Effect of stroke thrombolysis predicted by distal vessel occlusion detection

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Abstract: OBJECTIVE Among ischemic stroke patients with negative CT angiography (CTA), we aimed to determine the predictive value of enhanced distal vessel occlusion detection using CT perfusion post-processing (waveletCTA) for the treatment effect of IV thrombolysis (IVT). METHODS Patients were selected from 1,851 consecutive patients who had undergone CT perfusion. Inclusion criteria were (1) significant cerebral blood flow (CBF) deficit, (2) no occlusion on CTA, and (3) infarction confirmed on follow-up. Favorable morphologic response was defined as smaller values of final infarction volume divided by initial CBF deficit volume (FIV/CBF). Favorable functional outcome was defined as modified Rankin Scale score of 2 after 90 days and decrease in NIH Stroke Scale score of 3 from admission to 24 hours (NIHSS). RESULTS Among patients with negative CTA (n = 107), 58 (54%) showed a distal occlusion on waveletCTA. There was no difference between patients receiving IVT (n = 57) vs supportive care (n = 50) regarding symptom onset, early ischemic changes, perfusion mismatch, or admission NIHSS score (all > 0.05). In IVT-treated patients, the presence of an occlusion was an independent predictor of a favorable morphologic response (FIV/CBF: -1.43; 95% confidence interval [CI] -1.96, -0.83; = 0.001) and functional outcome (90-day modified Rankin Scale: odds ratio 7.68; 95% CI 4.33-11.51; = 0.039; NIHSS: odds ratio 5.76; 95% CI 3.98-8.27; = 0.013), while it did not predict outcome in patients receiving supportive care (all > 0.05). CONCLUSION In stroke patients with negative CTA, distal vessel occlusions as detected by waveletCTA are an independent predictor of a favorable response to IVT.

DOI: https://doi.org/10.1212/WNL.0000000000005519

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-151376
Accepted Version

Originally published at:
Kunz, Wolfgang G; Fabritius, Matthias P; Sommer, Wieland H; Höhne, Christopher; Scheffler, Pierre; Rotkopf, Lukas T; Fendler, Wolfgang P; Sabel, Bastian O; Meinel, Felix G; Dorn, Franziska; Ertl-Wagner, Birgit; Reiser, Maximilian F; Thierfelder, Kolja M (2018). Effect of stroke thrombolysis predicted by distal vessel occlusion detection. Neurology, 90(20):e1742-e1750.
DOI: https://doi.org/10.1212/WNL.0000000000005519
Effect of Stroke Thrombolysis Predicted by Distal Vessel Occlusion Detection

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Supplemental Data (eAppendix.pdf) is available for this submission.

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WORD COUNT MANUSCRIPT BODY: 2,710
WORD COUNT ABSTRACT: 240
CHARACTER COUNT TITLE: 76
NUMBER OF REFERENCES: 40
NUMBER OF FIGURES: 2
NUMBER OF TABLES: 3
SEARCH TERMS: Stroke [2], Embolism [5], CT [119]
AUTHORSHIP CONTRIBUTIONS:

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K.M.T. (study design, data analysis & interpretation, draft and revision of manuscript)

FUNDING:

None.

DISCLOSURES:

Dr. Kunz reports no disclosures.
Dr. Fabritius reports no disclosures.
Prof. Sommer reports no disclosures.
Dr. Höhne reports no disclosures.
Dr. Scheffler reports no disclosures.
Mr. Rotkopf, reports no disclosures.
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ABSTRACT

Objective: Among ischemic stroke patients with negative CT angiography (CTA), we aimed to determine the predictive value of enhanced distal vessel occlusion detection using CT perfusion-post-processing (waveletCTA) for the treatment effect of intravenous thrombolysis (IVT).

Methods: Patients were selected from 1,851 consecutive patients who had undergone CT perfusion. Inclusion criteria were: (1) significant cerebral blood flow (CBF) deficit, (2) no occlusion on CTA, and (3) follow-up-confirmed infarction. Favorable morphologic response was defined as smaller values of final infarction volume divided by initial CBF deficit volume (FIV/CBF). Favorable functional outcome was defined as modified Rankin Scale (mRS) score of ≤2 after 90 days, and decrease in National Institutes of Health Stroke Scale score of ≥3 from admission to 24h (∆NIHSS).

