A CLINICAL EVALUATION OF PRIMARY ANGIOPLASTY AND STENTING IN ACUTE MYOCARDIAL INFARCTION

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Van 't Hof, Adriaan Willem Johannes

A Clinical Evaluation of Primary Coronary Angioplasty and Stenting in acute Myocardial Infarction
Thesis Erasmus University Rotterdam (de Weezenlanden Series No. 23)
ISBN 90-74991-23-8
Key words: Myocardial Infarction, Reperfusion, Angioplasty, Stenting

Front cover: Rio Orinoco, Venezuela, South America

Publication and printing of this thesis was financially supported by the Netherlands Heart Foundation Utrecht, and the "Dr Cremers Foundation", Hospital de Weezenlanden, Zwolle

A CLINICAL EVALUATION OF PRIMARY ANGIOPLASTY AND STENTING IN ACUTE MYOCARDIAL INFARCTION

Een klinische evaluatie van primaire ballonangioplastiek en stenting als behandeling van het acute hartinfarct

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus Prof.dr P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 2 september 1998 om 15.45 uur
door

Adriaan Willem Johannes van 't Hof

geboren te Doornspijk

PROMOTIECOMMISSIE

PROMOTOR:	Prof.dr M.L. Simoons
CO-PROMOTOR:	dr F. Zijlstra
OVERIGE LEDEN:	Prof.dr P.W. Serruys Prof.dr W.Th. Hermens Prof.dr F.W.A. Verheugt

Design and Printing: Sketch, Madrid, Spain

"Take your time, think a lot, think of everything you 've got, for you will still be here tomorrow, but your dreams may not".

Cat Stevens, Father and Son, 1970

Aan Karin, Marlou, Lasse en mijn Ouders

CONTENTS

Chapter 1: Introduction and aims of the thesis ..... **Page 9**

Chapter 2: Reperfusion ..... **Page 35**

The Clinical Value of 12-lead Electrocardiogram after Successful Reperfusion Therapy for Acute Myocardial Infarction

Lancet 1997;350:615-619

Angiographic Assessment of Myocardial Reperfusion in Patients treated with Primary Angioplasty for Acute Myocardial Infarction: Myocardial Blush Grade

Circulation 1998;97:2302-2306

Chapter 3: Additional therapy ..... **Page 59**

Randomized Comparison of Coronary Stenting with Balloon Angioplasty in Selected Patients with Acute Myocardial Infarction

Circulation, 1998;97:2502-2505

Costs of stenting for acute myocardial infarction

Lancet 1998;351:1817(letter)

A Randomised Comparison of Intra-Aortic Balloon Pumping after Primary Coronary Angioplasty in High Risk Patients with Acute Myocardial Infarction

Submitted for publication

Chapter 4: Primary PTCA for which patients? ..... **Page 85**

Randomized Comparison of Primary Coronary Angioplasty with Thrombolytic Therapy in Low Risk Patients with Acute Myocardial Infarction

Journal of the American College of Cardiology 1997;29:908-912

Transferring Patients for Primary Angioplasty
A Retrospective Analysis of 104 Selected High Risk Patients with Acute Myocardial Infarction

Heart 1997;78:333-336

Chapter 5: Time to reperfusion ..... **Page 105**

Influence of Treatment Delay on Infarct Size and Clinical Outcome in Patients with Acute Myocardial Infarction treated with Primary Angioplasty

Journal of the American College of Cardiology, in press

Clinical Presentation and Outcome of Patients with Early, Intermediate and Late Reperfusion Therapy by Primary Coronary Angioplasty for Acute Myocardial Infarction

European Heart Journal 1998;19:118-123

Chapter 6: Restenosis and Reocclusion ..... **Page 129**

Incidence and Predictors of Restenosis after Primary Coronary Angioplasty for Acute Myocardial Infarction: The Importance of Age and Procedural Result

