vs no substantial reperfusion (mTICI 0–1–2A). Regression analyses were performed to compare the strength of the associations between reperfusion and good functional outcome (mRS 0–2) in patients with ICA, M1, and M2/3/4 occlusions. Including more distal lesions (M3 and M4) in the distal MCA group could obscure a potential beneficial effect of reperfusion on

clinical outcomes in patients with an occlusion of the M2. We therefore assessed the association between reperfusion and the primary and secondary outcomes separately in the subgroup of patients with an M2 obstruction. To assess the associations, a multivariate logistic regression model was created with good functional outcome as the dependent variable. The primary aim was to determine if the interaction between reperfusion and site of the AOL is an independent predictor in this model.

The base model included age, baseline NIHSS, AOL, reperfusion, and the 2-way interaction of AOL and reperfusion. During the preliminary variable selection, time to treatment, diabetes, history of stroke, and prior treatment with tissue plasminogen activator (tPA) were added, one at a time, to the base model. Variables that were significant at an $\alpha \leq 0.10$ were considered candidates for the final model. For the final model, variables were added sequentially starting with the variable with the lowest p value from the group of candidate predictors. We retained variables with p values ≤ 0.05 in the final model. All qualifying variables from the preliminary selection phase were considered along with their 2-way interaction with site of AOL.

We prespecified several secondary analyses based on different endpoints: (1) excellent functional outcome, defined as an mRS score 0–1 at day 90; (2) mortality at day 90; and (3) sICH. In a tertiary analysis, we used the full range of the mRS as the dependent variable. We compared the mRS distribution, divided into 6 categories (0, 1, 2, 3, 4, 5–6), between patients with and without reperfusion using ordinal logistic regression. The adjusted ordinal logistic regression was stratified according to age (dichotomized based on median age of all subjects), NIHSS (dichotomized based on median NIHSS of all subjects), and any other variable identified in the primary analysis. Finally, we conducted an exploratory analysis that was identical to the primary analysis but with reperfusion as an ordinal predictor variable, divided into 4 categories: 0–1, 2A, 2B, 3, instead of a dichotomous variable (mTICI 0–2A vs 2B–3).

RESULTS Data on 787 patients from IMS III, STAR, SWIFT, and DEFUSE 2 were pooled. Seventy-seven patients were excluded from the analysis because details on functional outcome, reperfusion, or AOL status were missing (figure e-1 on the *Neurology*® Web site at Neurology.org). Characteristics of the remaining 710 patients are reported in table 1. Differences in the baseline characteristics between studies reflect the differences

Table 1 Characteristics of studies included in the pooled analysis

	DEFUSE 2 (n = 99)	IMS III[a] (n = 312)	STAR (n = 185)	SWIFT (n = 114)	All (n = 710)
Year of publication/age, y, mean (SD)	2012/64.8 (16.1)	2013/65.8 (12.6)	2013/68.5 (12.4)	2012/67.9 (10.9)	66.7 (12.9)
Male sex, n (%) NIHSS	49 (49)	150 (48)	73 (39)	56 (49)	328 (46)
Median	16	18	17	18	17
IQR	11–20	14–21	13–20	14–20	13–20
Prestroke mRS					
Median (range)	0 (0–4)	0 (0–2)	0 (0–2)	0 (0–5)	0 (0–5)
2 or better, %	97	100	100	94	99
Medical history, %					
Diabetes mellitus	18	21	13	27	18
Prior stroke	14	11	14	19	12
IV thrombolysis	53	100	58	45	74
Site of occlusion, n (%)					
ICA	29 (29)	73 (23)	34 (18)	25 (22)	161 (23)
Proximal MCA	58 (59)	133 (43)	127 (69)	71 (62)	389 (55)
Distal MCA	12 (12)	106 (34)	24 (13)	18 (16)	160 (23)
M2	8 (8)	81 (26)	24 (13)	18 (16)	131 (19)
M3	4 (4)	19 (6)	0 (0)	0 (0)	23 (3)
M4	0 (0)	6 (2)	0 (0)	0 (0)	6 (1)
Onset to start of therapy, min					
Median	348	248	249	301	260
IQR	270–470	210–284	181–312	247–375	215–318
Reperfusion,[b] n (%)	46 (47)	124 (40)	164 (89)	79 (69)	413 (58)

Abbreviations: DEFUSE 2 = Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2; ICA = internal carotid artery; IMS III = Interventional Management of Stroke Trial; IQR = interquartile range; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; STAR = Solitaire FR Thrombectomy for Acute Revascularisation; SWIFT = Solitaire With the Intention for Thrombectomy.

