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Optimizing image-based patient selection for endovascular treatment

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Publication date
2023

Link to publication

Citation for published version (APA):
Hoving, J. W. (2023). *CT perfusion in acute ischemic stroke: Optimizing image-based patient selection for endovascular treatment*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 6

Association Between Computed Tomography Perfusion and The Effect of Intravenous Alteplase Prior To Endovascular Treatment in Acute Ischemic Stroke

Neuroradiology 2023; doi:10.1007/s00234-023-03139-4

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Abstract

Background and purpose

Intravenous alteplase (IVT) prior to endovascular treatment (EVT) is neither superior nor noninferior to EVT alone in acute ischemic stroke patients. We aim to assess whether the effect of IVT prior to EVT differs according to CT perfusion-(CTP) based imaging biomarkers.

Materials and Methods

We included patients from the MR CLEAN-NO IV trial with available CTP data. CTP data were processed using syngo.via (version VB40). We performed multivariable logistic regression to obtain the effect size estimates (adjusted common odds ratio a[c]OR) on 90-day functional outcome (modified Rankin Scale [mRS]) and functional independence (mRS 0-2) for CTP-based imaging biomarkers with two-way multiplicative interaction terms between IVT administration and the studied biomarkers.

Results

In 227 patients, median CTP-estimated core volume was 13(IQR 5-35) mL. The treatment effect of IVT prior to EVT on outcome was not altered by CTP-estimated ischemic core volume, penumbral volume, mismatch ratio, and presence of a target mismatch profile. None of the CTP-based imaging biomarkers were significantly associated with functional outcome after adjusting for confounders.

Conclusion

CTP-based imaging biomarkers were not statistically significantly associated with the treatment effect of IVT prior to EVT in directly admitted patients who presented within 4.5 hours after symptom onset. However, our study sample was limited and these results should be interpreted with caution. If these findings are confirmed in a pooled analysis, CTP-based imaging biomarkers should not be used to withhold alteplase from EVT-eligible patients within 4.5 hours after symptom onset.

Introduction

Six randomized trials recently compared the added value and risk of endovascular treatment (EVT) alone with intravenous thrombolysis (IVT) using alteplase prior to EVT in patients with acute ischemic stroke due to a large vessel occlusion in the anterior circulation.[1–6] The Chinese Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: A Multicenter Randomized Clinical (DIRECT-MT) [1] and Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation (DEVT) trial [2] showed non-inferiority of EVT alone whilst the other four trials (including The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands–NO IV) did neither show superiority nor non-inferiority of EVT alone.[3–6] Therefore, the recently published guideline from the European Stroke Organisation (ESO) and European Society for Minimally Invasive Neurological Therapy (ESMINT) recommends IVT prior to EVT over EVT alone.[7]

In general, patients with extensive hypoperfusion on baseline imaging are considered as more suitable candidates for EVT alone – hypothesizing that patients with more extensive hypoperfusion have a higher risk of hemorrhagic transformation after IVT using alteplase.[8,9] The extent of the baseline hypoperfusion is commonly assessed with CT perfusion (CTP).

The effect of IVT in patients who are eligible for EVT may be impacted by the baseline infarct volume.[9] CTP enables estimating the baseline ischemic core volume and could therefore potentially identify patients with reduced benefit from IVT, e.g. due to an increased risk of hemorrhagic transformation after IVT.[9–11] Thus far, one study has assessed the modification of IVT treatment effect prior to EVT by baseline infarct size, assessed with Alberta Stroke Program Early CT Score (ASPECTS), and found that baseline infarct size did not modify the treatment effect of IVT prior to EVT.[12] This study, however, did not include CTP-based ischemic core imaging biomarkers in the analysis.

In this post-hoc analysis of the MR CLEAN-NO IV trial, we determine whether the effect of IVT prior to EVT on functional outcome differs according to CTP-estimated ischemic core volume, penumbral volume, mismatch ratio, and presence of a target mismatch (TMM) profile in EVT-eligible patients who were directly presented to an EVT-capable center within 4.5 hours after symptom onset.

Methods

Patient selection

The MR CLEAN-NO IV trial was an international, multicenter, prospective randomized open-label clinical trial which randomized patients who were directly presented at an EVT-capable center – and were eligible for both IVT and EVT – to either IVT (0.9 mg alteplase per kg) prior to EVT or EVT alone between January 2018 and October 2020. The study methods and patient eligibility criteria were published previously.[13] In this post-hoc analysis, we included all patients with available baseline CTP results.