Results: Among patients with negative CTA (n=107), 58 (54%) showed a distal occlusion on waveletCTA. There was no difference between patients receiving IVT (n=57) vs. supportive care (SC) (n=50) regarding symptom onset, early ischemic changes, perfusion mismatch or admission NIHSS (all P>0.05). In IVT-treated patients, the presence of an occlusion was an independent predictor of a favorable morphologic response (FIV/CBF: β, -1.43; 95% CI, -1.96, -0.83; P=0.001) and functional outcome (90-day mRS: OR, 7.68; 95% CI, 4.33-11.51; P=0.039; ∆NIHSS: OR, 5.76; 95% CI, 3.98-8.27; P=0.013), while it did not predict outcome in patients receiving SC (all P>0.05).

Conclusion: In stroke patients with negative CTA, distal vessel occlusions as detected by waveletCTA are an independent predictor for a favorable response to IVT.
INTRODUCTION

Intravenous thrombolysis (IVT) is the mainstay of ischemic stroke therapy since 1995. Its goal is reperfusion of ischemic tissue by targeting occluded arteries, usually detected by computed tomography angiography (CTA). While some studies showed benefits of IVT in patients without occlusions on CTA, other studies did not. Several recent studies demonstrated larger treatment effects of IVT in patients with vessel occlusions.

The function of IVT relates to recanalization. However, recanalization does not always lead to reperfusion as suggested by pre-clinical and clinical observations. The no-reflow phenomenon refers to persisting perfusion lesions despite macrovascular recanalization and may be caused by microvascular obstruction. As spontaneous recanalization occurs, improved detection of blood clots as IVT targets may be important. Despite growing evidence, occlusions are not considered decision-relevant for IVT by current recommendations.

Angiography examinations are routinely performed as single-phase CTA to detect proximal occlusions, which are required for thrombectomy. However, drawbacks in CTA include low contrast-to-noise ratio, venous superimposition, and scan timing imprecisions, increasing the risk of missing vessel occlusions. About one third of centers routinely use CT perfusion (CTP), a dynamic acquisition of the brain. To overcome some CTA limitations, efforts were made to reconstruct angiographic data from CTP. Among these, CTP-based wavelet-transformed angiography (waveletCTA) enables distal occlusion detection in about 50% of patients without CTA evidence of occlusion but follow-up-confirmed infarction.

Therefore, our aim was to determine the predictive value of distal vessel occlusions detected by waveletCTA in patients with ischemic stroke but negative CTA.
METHODS

Study design, standard protocol approvals, registrations, and patient consents

The institutional review board of the LMU Munich (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München) approved this retrospective study, which was conducted according to the Helsinki Declaration of 2013, and waived requirement for informed consent. Based on a prospectively collected stroke registry, our initial cohort consisted of 1,851 consecutive patients who had undergone multiparametric CT including CTP for suspected ischemic stroke between December 2012 and December 2016.

Out of this cohort, we included all patients with

1. significant cerebral blood flow (CBF) deficits on CTP,
2. missing evidence of vessel occlusion on CTA, and
3. acute ischemic infarction as confirmed by follow-up MRI or CT within 72 hours.

We excluded patients with

1. non-diagnostic quality or incomplete raw datasets of CTP or CTA,
2. lacunar etiology of stroke, and
3. hemodynamic infarction pattern.

A significant CBF deficit was defined as the presence of a focal decrease in the color-coded CBF maps compared to the contralateral side on a minimum of two adjacent slices. 19 CTP exams had to be excluded based on non-diagnostic CTP quality or incomplete raw CTP datasets. Among 1,832 diagnostic CTP exams, we excluded 955 patients without CBF deficits, 655 patients with CTA-detected occlusions, 45 patients due to missing follow-up imaging, 29 patients due to missing infarction on follow-up imaging, 35 patients with confirmed lacunar
stroke and 6 patients with confirmed hemodynamic stroke. The flow chart of patient selection is shown in Figure 1. For the functional outcome analysis, patients with pre-stroke disability as assessed by the premorbid modified Rankin Scale with scores >1 and patients with missing clinical follow-up were excluded.

**CT examination protocol, image post-processing and wavelet transform**

All patients underwent standardized CT protocols consisting of non-contrast CT (NCCT), CTA, and CTP (the detailed acquisition protocol has been previously described\(^2^4\)). We used the angiographic reconstruction of waveletCTA from CT perfusion as described in detail and employed in previous studies.\(^2^4-^2^6\) Briefly, the principle of the algorithm is an analysis of each voxel's time attenuation curve with respect to its resemblance to the shape of a generic contrast bolus time attenuation curve. The wavelet transform then translates this resemblance into a power spectrum, of which the maximal values are interpreted as the angiographic signal intensity. An illustration of the angiographic reconstruction is provided in Figure e-1 in the Supplemental Data.

