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Original research

Bifurcation occlusions and endovascular treatment outcome in acute ischemic stroke

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ABSTRACT

Background A thrombus in the M1 segment of the middle cerebral artery (MCA) can occlude this main stem only or extend into the M1-M2 bifurcation. The occlusion pattern may affect endovascular treatment (EVT) success, as a bifurcated thrombus may be more prone to fragmentation during retrieval.

Objective To investigate whether bifurcated thrombus patterns are associated with EVT procedural and clinical outcomes.

Methods Occlusion patterns of MCA thrombi on CT angiography from MR CLEAN Registry patients were classified into three groups: main stem occlusion, bifurcation occlusion extending into one M2 branch, and bifurcation occlusion extending into both M2 branches. Procedural parameters, procedural outcomes (reperfusion grade and embolization to new territory), and clinical outcomes (24-48 hour National Institutes of Health Stroke Scale [NIHSS$_{FU}$] score, change in NIHSS scores between 24 and 48 hours and baseline Δ[NIHSS], and 90-day modified Rankin Scale [mRS] scores) were compared between occlusion patterns.

Results We identified 1023 patients with an MCA occlusion of whom 370 (36%) had a main stem occlusion, 151 (15%) a single branch, and 502 (49%) a double branch bifurcation occlusion. There were no statistically significant differences in retrieval method, procedure time, number of retrieval attempts, reperfusion grade, and embolization to new territory between occlusion patterns. Patients with main stem occlusions had lower NIHSS$_{FU}$ scores than patients with single (7 vs 11, p=0.01) or double branch occlusions (7 vs 9, p=0.04). However, there were no statistically significant differences in ΔNIHSS or in 90-day mRS scores.

Conclusions In our population, EVT procedural and long-term clinical outcomes were similar for MCA bifurcation occlusions and MCA main stem occlusions.

INTRODUCTION

Middle cerebral artery (MCA) occlusions are the most common large vessel occlusions in patients with acute ischemic stroke (AIS).[1] The configuration of the MCA is highly variable across patients.[2] Most often, the M1 main stem bifurcates into two M2 segments: the frontoparietal M2 and the temporal M2 (figure 1A).

A thrombus in the MCA can occlude the main stem only or extend into one or two of the M2 branches. This difference in occlusion pattern may affect endovascular treatment (EVT) success. For example, when the thrombus extends into both M2 branches, one stent retriever (or aspiration device) cannot capture both branches simultaneously, as it can only be extended into one branch. During EVT, the interventionalist positions the treatment device in one branch, expecting that the thrombus segment occluding the other branch will come along. However, these bifurcated thrombi can be refractory to retrieval, requiring multiple retrieval attempts aimed at alternating branches.[3–5] Increasing the number of retrieval attempts may reduce the chance of good outcome by increasing the procedure time, the risk of thrombus fragmentation and of other procedural complications.[6]

The use of two stent retrievers simultaneously has been reported for difficult cases where the bifurcated thrombus cannot be removed by a single stent retriever.[3–5 7–9] However, this novel technique has been reported only in individual case studies, which makes it questionable whether it is a safe technique to use.

In this study, we aim to investigate whether MCA bifurcation occlusions are different from MCA main stem occlusions for EVT procedural and clinical outcomes. Such information may support the development of (and need for) novel EVT techniques.

