Stroke

CLINICAL AND POPULATION SCIENCES

# Endovascular Thrombectomy in Young Patients With Stroke: A MR CLEAN Registry Study

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**BACKGROUND AND PURPOSE:** Acute ischemic stroke due to large vessel occlusion is uncommon in young adults. We assessed stroke cause in young patients and compared their outcomes after endovascular thrombectomy with older patients.

**METHODS:** We used data (March 2014 until November 2017) of patients with an anterior circulation large vessel occlusion stroke from the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry, a nationwide, prospective study on endovascular thrombectomy in the Netherlands. We compared young patients (18–49 years) with older patients (≥50 years). Outcomes included modified Rankin Scale score after 90 days (both shift and dichotomized analyses), expanded Thrombolysis in Cerebral Infarction score, and symptomatic intracranial hemorrhage. Analyses were adjusted for confounding.

**RESULTS:** We included 3256 patients, 310 (10%) were 18 to 49 years old. Young patients had lower median National Institutes of Health Stroke Scale scores (14 versus 16, $P<0.001$) and less cardiovascular comorbidities than older patients. Stroke etiologies in young patients included carotid dissection (16%), cardio-embolism (15%), large artery atherosclerosis (10%), and embolic stroke of undetermined source (31%). Clinical outcome was better in young than older patients (acOR for modified Rankin Scale shift: 1.8 [95% CI, 1.5–2.2]; functional independence [modified Rankin Scale score 0–2] 61 versus 39% [adjusted odds ratio, 2.1 [95% CI, 1.6–2.8]); mortality 7% versus 32%, adjusted odds ratio, 0.2 [95% CI, 0.1–0.3]). Symptomatic intracranial hemorrhage occurred less frequently in young patients (3% versus 6%, adjusted odds ratio, 0.5 [95% CI, 0.2–1.00]). Successful reperfusion (expanded Thrombolysis in Cerebral Infarction Score 2b-3) did not differ between groups. Onset to reperfusion time was shorter in young patients (253 versus 255 minutes, adjusted B in minutes 12.4 [95% CI, 2.4–22.5]).

**CONCLUSIONS:** Ten percent of patients with acute ischemic stroke undergoing endovascular thrombectomy were younger than 50. Cardioembolism and carotid dissection were common underlying causes in young patients. In one-third of cases, no cause was identified, indicating the need for more research on stroke cause in young patients. Young patients had better prognosis and lower risk of symptomatic intracranial hemorrhage than older patients.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** adult ■ dissection ■ odds ratio ■ reperfusion ■ thrombectomy



Endovascular treatment (EVT) is standard therapy for patients with acute ischemic stroke in the anterior circulation caused by intracranial large vessel occlusion (LVO).[1,2] As with stroke in general, most patients who receive EVT are relatively old. The median age of patients in the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials collaboration meta-analysis was 68 years.[1] In studies that reflect daily clinical routine,

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **aOR** | adjusted odds ratio |
| **ASPECTS** | Alberta Stroke Program Early CT Score |
| **ESUS** | embolic strokes of undetermined sources |
| **EVT** | endovascular thrombectomy |
| **ICA** | intracranial carotid artery |
| **IVT** | intravenous thrombolysis |
| **LVO** | large vessel occlusion |
| **MR CLEAN** | Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands |
| **mRS** | modified Rankin Scale |
| **OR** | crude odds ratio |
| **sICH** | symptomatic intracranial hemorrhage |
| **TOAST** | Trial of ORG 10172 in Acute Stroke Treatment |

median age was even higher, varying between 71[3] and 75 years.[4] Stroke due to LVO is uncommon in young patients (<50 years),[5] and as a result, data on the outcomes after EVT and underlying cause in these patients are limited. In the pooled analysis of patient-level data in the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials collaboration meta-analysis, 56% of patients aged 18 to 49 in the intervention group had a favorable outcome, compared with 47% in the control group. The direction of the effect seemed to favor EVT, albeit not statistically significant (adjusted common odds ratio of 1.36 [95% CI, 0.75–2.46]).[1] Literature specifically on EVT in young patients is scarce and little is known on outcomes and stroke cause in these patients. Most studies on stroke due to LVO in young patients had small sample sizes,[6,7] were single-center,[6] or did not focus specifically on EVT.[8–10] Therefore, the aim of the current study was to report stroke cause in young patients with LVO stroke who underwent EVT in a large nationwide registry. Additionally, we compared clinical and radiological outcomes after EVT between young and older patients.

