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Original research

Risk factors of unexplained early neurological deterioration after treatment for ischemic stroke due to large vessel occlusion: a post hoc analysis of the HERMES study

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2021-018214).

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Received 8 September 2021
Accepted 25 January 2022
Published Online First 15 February 2022

To cite: Bourcier R, Goyal M, Muir KW, *et al*. *J NeuroIntervent Surg* 2023;**15**:221–226.

ABSTRACT

Background Early neurological deterioration (END) after endovascular treatment (EVT) in patients with anterior circulation acute ischemic stroke (AIS) is associated with poor outcome. END may remain unexplained by parenchymal hemorrhage (UnEND). We aim to analyze the risk factors of UnEND in the medical management (MM) and EVT arms of the HERMES study.

Methods We conducted a post-hoc analysis of anterior AIS patients who underwent EVT for proximal anterior occlusions. Risk factors of UnEND, defined as a worsening of ≥4 points between baseline National Institutes of Health Stroke Scale (NIHSS) and NIHSS at 24 hours without hemorrhage, were compared between both arms using mixed logistic regression models adjusted for baseline characteristics. An interaction analysis between the EVT and MM arms for risk factors of UnEND was conducted.

Results Among 1723 patients assessable for UnEND, 160 patients experienced an UnEND (9.3%), including 9.1% (78/854) in the EVT arm and 9.4% (82/869) in the MM arm. There was no significant difference in the incidence of UnEND between the two study arms. In the EVT population, independent risk factors of UnEND were lower baseline NIHSS, higher baseline glucose, and lower collateral grade. In the MM population, the only independent predictor of UnEND was higher baseline glucose. However, we did not demonstrate an interaction between EVT and MM for baseline factors as risk factors of UnEND. UnEND was, similarly in both treatment groups, a significant predictor of unfavorable outcome in both the EVT (p<0.001) and MM (p<0.001) arms.

Conclusions UnEND is not an uncommon event, with a similar rate which ever treatment arm is considered. In the clinical scenario of AIS due to large vessel occlusion, no patient-related factor seems to increase the risk for UnEND when treated by EVT compared with MM.

INTRODUCTION

Early neurological deterioration (END) following acute ischemic stroke (AIS) is a serious clinical event strongly associated with poor outcome.[1 2] END has been defined as an increase in ≥4 points of the National Institutes of Health Stroke Scale (NIHSS) between baseline NIHSS and NIHSS at 24 hours (±12 hours) after treatment. In the HERMES study, straightforward causes such as symptomatic intracranial hemorrhage (SICH) split END from unexplained END (UnEND) when no such causes can explain the END.[3–5] Observed in 10–40% of patients after intravenous thrombolytics,[6–8] the incidence of UnEND after endovascular treatment (EVT) performed in AIS due to large vessel occlusion has been described in a few studies.[1 9] Because UnEND consistently predicts poor outcome, its prevention is of importance through the treatment of modifiable risk factors.

Recently, a retrospective analysis of EVT-treated patients in the multicenter French registry of mechanical thrombectomy (ETIS) has highlighted some modifiable risk factors for UnEND, including technical aspects of EVT, such as the number of thrombus retrieval attempts.[9] Beyond the risk of treatment failure without improvement of clinical outcome, even 'minimally' invasive EVT may lead to clinical deterioration. Hence, identifying a subgroup of patients for whom EVT may harm rather than improve outcome needs a comparison to a medical management arm (MM). In this study, we compared rates and risk factors of UnEND in the MM and EVT arms of the HERMES population.

METHODS

Patients in the randomized clinical trials of the HERMES group[10] (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)[11]; Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE)[12]; Thrombectomie des Artères Cerebrales (THRACE) trial[13]; Pragmatic Ischemic Thrombectomy Evaluation (PISTE)[14]; Extending

