Thrombus Migration in the Middle Cerebral Artery: Incidence, Imaging Signs, and Impact on Success of Endovascular Thrombectomy

Johannes Kaesmacher, MD; Christian Maegerlein, MD; Mirjam Kaesmacher; Claus Zimmer MD; Holger Poppert, MD; Benjamin Friedrich, MD; Tobias Boeckh-Behrens, MD; Justus F. Kleine, MD

**Background**—Thrombus migration (TM) in intracranial vessels during ischemic stroke has been reported in the form of case reports, but its incidence, impact on the technical success of subsequent endovascular thrombectomy and patients’ outcome have never been studied systematically.

**Methods and Results**—Retrospective analysis was done of 409 patients with isolated middle cerebral artery occlusions treated with endovascular thrombectomy. TM was observed (1) by analyzing discrepancies between computed tomographic angiography and digital subtraction angiography and (2) by comparing infarct pattern in the striatocapsular region with exact, angiographically assessed thrombus location within the M1-segment and the involvement of the middle cerebral artery perforators. Preinterventional infarction of discrepant regions (infarction in regions supplied by more proximal vessels than those occluded by the clot) was ensured by carefully reviewing available preinterventional multimodal imaging. Adequate imaging inclusion criteria were met by 325 patients. Ninety-seven patients showed signs of TM (26 with direct evidence, 71 with indirect evidence). There was no difference in the frequency of preinterventional intravenous recombinant tissue plasminogen activator administration between patients with TM and those without (63.9% vs 64.9%, P=0.899). TM was associated with lower rates of complete reperfusion (Thrombolysis in Cerebral Infarction score 3) (adjusted odds ratio 0.400, 95% CI 0.226-0.707). Subsequently, preinterventional TM was associated with lower rates of substantial neurologic improvement (adjusted odds ratio 0.541, 95% CI 0.309-0.946).

**Conclusions**—Preinterventional TM does not seem to be facilitated by intravenous recombinant tissue plasminogen activator and often occurs spontaneously. However, TM is associated with the risk of incomplete reperfusion in subsequent thrombectomy, suggesting increased clot fragility. Occurrence of TM may thereby have a substantial impact on the outcome of endovascularly treated stroke patients. (J Am Heart Assoc. 2017;6:e005149. DOI: 10.1161/JAHA.116.005149.)

**Key Words:** embolic stroke • endovascular recanalization • ischemic stroke • thrombectomy • thrombus • thrombus migration

Endovascular thrombectomy (ET) has evolved as the standard of care for patients suffering from acute ischemic stroke due to large vessel occlusions in the anterior circulation.¹⁻⁵ Timely⁶ and complete reperfusion⁷⁻⁸ is considered a key factor associated with salvaging the tissue at risk and good clinical outcomes. However, because of their different vascular architecture, not all regions supplied by the middle cerebral artery (MCA) are equally salvageable by ET.⁹⁻¹¹ Thrombi occluding the orifices of the lenticulostriate arteries have been shown to almost inevitably lead to striatocapsular infarction despite successful recanalization,¹¹ likely because they lack a collateral blood flow.¹² This is of clinical relevance, as more proximal M1 occlusions are associated with worse clinical outcome.¹³ Moreover, striatocapsular infarcts are often larger than might have been expected from the exact location of the thrombus (eg, involving the whole striatocapsular region despite the fact that the occlusion is confined to the lateral perforator group or even spares all perforators).¹¹,¹⁴,¹⁵ Three hypotheses have to be taken into account. First, secondary tissue damage that has arisen from either inflammatory tissue damage¹⁶,¹⁷ or delayed extrafocal degeneration¹⁸,¹⁹ may be the causal factor explaining these discrepancies. Second, occlusion of the...
perforator orifices during the course of thrombectomy has to be considered. Third and most likely, the “excess” infarction is related to thrombus migration (TM), ie, caused by a migrating thrombus that had blocked more proximal lenticulostrate arteries only temporarily but for a sufficiently long time to induce irreversible infarction in the dependent striatocapsular subterritories already prior to ET.

So far, TM has been described in a small cohort study in which reactive hyperemia in the MCA territory has been interpreted as a sign of TM15 or in studies in which sequential transcranial Doppler has been performed in patients suffering from intracranial large vessel occlusions.20,21 Further, TM has been witnessed and reported anecdotally in the form of case reports during diagnostic or therapeutic angiography or sequential CTAs.22-25 However, neither its incidence nor its dependency on the administration of intravenous (IV) recombinant tissue plasminogen activator (rtPA) or its relevance for ET has been studied systematically. This study aims to clarify whether a discrepancy between thrombus location and infarct size in the striatocapsular region supplied by the MCA perforators is possibly due to TM prior to ET. Further, we hypothesized that the occurrence of TM is a sign of thrombus instability and consequently has impact on the technical success of subsequent ET.