**Image analysis**

Early ischemic changes on NCCT were assessed using the Alberta Stroke Program Early CT Score (ASPECTS)\(^2^7\) in the case of middle cerebral artery (MCA) infarction. As there are no established scores for other vascular areas outside the MCA territory, we assessed such cases in a binary fashion determining either presence or absence of early ischemic changes\(^2^8\). All CTA examinations of the initial study cohort were reviewed in detail for vessel occlusions using multiplanar reconstructions with the option of maximum intensity projections by two
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experienced radiologists, a board-certified attending (W.H.S.) with over 10 years and a board-
certified fellow (K.M.T.) with over 6 years of experience in stroke imaging. CBF deficit, CBV
deficit and final infarction were volumetrically measured based on expert delineation using
OsiriX v.8.0.2 imaging software (Pixmeo, Bernex, Switzerland) as previously described29, an
approach that has been shown to be reliable and valid29-31. Cerebral blood flow (CBF)-cerebral
blood volume (CBV) mismatch was calculated as absolute volume (CBF deficit volume - CBV
deficit volume) and as relative mismatch ([CBF deficit volume - CBV deficit volume] / CBF
deficit volume). Final infarction volume (FIV) was assessed using diffusion-weighted MRI
(b=1000 s/mm²) or NCCT. Two readers independently evaluated the waveletCTA images with
respect to vessel occlusions and their location. Readers were blinded to all clinical data and
any other imaging studies or reconstructions.

Morphologic and functional outcome analysis

The primary morphologic outcome parameter was FIV. As secondary morphologic outcome,
we determined parameters that represent the morphologic course from ischemia to infarction
as applied in previous studies32-35, indicating the morphologic response to treatment. To
quantify the change from initial hemodynamic impairment to final infarcted tissue, we used
three calculated parameters as surrogates: FIV divided by the CBF deficit volume (FIV/CBF) is
a ratio of infarction to the initial ischemia. FIV divided by CBV deficit volume (FIV/CBV)
represents a ratio of infarction to initial ischemic core. FIV minus the ischemic core volume
divided by the ischemic penumbra volume ([FIV-CBV]/[CBF-CBV]) indicates the progression of
the ischemic area to the infarcted penumbra. For all three parameters alike, smaller values
imply more favorable morphologic outcomes.
The functional outcome was assessed using the modified Rankin Scale (mRS) score upon discharge and after 90 days. In addition, the National Institutes of Health Stroke Scale (NIHSS) score was assessed on admission and after 24 hours. 90-day mRS was defined as the primary functional outcome parameter. As secondary functional outcome parameters, discharge mRS and the change of the NIHSS score from admission to 24 hours (ΔNIHSS ≥3) as a marker of early neurological improvement were used. Pre-stroke disability was also evaluated using mRS. Clinical reasons for withholding IVT treatment are supplied in Table e-1 of the Supplemental Data.

**Statistical analysis**

We performed all statistical analyses using SPSS Statistics 23 (IBM, Armonk/NY, USA). Inter-reader agreement was assessed using Cohen’s $\kappa$. The study population was first stratified in four subgroups according to treatment status and detection of vessel occlusions. For the group comparison of categorical variables, a chi-squared test was performed. In case of continuous variables, group comparisons were analyzed by analysis of variance (ANOVA), in case of ordinal variables a Kruskal Wallis test was used. Multivariate linear and binary logistic regression analyses were performed to test the association between predictors and the dependent morphologic and functional outcome variables. These analyses were adjusted for age, sex, NIHSS on admission, early ischemic changes on NCCT, CBF deficit volume, CBV deficit volume as well as the relative CBF-CBV mismatch. All metric and ordinal variables are presented as median (interquartile range). Normal distribution was assessed using the Kolmogorov-Smirnov test. Categorical variables are presented as frequency and percentage. Two-sided $P$ values < 0.05 were considered to indicate statistical significance.
Data Availability

Anonymized data will be shared by request from any qualified investigator.
RESULTS

Patient Characteristics

The study population of 107 patients was analyzed in subgroups according to the treatment status (IVT vs. supportive care) and to the presence of a vessel occlusion as detected by waveletCTA (occlusion vs. no occlusion). The detailed patient characteristics are shown in Table 1. Overall, in 58 (54%) out of all patients with negative CTA, an occlusion was detected using waveletCTA. The inter-reader agreement of vessel occlusion detection was very good (Cohen’s $\kappa=0.864$).

