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ORIGINAL ARTICLE

Effect of Intravenous Alteplase Treatment on First-Line Stent Retriever Versus Aspiration Alone During Endovascular Treatment

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BACKGROUND: We aimed to assess whether the effect of intravenous alteplase treatment (IVT) before endovascular treatment (EVT) on outcome is modified by first-line technique during EVT in IVT eligible patients.

METHODS: This was a post hoc analysis from MR CLEAN-NO IV (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands - Intravenous Treatment Followed by Intra-Arterial Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion), a randomized trial of IVT followed by EVT versus EVT alone in patients presenting directly to EVT-capable centers. We included data from all patients who underwent EVT with a thrombectomy attempt. We compared patients treated with stent retriever (with or without aspiration) to aspiration alone as first-line EVT technique and assessed the interaction of first-line EVT technique with IVT treatment. Primary outcome was the 90-day modified Rankin Scale score, analyzed with mixed model ordinal regression for a shift towards better outcome. Secondary outcomes included successful reperfusion (extended Thrombolysis in Cerebral Infarction score 2b–3).

RESULTS: Of 473 included patients, 102 (21.6%) were treated with aspiration alone as first-line technique. In the full population, functional outcome was similar for patients treated with stent retriever versus aspiration only (adjusted common odds ratio [acOR], 1.07 [95% CI, 0.69–1.66]). We observed a significant interaction between IVT and first-line EVT technique (P=0.03). In the aspiration-only group, patients treated with EVT alone had worse functional outcome compared to those treated with IVT and EVT (acOR, 0.44 [95% CI, 0.21–0.90]). In the stent retriever group, functional outcome did not differ between patients treated with or without IVT (acOR, 1.08 [95% CI, 0.74–1.57]). There was no statistically significant interaction for successful reperfusion.

CONCLUSIONS: In MR CLEAN-NO IV, the treatment effect of IVT was modified by first-line EVT technique. Patients treated with aspiration only as first-line technique had worse clinical outcomes if they did not receive IVT. No such difference was observed in patients treated with stent retrievers. Confirmation by pooling with results from other trials is needed to confirm these findings.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: ischemic stroke ■ patients ■ reperfusion ■ stent ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

EVT	endovascular treatment
IVT	intravenous alteplase treatment

Data from 6 randomized trials comparing direct endovascular treatment (EVT) with intravenous alteplase treatment (IVT) before EVT are currently available. The Chinese DIRECT-MT (Direct Intra-Arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals), and DEVT (Direct Endovascular Treatment Versus Standard Bridging Therapy for Patients With Acute Stroke With Large Vessel Occlusion in the Anterior Circulation) showed noninferiority of direct EVT,[1,2] whereas in SKIP (The Randomized Study of Endovascular Treatment With Versus Without Intravenous Recombinant Tissue Plasminogen Activator in Acute Stroke With Internal Carotid Artery and Proximal Middle Cerebral Artery Occlusion), SWIFT-DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke), DIRECT-SAFE (A Randomized Controlled Trial of Direct Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval), and MR CLEAN-NO IV (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands - Intravenous Treatment Followed by Intra-Arterial Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion), noninferiority of direct EVT was not demonstrated.[3a,3–5] However, all trials reported similar outcomes after EVT, regardless of pretreatment with IVT. Although previous randomized trials demonstrated no difference in functional outcome or successful reperfusion based on first-line device technique during EVT (stent retriever alone or in conjunction with local aspiration versus aspiration alone as primary modality),[6–8] it is unclear whether the treatment effect of IVT before EVT on functional outcome is modified by the first-line technique during EVT in patients eligible for both interventions. Previous studies have shown that IVT affects thrombus composition by stimulating breakdown of the fibrin meshwork in the clot.[9] Modeling studies have suggested that thrombus composition may affect the efficacy of EVT devices.[10] For instance, removal of fibrin-rich clots with aspiration resulted in more distal emboli compared to stent retrievers.[11] For this post hoc analysis, we hypothesized that first-line device technique during EVT (stent retriever with or without aspiration versus aspiration only) would modify the effect of IVT as a result of changes in thrombus composition following IVT administration and that the effect of stent retrievers would be diminished by a reduced adhesiveness of the thrombus.[12]

