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ABSTRACT

BACKGROUND AND PURPOSE: Randomized trials in the late window have demonstrated the efficacy and safety of endovascular thrombectomy in large-vessel occlusions. Patients with M2-segment MCA occlusions were excluded from these trials. We compared outcomes with endovascular thrombectomy in patients with M2-versus-M1 occlusions presenting 6–24 hours after symptom onset.

MATERIALS AND METHODS: Analyses were on pooled data from studies enrolling patients with stroke treated with endovascular thrombectomy 6–24 hours after symptom onset. We compared 90-day functional independence (mRS $\leq$ 2), mortality, symptomatic intracranial hemorrhage, and successful reperfusion (expanded TICI = 2b–3) between patients with M2 and M1 occlusions. The benefit of successful reperfusion was then assessed among patients with M2 occlusion.

RESULTS: Of 461 patients, 367 (79.6%) had M1 occlusions and 94 (20.4%) had M2 occlusions. Patients with M2 occlusions were older and had lower median baseline NIHSS scores. Patients with M2 occlusion were more likely to achieve 90-day functional independence than those with M1 occlusion (adjusted OR = 2.13; 95% CI, 1.25–3.65). There were no significant differences in the proportion of successful reperfusion (82.9% versus 81.1%) or mortality (11.2% versus 17.2%). Symptomatic intracranial hemorrhage risk was lower in patients with M2-versus-M1 occlusions (4.3% versus 12.2%, P = .03). Successful reperfusion was independently associated with functional independence among patients with M2 occlusions (adjusted OR = 2.84; 95% CI, 1.11–7.29).

CONCLUSIONS: In the late time window, patients with M2 occlusions treated with endovascular thrombectomy achieved better clinical outcomes, similar reperfusion, and lower symptomatic intracranial hemorrhage rates compared with patients with M1 occlusion. These results support the safety and benefit of endovascular thrombectomy in patients with M2 occlusions in the late window.

ABBREVIATIONS: eTICI = expanded thrombolysis in cerebral infarction; IQR = interquartile range; SICH = symptomatic intracranial hemorrhage

Treatment of medium-vessel occlusion with endovascular thrombectomy is gaining attention among the stroke community. In a recent survey of 366 physicians, 59.2% of participants were willing to treat such patients immediately with endovascular thrombectomy without waiting for the effect of intravenous thrombolysis or the worsening of patient symptoms.[1] These preferences are partly based on evidence from observational studies and meta-analyses suggesting the safety and efficacy of endovascular thrombectomy among patients with medium-vessel occlusion treated within 6 hours from

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symptom onset.[2-5] The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration included 130 patients with M2 occlusion and showed the benefit of endovascular thrombectomy compared with medical treatment.[2] In addition, multiple prior studies showed similar endovascular thrombectomy benefits among patients with M2 occlusions.[3,4]

The safety and effectiveness of endovascular thrombectomy in patients with M2 occlusion in the late time window remain unknown. The late-window randomized trials that demonstrated the efficacy and safety of endovascular thrombectomy excluded patients with M2 occlusions. A recent individual patient data meta-analysis of randomized controlled trials of endovascular thrombectomy in the late window included only 15 patients with M2 occlusion of 505 patients.[6] Therefore, current guidelines from the American Stroke Association[7] recommend endovascular thrombectomy in the late window only in patients with large-vessel occlusions in the M1 segment and the ICA.[8,9]

Using data from a multicenter international registry, we evaluated the safety and clinical outcomes of endovascular thrombectomy in patients with M2 occlusion presenting between 6 and 24 hours from symptom onset or last known well.

MATERIALS AND METHODS

Data were used from the Selection Of Late-window Stroke for Thrombectomy by Imaging Collateral Extent (SOLSTICE) Consortium, an individual-patient-level analysis of 2 randomized trials and 6 prospective registries from North America, Europe, and South Korea using collateral imaging to select patients eligible for endovascular thrombectomy between 6 and 24 hours after symptom onset or last known well.[10] These include the Acute Stroke Registry and Analysis of Lausanne,[11] Lausanne, Switzerland; the National Thrombectomy Service Beaumont Hospital Registry,[12] Dublin, Ireland; the stroke registry of Turku University Hospital, Turku, Finland; the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial,[13] the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) trial,[14] the Italian Registry of Endovascular Thrombectomy,[15] Italy; the Precise and Rapid Assessment of Collaterals Using Multiphase CTA in the Triage of Patients with Acute Ischemic Stroke for IV or IA Therapy (PRove-IT) study;[16] and the Seoul National University Bundang Hospital stroke registry.[17] All included studies and registries were approved by local ethics review committees or analyzed only anonymized data as permitted by local legislation. Details regarding the included studies are summarized in the Online Supplemental Data. The pooled analysis of the main study was registered at PROSPERO (No. CRD42020222003).

