Abstract

**Background** Thrombolytic therapy for acute ischemic stroke raises several unsettled bioethical issues related to risk versus benefit. Excluding the National Institutes of Neurological Disorders and Stroke (NINDS) rt-PA trial, the risk of intracerebral hemorrhage averages 10.3%, and there is a 44% increase in the odds of death among fibrinolysis-treated patients. Some investigators have suggested that as yet unidentified subgroups may benefit despite an increased early risk of hemorrhage and death, while others have warned that the widespread use of thrombolysis cannot currently be recommended despite recent Food and Drug Administration approval. The NINDS rt-PA trial showed a net benefit, but the relative risk to benefit ratio in individual patients is uncertain because of incomplete subgroup analysis. We explore these and related issues by applying the bioethical principle of justification to the selection of stroke patients for thrombolysis.

**Summary of Comment** Justification of a therapy rests on the criteria of safety, efficacy (net benefit under ideal conditions), effectiveness (net benefit under routine conditions), efficiency (cost-effectiveness or cost benefit), and outcome (proportionality and informed consent). The ethical principal of proportionality states that positive outcomes must be proportional to negative outcomes; only the NINDS trial sets equipoise between risk and benefit. The relative risk to benefit ratio and cost-effectiveness of thrombolysis will likely vary among treating
physicians and patient subgroups. Although some potential selection factors such as early CT changes, National Institutes of Health Stroke Scale score >22, and age >77 years have been identified, it is not yet possible to predict response to treatment in individual patients. The effectiveness of thrombolysis outside of a clinical trial has not yet been demonstrated, and it is not clear that thrombolysis is cost-effective for all potential patient subgroups.

Conclusions No stroke thrombolysis regimen has met all five justification criteria. Proportional outcome standards that take into account patient preferences must be established. The risk to benefit ratio of thrombolysis in patient subgroups requires clarification and should incorporate cost-efficiency analyses. These issues should be kept in mind when considering thrombolysis therapy in patients with acute ischemic stroke and when designing clinical trials.

Key Words: cerebral ischemia • ethics, medical • thrombolysis

Introduction

Thrombolytic therapy for acute ischemic stroke raises several bioethical issues related to risk versus benefit. It is well established that intravenous thrombolysis for acute ischemic stroke increases the risk of clinically significant intracerebral hemorrhage. Excluding the NINDS rt-PA trial, the risk of symptomatic intracerebral hemorrhage with intravenous thrombolysis averages 10.3%, a 3.5-fold increase compared with control subjects, and there is a 44% increase in the odds of death among fibrinolysis-treated patients.

Three recent trials of intravenous streptokinase, AST, MAST-E, and MAST-I were stopped early because of an increased risk of death, largely due to intracerebral hemorrhage. In MAST-E, death due to intracerebral hemorrhage was 16 times more frequent in the streptokinase group. In MAST-I, 75% of all deaths in the streptokinase group were "cerebral" compared with 55% of deaths among control subjects. Although deaths due to intracerebral hemorrhage are not reported, presumably the excess mortality in the streptokinase group was due to the 10-fold and 16.6-fold increase in symptomatic intracerebral hemorrhage in the streptokinase-alone and streptokinase+aspirin groups, respectively. Despite the lack of any statistical benefit, MAST-I fomented a public controversy among its own investigators by emphasizing that patients who survive intravenous streptokinase treatment might have a lower rate of death and disability at 6 months.

In ECASS, there was a significant increase in symptomatic intracerebral hemorrhage in all rt-PA groups and a significant increase in deaths due to intracerebral hemorrhage in the intent-to-treat analysis (6.3% versus 2.4%; P=.02). In the NINDS trial, both symptomatic and fatal intracerebral hemorrhage were significantly higher in the rt-PA group. In the NINDS trial, 83% of symptomatic intracerebral hemorrhages in the rt-PA group occurred within 36 hours of treatment. In ECASS, 65% of fatal intracerebral hemorrhages occurred within 72 hours of stroke onset. The high 10-day mortality rates reported in the MAST-E and MAST-I trials also provide indirect evidence that the majority of hemorrhages occur within hours or days of treatment.

