

# Tissue plasminogen activator (tPA) for acute ischaemic stroke: why so much has been made of so little

## *Has enthusiasm overwhelmed judgement?*

ALTHOUGH ADVOCATES of the use of tissue plasminogen activator (tPA) in acute ischaemic stroke suggest that this “is one of the most important advances in stroke medicine”,<sup>1</sup> a recent Cochrane meta-analysis also supports “clinicians who choose...not to use the treatment at all”,<sup>2</sup> and all three major emergency medicine associations in North America have declined to endorse it as “standard of care”.<sup>3</sup>

In a recent issue of the Journal, Szoeki and colleagues’ audit of tPA use in a tertiary-care hospital concluded that “favourable outcomes...were similar to those achieved in international...trials in specialised centres”,<sup>4</sup> while an accompanying editorial highlighted that “the absolute benefits of stroke care unit management clearly outweigh those of...tPA administration”.<sup>1</sup> Several letters in this issue of the Journal raise important concerns about the report of Szoeki et al, as well as the overall risks and benefits of the use of tPA in ischaemic stroke (page 386).<sup>5-7</sup>

A single dose of aspirin provides benefit to about 15 times as many stroke patients as does tPA,<sup>1</sup> at far less risk. This is true even assuming tPA benefits one in every eight patients treated, which is based on a point estimate taken from the National Institute of Neurological Diseases and Stroke (NINDS) trial,<sup>8</sup> the only randomised controlled trial which found a benefit for its primary endpoint. This does not take into account the wide confidence intervals in the NINDS trial, the negative results of multiple other randomised controlled trials,<sup>9,10</sup> and the far worse results in non-expert hands. Even under a “maximum benefit” scenario, with further assumptions that overestimate the impact of tPA (including that it could be given safely and effectively to 10% of acute stroke patients, rather than the 1%–3% non-protocol-violation treatments in typical community studies),<sup>11,12</sup> tPA would have only minimally greater impact than aspirin.

Ultimately, regardless of who is correct about the available evidence, the overall impact of tPA in acute ischaemic stroke is *at most* marginal, which makes it difficult to understand why “so

much has been made of so little”.<sup>7</sup> Perhaps it has to do with enthusiasm for what is frequently called the “first treatment for stroke”, although, as noted, there are far more important (but far less dramatic) treatments available. Readers will have to decide for themselves whether it also has something to do with money,<sup>3</sup> or if this is truly “extending conspiracy theory to its limits”, as Donnan and colleagues claim (page 387).<sup>13</sup>

Previous critiques of the use of tPA in ischaemic stroke have raised the following issues:

- There is a paucity of positive evidence; all but one small randomised controlled trial failed to find benefit in the primary outcome, or found substantial harm.<sup>14,15</sup>
- Even in the NINDS trial, the benefit was primarily in patients treated less than 90 minutes after symptom onset<sup>16</sup> (almost no such patients exist in actual community practice), so the number needed to treat in the 91–180-minute group is surely far higher than the “eight patients needed to treat” widely quoted.
- “Effectiveness” in a community setting is far different from “efficacy” as reported in the NINDS trial (even if NINDS is taken at face value).<sup>15,16</sup>

Let me add the following observations. Most supporters of tPA claim that three trials involving streptokinase are irrelevant (including one done in Australia, with very negative results<sup>10</sup>). However, in the absence of studies directly comparing them, there is no reason to believe that tPA *should* be better than streptokinase for treating ischaemic stroke. In head-to-head cardiac megatrials (ISIS III, GISSI II, and GUSTO I), tPA consistently caused more intracerebral haemorrhage than streptokinase, which is likely to be even more important in patients with stroke. Furthermore, the GUSTO I trial, which provided the only remotely credible (albeit controversial) evidence suggesting tPA might be a bit more effective than streptokinase in coronary patients, was explicitly based on the notion that adjunctive intravenous heparin *must* be given with tPA — an approach *contraindicated* in stroke. Excluding streptokinase trials

from the analysis of thrombolytics in stroke because they happened to be negative is simply inappropriate.

Although Szoek et al's report is not strictly an "efficacy" study, neither is it a community practice "effectiveness" study, as treatment was by experts in a tertiary care facility. Thus, in no case should the results be extrapolated to other practice environments. Furthermore, it is critical to note the report's limitations:

- Most obviously, there were no randomised controls, and outcomes were measured unblinded to the use of tPA, creating enormous potential for measurement bias.

- The study failed to meet most of the methodological criteria considered critical for chart reviews<sup>17</sup> (eg, use of trained abstractors [ideally other than the authors], standardised abstraction forms and multiple independent reviewers for at least some of the charts, with some measure of agreement between reviewers; use of explicit criteria for coding of outcomes and explicit definitions for interpreting absent or inconsistent data).

- Outcomes among 30 patients receiving tPA may have been "consistent with" the NINDS result, but, given the small numbers and extremely wide confidence intervals, were also consistent with virtually *any* result.

- The report may well represent publication bias. Indeed, the most positive "effectiveness" study reported results from 57 of 83 centres that participated in a proprietary randomised controlled trial<sup>18</sup> — what happened to the other 26? The only two reports that included *all* patients receiving tPA in a given community each documented unacceptable outcomes.<sup>11,12</sup>

- Finally, there is the problem of interpretation bias. Szoek et al classified one of the deaths after tPA therapy as a protocol violation, which will allow advocates to claim the results "would have been even better if...". But this was based on an exclusion criterion that *was not* part of the NINDS protocol (ie, "early signs on computed tomography [CT] suggesting infarct of more than a third of the territory of the middle cerebral artery"), and despite the fact that the study's expert CT readers did not agree whether this patient even met that criterion! This example (out of many) should provide insight into the way the "spin" of enthusiastic authors can lead to conclusions that are rosier than results actually justify.

Many of us believe that thrombolytic therapy in stroke remains far from proven, so that its use should be restricted to further randomised controlled trials. This would not only enable us to determine whether this therapy produces more good than harm, or vice versa, but might also allow identification of subgroups in whom it is, or is not, indicated. We could then avoid giving a potentially fatal drug to a patient in whom it increases risk unacceptably, while also allowing current sceptics to use it in a different patient likely to benefit — assuming such patients, in either category, could be identified.

If tPA use becomes more widespread, a very small number of patients may receive great personal benefit, while a very few others may be subjected to great personal harm. However, the broader implications of this debate are substantial. Modern health policy traditionally rests on the "precautionary principle", which requires that no new practice be widely introduced until it is shown to be safe. This principle is under fierce attack in postmodern society by advocates of the contrary "Kehoe principle", which asserts that if something may have value it should be accepted unless it's proven dangerous.<sup>19</sup> It is, of course, almost

impossible to *prove* such danger, and, once approval is given, it may take many years — and a great deal of harm — before the decision can be reversed. Such was the case with leaded gasoline, which was termed "a gift of God" by its discoverer, Robert Kehoe, after whom this dangerous principle is named,<sup>19</sup> and which was used ubiquitously for over 60 years, despite widespread understanding of its terrible public health impact. Whether or not the medical community insists on real evidence that tPA will do more good than harm in acute ischaemic stroke will also reflect how we feel about the introduction of all manner of potentially beneficial, but also potentially dangerous, new treatments.

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