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CLINICAL AND POPULATION SCIENCES

Etiology of Large Vessel Occlusion Posterior Circulation Stroke: Results of the MR CLEAN Registry

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BACKGROUND: In patients with large vessel occlusion stroke of the anterior circulation, underlying cause is a determinant of outcome. Whether this is the case for posterior circulation large vessel occlusion stroke has yet to be determined. We aimed to report on cause in patients with posterior circulation stroke treated with endovascular thrombectomy and to analyze the association with functional outcome.

METHODS: We used data of patients with posterior circulation stroke included in the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) registry, a prospective multicenter observational study, between 2014 and 2018. Stroke cause was categorized into large artery atherosclerosis (LAA), cardioembolism, arterial dissection, embolic stroke of undetermined source (ESUS), other determined cause, or undetermined cause. For primary analysis on the association between cause and outcome, we used multivariable ordinal logistic regression analysis to estimate the adjusted common odds ratio for a shift towards a better functional outcome on the modified Rankin Scale at 90 days with LAA as a reference group. Secondary outcomes included favorable functional outcome (modified Rankin Scale score 0–3), National Institutes of Health Stroke Scale score at 24 to 48 hours, reperfusion on digital subtraction angiography, and stroke progression.

RESULTS: Of 264 patients with posterior circulation stroke, 84 (32%) had LAA, 48 (18%) cardioembolism, 31 (12%) dissection, and 14 (5%) ESUS. Patients with a dissection were younger (48 [interquartile range, 43–60] years) and had a lower National Institutes of Health Stroke Scale at baseline (12 [interquartile range, 6–31]) than patients with other cause. Functional outcome was better for patients with cardioembolism and ESUS compared to LAA (modified Rankin Scale adjusted common odds ratio, 2.4 [95% CI, 1.1–5.2], respectively adjusted common odds ratio, 3.1 [95% CI, 1.0–9.3]). Patients with a dissection had a lower chance of successful reperfusion compared with LAA (adjusted odds ratio, 0.20 [95% CI, 0.06–0.70]).

CONCLUSIONS: Unlike the anterior circulation, most frequent cause in our posterior large vessel occlusion stroke cohort is LAA followed by cardioembolism, dissection, and ESUS. Patients with cardioembolism and ESUS have a better prognosis for functional outcome after endovascular thrombectomy than patients with LAA.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: atherosclerosis ■ embolic stroke ■ ischemic stroke ■ reperfusion ■ thrombectomy

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*A list of all MR CLEAN Registry investigators is given in the Appendix.

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| Nonstandard Abbreviations and Acronyms | |
|--|--|
| BA | basilar artery |
| CTA | computed tomography angiography |
| ESUS | embolic stroke of undetermined source |
| eTICI | extended Thrombolysis in Cerebral Ischemia |
| EVT | endovascular treatment |
| IQR | interquartile range |
| IVT | intravenous thrombolysis |
| LAA | large artery atherosclerosis |
| LVO | large vessel occlusion |
| MR CLEAN | Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands |
| mRS | modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| PCS | posterior circulation stroke |
| TOAST | Trial of ORG 10172 in Acute Stroke Treatment |

Posterior circulation stroke (PCS) differs from anterior circulation stroke not only in incidence and outcomes but also in stroke mechanism.^{1–3} For instance, in the posterior circulation atherothrombosis is more often reported as underlying stroke cause than in the anterior circulation, while cardioembolism is less often described.^{4–7} In stroke caused by large vessel occlusion (LVO) of the anterior circulation, cause is associated with stroke severity, collateral status, and both short- and long-term functional outcome.^{8–10} Whether the cause of LVO of the posterior circulation is associated with functional outcome has yet to be determined.

Due to the fact that LVO of the posterior circulation is rare, available studies on cause are scarce compared to the anterior circulation. More insight on cause and outcome in PCS may help establish better management strategies for this devastating condition. The aim of the present study is (1) to describe the distribution of cause of LVO in PCS patients treated with endovascular thrombectomy (EVT) in current clinical practice and (2) to analyze the association between cause and functional outcome after EVT.

METHODS

Data Source: MR CLEAN Registry

The MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) registry is a prospective, nationwide registry, in which data were collected from consecutive acute stroke patients treated with EVT in clinical practice in the

Netherlands. The study protocol was evaluated by the medical ethics committee of the Erasmus MC in Rotterdam, and permission to perform the study as a registry was granted. Full methods of the MR CLEAN registry have been reported previously.¹¹

Source data will not be made available because of legislative issues on patient privacy but detailed analytic methods and study materials, including log files of statistical analyses, will be made available to other researchers on reasonable request to the first author. This article adheres to the STROBE guidelines which can be found in the [Supplemental Material](#).

