Distance to Thrombus in Acute Middle Cerebral Artery Occlusion
A Predictor of Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke

Benjamin Friedrich, MD*; Matthias Gawlitza, MD; Stefan Schob, MD; Carsten Hobohm, MD; Mariana Raviolo, MD; Karl-Titus Hoffmann, MD; Donald Lobsien MD*

Background and Purpose—In patients with acute middle cerebral artery (MCA) stroke, therapeutic decisions are influenced by the location of the occlusion. This study aimed to analyze clinical outcomes in patients with acute ischemic MCA stroke treated with systemic intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator, according to the location of the occlusion.

Methods—Of 621 patients screened, 136 with acute stroke and MCA occlusion confirmed by CT angiography were retrospectively included in this study. The distance from the carotid T to the thrombus (DT) on coronal maximum intensity projection images and the thrombus length were measured. The correlation between DT and the modified Rankin Scale score at 90 days was analyzed.

Results—DT was an independent predictor of clinical outcome in stroke patients treated with IVT. A long DT was significantly correlated with a good clinical outcome (modified Rankin Scale score at 90 days ≤2). A poor clinical outcome was exponentially more likely than a good outcome when the DT was <16 mm (P<0.001). The thrombus length was not correlated with the modified Rankin Scale score at 90 days. A long thrombus (>8 mm) occurred significantly more often in the proximal MCA than the distal MCA (P<0.001).

Conclusion—DT is an independent predictor of clinical outcome in patients with acute MCA occlusion treated with IVT.

In acute stroke with MCA occlusion confirmed by CT angiography and DT <16 mm, the likelihood of a good clinical outcome after treatment with IVT was exponentially <50%. This might warrant the evaluation of other therapy forms than IVT in patients with proximal MCA occlusion. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008454.)

Key Words: middle cerebral artery occlusion ■ outcomes assessment ■ stroke ■ thrombosis

Ischemic stroke is a leading cause of death and physical impairment. In intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator is currently the standard treatment for acute ischemic stroke, although other acute therapies, such as mechanical thrombectomy, are promising as a recently published major trial (A Multi-Center Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR-CLEAN]) could show and are frequently used in selected cases, despite previous futile published multicenter trials. Various factors have been analyzed to determine whether they can predict outcome in patients with acute middle cerebral artery (MCA) occlusion treated with IVT, including the location of the thrombus and thrombus length. A proximal occlusion seems to correlate with an unfavorable outcome, and a long thrombus is associated with poor recanalization. In studies and management guidelines, the location of the occlusion is often described according to the segments of the MCA occluded (M1, M2, M3, or M4). However, despite the frequent use of these descriptions, the definitions used for the segments are variable, especially for M1. The M1 segment is classically defined as extending to the insular branches, including the bifurcation of the MCA, but it was recently recommended that M1 should be defined as extending from the carotid T to the first bifurcation of the MCA. Reported outcomes after M1 occlusion are therefore difficult to compare without knowing the definitions used. Furthermore, descriptions of the location of the thrombus according to these 4 segments are imprecise, as the segments are relatively long. As the location of the thrombus seems to be clinically important, it has been recommended that it should be precisely described. One recently used approach is to divide the M1 segment into proximal and distal M1 segments, either

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according to the origins of the lenticular perforators or by simply splitting it in half. However, this method only addresses the M1 segment, and the precise location of thrombus in the other segments remains unclear. Introduction of an objective, easy-to-assess, and precise method of describing the location of thrombus in the MCA is therefore important.

In this study, we measured the length of the MCA from the carotid T to the beginning of the thrombus (distance to thrombus [DT]) to avoid the above-mentioned problems and to obtain a continuous numeric parameter for comparison with outcomes in patients with acute MCA occlusion treated with IVT.

