Treatment Time-Specific Number Needed to Treat Estimates for Tissue Plasminogen Activator Therapy in Acute Stroke Based on Shifts Over the Entire Range of the Modified Rankin Scale

Maarten G. Lansberg, MD, PhD; Maarten Schrooten, MD; Erich Bluhmki, PhD; Vincent N. Thijs, MD, PhD; Jeffrey L. Saver, MD

Background and Purpose—To make informed treatment decisions, patients and physicians need to be aware of the benefits and risks of a proposed treatment. The number needed to treat (NNT) for benefit and harm are intuitive and statistically valid measures to describe a treatment effect. The aim of this study is to calculate treatment time-specific NNT estimates based on shifts over the entire spectrum of clinically relevant functional outcomes.

Methods—The pooled data set of the first 6 major randomized acute stroke trials of intravenous tissue plasminogen activator was used for this study. The data were stratified by 90-minute treatment time windows. NNT for benefit and NNT for harm estimates were determined based on expert generation of joint outcome distribution tables. NNT for benefit estimates were also calculated based on joint outcome distribution tables generated by a computer model.

Results—NNT for benefit estimates based on the expert panel were 3.6 for patients treated between 0 and 90 minutes, 4.3 with treatment between 91 and 180 minutes, 5.9 with treatment between 181 and 270 minutes, and 19.3 with treatment between 271 and 360 minutes. The computer simulation yielded very similar results. The NNT for harm estimates for the corresponding time intervals are 65, 38, 30, and 14.

Conclusions—Up to 4½ hours after symptom onset, tissue plasminogen activator therapy is associated with more benefit than harm, whereas there is no evidence of a net benefit in the 4½- to 6-hour time window. The NNT estimates for each 90-minute epoch provide useful and intuitive information based on which patients may be able to make better informed treatment decisions. **(*Stroke*. 2009;40:2079-2084.)**

Key Words: biostatistics ■ number needed to treat ■ stroke ■ thrombolysis

Time to treatment is a critical factor in the outcome of patients with acute stroke who are treated with intravenous tissue plasminogen activator (tPA). The longer the delay between symptom onset and treatment, the less likely it is that a patient will achieve a good clinical outcome. This was convincingly demonstrated in a pooled data analysis of the first 6 major intravenous tPA acute ischemic stroke trials.[1] This study reported that the odds ratio (OR) of an excellent outcome with tPA compared with placebo gradually decreases from 2.8 for patients treated between 0 and 90 minutes, to 1.6 for 91 to 180 minutes, 1.4 for 181 to 270 minutes, and 1.2 for 271 to 360 minutes. Although the OR for an excellent outcome is an effect measure that provides an important perspective on the study results, it also has an important disadvantage as a guide to clinical decision-making. Among the wide range of outcome state changes valued by treating physicians, patients with stroke, and family members, the OR for an excellent outcome captures only a single health state transition. To make well-informed clinical decisions in the emergency room, physicians and patients would benefit from an effect measure that captures all beneficial and adverse effects of a treatment across the entire spectrum of functional outcomes.

The number needed to treat for benefit (NNTB) is an effect measure that indicates how many patients need to be treated with an intervention for one patient to experience a benefit. The number needed to treat (NNT) is generally recognized as an intuitively accessible effect measure that facilitates practitioner and lay public decision-making.[2]

The NNT is the inverse of the absolute risk difference and can easily be calculated for outcomes that are dichotomized (eg, alive versus dead). Like most neurological conditions,

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From the Stanford Stroke Center (M.G.L.), Stanford University Medical Center, Palo Alto, Calif; the Department of Neurology (M.S., V.N.T.), University Hospitals of Leuven, Leuven, Belgium; Vesalius Research Center (V.N.T.), Flemish Institute Biotechnology, Leuven, Belgium; Boehringer Ingelheim Pharma GmbH & Co (E.B.), Ingelheim, Germany; and the Stroke Center and Department of Neurology (J.L.S.), David Geffen School of Medicine at UCLA, Los Angeles, Calif.

Correspondence to Maarten G. Lansberg, MD, PhD, Stanford Stroke Center, 701 Welch Road, Suite B325, Palo Alto, CA 94304-9705. E-mail lansberg@stanford.edu

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however, stroke causes a wide spectrum of functional impairment and disability in addition to death. This range of potential outcomes cannot be captured by any single dichotomized end point. Virtually all acute stroke studies therefore measure clinical outcomes using ordinal scales, not binary categories, that assess outcome domains of global disability (modified Rankin Scale [mRS]), activities of daily living (Barthel Index), neurological deficit (National Institutes of Health Stroke Scale), and quality of life (eg, Stroke Impact Scale, Stroke Specific Quality of Life Scale).

