www.cardiologyrounds.ca JANUARY 2003 volume VIII, issue 1

CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Primary angioplasty in acute myocardial infarction

HAHN HOE KIM, MD and WARREN CANTOR, MD

The patient who suffers an acute ST-elevation myocardial infarction (STEMI) continues to present a difficult challenge to the treating physician. The ultimate therapeutic objective is to achieve rapid and sustained reperfusion of the occluded coronary artery in order to salvage the myocardium. This can be achieved medically, with immediate thrombolytic therapy, or mechanically, with percutaneous coronary intervention (PCI). Although both modalities improve clinical outcomes, primary PCI has been shown to be superior to thrombolysis in many randomized trials. Historically, primary PCI has been available exclusively to patients presenting at an angioplasty centre. However, recent evidence suggests that those arriving at community hospitals can be transferred to angioplasty centres for catheter-based reperfusion and have superior clinical outcomes compared to immediate thrombolysis. In this issue of *Cardiology Rounds*, we will review the literature on primary angioplasty and discuss its role in light of the most recent evidence.

Primary angioplasty versus thrombolysis

A number of randomized trials comparing primary PCI to thrombolysis were conducted prior to the era of stenting and glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors (Table 1).[1-7] Although none of these studies were individually powered to demonstrate a difference in mortality, a meta-analysis[8] showed both a significantly lower mortality (4.4% versus 6.5%, p=0.02) and a lower incidence of the composite of death and MI (7.2% versus 11.9%, p<0.001) with PCI. PCI was also associated with a much lower incidence of intracranial hemorrhage (0.1% versus 1.1%, p=0.0005). These favourable results were sustained during long-term follow-up. Mortality benefits of primary PCI have been reported to persist for up to 5 years in one study.[9] Similarly, the PAMI study group reported a lower incidence of death and reinfarction at 2 years.[10]

Cost-effectiveness analyses of primary PCI have shown the cost of this approach to be equivalent to thrombolysis, with beneficial effects on length of stay and readmission rates.[11,12,13]

Time to treatment

Prompt access to the catheterization laboratory is likely the most important factor behind the favourable results of primary PCI in these trials. It is noteworthy that in the 3 largest trials,[1,4,7]

- the mean time from symptom-onset to percutaneous transluminal coronary angioplasty (PTCA) was 3.8 hours, and
- the mean time from hospital arrival to balloon inflation – the door-to-balloon time) – was 67 minutes.

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Table 1: Primary angioplasty vs. thrombolysis trials					
Study	**No. pts.**	**Agent**	**Door to balloon time (min)**	**Primary endpoint**	**Results**
Zijlstra[1]	142	SK	62	i/ Recurrent ischemia ii/ Recurrent MI iii/ LVEF	Less recurrent ischemia, less recurrent MI, higher LVEF with PCI
Ribeiro[2]	100	SK	238	IRA patency at 48 hours	No significant difference
Grinfield[3]	112	SK	63	i/ ST resolution ii/ TIMI-3 flow rate	Improved ST resolution and higher TIMI-3 flow rate with PCI
PAMI[4]	395	tPA	60	Death/Reinfarction	Less death/reinfarction with PCI
Ribichini[5]	83	tPA	40	Death/reinfarction/ recurrent ischemia	Lower rate of ischemic events with PCI
Garcia[6]	189	tPA	84	Death/reinfarction/ stroke	Lower rate of ischemic events with PCI
Gusto IIb[7]	1138	tPA	114	Death/reinfarction/ stroke	Less events with PCI at 30 days, no difference at six months

(SK = Streptokinase, tPA = tissue-type plasminogen activator)
MI = myocardial infarction, LVEF = left ventricular ejection fraction, IRA = infarct-related artery

Of these two markers of time to treatment, the door-to-balloon time is the strongest predictor of outcome. In a prospective registry of over 27 000 patients undergoing primary PCI for acute MI, in-hospital mortality significantly increased if door-to-balloon time was delayed past 120 minutes.[14] In the same study, the time from symptom-onset to balloon inflation had little effect on outcome up to 12 hours. This may be considered counter-intuitive, as one would expect the time from symptom-onset to balloon inflation to more accurately reflect the extent of myocardial necrosis, and hence be more predictive of adverse events. However, symptom onset may not be a precise surrogate marker of artery occlusion and symptom duration may not accurately reflect infarction period. Therefore, a short door-to-balloon time appears to be the key to achieving improved outcomes.

