tom onset achieved greater neurologic recovery and experienced less disability than patients who received placebo. Additional data published by the NINDS investigators[3] and the US Food and Drug Administration medical officer's review of data submitted in support of a new drug application,[4] show a significant in baseline stroke severity between the tPA-treated and placebo groups in the NINDS trial. Statistical correction for this baseline imbalance has not been provided in published reports and commentaries concerning this trial. Because baseline stroke severity has a significant effect on stroke outcome, I believe that accurate interpretation the results of the NINDS trial, or any similar trial, is not possible without using a statistically appropriate analytic equation to account for the differences in stroke severity between the trial groups.

The TOAST stroke trial[5] demonstrated that very small differences in baseline stroke severity have large effects on stroke outcome. I applied stroke outcome information derived from this trial to the NINDS data.[6] My analysis indicates that the difference in stroke outcome between the treatment and placebo groups in the NINDS trial may be accounted for solely by the baseline imbalance in stroke severity between the groups.

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[The authors respond:]

Mann draws attention to 2 important points: (1) stroke outcome depends heavily on initial stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and (2) baseline imbalances in stroke severity could potentially affect the results of a stroke trial. However, the assertion that the NINDS tPA trial results are invalid is incorrect.

The original NINDS trial publication (1995)[1] reported the treatment and placebo groups to be well balanced in terms of initial stroke severity (median NIHSS 14 v. 15). According to further data published 5 years later in a post-hoc analysis,[2] it does appear that there were more patients in the tPA group with mild stroke (NIHSS 0–5) and fewer patients with very severe stroke (NIHSS > 20) compared to placebo. This imbalance was evident primarily in the 91–180 minute onset-to-treatment cohort and less prominent in the 0–90 minute cohort or in the entire study cohort. No baseline imbalances were in favour of the tPA group for patients with moderate or severe stroke (NIHSS 6–10, 11–15, 16–20). Mann speculates that the positive results of the NINDS trial were driven by this baseline imbalance in stroke severity. However, the actual data do not bear this out.

We obtained data directly from the NINDS investigators to clarify this issue (see Table 1). These data show that even if one excludes the subgroups with baseline imbalances (NIHSS 0–5 or > 20), the efficacy of tPA in the NINDS trial still holds true — a 16.6% absolute benefit for patients with moderate severity stroke (NIHSS 6–10) and a 10.4% absolute benefit for patients with severe stroke (NIHSS 11–20). This is reassuring since in clinical practice the major target of tPA therapy is patients with moderate to severe deficits. The overall benefit of tPA, therefore, does not appear to be driven by baseline imbalances in the very mild or very severe subgroups.

Contrary to Mann's speculation that there might be an excessive benefit in

Table 1: Three-month stroke outcomes in the NINDS tPA stroke trial by baseline stroke severity

	Baseline		90-day NIHSS score of 0–1				90-day mRS score of 0–1				Unadjusted odds ratio for favourable outcome (95% CI)
NIHSS score	% of placebo patients (n = 312)	% of tPA patients (n = 312)	% of placebo patients	% of tPA patients	Absolute benefit, % (95% CI)	NNT	% of placebo patients	% of tPA patients	Absolute benefit, % (95% CI)	NNT	
0–5	5.1	13.5	62.5	69.1	6.6 (–20.9 to 34.1)	15	81.3	78.6	–2.7 (–25.5 to 20.1)	–37	1.12 (0.36 to 3.49)
6–10	26.6	21.8	34.9	51.5	16.6 (0.9 to 32.2)	6	45.8	67.7	21.9 (6.5 to 37.3)	5	2.33 (1.32 to 4.09)
11–20	43.6	44.6	16.9	27.3	10.4 (0.7 to 20.1)	10	21.3	34.5	13.2 (2.7 to 23.7)	8	1.68 (1.05 to 2.67)
> 20*	24.7	20.2	2.6	6.4	3.8 (–3.2 to 10.8)	26	3.9	9.5	5.6 (–2.8 to 14.0)	18	1.45 (0.64 to 3.33)

Note: NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin scale, CI = confidence interval, tPA = tissue plasminogen activator, NNT = number needed to treat.
*The 95% CI, derived using the normal approximation to the binomial distribution, for this group may not be valid owing to small number for each treatment group.

the NIHSS 0–5 or > 20 subgroups driving the overall benefit attributable to tPA in the trial, actually much less benefit is derived for patients in these subgroups. Caution is advised in interpreting subgroup analysis, however, because this trial was not powered to determine efficacy in these subgroups.

These raw data are explored further in the multivariable analysis published by the NINDS investigators in which adjustment is made for baseline NIHSS score and other potential confounding variables.[3] tPA was the most important predictor of outcome and no interaction effects were seen, suggesting the effect of tPA was robust across all patient groups. Other important predictors were the interaction of age with baseline NIHSS score, diabetes, interaction of age with mean blood pressure and early CT ischemic changes. The interaction term NIHSS score by age implies that both age and baseline NIHSS were independent predictors of outcome; statistically, however, age modifies the effect of baseline NIHSS score such that at older ages the baseline NIHSS becomes increasingly important in magnitude as a predictor of outcome. Because of this, it is not possible to clinically interpret an odds ratio for baseline NIHSS score or age in isolation — only their interaction has clinical meaning, and it is correct to report only the interaction term as the NINDS investigators had done. Therefore, it is not true that adjustment for baseline NIHSS was not considered. The effect of tPA was robust even after accounting for baseline NIHSS score. Mann's reference to a Food and Drug Administration submission is not relevant here because it refers to a nonrandomized, open-label, dose-escalation study of angiographic recanalization, not the NINDS tPA stroke trial.

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