










Intra-arterial thrombolytics during endovascular thrombectomy for acute ischaemic stroke in the MR CLEAN Registry

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ABSTRACT

Introduction The efficacy and safety of local intra-arterial (IA) thrombolytics during endovascular thrombectomy (EVT) for large-vessel occlusions is uncertain. We analysed how often IA thrombolytics were administered in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, whether it was associated with improved functional outcome and assessed technical and safety outcomes compared with EVT without IA thrombolytics.

Methods In this observational study, we included patients undergoing EVT for an acute ischaemic stroke in the anterior circulation from the MR CLEAN Registry (March 2014–November 2017). The primary endpoint was favourable functional outcome, defined as an modified Rankin Scale score ≤ 2 at 90 days. Secondary endpoints were reperfusion status, early neurological recovery and symptomatic intracranial haemorrhage (sICH). Subgroup analyses for IA thrombolytics as primary versus adjuvant revascularisation attempt were performed.

Results Of the 2263 included patients, 95 (4.2%) received IA thrombolytics during EVT. The IA thrombolytics administered were urokinase (median dose, 250 000 IU (IQR, 1 93 750–2 50 000)) or alteplase (median dose, 20 mg (IQR, 12–20)). No association was found between IA thrombolytics and favourable functional outcome (adjusted OR (aOR), 1.16; 95% CI 0.71 to 1.90). Successful reperfusion was less often observed in those patients treated with IA thrombolytics (aOR, 0.57; 95% CI 0.36 to 0.90). The odds of sICH (aOR, 0.82; 95% CI 0.32 to 2.10) and early neurological recovery were comparable between patients treated with and without IA thrombolytics. For primary and adjuvant revascularisation attempts, IA thrombolytics were more often administered for proximal than for distal occlusions. Functional outcomes were comparable for patients receiving IA thrombolytics as a primary versus adjuvant revascularisation attempt.

Conclusion Local IA thrombolytics were rarely used in the MR CLEAN Registry. In the relatively small study sample, no statistical difference was observed between groups in the rate of favourable functional outcome or sICH. Patients whom required and underwent IA thrombolytics were patients less likely to achieve successful reperfusion, probably due to selection bias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A recent trial demonstrated that local intra-arterial thrombolytics during endovascular thrombectomy improved patient outcomes. However, it is uncertain how often intra-arterial thrombolytics are used and whether this positive effect is also present in daily clinical practice.

WHAT THIS STUDY ADDS

⇒ In this non-randomised, observational study from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry, local intra-arterial thrombolytics were rarely used. In the relatively small study sample, no statistical difference was detected between groups in the rate of favourable functional outcome or symptomatic intracranial haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ As local intra-arterial thrombolytics were rarely used and were not associated with favourable outcome, larger studies are needed to confirm a potential beneficial effect.

INTRODUCTION

Treatment of acute ischaemic stroke has been the centre of attention in recent decades. Starting from 1990, intracranial thrombi were treated by administration of systemic intravenous thrombolysis or local intra-arterial (IA) thrombolytics.^{1–5} Intravenous thrombolysis became standard of care after publication of the National Institute of Neurological Disorders and Stroke and European Cooperative Acute Stroke Study trials.^{4,5} In the years that followed, the effectiveness and safety of mechanical endovascular thrombectomy (EVT) was proven for patients with a large-vessel occlusion as an adjunct to intravenous thrombolysis.^{6–11}

Despite the success of EVT, approximately 55% of the patients are functionally dependent or deceased at 90 days after EVT.¹¹ This may be partially explained by incomplete macrovascular recanalisation or incomplete microvascular reperfusion.¹² Incomplete macrovascular recanalisation may be due to technical difficulties regarding clot removal, such as thrombus fragmentation to inaccessible distal territories,¹³ fibrin-rich thrombus composition¹⁴ and anatomical challenges, such as tortuous arteries.¹⁵ Incomplete microvascular reperfusion has been related to the presence of microthrombi or neutrophil extracellular traps.¹⁶ To improve macrovascular recanalisation rates, microvascular reperfusion and subsequently functional outcomes, local IA thrombolytics may be administered during EVT.

In the Prolyse in Acute Cerebral Thromboembolism¹ 2 and prematurely terminated Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial³ trials conducted before the introduction of EVT with stent retrievers and aspiration catheters, better functional outcomes and reperfusion rates were observed in patients treated with local IA thrombolytics than in patients treated without. Recent observational studies reported improved outcomes after use of local IA thrombolytics as adjuvant revascularisation attempt during EVT.^{17–19} These latter results could, however, not be confirmed by a meta-analysis.²⁰ Moreover, despite growing evidence on the safety of IA thrombolytics, there still is a fear of an increased risk of intracranial haemorrhage.^{17–23}

In this study, we analysed how often local IA thrombolytics were used during EVT in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry and whether IA thrombolytics were associated with improved functional outcome. We further assessed technical and safety outcomes compared with EVT without IA thrombolytics.