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# METHODS

## Data Availability

J.B. and J.M.C. had full access to the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry database, which contains data at the individual patient level. The data of the study cannot be made available to other researchers due to the lack of patient approval for shared coded data. Dutch law prohibits data sharing in these circumstances. We will, however, share syntax or output files of the statistical analyses for academic purposes upon reasonable request from the corresponding author.

## Study Design and Patients

This study used data from the MR CLEAN Registry. The MR CLEAN Registry was a nationwide, multicenter, prospective observational cohort study, including all patients treated with EVT in the Netherlands from March 2014 till January 2019. Details on the design and procedures of the MR CLEAN Registry have been published.[3]

For the current study, we used data from patients with an LVO of the anterior circulation, who were treated until November 2017 (MR CLEAN Registry part 1 and 2). Children (age below 18) were excluded. In case a patient had > 1 event, only the first event was included in the analysis. LVO of the anterior circulation was defined as occlusions of the intracranial carotid artery (intracranial carotid artery terminus), middle cerebral artery (M1, M2, M3) or anterior cerebral artery (A1, A2), as confirmed on computed tomographic angiography. Young stroke was defined as stroke that occurred in patients 18 to 49 years of age, and all other patients were categorized as older patients (age ≥50 years). In the remainder of this article, we will be using these definitions with regard to both groups. We adhered to the RECORD reporting guideline. The associated checklist can be found in the Supplemental Material.

EVT was defined as arterial puncture with the objective to perform mechanical thrombectomy. Interventionists chose their own method of intervention (ie, local aspiration, stent retriever, with or without intraarterial thrombolytic agent). An independent, experienced imaging core laboratory assessed all imaging. This laboratory was blinded to clinical findings but were informed on side of occlusion. Collaterals at baseline were scored at computed tomographic angiography using a 4-point scale,[11] with 0 indicating no collaterals (0% filling of the vascular territory downstream of the occlusion), 1 indicating poor collaterals (>0, but ≤50%), 2 indicating moderate collaterals (>50%, but <100%), and 3 indicating 100% filling of the vascular territory. Degree of reperfusion was scored with the expanded Thrombolysis in Cerebral Infarction score on digital subtraction angiography, ranging from 0 (no reperfusion) to 3 (excellent reperfusion). If the posttreatment angiogram only had a single view, a maximum score of 2A could be attained.

## Outcome Measures

Two investigators (J.B. and A.S.) assessed stroke cause in all young patients according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.[12] In addition, we added a category for embolic strokes of undetermined sources (ESUS), following published criteria.[12,13] To minimize the interrater variability, we used dual abstraction, classifying each case individually by 2 independent assessors (J.B. and A.S.). In case of any discrepancy, a third adjudicator (J.M.C.) decided on the classification. Cases were scored as ESUS if they had no stenotic extra- or intracranial atherosclerotic disease, major cardioembolic risk factor, or other specific cause. To qualify for the diagnosis of ESUS, patients had to have undergone at least a 12-lead ECG, echocardiography, cardiac monitoring for a minimum of 24 hours, and imaging of both extra- and intracranial carotids. Patients with a patent foramen ovale without any other

source of emboli were listed as ESUS, in accordance with the criteria of Hart et al.[13] If patients had >1 equally likely cause for stroke, we scored cause as stroke of undetermined cause: 2 or more possible causes. In young patients who underwent EVT twice and were thus listed twice in the Registry (n=5), only the first event was counted to minimize confounding effects.

To minimize missing data regarding stroke cause, investigators assessed all discharge letters for relevant information. If these data were inconclusive, additional information was requested from participating hospitals.

Our main clinical outcome measure was the shift in the modified Rankin Scale (mRS) score at 90 days. Secondary outcomes included functional independence (mRS score 0–2), successful reperfusion (expanded Thrombolysis in Cerebral Infarction score 2b-3), door to groin times in minutes, and onset to reperfusion time in minutes.