**Methods**

**Patient Selection**

Patients treated for ischemic stroke by our institution between January 1, 2009, and April 30, 2014, were retrospectively screened for eligibility. The inclusion criteria, according to criteria as published by Toni and colleagues, for the present study were as follows:

1. CT angiography (CTA)–proven vessel occlusion in the MCA territory.
2. Completed treatment with a full dose of IVT according to a previously published protocol. The thrombus length was measured on the CTA images, in accordance with the gold standard described in the study by Riedel and colleagues, and was categorized as <5, 5 to 8, or >8 mm based on their results.
3. Complete documentation of the clinical course, including the initial National Institutes of Health Stroke Scale (NIHSS) score, NIHSS score at 7 days, and modified Rankin Scale (mRS) score at 90 days (90d-mRS).
4. No additional vasculopathy in either a different intracranial territory or the cervical vessels (especially no relevant preceding stenosis).

**Image Analysis**

All CTA examinations were performed using a 64-section multidetector scanner (Brilliance 64, Philips, Best, The Netherlands) with a slice thickness of 1 mm. CTA images were reformatted in the coronal plane, and a 10-mm maximum intensity projection image was rendered using the free software Osirix (Pixmeo SARL, Switzerland). The exact location of the occlusion was determined, and DT was measured as the distance from the center of the carotid T to the beginning of the thrombus. The center of the carotid T was defined as the crossing point of the virtual elongation of the MCA, the internal carotid artery, and the proximal anterior cerebral artery. The DT was measured as a curved line along the center of the MCA (Figure 1). DT analysis was performed by a single rater (B.F.) with >5 years in stroke territory splitting it in half. However, this method only addresses the M1 segment, and the precise location of thrombus in the other segments remains unclear. Introduction of an objective, easy-to-assess, and precise method of describing the location of thrombus in the MCA is therefore important.

In this study, we measured the length of the MCA from the carotid T to the beginning of the thrombus (distance to thrombus [DT]) to avoid the above-mentioned problems and to obtain a continuous numeric parameter for comparison with outcomes in patients with acute MCA occlusion treated with IVT.

**Statistical Analysis**

Statistical analyses were performed using SPSS software version 20 (IBM, Armonk, NY). Data were tested for normality using the Shapiro–Wilk test. Correlations between clinical information and the DT or thrombus length were calculated using a correlation analysis with Spearman ρ. The probability of a good clinical outcome (defined as 90d-mRS ≤2) was calculated using logistic regression analysis. Differences between partially arbitrarily chosen groups of DT (<5 mm/5–10 mm/10–16 mm/16–30 mm/30 mm; the 16 mm value as a result of the logistic regression analysis) were analyzed with univariate analysis using ANOVA on ranks with a Tukey post hoc analysis followed by multivariate analysis. Noncontinuous variables like mRS and NIHSS are presented as median (interquartile range). All other data are shown as means±SD unless indicated otherwise. Statistical significance was set at P<0.05.

**Results**

Of 621 patients screened, 136 met the inclusion criteria for this study. The demographic characteristics of the patients are shown in the Table and Table I in the online-only Data Supplement.

We were able to identify the exact location of the occlusion and measure DT in all patients. The mean DT was 19±13.7 mm (range, 1–77 mm). Figure 1 shows a representative proximal occlusion and more distal occlusion (Figure 1A and 1B).

The probability of a good clinical outcome according to DT was evaluated using logistic regression analysis. There was an exponential relationship between DT and 90d-mRS. Logistic regression analysis showed that probability of good outcome was increasing with DT and became ≥50% at DT>16 mm (Figure 2; P<0.001).

There was a significant, however weak, negative correlation using Spearman ρ between DT and 90d-mRS (R= −0.21; P=0.014). There were also differences in outcome among different categories of DT: for DT <5 mm, only 20% of patients had a good clinical outcome; for DT >30 mm, 57% had a good clinical outcome (P=0.041). Statistical significance in good clinical outcome between DT<5 mm and DT=5 to 10 mm/DT=10 to 16 mm/DT=16 to 30 mm was shortly missed (P=0.054/0.061/0.087). The 90-day mortality rate was 55.6% in patients with DT<5 mm and 4.8% in patients with DT>30 mm (P=0.007; Figure 3A and 3B). There was no significant correlation using Spearman ρ between DT and the short-term change in neurological status (R=0.037; P=0.696), defined as the difference between the initial NIHSS score and the NIHSS score on day 7 after IVT (eg, DT<5 mm: NIHSS score improvement 4–2=2; DT>30 mm: NIHSS score improvement 3–1=2).