METHODS

Study design

This is a non-randomised, observational study of prospectively collected data from the MR CLEAN Registry between March 2014 and November 2017. The MR CLEAN Registry is a multicentre, observational study in which patients who were treated endovascularly (defined as arterial puncture in the angiography suite) for a large-vessel occlusion in the Netherlands were enrolled. The study design and patient eligibility criteria have been reported previously.²⁴

The medical ethics committee of the Erasmus University Medical Centre Rotterdam in the Netherlands evaluated the study and granted permission to carry out the study as an observational registry (MEC-2014-235).

Data will not be made available to other researchers as no patient approval has been obtained for sharing data. Syntax files will be made available from the corresponding author on reasonable request.

Participants

Patients with an acute ischaemic stroke due to a proximal occlusion in the anterior circulation who underwent EVT (defined as an attempt to remove or dissolve the intracranial occlusion by thrombectomy or local IA thrombolytics) were included. Exclusion criteria were age under 18 years, EVT in a non-MR CLEAN trial centre, initiation of EVT more than 6.5 hours after onset of symptoms, a prestroke modified Rankin Scale (mRS) score >2 and missing data on administration of local IA thrombolytics. The choice of interventional technique, use of local IA urokinase or alteplase and dose was left to the discretion of the interventionist.

Outcome measurement

The primary endpoint was favourable functional outcome, defined as an mRS score of ≤ 2 at 90 days after EVT, reflecting independency for activities of daily living.²⁵

The secondary endpoints were successful reperfusion, excellent reperfusion, early neurological recovery and occurrence of symptomatic intracranial haemorrhage (sICH). Successful reperfusion was defined as an extended Thrombolysis In Cerebral Infarction (eTICI) score of $\geq 2B$ immediately after EVT. Excellent reperfusion was defined as an eTICI score of $\geq 2C$ immediately after EVT.²⁶ If the anteroposterior or lateral digital subtraction angiography (DSA) run immediately after EVT was unavailable, the assessment was based on only one DSA view with an eTICI score of 2A being the highest possible grading.²⁴ Early neurological recovery was defined as a postprocedural National Institutes of Health Stroke Scale (NIHSS) score of 0 or 1 within 24 hours, or a decrease of 8 points relative to baseline.⁸ An intracranial haemorrhage was considered to be symptomatic if patients deteriorated neurologically (a decline of at least 4 points on the NIHSS) or died within 90 days after EVT and the haemorrhage was related to the clinical deterioration (according to the Heidelberg criteria).^{24 27}

Data collection

A core lab, blinded to the clinical characteristics and outcome (except for symptom side), evaluated imaging data on location of the intracranial occlusion, collateral status, time from stroke onset to recanalisation or last contrast bolus, eTICI score before and after EVT and presence of sICH within 90 days after EVT.

For each patient, data on revascularisation attempts during EVT were registered. For the first three thrombectomy passes, it was recorded in the MR CLEAN Registry what the passes entailed (local IA thrombolytics, stent retriever or aspiration). Also, procedural reports were included in the database. From these variables, we could extract whether or not IA thrombolytics had been administered during EVT. Local IA thrombolytics were administered during a primary revascularisation attempt if no prior thrombectomy passes had been performed. Local IA thrombolytics were administered during an adjuvant

revascularisation attempt if prior thrombectomy passes had been performed.

Additional reassessment of DSA images was performed by two neurointerventionists (MJ and RB) to acquire data on the most proximal location of the occlusion for which IA thrombolytics were administered. An occlusion was considered to be located proximally in case of an obstruction in the intracranial internal carotid artery, M1 or M2 segment, A1 or A2 segment or anterior communicating artery. An occlusion was considered to be located distally in case of an occlusion in the M3 of M4 segment, posterior communicating artery or posterior cerebral artery. Furthermore, additional data were collected on the procedural use of heparin. Procedural use of heparin was defined as administration of heparin either as a single bolus or continuously in saline flush during EVT.²⁸

Statistical analysis

Baseline characteristics, procedural characteristics and outcomes were presented for patients treated with and without local IA thrombolytics.

Based on previous data,²⁹ a sample size of 172 patients (86 patients per group) would have been required to detect an absolute difference in the rate of good functional outcome of 19%, assuming the rate of favourable functional outcome in the control group to be 63% (as was observed in the Chemical Optimization of Cerebral Embolectomy (CHOICE) trial),²⁹ to achieve a significance level of 5% (two-sided) and a power of 80%.

