Intravenous Thrombolysis Is Not Associated with Increased Time to Endovascular Treatment

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Keywords

Acute stroke intervention · Endovascular treatment of acute stroke · Intravenous thrombolytic therapy of stroke · Stroke organization · Workflow

Abstract

Background: Endovascular treatment (EVT) with or without intravenous thrombolysis (IVT) is effective and safe in ischemic stroke caused by large vessel occlusion, but IVT might delay time to EVT or increase risk of intracranial hemorrhage (ICH). We assessed the influence of prior IVT on time to treatment and risk of ICH in patients treated with EVT. **Methods:** We analyzed data from the MR CLEAN Registry and included patients with an anterior circulation occlusion treated with EVT who presented directly to an intervention center, between 2014 and 2017. Primary endpoint was the

door to groin time. Secondary outcomes were workflow time intervals and safety outcomes. We compared patients who received EVT only with patients who received IVT prior to EVT. **Results:** We included 1,427 patients directly referred to an intervention center of whom 1,023 (72%) received IVT + EVT. Adjusted door to CT imaging and door to groin time were shorter in IVT + EVT patients (difference 5.7 min [95% CI: 4.6–6.8] and 7.0 min [95% CI: 2.4–12], respectively) while CT imaging to groin time was similar between the groups. Early recanalization on digital subtraction angiography before EVT was seen more often after prior IVT (11 vs. 5.2%, aOR 2.4 [95% CI: 1.4–4.2]). Rates of symptomatic ICH were similar. **Conclusion:** Prior IVT did not delay door to groin times and was associated with higher rates of early recanalization, without increasing the risk of ICH. Our results do not warrant withholding IVT prior to EVT.

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Introduction

Intravenous thrombolysis (IVT) has long been the only available evidence-based recanalization therapy in acute ischemic stroke (AIS) [1]. After 2015, endovascular treatment (EVT) has become an additional treatment modality for anterior circulation AIS caused by large vessel occlusion (LVO) [2]. The majority of patients treated in these trials received IVT prior to EVT.

The treatment effect of both IVT and EVT is strongly time dependent. Every hour delay to EVT decreases the chance of good functional outcome by 5.3% and every hour delay in reperfusion by 7.7% [3]. There is an open question whether withholding IVT in patients with LVO could potentially lead to a faster workflow to EVT as it omits IVT decision making which may be associated with large delays [4, 5]. Avoiding this delay may result in better functional outcome and could decrease rates of intracranial hemorrhage.

Meta-analyses on IVT prior to EVT have shown mixed results where several post hoc analyses of randomized EVT trials and registries showed shorter times to treatment (4/11 of the included studies) when IVT was withheld, while others showed either no difference (2/11 of the included studies) or even longer times to treatment without IVT (5/11 of the included studies) [6, 7]. This might be explained by small sample sizes, differences in baseline characteristics or stroke logistics, and the inclusion of transferred patients where IVT was given as a bridging therapy. Our aim was to assess the influence of prior IVT on detailed workflow intervals and door to groin puncture time in a large sample set in daily practice.

Methods

Design and Patient Enrollment

We used data from the MR CLEAN Registry, a prospective and observational study in 17 centers that perform EVT for AIS in the Netherlands. Patient data were retrospectively analyzed from March 16, 2014, up to November 1, 2017. Recent results from an earlier part of this dataset containing data up to June 2016 analyzed clinical outcomes and some workflow outcomes [8]. This current analysis differs in the use of a larger dataset and inclusion of more detailed workflow intervals. We excluded patients referred from primary stroke centers, as IVT is often given as a bridging therapy during transfer which is not the topic of the current study.

Definitions and Measures

We grouped patients based on whether they received IVT + EVT or EVT only. Primary endpoint was emergency room (ER)

