Thrombolytic Therapy for Patients With Myocardial Infarction Who Are Older Than 75 Years
Do the Risks Outweigh the Benefits?

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Thrombolytic therapy represents a major advance in the care of patients with acute myocardial infarction (AMI) that has developed over the past 2 decades. In a meta-analysis of the 9 largest randomized trials conducted between 1982 and 1992 and involving 58,000 patients, this treatment was shown to reduce 35-day mortality, particularly in patients younger than 75 years who had evidence of ST-segment elevation or bundle-branch block and who were treated within 12 hours of the onset of symptoms. Among the 5,754 patients in these trials who were ≥75 years, thrombolytic therapy was associated with an absolute reduction in mortality of 1% (1 life saved for every 100 patients treated), a reduction that did not approach statistical significance. Given the powerful evidence of benefit in younger patients (including those between 65 and 74 years) and the potential benefit in older patients, guidelines for the care of AMI from the American Heart Association and the American College of Cardiology have supported the use of this treatment for patients ≥75 years who present with ST elevation within 12 hours of symptom onset as a class IIa indication, ie, one for which the “weight of evidence/opinion is in favor of usefulness/efficacy.”

Contrary to this perspective, an observational study by Thiemann et al in this issue of Circulation indicates that thrombolytic therapy is not beneficial and could actually be harmful in patients older than 75 years. These investigators assessed the 30-day mortality among patients aged 65 to 86 years in the United States who were treated for an AMI during 1994 and 1995. In a primary analysis of 7,864 patients who met clinical inclusion criteria for thrombolytic therapy, they compared those who did and who did not receive this treatment.

Their findings are quite surprising. Among the >5,000 patients aged 65 to 75 years, they found a relative reduction in 30-day mortality of 12% for those who received thrombolytic therapy, which is consistent with the results of randomized trials. However, among patients aged 76 to 86 years, thrombolytic therapy was associated with a statistically significant 38% relative increase in 30-day mortality. Patients who received thrombolytic therapy had an actual mortality rate of 18.0%, which is substantially higher than the expected mortality rate of 13.6% based on their clinical characteristics. Thus, for patients older than 75 years, this study suggests the possibility of 4 more deaths than expected for every 100 patients treated with thrombolytic therapy.

Should this observational study be the basis for withholding thrombolytic therapy from patients older than 75 years, even when such patients seem to be good candidates for this treatment? More specifically, does this study demonstrate a true harmful effect of thrombolytic therapy or could the results be an artifact of the ways in which the cohort was assembled or the data were collected and analyzed?

The study by Thiemann et al shares the potential limitations of observational studies, as the authors acknowledge, but it also has several strengths that merit serious consideration. They analyzed a well-specified cohort that was distilled from >210,000 patients in a national database; this cohort was one that could reasonably be expected to benefit from thrombolytic therapy without excessive risk. The authors also controlled for numerous factors that might confound the effect of thrombolytic therapy on mortality, such as Killip class and blood pressure. To reduce the possibility of selection bias in the choice of initial revascularization treatment, their primary analysis focused on patients treated at hospitals without the capacity to perform coronary angioplasty.

Thiemann et al also conducted numerous sensitivity analyses to determine whether their findings varied in a more inclusive cohort, specific subgroups of patients, or hospitals that offered coronary angioplasty. Across these analyses, their findings were generally consistent, with one notable exception. Rather than demonstrating a 2-way interaction of age with thrombolytic therapy, their stratified analyses depicted in Table 5 suggest a 3-way interaction of age and sex with this treatment. Among men, thrombolytic therapy had no significant impact on 30-day mortality for those aged 65 to 75 years (hazard ratio of 1.00) or those aged 76 to 86 years (hazard ratio of 1.12). However, women aged 65 to 75 years who received thrombolytic therapy had a nearly significant 26% relative reduction in mortality. A highly significant 60% relative increase in mortality existed for women aged 76 to 86 years who received this treatment. Although these figures

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seem startling, they must be interpreted with caution because they represent the outcome of a subgroup in an observational study.

