Development and validation of a post-procedural model to predict outcome after endovascular treatment for ischemic stroke (MR PREDICTS@24H)

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Key points

Question

Can we predict functional outcome for individual patients after endovascular treatment (EVT) for ischemic stroke?

Findings

We developed and validated a prognostic model using data from multiple clinical trials and routine practice of patients who received EVT within 12 hours after stroke onset. It includes nine pre- and post-procedural characteristics, has excellent discriminative ability and good calibration, and is online available for clinical use.

Meaning

MR PREDICTS@24H is a simple prognostication tool that can provide patients, family members, and physicians with reliable and accurate outcome expectations one day after EVT.

Abstract

Importance: Outcome prediction after endovascular treatment (EVT) for ischemic stroke is important to patients, family members, and physicians.

Objective: To develop and validate a model based on pre- and post-procedural characteristics to predict functional outcome for individual patients after EVT.

Design: Development of a predicton model in individual patient data from seven randomized controlled trials, performed between 2010 and 2015, within the HERMES collaboration; and external validation in data from the Dutch MR CLEAN Registry of patients treated in clinical practice between 2014 and 2017. Data were last analyzed in July 2022.

Setting: Multiple centers throughout different countries in Europe, North America, East Asia and Oceania (derivation cohort), and multiple centers in the Netherlands (validation cohort).

Participants: 781 of 1764 (derivation cohort) and 3260 of 3637 (validation cohort) adult ischemic stroke patients with an intracranial large vessel occlusion in the anterior circulation who underwent EVT within 12 hours of symptom onset or last seen well.

Main Outcome(s) and Measure(s): We assessed 19 variables, routinely available one day after EVT, by multivariable ordinal regression to predict functional outcome (modified Rankin Scale [mRS] score) 90 days after EVT. We used Akaike Information Criterion (AIC) to optimize model fit versus model complexity. Probabilities for functional independence (mRS 0-2) and survival (mRS 0-5) were derived from the ordinal model. Model performance was expressed with discrimination (C-statistic) and calibration.

Results: Patients of the derivation cohort (n=781) had a median age of 67 years (IQR 57-76) and 414/718 (53%) patients were men. This was respectively 72 years (IQR 61-80) and 1684/3260 (52%) for the validation cohort (n=3260). Nine variables were included in the model: age, baseline NIHSS, pre-stroke mRS, diabetes mellitus, occlusion location, collateral score, reperfusion grade, NIHSS at 24h, and symptomatic intracranial hemorrhage 24h after EVT. External validation in MR CLEAN Registry showed excellent discriminative ability for functional independence (C-statistic 0.91, 95%CI 0.90-0.92) and survival (0.89, 95%CI 0.88-0.90). The proportion of functional independence in MR CLEAN Registry was systematically higher than predicted by the model (41% vs 34%), while observed and predicted survival were similar (72% vs 75%). The model was updated and implemented for clinical use (https://mdmtest.shinyapps.io/test_24h).

Conclusion and relevance: MR PREDICTS@24H can be applied one day after EVT to accurately predict functional outcome for individual patients at 90 days, to provide reliable outcome expectations and personalize follow-up and rehabilitation plans. It will need further validation and updating for contemporary patients.

Introduction

Since the implementation of endovascular treatment (EVT) for ischemic stroke in daily clinical practice, physicians are confronted with questions from patients and family members about the extent of recovery they can expect, most often quite early after EVT. While at group level almost half of all patients treated with EVT recover to functional independence, outcomes of individual patients remain highly variable and depend on multiple factors.[1] For treating physicians it is therefore difficult to accurately predict individual outcomes after stroke. Results from previous research suggest that well-validated prognostic models are more accurate in predicting outcome than physicians.[2,3]

Most prediction models for patients undergoing EVT are based on pre-procedural data only and primarily serve to identify patients who may benefit from EVT.[4] A clinical prognostic model that can be used after EVT and takes into consideration both pre- and post-procedural characteristics – such as age, reperfusion grade, and neurological status one day after EVT – could provide physicians, patients, and family members with more reliable outcome expectations.[5-8] However, three externally validated models that were designed for early prognostication after EVT and include post-procedural characteristics were developed before the landmark trials were published.[7,9,10] The purpose of the present study was to develop and externally validate a contemporary prognostic model that can be applied one day after EVT to predict functional outcome.