Treatment Procedures

EVT was defined as actual arterial puncture in the angiography suite. Mechanical thrombectomy included stent retriever technique, thrombus aspiration, or a combination of both, with or without delivery of a thrombolytic agent. The method of EVT for each patient was left to the discretion of the treating physicians.

Patient Selection

For the present retrospective study, we included patients treated from March 2014 up to December 2018, who met the following inclusion criteria: age ≥ 18 ; occlusion of the vertebral, basilar, or posterior cerebral artery confirmed by baseline computed tomography angiography (CTA); with corresponding clinical symptoms of a posterior LVO.

Time Metrics

Time of first symptom onset was reported if witnessed, or time last known well if unwitnessed. In patients with transient or mild neurological symptoms with secondary worsening, the moment of secondary worsening was considered as the estimated time of LVO. Based on the course of symptoms, stroke presentation was divided into maximum deficit from onset, progressive deficit, or fluctuating deficit.

Imaging Assessment

The imaging core laboratory consisted of 8 observers (2 neuroradiologists, 6 interventional [neuro]radiologists) who were blinded for all clinical findings. Baseline noncontrast CT assessment included the posterior circulation-Acute Stroke Prognosis Early CT Score.¹² The posterior circulation-Acute Stroke Prognosis Early CT Score is graded from 0 to 10, with 1 point subtracted from 10 for any evidence of early ischemic changes in each defined region of the posterior circulation. Baseline CTA assessment included determination of the occluded arterial segment and posterior circulation collateral score.¹³ For the location of occlusion, the basilar artery (BA) was divided into 3 segments (proximal, middle, and distal) according to previously published research.¹⁴ The posterior circulation collateral score is a 10-point grading system, in which points are scored for patent collaterals supplying the vascular territory of the posterior circulation. Reperfusion status was evaluated on digital subtraction angiography according to the extended Thrombolysis in Cerebral Ischemia (eTICI) score.¹⁵ eTICI ranges from grade 0 (no reperfusion) to grade 3 (complete reperfusion) and successful reperfusion was defined as eTICI 2B or higher.

Stroke Cause

Stroke cause was determined by information from discharge letters and from reports of the imaging core laboratory. We partly used the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification to categorize stroke subtype into large artery atherosclerosis (LAA), cardioembolism, other determined cause, or undetermined cause.¹⁶ Based on more recent insights in stroke cause, we also incorporated the entities embolic stroke of unidentified source (ESUS) and arterial dissection.¹⁷ A patient was considered to have LAA in case of moderate to severe stenosis (>50%) of one of the vertebral arteries or stenotic or occlusive thrombosis of the BA due to atherosclerosis, as confirmed on vascular imaging by core lab adjudication.¹⁶ LAA as cause could include atherosclerosis in the extracranial segments V1–V3 of the vertebral arteries, the intracranial segment V4, or the BA. Cardioembolism was recorded in case high-risk sources of cardioembolism were present (Table S1).¹⁸ Unlike the traditional TOAST classification, in which arterial dissection is part of other determined cause, we decided to analyze this entity as a separate stroke subtype. Arterial dissection was defined as an intimal flap identified on CTA, enlargement of the artery, or typical aspect and location of occlusion (pearl and string sign or double lumen with distally tapered stenosis or occlusion) on CTA or digital subtraction angiography.¹⁹

A patient was considered to have ESUS when complete diagnostic workup showed no LAA, cardioembolism, dissection, or other cause. ESUS could include minor risk potentials for cardioembolic sources.¹⁷ Other determined cause could include nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. Undetermined cause consisted of patients with 2 or more causes identified, or patients without LAA, cardioembolism, dissection or other cause, but with incomplete diagnostic workup.

The extent of the diagnostic workup was determined by the treating physician. Diagnostic workup was considered incomplete if one of the following diagnostic assessments was missing: CTA which allows evaluation of proximal atherosclerosis; 12-lead ECG and Holter cardiac monitoring for at least 48 hours; or precordial echocardiography.

