Endovascular Treatment With or Without Prior Intravenous Alteplase for Acute Ischemic Stroke

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Background—It is unclear whether intravenous thrombolysis (IVT) with alteplase before endovascular treatment (EVT) is beneficial for patients with acute ischemic stroke caused by a large vessel occlusion. We compared clinical and procedural outcomes, safety, and workflow between patients treated with both IVT and EVT and those treated with EVT alone in routine clinical practice.

Methods and Results—Using multivariable regression, we evaluated the association of IVT+EVT with 90-day functional outcome (modified Rankin Scale), mortality, reperfusion, first-pass effect, and symptomatic intracranial hemorrhage in the MR CLEAN (Multicenter Randomised Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands) Registry. Of 1485 patients, 1161 (78%) were treated with IVT+EVT, and 324 (22%) with EVT alone. Patients treated with IVT+EVT had atrial fibrillation less often (16% versus 44%) and had better pre-stroke modified Rankin Scale scores (pre-stroke modified Rankin Scale 0: 73% versus 52%) than those treated with EVT alone. Procedure time was shorter in the IVT+EVT group (median 62 versus 68 minutes). Nontransferred IVT+EVT patients had longer door-to-groin-puncture times (median 105 versus 94 minutes). IVT+EVT was associated with better functional outcome (adjusted common odds ratio 1.47; 95% CI: 1.10–1.96) and lower mortality (adjusted odds ratio 0.58; 95% CI: 0.40–0.82). Successful reperfusion, first-pass effect, and symptomatic intracranial hemorrhage did not differ between groups.

Conclusions—In this observational study, patients treated with IVT+EVT had better clinical outcomes than patients who received EVT alone. This finding may demonstrate a true benefit of IVT before EVT, but its interpretation is hampered by the possibility of residual confounding and selection bias. Randomized trials are required to properly assess the effect of IVT before EVT. (***J Am Heart Assoc***. 2019;8:e011592. DOI: 10.1161/JAHA.118.011592.)

Key Words: endovascular treatment • large vessel occlusion • stroke • thrombectomy • thrombolysis

Endovascular treatment (EVT) has become standard of care for patients with acute ischemic stroke caused by an intracranial large vessel occlusion of the anterior circulation.[1] Patients included in the EVT trials received intravenous thrombolysis (IVT) with alteplase as standard care, unless they had a contraindication for IVT. Hence, all major guidelines recommend IVT in eligible patients before EVT.[2] In a recent meta-analysis of randomized trials, the effect of EVT was not influenced by IVT, raising the question of whether IVT is beneficial to patients with a large vessel occlusion.[1] Theoretical advantages of IVT before EVT include early reperfusion, faster procedural times, lysis of distal emboli, and improved microvascular reperfusion.[3] Potential

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Clinical Perspective

What Is New?

- The question of whether intravenous thrombolysis (IVT) should still be administered before endovascular treatment (EVT) in ischemic stroke patients was investigated in a large, nationwide registry of patients who underwent EVT, reflecting daily clinical practice.
- IVT administration appeared to delay the time until groin puncture in nontransferred patients.
- Various aspects of this debate, including clinical and safety outcomes, workflow implications, first-pass effect (successful reperfusion on first pass without rescue medication), and reperfusion of the occluded vessel before EVT were explored in 1 comprehensive study.

What Are the Clinical Implications?

- In addition to having better clinical outcomes, patients treated with IVT+EVT more often had reperfusion of the occluded vessel before EVT than patients treated with EVT alone.
- IVT remains the only available reperfusion therapy in about 6% of all patients, in whom the clot was not accessible because of technical reasons; however, successful reperfusion and first-pass effect did not differ between groups, implying that IVT does not facilitate the thrombectomy procedure.
- Until results of ongoing randomized trials are published, current guidelines should remain unchanged.

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disadvantages include delayed initiation of EVT, thrombus fragmentation, major bleeding, potential neurotoxicity, and disruption of the blood–brain barrier.[4–6]

Several studies examined the efficacy and safety of IVT before EVT, but the sample sizes of most studies were relatively small, and their results were inconclusive.[7–10]

The aim of our study was to compare clinical and procedural outcomes, safety, and workflow between acute ischemic stroke patients with a large vessel occlusion treated with both IVT and EVT to those treated with EVT alone using data of the MR CLEAN (Multicenter Randomised Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry.

Methods

Data, Materials, and Code Disclosure Statement

Data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, because no patient approval has been obtained for sharing coded data. However, syntax and output files of statistical analyses may be made available upon request.

Study Design

Details of the MR CLEAN Registry have been reported previously.[11] Briefly, the MR CLEAN Registry is an ongoing, nationwide, multicenter, prospective, observational phase IV study for centers that provide EVT in The Netherlands. Data are collected from consecutive patients who underwent EVT in 18 hospitals. All imaging of patients in the MR CLEAN Registry is adjudicated by an imaging core laboratory, whose members are blinded to clinical findings, except for symptom side. Safety parameters are scored by the complication committee, whose members are blinded to treatment center. A central medical ethics committee evaluated the study protocol of the MR CLEAN Registry and granted permission to carry out the study as a registry.

Study Population and Treatment

We included adult patients who were treated in a MR CLEAN trial center between March 2014 and June 2016, with a large vessel occlusion of the anterior circulation confirmed on computed tomography angiography or magnetic resonance angiography (intracranial carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]), and who underwent groin puncture within 6.5 hours after symptom onset. We excluded patients for whom it was unknown whether they received IVT.

IVT (0.9 mg/kg alteplase over 1 hour with 10% initial bolus) was administered at the first hospital of arrival, according to national guidelines. EVT consisted of mechanical thrombectomy with a stent retriever and/or thrombus aspiration, with or without local delivery of a thrombolytic agent.

