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Endovascular treatment for calcified cerebral emboli in patients with acute ischemic stroke

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OBJECTIVE Calcified cerebral emboli (CCE) are a rare cause of acute ischemic stroke. The authors aimed to assess the association of CCE with functional outcome, successful reperfusion, and mortality. Furthermore, they aimed to assess the effectiveness of intravenous alteplase treatment and endovascular treatment (EVT), as well as the best first-line EVT approach in patients with CCE.

METHODS The Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry is a prospective, observational multicenter registry of patients treated with EVT for acute ischemic stroke in 16 intervention hospitals in the Netherlands. The association of CCE with functional outcome, reperfusion, and mortality was evaluated using logistic regression models. Univariable comparisons were made to determine the effectiveness of intravenous alteplase treatment and the best first-line EVT approach in CCE patients.

RESULTS The study included 3077 patients from the MR CLEAN Registry. Fifty-five patients (1.8%) had CCE. CCE were not significantly associated with worse functional outcome (adjusted common OR 0.71, 95% CI 0.44–1.15), and 29% of CCE patients achieved functional independence. An extended Thrombolysis in Cerebral Infarction score ≥ 2B was significantly less often achieved in CCE patients compared to non-CCE patients (adjusted OR [aOR] 0.52, 95% CI 0.28–0.97). Symptomatic intracranial hemorrhage occurred in 8 CCE patients (15%) vs 171 of 3022 non-CCE patients (6%; p = 0.01). The median improvement on the National Institutes of Health Stroke Scale (NIHSS) was 2 in CCE patients versus 4 in non-CCE patients (p = 0.008). CCE were not significantly associated with mortality (aOR 1.16, 95% CI 0.64–2.12). Intravenous alteplase use in CCE patients was not associated with functional outcome or reperfusion. In CCE patients with successful reperfusion, stent retrievers were more often used as the primary treatment device (p = 0.04).

CONCLUSIONS While patients with CCE had significantly lower reperfusion rates and less improvement on the NIHSS after EVT, CCE were not significantly associated with worse functional outcome or higher mortality rates. Therefore, EVT should still be considered in this specific group of patients.

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KEYWORDS stroke; calcified cerebral emboli; endovascular treatment; vascular disorders; interventional neurosurgery

ABBREVIATIONS acOR = adjusted common OR; aOR = adjusted OR; ASPECTS = Alberta Stroke Program Early CT Score; CBS = clot burden score; CCE = calcified cerebral emboli; CTA = CT angiography; DSA = digital subtraction angiography; eTICI = extended Thrombolysis in Cerebral Infarction; EVT = endovascular treatment; HU = Hounsfield unit; ICA = internal carotid artery; IQR = interquartile range; MR CLEAN = Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Scale; NCCT = noncontrast CT; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; RF = resorcin-fuchsin; ROI = region of interest; ucOR = unadjusted common OR.

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Calcified cerebral emboli (CCE) are a rare cause of acute ischemic stroke with a reported relative frequency of 1.1%–1.3% in patients with acute ischemic stroke who underwent endovascular treatment (EVT),[1–3] and a relative frequency of 2.7% in all patients presenting with acute ischemic stroke.[4] It is unclear whether patients with acute ischemic stroke due to CCE benefit as much from intravenous alteplase treatment and EVT as other stroke patients. Moreover, the most suitable EVT approach for patients with CCE is unclear.

Treatment results in patients with CCE in the literature are inconsistent and data are scarce. Intravenous alteplase treatment appears to be less effective in patients with CCE based on several case reports, probably because alteplase only degrades fibrin and not the calcified part of the embolus.[4–17] Successful reperfusion after EVT with stent retrievers in CCE patients has been described in several case reports.[10,18–23] In two retrospective studies describing EVT in CCE patients, successful reperfusion was achieved in only 1 of 8 patients when stent retrievers were used and was not achieved in any of the 5 reported patients with mechanical aspiration thrombectomy.[1,2] In a recent cohort of 40 patients with CCE, successful reperfusion was achieved in 58% of patients and functional independence in 27%; in most of these patients (90%), a combined approach of stent retrieval and distal aspiration was used.[3]

The aim of this study was to assess the association of CCE with functional outcome, successful reperfusion, and mortality. Furthermore, we aimed to assess the effectiveness of intravenous alteplase treatment and EVT, as well as the best first-line EVT approach, in CCE patients.

Methods

Patient Selection

Patients included in this study were recruited from the Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry. The MR CLEAN Registry is a prospective, observational multicenter registry that collected data from patients treated with EVT for acute ischemic stroke due to intracranial large-vessel occlusion in 16 intervention hospitals in the Netherlands, since the completion of the MR CLEAN trial in March 2014.[24] All patients without contraindications received 0.9 mg/kg intravenous alteplase prior to EVT. The study protocol was evaluated by a central medical ethics committee in the Erasmus MC, and permission to conduct the study as a registry was granted.[24]

The current study reports on patients treated between March 14, 2014, and November 1, 2017. We used the following inclusion criteria: intracranial proximal occlusion in the anterior circulation, age ≥ 18 years, onset to groin puncture time < 6.5 hours, and treatment performed in a MR CLEAN trial center. We excluded patients treated after 6.5 hours because it was not standard of care to treat patients in the late time window during the inclusion period,[24] and inclusion would bias the estimation of CCE prevalence.

Imaging Analyses

All patients underwent the imaging protocol advised by the Dutch guidelines at baseline, including noncontrast CT (NCCT) and CT angiography (CTA). The following imaging characteristics were evaluated by the MR CLEAN Registry imaging core laboratory:[24] Alberta Stroke Program Early CT Score (ASPECTS) on baseline NCCT, and clot burden score (CBS), collateral score, presence of cervical carotid lesions, location of the occlusion, and presence of intracranial atherosclerosis on baseline CTA. We defined an ipsilateral cervical carotid stenotic lesion as an atherosclerotic carotid stenosis of less than 50%, and more than 50% ipsilateral to the intracranial occlusion. Reperfusion status was evaluated by the core laboratory on digital subtraction angiography (DSA) according to the extended Thrombolysis in Cerebral Infarction (eTICI) score.[25]

Noncalcified thrombi have an attenuation of 50–70 Hounsfield units (HUs),[4] and in previous reports the mean attenuation of CCE ranged between 92 and 327 HUs.[1,3,4,9,26] Therefore, we defined an intravascular attenuation ≥ 90 HUs (measured with the single-voxel measurement tool in RadiAnt DICOM viewer) at the site of the occlusion as CCE. To prevent overlap with vessel wall calcifications, linear and tubular calcifications at the occlusion site were excluded, and only round or ovoid calcifications were defined as CCE. If CCE were identified on NCCT but no occlusion was observed on CTA, DSA was used to confirm the location of the CCE, because CCE can appear isodense to contrast on CTA.[20,23] Examples of CCE are shown in Fig. 1.