Table 1. Baseline characteristics

	EVT only, <i>n</i> = 404	IVT + EVT, <i>n</i> = 1,023
Age, median (IQR)	73 (63–81)	71 (59–80)
Men	189/404 (47)	557/1,023 (54)
NIHSS at baseline, median (IQR) <i>n</i> = 1,397	15 (10–19)	16 (11–20)
Pre-mRS >2	81/396 (20)	116/1,011 (11)
History of		
Atrial fibrillation	164/401 (41)	170/1,011 (17)
Hypertension	211/395 (53)	500/1,010 (50)
Hypercholesterolemia	138/396 (35)	321/1,000 (32)
Diabetes mellitus	62/401 (15)	159/1,017 (16)
Previous stroke	115/403 (29)	138/1,017 (14)
Myocardial infarction	61/398 (15)	134/1,010 (13)
Antiplatelet use	121/403 (30)	323/1,016 (32)
Anticoagulation use	158/404 (39)	75/1,021 (7.4)
Local anesthesia only	259/390 (66)	610/952 (64)
Onset to door (<i>n</i> = 1,409)		
Median (IQR)	55 (24–123)	55 (38–93)
Mean (95% CI)	92 (80–103)	74 (70–77)
Door to needle, median (IQR), <i>n</i> = 1,023	N/A	24 (18–33)

Numbers are *n* (%) unless otherwise noted. EVT, endovascular treatment; IVT, intravenous thrombolysis; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; CI, confidence interval.

door entry to groin puncture time (DGT). Secondary endpoints were divided into workflow and safety endpoints.

We analyzed ER door to CT/MR imaging (DIT), CT/MR imaging to groin puncture (IGT), and groin puncture to reperfusion (GRT) times. Reperfusion was defined as achieving an extended treatment in cerebral ischemia (eTICI) of 2B or greater, or time of last contrast bolus as a surrogate when no reperfusion was achieved. If initial digital subtraction angiography (DSA) imaging revealed that the target occlusion was no longer present, this was defined as early recanalization on DSA. If no anesthetic management (general anesthesia or conscious sedation) was performed except for local groin puncture anesthesia, patients were regarded as being treated with local anesthesia only. Intracranial hemorrhage was defined symptomatic (sICH) if patients died or deteriorated neurologically (NIHSS ≥ 4), and the hemorrhage as defined by the Heidelberg bleeding classification was related to the clinical deterioration [9].

Statistical Analysis

We imputed missing data using multiple imputation. Due to nonnormality, workflow endpoints were log_e transformed and analyzed using linear regression. Time intervals were adjusted for age, sex, National Institutes of Health Stroke Scale score, baseline modified Rankin Scale score, systolic blood pressure, anticoagulation (coumarins or direct oral anticoagulants), and periprocedural local anesthesia only. Functional and safety endpoints were analyzed with ordinal regression models and adjusted for all previ-

Fig. 1. Flowchart of MR CLEAN Registry patients selected for analysis. EVT, endovascular treatment; IVT, intravenous thrombolysis.

Fig. 2. Workflow timeline of EVT only versus EVT + IVT treated patients. Times are shown in minutes, and intervals are shown as medians. Overarching workflow intervals (i.e., door to groin time) might not match the sum of individual parts due to summation of medians. EVT, endovascular treatment; IVT, intravenous thrombolysis; DTNT, door to needle time; DGT, door to groin time; Ima, imaging; Reper, reperfusion.

ously mentioned variables and additionally collateral score, time from onset to groin puncture (OGT), and occlusion segment. Statistical analyses were performed using Stata/SE 14.0 (StataCorp, College Station, TX, USA).

Results

Baseline Characteristics

Of the 3,637 patients included in the MR CLEAN Registry, we included 1,427 directly referred patients for current analysis (Fig. 1). IVT + EVT was performed in 1,023 (72%) patients (Table 1). Patients in the IVT + EVT group were slightly younger and more often men and had less

often prestroke disability, atrial fibrillation, previous stroke, or anticoagulant use (Table 1). Median door to IVT time was 24 min (95% CI: 18–33) (Fig. 2).

Primary Endpoint

Door to groin time was shorter in the IVT + EVT group (90 vs. 95 min, $p = 0.02$) (Table 2). After adjusting for baseline variables, door to groin time remained shorter in the IVT + EVT group (difference 7.0 min [95% CI: 2.4–12] or 7%).

