Thrombolytic Therapy With Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke

Where Do We Go From Here? A Cumulative Meta-Analysis

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Background and Purpose—Recombinant tissue plasminogen activator (rtPA; Actilyse) is not as widely used in clinical practice as it could be. Have new data since 1995 strengthened the evidence sufficiently to justify more widespread use of rtPA?

Methods—We performed a sequential year-to-year cumulative meta-analysis of randomized controlled trials of rtPA in acute ischemic stroke.

Results—Although the amount of data has doubled since 1995, effect estimates for key outcomes remain imprecise, and significant between-trial heterogeneity persists. In the most recent analysis, rtPA up to 6 hours after stroke yielded 55 fewer dead or dependent people per 1000 treated (95% CI, 18 to 92) despite some risk (nonsignificant excess of 19 deaths per 1000 patients treated; 95% CI, 6 fewer to 48 more). Severity of stroke, patient age, and aspirin use were possible sources of heterogeneity.

Conclusions—Despite doubling of the data since 1995, the magnitude of risks and benefits with rtPA remains imprecise. This gap in knowledge may be hindering clinical use of rtPA and can be filled only by new trials designed to address these specific issues. **(*Stroke*. 2003;34:1437-1442.)**

Key Words: meta-analysis ■ stroke, acute ■ stroke, ischemic ■ thrombolytic therapy

Recombinant tissue plasminogen activator (rtPA) is the most promising, yet controversial, treatment for acute ischemic stroke. Some guidelines urge the use of rtPA in selected patients.[1–3] Others have stated that thrombolysis "should be restricted to use in formal research protocols, or closely monitored programs, until there is further evidence that the benefits of this therapy outweigh the risks."[2,4] Although emergency physicians are sued for not using rtPA,[4] <2% of ischemic stroke patients in US community hospitals[5,6] and 6% in university hospitals[4] receive rtPA, and a third of US hospitals in 1 survey did not administer rtPA at all.[7]

Clinicians' concerns about rtPA (lack of a neurologist on site, size of the benefits and harms, lack of acute stroke units, treating older patients) may contribute to the low use of rtPA.[7–11] Perhaps stroke clinicians are unconvinced of the benefits because the adverse events occur close to rtPA administration and are dramatic (intracranial hemorrhage), whereas the benefit may become evident only later and be more apparent to the rehabilitationist. Perhaps the clinicians' reluctance[4,9] reflects a lack of detailed information guiding the treatment of individual patients. The current rtPA randomized trial data consist of about 2955 patients.[12] Despite evidence of benefit up to 6 hours,[12] the many "negative" trials may detract from the 1 "positive" trial.

Thrombolysis in acute myocardial infarction was different at a similar stage in its introduction into clinical practice 20 years ago. Although there was far stronger evidence (7000 patients in 33 trials),[13] the experts were against thrombolysis.[14] However, a meta-analysis of the data available at the time showed consistent evidence that thrombolysis reduced deaths.[14] Large trials[15] verified the meta-analysis, provided convincing evidence of the benefits, and had sufficient power for subgroup analyses to guide individual patient treatment. Clinical practice changed suddenly and dramatically. Cumulative meta-analysis would have made the evidence much clearer earlier, led to more rapid implementation of thrombolysis in routine practice, and avoided many deaths.

Can stroke physicians avoid cardiologists' errors and determine more quickly when there are enough data for rtPA in stroke?[16–18] Cumulative meta-analysis (performing a new meta-analysis each time the results of a new clinical trial are published) can determine whether more recent data have shifted the estimate of effect to support wider use of rtPA. If no shift has occurred, the analysis should help design new trials to answer remaining questions. We cumulatively ana-

