# Infarct volume after ischemic stroke as a mediator of the effect of endovascular thrombectomy on early postprocedural neurologic deficit

# Infarct volume after ischemic stroke as a mediator of the effect of endovascular thrombectomy on early postprocedural neurologic deficit

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*Objectives:* The beneficial effect of endovascular thrombectomy (EVT) on clinical outcome is assumed to be caused by reduced follow-up infarct volume (FIV), which could serve as an early imaging endpoint. However, the effect of EVT on the modified Rankin Scale (mRS) was poorly explained by FIV. NIHSS at 5-7 days could be a more specific measure of the effect of reperfusion therapy, as opposed to the mRS at 3 months. Therefore, we aimed to assess to what extent the effect of EVT on NIHSS is explained by FIV. *Materials and methods:* We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; $n$ = 500) trial to evaluate the mediating role of FIV within 1 week in the relationship between EVT and baseline adjusted NIHSS at 5−7 days. *Results:* Larger FIVs were associated with higher NIHSS after treatment (adjusted beta-coefficient (aβ) 0.47;95%CI 0.39-0.55). EVT was associated with smaller FIVs (β -0.35;95%CI-0.64 to -0.06) and lower NIHSS (β -0.63;95%CI-0.90 to -0.35). After adjustment for FIV, the effect of EVT on NIHSS decreased (aβ -0.47;95%CI-0.72 to -0.23), indicating that effect of EVT on neurologic deficit is partially mediated by FIV. Reduction of FIV explained 34% (95%CI;5%−93%) of the effect of EVT on the NIHSS at 5−7 days. *Conclusions:* Larger FIV was significantly associated with larger neurological deficits after treatment. Reduced infarct volume after EVT explains one third of treatment benefit in terms of neurological deficit. This suggests that FIV is of interest as an imaging biomarker of stroke treatment effect.

**Keywords:** Stroke—Endovascular treatment—Infarct volume—Treatment effect


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## Introduction

The modified Rankin Scale (mRS) at 3 months is currently used to evaluate stroke treatment success. The downside of a global measure at a relatively late timepoint is that several events, which are not necessarily stroke or treatment-related, could have occurred in the 90 days after stroke. This may have confounded the intervention outcome relation. This could explain why reduced follow-up infarct volume (FIV) only explained 12−14% of the effect of endovascular thrombectomy (EVT) measured on mRS, while it is presumed that the underlying mechanism of the beneficial effect of EVT is the prevention of lesion volume expansion.[1,2] It is not fully understood whether this limited explained proportion could be mainly attributed to imprecise quantification of the ischemic lesion or lack of specificity in measuring stroke-related outcome with the mRS.[3] Still, using such a 'late' measure will eventually limit new studies improving direct stroke related treatment success further. Earlier endpoints could attribute to more efficient clinical trial design.

An alternative primary stroke trial endpoint of interest is the National Institutes of Health Stroke Scale (NIHSS) score, indicating neurologic deficit.[4] This outcome measure could be considered an optimal primary endpoint for trials of acute treatment for ischemic stroke as this outcome measure is likely to balance between early imaging endpoints such as FIV and long-term patient-related outcome measures like the mRS. Previous studies found that NIHSS within 1 week after stroke treatment satisfied the requirements for a valid alternative endpoint. NIHSS assessed within 1 week after reperfusion therapy for ischemic stroke mediated a large part of the effect of intravenous thrombolysis (IVT) and EVT measured on mRS at 3 months.[5,6] Despite previous studies showed a relation between FIV and NIHSS, it is unclear up to what extent the effect of EVT measured on NIHSS is mediated by FIV.[5,7] A deeper understanding of the underlying mechanism of the effect of EVT between early imaging and clinical endpoints is needed before alternative endpoints are found suitable as a valid proxy to assess the effect of acute reperfusion therapies. Therefore, we aimed to assess to what extent the effect of EVT on baseline adjusted NIHSS is explained by FIV.