the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA)[15]; Randomized Trial of Revascularization with Solitaire FR Device vs Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT)[16]; and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial)[17] were included. Patients with AIS-large vessel occlusion (LVO) who had M1/M2 or intracranial carotid artery (ICA) occlusion for whom reperfusion results were assessed by a separate core laboratory for HERMES (not only the core laboratory of each individual study) were also included. Each trial enrolled patients according to its specific inclusion and exclusion criteria: SWIFT PRIME, with 195 patients from December 2012 through November 2014 in the USA and Europe; ESCAPE, with 315 patients from February 2013 through October 2014 in Canada, USA, South Korea, Ireland, and UK; EXTEND-IA, with 70 patients from August 2012 through October 2014 in Australia and New Zealand; REVASCAT, with 207 patients from November 2012 through December 2014 in Catalonia, Spain; MR CLEAN, with 500 patients between December 2010 and March 2014 in the Netherlands; PISTE, with 65 patients between April 2013 and April 2015 in the UK; and THRACE, with 412 patients between June 2010 and February 2015 in France. Data on patients eligible but not enrolled (eg, refusals or exclusions) were not available. END was defined as a worsening of ≥4 points between baseline NIHSS and NIHSS at 24 hours (±12 hours) after treatment. Baseline NIHSS refers to the last NIHSS obtained before angiography. Causes for END were classified as parenchymal hemorrhage (defined as a 1 or 2 stage of the European Cooperative Stroke Study classification) on day 1 imaging or as UnEND and constitute the primary end point of our study. UnEND was defined as END without parenchymal hemorrhage and constitutes the primary endpoint of the study.

We excluded patients with missing data for baseline or at 24 hours (+12 hours) after treatment.

MM definition, and inclusion and exclusion criteria of the seven randomized control trials (RCTs), have been extensively described in previous publications.[10 18]

All participants provided written informed consent according to each trial protocol, and each study was approved by the local ethics board.

A complete list of investigators in the HERMES group can be found in the online supplemental eAppendix.

STATISTICAL ANALYSIS

Continuous data were summarized using descriptive statistics: mean, SD, median, and range or IQR. Categorical variables were summarized using frequency counts and percentages. Analyses comparing between randomized groups were conducted under the principles of intent-to-treat, under which data were analyzed according to the treatment to which a subject was randomized, regardless of the treatment received. All hypothesis tests were two-sided, with p values <0.05 considered statistically significant. Simple two-group comparisons using t-tests or Wilcoxon's rank-sum for continuous variables, and Fisher's exact test for binomial variables, were conducted to find potential univariable risk factors of UnEND, by comparing patients with and without UnEND—that is, that UnEND were compared with END with parenchymal hemorrhage and no END lumped together; these analyses were performed separately in the EVT and MM arms. Candidates for comparison included age, sex, history of hypertension, diabetes mellitus, hyperlipidemia or atrial fibrillation, prior stroke, direct admission (vs transfer to stroke center), baseline systolic blood pressure, baseline NIHSS, baseline Alberta Stroke Program Early CT Score (ASPECTS), baseline glucose, pre-stroke modified Rankin Scale (mRS), site of occlusion, administration of tissue plasminogen activator (tPA) for intravenous (IV) thrombolysis, time from onset to randomization, and pre-treatment collateral grade.

Candidate characteristics with p<0.20 in univariable analyses for either the EVT or MM arms were then entered into a multivariable mixed-effects logistic regression model with UnEND as the dependent variable, with fixed effects for the above characteristics of interest and 'trial' as random effects variables in these models. Continuous characteristics were incorporated into the modeling using restricted cubic splines to permit non-linearity of effect. As with univariable analyses, these multivariable analyses were then performed separately on the EVT and MM arms. Odds ratios (ORs) and corresponding two-sided 95% confidence intervals (95% CIs) were computed by the Wald method and are presented for all risk factors in multivariable analyses, irrespective of their nominal statistical significance. Model fit and predictive strength were examined by use of the C-statistic for concordance and the Hosmer-Lemeshow goodness-of-fit test.

The association between UnEND and unfavorable outcome, defined as a 90-day mRS value >2 and using similar mixed logistic regression models adjusted for baseline characteristics, was investigated for both EVT and MM arms, and mRS outcomes categorized for display by treatment and UnEND status. Last, an interaction analysis between EVT and MM and various risk factors of UnEND was conducted. Statistical analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC) and R (version 3.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Whole population

Among 1764 patients across the seven HERMES trials, 1723 patients were assessable for END and UnEND status and constituted the primary analysis set for this report (figure 1). Demographics and baseline characteristics for the overall population are presented by the presence or absence of UnEND in online supplemental table 1. In total, 160 patients experienced an UnEND (9.3%, 95% CI 8.0% to 10.8%), including 9.1% (78/854) in the EVT arm and 9.4% (82/869) in the MM arm. At day 1, SICH was found in 3.6% (31/869) and 4.3% (32/744) in the MM arm and EVT arm, respectively.

