Eight years have passed since the US Food and Drug Administration approved recombinant tissue plasminogen activator (rtPA) for stroke thrombolysis. The regulatory authorities of Canada approved it in 1999 and those of Germany in 2000. The European Agency for the Evaluation of Medicinal Products (EMEA) approved it for all member states in 2002, although only conditionally. One condition was that all treated patients must be included in a register, the Safe Implementation of Thrombolysis in Stroke: a Multinational, Multicenter Monitoring Study of Safety and Efficacy of Thrombolysis in Stroke (SITS-MOST). The conditional approval of EMEA made stroke thrombolysis available for many more Europeans. Finally, we had a drug that had been shown effective in acute ischemic stroke and was approved in most developed countries. However, has it changed the way acute ischemic strokes are treated? The answer is no, or, to be exact, not on as wide a scale as it could have. Doctors and medical centers have been slow in changing their practices. And the reasons for it.2 Unfounded allegations have tried to deny the possibility of benefiting from thrombolytic therapy.8 Recently published series indicate that when patients are treated outside trials, doctors weigh the risks and benefits for individual patients, and then age alone is not an exclusion criterion in experienced hands.8-11

Many reliable data have been generated through systematic reviews. When the data sets of all 6 randomized IV rtPA trials (ie, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS], the European Cooperative Acute Stroke Study [ECASS], and the NINDS rtPA trials) were merged into a large data pool of 2775 acute stroke patients and analyzed, this pooled analysis clearly verified the safety and efficacy of thrombolysis within 3 hours from the onset of symptoms. It also suggested that the time window might be longer, possibly 4.5 hours, although all trials having a >3-hour time window had been underpowered to reveal it.7 The results of the pooled analysis confirmed the strong association between rapid treatment and favorable outcome. Odds of a favorable 3-month outcome increased as onset-to-treatment time decreased. Odds were 2.8 (95% CI, 1.8 to 4.5) for 0 to 90 minutes, 1.6 (95% CI, 1.1 to 2.2) for 91 to 180 minutes, 1.4 (95% CI, 1.1 to 1.9) for 181 to 270 minutes, and 1.2 (95% CI, 0.9 to 1.5) for 271 to 360 minutes in favor of the rtPA group. Hemorrhages were not associated with the onset-to-treatment time but only with rtPA treatment and age (ie, rtPA increased the risks of bleeding and so did age). Elderly patients had a higher risk of bleeding compared with younger patients.7 The role of age was obvious in the German Stroke Register1 and in the Calgary experience8 as well as in Ontario.9 The age and severity of stroke increase the risk of poor functional outcome and death. Thrombolysis cannot eliminate these basic predictors of stroke outcome as verified by the German and Canadian studies,1,8,9 but it is more important to keep in mind that thrombolysis with rtPA is by far the best acute therapy for their ischemic stroke for elderly patients as well as those with severe stroke. The pooled analysis revealed that mortality and disability are highest in early treatment intervals and that severity of stroke and age influence the outcome. This was clearly visible in the outcome of control patients randomized to receive placebo treatment. Furthermore, the therapeutic effect of rtPA was greater in those treated early despite more severe stroke.7 Early treatment significantly enhances the likelihood of confining the long-term disability to a minimum. The same holds true for elderly patients who have high mortality and morbidity from acute stroke but when treated with rtPA, have a symptomatic hemorrhage rate similar to that in younger patients treated with thrombolytics and a mortality rate similar to the natural history in older patients without rtPA. Accordingly, stroke patients >80 years of age should not be denied the possibility of benefiting from thrombotic therapy.8

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Stroke is available at http://www.strokeaha.org
Doubters of stroke thrombolysis still ponder whether the results of randomized controlled trials can be reproduced in the community. This was a reason why EMEA ordered that all treated patients must be enrolled in the SITS-MOST register to enable continuous monitoring of safety. There are already many data to verify the safe use of rtPA outside randomized trials, and more emerge continuously. Graham’s meta-analysis on safety of open series with 2639 patients showed a mean 13.4% death rate (i.e., better than that in the NINDS rtPA trial; 17.0%). The mean of symptomatic intracerebral hemorrhages was 5.2% in Graham’s meta-analysis and 6.4% in the NINDS trial. The mean of very favorable outcome was 37.1% in the meta-analysis and 39.0% in the NINDS trial. The case mix could not explain the good results of the open studies. In the NINDS rtPA trial and in Graham’s meta-analysis, the median pretreatment NIHSS score was 14. After Graham’s meta-analysis, many more open series have been published with similar results. Graham’s meta-analysis also revealed that the mortality rate was correlated with the percentage of protocol violations. Inexperience in delivering thrombolysis worsened the efficacy of treatment in the German Stroke Register. According to this register, there was an inverse relationship between the number of patients treated with rtPA and the risk of in-hospital death. In experienced centers, which followed published guidelines for IV thrombolysis, the results mirror the results of the pivotal NINDS rtPA trial. It is encouraging that the results of randomized clinical trials can be duplicated in the community. There are many ways how this target can be achieved. In rural areas, airlifts for stroke are an alternative. Stillman et al showed that it is possible to increase the number of ischemic stroke patients treated with thrombolytics up to 38% by establishing a coordinated program that links local emergency medical services and a comprehensive stroke center via a helicopter-based transport system. Another possibility is to organize a rural stroke network backed by a tertiary care center with a comprehensive stroke unit. The OSF Stroke Network experience verified that thrombolysis can be provided successfully at hospitals located in small towns. After the thrombolytic treatment, patients can be transferred to a comprehensive stroke center, if needed, and the results duplicate those of the NINDS trial. A more advanced system using modern telemedicine not only allows the transfer of the results of emergency computed tomography or MRI to a comprehensive stroke unit but also makes it possible to evaluate the patient via video transmission. The physician responsible for the care of a stroke patient in a rural hospital and a stroke specialist in a comprehensive stroke unit can evaluate the patient online and select the most appropriate therapy individually. The experience of the Telemedicine in Stroke in Swabia (TESS) study group demonstrated that this is feasible. Furthermore, investments per participating hospital were modest, at $8000 US dollars each. The early results of the SITS-MOST register presented at the 29th International Stroke Conference in San Diego, Calif, in February 2004 showed that thrombolysis can be equally well administered at the community level in Europe as in the USA.
present 3-hour time window is higher per million inhabitants in Finland than in any other European Union member country, although Finland is one of the largest and least densely populated countries of the union. Distances in northern Finland are long, but if a patient experiences an ischemic stroke at the Arctic Circle in Finnish Lapland, he/she has a fair chance to receive thrombolysis. If one has to experience stroke, Helsinki is the best place to have it because more patients have been enrolled in the SITS-MOST register in Helsinki than in any other European city. The Finnish experience shows that it is possible to improve the chain of recovery not only in your community but nationwide. It only takes motivation, education, and hard work to deliver thrombolysis for those eligible and in need of it.

References


Key Words: Advances in Stroke ■ emergency medical services ■ stroke, acute ■ stroke, ischemic ■ stroke outcome ■ thrombolysis ■ thrombolytic therapy
Thrombolysis: What More Does It Take?
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Stroke. 2005;36:200-202; originally published online January 6, 2005;
doi: 10.1161/01.STR.0000153058.54341.72
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
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