All patients underwent collateral imaging and were treated with endovascular thrombectomy. Perfusion imaging was performed in a subset of patients according to local institutional protocols. All included studies were approved by the local review board at each participating center.

For this study, we included patients with MCA occlusion and compared patients with M1 occlusions with patients with M2 occlusions. The M2 segment was defined as the segment starting from the first bifurcation of the proximal MCA excluding the anterior temporal branch and ending at the circular sulcus.[18]

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Online Supplemental Data).

Outcomes

The primary clinical outcome was functional independence defined as mRS $\leq$ 2 at 90 days. Secondary outcomes were mRS 0–1 at 90 days and safety outcomes, which included mortality within 90 days and the incidence of symptomatic intracranial hemorrhage (SICH) defined according to European-Australian Cooperative Acute Stroke Study 2 (ECASS2) definition.[19] Successful reperfusion was defined as expanded TICI (eTICI) $\geq$2b, corresponding to reperfusion of at least half of the affected arterial territory.

Statistical Analysis

Categoric data were presented as numbers (percentages), and continuous data, as median with interquartile range (IQR). We compared baseline characteristics and outcomes between M1 and M2 occlusion groups using the χ^2 test for categoric variables and the Mann-Whitney test for continuous variables. Mixed-effects logistic regression was then performed to determine whether M2 occlusion was associated with functional independence after adjusting for age, sex, and time from onset to reperfusion with the data source treated as a random-effects variable. To investigate the differential effect of time from onset to reperfusion on functional independence in patients with M2-versus-M1 occlusion, we performed interaction analyses by including the multiplicative interaction term in the regression model.

Furthermore, in patients with M2 occlusions, baseline characteristics were compared between patients who achieved successful reperfusion and those who did not. Because all patients in our data had undergone endovascular thrombectomy, we used successful reperfusion as a proxy for endovascular thrombectomy efficacy, similar to previously published studies.[20,21] Mixed-effects logistic regression was attempted to determine the association between successful reperfusion and functional independence at 90 days in the M2 occlusion group after adjusting for age, sex, NIHSS score, and time from onset to reperfusion ("study ID" was included as a random-effects variable). No imputation was performed because missing data were minimal (<5%).

All statistical tests were 2-sided, and P values $< .05$ were considered significant. Statistical analysis was performed using STATA 17 (StataCorp).

RESULTS

Of 461 patients, 94 (20.4%) had M2 occlusion and 367 (79.6%) had M1 occlusion. The study flow chart is shown in Fig 1.

Baseline demographics, imaging parameters, and outcomes are summarized in Table 1. Compared with patients with M1 occlusion, patients with M2 occlusion were older (75 [median IQR = 63–82] years versus 69 [IQR = 58–78] years, $P = .01$) and had a lower median NIHSS score (10 versus 16, $P < .001$) and a higher median ASPECTS (9 versus 8, $P < .001$). Arterial puncture to reperfusion time was longer in patients with M2 occlusions (median, 45 versus 30 minutes, $P = .001$). Other workflow times were not significantly different between patients with M2 and M1

occlusion. Rates of successful reperfusion were similar between the M2 and M1 occlusion groups (82.9% versus 81.1%, $P = .77$). The 90-day follow-up was available in 438/461 (95%) patients. The proportion of patients achieving 90-day functional independence (mRS 0–2) was higher in patients with M2 compared with M1 occlusions (59.6% versus 45.0%. $P = .02$) (Table 1 and Fig 2). Mortality rates in the patients with M2-versus-M1 occlusion were comparable (11.2% versus 17.2%, $P = .20$), while SICH occurred less frequently in the M2 occlusion group (4.3% versus 12.2%, $P = .03$) (Table 1). In multivariable analysis adjusting for age, sex, and time from onset to reperfusion, age (adjusted OR = 0.60 per decile increase; 95% CI, 0.51–0.71), time from onset to reperfusion (adjusted OR = 0.94 per 60-minute delay; 95% CI, 0.88–0.99), and M2 occlusion (adjusted OR = 2.13; 95% CI, 1.25–3.65) were independently associated with a higher likelihood of functional independence at 90 days. In the interaction analysis, there was no evidence of the heterogeneity of effect by time from onset to reperfusion when comparing patients with M2-versus-M1 occlusion ($p_{interaction} = 0.19$).

