CT perfusion in acute ischemic stroke

Optimizing image-based patient selection for endovascular treatment

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Chapter 7

Infarct evolution in patients with anterior circulation large vessel occlusion randomized to IV alteplase and EVT versus EVT alone

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Abstract

Background and purpose

Infarct evolution after endovascular treatment (EVT) varies widely among stroke patients and may be affected by baseline characteristics and procedural outcomes. Moreover, intravenous alteplase (IVT) and EVT may influence the relationship of these factors with infarct evolution.

Materials and Methods

We included patients from the MR CLEAN-NO IV trial with baseline CTP and follow-up imaging. Follow-up infarct volume (FIV) was segmented on 24-hour or 1-week follow-up DWI or NCCT. Infarct evolution was defined as the follow-up lesion volume – CTP core volume. Substantial infarct growth was defined as an increase in FIV>10 mL. We assessed whether infarct evolution was different for patients with IVT and EVT vs. EVT alone and evaluated the association of baseline characteristics and procedural outcomes with infarct evolution using multivariable regression.

Results

From 227 patients with CTP results available, 145 patients had follow-up imaging and were included in our analysis. For patients with IVT and EVT vs. EVT alone, baseline median CTP core volume was 17(IQR 4-35) mL vs. 11(IQR 6-24) mL. Median FIV was 13(IQR 4-48) mL vs. 17(IQR 4-50) mL. Collateral status and occlusion location were negatively associated with substantial infarct growth in patients with and without IVT prior to EVT.

Conclusion

No statistically significant difference in infarct evolution was found in directly admitted patients who received IVT and EVT within 4.5 hours after symptom onset vs. patients who underwent EVT alone. Collateral status and occlusion location may be useful predictors for infarct evolution prognosis in IVT-eligible patients who underwent EVT.

Introduction

Endovascular treatment (EVT) preceded by administering intravenous alteplase (IVT) is the current standard of care and is effective in patients with acute ischemic stroke.[1] A first meta-analysis of three Asian randomized controlled trials (RCTs) comparing EVT alone with IVT prior to EVT suggested non-inferiority of EVT alone.[2] However, four following RCTs – including the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)-NO IV trial (ISRCTN80619088) – did neither demonstrate superiority nor non-inferiority of EVT alone with regard to functional outcome at 90 days after stroke.[3–6] A recent expedited guideline from the European Stroke Organisation (ESO) and European Society for Minimally Invasive Neurological Therapy (ESMINT) – a meta-analysis of all six RCTs – recommended IVT prior to EVT over EVT alone.[7] Whilst there were no large differences in clinical outcome between the overall study groups in the RCTs, individual variations in infarct evolution may still be present.[5,6,8,9] This is clinically relevant since infarct evolution – and infarct growth in particular – is associated with functional outcome after EVT and differs from patient to patient.[10–18] Factors affecting – subacute – infarct evolution are: collateral status, occlusion location, onset-to-reperfusion time, reperfusion rate, total attempts, and early reocclusion of the target artery.[19–21] These factors may be influenced by IVT prior to EVT.

CTP acquisition allows for quantification of the cerebral blood flow to estimate the brain tissue viability and ischemic core volume on baseline imaging.[22] The estimated ischemic core may still evolve in the first days to weeks after stroke onset despite timely and adequate endovascular treatment.[17,23–25] To our knowledge, infarct evolution has not yet been compared between endovascularly treated acute ischemic stroke patients who were randomized for IVT and EVT vs. EVT alone.

In this post-hoc analysis of the MR CLEAN-NO IV trial, we aimed to assess whether the infarct evolution between baseline and follow-up imaging was different for patients who received IVT and EVT vs. EVT alone. Additionally, we aimed to identify which clinical and procedural outcomes are associated with infarct evolution in acute ischemic stroke patients who received IVT and EVT vs. EVT alone.

Methods

Patient selection

We included patients with baseline CTP and follow-up DWI or NCCT from the MR CLEAN-NO IV trial.[5] The MR CLEAN-NO IV trial included patients with acute ischemic stroke due to an intracranial proximal occlusion of the anterior circulation who were

directly admitted to an EVT-capable center between January 2018 and October 2020. If eligible for EVT and intravenous alteplase (IVT) administration within 4.5 hours, patients were randomly assigned to receive either EVT alone or IVT followed by EVT. Analyses were performed in the as-treated population. Details of the trial protocol were previously published.[26] A flowchart explaining the inclusion criteria of this study is provided in **Figure 1**.