Outcome Assessment

The primary outcome measure was the score on the modified Rankin Scale score (mRS) at 90 days, which is a 7-point scale ranging from 0 (no symptoms) to 6 (death).²⁰ The mRS was assessed via telephone interview as part of usual care for all patients with stroke in all centers. Secondary outcomes were favorable functional outcome, score on the National Institutes of Health Stroke Scale (NIHSS) at 24 to 48 hours,²¹ successful reperfusion (eTICI 2B–3), mortality at 90 days, and stroke progression (decline of at least 4 points on the NIHSS without hemorrhage on noncontrast CT). Consistent with other studies on PCS we defined favorable outcome as mRS score of 0–3.^{22,23}

Statistical Analysis

For our analysis, we used data from the MR CLEAN registry. For the main analysis, we compared the largest groups of determined etiologic subtype. Baseline characteristics and outcomes were described using standard statistics and presented as median (interquartile range [IQR]) or numbers and percentages (%), unless indicated otherwise. For the association between

cause and the primary outcome, we used univariable and multivariable ordinal logistic regression analysis to estimate the (adjusted) common odds ratio (OR). For this ordinal shift analysis, we inverted the mRS, which means higher common ORs indicate better functional outcome. The largest group of etiologic subtype was chosen as a reference group. In multivariable analysis, we adjusted for potential imbalances in prespecified prognostic variables: age, sex, NIHSS at baseline, baseline mRS, hypertension, use of anticoagulation (vitamin K antagonists or direct oral anticoagulants), intravenous thrombolysis, and duration from estimated time of LVO to time of groin puncture. Most of these confounders were obtained from patient records by researchers of the intervention center (age, sex, hypertension, use of anticoagulation, and intravenous thrombolysis). Hypertension was registered in case this was part of the medical history, and the patient was using antihypertensive medication. NIHSS and mRS at baseline were scored by the treating physician or (in case of NIHSS) retrospectively scored based on the recorded neurological examination, according to a standard score chart. Adjusted (a) ORs and betas (β) are reported with 95% CI. Supplemental Material 2 shows the result of the same multivariable analysis with the subgroup LAA divided into extracranial LAA and intracranial LAA, with extracranial LAA as the reference group.

All descriptive analyses include patients with complete data on that specific variable, while for the regression models, all patients were included after imputation of missing data. Statistical analyses and multiple imputation were performed with STATA/SE version 14.1 (StataCorp, TX). We ran 20 imputations based on the covariates and outcomes from multivariable analysis, complemented with the variables: use of general anesthesia, duration of EVT procedure, occlusion location, and intracranial hemorrhage.

RESULTS

Out of 5773 patients enrolled in the MR CLEAN registry between 2014 and 2018, 264 patients were treated with EVT for posterior LVO stroke. The distribution of the etiologic subtypes is shown in Figure 1. The most frequent determined etiologic subtypes were LAA (84/264 [32%]), cardioembolism (48/264 [18%]), dissection (31/264 [12%]), and ESUS (14/264 [5%]). LAA consisted of 56 patients with extracranial atherosclerosis (21%) and 28 patients with intracranial atherosclerosis (11%). In total, 81 patients had an undetermined cause: 46 (17%) because of incomplete diagnostic evaluation and 35 (13%) because of 2 or more potential causes of stroke.

Patient Characteristics

Significant differences between etiologic subtypes were found for age, history of hypertension, use of anticoagulation, administration of intravenous alteplase, course of symptoms, and use of general anesthesia during EVT (Table 1). Patients with dissection or ESUS as most likely cause of ischemic stroke were significantly younger (respectively, median 48 years; [IQR, 43–60], 54 years; [IQR, 39–71]) than patients with LAA (median 67; [IQR, 58–76]) or cardioembolism (median 69; [IQR, 60–77]).