To facilitate statistical comparisons despite the small number of observations in some of the categories, the mRS score was dichotomised into favourable and poor functional outcome, and the eTICI score into successful and unsuccessful reperfusion, and into excellent and non-excellent reperfusion. Univariable and multivariable logistic regression analyses were performed to analyse the association between local IA thrombolytics and primary and secondary endpoints.

For the primary endpoint, three stratified analyses were conducted to test for interaction between IA thrombolytics and intravenous thrombolysis, IA thrombolytics and procedural use of heparin and IA thrombolytics and EVT before versus after 1 January 2016. The significance of the interaction terms was tested in logistic regression models that consisted of the separate predictors and their joined effect. Furthermore, within the group of patients who were treated with local IA thrombolytics, three subgroup analyses were performed. We determined whether administration of local IA thrombolytics as primary revascularisation attempt was associated with favourable functional outcome or with successful reperfusion, and whether administration of local IA thrombolytics for a distal occlusion was associated with favourable functional outcome. An association between IA thrombolytics for a distal occlusion and successful reperfusion could not be analysed due to limited number of observations.

For the secondary endpoints successful reperfusion and excellent reperfusion, a sensitivity analysis was conducted

in which patients with a missing final two-directional DSA run were excluded.

In the multivariable analyses, results were adjusted for age, a medical history of atrial fibrillation and previous stroke, use of anticoagulation, NIHSS score at baseline, collateral score, intravenous thrombolysis, procedural use of heparin and time from groin puncture to recanalisation or last contrast bolus. For the primary endpoint, an additional multivariable analysis was conducted in which we adjusted for the aforementioned covariables and the postprocedural reperfusion status (eTICI score on a categorical scale) in an attempt to further reduce the selection bias (we hypothesised that patients treated with IA thrombolytics who initially had a poor TICI score, were more likely to have a favourable outcome due to delayed reperfusion). In the subgroup analyses, we only adjusted for NIHSS score at baseline and time from groin puncture to recanalisation or last contrast bolus due to the limited sample size. The choice of the covariables was based on standard adjustments,²⁴ and in addition on generally known associations related to stroke outcomes and significant differences that we found between the groups treated with and without local IA thrombolytics. Results of the logistic regression analyses were displayed as adjusted OR (aOR) with 95% CI.

Missing data were imputed using multiple imputations by chained equations. Statistical significance was set to $p < 0.05$. Analyses were performed with SPSS Statistics V.23.0 software (IBM, Armonk, New York).

RESULTS

In total, 3637 patients with acute ischaemic stroke were treated endovascularly in the Netherlands between March 2014 and November 2017. Of the 3180 patients who were included in the analysis of the MR CLEAN Registry, 2263 patients were eligible for inclusion in this study: 95 (4.2%) patients were treated with local IA thrombolytics and 2168 (96%) patients were treated without local IA thrombolytics (figure 1).

Baseline and procedural characteristics

Patients treated with local IA thrombolytics were younger, less likely to use anticoagulation, less often treated with a stent retriever or aspiration and had a longer duration from groin puncture to recanalisation or last contrast bolus. The number of revascularisation attempts, which included treatment with stent retrievers, aspiration or local IA thrombolytics, did not differ between patients treated with and without IA thrombolytics (table 1 and table 2).

The IA thrombolytics administered were urokinase ($n=63/95$ (66%)) or alteplase ($n=32/95$ (34%)), and the median doses were 250 000 IU (IQR, 193 750–250 000) and 20 mg (IQR, 12–20), respectively (table 2).

IA thrombolytics were administered more frequently as adjuvant than as primary revascularisation attempt ($n=65/91$ (71%) vs $n=26/91$ (29%)) and more frequently

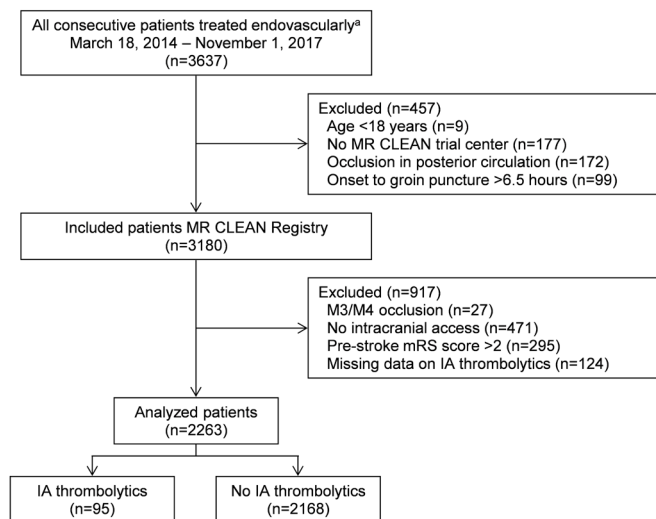


Figure 1 Flowchart of included patients. IA, intra-arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; M3, middle cerebral artery, third segment; M4, middle cerebral artery, fourth segment; mRS, modified Rankin Scale; n, number. ^aEndovascularly was defined as arterial puncture in the angiography suite.