Primary angioplasty performed at centres without on-site cardiac surgery

The institutions that participated in the trials above were all tertiary care centres with established PCI programs and available cardiac surgery, implying that the benefits of primary PCI were limited to patients who presented to such centres. The Atlantic C-PORT trial[15] showed that primary PCI was superior to thrombolysis (accelerated tissue-type plasminogen activator [tPA]), even when performed at centres without on-site cardiac surgery or extant elective PCI programs.

The 11 participating centres in the C-PORT trial all underwent rigorous development to establish a primary PCI program – a process that took approximately 3 months. The operators were required to perform a minimum of 50 interventions per year,[16] and the infrastructure developed for primary PCI set a door-to-balloon time goal of 90 minutes.

The C-PORT study randomized patients presenting within 12 hours after the onset of a STEMI to receive either primary PCI or accelerated tPA. The primary outcome measure was the composite of death, recurrent MI, and stroke at 6 months, with a target sample size of 2550 patients. However, due to a lack of funding, the study was terminated after a 3-year period of enrollment, during which 451 patients were recruited.

The goals of prompt intervention were met. The median door-to-balloon time was 101 minutes in the PCI group,

Table 2: Trials comparing thrombolysis versus patient transfer for primary PCI

Trial	No. Pts.	Transfer time (min)	Door to balloon time in transfer group (min)	Results
Vermeer[17] – *TL vs.TL and TF for PCI vs. TF for 1° PCI*	224	20-30	Approx. 110	– Transfer of patients with acute MI is safe and feasible – No significant difference in clinical endpoints between groups
PRAGUE[18] – *TL vs.TL and TF vs. TF for1° PCI*	300	35-38	Approx. 95	– Streptokinase was the thrombolytic agent used in the study – Lower reinfarction rate in the group transferred for primary PCI
Air PAMI[19] – *TL vs. TF for 1° PCI*	138	60	155	– Stopped early – 38% lower MACE in transfer group (not statistically significant)
DANAMI-2[20] – *TL vs. TF for 1° PCI*	1129	< 180	Approx. 100	– Significant reduction in 30-day MACE in primary PCI group, mainly driven by reduction in reinfarction
PRAGUE-2[21] – *TL vs. TF for 1° PCI*	850	n/a	n/a	– Overall, no mortality benefit of primary PCI over thrombolysis – Mortality benefit of primary PCI for subgroup of patients presenting 3-12 h after symptom-onset

TL = Thrombolysis, TF = Transfer, 1° PCI = Primary PCI, MACE = major adverse cardiac event

and the median time to treatment was 46 minutes in the thrombolysis group. Of the 225 patients randomized to primary PCI, 169 (75%) underwent angioplasty, with a 96% success rate. Stents were placed in 63% of the cases, and GP IIb/IIIa inhibitors were used in 76%. There was no need for emergency coronary artery bypass graft (CABG), nor were there any PCI-related complications that necessitated emergency transfer.

By intention-to-treat analysis, the composite endpoint was significantly lower in the primary PCI group than in the thrombolysis group (12.4% versus 19.9%, p=0.03), the difference mainly driven by a reduction in recurrent MI (5.3% versus 10.6%, p=0.04).

Therefore, although the statistical power of the trial was diminished by its premature termination, the C-PORT study showed that primary PCI can be done safely in properly primed facilities without on-site cardiac surgery, and can achieve lower rates of reinfarction than thrombolysis.

Community hospitals – Immediate thrombolysis versus transfer for primary PCI

The question of whether to treat patients arriving at centres without PCI capabilities with immediate thrombolysis or to transfer them to a PCI centre, has been examined in several trials (Table 2).[17-21]

• Air-PAMI[19] randomized "high risk" patients with STEMI to thrombolysis (tPA or streptokinase [SK]) or immediate transfer to a PCI centre for primary PCI. The target sample size was 430, but after 39 months and 138 patients, the study was terminated due to poor recruitment.