Safety outcomes included mortality at 90 days and symptomatic intracranial hemorrhage (sICH), defined as a 4-point increase on the National Institutes of Health Stroke Scale (NIHSS) and intracranial hemorrhage on follow-up noncontrast enhanced computed tomography according to the Heidelberg Bleeding criteria.[14]

## Missing Data

The reported baseline data are not imputed. Etiology is reported using descriptive statistics and was not imputed. Several of the variables used in our regression models had missing data. To assess whether we could use multiple imputation to account for missing values, we first assessed the fraction of missing information and the patterns underlying our missing data. A list of the variables with missing data, and the associated fractions of missing information are provided under separate heading (Table S1). We had no reason to assume that our data were missing not at random. Following Enders (2010),[15] we thus used multiple imputation (with Fully Conditional Specification, 50 iterations) to impute those covariates and outcomes that had missing values. All variables included in the multiple imputation model were both imputed and used as predictor, with the exception of age and sex (which were predictors only). We conducted sensitivity analyses to assess whether multiple imputation led to significant changes in both effect size and direct of the effects. No significant changes were observed.

## Statistical Analyses

Baseline characteristics are reported using descriptive statistics.

We analyzed functional status at 90 days, measured with the mRS, with a shift analysis using multiple logistic ordinal regression analysis. We estimated the adjusted common odds ratio for a shift in direction of better outcome on the mRS. For clinical outcome measures (mRS, favorable mRS, mortality), the data were fitted using multiple generalized linear regression models or logistic regression models, when appropriate. These models were adjusted for potential confounding by sex, baseline NIHSS, Alberta Stroke Program Early CT Score, collateral score, intravenous thrombolysis (IVT), onset to door time, and prestroke mRS. For radiological outcome measures and symptomatic intracranial hemorrhage, we adjusted for history of previous stroke or transient ischemic attack, use of anticoagulants, baseline NIHSS, baseline systolic blood pressure, IVT, onset to groin time, and use of general anesthesia during EVT. Analyses for workflow times were adjusted for baseline NIHSS, prestroke mRS, systolic blood pressure at baseline, administration of IVT, onset to door time, Alberta Stroke Program Early CT Score, and collateral score.

The main outcome of this study is reported as adjusted common odds ratio. The secondary outcomes of this study are reported as crude odds ratios and adjusted odds ratios with 95% CI. All *P* are based on a 2-tailed distribution. Statistical analyses were performed with SPSS (IBM SPSS Statistics, version 26, release 26.0.0.1, 64-bit edition).

## Ethical Approval

Ethical approval has been obtained from the central medical ethics committee of the Erasmus Medical Centre in Rotterdam, the Netherlands (MEC-2014-235). For UMC Utrecht, additional approval from the local ethics committee was obtained.

# RESULTS

Of 3637 patients included in the MR CLEAN Registry in the specified time period, 3256 patients were included in the analysis (Figure 1). Of these, 310 patients were 18 to 49 years old (10%, median age 44, 47% male) and 2946 were ≥50 years of age (90%, median age 74, 52% male).

Young patients had a lower baseline NIHSS score (14 versus 16, $P<0.001$) and lower baseline systolic blood pressure than older patients (136 versus 151 mm Hg, $P<0.001$) (Table 1). Young patients had lower baseline prestroke mRS and less often a history of (cardiovascular) diseases. There was a difference in use of IVT (80% versus 75%, $P=0.032$). Baseline process measures, such as onset to door time and door to needle time in minutes, did not differ between young and older patients. Young patients had better collateral score on baseline computed tomographic angiography (grade 0: 5% versus 6%, grade 1: 26% versus 37%, grade 2: 42% versus 38%, grade 3: 28% versus 19%, $P<0.001$).

Etiology was assessed for 310 strokes in young patients (Table 2). In 21 strokes, there were 2 possible causes (Table S2). The most common stroke etiologies in young patients were carotid dissection (n=50, 16.2%), cardioembolism (n=46, 14.8%), and large artery atherosclerosis (n=31, 10.0%). For 95 events (30.7%), no etiology was found despite a complete evaluation and thus these cases fulfilled the criteria of embolic stroke of undetermined source (ESUS). Of the patients with ESUS, 23 (7.4%) had a patent foramen ovale or atrial septum defect. Diagnostic evaluation was incomplete for 35 (11.3%) events.

mRS scores were available for 3044 patients and imputed for the remaining 212 (6.5%). Clinical outcomes and treatment times are listed in Table 3. Young patients had a better functional outcome than older patients (adjusted common odds ratio for a shift towards better outcome: 1.8 [95% CI, 1.5–2.2]; Figure 2).