for proximal than for distal occlusions ($n=67/88$ (76%) vs $n=21/88$ (24%)). IA thrombolytics as primary revascularisation attempt were administered for both proximal ($n=18/26$, 69%) and distal ($n=8/26$, 31%) occlusions. For adjuvant revascularisation attempts, IA thrombolytics were also administered for both proximal ($n=47/60$, 78%) and distal ($n=13/60$, 22%) occlusions (online supplemental table S1).

Outcome data

Primary endpoint

We observed comparable rates of favourable functional outcome between the groups treated with and without IA thrombolytics (49% vs 44%, respectively; OR, 1.18; 95% CI 0.78 to 1.80) (table 3, figure 2). After adjustments, no association was found between IA thrombolytics and favourable functional outcome (aOR, 1.16; 95% CI 0.71 to 1.90) (table 3). The direction of the results remained equal after additional adjustment for eTICI score (aOR, 1.31; 95% CI 0.79 to 2.19).

There was no significant interaction between IA thrombolytics and intravenous thrombolysis related to favourable functional outcome ($p=0.51$) and between IA thrombolytics and procedural use of heparin related to favourable functional outcome ($p=0.88$) (online supplemental figure S1). IA thrombolytics were less often used in EVT procedures performed after January 2016 ($n=53/1539$ (3.4%) vs $n=42/724$ [5.8%]; $p<0.01$). There was no significant interaction with IA thrombolytics related to favourable functional outcome ($p=0.27$) (online supplemental figure S1).

Secondary endpoints

Successful reperfusion was less often observed in patients treated with IA thrombolytics than in patients treated without (49% vs 67%, respectively; OR, 0.46; 95% CI 0.30 to 0.70; aOR, 0.57; 95% CI 0.36 to 0.90) (table 3). Compared with patients not treated with IA thrombolytics, the reperfusion status of patients treated with IA thrombolytics was numerically more often scored with a maximum eTICI score of 2A due to unavailability of a final anteroposterior or lateral DSA run ($n=258/2135$ (12%) vs $n=17/92$ (18%), respectively, $p=0.07$). Exclusion of those patients with a missing final two-directional DSA run did not change the direction of the results in both the unadjusted analysis (OR, 0.46; 95% CI 0.29 to 0.73) and adjusted analysis (aOR, 0.59; 95% CI 0.35 to 0.99).

Excellent reperfusion was also less often achieved in patients treated with IA thrombolytics than in patients treated without (32% vs 47%, respectively; OR, 0.54; 95% CI 0.35 to 0.85). In the adjusted analysis, the association between IA thrombolytics and excellent reperfusion did no longer exist (aOR, 0.68; 95% CI 0.43 to 1.09) (table 3). Exclusion of patients with a missing final two-directional DSA run did not change the directions of the results (OR, 0.58; 95% CI 0.36 to 0.93 and aOR, 0.74; 95% CI 0.45 to 1.21).

For patients treated with and without IA thrombolytics, the rates of early neurological recovery and sICH were comparable, and no associations were observed (table 3).

Subgroup analyses

Within the IA thrombolytics group, comparable proportions of favourable functional outcome ($n=13/24$ (54%) vs $n=28/60$ (47%), respectively; OR, 1.23; 95% CI 0.49 to 3.11) and successful reperfusion ($n=10/26$ (38%) vs $n=35/63$ (56%), respectively; OR, 0.51; 95% CI 0.20 to 1.29) were observed between patients who received IA thrombolytics as primary or adjuvant revascularisation attempt. Similarly for patients with a proximal or distal occlusion, the rate of favourable functional outcome was almost equal ($n=30/63$ (48%) and $n=9/19$ (47%), respectively; OR, 1.01; 95% CI 0.37 to 2.76).

In the adjusted analyses, no associations were found between IA thrombolytics as primary revascularisation attempt and favourable functional outcome (aOR, 0.83; 95% CI 0.30 to 2.33). Successful reperfusion was less often observed in patients treated with IA thrombolytics as primary revascularisation attempt than in those treated with IA thrombolytics as adjuvant revascularisation attempt (aOR, 0.34; 95% CI 0.12 to 0.95). Furthermore, there was no association between IA thrombolytics for distal occlusions and favourable functional outcome (aOR, 0.79; 95% CI 0.26 to 2.43) (online supplemental tables S2–S5).