Baseline imaging assessment

Baseline NCCT and CTA data were scored by an independent core lab of (neuro)radiologists. [13] Observers were blinded for all clinical information except for occlusion side.

CTP acquisition, post-processing, and quality assessment

CTP images were acquired according to local acquisition protocols per site. CTP data were centrally post-processed by an independent core laboratory using *syngo.via* (version VB40, Siemens Healthineers, Forchheim, Germany). The 'ischemic core' was estimated as: CBV <1.2 mL/100mL. Critically hypoperfused – yet not ischemic – tissue was defined as CBF <27 mL/100mL/min. A default smoothing filter was applied.[14] The penumbral volume was calculated as critically hypoperfused volume minus the ischemic core volume. The mismatch ratio was defined as the critically hypoperfused volume divided by the ischemic core volume. Presence of a TMM profile was defined as: ischemic core volume <70 mL, mismatch ratio >1.8, and penumbral volume ≥15 mL.[15] Visual quality assessment of the CTP results was performed by two experienced neuroradiologists (>10 and >15 years of experience).

Outcomes

The primary outcome was functional outcome – scored on the ordinal modified Rankin Scale (mRS) – at 90 days. The secondary outcome was functional independence (defined as mRS 0-2) at 90 days. Occurrence of symptomatic intracerebral hemorrhage (sICH) was the safety end point.

Statistical analyses

We report the adjusted common odds ratio (a[c]OR) with 95% confidence intervals (95% CI) for a shift towards improved functional outcome on the mRS at 90 days. Results are reported per 10 mL (or per 10 percentage point [p.p.] for mismatch ratio) increase. We used ordinal and binary uni- and multivariable logistic regression models with and without two-way multiplicative interaction terms (between the studied biomarkers and IVT administration) to assess whether the treatment effect of IVT prior to EVT was modi-

fied by CTP-estimated ischemic core, penumbral volume, mismatch ratio, and presence of a TMM profile. Similarly, we aimed to analyze the relationship between functional outcome and the abovementioned CTP-based infarct imaging biomarkers. We adjusted the multivariable regression models for the following variables: age, pre-stroke mRS, onset-to-randomization time, and NIHSS score at baseline. We performed sensitivity analyses to assess the rates of reperfusion after EVT (eTICI score), follow-up lesion volume (FLV), and functional independence for subgroups stratified by presence of a TMM profile. Baseline clinical and imaging characteristics of both treatment arms were compared using Mann-Whitney U and $\chi 2$ tests. Five (2%) patients had missing variables. These patients were excluded from our analyses. We considered a two-sided $p<0.05$ as statistically significant. Statistical analyses were performed using RStudio (R Statistical Software, v2022.02.2, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

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 are both available at www.NEJM.org. The MR CLEAN-NO IV trial was conducted in accordance with the revised Helsinki guidelines.

Results

A flowchart of patient selection is shown in **Figure 1**.

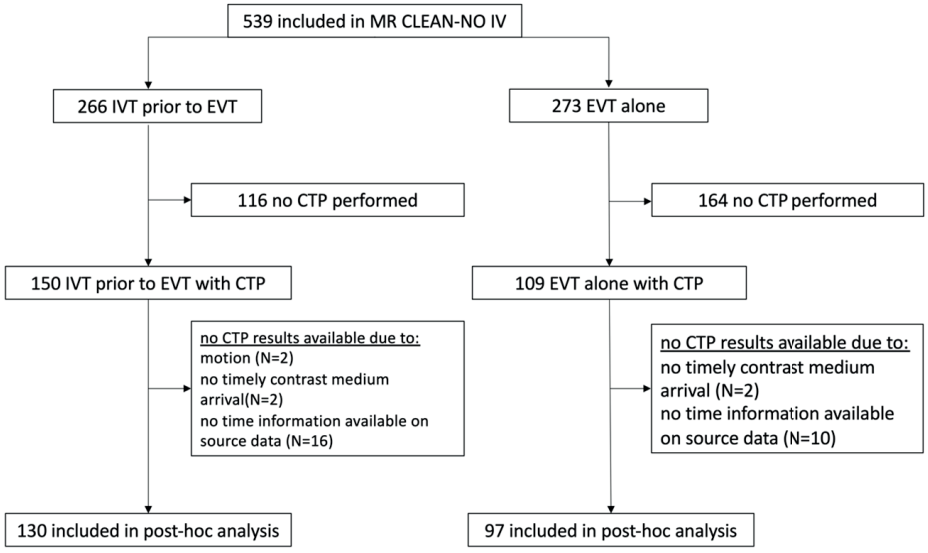

Figure 1. Flowchart of patient selection. CTP = CT perfusion, EVT = endovascular treatment, IVT = intravenous alteplase.

