

Thrombolytics in elderly patients: A triumph of hope over experience?

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The study reported by Jean-Marc Boucher and colleagues in this issue (page 1285)¹ provides a thought-provoking, sometimes surprising overview of Canadian care for patients with acute myocardial infarction (AMI). The authors studied 3741 consecutive patients admitted with confirmed AMI to the emergency departments of 44 Quebec hospitals between January 1995 and May 1996. They found that even among ideal candidates for thrombolysis (defined as patients with electrocardiographic ST elevation, no history of cerebrovascular disease and no absolute contraindications to thrombolysis, who arrived at the hospital within 12 hours of the onset of symptoms) the use of thrombolytic therapy decreased markedly with age, from 85.7% for patients aged less than 55 years to 69.6% for patients aged 75–84 years. Although at first glance such statistics may suggest poor compliance with guidelines for AMI treatment, if anything thrombolytic therapy is used more frequently in Canada than in the United States. In a reanalysis of the Cooperative Cardiovascular Project (CCP) data, we found that thrombolytics were given to 63.3% of ideal US candidates for this therapy aged 75–84 years. Canadian hospital formularies and budgets doubtless influence the choice of thrombolytic agent: 69% of Canadian patients received streptokinase intravenously and 31% received tissue plasminogen activator (t-PA), which is more effective for patients aged up to the age of 85 years, whereas in the United States 76% of CCP patients received t-PA intravenously.

As the authors acknowledge, the key question implicit in this study is whether the low use of thrombolytic therapy harms elderly patients with AMI with ST elevation. The discussion notes that Boucher and coworkers found a surprising overall “lack of association between thrombolytic therapy and improved [in-hospital] survival.” Although this finding may be a result of selection bias or chance, other studies have shown consistently that selection bias actually favours thrombolytic patients, who tend to be younger and healthier than those not treated with thrombolysis. Boucher and colleagues suggest that another possible explanation for the lack of thrombolytic benefit might lie in our recent report² that showed no benefit to thrombolytic therapy for patients over the age of 75 years. In our

study, the hazard ratio for 30-day survival for patients aged 65–75 years was 0.88 (95% confidence interval [CI] 0.69–1.12, $p = 0.29$), which is consonant with the results of randomized trials, whereas for patients aged 76–86 years there was a significant survival disadvantage, with a hazard ratio of 1.38 (95% CI 1.12–1.71, $p = 0.003$) and a particularly marked survival disadvantage among elderly women. These findings have been replicated by other investigators.³

The observation that the relative benefit of thrombolysis diminishes with age is not new. The classic Fibrinolytic Therapy Trialists’ (FTT) meta-analysis⁴ of placebo-controlled thrombolytic trials found a consistent trend ($p = 0.01$) for diminished relative thrombolytic benefit with age compared with placebo, from an odds ratio for 35-day mortality of 0.74 for patients aged less than 55 years to 0.96 for patients aged over 75 years. A recent, unpublished reanalysis of the FTT data,⁵ limited to patients with ST elevation or left bundle branch block who presented within 12 hours of the onset of symptoms, reportedly showed an odds ratio of 0.88 ($p = 0.03$), which is about half the relative benefit seen in younger patients, with 35-day mortality of 29.4% for placebo versus 26.0% for thrombolytics. Thus, responsible arguments for administering thrombolytics to elderly patients have always acknowledged a diminished relative benefit, but with the hope of a persistent absolute benefit of about 3 lives saved per 100 patients treated.

Unfortunately, the available evidence does not provide a definitive answer concerning thrombolytic benefit in patients over the age of 75 years. Like all thrombolytic trials, the FTT meta-analysis has a skewed population distribution: 10% of the patients were over the age of 75 years — most presumably in their mid-seventies — compared with 30% of the general population of patients with AMI⁶ and 14% of Boucher’s ideal candidates for thrombolysis. Extrapolating from the skewed FTT population to octogenarians may be perilous. Of the FTT population, about 40% of elderly patients took part in trials in which the control arm did not require ASA, and three-quarters took part in trials without routine heparin, which may have potentially exaggerated the apparent benefit of thrombolysis compared with conservative therapy. In addition, there may be large differences between thrombolytic efficacy in the

Management of patients over the age of 75 years with AMI with ST elevation

- A nuanced, common-sense approach seems reasonable, depending upon the patient's age, duration of symptoms, cardiac history, clinical condition and the available technology.
- In urban regions where urgent transfer for direct angioplasty is feasible, both randomized trials and observational data suggest that for elderly patients direct angioplasty may be preferable to thrombolysis. Limited resources in Canada, compared with the United States, may have made primary angioplasty rare: only 1.3% of the cohort studied by Boucher and colleagues received primary angioplasty.
- In the absence of angioplasty, thrombolysis probably should remain the mainstay of therapy for older patients who present with widespread ST elevation, anterior MI or left bundle branch block within perhaps 4–6 hours of the onset of sustained symptoms and without cardiogenic shock.
- For patients who present more than 6 hours after the onset of symptoms, in whom the potential benefit of thrombolytic therapy is lower and the risk is otherwise unchanged, or for those who have good left ventricular function and small, well-tolerated inferior or lateral infarctions, aggressive management with ASA, heparin, β -blockers and angiotensin-converting-enzyme inhibitors is appropriate.
- When elderly patients are treated with thrombolytics, strict adherence to protocol is imperative: contraindications should be rigorously excluded; heparin dosing should be reduced because elderly patients metabolize heparin slowly; and, in patients weighing less than 67 kg, weight-based thrombolytic-dosing nomograms are essential. Even these precautions may not improve the death toll of AMI in older patients, in whom excess mortality occurs in the first day or 2 after infarction and may not be due primarily to stroke or bleeding, raising the possibility of ventricular rupture¹¹ or arrhythmia.
- For elderly survivors of AMI, angiography and indicated revascularization should be strongly considered.