## Methods

We used individual patient data of patients enrolled in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands). In this trial, the effect of EVT within 6 h from symptom onset in addition to usual care (intervention group) versus usual care alone (control group) was evaluated in patients with a proximal intracranial arterial occlusion of the anterior circulation. Follow-up imaging by computed tomography angiography (CTA) or magnetic resonance angiography (MRA) was performed at 24 h after randomization to assess recanalization of the initial occluded segment. At 5 to 7 days after randomization, a non-contrast computed tomography (NCCT) scan was performed to assess FIV and hemorrhagic transformation. For this post-hoc analysis, patients were excluded if they died before the follow-up NCCT scan at 5-7 days could be performed or in case no NCCT scan was acquired prior to hemicraniectomy. Detailed information on the description of variables and the methods of MR CLEAN have been reported previously.[8] Ethical approval was obtained from the local institutional review boards of all participating centers, and written informed consent was obtained prior to randomization.[8]

### *Study measures*

Lesion volume at 5 to 7 days after randomization was semi-automatically identified on NCCT scans using validated software.[9] Lesion volumes were calculated by multiplying the number of voxels in the segmentation with the image voxel size. The segmentations were verified and corrected if needed by neuro-radiologists who were blinded to baseline characteristics and patient outcomes. Further details on the segmentation procedure have been described previously.[9,10] FIV assessed at 5 to 7 days after randomization was considered the potential imaging endpoint, also known as the mediating variable. Post-treatment neurologic deficit was measured according to the NIHSS assessed at 5 to 7 days after randomization by the attending physician. The NIHSS ranges from 0 to 42, with higher scores indicating more severe neurologic deficit.[4] Since NIHSS does not include death, we assigned patients who died within 1 week the maximum score of 42 to limit the risk of biased treatment effects by unequally distributed mortality rates over the treatment arms.[5] In the adjusted analyses, NIHSS at 5 to 7 days was adjusted for baseline NIHSS.[11]

### *Statistical analysis*

To understand the mediating role of FIV in the effect of EVT measured according to the NIHSS, we developed a statistical mediation model. To assess to what extent the effect of EVT (treatment) on the NIHSS at 5-7 days (outcome) can be explained by FIV (mediating variable, Fig. 1), we will use a mediation model according to the methods described by Baron and Kerry, and Vanderweele and Vansteelandt.[12,13]

Statistical validation of this model requires at least three conditions to be satisfied:

(1) There is a significant treatment effect on the outcome, pathway C;
(2) There is a significant treatment effect on the mediating variable, pathway A;

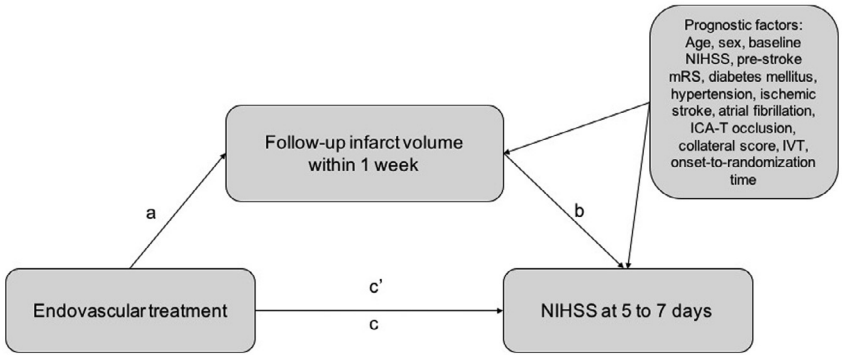


**Fig. 1.** *Mediation model.*

(3) There is a significant association between the mediating variable and the outcome while controlling for treatment, pathway B;
(4) The mediating variable explains part of the effect of treatment on the outcome, which means that the significant treatment effect on the outcome becomes not statistically significant or should be reduced (i.e., partial mediation) after adjusting for the mediating variable (pathway C′).[14–16]