Of 539 patients included in the MR CLEAN-NO IV trial, 259 (48%) patients underwent CTP at admission. CTP results were available for 227/259 (88%) patients. CTP data could not be processed for 32 patients for the following reasons: severe patient motion (n=2), no timely contrast medium arrival or incorrect timing CTP (n=6), and absence of time information on CTP source data (n=24).

In the included patients, median CTP ischemic core volume was 13 (IQR 5-35) mL, median penumbral volume was 114 (IQR 78-149 mL), and median mismatch ratio was 9.4 (IQR 4.6-18.7). Median ASPECTS at baseline was 9 (IQR 8-10). One hundred thirty (58%) patients received IVT prior to EVT. Any intracerebral hemorrhage occurred in 63 (28%) patients (27/97 [28%] patients with IVT prior to EVT vs. 36/130 [28%] patients who underwent EVT alone, p=0.5). Symptomatic intracerebral hemorrhage occurred in 12(5.3%) patients and did not differ per treatment arm (p=0.5). Baseline characteristics per treatment arms (i.e, IVT prior to EVT vs. EVT alone) are summarized in **Table 1**.

Table 1. Baseline and outcome characteristics of the MR CLEAN-NO IV post-hoc analysis 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, interquartinfarct growth range; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage. If the [known in] number is not shown, the variable was known for all patients.

Baseline characteristic	Overall MR CLEAN-NO IV CTP subgroup (n=227)	MR CLEAN-NO IV CTP subgroup – IVT prior to EVT (n=130)	MR CLEAN-NO IV CTP subgroup – EVT alone (n=97)	Overall MR CLEAN-NO IV population (n=539)
Age (yr) – median(IQR)	70(61-78)	70(61-78)	70(61-78)	71(62-79)
Female – n(%)	96(42)	58(45)	38(39)	234(43)
Baseline NIHSS – median(IQR)	16(11-20)	16(10-20)	16(11-20)	16(10-20)
Prior antiplatelet use – n(%)	83(37)	51(39)	32(33)	190(35)
Median systolic blood pressure (IQR) – mmHg	146(129-165)	146(128-164)	147(130-166)	150(133-169)
IVT administered – n yes(%)	130(57)	130(100)	0(0)	285(53)
Onset-to-imaging time (min) – median(IQR) [known in]	67(52-89) [n=147]	67(55-88)	69(51-91)	67(53-89) [n=170]
Onset-to-groin time (min) – median (IQR) [known in]	132(105-172) [n=214]	130(105-161)	135(107-180)	133(105-180) [n=511]
Onset-to-needle time (min) – median (IQR) [known in]	92(76-131) [n=120]	92(76-131)	NA	100(75-157) [n=260]
Imaging				
Occlusion location on baseline CTA – n(%)				
ICA	2(1)	0(0)	2(2)	4(1)
ICA-T	50(22)	23 (18)	27(28)	114(21)
M1	136(60)	85(65)	51(53)	330(61)
M2	37(16)	21(16)	16(17)	85(16)
Other	2(1)	1(1)	1(1)	5(1)
ASPECTS – median(IQR)	9 (8-10)	9 (8-10)	9 (8-10)	9(8-10)