Outcome Measures

The primary outcome was the modified Rankin Scale (mRS) score at 90 days. Secondary outcomes were an mRS score of 0 to 2 (functional independence) at 90 days; change in score on the National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 to 48 hours (delta NIHSS); door-(intervention center)-to-groin-puncture time; procedure time; onset-to-last-contrast-bolus time; first-pass effect (single pass/use of the device as first line of EVT, complete reperfusion of the large vessel occlusion and its downstream territory [eTICI 3] and no use of rescue therapy after use of the device)[12]; reperfusion before start of EVT (defined as a score ≥2B on the extended Thrombolysis in Cerebral Ischemia scale [eTICI] on first digital subtraction angiography); and successful reperfusion post-EVT (defined as an eTICI score ≥2B or ≥2C).[13]

Procedure time was defined as the moment of puncture of the femoral artery to successful reperfusion (eTICI ≥2B) or last contrast bolus (when successful reperfusion was not achieved or no target occlusion was seen during the intervention).

Onset-to-last-contrast-bolus time was defined as the duration from symptom onset or time of last seen well to successful reperfusion or last contrast bolus. Safety outcomes were mortality at 90 days, severe extracranial hemorrhage (ie, requiring surgery or blood transfusion), and symptomatic intracranial hemorrhage (sICH) according to the Heidelberg Bleeding Classification.[14]

Statistical Analysis

We compared patients treated with IVT+EVT with patients treated with EVT alone. For intergroup comparison, we used a χ^2 test, Fisher's exact test, Student t test, or Mann–Whitney U test. The mRS scores of patients treated with IVT+EVT were compared with those of patients treated with EVT alone by means of ordinal logistic regression. Binary outcomes were analyzed with logistic regression analysis and continuous outcomes with linear regression analysis. We made adjustments based on theoretical identification, known association with outcome, and empirical identification (ie, baseline imbalances). For all analyses, we made adjustments in a multivariable model for age, baseline NIHSS, history of diabetes mellitus, pre-stroke mRS, prior use of anticoagulant medication, onset-to-first-noncontrast-computed-tomography time, center (in case of sufficient [≥1] outcome events), and additional baseline imbalances ($P<0.05$) in the patients' medical histories. For clinical outcome measures, we made additional adjustments for baseline mean arterial pressure, occlusion location, collateral score,[15] and transfer from a primary stroke center. For door-to-groin-puncture time, procedure time, onset-to-last-contrast-bolus time, first-pass effect, reperfusion before start of EVT, and successful reperfusion, we additionally adjusted for occlusion location and transfer from a primary stroke center. For sICH and severe extracranial hemorrhage, we additionally adjusted for baseline mean arterial pressure, prior use of antiplatelet agents, and Alberta Stroke Program Early CT Score. We tested for collinearity between all variables in all analyses by measuring the variance inflation factor.

In a supplementary analysis, we compared the distribution of occlusion locations in patients with reperfusion before start of EVT to those without.

Missing data were imputed using multiple imputation based on relevant covariates and outcome. Adjusted (common) odds ratios [a(c)ORs] are reported with 95% CIs and all P values are 2-sided. Statistical analyses were performed with Stata software, version 14.1 (StatCorp, TX), and IBM SPSS Statistics for Windows, Version 24.0.

Sensitivity Analyses

We performed 2 sensitivity analyses. First, we conducted a 1:1 propensity score matching analysis to evaluate the association between IVT and functional outcome. Propensity scores representing the probability of receiving IVT were calculated for each patient in each multiple imputed data set, using a logistic regression model, based on the covariates used for the adjustments in our primary analysis. Patients from the EVT alone group were matched to patients in the IVT+EVT group in a 1:1 nearest-neighbor matching of the logit of the propensity score, with a caliper width of 0.20. Matching was performed without replacement and unpaired patients were excluded. We used an ordinal logistic regression analysis to compare functional outcomes of patients treated with IVT+EVT and EVT alone.

To explore residual confounding, we performed a second sensitivity analysis, in which we stratified for "history of atrial fibrillation." In this analysis, we used the outcome variables mRS at 90 days, functional independence at 90 days, mortality at 90 days, sICH, and eTICI ≥2B.

Results

During the study period, 1628 patients were recorded in the MR CLEAN Registry, of whom 140 did not meet the inclusion criteria. We further excluded 3 patients because it was unknown whether they had been treated with IVT. Of the 1485 included patients, 1161 (78%) were treated with IVT+EVT and 324 (22%) with EVT alone (Figure 1).

The most common reasons for withholding IVT were coagulation abnormalities and/or antithrombotic treatment (50%), recent surgery (15%), and presentation exceeding 4.5 hours after symptom onset or last seen well (14%) (Table 1).

Patients in the IVT+EVT group were younger (median 70 years versus 72 years, $P=0.03$), had less severe deficits (median NIHSS 16 versus 17, $P<0.01$), less often had atrial fibrillation (16% versus 44%, $P<0.01$) and previous ischemic stroke (14% versus 26%, $P<0.01$) than patients treated with EVT alone (Table 2). Patients treated with IVT+EVT also had a better pre-stroke mRS (mRS 0: 73% versus 52%, $P<0.01$).

In total, 656 (57%) patients with IVT+EVT were transferred from a primary stroke center, compared with 151 (47%) patients treated with EVT alone ($P<0.01$) (Table 3). The median door-to-needle time in patients treated with IVT+EVT was 25 minutes. Onset-to-noncontrast-computed-tomography time (median 67 versus 83 minutes, $P<0.01$) and onset-to-groin-puncture time (median 206 versus 215 minutes, $P=0.04$) were shorter in the IVT+EVT group.