Expert specification of joint outcome tables is a method to determine the NNT for benefit across the entire range of ordinal outcome scales from parallel group clinical trial data.[3] This method has been successfully applied to trials of intravenous fibrinolysis, intra-arterial fibrinolysis, neuroprotective therapy for acute ischemic stroke, and neuroprotective therapy for vasospasm after aneurysmal subarachnoid hemorrhage.[4] However, it has not previously been used to characterize how the degree of benefit of a therapy may vary with onset to treatment time.

The aim of this study was to determine the NNT benefit and NNT harm for each 90-minute treatment time window based on the pooled data from the first 6 major intravenous tPA stroke trials (National Institute of Neurological Diseases and Stroke [NINDS] 1 and 2, European Cooperative Acute Stroke Study [ECASS] I and II, and Alteplase Thrombolysis for acute Noninterventional Therapy in Ischemic stroke [ATLANTIS] A and B).

Methods

The pooled data set of the NINDS Parts 1 and 2, ECASS I and II, and ATLANTIS A and B trials was used for this study. The proportion of patients in the placebo and tPA groups achieving 3-month final outcome scores in each of the 7 mRS categories were tabulated separately for patients enrolled in 4 time epochs: 0 to 90 minutes, 91 to 180 minutes, 181 to 270 minutes, and 271 to 360 minutes.

Because the data from parallel group controlled trials do not specify the within-patient variance, the equivalent information was derived using the expert and algorithmic joint outcome table distribution specification methods as previously described in detail.[3,4]

Briefly, for each 90-minute treatment time window, joint distribution tables of individual patient outcomes for model populations of 1000 patients were generated. In the expert method, 7 expert clinicians highly experienced in acute stroke therapy each independently specified a joint outcome table under the injunction to indicate the biologically most plausible responder distribution compatible with the trial-specified group data. Experts were asked to redistribute patients in the joint distribution tables from the distribution on the mRS that is seen in the control arm to the distribution that is seen in the tPA arm. Each expert was provided with Excel spreadsheets that contained the joint distribution tables and the rate of parenchymal hematoma Type 2 for each time window. At the beginning of each expert session, patients were distributed along the diagonal of the distribution table reflecting the distribution of patients on the mRS in the control cohort. Based on their clinical experience, and constrained by the row and column marginals of the distribution tables, experts were then instructed to iteratively shift patients horizontally from the diagonal to yield a distribution on the mRS equal to that seen in patients treated with tPA. Experts started this process by moving a fraction of the patients horizontally to the right, reflecting patients who worsened due to tPA treatment. Experts typically used the difference in the parenchymal hematoma Type 2 rate between the control and tPA-treated groups as a guide to determine the fraction of patients that was shifted to the right. Subsequently, experts shifted patients from cells on the diagonal to cells left of the diagonal (indicating improved outcome with tPA) to achieve the target mRS distribution in the tPA-treated group.

NNTB and NNT harm (NNTH) estimates were calculated for each expert based on the number of patients that were shifted to the left and to the right, respectively, over the entire range of the mRS (7-point scale). $NNT_{netbenefit}$ was calculated based on the difference between patients shifted to the left and those shifted to the right. Because some patients perceive being severely disabled from a stroke as an equally or more undesirable an outcome as death, we also calculated NNTs based on a 6-point scale, in which a score of 5 on the mRS (severely disabled state) and a score of 6 (death) were condensed into one category. Based on all 5 expert assessments, the geometric means and 95% CIs of the geometric means were calculated for each NNT estimate.

An algorithm method was used to determine the maximum and minimum possible NNTBs for each time epoch independent of expert judgment of benefit distributions. This was achieved by taking the median harm of therapy distribution from the expert panel data and subsequently completing 2 joint outcome tables for each time epoch in a rule-based manner.[4] The maximum possible NNTB compatible with the data is derived by completing the table following the rule that every patient who benefits from therapy does so by improving only the minimum possible number of grades on the mRS. The minimum possible NNTB compatible with the data is derived by completing the table following the rule that every patient who benefits from therapy does so by improving the maximum possible number of grades compatible with the group data.

