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Association of Reperfusion After Thrombolysis With Clinical Outcome Across the 4.5- to 9-Hours and Wake-Up Stroke Time Window

A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials

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IMPORTANCE Intravenous alteplase reduces disability after ischemic stroke in patients 4.5 to 9 hours after onset and with wake-up onset stroke selected using perfusion imaging mismatch. However, whether the benefit is consistent across the 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke epochs is uncertain.

OBJECTIVE To examine the association of reperfusion with reduced disability, including by onset-to-randomization time strata in the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) randomized clinical trials.

DESIGN, SETTING, AND PARTICIPANTS Individual patient meta-analysis of randomized clinical trials performed from August 2001 to June 2018 with 3-month follow-up. Patients had acute ischemic stroke with 4.5-to 9-hours poststroke onset or with wake-up stroke were randomized to alteplase or placebo after perfusion mismatch imaging. Analysis began July 2019 and ended May 2020.

EXPOSURES Reperfusion was defined as more than 90% reduction in time to maximum of more than 6 seconds' lesion volume at 24- to 72-hour follow-up.

MAIN OUTCOMES AND MEASURES Ordinal logistic regression adjusted for baseline age and National Institutes of Health Stroke Scale score was used to analyze functional improvement in day 90 modified Rankin Scale score overall, including a reperfusion × time-to-randomization multiplicative interaction term, and in the 4.5- to 6-hours, 6- to 9-hours, and wake-up time strata. Symptomatic hemorrhage was defined as large parenchymal hematoma with a National Institutes of Health Stroke Scale score increase of 4 points or more.

RESULTS Reperfusion was assessable in 270 of 295 patients (92%), 68 of 133 (51%) in the alteplase group, and 38 of 137 (28%) in the placebo reperfused group ($P < .001$). The median (interquartile range) age was 76 (66-81) years in the reperfusion group vs 74 (64.5-81.0) years in the group with no reperfusion. The median (interquartile range) baseline National Institutes of Health Stroke Scale score was 10 (7-15) in the reperfusion group vs 12 (8.0-17.5) in the no reperfusion group. Overall, reperfusion was associated with improved functional outcome (common odds ratio, 7.7; 95% CI, 4.6-12.8; $P < .001$). Reperfusion was associated with significantly improved functional outcome in each of the 4.5- to 6-hours, 6- to 9-hours, and wake-up time strata, with no evidence of association between time to randomization and beneficial effect of reperfusion ($P = .63$). Symptomatic hemorrhage, assessed in all 294 patients, occurred in 3 of 51 (5.9%) in the 4.5- to 6-hours group, 2 of 28 (7.1%) in the 6- to 9-hours group, and 4 of 73 (5.5%) in the wake-up stroke in patients treated with alteplase (Fisher $P = .91$).

CONCLUSIONS AND RELEVANCE Strong benefits of reperfusion in all time strata without differential risk in symptomatic hemorrhage support the consistent treatment effect of alteplase in perfusion mismatch–selected patients throughout the 4.5- to 9-hours and wake-up stroke time window.

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Supplemental content

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Intravenous thrombolysis has been shown to improve functional outcome in patients with favorable perfusion imaging 4.5 to 9 hours after they were last known to be well and within 9 hours of the midpoint of sleep for those who wake with stroke symptoms. The impetus for the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND)[1] and European Cooperative Acute Stroke Study-4: Extending the Time for Thrombolysis in Emergency Neurological Deficits (ECASS4-EXTEND)[2] trials was the evidence from Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE)[3] and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)[4] studies that reperfusion improved outcome in patients with favorable perfusion imaging 3 to 6 hours after stroke onset and that alteplase increased reperfusion. EXTEND[1] and the subsequent systematic review and individual patient data meta-analysis[5] with ECASS4-EXTEND[2] and EPITHET[4] demonstrated overall benefit of intravenous alteplase with no statistical heterogeneity between the 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke strata. However, approximately 50% of patients had wake-up stroke, and therefore, the number of patients treated at 4.5 to 6 hours and 6 to 9 hours was relatively small. Therefore, we performed an analysis of functional outcomes by reperfusion status to further explore the benefits of treatment more than 4.5 hours after stroke onset.