The scores on the mRS at 90 days were more favorable in patients in the IVT+EVT group than in the EVT-alone group, and this difference persisted after adjustment for potential confounders (acOR 1.47; 95% CI: 1.10–1.96, Table 4, Figure 2). Functional independence at 90 days was achieved in 41% of patients with IVT+EVT, compared with 29% of patients with EVT
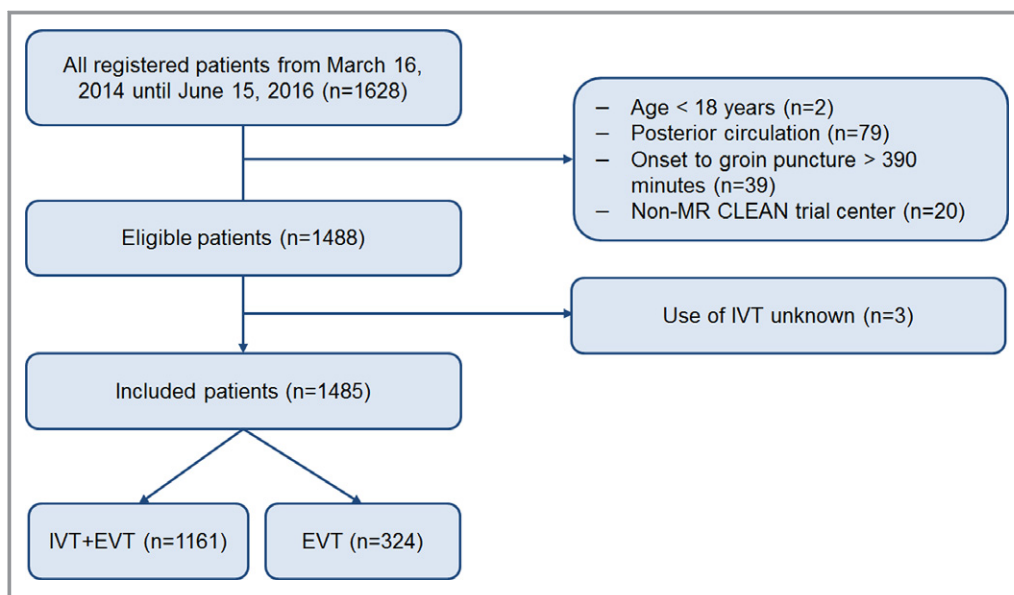
Figure 1. Flowchart of patient selection. EVT indicates endovascular treatment; IVT, intravenous thrombolysis; MR CLEAN, a Multicenter Randomized Controlled trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands.

alone (aOR 1.32; 95% CI: 0.85–1.87). Delta NIHSS was larger (adjusted β −1.5; 95% CI: −2.6 to −0.3) and mortality was lower in the IVT+EVT group (aOR 0.58; 95% CI: 0.40–0.82).

Among nontransferred patients, median door-to-groin-puncture time was longer in the IVT+EVT group (105 versus 94 minutes; adjusted β 9.5; 95% CI: 0.5–18.5), while among

Table 1. Reported Reasons for Withholding IVT

Reason for Withholding IVT*	Total (n=324), n (%)
Coagulation abnormalities and/ or antithrombotic treatment	163 (50)
Recent surgery	48 (15)
Time from symptom onset or last seen well exceeds 4.5 h	46 (14)
Recent ischemic stroke	29 (9.0)
Recent traumatic injury or current hemorrhage	20 (6.2)
Recent gastrointestinal or urogenital hemorrhage	12 (3.7)
Other, such as allergy for IVT, cerebellar metastasis, endocarditis, pregnancy	10 (3.1)
Recent ICH	8 (2.5)
SBP ≥185 mm Hg and/ or DBP ≥110 mm Hg	7 (2.2)
Unknown	5 (1.5)

DBP indicates diastolic blood pressure; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; SBP, systolic blood pressure.
*More than 1 reason may have been reported per patient.

transferred patients this was 47 minutes in both groups. We found no association between prior IVT and door-to-groin-puncture time for transferred patients only (adjusted β 0.5; 95% CI: −7.3 to 8.2), nor between prior IVT and onset-to-last-contrast-bolus time (adjusted β −3.5; 95% CI: −12.8 to 5.9). There also was no difference in the proportion of patients with first-pass effect (17% versus 16%; aOR 1.22; 95% CI: 0.79–1.90). We did find a faster median procedure time (62 versus 68 minutes, adjusted β −6.2; 95% CI: −11.0 to −1.3) in the IVT+EVT group. Reperfusion before start of EVT occurred more often in the IVT+EVT group than in the EVT-alone group (8.4% versus 2.8%, aOR 3.14; 95% CI: 1.47–6.73) (Table 4).

In the supplementary analysis in 85 of the 97 IVT+EVT patients who had reperfusion before EVT and in whom the occlusion location was known, 61 (72%) had a distal M1, M2, or M3 occlusion (Table 5).

The risk of severe extracranial hemorrhage (2.4% versus 1.5%, aOR 1.96; 95% CI: 0.66–5.81) and sICH (5.9% versus 5.3%, aOR 1.20; 95% CI: 0.64–2.25) did not differ between groups (Table 4).

Sensitivity Analyses

After applying 1:1 matching in each multiple imputed data set, sample sizes of both the IVT+EVT and EVT alone group ranged between 299 and 305. Baseline characteristics were similar in the 2 matched groups, with significant differences remaining in atrial fibrillation, prior use of direct oral anticoagulants, and prior use of vitamin K antagonists (Table 6). Prior IVT was still associated with better functional outcome at 90 days (cOR 1.42; 95% CI: 1.03–1.96).