DISCUSSION

Local IA thrombolytics were rarely used in the MR CLEAN Registry. No statistical difference was detected between

Table 1 Baseline characteristics

Characteristics	IA thrombolytics (n=95)	No IA thrombolytics (n=2168)	P value
Age, median (IQR), years	67 (56–76)	71 (60–79)	0.02
Male, n (%)	50/95 (53)	1186/2168 (55)	0.69
Medical history, n (%)			
Atrial fibrillation	14/95 (14.7)	491/2139 (23.0)	0.06
Diabetes mellitus	10/95 (10.5)	310/2153 (14.4)	0.29
Hypercholesterolemia	23/95 (24.2)	624/2067 (30.2)	0.21
Hypertension	43/95 (45.3)	1080/2126 (50.8)	0.29
Myocardial infarction	12/95 (12.6)	285/2129 (13.4)	0.83
Previous stroke	8/95 (8.4)	322/2150 (15.0)	0.08
Current smoker, n (%)	26/70 (37.1)	470/1664 (28.2)	0.11
Use of antiplatelet, n (%)	26/95 (27.4)	638/2138 (29.8)	0.61
Use of anticoagulation, n (%)	8/95 (8.4)	371/2151 (17.2)	0.03
Initial location occlusion on CTA, n (%)			
Left hemisphere	57/95 (60.0)	1117/2168 (51.5)	0.11
Intracranial ICA	30/95 (31.6)	590/2164 (27.3)	0.19
M1	46/95 (48.4)	1287/2164 (59.5)	
M2	19/95 (20.0)	281/2164 (13.0)	
A1	0/95 (0)	3/2164 (0.1)	
A2	0/95 (0)	3/2164 (0.1)	
Collateral status, n (%)			
Absent collaterals	6/91 (6.6)	136/2050 (6.6)	0.68
<50% of occluded area	32/91 (35.2)	752/2050 (36.7)	
50%–99% of occluded area	32/91 (35.2)	791/2050 (38.6)	
100% of occluded area	21/91 (23.1)	371/2050 (18.1)	
NIHSS score, median (IQR)	15 (9–19)	16 (11–19)	0.24
Intravenous thrombolysis, n (%)	77/95 (81.1)	1673/2163 (77.3)	0.40
Pre-intervention SBP, mean (SD), mm Hg	152 (27)	149 (25)	0.26

A1, anterior cerebral artery, first segment; A2, anterior cerebral artery, second segment; CTA, computed tomography angiography; IA, intra-arterial; ICA, internal carotid artery; M1, middle cerebral artery, first segment; M2, middle cerebral artery, second segment; n, number; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

groups in the rate of favourable functional outcome or sICH. Patients whom required and underwent IA thrombolytics were patients less likely to achieve successful reperfusion.

Overall, IA thrombolytics were administered in 4.2% patients of the included patients, which was substantially lower compared with other observational studies (10%). This discrepancy could be the result of different preferences and experiences of the interventionists.

Based on the rationale behind administration of local IA thrombolytics, namely, improving recanalisation rates and microvascular reperfusion, one could have expected an association between IA thrombolytics and favourable functional outcome at 90 days after EVT. This hypothesis was neither confirmed by our primary analysis, nor in subgroup analyses on additional periprocedural treatment (use of intravenous thrombolysis and use of heparin), moment of treatment (EVT before or after

January 2016), treatment approaches of local IA thrombolytics (primary or adjuvant revascularisation attempt) and indications for local IA thrombolytics (distal or proximal occlusion). Our results were consistent with a recently published meta-analysis, in which the use of local IA thrombolytics as adjuvant revascularisation attempt was not found to be associated with improved functional outcomes. Comparable to our study, the meta-analysis was only based on observational data, and, therefore, the results were considered to be inconclusive.²⁰ In the CHOICE trial, the rate of favourable functional outcome (defined as mRS score of 0 or 1) was found to be higher in patients treated with than without IA alteplase (59.0% (n=36/61) vs 40.4% (n=21/52); adjusted risk difference, 18.4%; 95% CI 0.3% to 36.4%). The differences in functional outcome between our study and the CHOICE trial may be due to the location and size of the intracranial occlusions. In our study, for both primary and adjuvant