The primary endpoint was major adverse cardiac events (MACE – death, reinfarction, stroke) at 30 days. For the 71 patients randomized to transfer, the mean traveling distance was 51 km, which took approximately 60 minutes. The median time from 1st hospital arrival to balloon treatment was 155 minutes. There was a 38% lower incidence of MACE in the transfer group, but this was not statistically significant due to the small sample size.

- Similarly, DANAMI-2[20] randomized 1129 patients with STEMI to thrombolysis (front-loaded tPA) or transfer for PCI (mean traveling distance of 50 km). During the same period, 443 patients who presented to a PCI centre were randomized to primary PCI or thrombolysis. Analysis of all 1572 patients showed a significant reduction of 30-day MACE in the primary PCI group (8.0% versus 13.7%, p=0.003). This benefit was independently observed in the 1129 patients who were transferred for primary PCI (8.5% versus14.2%, p=0.002). Most of the benefit was again driven by a reduction in the reinfarction rate (1.6% versus 6.3%, p<0.0001). Notably, the infrastructure implemented for transfer in this study allowed very expeditious implementation of primary PCI. The door-to-balloon time in the patients randomized to transfer was 115 minutes, only 10 minutes longer than in those patients who presented to a PCI centre.
- PRAGUE-2[21] was a 30-day mortality study where 850 patients with STEMI presenting to community hospitals were randomized to immediate thrombolysis or transfer to a PCI centre. In the intention-to-treat analysis, there was no significant reduction in 30-day mortality with transfer for primary PCI (6.8% versus 10.0%, p=0.12). Only the subgroup of patients presenting later (between 3-12 hours after symptom-onset), had a significant mortality benefit from transfer for primary PCI over thrombolysis (6.0% versus 15.3%, p < 0.02). This implies that early (< 3h) treatment with thrombolytics may achieve reperfusion rates comparable to those of primary PCI. Notably, the incidence of MACE, a secondary endpoint of this study, was significantly lower in the transfer group than in the thrombolysis group (8.4% versus 15.2%, p < 0.05).

Adverse events during patient transfer in these studies were extremely rare. The PRAGUE-2 trial reported the only death, and the incidence of successfully treated arrhythmias was less than 2%.

In summary, the results from these trials suggest that for patients with STEMI who present to community hospitals, transfer to a PCI centre for primary PCI is not only safe, but will result in better outcomes when compared to immediate treatment with thrombolysis. Most of the demonstrated benefit has been in reducing reinfarction, as opposed to mortality. Despite the time required for patient transfer, the door-to-balloon times were kept short. At present, there are very few regions in Ontario with the infrastructure to consistently achieve door-to-balloon times less than 120 minutes. In the absence of such an infrastructure, the proven benefits of immediate thrombolysis should not be withheld in favour of transfer for primary PCI, with the exception of patients with a contraindication to thrombolysis.

Pre-hospital fibrinolysis versus primary angioplasty

Thrombolytic therapy given prior to arrival in hospital has previously been shown to result in a 17% relative reduction in mortality over in-hospital thrombolysis.[22] More recent studies have confirmed the feasibility of pre-hospital fibrinolysis and its benefit in shortening time to treatment.[23,24] The aim of the recently published CAPTIM trial[25] was to compare thrombolysis (front-loaded tPA) administered in the field by mobile emergency-care units followed by transfer to a PCI centre, versus primary PCI. The primary endpoint was a composite of death, reinfarction and stroke at 30 days.

Due to insufficient funds, CAPTIM was terminated early, after 840 of the targeted 1200 patients were enrolled. Delivery of prompt revascularization was again successful. In the patients randomized to primary PCI, the mean door-to-balloon time was approximately 80 minutes, achieving TIMI-3 flow in 90% of the cases, with 75% stent use.