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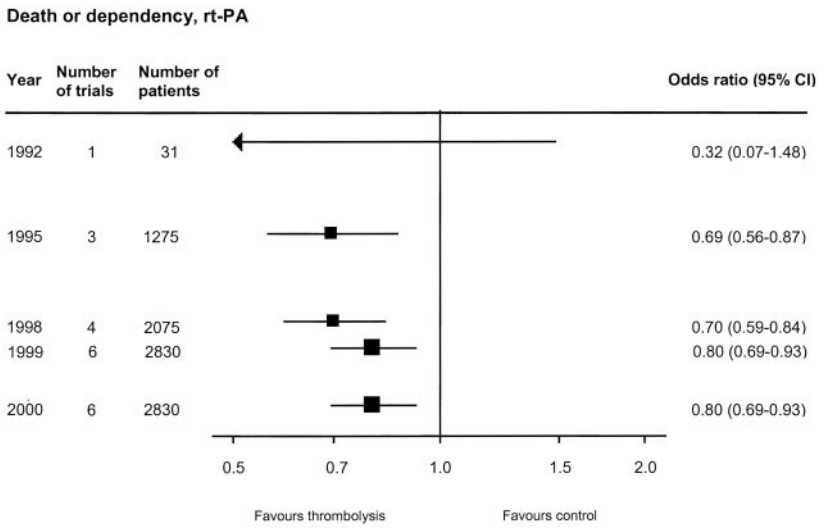

Figure 1. Cumulative meta-analysis showing effect of rtPA on death or dependency at the end of follow-up. Pooled ORs for subsequent years are shown as squares (area of square proportional to amount of data), and horizontal lines (95% CIs) are on a logarithmic scale. χ^2 refers to test of heterogeneity among trials contributing to the figure. Test for heterogeneity: $\chi^2=13.23$; df=5; $P=0.02$.

lyzed rtPA data specifically to highlight the strengths and weaknesses of the existing evidence.

Methods

Identification of Studies

Studies were identified from an ongoing systematic literature search, continuously updated since 1987.[12] Search methods, data extraction, verification, and trial details are published elsewhere.[12] There is a cumulative total of 17 published trials.[19–35] Others are ongoing (IST3, DIAS, ECASS 3, EPITHET) or await publication (Chinese intravenous urokinase trial; Q.T. Chen, personal communication, 2002).

Criteria for Inclusion of Studies

Truly randomized controlled trials of thrombolytic agents with control in patients with imaging-confirmed nonhemorrhagic stroke were included if treatment was started within 6 hours after stroke. Analyses were intention to treat.

Data Extraction

Data were extracted from each trial on the number of patients who were randomized to thrombolysis or control, who developed symptomatic or fatal intracranial hemorrhage within the first 7 to 10 days, and who were either dead or dependent on others in activities of daily living by the end of follow-up (usually 3 to 6 months).

Classification of Outcomes

Symptomatic intracranial hemorrhage (SICH) was defined as neurological deterioration or death temporally associated with the appearance of new intracranial hemorrhage on CT or necropsy. Patients were classified as having poor outcome if they were dead or dependent in activities of daily living at final follow-up. "Dependent" was defined as a score of 3 to 5 on the modified Rankin Scale[36] or a score of $\leq$60 on the Barthel Index.[37] Good functional outcome or independence (modified Rankin Scale, 0, 1, or 2 or Barthel Index 61 to 100) is the opposite of poor functional outcome.

Cumulative Meta-Analysis

Starting with 1992 (the year of publication of the first "modern" trial with a short time window),[27] we performed a separate analysis for each year in which new data emerged.[14] This method shows the impact of new data on the point estimates of treatment effect, the corresponding increase in precision (ie, reduction in the width of CIs), and temporal trends. A consistent point estimate with persistently wide CIs suggests that there may be a worthwhile treatment effect, but more data are needed to narrow the CIs. Persistent between-trial or between–time-point heterogeneity (ie, odds ratios [ORs] varied significantly year to year) suggests that more data are needed to provide statistically robust estimates of effect.

We first analyzed the effect of rtPA, the drug that is licensed and for which there are the most data. To determine the robustness of the results, we repeated the cumulative meta-analysis of the outcomes "death" and "death or dependency" for all agents. To determine whether there were adequate data for specific categories of patients, we repeated the analysis of death at end of follow-up (as the outcome with the most data) for various categories of patients using data from all trials.

The results are reported as ORs with 95% CIs calculated by the fixed- and random-effects method.[38] Heterogeneity of effect was assessed with the χ^2 test.