IVT was administered in 57 patients (53%), the remaining 50 patients received supportive care (SC). The detected vessel occlusions showed similar distribution across vascular segments in IVT- and SC-treated patients (all with $P>0.05$). Group comparisons showed no differences in age, sex, time from symptom onset, presence of early ischemic changes, ASPECTS, relative CBF-CBV mismatch, or admission NIHSS (all with $P>0.05$). waveletCTA-detected occlusions were not associated with the premorbid or admission functional status (all with $P>0.05$). Differences among the groups were observed for CBF deficit volume, primary morphologic outcome parameters (FIV) as well as primary (90-day mRS) and secondary functional outcome parameters (discharge mRS, $\Delta$NIHSS) (all with $P<0.05$). For further statistical analyses with respect to independent associations with morphologic and functional outcome parameters, regression analyses were performed.

Predictors of Morphologic Outcome

In both treatment groups, no association of waveletCTA-detected occlusions with the primary outcome parameter FIV was present (all with $P>0.05$); a moderate association for a favorable
outcome was observed within the IVT-treated group ($\beta$, -7.43; 95% CI, -14.86, 1.82; $P=0.107$).

In patients receiving IVT, the presence of waveletCTA-detected occlusions demonstrated an association with smaller values of the morphologic response parameters FIV/CBF ($\beta$, -1.43; 95% CI, -1.96, -0.83; $P=0.001$) and $[\text{FIV-CBV}]/[\text{CBF-CBV}]$ ($\beta$, -4.54; 95% CI, -7.02, -2.07; $P=0.001$), indicating a favorable response, whereas no associations were found for patients that received SC (all with $P>0.05$). The results of the regression analysis are presented in Table 2. Representative patient examples for the IVT treatment response are shown in Figure 2. Graphic representations of the morphologic outcome parameters are provided in Figure e-2 to Figure e-4 in the Supplemental Data.

**Predictors of Functional Outcome**

In patients receiving IVT, associations for the presence of a waveletCTA-detected occlusion with favorable primary (90-day mRS $\leq 2$: OR, 7.68; 95% CI, 4.33-11.51; $P=0.039$) and secondary functional outcome parameters (discharge mRS $\leq 2$: OR, 8.33; 95% CI, 3.74-12.45; $P=0.042$; $\Delta\text{NIHSS} \geq 3$: OR, 5.76; 95% CI, 3.98-8.27; $P=0.013$) were observed, whereas no associations were found for SC-treated patients (all with $P>0.05$). The results of the logistic regression analysis are presented in Table 3. Further, a mRS reduction shift analysis yielded comparable results (Table e-2 in the Supplemental Data). A visual representation of the clinical course of the NIHSS score between admission and 24 hours thereafter is provided in Figure e-5 in the Supplemental Data.
DISCUSSION

This study investigated the predictive value of waveletCTA-based detection of distal vessel occlusions, that are not evident on CTA, in acute ischemic stroke patients. Patients with such occlusions who received IVT, in contrast to patients who received only SC, had more favorable morphologic outcomes independent of established predictors such as admission NIHSS, early ischemic changes or CBF-CBV mismatch. With respect to functional outcome, IVT-treated patients with waveletCTA-detected occlusions, as opposed to patients treated with SC, had more favorable primary and secondary functional outcomes, particularly a better neurological improvement measured by the difference in the NIHSS scores between admission and 24 hours thereafter.

Regardless of the recent success of endovascular thrombectomy in patients with large-vessel occlusions, IVT is still the mainstay of ischemic stroke therapy in the majority of patients\textsuperscript{1, 17}. Stroke patients without evidence of a vessel occlusion are known to have better functional outcomes\textsuperscript{36, 37}. However, there is no consensus on the differential treatment effect of IVT in patients with compared to patients without vessel occlusions. While earlier studies suggest that patients without evidence of vessel occlusions benefit from IVT\textsuperscript{2, 3}, two recent large studies were not able to find a significant benefit of IVT for this patient subgroup\textsuperscript{4, 5}. Another recent study on patients with small perfusion deficits of less than 15 mL, of which only 15\% showed an occlusion, also showed no benefit of IVT regarding functional outcome\textsuperscript{38}. The evaluation of patients with waveletCTA regarding the presence or absence of distal vessel occlusions, however, allows to further classify patients with negative CTA. The differential treatment effect of IVT in patients with compared to patients without waveletCTA-detected occlusions in our study could represent a possible explanation for the differences that were
observed in the above-mentioned studies. From a pathophysiologic point of view, the vessel-occluding clot as the primary target of a thrombolytic therapy represents a possible reason for the larger IVT treatment effect observed in our study.