Methods

Study Population

A retrospective analysis of a prospective database including all consecutive patients subjected to digital subtraction angiography (DSA) with the intention to treat an isolated MCA occlusion between January 2007 and June 2016 (n=409) was carried out. We excluded patients with imaging inadequate to assess infarct extent (n=72) and patients with any other clinical condition that might interfere with clinical assessment of infarct severity (n=12, see study flowchart in Figure 1). The final study population consisted of 325 patients (297 M1 occlusions, 28 M2 occlusions). Baseline characteristics and risk factors were evaluated by reviewing patients’ clinical records. All procedures were in accord with the 1964 declaration of Helsinki and its later amendments and approved by the local ethics committee. Written informed consent of individual patients for this anonymized retrospective study was waived according to institutional guidelines.

Endovascular Treatment

Concordant with our institutional standard operating procedures, all stroke patients with CTA-proven large vessel occlusion in the anterior circulation were eligible for ET if the groin puncture could be performed within 6 hours after symptom onset and if the infarct on preinterventional noncontrast computed tomography (CT) did not exceed one-third of the MCA territory. Our center did not apply an age limit. Preinterventional IV rtPA was administered as a “bridging approach” if there were no contraindications (n=210; 64.6%). Procedures were performed under general anesthesia or conscious sedation. See Data S1 and S2 for device choice throughout the study period and device impact on rates of successful recanalizations. In total, 7 cases with spontaneous or IV rtPA-related partial or complete recanalizations as revealed by first intracranial DSA runs were observed throughout the study period. In these cases only diagnostic angiography was performed. Those cases were included in the analysis regarding factors associated with thrombus migration but were excluded for the analysis with regard to impact on technical success of thrombectomy because no maneuvers were performed.

Image Analysis

Technical Success of Thrombectomy

Thrombolysis in Cerebral Infarction (TICI)-graded recanalization success of ET was assessed by 2 neuroradiologists independently, with TICI-2b defined as reperfusion of more than 66% of the initially involved territory, according to the original TICI scale.26 In cases of discrepancies a consensus read was performed (see Kleine et al18 for interrater agreement). Successful recanalization was defined as ≥TICI-2b. First-pass recanalization was defined if ET was terminated after 1 maneuver (1 aspiration or 1 stent-retriever retrieval).

Definition of TM

Nearly all patients with an ischemic stroke in the anterior circulation had a thrombus movement or dislocation prior to its being “stuck” in the MCA (originating from either an internal carotid artery plaque or an atrial thrombus). However, the term “thrombus migration” in this case refers to a totally distinct pathophysiological process because either it describes how an atrial thrombus starts migrating into the aortic arch or it describes a process related to plaque rupture (eg, of an internal carotid artery plaque). We have defined thrombus migration as “secondly” occurring downstream migration in a vessel just as large as the thrombus diameter itself. Hence, the thrombus was stuck in the first place and started migrating again afterward.

Direct Evidence for TM

Preinterventional CT angiography (CTA) images were available in 221 cases (68.0%). A substantial difference between thrombus location on CTA images and thrombus location as revealed by first DSA runs was classified as direct evidence for TM (migration group A, see Figure 2).
Indirect Evidence for TM

Involvement of the MCA perforators (medial, middle, and lateral group, respectively) and the infarction of their respective supplied territory were classified as described in detail before (see Kleine et al for reliability and illustrations). Patients with infarction of any lenticulostriate artery territory, even if CTA and DSA revealed that the occlusion spared all MCA perforator groups, were classified as indirect evidence for TM (migration group B, see Figure 3). Additionally, patients in whom the infarct involved more proximal parts of the lenticulostriate territory than expected from the exact thrombus location were also classified as indirect evidence for thrombus migration (eg, infarct involves all proximal territories despite the occlusion being confined to the lateral perforator group, group C, see Figure 4).

Time Point of Discrepant Infarction

To ensure that the discrepancies between thrombus location and infarct size were due to preinterventional infarction and did not occur perinterventionally or postinterventionally, 2 experienced senior neuroradiologists (>5 years of experience) performed in consensus a detailed image analysis for all migration group B cases using all preinterventional images available: noncontrast CT, CTA, CT perfusion, DSA. Three criteria, if available, were taken into account to ensure preinterventional infarction: (1) preinterventional demarcation of the discrepant infarct area on noncontrast CT (see Figure 5, for example); (2) reactive hyper- or hypoperfusion as revealed on preinterventional CTP; and (3) basal ganglia blush and/or early venous drainage on first DSA runs as a sign of irreversible infarction (see Figure 5 for...
Based on a synopsis of these observations, the reader ultimately dichotomized cases with discrepancies regarding thrombus location and infarct size as evidence for preinterventional infarction or no evidence for preinterventional infarction. To exclude relevant a priori bias of the readers (ie, knowing that all cases to be rated had thrombus migration, which may have induced false positive ratings), all cases were mixed with an equal number of cases without TM, and specificity of the ratings were evaluated accordingly.