Overall, there was no significant difference in the occurrence of the primary endpoint between pre-hospital thrombolysis and primary PCI (8.2% versus 6.2%, p = 0.29). However, a significant number of patients who received pre-hospital fibrinolysis underwent rescue PTCA (26%). This is higher than in other studies, such as PAMI, which had a rescue PTCA rate of 7%.

Although this study showed that pre-hospital thrombolysis followed by transfer to a PCI centre is

equivalent to primary PCI for STEMI, the study's premature termination diminished its statistical power. It is possible that the transfer to a PCI centre, enabling ready access to PCI facilities, is the key element behind the favourable outcomes in the pre-hospital thrombolysis group.

Overall, the balance of clinical data weighs in favour of primary PCI as the preferred treatment modality for STEMI. A recent comprehensive meta-analysis[26] combined all of the major trials to-date on this topic and affirmed the benefit of primary PCI. This overview, involving 23 trials and 7739 patients, again demonstrated the superiority of primary PCI over thrombolysis in reducing the individual end-points of death, nonfatal reinfarction, and stroke. Although an increase in major bleeding was found with primary PCI, the bleeding mainly occurred at the vascular access sites. The risk of hemorrhagic stroke was significantly reduced by primary PCI.

GP IIb/IIIa inhibitors and facilitated PCI

Several studies have evaluated the role of abciximab in primary PCI.[27-32] Although no individual trial has shown a mortality benefit, the use of abciximab in the setting of primary PCI resulted in a significant reduction in reinfarction, recurrent ischemia, target vessel revascularization, and subacute thrombosis. The clinical advantage is especially evident when abciximab is given prior to arrival at the catheterization laboratory.[30] Therefore, there is merit in routine early administration of abciximab as an adjunctive therapeutic agent in primary PCI.

The term "facilitated PCI" describes the use of fibrinolytics, with or without GP IIb/IIIa inhibitors, followed by emergency coronary angiography and percutaneous revascularization, combining the benefits of pharmacologic reperfusion therapy with catheter-based reperfusion. Although preliminary studies show promise for facilitated PCI,[33] ongoing studies will more definitively determine the safety and clinical utility of this strategy in the setting of STEMI.

Conclusions

It is quite clear that when performed expeditiously by trained personnel, primary PCI is superior to thrombolysis for the treatment of STEMI, a conclusion that is supported by recent studies reflecting the evolution of patient care. The benefit of primary PCI is accessible to patients at centres without on-site cardiac surgery, as well as centres located within transfer range of a PCI centre, when the time between arrival and balloon inflation can be kept short (under 120 minutes). The adjunctive use of GP IIb/IIIa inhibitors results in favourable outcomes, and their role in conjunction with thrombolysis for facilitated PCI is currently being evaluated.

References

1. Zijlstra F, de Boer MJ, Hoorntje JC, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993; 328:680-4.
2. Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1993;22: 376-380.
3. Grinfield L, Berrocal D, Belardi J. Fibrinolysis vs. primary angioplasty in acute myocardial infarction: A randomized trial in a community hospital in Argentina. *J Am Coll Cardiol* 1996;22:222-A.
4. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;328: 673-679.
5. Ribichini F, Steffenino G, Dellavale A. Primary angioplasty versus thrombolysis in inferior acute myocardial infarction with anterior ST segment depression: A single center randomized study. *J Am Coll Cardiol* 1996;27:221-A.
6. Garcia E, Elizaga J, Soriano J. et al. Primary angioplasty versus thrombolysis with tPA in anterior myocardial infarction: Results from a single center trial. *J Am Coll Cardiol* 1997;29(Suppl.A):389-A.
7. The GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;336:1621-1628.
8. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;278:2093-2098.
9. Zijlstra F, Hoorntje JC, de Boer, MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999; 341:1413-9.
10. Nunn CM, O'Neill WW, Rothbaum D, et al. Long-term outcome after primary angioplasty: Report from the PAMI-1 Trial. *J Am Coll Cardiol* 1999;33:640-6.
11. Lieu TA, Lundstrom RJ, Ray GT, Fireman BH, Gurley RJ, Parmley WW. Initial cost of primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1996;28:882-9.
12. Stone GW, Grines CL, Rothbaum D, et al. Analysis of the relative costs and effectiveness of primary angioplasty versus tPA: The PAMI trial. The PAMI Trial Investigators. *J Am Coll Cardiol.* 1997;29:901-7.
13. Grines CL, Ellis S, Jones M, et al. Primary coronary angioplasty vs. thrombolytic therapy for acute myocardial infarction: Long-term follow-up of randomized trials. *Circulation* 1999;100 (Suppl I):1499.