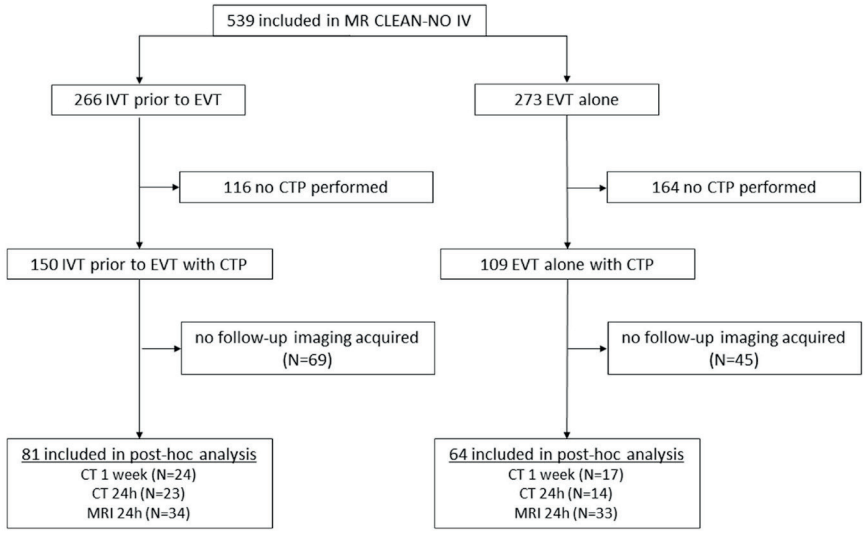

Figure 1. Flowchart of patient selection. CTP = CT perfusion, EVT = endovascular treatment.

Image acquisition and post-processing

Baseline CTP images were acquired according to site-specific baseline CT acquisition protocols. CTP data were centrally post-processed by an independent core lab using syngo.via (version VB40, Siemens Healthineers, Forchheim, Germany). The ischemic core was estimated using CBV <1.2 mL/100mL and the penumbra was estimated using CBF <27 mL/100mL/min.[27] A smoothing filter (smoothing strength 10mm) was applied.[27] Expert visual quality assessment of the CTP results was performed by two experienced neuroradiologists (>10 and >15 years of experience) and craniocaudal cropping was allowed to remove obvious artifacts at the level of the skull base.[28] Follow-up imaging was acquired at (median) 24-48h) DWI, 24h NCCT, or 5-7-day NCCT. DWI was the preferred modality for determining the follow-up infarct volume (FIV). If DWI was not available, follow-up NCCT was used to segment the FIV using a semi-automated segmentation method[29] with subsequent expert visual quality assessment (>15 years of experience). In case both 24h and 5-7d NCCT were available, the 5-7d NCCT was used to assess the FIV. If hemorrhagic transformation was present, the hemorrhagic regions

were included in the segmentation volume. Hemorrhagic transformation was scored by an independent core lab and defined according to the Heidelberg Bleeding Classification.[30] Recanalization on follow-up imaging was assessed on either CTA or MRA using the modified arterial occlusive lesion (mAOL) score.[31]

Infarct evolution and imaging assessment

We compared the infarct evolution and occurrence of substantial lesion growth between patients who received IVT and EVT vs. patients who underwent EVT alone. Infarct evolution was calculated by subtracting the CTP core volume from the FIV. Overestimation of the FIV by CTP was defined as CTP core volume > FIV. Substantial infarct growth was defined as an increase in FIV >10 mL. All imaging data were assessed by an independent core laboratory of (neuro)radiologists. Post-procedural reperfusion was assessed on post-procedural DSA. Successful reperfusion was defined as eTICI 2b-3 and complete reperfusion was defined as eTICI 3. Recanalization of the target artery was assessed on 24h follow-up CTA or MRA imaging. Incomplete patency of the target artery on follow-up imaging was defined as mAOL 0-1.[32]

