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After European Cooperative Acute Stroke Study 3 Mission Accomplished?

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The results of the third European Cooperative Acute Stroke Study (ECASS 3) show that patients with acute stroke, who could not make it to the hospital within the 3-hour treatment time window, still have a chance to benefit from intravenous alteplase if they can be treated within 4.5 hours of stroke onset.¹ They will not be exposed to an increased risk of brain hemorrhage compared with patients being treated earlier. The European Medicines Agency required this trial with its relatively close treatment time window, because authorities were afraid of an increased risk for patients treated after 3 hours. After approval to treat patients with stroke with alteplase until 4.5 hours after symptom onset, more patients being remote from stroke centers and brain imaging facilities will get a chance to be treated. However, “having more time does not mean we should be allowed to take more time” as the authors pointed out.¹ The door-to-needle time should be kept short giving the patients the best chances for recovery.

What is the probability that a patient with acute stroke will recover due to treatment with alteplase? In ECASS 3, 221 of 403 placebo-treated patients (55%; 95% CI, 50% to 60%) were disabled or dead (modified Rankin Scale [mRS]: 2 to 6) at 3 months after stroke and 199 of 418 alteplase-treated patients (48%; 95% CI, 43% to 52%; intent-to-treat analysis). This means that 7% of patients had a treatment benefit, but 93% of the patients had none corresponding to a number needed to treat of 14. To show an effect beyond chance in 29 patients, 821 patients had to be exposed to placebo or alteplase. The modest effect size is similar to that of other randomized, controlled trials on alteplase in acute ischemic stroke (Table); 87% to 98% of patients had no benefit from this treatment.

Although the effect size is in the range of other treatments, eg, the treatment of acute myocardial infarction, and is regarded as one of the most effective treatments in internal medicine,² the challenging question remains why so many patients do not benefit from intravenous alteplase infusion and, more importantly, how the effect size can be increased.

The effect may be even smaller in patients not included in these studies, eg, the elderly >80 years and patients being admitted later.

We have several answers that are quite simple or more sophisticated. A considerable proportion of patients (26% to 45% in randomized, controlled trials; Table) has a spontaneous good prognosis and does not need thrombolysis. It can be presumed that most of these patients do not have an occluded artery when treatment is initiated. A review of angiography studies revealed nonocclusion or early spontaneous recanalization in 221 of 775 patients (29%; 95% CI, 25% to 32%) within 6 hours of stroke onset.³ Other patients were falsely randomized. In ECASS 3, 43 patients in the alteplase group (10.3%) were excluded from per protocol analysis because they did not receive treatment, had uncontrolled hypertension, or did not meet the age or CT criteria (no brain hemorrhage or major ischemic lesion). Excluding these patients would have enhanced the effect size from 7% to 10% showing that at least some of the prespecified exclusion criteria were justified.

Another popular consideration is that major portions of ischemic brain tissue are already infarcted when alteplase is going to lyse the clot. The clear association between time to treatment and effect size illustrates that brain tissue can be rescued if arterial recanalization can be achieved early and justifies the slogan “time is brain.” What do we gain if we treat early with intravenous alteplase? Following the pooled analysis⁴ of randomized, controlled trials with alteplase, the absolute reduction of disability and death (mRS: 2 to 6) by alteplase is 12% for patients being treated within the first 90 minutes of symptom onset, 13% for treatment between 91 and 180 minutes, 5% for treatment between 181 and 270 minutes, and 1% for treatment between 271 and 360 minutes (Figure).

Accordingly, 87% of patients with stroke have no benefit even with early alteplase treatment. We cannot, thus, explain the missing treatment effect of alteplase with treatment delay for the majority of patients. The widespread emphasis on “mismatch” on acute stroke imaging and the assessment of

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Table. Disability and Death at 3 Months After Ischemic Stroke and Treatment With Alteplase in Randomized, Controlled Trials

Study	TTW (hours)	N		NIHSS (median)		Disability/Death mRS: 2–6		Effect Size	
		Placebo	Alteplase	Placebo	Alteplase	Placebo	Alteplase	Absolute	NNT
ECASS	0–6	307	313	13	12	71%	64%	7%	14
NINDS II	0–3	165	168	15	14	74%	61%	13%	8
ATLANTIS B	3–5	275	272			68%	66%	2%	50
ECASS 2	0–6	391	409	11	11	63%	60%	3%	33
ECASS 3	3–4.5	403	418	10	9	55%	48%	7%	14

TTW indicates treatment time window; NIHSS, National Institutes of Health Stroke Score; Effect Size, absolute reduction of disability and death at 3 months due to treatment with alteplase; NNT, number needed to treat; NINDS, National Institute of Neurological Disorders and Stroke rPA Stroke Study; ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke.

ischemic brain tissue at risk ignores that tissue at risk is very common in patients with acute stroke even after 6 hours.^{5,6} This discussion creates a distraction from other factors affecting the effectiveness of intravenous thrombolytics. The absence or presence of ischemic penumbra may predict whether the patient will benefit from reperfusion only if recanalization can be achieved, but does not predict whether alteplase will successfully recanalize obstructed arteries. It can be presumed that failure of arterial recanalization is the best explanation for the failure of alteplase in the majority of patients.