Methods

Derivation cohort

The model was developed with individual patient data from seven randomized controlled trials (RCTs) on EVT within the HERMES collaboration: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE.[1,11,12] These RCTs compared EVT – primarily performed with stent retrievers – with standard care in adult patients with ischemic stroke caused by a large vessel occlusion in the anterior circulation confirmed on computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Inclusion criteria varied between the RCTs.[1] All participants provided written informed consent according to each trial protocol, and each RCT was approved by the local ethics committee.

For this study, we included all patients randomized to EVT who underwent arterial puncture within 12 hours of symptom onset for an occlusion of the intracranial carotid artery (ICA), internal carotid artery terminus (ICA-T), or middle cerebral artery (segment M1 or M2).

Outcome measures

The primary outcome was functional outcome at 90 days, assessed with the modified Rankin Scale (mRS). The mRS is an ordinal scale used to measure the degree of disability in daily activities, and ranges from 0 (no symptoms) to 6 (death). [13] The mRS was modelled as the full ordinal scale and we subsequently extracted the probabilities for functional independence (defined as mRS 0-2) and survival (defined as mRS 0-5) from the predicted distribution.

Statistical analysis: Model development

To identify predictors of functional outcome after EVT, we pre-specified 19 pre- and post-procedural variables that can be assessed within one day after EVT, based on recent literature, expert opinion, clinical relevance, and availability in both the derivation and validation cohort. These variables were: age, sex, pre-stroke disability assessed with the mRS, diabetes mellitus (yes/no), hypertension (yes/no), previous stroke (yes/no), baseline stroke severity assessed with National Institutes of Health Stroke Scale (NIHSS), serum glucose, systolic blood pressure, IV treatment with alteplase (yes/no), baseline location of intracranial large vessel occlusion, baseline collateral score on single-phase CTA (grade 0 indicates no collateral filling; grade 1 indicates collateral filling ≤50%, but >0%; grade 2 indicates collateral filling >50%, but <100%; grade 3 indicates 100% collateral filling; all scored in the affected middle cerebral artery territory in comparison to the entire contralateral middle cerebral artery territory), [14,15] baseline Alberta Stroke Program Early CT Score (ASPECTS), time from symptom onset to arterial puncture, duration of the procedure (arterial puncture to last contrast bolus injection), general anesthesia (yes/no), radiological reperfusion grade (modified Treatment in Cerebral Infarction [mTICI] score) after EVT on digital subtraction angiography (DSA), NIHSS 24h after EVT, symptomatic intracranial hemorrhage (sICH) 24h after EVT (yes/no, as defined in each RCT). Trial was included as a fixed effect to account for possible study-level differences in prognosis in the EVT arms and statistical dependence of outcomes within trials.

We used ordinal logistic regression modelling, which assumes proportional odds, to determine the association of the potential predictors with functional outcome. We tested non-linearity of the relation

between continuous variables (age, systolic blood pressure, glucose, NIHSS at baseline, ASPECTS, time to arterial puncture, duration of the procedure, NIHSS at 24h) and the log odds of mRS with restricted cubic spline functions with three knots.