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Selection

We used data from MR CLEAN-NO IV, a randomized trial of IVT followed by EVT versus EVT alone in patients presenting directly to EVT-capable centers.[13] We included data from all patients who underwent at least one intracranial mechanical thrombectomy attempt at the clot. Patients in whom catheterization of the intracranial arteries failed or in whom only intracranial digital subtraction angiography was performed, were excluded. Rescue IVT (0.9 mg/kg) was permitted in patients allocated to EVT alone if there was incomplete reperfusion after EVT (score 0, 1, or 2A on the extended Thrombolysis in Cerebral Infarction scale), and IVT could be administered within 4.5 hours of stroke onset. We compared patients who underwent EVT with a stent retriever with or without concomitant aspiration on a distal access catheter as first-line technique during EVT to patients with a first-line technique of aspiration only. The technique for EVT, including the choice of guiding catheter, was at the discretion of the treating physician, but the use of stent retriever was recommended in the trial protocol. All relevant imaging was analyzed by an imaging core laboratory, whose members were blinded to treatment allocation and all clinical data except for symptom side. An adverse event committee evaluated the safety end points based on clinical data and reports from the imaging core lab. Detailed methods and primary results of the MR CLEAN-NO IV trial have been reported previously, including the results 8 prespecified subgroup analyses.[13,14]

Outcomes

The primary outcome was functional outcome as measured with the modified Rankin Scale score at 90 days after stroke (modified Rankin Scale, ranges from 0 [no disability]–6 [death]). Secondary outcomes were modified Rankin Scale dichotomized at 0 to 2 (indicating functional independence), mortality, successful reperfusion on the final intracranial angiogram (defined as an extended Thrombolysis in Cerebral Infarction score of 2B, 2C, or 3), successful reperfusion after the first EVT attempt, percentage of patients with recanalization on computed tomography angiography or magnetic resonance angiography at 24 hours (modified Arterial Occlusive Lesion score 2–3; range, 0 [no recanalization]–3 [complete recanalization]), occurrence of symptomatic intracranial hemorrhage (according to the Heidelberg criteria),[15] occurrence of subarachnoid hemorrhage (both symptomatic and asymptomatic), final lesion volume on magnetic resonance imaging at 24 hours or noncontrast computed tomography at 5 to 7 days or discharge, embolization in a new vascular territory, infarction in a new vascular territory on noncontrast computed tomography at 5 to 7 days or discharge, or diffusion-weighted magnetic resonance imaging at 24 hours.Scale

Statistical Analysis

For the primary outcome, we used ordinal logistic regression with multiplicative interaction terms between first-line device technique and treatment allocation to assess whether the association of IVT administration with functional outcome was modified. Then we assessed the effect of IVT before EVT compared to EVT alone in subgroups according to the first used device. We assessed binary outcomes using logistic regression and continuous outcomes using linear regression. All main analyses were performed according to the intention-to-treat principle. We adjusted all regression analyses for the variables prespecified in the MR CLEAN-NO IV statistical analysis plan[14] (age, prestroke modified Rankin Scale, onset-to-randomization time, National Institutes of Health Stroke Scale at baseline, and collateral score [ranges from 0, indicating no collaterals, to 3, indicating collateral flow to 100% of the affected territory]) with additional adjustment for occlusion location, the presence of a tandem lesion and use of balloon guide catheter as they might confound the association between first-line device choice and outcomes. To adjust for potential between-center differences, we used mixed-effects models including center of inclusion as random effect. As a sensitivity analysis, we also assessed whether there was an interaction when assessing first-line devices in 3 groups: stent retriever with aspiration, aspiration alone, and stent retriever alone. Moreover, we assessed all outcomes in an as-treated population for which we excluded patients who did not receive their allocated treatment (full dose IVT for IVT before EVT group and no IVT for EVT alone group).[14] We also reported all outcomes stratified by both treatment allocation and first-line EVT technique including absolute risk differences, with IVT before EVT patients as reference group. Missing data were imputed for the regression analyses only, using multiple imputation methods.[16] All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing 2018, www.r-project.org).

Ethical Approval and Informed Consent

The trial protocol for the MR CLEAN-NO IV trial was approved by Dutch (MEC-2017-368), Belgian (ID-RCB: 2018-A00764-51), and French (B322201939935, 19/20/987) ethical committees and the research board of each participating center. Patients or their representatives provided written informed deferred consent.[17]