[a] Only the IV + intra-arterial treatment arm of the IMS III trial is included in this pooled analysis.

[b] Modified Thrombolysis in Cerebral Infarction Scale ≥2B.

Table 2 Baseline characteristics stratified by reperfusion status

	Reperfusion (n = 413; 58%)	No reperfusion (n = 297; 42%)
Age, y, mean (SD)	66.9 (12.7)	66.4 (13.2)
Male sex, n (%)	178 (43)	150 (51)
NIHSS		
Median	17	17
IQR	13–20	14–21
IV thrombolysis, n (%)	277 (67)	246 (83)
Onset to start of endovascular therapy, min		
Median	259	264
IQR	212–322	221–316
Site of occlusion, n (%)		
ICA	87 (21)	74 (25)
Proximal MCA	251 (61)	138 (47)
Distal MCA	75 (18)	85 (29)
M2 branch	67 (16)	64 (22)
M3 branch	6 (1)	17 (6)
M4 branch	2 (1)	4 (1)

Abbreviations: ICA = internal carotid artery; IQR = interquartile range; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale.

in study design between studies, e.g., in IMS III all patients received IV tPA before endovascular therapy and in DEFUSE 2 the time window for treatment was longer than in the other studies. Baseline characteristics were well-matched between patients who did and who did not achieve endovascular reperfusion (mTICI 2B–3), except for a higher rate of IV tPA in patients who did not reperfuse (83%) than in patients with reperfusion (67%). This imbalance is explained by 2 characteristics of the IMS III trial. Patients who underwent endovascular therapy in IMS III had lower rates of reperfusion (40%) and a higher rate of IV tPA use (100%, because treatment with IV tPA was a prerequisite for inclusion) compared to patients from the other trials. Consequently, the observation of a higher rate of IV tPA use in patients who did not reperfuse (tables 1 and 2) is most likely due to confounding by IMS III. The site of the AOL was the ICA in 161, the proximal MCA in 389, and the distal MCA in 160 (M2 = 131, M3 = 23, and M4 = 6) patients. The distribution of postprocedure mTICI scores, stratified by AOL, is shown in figure e-2.

Reperfusion was associated with an increased rate of good functional outcome (mRS 0–2) in the overall population (odds ratio [OR] 3.4, 95% confidence interval [CI] 2.5–4.7), but there was a differential response to reperfusion according to AOL; the association between reperfusion and good functional outcome was stronger in patients with ICA and proximal MCA occlusions compared to patients with distal MCA occlusions ($p = 0.001$ for the difference in ORs between ICA and proximal MCA vs distal MCA occlusions; table 3 and figure 1). Age, baseline NIHSS, and time to treatment were additional predictors of good functional outcome, but adjusting for these variables had little influence on the association between reperfusion and good functional outcome, which remained stronger for patients with ICA and proximal MCA vs distal MCA occlusions (p for adjusted difference in ORs is 0.003; table 3 and figure e-2). Limiting the distal MCA cohort to patients with M2 occlusions (i.e., excluding patients with M3 and M4 lesions) also did not alter the results (table 3 and figure 1).

The effects of reperfusion on the secondary outcomes (excellent functional outcome, mortality, and sICH) are reported in table 3, figure 1, and figure e-3. The association between reperfusion and excellent functional outcome was significant in patients with ICA and proximal MCA occlusions but not in patients with distal MCA occlusions ($p = 0.003$ for the difference in ORs between ICA and proximal MCA vs distal MCA). When the distal MCA cohort was limited to patients with M2 occlusions, the association between reperfusion and excellent functional outcome was, however, also present in this group ($p = 0.04$). The amount of patients with M3/4 occlusions was too small, 29 patients, to draw any conclusions (figure e-4). Mortality was reduced with reperfusion in the overall cohort. This association was driven by fewer deaths with reperfusion among patients with ICA and proximal MCA occlusions but not among patients with distal MCA occlusions ($p = 0.01$ for the difference between the ORs for ICA and proximal MCA vs distal MCA). sICH was reduced with reperfusion in the overall cohort, and there was no interaction between the site of AOL and the association between reperfusion and sICH ($p = 0.5$).