Table 1. Continue

Baseline characteristic	Overall MR CLEAN-NO IV CTP subgroup (n=227)	MR CLEAN-NO IV CTP subgroup – IVT prior to EVT (n=130)	MR CLEAN-NO IV CTP subgroup – EVT alone (n=97)	Overall MR CLEAN-NO IV population (n=539)
CTA-CS – n(%) [known in]	[n=220]	[n=124]	[n=96]	[n=526]
0	14(6)	7(5)	7(7)	32(6)
1	57(26)	38(29)	19(20)	152(29)
2	99(45)	51(39)	48(50)	223(42)
3	50(23)	28(22)	22(23)	119(23)
Ischemic core volume on CTP (mL) – median(IQR)	13(5-35)	15(4-33)	12(7-40)	13(5-35) [n=227]
Penumbral volume on CTP (mL) – median(IQR)	114(78-149)	118(78-150)	109(81-145)	114(78-149) [n=227]
Mismatch ratio (p.p.) – median (IQR)	9.4(4.6-18.7)	9.0(4.7-20.1)	9.9(4.3-18.1)	9.4(4.6-18.7) [n=227]
Present target mismatch profile – n(%)	196 (86)	112(86)	84(87)	196(86) [n=227]
eTICI – n(%) [known in]	[n=204]	[n=113]	[n=91]	[n=480]
0	15(7)	10(8)	5(5)	36(8)
1	4(2)	3(2)	1(1)	6(1)
2a	16(8)	9(7)	7(7)	50(10)
2b	52(26)	26(20)	26(27)	109(23)
2c	25(12)	12(9)	13(13)	59(12)
3	92(45)	53(41)	39(40)	220(46)
Outcomes				
Poor functional outcome (mRS 5-6)– n(%)	54(24)	28(22)	26(27)	153(28)
Functional independence (mRS 0-2)– n(%)	125(55)	71(55)	55(57)	270(50)
Mortality at 90 days – n(%)	34(15)	18(14)	16(17)	98(18)
sICH – n(%)	12(5)	8(6)	4(4)	30(5)

A detailed presentation of the univariable associations of clinical and imaging parameters (i.e., CTP-based imaging biomarkers, ASPECTS, age, pre-stroke mRS, baseline NIHSS, and onset-to-randomization time) with improved functional outcome and functional independence is given in **Supplemental Table I** and **Supplemental Table II**.

Association between CTP ischemic core volume and functional outcome

CTP-estimated ischemic core volume was inversely associated with improved functional outcome at 90 days in the baseline univariable ordinal regression analysis (OR per 10 mL 0.81 [95% CI 0.75-0.87], $p<0.001$) and in ordinal regression with a multiplicative interaction term applied (i.e., CTP ischemic core volume × IVT administration) (OR 0.73 [95% CI 0.54-0.95], $p=0.02$). After adjusting for confounders, this association was no longer statistically significant (a[c]OR per 10 mL 0.80 [95% CI 0.60-1.04]). The treatment effect of IVT prior to EVT was not modified by CTP ischemic core volume at baseline (a[c] OR per 10 mL 1.01 [95% CI 0.86-1.19]). Detailed results of the multivariable regression analysis are provided in **Supplemental Table III**.

Association of CTP penumbral volume and mismatch ratio with improved functional outcome

In univariable analysis, penumbral volume was not associated with improved functional outcome at 90 days. Yet, mismatch ratio was associated with improved functional outcome at 90 days (OR per 10 p.p. 1.17 [95% CI 1.06-1.31], $p<0.01$). After adjustment for confounders, both CTP-estimated penumbral volume and mismatch ratio were not statistically significantly associated with improved functional outcome at 90 days. The treatment effect of IVT prior to EVT was not modified by either the penumbral volume or mismatch ratio at baseline. A complete overview on the prognostic value of CTP-estimated penumbral volume and mismatch ratio is provided in **Supplemental Table III**.

Association between CTP parameters and functional independence (mRS 0-2)

One hundred twenty-five of 227 (55%) achieved functional independence at 90 days (71/130 [55%] patients with IVT prior to EVT vs. 54/97 [56%] patients who underwent EVT alone, p=0.8). In univariable analysis, CTP ischemic core volume (OR per 10 mL 0.80 [95% CI 0.71-0.88], p<0.001) and CTP mismatch ratio (OR per 10 p.p. 1.17 [95% CI 1.02-1.37], p=0.04) were significantly associated with achieving functional independence at 90 days. Penumbral volume was not statistically significantly associated with achieving functional independence at 90 days (OR per 10 mL 0.97 [95% CI 0.92-1.03]). **Figure 2** shows the unadjusted correlations between CTP-based imaging biomarkers with the probability of achieving functional independence at 90 days per study arm.

