The Likelihood of Being Helped Versus Harmed

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Thrombolytic Therapy for Acute Ischemic Stroke

See related article, pages 2279–2283.

Symptomatic intracerebral hemorrhage (SICH) risk is the factor most likely to preclude tissue plasminogen activator (tPA) use by emergency physicians. Of the 40% of respondents to the American College of Emergency Physicians survey about tPA for acute ischemic stroke who would not use tPA in the ideal setting reported that this was attributable to SICH risk.1 From the same survey, we learned that in the respondents’ minds, the highest clinically acceptable mean risk of SICH was 3.4% (compared with 6.4% risk reported in the tPA arm of the National Institute of Neurological Disorders and Stroke [NINDS] trial).

The American Academy of Emergency Medicine (AAEM) has created an educational tool entitled “tPA for Stroke—Potential Benefit, Risk, and Alternatives,” dated May 3, 2007, that was circulated to its membership.2 The document was designed to help emergency physicians inform patients and family members about the pros and cons of tPA for stroke in appropriate patients. The tool emphasizes how important it is for physicians to weigh the possibility of benefit (improved function at 3 months) against the possibility of harm (severe bleeding or death). The AAEM has produced an accompanying illustration to pictorially and quantitatively convey the probabilities of “good recovery,” “poor or no recovery,” and “brain bleed and death” with and without tPA in cohort of acute ischemic stroke patients. In reviewing the potential benefit, the illustration suggests that 8 of 18 stroke patients who receive tPA will have a good recovery by 3 months after the event. This is compared to 6 of 18 stroke patients who recover substantially with good outcome without tPA. Even more importantly, in reviewing the potential risk, the illustration suggests that bleeds into the brain, with high probability of death, will occur in 1 of 18 patients receiving tPA. No patients in the diagram are visualized to experience an intracerebral bleed or die without tPA. Using this educational resource, an emergency physician, with patient and family members about the pros and cons of tPA for stroke, would naturally conclude that for every 18 stroke patients treated with tPA, 9 would have a good recovery related to tPA, 9 would have poor or no recovery regardless of tPA, and 1 would have an intracerebral hemorrhage and die related to tPA. The illustration tool conveys the most widely publicized ballpark number needed to harm (NNH) for tPA in acute ischemic stroke, ≈17 (the number of stroke patients who would need to be treated before one adverse side effect [SICH and possible death] of the treatment will occur). Use of such a tool in clinical practice would be problematic, misleading, and would erroneously convey an unfavorable benefit-risk ratio.

The NNH is the inverse of the absolute risk increase. In other words, it reflects the number of patients who would need to be treated over a specific period of time before 1 adverse side effect of the treatment will occur.3 It is simply another quantitative expression of the absolute risk increase, in the same way that the clinically popular number needed to treat (NNT) is another expression of the absolute risk reduction. When discussing the NNH, it is important to specify the treatment, its duration, and the adverse side effect it can cause. The NNH, if the adverse side effect is protocol-defined SICH in NINDS Trials 1 and 2, has been determined to be 17.2, but does not represent the most clinically relevant NNH for tPA in stroke.4–6 The NNH for protocol-defined SICH is regularly referred to as representing the NNH for tPA, as in the AAEM tool above.2,7 Saver, in this issue of Stroke, correctly argues that NNH for protocol-defined SICH is not the most appropriate NNH for tPA, for at least 3 fundamental reasons.8 First, the NINDS trials used a very conservative protocol definition of clinical worsening. Second, many patients have hemorrhages temporally associated with, but not causally related to, early worsening. Third, even among the subset of patients in whom hemorrhage causes early worsening, many do not have their final outcome altered as a result. For these fundamental reasons, the most important NNH value for patient and treating physician to consider when making tPA treatment decisions is not the NNH with adverse side effect defined as hemorrhage temporally associated with early worsening of any degree, but rather the NNH with adverse side effect defined as SICH resulting in a worsened final functional outcome.