If thrombolytic therapy is truly causing harm in patients older than 75 years, particularly women, what are the potential mechanisms of this effect? Risks of cerebral hemorrhage have long been recognized with thrombolytic therapy, especially among patients older than 75 years, and this risk is higher in women than in men. Thiemann et al also found that the incidence of new strokes was higher among patients older than 75 years who received thrombolytic therapy than in those who did not. In addition, they reported a higher rate of transfusions among patients who received thrombolytic therapy, but presumably only a fraction of these patients died within 30 days. Lacking data on the specific causes of death in their cohort, they speculated that thrombolytic therapy may have been associated with excessive anticoagulation or higher rates of cardiac rupture among patients older than 75 years. Reperfusion-related arrhythmias may also have contributed to increased mortality.

Are there other differences between the “younger old” (65 to 75 years) and the “older old” (76 to 86 years) that can explain these results? Animal studies have demonstrated progressive and accelerating apoptosis, causing a dropout of myocytes, accompanied by increased interstitial fibrous tissue in the senescent heart. Hearts of aged animals are more susceptible to injury after reperfusion and exhibit a reduced contractile recovery from ischemia and hypoxia.

As the use of thrombolytic therapy has come of age over the past 20 years, so has the field of health services and outcomes research. Observational studies of healthcare delivery in community practice have the potential to complement randomized trials that are frequently conducted in academic medical centers. For example, randomized trials of carotid endarterectomy have demonstrated clear benefits of this procedure and low complication rates when performed by experienced surgeons. However, when a broader group of surgeons and hospitals perform carotid endarterectomy, higher complication rates among low-volume surgeons may offset much of the potential benefit of this procedure.

Randomized and observational data have also been compared directly in the Bypass Angioplasty Revascularization Investigation (BARI). In the randomized component of this study, diabetic patients who received coronary angioplasty had worse outcomes than those who received coronary artery bypass surgery, but the observational BARI registry found equivalent outcomes for these 2 procedures when physicians’ judgment and patients’ preferences, rather than a randomization protocol, were used to determine treatment. After incorporating clinical and socioeconomic factors influencing treatment selection into the analysis of BARI registry data, the results for diabetic patients were more similar to the findings of the randomized trial. Thus, observational studies must be carefully evaluated and cautiously interpreted when they move beyond describing patterns of care to assessing treatments and outcomes. Because physicians and patients may choose treatments on the basis of criteria that are not readily apparent in observational data, these unobserved selection effects may obscure true treatment effects, as suggested by the BARI findings.

What further research is needed to understand the provocative findings of Thiemann et al? The possibility remains in their study that patients older than 75 years who received thrombolytic therapy differed from other patients in unmeasured ways that increased their risk and would explain their higher mortality. Ideally, new randomized trials of reperfusion therapies would focus on patients older than 75 years who present with AMI and overcome prior obstacles to such research. These trials should compare thrombolytic therapy with placebo treatment in hospitals that do not offer primary angioplasty, and they should compare thrombolytic therapy with primary angioplasty in hospitals that do offer the latter procedure. Because the combination of reduced-dose thrombolytic therapy and platelet glycoprotein IIb/IIIa inhibition seems to enhance microvascular perfusion, this regimen may be particularly favorable in the elderly, in whom the propensity for reperfusion injury may be enhanced.

Previous randomized trials have suggested benefits of primary angioplasty over thrombolytic therapy in the elderly. A recent observational study of a cohort that overlaps with the population studied by Thiemann et al has shown a marked reduction in 30-day mortality for primary angioplasty relative to thrombolytic therapy in the elderly. However, primary angioplasty is not available at the hospitals where most elderly patients present with AMI.

Therefore, the current state of reperfusion strategies for AMI patients older than 75 years satisfies a primary rationale for randomized trials: clinical uncertainty about the best course of action. This problem can no longer be neglected. Patients older than 75 years now constitute almost one-third of all patients with acute MI, and this percentage is growing rapidly as the population ages.

In the absence of new randomized trials to resolve these questions, data from earlier trials and new observational studies can be used to define more clearly the predictors of positive and negative outcomes of reperfusion therapies for patients older than 75 years. Some older patients certainly benefit from thrombolytic therapy, but many face an increased risk of cerebral hemorrhage and other complications that can be disabling or fatal. Discerning physicians must recognize that age per se does not cause positive or negative outcomes of thrombolytic therapy, but rather that it is a marker for underlying pathophysiologic factors and comorbid illnesses that may influence treatment effects.

References


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