Workflow Endpoints

Adjusted door to imaging time was 5.7 min (95% CI: 4.6–6.8) or 35% shorter in the IVT + EVT group while

Table 2. Primary and secondary outcomes

	EVT only, <i>n</i> = 404	IVT + EVT, <i>n</i> = 1,023	<i>p</i> value	Unadjusted β in minutes (95% CI)	Adjusted β in minutes (95% CI)
Door to groin, min	95 (72–132)	90 (70–118)	0.02	–7.1 (–11 to –2.8)	–7.0 (–12 to –2.4)
Onset to groin, min	170 (124–265)	155 (120–213)	<0.01	–17 (–24 to –8.7)	–17 (–26 to –8.7)
Door to CT, min	16 (10–27)	12 (8–18)	<0.01	–5.5 (–6.6 to –4.5)	–5.7 (–6.8 to –4.6)
CT to groin, min	73 (54–101)	75 (57–104)	0.11	2.3 (–2.0 to 6.6)	2.9 (–1.7 to 7.6)
Groin to reperfusion ^b , min	52 (34–79)	51 (32–78)	0.64	–1.4 (–5.1 to 2.3)	–1.8 (–5.8 to 2.7)
	EVT only, <i>n</i> = 404	IVT + EVT, <i>n</i> = 1,023	<i>p</i> value	Unadjusted (c) OR (95% CI)	Adjusted (c) OR (95% CI)
mRS, median (IQR)	2 (4–6)	1 (3–5)	<0.01	1.6 (1.3–2.0)	1.2 (0.9–1.6)
sICH, <i>n</i> (%)	21/404 (5.2)	63/1,023 (6.2)	0.49	1.2 (0.7–2.0)	1.1 (0.7–2.0)
Early recanalization on DSA ^a , <i>n</i> (%)	20/384 (5.2)	110/966 (11)	<0.01	2.3 (1.4–3.8)	2.4 (1.4–4.2)
eTICI score ^{b, c} , <i>n</i> (%)			0.429	1.1 (0.8–1.3)	1.0 (0.8–1.4)
0	22/307 (7.2)	51/729 (7.1)			
1	11/307 (3.6)	15/429 (2.1)			
2A	49/307 (17)	123/729 (17)			
2B	71/307 (23)	180/729 (25)			
2C	54/307 (18)	101/729 (14)			
3	100/307 (33)	259/729 (36)			

On the left are shown unimputed and unadjusted data reported as median (IQR) unless otherwise noted. On the right, the differences in imputed time variables with the EVT-only group as reference are shown. Positive numbers denote a longer workflow interval for the IVT + EVT group. EVT, endovascular treatment; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; CI, confidence interval. ^a Only if intracranial access was achieved (94.6% of patients). ^b Only in patients with a device attempt. ^c Only when 2 directional postprocedure DSA images were available.

imaging to groin time was similar (2.9 min in favor of IVT + EVT [95% CI: –1.7 to 7.6]). Groin to reperfusion time was not significantly different (1.8 min in favor of IVT + EVT [95% CI: –2.7 to 5.8]). Finally, onset to groin time was 17 min (95% CI: 8.7–26) or 10% shorter in the IVT + EVT group.

Functional, Technical, and Safety Endpoints

Unadjusted common odds of a 1 point shift toward better functional outcome on the mRS was 1.6 (95% CI: 1.3–2.0) in favor of EVT + IVT. However, after adjusting for baseline differences this shift was no longer significant (acOR 1.2 [95% CI: 0.9–1.6]) (Table 2). There was a higher adjusted odds of early recanalization on DSA (11 vs. 5.2%, aOR 2.4; 95% CI: 1.4–4.2) after treatment with IVT. In patients in which an actual device attempt was made, there were no differences in reperfusion rate after treatment (eTICI score acOR 1.0 [95% CI: 0.8–1.4]). There were no differences in sICH (5.2 vs. 6.2%; OR 1.1 [95% CI: 0.7–2.0]).

Discussion

In this study, we found that prior IVT was associated with a shorter door to groin time (7.0 min or 7%) compared with EVT only, mainly due to a shorter door to imaging time. The shorter door to imaging time found in IVT + EVT patients might be due to longer decision times in patients ineligible for IVT, reflecting the more complex pathology in these patients, and local protocols might have been focused on IVT + EVT. Imaging to groin times were similar, meaning after LVO detection these patients were processed at a similar speed. Addition of IVT did not shorten groin to reperfusion time but was associated with a higher rate of early recanalization on DSA. The actual early recanalization rate might have been higher as we have information only on patients who received groin puncture and not on patients with improved clinical status due to early recanalization. The ability to achieve good reperfusion rates if a patient was treated with a device or thrombosuction did not seem to be influenced by the concurrent administration of IVT. Although there was a

trend toward better functional outcome in the unadjusted mRS when IVT was given, this trend became nonsignificant after adjusting for baseline imbalances including prestroke dependence.