Saver’s study was undertaken to derive NNH values for the impact of SICH upon the final 3-month score on a widely used stroke trial measure of global disability, the modified Rankin Scale (mRS). Although the rates of adverse outcomes in patients who experienced SICH after tPA are easily identified and portrayed pictorially in diagrams such as that promoted by AAEM, they grossly overestimate the net harm of this therapy. Saver cleverly derived a 15 variable prognostic model from placebo group patients enrolled in NINDS tPA trials 1 and 2 and used it to predict final global disability...
outcome for tPA-related SICH patients had they been treated with placebo, rather than tPA. The end result of this well conceived and methodologically sound design was the ability to truly compare the observed 3-month mRS outcomes among the patients experiencing SICH after tPA and the predicted outcomes had they been treated with placebo. The NNH for 1 more patient to have a final disabled or dead outcome (mRS ≥3) attributable to tPA-related SICH was 707; for severely disabled or dead outcome (mRS ≥4) was 126; for fatal outcome 36.5; and for worsened outcome by any degree (≥1 mRS grade) was between 29.7 and 40.1.8 In other words, for every 100 acute ischemic stroke patients treated with tPA, ≈3 will ultimately be deleteriously affected and experience a worse final global functional outcome as a result of tPA-related SICH. The main limitation of the study is the small sample size and its impact on precision. Had the same analysis been conducted on a substantially larger pooled dataset of all major intravenous tPA trials, the precision would be increased.

A more clinically relevant tool for acute stroke patients, family members, and their treating physicians would be one that illustrates how for every 100 acute ischemic stroke patients treated with tPA, ≈32 will benefit9 and 3 will be harmed as a result of tPA-related SICH.8 This would have quite a different impact than the ≈2 in 18 that benefit and 1 in 18 that are harmed in the AAEM tool illustration, discussed above.2 If we return for a moment to the American College of Emergency Physicians survey we are reminded that in the respondents’ minds, the highest clinically acceptable mean risk of SICH was 3.4%.1 By more sensibly defining tPA-related SICH, as Saver has done, the risk is actually at (100/29.7=3.4%) or below (100/40.1=2.5%) this maximally acceptable risk.

When applying information about adverse effects in clinical practice, it is helpful to use the expression “likelihood of being helped versus harmed” (LHH).10 This meaningful measure incorporates information about benefit and harm and expresses the pros (benefits) and cons (harm) of a treatment in a single value. The LHH is simply the ratio of the NNH and the NNT: LHH = NNH/NNT. An LHH >1 means that the expected benefits outweigh the possible harm, and an LHH <1 means that the possible harm outweighs the expected benefits. The average estimated NNT for 1 additional patient to have a better outcome by 1 or more grades on the mRS as a result of tPA treatment is 3.1 (95% CI, 2.6 to 3.6).9 The NNH for 1 more patient to have a worsened outcome by any degree (≥1 mRS grade) attributable to tPA-related SICH is between 29.7 and 40.1.8 Therefore, the LHH could be expressed as ≈30/3=10. When expressed in this fashion, it is evident that intravenous tPA is 10 times more likely to help than to harm eligible patients with acute ischemic stroke.

Saver’s assistance in deriving clinically relevant NNT9 and NNH8 for intravenous tPA in acute ischemic stroke will assist patients, family members, physicians, payers, and policymakers to more sensibly compare the benefits and harm conferred by this therapy.

Disclosures
B.M.D. has several conflicts of interest to report: (1) Consultant/Advisory Board: Genentech; (2) Steering Committee/Advisory Board: Neurobiological Technologies; (3) Steering Committee: Vernalis UK VASTT Trial; (4) Other Research Support: NIH-NINDS IMS 3 Trial Site Investigator; (5) Other Research Support: Neurobiological Technologies Ancrod Stroke Program Trial Site Investigator; (6) Other Research Support: Vernalis UK V10153 VASTT Trial Site Investigator.

References
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