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Association of Time From Stroke Onset to Groin Puncture With Quality of Reperfusion After Mechanical Thrombectomy
A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials

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Supplemental content

IMPORTANCE Reperfusion is a key factor for clinical outcome in patients with acute ischemic stroke (AIS) treated with endovascular thrombectomy (EVT) for large-vessel intracranial occlusion. However, data are scarce on the association between the time from onset and reperfusion results.

OBJECTIVE To analyze the rate of reperfusion after EVT started at different intervals after symptom onset in patients with AIS.

DESIGN, SETTING, AND PARTICIPANTS We conducted a meta-analysis of individual patient data from 7 randomized trials of the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) group. This is a multicenter cohort study of the intervention arm of randomized clinical trials included in the HERMES group. Patients with anterior circulation AIS who underwent EVT for M1/M2 or intracranial carotid artery occlusion were included. Each trial enrolled patients according to its specific inclusion and exclusion criteria. Data on patients eligible but not enrolled (eg, refusals or exclusions) were not available. All analyses were performed by the HERMES biostatistical core laboratory using the pooled database. Data were analyzed between December 2010 and April 2015.

MAIN OUTCOMES AND MEASURES Successful reperfusion was defined as a modified thrombolysis in cerebral infarction score of 2b/3 at the end of the EVT procedure adjusted for age, occlusion location, pretreatment intravenous thrombolysis, and clot burden score and was analyzed in relation to different intervals (onset, emergency department arrival, imaging, and puncture) using mixed-methods logistic regression.

RESULTS Among the 728 included patients, with a mean (SD) age of 65.4 (13.5) years and of whom 345 were female (47.4%), decreases in rates of successful reperfusion defined as a thrombolysis in cerebral infarction score of 2b/3 were observed with increasing time from admission or first imaging to groin puncture. The magnitude of effect was a 22% relative reduction (odds ratio, 0.78; 95% CI, 0.64-0.95) per additional hour between admission and puncture and a 26% relative reduction (odds ratio, 0.74; 95% CI, 0.59-0.93) per additional hour between imaging and puncture.

CONCLUSIONS AND RELEVANCE Because the probability of reperfusion declined significantly with time between hospital arrival and groin puncture, we provide additional arguments for minimizing the intervals after symptom onset in anterior circulation acute ischemic stroke.

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The challenges in the field of acute ischemic stroke (AIS) owing to large-vessel occlusion (LVO) focus on reducing time to reperfusion, optimizing imaging methods for patient selection, and evaluating the best technical approach.[1,2] Reperfusion is significantly associated with clinical outcome in patients undergoing endovascular thrombectomy (EVT).[3,4] Reperfusion is commonly scored with the modified thrombolysis in cerebral infarction (mTICI) grading scale, with 0 indicating persistent complete occlusion and 3 indicating complete reperfusion.[5] Because grade 2b was shown to be the best cutoff for predicting favorable outcome at 90 days, grades 2b and 3 are termed *successful reperfusion*.[6,7] A pooled analysis of the first 5 randomized clinical stroke trials, which predominantly used stent retrievers as the primary approach, demonstrated that successful reperfusion was obtained in 71% of patients, whereas the rate of mTICI 0 to 2a varied from 12% to 41%.[1] Successful reperfusion is influenced by device choice and strategy, use of intravenous (IV) alteplase, collateral status, and thrombus size, location, or composition.[8-15] Thrombus composition and characteristics may change rapidly over time after occlusion.[16] Although time to successful reperfusion strongly affects clinical outcome,[2] few data exist describing the effect of time on the rate of successful reperfusion. In this meta-analysis of the HERMES population, we aimed to analyze the rate of successful reperfusion as a function of interval times in patients with AIS-LVO treated with EVT.

Key Points

Question Is the quality of reperfusion rated with the thrombolysis in cerebral infarction score associated with longer hospital arrival to groin puncture time?

Findings In this meta-analysis, the rate of successful reperfusion, defined as a thrombolysis in cerebral infarction score of 2b-3 at the end of the procedure, decreased as time elapsed after arrival at the stroke endovascular center.