Table 2. Baseline Characteristics

	IVT+EVT (n=1161)	EVT (n=324)	*P* Value
Age (y), median (IQR)	70 (59–79)	72 (63–80)	0.03
Men, n (%)	621 (54)	171 (53)	0.82
NIHSS, median (IQR)*	16 (11–20)	17 (13–20)	<0.01
Systolic BP, mean mm Hg (SD)†	150 (24)	149 (26)	0.85
Diastolic BP, mean mm Hg (SD)‡	82 (15)	82 (17)	0.77
Medical history			
Atrial fibrillation, n (%)	186/1144 (16)	141/320 (44)	<0.01
Diabetes mellitus, n (%)	197/1155 (17)	56/321 (17)	0.87
Hypertension, n (%)	562/1145 (49)	180/321 (56)	0.03
Ischemic stroke, n (%)	164/1154 (14)	83/322 (26)	<0.01
Myocardial infarction, n (%)	163/1142 (14)	64/314 (20)	<0.01
Peripheral artery disease, n (%)	99/1139 (8.7)	36/318 (11)	0.15
Pre-stroke mRS, n (%)			<0.01
0	826/1138 (73)	165/320 (52)	
1	132/1138 (12)	57/320 (18)	
2	70/1138 (6.2)	38/320 (12)	
≥3	110/1138 (9.7)	60/320 (19)	
Medication			
Direct oral anticoagulants, n (%)	10/1141 (0.9)	27/318 (8.5)	<0.01
Vitamin K antagonists, n (%)	70/1150 (6.1)	120/324 (37)	<0.01
Antiplatelets, n (%)	391/1146 (34)	100/320 (31)	0.34
Imaging			
Occlusion location on CTA, n (%)			0.32
ICA	70/1101 (6.4)	12/307 (3.9)	
ICA-T	241/1101 (22)	71/307 (23)	
M1	637/1101 (58)	186/307 (61)	
M2	142/1101 (13)	33/307 (11)	
Other‖	11/1101 (1.0)	5/307 (1.6)	
ASPECTS, median (IQR)§	9 (7–10)	9 (7–10)	0.76
Collateral score, n (%)			0.74
Grade 0	72/1105 (6.7)	24/303 (7.9)	
Grade 1	365/1105 (34)	95/303 (31)	
Grade 2	41/1105 (39)	117/303 (39)	
Grade 3	221/1105 (21)	67/303 (22)	

ASPECTS indicates Alberta Stroke Program Early CT Score; BP, blood pressure; CTA, computed tomography angiography; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
Missing: *30; †42; ‡47; §64.
‖Other: occlusions in segment 1 or 2 of the anterior cerebral artery (A1: n=3; A2: n=3) or segment 3 of the middle cerebral artery (M3, n=9), or no occlusion visible (n=12) on CTA after adjudication by the imaging core laboratory.

We next stratified the analysis for atrial fibrillation. Among 327 patients with atrial fibrillation, 186 underwent IVT+EVT and 141 EVT alone. Of the 1137 patients without atrial fibrillation, 958 underwent IVT+EVT and 179 EVT alone. A comparison of baseline characteristics within the strata is shown in Table 7. The association between prior IVT and better functional outcome at 90 days remained statistically significant among patients without atrial fibrillation (acOR

Table 3. Workflow* and Treatment Characteristics

	IVT+EVT (n=1161)	EVT (n=324)	P Value
Transferred from primary stroke center, n (%)	656 (57)	151 (47)	<0.01
Onset-to-first-NCCT time[†]	67 (51–103)	83 (52–142)	<0.01
Door-to-needle time[‡]	25 (19–33)	NA	
Onset-to-groin-puncture time[‖]	206 (160–260)	215 (158–294)	0.04
Door-to-groin-puncture time[‖§]	128 (97–165)	115 (85–165)	0.08
Performed procedure, n (%)			
Catheterization—no access to target occlusion	64 (5.5)	16 (5.0)	<0.01
DSA—no target occlusion present	108 (9.3)	11 (3.4)	
Thrombectomy—thrombus retrieval attempted	983 (85)	294 (91)	
Other—procedure ended before attempt	6 (0.5)	3 (0.9)	

DSA indicates digital subtraction angiography; EVT, endovascular treatment; IQR, interquartile range; IVT, intravenous thrombolysis; NA, not applicable; NCCT, noncontrast computed tomography.
*All times are in minutes—median (IQR).
Missing: [†]495; [‡]319; [§]447.
[‖]Includes both transferred and nontransferred patients; door-time is door of first hospital.

1.72; 95% CI: 1.23–2.42, Table 8). However, among patients with atrial fibrillation, there was no association between prior IVT and functional outcome (acOR 1.06; 95% CI: 0.63–1.81). We also found a higher percentage of sICH in patients with atrial fibrillation who were treated with IVT+EVT, but this difference was not statistically significant (5.9% versus 2.8%, aOR 2.18; 95% CI: 0.60–7.91).

Discussion

In our study—in which we compared clinical and procedural outcomes, safety, and workflow in patients with acute ischemic stroke and an intracranial large vessel occlusion of the anterior circulation treated with IVT+EVT to those treated with EVT alone—we found that the combination of EVT with IVT was associated with a better clinical outcome than treatment with EVT alone.

A number of observational studies have previously addressed the additional benefit of IVT before EVT. These studies mostly had small sample sizes (range: 66–500 patients, with the exception of 1 study of 1166 patients) and had varying results.[7–9,16–18] A post hoc, pooled analysis of the SWIFT (Solitaire With the Intention for Thrombectomy) and STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization) studies showed no statistically significant benefit of IVT followed by EVT over EVT alone.[9] However, contrary to our study, the effect of IVT was awaited before initiating EVT in the majority of cases, possibly decreasing the chances of good functional outcome. Two other studies performed a propensity score matching analysis comparing patients who received IVT before EVT with IVT-eligible patients who underwent EVT alone, and also found no difference in

functional independence between the 2 groups.[8,10] In only 2 studies with data of 66 and 131 patients, a score on the mRS of 0 to 2 at 90 days was more common in the IVT+EVT group, which is in line with our results.[16,17] Notably, all previous studies used a dichotomized mRS as outcome measure for regression analyses, which has less statistical power than an ordinal analysis, and may thus lead to false-negative results.

In accordance with previous studies, prior use of IVT was not associated with a higher percentage of successful reperfusion,[8,9,18] nor was it associated with a higher percentage of first-pass effect, a relatively new measure of successful thrombectomy.[12] Conversely, procedure times were shorter in the IVT+EVT group. This implies that it may have been more difficult to gain intracranial access in the EVT alone group. It further implies that IVT does not facilitate the procedure by softening the thrombus. The latter could also have been influenced by differences in stroke cause between the 2 groups (ie, caused by a higher percentage of atrial fibrillation in the EVT-alone group) potentially leading to different clot characteristics.[19] However, if that were the case, the differences in successful reperfusion and first-pass effect would have been larger. Also, this association between clot characteristics and cause remains unclear,[19] and we did account for this imbalance in our multivariable analysis. Further, it is possible that the higher percentage of oral anticoagulation use in the EVT-only group influenced the occurrence of successful reperfusion, despite our attempts to adjust for this imbalance. However, there is currently no evidence that oral anticoagulation use and successful reperfusion are associated with one another.