Results

Characteristics of Included and Excluded Trials

Fourteen trials met the inclusion criteria.[19–32] Three older trials with longer time windows were excluded.[33–35] The NINDS[19] trial was included, although the Food and Drug Administration (FDA) stated that the data available were not strictly "intention to treat"[39] (Clinical Review 2, page 20). Not all trials provided data for every outcome. Further details are available elsewhere.[12]

Functional Outcome: Death or Dependency at the End of Follow-Up

Between 1992 and 2001, the number of patients in rtPA trials increased from 31 (1 trial)[27] to 2830 (7 trials)[19–24,26] (Figure 1). In the cumulative meta-analysis, the point estimate remains consistent from 1995 on (0.69 to 0.80 in 1999). The 95% CIs narrow from a spread of 0.31 in 1995 to 0.22 in 1999. For 1000 patients treated with rtPA up to 6 hours after stroke, 55 (95% CI, 18 to 92) fewer patients would be dead or dependent at the end of follow-up. There was significant heterogeneity between trials ($P=0.02$) but not between time points ($P=0.45$).

Deaths by the End of Follow-Up

Overall, there was a nonsignificant trend for an increase in deaths (2955 patients; OR, 1.16; 95% CI, 0.95 to 1.43; Figure 2). The 95% CIs range from a reduction of 6 deaths to an increase of 48 deaths per 1000 patients treated, with signifi-

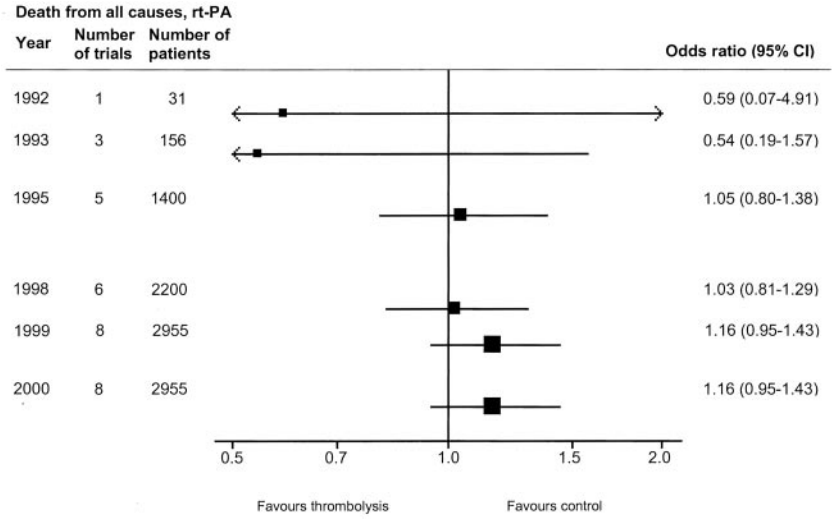

Figure 2. Cumulative meta-analysis showing effect of rtPA on death alone at the end of follow-up. Same conventions as in Figure 1. Test for heterogeneity: $\chi^2=14.42$; df=7; $P=0.04$.

cant heterogeneity between trials ($P=0.04$) but not between time points ($P=0.69$).

Intracranial Hemorrhage Within 7 to 10 Days

The estimates of SICH did not change materially from the mid 1990s to the present (Figure 3). SICH occurred among 153 of 1496 (10%) allocated to rtPA and 46 of 1459 (3%) allocated to control (OR, 3.1; 95% CI, 2.3 to 4.2; absolute excess 62 SICHs per 1000 patients treated). Fatal intracranial hemorrhage occurred in 62 of 1496 (4%) allocated to rtPA and 14 of 1459 (1%) allocated to control (OR, 3.6; 95% CI, 2.3 to 5.7; absolute excess 25 fatal intracranial hemorrhages per 1000 patients treated). Intracranial hemorrhage showed no heterogeneity between rtPA trials up to 6 hours ($P=0.11$) or between time points ($P=0.26$).

Are the Effects of rtPA Consistent With Thrombolytic Agents in General?

These results for rtPA were supported by trials of other thrombolytic agents that provide a similar amount of data as for rtPA (12 trials total, 4342 patients). Thrombolysis significantly reduced death or dependency compared with control (OR, 0.82; 95% CI, 0.75 to 0.96; ≈40 more alive and independent patients per 1000 treated). The point estimate (OR) was consistent from 1995 on (0.76 to 0.82 in 2000), and the 95% CIs narrowed (a spread of 1.41 in 1992 to 0.19 in 2000), with borderline significant heterogeneity between trials ($P=0.07$) but not between time points ($P=0.72$). Thrombolysis significantly increased the proportion of patients who died (40 more deaths per 1000 patients treated; 95% CI, 20 to 70). The point estimate is consistent from 1995 on, and the 95% CI narrows some (from 0.55 to 0.41 in 2000) with persistent heterogeneity between trials ($P=0.0009$) but not between time points ($P=0.72$).

