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Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis

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IMPORTANCE Endovascular thrombectomy with second-generation devices is beneficial for patients with ischemic stroke due to intracranial large-vessel occlusions. Delineation of the association of treatment time with outcomes would help to guide implementation.

OBJECTIVE To characterize the period in which endovascular thrombectomy is associated with benefit, and the extent to which treatment delay is related to functional outcomes, mortality, and symptomatic intracranial hemorrhage.

DESIGN, SETTING, AND PATIENTS Demographic, clinical, and brain imaging data as well as functional and radiologic outcomes were pooled from randomized phase 3 trials involving stent retrievers or other second-generation devices in a peer-reviewed publication (by July 1, 2016). The identified 5 trials enrolled patients at 89 international sites.

EXPOSURES Endovascular thrombectomy plus medical therapy vs medical therapy alone; time to treatment.

MAIN OUTCOMES AND MEASURES The primary outcome was degree of disability (mRS range, 0-6; lower scores indicating less disability) at 3 months, analyzed with the common odds ratio (cOR) to detect ordinal shift in the distribution of disability over the range of the mRS; secondary outcomes included functional independence at 3 months, mortality by 3 months, and symptomatic hemorrhagic transformation.

RESULTS Among all 1287 patients (endovascular thrombectomy + medical therapy [n = 634]; medical therapy alone [n = 653]) enrolled in the 5 trials (mean age, 66.5 years [SD, 13.1]; women, 47.0%), time from symptom onset to randomization was 196 minutes (IQR, 142 to 267). Among the endovascular group, symptom onset to arterial puncture was 238 minutes (IQR, 180 to 302) and symptom onset to reperfusion was 286 minutes (IQR, 215 to 363). At 90 days, the mean mRS score was 2.9 (95% CI, 2.7 to 3.1) in the endovascular group and 3.6 (95% CI, 3.5 to 3.8) in the medical therapy group. The odds of better disability outcomes at 90 days (mRS scale distribution) with the endovascular group declined with longer time from symptom onset to arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96 to 3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30 to 3.00), ARD, 30.2%; cOR at 8 hours,1.57 (95% CI, 0.86 to 2.88), ARD, 15.7%; retaining statistical significance through 7 hours and 18 minutes. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76 to 0.93]; ARD, −6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71 to 0.92], ARD, −5.2% [95% CI, −8.3% to −2.1%]), but no change in mortality (OR, 1.12 [95% CI, 0.93 to 1.34]; ARD, 1.5% [95% CI, −0.9% to 4.2%]).

CONCLUSIONS AND RELEVANCE In this individual patient data meta-analysis of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit became nonsignificant after 7.3 hours.

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Editorial page 1265

Supplemental content

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Five randomized trials have demonstrated the benefit of second-generation endovascular recanalization therapies (primarily stent retrievers) over medical therapy alone among patients with acute ischemic stroke due to large-vessel occlusions.[1-6] However, uncertainties remain about the benefit and risk of endovascular intervention when undertaken more than 6 hours after symptom onset as well as the degree to which benefit varies with time within the first 6 hours after symptom onset. In addition, evaluation of the workflow speeds achieved in the trials could guide time targets for quality improvement in clinical practice. National guidelines and consensus statements in the United States, Europe, and Canada recommend endovascular recanalization up until 6 hours after symptom onset, but thrombectomy devices are cleared by the US Food and Drug Administration for use up to 8 hours after symptom onset, and the Canadian guidelines additionally recommend thrombectomy for selected patients up to 12 hours after symptom onset.[7-9]

cOR *common odds ratio*

ICA *internal carotid artery*

IV tPA *intravenous tissue plasminogen activator*

MCA *middle cerebral artery*

mRS *modified Rankin Scale*

mTICI *modified Thrombolysis in Cerebral Infarction*

To address these uncertainties regarding temporal aspects of endovascular recanalization therapy, the investigators from the 5 trials agreed to pool their individual patient data for analysis. The objectives of this pooled analysis were to delineate the period in which endovascular thrombectomy is associated with benefit and to investigate the extent to which treatment delay is related to the association of endovascular intervention with functional outcomes, mortality, and symptomatic intracranial hemorrhage, with greater power and precision than achievable in analyses of individual trials.[10-13]

Key Points

Question What is the relation between time to treatment and outcome from endovascular mechanical thrombectomy for acute ischemic stroke?

Findings In this meta-analysis of pooled individual patient data from 1287 adults in 5 randomized trials, compared with medical therapy alone, thrombectomy up to 7.3 hours after symptom onset was associated with improved outcomes. Rates of functional independence after thrombectomy were 64% with reperfusion at 3 hours vs 46% with reperfusion at 8 hours.

Meaning In acute ischemic stroke due to large-vessel occlusion, endovascular mechanical thrombectomy should be initiated as soon as possible within the first 7 hours after symptom onset.

Methods

Study Design and Inclusion Criteria

A detailed description of the analytic approach is provided in the statistical analysis plan (Supplement 1). The study investigators established the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration to undertake meta-analysis of pooled individual patient data. The collaboration included all randomized phase 3 trials in which stent retrievers or other second-generation devices were used in the majority of endovascular interventions for treatment of acute ischemic stroke, and for which a peer-reviewed, complete primary results manuscript was published by July 1, 2016. PubMed search and inquiry among collaborators and colleagues was performed to confirm that all eligible trials were included (eTable 1 in Supplement 2).[14,15] Comparative design features of the contributing trials have been described.[6] All included trials enrolled patients with ethics approval from the local institutional boards at participating sites. The trials enrolled patients using prospective (4 trials) or prospective and deferred (1 trial) written informed consent from patients or their legally authorized representatives.