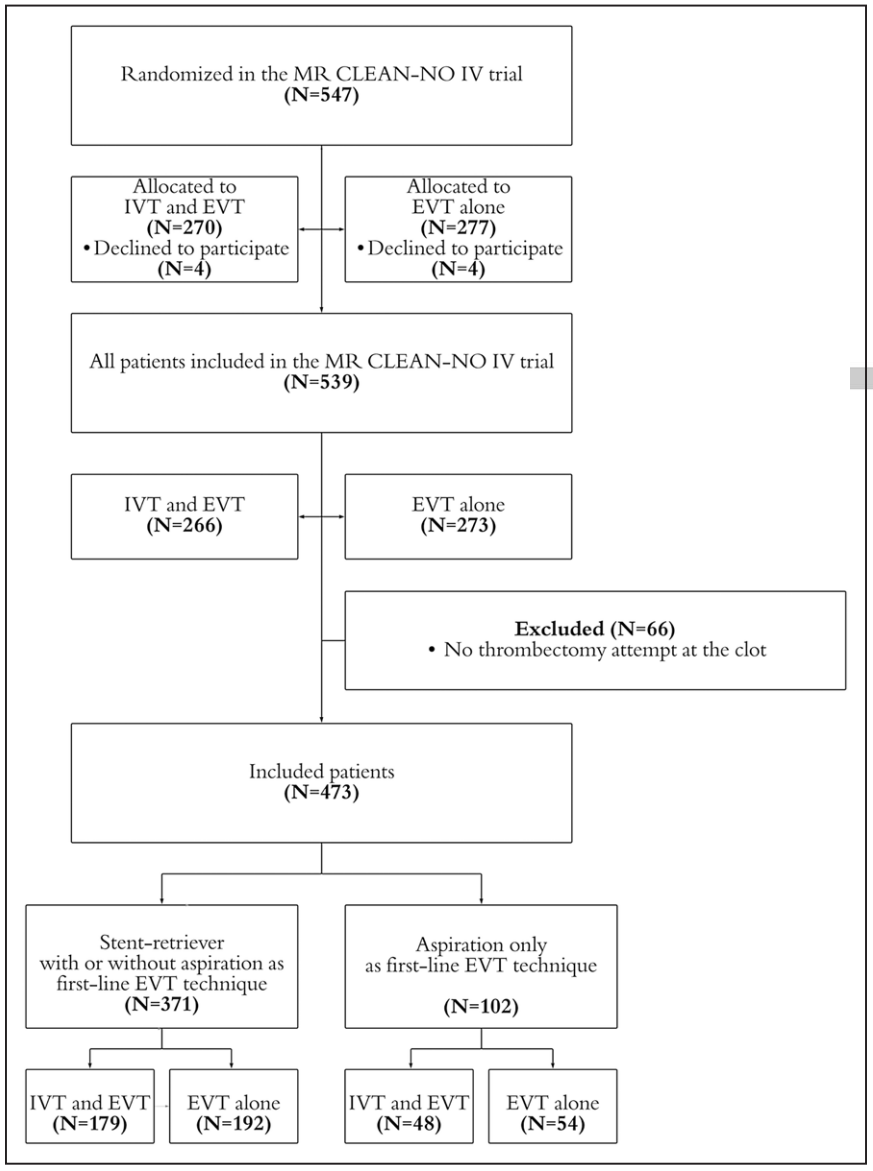

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of patient inclusion. Reasons for no thrombectomy attempt at the clot: 13 patients were ineligible according to local physician, 13 patients due to clinical improvement, 17 patients due to access problems, 20 patients due to complete recanalization of target vessel or no remaining treatable intracranial occlusion according to local interventionist, 2 patients due to respiratory distress and not suited for intubation, and 1 patient due to arterial perforation and halted procedure. EVT indicates endovascular treatment; IVT, intravenous alteplase treatment; and MR CLEAN-NO IV, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands-Intravenous Treatment Followed by Intra-Arterial Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion.

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Table 1. Baseline Characteristics Stratified by Both First-Line EVT Technique and IVT Treatment Allocation