METHODS

Patient selection

Patients included in this study were recruited from the MR CLEAN Registry, a multicenter prospective observational registry of all patients undergoing EVT for AIS in the Netherlands.[10] This registry was approved by the central medical ethics committee of the Erasmus Medical Center Rotterdam, which served as the review board of all participating centers and granted permission to carry out the study as a registry (MEC-2014-235). All patients or legal representatives were provided with oral and written information on the registry and had the opportunity to withdraw consent to use their data.
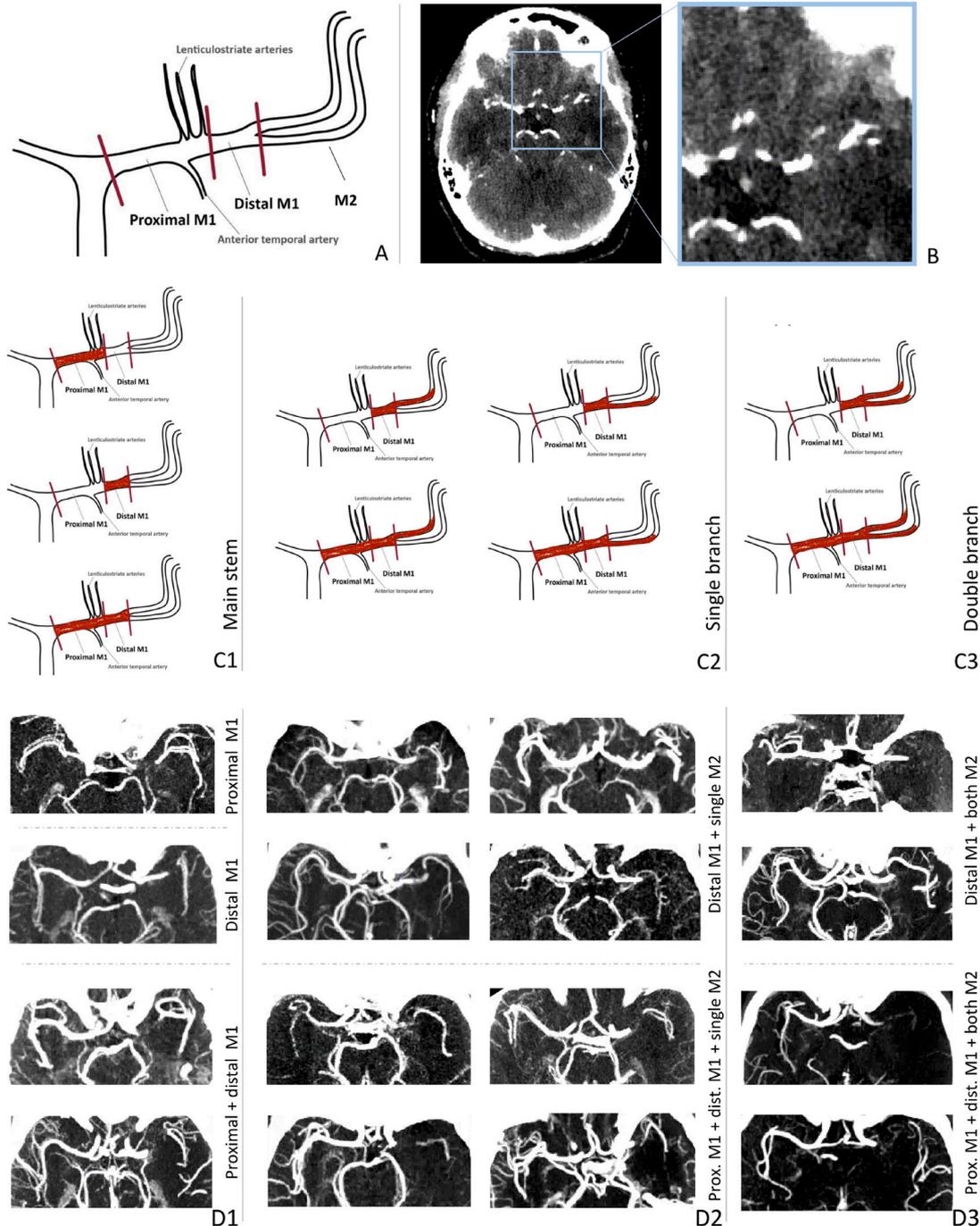
Figure 1 (A) Middle cerebral artery (MCA) configuration: proximal M1, distal M1 and the M2 bifurcation: frontoparietal M2 and temporal M2. (B) Axial view of a CT angiography (CTA) scan showing a proximal M1 occlusion, identifiable by a sudden stop of contrast filling. (C) Classification of MCA occlusion patterns: C1, main stem; C2, single branch; and C3, double branch occlusions. (D) Examples of thin-slab maximum intensity projections of CTA scans showing each occlusion pattern. Some scans are mirrored so all occlusions can be found on the right. (D1) Main stem occlusions where proximal M1, distal M1, or both proximal and distal M1 are occluded, from top to bottom. (D2) Single branch occlusion where the proximal and/or distal M1 and only one M2 branch (temporal or frontoparietal) are occluded. (D3) Double branch occlusion where the proximal and/or distal M1 and both M2 branches are occluded.