Outcomes

Two approaches were used to analyze the association between treatment time and outcomes: (1) the association of time with differences in outcome between treatment strategies was analyzed in an intention-to-treat manner, comparing patients allocated to treatment with endovascular thrombectomy + medical therapy (endovascular group) vs patients allocated to medical therapy alone (medical therapy group); (2) the association between time and outcome with substantial endovascular reperfusion was analyzed in the subset of endovascular group patients with modified Thrombolysis in Cerebral Infarction (mTICI) scale scores of 2b or 3.[16]

Efficacy outcomes analyzed at 3 months were (1) degree of disability, assessed across 6 levels of the modified Rankin Scale (mRS), with ranks 5 and 6 combined into a single worst outcome rank; (2) functional independence, defined as mRS scores of 0 through 2; and (3) excellent outcome, defined as mRS score of 0 through 1. Safety outcomes evaluated were 90-day mortality, symptomatic intracranial hemorrhage within 36 hours, and radiologic major intracerebral parenchymal hematoma within 36 hours. Symptomatic intracranial hemorrhage was classified according to the definitions of symptomatic intracranial hemorrhage used in each trial. Major parenchymal hematoma was defined as parenchymal hematoma type 2.[17]

Statistical Analysis

A detailed description of the analytic approach is provided in the statistical analysis plan, which was modified from the preanalysis document to incorporate additional analyses based on the initial findings (eAppendix in Supplement 1). Briefly, probability of each outcome as a function of time was analyzed using mixed-method ordinal logistic regression for ordinal outcomes and mixed-method binary logistic regression for binary outcomes, with trial and trial-by-treatment interaction as random-effects variables. In the main analyses, models were constructed of the linear dependence of the log odds of a particular outcome on allocation to endovascular vs medical therapy groups and time interval (a linear variable). For models including both randomized groups, the interaction of time and treatment assignment was also included. In addition to these linear models, exploratory nonlinear models were constructed of the relations of outcomes with time to reperfusion by analyzing each

modified Rankin Scale (mRS) cut point in 6 separate, binary mixed-method logistic regression models, using a locally weighted scatterplot smoothing (LOWESS) regression technique. The common odds ratio (cOR) of the ordinal shift in the distribution of disability over the range of the mRS was the primary effect measure estimated from these models. The proportion of patients having better outcome by 1 or more disability levels on the mRS (absolute risk difference) was calculated by averaging values derived using the algorithmic joint outcome table and permutation test methods.[18,19]

For binary outcomes, absolute risk differences were calculated as differences of predicted proportions from logistic regression models. Variables included in adjusted analyses were age (a linear variable), sex (binary variable), baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score), target occlusion location (a 3-level categorical variable—internal carotid artery [ICA], M1 middle cerebral artery [MCA], M2 MCA), entry Alberta Stroke Program Early Computed Tomography Score (ASPECTS; linear variable), and pretreatment intravenous (IV) tissue plasminogen activator (tPA [alteplase]; binary variable). Race/ethnicity was not included both because collection of race data was legally prohibited in some countries where studies were performed and because race/ethnicity is not a known major independent determinant of outcome from large-vessel ischemic stroke.

In all 5 trials, all patients eligible for IV tPA received it; only patients with contraindications to IV tPA did not receive it. Subgroups analyzed included IV tPA–treated vs IV tPA–ineligible patients, target occlusion location, extent of cerebral infarction at entry on the ASPECTS scale, and mode of arrival (direct from out-of-hospital setting to endovascular hospital [direct arrival patients] vs interhospital transfer from outside initial receiving hospital [transfer patients]).

An independent statistician collated, cleaned, and merged the data. A minimum data set was designed by the collaborative authors and retrieved by each study statistician and submitted to the independent statistician. Data definitions were harmonized, and when data queries arose, detailed information was sought from each trials' data center and statistician. Additional data checking (eg, for sequence generation, data consistency, and completeness) was performed by comparing independent analysis of the acquired data to published results and to unpublished summaries provided by the collaborative authors. Final analyses were performed on the collated and merged data set after the above steps.

For comparisons of treatment groups, time intervals analyzed included (1) symptom onset to randomization; (2) symptom onset to expected arterial puncture; (3) arrival at the emergency department door to randomization; and (4) arrival at the emergency department door to expected arterial puncture. Symptom onset time was time the patient was last known to be well. Symptom onset-to-expected arterial puncture time was derived by adding to the symptom onset-to-randomization value for each patient in both the endovascular and medical therapy groups (the study mean for the time from randomization to arterial puncture of the trial in which they participated). Symptom onset-to-expected arterial puncture time was considered the lead analytic time interval, as it is the time interval used in national guidelines for treatment recommendations.[7-9] For analysis of the association with outcome of time of revascularization among the subset endovascular group patients achieving substantial reperfusion (mTICI score of 2b or 3), the primary time interval analyzed was symptom onset to actual substantial reperfusion. Analyses of symptom onset-to-treatment event time intervals always included both direct arrival and transfer patients. Analyses of emergency department door-to-treatment event time intervals were confined to direct arrival patients (because transfer patients, having undergone workup at outside facilities, often had paradoxical short emergency department door-to-treatment event and long symptom onset-to-treatment event times.)

All effect size estimates were provided with their 95% CIs; *P* values were 2-sided with values less than .05 considered statistically significant, without adjustment for multiple comparisons. Statistical analyses were performed in SAS (SAS Institute), version 9.3. Graphical output was obtained from R (R Foundation for Statistical Computing), version 3.2.