Statistical analysis

Baseline clinical and imaging variables were compared between patients with IVT prior EVT vs. EVT alone using Mann-Whitney U tests or χ^2 tests. The primary outcome in this study was infarct evolution in mL. To assess the association of IVT prior to EVT with substantial infarct growth (i.e., positive infarct evolution >10 mL), we performed uni- and multivariable logistic regression analysis adjusted for the following potential confounders: ASPECTS, CTA collateral score, onset-to-reperfusion time, reperfusion rate (scored on the eTICI scale), occlusion location, total attempts, occurrence of any hemorrhagic transformation, and reocclusion rates on follow-up CTA or MRA (scored on the mAOL scale). We checked our model for multicollinearity by determining the variance inflation factor (VIF) values of all variables included in the model. Infarct evolution between patients with successful reperfusion vs. unsuccessful reperfusion was compared using Mann-Whitney U tests. We performed a sensitivity analysis for patients who received 24h follow-up DWI and NCCT imaging to evaluate whether including 1-week follow-up NCCT FIVs would affect our findings. We performed a sensitivity analysis for patients with tandem lesions, since tandem lesions (i.e., occlusion or stenosis of the internal carotid artery with a concomitant intracranial occlusion) are known to be associated with lower reperfusion rates and therefore may show different infarct evolution.[33] Furthermore, we exploratively assessed whether our results were consistent in a subgroup of patients without hemorrhagic transformation as large hemorrhages which between baseline and follow-up imaging can strongly affect FIV assessment. Both sensitivity analyses are reported in the **Supplemental Material** (**Appendix A**).

Protocol approval and patient consent

The MR CLEAN-NO IV trial protocol was approved by national central ethical committees and by research boards at each participating center. The final versions of the trial protocol and statistical analysis plan (both available at www.nejm.org). The MR CLEAN-NO IV trial was conducted in accordance with the revised Helsinki guidelines.

Data availability

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data. All syntax files and output of statistical analyses are available upon reasonable request.

Results

From 539 patients included in the MR CLEAN-NO IV trial, 227 had available CTP results. Of these 227 patients, 145 patients follow-up imaging and were included in our post-hoc analysis. Eighty-one (56%) patients received IVT and EVT. Baseline characteristics, such as age, sex, and baseline NIHSS were comparable for patients who received IVT and EVT vs. patients who underwent EVT alone. Median (IQR) baseline CTP-estimated ischemic core volume was 17 (4-35) mL vs. 11 (6-24) mL (p=0.5). Median FIV was 13 (IQR 4-48) mL vs. 17 (IQR 4-50) mL (p=1.0). CTP ischemic core overestimation >10 mL occurred in 17/81 (21%) vs. 9/64 (14%) patients and occurred primarily in the white matter. The time between baseline CTP and follow-up imaging was comparable (27 vs. 33 hours, p=0.3). Good functional outcome occurred in 45/81 (56%) patients who received IVT and EVT vs. in 37/64 (58%) patients who received EVT alone (OR 0.86 [95% CI 0.42-1.73], p=0.7). Four (3%) patients showed early recanalization (i.e., recanalization prior to EVT). Two patients with early recanalization received IVT prior to EVT. An example of a patient with a left-sided M1 occlusion and baseline CTP-estimated core of 65 mL is shown in **Figure 2**.