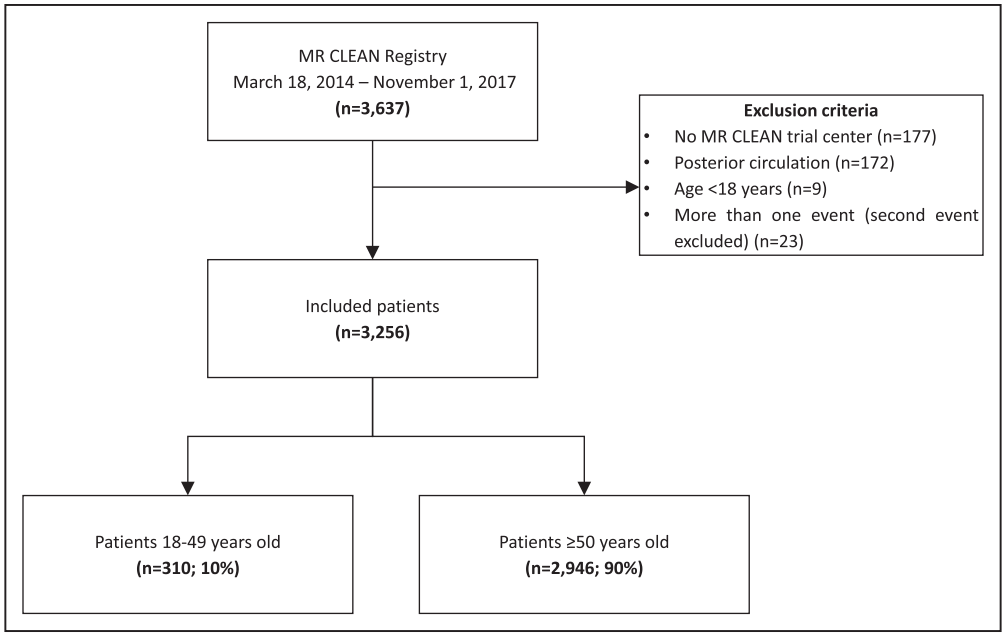


**Figure 1. Flowchart of included patients.**
MR CLEAN indicates Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands.

Functional independence (mRS score 0–2) was more frequent in young patients than older patients (61% versus 39%, adjusted odds ratio 2.1 [95% CI, 1.6–2.8]). Mortality was substantially lower in young patients (7% versus 32%, adjusted odds ratio 0.2 [95% CI, 0.1–0.3]). Young patients less frequently developed an sICH (3% versus 6%, adjusted odds ratio, 0.5 [95% CI, 0.2–1.0]). Door to groin time was slightly worse in young patients after adjustment for potential confounders (69 versus 61 minutes, adjusted B in minutes 6.4 [95% CI, 0.5–12.2]). Periprocedural complications were similar in both groups (Table S3).

## DISCUSSION

This study set out to asses clinical and radiological outcomes after EVT, and to identify stroke cause in young patients with stroke treated with EVT. We observed that young patients (18–49 years) had a significantly better clinical outcome than those ≥50 years of age and a lower risk of death or symptomatic intracranial bleeding. Cardioembolic disease (14.8%) and carotid dissections (16.2%) were found to be the most common causes of stroke caused by LVO in younger patients, followed by large artery atherosclerosis (10.0%). However, in one-third of patients, no stroke cause was identified despite extensive diagnostic work-up, and these patients fulfilled the criteria for ESUS. In a further 6.8%, 2 or more possible causes were present.