Key Points

Question Does the benefit of reperfusion in patients with ischemic stroke with perfusion imaging mismatch vary in trials of intravenous thrombolysis beyond 4.5 hours?

Finding In this meta-analysis of 2 randomized clinical trials that included 295 patients, reperfusion was strongly associated with improved functional outcomes in 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke time epochs with no heterogeneity in the beneficial association of reperfusion with outcomes by time to randomization and similar risk of symptomatic intracerebral hemorrhage.

Meaning These data provide reassurance that the benefits and risks of thrombolysis-induced reperfusion are consistent across the 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke patient groups selected using perfusion mismatch.

Methods

EXTEND[1] was a randomized clinical trial of alteplase vs placebo in 225 patients with computed tomography perfusion- or magnetic resonance perfusion-diffusion mismatch. Mismatch was defined as a difference between the critically hypoperfused (time to maximum, >6 seconds) region and the

Table. Baseline Characteristics of Patients With or Without Reperfusion

Characteristic	No. (%)		*P* value
	Reperfusion	Without reperfusion	
No.	106	164	NA
Age, mean (SD), y	72.4 (12.9)	72.1 (12.4)	.72
Male	49 (46.2)	100 (61.0)	.02
NIHSS score, median (IQR)[a]	10 (7-15)	12 (8-17.5)	.06
Received intravenous alteplase	68 (64.2)	65 (39.6)	<.001
Atrial fibrillation	47 (44.3)	55 (33.5)	.10
Hypertension	73 (68.9)	115 (70.1)	.89
Diabetes mellitus	22 (20.8)	35 (21.3)	.99
Smoking	42 (39.6)	62 (37.8)	.89
Geographic region[b]			
Australia/NZ/Europe	95 (89.6)	133 (81.1)	.11
Asia	11 (10.4)	31 (18.9)	
Stroke onset to randomization time			
4.5 h-6 h	31 (29.2)	46 (28.0)	.99
6 h-9 h	21 (19.8)	32 (19.5)	
Wake-up strokes	54 (50.9)	86 (52.4)	
Time from stroke onset to initiation of intravenous therapy, median (IQR), min[c]	476 (360-671)	491.5 (355-658)	.95
Imaging			
Large vessel occlusion, No./total No. (%)[d]	65/106 (61.3)	125/164 (76.2)	.01
Ischemic core volume at initial imaging, median (IQR)[e]	7.3 (0-18.2)	9.9 (0-29.0)	.04
Perfusion lesion volume at initial imaging, median (IQR)[f]	57.2 (31.4-113.6)	85.2 (52.4-133.3)	<.001

Abbreviations: IQR, interquartile range; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NZ, New Zealand.

[a] Scores on the NIHSS range from 0 (normal) to 42 (death), with lower scores indicating less severe stroke.

[b] Geographic region defined as Australia/NZ/Europe (Finland) vs Asia (Taiwan).

