

GARY S. FRANCIS, MD

Director, Coronary Intensive Care Unit, Cleveland Clinic, and George M. and Linda H. Kaufman Center for Heart Failure; Professor of Medicine, Health Sciences Center, Ohio State University

Fibrinolytic therapy in the elderly: Making sense of troubling new findings

FIBRINOLYTIC THERAPY for acute myocardial infarction (MI) has been a major advance of the past 20 years. However, any physician who has used it in a large number of patients has seen a patient rapidly develop an intracerebral hemorrhage. Most patients with this catastrophic complication die or are left with serious neurologic consequences. Although the overall incidence is low (< 1%), when intracerebral hemorrhage occurs there are few treatment options and no clear evidence that the process can be reversed.

Patients older than 75 years have a threefold to fivefold higher incidence of intracerebral hemorrhage than younger patients.¹ Even after adjustment for other factors, such as type of fibrinolytic agent, body weight, blood pressure on admission, and age, patients older than 65 years are twice as likely to experience intracerebral hemorrhage.

More troubling, two recent observational studies reported a higher mortality rate in elderly patients who received fibrinolytic therapy than in those who did not. Thiemann et al² found that, among patients 76 to 86 years old who received fibrinolytics, the mortality rate at 30 days was 18.0%, compared with 15.4% among similar patients who did not receive fibrinolytics. The hazard ratio was 1.38 (95% CI 1.12 to 1.71, $P = .003$). Soumerai et al³ reported similar observations at the recent 23rd annual meeting of the American Society of General Internal Medicine, held in Boston, May 4–6, 2000.

Therefore, the current data suggest that fibrinolytic therapy is not ideal in elderly patients. Notably, however, these data are from observational studies, which lack the rigor of randomized controlled trials and generally can only suggest a new hypothesis. They

cannot be considered conclusive and do not carry the weight of a primary end point from a randomized trial.

In fact, aggregate data from six previous large clinical trials indicate that the elderly may benefit from fibrinolytic therapy at least as much as younger patients, and possibly even more (FIGURE 1). This is because the elderly suffer more serious clinical events, including death, as a consequence of acute MI. It is believed the elderly derive “more bang for the buck” from fibrinolytic therapy, and currently available observational data continue to support judicious use of fibrinolytic treatment in the elderly.^{4–8}

LOOKING FOR ALTERNATIVES

As the American population ages, elderly patients with acute MI will become more and more common, and it will become imperative to find the safest and most reliable treatment for them.

Percutaneous coronary intervention

Primary percutaneous coronary intervention may be a safer alternative⁹ but is not realistic for most hospitals, as it must be done very quickly by a highly trained, experienced team. The time “from door-to-balloon” is critically important for outcome success¹⁰ and should be less than 2 hours.

Low-dose fibrinolytics plus full-dose glycoprotein IIb/IIIa inhibitors

Two large clinical trials are now testing a new treatment strategy that may prove safer: the combination of fibrinolytics in reduced doses plus glycoprotein (GP) IIb/IIIa inhibitors in full doses.

Data still support judicious use of fibrinolytics in the elderly



Fibrinolytic therapy for acute MI is beneficial in all age groups

AGE (YEARS)	FIBRINOLYTIC GROUP			CONTROL GROUP		
	NO. OF PATIENTS	NO. WHO DIED	% WHO DIED	NO. OF PATIENTS	NO. WHO DIED	% WHO DIED
75+	2494	604	(24.2%)	2541	661	(26.0%)
65-74	7189	1017	(14.1%)	7013	1159	(16.5%)
55-64	4680	1107	(7.5%)	14232	1368	(9.6%)
< 55	7600	272	(3.6%)	7394	346	(4.7%)

