Tailoring therapy to best suit ST-segment elevation myocardial infarction: searching for the right fit

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> The true rate of advances in medicine is not to be tested by the work of single men, but by the practical capacity of the mass. The truer test of national medical progress is what the county doctor is.
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> —S. Weir Mitchell
> American novelist (1829–1914)
> *Familiar Medical Quotations* (Little, Brown, 1968)

Strident calls to divert patients with acute ST-segment elevation myocardial infarction (STEMI) for percutaneous coronary intervention (PCI) in lieu of fibrinolysis have generated major debate within the cardiovascular arena.[1–3] This debate has created doubt among community physicians who provide first-line care for such patients as to what should be regarded as optimal therapy. Although we support timely evolution of both the content and the delivery of cardiac care in Canada, we will illustrate in this commentary why the case for wholesale application of PCI is currently unpersuasive.

Problems with the evidence favouring PCI

The results of a recent meta-analysis comparing fibrinolysis and PCI in patients with STEMI favoured the latter form of therapy.[4] However, half of the 23 trials included fewer than 100 patients per treatment arm, and 8 used streptokinase as the fibrinolytic agent.[4] When the analysis was restricted to comparisons with accelerated tissue plasminogen activator, a superior fibrinolytic regimen, PCI's mortality advantage became nonsignificant (absolute reduction of 1.2%, $p = 0.081$), despite a 1% excess in hemorrhagic stroke with fibrinolysis.[5] Primary PCI also extracted an additional price of a 2% absolute excess in major hemorrhage ($p = 0.032$). Therefore, we concur with Melandri[5] that this meta-analysis should be regarded as hypothesis-generating rather than definitive.

The recent Danish multicentre randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction (known as DANAMI-2)[6,7] compared standard fibrinolytic therapy with transfer for PCI for patients with STEMI presenting to community hospitals. The group that received primary PCI had significantly lower rates of a composite endpoint of death, reinfarction and disabling stroke (8.5% v. 14.2%, $p = 0.002$). This result was largely driven by lower rates of reinfarction (1.9% v. 6.2%, $p < 0.001$) and of disabling stroke (1.1% v. 2.0%, $p = 0.15$) without a commensurate difference in mortality rate. Germane to this issue was the fact that the protocol recommended repeat fibrinolysis for recurrent infarction or ischemia, rather than the more conventional timely referral for mechanical co-intervention. Moreover, the unusually high rate of intracranial hemorrhage in the fibrinolytic arm may have been mediated by the unconventional inclusion of patients with prior stroke (which had occurred nearly twice as often among fibrinolytic-treated patients) and an aggressive anticoagulant regimen with non-weight-adjusted heparin. Careful consideration of the study conditions reveals major logistic impediments to general application of a policy of transferring STEMI patients from community hospitals for invasive therapy: physicians were required to accompany patients during transport, and an around-the-clock cardiac catheterization team was available.[6] Finally, the sickest patients were not transported, namely those with cardiogenic shock or severe heart failure and those requiring ventilation. These issues engender caution concerning the use of DANAMI-2 as the basis for a major change in practice.

The importance of timing

It must be emphasized that reperfusion of the infarct-related artery in the shortest amount of time is central to this debate. The PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE-2) trial compared streptokinase with PCI and showed a 30-day mortality trend favouring PCI (6.8% v. 10%, $p = 0.12$) in STEMI patients randomized up to 12 hours after symptom onset.[8] However, there was no difference between streptokinase and PCI in the 551 patients treated within 3 hours (7.4% v. 7.3%). Furthermore, transfer from community centres for PCI was not without risk: 2 patients died in transit, and 3 others experienced successfully treated ventricular fibrillation. The Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial compared prehospital fibrinolysis with PCI for patients with STEMI and found 30-day mortality rates of 3.8% for accelerated tissue plasminogen activator and 4.8% for PCI.[9] By 1 year these rates were 5.4% and 7.3% ($p = 0.27$) respectively. When the cohort randomized within 2 hours (57% of the patients) was examined, this mortality advantage for fibrinolysis over PCI widened: 2.2% v. 5.7% ($p < 0.04$).[10] The recent Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT 3+) study of prehospital fibrinolysis

(which involved a significant Canadian contribution) demonstrated that it is feasible to treat more than half of STEMI patients within 2 hours of symptom onset.[11,12]

A new analysis of recent trials is also insightful.[13] This analysis examined the PCI-related time delay and found that the absolute mortality reduction favouring primary PCI was progressively smaller for each additional 10-minute delay. Once the PCI-related time delay reached 62 minutes, the mortality rate was nearly equivalent between patients treated with fibrinolysis and those treated with PCI.[13]