In a tertiary analysis, we assessed the effect of reperfusion on the distribution of mRS scores at day 90, stratified by AOL. Reperfusion was associated with better functional outcome when analyzed over the full distribution of mRS scores in patients with ICA occlusions (OR 2.9; 95% CI 1.6–5.2) and proximal MCA occlusions (OR 5.0; 95% CI 3.3–7.4), but not in patients with distal MCA occlusions (OR 1.2; 95% CI 0.7–2.1) (figure 2). We identified an interaction between reperfusion status and site of AOL (ICA and proximal MCA vs distal MCA; $p < 0.001$). This result was unaltered after adjusting for baseline predictors of outcome (figure e-5). The

Table 3 Effect of reperfusion on clinical outcomes in pooled analysis of endovascularly treated patients

	Overall (n = 710)	ICA (n = 161)	Middle cerebral artery			p Value for interaction[a]
			Proximal (M1) (n = 389)	Distal (M2/3/4) (n = 160)	M2 (n = 131)	
Good functional outcome (mRS 0–2)						
No. (%) with reperfusion	224 (54)	39 (45)	145 (58)	40 (53)	34 (51)	
No. (%) without reperfusion	72 (26)	14 (19)	25 (18)	38 (45)	26 (41)	
RR (95% CI)	2.1 (1.7–2.6)	2.4 (1.4–4.0)	3.2 (2.2–4.6)	1.2 (0.9–1.6)	1.2 (0.9–1.8)	
OR (95% CI)	3.4 (2.5–4.7)	3.5 (1.7–7.2)	6.2 (3.8–10.2)	1.4 (0.8–2.6)	1.5 (0.8–3.0)	0.001
OR (95% CI) adjusted[b]	4.3 (2.9–6.2)	5.2 (2.2–12.5)	6.9 (3.9–12.0)	2.2 (1.0–4.7)[c]	2.1 (0.9–4.9)	0.003
Excellent functional outcome (mRS 0–1)						
No. (%) with reperfusion	164 (40)	23 (26)	111 (44)	30 (40)	27 (40)	
No. (%) without reperfusion	48 (16)	9 (12)	14 (10)	25 (29)	15 (23)	
OR (95% CI)	3.4 (2.4–4.9)	2.6 (1.1–6.0)	7.0 (3.8–12.9)	1.6 (0.8–3.1)	2.2 (1.0–4.7)	0.003
OR (95% CI) adjusted[b]	4.1 (2.7–6.2)	3.1 (1.2–7.9)	7.6 (3.9–14.8)	2.3 (1.0–5.4)[c]	3.0 (1.1–7.8)	0.01
Mortality						
No. (%) with reperfusion	52 (13)	16 (18)	25 (10)	11 (15)	9 (13)	
No. (%) without reperfusion	83 (28)	29 (39)	41 (30)	13 (15)	11 (17)	
OR (95% CI)	0.4 (0.3–0.5)	0.3 (0.1–0.7)	0.2 (0.1–0.4)	0.9 (0.3–2.2)	0.7 (0.3–1.9)	0.01
OR (95% CI) adjusted[b]	0.3 (0.2–0.5)	0.4 (0.2–0.7)	0.3 (0.2–0.5)	1.0 (0.4–2.3)	0.8 (0.3–2.2)	0.03
Symptomatic intracranial hemorrhage						
No. (%) with reperfusion	14 (3)	5 (6)	6 (2)	3 (4)	3 (5)	
No. (%) without reperfusion	30 (10)	9 (12)	14 (10)	7 (8)	6 (9)	
OR (95% CI)	0.3 (0.2–0.6)	0.4 (0.1–1.4)	0.2 (0.1–0.6)	0.5 (0.1–1.9)	0.5 (0.1–1.9)	0.5
OR (95% CI) adjusted[b]	0.3 (0.2–0.6)	0.6 (0.2–2.1)	0.2 (0.1–0.5)	0.5 (0.1–2.3)	0.5 (0.1–2.6)	0.5

Abbreviations: CI = confidence interval; ICA =internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; OR = odds ratio; RR = relative risk.
[a] *p* Value for interaction between reperfusion and arterial occlusive lesion (ICA/proximal MCA vs distal MCA).
[b] Adjusted for age, baseline NIH Stroke Scale score, and time to treatment.
[c] $p = 0.06$.