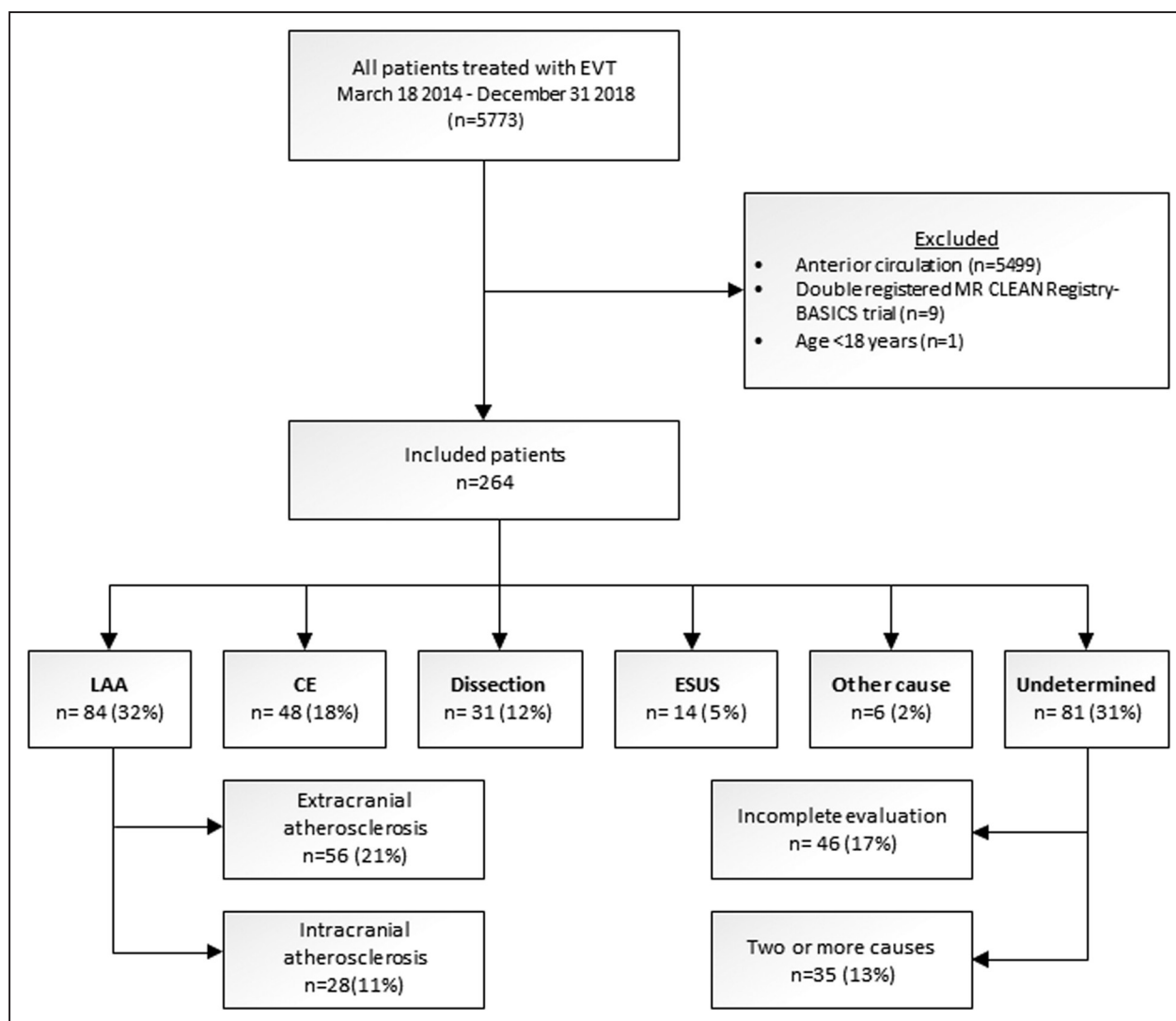


Figure 1. Flowchart patient selection.

BASICS indicates Basilar Artery International Cooperation Study; CE, cardioembolic; ESUS, embolic stroke of undetermined source; EVT, endovascular thrombectomy; LAA, large artery atherosclerosis; and MR CLEAN, Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands.

Hypertension was most prevalent in patients with LAA (65%) and cardioembolism (61%). Administration of intravenous thrombolysis was highest in patients with a dissection (61%) or ESUS (71%). Patients with cardioembolism or ESUS most often had maximum symptoms from stroke onset (respectively, 67% and 54%), while patients with LAA and dissection most often presented with progressive deficit (respectively, 48% and 43%). Thrombi seemed to be more distally located (distal BA) for cardioembolism (49%) and ESUS (50%) compared with LAA (29%) and dissection (30%; $P=0.07$).

Outcomes

The distribution of 90-day mRS scores is provided by etiologic subtype in Figure 2. Compared with LAA, better outcome was found for patients with cardioembolism (2.21 [95% CI, 1.1–4.3]), dissection (2.99 [95% CI, 1.4–6.5]),

and ESUS (5.09 [95% CI, 1.8–14.7]; Table 2). After adjustment for potential prognostic factors, better functional outcome remained for patients with cardioembolism (adjusted common OR, 2.48 [95% CI, 1.2–5.3]) and ESUS (adjusted common OR, 3.03 [95% CI, 1.0–9.0]).