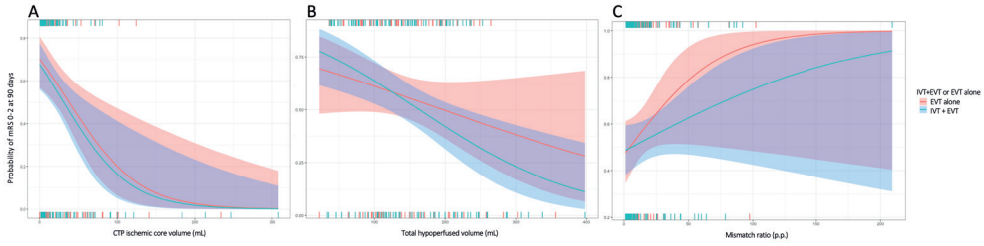

Figure 2. Probability of functional independence for univariable models considering (A) CTP-estimated ischemic core volume, (B) total hypoperfused volume (i.e., core + penumbra volume), and (C) mismatch ratio. Associations are shown for patients who received IVT prior to EVT (blue) and who underwent EVT alone (red). CTP, Computed Tomography Perfusion; EVT = endovascular treatment; IVT = intravenous alteplase; mRS = modified Rankin Scale score.

Detailed results of the multivariable regression analysis on functional independence are provided in **Supplemental Table IV**. None of the CTP-based imaging biomarkers were statistically significantly associated with the occurrence of any intracerebral hemorrhage.

Association between CTP parameters and sICH and any intracerebral hemorrhage

None of the CTP-based imaging biomarkers or clinical parameters were statistically significantly associated with the occurrence of sICH or any intracerebral hemorrhage. Detailed results of the univariable associations of clinical and imaging parameters with sICH are given in **Supplemental Table V**.

Target mismatch (TMM) profile

One hundred ninety-six (86%) patients had a TMM profile. Patients with a TMM profile equally often received IVT prior to EVT compared to patients without a TMM profile (57% vs. 58%). One hundred fourteen (58%) patients with a TMM profile achieved functional independence at 90 days vs. 8 (31%) of patients without a TMM profile (p<0.01). Presence of a TMM profile was statistically significantly associated with functional independence at 90 days in univariable analysis (OR 3.13 [95% CI 1.34-7.94], p=0.01), but not after adjusting for confounders (a[c]OR 1.18 [95% CI 0.04-35.33], p=0.9). Forty (20%) patients with a TMM profile showed poor outcome (i.e., mRS 5-6) at 90 days compared to thirteen (50%) of patients without a TMM profile. The distributions of the mRS scores at 90 days for patients with and without a TMM profile stratified by treatment allocation is shown in **Figure 3**.

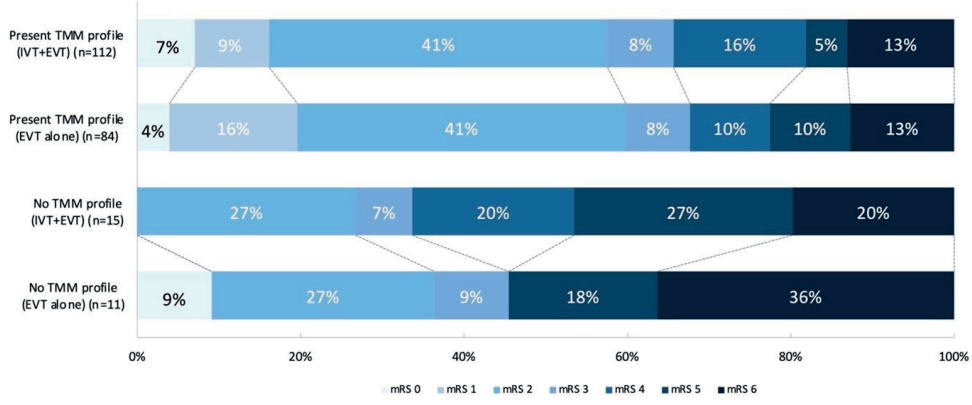

Figure 3. Distribution of scores on the Modified Rankin Scale score at 90 days in the MR CLEAN-NO IV CTP subgroup for patients with (n=196) and without (n=26) a target mismatch (TMM) profile on CTP imaging who underwent IVT and EVT vs. EVT alone CTP, Computed Tomography Perfusion, mRS = modified Rankin Scale score at 90 days.

