CORONARY DISEASE

Acute myocardial infarction:
primary angioplasty

Felix Zijlstra

Department of Cardiology, Hospital De Weezenlanden, Zwolle,
The Netherlands

The treatment of myocardial infarction has evolved considerably over the past decades. Reported mortality rates have fallen as a result of a variety of factors, including earlier diagnosis and treatment of the acute event, improved management of complications such as recurrent ischaemia and heart failure, and general availability of pharmacological treatments such as aspirin, β blockers, and angiotensin converting enzyme inhibitors.¹ Most attention, however, has been focused on treatments that may restore antegrade coronary blood flow in the culprit artery of the patient with evolving acute myocardial infarction. The two methods to achieve this goal are thrombolytic treatment and immediate coronary angiography followed by primary angioplasty if appropriate.¹

History of angioplasty for acute myocardial infarction

Angioplasty for acute myocardial infarction was first described as a rescue treatment in the case of failed intracoronary thrombolysis, and was studied extensively as adjunctive therapy, performed immediately (within hours), early (within 1–2 days), late (after two days), or elective for inducible ischaemia and/or postinfarction angina, after intravenous thrombolytic treatment. Primary angioplasty, without the use of thrombolytic treatment, was described in 1983.² It can be applied as an alternative reperfusion therapy in candidates for thrombolytic treatment, and is the only reperfusion option in many patients with acute myocardial infarction ineligible for thrombolytic treatment.

Pathophysiological considerations and concomitant pharmacological treatment

Studies based on necropsy, angiography, and angiography have shown that formation of a

coronary thrombus on an atherosclerotic plaque, leading to total or subtotal occlusion of the coronary artery, is the key event that causes acute ischaemic syndromes. The initial event in coronary thrombus formation usually is disruption or fissuring of the plaque. Typically this is a lipid laden plaque with a thin cap, and most of these plaques are not haemodynamically significant before rupture. At the site of rupture, platelets adhere to the arterial wall and release vasoconstricting and aggregating substances. A platelet thrombus is formed, the coagulation system is activated, and the end product is a coronary thrombus consisting of aggregated platelets stabilised by fibrin. The result of a mechanical approach to reperfusion is therefore critically dependent on the concomitant use of adjunctive pharmacotherapy to counterbalance the many factors that predispose to further thrombus formation, distal embolisation, and reocclusion of the coronary artery. A brief overview is given in table 1. Meticulous attention to the clinical and haemodynamic condition of the patient and strict adherence to guidelines for the adjuvant treatments will have a profound beneficial effect, irrespective of the mode of reperfusion therapy.

Advantages of acute coronary angiography

The safety and diagnostic potential of coronary angiography during the early hours of acute myocardial infarction have been reported more than 20 years ago.³ In addition to being a prelude to angioplasty, acute coronary angiography offers several advantages. Patient management after the acute event is facilitated by the knowledge of the coronary anatomy, and allows identification of a large subgroup of patients that can be discharged very early (2–3 days) after the acute event,⁴ as well as the 5–10% of patients who have an indication for elective coronary artery bypass grafting on anatomical grounds, such as left main disease and/or triple vessel disease with involvement of the proximal left anterior descending coronary artery.⁵ Some patients presenting with symptoms and signs of acute myocardial infarction should not undergo reperfusion therapy and this can only be ascertained by angiography—for example, patients with spontaneous reperfusion of the infarct related coronary artery, or patients with a cardiac event without thrombotic occlusion of a coronary artery or non-cardiac condition, that may mimic acute myocardial infarction.

Finally, patients with aortic dissections extending into the aortic root or with a coronary anatomy unsuitable for angioplasty can be considered for acute surgical intervention.

Correspondence to:
Dr F Zijlstra, Hospital
De Weezenlanden,
Department of
Cardiology, Groot
Wezenland 20, 8011 JW
Zwolle, The
Netherlands
f.zijlstra@diagram-zwolle.nl

Table 1 Adjunctive pharmacotherapy during and after primary angioplasty

Drug	Target	Acute	Chronic
Aspirin	Platelets	+	+
Glycoprotein IIa/IIIb antagonists	Platelets	+	–
Clopidogrel (after stenting)	Platelets	+	4 weeks
Nitrates ic and/or iv	Vasospasm	+	–
Heparin	Thrombin	+	–
β Adrenergic blockers	Sympathetic receptor	+	+
ACE inhibitor	Heart failure prevention	?	+

Do not forget adequate sedation and pain relief!
ic, intracoronary; iv, intravenous; ACE, angiotensin converting enzyme.