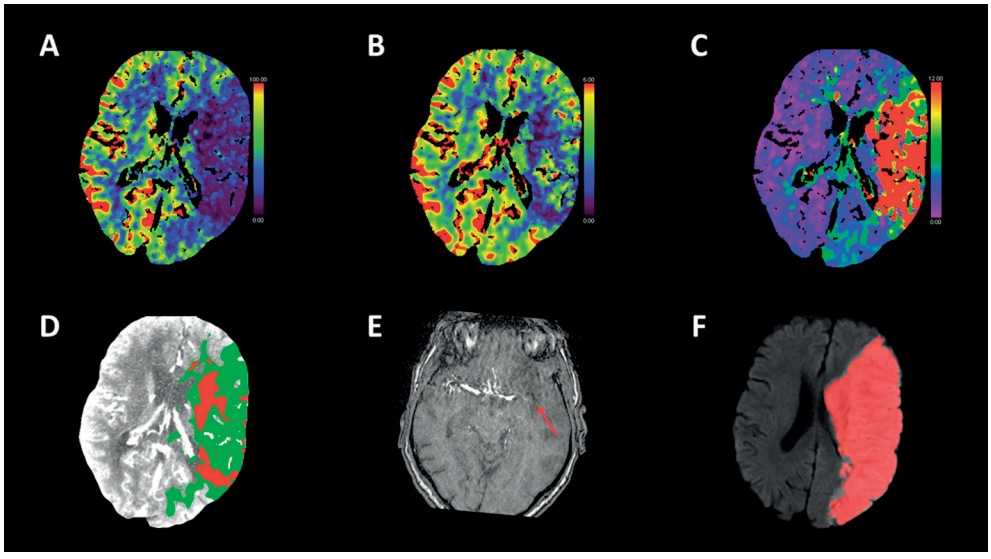

Figure 2. Baseline CTP of a patient with a left-sided M1 occlusion with substantial infarct growth with complete reperfusion (eTICI 3) after 5 attempts within 195 minutes after onset. Collateral score at baseline CTA (not shown) was 0. The CBF, CBV, and Tmax parameter maps are shown in panels A-C. (D) Ischemic core (red) and penumbra (green) estimations. (E) Follow-up MRA showed a reoccluded M1 with visible calcified embolus (red arrow; mAOL 0). (F) Follow-up DWI acquired at 15 hours after baseline imaging with FIV segmentation (red). CBF = cerebral blood flow; CBV = cerebral blood volume; CTP = CT perfusion; DWI = diffusion-weighted imaging; eTICI = expanded treatment in cerebral infarction; FIV = follow-up infarct volume; mAOL = modified arterial occlusive lesion; MRA = magnetic resonance angiography; Tmax = time-to-maximum.

This patient underwent successful EVT alone (eTICI 3) with an onset-to-reperfusion time of 195 minutes. Follow-up CTA showed a visible calcified embolus in the left M1 (mAOL 0). Follow-up DWI showed substantial infarct growth (384 mL). See **Table 1** for a complete description of baseline, procedural, and outcome characteristics stratified per study subgroup.

Table 1. Baseline, imaging, and clinical outcome characteristics of the MR CLEAN-NO IV CTP with follow-up imaging subgroup compared to the overall MR CLEAN-NO IV trial cohort. ASPECTS, Alberta Stroke Program Early CT Score; CTA-CS; Computed Tomography Angiography Collateral Score; CTP, Computed Tomography Perfusion; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IVT, IV alteplase; IQR, interquartile range; mAOL, modified arterial occlusive lesion; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage. If the [known in] number is not shown, the variable was known for all patients.

Baseline characteristics	**CTP with FU imaging population – IVT and EVT subgroup (n=81)**	**CTP with FU imaging population – EVT alone (n=64)**	**Overall CTP with FU imaging substudy population (n=145)**	**Overall MR CLEAN-NO IV population (n=539)**
Age (yr) – median(IQR)	71(61-78)	70(61-78)	70(61-78)	71(62-79)
Female – n(%)	31(38)	25(39)	56(39)	234(43)
Baseline NIHSS – median(IQR)	16(9-20)	15(11-19)	16(10-20)	16(10-20)
IVT administered – n yes(%)	81(100)	0(0)	81(56)	285(53)
Onset-to-imaging time (min) – median(IQR) [known in]	68(60-102)	67(48-88)	67(52-101) [n=91]	67(53-89) [n=170]
Onset-to-groin time (min) – median (IQR) [known in]	137(106-168)	140(111-180)	138(107-174) [n=140]	133(105-180) [n=511]
Onset-to-needle time (min) – median (IQR) [known in]	99(77-139) [n=73]	NA	99(77-139) [n=73]	100(75-157) [n=260]
Imaging characteristics				
Occlusion location on baseline CTA – n(%)				
ICA	0(0)	0(0)	0(0)	4(1)
ICA-T	16(20)	22(34)	38(26)	114(21)
M1	49(61)	29(45)	78(54)	330(61)
M2	16(20)	12(19)	28(19)	85(16)
Other	0(0)	1(2)	1(1)	5(1)
ASPECTS – median(IQR)	9(8-10)	9(8-10)	9(8-10)	9(8-10)
CTA-CS – n(%) [known in]	[n=77]	[n=64]	[n=141]	[n=526]
0	6(8)	4(6)	10(7)	32(6)
1	22(29)	11(17)	33(23)	152(29)
2	32(42)	33(52)	65(45)	223(42)
3	17(22)	16(25)	33(23)	119(23)