There was no significant difference in the incidence of UnEND between the two study arms. Older age, lower NIHSS at baseline, higher level of glucose, higher systolic blood pressure, higher pre-stroke mRS, proximal occlusion location, lower ASPECTS at baseline, and lower collateral grade were associated with UnEND in univariable analysis of the whole included population.

UnEND in the EVT population

Baseline and treatment characteristics according to the presence or absence of UnEND in the EVT arm are reported in online supplemental table 2. In univariable analyses, a greater incidence of UnEND was significantly associated with older age, higher baseline glucose, higher systolic blood pressure, history of diabetes mellitus, higher pre-stroke mRS, lower ASPECTS at baseline, and lower collateral grade.

In multivariable analysis, independent risk factors of UnEND were lower baseline NIHSS, higher baseline glucose, and lower collateral grade (table 1). The multivariable model showed

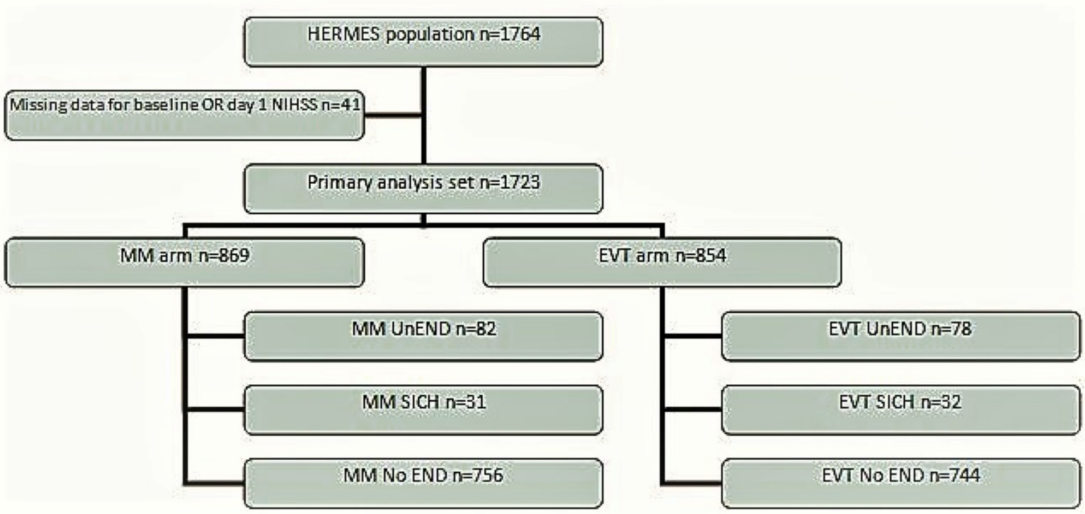

Figure 1 Study flow chart. END, early neurological deterioration; EVT, endovascular treatment; MM, medical management; OR, odds ratio; SICH, symptomatic intracranial hemorrhage; UnEND, unexplained early neurological deterioration .

good predictive discrimination (C-statistic 0.77) and calibration as measured by the Hosmer-Lemeshow goodness-of-fit test (p=0.82).

UnEND in the MM population

Patient and treatment characteristics according to the presence or absence of UnEND in the MM arm are reported in online supplemental table 3. In univariable analyses, a greater incidence of UnEND was significantly associated with lower baseline NIHSS and lower collateral grade as well as site of occlusion, with ICA occlusion associated with greater incidence of UnEND.

In multivariable analysis, the only independent predictor of UnEND was higher baseline glucose (table 2). As with the analysis of EVT subjects, the multivariable model for MM showed good predictive discrimination (C-statistic 0.73) and calibration as measured by the Hosmer-Lemeshow goodness-of-fit test (p=0.73).

Table 1 Multivariable analysis of risk factors of unexplained early neurological deterioration in the endovascular treatment arm