Primary angioplasty in patients eligible for thrombolytic treatment

An overview of short term results of 10 comparisons⁶ of the two approaches has shown that, compared to thrombolysis, primary angioplasty results in a lower mortality (4.4% *v* 6.5%; relative risk 0.66, 95% confidence interval (CI) 0.46 to 0.94), translating into an absolute benefit of two lives saved per 100 patients treated with angioplasty compared with thrombolysis. The reduction in the combination of death or non-fatal reinfarction after angioplasty compared with thrombolysis is even more striking (11.9% *v* 7.2%; relative risk 0.58, 95% CI 0.44 to 0.76). With respect to safety, stroke was reduced from 2.0% with thrombolysis to 0.7% with angioplasty (relative risk 0.35, 95% CI 0.14 to 0.77).

Recently, long term follow up data were published of 395 patients randomly assigned to treatment with angioplasty or intravenous streptokinase.⁷ Clinical information was collected for a mean (SD) of 5 (2) years, and medical charges were compared. A total of 194 patients were assigned to undergo angioplasty and 201 to receive streptokinase. Mortality was 13% in the angioplasty group, as compared with 24% in the streptokinase group (relative risk 0.54, 95% CI 0.36 to 0.87). Non-fatal reinfarction occurred in 6% and 22% of the two groups, respectively (relative risk 0.27, 95% CI 0.15 to 0.52). The combined incidence of death and non-fatal reinfarction was lower for early events (within the first 30 days), with a relative risk of 0.13 (95% CI 0.05 to 0.37), as well as for late events (after 30 days), with a relative risk of 0.62 (95% CI 0.43 to 0.91). The rates of readmission for heart failure and ischaemia were lower in patients from the angioplasty group than in the streptokinase treated patients. Total medical charges per patient were similar in the angioplasty group (\$16 090) and the streptokinase group (\$16 813).

That costs are not higher, and in fact may even be lower for primary angioplasty than for thrombolysis, has been shown in several settings.⁸ Given the superior safety and efficacy of primary angioplasty, this treatment is now preferred when logistics allow this approach. The results of primary angioplasty are in part dependent on the setting in which it is performed, and therefore the results from various hospitals may differ considerably. This is a consequence of the fundamental difference between a procedure and pharmacotherapy,⁹ and has also been shown for angioplasty for stable and unstable angina. Quality control, outcome monitoring, and adherence to guidelines and recommendations of task forces of the European Society of Cardiology¹ and the American College of Cardiology/American Heart Association are therefore of crucial importance.

Table 2 Additional data* from the overview of 10 comparisons between angioplasty and thrombolysis: outcome of patients with early (< 2 hours), intermediate (2–4 hours), and late (> 4 hours) presentation

	Early	Intermediate	Late
30 days mortality (%)			
Angioplasty	3.9	4.1	4.7
Thrombolysis	5.0	6.3	12.1
Death and reinfarction (%)			
Angioplasty	6.0	8.2	7.7
Thrombolysis	12.5	13.4	20.0
Death, reinfarction and stroke (%)			
Angioplasty	6.5	9.0	8.8
Thrombolysis	13.9	15.7	22.5

*Presented at the American College of Cardiology annual meeting, Anaheim 1999.

Stents

In the early years of coronary stenting the presence of an intraluminal thrombus was considered a relative contraindication for stenting. The anticoagulation regimens that were used resulted in a high risk of bleeding and vascular complications. Stenting was therefore restricted to bail-out situations, such as flow limiting dissections or severe residual stenosis despite balloon dilatations. Despite these two problems, the initial results of stenting were quite favourable. In particular, after the development of safe and effective antiplatelet agents, stenting has had a profound effect on the performance and results of primary angioplasty both in the acute phase and during follow up (table 1). Randomised trials have shown a lower adverse event rate after stenting compared to balloon angioplasty.¹⁰ The impact of stenting is also pertinent to the costs; by reducing the rate of restenosis, stent eligible patients have a reduced need for repeat hospitalisation and procedures.

