EDITORIAL COMMENT

Overutilization and Underutilization of Thrombolysis in Routine Clinical Practice*

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This issue of the *Journal* includes an important new analysis of the TRACE (TRAndolapril Cardiac Evaluation) database that was set up to identify eligible patients for the subsequent randomized trial of angiotensin-converting enzyme (ACE) inhibition in acute myocardial infarction (MI) (1). This database is unique in that the TRACE investigators identified and followed up an unusually high proportion of all cases of MI occurring in Denmark in 1990 to 1992. All the 27 coronary care units were the only units in their respective regions, and so this survey produces a reliable snapshot of clinical practice.

The collaborators collected clinical, electrocardiogram (ECG) and echocardiographic data on all of approximately 6,500 patients admitted to the hospital with enzymatically determined acute MI, and then obtained follow-up data on stroke and survival. The decision to use thrombolytic therapy was left to the judgment of their physicians, with no set criteria beyond the general consensus at the time. Forty percent received lytic therapy, a reasonable figure by international standards. Ninety-five percent received streptokinase as the lytic agent. The present investigation retrospectively examined these decisions in the light of the first Fibrinolytic Therapy Trialists (FTT) collaborative group, published two years after the original Danish survey (2).

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In this issue of the *Journal*, Ottesen et al. (3) judged whether the earlier decisions on the utilization of thrombolytics were appropriate, both for overutilization of lytic therapy in the 40% who received it, and for underutilization in the remainder who were not given it. Mortality follow up was to mid-1998; only 39 patients lacked survival data.

These data are now particularly relevant in view of the recent analysis of the U.S. Medicare database, which suggested that thrombolytic therapy may be harmful in patients >75 years with acute MI (4).

In the U.S., tissue plasminogen activator (tPA) is the predominant choice in view of the GUSTO-I results, whereas European practice—especially eight years ago—favored streptokinase because of its much lower cost, and perhaps because of the lack of evidence of superiority for tPA in the non-North American patients enrolled in GUSTO-I (about half the study population) (5). Unlike the recent Medicare experience, the current analysis finds no evidence of adverse effects in older patients, especially for stroke.

The mortality (in those receiving thrombolysis) was lower even in those with a prior history of stroke, a contraindication (i.e., overutilization of thrombolysis). Using the benefit of hindsight, the authors found that there was a substantial “inappropriate” use of lytic therapy. Of the 2,781 patients who had a conventional indication but no contraindications, 66% received it, which is commendably high by many national surveys, in which underuse is even higher. Sixty percent had no indications, or at least one contraindication or both, but 851 of these 3,811 patients were actually given lytic therapy (i.e., overutilization). Of these, 620 patients had no conventional indication—usually because of hospital admission >12 h from onset (60%) or no ST elevation (55%). The most common contraindication was a prior history of stroke (52%), or ulcer (9%). No cases of uncontrolled hypertension were treated. Ninety-nine of 540 (18%) patients with prior stroke actually received lytic therapy; in these, the hospital incidence of stroke was reassuringly low at 1.0% and certainly not higher than in those not treated, of whom 1.7% experienced a stroke; but patients who did get lytic therapy (in this nonrandomized comparison) had a lower risk profile.

The authors are careful and correct to point out that in their analysis of this observational but nonrandomized data, one can only draw tentative conclusions. I agree with their comment that thrombolysis is underused not only in entirely eligible patients (where underutilization is between 30% and 50% in many surveys), but it is also underused in high risk patients with conventional contraindications, such as prior stroke or peptic ulcer, perhaps in the remote past. They conclude that their data show that ordinary physicians are able to balance these risks and select such patients so that the risk is acceptable.

The value of these new data is to contrast real life with clinical trials. The latter always enroll fitter and often younger patients than the “garden” variety seen in district hospitals. Important risks, such as cerebral hemorrhage, are underestimated in trials.

I believe that these data, when contrasted with the Medicare database (4), once more raise questions about the safety in elderly patients of more aggressive agents such as tPA and of more aggressive regimens of tPA. Unpublished but widely circulated data from the FTT overview showed an increasing incidence of intracranial hemorrhage with increasing age for tPA compared with streptokinase, which reached a fourfold to fivefold greater incidence in the oldest age group. Even without lytic therapy, there is an increased
risk of stroke with increasing age; however, the absolute benefit of thrombolysis is greater in the elderly (2).

In the past, we have criticized the prevailing U.S. view of the superiority of tPA over streptokinase in terms of its mortality benefit (6,7), and the greater safety of streptokinase, especially in the old.

We agree with the authors of the present analysis and those of the recent Medicare analysis that there is a pressing need for new randomized trials of thrombolysis in elderly patients. I would add that it would be worthwhile to revisit GUSTO-I in an elderly population, taking care not to discontinue streptokinase therapy when symptomless hypotension occurs—this may, in fact, partly explain the lower incidence of cerebral hemorrhage with the older, cheaper streptokinase and the apparent superiority of tPA in GUSTO-I.

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REFERENCES
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