We included patients with AIS aged 18 years or older, with an MCA occlusion, who underwent EVT with a stent retriever (with or without aspiration) or aspiration device between March 2014 and November 2017. Patients without contraindications received 0.9 mg/kg of intravenous alteplase prior to EVT. The EVT approach and choice of material was left to the individual interventionalist. Source data for this study are not available owing to privacy regulations, but analysis methods, codes, and results are available from the corresponding author on reasonable request.

Data collection

All patients underwent a standard stroke imaging protocol at baseline, consisting of baseline non-contrast computed tomography (NCCT) and CT angiography (CTA). The MR CLEAN Registry imaging core laboratory, which has been involved in

all major clinical studies of the MR CLEAN Registry, assessed occlusion location, clot burden score (CBS), Alberta Stroke Program Early CT Score (ASPECTS), and collateral score. Core laboratory members were blinded to all clinical information except symptom side.[10]

Occlusion pattern classification

MCA segments were defined as follows: proximal M1, distal M1, M2-frontoparietal, and M2-temporal (figure 1A). M3 and more distal MCA segments were not considered in this study. The MR CLEAN Registry central imaging core laboratory assessed which MCA segments were occluded based on the contrast-filling defects found on baseline CTA (figure 1B). The central imaging core laboratory in charge of the CTA modality consisted of 31 interventional neuroradiologists with at least 5 years of experience assessing CTA scans in daily clinical practice. Each observer assessed a subset of the total number of these CTA scans. For the scoring, three views (axial, sagittal, and coronal) were used, aided with a maximum intensity projection of the CTA scan, if available. To ensure scoring-homogeneity, the observers were provided with training and guidelines of relevant definitions of each occlusion segment, including the scheme shown in figure 1A. The scoring of bifurcating M2 branches was performed based on the perfusion territory (frontoparietal vs temporal). This criterion was also applied for special cases like trifurcations or early bifurcations. If the scoring was not clear, the scoring was reviewed by a senior radiologist. Based on the scored occluded segment(s), we distinguished between patients with:

▶ An MCA **main stem** occlusion, where the proximal M1, distal M1, or both segments are occluded, but no M2 branches are occluded.

▶ A bifurcated thrombus with occlusion of the M1 segment and only one M2 branch (temporal or frontoparietal), i.e., **single branch** occlusion.

▶ A bifurcated thrombus with occlusion of the M1 segment and both M2 branches (temporal and frontoparietal), i.e., **double branch** occlusion.

A complete overview of these patterns is displayed in figure 1C,D.

EVT outcomes

For each occlusion pattern group, we compared the retrieval method (stent retriever vs aspiration), duration of EVT procedure, number of retrieval attempts, reperfusion grade, and presence of an embolus in a new (previously unaffected) vascular territory (ENT). Both reperfusion grade and ENT were assessed by the MR CLEAN Registry imaging core laboratory. Reperfusion grade after EVT was scored on digital subtraction angiography (DSA) according to the expanded Thrombolysis in Cerebral Infarction (eTICI) scale, ranging from 0 (no reperfusion) to 3 (complete reperfusion) and including a 2c score (99% reperfusion).[10] If only one DSA view was available a maximum of 2a was scored. The presence of ENT was identified on the last DSA run and defined as a remaining occlusion not matching the primary target occlusion on the first DSA run.

Functional outcome

Stroke severity at 24 to 48 hours' follow-up was assessed using the National Institutes of Health Stroke Scale ($NIHSS_{FU}$).[11] Change in NIHSS score between hospital presentation and follow-up was calculated according to: $\Delta NIHSS = NIHSS_{FU} - NIHSS_{BL}$. A negative $\Delta NIHSS$ value implies clinical improvement and a positive value means clinical deterioration. Patients' functional outcome was assessed with the modified Rankin scale (mRS) at 90 days through telephone or in-person interviews by trained nurses.[12] Presence of symptomatic intracranial hemorrhage (sICH) on follow-up NCCT was assessed by the MR CLEAN Registry core laboratory using the Heidelberg bleeding criteria for hemorrhage classification.[13]