**Table 2** Procedural variables

Characteristics	IA thrombolytics (n=95)	No IA thrombolytics (n=2168)	P value
Thrombectomy technique, n (%) [*]			
Stent retriever	61/95 (64.2)	1647/2168 (76.0)	0.01
Aspiration	21/95 (22.1)	884/2168 (40.8)	<0.001
Other	9/95 (9.5)	141/2168 (6.5)	0.26
Total revascularisation attempts, n (%)			
1	19/67 (28.4)	803/1994 (40.3)	0.09
2	24/67 (35.8)	470/1994 (23.6)	
3	10/67 (14.9)	316/1994 (15.8)	
≥4	14/67 (20.9)	405/1994 (20.3)	
IA thrombolytics, n (%)			
Urokinase†	63/95 (66.3)	N/A	
Alteplase‡	32/95 (33.7)	N/A	
IA thrombolytics attempt, n (%)			
Primary attempt	26/91 (28.6)	N/A	
Adjuvant attempt	65/91 (71.4)	N/A	
Location occlusion IA thrombolytics, n (%)			
Proximal occlusion	67/88 (76.1)	N/A	
Distal occlusion	21/88 (23.9)	N/A	
General anaesthesia, n (%)	32/90 (35.6)	562/2091 (26.9)	0.07
Time from stroke onset to groin puncture, median (IQR), minutes	200 (154–250)	190 (150–245)	0.37
Time from groin puncture to recanalisation or last contrast bolus, median (IQR), minutes	72 (58–108)	60 (40–85)	<0.001
[*] Sum may be less than 100% due to administration of IA thrombolytics only, or exceed 100% due to a combination of treatment techniques.			
†Median dose was 250 000 IU (IQR, 193 750–250 000).			
‡Median dose was 20 mg (IQR, 12–20).			
IA, intra-arterial; n, number; N/A, not applicable.			

revascularisation attempts, proximal occlusions more often constituted the target lesion. In the CHOICE trial, a positive treatment effect on functional outcome was particularly found in the subgroup of patients with an eTICI score of 2C or 3. Our study population may, therefore, have consisted of patients in whom clot removal was more difficult and treatment response to local IA thrombolytics was lower. Since the CHOICE trial only included patients with successful reperfusion and was terminated early due to implications of the COVID-19 pandemic, the results cannot be generalised to patients with incomplete reperfusion (eTICI scores of ≤2B).²⁹

Contrary to the supposed therapeutic effect of local IA thrombolytics on recanalisation, successful reperfusion (and excellent reperfusion in the unadjusted analysis) was less often achieved in patients treated with than in those treated without IA thrombolytics. This overall result could be due to the low rate of successful recanalisation among the subgroup of patients treated with IA thrombolytics as primary revascularisation attempt. Importantly, the inverse association between local IA thrombolytics and successful reperfusion did not translate into less

favourable outcome. The discrepancy between the supposed effect of IA thrombolytics and our results suggests that the impaired recanalisation with local IA thrombolytics may be explained by other factors. First, we hypothesised that the reperfusion status of patients treated with IA thrombolytics might have been underestimated, as it was more often scored with a maximum eTICI score of 2A due to unavailability of a final two-directional DSA run. Our hypothesis was not confirmed, however, in the sensitivity analysis. Second, due to the non-randomised design, the local IA thrombolytics group may have consisted of patients with more ‘difficult’ procedures in whom successful reperfusion could not be achieved after intravenous thrombolysis or thrombectomy attempts. This latter argument may also hold for other observational studies, which predominantly showed comparable reperfusion rates between patients treated with and without IA thrombolytics as adjuvant revascularisation attempt.^{17 20–23}

We did not find an association between IA thrombolytics and sICH, even though the majority of patients were previously treated with intravenous thrombolysis

Table 3 Secondary outcome variables

Characteristics	IA thrombolytics (n=95)	No IA thrombolytics (n=2168)	OR	95% CI	aOR*	95% CI
Favourable functional outcome, n (%)†	43/88 (48.9)	897/2018 (44.4)	1.18	0.78 to 1.80	1.16	0.71 to 1.90
Successful reperfusion, n (%)‡	45/92 (48.9)	1429/2120 (67.4)	0.46	0.30 to 0.70	0.57	0.36 to 0.90
Excellent reperfusion, n (%)§	29/92 (31.5)	992/2120 (46.8)	0.54	0.35 to 0.85	0.68	0.43 to 1.09
Early neurological recovery, n (%)¶	6/91 (6.6)	153/1962 (7.8)	0.83	0.36 to 1.93	0.96	0.40 to 2.29
Symptomatic intracranial haemorrhage, n (%)**	5/95 (5.3)	129/2168 (6.0)	0.88	0.35 to 2.20	0.82	0.32 to 2.10

*Results were adjusted for age, a medical history of atrial fibrillation and previous stroke, use of anticoagulation, National Institutes of Health Stroke Scale score at baseline, collateral score, intravenous thrombolysis, procedural use of heparin and time from groin puncture to recanalisation or last contrast bolus.

†Favourable functional outcome was defined as an modified Rankin Scale score of ≤ 2 at 90 days after EVT.