We used univariable and multivariable regression analysis with Akaike's Information Criterion (AIC) to balance model fit versus model complexity in a stepwise procedure. Effectively, this implies selection with p <0.157 for potential predictors with 1 degree of freedom. The final model was labelled 'Multivariable outcome prediction after endovascular treatment for ischemic stroke at 24 hours' (acronym: MR PREDICTS@24H). Predictor effects were expressed as adjusted (common) odds ratios (a[c]ORs) with 95% confidence intervals (CI). To obtain more insight into the relative importance of NIHSS at 24h, we made a model with NIHSS alone. We also performed additional analyses with final infarct volume (FIV) - assessed between 12 hours and 2 weeks - which was not included in the final model because it is not routinely used in clinical practice and not available in the validation cohort. The comparison of the models of NIHSS at 24h alone and FIV alone with, and the contribution of addition of FIV to the final model on the model fit were tested using the log-likelihood ratio

We assessed the internal validity of the final model with bootstrap resampling to calculate the degree of optimism in model performance. To correct for this optimism, we shrunk the regression coefficients in the final model using penalized regression (penalized function in the rms package for R statistical software).

Validation cohort

For external validation we used data from the MR CLEAN Registry, a nationwide prospective, observational study in 18 centers that provide EVT in the Netherlands. [16] Data were collected from consecutive patients with ischemic stroke who had undergone EVT since March 2014, after the last patient was included in the MR CLEAN trial. The medical ethics committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands granted permission to carry out the study (MEC-2014-235) as a registry, for which no consent was necessary.

We included patients with ischemic stroke who were enrolled in the MR CLEAN Registry, treated with EVT between March 16, 2014 and November 1, 2017 in centers that participated in the MR CLEAN trial. Included patients were aged 18 years or older, had an occlusion of the ICA(-T) or middle cerebral

artery (M1 or M2) on CTA or MRA, and had undergone arterial puncture within 12 hours after symptom onset.

Statistical analysis: Model validation and updating

External validation was performed with the regression coefficients of MR PREDICTS@24H and the model intercept as estimated for the MR CLEAN trial. Model performance was assessed in terms of discrimination and calibration. Discrimination refers to the ability of the model to distinguish between patients with good and poor outcome. The discriminative ability of the model at internal and external validation was quantified with the concordance statistic (C-statistic). [17] We calculated Harrell's C-statistic for the ordinal mRS and for the predictions of functional independence (mRS 0-2 vs mRS 3-6) and survival (mRS 0-5 vs mRS 6). Calibration refers to the level of agreement between observed outcomes to predicted probabilities. We assessed calibration of predictions graphically by plotting the observed proportion of functional independence or survival in the validation cohort against the predicted probability of functional independence or survival based on the derivation cohort. Calibration was quantified with the calibration slope and calibration intercept of these plots. The calibration slope should ideally be equal to 1, meaning that the effects of predictors are equal in the derivation cohort as compared to those in the validation cohort. The intercept should ideally be 0, and indicates whether the predictions based on the model are systematically too high or too low in the validation cohort. [17] The 95% CI's of the c-statistic, calibration slope, and calibration intercept were calculated with bootstrap resampling with 2000 replications.

After validation, we refitted the model coefficients of the predictors on the MR CLEAN Registry data. Additionally, we replaced the variable mTICI for eTICI, [18,19] and added a missing category for collateral score, because this scoring system might not (yet) be common practice everywhere.

We implemented the updated final model in a web application that provides predictions of functional outcome at 90 days for individual patients with ischemic stroke based on routinely available information one day after EVT. It displays the predicted probabilities of functional independence and survival based on the intercept of the MR CLEAN Registry.

Following HERMES policy, patients with missing outcomes were excluded. Missing predictor data were imputed by multiple regression imputation based on relevant study, covariates, intervention, and outcome. According to MR CLEAN Registry policy, missing data, including mRS, were imputed by

multiple imputation using additive regression based on relevant baseline covariates and outcomes. Statistical analyses were performed with R statistical software (version 3.5.1). This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist: Prediction Model Development and Validation.