Statistical analyses

In this exploratory study, we compared baseline clinical characteristics, EVT outcomes, and patient functional outcomes for the three occlusion patterns. Numerical data were reported as medians with IQR, and categorical data as numbers and percentages. The Kruskal-Wallis test was used to compare numerical data and the χ^2 test (or Fisher exact test) for categorical data. Statistical significance was set at $p < 0.05$. If a variable was statistically significantly different between the three groups, a post hoc analysis was performed to assess the pairwise differences: Mann-Whitney U test for numerical data, and pairwise χ^2 test (with Bonferroni corrections) for categorical data. To further evaluate the effect of observed baseline differences, we performed a subgroup analysis to investigate if similar trends in outcome variables are observed after stratification based on age. We further performed a subgroup analysis where we stratified the population based on the used first-line EVT approach (stent retriever (with or without aspiration) or aspiration alone). In addition, for each occlusion pattern, we assessed the impact of proximal M1 occlusions. All analyses were performed with IBM SPSS statistics package software (version 26.0).

RESULTS

Our study population consisted of 1023 patients. The patient inclusion flow chart can be found in the online supplemental figure S1. Of all included patients, 370/1023 (36%) patients had an MCA main stem occlusion, 151/1023 (15%) had a single branch occlusion, and 502/1023 (49%) had a double branch occlusion (online supplemental table S1).

Baseline characteristics

Baseline characteristics of the three subgroups can be found in table 1. Patients with main stem occlusions were slightly younger than patients with single branch (70 years vs 74 years, p=0.03) and double branch occlusions (70 years vs 73 years, p=0.03). Patients with main stem occlusions had a higher collateral score than patients with single branch and double branch occlusions (p<0.01). Main stem occlusions resulted in higher CBS than single branch (8 vs 7, p<0.01) and double branch occlusions (8 vs 6, p<0.01).

EVT outcomes

Stent retrievers were used as a first-line device in 72% of patients with main stem occlusions, in 75% of patients with single branch, and in 73% of patients with double branch occlusions (p=0.77). There were no statistically significant differences in duration of EVT procedure, number of retrieval attempts, reperfusion grade, and presence of ENT between the three groups (table 2).

Functional outcome

Patients with a main stem occlusion had lower $NIHSS_{FU}$ scores than patients with single branch (7 vs 11, p=0.01) and double branch occlusions (7 vs 9, p=0.04) (figure 2A).

Ischemic stroke

Table 1 Baseline characteristics of the three occlusion pattern groups

Baseline characteristics	Main stem (n=370)	Single branch (n=151)	Double branch (n=502)	P value
Age – median (IQR)	**70 (59–79)**	**74 (62–82)**	**73 (63–80)**	**0.03**
Sex, female – no./total (%)	174/370 (47)	73/151 (48)	255/502 (51)	0.54
Medical history – no./total (%)				
Previous stroke	60/368 (16)	27/149 (18)	93/500 (19)	0.67
Diabetes mellitus	63/369 (17)	18/150 (12)	87/500 (17)	0.27
Hypertension	185/364 (51)	83/147 (56)	274/495 (55)	0.33
Atrial fibrillation	87/367 (24)	37/147(25)	132/499 (26)	0.66
Pre-stroke mRS score – no./total (%)				0.43
0	243/363 (67)	91/147 (62)	327/491 (67)	
1	57/363 (16)	25/147 (17)	63/491 (13)	
2	26/363 (7)	8/147 (5)	35/491 (7)	
≥3	37/363 (10)	23/147 (16)	66/491 (13)	
Systolic blood pressure† (mm Hg) – median (IQR)	150 (130–166)	149 (130–165)	146 (130–162)	0.77
Diastolic blood pressure‡ (mm Hg) – median (IQR)	80 (71–91)	80 (70–90)	80 (70–90)	0.44
$NIHSS_{BL}$§ – median (IQR)	15 (11–18)	16 (12–20)	15 (11–19)	0.11
$ASPECTS_{BL}$¶ – median (IQR)	9 (8–10)	9 (8–10)	9 (8–10)	0.99
CS – no./total (%)				**<0.01**
0	**8/358 (2)**	**0/150 (0)**	**28/492 (6)**	
1	**75/358 (21)**	**56/150 (37)**	**179/492 (36)**	
2	**143/358 (40)**	**80/150 (53)**	**209/492 (42)**	
3	**132/358 (37)**	**14/150 (10)**	**76/492 (15)**	
CBS	**8 (6–8)**	**7 (5–7)**	**6 (4–6)**	**<0.01**
Treatment and workflow				
IVT – no./total (%)	277/370 (75)	112/151 (74)	365/502 (73)	0.66
Transferred patients – no./total (%)	191/370 (52)	89/151 (59)	281/502 (56)	0.24
Stroke onset* to first hospital presentation** (min) – median (IQR)	55 (38–104)	57 (40–105)	57 (40–101)	0.72
Hospital presentation to IVT†† (min) – median (IQR)	25 (19–32)	23 (17–33)	24 (18–33)	0.41
Stroke onset* to groin puncture (min) – median (IQR)	193 (150–255)	209 (160–270)	192 (147–255)	0.12

