This is a clear case. Yes! The patient should immediately be treated with the standard dose of rt-PA as per approval in Europe and many other countries on this planet. After the results of all pooled analyses (National Institute of Neurological Disorders and Stroke [NINDS], European Cooperative Acute Stroke Study 1–2 [ECASS 1–2], Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]), Cochrane Analyses, Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR), and others,1 the effect size with an odds ratio for a favorable (modified Rankin Scale, 0–1) versus unfavorable outcome was established at ≈1.4 from 3 to 4.5 hours. Safety in terms of bleedings did not differ from what was seen within the first 3 hours and neither did mortality. Then came ECASS 3, positive for the primary end point.2 The European conditional approval was changed to a full approval in 2010 by the European Medicines Agency (EMA) taking the congruent results of the pooled analyses, meta-analyses, SITS-ISTR, and ECASS 3 into account. According to label and guidelines, this patient fulfills all criteria for treatment also in a legal obligatory sense in the country of these authors. Apart from that, in many countries, withholding a treatment that is off label but where there is firm scientific evidence that it causes benefit and no harm can be judged and accounted for as malpractice by court with all due consequences.

Is advanced imaging necessary to make this decision? Why, No?! Would a lacunar versus nonlacunar syndrome make a difference here? No!! It would not make a difference within 3 hours, would it? And what about an MRI without perfusion imaging/diffusion weighted imaging mismatch or with proof of a lacunar stroke, would this make a difference? Hell, no!!! There is no evidence at all for this conclusion. And is there any reason to believe that rt-PA does not work in the 3- to 4.5-hour time window or that it does work only in "a carefully selected set of patients"? What the h…, No, No No!!!! It is a widely held misbelief that ECASS 3 looked at carefully selected patients only. In fact, ECASS 3 inclusion criteria followed exactly the stricter label of rt-PA as it was given by the EMEA in 2002 and extended in 2004, with 1 exception, the 3- to 4.5-hour time window. By label, Europe and many other countries exclude patients >80, National Institutes of Health Stroke Scale >25, diabetes mellitus and...
prior stroke, among other criteria, from intravenous thrombolysis. It is daily practice, however, that these criteria are not followed to the letter, especially after several analyses from the Virtual International Stroke Trials Archive (VISTA) group and thrombolysis trialists (references 15–18, 20–21, and 28, summarily discussed in Frank et al3), as well as IST-3. In fact, even IST-3, a randomized off-label thrombolysis trial, was nearly positive for the primary end point and positive for a change across the whole range of the Oxford Handicap Scale (which in practical terms is nearly identical to the modified Rankin Scale). Furthermore, most countries on this planet have a label similar or equal to the European label including the whole of Europe, Australasia, Russia, some countries in Africa and South America. In fact, the US label is the exception to the rule, not vice versa. As a consequence, in countries such as Germany, currently 10% of all patients with ischemic stroke receive thrombolytic therapy, with much lower door-to-needle times than recently reported in a Get With the Guidelines study, where only 18% of the golden hour patients received rt-PA within 60 minutes from door to needle.5

Final Comments

1. These authors understand the difficulty of adapting a label change in the United States and Canada, necessitating 2 different labels for the 2 time windows as opposed to Europe, where just the time window was extended.

2. These authors cannot follow the actual class I level B rating of thrombolysis within 3 to 4.5 hours1 when compared with the same rating given for, for example, decompressive surgery in space occupying cerebellar infarction or thrombectomy. Strikingly, there seemed to be little hesitation to treat many patients with thrombectomy during the past few years with no evidence-based proof of efficacy over standard intravenous thrombolysis.

3. For us, as stroke physicians in a country were the described patient falls into the label of rt-PA, which is based on clear evidence from many analyses and more importantly a positive randomized controlled large clinical trial, there is only 1 rational conclusion to the question: the patient must be treated, quod erat demonstrandum.

Disclosures

Drs Schellinger and Köhrmann received honoraria, travel grants, and consulting fees from Boehringer Ingelheim and Cerevast, and both are members of the steering committee for ECASS 4 EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) and CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke).

References


Key Words: controlled clinical trials, randomized ▪ stroke ▪ thrombolytic therapy
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