**Clinical Outcome and Classification of Hemorrhagic Transformation**

Clinical outcomes were measured as NIH Stroke Scale (NIHSS) scores at the day of discharge, which were assessed by a qualified stroke neurologist. Patients who died during the acute hospital stay were assigned a score of 42. A difference between baseline NIHSS and NIHSS at discharge ≥8 or an NIHSS score at discharge ≤1 was classified as “substantial neurologic improvement,” as this outcome measure has been shown to be a very sensitive parameter for stroke treatment effects.30

**Statistical Analyses**

All analyses were performed using IBM SPSS Statistics, release 23.0 (IBM, Armonk, NY). Frequency counts were compared using the Fisher exact test. Non–normally distributed data were compared using the Mann-Whitney U test, and normally distributed data sets were compared using the t test for independent samples. Logistic regression models were used to evaluate the impact of different variables on dichotomized outcome or technical success parameters. In total, 3 different logistic regression models were used (see Table S1): 1 technical (logistic regression model 1, LRM-1), adjusting for factors that have been associated with different physical clot properties, including patient’s age and time to first DSA series,31,32 prior administration of IV rtPA33 and

**Figure 2.** Thrombus migration vs stable clot position on sequential CTA/DSA. Upper row (A+B), case with direct evidence of thrombus migration; (A) coronary CTA reformation with 10 mm maximum intensity projection shows proximal MCA occlusion on the right side (arrow); (B) initial DSA runs before recanalization revealed significant thrombus dislocation (see arrow) to the distal M1-segment/Truncus inferior (migration group A); lower row (C+D), case with stable clot position; (C) coronary CTA reformation with 10 mm maximum intensity projection displays proximal thrombus end after MCA bifurcation (arrow); (D) unchanged thrombus position on first DSA runs before recanalization (arrow). CTA, computed tomographic angiography; DSA, digital subtraction angiography; MCA, middle cerebral artery.
device choice and 2 outcome models (logistic regression model 2 and 3, LRM-2 and LRM-3, respectively), which adjust for major outcome determinants in acute stroke, both including baseline NIHSS, time from symptom onset to recanalization, and age. LRM-3 additionally corrects for successful recanalization and rates of complete (TICI-3) recanalization.

Results

Patients

A set of 325 patients was included. Mean age was 71.9±14.4 years. Successful recanalization was achieved in 80.3% of patients (n=261). In 117 cases postinterventional DSA runs revealed complete reperfusion (TICI-3, 36.0%, n=117). Patients presented with severe neurological deficits (median baseline NIHSS 14) and improved to a median NIHSS of 7 at the day of discharge. Mean time from symptom onset to first DSA runs, precisely determinable for 305 patients, was 219.2±77.5 minutes.

Thrombus Migration

In total, 97 (29.8%) patients with signs of TM were identified. Twenty-six showed discrepancies of thrombus location between CTA and initial DSA runs (migration group A), 29 patients had a striatocapsular infarct despite the occlusion sparing all perforators, as revealed on a synopsis of CTA and first DSA runs (migration group B). Forty-two patients had a striatocapsular territory infarction that clearly exceeded the regions that were suggested by the exact perforator group.
involvement (migration group C). There were no differences in age (70.5±16.8 vs 72.5±13.3, \( P = 0.288 \)), sex (female: 53.6% vs 53.7%, \( P = 1.000 \)), baseline NIHSS (15 vs 14, \( P = 0.569 \)), the frequency of bridging thrombolysis (63.9% vs 64.6%, \( P = 0.899 \)), and risk factor distribution between patients with TM compared to those without signs of TM (see Table). Rates

**Figure 4.** Proximal striatocapsular infarct despite an occlusion confined to the lateral perforator group. A, First DSA runs before endovascular thrombectomy was performed revealed an occlusion involving only the lateral perforator group (see white arrows in A) while the proximal and middle perforator groups were perfused; B, postinterventional DSA runs revealed reperfusion of the lateral perforator group (see white arrows in B); C, postinterventional imaging revealed a complete striatocapsular infarction corresponding to a complete occlusion of all MCA perforators (migration group C).

**Figure 5.** Signs of preinterventional infarction. A, Distal MCA occlusion with clear evidence of preinterventional infarction of the striatocapsular region. First DSA runs prior to endovascular treatment revealed full perfusion of all perforators (compare pre- and postinterventional DSA, left side upper and lower row). Preinterventional CT before DSA revealed demarcation of striatocapsular infarcts (see arrows) and hypodensities on “stroke window” settings (right side lower row). B, Case with distal MCA occlusion and clear evidence of preinterventional infarction of the striatocapsular region. First DSA runs prior to endovascular treatment revealed full perfusion of all MCA perforators but basal ganglionic blush (see black arrows, left side lower row) and early venous drainage (left side, white arrows), suggesting an already occurred infarction. Postinterventional DWI (right side upper row) and FLAIR-sequence revealed complete striatocapsular infarct corresponding to a complete occlusion of all MCA perforators. CT, computed tomography; DSA, digital subtraction angiography; DWI, diffusion weighted imaging; FLAIR, fluid attenuation inversion recovery; MCA, middle cerebral artery.
of TM did not differ between patients receiving IV rtPA and those ineligible (13.5% vs 8.8%, \( P = 0.386 \)) also when analysis was confined to patients with sequential imaging available \((n = 221)\) and when only migration group A \((n = 26)\) is defined as TM. In this cohort the time window of TM is restricted to the interval after lysis (Table S2). Further, in 61 cases TM occurred without any association to IV rtPA administration. Either patients were ineligible for IV rtPA \((n = 35)\) or TM occurred prior to the administration of IV rtPA \((n = 26; \text{see Data S1})\).
Thrombus Migration Prior to Stroke Thrombectomy  Kaesmacher et al