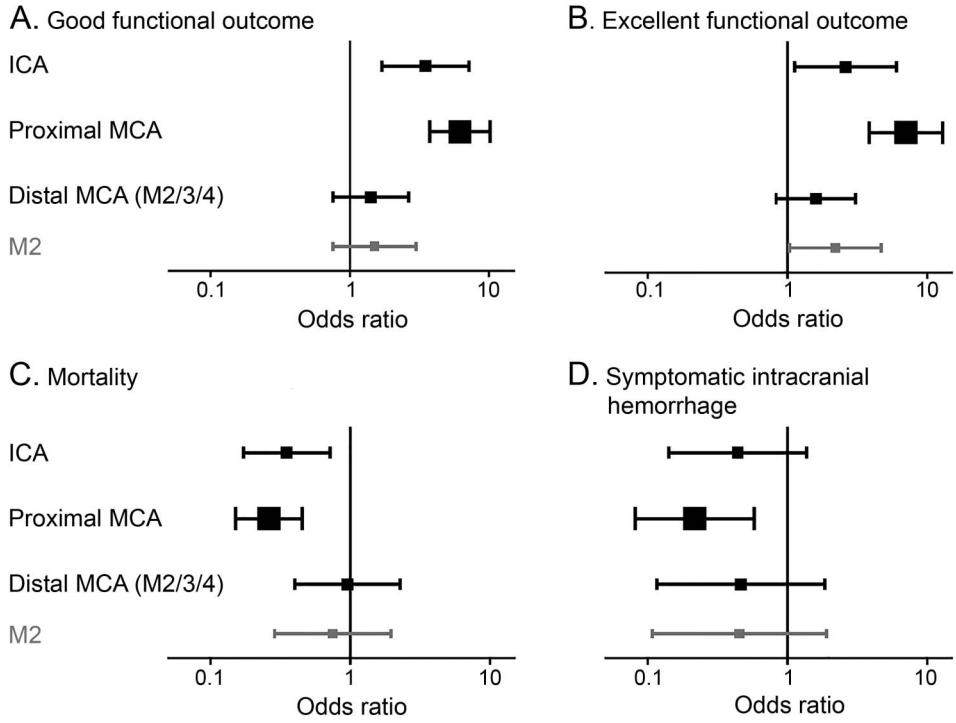
results were also unaltered when the distal MCA cohort was limited to patients with M2 occlusions.

In an exploratory analysis, the association between reperfusion and good functional outcome was assessed using the full range of the mTICI scale (i.e., 4 categories: 0–1, 2A, 2B, and 3; figure e-6). Based on this analysis, a 1-point increase in mTICI category was associated with an OR of 2.0 (95% CI 1.4–2.9) for good functional outcome in patients with ICA occlusions and an OR of 2.2 (95% CI 1.8–2.8) for proximal MCA occlusions. These associations remained present after adjusting for baseline predictors. The linear assumption between reperfusion, assessed as an ordinal variable, and good functional outcome was not met in patients with distal MCA occlusions (figure e-6).

DISCUSSION In this pooled analysis of stroke patients who underwent acute endovascular treatment, reperfusion was associated with an increased chance of good and excellent functional outcome. This effect was strongest in patients with ICA and proximal MCA occlusions and less pronounced in patients with more distal MCA lesions (i.e., occlusions of the second or more distal branch of the MCA).

The chosen clinical endpoint may influence the ability to demonstrate a benefit of reperfusion in patients with distal MCA occlusions. In patients with M2 occlusions, reperfusion was not associated with good functional outcome (mRS 0–2), but it was associated with excellent functional outcome (mRS 0–1). When the 131 patients with M2 lesions were pooled with the 29 patients with M3/4 lesions, neither association was significant, supporting the hypothesis that the natural history in the most distal lesions may be so favorable that there is little room to demonstrate improved outcomes with reperfusion even when excellent clinical outcome is the endpoint.[15] Our pooled analysis has a very small sample of patients with M3/4 occlusions, hampering

Figure 1 Associations between reperfusion and clinical outcomes stratified by arterial occlusive lesion



Graphs show the odds ratios for the associations between reperfusion and good functional outcome defined as modified Rankin Scale (mRS) score of 0–2 (A), excellent functional outcome defined as mRS of 0–1 (B), mortality (C), and symptomatic intracranial hemorrhage (D). Effects are shown separately for patients with internal carotid artery (ICA), proximal middle cerebral artery (MCA), distal MCA, and M2 occlusions. Corresponding odds ratios and their 95% confidence intervals are listed in table 3.