This means that when treatment allocation and FIV are both used to predict NIHSS, FIV should still be a significant predictor, while the effect of EVT on NIHSS should be reduced compared to the effect of EVT on NIHSS without including FIV as a covariate.[14]

In patients with missing FIVs, values of infarcted volumes were imputed based on relevant baseline covariates, allocated treatment and functional outcome.[17] Due to a skewed distribution of FIV measurements, the confidence interval of the difference of measured median FIVs between both treatment groups was constructed by bootstrapping with 1000 replications. For the same reason, FIV was transformed to $\sqrt[3]{FIV}$ to achieve linearity for linear regression models. Pathway A, B, C and C′ were tested with linear regression models without and with adjustments for NIHSS at baseline, age, sex, medical history of diabetes mellitus, stroke, atrial fibrillation, hypertension, pre-stroke mRS, internal carotid artery terminus (ICA-T) occlusion, collateral score, IVT and time from stroke onset to randomization.

Effect estimates were presented as beta coefficients with corresponding 95% confidence interval (CI). To assess the proportion of the effect of EVT on NIHSS at 5–7 days that was explained by FIV, the beta coefficient of the indirect effect of EVT in pathway A-B was divided by the beta coefficient of the direct effect of EVT in pathway C.[16,18] The CI for the explained proportion of the effect of EVT by FIV was calculated with bootstrapping including 1000 replications. Since the 95%CI can exceed 0% and 100% based on this approach, we truncated the lower bound to 0% and the upper bound to 100%. All analyses were performed in R statistical software (version 4.0) with packages foreign, rms, gvlma and boot.

### *Sensitivity analysis*

We performed two sensitivity analyses. First, we imputed the NIHSS score for patients who died within 1 week instead of assigning them a score of 42 and we imputed FIV for patients who died or underwent hemicraniectomy before the NCCT scan at 5–7 days could have been performed. Second, we replaced missing FIVs at 5–7days with FIV assessed from NCCT scans acquired at 24 h after randomization.

## Results

### *Study population*

For the current study, we included 436 patients in our primary analysis after excluding 60 patients who died before the NCCT scan at 5–7 days after initial treatment could be performed and four patients in whom no NCCT was performed before hemicraniectomy (Fig. 2). In 99/436 (22.7%) patients no FIV could be assessed from NCCT at 5–7 days as no NCCT scan was performed due to early discharge ($n$ = 91) or because of poor scan quality ($n$ = 8). Baseline characteristics are shown per treatment allocation in Table 1. Median FIV in all patients was 67 mL (IQR 30–124), 53 mL (IQR 24–116) in the intervention arm and 81 mL (IQR 35-127) in the control arm.

### *Mediation analysis*

In step 1 of the mediation analysis, we tested the association between treatment allocation (i.e. usual care plus EVT versus usual care alone) and NIHSS at 5–7 days. Treatment allocation was a significant predictor of NIHSS at 5-7 days, EVT resulted in lower NIHSS compared to usual care (ß-coefficient -0.63, 95%CI -0.90 to -0.35). In step 2, we tested the association between treatment allocation and FIV. EVT was significantly associated with a reduction in transformed FIV (ß-coefficient -0.35, 95%CI -0.64 to -0.06). In step 3, we tested the association between FIV and NIHSS, with adjustment for treatment allocation.