Discussion

This study shows 4 major findings: (1) TM should be regarded as the first and foremost reason causing discrepancies between exact occlusion site (perforator involvement) and infarct size in the striatocapsular region supplied by the MCA; (2) TM is not infrequent, occurring in at least one-third of MCA occlusions; (3) the occurrence of TM does not seem to be facilitated by the use of IV rtPA and often occurs spontaneously; (4) TM independently predicted lower rates of complete recanalization, presumably as a sign indicating increased thrombus fragility, and hence was associated with lower rates of neurologic improvement.

The results were derived from a large prospective cohort of patients with a baseline severity symptom onset to DSA, etc) highly comparable to those of the large randomized trials. The data presented are thus representative of current standards in endovascular treatment of large vessel occlusions.

Olsen et al were the first to observe discrepancies among infarct size, reactive hyperemia, and thrombus location and suggested a model of “embolic migration” in MCA occlusions. Since then, further cases with clear discrepancies between infarct size and thrombus location have been reported. Saito et al observed discrepancies between thrombus location as revealed by DSA and infarct extent in the striatocapsular region. They reported 5 cases in which the occlusion was confined to the distal M1 segment or M2 branches, but the infarct involved the basal ganglia. Further, in a previous large-cohort study the correlation of infarct extent and exact thrombus location within the striatocapsular region was systematically investigated. Our results suggest that TM occurs frequently and causes preinterventional infarction of more proximal territories than expected by the thrombus location on preinterventional angiography imaging (CTA/DSA). The data presented also underscore that the literature on that topic may underestimate its incidence and especially its relevance for endovascular stroke therapy.

Interestingly, TM was found to occur with the same frequency in patients receiving IV rtPA as in those ineligible for IV treatment. Although TM has been reported after the use of IV rtPA, the evidence was clearly insufficient to conclude that IV rtPA favors TM. In contrast, our data militate against those assumptions, at least in the setting of timely subsequent ET. No significant association between IV rtPA and thrombus migration could be observed in group A cases, and in 61 out of 97 cases, TM occurred without administration of IV rtPA. Hence, our data suggest that TM is a phenomenon that is not predominantly caused by medical therapy; rather, it indicates that other factors (ie, thrombus histology and vessel anatomy) may be major predisposing factors.

Discrepancies between thrombus locations as revealed by CTA and subsequent DSA may also be caused by proximal thrombolysis, leaving more distal parts of the thrombus as the “newly formed” proximal end of the thrombus. However, first, this would imply that proximal thrombolysis accounts for discrepancies of roughly more than 10 to 20 mm, and second, as mentioned above, the administration of IV rtPA was not associated with the occurrence of these discrepancies. Another study has suggested that the use of IV rtPA affects thrombus stability and technical success of subsequent ET in distal MCA occlusions. However, the effects on complete reperfusion of TM seem to be independent of prior use of IV rtPA, as we corrected for this potential confounding effect of IV rtPA regarding this issue in multiple logistic regression.

The poorer outcome of patients with TM was shown to be mediated mainly through lower rates of complete recanalizations (see impact of adding rates of TICI-3 recanalizations to the logistic regression model). Logically, lower rates of TICI-3 recanalizations have been associated with less favorable neurologic outcome; however, its association with TM has never been studied so far. Incomplete recanalization in the setting of preinterventional TM may be caused by either preprocedural thrombus fragmentation during the course of migration or by increased rates of periprocedural thrombus fragmentation because migrated thrombi may generally be more fragile during the thrombectomy maneuver. We propose that preinterventional thrombus fragmentation might be the less prevalent event causing incomplete recanalization, as most intracranial thrombi have been shown to be unilocular. However, if pretherapeutic fragmentation of a thrombus is present, it is associated with poorer treatment effects of IV rtPA and ET. In contrast to the presumably low incidence of fragmented thrombi prior to endovascular treatment, periprocedural thrombus fragmentation during thrombectomy has been described as a common risk in endovascular stroke therapy. Several factors influencing its incidence have been suggested, including proximal flow modulation, device characteristics, and thrombus architecture. This study
also implies that if a sign of TM is observable on first DSA runs, it is desirable to pull out all the stops to reduce the—in this case a priori increased—risk of perinterventional thrombus fragmentation and adjust the technical approach and safety considerations accordingly, eg, by using aspiration techniques or additional proximal flow modulation.