14. Cannon C, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute MI. *JAMA* 2000;283:2941-47.
15. Aversano T, Aversano LT, Passamani E, et al. Thrombolytic therapy vs. primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery. *JAMA* 2002;287:1943-1951.
16. Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol.* 1993;22:2033-2054.
17. Vermeer F, Oude Ophuis AJ, vd Berg EJ, et al. Prospective randomized comparison between thrombolysis, rescue PTCA and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999;82:426-431.
18. Widimsky P, Groch L, Zelizko M, et al. Multicentre randomized trial comparing transport to primary angioplasty vs. immediate thrombolysis vs. combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory – The PRAGUE Study. *Eur Heart J* 2000;21:823-831.
19. Grines CL, Westerhausen DR, Grines LL, et al. A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in patients with high-risk myocardial infarction. *J Am Coll Card* 2002;39:1713-9.
20. Andersen H. DANAMI-2: The Danish trial in acute coronary angioplasty in acute myocardial infarction. *Clin Cardiol* 2002;25: 301.
21. Widimsky P. PRAGUE-2 trial. Paper presented at: The 24th Congress of the European Society of Cardiology; September 21, 2002; Berlin, Germany.
22. The European Myocardial Infarction Project Group. Prehospital fibrinolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993;329:383-389.
23. Morrow DA, Antman EA, Assaad S, et al. Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction – Results of the ER-TIMI 19 trial. *J Am Coll Cardiol* 2002;40:71-7.
24. Wallentin L. ASSENT 3+ trial. Paper presented at: The American Heart Association 75th Scientific Sessions; November 20, 2002; Chicago, Illinois.
25. Bonnefoy E, Lapostolle F, Leizorovica A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomized study. *Lancet* 2002;360:825-829.
26. 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.
27. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 2000;343:385-391.
28. Brener SJ, Barr LA, Burchenal JEB, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. *Circulation* 1998;98:734-741.
29. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-2701.
30. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting in acute MI (ADMIRAL trial) *N Engl J Med* 2001;344:1895-1903.
31. Stone GW, Grines CL, Cox DA, et al. A prospective, randomized trial comparing primary balloon angioplasty with or without abciximab to primary stenting with or without abciximab in acute myocardial infarction – primary endpoint analysis from the CADILLAC trial. *Circulation* 2000;102:II-664.
32. Cantor W and Linde J Catheter-based reperfusion for acute myocardial infarction *Cardiology Rounds* 2001;6(3):1-6.
33. Zeymer U, Ludwigshafen C, Roe MT, et al. Effects of facilitated percutaneous coronary intervention on myocardial perfusion and clinical outcome in patients treated with reduced dose tenecteplase and eptifibatide for acute myocardial infarction. Abstract #105675 from: The American Heart Association 75th Scientific Sessions; November 17-20, 2002; Chicago, Illinois.

Upcoming meetings

3-6 March, 2003
The 18th Annual Interventional Cardiology 2003: The International Symposium
Snowmass, Colorado
CONTACT: Cheryl Russell
Tel. 714-799-1617
Fax: 714-799-1686
Email: education@promedica-intl.com

30 March-2 April, 2003
Annual Meeting of the American College of Cardiology
Chicago, Illinois
CONTACT: Tel. 800-253-4636
Email: resource@acc.org

7-10 May, 2003
26th Annual Meeting of the Society for Cardiac Angiography and Interventions
Boston, MA
CONTACT: The Society for Cardiac Angiography and Interventions
Tel. 1-301-897-5400
Fax: 1-301-581-3408
Email: info2@scai.org

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.