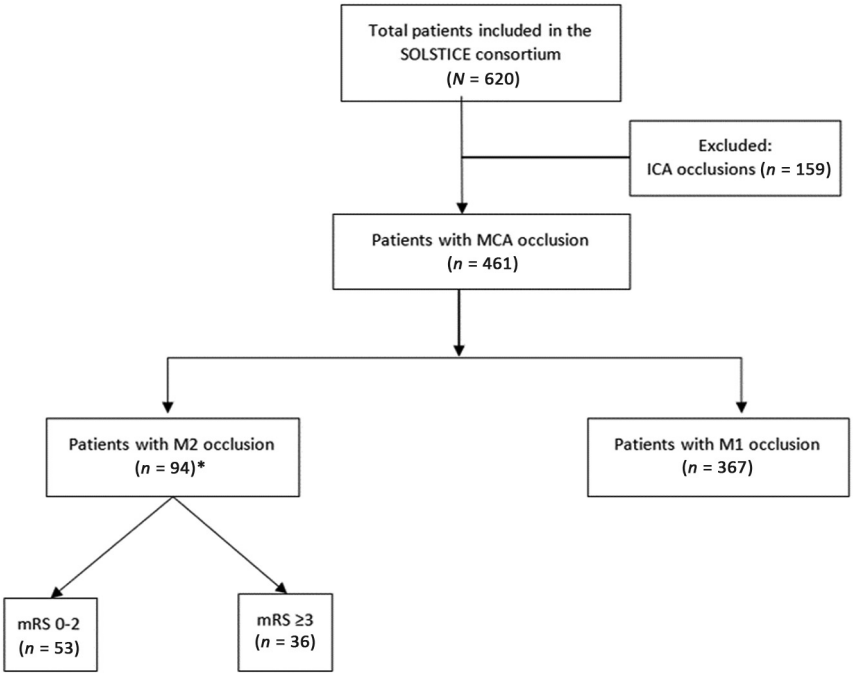

FIG 1. Study flow chart for SOLSTICE. The *asterisk* indicates that 5 patients did not have 90-day follow-up data.

M2 Subgroup

Among the 94 patients with M2 occlusion, 89 (95%) had 90-day follow-up data. Functional independence (mRS 0–2) was achieved in 53/89 (59.6%) patients, and successful reperfusion (eTICI ≥2b) was seen in 78/94 (83.0%). Patients with successful reperfusion had longer onset-to-reperfusion times (median, 762 [IQR = 586–968] minutes versus 540 [IQR = 511–663] minutes, $P = .03$) and higher ASPECTS scores (median 10 [IQR = 8–10] versus median 8

Table 1: Patient baseline characteristics and outcomes stratified by MCA occlusion location[a]

Characteristic	M2 Occlusion (*n* = 94)	M1 Occlusion (*n* = 367)	Missing
Age (median) (IQR) (yr)[b]	75 (63–82)	69 (58–78)	0
Female sex	51 (54.3)	193 (52.6)	0
Stroke presentation			
Wake-up stroke	49/93 (52.7)	187/349 (53.6)	19
Baseline NIHSS (median) (IQR)[b]	10 (7–15)	16 (11–20)	1
Tandem cervical occlusion	10 (10.6)	46 (12.5)	0
IV Alteplase	12 (12.8)	34 (9.3)	0
Time metrics (median) (IQR) (min)			
Time from onset to ED door	545 (368–730), [*n* = 91]	538 (405–692), [*n* = 342]	28
Time from onset to CT scan	579 (416–735), [*n* = 91]	551 (430–710), [*n* = 359]	11
Time from onset to puncture	744 (485–900), [*n* = 87]	631 (521–815), [*n* = 348]	26
Time from onset to reperfusion	762 (530–968), [*n* = 85]	671 (570–848), [*n* = 333]	26
Time from puncture to reperfusion[b]	45 (26–64), [*n* = 85]	30 (19–50), [*n* = 333]	25
Imaging factors			
ASPECTS[b]	9 (8–10)	8 (7–9)	2
Use of perfusion imaging	67 (71.3)	223 (60.7)	0
Outcomes			
Final TICI 2b–3	78 (82.9)	297 (81.1)	1
Final TICI 2c–3	29 (30.8)	119 (32.4)	1
SICH[b]	4/92 (4.3)	41/337 (12.2)	32
90-Day mRS (median) IQR)	2 (1–3) [*n* = 89]	3 (1–5) [*n* = 349]	23
90-Day mRS = 0–1	36/89 (40.4)	102/349 (29.2)	23
90-Day mRS = 0–2[b]	53/89 (59.6)	157/349 (45.0)	23
90-Day mortality	10/89 (11.2)	60/349 (17.2)	23