Results

Derivation cohort

The HERMES cohort consisted of 781 patients (eFigure 1 in Data supplement), with a median age of 67 years (IQR 57-76). 414 (53%) patients were men, and their median baseline NIHSS score was 17 (IQR 14-21) (Table 1). Substantial reperfusion (i.e., mTICI ≥2B) was achieved in 544/715 (76%) patients. The median NIHSS score at 24h was 9 (IQR 4-16), the median mRS score at 90 days was 3 (IQR 1-4), 371 patients (48%) achieved functional independence, and 671 (86%) survived up to 90 days.

Model development

All pre-specified variables, with the exception of treatment with IV alteplase and previous stroke, were predictors of outcome in univariable analysis (Table 2). Based on the multivariable analysis, nine pre- or post-procedural variables were included in the final model: age, baseline NIHSS, pre-stroke mRS, diabetes mellitus, occlusion location, collateral score, mTICI after EVT, NIHSS at 24h, and sICH (Table 2). The final model had an ordinal C-statistic of 0.85 for the ordinal mRS. The discriminative ability of NIHSS at 24h alone was lower than the final model (0.83; $p<0.001$), as was FIV alone (0.76; $p<0.001$). By adding FIV to the final model, the discriminative ability increased from 0.85 to 0.86 ($p<0.001$). The internally validated C-statistic of the final model, corrected for optimism, was 0.84 for the ordinal mRS, 0.91 for functional independence, and 0.86 for survival (Table 3).

Patient population in validation cohort

The MR CLEAN Registry consisted of 3260 patients (eFigure 2 in Data supplement). The median age was 72 years (IQR 61-80), 1684 (52%) were men, and the median baseline NIHSS score was 16 (IQR 11-19). Patients in the validation cohort less often had atrial fibrillation (24% vs 34%), but more often pre-stroke disability (mRS of 2 or higher: 20% vs 4.6%) and worse collateral scores (collateral score of 0-1: 42% vs 15%) than in the derivation cohort. Fewer patients in the validation cohort had M1

occlusions (58% vs 65%), and time from stroke onset to arterial puncture was shorter (median 195 minutes [IQR 150-255] vs 240 [IQR 185-299]). 2245/3248 (75%) patients were treated with IV alteplase, compared to 678/781 (87%) patients in the derivation cohort. Other baseline patient, baseline imaging, and treatment characteristics were similar between the two cohorts (Table 1). Substantial reperfusion (i.e., mTICI ≥2B) was achieved in 1956/3173 (62%) patients. In the validation cohort the median NIHSS score at 24h was 10 (IQR 4-17), the median mRS was 3 (IQR 2-6), 1235/3047 patients (41%) achieved functional independence, and 2164/3047 (71%) survived up to 90 days.

External validation

In the validation cohort, we found predictor effects similar to those in the derivation cohort (eTable 1 in Data supplement). The externally validated C-statistics were 0.84 (95%CI 0.83-0.84) for the ordinal mRS, 0.91 (95%CI 0.90-0.92) for functional independence, and 0.89 (95%CI 0.88-0.90) for survival (Table 3). Calibration plots showed that the observed proportion of patients achieving functional independence was systematically higher than predicted based on the model (intercept 0.61, slope 0.98). The mean observed probability of functional independence was 41%, while the model predicted a mean of 34% (Figure 1A). Observed survival was somewhat lower than predicted (intercept -0.25, slope 0.87). The observed probability of survival was 72%, while the model predicted 75% (Figure 1B).

Final model

The regression equation of the model, is available in the Data Supplement. The online tool is accessible for clinical use at https://mdmtest.shinyapps.io/test_24h (*temporary link*) (Figure 2).

Discussion

MR PREDICTS@24H can be used within one day after EVT for ischemic stroke to accurately predict functional outcome at 90 days after EVT. The model consists of nine routinely available pre- and post-procedural clinical and radiological characteristics and showed excellent discriminative ability and good calibration. Through validation and updating the model was optimized for use in contemporary clinical practice.