NNTBs were also generated using a fully automated, iterative method implemented by Microsoft as Perl scripts to simulate the redistribution in the joint distribution table. Again, for each 90-minute epoch, the median harm of therapy distribution is taken from the expert panel data. When the set of all possible distributions was large (>250 000), a random sample of distributions was generated. For each time window, a maximum of 48 hours of computing time was allotted to generate such a sample. When the set of all possible distributions was small, all possible distributions were sought. The mean NNTB was derived from the generated distributions.

Values for the number of patients who benefit (and are harmed) per 100 treated patients were calculated by dividing 100 by each NNTB (and NNTH) value. The help-to-harm ratio was calculated by dividing the NNTB by the NNTH. $NNT_{netbenefit}$ was defined as the number of patients that need to be treated so that the number of patients that benefits minus the number of patients that is harmed equals one. The NNT net benefit was calculated by: $NNT_{netbenefit} = 1/(1/NNTB - 1/NNTH)$.

Baseline variables of tPA- and placebo-treated patients were compared using the t test for normally distributed data, the Mann–Whitney U test for nonnormally distributed data, and the χ^2 test for binary data. NNTs for different treatment time windows were compared using analysis of variance.

Results

Key baseline variables predictive of functional outcome that were compared among treatment groups for this study included age and National Institutes of Health Stroke Scale score, history of diabetes, history of stroke, gender, and serum glucose (Table 1). The variables were well matched between placebo and control groups in each treatment time window with the exception of National Institutes of Health Stroke Scale score in the 91- to 180-minute time window. In this time window, median National Institutes of Health Stroke Scale score was 11.5 in the tPA arm compared with 13.0 in the placebo arm ($P=0.009$).

Table 2 lists the NNT estimates for all analyses. The NNTB based on the expert panel assessments progressively increases and the NNTH progressively decreases with longer treatment time windows ($P<0.001$, analysis of variance).

Table 1. Baseline Characteristics of Placebo and tPA-Treated Patients Stratified by 90-Minute Treatment Time-Windows

Variable	Time Window, Minutes	Placebo	tPA
Age	0–90	66±12	68±11
	91–180	66±12	67±11
	181–270	66±11	65±12
	271–360	65±12	66±11
Female	0–90	42.7%	38.5%
	91–180	39.0%	41.1%
	181–270	35.0%	42.8%
	271–360	41.7%	40.7%
National Institutes of Health Stroke Scale score	0–90	15 (10–19)	15 (10–20)
	91–180	13 (9–19)	11.5 (7–18)*
	181–270	12 (8–16)	11 (8–16)
	271–360	10 (7–14)	10 (7–16)
Glucose, mg/dL	0–90	142±73	150±78
	91–180	149±73	141±61
	181–270	139±57	146±60
	271–360	140±60	141±67
History of stroke	0–90	10.7%	9.9%
	91–180	13.7%	15.6%
	181–270	16.8%	15.6%
	271–360	17.7%	18.2%
History of diabetes mellitus	0–90	16.7%	21.1%
	91–180	20.0%	20.9%
	181–270	17.8%	19.2%
	271–360	19.9%	18.6%

Values are means and SD for age and glucose and medians and interquartile range for National Institutes of Health Stroke Scale score.

*P=0.009 (2-sided Mann–Whitney U test, normal approximation).

Results are similar whether the full range of the mRS is considered (7 strata) or the modified Rankin Scale is condensed into 6 strata by merging severe disability (mRS of 5) and death (mRS of 6) into one category.

The NNT estimates were used to calculate 3 alternative but related effect measures. The number of patients that benefit and number of patients that is harmed for every 100 patients treated is displayed in the Figure; the help-to-harm ratio for the four 90-minute treatment time windows is 18.1, 8.8, 5.0, and 0.7, respectively; and the $NNT_{netbenefit}$ for the four treatment time windows is 3.8, 4.9, 7.4, and infinity, respectively. Each of these effect measures illustrates, in a different way, that in the 0- to 90-minute time window, the number of patients that benefit from treatment far exceeds the number of patients that is harmed by treatment and that this excess declines when patients are treated at later times; in the 271- to 360-minute time windows, the numbers are reversed with patients who are harmed by treatment outnumbering those who benefit.