Interestingly, waveletCTA-detected occlusions in IVT-treated patients were associated with favorable morphologic outcome parameters FIV/CBF and [FIV-CBV]/[CBF-CBV], which both consider the ischemic penumbra, but not FIV/CBV, which only accounts for the progression of the ischemic core to the final infarction. This could be explained by the pathophysiologic concept that distinguishes irreversibly damaged brain tissue (ischemic core) and potentially salvageable tissue-at-risk (ischemic penumbra). Integrating our observations in this concept, IVT might therefore be unable to influence the progression of the ischemic core to the final infarction irrespective of available therapeutic targets in the form of vessel occlusions.

Despite proven ischemic lesions on CTP imaging, we only observed underlying vessel occlusions in about half of the patients. Possible explanations are that (a) spontaneous recanalization has already occurred by the time of admission\textsuperscript{14, 15} or that (b) waveletCTA misses smaller occlusions due to the limited spatial resolution of contemporary CT imaging.

The presence of a high-grade extracranial stenosis was very low in the study population and evenly distributed across the subgroups. We therefore consider it unlikely that the ischemic lesions could have resulted from an extracranial stenosis.

The persistence of perfusion lesions despite macrovascular recanalization, also termed the no reflow-phenomenon, has been observed by several basic science studies on ischemic stroke\textsuperscript{7, 11, 12} as well as in human clinical ischemic stroke trials\textsuperscript{8-10}. It is known that oxidative stress signals resulting from hypoperfusion lead to microvascular obstruction mediated by capillary pericytes\textsuperscript{11, 12}. Targeting this mechanism conferred neuroprotection and improved outcomes in animal models of ischemic stroke\textsuperscript{13}, yet the relevance in humans remains unclear. In this
pathophysiological context, the added value of waveletCTA may be to triage patients with acute ischemic perfusion lesions based on the presence of a macrovascular occlusion, which represents the main target of IVT.

Despite the well-proven benefits of IVT, undertreatment of stroke patients remains an issue\textsuperscript{39}. A recent survey demonstrated that CTA findings are important influencing factors for 41% of North American neurologists regarding their decision of IVT administration\textsuperscript{40}. Thus, the identification of additional occlusions using angiographic CTP postprocessing techniques may support the decision-making process to increase diagnostic confidence and the use of IVT. However, in the light of equivocal data on the benefit of IVT in patients without evidence of occlusions on CTA, this aspect is not considered in the current guidelines on stroke management\textsuperscript{16, 17}.

There are limitations to this study that need to be considered when interpreting the results. First, this is a single-center study with a limited number of patients. However, as our results were consistent among different morphologic and functional parameters, we assume that larger studies will come to similar conclusions. Second, the retrospective design of our study makes it potentially prone to selection bias. Yet, all enrolled patients were recruited from a prospectively collected stroke registry and standardized stroke protocols were applied to minimize this potential bias. Third, based on the study design, no diagnostic standard of reference for waveletCTA-detected occlusions is available. However, in a previous diagnostic accuracy study using stroke patients with CTA-proven occlusions and control patients without follow-up infarction, waveletCTA demonstrated high specificity for occlusion detection\textsuperscript{24}. On the other hand, it should be acknowledged that the sensitivity of waveletCTA may be limited and that other reconstruction techniques may yield similar results. Four, expert visual delineation of CTP lesions was applied for volumetric assessment as the manufacturer's
automated analysis was not applicable to all vascular territories and misclassification of medium-sized lesions was observed. As no threshold could be applied in this approach, a differentiation from benign oligemic changes is potentially limited. Yet, all patients were included on the basis of a follow-up confirmed infarction. Moreover, reliability and validity of this approach has been shown by several studies\textsuperscript{29-31}. Nevertheless, further studies with larger patient cohorts will need to be conducted to validate the prognostic relevance of distal vessel occlusions with respect to efficacy and safety of IVT.