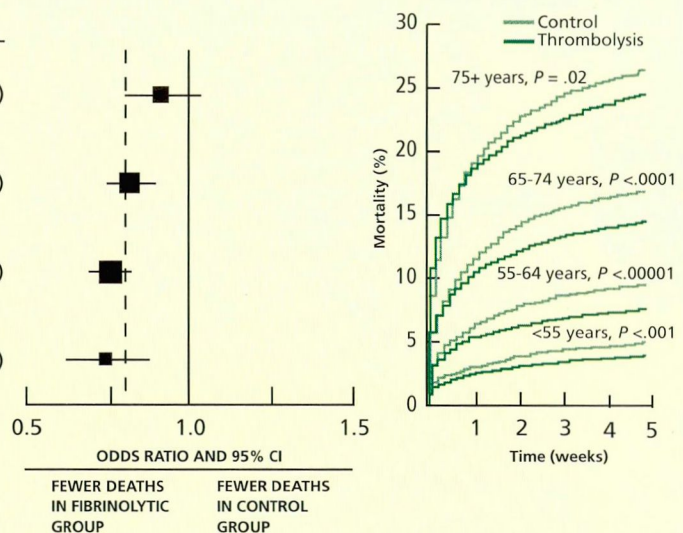


FIGURE 1. Summary data from trials of fibrinolytic therapy in acute MI (ISIS, GISSI, EMERAS, USIM, ISAM, and AIMS) by age group. Patients 75 years and older had an absolute reduction in mortality of 18 lives saved per 1,000 patients treated. The dashed line shows the odds ratio for the entire cohort.

ADAPTED FROM FIBRINOLYTIC THERAPY TRIALISTS (FTT) COLLABORATIVE GROUP. INDICATIONS FOR FIBRINOLYTIC THERAPY IN SUSPECTED ACUTE MYOCARDIAL INFARCTION: COLLABORATIVE OVERVIEW OF MORTALITY AND MAJOR MORBIDITY RESULTS FROM ALL RANDOMIZED TRIALS OF MORE THAN 1,000 PATIENTS. LANCET 1994; 343:311-322.

GUSTO IV (the fourth Global Use of Strategies to Open Occluded Arteries trial) is randomizing patients with ST-T elevation acute MI to receive either reteplase (Retavase; recombinant plasminogen activator; r-PA) in half doses plus abciximab (ReoPro, a GP IIb/IIIa inhibitor) in full doses, or reteplase in full doses.

INTRO-MI (Integrilin and Reduced Dose of Thrombolytics in Acute MI), soon to be reported, is similar but is using half doses of alteplase (Activase; tissue plasminogen activator; t-PA) and full doses of eptifibatid (Integrilin), vs full doses of t-PA. It has a much smaller number of elderly patients than does GUSTO IV.

In principle, the rate of intracerebral hemorrhage should be less with the combination of half-dose fibrinolytic therapy and GP IIb/IIIa inhibitors than with full-dose fibrinolytics. Nevertheless, these clinical trials will be observational, ie, the primary end point is not

intracerebral hemorrhage, and some risk of intracerebral hemorrhage will remain whenever fibrinolytic drugs are used. Moreover, fibrinolytic drugs are conventionally used with heparin, which likely adds to their propensity to cause spontaneous bleeding.

There is concern that the recent report of Thiemann et al² may slow randomization of elderly patients into GUSTO IV, a tragic consequence if it occurs.

■ LIVING WITH UNCERTAINTY

For now, we must live with uncertainty about the best course of action for patients older than age 75 with ST-T elevation acute MI. Age remains the most powerful and consistent predictor of mortality in patients with acute MI. To deny older patients fibrinolytic therapy for fear of inducing a fatal intracerebral hemorrhage may not be prudent in the absence of firm data from a randomized trial.




We need a randomized, controlled trial to settle this controversy.¹¹ Previous attempts to perform such a clinical trial failed because of low randomization rates.¹² The combination of half-dose fibrinolytic therapy and a GP IIb/IIIa antagonist may prove to be a safer alternative, but data on this new strategy are not yet available.