In the MR CLEAN Registry, about 10% of patients treated by EVT were young patients with stroke. This is in line with other data on patients treated by EVT and of patients with ischemic stroke overall, where around 10% of patients are 18 to 49 years old.[1,16] At baseline, a significant difference in collateral grade was found, with a better collateral grade in younger patients. Earlier studies noted a similar relation between collateral status and higher age,[17–19] for which the pathophysiological mechanism remains to be elucidated. We found that a significantly larger proportion of young patients with stroke directly presented at an intervention center rather than a regional primary stroke center, when compared with older patients. A possible explanation could be that interventional hospitals are mostly located in urban areas with a relatively younger population. Another explanation could be that paramedics may be inclined to bring young patients with a suspected stroke and severe neurological deficits directly to a comprehensive stroke center. Interestingly, there was no significant difference in onset to door time of the intervention hospital, although the younger patients more frequently presented directly at the intervention hospital. This may suggest a prehospital delay in the young patients with stroke. Furthermore, the door to groin time at the intervention hospital was longer for younger patients. This could be due to a longer work-up for younger patients who presented directly to an intervention hospital, as compared with older patients who already had a work-up at an auxillary hospital. There was a significant difference in treatment with IVT, with more younger patients being treated with IVT. This is likely due to the fact the older patients use oral anticoagulants significantly more often, due to which IVT can be contraindicated.

Earlier studies have shown that cervical dissection and nonarrhythmic heart disorders are frequent causes of stroke in young patients,[6,10,17,20] which is similar to our

**Table 1. Baseline Characteristics**

| | Age 18–49 y (n=310) | Age ≥50 y (n=2946) | *P* value |
|---|---|---|---|
| Age median (IQR) | 44 (39–47) | 74 (65–81) | NA |
| Male–n (%) | 145 (47) | 1542 (52) | 0.064 |
| Mean systolic blood pressure, mm Hg±SD* | 136 (±21) | 151 (±25) | <0.001 |
| Mean diastolic blood pressure, mm Hg±SD† | 81 (±17) | 82 (±15) | 0.262 |
| Median NIHSS (IQR)‡ | 14 (10–18) | 16 (11–20) | <0.001 |
| IVT treatment, n (%) | 249/310 (80) | 2191/2934 (75) | 0.032 |
| Prestroke mRS score ≥3, n/total n (%) | 13/307 (4.2) | 352/2879 (12.2) | <0.001 |
| Medical history | | | |
| Previous stroke/TIA | 24/309 (7.8) | 506/2920 (17.3) | <0.001 |
| Atrial fibrillation | 18/308 (5.8) | 744/2905 (25.6) | <0.001 |
| Diabetes | 12/309 (3.9) | 515/2923 (17.6) | <0.001 |
| Hypertension | 46/307 (15.0) | 1629/2883 (56.5) | <0.001 |
| Hypercholesterolemia | 34/307 (11.1) | 922/2806 (32.9) | <0.001 |
| Coronary artery disease | 13/309 (4.2) | 435/2880 (15.1) | <0.001 |
| Use of antiplatelet therapy before event, n/total n (%) | 36/3083 (11.7) | 964/2908 (33.1) | <0.001 |
| Use of antihypertensive agents before event, n/total n (%) | 49/307 (16.0) | 1674/2888 (58.0) | <0.001 |
| Use of anticoagulation before event, n/total n (%) | 31/308 (10.1) | 557/2926 (19.0) | <0.001 |
| Use of statins before event, n/total n (%) | 34/307(11.1) | 1086/2876 (37.8) | <0.001 |
| Location of occlusion, n/total n (%) | | | <0.001 |
| Intracranial ICA | 21/300 (7.0) | 139/2827 (4.9) | |
| ICA-T | 58/300 (19.3) | 598/2827 (21.2) | |
| M1 | 178/300 (59.3) | 1628/2827 (57.6) | |
| M2 | 39/300 (13.0) | 432/2827 (15.3) | |
| Other | 4/300 (1.3) | 30/2827 (1.06) | |
| Median ASPECTS (IQR)§ | 9 (7–10) | 9 (8–10) | 0.211 |
| Collateral grade, n/total n (%) | | | <0.001 |
| 0 Absent collaterals | 13/290 (4.5) | 173/2761 (6.3) | |
| 1 Filling <50% of occluded area | 76/290 (26.2) | 1018/2761 (36.9) | |
| 2 >50% but <100% | 121/290 (41.7) | 1060/2761 (38.4) | |
| 3 100% of occluded area | 80/290 (27.6) | 510/2761 (18.5) | |
| Referred patients, n/total n (%) | 145/310 (46.8) | 1631/2945 (55.4) | 0.002 |
| Median onset to door time (intervention hospital)‖ | 126 (50–214) | 136 (68–193) | 0.412 |
| Median onset to door time (initial hospital)¶ | 60 (35–138) | 53 (37–90) | 0.097 |
| Median door to needle (IVT) time# | 24 (19–34) | 24 (18–33) | 0.112 |