In our study on acute ischemic stroke patients, distal vessel occlusions as detected using wavelet-based CTP post-processing predicted a favorable response to IVT and may have potential implications in clinical decision-making.
ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

W.G.K. (concept and design of the study, acquisition and analysis of data, drafting manuscript and figures); M.P.F. (acquisition and analysis of data, drafting manuscript and figures); W.H.S. (concept and design of the study, acquisition and analysis of data, drafting manuscript and figures); C.H. (acquisition and analysis of data); P.S. (acquisition and analysis of data); L.R. (acquisition and analysis of data); W.P.F. (drafting manuscript); B.O.S. (drafting manuscript); F.G.M. (drafting manuscript); F.D. (drafting manuscript); B.E.-W. (drafting manuscript); M.F.R. (drafting manuscript); K.M.T. (concept and design of the study, acquisition and analysis of data, drafting manuscript and figures)

CONFLICTS OF INTEREST

Nothing to report.
REFERENCES


**FIGURE LEGENDS**

**Figure 1.** Flow chart of patient selection

Abbreviations: CBF, cerebral blood flow; mRS, modified Rankin Scale; CTA, CT angiography; CTP, CT perfusion.

**Figure 2.** Patient examples for the intravenous thrombolysis treatment response

59- and 56-year-old male patients A and B presented with a right-sided hemiparesis and similar NIHSS scores on admission, TfSO, ASPECT scores and CTP mismatch. Both patients received immediate IVT treatment. In patient A, a M3 segment vessel occlusion not evident on CTA was identified using waveletCTA (white arrow). In contrast, no occlusions were evident in patient B, neither on CTA nor on waveletCTA. Patient A showed a favorable morphologic and clinical outcome (final infarction volume: 1.2 mL, CBF deficit volume: 16.5 mL, 90-day mRS: 1). Patient B demonstrated an unfavorable morphologic as well as clinical outcome (final infarction volume: 25.4 mL, CBF deficit volume: 28.2 mL, 90-day mRS: 3). CTA and waveletCTA are presented as maximum intensity projections.

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; CTP, CT perfusion; DWI, diffusion-weighted imaging; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; CTA, CT angiography; TfSO, time from symptom onset; mRS, modified Rankin Scale.
TABLES

Table 1. Patient Characteristics Stratified by IV Thrombolysis Treatment and Occlusion Detection

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<th>IV Thrombolysis (n=57)</th>
<th>Supportive Care (n=50)</th>
<th>P Value</th>
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<td></td>
<td>Occlusion (n=35)</td>
<td>No Occlusion (n=22)</td>
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<tr>
<td>Age</td>
<td>75 (67-83)</td>
<td>71 (67-79)</td>
<td>73 (64-79)</td>
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<tr>
<td>Male sex</td>
<td>24 (68.6%)</td>
<td>11 (50.0%)</td>
<td>16 (69.6%)</td>
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<td>Time from symptom onset*</td>
<td>105 (90-150)</td>
<td>153 (105-210)</td>
<td>105 (60-210)</td>
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<td>MCA stroke</td>
<td>29 (82.9%)</td>
<td>17 (77.3%)</td>
<td>18 (78.3%)</td>
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<td>Imaging data</td>
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<tr>
<td>Early ischemic changes</td>
<td>10 (28.6%)</td>
<td>6 (27.3%)</td>
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<td>ASPECTS</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
<td>9 (9-10)</td>
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<td>Extracranial ≥70% stenosis</td>
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<td>1 (4.5%)</td>
<td>1 (4.3%)</td>
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<td>CBF deficit volume</td>
<td>24 (13-39)</td>
<td>8 (2-18)</td>
<td>18 (13-30)</td>
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<tr>
<td>CBV deficit volume</td>
<td>5 (2-11)</td>
<td>3 (2-6)</td>
<td>6 (2-16)</td>
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<td>CBF-CBV mismatch %</td>
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<td>68 (48-81)</td>
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<td>Final infarction volume</td>
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<td>7 (2-22)</td>
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<td>Functional data</td>
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<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Discharge mRS*</td>
<td>1 (1-2)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>90-day mRS*</td>
<td>1 (0-1)</td>
<td>1 (1-3)</td>
<td>3 (2-6)</td>
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<tr>
<td>Cardiovascular risk factors</td>
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</tr>
<tr>
<td>Arterial hypertension</td>
<td>25 (71.4%)</td>
<td>11 (50.0%)</td>
<td>14 (63.6%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (28.6%)</td>
<td>6 (27.3%)</td>
<td>10 (45.5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (37.1%)</td>
<td>3 (13.6%)</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9 (25.7%)</td>
<td>7 (31.8%)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (20.0%)</td>
<td>4 (18.2%)</td>
<td>6 (27.3%)</td>
</tr>
<tr>
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<tr>
<td>Etiology of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>11 (31.4%)</td>
<td>10 (45.5%)</td>
<td>10 (43.5%)</td>
</tr>
<tr>
<td>Arterio-arterial</td>
<td>13 (37.1%)</td>
<td>9 (40.9%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Other determined</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>10 (28.6%)</td>
<td>3 (13.6%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>2 (5.7%)</td>
<td>1 (4.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>2 (5.7%)</td>
<td>0 (0.0%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Type 1 (0.0%)</td>
<td>Type 2 (0.0%)</td>
<td>Extraischemic ICH (2.9%)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Parenchymal hematoma Type 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Extraischemic ICH</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Space-occupying edema</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Values presented are no. (%) for categorical and median (interquartile range) for ordinal and continuous variables. Proportion analysis tests for categorical variables were performed using the $\chi^2$ test. Nonparametric tests for continuous variables were performed using ANOVA, and for ordinal variables using the Kruskal Wallis test.