This study has several limitations beyond the common limitations of an observational study. The results are likely to underestimate the true incidence of TM for several reasons. First, the discrepancies observable between CTA and DSA represent a short time period, and TM may occur before (false negative direct evidence for TM). Second, TM may occur in the distal M1 segment without reliable indirect imaging signs because this occlusion pattern lacks end-artery involvement (false negative indirect evidence for TM). Third, TM may occlude perforators for such a short time that irreversible ischemia does not occur (false negative indirect evidence for TM). Fourth, in 27 patients the time interval of thrombus migration cannot be narrowed down (Data S1). Correlations in these 27 patients are thus prone to biases. If patients receive IV rtPA but thrombus migration had occurred already, these cases may suggest a false positive “pseudocorrelation” between use of IV rtPA and the occurrence of thrombus migration. However, that bias should be primarily kept in mind if any statistical association between IV rtPA and thrombus migration had been observed. This was not the case, and, relatively speaking, it strengthens our conclusion that IV rtPA does not seem to facilitate thrombus migration. Fifth, our outcome analysis is based on discharge NIHSS scores and not on 3-month modified Rankin Scale scores, the most commonly used outcome measure in current stroke research. The NIHSS, however, is a dedicated scoring system more directly reflecting the multifaceted and complex neurologic damage caused by ischemic lesions. Further, short-term NIHSS scores have been shown to be a sensitive outcome measure in detecting small treatment effects and are less prone to confounding effects such as age and comorbidities. This particularly holds true because our institution did not apply an age limit, and thus, a considerable portion of octo- and nonagenarians were included (n=103). The mentioned reasons make this outcome measure particularly suitable for the purpose of this study, which is detecting small, TM-associated shifts in outcomes due to decreased rates of complete reperfusion. Last, we have ensured preinterventional infarct signs on multimodal imaging are generally subtle, and it is relatively difficult to ensure infarction of, eg, a small more proximally located territory on a native preinterventional CT or detect a blush or AV shunt affecting only the more proximal perforator group but sparing the medial ones. Of note, however, if the analysis had been redone and limited to migration group A and B cases as “confirmed” thrombus migration, the results would have remained basically the same.

Conclusion

TM occurs frequently, at least in about one-third of MCA occlusions. TM does not seem to be facilitated by the administration of IV rtPA and often occurs spontaneously. However, TM was associated with lower rates of complete reperfusion in subsequent ET, suggesting increased clot fragility. Occurrence of TM thereby has substantial impact on the outcome of endovascularly treated stroke patients.

Sources of Funding

This work was supported by the German Research Foundation and the Technical University of Munich in the framework of the Open Access Publishing Program.

Disclosures

None.

References

1. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serénia J, Abeleira S, Ribó M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallof M, Davalos A; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–2306.

2. Saver JL, Goyal M, Bonafe A, Diener H, Levy EJ, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Noegueira RG, Siddiqui AH, Yavagal DR, Baxter BW, De Vlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285–2295.

3. Campbell BC, Mitchell PJ, Kleing T, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oexley TJ, Wu TY, Brooks M, Simpson MA, Mittef F, Levi CR, Krause M, Harrington TJ, Fauler KC, Steinfort BS, Priglinger M, Ang T, Scoope R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers I, Ma H, Desmond PM, Donnan GA, Davis SM; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–1018.

4. Goyal M, Demchuk AM, Menon BK, Eesa M, Kremel J, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Karmal NR, Montanera WJ, Poppe AY, Rycikborst KJ, Silver FT, Shuabi A, Rampier D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linas G, Mandzba JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morris WJ, Weil A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–1030.

5. Berkhemer OA, Fransen PS, Beaum D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermel MJ, van Walderveen MA, Staals J, Hofmeier J, van Oostayaen JA, Lycklama a Nijholt GJ, Boiten J.
Thrombus Migration Prior to Stroke Thrombectomy

Kaesmacher et al

Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.

6. Sheth SA, Jahan R, Gralla J, Pereira VM, Nogueira RG, Levy EI, Zaidat OO, Saver JL; Trialists S-S. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol*. 2015;78:584–593.

7. Yoo AJ, Simonsen CZ, Prabhakaran S, Chaudhry ZA, Issa MA, Fugate JE, Linfante I, Liebeskind DS, Khatri P, Jovin TG, Kallmes DF, Dabus G, Zaidat OO; Cerebral Angiographic Revascularization Grading Collaborators. Refining angiographic biomarkers of revascularization: improving outcome prediction after intracerebral hemorrhage. *Stroke*. 2013;44:2509–2512.

8. Kleine JF, Wunderlich S, Zimmer C, Kaesmacher J. Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg*. 2017;9:117–121.