Results

The systematic search identified 5 trials enrolling 1287 participants (eTable 1-2 and eFigure 1 in Supplement 2). Data from all patients in all trials were included; across all possible time points and outcomes, data availability was 99.2% (eTable 4 in Supplement 2). Formal assessment of trial quality was high for all 5 trials, although potential sources of bias included blinding of outcome raters but not participants in all and early stopping due to overwhelming efficacy in 4 trials (eTable 5 in Supplement 2).

Overall, 634 participants were assigned to the endovascular group and 653 participants to the medical therapy group. Characteristics of patients in each treatment group and in different time windows are shown in **Table 1**. The treatment groups were well matched with respect to age, sex, baseline stroke severity, site of target occlusion, and time to randomization (eTable 6 in Supplement 2). Although all trials administered IV tPA to all tPA-eligible patients in both treatment groups, randomized assignment resulted in slightly less frequent IV tPA use in the endovascular group than in the medical therapy group (83% for the endovascular group vs 87% for the medical therapy group, $P = .04$). The median time from symptom onset to randomization was 196 minutes (IQR, 142-267; full range, 37-713) (eFigure 2 in Supplement 2).

Endovascular intervention was associated with a substantially lower degree of patient disability at 3 months, with mRS scores of 2.9 (95% CI, 2.7-3.1) in the endovascular group and 3.6 (95% CI, 3.5-3.8) in the medical therapy group. In the endovascular group, the cOR of a less-disabled outcome with thrombectomy was 2.49 (95% CI, 1.76-3.53); absolute risk difference (ARD), 38.1% ($P < .001$), with earlier treatment associated with greater magnitude of benefit (**Table 2**, **Figure 1**, and eTables 7-8 and eFigure 3 in Supplement 2). Considering all mRS disability levels concurrently, increasing delays were associated with higher levels of disability among patients in the endovascular group and there was no change over time in the medical therapy

Table 1. Selected Baseline Characteristics of Patients in Participating Trials According to Entry Time Window and by Treatment Group

	Symptom Onset-to-Randomization Time Interval, min				Treatment Group	
	30-120	121-240	241-360	>360	Endovascular Thrombectomy	Medical Therapy
No. of patients[a]	194	657	352	79	634	653
Age, mean (SD), y	68.7 (11.8)	66.5 (12.9)	65.8 (13.5)	64.5 (14.7)	66.3 (13.2)	66.7 (12.9)
Age, No. (%)						
18-79	159 (82)	548 (83.4)	307 (87.7)	68 (86.1)	527 (83.1)	558 (85.8)
≥80	35 (18)	109 (16.6)	43 (12.3)	11 (13.9)	107 (16.9)	92 (14.2)
Women, No. (%)	103 (53.1)	302 (46)	157 (44.7)	42 (53.2)	304 (47.9)	301 (46.2)
Medical history, No. (%)						
Atrial fibrillation	74 (38.1)	198 (30.1)	125 (35.6)	27 (34.2)	209 (33)	215 (33)
Hypertension	124 (63.9)	373 (56.8)	197 (56.1)	46 (58.2)	352 (55.5)	388 (59.5)
Hyperlipidemia	64 (33)	228 (34.7)	120 (34.2)	31 (39.2)	207 (32.6)	236 (36.2)
Diabetes	43 (22.2)	114 (17.4)	50 (14.2)	11 (13.9)	103 (16.2)	115 (17.6)
Prior stroke or TIA	27 (13.9)	78 (11.9)	42 (12)	7 (8.9)	79 (12.5)	76 (11.7)
Prior or current smoker	49 (30.4)	221 (35.4)	116 (34.4)	17 (26.2)	194 (33.2)	210 (34.7)
Baseline glucose, mean (SD), mg/dL	135.9 (90.4)	134.2 (83.5)	131.6 (43.5)	124.2 (31.3)	134.4 (83.6)	131.9 (62.1)
Prestroke mRS, No. (%)[b]						
0	154 (79.4)	532 (81)	297 (84.4)	72 (91.1)	524 (82.6)	533 (81.6)
1	30 (15.5)	92 (14)	36 (10.2)	4 (5.1)	78 (12.3)	84 (12.9)
2	6 (3.1)	19 (2.9)	10 (2.8)	2 (2.5)	20 (3.2)	17 (2.6)
3-5	4 (2.1)	14 (2.1)	9 (2.6)	1 (1.3)	12 (1.9)	19 (2.9)
NIHSS score, mean (SD)[c]	17.2 (5.6)	17 (5.3)	16.5 (5.1)	16.1 (5.5)	16.8 (5.1)	16.8 (5.5)
1-10	25 (13)	87 (13.3)	48 (13.7)	12 (15.4)	74 (11.7)	98 (15.1)
11-15	45 (23.3)	145 (22.1)	86 (24.5)	32 (41)	168 (26.6)	142 (21.9)
16-20	69 (35.8)	253 (38.6)	136 (38.7)	17 (21.8)	237 (37.6)	238 (36.7)
≥21	54 (28)	170 (26)	81 (23.1)	17 (21.8)	152 (24.1)	170 (26.2)
Mode of arrival, No. (%)						
Direct	187 (97.9)	496 (75.5)	133 (37.8)	52 (66.7)	441 (69.8)	428 (66)
Transfer	4 (2.1)	161 (24.5)	219 (62.2)	26 (33.3)	191 (30.2)	220 (34)
Pretreatment IV-tPA, No. (%)	166 (85.6)	585 (89.0)	306 (86.9)	36 (45.6)	526 (83.0)	569 (87.1)
Occlusion location, No. (%)						
ICA	62 (32.1)	141 (21.8)	55 (16.2)	17 (21.8)	133 (21.3)	144 (22.5)
M1 MCA	120 (62.2)	455 (70.2)	259 (76.2)	56 (71.8)	439 (70.5)	452 (70.6)
M2 MCA	11 (5.7)	52 (8)	26 (7.6)	5 (6.4)	51 (8.2)	44 (6.9)
ASPECTS, mean (SD)[d]	9 (1.4)	8.4 (1.7)	7.8 (2)	8.0 (1.6)	8.3 (1.7)	8.3 (1.8)
9-10	143 (75.3)	367 (56.2)	142 (41.2)	33 (45.8)	325 (52.4)	361 (56.1)
7-8	38 (20)	195 (29.9)	133 (38.6)	31 (43.1)	212 (34.2)	188 (29.2)
5-6	5 (2.6)	64 (9.8)	45 (13)	6 (8.3)	58 (9.4)	62 (9.6)
0-4	4 (2.1)	27 (4.1)	25 (7.2)	2 (2.8)	25 (4)	33 (5.1)
Symptom onset-to-randomization time, median (IQR), min	101 (86-112)	176 (148-207)	284 (262-314)	410 (383-525)	196 (142-260)	196 (142-270)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; IQR, interquartile range; IV tPA, intravenous tissue plasminogen activator (alteplase); MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Sum of patients in the time interval columns is 5 fewer than the sum of patients in the treatment group columns because randomization time was not documented in 5 patients. eTable 2 provides further information on data availability for event times and outcomes (Supplement 2).