In a multivariate analysis, DT turned out to be an independent predictor of good clinical outcome with on odds ratio of 1.68 (95% confidence interval, 1.49–1.72), independent...
of all other clinical variables tested for (risk factors, Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification, baseline NIHSS, thrombus length, and time to treatment; Table II in the online-only Data Supplement). None of the obtained parameters were distributed normally.

We analyzed the clinical outcome according to the thrombus length. There was no significant correlation between the thrombus length and 90d-mRS ($R=0.153; P=0.32$), and there were no significant differences in clinical outcome among different categories of thrombus length ($P=0.698$). There was a highly significant negative correlation between DT and thrombus length: a longer thrombus occurred significantly more often with a short DT than with a long DT ($R=0.529; P<0.001$; Figure 4A and 4B).

### Discussion

We found that DT was a highly significant predictor of clinical outcome in patients with acute MCA occlusion treated with IVT.

There are few recent studies that compared the location of MCA occlusion on angiography (CTA or digital subtraction angiography) with clinical outcomes in patients with ischemic stroke. The likelihood of an unfavorable outcome was reported to increase with a more proximal occlusion in patients treated with IVT or mechanical thrombectomy. Studies used analyses based on the occluded MCA segment and restricted their comparisons to M1 segment occlusion with or without M2 segment occlusion. In their CT-based study, Rohan and colleagues$^8$ found that the length of M1 occlusion was significantly correlated with the clinical outcome. They measured the stump length, which is comparable with the DT we measured, but excluded it as a parameter from the outcome correlation analysis. Furthermore, they used a complicated analytic method based on evaluation of 4D-CTA images on dedicated workstations, which makes clinical application of their method in the acute setting difficult. In another angiography-based study, Behme and colleagues$^9$ analyzed patients treated by mechanical thrombectomy after M1 occlusion. They split the location of the M1 occlusion into 2 groups: a proximal group with occlusion of the lenticulostriate perforators visible on digital subtraction angiography, and a distal group without occlusion of the lenticulostriate perforators. They found that patients with proximal M1 occlusion had unfavorable outcomes compared with patients with distal M1 occlusion. These findings indicate the importance of determining the exact location of the vascular occlusion in MCA stroke when evaluating the prognosis or making therapeutic decisions. However, use of this system is restricted to assessment of the proximal segments of the MCA, and the complicated analytic method makes it difficult to compare findings among studies and difficult to use the system in acute settings. Measurement of the DT as in the present study seems to be more precise and more useful.

In their 2011 study, Riedel and colleagues$^9$ found that a thrombus length of ≥8 mm measured by their previously described noncontrast CT method was associated with a low rate of recanalization after IVT (<1%). They also found that patients with a long thrombus were unlikely to have a good clinical outcome. In our study, we found no correlation between thrombus length and the clinical outcome measured by 90d-mRS. However, a longer thrombus was significantly more frequent with a shorter DT. These data could be interpreted as if the location of the thrombus therefore seems to have a greater impact on the clinical outcome than thrombus length. It is possible that the effects on outcome attributed to recanalization in the study by Riedel and colleagues$^9$ were because of the location of the thrombus, which they did not include in their analyses.

The benefit of treatment of stroke with IVT has been shown in several large multicenter trials.$^7$ In many of these trials, the
type of occlusion was not included in the analyses and was not considered in the inclusion criteria. However, our data in combination with other published data suggest that the outcome after IVT varies according to the location of the occlusion. A recently published subgroup analysis of several large stroke studies found that patients with a single distal MCA occlusion (the equivalent of a long DT) had a high likelihood of a good clinical outcome independent of successful recanalization, which is the objective of IVT. As patients with a short DT have a poor outcome after MCA stroke treated with IVT, and the clinical outcome after distal MCA occlusion may be independent of the initial treatment success, it may be necessary to reconsider which patients actually benefit from IVT. Considering our results in combination with previously published results, it is possible that only patients with a specific type of occlusion benefit from IVT, for example, as those with a DT between 16 and 30 mm and a thrombus length of <5 mm. In a subgroup analysis of our data, these patients had the highest rate (>80%) of a good clinical outcome. However, because of the small sample size of this subgroup, this tendency did not reach significance and must be interpreted with caution.

