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: 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. Of ischemic stroke patients treated in community hospitals, only 1.6% to 2.7% receive thrombolysis, and of those treated in academic hospitals or specialized stroke centers, only 4.1% to 6.3% receive thrombolysis.¹ There are many practical reasons for it.² Unfounded allegations have tried to deny the results of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial,³ but the results from reanalysis of the NINDS trial verified the original observations.⁴ Although there is a need for more information about many still open questions related to delivery of thrombolysis for stroke patients,⁵ a far more burning problem is how to administer thrombolysis in a community on a wide scale. Even in many parts of the developed world, basic resources for good care of stroke patients need to be built to develop a well functioning stroke triage.⁶

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 greatest 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 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
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 (ie, 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.1–10,12–13

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, airflights for stroke is 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 online 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 the 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. The results of the register were similar to the results of the pooled analysis of ATLANTIS, ECASS, and NINDS rtPA trials. The mean death rate was 17%, and the rate of symptomatic intracerebral hemorrhage was 3.3%, defined as clinical deterioration of ≈4 points on the NIHSS combined with large intracerebral hemorrhage. These outcome parameters have since then stayed at the same level, whereas the number of patients in the register is increasing fast. At present, more than half of the hospitals involved in the register are inexperienced in administering rtPA for ischemic stroke. The definition of an inexperienced center in the SITS-MOST register is a stroke center that was not involved in ECASS or ECASS II trials or has treated <5 ischemic stroke patients with IV rtPA before joining the SITS-MOST register.

NINDS sponsored a symposium titled Improving the Chain of Recovery for Acute Stroke in Your Community December 12–13, 2002, in which the NINDS Task Force proposed practical recommendations how to conquer the obstacles preventing wide-scale administration of thrombolysis. The summary of the symposium was finalized and published by the National Institutes of Health. It includes the following key topics: increasing recognition and rapid response to stroke, choosing your level of care, professional education, templates for organizing stroke triage, incentives for enhancing stroke care, and provider support systems for acute stroke. On the basis of a systematic review of barriers to deliver thrombolysis for acute stroke, Kwan et al listed the following obstacles: the patient or his/her family did not recognize symptoms or failed to seek urgent help, a general practitioner rather than emergency medical services was called first, the paramedics and emergency department staff triaged stroke as nonurgent, delays in neuroimaging, inefficient process of in-hospital emergency stroke care, difficulties in obtaining consent for thrombolysis, and the physicians’ uncertainty about administering thrombolysis. The NINDS Task Force and Kwan et al came to almost identical lists of barriers to be conquered.

Many unsolved questions connected with thrombolysis wait for future trials. The extension of the time window beyond 3 hours could make thrombolysis available to a much larger stroke population. The results of the Desmoteplase In Acute Ischemic Stroke (DIAS) trial published in the January 2005 issue of Stroke suggest that it may be possible to extend the time window for thrombolysis with a new agent up to 9 hours when modern neuroimaging is used to select patients. In randomized trials, the same treatment is given to all eligible patients based on randomization, whereas in clinical practice, doctors must weigh the risks and benefits of all possible treatments for a stroke patient in a complex situation that has never been or most likely never will be studied in randomized clinical trials. Even the best guidelines on how to provide thrombolysis will become outdated sooner or later and should therefore be regularly updated to correspond with the most recent evidence. However, the daily clinical practice does not justify waiting for results of new trials or updated guidelines. If doctors are not willing to evaluate patients and deliver thrombolysis for eligible patients 24 hours per day, 7 days per week, it is a problem that no new trials or updated guidelines can solve. According to the SITS-MOST register, a stroke patient’s likelihood to receive IV rtPA within the
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


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