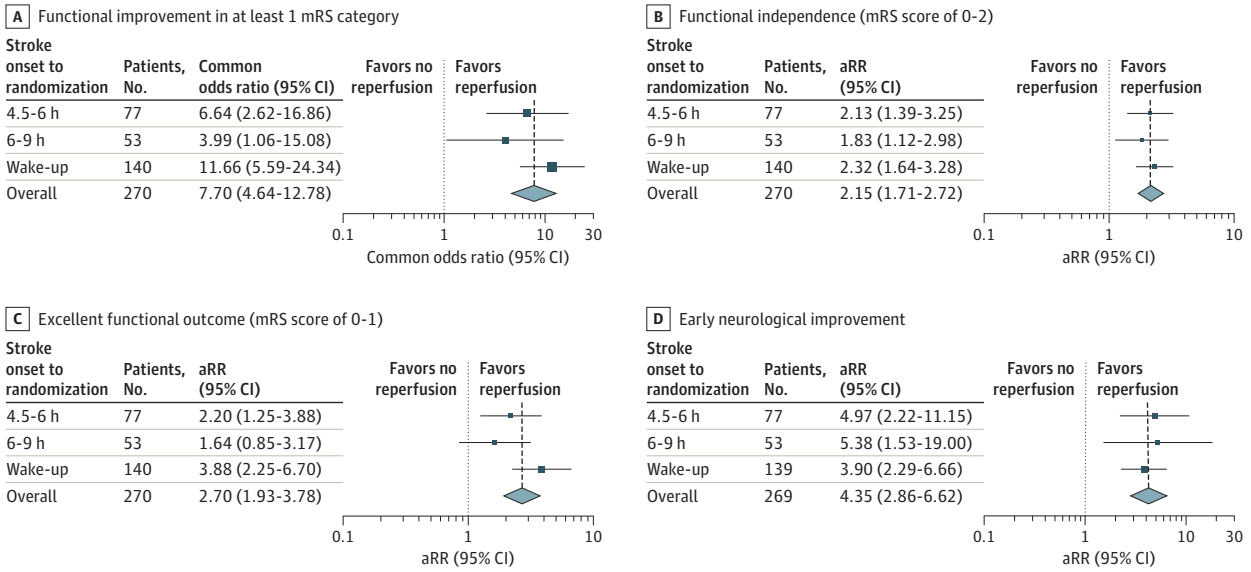
[c] Stroke onset defined as the time the patient was last known to be well.

[d] Large vessel occlusion defined as occlusion of the internal carotid artery, first division middle cerebral artery, and proximal portion of the second division of middle cerebral artery.

[e] Ischemic core volume defined as relative cerebral blood flow less than 30% of the normal brain tissue.

[f] To define the ischemic tissue at risk of infarction, a perfusion lesion was defined as one with time to maximum delay of more than 6 seconds.

Figure 1. Forest Plot of the Association of Reperfusion With Functional Outcome Assessed Using the Modified Rankin Scale (mRS) at 90 Days by Time to Randomization Epoch and Overall



A, Functional improvement by at least 1 mRS category (ordinal analysis merging categories, 5-6). B, Functional independence (mRS score, 0-2). C, Excellent functional outcome (mRS score, 0-1). D, Early neurological improvement (8-point reduction in National Institutes of Health Stroke Scale score or reaching 0-1 at day 3). aRR indicates adjusted risk ratio.

irreversibly injured ischemic core (estimated as relative cerebral blood flow <30% of normal brain[6]) of more than 10 mL; a mismatch ratio of critically hypoperfused to ischemic core volume more than 1.2; and a core volume less than 70 mL. Mismatch was automatically determined using RAPID software (iSchemaView) to assess eligibility for the trial. The details of methodology[7] and main results[1] have been published previously. EPITHET[4] was a randomized clinical trial of alteplase vs placebo in 100 patients who were treated 3 to 6 hours after stroke onset (this analysis only included those treated 4.5 to 6 hours after onset). All patients had magnetic resonance perfusion-diffusion imaging, but mismatch was not required for study eligibility. Reperfusion was defined as more than 90% reduction in time to maximum of more than 6 seconds' lesion volume between baseline and 24-hour perfusion imaging in EXTEND[1] and between baseline and day 3 imaging in EPITHET.[4] Only patients with known reperfusion status were included in this meta-analysis, which followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline of individual participant data. Data from ECASS4[2] (the only other relevant trial in the systematic review[5]; eFigure 1 in the Supplement) were not included because follow-up perfusion imaging was not routinely acquired. The studies were approved by the Melbourne Health Human Research Ethics Committee, and all participants or their legal representative gave written informed consent. The data that support these analyses are available from the corresponding author on request. Data were collected between August 2001 and June 2018.