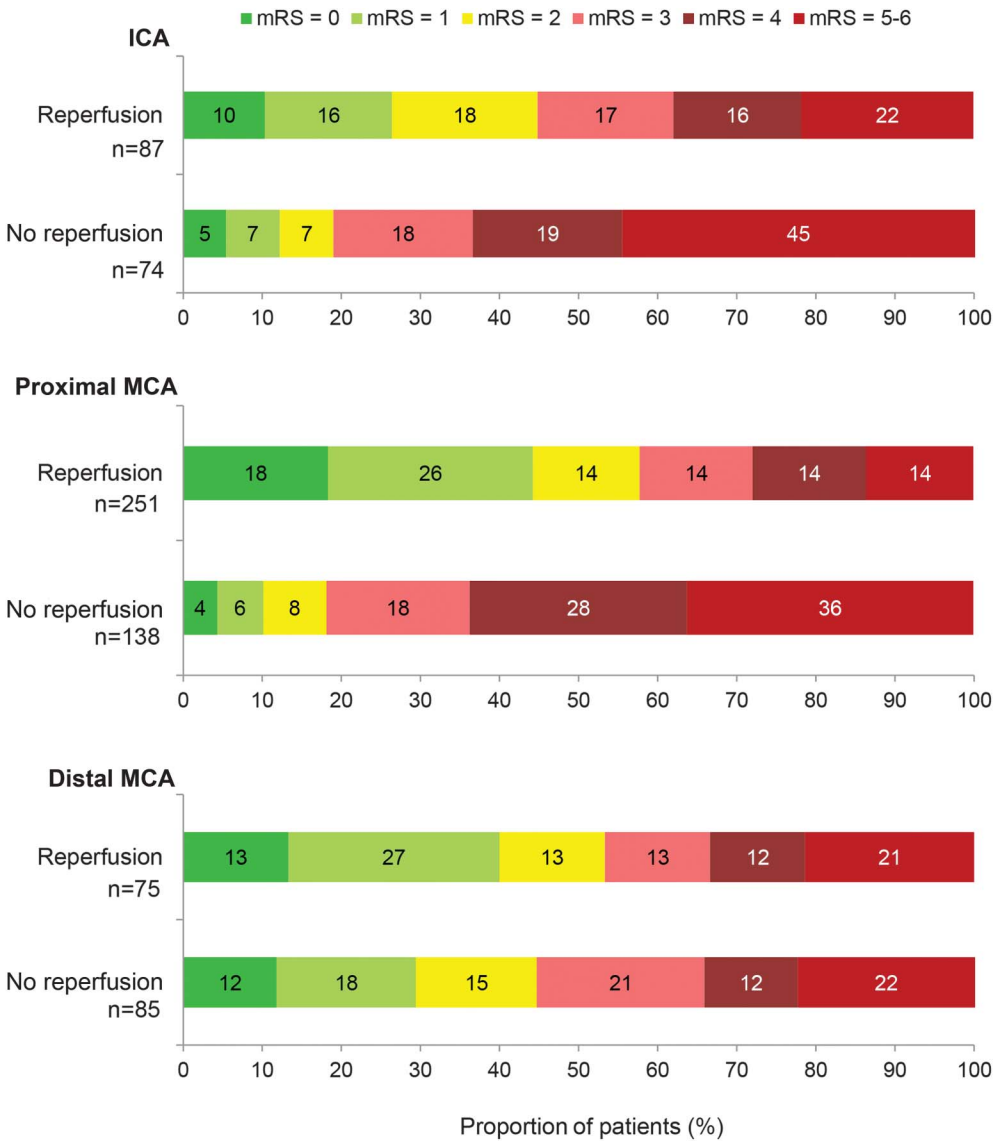
conclusions to be drawn about reperfusion and clinical outcomes in this subgroup.

Data on the association between reperfusion and good functional outcome in patients with M2 occlusions following endovascular treatment have been inconclusive.[16–19] These differing results may be due to variations in the population of patients who were included. Additionally, among patients with M2 occlusions, there may be variability in the association between reperfusion and favorable clinical outcome as a result of variable interpretations of what constitutes an M1 vs an M2 occlusion. Differences between studies in the definition of M1 vs M2 occlusions might have influenced our pooled study since we relied on the AOL ratings of the original studies. Due to a restrictive definition of M1 occlusions in IMS III, it is likely that some lesions were rated as M1 occlusions in the DEFUSE 2, STAR, and SWIFT studies, but as M2 occlusions in IMS III. Consequently, we might have found an even stronger interaction between reperfusion and site of AOL (ICA and proximal MCA vs distal MCA) if a uniform definition had been applied in all studies.