For secondary outcomes: favorable functional outcome was highest in patients with cardioembolism (adjusted OR, 3.28 [95% CI, 1.3–8.3]), and NIHSS lowest in patients with cardioembolism (adjusted β , -6.31 [95% CI, -10.8 to -1.8]) and ESUS (adjusted β , -12.32 [95% CI, -19.2 to -5.5]) compared with LAA. The OR for successful reperfusion was lowest in patients with a dissection (adjusted OR, 0.22 [95% CI, 0.06–0.7]) compared with LAA. The risk of death at 90 days was lowest for patients with cardioembolism (adjusted OR, 0.35 [95% CI, 0.1–0.9]) and ESUS (adjusted OR, 0.19 [95% CI, 0.04–1.0]) compared with LAA. Stroke progression was not significantly different between groups.

Table 1. Baseline Characteristics of Posterior Circulation Stroke Patients by Etiologic Subtype

| | LAA | CE | Dissection | ESUS | P value |
|---|---------------|---------------|---------------|---------------|---------|
| | N=84 | N=48 | N=31 | N=14 | |
| Age, y, median (IQR) | 67 (58–76) | 69 (60–77) | 48 (43–60) | 54 (39–71) | <0.001 |
| Male sex, n (%) | 53 (63) | 23 (48) | 15 (48) | 10 (71) | 0.17 |
| Medical history | | | | | |
| Hypertension, n (%) | 53/82 (65) | 28/46 (61) | 6/30 (20) | 3/14 (21) | <0.001 |
| Hypercholesterolemia, n (%) | 18/82 (22) | 13/46 (28) | 3/28 (11) | 1/13 (8) | 0.19 |
| Diabetes, n (%) | 19/84 (23) | 6/47 (13) | 2/30 (7) | 1/14 (7) | 0.12 |
| Previous ischemic stroke, n (%) | 20/83 (24) | 6/47 (13) | 4/30 (13) | 1/14 (7) | 0.21 |
| Prestroke modified Rankin Scale score, n (%) [*] | | | | | 0.26 |
| <3 | 74 (93) | 39 (85) | 27 (93) | 14 (100) | |
| ≥3 | 6 (8) | 7 (15) | 2 (7) | 0 | |
| Intoxication and medication | | | | | |
| Current smoking, n (%) | 16/53 (30) | 10/36 (28) | 7/23 (30) | 2/13 (15) | 0.75 |
| Antiplatelet use, n (%) | 20/81 (25) | 13/47 (28) | 4/29 (14) | 1/14 (7) | 0.25 |
| Anticoagulation use, n (%) | 5/80 (6) | 16/47 (34) | 0 | 0 | <0.001 |
| Statin use, n (%) | 25/80 (31) | 17/47 (36) | 5/28 (18) | 1/14 (7) | 0.10 |
| Clinical | | | | | |
| Mean (SD) systolic blood pressure, mm Hg† | 154 (30) | 145 (27) | 147 (28) | 132 (26) | 0.82 |
| Intravenous alteplase treatment, n (%) | 37 (44) | 15 (31) | 19 (61) | 10 (71) | 0.01 |
| NIHSS, median (IQR)‡ | 17 (10–29) | 14 (7–20) | 12 (6–31) | 19 (7–35) | 0.06 |
| Glasgow Coma Scale score (median)‡ | 11 (6–13) | 11 (7–14) | 10 (4–15) | 11 (6–15) | 0.54 |
| Course of symptoms, n (%)§ | | | | | 0.02 |
| Maximum from onset | 29 (36) | 30 (67) | 9 (32) | 7 (54) | |
| Progressive deficit | 38 (48) | 9 (20) | 12 (43) | 4 (31) | |
| Fluctuating deficit | 13 (16) | 6 (13) | 7 (25) | 3 (21) | |
| Imaging | | | | | |
| Pc-ASPECTS on NCCT, median (IQR) | 10 (9–8) | 10 (9–8) | 10 (8–8) | 10 (10–7) | 0.10 |
| Level of occlusion on noninvasive vessel imaging (on CTA), n (%)¶ | | | | | 0.07 |
| No occlusion | 3 (4) | 1 (2) | 2 (7) | 0 | |
| Intracranial vertebral artery | 6 (7) | 2 (4) | 5 (17) | 0 | |
| BA | | | | | |
| Total BA | 10 (12) | 5 (11) | 7 (23) | 0 | |
| Proximal/middle BA | 31 (38) | 9 (19) | 4 (13) | 4 (29) | |
| Distal BA | 24 (29) | 23 (49) | 9 (30) | 7 (50) | |
| Posterior cerebral artery | 8 (10) | 7 (15) | 3 (10) | 0 | |
| PC-collateral score, median (IQR)‡ | 7 (5–8) | 7 (6–8) | 7 (5–8) | 7 (6–7) | 0.07 |
| Procedure | | | | | |
| Duration eLVO to groin, min, median (IQR)** | 260 (190–385) | 236 (177–365) | 208 (171–309) | 235 (185–370) | 0.77 |
| Duration door to groin, min, median (intervention center; IQR)†† | 79 (40–134) | 92 (44–132) | 77 (61–111) | 82 (53–145) | 0.78 |
| Duration of procedure, min, median (IQR)‡‡ | 64 (41–105) | 47 (35–93) | 59 (35–80) | 45 (33–81) | 0.42 |
| Use of general anesthesia, n (%)§§ | 40 (49) | 19 (40) | 24 (77) | 8 (57) | 0.01 |
| Device used for first attempt | | | | | |
| Stent retriever, n (%) | 39/70 (56) | 32/43 (74) | 11/20 (55) | 9/14 (64) | 0.22 |
| Aspiration device, n (%) | 24/70 (34) | 10/43 (23) | 7/20 (35) | 4/14 (29) | 0.63 |
| Stent placement at occlusion location, n (%) | 14/76 (18) | 1/46 (2) | 4/31 (13) | 1/13 (8) | 0.06 |