Note:—ED indicates emergency department.

[a] Values are expressed as median (IQR) or No. (%). Data are for the entire population unless otherwise specified in brackets.

[b] Significant difference between groups.

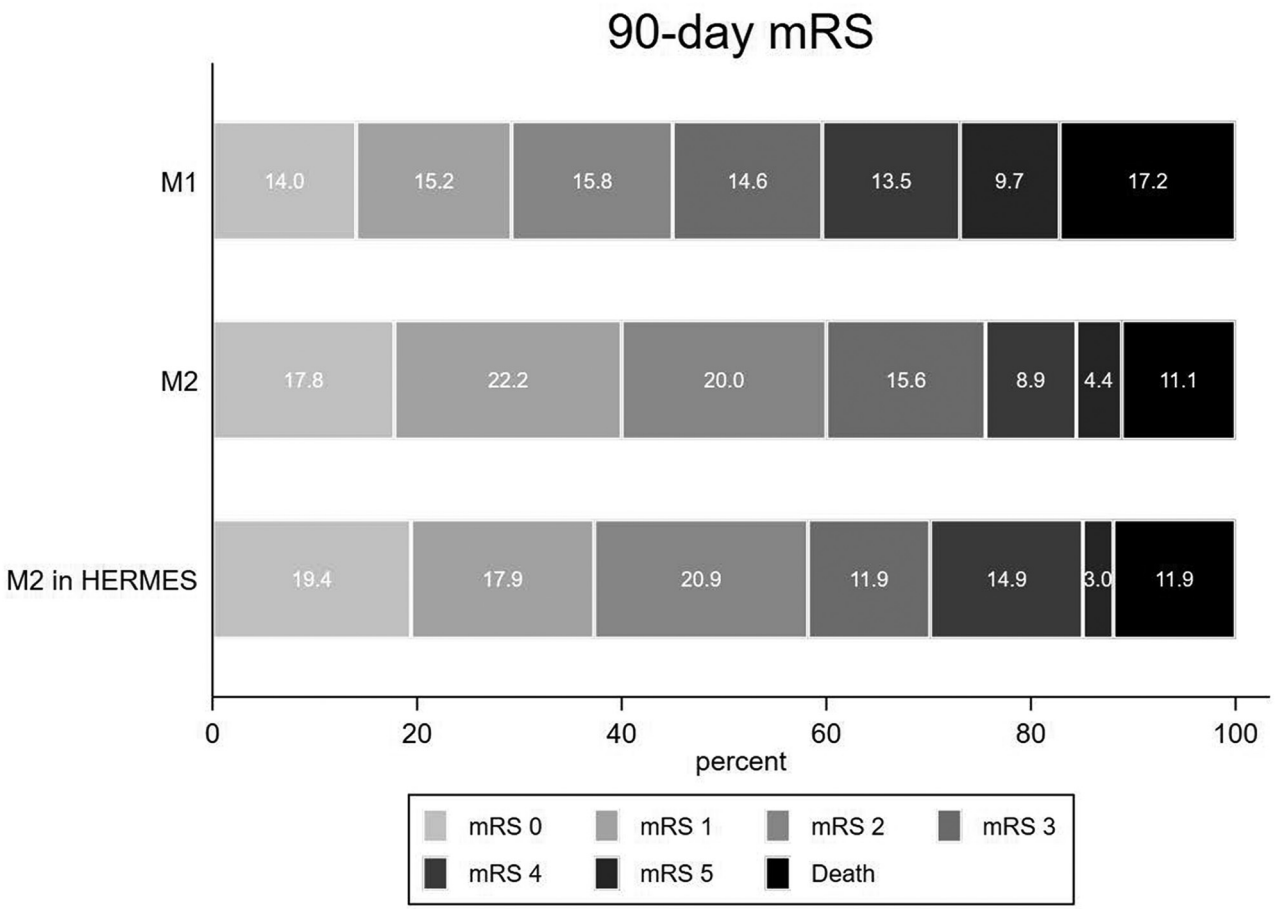

FIG 2. mRS distribution at 90 days in patients with M1 and M2 occlusion in this study versus patients with M2 occlusion treated with endovascular thrombectomy in the HERMES collaboration.