Discussion

The NNT is an effect measure that has gained popularity, because it is both statistically valid and intuitively accessible and therefore particularly suitable for clinical decision-making.[2] Using previously described expert-based and expert-independent algorithmic methods to delineate shifts over the entire range of the mRS when patients with stroke are treated with intravenous tPA, we estimated NNTs for each 90-minute treatment time window up to 6 hours.[3] The biologically most likely NNTB for patients treated in the 0- to 90-minute time window was 3.6, in the 91- to 180-minute time window 4.3, in the 181- to 270-minute time window 5.9, and in the 271- to 360-minute time window 19.3. Biologically most likely NNTH values for these time windows were 65, 38, 30, and 14, respectively. These are useful estimates that clinicians can use in the acute setting to inform patients with stroke and/or their family members of the benefits and risks associated with intravenous tPA treatment.

The NNT effect measure is often used for treatments that carry no significant risk. In such settings, it may be straightforwardly interpreted as the number of patients that need to be treated with a certain intervention or medication for one patient to experience a benefit. However, because tPA treatment can lead to both improved as well as worsened outcomes, knowing only the NNT for one patient to benefit from tPA is not sufficient. Therefore, the data were analyzed in terms of both the NNT for one patient to benefit (NNTB) and the NNT for one patient to be harmed (NNTH). The same data were also reported as the number of patients that benefit and the number of patients that are harmed per 100 patients treated. The gradual decline in the percentage of patients that benefits and the gradual incline in the percentage of patients harmed by tPA therapy is illustrated in the Figure. Although these methods describe the effect of tPA in an intuitive way, the need to use 2 variables (one for benefit and one for harm) introduces modest complexity. Some people may therefore favor combining both variables into one common effect measure. This can be achieved by reporting the help-to-harm ratio defined as the NNTB divided by the NNTH. The help-to-harm ratio is 18.1, 8.8, 5.0, and 0.7 for the 4 90-minute treatment time windows, respectively, indicating that in the 0- to 90-minute window, intravenous tPA benefits 18 patients for every one patient it harms; in the 270-to 360-minute window, intravenous tPA benefits 0.7 patients for every one patient it harms. $NNT_{netbenefit}$ is an alternative effect measure that incorporates benefit and harm into a single metric. $NNT_{netbenefit}$ summarizes the effectiveness of tPA in the most straightforward and intuitive way and is therefore suitable for use in the acute setting when physicians need to inform patients and their families of the effectiveness of tPA. Based on the $NNT_{netbenefit}$ calculations in this study, we can inform patients who could receive tPA within the first 90 minutes that, taken the relatively small risk of treatment into account, one patient benefits for every 3.8 patients who are treated. For patients who can be treated in the 91- to 180-minute window, this number is 4.9 and for patients treated in the 181- to 270-minute window, it is 7.4. For patients treated between 270 and 360 minutes, the $NNT_{netbenefit}$ is infinity, indicating that there is no net benefit of treatment in this time window.

In the 271- to 360-minute treatment time window, the patients harmed by treatment outnumber those that benefit. This is clearly illustrated in the Figure and by the fact that the

Table 2. NNT Estimates for tPA Therapy Stratified by 90-Minute Treatment Time-Windows

Treatment Time Window, Minutes	0–90	91–180	181–270	271–360
Expert panel				
7-strata				
NNTB	3.6 (3.1–4.2)	4.3 (3.6–5.3)	5.9 (4.3–8.2)	19.3 (12.0–31.0)
NNTH	65 (38–111)	38 (24–61)	30 (20–45)	14.0 (10.5–17.8)
6-strata				
NNTB	3.7 (3.1–4.3)	4.3 (3.6–5.3)	5.9 (4.3–8.2)	19.4 (12.1–31.0)
NNTH	82 (42–160)	49 (31–77)	36 (24–53)	16.1 (13.8–18.8)
Computer simulation				
NNTB	3.4 (2.4–4.4)	4.3 (3.1–5.5)	6.7 (5.9–7.5)	18.4 (14.0–22.7)
Maximum possible benefit				
NNTB	2.0	2.9	3.9	12.1
Minimum possible benefit				
NNTB	6.7	7.0	9.7	30
Median expert				
NNTB	3.9	4.0	6.5	17
NNTH	71	37	33	13

Values are means and 95% CIs when applicable. The median NNTH distribution of all experts was used as a basis for computation of maximum and minimum possible NNTBs and for the computer-generated NNTB estimates. NNT estimates are based on shifts over the entire range of the mRS (7-strata) unless otherwise specified.

