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. 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.

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. 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 angioscopy 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 reclosure 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. 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, 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. 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.

Table 1 Adjunctive pharmacotherapy during and after primary angioplasty

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Platelets</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glycoprotein IIa/IIIb antagonists</td>
<td>Platelets</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clopidogrel (after stenting)</td>
<td>Platelets</td>
<td>+</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Nitrates ic and/or iv</td>
<td>Vasospasm</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Heparin</td>
<td>Thrombin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>β Adrenergic blockers</td>
<td>Sympathetic receptor</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Heart failure prevention</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

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 comparisons 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), translated 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. 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. 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 a consequence of the fundamental difference between a procedure and pharmacotherapy, 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 Cardiology 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

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Intermediate</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days mortality (%)</td>
<td>3.9</td>
<td>4.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>5.0</td>
<td>6.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.35</td>
<td>0.14</td>
<td>0.77</td>
</tr>
<tr>
<td>Death and reinfarction (%)</td>
<td>6.0</td>
<td>8.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>12.5</td>
<td>13.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>13.9</td>
<td>15.7</td>
<td>22.5</td>
</tr>
</tbody>
</table>

*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. 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...
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. Further-more, 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. This is illustrated in fig 1, and a clinical priority list is given in the box above.

### Priority list for referral for primary angioplasty

1. Patients with signs of a large myocardial infarction ($\geq 15$ mm cumulative ST segment elevation and/or $\geq 7$ leads of the 12 lead ECG with $\geq 1$ 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).
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. 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. 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 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 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, and where angioplasty is not available it allows the prehospital and more rapid administration of thrombolytic therapy.

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 heparin and with thrombolytics 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 option and should be studied for this specific purpose, 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.

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. 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. 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 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 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, and where angioplasty is not available it allows the prehospital and more rapid administration of thrombolytic therapy. 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 heparin and with thrombolytics 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 option and should be studied for this specific purpose, 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.

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