ASPECTS indicates Alberta Stroke Program Early CT Score; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IQR, interquartile range; IVT, intravenous thrombolysis; M1, first segment of middle cerebral artery, right after ICA; M2, second, more distal segment of middle cerebral artery; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Missing data n (%):

*Young patients 5 (1.6), older patients 82 (2.8).

†Young patients 5 (1.6), older patients 91 (3.1).

‡Young patients 6 (1.9), older patients 47 (1.6).

§Young patients 10 (3.2), older patients 98 (3.3).

‖Young patients 18 (5.8), older patients 141 (4.8).

¶Young patients 209 (67.4%), older patients 1809 (61.4).

#Young patients 113 (36.5), older patients 1230 (41.8).

findings. It is of note that these studies included young patients with stroke overall, not only patients with an LVO. We found that 16.2% of young patients had carotid dissection as etiology for stroke due to LVO. In the 21 patients where >1 possible cause was identified carotid dissection was found in 9 patients. Therefore, in total carotid dissection was prevalent in 19% of all young patients with stroke. An earlier MR CLEAN trial and MR CLEAN Registry study showed that in the total cohort from 2014 to 2016, only 4.7% had a carotid dissection. However, this study included young and older patients and was not set out to assess young patients. The authors

**Table 2. Stroke Etiology in Young Patients (Age 18–49) (n=310)**

| | n=310 |
|---|---|
| Large artery atherosclerosis | 31 (10.0) |
| Cardioembolic | 46 (14.8) |
| Stroke of other determined etiology | 82 (26.5) |
| Extracranial carotid dissection | 50 (16.2) |
| Carotid web | 7 (2.3) |
| Vasculitis | 2 (0.6) |
| Nonmalignancy-associated coagulopathy | 11 (3.6) |
| Malignancy | 5 (1.6) |
| Drug misuse | 1 (0.3) |
| Iatrogenic | 1 (0.3) |
| Remaining causes | 5 (1.6) |
| Stroke of undetermined etiology | 151 (48.7) |
| 2 or more possible causes | 21 (6.8) |
| ESUS* | 95 (30.7) |
| Incomplete diagnostic evaluation | 35 (11.3) |

CT indicates computed tomography; ESUS, embolic stroke of undetermined source; and MRI, magnetic resonance imaging.

*ESUS could only be attributed in case of a negative evaluation, which required a minimum diagnostic assessment according to criteria ESUS: brain CT or MRI ruling out intracranial hemorrhage, 12-lead ECG, precordial echocardiography, cardiac monitoring for at least 24 h, imaging of extra- and intracranial carotid arteries.

conclude that carotid dissection by itself should not be a contraindication for EVT as EVT in patients with carotid dissection does result in neurological improvement.

In our study, in 48.7% of patients, no (single) cause was identified. In 6.8% of patients, 2 or more causes were found; this may contribute to a higher percentage of patients with unknown cause than found in literature. About one-third of all included events in young patients was classified as ESUS. Of the patients with ESUS, 7.4% had a patent foramen ovale or atrial septum defect. Rates of unknown cause in the literature vary between 20% and 40%.[10,17–19] This variation may be due to differences in criteria used to determine what work-up is required to establish undermined cause; none of the referenced articles used the ESUS criteria.[10,17–19] The fact that in our study one-third of patients was identified as ESUS and thus no cause could be found despite a thorough work-up suggests that further research on risk factors and potential causes in this patient group is necessary. Earlier studies on young stroke cause included a higher proportion of strokes due to small vessel disease.[8,16,21] Since we only included patients treated by EVT, strokes caused by small vessel disease were not included in our cohort. In ischemic stroke in the older population (≥50), cardioembolism and large artery atherosclerosis are the most common causes.[22]

Our finding that young patients with stroke have a good clinical outcome with a high rate of favorable outcomes (61%–87%) and low mortality is in line with previous reports.[8,9,17,19] With regard to mortality and sICH, Shi et al[23] observed no significant difference between young patients with stroke and those over 50 years after IVT. Our findings, however, do suggest a difference in mortality and sICH, both in favor of young stroke patients, with similar reperfusion rates. Possible explanations for a better clinical outcome could be that young patients with stroke are overall healthier with less (cardiovascular) comorbidity. Another explanation could relate to more exhaustive rehabilitation options for young patients.