help-to-harm ratio is less than one and the $NNT_{netbenefit}$ is infinite in this late treatment time window. At first, these results seem at odds with the results of the pooled analysis, which demonstrated increased odds for excellent outcome, albeit not significant, for patients treated between 271 and 360 minutes (OR, 1.04; 95% CI, 0.84 to 1.29).[1] Closer inspection of the distribution on the mRS of placebo- and tPA-treated patients in the 271- to 360-minute time window explains the apparent discrepancy. In this time window, the rate of excellent outcome, defined as a mRS of 0 to 1, is 37% with tPA versus 36% with placebo.[1] Thus, when the data are analyzed based solely on the proportion of patients that achieve an excellent outcome, tPA used in the 271- to 360-minute time window is associated with a 1% absolute increased chance of good outcome. However, this type of analysis ignores the 5% absolute increased chance of death that is also associated with tPA treatment in the 271- to 360-minute time window.[1] The fact that the absolute increased risk of death with tPA (5%) exceeds the absolute increased chance of a good outcome (1%) is consistent with the NNT analysis over the entire range of outcomes, which demonstrates that more patients are harmed than helped by tPA in the 271- to 360-minute treatment time window. The cause of the excess deaths in the tPA-treated population in the 271- to 360-minute time window may, in part, be related to ECASS 1 patients making up a relatively large proportion of the total number of patients in this time window. Whereas 90-day mortality rates were similar for tPA- and placebo-treated patients in ECASS 2,[5] the 90-day mortality rate was higher in tPA-treated patients (22.4%) compared with placebo (15.8%) in ECASS 1.[6] The higher dose of tPA used in ECASS 1 (1.1 mg/kg) is likely a contributing factor responsible for the increased mortality associated with tPA treatment in this study.

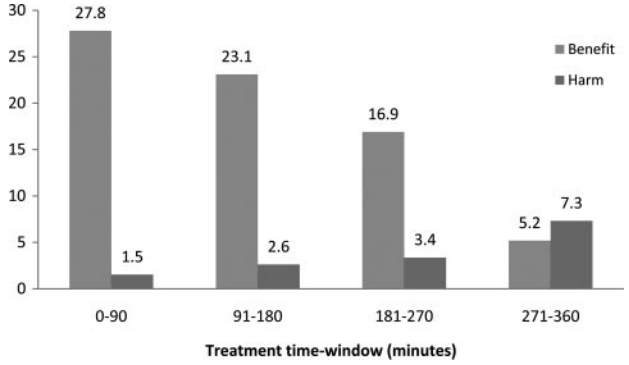

Figure. Number of patients who benefit and are harmed per 100 patients treated in each time window.

The suggestion of potential benefit for patients treated in the 271- to 360-minute time window is illustrative of the effect that can result from dichotomization of an ordinal outcome scale such as the mRS. NNT estimates based on a mRS dichotomized into an excellent outcome category (defined as mRS 0 to 1) and a nonexcellent outcome category (defined as mRS 2 to 6) are quite different from those reported in this article. This difference results from only counting shifts across the mRS 1 to 2 divide in the dichotomized approach versus counting shifts across all 6 mRS divisions in the $NNT_{netbenefit}$ approach used in our study. For example, for treatment within the first 90 minutes, the NNT based on a dichotomized mRS is higher (8.3) than the $NNT_{netbenefit}$ reported in this article (3.8). This underestimation of the treatment effect by the method that is based on the dichotomized mRS results from an inability to detect positive

shifts that occur within the mRS 2 to 6 range and within the mRS 0 to 1 range. Conversely, in the 271- to 360-minute time window, the NNT based on the dichotomized mRS overestimates the treatment effect of tPA because it does not account for negative shifts occurring within the mRS 2 to 6 range. In this treatment time window, the NNT based on the dichotomized approach is 100 compared with a $NNT_{netbenefit}$ that is infinite.

Utility research has shown that a substantial proportion of healthy elderly individuals consider a severely disabled post-stroke state (mRS of 5) to be an outcome that is equally or more undesirable than death (mRS of 6).[7] Such patients would therefore view a shift from mRS 6 to mRS 5 as not being a benefit of therapy. To account for this, we ran a secondary analysis in which we condensed the 7-point mRS to a 6-point scale by combining the mRS 5 and 6 categories into one. This change did not have a significant effect on the study results (Table 2). The primary results of our study, based on shifts over the full 7-level range of the mRS, therefore provide a reasonable estimate of the expected effect of tPA regardless of a patient's perception of the utility of being severely disabled versus dead.