Patients with suspicion of CCE were selected on NCCT by A.A.E.B., who received a 4-week training in stroke CT interpretation before starting patient selection. All selected cases were discussed with two experienced interventional neuroradiologists (B.J.E. and C.B.L.M.M.) and were only included if consensus was reached on the aforementioned items. After inclusion, we performed additional measurements of CCE attenuation and length in ITK-SNAP (version 3.4) to provide verifiable, repeatable, and comparable measurements. Prior to performing these measurements, thin-slice (≤ 2.5 mm) baseline NCCT and CTA scans were coregistered using Elastix imaging registration software.[27] Thick-slice NCCT scans were excluded to prevent underestimation of CCE attenuation.[28]

CCE Attenuation

The method for the assessment of absolute CCE attenuation was adapted from Santos et al.[29] CCE attenuation was measured in the proximal, middle, and distal part of the embolus using three separate spherical volumes with a radius of 1 mm (Supplemental Fig. I). Based on the CT attenuation values of these regions of interest (ROIs), the average absolute attenuation of the CCE in HUs was determined.

CCE Length

Dutra et al.[30] determined thrombus length on CTA; however, consistent with previous reports, CCE appeared isodense to contrast on CTA in many of our patients.[20,23] Therefore, CCE length was estimated on NCCT by measuring the distance between the proximal and distal border of the CCE in the plane that was most perpendicular

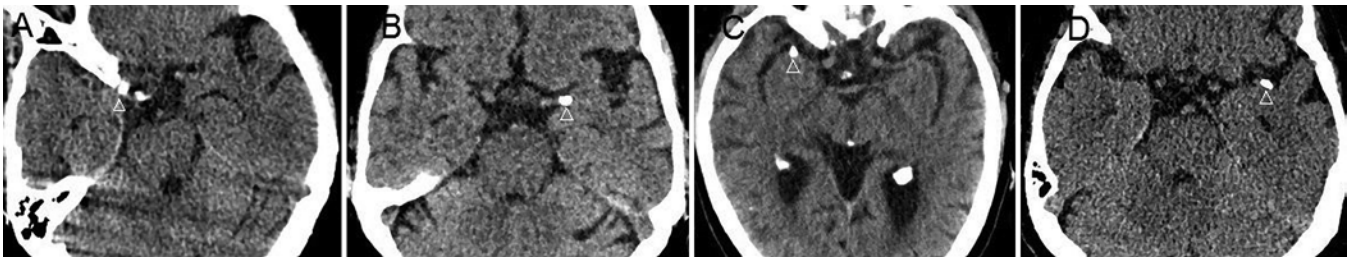

FIG. 1. Examples of CCE (*arrowheads*) on NCCT in the right ICA (**A**), in the left proximal M_1 vessel segment of the middle cerebral artery (MCA; **B**), in the right distal M_1 vessel segment of the MCA (**C**), and in the left M_2 vessel segment of the MCA (**D**). Window width = 80 HUs, window level = 40 HUs.

to the longest length of the CCE (Supplemental Fig. II). In case of curved CCE, measurements were performed individually for each segment in the plane most parallel to the course of the vessel (axial, sagittal, or coronal) and then added together. CTA images were used as reference for vessel anatomy and contrast detection in each case.

Histological Analysis

Collected thrombi were immediately stored after EVT in 4% buffered formaldehyde until embedding in paraffin. For each thrombus, two representative longitudinal 5-μm sections were cut, generally at a depth of 170 μm and the second at a depth of 230 μm using a Microm HM335 S microtome (Microm International GmbH). The two sections were fixed on a glass slide followed by H&E and resorcin-fuchsin (RF) staining. Slides were digitized at magnification ×20 (228 nm/pixel) using a Hamamatsu Nano-Zoomer scanner (Hamamatsu Photonics K.K.), and raw Hamamatsu.ndpi data files were stored. Sections were analyzed for the presence of calcifications visually and with micro-CT imaging. The presence of vessel wall in the thrombus was demonstrated with RF staining, which stains elastic fibers in the internal and external elastic lamina of the vessel wall.

EVT Procedure

EVT was defined as entry into the angiography suite and receiving arterial puncture. The method of EVT was left to the discretion of the treating neurointerventionist. EVT consisted of arterial catheterization with a microcatheter to the intracranial occlusion location if possible, followed by stent retrieval or aspiration thrombectomy, or a combined approach. If a patient's condition deteriorated after EVT, follow-up CT imaging was performed.

Outcomes

The primary outcome was the ordinal modified Rankin Scale (mRS) score at 90 days.[31,32] The mRS is a 7-point scale, ranging from 0 (no symptoms) to 6 (death). The mRS score at 90 days was assessed as part of usual care. Functional independence was defined as an mRS score of 0–2. Secondary outcomes were successful reperfusion, median difference between baseline National Institutes of Health Stroke Scale (NIHSS) score and NIHSS score after 24–48 hours (Δ NIHSS), and mortality at 90 days. Successful reperfusion was defined as an eTICI score of 2B or more. To be classified as successful reperfusion, complete post-intervention DSA imaging, including anteroposterior and lateral views, was mandatory. If a lateral view was missing, an eTICI score of 2A was the highest possible score.

Statistical Analysis

Continuous data are displayed as medians and interquartile ranges (IQRs). Categorical data are displayed as frequencies and percentages. We compared baseline, treatment, and outcome characteristics of patients with and patients without CCE. Among CCE patients, treatment characteristics in patients with and those without successful reperfusion and functional independence were compared in univariable comparisons. Treatment characteristics included intravenous alteplase treatment prior to EVT, onset to reperfusion time, use and type of balloon guide catheter, primary treatment modality (stent retriever or aspiration), number of attempts, and duration of procedure.

Univariable comparisons were made using the Fisher's exact test, Pearson chi-square test, Pearson chi-square test for trend, or Mann-Whitney U-test, as appropriate to the type of data. A p value < 0.05 was considered significant. Ordinal logistic regression was used to evaluate the association between CCE and ordinal mRS score in the primary outcome analysis, resulting in an unadjusted and an adjusted common odds ratio (ucOR and acOR, respectively) for a 1-step shift toward a better functional outcome. Adjustments were made for age, sex, atrial fibrillation, level of occlusion, ipsilateral cervical carotid stenotic lesion, and intravenous alteplase treatment. Binary logistic regression was performed to assess the association between CCE, successful reperfusion, and mortality.