We found that patients in the IVT+EVT group more frequently had reperfusion before start of EVT (eTICI ≥2B on

Table 4. Primary, Secondary,* and Safety Outcomes Among Patients Treated With IVT+EVT Versus EVT Alone

	IVT+EVT (n=1161)	EVT (n=324)	P Value	(c)OR/β (95% CI)	Adjusted (c)OR/β (95% CI)[†]
Primary outcome					
mRS at 90 d, median (IQR)[‡]	3 (2–6)	4 (2–6)	<0.01	1.80 (1.43–2.26)	1.47 (1.10–1.96)[††]
Secondary outcomes					
mRS 0–2 at 90 d, n (%)	431/1061 (41)	86/299 (29)	<0.01	1.65 (1.25–2.17)	1.32 (0.85–1.87)[††]
ΔNIHSS, median (IQR)[§]	−4 (−9 to 0)	−3 (−8 to 1)	0.02	−0.9 (−1.9 to 0.2)	−1.5 (−2.6 to −0.3)[††]
Door-intervention center-to-groin-puncture time for transferred patients[‖]	47 (31–69)	47 (30–71)	0.72	−0.8 (−7.2 to 5.7)	0.5 (−7.3 to 8.2)[‡‡]
Door-intervention center-to-groin-puncture time for nontransferred patients[¶]	105 (79–130)	94 (73–125)	0.08	10.5 (2.2–18.8)	9.5 (0.5–18.5)[‡‡]
Procedure time[#]	62 (39–87)	68 (45–95)	<0.01	−5.6 (−9.9 to −1.3)	−6.2 (−11.0 to −1.3)[‡‡]
Onset-to-last-contrast-bolus time**	265 (215–324)	277 (221–355)	<0.01	−19.6 (−29.5 to −9.7)	−3.5 (−12.8 to 5.9)[‡‡]
First-pass effect[¶¶]	147/842 (17)	41/259 (16)	0.543	1.20 (0.83–1.74)	1.22 (0.79–1.90)[§§]
Reperfusion (eTICI ≥2B) before start of EVT, n (%)	97/1161 (8.4)	9/324 (2.8)	<0.01	3.19 (1.59–6.39)	3.14 (1.47–6.73)[§§]
Successful reperfusion post-EVT (eTICI ≥2B), n (%)	672/1143 (59)	175/321 (54)	0.17	1.19 (0.92–1.52)	1.05 (0.77–1.43)[‡‡]
Post-EVT eTICI ≥2C, n (%)	456/1143 (40)	120/321 (37)	0.42	1.11 (0.86–1.43)	0.98 (0.72–1.33)[‡‡]
Safety outcomes					
Mortality at 90 d, n (%)	275/1161 (24)	122/324 (38)	<0.01	0.51 (0.40–0.67)	0.58 (0.40–0.82)[††]
Severe extracranial hemorrhage, n (%)	28/1161 (2.4)	5/324 (1.5)	0.35	1.58 (0.60–4.12)	1.96 (0.66–5.81)[‖‖]
Symptomatic ICH, n (%)	69/1161 (5.9)	17/324 (5.3)	0.64	1.14 (0.66–1.97)	1.20 (0.64–2.25)[‖‖]

(c)OR indicates common odds ratio; eTICI, extended Thrombolysis in Cerebral Ischemia scale; EVT, endovascular treatment; ICH, intracranial hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; ΔNIHSS, NIHSS at 24 to 48 hours minus baseline NIHSS.

*All times are in minutes—median (IQR).

[†]All analyses were adjusted for: age (y), baseline NIHSS, history of atrial fibrillation, diabetes mellitus, hypertension, ischemic stroke, myocardial infarction, pre-stroke mRS, prior use of anticoagulant medication, onset-to-first noncontrast CT (NCCT) time.

Missing: [‡]125; [§]167; [‖]35; [¶]96; [#]156; **87.

[††]Additionally adjusted for: baseline mean arterial pressure (MAP), occlusion location, collateral score, transfer from a primary stroke center, center.

[‡‡]Additionally adjusted for: occlusion location, transfer from a primary stroke center, center.

[§§]Additionally adjusted for: occlusion location, transfer from a primary stroke center.

[‖‖]Additionally adjusted for: baseline MAP, prior use of antiplatelet agents, Alberta Stroke Program Early CT Score.

[¶¶]In patients with at least 1 attempt at thrombectomy with a device (n=1101/1267).

first digital subtraction angiography) than in the EVT-alone group. Reperfusion before start of EVT in the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times) trial and MR CLEAN trial was found in 4.8% and 3.7% of patients, respectively, compared with 8% in our study.[20,21] Our supplementary analysis showed that patients with reperfusion before EVT had more distally located occlusions, supporting the hypothesis that IVT is most effective in more distally located thrombi.[22] However, these numbers are small and there may be underreporting of those patients who recovered before EVT because these patients were not included in the MR CLEAN Registry. Moreover, results of the recent EXTEND-IA TNK (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) study suggest that tenecteplase may be a more effective fibrinolytic drug than alteplase in patients with a large vessel occlusion.[23] Whether tenecteplase can replace alteplase as

the preferred drug for IVT requires further study.[24] Conversely, the use of IVT before EVT may also pose a higher risk of emboli migrating to a previously uninvolved territory or thrombus migration to more distal arterial branches that cannot be reached with EVT, which is associated with a worse prognosis.[25] In our study, embolization to a new territory and thrombus migration were not documented. However, the postprocedural eTICI score of ≥2C was similar in both groups. This finding suggests that IVT contributes mainly to faster recanalization, rather than causing thrombus migration.