Nevertheless, there are important caveats in our current knowledge of the role of stenting for acute myocardial infarction. Firstly, the benefit of stenting to reduce the rate of restenosis and the need for repeat revascularisation procedures is clear, but the effect of stenting on mortality seems to be absent.

Secondly, (almost) all stent trials have enrolled patients after diagnostic angiography, and excluded many patients after diagnostic angiography, deemed “not suitable” for stenting. Results of trials that enroll all patients with acute ST elevation myocardial infarction, and with randomisation before vascular access is obtained, are urgently needed. At the present time, stenting can be advocated for bail-out situations, and to reduce restenosis in selected suitable candidates. Further improvements will come from new stent designs and possibly from stents covered with drugs or materials that prevent thrombosis or restenosis, or both.

Which patients benefit most?

Only a minority of patients with acute myocardial infarction are presented to a hospital with the facilities to provide primary angioplasty to

Figure 1. A 46 year old male patient presented in profound cardiogenic shock. His ECG showed a sinus rhythm, right bundle branch block with left axis deviation, and ST elevation in all anterior and lateral leads. Following referral and transportation to our hospital, coronary angiography showed a normal right coronary artery (not shown), and a total occlusion of the left main coronary artery (A). After balloon angioplasty and stenting (B), patency was restored (C). The patient was supported for three days with an intra-aortic balloon pump. He made a full recovery and currently, more than a year after the acute event, he is asymptomatic and has resumed his former activities, except smoking.

Priority list for referral for primary angioplasty

- (1) Patients with signs of a large myocardial infarction (≥ 15 mm cumulative ST segment elevation and/or ≥ 7 leads of the 12 lead ECG with ≥ 1 mm ST segment deviation), and contraindications for thrombolytic treatment
- (2) Patients eligible or not eligible for thrombolytic treatment, and two or more high risk characteristics:
 - age > 70 years
 - anterior wall myocardial infarction
 - heart rate > 100 beats/min
 - systolic blood pressure < 100 mm Hg
 - previous myocardial infarction
 - previous coronary artery bypass grafting
 - diabetes
- (3) Patients eligible or not eligible for thrombolytic treatment, with one or fewer high risk characteristics, but with signs of a large (see 1) myocardial infarction.

Whether all patients with acute ST elevation myocardial infarction should be referred is currently being investigated in the DANAMI-2 study (a large multicentre, almost nationwide trial in Denmark comparing thrombolysis in the nearest facility (including transportation) with primary angioplasty, which is expected to be completed in 2001), and also in the PRAGUE-2 study (a similar nationwide trial in the Czech Republic).

all patients with acute myocardial infarction. Most patients are presented in settings—at home, in an ambulance, an emergency room or another hospital facility—that permit the immediate use of thrombolytic treatment, but need additional referral and transportation to allow primary angioplasty. This can be organised safely, but the additional time delay will offset some of the benefit, even though time to therapy is less important for clinical outcome after primary angioplasty compared to thrombolytic treatment (table 2).

One of the first attempts to provide and study primary angioplasty from a community perspective has recently been published, and several larger trials are underway.¹¹ Furthermore, reports have consistently shown that the risk of transportation for primary angioplasty is lower than the risk of stroke associated with the use of thrombolytic treatment. In general, it can be stated that the higher the risk of the patient, the greater the potential benefit of primary angioplasty.¹² This is illustrated in fig 1, and a clinical priority list is given in the box above.

Figure 2. The importance of myocardial reperfusion. Kaplan-Meier survival curves of 398 patients who underwent successful primary angioplasty. ST-T segment elevation resolution on the 12 lead ECG one hour after angioplasty. Complete, complete normalisation of the ST segments; Partial, partial normalisation of the ST segments; No, continuing ST segment elevation. Adapted with permission from AWJ van 't Hof, thesis.