Missing data (Supplemental Tables I and II) were imputed using multiple imputation for regression analyses only, not for descriptive analyses.[33] Multiple imputation was performed on the variables listed in Supplemental Table I. All statistical analyses were performed with SPSS Statistics (version 25.0, IBM Corp.).

Sensitivity Analysis

We conducted a 1-to-1 (1:1) propensity score matching analysis to evaluate the association between CCE and functional outcome. Propensity scores representing the probability of having CCE were calculated for each patient in each multiple imputed data set, using a logistic regression model, based on the following covariates: age, atrial

TABLE 1. Baseline characteristics of patients with and patients without CCE

Characteristic	CCE	Non-CCE	p Value
No. of patients	55	3022	
Median age (IQR), yrs	76 (71–82)	72 (61–80)	**0.004**
Males, n (%)	21 (38)	1583 (52)	**0.04**
Medical history, n (%)			
Previous stroke	6 (11)	507 (17)	0.24
Previous myocardial infarction	7 (13)	418 (14)	0.81
Diabetes	8 (15)	482 (16)	0.76
Hypertension	35 (64)	1541 (52)	0.09
Previous atrial fibrillation	5 (9)	729 (25)	**0.008**
Hypercholesterolemia	21 (42)	886 (31)	0.09
Current smoker	12 (31)	650 (28)	0.69
Anticoagulation (vitamin K antagonists)	0	392 (13)	**0.004**
Clinical presentation			
Median baseline NIHSS score (IQR)	16 (11–19)	16 (11–19)	0.64
Pre-stroke mRS score, n (%)			0.59
0–2	48 (91)	2606 (88)	
≥3	5 (9)	351 (12)	
Imaging characteristics			
Level of occlusion on CTA, n (%)			**<0.001**
ICA	1 (2)	774 (26)	
M_1	36 (67)	1699 (58)	
M_2	16 (30)	441 (15)	
Other*	1 (2)	22 (1)	
Median CCE length (IQR), mm†	6 (4–7)	NA	
Median CCE absolute attenuation (IQR), HUs†	184 (142–276)	NA	
Range of CCE absolute attenuation, HUs‡	59–461	NA	
Median CBS (IQR)	6 (4–8)	6 (4–8)	0.94
Median ASPECTS (IQR)	9 (8–10)	9 (8–10)	0.62
Collaterals, n (%)			0.35
0% filling of the occluded territory	6 (12)	179 (6)	
>0% and ≤50% filling of the occluded territory	20 (39)	1030 (36)	
>50% and <100% filling of the occluded territory	15 (29)	1119 (39)	
100% filling of the occluded territory	11 (21)	544 (19)	
Intracranial atherosclerosis, n (%)	32 (59)	1755 (61)	0.84
Ipsilateral cervical carotid stenotic lesion, n (%)§	37 (80)	1442 (53)	**<0.001**
Ipsilateral atherosclerotic carotid artery stenosis <50%, n (%)	31 (67)	1203 (45)	**0.002**
Ipsilateral atherosclerotic carotid artery stenosis >50%, n (%)	6 (13)	239 (9)	0.30
Intravenous alteplase treatment, n (%)	49 (89)	2301 (76)	**0.03**
Median onset to groin puncture time (IQR), mins	210 (159–255)	193 (150–250)	0.17

M_1/M_2 = middle cerebral artery segments; NA = not available.
Boldface type indicates statistical significance. Missing values are listed in Supplemental Tables I and II.
* Other = none, M_3, A_1, and A_2 vessel segments.
† Measurements were performed on thin-slice (≤ 2.5-mm) baseline NCCT and CTA images in CCE patients (n = 23).
‡ In 4 patients with small CCE (≤ 5 mm), the measured average absolute attenuation was < 90 HUs.
§ Ipsilateral cervical carotid stenotic lesions included both atherosclerotic carotid stenosis < 50%, and > 50% ipsilateral to the intracranial occlusion.

fibrillation, level of occlusion, and ipsilateral cervical carotid stenotic lesion. CCE patients were matched with non-CCE patients in a 1:1 nearest-neighbor matching with a matching tolerance of 0.001. Matching was performed without replacement. After matching each multiple imputed data set, we merged these 5 data sets and used ordinal logistic regression to compare functional outcome of CCE and non-CCE patients. We adjusted for baseline variables vthat remained significantly different after propensity score matching (age, diabetes, collateral score, CBS).

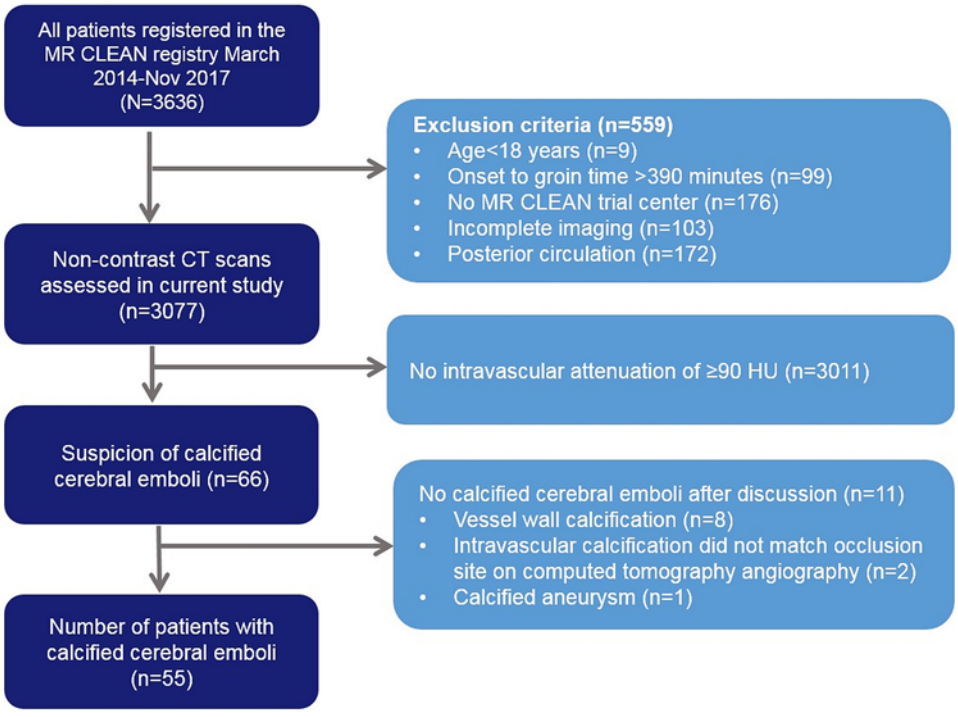

FIG. 2. Flowchart of the patient selection procedure. Vessel wall calcifications are linear/tubular intravascular calcifications at the occlusion site. Vessel wall calcifications were located in the carotid siphon (n = 1), carotid terminus (n = 5), and M_1 vessel segment (n = 2). Figure is available in color online only.