[b] The mRS ranges from 0 to 6, with higher scores indicating greater degree of disability.

[c] NIHSS ranges from 0 to 42, with higher scores indicating more severe neurologic deficits.

[d] ASPECTS ranges from 0 to 10, with higher scores indicating a smaller infarct core.

group (Table 2, Figure 1). The degree of benefit from thrombectomy nominally declined with longer times from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96-3.98), ARD for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30-3.00), ARD, 30.2%; cOR at 8 hours, 1.57 (95% CI, 0.86-2.88), ARD, 15.7%. Odds of functional independence (mRS 0-2) similarly declined: OR at 3 hours, 2.83 (95% CI, 2.07-3.86), ARD, 23.9% (95% CI, 12.5%-35.2%); OR at 6 hours, 2.32

Table 2. Association of a 1-Hour Treatment Delay With Disability Level, Functional Independence (mRS 0-2), and Mortality at 3 Months in the Endovascular Thrombectomy vs Medical Therapy Groups

	Endovascular Thrombectomy		Medical Therapy		*P* Value for Interaction With Treatment Group
	OR (95% CI) per 1-Hour Delay	ARD, % (95% CI) per 1-Hour Delay[a]	OR (95% CI) per 1-Hour Delay	ARD, % (95% CI) per 1-Hour Delay[a]	
Symptom Onset-to-Randomization Time Interval					
mRS shift[b]	0.88 (0.81 to 0.96)	−4.7	0.98 (0.89 to 1.07)	−0.5	.10
mRS 0-2	0.87 (0.79 to 0.97)	−3.4 (−5.8 to −0.8)	0.92 (0.81 to 1.05)	−1.6 (−3.9 to 1.0)	.49
Mortality	1.11 (0.96 to 1.27)	1.4 (−0.5 to 3.4)	0.88 (0.76 to 1.03)	−1.9 (−3.9 to 0.5)	.03
Symptom Onset-to-Arterial Puncture Time Interval (Expected)[c]					
mRS shift[b]	0.88 (0.80 to 0.96)	−5.3	0.98 (0.89 to 1.08)	−0.5	.07
mRS 0-2	0.87 (0.78 to 0.96)	−3.4 (−6.1 to −1.0)	0.93 (0.82 to 1.06)	−1.4 (−3.7 to 1.2)	.37
Mortality	1.12 (0.97 to 1.30)	1.5 (−0.4 to 3.7)	0.88 (0.76 to 1.02)	−1.9 (−3.9 to 0.5)	.02
Symptom Onset-to-Reperfusion Time Interval (Expected)[d]					
mRS shift[b]	0.87 (0.79 to 0.95)	−6.1	0.99 (0.90 to 1.09)	−0.4	.046
mRS 0-2	0.85 (0.77 to 0.95)	−4.0 (−6.4 to −1.3)	0.94 (0.83 to 1.06)	−1.2 (−3.5 to 1.2)	.25
Mortality	1.16 (1.01 to 1.32)	2.0 (0.1 to 4.0)	0.88 (0.76 to 1.02)	−1.9 (−3.9 to 0.5)	.048
Symptom Onset-to-ED Arrival Time Interval					
mRS shift[b]	1.01 (0.93 to 1.09)	0	0.99 (0.91 to 1.08)	0	.79
mRS 0-2	1.00 (0.93 to 1.08)	0.0 (−1.8 to 1.9)	0.95 (0.81 to 1.10)	−1.0 (−3.9 to 1.9)	.52
Mortality	1.01 (0.88 to 1.16)	0.1 (−1.6 to 2.0)	0.90 (0.78 to 1.03)	−1.6 (−3.5 to 0.4)	.21
ED Arrival-to-Randomization Time Interval					
mRS shift[b]	0.56 (0.46 to 0.68)	−16.2	0.97 (0.81 to 1.16)	−1.2	<.001
mRS 0-2	0.55 (0.43 to 0.71)	−14.1 (−19.2 to −8.3)	0.96 (0.75 to 1.24)	−0.8 (−5.2 to 4.4)	.002
Mortality	1.42 (1.08 to 1.88)	5.1 (1.0 to 10.1)	0.95 (0.72 to 1.26)	−0.8 (−4.5 to 3.8)	.049
ED Arrival-to-Arterial Puncture Time Interval (Expected)[e]					
mRS shift[b]	0.56 (0.47 to 0.67)	−16.8	0.98 (0.82 to 1.16)	−1.2	<.001
mRS 0-2	0.55 (0.43 to 0.71)	−14.1 (−19.2 to −8.3)	0.94 (0.74 to 1.19)	−1.2 (−5.4 to 3.5)	.001
Mortality	1.44 (1.11 to 1.87)	5.4 (1.4 to 10.0)	0.98 (0.75 to 1.27)	−0.3 (−4.0 to 3.8)	.03
ED Arrival-to-Reperfusion Time Interval (Expected)[f]					
mRS shift[b]	0.57 (0.48 to 0.67)	−16.7	0.95 (0.80 to 1.12)	−2.2	<.001
mRS 0-2	0.56 (0.45 to 0.70)	−13.7 (−18.2 to −8.6)	0.91 (0.73 to 1.13)	−1.8 (−5.7 to 2.4)	.001
Mortality	0.91 (0.88 to 0.93)	−1.2 (−1.6 to −0.9)	1.06 (0.84 to 1.33)	0.9 (−2.5 to 4.8)	.02