Effects in Subgroups of Patients (All Agents Combined)

To examine sources of heterogeneity between trials, we undertook exploratory analyses (Figure 4) using death at the end of follow-up because, although this outcome included the most data and was probably the most accurate, it still showed heterogeneity ($\chi^2=39$, $df=14$, $2P=0.003$) and because death is the most important hazard and may be the main reason that

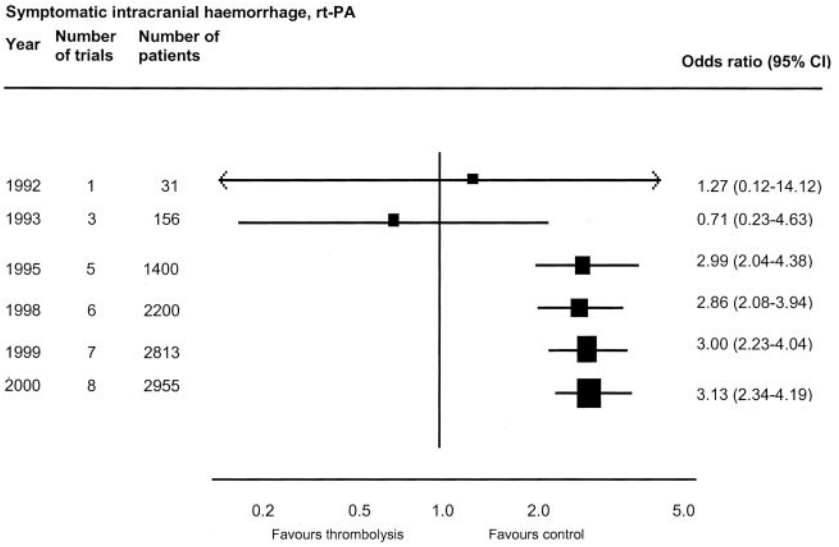

Figure 3. Cumulative meta-analysis showing effect of rtPA on SICH within 7 to 10 days. Same conventions as in Figure 1. Test for heterogeneity: $\chi^2=11.84$; df=7; $P=0.11$.

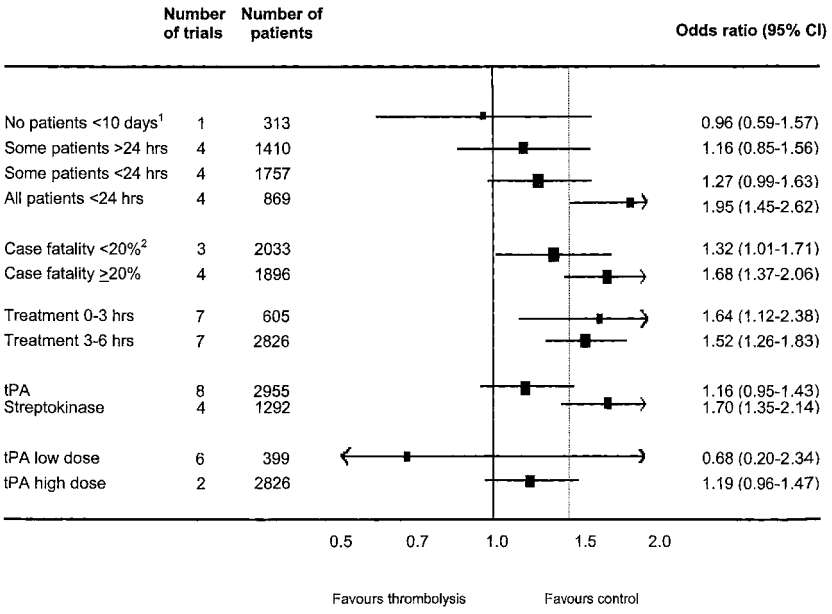

Figure 4. Effects of thrombolytic treatment (all agents) on death by the end of follow-up in different categories of patients. Dotted line shows the effect for all patients combined (OR, 1.34). Analysis of patients treated in the 0-to-3 and 3-to-6-hour windows is restricted to trials randomizing patients >3 hours after stroke onset (ie, up to 4, 5, or 6 hours). High-dose rtPA equals the dose used in myocardial infarction; low dose is about half of that dose. [1]Permitted use of antithrombotic agents; [2]case fatality in control group (of trials of >100 patients in the control group).

use of thrombolysis is discouraged. The absence of data from older patients precluded analysis of the effect of thrombolysis at different ages (only 42 were >80 years of age in rtPA trials).[39]

Concomitant Use of Antithrombotic Agents

Trials were categorized according to the permitted use of antithrombotic agents (aspirin and heparin). There is a trend toward higher case fatality with more frequent and earlier antithrombotic agent use.