Primary PCI delivered promptly for patients with STEMI (i.e., administered by experienced operators within 90 minutes of first medical contact) constitutes excellent therapy; however, achieving this standard, both within trials and more generally, is problematic.[14] Moreover, the timing of PCI is heavily biased toward conduct during usual working hours.[15] The resource and personnel implications of a 24 hours/day, 7 days/week PCI program for all STEMI patients represent a legitimate concern, and commensurate delays in door-to-balloon time are associated with worsened outcomes.[16,17] We believe that the recent Netherlands experience from a recognized centre of PCI excellence, which indicates that the performance of PCI during "off hours" has a significant negative effect on both PCI quality and patient outcome, should be heeded.[18]

Resource implications

Although some economic arguments have been made in support of primary PCI, these lack rigour and often do not reflect the true use of ancillary devices and drugs.[16,19] In particular, from where will the additional resources required for optimal cardiac care be derived? Some may be available through internal reallocation; for example, it seems clear that appropriate risk stratification can facilitate early discharge of more than half of low-risk STEMI patients, which would thereby reduce needless hospital costs.[20] Nonetheless, any policy mandating the emergent transfer of all patients with STEMI from community hospitals to tertiary care centres for PCI would carry an enormous cost and would undoubtedly necessitate additional resources or reallocation of current ones from other health care sectors.

A logical coexistence

Primary PCI is unquestionably superior in preventing reinfarction, but this advantage is attenuated when mechanical intervention is undertaken for failed fibrinolysis (i.e., recurrent ischemia or inadequate reperfusion after fibrinolysis). In the CAPTIM trial, this occurred in 26% of patients.[3,9] Careful bedside assessment of the extent of ST resolution from its admission height to 60 to 90 minutes after fibrinolysis can help to identify low-risk (more than 70% ST resolution), intermediate-risk (30% to 70%) and high-risk (less than 30%) patients, thereby assisting in the identification of those most appropriate for mechanical co-intervention.[21] Strategic partnerships between community hospitals and regionalized special centres for tertiary cardiac care will be required to ensure a seamless approach to and comprehensive pattern of cardiac care.[22] When contraindications to fibrinolysis exist and for patients with cardiogenic shock, PCI is unquestionably the most appropriate standard of care,[23] and it should be available for these situations.

Future directions

Whereas PCI proponents understandably herald achievement of enhanced perfusion of the infarct-related coronary artery, less attention has been directed to the estimated 36% of patients in whom there is a failure to resolve the initial epicardial injury pattern evident on the admission electrocardiogram (ECG).[24] This failure appears to signal impaired coronary flow at the microcirculatory level, which causes greater morbidity and mortality. Current research promises new opportunities to combat these problems, including the use of intracoronary devices to aspirate or catch distal coronary emboli and pharmacologic therapy to combat the inflammatory response caused by balloon angioplasty and stent insertion.[22,25]

Because of limited availability of tertiary care centres in Canada (less than 10% of all hospitals), substantial disparities in the quality of ambulance and prehospital services, and major advances in the content of care, we agree that there is an urgent need for a national program that would provide not only a systematic inventory of these issues, but also constructive suggestions regarding the allocation or reallocation of resources necessary to achieve progress in these areas (see Table 1).[19]

In the interim, withholding fibrinolytic therapy when it is medically indicated, to allow transfer of patients for primary PCI, should not be regarded as standard care unless PCI can be achieved within 90 minutes of first medical contact. Achieving this standard around the clock is a substantial challenge, even in the most experienced centres.[3,14,16] Whether pharmacologic or mechanical approaches are

Table 1: Six steps to enhance early reperfusion

Enhance patient and public education regarding the symptoms of acute myocardial infarction
Improve all aspects of 911 response, prehospital care and field communication
Promptly evaluate risk of acute ST-segment elevation myocardial infarction and risk of fibrinolytic therapy, and select best reperfusion therapy, with triage to most appropriate facility using pre-established algorithm or care map
Carefully evaluate response to reperfusion therapy and follow with appropriate intervention
Improve current pharmacologic and mechanical therapies
Develop specialized regional heart centres to promptly receive high-risk patients

used to achieve timely reperfusion will depend on local circumstances.[3,14,26] Substantial unrealized opportunities exist in Canada to enhance the process of prehospital care, and the argument for pursuing them is especially compelling given that public education programs have been unsuccessful in shortening the time from symptom onset to call for medical assistance.[27,28] These initiatives include reliable transmission of prehospital 12-lead ECG recordings, presence of paramedics trained in their interpretation, and computer-assisted algorithms to expedite diagnosis, therapy and triage before hospital admission. National standards for prehospital management should be responsive to demographic characteristics and geography. We encourage clinicians to consider participating in clinical research studies to advance our store of knowledge and to improve the care of our patients.