Abbreviations: ARD, absolute risk difference; ED, emergency department; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; OR, odds ratio.

[a] Absolute risk difference (negative values indicate lower absolute rate with later therapy; positive values indicate higher absolute rate with later therapy).

[b] mRS shift: common OR over 6 levels of the 7-level modified Rankin Scale (with mRS strata 5 and 6 as the worst outcome level).

[c] Derived by adding to the actual symptom onset–to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated. Arterial puncture is considered procedure start.

[d] Derived by adding to the actual symptom onset–to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI score of 2b or 3) of the trial in which they participated.

[e] Derived by adding to the actual ED arrival–to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated.

[f] Derived by adding to the actual ED arrival–to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI score of 2b or 3) of the trial in which they participated.

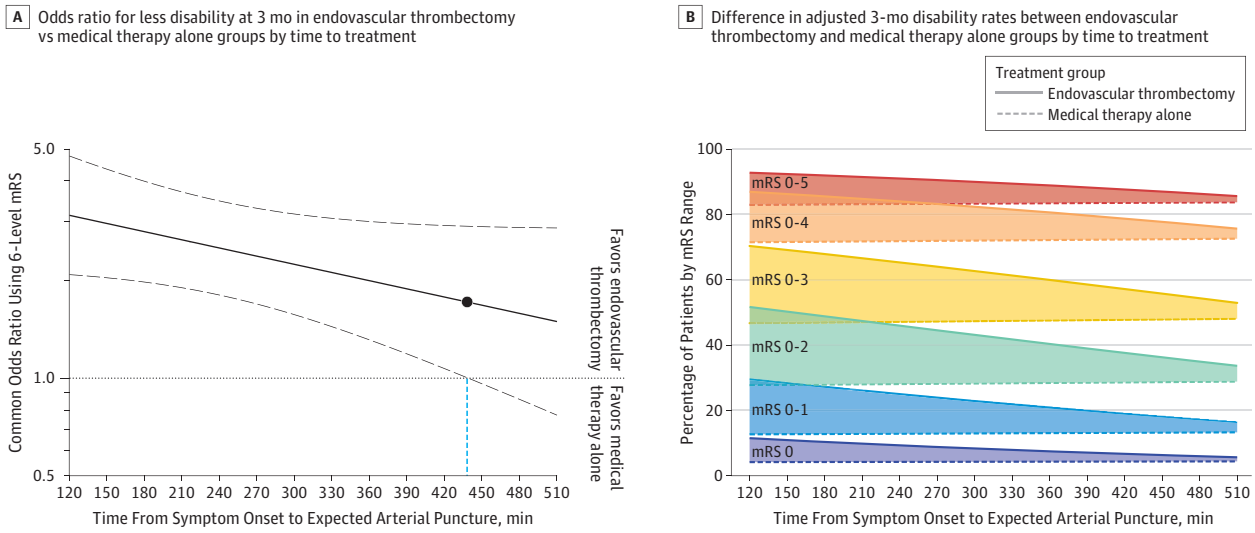
(95% CI, 1.56-3.44), ARD, 18.1% (95% CI, 5.7%-30.5%); OR at 8 hours, 2.03 (95% CI, 1.03-3.99), ARD, 14.3% (95% CI, 0.1%-28.5%). The time at which the lower 95% CI for estimated treatment benefit first crossed 1.0 and was no longer statistically significant was at an symptom onset-to-expected arterial puncture time of 7 hours and 18 minutes (Figure 1).

Treatment effect was not significantly modified by the symptom onset-to-emergency department arrival time interval. However, pronounced treatment effect modification was observed with time intervals beginning from emergency-department arrival (Table 2). Excellent outcome (mRS 0-1), symptomatic hemorrhage, and major parenchymal hematoma did not show interactions of time with treatment group (eTable 9 and eFigure 4 in Supplement 2).

Among the 634 patients randomized to the endovascular group, arterial puncture was performed in 607 (95.7%) and thrombectomy intervention in 563 (88.8%). The most common reason for nonintervention was interval resolution of target occlusion (eTable 10 in Supplement 2). Among the 549 patients who underwent an endovascular thrombectomy intervention and had resulting mTICI scores documented, substantial reperfusion was achieved in 390 (71.0%). Among the 607 patients who had an arterial access puncture, the median time from symptom onset to arterial puncture was 238 minutes (IQR, 180-302) and from symptom onset to reperfusion 301 minutes (IQR, 226-384) (eFigure 2 in Supplement 2).