9. Bozzao L, Fantozzi LM, Bastianello S, Bozzao A, Fieschi C. Early collateral blood supply and late parenchymal brain damage in patients with middle cerebral artery occlusion. *Stroke*. 1989;20:725–740.

10. Decavel P, Vuiller F, Moulin T. Lenticulostriate infarction. *Front Neurol*. 2013;3:169.

11. Kleine JF, Beller E, Zimmer C, Kaesmacher J. Lenticulostriate infarctions after revascularization in patients presenting with acute stroke. *J Neurointerv Surg*. 2015;7:559–563.

12. Behme D, Kowall A, Weber W, Mptotsaris A. M1 is not M1 in ischemic stroke: the disability-free survival after mechanical thrombectomy differs significantly between proximal and distal occlusions of the middle cerebral artery M1 segment. *J Neurointerv Surg*. 2015;7:559–563.

13. Saito I, Segawa H, Shiokawa Y, Taniguchi M, Tsutsumi K. Middle cerebral artery occlusion: correlation of computed tomography and angiography with clinical outcome. *Stroke*. 1987;18:863–868.

14. Olsen TS, Lassen NA. A dynamic concept of middle cerebral artery occlusion and cerebral infarction in the acute state based on interpreting severe hyposmia as a sign of embolic migration. *Stroke*. 1984;15:458–468.

15. Gauderti M, De Lazzarondo SM, Vivien D. The “inflammatory penumbra” in ischemic stroke: from clinical data to experimental evidence. *Eur Stroke J*. 2016;20:1–27.

16. De Meyer SF, Denomre F, Langhauser F, Geuss E, Fluri F, Kleinschnitz C. Thrombomigration in stroke brain. *Stroke*. 2016;47:1165–1176.

17. Winter B, Brunecker P, Fiebach JB, Jungehulsing GJ, Kronenberg G, Endres M. Lenticulostriate infarction. *Stroke*. 1992;23:328–332.

18. Wintzer P, Heindel W, Cnyrim C, Niederstadt T, Chapot R, Heindel W. Lenticulostriate infarction: a sign of embolic migration. *Stroke*. 1998;29:1192–1195.

19. Yoon JH, Shin YS, Lim YC, Kim HS, Nam HS, Heo JH. Distal migration of carotid thrombus in a patient using oral contraceptives: a case report. *J Neurointerv Surg*. 2016;8:413–417.
Data S1.

Information on device choice

In total 18 patients with isolated MCA occlusions were treated in the years 2007 and 2008. Most of the patients subjected to angiography in this time period were treated either with the Phenox Clot retriever (PCR), intraarterial-thrombolysis using rtPA, the Merci-Retriever or a combination of the latter. We refer to those endovascular treatment regimens as ‘older devices’. In three cases the Solitaire AB Neurovascular Remodeling Device was used in its unfolded state for thrombus retrieval, which has been reported by other groups. Our institution was one of the first using this technique which had later on led to the development of the Solitaire™ FR Revascularization Device. In total, throughout the years 2007 to 2009 26 patients were treated with what we had defined as ‘older devices’ (see above). Usage of ‘older devices’ tended to be associated with lower rates of successful recanalization (65.4% vs 81.6%, p=0.068). Further, introduced in 2014, a total of 25 patients were treated with aspiration devices (ADAPT), 15 of them with adjunctive usage of stent-retrievers. In all other cases ‘up-to-date stent-retrievers’ were used (e.g. Trevo, Solitaire, pREset). Here, the rate of successful recanalizations did not differ between the devices which corroborates findings derived from the MR CLEAN study. The frequency of using older techniques (p=0.372) and aspiration devices (p=0.171) did not differ between patients with TM and those without. Further, TM was independently associated with lower rates of TICI-3 recanalization (adjusted OR: 0.400, 95%-CI: 0.226-0.707, p=0.002) after additionally adjusting for both, usage of aspiration devices and usage of ‘older devices’ in the logistic regression model used in the study. Additionally, we repeated statistical analysis confined to cases with ‘up-to-date’ equipment. TM was still found to be an independent risk factor for incomplete recanalizations. We thus believe that device choice did not severely bias our analysis regarding the influence of TM on recanalization success.
Data S2.

Time intervals of thrombus migration

In general, it is impossible to assess the exact time point of thrombus migration. However, time intervals can be narrowed down in the majority of cases (n=70/97).

1) In group A (n=26), the time interval is defined by the time from CTA imaging to intracranial DSA series. These patients have either received IV rtPA in a timely manner after CTA (n=19) or they were ineligible and bridging therapy was withheld (n=7). This group thus allows for conclusions regarding a potential effect of IV rtPA. However, no significant effect was observed: When analyzing all patients with available imaging (n=221) frequency of thrombus migration as revealed by direct evidence did not differ between patients receiving IV rTPA and those ineligible (13.5% vs 8.8%, p=0.386).