	Stent retriever (N=371)		Aspiration only (N=102)	
	IVT and EVT; n=179	EVT alone; n=192	IVT and EVT; n=48	EVT alone; n=54
Median age (IQR), y	69 (62–77)	73 (63–79)	69 (57–76)	70 (61–80)
Male sex, n (%)	95/179 (53.1)	116/192 (60.4)	31/48 (64.6)	28/54 (51.9)
Median NIHSS score (IQR)	17 (11–20)	16 (10–20)	17 (12–19)	18 (13–20)
Medical history, n (%)				
Previous ischemic stroke	31/179 (17.3)	39/192 (20.3)	6/48 (12.5)	7/54 (13.0)
Atrial fibrillation	15/179 (8.4)	22/192 (11.5)	6/48 (12.5)	7/54 (13.0)
Diabetes mellitus	34/179 (18.9)	30/192 (15.6)	6/48 (12.5)	7/54 (13.0)
Hypertension	100/179 (55.9)	89/192 (46.4)	21/47 (44.7)	23/54 (42.6)
Prestroke modified Rankin Scale score, n (%)				
0	127/179 (70.9)	133/192 (69.3)	37/48 (77.1)	39/53 (73.6)
1	32/179 (17.9)	35/192 (18.2)	7/48 (14.6)	11/53 (20.8)
2	18/179 (10.1)	17/192 (8.9)	2/48 (4.2)	3/53 (5.7)
≥3	2/179 (1.2)	7//192 (3.6)	2/48 (4.2)	0/53 (0.0)
Median systolic blood pressure (IQR), mm Hg	149 (130–168)	149 (135–166)	150 (123–169)	146 (135–163)
Median glucose level (IQR), mmol/L*	6.9 (6.0–8.6)	6.6 (5.8–7.6)	6.5 (6.0–7.7)	6.8 (6.0–7.7)
Median ASPECTS (IQR)†	9 (8–10)	9 (8–10)	9 (8–10)	9 (8–10)
Intracranial occlusion location on CT/MRI, n (%)				
Intracranial ICA	0/179 (0.0)	4/192 (2.1)	0/48 (0.0)	0/54 (0.0)
ICA-T	35/179 (19.6)	41/192 (21.4)	13/48 (27.1)	15/54 (28.3)
M1	119/179 (66.5)	114/192 (59.4)	31/48 (64.6)	32/54 (60.4)
Proximal M2	25/179 (14.0)	9/192(8.9)	3/48 (6.2)	6/54 (11.3)
None	0/179 (0.0)	0/192 (0.0)	1/48 (2.1)‡	0/54 (0.0)
Tandem lesion, n (%)§	28/169 (16.6)	33/182 (18.1)	4/45 (8.9)	7/52 (13.5)
Collateral score, n (%)				
0	11/174 (6.3)	13/190 (6.8)	1/47 (2.1)	4/53 (7.5)
1	56/174 (32.2)	54/190 (28.4)	18//47 (38.3)	16/53 (30.2)
2	71/174 (40.8)	75/190 (39.5)	21/47 (44.7)	28/53 (52.8)
3	36/174 (20.7)	48/190 (25.3)	7/47 (14.9)	5/53 (9.4)
Median duration (IQR), min				
From stroke onset to randomization	90 (72–149)	94 (69–143)	92 (68–139)	88 (72–121)
From stroke onset to start of alteplase‖	99 (77–155)	NA	88 (69–134)	NA
From stroke onset to groin puncture¶	130 (105–180)	130 (104–180)	144 (109–176)	129 (104–168)
From stroke onset to first reperfusion†	168 (140–225)	180 (148–238)	173 (153–215)	169 (136–204)

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; EVT, endovascular treatment; ICA internal carotid artery; ICA-T internal carotid artery terminus; IQR, interquartile range; IVT, intravenous alteplase treatment; MRI, magnetic resonance imaging; NA, not applicable; and NIHSS, National Institutes of Health Stroke Scale.

*Missing for 4 patients in the stent retriever group (2 EVT alone group) and 1 patient in the aspiration-only group (EVT alone group).

†Missing for 70 patients in the stent retriever group (39 EVT alone group) and 27 patients in the aspiration-only group (18 EVT alone group).

‡Extracranial ICA occlusion.

§Tandem lesion is defined as an intracranial target occlusion with ipsilateral extracranial carotid dissection, significant atherosclerotic stenosis, or atherosclerotic occlusion.

‖Data from 178 patients in the stent retriever group and 44 patients in the aspiration-only group.

¶Missing for 1 patient in the stent retriever group and 1 patient in the aspiration-only group, both in the IVT and EVT groups.

RESULTS

Patient Characteristics

Out of 539 patients included in MR CLEAN-NO IV, 473 underwent an intracranial thrombectomy attempt at the clot and were included in the current study (Figure 1). In total, 371 patients were treated with a stent retriever as first-line device, of which 192 were allocated to EVT alone, and 102 patients were treated with aspiration alone as first-line EVT technique, of which 54 were allocated to EVT alone. Baseline characteristics are presented in Table 1. In patients treated with a stent retriever as first-line EVT technique, concomitant aspiration on a distal access catheter was used in 80 out of 179 (44.7%) in the IVT and EVT group and 99 out of 192 (51.7%) in the EVT alone group (Table 2). A balloon guide catheter was used in the

Table 2. Procedure Characteristics Stratified by Both First-Line EVT Technique and IVT Treatment Allocation