Meaning Fast reperfusion is a major modifiable factor associated with better clinical outcome when successful reperfusion is achieved, and the intermediary outcome, the rate of successful reperfusion, is higher with faster in-hospital process times.

Methods

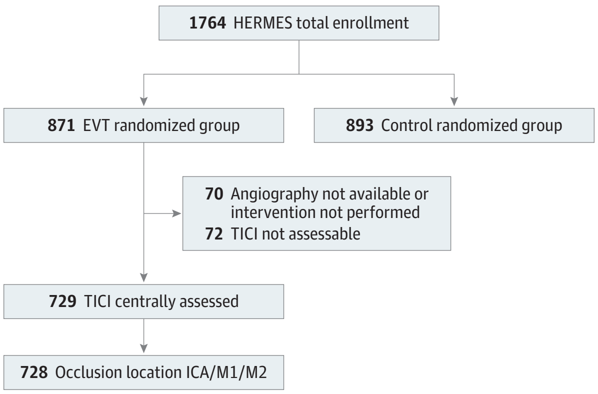
Patients in the intervention (EVT) arms of randomized clinical trials of the HERMES group (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN]; Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE]; Thrombectomie des Artères Cerebrales [THRACE] trial; The Pragmatic Ischaemic Thrombectomy Evaluation [PISTE]; Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial [EXTEND-IA]; Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset [REVASCAT]; and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME] trial) were included. Patients with AIS-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. A complete list of investigators in the HERMES group can be found in the eAppendix in the Supplement. 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 United States and Europe; ESCAPE, with 315 patients from February 2013 through October 2014 in Canada, the United States, South Korea, Ireland, and the United Kingdom; 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 United Kingdom; 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. The primary end point was the rate of successful reperfusion, defined as an mTICI 2b/3 at the end of the EVT procedure (eTable 1 in the Supplement). We also evaluated the potential association between different intervals from onset to groin puncture and the clot burden score (CBS). The CBS was scored on a scale of 0 to 10, according to Puetz et al,[17] with a score of 2 subtracted if the thrombus was found in either of the supraclinoid ICAs or the proximal or the distal half of the MCA trunk, and a score of 1 subtracted if the thrombus was found in the infraclinoid ICA, anterior cerebral artery, and for each affected M2 branch. Thus, a score of 10 indicates absence of thrombus and a score of 0 indicates a complete multisegment occlusion of the anterior circulation. Interval times were defined according to individual trial definitions. All participants provided written informed consent according to each trial protocol, and each study was approved by the local ethics board.

Statistical Analysis

Probability of successful reperfusion as a function of time was analyzed using mixed-methods logistic regression, with trial as a random effect. Models were constructed for the dependence of the log odds of reperfusion on time intervals including time from stroke onset,[1] arrival at the emergency department,[2] and imaging to arterial puncture.[3] Potential nonlinear effects of time were also investigated, including exploratory nonlinear models using locally weighted scatterplot smoother regression.

Logistic regression models were adjusted for age (a linear variable), centrally adjudicated target occlusion location (a 3-level categorical variable: ICA, M1 middle cerebral artery [MCA], and M2 MCA), and pretreatment IV tissue plasminogen activator (binary variable). In addition to the full cohort, subgroup analyses were conducted to examine the association between reperfusion and time in patients imaged either with computed tomography or magnetic resonance imaging.

Figure 1. Study Flowchart



EVT indicates endovascular treatment; ICA, intracranial carotid artery; M1/M2, first and second segment of the middle cerebral artery; TICI, thrombolysis in cerebral infarction.