Patency of the artery and reperfusion of the myocardium

In experiments with temporary occlusion of a coronary artery in animals, it has been shown that restoration of antegrade flow in the epicardial coronary artery does not always result in effective reperfusion of the affected myocardium, because of damage to the distal microvasculature. This has been called the “no-reflow” phenomenon. Studies of the ST segment changes on the ECG, the appearance of radiographic contrast during angiography in the myocardium, intracoronary Doppler flow measurements, contrast echocardiography, and magnetic resonance imaging have shown that in a considerable number of patients, flow into the distal myocardium is not normal or even absent despite a patent epicardial coronary artery.¹³ Clinical data show that patients with evidence of adequate myocardial perfusion have an excellent clinical outcome, whereas almost all major adverse clinical events after reperfusion therapy occur in patients with signs of the “no-reflow” phenomenon.¹³ The prognostic importance of signs of myocardial reperfusion is illustrated in fig 2. In day-to-day clinical practice 12 lead electrocardiography, in particular resolution of the ST segment elevations after reperfusion therapy, is an excellent and simple method^{14 15} that can be applied after all forms of reperfusion therapy. Several approaches are under investigation to improve myocardial perfusion and to maintain or restore microvascular integrity in infarct patients—for example, with adjuvant antiplatelet agents, metabolic support or mechanical devices that may prevent distal embolisation.

Future developments

Developments in both mechanical and pharmacological treatments for acute myocardial infarction will continue. If we define our goal

Key points

- Restoration of antegrade coronary blood flow in the culprit artery of the patient with evolving acute myocardial infarction is of paramount importance
- Primary angioplasty can be applied as an alternative reperfusion therapy in candidates for thrombolytic treatment and is the only reperfusion option in all other patients
- Primary angioplasty results in two lives saved per 100 patients treated compared with thrombolysis
- Primary angioplasty results in a lower risk of stroke and reinfarction compared with thrombolysis
- The higher the risk of the patient, the greater the potential of primary angioplasty compared with thrombolysis

for the future as effective myocardial reperfusion within two hours after symptom onset in all patients with acute infarction, it is clear that we still have a long way to go. Earlier diagnosis by 12 lead electrocardiography at home or in the ambulance, rapid transportation, and institution of the best available option should be the first priorities. Prehospital diagnosis allows preparations before the arrival of the patient and results in an important improvement in the delivery of reperfusion therapy. In patients treated with primary angioplasty it results in a reduction in time to first balloon inflation by 30–40 minutes,¹⁶ and where angioplasty is not available it allows the prehospital and more rapid administration of thrombolytic treatment. Prehospital diagnosis offers as an additional advantage the possibility to consider pharmacological pretreatment on the way to the catheterisation laboratory. Trials with very high doses of heparin¹⁷ and with thrombolytics¹⁸ have been reported, but did not show clear clinical benefits in spite of a somewhat higher initial patency of the infarct related artery, at the expense of higher bleeding rates. Glycoprotein IIb/IIIa antagonists are an attractive option¹⁹ and should be studied for this specific purpose,²⁰ as well as various forms of metabolic support, such as glucose–insulin–potassium.

Although more research is required into many facets of primary angioplasty, it is clear that this treatment is here to stay. Planning for infarct angioplasty needs to be coordinated and clinical protocols agreed by all involved in the care of patients with acute myocardial infarction. The additional benefits and limitations of new drugs, devices, and combinations of both will be investigated and may lead to improved patient outcome, but in the years to come, most benefit for our patients will come from dedicated application of the therapeutic possibilities that are available today.