Results

Baseline Characteristics

We included 3077 patients from the MR CLEAN Registry. Fifty-five patients (1.8%) had CCE (Fig. 2). CCE patients were older and more often women (Table 1). Furthermore, CCE patients less often had atrial fibrillation compared to non-CCE patients. None of the CCE patients used anticoagulation compared to 13% (n = 392/3022) of the non-CCE patients (p = 0.004). The most common occlusion sites in CCE patients were M_1 and M_2 vessel segments (Fig. 3). In 1 CCE patient, no occlusion was detected on CTA, while on DSA an M_2 occlusion was seen (Supplemental Fig. III). Eight (15%) of 55 CCE patients had multiple CCE. Median CCE attenuation and length were 184 HUs (range 59–461 HUs) and 6 mm, respectively. In 4 patients with small CCE (≤ 5 mm), the measured average absolute attenuation was < 90 HUs. The median attenuation of small CCE was 145 HUs (range 59–461 HUs) compared to 229 HUs (range 142–381 HUs) of larger CCE (> 5 mm; p = 0.04). Ipsilateral cervical carotid stenotic lesions were more often present in CCE patients compared to non-CCE patients (80% [n = 37/46] vs 53% [n = 1442/2699], p < 0.001). CCE patients more often received intravenous alteplase prior to EVT compared to non-CCE patients (89% [n = 49/55] vs 76% [n = 2301/3022], p = 0.03).

Treatment Characteristics

Onset to reperfusion time was significantly longer in CCE patients compared to non-CCE patients (median 281 vs 250 minutes, p = 0.01), mainly driven by the longer EVT

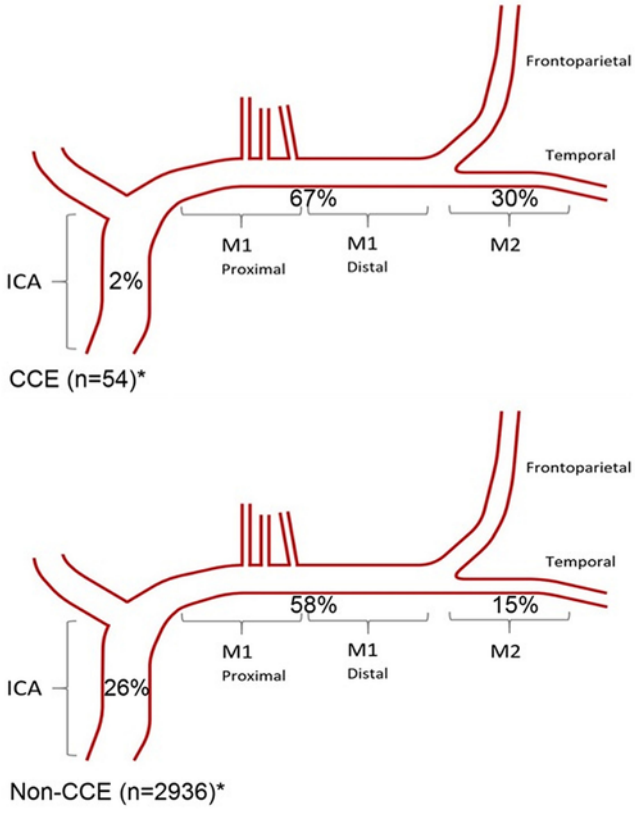

FIG. 3. Distribution of occlusion location in patients with CCE and patients without CCE (non-CCE). *Number of patients with available occlusion location. Figure is available in color online only.

TABLE 2. Treatment characteristics and outcome in patients with and patients without CCE

Treatment Characteristics and Outcomes	CCE	Non-CCE	p Value
Characteristics			
Median onset to reperfusion time (IQR), mins*	281 (223–336)	250 (198–311)	**0.01**
Performed procedure, n (%)			0.44
Target occlusion not accessible	1 (2)	175 (6)	
DSA only, spontaneous reperfusion	6 (11)	267 (9)	
EVT	48 (87)	2572 (85)	
Median no. of attempts (IQR)	2 (1–4)	2 (1–3)	0.21
Median procedure duration (IQR), mins	75 (47–87)	58 (38–83)	**0.03**
Balloon guide catheter, n (%)	25 (63)	1369 (63)	0.97
Primary treatment device, n (%)			0.77
Stent retriever	30 (68)	1708 (72)	
Aspiration device	14 (32)	634 (27)	
Intraarterial thrombolysis	0	21 (1)	
Per-procedural complications assessed on DSA, n (%)			
Distal occlusion	5 (10)	406 (15)	0.33
New clot in different vascular territory	0	132 (5)	0.17
Evidence of vessel perforation on DSA	1 (2)	52 (2)	0.61
Serious adverse events, n (%)			
Stroke progression	5 (9)	272 (9)	1.00
New ischemic stroke	0	47 (2)	1.00
Symptomatic intracranial hemorrhage	8 (15)	171 (6)	**0.01**
Pneumonia	10 (18)	335 (11)	0.098
Readmission due to recurrent stroke†	2 (4)	15 (0.5)	**0.04**
Outcomes			
Posttreatment eTICI score, n (%)			**0.01**
0	10 (18)	487 (17)	
1	4 (7)	82 (3)	
2A	17 (31)	544 (19)	
2B	10 (18)	658 (22)	
2C	5 (9)	319 (11)	
3	9 (16)	856 (29)	
Median NIHSS 24–48 hrs post-EVT (IQR)	13 (6–20)	10 (4–17)	0.11
Median Δ NIHSS (IQR)‡	2 (–3 to 8)	4 (0–9)	**0.008**
mRS score at 3-mo follow-up, n (%)			0.09
0–2	15 (29)	1159 (41)	
3–6	36 (71)	1664 (59)	
Mortality, n (%)	18 (35)	808 (29)	0.30

Boldface type indicates statistical significance. Missing values are listed in Supplemental Tables I and II.

* Or last contrast bolus.

† Readmission due to recurrent stroke included transient ischemic attack, retinal artery ischemia, and new ischemic stroke within 3 months after EVT.