ideal world of randomized trials and effectiveness in community practice. Patients in the real world tend to present later than those enrolled in randomized trials, to have greater comorbidity and to have higher rates of protocol violations. It is quite possible that the results of thrombolytic therapy in community practice may be different from those in randomized trials.

The study by Boucher and coworkers contains another surprise: an adjusted odds ratio for in-hospital mortality of 0.66 (95% CI 0.50–0.87) at hospitals with angiographic capability compared with those without catheterization laboratories. This is in contrast to a nationwide US study⁷ that

found no significant survival advantage due to hospital technology alone. The apparent survival advantage for Canadian patients at hospitals with better technology may be merely a result of inadequate risk adjustment. But the disparity could also be caused in part by the underuse of angiography, which has also been implicated south of the border;⁸ by poorer outcomes at rural centres;⁷ or by a survival advantage at centres where a greater number of patients are treated⁷ that is independent of technology. If this marked survival differential is confirmed by other studies, then it deserves urgent policy review.

A decade ago a randomized trial of thrombolytic therapy⁹ in elderly patients was stopped, largely because physicians were unwilling to assign patients randomly to nonthrombolytic therapy, an attitude that with hindsight may have been a triumph of hope over experience. Published randomized trials of thrombolytic therapy have concentrated on young cohorts of patients with AMI who have a relatively low mortality rate, whereas in community practice more than half of deaths from AMI occur in patients aged 75 years or more, a proportion that will continue to rise as the population ages. The prospect of conducting new inclusive, community-based randomized trials to determine the effectiveness of thrombolytics in elderly patients with AMI — a question deemed settled (albeit by consensus more than by proof) for nearly a decade — raises the following 2 concerns: that stand-alone thrombolytic therapy may soon be superseded by other therapies, such as primary angioplasty, facilitated angioplasty or combinations of low-dose thrombolytic drugs with glycoprotein IIb/IIIa inhibitors; and that the pharmaceutical industry, without whose support randomized trials seldom occur, is unlikely to finance studies of drugs that have already been approved. These generic objections apply whenever new findings cast doubt on the effectiveness of approved drugs. But thrombolytic therapy remains the mainstay of community treatment for elderly patients with AMI associated with ST elevation, and to date trials of new therapies have provided no new guidance about effectiveness or toxicity in elderly patients. Despite the logistical difficulties involved in randomized trials in subgroup populations, trials focused specifically on the cohort with the highest mortality—the elderly population — are urgently needed.¹⁰

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References

1. Boucher JM, Racine N, Huynh Thanh T, Rahme E, Brophy J, LeLorier J, et al. Age-related differences in in-hospital mortality and the use of thrombolytic therapy for acute myocardial infarction. *CMAJ* 2001;164(9):1285-9. Available: www.cma.ca/cmaj/vol-164/issue-9/1285.asp
2. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial

- infarction who are older than 75 years. *Circulation* 2000;101:2239-46.
3. Berger AJ, Radford MJ, Wang Y, Krumholz HM. Thrombolytic therapy in older patients. *J Am Coll Cardiol* 2000;36:366-74.
 4. Fibrinolytic Therapy Trials' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22.
 5. White HD. Thrombolytic therapy in the elderly. *Lancet* 2000;356:2028-30.
 6. Goldberg RJ, McCormick D, Gurwitz JH, Yarzebski J, Lessard D, Gore JM. Age-related trends in short- and long-term survival after acute myocardial infarction: a 20-year population-based perspective (1975-1995). *Am J Cardiol* 1998;82:1311-7.
 7. Thiemann DR, Coresh J, Oetgen WJ, Powe NR. The association between hospital volume and survival after acute myocardial infarction in elderly patients. *N Engl J Med* 1999;340:1640-8.
 8. Guadagnoli E, Landrum MB, Peterson EA. Appropriateness of coronary angiography after myocardial infarction among Medicare beneficiaries: managed care versus fee for service. *N Engl J Med* 2000;343:1460-6.
 9. Ross AM. The TTOPP study: lessons from an aborted trial. *J Myocardial Ischemia* 1990;2:65-9.
 10. 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;101:2224-6.
 11. Maggioni AP, Maseri A, Fresco C, Franzosi MG, Mauri F, Santoro E, et al. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. *N Engl J Med* 1993;329:1442-8.

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