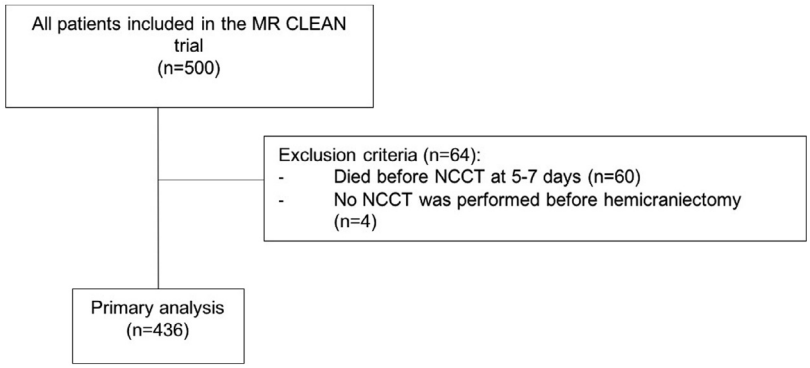


**Fig. 2.** *Flowchart of patients included in the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke (MR CLEAN).* Abbreviations*: n, number; NCCT, non-contract computed tomography.*

A larger FIV was significantly associated with higher NIHSS (adjusted ß-coefficient 0.47 per 10 mL, 95%CI 0.39−0.55). The effect of EVT on NIHSS remained statistically significant after adjustment for FIV (ß-coefficient -0.47, 95%CI -0.72 to -0.23, Table 2). We found that a reduction in FIV explained 34% (95%CI 5 - 93%) of the beneficial effect of EVT on NIHSS 5-7 days after treatment. Adjusted estimates were similar to unadjusted estimates.

### *Sensitivity analysis*

In the first sensitivity analysis, we also included 35 patients in the intervention group and 29 patients in the control group who died within one week or underwent hemicraniectomy before NCCT. For patients who died within 7 days, NIHSS at 5-7 days was set at 42. FIV measures were imputed based on single imputation based on chained equations. Steps of the analysis were consistent with the primary analysis, with an explained proportion of the effect of EVT by FIV of 32% (95% CI 0 to 100%), Table I of the Supplemental material). In the second sensitivity analysis, missing 5-7 days NCCT derived FIVs were replaced by FIVs assessed from 24 h NCCT, resulting in an explained mediated effect of 43% (95%CI 8 to 100%, Table I of the Supplemental material). For the latter analysis, FIVs from 24 h NCCT were not available for 30 patients.

## Discussion

In this study, we explored the role of FIV in explaining treatment effect on early neurologic deficit according to the NIHSS within 1 week after treatment. Smaller FIVs were significantly associated with lower NIHSS scores within 1 week after randomization. We observed that FIV partially explained the beneficial effect of EVT on NIHSS, although the explained proportion was still relatively small considering the relation between lesion volume and NIHSS. Thirty-four percent of the variance in NIHSS within 1 week after treatment could be explained by a difference in FIV. This suggests that quantification of the lesion could be a potential alternative early outcome to consider for the evaluation of new stroke treatments in addition to the NIHSS and mRS. Compared to the mRS, a larger proportion of the effect of EVT on NIHSS was explained by FIV, however, FIV did not explain a large proportion of the effect of EVT on neurologic deficit.

No previous study evaluated to what extent the beneficial effect of EVT on NIHSS could be explained by FIV.[1,2] One explanation for the limited explained proportion might be an inadequate quantification of the infarcted tissue volume which could be a result of oversimplification of the deleterious effects of infarcted tissue. This is supported by previous findings showing better prediction of functional outcome by including information on infarct location and the ratio of gray versus white matter loss, in addition to lesion volume, addressing the complexity of brain function in relation to the ischemic injury.[3,19,20] Besides, lesion volume might be a better predictor of clinical outcome when information on the capacity of a patient's brain to compensate for an acute ischemic event, in addition to age and baseline functional status, is taken into account.[21] Third, additionally factors can still contribute to the variation in NIHSS at 5-7 days after treatment (i.e. pneumonia, symptomatic intracranial hemorrhage) which are not fully captured by FIV.[22] Yet, to optimally evaluate the effect of a medical intervention, clinical trials should include endpoints that are both sensitive to detect treatment effects (e.g. early treatment specific endpoints such as asymptomatic bleeding, infarct volume and NIHSS) as well as clinically relevant, meaning a direct measure of something important to the patient (e.g. survival, level of daily functioning).[23] Therefore, selection of trial endpoints is important as it is expected to result in more efficient clinical trial design by minimizing the number of subjects required to be able to detect differences between stroke treatments at shorter follow-up time, consequently reducing trial costs and duration. Our findings suggest that quantification of lesion volume as an early important imaging endpoint might be relevant to assess the differences in ischemic stroke treatment. Future studies should focus on the thorough understanding of the