‡ Median difference between baseline NIHSS score and NIHSS score 24–48 hours post-EVT.

procedure duration (75 minutes in CCE patients compared to 58 minutes in non-CCE patients, p = 0.03; Table 2). Symptomatic intracranial hemorrhage occurred in 15% (n = 8/55) of the CCE patients and in 6% (n = 171/3022) of the non-CCE patients (p = 0.01). Four of 8 cases of symptomatic intracranial hemorrhage occurred in the 6 CCE patients not receiving intravenous alteplase. The percentage of patients with vessel perforation visible on DSA (2%) was comparable between CCE and non-CCE patients. Readmission due to recurrent stroke within 3 months after EVT occurred in 4% (n = 2/55) of the CCE patients and in 1% (n = 16/3022) of the non-CCE patients (p = 0.04).

In Table 3, treatment characteristics in CCE patients with and those without successful reperfusion and functional independence are compared. Intravenous alteplase use in CCE patients was not associated with reperfusion or

TABLE 3. Treatment characteristics and follow-up imaging in CCE patients

Treatment Characteristic	Reperfusion Score			Functional Outcome		
	eTICI <2B, n = 31	eTICI ≥2B, n = 24	p Value	mRS ≤2, n = 15	mRS ≥3, n = 36	p Value
Intravenous alteplase, n (%)	27 (87)	22 (92)	0.69	14 (93)	31 (86)	0.66
Median onset to reperfusion time (IQR), mins*	290 (240–339)	278 (213–340)	0.63	250 (190–302)	303 (225–346)	0.12
Performed procedure, n (%)			0.31			0.05
Target occlusion not accessible	1 (3)	0		0	1 (3)	
DSA only, spontaneous reperfusion	1 (3)	5 (21)		5 (33)	1 (3)	
EVT	29 (94)	19 (79)		10 (67)	34 (94)	
Median no. of attempts (IQR)	3 (1–4)	2 (1–2)	0.25	2 (1–2)	2 (2–4)	0.09
Median procedure duration (IQR), mins	79 (68–90)	65 (35–80)	0.06	35 (17–75)	80 (68–90)	**0.002**
Balloon guide catheter, n (%)	14 (64)	11 (61)	0.87	7 (58)	16 (64)	1.00
Primary treatment device, n (%)						0.65
Stent retriever	16 (57)	14 (88)	**0.04**	6 (86)	22 (67)	
Aspiration device	12 (43)	2 (13)		1 (14)	11 (33)	
Follow-up CT, n (%)†	16 (52)	9 (38)	0.30	5 (33)	20 (56)	0.15
Persistent CCE, n (%)	13 (81)	3 (33)	0.12	1 (33)	15 (79)	0.43
CCE migrated more distally, n (%)	3 (23)	2 (67)	0.56	0	5 (33)	1.00

Boldface type indicates statistical significance. Missing values are listed in Supplemental Tables I and II.

* Or last contrast bolus.

† Follow-up CT imaging was performed in 25 CCE patients; in 22 patients, follow-up CT scans were available for analysis.

functional outcome (p = 0.69 and p = 0.66, respectively). In CCE patients with successful reperfusion, procedure duration was shorter than in patients without successful reperfusion: 65 minutes in patients with successful reperfusion compared to 79 minutes in patients without successful reperfusion (p = 0.06). In CCE patients with successful reperfusion, a stent retriever was significantly more often used as the primary treatment device (p = 0.04). In patients who achieved functional independence, the median procedure duration of EVT was 35 minutes compared to 80 minutes in patients who did not achieve functional independence (p = 0.002).

Postintervention Imaging

Postintervention NCCT was performed in 25 CCE patients, and in 16 (73%) of 22 patients a persistent CCE was noted. In 9 patients with successful reperfusion, postintervention imaging was performed; 3 of them had persistent CCE (Table 3). In 2 of these patients, distal dispersion of the CCE occurred, and in 1 patient, spontaneous reperfusion occurred while the CCE persisted at the same location. None of the patients with persistent CCE on postintervention imaging experienced recurrent stroke within 3 months after EVT.

Histology

Three thrombi of CCE patients were present in the MR CLEAN biobank. Analysis revealed the presence of calcium, scattered in several places throughout the thrombus (Fig. 4). The presence of calcium was confirmed with micro-CT imaging (Supplemental Fig. IV). No calcifications were found in the other two thrombi upon histological analysis and micro-CT imaging, but macrophage giant cells, cholesterol, and vessel wall were present, indicative of atheroma and fibrous plaque, respectively. In the 2 patients in whom no calcifications were found on histological analysis, postintervention imaging was performed, and a persistent CCE was seen at the same location in 1 patient.

Primary Outcome

After 3 months, 29% of CCE patients achieved functional independence (n = 15/51) versus 41% (n = 1159/2823) of non-CCE patients (p = 0.09; Fig. 5, Table 2). CCE presence showed a nonsignificant trend toward worse functional outcome (ucOR 0.66, 95% CI 0.41–1.07, and acOR 0.71, 95% CI 0.44–1.15).

Secondary Outcomes

Successful reperfusion was achieved in 24 CCE patients (44%) and in 1833 (63%) of 2946 non-CCE patients. CCE were significantly associated with a lower chance of successful reperfusion (OR 0.52, 95% CI 0.28–0.95, and adjusted OR [aOR] 0.52, 95% CI 0.28–0.97).

Δ NIHSS Score

CCE patients achieved a median improvement of 2 points on the NIHSS 24–48 hours after EVT, while non-CCE patients achieved a median improvement of 4 points (p = 0.008; Table 2).

Mortality at 90 Days

Death at 90 days was observed in 18 (35%) of 51 CCE patients and in 808 (29%) of 2823 non-CCE patients (Table 2). The presence of CCE was not significantly associated with mortality (OR 1.25, 95% CI 0.71–2.21, and aOR 1.16, 95% CI 0.64–2.12).