Characteristic	OR	95% LCL	95% UCL	P value
Age (years)	1.04	0.99	1.09	0.17
Age (years)*	0.97	0.93	1.02	0.29
NIHSS at baseline	0.87	0.78	0.97	0.01
NIHSS at baseline*	1.07	0.94	1.22	0.32
Glucose	1.04	1.01	1.06	0.01
Glucose*	0.97	0.94	0.99	0.01
Systolic BP	1.01	0.98	1.04	0.50
Systolic BP*	1.01	0.98	1.04	0.72
Diabetes mellitus	1.09	0.57	2.07	0.80
Prior stroke	1.64	0.79	3.44	0.18
Pre-stroke mRS	1.58	0.97	2.57	0.06
Site of occlusion: ICA	2.05	0.55	7.65	0.29
Site of occlusion: M1	1.78	0.50	6.35	0.38
Site of occlusion: M2	1.35	0.28	6.60	0.71
ASPECTS	0.90	0.78	1.03	0.14
Collateral grade	0.58	0.38	0.87	0.01
Onset to randomization (min)	1.00	0.99	1.01	0.84
Onset to randomization (min)*	1.00	0.99	1.02	0.51

*Particular lines indicate multiple odds ratios due to spline modeling; OR calculated using patients without early neurological deterioration as reference group.
ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; ICA, internal carotid artery; LCL, lower confidence limits; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; UCL, upper confidence limits.

Table 2 Multivariable analysis of risk factors of unexplained early neurological deterioration in the medical management arm

Characteristic	OR	95% LCL	95% UCL	P value
Age (years)	0.99	0.95	1.03	0.63
Age (years)*	1.03	0.99	1.07	0.28
NIHSS at baseline	0.95	0.86	1.06	0.29
NIHSS at baseline*	0.96	0.83	1.11	0.63
Glucose	1.03	1.00	1.05	0.03
Glucose*	0.98	0.95	1.00	0.04
Systolic BP	0.99	0.97	1.02	0.56
Systolic BP*	1.01	0.99	1.04	0.32
Diabetes mellitus	1.12	0.56	2.22	0.83
Prior stroke	1.42	0.66	3.06	0.66
Pre-stroke mRS	1.27	0.75	2.14	0.35
Site of occlusion: ICA	1.93	0.60	6.18	0.37
Site of occlusion: M1	0.72	0.23	2.28	0.39
Site of occlusion: M2	0.91	0.21	3.89	0.61
ASPECTS	0.90	0.79	1.02	0.12
Collateral grade	0.85	0.57	1.26	0.14
Onset to randomization (min)	1.00	0.99	1.01	0.77
Onset to randomization (min)*	1.00	0.99	1.01	0.93

*Particular lines indicate multiple odds ratios due to spline modeling; OR calculated using patients without early neurological deterioration as reference group.
ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; ICA, internal carotid artery; LCL, lower confidence limits; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; UCL, upper confidence limits.

Table 3 Interaction analysis of risk factors versus treatment arm for unexplained early neurological deterioration

Characteristic	Interaction: treatment by predictor p value
Age (years)	0.15
Age (years)*	0.10
NIHSS at baseline	0.38
NIHSS at baseline*	0.39
Glucose	0.56
Glucose*	0.59
Systolic BP	0.36
Systolic BP*	0.63
Diabetes mellitus	0.98
Prior stroke	0.62
Pre-stroke mRS	0.73
Site of occlusion: ICA	0.78
Site of occlusion: M1	0.19
Site of occlusion: M2	0.54
ASPECTS	0.78
Collateral grade	0.25
Onset to randomization (min)	0.90
Onset to randomization (min)*	0.85

*Particular lines indicates multiple p values due to spline modeling.
ASPECTS, Alberta Stroke Program Early CT Score; BP, blood pressure; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

UnEND and outcome

UnEND was, similarly in both treatment groups (p=0.36), a significant predictor of unfavorable outcome (defined as a 90-day mRS value >2) in both the EVT (p<0.001) and MM (p<0.001) arms. The association between UnEND and unfavorable outcome, using similar mixed logistic regression models adjusted for baseline characteristics, was displayed by treatment and UnEND status (online supplemental figure 1).

Last, an interaction analysis between EVT and MM and various risk factors of UnEND was conducted. No statistically significant interaction effects were found, meaning that no significant differences in EVT benefit over MM by risk factor were detected (table 3).

DISCUSSION

We confirmed that UnEND, defined as an increase in ≥4 points of the NIHSS between baseline NIHSS and NIHSS at 24 hours after treatment excluding SICH, is a strong predictor of unfavorable outcome at 3 months. The main finding of our study is that the UnEND rate observed in the EVT arm is similar to that observed in the MM arm, with higher baseline glucose and lower collateral grade demonstrated as the strongest independent risk factors.

Of particular interest, the interaction analysis shows that, in the clinical scenario of AIS due to LVO, no patient-related factor seems to increase the risk for UnEND when treated by EVT compared with MM.