2) When indirect evidence suggests thrombus migration and no discrepancies between CTA and DSA series were observable, thrombus migration had to be occurred prior to any treatment. These cases of thrombus migration thus clearly occurred without any association to IV rtPA (n=44).
Table S1. Logistic regression models used in the study

| LR Model |   |   |   |   |   |   |   |
|----------|---|---|---|---|---|---|---|
| 1        | X | X | 0 | 0 | X | 0 | X |
| 2        | X | 0 | X | X | 0 | 0 | 0 |
| 3        | X | 0 | X | X | 0 | X | 0 |

LR, logistic regression; X, variable included into model; 0, variable not included into model; SR, successful recanalization; TICI-3-R, TICI-3 recanalization

Table S2. TM confined to patients with available sequential imaging and migration group A

| Patients with available sequential imaging (n=212) | No TM as revealed by sequential imaging (n=195) | TM (Group A) (n=26) | p   |
|-------------------------------------------------|-----------------------------------------------|---------------------|-----|
| Drip and Ship                                   | 19.0%                                         | 30.8%               | 0.193|
| IV rtPA                                         | 62.6%                                         | 73.1%               | 0.386|
| Time-to-lysis                                   | 110 (80-149)                                  | 100 (80-138)        | 0.505|
| Lysis-to-recanalization                         | 126 (87-179)                                  | 157 (108-243)       | 0.147|
| CTA to first DSA series                         | 77 (56-112)                                   | 113 (70-151)        | 0.043*|

*, p<0.05
### Table S3. Ratings of signs of preinterventional infarction

Ratings of signs of preinterventional infarction of migration group B (striatocapsular infarction despite no perforator occlusion) cases and respective controls (no striatocapsular infarction corresponding to an occlusion which spares all perforators)

| Case | Preinterventional demarcation on NCT | Hyperemia or Hypoperfusion on CTP | Perforator blush and early venous drainage | Synopsis |
|------|-------------------------------------|----------------------------------|------------------------------------------|----------|
| #1   | 0                                   | 1                                | 0                                        | 1        |
| #2   | 1                                   | 1                                | 1                                        | 1        |
| #3   | 0                                   | 1                                | 0                                        | 1        |
| #4   | 1                                   | 99                               | 0                                        | 1        |
| #5   | 1                                   | 1                                | 1                                        | 1        |
| #6   | 1                                   | 1                                | 1                                        | 1        |
| #7   | 1                                   | 1                                | 1                                        | 1        |
| #8   | 0                                   | 1                                | 1                                        | 1        |
| #9   | 0                                   | 99                               | 1                                        | 1        |
| #10  | 1                                   | 99                               | 0                                        | 1        |
| #11  | 99                                  | 99                               | 1                                        | 1        |
| #12  | 99                                  | 99                               | 1                                        | 1        |
| #13  | 99                                  | 99                               | 1                                        | 1        |
| #14  | 1                                   | 99                               | 0                                        | 1        |
| #15  | 99                                  | 99                               | 1                                        | 1        |
| #16  | 99                                  | 99                               | 1                                        | 1        |
| #17  | 1                                   | 1                                | 1                                        | 1        |
| #18  | 99                                  | 99                               | 1                                        | 1        |
| #19  | 99                                  | 99                               | 1                                        | 1        |
| #20  | 1                                   | 0                                | 0                                        | 1        |
| #21  | 1                                   | 1                                | 1                                        | 1        |
| #22  | 99                                  | 99                               | 0                                        | 1        |
| #23  | 0                                   | 0                                | 0                                        | 0        |
| #24  | 99                                  | 99                               | 0                                        | 1        |
| #25  | 1                                   | 99                               | 0                                        | 1        |
| #26  | 99                                  | 99                               | 1                                        | 1        |
| #27  | 99                                  | 99                               | 1                                        | 1        |
| #28  | 0                                   | 99                               | 0                                        | 0        |
| #29  | 1                                   | 99                               | 1                                        | 1        |
| #1C  | 0                                   | 0                                | 0                                        | 0        |
| #2C  | 0                                   | 1                                | 1                                        | 1        |
| #3C  | 0                                   | 0                                | 0                                        | 0        |
| #4C  | 0                                   | 0                                | 99                                       | 0        |
| #5C  | 0                                   | 0                                | 0                                        | 0        |
| #6C  | 0                                   | 0                                | 0                                        | 0        |
|   |   |   |   |   |
|---|---|---|---|---|
| #7C | 0 | 0 | 0 | 0 |
| #8C | 0 | 0 | 0 | 0 |
| #9C | 0 | 0 | 0 | 0 |
| #10C | 0 | 0 | 0 | 0 |
| #11C | 0 | 0 | 0 | 0 |
| #12C | 0 | 0 | 0 | 0 |
| #13C | 0 | 0 | 0 | 0 |
| #14C | 0 | 0 | 0 | 0 |
| #15C | 0 | 0 | 0 | 0 |
| #16C | 0 | 0 | 0 | 0 |
| #17C | 0 | 0 | 0 | 0 |
| #18C | 0 | 0 | 0 | 0 |
| #19C | 0 | 0 | 0 | 0 |
| #20C | 0 | 0 | 0 | 0 |
| #21C | 0 | 0 | 0 | 0 |
| #22C | 0 | 0 | 0 | 0 |
| #23C | 0 | 0 | 0 | 0 |
| #24C | 99 | 99 | 0 | 0 |
| #25C | 0 | 0 | 0 | 0 |
| #26C | 0 | 0 | 0 | 0 |
| #27C | 0 | 0 | 0 | 0 |
| #28C | 0 | 0 | 0 | 0 |
| #29C | 0 | 0 | 0 | 0 |
Table S4. Comparison of baseline characteristics of patients with direct and indirect evidence of TM and those without signs of TM