Previous results from a smaller and earlier sample set of the MR CLEAN Registry demonstrated a slightly longer door to groin time in directly referred patients treated with IVT, while we found a shorter door to groin time in these patients [8]. They did not look at functional and safety outcomes in directly referred patients separately but did demonstrate a higher odds of a favorable shift on the mRS for all (directly referred and transferred) IVT treated patients. Our results are similar although we were not able to demonstrate a significant shift toward better functional outcome after adjusting for baseline imbalances. This difference, as well as the longer door to groin time, might be explained by workflow optimization since our dataset includes more recent patient data up to November 2017. A meta-analysis including 2,920 patients from 12 mostly small single-center studies and 2 larger trials looked at onset to groin times and outcomes between EVT only and EVT + IVT treated patients [6]. We observed shorter onset to groin times in both groups compared to most studies in the meta-analysis. The 4 included studies that observed shorter workflow times when IVT was given generally had larger differences between the 2 groups than our observed 17 min difference. This larger difference could possibly be because these studies investigated patients between 2010 and 2014 when the EVT workflow might not have been optimized, and due to some studies reporting means instead of medians. We were able to demonstrate similar results in functional and safety endpoints compared to the combined estimate of all included studies with a slight improvement in mRS in IVT treated patients and similar risk of sICH. It should be noted that some of these studies included patients transferred from primary stroke centers where IVT is often given as a bridging strategy. Our results might therefore not be directly comparable to these studies. Patients transferred from primary stroke centers often receive part of their diagnostic workup and IVT in the primary stroke center. Therefore, their intervention center door to groin times can be much shorter, leading to a biased result. In our analysis, we looked only at directly referred patients that received their entire diagnostic workup and IVT treatment in the intervention center, reducing this bias.

Other workflow intervals we analyzed (door to imaging and imaging to groin time) suffer from a lack of reported data with few prior studies reporting broadly sim-

ilar time windows [7, 10]. One single-center study in Germany saw shorter door to groin puncture, door to imaging, and imaging to groin puncture times when IVT was given before EVT. Their times were overall shorter, possibly due to the single-center nature of their study [10]. Post hoc analysis of the Solitaire With the Intention for Thrombectomy (SWIFT) and Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) studies saw no difference in door to groin puncture times [7]. They did not look at more detailed workflow intervals. However, in both the single-center German study and the post hoc analysis of SWIFT and STAR patients treated with IVT as a bridging strategy were included.

Door to IVT administration times (DTNT) were short (24 min) compared to previous Dutch studies and studies in stroke networks of different countries [11–13]. Withholding IVT prior to EVT could potentially result in a larger reduction in door to groin time when IVT is withheld in stroke networks with a longer DTNT [3]. However, in case of long DTNTs it is likely that other workflow aspects show large delays as well.

Early recanalization rate was higher when IVT was given (11 vs. 5%). This higher rate of early recanalization is one of the main reasons that IVT is given before EVT and could lead to a higher chance of good outcome [14]. However, in our analysis differences in clinical outcome between IVT + EVT and EVT only were mainly explained by baseline differences. It must be noted that the overall rate of early recanalization was low (11%), showing that in large vessel occlusion anterior circulation stroke patients, the benefit of early recanalization due to IVT is still small [15].

Our study has several strengths including the large number of directly referred patients in a multicenter, nationwide registry of all patients treated with EVT. We had data available not only on onset to groin and door to groin times, but also on intermediate workflow intervals, which allows a more detailed view on intrahospital logistics.

Our main limitation was that IVT was often not given to patients due to contraindications. This resulted in the EVT-only group having a larger proportion of patients who were prestroke dependent (pre-mRS >2), or had a history of previous stroke or atrial fibrillation, and as a result had a higher use of anticoagulation medication. Higher rates of atrial fibrillation might imply higher rates of cardioembolic stroke etiologies and potentially better functional outcome [16]. Higher rates of prestroke dependence will limit the final achievable mRS score as patients cannot improve beyond their baseline status. However, these prestroke-dependent patients seem to have a

similar EVT treatment effect [17]. Overall, we cannot exclude that there might have been some residual bias despite adjusting for baseline imbalances. Randomized clinical trials, such as MR CLEAN-NOIV (ISRCTN80619088), are therefore necessary to further investigate this topic. Additionally, patients that experienced sICH or early recanalization directly after IVT may have never been offered for EVT so rates of sICH and early recanalization may not be fully comparable.