## Strengths and Limitations

This study has several limitations to consider. First, our data were collected in a prospective database in which certain etiologies were documented, mostly based on findings during admission (eg, atrial fibrillation status). However, rare causes seen in young stroke that are frequently diagnosed during outpatient visits after additional testing (eg, patent foramen ovale, antiphospholipid syndrome) as well as certain risk factors (eg, oral contraceptive use, migraine) were not systematically collected, requiring additional enquiries to participating hospitals. Retrospectively, we were unable to retrieve a definite cause for all patients, for instance, because some patients were lost to follow-up. The additional work-up in young patients with stroke also varied among hospitals. For example, there are differences in duration of cardiac monitoring, whether or not a carotid ultrasound is performed, and the extent to which additional laboratory tests are performed, including toxicology screens and a hypercoagulable work-up. Another limitation is the risk of interobserver variability, as multiple researchers have screened the discharge letters of the patients, which may have led to different interpretation. We attempted to overcome this potential variability by having both researchers read the discharge letters and by discussing uncertain cases with an expert panel, we attempted to minimize any inconsistencies.

By definition, large artery atherosclerosis is a cause for ischemic stroke in case of a symptomatic significant stenosis of the internal carotid artery, but also in case of atherosclerosis in the middle or anterior cerebral artery of >50%. However, in the MR CLEAN Registry, there is no data collection of atherosclerosis in the middle or anterior cerebral artery, nor on nonstenotic atherosclerosis. The fact that these parameters were not included in the data may have led to an underestimation of large artery atherosclerosis.

We only determined cause in young patients with stroke, as one of our aims of this study was to determine whether the cause specifically in young patients with stroke with an LVO differs from young patients with stroke with ischemic stroke overall. Therefore, we were unable to compare stroke cause between young and old patients.

**Table 3. Outcomes**

| | Age 18 to 49 y (n=310) | Age ≥50 y (n=2946) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| mRS (median, IQR)* | 2 (1 to 3) | 3 (2 to 6) | 2.22 (1.81 to 2.73) | 1.79 (1.45 to 2.22) |
| mRS score 0 to 2† | 189 (61.0) | 1144 (38.8) | 2.46 (1.94 to 3.13) | 2.13 (1.64 to 2.76) |
| eTICI 2b-3‡ | 199 (64.2) | 1803 (61.2) | 1.10 (0.85 to 1.41) | 1.00 (0.76 to 1.30) |
| Mortality at 90 d† | 21 (6.8) | 939 (31.9) | 0.16 (0.10 to 0.24) | 0.18 (0.11 to 0.29) |
| Symptomatic ICH‡ | 9 (2.9) | 183 (6.2) | 0.43 (0.21 to 0.89) | 0.47 (0.23 to 0.97) |
| | Young patients (n=315) | Older patients (n=2964) | Unadjusted B, min (95% CI) | Adjusted B in minutes (95% CI) |
| Median onset to reperfusion time, min (IQR)§ | 253 (198 to 337) | 255 (200 to 317) | 12.69 (0.25 to 25.13) | 12.43 (2.40 to 22.47) |
| Median door (referral hospital) to groin time, min (IQR)§ | 176 (132 to 235) | 167 (130 to 216) | 4.22 (−7.96 to 16.40) | 5.13 (−7.24 to 17.50) |
| Median door (intervention hospital) to groin time, min (IQR)§ | 69 (40 to 100) | 61 (35 to 92) | 5.43 (−0.37 to 11.23) | 6.35 (0.54 to 12.16) |
| Median duration of procedure, min (IQR)§ | 55 (35 to 85) | 60 (39 to 84) | −1.81 (−5.91 to 2.29) | −0.05 (−4.23 to 4.14) |

Imputed data. B=difference in time, min. eTICI indicates expanded Treatment in Cerebral Infarction; ICH, intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; and OR, odds ratio.