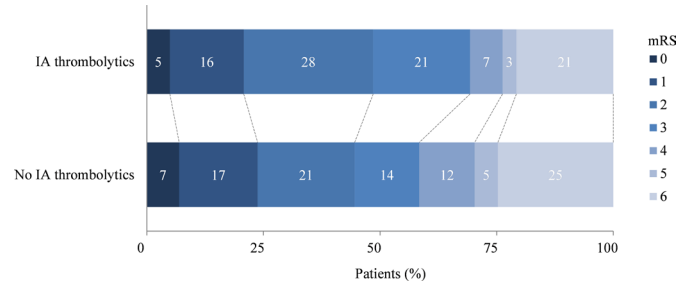
‡Successful reperfusion was defined as extended Thrombolysis In Cerebral Infarction score of $\geq 2B$.

§Excellent reperfusion was defined as extended Thrombolysis In Cerebral Infarction score of $\geq 2C$.

¶Early neurological recovery was defined as National Institutes of Health Stroke Scale score of 0 or 1 within 24 hours postprocedural, or a decrease of 8 points relative to baseline.

**An intracranial haemorrhage was considered to be symptomatic if patients deteriorated neurologically (a decline of at least four points on the National Institutes of Health Stroke Scale) or died within 90 days after endovascular thrombectomy and the haemorrhage was related to the clinical deterioration (according to the Heidelberg criteria).

aOR, adjusted OR; IA, intra-arterial; n, number.


Figure 2 Distribution on the modified Rankin Scale. IA, intra-arterial; mRS, modified Rankin Scale.

and procedure duration of EVT itself was longer. Previous studies focusing on IA thrombolytics as primary revascularisation attempt showed an increased risk of intracranial haemorrhages after administration of IA thrombolytics,²³⁰ while in most of the recent studies (focusing on IA thrombolytics as adjuvant revascularisation attempt), this association was no longer being observed.^{17 19–23} The comparable sICH rates that were found in recent studies, and also in our study, could be the result of the increased experience of interventionists and the more advanced devices in use today, reducing the risk of vessel wall injury. The influence of the type and dose of IA thrombolytics on sICH is unclear. In a meta-analysis of five randomised clinical trials, an increased risk of sICH was observed in patients treated with IA thrombolytics, whereas this was not found in any of the individual studies.³⁰ The increased risk of sICH might be the result of the higher dose of IA thrombolytics used in some of the studies, however, its impact on the risk of sICH could not be reliably assessed due to the different eligibility criteria and protocols used.^{3 31 32}

Our study has several limitations. First, results might have been affected by selection bias and confounding by indication as, due to the non-randomised, retrospective study design, no uniform protocol existed on the use of local IA thrombolytics, the type of thrombolytic agent and dose. The control group may therefore not have entirely matched the intervention group in terms of ‘difficulty’ of the EVT procedure and impossible or failed thrombectomy attempts (the latter was, however, not reflected in the number of revascularisation attempts). This could potentially have led to an underestimation of the rate of favourable functional outcome in patients treated with local IA thrombolytics. Second, for four patients, the exact revascularisation attempt of local IA thrombolytics was unknown. Moreover, for all patients, eTICI scores immediately before and after administration of IA thrombolytics were lacking. DSA images were, therefore, reassessed, but unfortunately, the exact timing of administration of IA thrombolytics, and consequently the eTICI scores before and after each attempt, could not be determined. Unavailability of the data hampered more accurate composition of the control group and determination of the precise effect of IA thrombolytics on reperfusion rates. Third, the effect of local IA thrombolytics on microvascular reperfusion status could not be

assessed because the protocol of the MR CLEAN Registry did not include postprocedural perfusion imaging^{12 33} and/or transcranial Doppler.³⁴ Fourth, although we did our best efforts to minimise missing data on the treatment with local IA thrombolytics, 124 patients had to be excluded, which may have biased the results in unpredictable ways and influenced the precision of the effect estimates. Finally, some of the secondary endpoints could not be analysed separately for patients treated with IA thrombolytics as primary versus adjuvant recanalisation attempt and for a distal versus proximal occlusion due to small sample sizes. Also, the effect of the type and dose of thrombolytic agents could not be studied due to small sample sizes. Furthermore, as the underlying reasons to administer local IA thrombolytics were not reported in the MR CLEAN Registry, we could only hypothesise on the indications. These limited data may have hampered an in-depth understanding of the results.

CONCLUSION

Local IA thrombolytics were rarely used in the MR CLEAN Registry. In the relatively small study sample, no statistical difference was observed between groups in the rate of favourable functional outcome or sICH. Patients whom required and underwent IA thrombolytics were patients less likely to achieve successful reperfusion, probably due to selection bias.