Table 1. Baseline Characteristics of Included Patients

Characteristic	Mean (SD)	No.	Median (IQR)	No./Total No. (%)
Age, y	65.4 (13.5)	728	67.0 (56.8-76.0)	NA
Female	NA	728	NA	345/728 (47.4)
Hypertension	NA	728	NA	388/726 (53.4)
Hyperlipidemia	NA	728	NA	246/712 (34.6)
Diabetes mellitus	NA	728	NA	107/727 (14.7)
Atrial fibrillation	NA	728	NA	205/591 (34.7)
NIHSS score at baseline	NA	728	17.0 (14.0-20.0)	NA
ASPECTS at baseline	NA	728	8.0 (7.0-9.0)	NA
Onset to arterial puncture, min	250.4 (95.6)	714	239.0 (184.3-299.0)	NA

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; IQR, interquartile range; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

Effect size estimates are provided with their corresponding 95% confidence intervals; *P* values are 2-sided with values less than .05 considered statistically significant. Statistical analyses were performed in SAS, version 9.4 (SAS Institute Inc). Graphic output was obtained from R, version 3.3 (R Foundation for Statistical Computing).

Results

Among 871 patients assigned to endovascular therapy across the 7 HERMES trials, 729 had mTICI scores assessed by the central imaging core laboratory and 728 had ICA or MCA occlusion; these 728 patients constituted the primary analysis set for this report (**Figure 1**). Demographics and baseline characteristics are presented in **Table 1**. Median onset to arterial access time was 239 minutes (interquartile range [IQR], 184-299 minutes).

Successful reperfusion was associated with shorter times to arterial access (**Figure 2**; **Table 2**). Onset to arterial access time was not associated with mTICI 2b/3 reperfusion, but both computed tomography to arterial access and door to arterial access were. This effect persisted in subgroups of patients imaged with computed tomography and magnetic resonance imaging, where odds ratios within the subgroups were similar to those observed in the overall cohort.

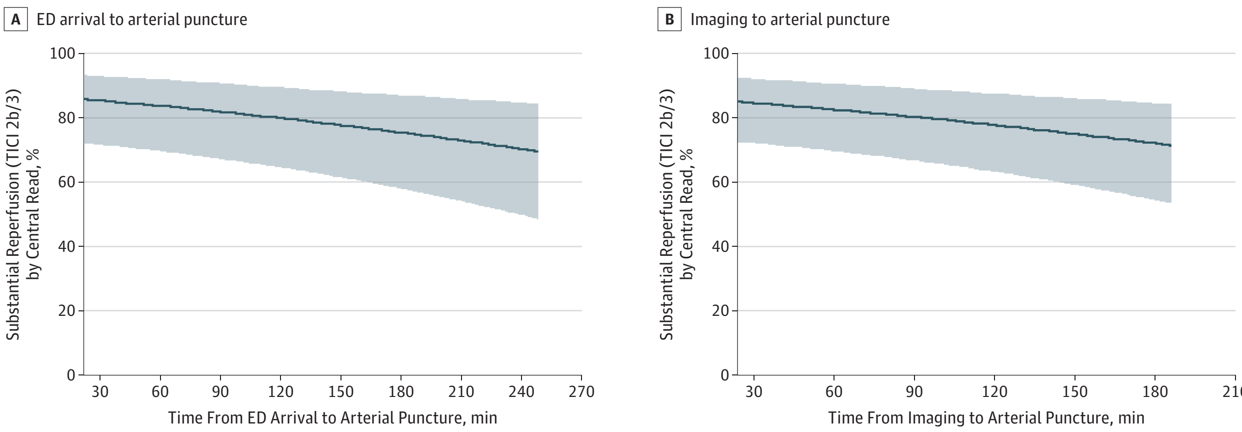
Observed rates of reperfusion in various time subgroups are summarized in Table 2, while modeled probabilities of reperfusion with time as a continuous predictor are displayed in Figure 2. Similar to the analysis of odds ratios in previous paragraphs, rates of TICI 2b/3 decreased with longer time since onset, with odds ratio 0.78 (95% CI, 0.64-0.95) per additional hour in admission to puncture and odds ratio of 0.74 (95% CI, 0.59-0.93) per additional hour in imaging-to-puncture delays. In this study, every additional hour between arrival at the emergency department and groin puncture was associated with a 22% reduction in the odds of TICI 2b/3 reperfusion. Furthermore, every additional hour between imaging and groin puncture was associated with a 26% reduction in the odds of TICI 2b/3 reperfusion; this time interval had the strongest association with final reperfusion. One notable exception was the subgroup of onset to arterial puncture of more than 360 minutes (6 hours), for which reperfusion rates were substantially higher than for patients with onset to puncture between 300 and 360 minutes. An increased reperfusion rate in late time intervals was not observed with intervals beginning with imaging or emergency department arrival times. Last, the CBS did not vary by intervals from onset to groin puncture (eTable 2 in the Supplement).