Stroke Severity at Baseline

None of the rtPA trials used centralized telephone randomization. Although not statistically significant in individual trials, even a modest imbalance in key baseline prognostic factors could affect the estimate of treatment effect. The FDA considered that baseline imbalance was likely to have been important in the NINDS trial[39] (Clinical Review 2, pages 25 and 26). Stroke severity was assessed differently in the trials, so we compared trials with low (<20%) and high (≥20%) case fatality in the control group (in trials of >100 patients in the control group). There was a nonstatistically significant trend toward thrombolysis being associated with more deaths in patients with severe strokes (OR, 1.32 and 1.68 in trials with case fatality <20% and ≥20%, respectively; $2P=0.24$).

Time to Randomization

Analysis of the effect of time may be strongly influenced by the NINDS trial,[19] which provided 50% of the data on patients randomized within 3 hours. Therefore, from the 7 most recent trials randomizing patients beyond 3 hours (ie, up to 6 hours), we compared patients treated under 3 and 3 to 6 hours (ie, each trial then became its own internal control).[20–23,27–29] Comparing patients randomized within 3 hours with those randomized at 3 to 4 hours,[27] 3 to 5 hours,[23] or 3 to 6 hours[20–22,28,29] showed no definite difference in the risk of death (randomized within 3 hours: OR, 1.64; randomized 3 to 6 hours: OR, 1.52; for the difference between the 2 ORs, $2P=0.73$; Figure 4).

When analysis of death or dependency was restricted to patients randomized within 3 hours (all trials), there was no evidence of heterogeneity ($\chi^2=6.37$, $df=8$, $2P=0.61$), and the result became more favorable for thrombolysis (all agents) (OR, 0.66; 95% CI, 0.52 to 0.82), corresponding to 100 (95% CI, 50 to 160) fewer dead or dependent patients per 1000 treated. Exclusion of the NINDS study[19] (50% of the data within 3 hours) did not substantially alter this conclusion (OR, 0.70; 95% CI, 0.50 to 0.97). For rtPA trials, there were 110 (95% CI, 50 to 170) fewer dead or dependent patients per 1000 treated.

Type and Dosage of Thrombolytic Agent

We compared case fatality in groups receiving different types or doses of thrombolytic agent. There was no clear evidence of any overall difference in total case fatality between trials of recombinant prourokinase (OR, 0.75; 95% CI, 0.40 to 1.41), rtPA (OR, 1.16; 95% CI, 0.95 to 1.43), or streptokinase (OR, 1.70; 95% CI, 1.35 to 2.14) ($\chi^2=4.78$, $P=0.19$) or between trials that used low- or high-dose rtPA (OR, 0.68; 95% CI, 0.20 to 2.35; and OR, 1.19; 95% CI 0.96 to 1.47, respectively; $\chi^2=0.75$; $P=0.39$).

Discussion

Since 1995, the number of patients in randomized controlled trials of thrombolysis for acute ischemic stroke has more than doubled, bringing the total to 5210 patients in 17 trials, including 2955 in 8 trials of rtPA. Cumulative analysis confirms that there are net benefits despite the definite hazards. For every 1000 patients treated with rtPA up to 6 hours, ≈55 more patients will be independent at the end of follow-up, including the "cost" of ≈20 extra deaths. However, the statistical heterogeneity and wide CIs indicate that these estimates of rtPA effects are unreliable. The true effect of rtPA might be considerably better or considerably worse than suggested here. Current evidence indicates that additional trial data are still required to increase reliability and settle several questions.

The wide CIs make it difficult to assess the exact size of the benefit. The 95% CI for death at the end of follow-up is compatible with both a 10% reduction and a 40% increase in the odds of death. The CIs for most of the other outcome measures were even wider.