Discussion

This post-hoc analysis of the MR CLEAN-NO IV trial showed that the treatment effect of IVT prior to EVT in the hyperacute – 0-4.5h – time window was not statistically significantly modified by CTP ischemic core volume, penumbral volume, mismatch ratio, or presence of a TMM profile. In addition, our results did not show an association between CTP-based imaging biomarkers and the occurrence of sICH. However, our study sample was limited and therefore the results should be interpreted with caution. Until replicated in a pooled analysis, our findings provide preliminary evidence that CTP-based imaging biomarkers may not be able identify patients who are less likely to benefit from IVT prior to EVT.

Similar to our findings, a recent substudy of the DIRECT-MT trial demonstrated that the extent of infarction on baseline imaging – estimated using ASPECTS – was not associated with functional outcome at 90 days in the DIRECT-MT population.[12] Furthermore, the post-hoc analysis of the DIRECT-MT trial showed that the baseline infarct size did not modify the treatment effect of IV alteplase prior to EVT. Also, they showed that patients with extensive baseline infarction (i.e., ASPECTS 0-4) are highly unlikely to achieve functional independence at 90 days regardless of IVT administration prior to EVT.[12] More specifically, in the DIRECT-MT trial, only 3/25 (12%) patients with ASPECTS 0-4 achieved functional independence in the EVT alone arm compared to 5/31 (16%) of patients with ASPECTS 0-4 in the IVT prior to EVT arm. Due to the low number of patients with large CTP-estimated ischemic core volumes in the MR CLEAN-NO IV trial, our results might therefore not be applicable to patients with extensive perfusion deficits on baseline CTP.

Our findings are in contrast with a previous observational study from the MR CLEAN Registry, which collected data from stroke patients in the same healthcare system as the MR CLEAN-NO IV trial and found that CTP ischemic core volume was associated with functional outcome at 90 days.[16] Although the rate of IVT prior to EVT was higher in the MR CLEAN Registry (i.e., 72%) and patients who present later in the 0-6h time window may have more established infarcts, it is most likely that the contradictory conclusions can be explained by the limited sample size in both studies in addition to the fact that the accuracy of CTP may be different for patients who present in the hyperacute (i.e., 0-4.5h) vs. the early (0-6h) time window.[17]

Several limitations of our analysis should be noted. First, CTP was performed according to local acquisition protocols and therefore not routinely acquired in every admitted suspected stroke patient. As differences in acquisition protocols may influence the CTP results [18], this could have affected our results. However, all CTP data were centrally

processed using a single software package using a previously validated procedure. Also, CTP data used in this study reflect CTP in daily clinical practice.[14]. Furthermore, these acquisition-related differences in CTP results are commonly largely driven by differences in contrast medium injection protocols [18] 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. Second, only 259/539 (48%) patients included in the MR CLEAN-NO IV trial underwent baseline CTP imaging – depending on the local imaging protocol of the stroke center. Together with the fact that 32 CTP datasets could not be processed, this resulted in a relatively limited sample size. Third, the MR CLEAN-NO IV trial only included directly admitted patients who could be treated within 4.5 hours after stroke onset. Therefore, our results are not generalizable to the extended – 0-6h and 0-9h – time windows for IVT administration in acute ischemic stroke patients.

Conclusion

In directly admitted acute ischemic stroke patients who presented within 4.5 hours after symptom onset, CTP-based imaging biomarkers did not statistically significantly alter the treatment effect of IVT prior to EVT. However, our study sample was limited and therefore the results should be interpreted with caution. Until these results are confirmed in a pooled analysis of all randomized trials on EVT alone, CTP-based imaging biomarkers should not be used to withhold alteplase from EVT-eligible patients within 4.5 hours after symptom onset.

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Supplemental Material

Supplemental Table I. Univariable analysis of improved functional outcome (mRS) at 90 days. ASPECTS = Alberta Stroke Program Early CT Score; IVT = intravenous alteplase; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; OR = Odds Ratio.

Variables	OR (95% CI)	P value
CTP ischemic core volume (per 10 mL)	**0.81 (0.75-0.87)**	**<0.001**
CTP penumbral volume (per 10 mL)	0.98 (0.94-1.03)	0.49
CTP mismatch ratio (per 10 percentage point)	**1.17 (1.06-1.31)**	**<0.01**
Present CTP target mismatch (TMM) profile	**3.15 (1.51-6.57)**	**0.002**
ASPECTS	**1.17 (1.00-1.37)**	**0.05**
Age (per year)	**0.96 (0.94-0.98)**	**<0.001**
Pre-stroke mRS	**0.62 (0.46-0.82)**	**0.001**
NIHSS at baseline (per point)	**0.88 (0.85-0.92)**	**<0.001**
Onset-to-randomization time (per 10 min)	**0.95 (0.91-0.99)**	**0.01**
IVT administration	0.99 (0.61-1.59)	0.96

Supplemental Table II. Univariable analysis of functional independence (mRS 0-2). ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; IVT = intravenous alteplase; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; OR = Odds Ratio.