Level of occlusion: vertebral artery means no further distal occlusions; proximal/middle BA means no distal BA occlusion; distal BA may include a more proximal occlusion; posterior cerebral artery means no occlusion of the BA. BA indicates basilar artery; CE, cardioembolic; CTA, computed tomographic angiography; eLVO, estimated time of large vessel occlusion; ESUS, embolic stroke of undetermined source; IQR, interquartile range; LAA, large artery atherosclerosis; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; and Pc-ASPECTS, posterior circulation-Acute Stroke Prognosis Early CT Score.

^{*}n=169, missing in 8 patients.

[†]n=170, missing in 7 patients.

[‡]n=174, missing in 3 patients.

[§]n=175, missing in 2 patients.

[§]n=167, missing in 10 patients.

^{||}n=175, missing in 2 patients.

[¶]n=173, missing in 4 patients.

[#]n=171, missing in 6 patients.

^{**}n=162, missing in 15 patients.

^{††}n=166, missing in 11 patients.

^{‡‡}n=164, missing in 13 patients.

^{§§}n=173, missing in 4 patients.

^{|||}n=166, missing in 11 patients.

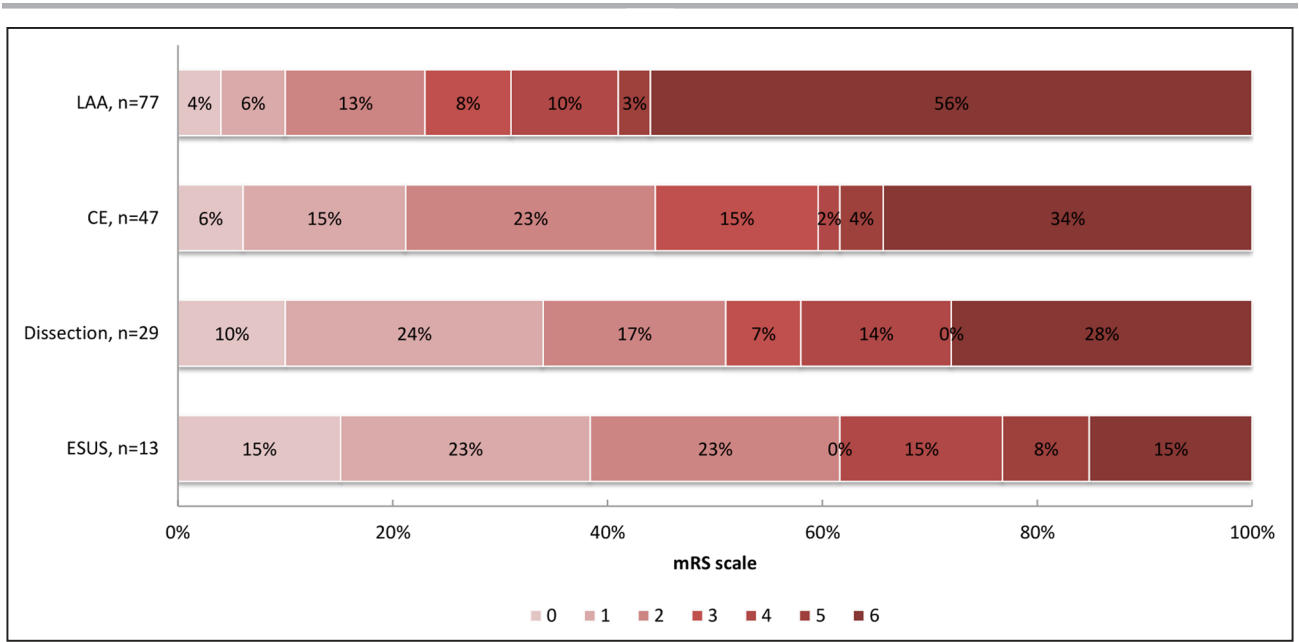


Figure 2. The modified Rankin Scale (mRS) distribution at 90 d by etiologic subtype.
CE indicates cardioembolic; ESUS, embolic stroke of undetermined source; and LAA, large artery atherosclerosis.

Table S2 shows outcomes of patients with PCS by etiologic subtype when LAA is divided into extracranial atherosclerosis and intracranial atherosclerosis. All outcome measures of patients with intracranial atherosclerosis were not significantly different from patients with extracranial atherosclerosis.

DISCUSSION

In this nationwide multicenter registry of patients with posterior LVO stroke treated with EVT, most frequent cause was LAA (32%) followed by cardioembolism

(18%), dissection (12%), and ESUS (5%). This is in line with autopsy series of patients with BA occlusions, which revealed atherosclerosis as the most common cause, and this was usually extensive beyond the BA alone.^{24,25} In clinical studies on posterior LVO various proportions of stroke subtypes have been reported. In Asian cohorts, LAA is reported as main cause of posterior circulation ischemic stroke in up to 80%.^{23,26–28} The prevalence of LAA, including the ratio extracranial versus intracranial atherosclerosis, in our cohort was in line with other registries with a predominantly White population (24%–36%).^{29–35} These studies, however, report much higher