Discussion

The main finding of this study is that the rate of successful reperfusion, defined as an mTICI 2b/3 at the end of the procedure, decreased as time elapsed after arrival at the stroke endovascular center. Hence, time is doubly important in the setting of AIS-LVO. First, the time to effective reperfusion is a major potentially modifiable factor associated with better clinical outcomes, and second, the intermediary outcome, the rate of successful reperfusion, is higher with faster in-hospital process times. A component of improved outcomes owing to overall faster onset to reperfusion times is faster in-hospital treatment times. Our results could be confusing compared with the results of the late time studies.[18,19] Importantly, even if the reperfusion rate declines as time elapses, patients recanalized in later times continue to have better clinical outcome compared with those without reperfusion.

Notably, the total onset-to-arterial access time was not statistically associated with reperfusion outcomes in this analysis, possibly because several of the trials used imaging selection criteria to choose patients (thereby selecting those more likely to be slow progressors), and 1 trial examined an extended 12-hour eligibility window from stroke onset.

Figure 2. Modeled Probability of Thrombolysis in Cerebral Infarction (TICI) Score of 2b/3 by Workflow Time



Modeled probabilities of TICI score of 2b/3 outcome by workflow time, computed using logistic regression with covariates analogous to those in Table 2. Results are displayed as the point estimate for probability of TICI 2b/3 modeled by time along with the corresponding 95% confidence interval. ED indicates emergency department.

Table 2. Association of Delays in Workflow With TICI 2b/3 Outcome[a]

Outcome/Predictor	No.	OR (95% CI)	*P* Value
TICI 2b/3 by workflow predictors: all patients (adjustments: age, alteplase, and occlusion location)			
Onset to arterial puncture, per 60 min	714	0.92 (0.81-1.03)	.15
Imaging to arterial puncture, per 60 min	670	0.74 (0.59-0.93)	.01
ED arrival to arterial puncture, per 60 min	680	0.78 (0.64-0.95)	.01
TICI 2b/3 by workflow predictors: CT (adjustments: age, alteplase, occlusion location, and collateral grade)			
Onset to arterial puncture, per 60 min	541	0.93 (0.82-1.06)	.26
Imaging to arterial puncture, per 60 min	499	0.83 (0.64-1.08)	.17
ED arrival to arterial puncture, per 60 min	508	0.81 (0.65-1.02)	.07
TICI 2b/3 by workflow predictors: MR (adjustments: occlusion location only due to sample size)			
Onset to arterial puncture, per 60 min	117	0.97 (0.64-1.48)	.89
Imaging to arterial puncture, per 60 min	117	0.54 (0.30-0.99)	.05
ED arrival to arterial puncture, per 60 min	117	0.60 (0.34-1.07)	.09

Abbreviations: CT, computed tomography; ED, emergency department; MR, magnetic resonance; OR, odds ratio; TICI, thrombolysis in cerebral infarction.

[a] The association of time with the binary outcome of TICI 2b/3 following the procedure, including odds ratios (where values <1 represent diminishing rates of TICI 2b/3 as time increases), their corresponding 95% confidence intervals, and *P* values. Odds ratios are scaled per 60 minutes of delay in each listed interval and are computed via logistic regression including the listed covariate adjustments.

Long times from onset to arterial access in some cases could be dominated by onset to hospital arrival time even when in-hospital process times were short, and this patient group may have had additionally rigorous selection prior to transfer, diluting any possible demonstration of effect. Similarly, patients in later time epochs might have had blood flow stasis and new thrombus formation, increasing the total thrombus burden around the original thrombus.[20] However, in our analysis, we did not find any association between CBS and time between onset and imaging.