	Stent retriever (N=371)		Aspiration only (N=102)	
	IVT and EVT; n=179	EVT alone; n=192	IVT and EVT; n=48	EVT alone; n=54
Additional intraarterial alteplase administered, n (%)	0/174 (0.0)	10/182 (5.5)	0/48 (0.0)	3/54 (5.6)
Dose, mg, median (IQR)	NA	5 (5–20)	NA	10 (7.5–10)
Rescue IVT administered	NA	11/190 (5.8)	NA	2/52 (3.8)
Periprocedural heparin administered	19/178 (10.7)	37/192 (19.3)	11/46 (23.9)	19/54 (35.2)
Total number of thrombectomy attempts, median (IQR)	1 (1-2)	1 (1-3)	1 (1-2)	1 (1-3)
Use of balloon guide catheter, n (%)	126/179 (70.4)	133/192 (69.3)	12/48 (25.0)	20/54 (37.0)
Procedure under general anesthesia, n (%)	25/177 (14.1)	29/189 (15.3)	9/48 (18.8)	8/53 (15.1)
Extracranial carotid artery stenting, n (%)	8/179 (4.5)	13/191 (6.8)	5/44 (11.4)	3/54 (5.6)
Percutaneous transluminal angioplasty, n (%)	12/179 (6.7)	18/190 (9.5)	4/45 (8.9)	5/54 (9.3)
Intracranial occlusion location on DSA, n (%)				
Intracranial ICA	32/178 (18.0)	40/189 (21.2)	6/48 (12.5)	18/53 (34.0)
M1	109/178 (61.2)	111/189 (58.7)	32/48 (66.7)	25/53 (47.1)
M2	34/178 (19.1)	35/189 (18.5)	9/48 (18.8)	10/53 (18.9)
Other*	3/178 (1.7)	3/189 (1.6)	0/48 (0.0)	0/53 (0.0)
None	0/178 (0.0)	0/189 (0.0)	1/48 (2.1)	0/53 (0.0)
Combination of stent retriever and aspiration, n (%)	80/179 (44.7)	99/192 (51.7)	0/48 (0.0)	0/53 (0.0)
Conversion from aspiration only to stent retriever, n (%)†	0 (0.0)	0 (0.0)	12/48 (25.0)	20/54 (37.0)
Conversion from stent retriever to aspiration only, n (%)‡	8/179 (4.5)	18/192 (9.4)	0 (0.0)	0 (0.0)
Duration of procedure, median (IQR)	46 (30–63)	52 (34–89)	43 (29–58)	46 (32–67)

DSA indicates digital subtraction angiography; EVT, endovascular treatment; ICA internal carotid artery; IQR, interquartile range; IVT, intravenous alteplase treatment; and NA, not applicable.

*Other locations n (%): A2: 1 (0.3), M3: 3(0.8), M4:1 (0.3).

†From aspiration only to stent retriever without aspiration: 11 (5 EVT alone group); to stent retriever with aspiration: 21 (14 EVT alone group).

‡From stent retriever without aspiration to aspiration only 17 (13 EVT alone group). From stent retriever with aspiration to aspiration only: 9 (5 EVT alone group) Conversion from stent retriever with aspiration to stent retriever only: 2 (1 EVT alonegroup), conversion from stent retriever without aspiration to stent retriever with aspiration: 15 (12 EVT alone group).

stent retriever group in 126 out of 179 (70.4%) patients allocated to IVT and EVT and 133 out of 192 (69.3%) allocated to EVT alone and in the aspiration-only group in 12 out of 48 (25.0%) patients allocated to IVT and EVT group and 20 out of 54 (37.0%) allocated to EVT alone.

In the first-line aspiration-only group, treatment strategy was changed to stent retriever (with or without concomitant aspiration on a distal access catheter) in 12 out of 48 (25.0%) patients in the IVT and EVT group and 20 out of 54 (37.0%) in the EVT alone group after a median of 1 (interquartile range, 1–2) attempt. In the stent retriever group, treatment strategy was changed to aspiration only in 8 out of 179 (4.5%) patients in the IVT and EVT group and 18 out of 192 (9.4%) in the EVT alone group after a median of 2 (interquartile range, 1–2) attempts. Baseline and procedural characteristics stratified by first-line EVT technique only are represented in Tables S1 and S2.

Primary Outcome

In all patients with a thrombectomy attempt, functional outcome was similar for patients treated with stent retriever versus aspiration only (adjusted common odds ratio [acOR] 1.07 [95% CI, 0.69–1.66]), and patients treated with EVT alone did not show improved outcome compared to IVT and EVT (acOR, 0.89 [95% CI, 0.64–1.24]). For overall functional outcome (Figure 2), we observed a significant interaction between the treatment effect of IVT and first-line EVT technique (P=0.03; Figure 3). In the aspiration-only group, patients treated with EVT alone had worse functional outcome compared to those who were treated with IVT and EVT (acOR, 0.44 [95% CI, 0.21–0.90]). In the stent retriever group, functional outcome did not differ between patients treated with or without IVT (acOR, 1.08 [95% CI, 0.74–1.57]).

Secondary Outcomes

We observed no statistically significant interaction between the treatment effect of IVT and first-line EVT technique for any of the secondary outcomes, including mortality and successful reperfusion. Of note, although successful reperfusion rates were slightly lower after EVT alone in the stent retriever group (aOR EVT alone, 0.78 [95% CI, 0.44–1.39]), this difference was more pronounced in the aspiration-only group (aOR EVT alone, 0.35 [95% CI 0.12–1.04]; Figure 3). However, these differences were not statistically significant nor was there a significant interaction (P=0.21). Outcomes stratified by both treatment allocation and first-line EVT technique, including absolute