While the risk of symptomatic intracerebral hemorrhage is increased in all reported studies, no net benefit has been demonstrated for intravenous thrombolysis in acute stroke, with the exception of the NINDS rt-PA trial. The NINDS trial reported an 11% to 13% absolute increase in favorable outcomes at 90 days among patients...
treated within 3 hours with intravenous rt-PA. The net benefit of rt-PA was seen "consistently" in subgroups categorized by age, stroke subtype ("small-vessel" versus "large-vessel" versus "cardioembolic"), stroke severity, and aspirin use. Despite these results and subsequent Food and Drug Administration approval of intravenous rt-PA for selected patients with ischemic stroke of <3 hours duration, the MAST-E investigators recently stated that the "widespread use of thrombolytic therapy in patients with acute stroke cannot be recommended [until] specific characteristics of [responders] are identified."4

With this brief background, we would like to explore under what current circumstances we can justify exposing ischemic stroke patients to an increased acute risk of hemorrhage and death from thrombolysis. The crucial notion is contained in the word "justify." Justify means to move closer to a norm or standard, such as to justify the text in a document by word processing. More precisely, justify means to prove or show something to be right or reasonable.

Interwoven in the word "justify" are scientific, ethical, and economic standards. Schwartz2 has suggested four criteria for evaluation of medical therapies (Table 1). Traditionally, new therapies have been justified on the basis of randomized clinical trials that demonstrate safety and efficacy, ie, a net benefit under ideal circumstances (so-called level 1 evidence). However, in the emerging healthcare environment, safety and efficacy are no longer sufficient to justify a new therapy. Schwartz states: "The market is now requiring that in addition to being safe and efficacious, interventions also must be demonstrated to be both effective, ie, to provide benefit under routine circumstances, and efficient, ie, the benefit obtained is worth the cost." Clinical health economics examines the "efficiency" or "value" of a therapy. Are the health benefits derived worth the monetary costs? This relatively new, increasingly important, and for many physicians uncomfortable discipline helps decide how best to spend limited resources through cost-benefit or cost-effectiveness analysis of new therapies. That is, a therapy must show benefit over risk as justified by the standard of socially responsible use of resources.

View this table:  Table 1. Criteria for Justification of Medical Interventions
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To this list should be added outcome justification criteria. Outcome justification relies on the ethical principle of informed consent, which acknowledges the right of persons to accept clinical risk freely and with an accurate understanding of the degree and type of risk and the principle of proportionality.10 The principle of proportionality acknowledges that all actions have positive and negative effects but accepts the risk of negative effects as long as the positive effects are proportional.

The "benefit" of a therapy describes the assessment of outcomes as positive or negative. Hence, the choice of outcome variables and standards strongly influences not only the statistical results of a trial but also their ethical justification and clinical validity. Our notions about how to assess stroke outcomes have evolved over several years. Early acute stroke trials, and initially even the NINDS rt-PA trial, defined a "favorable" outcome as a somewhat arbitrary change in a stroke scale score, which may or may not be clinically relevant. More recent acute stroke trials have turned to specific functional assessments such as activities of daily living (eg, the Barthel Index) or a more global disability index (eg, a modified Rankin scale) at 90 days as the primary outcome measure.
Although they are an improvement over stroke scale scores, functional scales also pose difficulties. The "ceiling effect" of the Barthel Index is well known; patients may have a significant neurological disability yet adapt to be able to perform activities of daily living. A modified Rankin score of \( \leq 2 \) is often equated with mild disability and a "favorable" outcome. However, in the original Rankin scale the distinction between a score of 2 or 3 is ambiguous, and there are no published guidelines to increase uniformity of scoring.\(^\text{11}\)

Lack of standardization in stroke outcome end points, as well as in other variables, makes comparisons between studies difficult. MAST-I defined a "favorable" outcome as a modified Rankin score of \( \leq 2 \) at 6 months as determined by a telephone interview. The 6-month end point and telephone interview raise further questions about the reliability of the outcome standard in this trial. In ECASS, the only significantly positive primary outcome in the target population was a 1-point improvement in the median modified Rankin score at 90 days (ie, 2 versus 3).

The NINDS trial set a new standard for assessing benefit by switching the primary end point from a 4-point NIHSS score improvement to essentially full neurological recovery at 90 days. This rigorous new standard sets proportionality between risk (death or severe disability) and benefit (full neurological recovery) and makes the net positive results convincing. However, the distribution of moderate disability was not emphasized in the NINDS trial, yet it is a more frequent outcome after acute stroke.

Some investigators have questioned whether global assessments of functional outcome such as the Barthel Index or modified Rankin scale should be supplanted by quality of life assessment in stroke survivors.\(^\text{12}\) Quality of life assessment distinguishes between impairments, disabilities, and handicaps (Table 2). Handicap refers to a patient's ability to fulfill normally expected social roles. Quality of life assessment encompasses at least four domains: physical, functional, psychological, and social (Table 3). The patient's perceived ability to fulfill social roles is of major importance for the assessment of personal quality of life. Handicap assessment identifies activities such as recreation, communication, mobility, cognition, and social interaction as indicators of quality of life.