Table 1. Continue

Baseline characteristics	CTP with FU imaging population – IVT and EVT subgroup (n=81)	CTP with FU imaging population – EVT alone (n=64)	Overall CTP with FU imaging substudy population (n=145)	Overall MR CLEAN-NO IV population (n=539)
Baseline ischemic core volume on CTP (mL) – median(IQR)	17(4-35)	11(6-24)	14(4-33)	13(5-35) [n=223]
Baseline penumbra volume on CTP (mL) – median(IQR)	114(79-157)	106(82-142)	111(80-150)	114(78-149) [n=223]
eTICI – n(%) [known in]	[n=73]	[n=60]	[n=133]	[n=480]
0	7(10)	2(3)	9(7)	36(8)
1	2(3)	1(2)	3(2)	6(1)
2a	5(7)	4(7)	9(7)	50(10)
2b	18(25)	20(33)	38(29)	109(23)
2c	9(12)	6(10)	15(11)	59(12)
3	32(44)	27(45)	59(44)	220(46)
mAOL at 24h follow-up imaging – n(%)	[n=73]	[n=59]	[n=132]	[n=422]
[known in]	4(6)	8(14)	12(9)	35(8)
0	3(4)	1(2)	4(3)	8(2)
1	4(6)	7(12)	11(8)	36(9)
2	62(85)	43(73)	105(80)	343(81)
3				
Procedural and clinical outcome characteristics				
First line stent retriever – n(%) [known in]	57(83)	46(78)	103(81)	371(78) [n=474]
Number of retrieval attempts – median(IQR)	2(2-3)	2(2-4)	2(2-3)	2(2-3)
Infarct evolution (mL) – median(IQR)	0.3 (-6.0; 26.2)	1.8 (-5.7; 22.9)	1.3 (-5.7; 25.4)	N/A
Poor functional outcome (mRS 5-6)– n(%)	16(20)	13(20)	29(20)	153(28)
Functional independence (mRS 0-2)– n(%)	45(56)	37(58)	82(57)	270(50)
Mortality at 90 days – n(%)	10(12)	9(14)	19(13)	98(18)
sICH – n(%)	0(0)	0(0)	0(0)	1(0)

Association of baseline characteristics and procedural outcomes with infarct evolution

Univariable analyses showed that better collateral status was negatively associated with substantial infarct growth and early reocclusion of the target artery at 24h follow-up imaging was positively associated with substantial infarct growth. In addition, the number of attempts during EVT and the occurrence of any hemorrhage were positively associated with substantial infarct growth (**Supplemental Material, Appendix B, Table I**). Notably, reperfusion (eTICI) was not associated with infarct evolution. The distribution

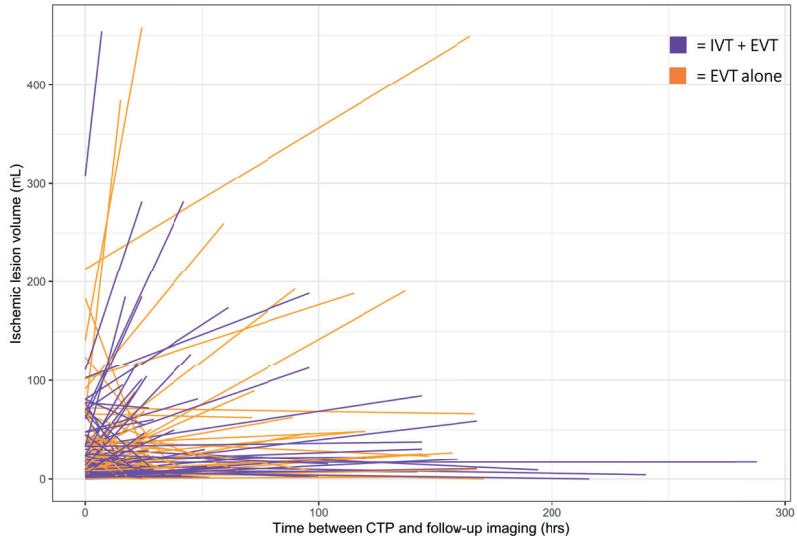

Figure 3. Infarct evolution between baseline CTP imaging and follow-up imaging on either DWI or NCCT for patients who received IVT and EVT (purple) and patients who underwent EVT alone (orange). (A) The left panel shows data for all included patients. (B) The right panel only shows data for patients who had follow-up imaging within 24 hours posttreatment. CTP = computed tomography perfusion, DWI = diffusion-weighted imaging, EVT = endovascular treatment, NCCT = non-contrast CT.

of infarct evolution stratified by reperfusion subgroup is displayed in **Figure 3**.

After adjustment for confounders, better collateral status and more distal occlusion location were negatively associated with substantial infarct growth. The number of attempts during EVT and the occurrence of any hemorrhage were positively associated with substantial infarct growth. Early reocclusion of the target artery was not associated with substantial infarct growth in multivariable analysis. For all included variables, the VIFs were <1.5, indicating no correlation between the included independent variables (**Supplemental Material, Appendix B, Table II**). An exploratory analysis in a subgroup of patients without any hemorrhagic transformation (n=103) consistently showed that

better collateral status and more distal occlusion location were negatively associated with substantial infarct growth.