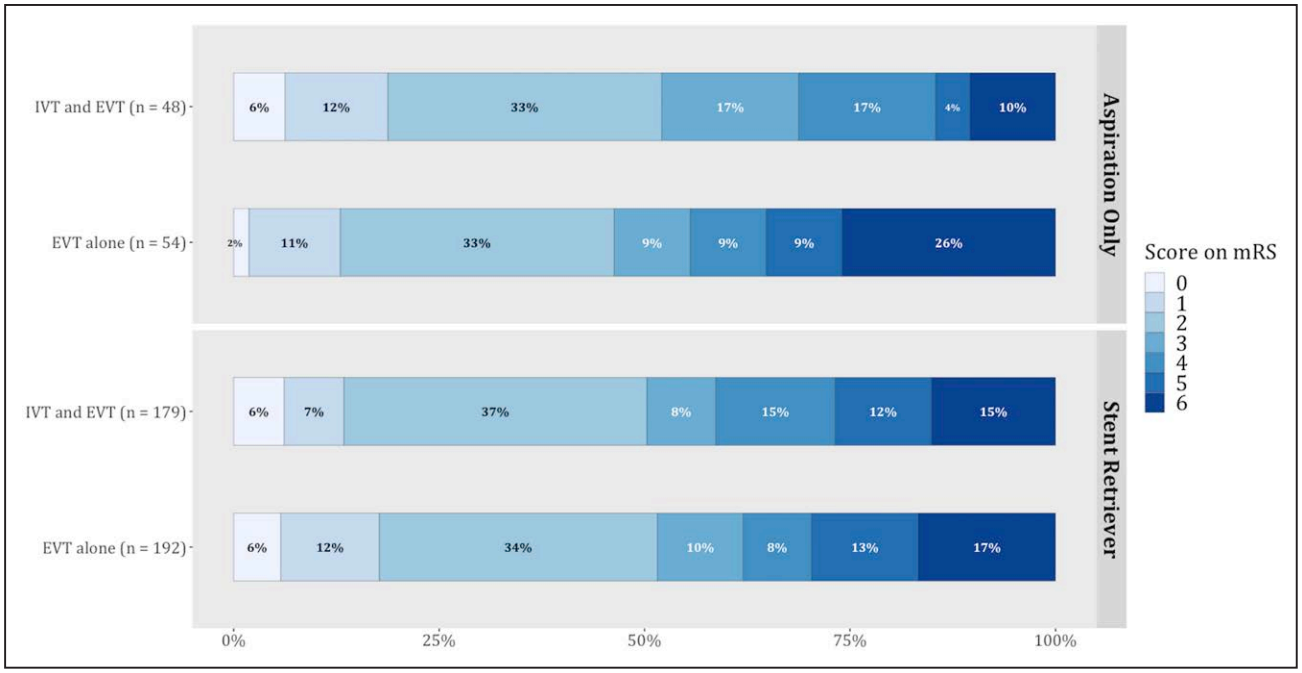

Figure 2. Functional outcome at 90 d according to intravenous alteplase treatment (IVT) allocation and first-line endovascular treatment (EVT)-technique.
mRS indicates modified Rankin Scale.

risk differences, are reported in Table S3. Full range of extended Thrombolysis in Cerebral Infarction scores, recanalization scores at 24 hours, and causes of mortality stratified by treatment allocation and first-line EVT technique are represented in Tables S4–S6. Results in the as-treated population (consisting of 453 patients: 358 in the stent retriever group of which 189 treated with EVT alone and 95 in the aspiration-only group of which 53 treated with EVT alone) were similar (Figure S1). When categorizing first-line device type into 3 groups, we observed there is a significant interaction for the treatment effect of IVT before EVT when comparing stent retrievers combined with aspiration with aspiration alone (P=0.01) but not when comparing with stent retriever alone (P=0.25). In the aspiration-only group, patients treated with EVT alone had worse functional outcome compared to those who were treated with IVT and EVT. In both the stent retriever plus aspiration group and stent retriever alone group, functional outcome was not statistically different between patients treated with or without IVT (Table S7, Figure S2).

DISCUSSION

In this post hoc analysis of the MR CLEAN-NO IV trial, in which patients were randomized for IVT before EVT, the treatment effect of IVT was modified by first-line EVT technique. Among patients treated with aspiration only as first-line EVT technique, we observed worse clinical outcomes when IVT was omitted. No such difference was seen among patients treated with stent retrievers as first-line EVT technique. We observed no statistically significant effect modification by first-line EVT technique for any of the other outcomes.

Recently, a substudy of the SKIP trial reported no significant interaction between IVT treatment and first-line EVT technique for successful reperfusion, after first or last attempt, or the number of attempts during EVT.[18] However, the authors reported that in patients treated with stent retrievers, prior IVT was associated with successful reperfusion after the first attempt and fewer attempts during EVT. This was not observed for patients treated with aspiration only. The difference in results of these radiological outcomes may be explained by the small sample size and the difference in used IVT dosage of 0.6 mg/kg rather than 0.9 mg/kg. Importantly, this study did not assess interaction for any clinical outcomes, including functional outcome.