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REFERENCES

- del Zoppo GJ, Higashida RT, Furlan AJ, *et al*. Proact: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke* 1998;29:4–11.
- Furlan A, Higashida R, Wechsler L, *et al*. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. *JAMA* 1999;282:2003–11.
- Ogawa A, Mori E, Minematsu K, *et al*. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (melt) Japan. *Stroke* 2007;38:2633–9.
- National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–8.
- Hacke W, Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European cooperative acute stroke study (ECASS). *JAMA* 1995;274:1017–25.
- Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
- Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–30.
- Campbell BCV, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009–18.
- Saver JL, Goyal M, Bonafe A, *et al*. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372:2285–95.

- 10 Jovin TG, Chamorro A, Cobo E, *et al*. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;372:2296–306.
- 11 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
- 12 Ng FC, Churilov L, Yassi N, *et al*. Prevalence and significance of impaired microvascular tissue reperfusion despite macrovascular angiographic reperfusion (no-reflow). *Neurology* 2022;98:e790–801.
- 13 Kaesmacher J, Boeckh-Behrens T, Simon S, *et al*. Risk of thrombus fragmentation during endovascular stroke treatment. *AJNR Am J Neuroradiol* 2017;38:991–8.
- 14 Gunning GM, McArdle K, Mirza M, *et al*. Clot friction variation with fibrin content; implications for resistance to thrombectomy. *J Neurointerv Surg* 2018;10:34–8.
- 15 Kim BM. Causes and solutions of endovascular treatment failure. *J Stroke* 2017;19:131–42.
- 16 Dalkara T, Arsava EM. Can restoring incomplete microcirculatory reperfusion improve stroke outcome after thrombolysis? *J Cereb Blood Flow Metab* 2012;32:2091–9.
- 17 Yi T-Y, Chen W-H, Wu Y-M, TY Y, YM W, *et al*. Adjuvant intra-arterial rt-PA injection at the initially deployed solitaire stent enhances the efficacy of mechanical thrombectomy in acute ischemic stroke. *J Neurol Sci* 2018;386:69–73.
- 18 Kaesmacher J, Abdullayev N, Maamari B, *et al*. Safety and angiographic efficacy of intra-arterial fibrinolytics as adjunct to mechanical thrombectomy: results from the infinity registry. *J Stroke* 2021;23:91–102.
- 19 Kaesmacher J, Bellwald S, Dobrocky T, *et al*. Safety and efficacy of intra-arterial urokinase after failed, unsuccessful, or incomplete mechanical thrombectomy in anterior circulation large-vessel occlusion stroke. *JAMA Neurol* 2020;77:318–26.
- 20 Kaesmacher J, Meinel TR, Kurmann C, *et al*. Safety and efficacy of intra-arterial fibrinolytics as adjunct to mechanical thrombectomy: a systematic review and meta-analysis of observational data. *J Neurointerv Surg* 2021;13:1073–80.
- 21 Zaidi SF, Castonguay AC, Jumaa MA, *et al*. Intraarterial thrombolysis as rescue therapy for large vessel occlusions. *Stroke* 2019;50:1003–6.
- 22 Anadani M, Ajinkya S, Alawieh A, *et al*. Intra-arterial tissue plasminogen activator is a safe rescue therapy with mechanical thrombectomy. *World Neurosurg* 2019;123:e604–8.
- 23 Heiferman DM, Li DD, Pecoraro NC, *et al*. Intra-arterial alteplase thrombolysis during mechanical thrombectomy for acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2017;26:3004–8.
- 24 Jansen IGH, Mulder MJHL, Goldhoorn R-JB, *et al*. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (Mr clean registry). *BMJ* 2018;360:k949.
- 25 van Swieten JC, Koudstaal PJ, Visser MC, *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7.
- 26 Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;34:e109–37.
- 27 von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
- 28 Benali F, Hinsenveld WH, van der Leij C, *et al*. Effect of heparinized flush concentration on safety and efficacy during endovascular thrombectomy for acute ischemic stroke: results from the MR CLEAN Registry. *Cardiovasc Intervent Radiol* 2021;44:750–5.
- 29 Renú A, Millán M, San Román L, *et al*. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the choice randomized clinical trial. *JAMA* 2022;327:826–35.
- 30 Lee M, Hong K-S, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. *Stroke* 2010;41:932–7.
- 31 Keris V, Rudnicka S, Vorona V, *et al*. Combined intraarterial/intravenous thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol* 2001;22:352–8.
- 32 Macleod MR, Davis SM, Mitchell PJ, *et al*. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. *Cerebrovasc Dis* 2005;20:12–17.
- 33 Rubiera M, Garcia-Tornel A, Olivé-Gadea M, *et al*. Computed tomography perfusion after thrombectomy: an immediate surrogate marker of outcome after recanalization in acute stroke. *Stroke* 2020;51:1736–42.
- 34 Ng FC, Coulton B, Chambers B, *et al*. Persistently elevated microvascular resistance postrecanalization. *Stroke* 2018;49:2512–5.