Table 2: Primary and secondary outcomes in patients with M2 occlusion stratified by successful reperfusion[a]

	Successful Reperfusion (n = 75)	Unsuccessful Reperfusion (n = 14)	P Value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
90-Day mRS 0–2	48 (64.0)	5 (35.7)	.07	3.20 (0.97–10.52)	2.84 (1.11–7.29)[b]
90-Day mRS 0–1	33 (44.0)	3 (21.4)	.14	2.88 (0.74–11.17)	2.52 (0.82–7.67)
90-Day mortality	8 (10.7)	2 (14.3)	.65	0.72 (0.13–3.79)	0.13 (0.02–0.67)[b]
SICH	4 (5.3)	0 (0.0)	.99	–	–

Note:—En dash indicates that logistic regression was not performed because of the low number of events ($n < 10$).

[a] Data on 90-day mRS was missing for 5 patients. Regression analyses were not performed for SICH because the number of events was zero in the unsuccessful reperfusion group. Successful reperfusion was defined as a final eTICI 2b–3. The numbers in parentheses in columns 2 and 3 indicate percentages.

[b] Significant results.

[IQR = 7–9], $P = .03$). No significant difference was noted for the remaining baseline characteristics (Online Supplemental Data).

Effect of Successful Reperfusion in Patients with M2 Occlusion. Patients with successful reperfusion more often achieved 90-day functional independence (48/78, 64.0%) than those with unsuccessful reperfusion (5/16, 35.7%; $P = .07$). Similarly, higher proportions of 90-day mRS 0–1 (44.0% versus 21.4%, $P = .14$) and reduced 90-day mortality (10.7% versus 14.3%, $P = .65$) were seen in successfully reperfused patients. Proportions of SICH were numerically higher but not significantly different in the successful reperfusion group (0% versus 5.3%, $P = .99$) (Table 2).

In multivariable regression analyses adjusting for age, sex, NIHSS score, and time from onset to reperfusion, successful reperfusion was significantly associated with functional independence (adjusted OR = 2.84; 95% CI, 1.11–7.29), 90-day mortality (adjusted OR = 0.13; 95% CI, 0.02–0.67), but not with 90-day mRS 0–1 (adjusted OR = 2.52; 95% CI, 0.82–7.67) (Table 2 and Online Supplemental Data). Regression analysis for SICH was not performed because there was no event in the unsuccessful reperfusion group.

DISCUSSION

In this multicenter international study of patients with stroke presenting in the late window and treated with endovascular

Table 3: Comparison of clinical outcomes in patients with M2 occlusions treated with endovascular thrombectomy in the current study versus the HERMES collaboration study[a]

	Current Study (n = 94)	HERMES (n = 67)
Final TICI 2b–3	82.9% (78/94)	59.2% (40/67)
SICH	4.3% (4/92)	0.0% (0/67)
90-Day mRS = 0–1	40.4% (36/89)	37.3% (25/67)
90-Day mRS = 0–2	59.6% (53/89)	58.2% (39/67)
90-Day mortality	11.2% (10/89)	11.9% (8/67)

[a] Data are percentages (n/N).

thrombectomy, patients with M2 occlusion were more likely to achieve functional independence at 90 days and had a lower risk of SICH compared with patients with M1 occlusion. There were no differences in successful reperfusion rates between the 2 groups. Among patients with M2 occlusion receiving endovascular thrombectomy, successful reperfusion was independently associated with higher rates of functional independence and lower mortality at 90 days. While patients with M2 occlusions are predicted to have less severe initial stroke and therefore better outcomes compared with patients with M1 occlusions regardless of time window, it is relevant that we have empirically shown that there is no evidence of harm in this population of patients in the late window and, indeed, that the direction of effect on clinical outcomes is strongly positive.