Infarct evolution for patients who received IVT and EVT vs. EVT alone

Substantial infarct growth (i.e., infarct growth >10 mL) occurred in 27/81 (33%) patients with IVT and EVT vs. 27/64 (42%) patients who underwent EVT alone (p=0.3). After adjustment for confounders, substantial infarct growth was not significantly associated with occurrence of administration of IVT and EVT (aOR 0.63 [95% CI 0.30-1.32], p=0.2). Boxplots showing the infarct growth per subgroup are provided in **Figure 4.**

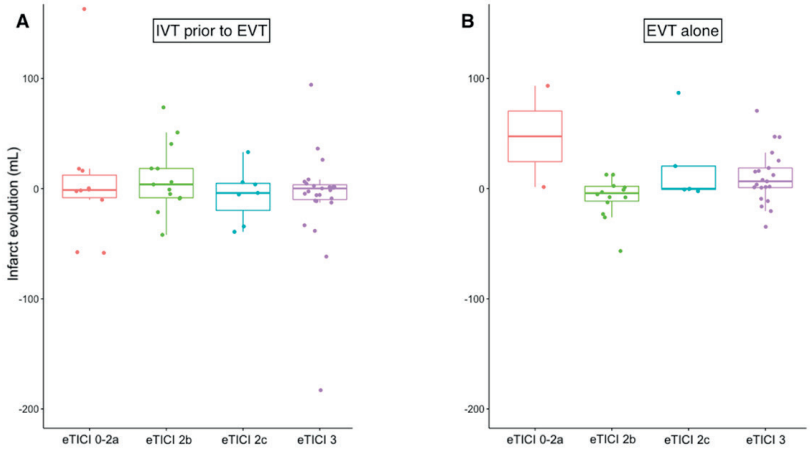

Figure 4. Boxplots showing infarct evolution (mL) for patients who received IVT and EVT (A) and patients who underwent EVT alone (B) with eTICI 0-2a vs. eTICI 2b vs. eTICI 2c vs. eTICI3 reperfusion. eTICI = extended Thrombolysis in Cerebral Ischemia.

Infarct evolution for patients with and without successful reperfusion

One hundred twelve (84%) patients achieved successful reperfusion after EVT. Patients with successful reperfusion showed lower median infarct evolution rates compared to patients without successful reperfusion (1 [IQR -7; 20] mL vs. 15 [IQR -2; 71] mL), although this difference was not statistically significant (p=0.2). From 59 patients with complete reperfusion (i.e., eTICI 3), 20 (34%) showed substantial infarct growth.

Effect of follow-up CT- or MR-angiography recanalization status on infarct evolution

Follow-up CTA or MRA was available for 132 patients and showed incomplete patency of the target artery in 10% of patients receiving IVT and EVT vs. in 15% of patients receiving EVT alone. However, this difference was not statistically significant (p=0.3). In

multivariable analysis, early reocclusion of the target artery – assessed on follow-up CTA or MRA – was not associated with infarct growth (aOR 1.48 [95% CI 0.28-7.83]).

Discussion

In this post-hoc analysis of the MR CLEAN-NO IV trial, we did not observe a statistically significant difference in infarct evolution between directly admitted patients who received IVT and EVT vs. patients who underwent EVT alone within 4.5 hours after symptom onset. Overall, successful reperfusion rates were similar in patients who received IVT and EVT vs. EVT alone. Furthermore, our results demonstrated that collateral status, occlusion location, the number of attempts during EVT, and occurrence of any hemorrhage were significantly associated with substantial infarct growth in patients who received IVT and EVT or EVT alone within 4.5 hours after symptom onset.