Because there is a paucity of data from randomized controlled trials on patients with distal MCA occlusions, we could only investigate the effect of reperfusion, and not the effect of endovascular treatment, in relation to the site of the AOL. The results should be interpreted in this context. They indicate that the association between reperfusion and good clinical outcomes is stronger in patients with proximal occlusions compared to distal occlusions. Patients with distal MCA occlusions might experience less benefit from reperfusion because they have less brain tissue at risk of infarction (i.e., less brain tissue that can be salvaged with reperfusion) compared to patients with more proximal MCA or ICA occlusions. This finding may be useful in the design of future trials, specifically for the estimation of the expected effect size. Our results, however, do not indicate that patients with distal MCA occlusions do not benefit from endovascular therapy. Patients with distal MCA occlusions should, therefore, not be excluded from endovascular therapy or from future trials of endovascular therapy based on the results of this study. In contrast, the results underscore the need for additional clinical trial data to determine the effect of endovascular therapy in this subgroup.

We also assessed the effect of reperfusion on sICH. A large meta-analysis, including patients who received IV thrombolysis, endovascular therapy, or no active treatment, did not show an association

Figure 2 Distribution of 90-day functional outcome according to the modified Rankin Scale (mRS) stratified by reperfusion status and arterial occlusive lesion (AOL)



The graphs show the distribution of 90-day functional outcomes according to the mRS score stratified by reperfusion status and AOL (internal carotid artery [ICA], proximal middle cerebral artery [MCA], and distal MCA occlusions). Reperfusion is associated with better functional outcomes, assessed using the full distribution of mRS scores, in patients with ICA (odds ratio [OR] 2.9; 95% confidence interval [CI] 1.6–5.2) and proximal MCA occlusions (OR 5.0; 95% CI 3.3–7.4), but not in patients with distal MCA occlusions (OR 1.2; 95% CI 0.7–2.1).

between recanalization and sICH.[1] Here we report reduced sICH rates in patients with reperfusion following endovascular therapy. We acknowledge that determining the association between reperfusion and sICH has been confounded by the various definitions of sICH used across trials. Therefore, these findings would need to be confirmed in other cohorts, ideally using a more uniform definition of sICH.

This study has some limitations. Data were pooled from several studies with variations in design, which introduces variability in the analysis. The variation in time to treatment between the various studies could potentially have influenced the results. However, adjusting the analyses for time to treatment and other baseline predictors of outcome did not alter the results. The association between reperfusion and outcome was studied in patients treated with a wide variety of intra-arterial therapies. Although there is no evidence that the response to reperfusion differed depending on the method of endovascular treatment used, this cannot be excluded. As reported above, another factor, which could have influenced the results, is the variability in the definition of M1 and M2 lesions in the various studies. Variability between studies in the way core laboratories defined mTICI scores may also have affected our results. Importantly,

it is unlikely that any variability in angiographic assessments would have systematically biased the results of our analyses. Another limitation is that we were merely able to adjust the results for predictors of outcome that were assessed in all studies. Predictive variables that were only collected in selected trials, such as MRI or computed tomography perfusion mismatch pattern and the Alberta Stroke Program Early CT Score (ASPECTS), could therefore not be taken into account.[8,20] Finally, it would have been of interest to study the association between reperfusion and clinical outcomes in more detailed subgroups. For example, we were unable to compare proximal vs distal ICA lesions, because this classification was unavailable.

Our findings from a large pooled data analysis of acute stroke patients enrolled in prospective endovascular stroke studies suggest that there is a differential response to reperfusion based on site of AOL. Specifically, the beneficial effect of endovascular reperfusion is more pronounced for patients with proximal (ICA and proximal MCA) occlusions than for patients with more distal MCA occlusions.

AUTHOR CONTRIBUTIONS

R.L. designed the study, collected, analyzed, and interpreted data, and wrote the manuscript. S.A.H. analyzed and interpreted the data and wrote the manuscript. D.S.L. designed the study and collected data. T.A.T. designed the study and collected data. A.M.D. designed the study and collected data. R.G.N. designed the study and collected data. M.P.M. designed the study and collected data. R.J. designed the study and collected data. J.G. designed the study and collected data. A.J.Y. designed the study and collected data. S.D.Y. designed the study and collected data. Y.Y.P. designed the study and collected data. J.L.S. designed the study and collected data. V.M.P. designed the study and collected data. J.P.B. designed the study and collected data. G.W.A. designed the study and collected data. M.G.L. designed the study, collected, analyzed, and interpreted data, and wrote the manuscript. All authors reviewed and revised the manuscript.

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DISCLOSURE

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Effect of endovascular reperfusion in relation to site of arterial occlusion

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