Of the previous trials investigating stent retrievers versus aspiration as first-line technique only, the ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization) assessed heterogeneity of the effect of aspiration only as first-line technique in subgroups according to IVT, but no statistically significant difference regarding successful reperfusion rates was reported.[6–8] Although we also did not observe a statistically significant interaction between treatment effect of IVT and first-line EVT technique with successful reperfusion as outcome, the point estimate reported in the ASTER trial favored direct aspiration in patients not treated with IVT as opposed to our findings. Similarly, in a recent post hoc

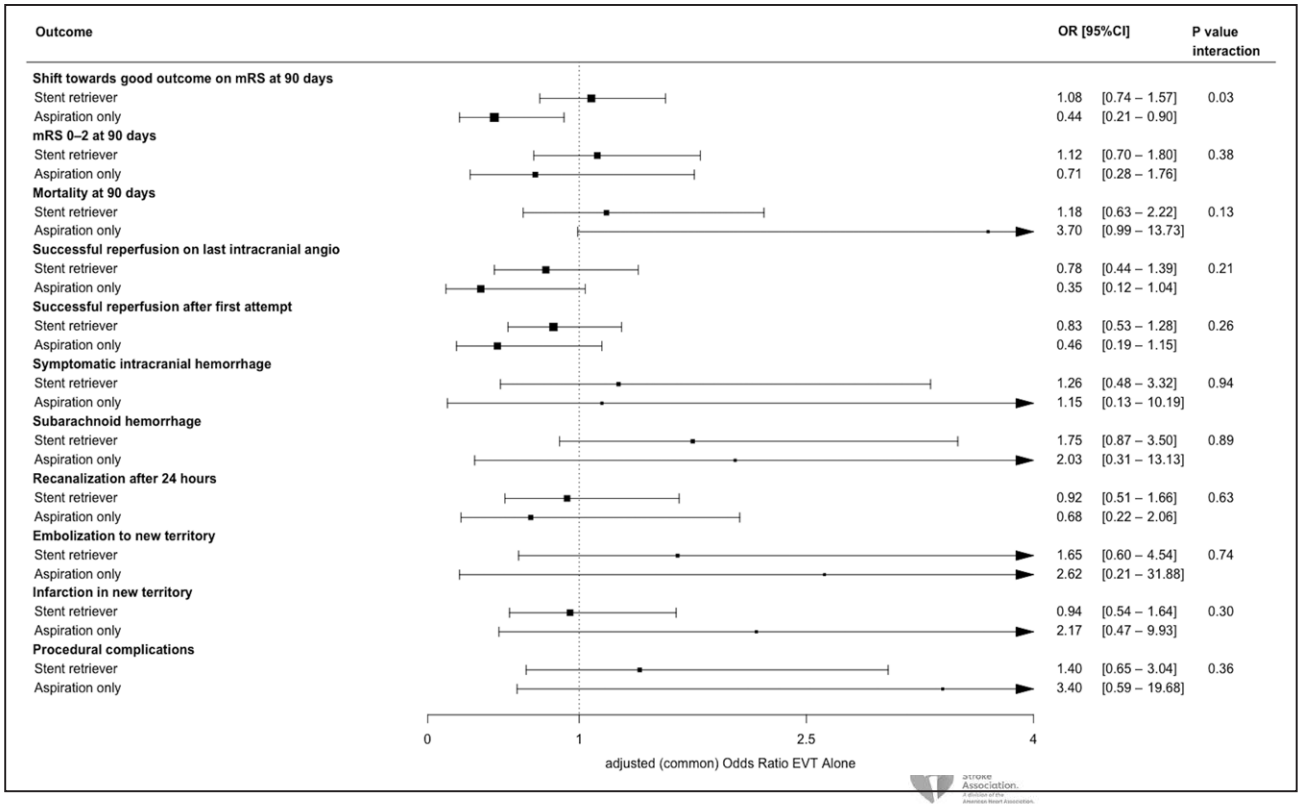

Figure 3. Treatment effect endovascular treatment (EVT) alone in patients treated with stent retriever or aspiration only as first-line EVT technique.

Mixed-effects regression models with including center as random effect adjusted for age, prestroke modified Rankin Scale, onset-to-randomization time, baseline National Institutes of Health Stroke Scale, collateral score, occlusion location, the presence of a tandem lesion, and use of balloon guide catheter. OR indicates odds ratio.

analysis of COMPASS (Aspiration Thrombectomy Versus Stent Retriever Thrombectomy as First-Line Approach for Large Vessel Occlusion) better reperfusion rates were observed in patients treated with aspiration without prior IVT compared with those treated with IVT.[19] However, the authors did not formally test for the presence of an interaction between first-line EVT technique and prior IV administration for any of their clinical or radiological outcomes. It is unclear what the cause of the discrepancy in results between our study and theirs is. It may be explained by differences in the included patient population between the trials. The ASTER and COMPASS trials included patients transferred from primary stroke centers to comprehensive stroke centers and patients with contraindications for IVT including presentation outside the IVT time window, anticoagulation use, or high blood pressure levels, confounding the comparison. Several of these variables may affect thrombus composition.[9] Moreover, the analyses in the ASTER and COMPASS trials were unadjusted for potential confounders. Last, functional outcome was not assessed in subgroups according to IVT status in the ASTER trial.