EVT has become the standard of care for AIS-LVO.[19] However, we confirmed that some patients, despite rapid and successful recanalization, suffered UnEND. We failed to demonstrate an interaction between EVT and MM for baseline factors as risk factors of UnEND. Risk factors of UnEND may help in selecting patients for EVT. Artificial intelligence and machine learning represent promising tools to determine whether EVT will be beneficial or harmful on an individual basis for AIS-LVO patients,[20] but until then the positive predictive value of any simple 'algorithm' should be as high as possible to avoid withholding an evidence-based treatment from otherwise suitable patients for EVT.

SICH represented ~20% of all causes of END, with specific management according to published guidelines.[19] However, over half of all ENDs have no clear cause, as was confirmed in two large studies reporting that 70% of all ENDs following intravenous thrombolysis (IVT) alone or IVT followed by endovascular treatment were UnEND.[7 21] Hence, no guidelines are available for this situation of UnEND, and no clear action is usually taken to prevent its occurrence and poor outcomes.

No study has assessed the incidence of UnEND in IVT versus EVT-treated samples. Our study provides more insight into the incidence of UnEND following EVT (9.1%). This incidence was higher than that reported recently by ETIS, where UnEND was described in 128/1925 patients (6.6%).[8] Differences in UnEND definition may explain in part such a difference.[9]

Considering that some patients did not achieve good reperfusion, we found a rate of 9.4% UnEND in the MM group. Similar rates of UnEND (8–13%) after MM were previously described.[5 7] Since reperfusion at 24 hours was not assessed in the present study, we cannot confirm the absence of reperfusion at 24 hours as a factor associated with UnEND, as suggested by Seners *et al* in their multivariable analysis of a single center retrospective study.[7] In a retrospective single-center analysis of 1146 patients who experienced successful recanalization for acute ischemic stroke in the anterior circulation, the extent of infarction and the involvement of motor cortex and internal capsule, as well as higher premorbid mRS, end-stage renal failure, high glucose level on admission, absence of bridging IV lysis, general anesthesia, and a longer therapy interval, were independent predictors for failure of early neurological improvement.[22]

Several risk factors of UnEND after EVT have been previously suggested, including diabetes, pre-stroke mRS ≥2, general anesthesia, admission systolic blood pressure, older age, higher number of passes, indirect admission to a comprehensive stroke center, and lower initial NIHSS score.[9]

In the EVT arm, we found that low baseline NIHSS was a significant predictor of UnEND, implying that less severe strokes were more likely to result in UnEND. This relationship is a form of regression to the mean, since the primary basis for declaring UnEND is increasing NIHSS and changed scores in general tend to be negatively correlated with baseline values. Furthermore, as well demonstrated by perfusion imaging studies, the NIHSS score reflects the neurological deficits and the symptomatic ischemic tissue (core and penumbra) rather than the surrounding asymptomatic tissue (benign oligemia or normally perfused tissue).[23] Thus, lower NIHSS patients potentially suffer from vascular impairments with hypoperfusion areas in the acute phase that lead to infarction progression.[24 25] What is being observed in EVT datasets confirms what was known previously in the prior stroke literature, including on IVT.[26 27] This phenomenon might be even larger in magnitude because so many EVT patients improve after treatment.

Among modifiable admission factors, higher baseline glucose was, in both arms, a predictor of UnEND. Publications have proven a link between pre-existing hyperglycemia and increased cerebral ischemia/reperfusion injury in the setting of AIS.[28 29] Several mechanisms might explain this association. First, neuronal death in the hypoperfused or oligemic tissue may be

favored by increased brain lactate produced from high glycemia level. Hence, insulin therapy, which reduces blood glucose levels, may decrease brain lactate level. Studies into this area are needed, since neuronal death may also be favored by hypoglycemic episodes caused by insulin therapy. Second, by neutrophil priming and margination in the downstream microvascular territories, hyperglycemia generates a deleterious environment prone to rapid initiation and development of thrombo-inflammation, even in cases of successful final reperfusion. Finally, an impaired fibrinolytic response in the setting of hyperglycemia was also suggested, with acute hyperglycemia state associated with lower recanalization rates in patients treated with IV-tPA. In the case of EVT, combined data from three trials demonstrated that higher glucose levels reduced the likelihood of a favorable outcome[29] among patients with good pretreatment collaterals that may also contribute to UnEND. Consequently, LVO patients with good collaterals could be a potential target group for acute glucose lowering treatment.