Unfortunately, in all randomized, controlled trials testing alteplase, the pathology and site of arterial occlusion and the time of recanalization were not recorded. We do not know how many patients without arterial occlusion were treated, whether recanalization was achieved, whether and when recanalization led to reperfusion, whether reocclusion hampered the effect of recanalization, and in which patient was recanalization associated with clinical recovery. Using digital subtraction angiography >10 years ago, we observed partial and complete recanalization in 22 of 77 patients with acute hemispheric stroke (29%; 95% CI, 20% to 39%) being treated with intravenous and intra-arterial thrombolysis.⁷ A recent Doppler ultrasound-based study found complete recanalization of the middle cerebral artery (stem and branches) in 32% of 99 alteplase-treated patients at 6 hours after stroke onset and partial recanalization in 21%.⁸ No recanalization was associated with disability and death (mRS: 3 to 6) in 90% (74% to 97%), whereas full recanalization was associated with disability and death in 14% (3% to 51%) of patients only and partial recanalization in 64% (39% to 84%), meaning that full recanalization reduced the risk of disabling stroke for

76% of patients and partial recanalization for 26%. A meta-analysis of the impact of recanalization on ischemic stroke outcome revealed good outcome (mRS: 0 to 2) in 51% of patients being recanalized within 6 hours of stroke onset versus 11% of nonrecanalized patients (effect size: 40%).⁹ An analysis of 1905 patients with a hyperdense middle cerebral artery, indicating occlusion, before treatment with alteplase showed that persistence of middle cerebral artery hyperdensity after treatment was associated with disability and death (mRS: 3 to 6) in 81% of 788 patients in contrast to 58% of 831 patients with disappearance of this sign of occlusion.¹⁰ Achieving recanalization seems thus to be approximately 10-fold more effective for clinical outcome after ischemic stroke than the time point of treatment or visualization of penumbra.

Further efforts in stroke research should focus on the target of treatment: the diseased arterial system, the type and volume of clot, and possibilities to identify the best chances for early arterial recanalization. We should study in which type of arterial obstruction thrombolytics fail or achieve recanalization. This is the first step. We should identify factors that inhibit recanalization. Some are already under suspicion: clots with large volumes, calcified clots, nonblood obstructions, some clot within tight stenoses, middle cerebral artery occlusions distally from internal carotid artery stenoses or occlusions,¹¹ and so on. We have now the means to directly diagnose the arterial disease with noninvasive and quick Doppler ultrasound, CT angiography or MR angiography, and vessel wall imaging. Only with the diagnostic test of arterial recanalization can we understand why patients do not improve despite recanalization.

Nevertheless, it is evident that patients with stroke have a chance to get better after minimal diagnostics with nonenhanced CT only and can thus be treated with alteplase widespread and remote from experienced stroke centers. The time for diagnostic testing matters, but guiding successful arterial recanalization is much more important for the patient. We may continue with black box treatment where no other possibilities exist and accept a relatively small effect size. Treatment with alteplase is better than no treatment or late treatment. We should change the paradigm, however, where the diagnostic tools are ready available and test additional and other treatments to achieve recanalization. The effect of

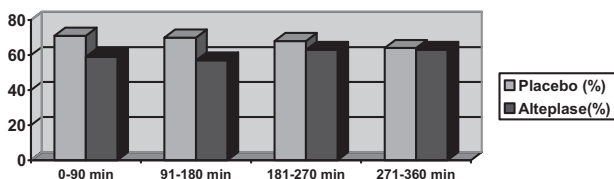


Figure. Patients with disability and death (modified Rankin Scale: 2 to 6) in acute stroke trials with alteplase.⁴

recanalization treatment should be monitored. We can better accomplish our mission if we better understand the conditions for recanalization and subsequent recovery and focus our treatment trials more on the causes of ischemic stroke, the diseased vascular system, and further study the conditions of reperfusion therapy.

Disclosures

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