Table 2. Outcomes of PCS Patients Treated With EVT by Etiologic Subtype

| Outcome | LAA | CE | | Dissection | | ESUS | |
|--------------------------|-----|------------------------|-----------------------|------------------------|----------------------|------------------------|------------------------|
| | OR | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
| Primary outcome | | | | | | | |
| mRS score at 90 d | 1 | 2.21 (1.1 to 4.3) | 2.48 (1.2 to 5.3) | 2.99 (1.4 to 6.5) | 1.44 (0.6 to 3.5) | 5.09 (1.8 to 14.7) | 3.03 (1.0 to 9.0) |
| Secondary outcomes | | | | | | | |
| mRS score of 0–3 at 90 d | 1 | 2.89 (1.4 to 6.1) | 3.28 (1.3 to 8.3) | 2.66 (1.1 to 6.3) | 1.07 (0.4 to 3.2) | 3.54 (1.1 to 11.8) | 2.25 (0.6 to 88) |
| NIHSS 24 h, β | 1 | −7.31 (−11.8 to −2.8) | −6.31 (−10.8 to −1.8) | −3.91 (−9.1 to 1.3) | −2.97 (−8.6 to 2.7) | −11.12 (−18.2 to −4.0) | −12.32 (−19.2 to −5.5) |
| Reperfusion on DSA | 1 | 1.58 (0.6 to 4.1) | 1.17 (0.4 to 3.5) | 0.47 (0.2 to 1.2) | 0.22 (0.06 to 0.7) | 1.12 (0.3 to 4.5) | 0.66 (0.1 to 3.0) |
| Death at 90 d | 1 | 0.41 (0.2 to 0.9) | 0.35 (0.1 to 0.9) | 0.30 (0.1 to 0.8) | 0.58 (0.2 to 1.8) | 0.14 (0.03 to 0.7) | 0.19 (0.04 to 1.0) |
| Stroke progression | 1 | 0.36 (0.1 to 1.1) | 0.26 (0.06 to 1.0) | 0.94 (0.3 to 2.7) | 0.88 (0.3 to 3.1) | 0.66 (0.1 to 3.2) | 0.83 (0.1 to 4.7) |

OR for main cause association with outcome variables: CE, dissection, or ESUS compared with LAA, estimated with logistic regression analyses. Adjustments were made for age, sex, NIHSS at baseline, mRS at baseline, hypertension, use of anticoagulation, intravenous thrombolysis, duration from estimated time of large vessel occlusion to groin puncture. β indicates regression coefficient, estimated with linear regression analyses; CE, cardioembolic; CTA, computed tomographic angiography; DSA, digital subtraction angiography; ESUS, embolic stroke of undetermined source; EVT, endovascular thrombectomy; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratios; and PCS, posterior circulation stroke.