Our results showed that reocclusion on follow-up imaging was not uncommon. However, frequencies of reocclusion were comparable between both groups. Interestingly, reocclusion on follow-up imaging was not statistically significantly associated with substantial infarct growth after adjusting for potential confounders. However, this non-intuitive finding might be explained by the fact that our sample size was limited and therefore potentially underpowered to detect a clear association. The observed rates of reocclusion on follow-up imaging are in line with a previous study assessing vessel patency at 24h follow-up imaging using the mAOL score.[34] Other studies assessing reocclusion after EVT reported rates of early reocclusion ranging from 3-9%. However, these studies did use different imaging techniques and grading systems to assess the vessel patency on follow-up imaging (e.g, 24h follow-up angiography using the Qureshi grading scheme).[35,36]

Our results showed that substantial infarct growth was associated with the number of attempts during EVT, which is in line with a previous large prospective study from multiple stroke registries.[20] In addition, our results suggested that in the hyperacute (0-4.5h) time window, patients with poor collaterals have a higher likelihood of substantial infarct growth compared to patients with good collaterals. This is also in concordance with previous research in stroke patients who underwent EVT within 6 hours after symptom onset.[19,21]

If replicated, the relatively high frequency of reocclusion within 24 hours after endovascular treatment could imply that there might be potential added benefit of thrombolytic therapy in addition to EVT to improve functional outcome after stroke. This would also be in line with the preliminary findings from the CHOICE trial which showed that

adjunct intra-arterial alteplase in large vessel occlusion stroke patients resulted in a greater likelihood of excellent neurological outcome at 90 days.[37] Also, they showed that additional intra-arterial thombolysis was associated with an increased likelihood of achieving excellent angiographic reperfusion (i.e., eTICI 2c-3) However, the proportion of patients with infarct growth between baseline and follow-up imaging was not statistically significantly different between both study groups. This could imply that additional factors – such as for example microvascular perfusion – may also contribute to functional outcome at 90 days and that these factors might be affected by additional thrombolytic therapy in EVT-treated patients.

Several limitations to our study should be noted. First, selection bias may have been introduced as CTP was not mandatory for inclusion in the MR CLEAN-NO IV trial and CTP was acquired according to local imaging protocols. Of note, not all centers routinely acquired CTP in every admitted suspected stroke patient. a total of 227 [41%] patients in the MR CLEAN-NO IV had CTP available from 17 participating centers. Of these 227 patients, 145 (64%) of the patients had baseline CTP with follow-up NCCT or MRI available, which lead to a relatively small sample size. However, the baseline, imaging and outcome characteristics of patients without follow-up imaging were comparable to the overall MR CLEAN-NO IV population. Second, the MR CLEAN-NO IV trial had no standardized CTP acquisition protocol and CTP data were acquired according to local acquisition protocols per site which could have introduced differences in CTP ischemic core volume estimations.[38] However, all CTP data were centrally processed using a previously described single post-processing protocol.[27] Furthermore, differences in CTP results which are caused by differences in acquisition protocols are commonly largely driven by differences in contrast medium injection protocols[38] and since the particular contrast medium injection protocols from centers in the MR CLEAN-NO IV were similar, we expect that the effect of using data from different acquisition protocols is limited. Third, FIV was measured on both – 24h and 1-week – follow-up NCCT and MRI. This could have affected the accuracy of our FIV assessments as it is known that edema affects the FIV on NCCT after stroke and it can be challenging to distinguish edema from infarcted tissue on NCCT.[39] However, the FIVs were not different for patients who received (median) 24h FU DWI vs. patients with 24h FU NCCT. In addition, it has been demonstrated that FIV assessed on 24h NCCT is equally strongly associated with functional outcome as the FIV measured on 1-week NCCT – despite that infarct growth between 24h and 1-week imaging is common.[24] Fourth, hemorrhagic regions were included in the final infarct lesion, which could have affected our results. An exploratory analysis in a subgroup of patients without any hemorrhagic transformation (n=103) consistently showed that collateral status and occlusion location were associated with substantial infarct growth. Excluding all patients with hemorrhagic transformation from our analyses could potentially introduce bias as it is not well-known how infarct growth

changes over time and what the tempo of blood-brain barrier disruption and development of hemorrhagic transformation is.[40]

It is known that CTP may overestimate the FIV (i.e. the 'ghost infarct core concept') – especially in patients with successful reperfusion in the early time window.[41] However, rates of overestimation >10 mL were comparable with rates previously reported in a post-hoc analysis of the HERMES collaboration.[42] Similarly, we found that CTP ischemic core overestimation by *syngo.via* predominantly occurred in the white matter. As previous studies have shown that ischemic core thresholds might differ between grey and white matter[43], future studies focusing on improving white matter ischemic core estimation by syngo.via, should consider this. Finally, the timing of follow-up scans had a wide range (1-288h posttreatment). As we showed that infarct growth was common in our population, the timing of follow-up imaging could have affected the accuracy of FIV measurements. A pooled analysis on this topic from all trials investigating the non-inferiority of EVT alone, is warranted for confirmation whether infarct growth differs between patients who received IVT and EVT vs. patients who underwent EVT alone. Ideally, follow-up imaging should be acquired at similar time points using a single modality.