This study is limited by its single-center, retrospective design and the relatively small number of patients. Because of the retrospective design, no data of vessel recanalization was available to evaluate this aspect in the light of our results. Another limitation is that only one, although experienced, rater measured the DT values and therefore we were not able to assess inter-rater reliability. Furthermore, the thrombus length as measured in this study has to be compared with caution.

Figure 3. Correlation between 90d-mRS and DT. A, There was a highly significant, however weak, correlation between DT and the clinical outcome as assessed by 90d-mRS after treatment with intravenous thrombolysis using recombinant tissue plasminogen activator ($R=−0.21; P=0.014$). B, There were significant differences in clinical outcome and mortality among patients in different categories of DT ($P=0.022$) with post hoc significances for DT<5 mm vs DT=16 to 30 mm and DT>30 mm ($P=0.041$ and $P=0.032$, respectively). DT indicates distance from the carotid T to the thrombus; and 90d-mRS, modified Rankin Scale score at 90 days.

Figure 4. Correlation between thrombus length and outcome. A, There were no significant differences in clinical outcome among different categories of thrombus length ($P=0.698$). B, A longer thrombus occurred significantly more often with a shorter distance from the carotid T to the thrombus ($R=0.529; P<0.001$).
with the studies of Riedel et al. 201014 and 201115 because the measurement could not be performed in exactly the same way because of the retrospective design and the imaging data available.

In conclusion, we found that DT was a highly significant predictor of clinical outcome in patients with acute MCA occlusion treated with IVT. Based on our results in combination with previously published results, IVT might not be the ideal treatment for all patients with acute MCA stroke and other therapy forms, for example mechanical thrombectomy, might be warranted. Advanced and easily obtainable imaging analysis that includes measurement of the DT and thrombus length may provide information that can improve patient triage and may enable specifically tailored therapy, thereby improving overall patient outcomes. The results could also play an important role for future multicenter trials as they enable to evaluate the benefit of IVT versus other treatment options exactly in those patients that have a low probability of a good clinical outcome with IVT.

Disclosures
None.

References
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### Supplemental Material

**Supplemental Table I: Patient characteristics based on DT subgroups**

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<th>0-5 mm</th>
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<td>30</td>
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<td>65%</td>
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<td>77 +/- 9</td>
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<td></td>
<td></td>
<td>(46; 91)</td>
<td>(53; 95)</td>
<td>(61; 92)</td>
<td>(27; 94)</td>
<td>(49; 88)</td>
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<td>17 (4 – 20)</td>
<td>16 (12 – 18)</td>
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<td>5 (2 -14)</td>
<td>3 (1 – 11)</td>
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<td><strong>Risk factors, n (%)</strong></td>
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<td>123 +/- 45</td>
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Supplemental Table II: Results of the logistic regression analysis in regard of good clinical outcome (90d-mRS ≤2)

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<td>Thrombuslength</td>
<td>1.848</td>
<td>0.597 - 5.7</td>
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Abstract

Distance to Thrombus in Acute Middle Cerebral Artery Occlusion
A Predictor of Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke

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図3 90d-mRSとDTの相関。A：DTと組換え型組織プランギノーゲン活性化因子を用いた静脈内血栓溶解療法後90日mRSで評価した臨床転帰の相関は有意であったが、弱かった (r = -0.21; P = 0.014)。B：DTの違いによって患者間で臨床転帰と亡別率に有意差が認められる (P = 0.022)。post hoc 検定ではDTが＜5 mmと16～30 mmもしくは＞30 mmに有意差があることが明らかになった (それぞれP = 0.041, P = 0.032)。DT：頚動脈から血栓までの距離。90d-mRS：90日目の変化 Rankin スコア。