The Barthel Index and the modified Rankin scale measure disability rather than handicap.\(^\text{13}\) Physical disabilities do not always have a negative impact on quality of life. Conversely, stroke survivors with little or no physical disability can experience a significantly compromised quality of life. Bamford et al\(^\text{14}\) have suggested an amended Oxford Handicap Scale based on the Rankin scale that assesses handicap from stroke, but it has not been fully validated or widely used in acute stroke trials. There are many other quality of life instruments, but

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View this table:  **Table 2. Factors Determining Disease Impact on Patient Health**
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View this table:  **Table 3. Domains of Quality of Life Assessment**
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their applicability to acute stroke clinical trial outcome assessment remains investigational. Among other difficulties, handicap is strongly influenced by cultural, environmental, and personal factors that may be difficult and impractical to directly measure in large clinical trials.

The MAST-I investigators advised evaluating "all the clinical and ethical implications of early risk and potential benefit from thrombolytic drugs from the patient's point of view" (the emphasis is ours). If they were referring to informed consent, this requires that information about risks (negative outcomes) be communicated to patients in terms they comprehend. The purpose of this communication is to provide information about risks and benefits that patients can assess according to their personal goals and values, as well as according to the degree of risk taking they can tolerate. The situation with thrombolysis in acute stroke is analogous to investing in the stock market, where there are different levels of return for different financial risks; some investors opt for high-risk growth funds, while others prefer a guaranteed savings account at the bank.

Several studies have documented major discrepancies between patients' and providers' perceptions of functional capabilities and preferences. Patients at risk for stroke fear disabling paralysis more than death, but preferences of patients with completed strokes have not been well studied. It is not known whether stroke survivors consider a "favorable" outcome to be the ability "to look after oneself" or to perform activities of daily living while being "unable to carry out all previous activities." (Which activities are not specified by the Rankin scale. Are they activities important to this patient?) Informed-consent documents typically describe potential benefits in very general terms, eg, "Your participation in this study may reduce your disability following your stroke." Perhaps we should translate assessment scales into more realistic measures of quality of life that patients understand: "This treatment may increase your chances to drive, to play with your children, to write an article, to play music again." Patients at risk for stroke could also clarify in their living wills what they consider a "minimal" acceptable disability or handicap.

If the MAST-I investigators are suggesting that treatment should be selected on the basis of the individual patient's specific stroke problem, the dilemma of applying the results of large clinical trials to a patient in the emergency department at 3 AM is well known. This difficulty arises from several reasons: (1) subgroups are not well defined in large trials, (2) the entry criteria in clinical trials are very restricted so that many more patients are excluded than treated, (3) specific information important in clinical decision making is missing from clinical trials (eg, precise stroke etiology, vascular data), and (4) there are conflicting data in the literature.

Making large clinical trials more relevant to individual patients requires analysis of clinically important subgroups. Unfortunately, despite bedside relevance, most subgroup analyses have insufficient power to be statistically conclusive. Subgroup and multivariate analyses nonetheless help identify patient characteristics associated with better or worse outcome after stroke, although these same variables do not necessarily distinguish those patients most likely to benefit from therapy. The MAST-I investigators could not identify any subgroup, with the marginal exception of those treated <3 hours from onset, who had a lower early mortality rate. The AST trial also found a trend toward improved outcomes but no net benefit among the 70 patients treated with intravenous streptokinase within 3 hours from stroke onset. Accordingly, intravenous streptokinase cannot be justified for any acute stroke patient population on the basis of current data.

The situation with 6-hour intravenous rt-PA is somewhat more complex. The intent-to-treat analysis in ECASS, reflective of the community experience, was negative. ECASS could not confirm a benefit in patients treated within 3 hours of stroke onset, possibly because patients with more severe strokes presented to the hospital...
sooner in this trial. However, ECASS suggested that a benefit for 6-hour intravenous rt-PA might be demonstrable at 90 days in a "target population" without early signs of infarction on CT. Patients with early CT signs presumably have large infarcts with a worse natural history and may also have a higher risk of fatal brain hemorrhage. As the investigators point out, the actual number of CT violators excluded from this target population was small, yet it made the difference between a net positive or negative outcome. Thus, the margin for error is small with this intravenous rt-PA regimen. The therapy may be "efficacious" within a rigidly controlled clinical trial, but it would likely prove "ineffective" and dangerous in the community setting and therefore cannot be justified. Similarly, although the efficacy of intravenous rt-PA in selected patients with stroke duration of <3 hours has been demonstrated within a clinical trial, the effectiveness of intravenous rt-PA in the community setting remains to be documented.