1. **The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology.** Acute myocardial infarction: pre-hospital and in-hospital management. *Eur Heart J* 1996;**17**:43–63.
2. **Hartzler GO, Rutherford BD, McConahay DR, et al.** Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983;**106**:965–73.
 - The first description in a large series of patients of primary angioplasty without the concomitant use of thrombolytic drugs. It established the safety and efficacy of angioplasty in order to obtain a patent infarct related artery.
3. **DeWood MA, Spores J, Notske R, et al.** Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.
 - The first large study that documented the safety and diagnostic potential of coronary angiography during acute myocardial infarction. It showed that most patients presenting with acute ST segment elevation myocardial infarction have a total occlusion of a major epicardial coronary artery and that thrombosis is involved in many patients.
4. **Grines CL, Marselese DL, Brodie B, et al for the PAMI-II Investigators.** Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. *J Am Coll Cardiol* 1998;**31**:967–72.
5. **Every NR, Maynard C, Cochran RP, et al for the Myocardial Infarction Triage and Intervention Investigators.** Characteristics, management, and outcome of patients with acute myocardial infarction treated with bypass surgery. *Circulation* 1996;**94** (suppl II):81–6.
 - A report from the MITI investigators, describing 1299 patients who underwent bypass surgery early in the course of acute myocardial infarction. In selected patients with acute myocardial infarction, bypass surgery is associated with a low repeat procedure use and excellent long term survival.
6. **Weaver WD, Simes RJ, Betriu A, et al for the Primary Coronary Angioplasty vs. Thrombolysis Collaboration Group.** Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative overview. *JAMA* 1997;**278**:2093–8.
 - An overview of 10 randomised comparisons of thrombolytic treatment and primary angioplasty.
7. **Zijlstra F, Hoorntje JCA, 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.
8. **Lieu TA, Gurley RJ, Lundstrom RJ, et al.** Projected cost-effectiveness of primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1997;**30**:1741–50.
9. **Canto JG, Every NR, Magid DJ, et al.** The volume of primary angioplasty procedures and survival after myocardial infarction. *N Engl J Med* 2000;**342**:1573–80.
 - A nice illustration of the fact that angioplasty is a procedure, and that therefore the results are dependent on both the operator and the general setting in which the procedure is performed. Hospitals with the greatest number of interventions had a lower mortality (2.0 fewer deaths per 100 patients treated). There was no relation between the number of thrombolytic interventions and mortality among patients who received thrombolytic treatment.
10. **Grines CL, Cox DA, Stone GW, et al for the Stent Primary Angioplasty in Myocardial Infarction Study Group.** Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med* 1999;**341**:1949–56.
 - Important stent trial that shows unequivocally that stents result in a reduced rate of recurrent ischaemic events. However, TIMI flow after the procedure and mortality were at least as good after "plain old balloon angioplasty" with some bail-out stenting compared to primary stenting.
11. **Widimsky P, Groch L, Zelizko M, et al on behalf of the PRAGUE Study Group Investigators.** 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**:823–31.
 - One of the first attempts to deliver and study primary angioplasty on a "nationwide" scale. The results of the ongoing DANAMI-2 and PRAGUE-2 studies may have a profound impact on the care of the many patients with acute myocardial infarction presenting to a community hospital without a catheterisation laboratory.
12. **O'Neill WW, de Boer MJ, Gibbons RJ, et al.** Lessons from the pooled outcome of the Pami, Zwolle and Mayo Clinic randomized trials of primary angioplasty versus thrombolytic therapy of acute myocardial infarction. *J Invasive Cardiol* 1998;**10**:4A–10A.
 - Observations based on pooled data from three randomised trials performed a decade ago. Two of the conclusions are that the results of angioplasty are less time dependent in comparison with the results of thrombolytic treatment, and that the benefits of angioplasty compared to thrombolysis are most pronounced in patients with high risk characteristics.
13. **Iliceto S, Marangelli V, Marchese A, et al.** Myocardial contrast echocardiography in acute myocardial infarction: pathophysiological background and clinical applications. *Eur Heart J* 1996;**17**:344–53.
 - A nice example of one of the many ways by which we can study myocardial reperfusion after the restoration of patency of the epicardial infarct related coronary artery.
14. **Schröder R, Dissmann R, Bruggemann T, et al.** Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;**24**:384–91.
 - One of the first reports that showed the prognostic importance of ST segment elevation resolution after thrombolytic treatment. It was subsequently established that this simple electrocardiographic parameter is of similar value after successful primary angioplasty.
15. **van 't Hof AWJ, Liem AL, de Boer MJ, et al on behalf of the Zwolle Myocardial Infarction Study Group.** Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *Lancet* 1997;**350**:615–9.
16. **Zijlstra F.** Long-term benefit of primary angioplasty compared to thrombolytic therapy for acute myocardial infarction. *Eur Heart J* 2000;**21**:1487–9.
17. **Liem AL, Zijlstra F, Ottervanger JP, et al.** High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the heparin in early patency (HEAP) randomized trial. *J Am Coll Cardiol* 2000;**35**:600–4.
18. **Ross AM, Coyne CS, Reiner JS, et al for the PACT Investigators.** A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction; the PACT trial. *J Am Coll Cardiol* 1999;**33**:1528–33.
19. **Brener SJ, Ban, LA, Burchenal JEB, et al on behalf of the RAPPORT Investigators.** Randomised, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. *Circulation* 1998;**98**:734–41.
20. **van den Merkhof LFM, Zijlstra F, Olsson H, et al.** Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. Results of the glycoprotein receptor antagonist patency evaluation (Grape) pilot study. *J Am Coll Cardiol* 1999;**33**:1528–33.