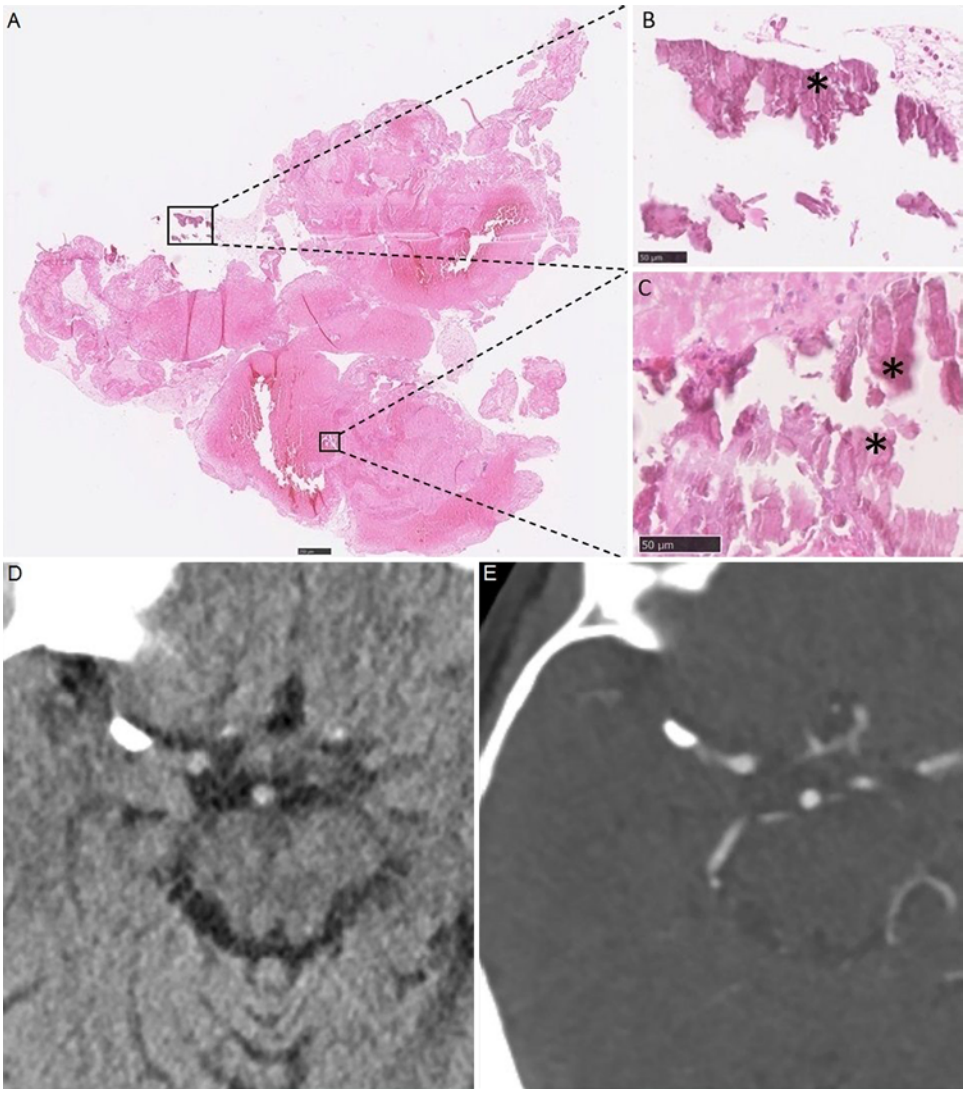

FIG. 4. Histology and CT imaging of a calcified cerebral embolus. Overview (**A**) and details (**B and C**) of a thrombus retrieved by endovascular thrombectomy. Shown is a thrombus that typically consists of erythrocytes and leukocytes within a fibrin- and platelet-rich matrix. In this thrombus, calcified areas were found (*). H&E. Bar = 250 µm (A), 50 µm (B and C). On NCCT (**D**) and CTA (**E**), the calcified cerebral embolus is clearly visible in the right distal M_1 vessel segment of the MCA. Figure is available in color online only.

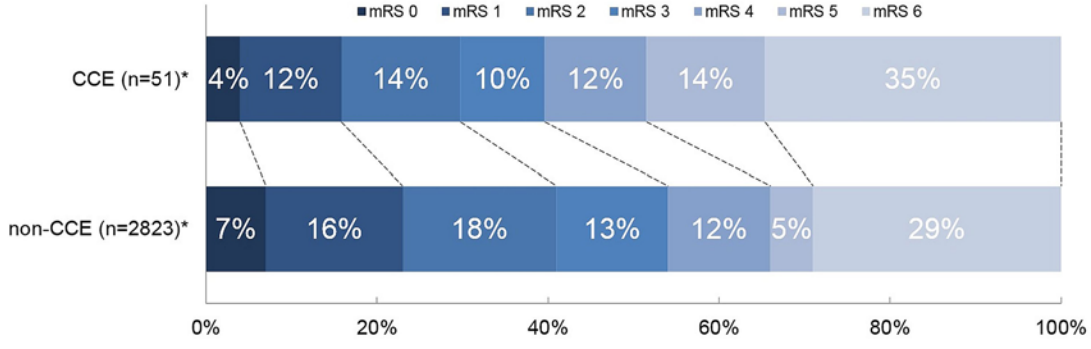

FIG. 5. Distribution of the mRS score after 3 months in patients with CCE and patients without CCE (non-CCE). *Number of patients with available mRS score. Figure is available in color online only.

Sensitivity Analysis

After propensity score matching, the sample size of both the CCE and non-CCE groups was 55. Baseline characteristics were similar in the 2 matched groups, except collateral score, which was higher in the non-CCE group (Supplemental Table III). The presence of CCE was not significantly associated with worse functional outcome (ucOR 0.90, 95% CI 0.39–2.09, and acOR 0.88, 95% CI 0.33–2.33).

Discussion

CCE were present in 55 patients (1.8%) of the MR CLEAN Registry. We demonstrated that in CCE patients, reperfusion rates were significantly lower than in non-CCE patients. Also, CCE patients showed less improvement on the NIHSS after EVT. Despite these findings, CCE were not significantly associated with worse functional outcome or mortality.

The frequency of CCE in our study (1.8%) was comparable to the previously reported frequencies of 1.1%–2.7%.[1–4] The median attenuation of CCE was 184 HUs, with a minimum attenuation of 59 HUs. The minimum of 59 is slightly lower than the 90 HU cutoff value used for patient inclusion, because during inclusion a single-voxel measurement in RadiAnt DICOM Viewer was used. In the more complete thrombus characteristics measurement workflow in ITK-SNAP, the average of three slightly larger ROIs was used, to take potential heterogeneity within a thrombus into account. The measurement performed in ITK-SNAP may be more affected by partial volume effect in small CCE thrombi, lowering the resulting measured HUs.

Only a few studies have provided histological evidence to confirm the CT imaging diagnosis of CCE.[19,34,35] We performed histological analysis and micro-CT imaging of three available extracted thrombus fragments of CCE patients and were able to confirm the presence of calcium in 1 case. In the 2 remaining patients, we could not identify calcifications in the sections taken from the extracted thrombus fragment. In 1 patient, this was caused by failure to remove the CCE, as demonstrated on postinterventional imaging. In the other patient, it is possible that the calcified part of the thrombus was not present in the investigated thrombus fragment, or not yet cut. The former is supported by a previous study that described that CCE mostly have attached thrombi or will form an adjacent thrombus at the site of the intracranial occlusion location.[36] Together with the observation that CCE are often only small emboli, it is likely that the CCE fragment itself may not be present in a histologically analyzed thrombus fragment.