*Time of stroke onset was defined as the time of witnessed symptom onset or, if unknown, as the time the patient was last seen well.
†Missing value: 26.
‡Missing value: 31.
§Missing value: 13.
¶Missing value: 1.
**Missing value: 185.
††Missing value: 429
ASPECTS, Alberta Stroke Programme Early CT Score; BL, baseline; CBS, clot burden score; CS, collateral score; CT, computed tomography; IQR, interquartile range; IVT, intravenous treatment with alteplase; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

However, there were no statistically significant differences in the ΔNIHSS scores for the three occlusion patterns (online supplemental table S2). Patients with main stem thrombi had slightly lower mRS scores at 90 days than patients with bifurcated thrombi (figure 2B), although these differences were not statistically significant (p=0.58). There were no significant differences in the occurrence of sICH (online supplemental file 2).

The subgroup analysis, stratified by the median age of the study population, showed similar trends in older patients (age >72 years): main stem occlusion had lower $NIHSS_{FU}$ scores than patients with single branch occlusions (8 vs 13, p=0.01), but were not significantly different from double branch occlusions (8 vs 11, p=0.07) after adjusting with Bonferroni corrections. For younger patients (age <72 years): the three groups showed a median $NIHSS_{FU}$ score of 7 (p=0.46) (online supplemental table S3).

Subgroup analysis: first-line EVT approach
Stent retriever
The results of the stent-retriever subgroup analysis can be found in online supplemental table S4. We found no differences in EVT outcomes. Patients with main stem occlusions had lower $NIHSS_{FU}$ scores than patients with single branch occlusions (7 vs 10, p=0.03), but were not significantly different from double branch occlusions (7 vs 9, p=0.07) after Bonferroni corrections. There were no differences in ΔNIHSS or in mRS scores. We found differences in the occurrence of sICH between the three groups; however these differences did not remain when performing a post hoc analysis with Bonferroni corrections.

Aspiration
We found no differences in EVT or functional outcomes for the three occlusion patterns for patients treated with aspiration.

Table 2 EVT outcomes: first-line device used, duration of EVT procedure, number of retrieval attempts, eTICI scores, and ENT

EVT outcomes	Main stem, n=370	Single branch, n=151	Double branch, n=502	P value
First-line device				0.77
Stent retriever	268/370 (72)	114/151 (75)	368/502 (73)	
Aspiration	102/370 (28)	37/151 (25)	134/502 (27)	
Procedural time* (min) – median (IQR)	55 (36–80)	60 (37–89)	56 (38–83)	0.62
Retrieval attempts – no./total (%)				0.38
1	146/343 (42)	67/144 (47)	194/476 (41)	
2	68/343 (20)	28/144 (19)	127/476 (27)	
3	61/343 (18)	24/144 (17)	72/476 (15)	
4	33/343 (10)	10/144 (7)	34/476 (7)	
≥5	35/343 (10)	15/144 (10)	49/476 (10)	
eTICI scores – no./total (%)				0.55
0	27/362 (7)	14/148 (9)	35/494 (7)	
1	14/362 (4)	7/148 (5)	8/494 (2)	
2a	72/362 (20)	30/148 (20)	105/494 (21)	
2b	73/362 (20)	31/148 (21)	107/494 (22)	
2c	43/362 (12)	14/148 (9)	67/494 (14)	
3	133/362 (37)	52/148 (35)	172/494 (35)	
ENT – no./total (%)	11/336 (3)	6/138 (4)	22/465 (5)	0.59

*Missing values: 71.
ENT, embolization to new (previously unaffected) vascular territory; eTICI, expanded Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; IQR, interquartile range.