Even well-designed trials with net positive results can leave individual treatment questions unsettled. The NINDS trial reported a "consistent" benefit across all stroke types regardless of severity, but is this precise enough to justify individual patient treatment decisions? What is the specificity of the diagnostic criteria used to define stroke type? Was the 11% to 13% absolute benefit and 6.4% symptomatic brain hemorrhage rate the same for clinically relevant subgroups? The package insert for Activase suggests not, since for patients with an NIHSS score >22 or aged >77 years the "trends toward increased risk for symptomatic intracerebral hemorrhage were more prominent" and, although still favorable, outcomes were "reduced." No details are provided. How, then, should the relative risk and benefit of intravenous rt-PA be phrased to such patients?

In uncontrolled pilot studies of 3-hour intravenous rt-PA, these same investigators reported no benefit and poor outcomes in patients with an NIHSS score >20 and mainstem middle cerebral artery occlusion. How did such patients fare in the NINDS trial? In the absence of vascular information, can they be, or should they be, reliably identified? Many investigators have reported higher recanalization rates with intra-arterial thrombolysis for large-vessel intracranial occlusions, but no clinical trial has demonstrated efficacy on the basis of vascular diagnosis or intra-arterial thrombolysis. Is it therefore more justifiable, when confronted with an 80-year-old patient with a 2.5-hour-old main-stem middle cerebral artery thrombosis and an NIHSS score of >22, to give intravenous rt-PA or local intra-arterial thrombolysis by "compassionate" use or to do nothing? Ideally, important patient subgroups should be randomized into a clinical trial comparing a potential new treatment (eg, intra-arterial thrombolysis) with an approved treatment or, when none exists, placebo. Clinical trials should also more precisely identify important subgroups prospectively when calculating sample sizes. Unfortunately, clinical trials take years to complete and may not be feasible for every therapy or patient subgroup. Until such data are available, physicians must ethically reconcile personal bias and uncontrolled but clinically specific observations with controlled but often less specific trial results.

Last, as societies confront limited healthcare resources, the justification of a new therapy may require not only demonstration of efficacy and effectiveness but also efficiency. Is thrombolysis for acute stroke cost-effective? A common cost-effectiveness benchmark is $50 000 per life-year added. Ratios less than this are considered "economically justified." Ratios above $100 000 are "economically unjustified," and the middle zone is uncertain. The cost-effectiveness ratio for rt-PA in the GUSTO trial (in which there would be 11 extra survivors at 1 year per 1000 shifted to rt-PA) was $32 678. Unfortunately, since no study has shown improved stroke survival with thrombolysis, benefit must be measured as years of disability prevented or some other index of quality of life, and available data in stroke survivors is very limited.

In the managed-care environment, the potential exists for the overzealous application of cost-effectiveness...
analysis in patients with acute stroke. Cost-effectiveness ratios are useful for formulating general healthcare policies to optimize utilization of resources, but a bioethical dilemma arises when individual treatment goals clash with broader societal priorities. Many accepted therapies appear economically unattractive when subjected to cost-effectiveness analysis but may well be medically appropriate for an individual patient. Cost-effectiveness analysis is also greatly influenced by study methodology, model assumptions, and patient characteristics. Cost-effectiveness analysis must therefore take into account the highly variable natural history of acute ischemic stroke. To return to our earlier example, it might be questioned whether thrombolysis is cost-effective for patients over 80 years of age with an NIHSS score of >22.

And so we return to the original issue: Under what current circumstances can we justify exposing ischemic stroke patients to an increased acute risk of hemorrhage and death from thrombolysis? Recently published guidelines are helpful but cannot fully address many of the questions raised here. We agree that the answer must ultimately be based on "the patient's point of view," but how can that point of view be well informed when we lack solid data both on patient preferences and the ability of stroke therapy to satisfy these preferences within relevant subgroups? We must search for data that will conform to the principle of proportionality and establish proportional outcome standards in acute stroke trials. These important scientific and ethical goals will be reached only if we demand rigorous assessment of patient satisfaction with the results of therapy. We must also anticipate potential conflict between patient and physician preferences and societal needs as acute stroke therapies become more complex and expensive. There can be no completely satisfying answer to the question "Under what current circumstances can we justify exposing ischemic stroke patients to an increased acute risk of hemorrhage and death from thrombolysis?" as long as the data are incomplete. We hope, however, that we have illustrated that the answer depends not only on how one looks at the question but also through whose eyes.

Selected Abbreviations and Acronyms

- AST = Australian Streptokinase Trial
- ECASS = European Cooperative Acute Stroke Study
- MAST-E = Multicenter Acute Stroke Trial–Europe
- MAST-I = Multicenter Acute Stroke Trial–Italy
- NIHSS = National Institutes of Health Stroke Scale
- NINDS = National Institute of Neurological Disorders and Stroke
- rt-PA = recombinant tissue plasminogen activator

Footnotes

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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