Several other prognostic models for patients treated with EVT also combined pre- and post-procedural characteristics. [5-10,20-26] However, some models include rather homogenous patient populations limiting the generalizability of their findings; other models have methodological shortcomings in model development, such as a small sample size for the amount of tested variables, dichotomization of variables, or no internal validation. Importantly, most models lack external validation. Of the four models that have been externally validated, the SNARL score included symptomatic intracranial hemorrhage, NIHSS at baseline, age, reperfusion grade, and location of the occlusion, and concluded that adding post-procedural characteristics would improve outcome prediction. [7] The POST score was based on age, infarct volume and hemorrhagic complications, [10] while the BRANCH scale included baseline blood glucose, reperfusion grade, age, baseline NIHSS score, change in blood glucose after 48h, and symptomatic intracranial haemorrhage. [9] However, these three models were derived from cohorts of patients treated before the landmark trials were published and EVT became the standard of care using second-generation devices. They also all did not include NIHSS or another measure of neurological status after EVT. The DEFIANT score was developed and externally validated after these landmark trials and did include (discharge) NIHSS in their model, as well as age and any hemorrhage (at discharge). [26,27] While MR PREDICTS@24H may be used to predict outcome 24 hours after EVT, the DEFIANT score was developed to better understand the phenomenon of delayed functional independence, and is meant to be used at discharge for patients who are not functionally independent. Given the sample size of the validation cohort (n=79), the DEFIANT score needs to be further validated to assess its performance in different populations.We found NIHSS at 24h to be the strongest independent outcome predictor of all nine included variables. This substantiates previous findings that the post-procedural NIHSS score is a major predictor of long-term functional outcome. [6,7,24,28-30] Although ASPECTS at baseline was not included in the current model, it might also become an independent predictor of outcome in populations including patients with lower ASPECTS resulting from the recent positive results for EVT in patients with large ischemic cores at baseline. [31-33] Interestingly, time from stroke onset to arterial puncture was not included in MR PREDICTS@24H. We emphasize that this does not mean that time is not important for the prediction of outcome after EVT, but suggest that the well-established effect of time on outcome[34] is captured in other (post-procedural) characteristics, such as the NIHSS at 24h. Two models, the POST score and GADIS score, [10,23] included follow-up infarct volume, as this is known to be a strong independent predictor of outcome

after EVT. [35] In our study FIV improved the performance of the model. FIV was assessed on follow-up between 12 hours and 2 weeks, so the observed improvement is probably an overestimation of the improvement with assessment one day after EVT. In addition, in many countries, including the Netherlands, patients do not routinely undergo follow-up CT or MRI. As MR PREDICTS@24H was specifically designed for use in clinical practice within one day after EVT, FIV was not considered for inclusion in the model. Moreover, as there is a desire to inform patients and their family members quickly after treatment, other post-procedural characteristics beyond one day that may also influence functional outcome, such as the occurrence of pneumonia or (the intensity) of rehabilitation were not analyzed. In addition, several important prognostic factors, such as socio-economic status, cultural expectations and treatment restrictions, were unavailable.

This model may be of use to neurologists, stroke physicians, and rehabilitation specialists, resulting in more homogeneous outcome prediction across different physicians. By providing more objective data of expected outcomes, the model can be used to guide physicians in adapting and personalizing their patients' follow-up and rehabilitation plans, including discharge destination. The accuracy of outcome prediction by physicians alone has shown to be insufficient for these types of decisions. [36] However, treatment decisions such as treatment restrictions or the intensity of rehabilitation probably contributed to the predicted outcome at 90 days. This limitation applies to the large majority of prediction models after stroke. Nonetheless, a more accurate estimation of a patients' prognosis could also be used in certain other situations, such as assisting families in planning long-term housing arrangements. External factors, such as housing circumstances and social support become more important when a poor outcome is likely. Furthermore, prediction of outcome provides us with probabilities; even with a 99% predicted probability of survival, the patient might still die. In addition, outcome predictions are most uncertain and potentially inaccurate in patients who are underrepresented in the development population, such as those who are very old or have a high pre-stroke mRS; or in uncommon combinations, such as a low NIHSS at 24h despite sICH. As a prognostic model cannot replace clinical judgement, particularly in these patients, MR PREDICTS@24H should be used as a complementary tool to aid the treating physician.