Functional outcome was assessed by clinicians who were blinded to treatment allocation at 90 days after stroke using the modified Rankin Scale (mRS). The National Institutes of Health Stroke Scale (NIHSS) score was assessed pretreatment and at day 3. Early neurologic improvement was defined as a reduction of 8 points or more on the NIHSS between baseline and 3 days or reaching 0 to 1. Symptomatic hemorrhage was defined as parenchymal hematoma type 2 (occupying >30% of the infarcted territory with mass effect) associated with an NIHSS increase of 4 points or more within 36 hours of treatment.[8]

Statistical analysis was performed using Stata version 15 (StataCorp). Ordinal logistic regression was used to analyze the entire range of the mRS at 90 days (merging categories 5-6), adjusted for baseline NIHSS score and age and including a reperfusion × time-to-randomization multiplicative interaction term. A fixed effect term for trial of origin was also included in the models to account for differences between EXTEND[1] and EPITHET.[4] The association of reperfusion with functional independence (mRS score, 0-2), excellent functional outcome (mRS score, 0-1), and early neurological improvement were also analyzed using modified Poisson regression with robust error estimation,[9] adjusted for baseline NIHSS score and age. The analyses were repeated in the 4.5- to 6-hours, 6- to 9-hours, and wake-up time strata. Two-sided *P* values were significant at .05.

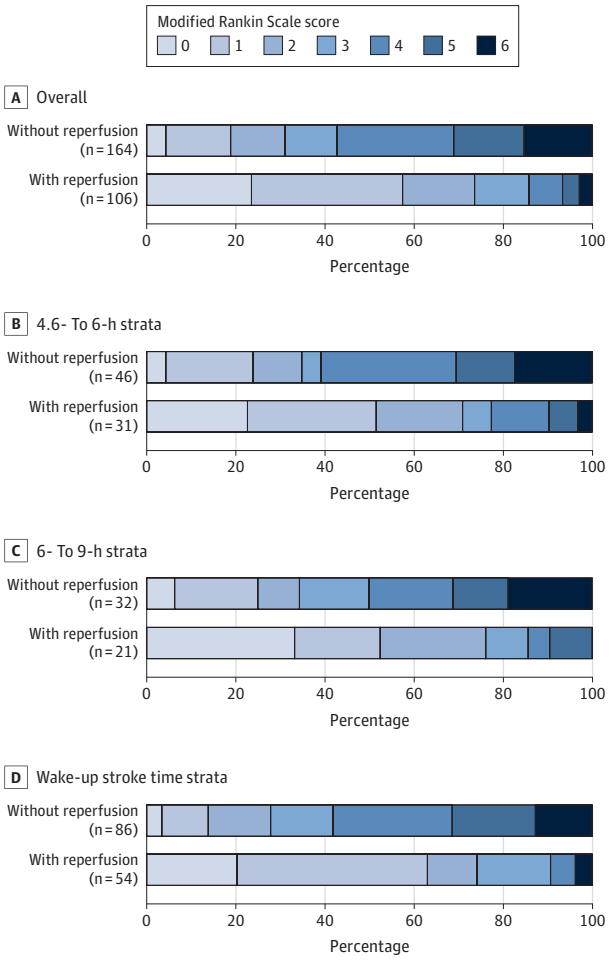
A secondary analysis was performed in the subgroup who met the EXTEND trial[1] mismatch criteria based on core laboratory automated perfusion mismatch assessment: imaging data were reprocessed at the central core laboratory using

RAPID software and an experienced imaging scientist (B.C.V.C.), blinded to treatment group and reperfusion status, reviewed all RAPID output and removed artifacts. Analysis began July 2019 and ended May 2020.