Variables	OR (95% CI)	*P* value
CTP ischemic core volume (per 10 mL)	**0.80 (0.71-0.88)**	**<0.001**
CTP penumbral volume (per 10 mL)	0.97 (0.92-1.03)	0.34
CTP mismatch ratio (per 10 percentage point)	**1.17 (1.02-1.37)**	**0.04**
Present CTP target mismatch (TMM) profile	**3.13 (1.34-7.94)**	**0.01**
ASPECTS	1.12 (0.95-1.34)	0.18
Age (per year)	**0.95 (0.93-0.97)**	**<0.001**
Pre-stroke mRS	**0.57 (0.39-0.81)**	**0.002**
NIHSS at baseline (per point)	**0.88 (0.84-0.93)**	**<0.001**
Onset-to-randomization time (per 10 min)	**0.93 (0.89-0.98)**	**0.01**
IVT administration	0.94 (0.55-1.59)	0.81

Supplemental Table III. Multivariable analysis of improved functional outcome (mRS) at 90 days. ASPECTS = Alberta Stroke Program Early CT Score; intravenous alteplase; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; aOR = adjusted Odds Ratio.

Variables	aOR(95% CI)	*P* value
CTP ischemic core volume (per 10 mL)	0.80 (0.60-1.04)	0.10
Age (per year)	**0.97 (0.95-0.99)**	**0.002**
Pre-stroke mRS	**0.59 (0.41-0.80)**	**<0.001**
Onset-to-randomization time (per 10 min)	**0.92 (0.88-0.97)**	**<0.001**
NIHSS at baseline (per point)	**0.90 (0.86-0.94)**	**<0.001**
IVT administration	1.24 (0.65-2.37)	0.52
CTP ischemic core volume × IVT administration	1.01 (0.86-1.19)	0.89
CTP penumbral volume (per 10 mL)	1.10 (0.93-1.30)	0.28
Age (per year)	**0.97 (0.95-0.98)**	**0.001**
Pre-stroke mRS	**0.72 (0.52-0.99)**	**0.049**
Onset-to-randomization time (per 10 min)	**0.93 (0.89-0.97)**	**0.001**
NIHSS at baseline (per point)	**0.87 (0.83-0.91)**	**<0.001**
IVT administration	2.05 (0.61-7.02)	0.25
CTP penumbral core volume × IVT administration	0.95 (0.86-1.05)	0.31
CTP mismatch ratio (per 10 percent points)	1.07 (0.71-1.66)	0.75
Age (per year)	**0.97 (0.95-0.99)**	**0.001**
Pre-stroke mRS	**0.65 (0.47-0.91)**	**0.013**
Onset-to-randomization time (per 10 min)	**0.92 (0.88-0.97)**	**0.001**
NIHSS at baseline (per point)	**0.88 (0.84-0.92)**	**<0.001**
IVT administration	**1.02 (0.54-1.92)**	**0.954**
CTP mismatch ratio × IVT administration	1.05 (0.82-1.34)	0.69
Present CTP target mismatch (TMM) profile	1.64 (0.13-21.2)	0.7
Age (per year)	**0.97(0.95-0.98)**	**<0.001**
Pre-stroke mRS	**0.65 (0.47-0.90)**	**0.01**
Onset-to-randomization time (per 10 min)	**0.93 (0.88-0.97)**	**0.001**
NIHSS at baseline (per point)	**0.87 (0.84-0.91)**	**<0.001**
IVT administration	0.77 (0.19-3.16)	0.7
CTP target mismatch profile × IVT administration	1.59 (0.35-7.14)	0.5
ASPECTS	1.23 (0.71-2.21)	0.47
Age (per year)	**0.96 (0.94-0.98)**	**<0.001**
Pre-stroke mRS	**0.72 (0.52-0.99)**	**0.04**
Onset-to-randomization time (per 10 min)	**0.93 (0.89-0.98)**	**0.003**
NIHSS at baseline (per point)	**0.88 (0.84-0.92)**	**<0.001**
IVT administration	1.57 (0.09-31.3)	0.76
ASPECTS × IVT administration	0.97 (0.69-1.34)	0.85

Supplemental Table IV. Multivariable analysis of functional independence (mRS 0-2). ASPECTS = Alberta Stroke Program Early CT Score; IVT = intravenous alteplase; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; aOR = adjusted Odds Ratio.