Evolution of thrombus composition and properties could also explain an increase rate of EVT failure over time. Studies on human thrombus retrieved from patients with AIS-LVO have revealed varying compositions.[21-23] As time elapses, the biochemical composition of thrombus changes,[24] the hemoglobin passes through several forms prior to red blood cell lysis and break down into ferritin and hemosiderin.[16] Afterwards, activation of coagulation pathways results in the formation of hemostatic fibrin plugs, and red blood cells become trapped within a fibrin mesh.[25,26] This modification of thrombus properties might account for the difference in reperfusion rates with increasing time from onset. Indeed, a fibrin-rich thrombus can be difficult to engage in the stent retriever and is more adherent to the vessel wall.[11,12]

Neutrophil extracellular traps form through the release of decondensed chromatin that is lined with granular components. Apart from thrombus modification over time, neutrophil extracellular traps have been identified as key players involved in the formation of thrombi of various origins and in their adhesion to the vessel wall.[27] Neutrophil extracellular traps are fibrous networks that form through the release of extracellular DNA from neutrophils, contributing to the scaffold of thrombus. As time elapses after occlusion, extracellular DNA and histones modify the structure of fibrin, rendering it more resistant to mechanical and enzymatic destruction. Neutrophil extracellular traps may participate in the interaction between the thrombus and the arterial wall or between the thrombus and the EVT device, thus increasing the difficulty of thrombus removal during EVT. The link between occlusion duration and neutrophil extracellular trap content was supported by a previous study,[28] demonstrating the need for a higher number of device passes to achieve a successful reperfusion.

While the probability of successful reperfusion decreased in our study with all intervals, the association was much more pronounced when arrival at the emergency department or imaging to groin puncture were considered compared with onset to groin puncture. These results are similar to those described in a previous study[2] that analyzed intervals and clinical outcomes. A potential explanation is the differential reliability of documented times for stroke onset vs emergency department arrival. Time of emergency department arrival is generally accurately documented in patient medical records. In contrast, the time of stroke onset (last known well) is often imprecisely determined or documented.[29] This emphasizes the need for improvement of modifiable in-hospital delays and may include intervals for patient transfer, imaging, or procedural factors, although it is not possible to define from the data available which specific components might be most usefully modified.

One notable exception to the association between time and successful reperfusion was the subgroup in whom onset to arterial puncture was more than 360 minutes (6 hours), for which the reperfusion rate was substantially higher than for patients with onset-to-puncture times between 300 and 360 minutes. This pattern of substantially increased reperfusion in late time windows was not observed with the imaging or emergency department arrival-to-puncture intervals. This observation may be an artifact of the definition of stroke-onset time as the last time the patient was seen well. Two trials, ESCAPE and REVASCAT, enrolled patients later than 6 hours from stroke onset and in so doing included patients with unwitnessed stroke, whose true stroke onset to treatment time was likely shorter.

Strengths and Limitations

Our analysis has several strengths because we were able to adjust our results for known factors of reperfusion, including intravenous alteplase treatment prior to EVT[30-32] and (in the computed tomography–selected subgroup) collateral status.[33,34] Potential limitations include differences in study entry criteria and patient characteristics among the trials that are a source of potential bias. Second, owing to multiple imaging modalities performed in the different trials, thrombus imaging characteristics were not analyzed but may have influenced reperfusion rates.[35-37] Third, a 2018 study[9] demonstrates that the number of EVT passes, an unreported variable in these studies, is itself associated with the probability of successful reperfusion.[9] Last, we were not able to analyze EVT procedural detail such as device selection, use of contact aspiration alone or combined with stent-retriever, or the use of balloon guide catheter.

Conclusions

In this post hoc analysis of the HERMES population, the probability of reperfusion declined significantly with time between hospital arrival and groin puncture. We provide additional arguments for minimizing the time intervals after symptom onset in anterior circulation AIS-LVO. Hence, the importance of reducing intrahospital delays after onset of symptom is highlighted because the rate of successful reperfusion itself is directly affected by shorter time intervals before groin puncture.

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