American Heart Journal, in press

Chapter 7: General Discussion and Closing Remarks ..... **Page 147**

Ten Commandments of Primary PTCA ..... **Page 165**

Summary ..... **Page 167**

Samenvatting ..... **Page 172**

Dankwoord ..... **Page 177**

Curriculum Vitae ..... **Page 179**

CHAPTER 1

Introduction and Aims of the Thesis

Introduction and aims of this thesis

History of reperfusion therapy for acute myocardial infarction

In 1949 the fibrinolytic effect of streptococcal fibrinolysin (streptokinase) was described for the treatment of fibrous, purulent or sanguineous pleural exudations (1). The effect of this lytic agent in patients with acute myocardial infarction was described by Fletcher in 1958 (2). In the late nineteenseventies the pathofysiologic mechanism underlying acute myocardial infarction was recognised. In the majority of patients with acute myocardial infarction a completely occluded coronary artery is present at immediate angiography (3-5), caused by the formation of a platelet rich thrombus on a ruptured atherosclerotic plaque (6,7). Reperfusion therapy is aimed at removal of this obstructing clot which can be achieved by thrombolytic agents (given directly into the coronary artery or intravenously) or by mechanical intervention (Percutaneous Transluminal Coronary Angioplasty (PTCA)) or by a combination of these two. Rentrop et al. described his experience with intracoronary administration of streptokinase in 1979 (8). In 1983 it was shown in small trials that the intracoronary administration of streptokinase was beneficial compared to placebo treatment (9,10) and later, larger randomised trials demonstrated convincingly that intravenous fibrinolytic therapy re-establishes coronary patency, thereby limiting infarct size and preserving left ventricular function resulting in improved survival (11, 12). In 1982, Meyer reported a case in which he successfully re-opened an infarct related vessel with a guide wire and a balloon after failed thrombolytic therapy (rescue PTCA,13). One year later Hartzler was the first to describe his experience with primary coronary angioplasty (mechanical revascularization without antecedent thrombolysis) (14)

Deferred and Rescue Angioplasty

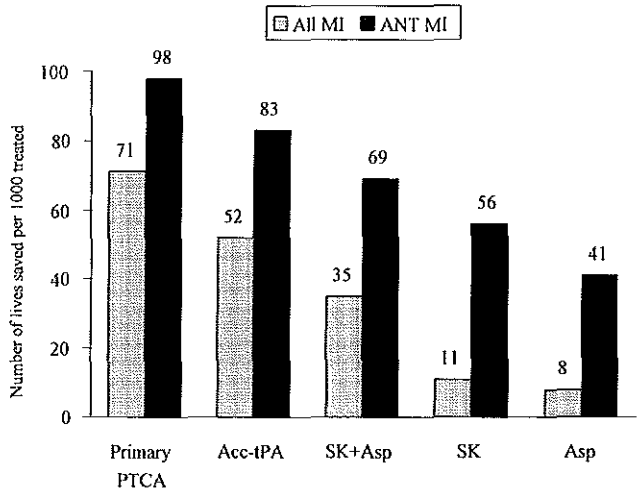
The combination of thrombolysis and PTCA seemed attractive and was studied by different groups of investigators. After the disappointing results of routine angioplasty for patients in whom a severe residual stenosis was present after thrombolysis or in whom thrombolysis had failed (15-24), PTCA was regarded as the "poor relation" in the management of acute myocardial infarction. Instead large scale studies were planned to compare different thrombolytic regimes and this resulted in megatrials like GISSI-2, ISIS-3, and GUSTO-1 (25-27), from which the latter included more than 40.000 patients and was published in 1993.
The Thrombolysis and Myocardial Infarction (TIMI) phase 1 trial introduced a standard for flow assessment in the infarct related vessel after thrombolytic therapy (28). This angiographic definition of perfusion of the epicardial coronary vessel was based on the assumption that grades 0 and 1 are effectively occluded and grades 2 and 3 provide adequate reperfusion. This scoring system has been commonly used to assess the immediate effectiveness of reperfusion therapy. From the trials which compared different lytic agents, it became evident that the best thrombolytic regime, the accelerated administration of recombinant tissue Plasminogen Activator (rtPA), resulted in successful reperfusion (TIMI 2 or 3 flow) in 80% of patients and TIMI 3 flow in only 60% of patients (29). This led to a re-evaluation of primary angioplasty as a possible more effective treatment modality (30). In 1993 three randomised trials of thrombolytic therapy versus primary coronary angioplasty for acute myocardial infarction were published in the same issue of the New England Journal of Medicine (31-33). The results of these trials were in favour of primary angioplasty and showed that it was possible to achieve TIMI grade 3 flow through the infarct related vessel in more than 90% of patients which was associated with a very low in-hospital mortality of 2-3%. This information influenced daily practice in many institu-

tions with facilities for interventional cardiology around the world and raised the question whether thrombolytic therapy was still the best treatment in a patient with acute myocardial infarction.