|                           | Direct evidence TM (Group A, n=26) | Indirect Evidence TM (Groups B and C, n=71) | P - Direct vs Indirect evidence TM | No TM (n=229) | P - Direct evidence TM vs No TM | P - Indirect Evidence TM vs No TM |
|---------------------------|------------------------------------|---------------------------------------------|----------------------------------|---------------|---------------------------------|-----------------------------------|
| Age                       | 73.1 +/- 19.9                      | 69.5 +/- 15.5                               | 0.406                            | 72.5 +/- 13.3 | 0.880                           | 0.142                             |
| sex, female               | 57.7% (15)                         | 52.1% (37)                                  |                                  | 53.7 (122)    | 0.836                           | 0.892                             |
| Baseline NIHSS            | 14 (9-17)                          | 15 (12-18)                                  | 0.194                            | 14 (11-17)    | 0.477                           | 0.267                             |
| Risk factors              |                                    |                                             |                                  |               |                                 |                                   |
| - Hypertension            | 73.1% (19)                         | 78.6% (55)                                  | 0.592                            | 74.8 (169)    | 0.815                           | 0.633                             |
| - Diabetes                | 26.9% (7)                          | 20.0% (14)                                  | 0.579                            | 15.9 (36)     | 0.171                           | 0.466                             |
| - AF                      | 57.7% (15)                         | 52.9% (37)                                  | 0.818                            | 52.7 (119)    | 0.682                           | 1.000                             |
| - Prior                   | 23.1% (6)                          | 17.1% (12)                                  | 0.560                            | 18.1 (41)     | 0.594                           | 1.000                             |
| Hemisphere, left          | 53.8% (14)                         | 42.3% (30)                                  | 0.361                            | 50.0 (114)    | 0.837                           | 0.278                             |
| Wake-up stroke            | 7.7% (2)                           | 5.6% (4)                                    | 0.657                            | 6.1% (14)     | 0.672                           | 1.000                             |
| Time-to-first DSA run (min)| 201 (167-239)                     | 214 (177-273)                               | 0.217                            | 206 (158-258) | 0.822                           | 0.135                             |
| IV rtPA bridging (%)      | 73.1% (19)                         | 60.6% (43)                                  | 0.341                            | 64.9% (148)   | 0.515                           | 0.572                             |
| Successful recanalization (%) | 76.9% (20)                  | 74.6% (54)                                  | 1.000                            | 82.5% (188)   | 0.590                           | 0.169                             |
| TICI-3 recanalization (%)  | 23.1% (6)                          | 19.7% (14)                                  | 0.779                            | 42.5% (97)    | 0.060                           | <0.001**                          |
| First-pass Recanalization (%) | 30.8% (8)               | 19.7% (14)                                  | 0.280                            | 28.1% (64)    | 0.819                           | 0.215                             |
| Time-to-recanalization (min)| 259 (239-328)        | 279 (241-332)                                | 0.532                            | 264 (204-320) | 0.492                           | 0.088                             |

TM, thrombus migration; AF, atrial fibrillation; TIA, transient ischemic attack; DSA, digital subtraction angiography; PH, parenchymal hemorrhage; **, p<0.001
Supplemental References:

1. Dippel DW, Majoie CB, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Lingsma HF, Koudstaal PJ, Treurniet KM, van den Berg LA, Beumer D, Fransen PS, Berkhemer OA, Investigators MC. Influence of device choice on the effect of intra-arterial treatment for acute ischemic stroke in MR CLEAN (multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands). *Stroke*. 2016;47:2574-2581
Thrombus Migration in the Middle Cerebral Artery: Incidence, Imaging Signs, and Impact on Success of Endovascular Thrombectomy

Johannes Kaesmacher, Christian Maegerlein, Mirjam Kaesmacher, Claus Zimmer, Holger Poppert, Benjamin Friedrich, Tobias Boeckh-Behrens and Justus F. Kleine

*J Am Heart Assoc.* 2017;6:e005149; originally published February 15, 2017; doi: 10.1161/JAHA.116.005149

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://jaha.ahajournals.org/content/6/2/e005149