In the EVT arm, we found that the occurrence of UnEND was associated with a lower baseline collateral grade. Collateral grades have been shown to play a major role in the sustenance of the ischemic penumbra before reperfusion. More robust collateral grades are associated with better reperfusion, and subsequent better clinical outcomes even when adjusted for age, history of diabetes, baseline NIHSS, and ASPECTS.[30]

Contrary to a previous study focusing on EVT,[9] we did not find a statistically significant association between higher baseline systolic blood pressure and UnEND in our multivariable analysis. Management of blood pressure for AIS-LVO is still a conundrum to be clarified. On the one hand, lowering blood pressure may contribute to the development of END by reducing cerebral perfusion pressure.[31] On the other hand, increased blood pressure may be associated with poor functional outcome for the reason of cerebral edema or hemorrhagic transformation.[32] In the present study, the fact that higher baseline systolic blood pressure was not associated with UnEND may be explained by the exclusion of patients with early SICH.

In comparison with the mothership paradigm, transferred patients have been reported to be more likely to suffer worse clinical outcomes, due to the increased time to groin puncture and reperfusion.[33 34] However, including 'onset to randomization' in our multivariable model, secondary transfer was not associated with UnEND.

Our study presents some limitations since, to ensure data completeness, only cases of END occurring within the first 24 hours after stroke were taken into account, even though it is known that END can also occur later. Thus, early systemic infections, early recurrent stroke, and cardiorespiratory adverse events were not evaluated here, even though they might account in some cases for UnEND, especially in patients with an underlying frailty. However, most of the specific procedural EVT-related complications occur in <48 hours and the vast majority begin within 24 hours. Hence, not having data at a 24–48 hour interval is a relatively minor limitation for the purposes of this between-groups analysis. Furthermore, fluctuation in the patients' NIHSS before EVT would lead to include or exclude a patient from the primary cohort of the study. However, we have not been able to control this parameter from the data recorded in the HERMES database. Beyond hemorrhage, UnEND can also result from other adverse events, social support or depression, which are variables that were not captured in the HERMES dataset.[35] As UnEND is often classified as END secondary to ischemic progression, it would have been interesting to evaluate ischemia progression on control imaging at 24 hours to determine potential UnEND without ischemic progression and specific mechanisms. We were unable to record the ASPECTS at day 1 and the patients who experienced a malignant edema after stroke in the HERMES study. Consequently, only patients with parenchymal hemorrhage were excluded from the UnEND group. However, in the HERMES study there were only 9% (121/1278) of patients included with a baseline ASPECTS <5, making the occurrence of malignant edema likely low.[10] Indeed, the observed effect could be related to a modification or an increase in the hypoperfused or already infarcted territories. We were also unable to record technical details of EVT such as the number of passes of thrombectomy. Indeed, independently of time, the number of passes required to achieve successful reperfusion during EVT was related to UnEND in a previous study.[9] Last, since the reperfusion results in the MM arm were not systematically recorded in the HERMES studies, we did not consider the final Thrombolysis In Cerebral Infarction (TICI) score in the EVT arm analysis. Indeed, studies that have searched for predictors of UnEND after MM have included in the UnEND group patients not achieving good reperfusion. As a consequence, the absence of reperfusion at 24 hours was the only factor associated with UnEND in the multivariate analysis.[6] In a previous study of EVT, failure of recanalization represented half of the cause of UnEND.[9] However, our study reports factors such as baseline NIHSS, higher baseline glucose, and lower collateral grade associated with UnEND that aim at questioning, or not, the pre-treatment patient's selection.

CONCLUSION

In this meta-analysis of seven RCTs into EVT for LVO stroke, we found that UnEND is not an uncommon event, with similar rates in both EVT and MM groups. Comparing EVT and MM arms from a large RCT population, we did not demonstrate any argument to withhold EVT from suitable patients on the basis of UnEND risk. UnEND is predictive of a poor 3 month outcome, with higher baseline glucose and lower collateral grade demonstrated as the strongest independent predictors. Future studies should explore the pathophysiology of non-modifiable factors associated with UnEND and the need for effective therapeutic strategies for UnEND prevention.

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Funding The HERMES Collaboration was funded by a grant from Medtronic LLC to the University of Calgary.

Competing interests PW is member of the editorial board of the Journal of Neurointerventional Surgery.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Please contact us.

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