A major strength of this study is that it was developed on a large heterogeneous dataset generated from ischemic stroke patients treated with EVT in many different countries throughout Europe, North America, East Asia and Oceania. It was externally validated in a large Dutch registry which includes

patients treated in clinical practice. This registry is more heterogeneous than RCTs in terms of patient characteristics, representing current clinical practice. This makes the model widely applicable and improves its applicability in daily clinical practice. The increasing experience with EVT over time, resulting in better outcomes, is likely the cause of the suboptimal calibration, which is why the model was updated. Unfortunately for several reasons, prognostic models have been adopted to a limited extent only by the stroke community. [37] Models are perceived as being too complicated, too generic or not intuitive enough, or may require information that is not routinely available. Therefore, we aimed to develop and directly externally validate a simple online clinical tool, based on routinely available pre- and post-procedural characteristics. Finally, patients who had undergone EVT after 12 hours of symptom onset, those with low ASPECTS, or those with posterior circulation stroke were not included in HERMES nor in MR CLEAN Registry. It stands to reason, however, that especially for patients who underwent EVT after 12 hours of symptom onset, predictions of the current model will still be accurate. Yet, to make MR PREDICTS@24H applicable to a wider range of patients, it needs to be externally validated in datasets beyond the current development and validation data, and then be updated to keep predictions up to date for contemporary patients.

Conclusions

MR PREDICTS@24H includes nine pre- and post-procedural clinical and radiological characteristics and can be applied one day after EVT to accurately predict functional outcome at 90 days. It provides patients, family members and physicians with reliable outcome expectations, and may assist physicians in personalizing their patients' follow-up and rehabilitation plans. The model is online available for clinical use and will need further validation and updating to optimally support stroke care.

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Author Contributions

VC and EV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Study concept and design: VC, EV, BR, MJHLM, AvdL, DWJD, and HFL

Acquisition, analysis, or interpretation of data: VC, EV, MJHLM, BR, EWS, MJHW, GJL, HBvdW, MG, BCVC, KWM, FG, SBra, PW, AD, TGJ, MDH, PJM, AMD, JLS, AvdL, SBro, DWJD, and HFL (all authors)

Drafting first version of the manuscript: VC

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Conflict of interest Disclosures

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Data Sharing Statement

The tool will be publicly accessible online and the full regression equation can be found in the Data Supplement. Additional information is available from the corresponding author upon reasonable request. Individual patient data will not be made available. HERMES data are available via the VISTA-Endovascular repository.

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Figure legends

Figure 1. Calibration plots for A. Functional independence (mRS 0-2) and B. Survival (mRS 0-5) in validation cohort (n=3260)

Abbreviations: mRS, modified Rankin Scale.

A. The overall observed proportion of patients with mRS 0-2 in the validation cohort was higher than the predicted proportion using our model (41% vs 32%). The linear bar chart shows the distribution of patients with (=1) or without (=0) the observed outcome.

B. The overall observed proportion of patients with mRS 0-5 in the validation cohort was similar to the predicted proportion using our model (72% vs 75%). The linear bar chart shows the distribution of patients with (=1) or without (=0) the observed outcome.

Figure 2. Screenshot of the online tool

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ICA(-T), internal carotid artery(-terminus); ICH, intracranial hemorrhage; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; eTICI, extended Thrombolysis in Cerebral Infarction; RCT, randomized controlled trial