**Table 1.** *Baseline characteristics.*

| | Intervention group ($n$ = 198) | Control group ($n$ = 238) |
|---|---|---|
| **Patient characteristics** | | |
| Age, median [IQR] | 63 [53-73] | 66 [55-76] |
| Male sex, n (%) | 117 (59) | 134 (56) |
| NIHSS, median [IQR] | 17 [14-21] | 17 [14-22] |
| Left hemisphere, n (%) | 93 (49) | 118 (54) |
| SBP, mean (SD) | 143 (24) | 144 (25) |
| IVT, n (%) | 177 (89) | 216 (91) |
| **Medical history, n (%)** | | |
| Previous stroke | 23 (12) | 20 (8.4) |
| Atrial fibrillation | 54 (27) | 65 (27) |
| Hypertension | 80 (40) | 113 (48) |
| Diabetes mellitus | 23 (12) | 29 (12) |
| Myocardial infarction | 24 (12) | 35 (15) |
| Pre-stroke mRS | | |
| 0 | 166 (84) | 192 (81) |
| 1 | 17 (8.6) | 25 (11) |
| 2 | 8 (4.0) | 12 (5.0) |
| ≥ 3 | 7 (3.5) | 9 (3.8) |
| **Imaging, n (%)** | | |
| Occluded segment | | |
| ICA | 1 (0.5) | 3 (1.3) |
| ICA-T | 50 (25) | 65 (27) |
| M1 | 129 (65) | 146 (62) |
| M2 | 17 (8.6) | 21 (8.9) |
| A2 | 1 (0.5) | 2 (0.8) |
| ASPECTS subgroups | | |
| 0 - 4 | 6 (3) | 12 (5.1) |
| 5 - 7 | 42 (21) | 29 (12) |
| 8 - 10 | 150 (76) | 194 (83) |
| Collateral score | | |
| Absent | 4 (2.0) | 10 (4.3) |
| filling <50% of occluded area | 57 (29) | 50 (21) |
| filling ≥50% but less <100% | 76 (38) | 105 (45) |
| filling 100% of occluded area | 61 (31) | 70 (30) |
| **Workflow** | | |
| Time from stroke onset to randomization, min,median [IQR] | 200 [150-250] | 194 [149-267] |

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA-(T), internal carotid artery (terminus); IQR, interquartile range; IVT, intravenous thrombolysis; M(*segment*), middle cerebral artery; min, minutes; mRS, modified Rankin Scale; n, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; SBP, systolic blood pressure; y, year. Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (percentage).

relation between stroke treatment mechanisms and disease course. The evaluation of more sophisticated imaging approaches to increase insight into the pathophysiological process underlying the effect of acute reperfusion therapies for ischemic stroke could be considered. Detailed quantification of the lesion after stroke using MRI is likely to provide more accurate information on the brain tissue status and therefore be a better early imaging endpoint of interest for further reperfusion studies.

This study has several limitations. First, FIV measurements might be less accurate on CT compared to MRI, and treatment may have other pathophysiological effect that cannot be seen on CT. Furthermore, later measurements of FIV might have resulted in more precise estimates of dead tissue. However, a previous study evaluating the relation between FIV and functional outcome observed similar strengths of relation for both MRI and CT with mRS, as well as for early versus late measurements.[24] Second, by selecting the last scan of each patient for FIV assessment could have led to a bias, as it is likely that in patients with complications and neurologic deterioration more late imaging was performed. Third, both follow-up imaging and NIHSS assessment were performed within 1 week after randomization. To examine to