There is one previous analysis that estimated NNTB and NNTH for tPA treatment using expert generation of joint outcome distribution tables.[3] This study differed from the current study in 2 ways: (1) it estimated NNT values for tPA treatment in a single broad time window, 0 to 3 hours; and (2) it was based on data from the 2 NINDS trials rather than all 6 of the first intravenous TPA trials. The current study is the first to estimate NNTs based on expert generation of joint outcome distribution tables for each 90-minute treatment time interval up to 6 hours. The prior study yielded an NNTB for tPA treatment within 3 hours that was slightly more favorable at 3.1 and an NNTH that was slightly less favorable at 30.1 compared with the results of the current study. Several differences account for this discrepancy. First, current values were derived from group outcomes pooled from all 6 of the first intravenous TPA trials rather than just the 2 NINDS tPA trials. The ECASS 1 and 2 and ATLANTIS A and B studies contributed almost no patients to the pooled data for the 0- to 90-minute time window, but they did contribute patients to the 91- to 180-minute time window. A relatively lesser effect of tPA in the 91- to 180-minute time window in ECASS and ATLANTIS subjects compared with NINDS subjects may have contributed to the slightly reduced effect of tPA that was observed in our study compared with the previous NNT analysis. Second, compared with the previous study, the experts for the current study on average projected greater shifts in patients who benefit (ie, patients who improve, improve by more points on the mRS) and greater shifts in patients who are harmed (ie, patients who worsen, worsen by more points). Specifically, the mean shift on the mRS for patients who improved was 1.80 in our study compared with 1.76 in the prior study and the mean shift on the mRS for patients who worsened was 1.91 in our study compared with 1.62 in the prior study.

This study has limitations. First, ECASS 3 has provided more data on tPA therapy in the 3- to 4.5-hour time window than what was available at the time that this study was conducted.[8] Because the ECASS 3 database has not yet been merged with the pooled data set of the first 6 major tPA stroke trials, these data could not be integrated in the current study. However, because the OR for good outcome associated with tPA was similar between ECASS 3 and the 3- to 4½-hour time window cohort of the pooled data set, it is unlikely that inclusion of ECASS 3 data would have significantly altered the results of our study. Second, the imbalance in the median National Institutes of Health Stroke Scale score in favor of tPA-treated patients in the 91- to 180-minute time window is a limitation of this study. As a result, the NNTB reported for the 91- to 180-minute time window may be biased in favor of tPA treatment and hence the true NNTB in that time window may be slightly higher than the reported 4.3 (95% CI, 3.6 to 5.3).

This study is the first to use an iterative computer simulation method for generating joint outcome distribution tables to estimate NNTB for tPA therapy. The computer simulation yielded NNTB estimates that were close to the expert panel's mean estimates. The similarity in results between the 2 methods provides reasonable evidence for the validity of using an expert panel to determine NNTBs. Limitations of an unstructured computer simulation approach are that (1) the degrees of freedom of the matrix is so large that calculating every single possible solution is practically unfeasible; and (2) calculating a sample of all distributions without using any built-in constraints suffers from the random person effect, rendering biologically implausible results. Therefore, the NNTH of the median expert was used as a built-in constraint, limiting the degrees of freedom of the matrix and improving its biological plausibility by removing the random person effect. Although nearly the same, the NNTBs generated by the iterative computer simulation method were consistently slightly less than those generated by the pooled experts. This difference has biological relevance. The group outcome data from the pooled trials provide a total amount of benefit that can be allocated variously to individual patients. When each patient benefits a great deal from therapy, each patient consumes more of the total benefit indicated by the group distributions, and a smaller proportion of patients experience some benefit; conversely, when each patient benefits to a small degree, a greater proportion of patients experience some benefit. That the expert-specified NNTB is larger than the median of all possible NNTBs determined by iterative simulations indicates that the experts project that individual patients who benefit from lytic therapy do so substantially.

In summary, this study determined treatment time-specific NNTs based on shifts over the entire range of possible clinical outcomes. The results provide new insights into the treatment effect of tPA therapy in acute stroke that may facilitate the relay of efficacy data from treating physicians to stroke victims. Up to 4½ hours after symptom onset, the number of patient that benefit from treatment outweighs those who are harmed, whereas beyond 4½ hours, tPA therapy does not appear to have a net benefit. The results based on generation of joint outcome distribution tables by an expert panel were bounded by algorithmic calculations and validated using a computer simulation.

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