Patients older than 75 years, and particularly African American women, are at higher risk of bleeding if they have any of the following^{13,14}:

- Low body weight

- Systolic blood pressure greater than 175 mm Hg on entry
- Pulse pressure greater than 40 mm Hg if the systolic blood pressure is 120 mm Hg or more on admission
- A higher Killip class
- A previous cerebrovascular accident
- An anterior acute MI.

The observation that elderly patients have a higher mortality with fibrinolytic therapy is disturbing, but until more data become available, it may not warrant wholesale changes in our current practice. 

REFERENCES

1. Gurwitz JH, Gore JM, Goldberg RJ, et al. Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998; 129:597–604.
2. Thiemann DR, Coresh J, Schulman ST, Gerstenblith, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 2000; 101:2239–2246.
3. Soumerai SB, McLaughlin TJ, Ross-Degnan D, Gurwitz JH. Inappropriate use of thrombolytics and excess mortality in the elderly [abstract]. *J Gen Intern Med* 2000; 15(Suppl 1):147.
4. Muller DWM, Topol EJ. Selection of patients with acute myocardial infarction for thrombolytic therapy. *Ann Intern Med* 1990; 113:949–960.
5. White HD, Barbash GI, Califf RM, et al. Age and outcome with contemporary thrombolytic therapy. *Circulation* 1996; 94:1826–1833.
6. Gurwitz JH. Coronary thrombolysis for the elderly: Is clinical practice really lagging behind evidence of benefit? *JAMA* 1997; 277:1723–1724.
7. Gottlieb S, Goldbourt U, Boyko V, et al. Improved outcome of elderly patients (> 75 years of age) with acute myocardial infarction from 1981–1983 to 1992–1994 in Israel. *Circulation* 1997; 95:342–350.
8. Straznicki IT, French Jk, White HD, Califf RM. Fibrinolysis for acute myocardial infarction in the elderly patient: is it effective or too dangerous? *Am J Geriatr Cardiol* 1998; 7:22–23.
9. The GUSTO IIb investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997; 336:1621–1628.
10. Berger PB, Ellis SG, Holmes DR, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction. *Circulation* 1999; 100:14–21.
11. Ayanian JZ, Braunwald E. Thrombolytic therapy for patients with myocardial infarction who are older than 75 years: Do the risks outweigh the benefits? *Circulation* 2000; 101:2224–2226.
12. Feit F, Breed J, Anderson JL, et al. A randomized, placebo-controlled, trial of tissue plasminogen activator in elderly patients with acute myocardial infarction [abstract]. *Circulation* 1990; 82(Suppl III): III-666.
13. Maggioni AP, Franzosi MG, Santoro E, et al. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. *N Engl J Med* 1992; 327:1–6.
14. Selker HP, Beshansky JR, Schmid CH, et al. Presenting pulse pressure predicts fibrinolytic therapy-related intracranial hemorrhage: Thrombolytic predictive instrument (TPI) project results. *Circulation* 1994; 90:1657–1661.

ADDRESS: Gary S. Francis, MD, Department of Cardiology, F25, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail: francig@ccf.org.

Recent findings are troubling, but may not warrant wholesale changes

We Welcome Your Letters

WE ENCOURAGE YOU TO WRITE, either to respond to an article published in the *Journal* or to address a clinical issue of importance to you. You may submit letters by mail, fax, or e-mail.

MAILING ADDRESS

Letters to the Editor
Cleveland Clinic Journal of Medicine
 9500 Euclid Ave., NA32
 Cleveland, OH 44195

FAX

216.444.9385

E-MAIL ccjm@ccf.org

Please be sure to include your full address, phone number, fax number, and e-mail address. Please write concisely, as space is limited. Letters may be edited for style and length. We cannot return materials sent. Submission of a letter constitutes permission for the *Cleveland Clinic Journal of Medicine* to publish it in various editions and forms.