Abbreviations: ANOVA, analysis of variance; ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; ICH, intracranial hemorrhage; IV, intravenous; MCA, middle cerebral artery; mRS, modified Rankin Scale; n.a., not applicable; NIHSS, National Institutes of Health Stroke Scale. Bold P values are statistically significant.

* Missing values: Time from symptom onset 31/107, Discharge mRS 4/107, 24-hour NIHSS 4/107, 90-day mRS 17/107.
Table 2. Distal Vessel Occlusions and Morphologic Outcome in Treatment Subgroups

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Intravenous Thrombolysis</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Final infarction volume (FIV)</td>
<td>β (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Distal vessel occlusion</td>
<td>-7.43 (-14.86; 1.82)</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td>Ratio of final infarction volume to admission total ischemic volume (FIV/CBF)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Distal vessel occlusion</td>
<td>-1.43 (-1.96; -0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Ratio of final infarction volume to admission core ischemic volume (FIV/CBV)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Distal vessel occlusion</td>
<td>-1.92 (-4.76; 0.92)</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>Ratio of final penumbral infarction volume to admission penumbral ischemic volume ([FIV-CBV]/[CBF-CBV])&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Distal vessel occlusion</td>
<td>-4.54 (-7.02; -2.07)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

A multivariate linear regression analysis was performed for the indicated morphologic outcome parameters for the patients receiving intravenous thrombolysis or supportive care.

<sup>a</sup> Adjusted for age, sex, admission NIHSS, early ischemic changes, size of the perfusion deficit on CBF and CBV as well as the percentage of CBF-CBV mismatch.

<sup>b</sup> Total ischemic volume is based on the size of the CBF perfusion deficit.

<sup>c</sup> Core ischemic volume is based on the size of the CBV perfusion deficit.

<sup>d</sup> Penumbral ischemic volume is calculated as the size of the CBF minus the CBV perfusion deficit.

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; NIHSS, National Institutes of Health Stroke Scale. Bold values indicate statistical significance.
### Table 3. Distal Vessel Occlusions and Functional Outcome in Treatment Subgroups

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Intravenous Thrombolysis</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>90-day mRS ≤2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal vessel occlusion(^a)</td>
<td>7.68 (4.33; 11.51)</td>
<td><strong>0.039</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.71 (0.46; 6.37)</td>
</tr>
<tr>
<td>Discharge mRS ≤2</td>
<td>8.33 (3.74; 12.45)</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.64 (0.02; 17.62)</td>
</tr>
<tr>
<td>NIHSS improvement from admission to 24 hours (ΔNIHSS ≥3)</td>
<td>5.76 (3.98; 8.27)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 (0.01-18.77)</td>
</tr>
</tbody>
</table>

A binary logistic regression analysis was performed for the indicated functional outcome parameters for the patients receiving intravenous thrombolysis or supportive care.

\(^a\) Adjusted for age, sex, admission NIHSS, early ischemic changes, size of the perfusion deficit on CBF and CBV as well as the percentage of CBF-CBV mismatch.

Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio. Bold values indicate statistical significance.