Results

Reperfusion was assessable in 270 of 295 patients (92%), which included 215 of 225 patients (95.6%) from EXTEND[1] and 55 of 70 patients (78.6%) from EPITHET.[4] The median (interquartile range [IQR]) age was 75 (65-81) years, and 149 of 270 (55%) were male. Alteplase was associated with significantly increased reperfusion vs placebo (alteplase: 68 of 133 [51%] vs placebo: 38 of 137 [28%]; risk ratio, 1.84; 95% CI, 1.34-2.53; $P < .001$). Patients with reperfusion vs without reperfusion did not differ significantly in median (IQR) age (76 [66-81] years vs 74 [64.5-81] years) or median (IQR) baseline NIHSS score (10 [7-15] vs 12 [8.0-17.5]). Patients with reperfusion had smaller core and hypoperfusion lesion volumes and were less likely to have large vessel occlusion (**Table** and eTable 1 in the Supplement). In ordinal logistic regression analysis, reperfusion was associated with a common odds ratio of 7.7 (95% CI, 4.6-12.8; $P < .001$) for improvement by at least 1 mRS category. In each of the 4.5- to 6-hours, 6- to 9-hours, and wake-up time strata, reperfusion was associated with significant improvements in ordinal analysis of mRS score, mRS score of 0 to 2, and early neurological improvement, but the 95% CI crossed unity for mRS score of 0 to 1 in the 6- to 9-hours group (**Figure 1** and **Figure 2**). No evidence of association between time to randomization and beneficial effect of reperfusion was found ($P = .63$; Figure 1A). Results in 226 of 270 patients (83.7%) who met automated perfusion mismatch criteria were similar (eFigure 2 and eTable 2 in the Supplement). Symptomatic hemorrhage, assessed in all 295 patients, occurred in 3 of 51 (5.9%) in the 4.5- to 6-hours group, 2 of 28 (7.1%) in the 6- to 9-hours group, and 4 of 73 (5.5%) in the wake-up stroke in the alteplase-treated patients (Fisher $P = .91$; eTable 3 in the Supplement).

Figure 2. Distribution of Modified Rankin Scale in All Patients With and Without Reperfusion



Discussion

This study has demonstrated strong and consistent benefits of reperfusion in patients with favorable perfusion imaging in each of the 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke strata of onset-to-treatment time in the EXTEND[1] and EPITHET[4] trials. There was no evidence of differential risk of symptomatic intracerebral hemorrhage in these strata. This provides reassurance that the benefits of intravenous alteplase are also likely to be consistent across the strata in patients with perfusion mismatch.

Our results are consistent with the neutral effect of time to treatment in previous studies of perfusion mismatch–selected patients treated with both intravenous thrombolysis[3] and endovascular thrombectomy[10-13] beyond standard time windows. There was little difference in the association of reperfusion with outcomes between those originally included in the studies and those who met perfusion mismatch criteria on central reanalysis by the core laboratory. However, the number of patients excluded by central reanalysis was small and mainly affected the 4.5- to 6-hours stratum, contributed to by the EPITHET study.[4]

Limitations

Limitations of this study include that the true onset time in these patients was often unknown and may have been within 4.5 hours in some patients. However, all of these patients were ineligible for thrombolysis using the standard criterion of less than 4.5 hours since the patient was last known to be well. Patients excluded because of lack of reperfusion data may have been more severely affected. The assessment of reperfusion at 24 hours in EXTEND[1] and 3 days in EPITHET[4] may have included patients who had reperfusion too late to salvage the hypoperfused brain regions. However, the effect of this would be to reduce the strength of the observed association between reperfusion and functional outcome.

Conclusions

In conclusion, reperfusion was associated with improved functional outcome within the 4.5- to 6-hours, 6- to 9-hours, and wake-up stroke epochs with no evidence of an interaction by the time since last known well to treatment. The risk of symptomatic intracerebral hemorrhage appeared stable across time epochs. These data provide support for implementation of intravenous thrombolysis in patients who fall within the full time window up to 9 hours since last known well or midpoint of sleep and who were eligible in the EXTEND trial.[1] Further trials will test whether intravenous thrombolysis can benefit patients with perfusion mismatch up to 24 hours after the time they were last known to be well (NCT03785678 and NCT04454788).

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Statistical analysis: Campbell, Churilov, Sharma, Bivard.
Obtained funding: Levi.
Administrative, technical, or material support: Hsu, Wijeratne, Sharma, Bivard.
Supervision: Parsons, Yan, Desmond, Levi, Bivard, Donnan, Davis.

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