Tables

Table 1. Overview of derivation cohort and validation cohort

	Derivation cohort HERMES (n=781)	Validation cohort MR CLEAN Registry (n=3260)
Baseline patient characteristics		
Age (years)	67 (57 – 76)	72 (61 – 80)
Men	414/781 (53%)	1684/3260 (52%)
NIHSS	17 (14 – 21)	16 (11 – 19)
Systolic blood pressure (mmHg)	144 (130 – 159)	150 (131 – 165)
Serum glucose (mmol/L) (mg/dL)	6.7 (5.9 – 7.8) 120 (106 – 140)	6.8 (5.9 – 8.1) 122 (106 – 146)
Previous stroke	89/777 (11%)	544/3233 (17%)
Hypertension	426/779 (55%)	1676/3194 (52%)
Atrial fibrillation	217/640 (34%)	770/3217 (24%)
Diabetes mellitus	120/780 (15%)	524/3236 (16%)
Pre-stroke mRS		
0	501/605 (83%)	2160/3188 (68%)
1	76/605 (13%)	421/31888 (13%)
2	19/605 (3.1%)	239/3188 (7.5%)
≥3	9/605 (1.5%)	368/3188 (12%)
Baseline imaging characteristics		
Occlusion location		
ICA(-T)	198/733 (27%)	818/3121 (26%)
M1	473/733 (65%)	1804/3121 (58%)
M2 or other*	62/733 (8.5%)	499/3121 (16%)
ASPECTS	8 (7 – 9)	9 (7 – 10)
Collateral score		
0	5/602 (0.8%)	187/3053 (6.1%)
1	81/602 (14%)	1094/3053 (36%)
2	268/602 (45%)	1181/3053 (39%)
3	248/602 (41%)	591/3053 (19%)
Treatment characteristics		
Treatment with IV alteplase	678/781 (87%)	2445/3248 (75%)
Time from stroke onset to arterial puncture	240 (185 – 299)	195 (150 – 255)
General anesthesia	227/776 (29%)	775/3063 (25%)
Duration of the procedure	64 (40 – 91)	59 (38 – 83)
Outcome measures		
Reperfusion grade (mTICI)		
0	54/715 (7.6%)	531/3173 (17%)
1	19/715 (2.7%)	94/3173 (3.0%)
2A	98/715 (14%)	592/3173 (19%)
2B	483/715 (68%)	715/3173 (23%)†
2C	NA	339/3173 (11%)†
3	61/715 (8.5%)	902/3173 (28%)
NIHSS at 24h	9 (4 – 16)	10 (4 – 17)
SICH at 24h	28/770 (3.6%)	192/3245 (5.9%)
FIV 12h – 2 weeks (mL)	34 (11 – 103)	N/A
mRS score at 3 months	3 (1 – 4)	3 (2 – 6)
mRS 0-2 at 3 months	371/781 (48%)	1235/3047 (41%)
Survival at 3 months	671/781 (86%)	2164/3047 (71%)

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale score; ICA(-T), intracranial carotid artery (terminus); M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2;

ASPECTS, Alberta Stroke Program Early CT Score; IV, intravenous; mTICI, modified treatment in cerebral infarction; SICH, symptomatic intracranial hemorrhage; FIV, follow-up infarct volume; N/A, not applicable. Categorical values are presented in n. (%) and continuous values in median (IQR). Missing continuous values (n derivation cohort,n validation cohort): age 0,15; NIHSS baseline 4,55; systolic blood pressure 1,89; serum glucose 26,371; ASPECTS 8,109; time from stroke onset to arterial puncture 0,15; duration of the procedure 174,291; NIHSS at 24h 25,333.
*Other occlusion location (M3 or anterior cerebral artery segment 1 or 2) by core lab: in HERMES (n=1), in MR CLEAN Registry (n=25).
†extended TICI score MR CLEAN Registry: 2B (n=715), 2C (n=339).