The median door-to-groin-puncture time was 11 minutes longer in nontransferred patients in the IVT+EVT group, which indicates that administration of IVT might contribute to a small delay in start of EVT. This difference was shorter than the 32-minute mean delay in the STAR (Solitaire FR Thrombectomy for Acute Revascularization) trial.[26] This suggests that, with the increased experience in intervention centers, delayed start of EVT because of IVT administration has become less of an issue.
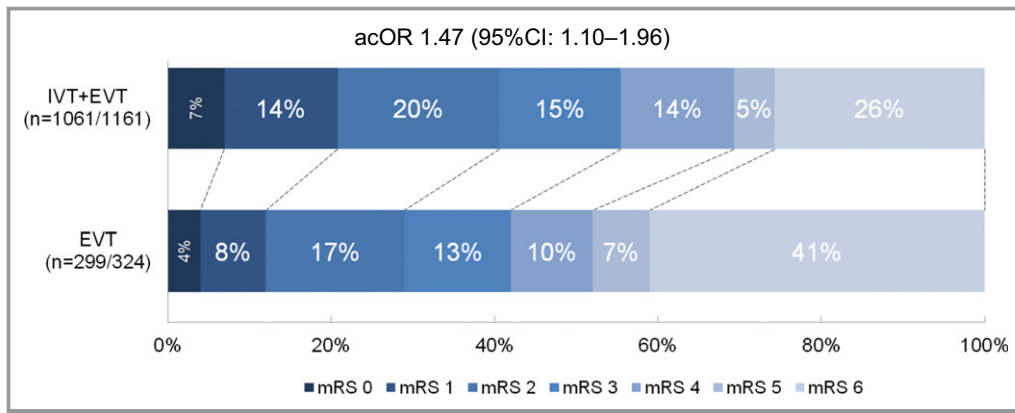
Figure 2. Distribution of the modified Rankin Scale score at 90 days in IVT+EVT group vs EVT-alone group (%)*. acOR indicates adjusted common odds ratio; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale. *The mRS 0 to 5 group contains 125 missing cases, whereas the mRS 6 group is complete. Therefore, this figure over-represents mortality in both groups.

Our study showed a reduction in mortality in favor of IVT+EVT versus EVT alone, which is in contrast with previous studies.[18,27,28] Conversely, 1 previous study reported a lower mortality in the EVT-alone group.[8] Importantly, the IVT+EVT group of this study was matched with patients who were eligible for IVT but were treated with EVT alone at the physician's discretion. Because the current standard of care in The Netherlands is to always give IVT except when contraindicated, we could not perform a similar analysis.

The occurrence of sICH and severe extracranial hemorrhage did not differ between both groups, which is in line with most previous studies.[7,9,16,18] In the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) meta-analysis, the risk of sICH was similar in the IVT+EVT group and IVT alone group.[1] This suggests that the occurrence of sICH can be mainly attributed to IVT rather than to EVT. Therefore,

our results might be a hallmark of residual (ie, unmeasured) confounding.

The stratified analysis revealed that the benefit of IVT before EVT was not present in patients with pre-existing atrial fibrillation. While this sensitivity analysis must be interpreted with caution, it could imply that IVT has a lower treatment effect in patients with a large vessel occlusion caused by embolism from the heart than in patients with stroke of other etiology. For instance, it may be that cardiac thrombi have a different composition or age than thrombi of noncardiac origin.[29] Another potential explanation could be the risk of sICH. The proportion of patients who developed a sICH after EVT alone (ie, without prior IVT) was almost 5% higher in patients without atrial fibrillation than in patients with atrial fibrillation (7.3% versus 2.8%, Table 8), which could partly explain the worse outcome of patients without atrial fibrillation who received EVT alone. On the

Table 5. No Recanalization Versus Recanalization Before Start of EVT in Patients With and Without IVT Per Occlusion Location*

	IVT+EVT		EVT	
	No Recanalization Before Start of EVT (n=1015)	Recanalization Before Start of EVT (n=85)	No Recanalization Before Start of EVT (n=299)	Recanalization Before Start of EVT (n=8)
Occlusion location, n (%)*				
ICA	66 (94)	4 (5.7)	12 (100)	0 (0)
ICA-T	236 (98)	5 (2.1)	71 (100)	0 (0)
Proximal M1	273 (94)	15 (5.2)	71 (95)	4 (5.3)
Distal M1	310 (89)	39 (11)	111 (100)	0 (0)
M2/M3	125 (85)	22 (15)	34 (92)	3 (8.1)
A1/A2	5 (100)	0 (0)	0 (0)	1 (100)

A1 indicates segment 1 of the anterior cerebral artery; A2, segment 2 of the anterior cerebral artery; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; IVT, intravenous thrombolysis; M1, segment 1 of middle cerebral artery; M2, segment 2 of middle cerebral artery; M3, segment 3 of middle cerebral artery.
*Missing data on occlusion location: 66. We excluded 12 patients in whom no occlusion was visible on computed tomography angiography after adjudication by the imaging core laboratory.

Table 6. Baseline Characteristics After Propensity Score Matching

	IVT+EVT (n=305)	EVT (n=305)	*P* Value
Age (y), median (IQR)	72 (59–82)	72 (63–80)	0.61
Men, n (%)	165/305 (54)	163/305 (53)	0.87
NIHSS, median (IQR)	16 (11–20)	17 (13–20)	0.13
Systolic BP, mean mm Hg (SD)	149 (25)	149 (26)	0.74
Diastolic BP, mean mm Hg (SD)	82 (16)	82 (17)	0.99
Medical history			
Atrial fibrillation, n (%)	102/305 (33)	126/305 (41)	0.045
Diabetes mellitus, n (%)	61/305 (20)	51/305 (17)	0.30
Hypertension, n (%)	157/305 (52)	167/305 (55)	0.42
Ischemic stroke, n (%)	62/305 (20)	74/305 (24)	0.24
Myocardial infarction, n (%)	53/305 (17)	62/305 (20)	0.35
Peripheral artery disease, n (%)	31/305 (10)	35/305 (11)	0.60
Pre-stroke mRS, n (%)			0.06
0	192/305 (63)	161/305 (53)	
1	41/305 (13)	54/305 (18)	
2	23/305 (7.5)	36/305 (12)	
≥3	49/305 (16)	54/305 (18)	
Medication			
Direct oral anticoagulants, n (%)	10/305 (3.3)	23/305 (7.5)	0.02
Vitamin K antagonists, n (%)	66/305 (22)	107/305 (35)	<0.01
Antiplatelets, n (%)	97/305 (32)	98/305 (32)	0.93
Imaging			
Occlusion location on CTA, n (%)			0.65
ICA	16/305 (5.3)	12/305 (3.9)	
ICA-T	69/305 (23)	77/305 (25)	
M1	174/305 (57)	180/305 (59)	
M2	41/305 (13)	33/305 (11)	
Other*	5/305 (1.6)	3/305 (1.0)	
ASPECTS, median (IQR)	8 (7–10)	9 (7–10)	0.66
Collateral score, n (%)			0.82
Grade 0	20/305 (6.6)	24/305 (7.9)	
Grade 1	101/305 (33)	94/305 (31)	
Grade 2	120/305 (39)	117/305 (38)	
Grade 3	64/305 (21)	70/305 (23)	