A more precise definition of the effect of rtPA in specific patients (age, severity, time to treatment, aspirin use) is needed to derive a more precise profile for the likely risk-to-benefit ratio that is tailored for individual patients. For example, for patients treated within 3 hours, the risk of death at the end of follow-up was equivalent to ≈20 more (95% CI, 20 fewer to 70 more) dead patients per 1000 patients treated. However, comparing patients treated within 3 hours and those treated between 3 and 6 hours in the same trials (therefore controlling for between-trial differences) failed to show a greater benefit of early treatment. It is very likely that earlier treatment is better, but the size of the benefit in different time windows is susceptible to both random and systematic errors[15] (eg, not only may patients with severe stroke present earlier,[40] but the severity of stroke may confound the analysis because stroke outcome is closely related to baseline stroke severity in a nonlinear fashion).[41] The effect of rtPA may vary with stroke severity and not necessarily linearly. Several other variables might contribute to the heterogeneity (eg, age, presence of visible infarction, intensity of blood pressure control), but we did not have appropriate data. An individual patient data meta-analysis (currently underway for 5 rtPA trials; T. Brott, MD, personal communication, 2002) may help, although it is not possible to completely correct imbalances in a posthoc analysis or fill gaps for data not collected.

More patients and longer follow-up are needed to confirm whether better long-term survival outweighs early hazard. The focus on SICH has overlooked the effect of thrombolysis on severe infarct edema. This potentially fatal event has not been recorded. Severe infarct edema may be less frequent in rtPA-allocated patients (see Clinical Review 2, page 39, Reference 39). Calling small hemorrhages within a large infarct symptomatic may have overestimated SICH. Intracranial hemorrhage should therefore merely be considered a surrogate outcome.

Should age >80 years (or other feature) preclude thrombolysis? Elderly patients and patients treated between 3 and 6 hours are far more common than younger patients treated within 3 hours. The number of patients who benefit may therefore be far higher in the former groups despite a more marginal effect. Patients 80 to 89 years of age were 60% less likely and those 90 to 99 years of age were 85% less likely to be offered rtPA than patients <60 years of age.[7] Treatment effects may differ in magnitude but rarely change direction (eg, from benefit to harm) in different subgroups of patients.[42] Restricting treatment to a few selected patients may therefore deprive many others of modest but still worthwhile benefits. All rtPA trials except NINDS excluded patients >80 years of age, and NINDS included only 42 patients >80 years of age (Reference 39, Clinical Review 2, page 27), but stroke increases with age and is likely to rise. In the United Kingdom, ≈100 000 patients have a first-ever stroke, and ≈20,000 of these are 80 to 99 years of age[43] (≈140 000 per year in the United States). Routine use of rtPA in patients 80 to 99 years of age is difficult to justify with trial data from only 42 patients. But should older patients be denied this potentially disability-avoiding therapy?

Cost-effectiveness analyses of rtPA require better data. A recent analysis from the perspective of the UK National Health Service (NHS) suggested a 78% probability of gain in quality-adjusted survival during the first year at a cost of ≤13 581 per quality-adjusted life-year gained.[44] Over a lifetime, rtPA was associated with a cost saving of ≤96 565 per quality-adjusted life-year. However, the estimates were imprecise; under several plausible economic assumptions, rtPA was much less cost effective than standard care, and under others, it was a great deal more cost effective. Healthcare purchasers will not be persuaded to invest in rtPA without more precise cost-effectiveness estimates. These estimates absolutely depend on more data from new randomized trials.

A Way Forward?

It is 44 years since the first trial of thrombolysis in acute stroke was published,[45] 20 years since the publication of the first trial included in the Cochrane Review,[33] and 7 years since the first "positive" thrombolysis trial in acute stroke.[19] Yet, the treatment is not widely used even where licensed.[7] When there was disagreement on the available evidence, the cardiologists' solution was to obtain more trial data. In the mid 1980s, there were 1 major positive myocardial infarction trial[46] and a positive overview of several inconclusive trials.[13] Despite this, clinical practice did not change[47] until the very large ISIS-2 trial[15] was published.

The evidence to date on rtPA in stroke, while encouraging, is still not persuasive. Many stroke patients may be denied an effective treatment. Further large-scale trials[47] may be the only way to shift clinicians' opinion and train more clinicians to administer the therapy safely and equitably to a wider range of patients than at present.

Acknowledgments

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