Variables	aOR(95% CI)	*P* value
CTP ischemic core volume (per 10 mL)	0.89 (0.60-1.29)	0.55
Age (per year)	**0.95 (0.92-0.97)**	**<0.001**
Pre-stroke mRS	**0.57 (0.37-0.87)**	**0.01**
Onset-to-randomization time (per 10 min)	**0.90 (0.84-0.96)**	**0.001**
NIHSS at baseline (per point)	**0.90 (0.84-0.95)**	**<0.001**
IVT administration	1.02 (0.42-2.46)	0.96
CTP ischemic core volume × IVT administration	0.93 (0.72-1.18)	0.55
CTP penumbral volume (per 10 mL)	1.20 (0.96-1.50)	0.1
Age (per year)	**0.95 (0.92-0.97)**	**<0.001**
Pre-stroke mRS	**0.66 (0.42-0.99)**	**0.05**
Onset-to-randomization time (per 10 min)	**0.91 (0.85-0.96)**	**0.002**
NIHSS at baseline (per point)	**0.86 (0.81-0.91)**	**<0.001**
IVT administration	3.42 (0.69-17.55)	0.14
CTP penumbral core volume × IVT administration	0.89 (0.78-1.01)	0.07
CTP mismatch ratio (per 10 percentage points)	1.25 (0.68-2.58)	0.51
Age (per year)	**0.95 (0.92-0.98)**	**<0.001**
Pre-stroke mRS	**0.63 (0.40-0.95)**	**0.033**
Onset-to-randomization time (per 10 min)	**0.92 (0.88-0.97)**	**0.002**
NIHSS at baseline (per point)	**0.87 (0.82-0.92)**	**<0.001**
IVT administration	**0.86 (0.38-1.98)**	**0.72**
CTP mismatch ratio × IVT administration	0.97 (0.65-1.39)	0.86
Present CTP target mismatch (TMM) profile	1.18 (0.04-35.2)	0.92
Age (per year)	**0.95 (0.92-0.98)**	**<0.001**
Pre-stroke mRS	**0.62 (0.40-0.94)**	**0.03**
Onset-to-randomization time (per 10 min)	**0.91 (0.85-0.96)**	**0.002**
NIHSS at baseline (per point)	**0.87 (0.82-0.92)**	**<0.001**
IVT administration	0.48 (0.07-3.20)	0.4
CTP target mismatch profile × IVT administration	1.95 (0.35-7.14)	0.5
ASPECTS	1.00 (0.49-2.15)	0.99
Age (per year)	**0.95 (0.92-0.97)**	**<0.001**
Pre-stroke mRS	**0.65 (0.42-0.98)**	**0.04**
Onset-to-randomization time (per 10 min)	**0.91 (0.85-0.96)**	**0.002**
NIHSS at baseline (per point)	**0.87 (0.82-0.92)**	**<0.001**
IVT administration	10.46 (0.01-24.01)	0.69
ASPECTS × IVT administration	1.08 (0.69-1.66)	0.72

Supplemental Table V. Univariable analysis of symptomatic intracerebral hemorrhage (sICH).
ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; IVT, intravenous alteplase; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, Odds Ratio.

Variables	OR (95% CI)	*P* value
CTP ischemic core volume (per 10 mL)	0.94 (0.73-1.09)	0.55
CTP penumbral volume (per 10 mL)	0.98 (0.87-1.10)	0.75
CTP mismatch ratio (per 10 percentage point)	1.00 (0.71-1.21)	1.0
Present CTP target mismatch (TMM) profile	1.49 (0.27-27.74)	0.71
ASPECTS	1.08 (0.76-1.74)	0.71
Age (per year)	1.03 (0.98-1.08)	0.26
Pre-stroke mRS	1.67 (0.89-2.93)	0.09
NIHSS at baseline (per point)	1.01 (0.92-1.11)	0.86
Onset-to-randomization time (per 10 min)	1.02 (0.91-1.13)	0.65
IVT administration	1.52 (0.47-5.85)	0.50