We must rise to these challenges, under leadership provided by the Canadian Cardiovascular Society in cooperation with other stakeholders and policy-makers. Progress will require careful audit and feedback, as well as a new spirit of genuine collaboration, which we hope can be aligned with the Health Council of Canada recommended by Romanow.[29]

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References

1. Stone GW. Primary angioplasty versus "earlier" thrombolysis — time for a wake-up call. *Lancet* 2002;360:814-6.
2. Grines CL, Serruys P, O'Neill W. Fibrinolytic therapy. Is it a treatment of the past? *Circulation* 2003;107:2538-42.
3. Armstrong PW, Collen D, Antman E. Fibrinolysis for acute myocardial infarction. The future is here and now. *Circulation* 2003;107:2533-7.
4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
5. Melandri G. Primary angioplasty or thrombolysis for acute myocardial infarction? [letter]. *Lancet* 2003;361:966.
6. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al; DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349(8):733-42.
7. Andersen HR, Nielsen TT, Vesterlund T, Grande P, Adilgaard U, Thayssen P, et al; DANAMI-2 Investigators. Danish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction: rationale and design of DANish trial in Acute Myocardial Infarction-2 (DANAMI-2). *Am Heart J* 2003;146:234-41.
8. Widimský P, Bud?šínský T, Vorá? D, Groch L, Zelizko M, Aschermann M, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial–PRAGUE 2. *Eur Heart J* 2003;24:94-104.
9. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, et al; Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;360:825-9.
10. Touboul P. Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM). Presented at the 18th International Symposium on Thrombolysis and Interventional Therapy in Acute Myocardial Infarction; 2001 Nov 16.
11. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Amtz HR, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS Randomized Trial in Acute Myocardial Infarction. *Circulation* 2003;108:135-42.
12. Welsh RC, Travers A, Sosnowski T, Williams R, Senaratne M, Lakhani Z, et al. Pre-hospital fibrinolysis: Is it safe, feasible, and efficient in a large urban North American Centre? [abstract]. *J Am Coll Cardiol* 2002:39(5 Suppl A):279A.
13. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: Is timing (almost) everything? *Am J Cardiol*. In press.
14. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;24:28-66.
15. Angeja BG, Gibson CM, Chin R, Frederick PD, Every NR, Ross AM, et al; Participants in the National Registry of Myocardial Infarction 2-3. Predictors of door-to-balloon delay in primary angioplasty. *Am J Cardiol* 2002;89:1156-61.
16. Natarajan MK, Yusuf S. Primary angioplasty for ST-segment elevation myocardial infarction: Ready for prime time? *CMAJ* 2003;169(1):32-5.
17. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941-7.
18. Henriques JP, Haasdijk AP, Zijlstra F; Zwolle Myocardial Infarction Study Group. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. *J Am Coll Cardiol* 2003;41:2138-42.
19. Ghali WA, Donaldson CR, Knudtson ML, Lewis SJ, Maxwell CJ, Tu JV. Rising to the challenge: transforming the treatment of ST-segment elevation myocardial infarction. *CMAJ* 2003;169(1):35-7.
20. Newby LK, Eisenstein EL, Califf RM, Thompson TD, Nelson CL, Peterson ED, et al. Cost effectiveness of early discharge after uncomplicated acute myocardial infarction. *N Engl J Med* 2000;342:749-55.
21. Schröder R, Wegscheider K, Schröder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. *J Am Coll Cardiol* 1995;26:1657-64.
22. Topol EJ, Kereiakes DJ. Regionalization of care for acute ischemic heart disease. A call for specialized centers. *Circulation* 2003;107:1463-6.
23. Armstrong PW. New advances in the management of acute coronary syndromes: 2. Fibrinolytic therapy for acute ST-segment elevation myocardial infarction. *CMAJ* 2001;165(6):791-7.
24. Claeys MJ, Bosmans J, Veenstra L, Jorens P, De Raedt H, Vrints CJ. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: importance of microvascular reperfusion injury on clinical outcome. *Circulation* 1999;99:1972-7.
25. Granger CB, Mahaffey KW, Weaver WD, Theroux P, Hochman JS, Filloon TG, et al. Effect of pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to primary percutaneous coronary intervention in acute myocardial infarction: complement inhibition in myocardial infarction treated with angioplasty (COMMA) Trial. *Circulation*. In press.
26. Eagle KA, Goodman SG, Avezum A, Badaj A, Sullivan CM, Lopez-Sendon J; GRACE investigators. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet* 2002;359:373-7.
27. Welsh RC, Ornato J, Armstrong PW. Prehospital management of acute ST-elevation myocardial infarction: a time for reappraisal in North America. *Am Heart J* 2003;145:1-8.
28. Luepker RV, Raczynski JM, Osganian S, Goldberg RJ, Finnegan JR Jr, Hedges JR, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: the Rapid Early Action for Coronary Treatment (REACT) trial. *JAMA* 2000;284:60-7.
29. Romanow RJ. *Building on values: the future of health care in Canada*. Saskatoon: Commission on the Future of Health Care in Canada; 2002.

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