**Table 2.** *Explained proportions and effect sizes in the mediation analyses of the effect of intervention on National Institutes of Health Stroke Scale (NIHSS) mediated by follow-up infarct volume (FIV).*

| | | Primary analysis ($n$ = 436) | | | |
|---|---|---|---|---|---|
| | | Unadjusted analysis | | Adjusted analysis | |
| Steps of analysis | Pathway* | Effect estimate† | (95%CI) | Effect estimate† | (95%CI) |
| I | c | -0.63 | -0.90 to -0.35 | NA | NA |
| II | a | -0.35 | -0.64 to -0.06 | NA | NA |
| III | b | 0.47 | 0.39 to 0.55 | 0.39 | 0.31 to 0.47 |
| | c' | -0.47 | -0.72 to -0.23 | NA | NA |
| ß $_{FIV}$ # | | 0.45 | 0.37 to 0.53 | NA | NA |
| Explained proportion | | 34% | 5% to 93% | | |

*Each pathway is shown in Fig. 1.
†Beta coefficient.
#Beta coefficient of FIV (mediator) in pathway c' must be a significant predictor of the dependent variable, while controlling for the independent variable. Patients who died within 7 days after randomization and patients who underwent hemicraniectomy before NCCT were excluded for this analysis. For this analysis, NIHSS at 5-7 days was transformed for normal distribution of the residuals (√NIHSS).Abbreviations: 95%CI, 95% confidence interval.

what extent FIV mediates the relationship between EVT and NIHSS, assessment of FIV should be performed before assessment of NIHSS. However, it is likely that the estimated infarcted volume at 5-7 days after stroke does not differ significantly over a time span of several hours. As previously suggested, evolution of infarct lesion was associated with worse functional outcome.[25] Fourth, despite mediation analysis is increasingly applied in biomedical sciences to gain insight in the identification of early endpoints, different statistical approaches may in likewise manner be suitable to estimate the proportion of the mediation, such as calculating the product of regression coefficients, rather than the difference between them.[26] However, this is a larger concern for ordinal outcome measures, such as the ordinal mRS compared to continuous outcome measures.[27] Finally, to obtain trustworthy results from mediation analysis, unmeasured confounding must not exist between parameters in the hypothetical causal model (Fig. 1). This is a strong assumption, especially when we consider that the independent contributions of the interconnected biological processes to the final neurological outcome are not fully understood and are likely to vary among patients. However, we can expect that this unmeasured confounding effect is minimal, as patients were randomized and observers were blinded to information related to patients' status.

## Conclusion

Larger FIV was significantly associated with larger neurological deficits after stroke treatment. Reduction in infarct volume after EVT explains one third of the treatment benefit in terms of neurological deficit. This suggests that FIV might be of interest as an imaging biomarker of stroke treatment effect.

## Disclosures

Dr van Doormaal, reports consulting fees from Stryker. Dr van Zwam chairs DSMBs of WETRUST, Solonda and InExtremis studies, and received speaker fees from Stryker, Cerenovus and NicoLab, all paid to institution. Dr Majoie reports grants from CVON/Dutch Heart Foundation, TWIN Foundation, European Commission, Healthcare Evaluation Netherlands, and Stryker (paid to institution); and is (minority interest) shareholder of NicoLab. Dr Marquering is co-founder and shareholder of Nicolab. Dr Roozenbeek reports funding from the Dutch Heart Foundation and the Netherlands Organization of Health Research and Development, paid to institution. Dr Dippel and Dr van der Lugt report unrestricted grants from Stryker, Penumbra, Medtronic, Cerenovus, Thrombolytic Science, LLC, Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organization for Health Research and Development, Health Holland Top Sector Life Sciences & Health, and Thrombolytic Science, LLC for research, paid to institution. The other authors report no conflicts.

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enrolment, data collection, analysis, writing of the manuscript, approval of the manuscript, and decision to submit the manuscript for publication.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2022.106906.

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