There is some evidence supporting the safety and efficacy of endovascular thrombectomy in patients with M2 occlusion in the early window,[3,22-26] with a patient-level meta-analysis from the HERMES collaboration showing a beneficial effect of endovascular thrombectomy over best medical care (adjusted OR = 2.39 for mRS 0–2 at 90 days).[2] Evidence regarding the benefit of endovascular thrombectomy in patients with M2 occlusions presenting late is, however, minimal. In this study, we noted higher proportions of successful reperfusion in patients with M2 occlusions than in those reported in the HERMES collaboration (82.9% versus 59.2%) (Fig 2 and Table 3).[2] This difference might be attributed to secular improvement in thrombectomy device technology across the years[27,28] and the increased experience of neurointerventionalists since 2015, when endovascular thrombectomy became the standard of care.[29]

Rates of functional independence were higher in patients with M2-versus-M1 occlusions in our study. This outcome is both predicted and concordant with a previous meta-analysis of 12 studies in the early time window comparing outcomes in patients with M2-versus-M1 segment occlusions.[4] The rates of functional independence in our study were similar to those reported in patients with M2 occlusion in the HERMES collaboration (59.6% versus 58.2%). Additionally, mortality in patients with M2 occlusions was similar between this study and the HERMES collaboration (11.2% versus 11.9%) (Table 3),[2] suggesting that endovascular thrombectomy of M2 occlusion may be similarly effective and safe in the late window.

The risk of SICH in our patients with M2 occlusion was slightly higher compared with patients with M2 occlusion in the HERMES collaboration (4.3%, 4/92, versus 0.0%; 0/67). However, this risk was significantly lower than that of patients with M1 occlusion in this study. Prior studies in the early time window reported varying results. A meta-analysis of 1080 patients with M2 occlusion found a higher risk of SICH compared with patients with M1 occlusion (15% versus 4.7%).[4] Other studies described a similar or lower risk of SICH in patients with M2-versus-M1 occlusion.[30,31] The endovascular thrombectomy procedure for M2 occlusions can be technically challenging, given the small size of the vessel, tortuous course, and distal location. This issue was reflected in the longer median procedural times in patients with M2-versus-M1 occlusion in this study (45 versus 30 minutes).[32] However, this difference was not translated into a lower rate of successful reperfusion or 90-day functional independence.

Prior studies identified various predictors of favorable outcomes among patients with M2 occlusion presenting early.[3,25,31,33] In a study by Jumaa et al,[3] a history of hypertension, baseline NIHSS, prestroke mRS, and time from puncture to reperfusion were associated with functional outcome. In this study, age, baseline NIHSS, time from onset to reperfusion, and successful reperfusion were associated with functional outcomes among patients with M2 occlusion. Successful reperfusion was the strongest predictor of functional independence with an adjusted OR of 2.84. A previous multicenter French registry in the early time window showed similar results, with a comparable effect size of successful reperfusion (adjusted OR = 2.79), corroborating our results.[34]

Our study has several limitations. First, we included studies from different centers with varying institutional protocols and inclusion criteria, potentially introducing sampling biases. Second, we did not have a control, non-endovascular thrombectomy arm and, therefore, cannot comment on the outcome of patients with M2 occlusions in the late time window if not treated with endovascular thrombectomy. It is likely that in this retrospective data, only patients with a high likelihood of benefit from endovascular thrombectomy judged by the treating physician were treated. However, our results of patients who were treated in prospective registries were similar to results of the HERMES collaboration, supporting the safety and good outcome among patients with M2 occlusion treated with endovascular thrombectomy in routine practice. Third, procedural techniques or associated complications were not collected in this study. The risk of SICH was, however, low overall. Fourth, information regarding the type of M2 occlusion (proximal-versus-distal, dominant-versus-nondominant) and procedural details such as the number of passes, the use of a stent retriever versus contact aspiration, and general anesthesia versus sedation were not collected in this study, possibly influencing our results. Fifth, the sample size of patients with M2 occlusion was relatively small, precluding subgroup analyses.

CONCLUSIONS

In this multicenter international analysis of patients treated with endovascular thrombectomy in the late time window, patients with M2 occlusion achieved better safety and functional outcomes than those with M1 occlusion. The rates of functional independence and mortality are similar to those in prior studies treating M2 occlusions in the earlier time window. These results provide some support for the safety of endovascular thrombectomy in patients with M2 occlusion presenting late after stroke onset or last known well.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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