Table 2. Main effects in derivation cohort (HERMES, n=781) presented as common odds ratios* with 95% confidence intervals

	Univariable models	Multivariable model
Age, per year		
<65 years	0.99 (0.97 – 1.01)	1.00 (0.98 – 1.02)
≥65 years	0.94 (0.92 – 0.96)	0.94 (0.91 – 0.96)
Sex, male	1.12 (0.87 – 1.44)	
Baseline NIHSS, per point	0.91 (0.88 – 0.93)	1.03 (1.00 – 1.06)
Systolic blood pressure, per 10 mmHg	0.87 (0.82 – 0.91)	0.97 (0.91 – 1.03)
Glucose, per 30 mmol/L		
<120 mmol/L	0.55 (0.39 – 0.79)	0.95 (0.68 – 1.34)
≥120 mmol/L	0.89 (0.81 – 0.98)	0.97 (0.89 – 1.07)
Treatment with IV alteplase	1.07 (0.72 – 1.60)	N/A
Previous stroke	0.84 (0.57 – 1.25)	N/A
Hypertension	0.76 (0.59 – 0.98)	0.95 (0.71 – 1.38)
Atrial fibrillation	0.75 (0.56 – 0.99)	1.04 (0.76 – 1.43)
Diabetes mellitus	0.47 (0.33 – 0.67)	0.50 (0.33 – 0.75)
Pre-stroke mRS, per point	0.52 (0.40 – 0.68)	0.61 (0.46 – 0.82)
Occlusion location		
ICA(-T)	1.0 (reference)	1.0 (reference)
M1	1.58 (1.19 – 2.11)	1.26 (0.91 – 1.74)
M2 or other	2.37 (1.42 – 3.94)	2.04 (1.16 – 3.60)
Collateral score, per point	1.78 (1.46 – 2.17)	1.24 (0.93 – 1.65)
ASPECTS	1.35 (1.18 – 1.53)	1.00 (0.92 – 1.10)
Time from stroke onset to arterial puncture, per 30 minutes	0.95 (0.91 – 0.99)	0.97 (0.93 – 1.01)
General anesthesia	0.71 (0.53 – 0.95)	0.98 (0.70 – 1.37)
Post-procedural reperfusion grade (mTICI), per point	1.73 (1.48 – 2.01)	1.20 (1.02 – 1.41)
NIHSS at 24h, per point		
<12 points	0.72 (0.68 – 0.75)	0.71 (0.68 – 0.75)
≥12 points	0.85 (0.82 – 0.89)	0.86 (0.83 – 0.90)
SICH at 24h	0.11 (0.05 – 0.24)	0.29 (0.11 – 0.79)

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; N/A, not applicable; mRS, modified Rankin Scale, ICA(-T); intracranial carotid artery(-terminus); M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; ASPECTS, Alberta Stroke Program Early CT Score; mTICI, modified treatment in cerebral infarction; SICH, symptomatic intracranial hemorrhage.

Common odds ratios reflect the effect on the reversed modified Rankin Scale (an odds ratio >1 corresponds with better functional outcome). Variables with a p<AIC (Akaike's Information Criterion; p<0.157 for potential predictors with 1 degree of freedom) in univariable analysis, were entered into the multivariable model.

Table 3. Performance measures* with 95% confidence intervals in derivation cohort (n=781) and validation cohort (n=3260)

	Ordinal mRS	Functional independence (mRS 0-2)	Survival (mRS 0-5)
Internal validation			
C-statistic	0.84	0.91	0.87
External validation			
C-statistic	0.84 (0.83 – 0.84)	0.91 (0.90 – 0.92)	0.89 (0.88 – 0.90)
Calibration intercept	N/A	0.61 (0.50 – 0.74)	-0.25 (-0.37 – -0.13)
Calibration slope	N/A	0.98 (0.92 – 1.05)	0.86 (0.80 – 0.94)

Abbreviations: mRS, modified Rankin Scale; C-statistic, concordance statistic; N/A, not applicable.

*The C-statistic is a measure for the ability to distinguish between patients with a low and high probability of good outcome. It can vary between 0.5 for a non-informative model and 1 for a perfectly discriminating model. The calibration intercept reflects the calibration-in-the-large, indicating whether predicted probabilities are systematically too low or too high, and should ideally be equal to 0. The calibration slope reflects the strength of the predictors and should ideally be equal to 1.