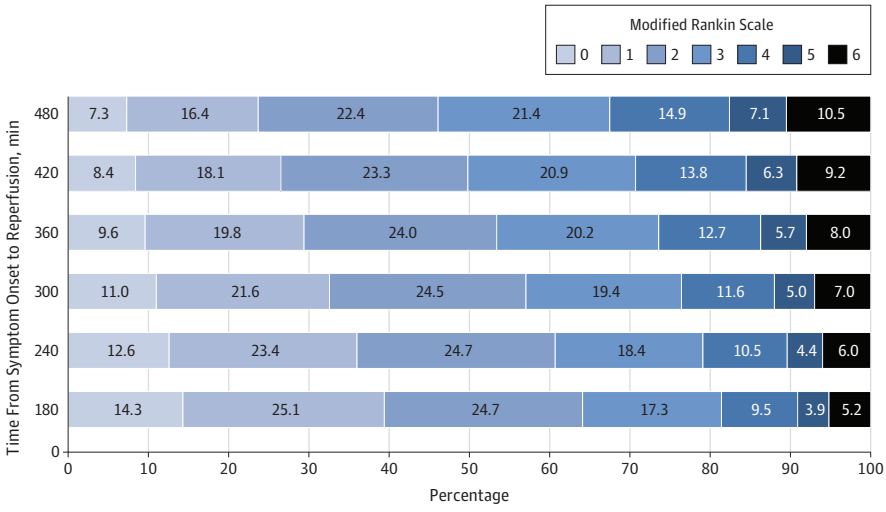
Among the endovascular group patients in whom substantial reperfusion was achieved, delay in symptom symptom onset-to-reperfusion times was associated with increased levels of 3-month disability (**Figure 2**; eTable 11 and eFigure 5 in Supplement 2). Considering outcome distributions across all mRS health states, for every 9-minute delay in symptom symptom onset-to-substantial endovascular reperfusion time, 1 of every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS). The probability of functional independence (mRS 0-2) at 3 months declined from 64.1% with symptom onset-to-reperfusion time of 180 minutes to 46.1% with symptom onset-to-reperfusion time of 480 minutes (Figure 2). The associations of time delay with poorer outcomes were

Figure 1. Association of Time From Symptom Onset to Expected Time of Endovascular Thrombectomy Procedure Start (Arterial Puncture) With Disability Levels at 3 Months in Endovascular (n = 633) vs Medical Therapy (n = 645) Groups



mRS indicates modified Rankin Scale. Time was analyzed as a continuous variable. Data were adjusted for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator. A, The 6-level mRS combined ranks 5 and 6 into a single worst outcome rank. The solid curve indicates the best linear fit between the common odds ratio for improved outcome over the 6-level mRS. The dashed curves indicate 95% CIs. The *P* value for interaction was .07. The lower bound of the 95% CI crosses 1.0 at 438 minutes (vertical blue dashed line). When the 7-level mRS was analyzed, with rank 5 considered a better outcome than rank 6, the lower bound of the 95% CI crossed 1.0 at 418 minutes. B, Upper solid line of each colored band indicates outcome rate in the endovascular thrombectomy group; lower dashed line of each band indicates outcome rate in the medical care only group. The widths of the colored bands indicate the absolute differences between the endovascular thrombectomy and medical therapy groups for that mRS cut point at each time point. Categories are cumulative, so that mRS 0-3 includes all patients with outcomes of mRS 0-3. For example, at the symptom onset to expected arterial puncture time of 300 minutes, the x intercepts indicate outcome rates (mRS 0: 8.3% for the endovascular thrombectomy group vs 4.3% for the medical therapy group; mRS 0-1: 22.9% for the endovascular thrombectomy group vs 12.9% for the medical therapy group; mRS 0-2: 43.1% for the endovascular thrombectomy group vs 28.2% for the medical therapy group; mRS 0-3: 62.7% for the endovascular thrombectomy group vs 47.3% for the medical therapy group; mRS 0-4: 82.4% for the endovascular thrombectomy group vs 72.0% for the medical therapy group; mRS 0-5: 90.0% for the endovascular thrombectomy group vs 83.3% for the medical therapy group).

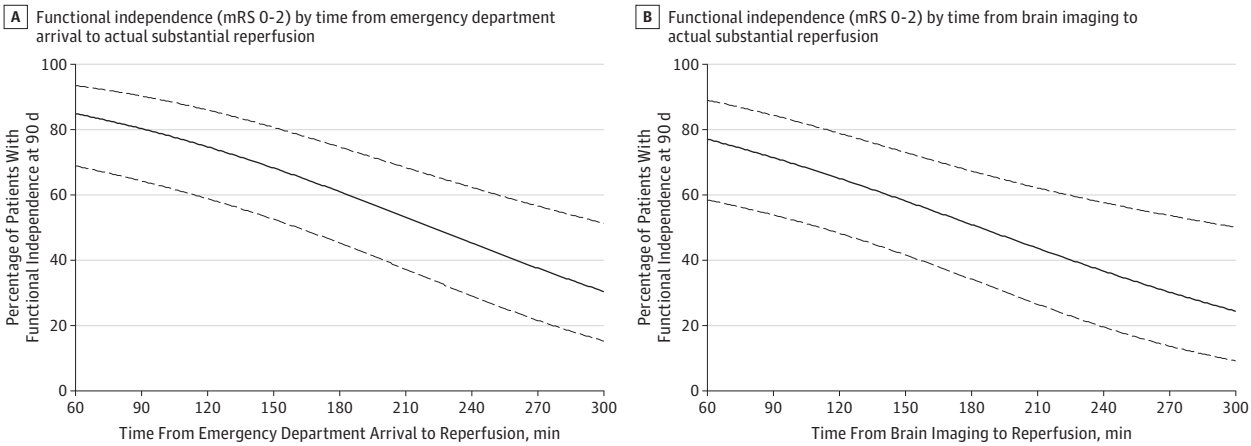
Figure 2. Association of Time From Symptom Onset to Actual Reperfusion Among Patients in the Endovascular Thrombectomy Group Achieving Substantial Reperfusion With 90-Day Disability Outcomes Using an Adjusted Ordinal Logistic Regression Model