Successful reperfusion was achieved in 44% of the CCE patients and was more often achieved when using a stent retriever as a primary treatment device. Therefore, consistent with previous studies, stent retrieval—with or without simultaneous aspiration—might be a better first-line approach for CCE than the use of an aspiration device alone,[2,3] although our study was not sufficiently powered for this analysis. A recent in vitro study showed that a combined technique of stent retrieval with flow arrest and manual aspiration using a balloon guide catheter was the most successful approach to remove CCE.[36] This was supported by a clinical study in which first-pass reperfusion in CCE patients was most often achieved with a combined approach of distal aspiration and stent retrieval.[3] In that study, a combined approach was used in 90% of the patients, which might explain the higher reperfusion rate of 58% compared to our CCE cohort. Furthermore, symptomatic intracranial hemorrhage occurred in 5% of the patients in that study, which is less than in our CCE patient cohort.[3] This might have been caused by the greater proportion of CCE patients receiving intravenous alteplase treatment in our study. However, the observation that intracranial hemorrhage occurred more often in CCE patients who were not treated with intravenous alteplase suggests that EVT contributed to this complication as well. In only 1 CCE patient, a vessel perforation was seen on DSA, but in 2 other CCE patients, symptomatic intracranial hemorrhage was visualized on NCCT within an hour after EVT, which makes it very likely that these bleedings were also directly attributable to EVT. Moreover, longer EVT procedure times in CCE patients imply that removing CCE was more difficult compared to patients without CCE. This was supported by a recent in vitro study, which showed that compressive stiffness of CCE was 4–5 times greater than that of blood thrombi.[36] Therefore, it is possible that in CCE patients more traction was applied to remove the embolus than in non-CCE patients, causing vascular damage leading to per-procedural symptomatic intracranial hemorrhage.

CCE patients more often received intravenous alteplase treatment prior to EVT compared to non-CCE patients, probably because non-CCE patients more often had atrial fibrillation and used anticoagulation, which is a contraindication for intravenous alteplase treatment. Additionally, it may be believed that alteplase does not help with recanalization in CCE, because its fibrin-degrading properties may have little effect on emboli consisting primarily of calcified material and atheroma. Reperfusion and functional outcome were comparable in patients with CCE who received intravenous alteplase treatment and those who did not, which could support this belief. However, our study was not significantly powered to draw definite conclusions from this finding. Furthermore, all 6 cases of spontaneous reperfusion occurred in patients with CCE who received intravenous alteplase prior to EVT. Therefore, it is likely that intravenous alteplase treatment and EVT both contribute to partial blood flow restoration by resolving or removing the softer, mostly fibrin-rich thrombus proximal from or surrounding the CCE.[36] This is further supported by the finding that in our study, distal dispersion of CCE only occurred in patients who received intravenous alteplase treatment prior to EVT.

Readmission due to recurrent stroke within 3 months after EVT occurred more often in CCE patients, which might have been caused by undiagnosed embolic sources. Ipsilateral cervical carotid stenotic lesions were more often present in patients with CCE. Possibly, the source of CCE is a calcified plaque in the extracranial carotid arteries. This finding is consistent with previous studies, in which 30% of CCE originated from a carotid atherosclerotic plaque. Furthermore, histological analysis in our study indicated the presence of atheroma and appears to

corroborate this as a potential source. Other important reported sources of CCE were the aortic arch and calcified heart valves.[3,4]

The proportion of patients achieving functional independence (29%) was in line with the 26% rate in a previously reported CCE patient cohort. However, the mortality rate in that study was 56%, much higher than the 35% in our cohort.[3] Perhaps the greater number of proximal CCE locations (M_1 and internal carotid artery [ICA] were the most common occlusion sites) and greater CCE length in that study compared to ours might have contributed to the higher mortality rate.[3]

There was no significant association between CCE and functional outcome, which became even more apparent after propensity score matching demonstrated a point estimate of the OR of 0.88. In addition, more CCE patients achieved functional independence than in the control group of the MR CLEAN trial, which is currently the best available control group for evaluating a treatment effect in CCE patients.[37] Patients in the control group of the MR CLEAN trial were assigned to usual care, which included intravenous alteplase if eligible. In the control group, 19% of patients achieved functional independence and 22% died.[37] In our CCE cohort, functional independence was achieved in 29% of the patients. However, our mortality rate was 35%, which is much higher than that of the MR CLEAN control group. This higher mortality rate is probably explained by the higher median age and the higher prevalence of symptomatic intracranial hemorrhage in the CCE group compared to the MR CLEAN control group. Because the proportion of CCE patients achieving functional independence is considerably higher after EVT when compared to the MR CLEAN control group, together with the finding that the presence of CCE is not associated with worse functional outcome, EVT should not be withheld in these patients.

There are limitations to our study. First, because the incidence of CCE is low, our CCE patient cohort was small, which limited statistical analyses. However, our reported CCE study cohort was obtained from a large cohort of consecutive patients with acute ischemic stroke and is the largest sample to date. Second, all CCE patients were selected by a trained observer (A.A.E.B.), which might have reduced the sensitivity of detecting CCE because only suspected cases as selected by A.A.E.B. were discussed with experienced neuroradiologists (B.J.E. and C.B.L.M.M.). However, A.A.E.B. received a 4-week training in stroke CT interpretation before starting patient selection, and our reported CCE frequency of 1.8% was comparable to the reported relative frequency range of 1.1%–2.7% in the literature.[1–4] Third, our data were obtained from 16 intervention hospitals in the Netherlands, which might have caused procedural differences that interfere with clinical outcome. However, this makes the results of this study more generalizable to real-world clinical practice. Finally, we were not able to provide a recommendation about the best first-line EVT approach and the benefit of intravenous alteplase treatment in patients with CCE, because our study was not sufficiently powered for these analyses. Future research should therefore focus on analyzing different treatment approaches in CCE patients.

Conclusions

Acute ischemic stroke due to CCE was associated with significantly lower reperfusion rates and less improvement on the NIHSS after EVT. However, CCE were not significantly associated with worse functional outcome or higher mortality rates, and almost 30% of CCE patients achieved functional independence. Successful reperfusion was more often achieved with a stent retriever than with aspiration as the primary treatment approach. EVT should still be considered in this specific group of patients.