Conclusion

In patients treated with EVT, those who received IVT did not have longer door to groin times, although they might benefit from targeted optimizations in door to imaging times. IVT prior to EVT led to more frequent early recanalization on DSA. We found no difference in reperfusion rate nor in sICH. Our results do not warrant withholding IVT prior to EVT.

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Statement of Ethics

Ethics approval was granted by the central medical ethics committee of the ErasmusMC Rotterdam, the Netherlands (MEC-2014-235), and the need for individual patient consent was waived.

References

- 1 Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274(13):1017–25.
- 2 Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723–31.
- 3 Mulder MJHL, Jansen IGH, Goldhoorn RJB, Venema E, Chalos V, Compagne KCJ, et al. Time to endovascular treatment and outcome in acute ischemic stroke. *Circulation*. 2018;138(3):232–40.
- 4 Nedeltchev K, Arnold M, Brekenfeld C, Isenegger J, Remonda L, Schroth G, et al. Pre- and in-hospital delays from stroke onset to intra-arterial thrombolysis. *Stroke*. 2003;34(5):1230–4.
- 5 Sloane B, Bosson N, Sanossian N, Saver JL, Perez L, Gausche-Hill M. Is door-to-needle time reduced for emergency medical services transported stroke patients routed directly to the computed tomography scanner on emergency department arrival? *J Stroke Cerebrovasc Dis*. 2020;29(1):104477.
- 6 Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, et al. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke*. 2017;48(9):2450–6.
- 7 Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Dávalos A, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR studies. *JAMA Neurol*. 2017;74(3):268–74.
- 8 Chalos V, LeCouffe NE, Uyttenboogaart M, Lingsma HF, Mulder MJHL, Venema E, et al. Endovascular treatment with or without prior intravenous alteplase for acute ischemic stroke. *J Am Heart Assoc*. 2019;8(11):e011592.
- 9 von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46(10):2981–6.
- 10 Heinrichs A, Nikoubashman O, Schürmann K, Tauber SC, Wiesmann M, Schulz JB, et al. Relevance of standard intravenous thrombolysis in endovascular stroke therapy of a tertiary stroke center. *Acta Neurol Belg*. 2018;118(1):105–11.
- 11 Kuhrij LS, Marang-van de Mheen PJ, Marang-van de Mheen PJ, van den Berg-Vos RM, de Leeuw F-E, Nederkoorn PJ. Determinants of extended door-to-needle time in acute ischemic stroke and its influence on in-hospital mortality: results of a nationwide Dutch clinical audit. *BMC Neurol*. 2019;19(1):265.
- 12 Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79(4):306–13.
- 13 Meretoja A, Keshkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: save a minute-save a week. *Neurology*. 2017;88(22):2123–7.
- 14 Serna Candel C, Aguilar Pérez M, Hellstern V, AlMatter M, Bätzner H, Henkes H. Recanalization of emergent large intracranial vessel occlusion through intravenous thrombolysis: frequency, clinical outcome, and reperfusion pattern. *Cerebrovasc Dis*. 2019;48(3–6):115–23.
- 15 Tsvigoulis G, Katsanos AH, Schellinger PD, Köhrmann M, Varelakis P, Magoufis G, et al. Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions. *Stroke*. 2018;49(1):232–5.
- 16 Tiedt S, Herzberg M, Küpper C, Feil K, Kellert L, Dorn F, et al. Stroke etiology modifies the effect of endovascular treatment in acute stroke. *Stroke*. 2020;51(3):1014–6.
- 17 Goldhoorn RB, Verhagen M, Dippel DWJ, van der Lugt A, Lingsma HF, Roos YBWEM, et al. Safety and outcome of endovascular treatment in prestroke-dependent patients. *Stroke*. 2018;49(10):2406–14.

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Author Contributions

Dr. Hinsenveld contributed in patient enrollment, literature search, study design, data collection, data analysis, data interpretation, and writing of the manuscript. Dr. de Ridder contributed in literature search, study design, data analysis, data interpretation, and writing of the manuscript. Drs. Van Oostenbrugge, Van Zwam, Vos, Coutinho, Lycklama à Nijeholt, Boiten, and Schoneville contributed in patient enrollment, data collection, and critical review of the manuscript.