Data are from the 390 endovascular group patients in whom substantial reperfusion (modified Thrombolysis in Cerebral Infarction score of 2b or 3) was achieved. Rows are intercepts from a single model using all 390 patients, treating time as a continuous variable. Model adjusted for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator.

magnified in the time segment from emergency department arrival through reperfusion (Table 2; eFigure 6 in Supplement 2). Considering outcome distributions across all mRS health states, for every 4-minute delay in emergency department door-to-reperfusion time, 1 of every 100 treated patients had a worse disability outcome (eTable 12 in Supplement 2). Among

Figure 3. Relation Between In-Hospital Treatment Speeds and Functional Independence (mRS 0-2) at 3 Months Among Direct Arrival Patients in the Endovascular Thrombectomy Group Achieving Substantial Reperfusion (mTICI score, 2b or 3)



mRS indicates modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction. Data are from the 390 endovascular group patients in whom substantial reperfusion (mTICI score, 2b or 3) was achieved. Curves were obtained from logistic regression of outcome on time as a continuous variable, after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator. Solid curves indicate point estimates. Dashed curves indicate 95% CIs. Substantial reperfusion was defined as mTICI score of 2b or 3 flow at the end of intervention.

direct arrival patients, functional independence at 3 months was more frequent both with faster emergency department door-to-reperfusion and brain imaging-to-reperfusion times (**Figure 3**). Rates of mortality, symptomatic intracranial hemorrhage, and major parenchymal hematoma did not significantly change with longer delay to reperfusion (eTable 13 in Supplement 2).

Rates of functional independence at 3 months declined with delay in symptom onset-to-reperfusion time in a parallel manner in 6 of the 7 analyzed subgroups: age, baseline stroke severity, clot location, initial extent of cerebral infarction (ASPECTS), patient arrival directly or by transfer, and time from symptom onset to IV tPA start (eFigure 7 in Supplement 2). In contrast, rates of independent outcome declined more steeply in patients treated with IV tPA vs tPA-ineligible patients (7.4% per hour [95% CI, 3.8% to 10.9%] for patients treated with IV tPA vs 3.4% [95% CI, −0.5% to 7.3%] for tPA-ineligible patients, $P = .047$).

Workflow time intervals differed between direct arrival patients and transfer patients (eTable 11 and eFigure 8 in Supplement 2). Transfer patients had faster processes of care at the endovascular hospital than direct arrival patients, with emergency department door-to-arterial puncture times of 81 minutes (IQR, 58-105) for transfer patients vs 116 minutes (IQR, 83-160) for direct arrival patients, $P < .001$. But the longer symptom onset to arrival times (207 minutes [IQR, 160-256] for transfer patients vs 65 minutes [IQR, 44-116] for direct arrival patients, $P < .001$) resulted in overall longer symptom onset-to-randomization intervals (260 minutes [IQR, 215-310] for transfer patients vs 165 minutes [IQR, 125-226] for direct arrival patients, $P < .001$). Considering all endovascular group patients, high proportions (62%-81%) were treated within the time intervals recommended by multispecialty guidelines in effect at the time of study conduct,[20] but low proportions (4%-13%) were treated within more recently promulgated "ideal" target intervals (eTable 14 in Supplement 2).[21]

Discussion

This study provides additional evidence regarding the association between treatment time and the benefit of endovascular reperfusion. Compared with best medical therapy alone, endovascular thrombectomy therapy was associated with improved outcomes when procedure start (arterial puncture) could be performed within the first 7.3 hours after symptom onset among patients meeting the brain imaging entry criteria for inclusion in these randomized trials. Moreover, within this period, functional outcomes were better the sooner after symptom onset that endovascular reperfusion was achieved, emphasizing the importance of programs to enhance patient awareness, out-of-hospital care, and in-hospital management to shorten symptom onset-to-treatment times.

The magnitude of the association between time to treatment and outcome was clinically meaningful. Based on the current study, and assuming the findings are generalizable to the population of patients with acute ischemic stroke due to large-vessel occlusion, among every 1000 patients achieving substantial endovascular reperfusion, for every 15-minute faster emergency department door-to-reperfusion time, an estimated 39 patients would have a less-disabled outcome at 3 months, including 25 more who would achieve functional independence (mRS 0-2). The findings that in-hospital processes of care are directly associated with improved functional outcome is noteworthy. In addition to faster time from emergency department door to reperfusion, faster time from brain imaging to reperfusion was associated with better 3-month functional outcomes. These findings are largely

consistent with those of prior endovascular intervention observational cohorts and trials[22-24] and of studies of intravenous thrombolysis.[25,26]