*mRS presented as common odds ratio.

†mRS, mRS score 0 to 2, and mortality adjusted for prestroke mRS, NIHSS at baseline, ASPECTS at baseline, collateral score, sex, IVT yes/no, onset to door time.

‡sICH not imputed as there were no missing values. eTICI, sICH adjusted for previous stroke, use of anticoagulation, NIHSS at baseline, systolic blood pressure at baseline, IVT yes/no, onset to groin time, and use of general anesthesia

§Onset to reperfusion time, door to groin time referral and intervention hospital adjusted for: baseline NIHSS, prestroke mRS, systolic blood pressure at baseline, IVT yes/no, onset to door time, ASPECTS, and collateral score.

Another limitation is that our study has no control group, as the MR CLEAN Registry does not include data on stroke patients who did not undergo EVT. Therefore, we cannot compare outcomes between patients who underwent EVT to patients who did not undergo EVT.

A strength of this study is the fact that in the MR CLEAN registry uniform data regarding baseline and outcome variables are collected, allowing the comparison between young stroke patients and those over 50 years of age, thereby providing more specific information on the young stroke population with an LVO. Another strength is the large number of young patients with stroke included in the study, enabling the characterization of this specific subgroup of young patients with stroke about cause. Our study thereby provides new information about an important subgroup of patients with LVO, as well as an important subgroup of young patients with stroke.

We anticipate that the findings of this study contribute to improvement of additional work-up in young patients treated with EVT and may aid in counseling of these patients and relatives regarding expected outcomes.

## Conclusions

In our study, 10 percent of patients with stroke treated with EVT was <50 years of age. The underlying cause was most often cardioembolic or carotid dissection, which is in accordance with earlier data on cause in ischemic stroke in young patients with stroke overall. However,

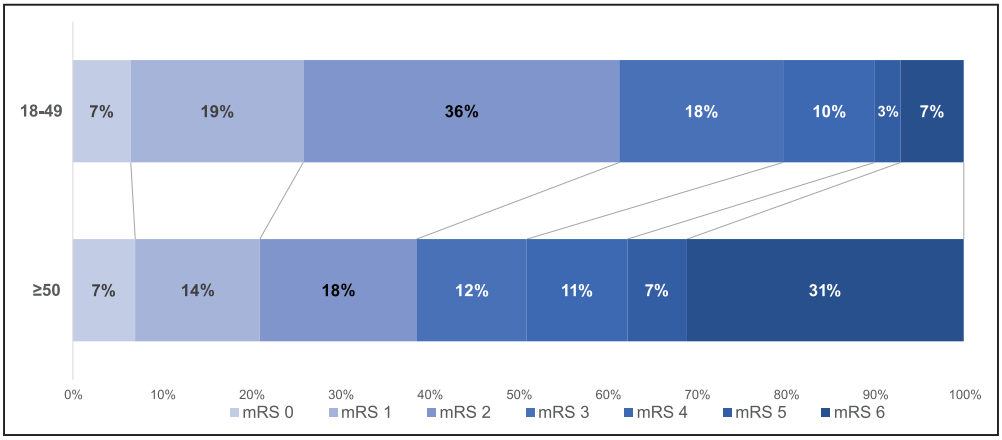


**Figure 2. Modified Rankin Scale score (mRS) at 90 d.**
Stacked bar-chart showing percentages for each mRS score, with on the *x*-axis: percentage of patients with certain mRS, and on the *y*-axis: dichotomized age. Unadjusted common odds ratio for a shift towards a better outcome 2.22 (95% CI, 1.81–2.73). Adjusted common odds ratio for a shift towards a better outcome 1.79 (95% CI, 1.45–2.22).

in about one-third no cause was identified despite an extensive work-up, indicating that more research is needed on risk factors and cause in young stroke patient. Young patients had higher chances of recovery toward independency after EVT and had lower mortality and sICH rates when compared with older patients, despite similar recanalization rates.

## ARTICLE INFORMATION

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### Supplemental Material

MR CLEAN Registry Investigators
Table S1–S3
RECORD Reporting Checklist

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