Baseline characteristics of set 1 of 5 imputed data sets are provided. ASPECTS indicates Alberta Stroke Program Early CT Score; BP, blood pressure; CTA, computed tomography angiography; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
*Other: occlusions in segment 1 or 2 of the anterior cerebral artery (A1: n=2; A2: n=2) or no occlusion visible (n=4) on CTA after adjudication by the imaging core laboratory.

other hand, the difference in response to IVT in patients with atrial fibrillation could also be the result of residual confounding.

Finally, it is important to consider the implications of withholding IVT in patients eligible for both IVT and EVT, in whom EVT may be delayed or not feasible. This is the case, for example, when the clot is not accessible because of technical reasons such as arterial tortuosity and extracranial carotid stenosis or occlusion.[30] In the MR CLEAN trial and Registry, this occurred in 5% and 6% of all patients, respectively, as

Table 7. Baseline Characteristics Among Patients Treated With IVT+EVT Versus EVT Alone, Stratified by Past Medical History of Atrial Fibrillation

	Patients With Atrial Fibrillation			Patients Without Atrial Fibrillation		
	IVT+EVT (n=186)	EVT (n=141)	P Value	IVT+EVT (n=958)	EVT (n=179)	P Value
Age (y), median (IQR)	77 (68–84)	77 (69–83)	0.75	69 (57–78)	68 (58–76)	0.54
Men, n (%)	87/186 (47)	70/141 (50)	0.61	525/958 (55)	100/179 (56)	0.79
NIHSS, median (IQR)*	16 (12–21)	17 (13–20)	0.36	15 (11–19)	16 (12–20)	0.04
Systolic BP, mean mm Hg (SD)†	148 (130–165)	150 (132–166)	0.54	150 (131–165)	147 (130–165)	0.21
Diastolic BP, mean mm Hg (SD)‡	84 (70–95)	80 (70–94)	0.70	80 (70–90)	80 (66–92)	0.77
Medical history						
Diabetes mellitus, n (%)	34/186 (18)	30/139 (22)	0.46	158/958 (16)	25/178 (14)	0.41
Hypertension, n (%)	114/184 (62)	98/140 (70)	0.13	438/947 (46)	79/177 (45)	0.69
Ischemic stroke, n (%)	36/186 (19)	39/141 (28)	0.08	126/957 (13)	43/178 (24)	<0.001
Myocardial infarction, n (%)	27/184 (15)	30/136 (22)	0.09	134/949 (14)	33/176 (19)	0.11
Peripheral artery disease, n (%)	17/181 (9.4)	16/139 (12)	0.54	78/948 (8.2)	20/176 (11)	0.18
Pre-stroke mRS, n (%)			0.27			<0.001
0	111/185 (60)	72/140 (51)		707/938 (75)	91/176 (52)	
1	27/185 (15)	23/140 (16)		103/938 (11)	32/176 (18)	
2	18/185 (9.7)	12/140 (8.6)		48/938 (5.1)	26/176 (15)	
≥3	29/185 (16)	33/140 (24)		80/938 (8.5)	27/176 (15)	
Medication						
Direct oral anticoagulants, n (%)	7/183 (3.8)	22/138 (16)	<0.001	3/944 (0.3)	5/177 (2.8)	<0.01
Vitamin K antagonists, n (%)	52/183 (28)	83/141 (59)	<0.001	18/952 (1.9)	35/179 (20)	<0.001
Antiplatelets, n (%)	60/183 (33)	33/139 (24)	0.08	327/949 (35)	66/177 (37)	0.47
Imaging						
Occlusion location on CTA, n (%)			0.02			0.74
ICA	5/175 (2.9)	4/137 (2.9)		65/913 (7.1)	8/165 (4.8)	
ICA-T	30/175 (17)	31/137 (23)		208/913 (23)	38/165 (23)	
M1	104/175 (59)	91/137 (66)		522/913 (57)	93/165 (56)	
M2	35/175 (20)	10/137 (7.3)		106/913 (12)	23/165 (14)	
Other‖	1/175 (0.6)	1/137 (0.7)		12/913 (1.3)	3/165 (1.8)	
ASPECTS, median (IQR)§	9 (7–10)	9 (7–10)	0.37	9 (7–10)	9 (7–10)	0.51
Collateral score, n (%)			0.98			0.33
Grade 0	14/168 (8.3)	10/132 (7.6)		56/893 (6.3)	14/167 (8.4)	
Grade 1	56/168 (33)	42/132 (32)		304/893 (34)	51/167 (31)	
Grade 2	70/168 (42)	58/132 (44)		341/893 (38)	58/167 (35)	
Grade 3	28/168 (17)	22/132 (17)		192/893 (22)	44/167 (26)	

ASPECTS indicates Alberta Stroke Program Early CT Score; BP, blood pressure; CTA, computed tomography angiography; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, terminal internal carotid artery; IVT, intravenous thrombolysis; IQR, interquartile range; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
Missing: *29; †40; ‡45; §64.
‖Other: occlusions in segment 1 or 2 of the anterior cerebral artery, segment 3 of the middle cerebral artery, or no occlusion visible on CTA after adjudication by the imaging core laboratory.

opposed to the other randomized controlled trials that used more strict selection criteria and that reported percentages between 2% and 3.6%.[20,21,31,32] In such cases, IVT remains the only available reperfusion therapy.