proportions of cardioembolism compared with our cohort (30%–43%). The considerable number of patients with incomplete diagnostic workup may have led to an underestimation of cardioembolism in our study. The proportion of dissections in our cohort is slightly higher compared with previous studies (6%–8%).²⁹

In contrast to anterior circulation stroke, multivariable analysis showed better functional outcome for cardioembolism and ESUS compared with LAA and arterial dissection.⁸ Two studies on PCS have shown that distal BA occlusions are associated with better clinical recovery.^{36,37} In our study, occlusion location was not significantly different between stroke subtypes, but we did see a relatively high proportion of distal BA occlusions in cardioembolism and ESUS ($\pm 50\%$). Also, we found a difference in course of symptoms between etiologic subtypes. When stroke symptoms are maximum from onset rather than stuttering or progressive, which is the case for cardioembolism and ESUS, this may facilitate fast determination of diagnosis and further treatment. In our cohort, this was not supported by shorter duration times (eg, estimated time from LVO to groin/door to groin) for cardioembolism or ESUS. Notably, we did find a nonsignificant difference in duration of procedure, in favor of cardioembolism and ESUS.

It should be noted that with the lack of a control group, we did not investigate any interaction of stroke cause with treatment effect of EVT. Therefore, our results do not justify the use of etiologic subtype for treatment decisions.

Based on difference in stroke mechanism (thrombosis versus embolism) we performed additional analysis on intracranial atherosclerosis versus extracranial atherosclerosis and the association with functional outcome. In patients with slowly occluding intracranial atherosclerotic lesions, the cerebral circulation could adapt (for instance by improvement of collateral flow), resulting in better outcome in case of LVO. However, a previous study found higher risk of stroke recurrence in patients with intracranial stenosis of the posterior circulation compared with extracranial stenosis of the vertebral arteries.³³ Although we did not record stroke recurrence, we found no difference in functional outcome after 90 days of follow-up.

The univariable association between dissection and favorable outcome diminished after adjustment and was thus most likely dependent on age, stroke severity, and comorbidity. The lower chance of successful reperfusion is an important finding that will hopefully be used as an incentive for future improvements of EVT technique. Because successful reperfusion was not significantly different between etiologic subtypes, we think the impact on cause-based clinical outcomes should be limited. Moreover, we did not adjust for reperfusion in our multivariable analysis, but we chose to analyze this variable as an outcome measure.

In line with previous studies on ESUS, we found similarities between cardioembolism and ESUS, such as course of symptoms and level of occlusion, suggesting undiagnosed cardiac source in ESUS.³⁸

The strength of our study is the use of a large database of posterior LVO stroke patients with ample distribution of etiologic subgroups. Moreover, all outcome measures have been collected prospectively according to protocol, except for reperfusion status which was determined by core lab observers who were blinded for all clinical information.

The main limitation of our study is inherent to the use of observational data with variation in treatment protocols and patients selection paradigms. However, this variation in approach also allows us to gain more details on the actual patients presenting in routine clinical practice.

Second limitation is the lack of standardized diagnostic workup for ischemic stroke. The large proportion of undetermined stroke cause is most likely due to the high mortality rate as additional analysis showed worse clinical outcome for the group with undetermined cause. Although this difference was not significant we cannot rule out residual bias on the association with functional outcome. Third limitation concerns the use of posterior circulation-Acute Stroke Prognosis Early CT Score and eTICI score. Early ischemic changes of the posterior circulation are less accurately captured on noncontrast CT. Nevertheless, posterior circulation-Acute Stroke Prognosis Early CT Score has been validated in predicting unfavorable functional outcome.³⁹ The eTICI score is known to have a lower interobserver agreement in the posterior compared with the anterior circulation.⁴⁰ Finally, although we used multivariable logistic regression analysis, bias by unmeasured confounders may not be completely removed.

CONCLUSIONS

Unlike the anterior circulation, most frequent determined cause of patients treated with EVT for posterior circulation stroke was LAA followed by cardioembolism, arterial dissection, and ESUS. Patients with a dissection were younger, had a lower NIHSS at baseline, and had a lower chance of successful reperfusion compared with other etiologic subtypes. Patients with cardioembolism and ESUS had a better prognosis for functional outcome after EVT than patients with LAA.

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Supplemental Material

Supplemental Material S1–S3

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