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References

1. Dobrocky T, Piechowiak E, Cianfoni A, et al. Thrombectomy of calcified emboli in stroke. Does histology of thrombi influence the effectiveness of thrombectomy? *J Neurointerv Surg*. 2018;10(4):345–350.
2. Koh E, Kwak HS, Chung GH. Manual aspiration thrombectomy in patients with acute stroke-related calcified cerebral emboli. *J Stroke Cerebrovasc Dis*. 2017;26(10):2050–2054.
3. Maurer CJ, Dobrocky T, Joachimski F, et al. Endovascular thrombectomy of calcified emboli in acute ischemic stroke: a multicenter study. *AJNR Am J Neuroradiol*. 2020;41(3):464–468.
4. Walker BS, Shah LM, Osborn AG. Calcified cerebral emboli, a "do not miss" imaging diagnosis: 22 new cases and review of the literature. *AJNR Am J Neuroradiol*. 2014;35(8):1515–1519.
5. Gokhale S, Lahoti S, Rojas R, Caplan LR. Tissue plasminogen activator and calcific emboli. *JAMA Neurol*. 2013;70(5):642–643.
6. Halloran JI, Bekavac I. Unsuccessful tissue plasminogen activator treatment of acute stroke caused by a calcific embolus. *J Neuroimaging*. 2004;14(4):385–387.
7. Okazaki S, Sakaguchi M, Sugiyama Y, et al. Ineffective thrombolytic therapy for calcified cerebral emboli originated from calcified internal carotid artery stenosis. Article in Japanese. *Rinsho Shinkeigaku*. 2009;49(5):281–284.
8. Smeeing DP, Kappelle LJ, Hendrikse J. Calcified cerebral embolism as a cause of ischemic stroke. Article in Dutch. *Ned Tijdschr Geneeskd*. 2015;159:A8946.
9. Raghib MF, Mutzenbach JS, Rösler C, et al. Acute treatment of stroke due to spontaneous calcified cerebral emboli causing large vessel occlusion. *J Clin Neurosci*. 2018;47:56–61.
10. O'Cearbhaill R, Moriarty HK, Crosbie I, et al. Calcified cerebral emboli: a case series and review of literature. *J Syst Integr Neurosci*. 2016;2(3):180–183.
11. Acha O, Novo F, Espina B, et al. Spontaneous cerebral calcific embolus from the aortic arch. *Clin Neurol Neurosurg*. 2009;111(10):862–863.
12. Gschwind M, Binaghi S, Zekeridou A, Michel P. Neurological picture. Dispersion and 'salted pretzel sign' from thrombolysis of a spontaneous calcified embolus in an acute stroke. *J Neurol Neurosurg Psychiatry*. 2013;84(1):111–112.
13. Ishiyama H, Okazaki S, Saito K, et al. Rolling stones sign as hard and fast evidence of calcified cerebral emboli. *Neurology*. 2018;91(1):41–43.
14. Kavanagh EC, Fenton DM, Heran MK, et al. Calcified cerebral emboli. *AJNR Am J Neuroradiol*. 2006;27(9):1996–1999.
15. Kissela BM, Kothari RU, Tomsick TA, et al. Embolization of

calcific thrombi after tissue plasminogen activator treatment. *J Stroke Cerebrovasc Dis*. 2001;10(3):135–138.
16. Liang JW, Weinberger J, Tansy A. Utility of carotid ultrasonography in management of an atypical high vascular-risk patient with recurrent calcified cerebral embolic stroke. *J Stroke Cerebrovasc Dis*. 2017;26(8):e156–e159.
17. Seike N, Matsumoto K, Hirota Y, Kobessho H. Effective thrombolytic therapy for calcified cerebral embolism originating from a calcified plaque in the internal carotid artery. Article in Japanese. *Rinsho Shinkeigaku*. 2014;54(11):916–919.
18. Kwak HS, Park JS. Successful recanalization using the Embolus Retriever with Interlinked Cage for acute stroke due to calcified cerebral emboli. *Interv Neuroradiol*. 2018;24(6):674–677.
19. Ramírez-Moreno JM, Trinidad-Ruiz M, Ceberino D, Fernández de Alarcón L. Mechanical thrombectomy during ischaemic stroke due to a calcified cerebral embolism. *Neurologia*. 2017;32(4):270–273.
20. Uneda A, Kanda T, Suzuki K, et al. Acute cerebral artery occlusion by a calcified embolus with false patency sign on computed tomographic angiography. *J Stroke Cerebrovasc Dis*. 2017;26(1):e5–e7.
21. Fassa AA, Mazighi M, Himbert D, et al. Successful endovascular stroke rescue with retrieval of an embolized calcium fragment after transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2014;7(1):125–126.
22. Salinas P, Moreno R, Frutos R, Lopez-Sendon JL. Neurovascular rescue for thrombus-related embolic stroke during transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2013;6(9):981–982.
23. Yogendrakumar V, Patro S, Dowlatshahi D, et al. Calcified embolus mimics patent middle cerebral artery on CT angiogram. *Pract Neurol*. 2017;17(4):307–309.
24. Jansen IGH, Mulder MJHL, Goldhoorn RB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949.
25. Liebeskind DS, Bracard S, Guillemin F, et al. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg*. 2019;11(5):433–438.
26. Maeda T, Kamide T, Kikkawa Y, et al. Incidence and predictors of calcified cerebral emboli detected in patients who underwent endovascular procedures. *Clin Neurol Neurosurg*. 2020;192:105715.
27. Klein S, Staring M, Murphy K, et al. elastix: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging*. 2010;29(1):196–205.
28. Tolhuisen ML, Enthoven J, Santos EMM, et al. The effect of non-contrast CT slice thickness on thrombus density and perviousness assessment. In: Cardoso MJ, Arbel T, Gao F, et al, eds. *Molecular Imaging, Reconstruction and Analysis of Moving Body Organs, and Stroke Imaging and Treatment*. Springer International Publishing; 2017.
29. Santos EM, Yoo AJ, Beenen LF, et al. Observer variability of absolute and relative thrombus density measurements in patients with acute ischemic stroke. *Neuroradiology*. 2016;58(2):133–139.
30. Dutra BG, Tolhuisen ML, Alves HCBR, et al. Thrombus imaging characteristics and outcomes in acute ischemic stroke patients undergoing endovascular treatment. *Stroke*. 2019;50(8):2057–2064.
31. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3):1091–1096.
32. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604–607.
33. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087–1091.
34. Hickey TB, Honig A, Ostry AJ, et al. Iatrogenic embolization following cardiac intervention: postmortem analysis of 110 cases. *Cardiovasc Pathol*. 2019;40:12–18.
35. Mohammadkhani M, Schaefer P, Koroshetz W, Hedley-Whyte ET. Mitral annulus calcareous brain emboli. *Neurology*. 2000;54(4):817.
36. Johnson S, McCarthy R, Fahy B, et al. Development of an in vitro model of calcified cerebral emboli in acute ischemic stroke for mechanical thrombectomy evaluation. *J Neurointerv Surg*. 2020;12(10):1002–1007.
37. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11–20.

Disclosures

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