Results of the aspiration subgroup analysis can be found in online supplemental table S5.

Impact of proximal M1 occlusions
We found similar EVT procedural and functional outcomes in main stem and single branch patients with and without an occluded proximal M1 segment. The results can be found in the online supplemental tables S6 and S7.

We found significant differences in the distribution of eTICI scores in patients with a double branch occlusion: double branch patients with a proximal M1 occlusion had less often 2a scores than patients without a proximal M1 occlusion (12% vs 25%, p=0.04 after Bonferroni corrections). Double branch patients with a proximal M1 occlusion also had higher median $NIHSS_{FU}$ scores than patients without a proximal M1 occlusion (11 vs 8, p<0.01). However, we found similar $\Delta NIHSS$ and 90-day mRS scores in both groups. The results can be found in the online supplemental table S8.

DISCUSSION
In this study, we found no differences in EVT procedural outcomes based on MCA occlusion pattern groups, when comparing main stem, single branch, and double branch occlusions. We found that patients with main stem occlusions had better NIHSS scores at 24-48 hours than patients with bifurcated thrombi; however, there were no differences in $\Delta NIHSS$ scores or in long-term functional outcomes as measured with the 90-day mRS.

MCA main stem and bifurcation occlusions have previously been compared in 62 patients, where lower rates of successful recanalization were found in patients with bifurcated thrombi than in main stem thrombi, but no differences in long-term functional outcomes.[14] Studies comparing M1 and M2 occlusions have reported similar results for recanalization and complication rates.[15 16] Proximal and distal M1 occlusions have also been associated with similar post-EVT clinical outcomes.[17] Other studies showed that shorter distance from the internal cerebral artery terminus to an MCA occlusion is related to higher rates of successful recanalization after EVT.[18]

Successful recanalization of an MCA artery depends on multiple factors besides the occlusion pattern/location - to enumerate a few: MCA tortuosity has been associated with reduced stent-retriever thrombectomy success.[19] Smaller thrombi have been related to fewer EVT attempts, higher rates of successful recanalization, and better functional outcomes after EVT.[20 21] Red blood cell-rich thrombi may be more prone to fragmentation during retrieval than fibrin-rich thrombi.[22] The occlusion dynamics (ie, the way the thrombus occludes the vessel) might affect thrombus removal: emboli can be bent and folded while traveling along the vascular system before they obstruct a vessel.[23 24] Ultimately, all these thrombus characteristics result in a wide spectrum of
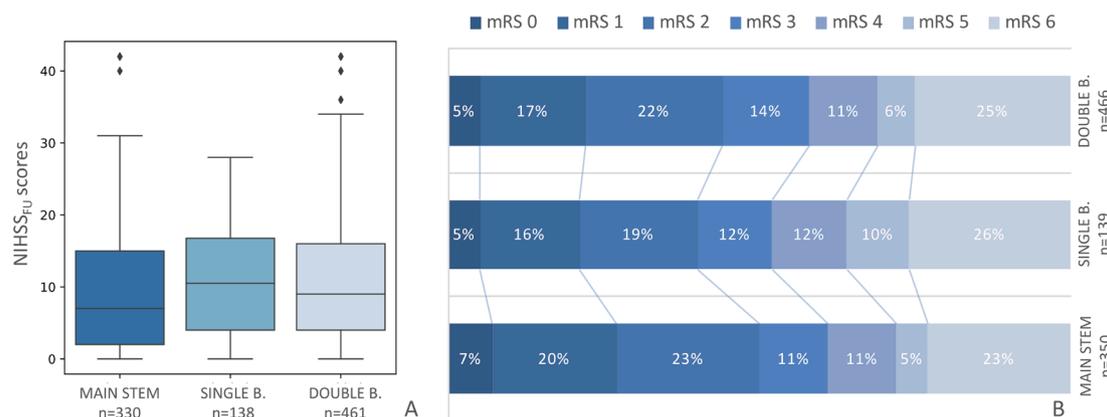
Figure 2 2(A) Neurological deficit assessed by the National Institutes of Health Stroke Scale (NIHSS) scores at 24–48 hours ($NIHSS_{FU}$) for patients with main stem, single branch, and double branch middle cerebral artery (MCA) occlusions. Patients with main stem occlusions have lower $NIHSS_{FU}$ scores than patients with single branch (p=0.01) and double branch (p=0.04) occlusions. (B) Functional outcome assessed by the modified Rankin scale (mRS) at 90 days for patients with a main stem, single branch, and double branch MCA occlusions. Between-group differences are not significant (p=0.58).