Use of brain imaging to exclude patients with a large core of permanently infarcted brain tissue in the trials in this pooled analysis may have influenced the strength of the association between symptom onset-to-randomization and symptom onset-to-reperfusion times and outcomes. Four of the 5 trials formally excluded patients with large ischemic cores evident on initial brain imaging from study participation.[2-5] The fifth trial required investigator and treating physician uncertainty regarding patient potential to benefit from therapy,[1] which may have resulted in informal exclusion of some patients with large cores. In the current study, patients with moderate infarct core volumes (ASPECT score, 7-8) had a shallower decline in benefit with longer symptom onset-to-reperfusion than patients with minor infarct core volumes (ASPECT score, 9-10). The exclusion of patients with even larger cores from the trials likely attenuated the relationship between symptom onset-to-reperfusion time and frequency of good functional outcomes. Similarly, in a population with more patients with large, already-established infarcts, symptom onset-to-reperfusion time would likely have greater association with mortality than in the trials pooled in this study.[24]

A time-by-treatment group interaction was observed for the interval from emergency department arrival to randomization, but not from symptom onset to emergency department arrival. There are several possible reasons the stronger association of time intervals after arrival with outcome. One is the application of study entry criteria after emergency department arrival. By eliminating patients with clinical features that indicated a very mild ischemic injury, and clinical and brain imaging features that indicated an advanced and extensive injury, the entry criteria likely filtered out patients who experienced very slow or very fast progression during the symptom onset-to-emergency department door period. A second likely source is 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.[27] In some patients, symptom onset occurs during sleep and the actual symptom onset time is not known. In others, the neurologic deficit may render the patient unable to accurately observe or report the time of symptom onset. A third possibility is physiological. Human cerebral ischemic injury may follow an exponential or sigmoid growth trajectory, with more rapid progression at intermediate after-symptom onset times than early after-symptom onset times. Available human serial brain imaging studies have not strongly suggested that the infarct growth curve has a sigmoid shape but have been relatively small and underpowered.[28,29]

Patient characteristics also were related to the association of symptom onset-to-reperfusion time with outcomes. At all symptom onset-to-reperfusion times, absolute rates of functional independence at 3 months were higher for patients younger than 80 years than those 80 years and older, although both declined at a similar pace with longer treatment intervals. Absolute rates were also higher at all time points (with parallel declines with longer symptom onset-to-reperfusion time) for patients with moderate-presenting neurologic deficits (NIHSS score, 10-19) compared with severe (NIHSS score, ≥20). In contrast, although longer symptom onset-to-reperfusion times were associated with a lower frequency of functional independence for M1 MCA occlusions, these longer times tended not to be associated with functional independence rates for ICA occlusions. ICA occlusions had relatively modest rates of functional independence at all analyzed symptom onset-to-reperfusion intervals. Potentially, patients with ICA occlusions who were prone to rapid infarct progression were excluded from the studies by the requirement for small or moderate core infarct size at entry. Patients receiving IV tPA had steeper declines in functional independence with longer symptom onset-to-reperfusion times than tPA-ineligible patients. These findings may reflect that the comorbidities constituting contraindications to tPA in the tPA-ineligible patients limited their ability to achieve high functional independence rates, even when reperfusion occurred early.

The results of this study reinforce guideline recommendations to pursue endovascular treatment when arterial puncture can be initiated within 6 hours of symptom onset,[7-9] and provide evidence that potentially supports strengthening of recommendations for treatment from 6 through 7.3 hours after symptom onset. Although point estimates suggested that benefit may continue to accrue up to and beyond 8 hours, there were insufficient numbers of patients in the extended time window to provide firm insights. These observations underline the importance of enrollment of brain imaging–selected patients in ongoing randomized trials evaluating endovascular reperfusion patients in longer time windows (NCT02142283, NCT02586415).

The findings also provide data useful for the refinement of guidelines on speed-of-care processes in patients undergoing endovascular reperfusion. The process time intervals in the pooled trial data set fall between the extremely lenient current multispecialty recommendations and extremely stringent ideal recommendations.[20,21] These time windows represent a good foundation upon which to further improve in practice as centers become proficient at routinely performing endovascular therapies and the need to obtain research-informed consent is no longer present. For continuous quality improvement programs, reasonable time targets for care processes might be those near the best 25th percentile in the pooled trial database, which would include 50 minutes for brain imaging–to–arterial puncture time, 75 minutes for emergency department door-to-arterial puncture time, and 110 minutes for emergency department door-to-reperfusion time.

Several potential limitations should be considered in interpreting the results of this study. First, differences in entry criteria and patient characteristics among the trials is a source of potential bias; random-effects models were used to mitigate potential confounding. Second, several different time intervals in the delivery of endovascular thrombectomy are potentially relevant when analyzing treatment delay and

treatment group interaction, including symptom onset to randomization, symptom onset to expected procedure start, and symptom onset to expected reperfusion. The primary analysis used the time interval that is the focus of national guideline recommendations, symptom onset to expected arterial puncture, and results for other intervals were also analyzed.[7-9] Third, functional outcomes were assessed at 3 months. Some further improvement may occur subsequently, especially among patients with more severe strokes. However, studies have shown that functional status at 3 months correlates well with functional status at 1 year.[30] Fourth, the definition of symptomatic intracranial hemorrhage varied in minor ways across studies; to mitigate this, a uniform radiologic variable was also examined—major parenchymal hematoma. Fifth, the results of this study are not generalizable to patients who would not meet the entry criteria of the component trials. However, the pooled patients were treated at many centers in multiple countries on 4 continents, suggesting wide applicability.

Conclusions

In this individual patient data meta-analysis of 5 randomized clinical trials of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit was greatest with time from symptom onset to arterial puncture for thrombectomy of under 2 hours and became nonsignificant after 7.3 hours.

ARTICLE INFORMATION

Correction: This article was corrected online for an error in eTable 7 of Supplement 2 on December 19, 2016.

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