Table 8. Functional and Safety Outcomes Among Patients Treated With IVT+EVT Versus EVT Alone, Stratified by Past Medical History of Atrial Fibrillation

	Patients With Atrial Fibrillation				Patients Without Atrial Fibrillation			
	IVT+EVT (n=186)	EVT (n=141)	(c)OR (95% CI)	Adjusted (c)OR (95% CI)*	IVT+EVT (n=958)	EVT (n=179)	(c)OR (95% CI)	Adjusted (c)OR (95% CI)*
mRS at 90 d, median (IQR)†	4 (2–6)	5 (2–6)	1.33 (0.89–1.98)	1.06 (0.63–1.81)‡	3 (2–5)	4 (2–6)	1.74 (1.31–2.31)	1.72 (1.23–2.42)‡
mRS 0–2 at 90 d, n (%)	52/174 (30)	33/131 (25)	1.28 (0.78–2.12)	0.78 (0.37–1.65)‡	373/872 (43)	53/166 (32)	1.62 (1.15–2.27)	1.53 (0.97–2.42)‡
Mortality at 90 d, n (%)	65/186 (35)	57/141 (40)	0.80 (0.51–1.25)	0.87 (0.46–1.64)‡	204/958 (21)	64/179 (36)	0.50 (0.35–0.70)	0.44 (0.28–0.68)‡
Symptomatic ICH, n (%)	11/186 (5.9)	4/141 (2.8)	2.3 (0.72–7.39)	2.18 (0.60–7.91)§	56/958 (5.8)	13/179 (7.3)	0.81 (0.43–1.51)	0.94 (0.46–1.92)§
Successful reperfusion post-EVT (eTICI ≥2B), n (%)	95/186 (51)	76/139 (55)	0.85 (0.55–1.31)	0.73 (0.44–1.21)	568/940 (60)	97/178 (55)	1.28 (0.93–1.76)	1.15 (0.80–1.66)

(c)OR indicates common odds ratio; eTICI, extended Thrombolysis in Cerebral Ischemia scale; EVT, endovascular treatment; ICH, intracranial hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale score.

*All analyses were adjusted for: age (y), baseline National Institutes of Health Stroke Scale (NIHSS), diabetes mellitus, hypertension, ischemic stroke, myocardial infarction, pre-stroke mRS, prior use of anticoagulant medication, onset-to-first noncontrast CT (NCCT) time.

†Missing: 122.

‡Additionally adjusted for: baseline mean arterial pressure (MAP), occlusion location, collateral score, transfer from a primary stroke center, center.

§Additionally adjusted for: baseline MAP, prior use of antiplatelet agents, Alberta Stroke Program Early CT Score.

Whether patients with acute ischemic stroke who are eligible for EVT should still receive intravenous alteplase is currently heavily debated among stroke physicians and researchers. In the present study, we explored many aspects of this debate. In addition to comparing clinical and safety outcomes in patients with IVT+EVT to those with EVT alone, we also included a complete assessment of workflow and procedural outcomes. Other strengths of our study include its comprehensive statistical approach, the large sample size, adherence to current protocols (eg, not awaiting the effect of IVT), and central adjudication of neuro-imaging, outcomes, and complications. Moreover, the data come from a nation-wide registry and therefore reflect routine clinical practice. Similar to other studies that have tried to examine the added benefit of IVT before EVT, the main limitation of our study is the fact that it was nonrandomized. Patients in the EVT-alone group were selected based on contraindications for IVT. We also found that patients in the EVT-alone group more often had a pre-stroke disability, had a higher NIHSS at baseline, and were more often presented outside the 4.5-hour time window for IVT (reflected in the 16 minutes shorter onset-to-first noncontrast-computed-tomography time in patients with IVT+EVT). These factors are all associated with a worse prognosis.[33,34] The apparent benefit of prior IVT on functional outcome remained after adjustment for these factors and after propensity score matching based on these variables, yielding comparable point estimates of 1.47 and 1.42, respectively, but not after stratification for atrial fibrillation. Therefore, we still cannot exclude the possibility of residual confounding. Secondly, we had no data on whether the full dose of alteplase was administered in each patient who was treated with IVT. However, the Dutch stroke guideline does not advise on halting infusion of alteplase after groin puncture and/or recanalization. Since this guideline is well adhered to in The Netherlands, patients most likely received the full dose of alteplase.[35] Thirdly, patients who had a sICH before EVT and those who recovered before EVT are not represented in our study, since both types of patients would not have received EVT and were thus not recorded in the Registry.

Our data show that, in daily clinical practice, administering IVT before EVT has advantages and disadvantages. Because this is a nonrandomized study, we cannot firmly conclude whether IVT before EVT is beneficial to patients with acute ischemic stroke caused by an intracranial large vessel occlusion. Patients treated with both IVT and EVT had a better functional outcome and lower mortality at 90 days than those with contraindications for IVT who were treated with EVT alone, also after adjustment for potential confounders and after propensity score matching. Notably, in patients with atrial fibrillation, IVT may not be beneficial before EVT. Our results may indicate a true added benefit of IVT before EVT in select patient groups, but the interpretation is hampered by the possibility

of residual confounding or selection bias, which cannot be overcome by multivariable regression analysis or propensity score matching. MR CLEAN-NO IV (ISRCTN10888758), SWIFT-DIRECT (NCT03192332), DIRECT-SAFE (NCT03494920), and DIRECT-MT (NCT03469206), the 4 ongoing randomized clinical trials that directly compare both treatment strategies, will provide conclusive results on this topic. Meanwhile, IVT should not be withheld in patients outside these trials who are eligible for both IVT and EVT.

Appendix

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