**We will try to publish authors' responses in the same edition with readers' comments. Time constraints might prevent this in some cases. The problem is compounded in a bimonthly journal where continuity of comment and redress are difficult to achieve. When the redress appears 2 months after the comment, 4 months will have passed since the original article was published. Therefore, we would suggest to our readers that their correspondence about published papers be submitted as soon as possible after the article appears.**

### Thrombolysis in Acute Ischemic Stroke

*To the Editor:* I was pleased to see the addition of the new feature, STEPped Care: An Evidenced-based Approach to Drug Therapy. It is the natural next step in the pursuit of a rational, considered approach to the medical literature. With the explosion of POEMs in multiple journals, applying the same rigor to new pharmaceutical modalities seems appropriate and forward-looking.

Unfortunately, the first article in the series falls below the standards set by proponents of evidence-based medicine. In their article on thrombolysis in acute ischemic stroke, Luisi and Hume[1] consider the results of two large studies of recombinant tissue plasminogen activator (rt-PA) and stroke. The ECASS study describes a higher mortality and no significant improvement in functional outcomes in patients given rt-PA compared with placebo.[2] The NINDS study showed an increase in the rate of symptomatic intracranial hemorrhage but no increase in overall mortality.[3] Functional status was significantly better in the treatment group compared with the placebo group.

Attempting to reconcile variant findings into a cohesive recommendation is very difficult. It requires that differing results be accounted for and that care be taken not to favor the findings of one study over another without clear justification. Luisi and Hume did an excellent job of discussing the results of the studies. They fell short in their final interpretation, concluding that the use of thrombolytics in acute stroke is both safe and effective when used in a specified fashion.

The conclusion is surprising for a number of reasons. First, it does not reconcile the results of the component studies. It simply excludes the ECASS study (ie, 50 percent of the studies under consideration). The justification for exclusion is weak. Admittedly, several patients were excluded for protocol violations in the ECASS study. Interestingly, 60.6 percent of those violations resulted from reinterpretation of computed tomographic (CT) head scans. A tenet of evidence-based medicine is the applicability of the findings to the population at large. The radiologists involved in the study were specially trained in the evaluation of acute stroke. Given their variable interpretations despite the high level of training, how consistent would be the results of CT scans performed in community hospitals? Radiology support in this setting is often patchy and, at best, involves a teleradiology link to a radiologist at another site. If one is to consider how these studies would play out in a real-life setting, the exclusion of the ECASS study seems unjustifiable.

Second, even if the ECASS can be excluded, making the recommendation for the use of rt-PA comes from one study only. Instead of appropriate caution for the introduction of a potentially lethal modality, the authors simply echo support for the published recommendations.[4,5] Giving this support, without confirmation or reproduction of the findings, seems hard to justify.

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4. Adams HP Jr, Brott TG, Furlan AJ, Gomez CR, Grotta J, Helgason CM, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke 1996;27:1711-8.
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The above letter was referred to the authors of the article in question, who offer the following reply.

*To the Editor:* We strongly agree with Dr. Hicks that further research into the use of rt-PA in acute ischemic stroke is urgently needed. Many questions have yet to be answered. While the appropriate use of thrombolytic agents in acute myocardial infarction has been well defined through many studies, information on recombinant tissue plasminogen activator (rt-PA) in acute ischemic stroke is based on two studies, only one of which was truly positive. Studies with streptokinase have been consistently negative. Unlike other topics and disease states to be discussed in this feature, few other therapeutic options can be offered to patients with an acute ischemic stroke. The critical question remains whether the recommendation to use throm-

bolytics is premature, as the first tenet of patient care must always be to do no harm.

In our paper we discussed the limitations of ECASS and indicated that the intention-to-treat analysis was closer to what might be expected in routine practice. Our point was to emphasize that ECASS is essentially a negative, not positive, study, as has been suggested. Furthermore, the ECASS results might have been due to the higher dose of rt-PA given or the longer time to treatment. In addition, we did not imply that the casual administration of a thrombolytic was safe and effective. The "specified fashion" represents the only conditions under which the drug may be administered, given the current state of knowledge. Outside the inclusion and exclusion criteria of the NINDS study, at a minimum, there is no evidence of its safety. Individual institutions must develop protocols that ensure these criteria are met. Is even this enough, however?

Two recent studies have underscored the difficulty in using rt-PA safely in actual practice.[1,2] Conducted in 1995, before recent campaigns to increase public awareness of signs of a stroke, a population-based study reported that only 57 percent of respondents were able to name correctly one of the five established warning signs. Among persons older than 75 years, only 47 percent could correctly name one. If patients cannot recognize warning signs, they will not seek care within the requisite 3 hours. More importantly, can the physicians who would most likely make the decision to use rt-PA recognize an intracerebral hemorrhage on a CT scan with 100 percent sensitivity? In a recent study, only 17 percent of emergency physicians, 40 percent of neurologists, and 52 percent of general radiologists achieved this level of discrimination.

The NINDS trial reported a significant positive change in functional outcome at 3 months in those patients who received rt-PA for acute ischemic stroke. A recent analysis of the NINDS data, using a Markov model, estimated an increase in hospital costs of $1.7 million for every 1000 patients treated, with a decrease in rehabilitation costs of $1.3 million and a decrease in nursing home costs of $4.8 million. Also, more patients who received rt-PA were discharged to home than to an inpatient rehabilitation facility or a nursing home (48 versus 36 percent, $P = 0.02$).[3]

Although we believe that we did not simply echo national guidelines and that we appropriately stressed the need for caution in the use of thrombolytics throughout the article, clearly this is the overriding concern for everyone and, in reality, cannot be overemphasized. The bottom line remains: if conditions of NINDS at a minimum cannot be assured, thrombolytic agents should not be administered.

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**References**

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3. Fagan SC, Morgenstern LB, Petitta A, Ward RE, Tilley BC, Marler JR, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. Neurology 1998;50:883-90

**Benefits of Lipid-Lowering Therapy**

*To the Editor:* In a letter to the editor in the May-June 1998 issue of JABFP, Froom et al stated that we "imply that there are primary prevention trials other than the ones we reviewed; there are none. They imply that there are primary prevention trials in women and the elderly; there are none."[1]

At the time of our editorial, the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) had been presented at an international scientific meeting but were not yet published.[2] These data have since been published and corroborate our assertion that lipid-lowering therapy for primary prevention of acute coronary events is beneficial in populations other than middle-aged men.[3]

In this study, 6605 persons (including 997 women) with low-density lipoprotein cholesterol levels greater than 130 mg/dL were randomized to receive either lovastatin or placebo therapy and were followed for an average of 5.2 years. Patients were as old as 78 years when the study was completed. There was a 40 percent reduction in fatal and nonfatal coronary events, and there was a 25 percent reduction in myocardial infarctions and cardiac deaths. Women and older patients benefited from lipid-lowering therapy as much as men and younger patients. Only 63 patients needed treatment to prevent one heart attack or fatal cardiac event. This finding is what would be expected, because the population was at slightly lower risk than were the patients in the West of Scotland Coronary Prevention Study.[4]

Coincidentally, the exact same number of men older than 50 years needed to be treated with aspirin to prevent one heart attack in the Physician's Health Study.[5] This number is much lower than the number needed to treat to prevent one stroke in patients with mild hypertension.

We were unable to present these data when we wrote the editorial because they had not been published. The AFCAPS/TexCAPS study adds to the overwhelmingly consistent and positive clinical trial data concerning the benefits of lipid-lowering therapy in both sexes and across the age spectrum. We only wish other generally accepted aspects of medical care were so carefully studied and validated.

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