There was a considerable change in device strategy following an unsuccessful previous attempt, most commonly in the aspiration-only group compared with the stent retriever group. If one first-line strategy fails to achieve reperfusion, this likely results in more frequent device changes to achieve reperfusion. We decided not to adjust for this as we believe a change in strategy during the procedure lies on the causal path of the association between first-line device strategy and outcomes.

Observational data have shown that the use of balloon guide catheter is associated with better functional outcome and reperfusion rates.[20] We observed a lower proportion of patients treated with a balloon guide catheter in the aspiration-only group. However, in the aspiration-only group, the proportion of patients treated with a balloon guide catheter was higher in those treated with EVT only. Hence, the worse functional outcome in this group is not explained by discrepancies in the use of balloon guide catheters.

Although we did not observe significant interactions for any of the secondary outcomes, the worse functional outcome among patients treated with aspiration without IVT compared to patients treated with IVT may be explained by the lower revascularization rates. As previous studies have shown, IVT affects thrombus composition by promoting the dissolvement of fibrin fibers resulting in a more porous clot[21,22] and thrombi retrieved during EVT are significantly smaller in patients treated with IVT.[23] IVT primarily affects the superficial layers of fibrin in the clot.[9] This could

reduce the clot-vessel wall friction, which is shown to be higher in fibrin-rich clots,[10] allowing for easier removal of the clot. The effect of reduced clot-vessel wall adhesion may be more pronounced in patients treated with aspiration only because the aspiration catheter only makes contact with the most proximal part of the clot. A stent retriever possibly increases the contact surface area with the thrombus when it is deployed. Therefore, this technique might be less dependent on changes in thrombus composition. This proposed mechanism is in contrast with our hypothesis. The recently published CHOICE trial (Chemical Optimization of Cerebral Embolectomy in Patients With Acute Stroke Treated With Mechanical Thrombectomy) demonstrated that intraarterial IVT improve functional outcome, most likely by dissolving microthrombi that are not detected in digital subtraction angiography.[24] It may be that aspiration only as first-line technique results in more microthrombi, resulting in worse outcome without IVT. Finally, we cannot exclude that patients treated with aspiration first and without IVT were more challenging cases due to chance and despite randomization for IVT, which could partially explain the worse outcome.

In the aspiration-only group, we observed statistically nonsignificant higher mortality rates when patients were not treated with IVT. We were unable to identify a clear difference in causes of mortality. It may be that the slightly worse reperfusion rates, and thus poorer recovery, in this group results in a higher susceptibility to a variety of complications. However, given the nonsignificance and absence of differences in adverse outcomes and procedural complications, the difference may be coincidental.

This study has several limitations. First, as this was a post hoc analysis of the MR CLEAN-NO IV trial and not a prespecified analysis, these results should be interpreted with caution. No other post hoc analyses have been published at the time of writing. Second, the sample size of patients undergoing aspiration alone as first-line EVT technique is small since the use of stent retriever as first attempt was recommended per trial protocol in MR CLEAN-NO IV. However, it is the largest sample in a population randomized for IVT before EVT reported to date. Third, the treatment contrast of first-line EVT technique was not randomized. To account for this, we adjusted for multiple potential confounders, in addition to center effect. However, the risk of residual confounding obviously remains. Last, these results only pertain to patients presenting within 4.5 hours of stroke onset who presented directly at a stroke intervention center and who were eligible for IVT according to the Dutch guidelines and not to patients transferred from a primary stroke center or patients with a contraindication to IVT.[25]

Due to the post hoc design of this study, limited sample size and conflicting prior evidence from subgroup analyses of trials randomizing for first-line EVT, pooling of the results of other trials on IVT before EVT versus EVT alone is necessary to confirm our findings before making recommendations for clinical practice. If confirmed, this will have ramifications for the choice of first-line EVT technique in patients not undergoing IVT before EVT or the administration of IVT before EVT.

CONCLUSIONS

In MR CLEAN-NO IV, the treatment effect of IVT appeared to be modified by first-line EVT technique. We observed worse functional outcomes among patients treated with aspiration only as first-line technique without prior IVT. No such association was observed in patients treated with stent retrievers as first-line EVT technique.

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Supplemental Material

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APPENDIX

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