Conclusion

No statistically significant difference in infarct evolution was found in patients who received IVT and EVT vs. patients who underwent EVT alone. Collateral status, occlusion location, and number of attempts during EVT are significantly associated with substantial infarct growth in IVT-eligible patients who undergo EVT.

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Supplemental Material

Appendix A

Sensitivity analysis of patients with 24h follow-up DWI and CT imaging

One hundred and four of 145 (72%) patients received 24h follow-up imaging. Of those, 67/145 (46%) patients received a follow-up DWI at median 27 (IQR 23-40) hours. Thirty-seven (26%) patients received follow-up CT imaging at median 24 (IQR 18-25) hours. Baseline characteristics were comparable to the overall study population. Median CTP ischemic core volume was 12 (IQR 4-29) mL. Median FIV was 11 (IQR 3-41) mL. Substantial infarct growth occurred in 15/57 (26%) patients who received IVT prior to EVT (median lesion evolution -1 [IQR -9; 14] mL) vs. in 17/47 (36%) patients who underwent EVT alone (median lesion evolution 1 [IQR -6; 20] mL, p=0.3). Patients with 24h DWI had similar rates of successful reperfusion (51/67 [76%]) compared to patients with follow-up CT at 24h (28/37 [76%]) and follow-up CT at 1 week (33/41 [80%]). In addition, the infarct evolution was comparable between patients with 24h DWI (median 1 mL) and 24h CT (median -1 mL). Patients with 1-week CT did show significantly different infarct evolution (median infarct growth 13 mL) compared to patients with 24h CT- or DWI imaging (p=0.02).

Sensitivity analysis of patients with tandem lesions

Nineteen (13%) patients had a tandem lesion on baseline CTA. Eight (42%) patients with a tandem lesion received IVT prior to EVT. Patients with a tandem lesion had a longer median onset-to-groin time (175 minutes) compared to patients without tandem lesions (135 min) (p<0.001). All other baseline characteristics were similar. Infarct growth occurred in 5/8 (63%) tandem lesion patients who received IVT prior to EVT versus 5/11 (46%) patients with EVT alone (p=0.5).

Appendix B

Supplemental Table I. Univariable analysis of substantial infarct growth (>10 mL). ASPECTS, Alberta Stroke Program Early CT Score; CI, Confidence Interval; CTA; Computed Tomography Angiography; IVT, intravenous alteplase; mRS, modified Rankin Scale; N, number of patients included in analysis; OR, Odds Ratio.

Characteristic	N	OR	95% CI	p-value	q-value*
IVT administration	145	0.69	0.35, 1.35	0.27	0.31
ASPECTS	145	0.84	0.68, 1.04	0.10	0.15
CTA collateral score	141	0.59	0.39, 0.89	0.011	0.033
Onset-to-reperfusion time (min)	145	1.00	1.00, 1.01	0.31	0.31
eTICI score	133	0.80	0.63, 1.02	0.067	0.12
Reocclusion	132	3.70	1.28, 11.6	0.016	0.036
Occlusion location	145	1.36	0.84, 2.24	0.22	0.28
Total attempts during EVT	145	1.49	1.18, 1.92	<0.001	0.002
Any hemorrhage	145	6.96	3.21, 15.8	<0.001	<0.001

* False discovery rate correction for multiple testing

Supplemental Table II. Multivariable analysis of substantial infarct growth (>10 mL). ASPECTS, Alberta Stroke Program Early CT Score; CI, Confidence Interval; CTA; Computed Tomography Angiography; IVT, intravenous alteplase; OR, Odds Ratio.

Characteristic	OR	95% CI	p-value
IVT administration	0.46	0.17, 1.21	0.12
ASPECTS	0.82	0.61, 1.13	0.2
CTA collateral score	0.42	0.22, 0.77	0.006
Onset-to-reperfusion time (min)	1.00	0.99, 1.01	0.7
eTICI score	0.85	0.58, 1.25	0.4
Reocclusion	2.49	1.24, 5.32	0.013
Occlusion location	1.48	0.28, 7.83	0.6
Total attempts during EVT	1.48	1.06, 2.14	0.026
Any hemorrhage	6.23	2.30, 18.4	<0.001