biomechanical responses, which may affect thrombus-device interaction, and therefore thrombus retrieval.[25–27]

We found higher $NIHSS_{FU}$ scores in patients with MCA main stem thrombi than in those with bifurcated thrombi, while the 90-day mRS scores remained similar. NIHSS scores at 24-48 hours may better reflect consequences of the procedure than mRS scores at 3 months. The mRS score lacks specificity compared with the NIHSS score, since it accounts for all patient disabilities (even if they are not related to the AIS) and is a more coarse scale, including 7 rather than 42 levels.[28] The longer the time between treatment and outcome assessment, the more probable that the outcome score will be affected by other factors, such as patient comorbidities or adverse effects at a later stage.

On the other hand, given that the procedural parameters were similar between the three groups, the observed difference in $NIHSS_{FU}$ scores might be due to other between-group differences, e.g., age, and not because of the occlusion patterns. The stratification analysis showed that when comparing patients with similar ages, the distribution of $NIHSS_{FU}$ scores remain different only for older patients.

The occlusion pattern can affect the length and complexity of procedures (which are associated with functional outcome), and it can also directly affect the functional outcome of the patient, regardless of the treatment. Main stem occlusions are less extensive (higher CBS) than bifurcation occlusions. A higher CBS has previously been related to better patient functional outcome.[29] However, we found no such differences in functional outcome among the occlusion pattern groups.

In patients with double branch occlusions, we found that patients without an occluded proximal M1 segment had more eTICI 2a scores than patients with an occluded proximal M1, while the other eTICI categories remained similar. An eTICI score of 2a implies partial reperfusion ($\leq 50\%$) of the target vascular territory. A bifurcated thrombus also occluding the proximal M1 segment could potentially better integrate with the stent since it has a larger stent-thrombus contact area, and therefore has a lower chance of fracture during retrieval than a shorter thrombus occluding only the distal M1 segment and the bifurcation. On the other hand, this finding could also be due to other factors, e.g., an uneven distribution of the single DSA views over the patients might also have caused this difference in eTICI 2a scores. Nevertheless, the ΔNIHSS and 90-day mRS scores remained similar for both groups.

The use of dual stents has been reported in the literature as a solution for refractory thrombi located in bifurcations.[3–5] This approach was not used in our patient cohort. In our patient cohort, bifurcation occlusions are not different from main stem occlusions for EVT outcomes, and therefore our results do not a priori encourage the use of a double stents for bifurcated thrombi. However, the thrombus imaging and histological characteristics of these refractory thrombi should be further studied and considered when developing novel EVT techniques.

Limitations

Occlusion patterns were scored on single-phase CTA by human eye. As such, some inaccuracy and interobserver variability might have been introduced. Poor distal contrast filling might have caused misclassification. Patients with a double branch occlusion might be misclassified if there is a main stem occlusion in combination with poor collateral distal filling. This might be reflected in the EVT outcomes: patients with double branch occlusions had similar outcomes to patients with main stem occlusions, and had better outcomes than patients with single branch occlusions. Assessment on multiphase CTA could improve the classification of the occlusion pattern. Combined CTA- and NCCT-based thrombus segmentations, although time consuming, could more accurately assess the occlusion pattern and additionally provide information on the clot burden. However, the occlusion segment classification presented in this study was performed as done in current clinical practice: based only on CTA scans.

Interobserver variability was not assessed in this study. However, previous studies have shown that, among experienced observers (>5 years), interobserver agreement was substantial for the assessment of CTA scans.[30]

The occlusion patterns illustrated in this study are an oversimplification of all the complex patterns that can be found.

CONCLUSION

In our population, EVT procedural and clinical outcomes are similar for patients with MCA main stem and patients with MCA bifurcation occlusions. More research should be conducted to justify the use of a more aggressive EVT approach for bifurcation thrombi.

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