Editorial

Treating Patients With Ischemic Stroke With Tissue Plasminogen Activator in the 3.5- to 4-Hour Window
Numbers Support Benefit but the Message Is to Still Go Fast

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Numbers needed to treat (NNT) is a powerful tool that has been proposed to translate research findings of treatment effects to an intuitive figure for clinical settings or for policy-making purposes. It is a measure of clinical benefits that describes the number of individuals who would need to be treated to prevent the occurrence of 1 outcome event.[1] NNT, most commonly, is simply calculated by the inverse of the absolute risk difference between 2 treatment options.

However, important limitations should be considered when using NNT in communicating research findings. First, as with all relative or absolute treatment effect measures, causality must be assumed, which even in the setting of randomized controlled trials is not guaranteed if, for example, compliance or follow-up rates differ according to treatment groups or blinding of treatments cannot be achieved. Second, NNT is specific to a comparison of treatment effects in 1 study population. Thus, it should be considered specific to a particular comparison and not necessarily to a particular therapy.[2] Strictly speaking, NNT only applies to patients of a specific trial and the application of this NNT to any other setting is an extrapolation, which may or may not be valid. Third, the NNT will vary across groups with different baseline risks for the outcome, even if the overall drug effect is similar across groups.[3] As an example, a meta-analysis of the effect of antihypertensive drugs on mortality is often used in which the NNT for antihypertensive therapy to prevent 1 death ranges considerably from 1157 in healthy young women to 17 in older men with vascular high-risk profile.[2,4] Thus, there is likely not 1 single NNT number applicable to all patients.[5] Further, NNT do not incorporate a measure as to when an outcome occurs in relation to drug use, which in the case of testing acute treatment effects is of lesser importance. Last, when communicating NNT to patients or policy-makers, one has to keep in mind that the interpretation of such

a measure will likely lead to more conservative treatment decisions.[6,7] This may not be surprising because the NNT also points out how many patients receive a treatment for "nothing" and underscore overall difficulties in communicating research findings with NNT.[8] In some settings, it may be more intuitive to use a ratio of NNT-to-benefit to the NNT-to-harm to communicate study results.

In this issue of *Stroke*, Saver et al[9] investigate the NNT-to-benefit and NNT-to-harm ratio for intravenous tissue plasminogen activator (tPA) in the 3- to 4.5-hour window among patients with ischemic stroke who participated in the ECASS 3 trial.[9] Because the evaluated functional outcome, the modified Rankin Scale (mRS), has 7 ordinal levels, NNT values had to be estimated by applying a somewhat complex methodology, which, however, does not change the principal interpretation of the NNT. The NNT was derived by expert specification, applied algorithms, as well as random sampling from joint distributions. In the primary analysis, the NNT for a change of ≥1 grade on the mRS score was calculated, which implies a linear effect of the treatment on the outcome. The authors estimated that the most plausible NNT-to-benefit from the expert analysis was 6 (95% CI, 5.6–6.7) and the most plausible NNT-to-harm was 38 (95% CI, 34.6–40.5). The ratio of these 2 NNT values, ie, the likelihood of harm to help, is 6, indicating that ≈6-times more patients with ischemic stroke would benefits from tPA therapy given in the 3- to 4.5-hour window than having a resulting harm of that therapy. Applying these results to 100 patients with ischemic stroke treated with tPA in the 3- to 4.5-hour time window, ≈16 will have a better and ≈3 will have a worse outcome.

A close inspection of the data reveals, however, a substantial source of heterogeneity when comparing benefits and harm in dichotomized mRS classes. Although most comparisons of net NNT-to-benefit-to-harm indicate a benefit, the contrast of the 2 most severe functional outcomes (mRS, 5 or 6) to all better functional outcomes indicate substantial harm. Whereas this finding may be attributable to chance, it raises questions as to whether the treatment effect is steady across the mRS and whether the avoidance of this clinically important outcome (ie, avoiding dependency or death from stroke) should be addressed differently in future studies.

The authors then compare the NNT analysis from ECASS 3 to the NNT analysis from the NINDS tPA Study, in which a 1- to 3-hour window was used to treat patients with ischemic stroke with tPA. Across all 7 levels of the mRS, the NNT-to-harm was similar as in the ECASS 3 trial (3/100 patients), but the benefit was doubled in the 1- to 3-hour

window (32/100 patients) as compared with the 3- to 4.5-hour window (16/100 patients).

How do these results translate to everyday clinical practice? As discussed by the authors, the NNT-to-benefit/harm results are limited to patients who, based on inclusion and exclusion criteria, would have participated in ECASS 3 and may differ for other stroke patients. Indeed, at least the results of harm attributable to tPA vary strongly across different target populations.[10] Thus, an important aim will remain to identify patients with ischemic stroke who benefit the most and who have less detrimental effects from tPA therapy. In this regard, the NNT should not be viewed as the deterministic value for all clinical settings but may serve as an additional guide to support treatment decisions based on individual patient characteristics. Although the NNT from ECASS 3 support benefits from tPA therapy applied in the 3- to 4.5-hour window, the contrast of the NNT to benefit from ECASS 3 and the NINDS trial even more strongly underscores the importance of applying tPA treatment as early as possible.

Disclosures

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