Criticism and results from other trials

Many criticised the results, suggesting that the evidence was obtained from only three, relatively small sized randomised trials, in which the work was done by highly experienced and dedicated, high volume operators, in selected patients (34,35). There was doubt whether these results would be reproducible in all day routine clinical practice, often referred to as the 'real world'.
To address this question a substudy of the GUSTO 2 trial randomised 1138 patients to receive either the best thrombolytic agent so far (accelerated tPA) or primary angioplasty. This study was performed in 57 centres over the world. The results have recently been published and were in favour of the angioplasty group (36). However, the reduction in the primary end point: a combination of death, reinfarction and stroke, was not as marked as in the first randomised trials (31-33). Later, it became evident that the relative long treatment delay (1.9 hours) and the considerable number of PTCA assigned patients, who did not undergo angiography (6%) or angioplasty (19%), may partially be responsible for this finding (37). Nevertheless the authors concluded that primary angioplasty is an effective alternative therapy. Three published registries showed conflicting results. The Myocardial Infarction Triage and Intervention project registry (MITI, retrospective, non-randomised, 12,331 patients from 19 centres) and the recently published National Registry of Myocardial Infarction-2 (NRMI, retrospective, non-randomised, including 29,644 patients) registry data failed to show a difference in outcome between thrombolytic therapy and primary angioplasty (38,39). However, in these registries only 10-15% of patients underwent primary angioplasty and suggests a selection bias. In contrast, the German Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärtze (ALKK) registry, which is a good reflection of common practice in a large part of Germany (4625 patients from 63 centres), documented results for patients treated with primary angioplasty comparable to the first randomised trials (40). A recent meta-analysis of all randomised trials comparing thrombolysis and primary angioplasty in myocardial infarction, comprising 2606 patients, showed a 34% reduction in total mortality at 30 days for patients treated with primary angioplasty, equivalent to the saving of 21 lives per thousand patients treated. The FTT analysis found the same mortality reduction when comparing fibrinolytic therapy with placebo (12). In addition it was found that angioplasty was associated with a significant reduction in the incidence of hemorrhagic stroke (0.08 vs 1.1%, p=0.0005) (41). Figure 1 shows a comparison of the number of lives saved for different reperfusion strategies.

Figure 1



Comparison of number of lives saved per 1000 patients treated at 30 days following acute myocardial infarction (MI) for different reperfusion strategies and aspirin. Acc-tPA: accelerated tPA;SK: streptokinase, Asp: aspirin. The figures have been derived by taking the overall mortality rate in control patients as 11.5% for all MIs and 16.9% for anterior Mis (taken from FTT's collaborators study (12)). Mortality rate for primary angioplasty for the overall population and for anterior MIs was taken as 4.4% (from meta-analysis of primary PTCA (41)) and 7.1% (taken from GUSTO-IIb (36)); respectively; for accelarated tPA as 6.3% and 8.6% respectively (taken from GUSTO I (27); for streptokinase with aspirin as 8% and 10%, respectively; for streptokinase alone 10.4% and 11.3%; and for aspirin as 10.7% and 12.8%, respectively (taken from ISIS-2 study (42). Reprinted with permission from Heart (BMJ publishing group, Beatt K, et al, Heart 1997(suppl 2);78:12-15).

Guidelines

Recently, the European Society of Cardiology recently stated in its guidelines that primary angioplasty "may have a special role in the treatment of patients with cardiogenic shock and in those with contra-indications for thrombolytic therapy" (43). The American College-American Heart Association task force recommended primary angioplasty as a first choice option for the treatment of acute myocardial infarction, provided that it can be done within a certain time window and with support from experienced personnel in high volume centres (44).
In summary, after an initial period of doubt about the role of mechanical opening of an occluded infarct related vessel, primary angioplasty has developed into a first choice option for many patients with acute myocardial infarction.

Lessons learned from thrombolytic trials

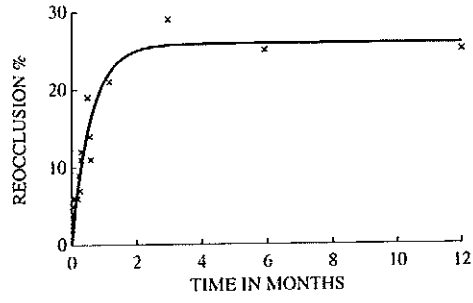
The open infarct-artery hypothesis

Complete reperfusion

Rapid and sustained patency of the infarct related vessel is the main goal of therapy in patients with acute myocardial infarction (45,46). This was illustrated in the GUSTO-1 angiographic substudy. Front-loaded rtPA achieved earlier and more complete reperfusion than other thrombolytic regimes and this resulted in an absolute mortality reduction of 1% at 30 days (27, 47). Thirty day and long term (2 years) mortality could be accurately predicted from the status of perfusion of the infarct related artery at 90 minutes (48). Furthermore it has been shown that incomplete perfusion (TIMI 2 flow) is almost as bad as no reperfusion (49-51). However, it is not only important to open the vessel as quick as possible but also to prevent it from restenosis and reocclusion. A high grade stenosis of the infarct related artery may negatively influence left ventricular function and long-term prognosis (52,53). Various studies have shown the importance of

an open infarct related vessel for long term clinical outcome (54-56). In this regard the APRICOT (Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis) study has made an important contribution and showed the detrimental effects of reocclusion of the infarct related vessel on left ventricular function and clinical outcome (57).

Figure 2



Incidence of reocclusion after thrombolysis. The x axis represents the time between the initiation of thrombolytic therapy and the time of follow-up angiography. Reprinted with permission from the American College of Cardiology, J Am Coll Cardiol 1996;27:766-73).

Reocclusion

The incidence of reocclusion is high in the early days after thrombolysis and increases to about 20-30% at 3 months to 1 year after infarction (Figure 2, 58). Risk factors for reocclusion are a severe residual stenosis of the infarct related vessel (59-61), which is not a rare phenomenon in patients after thrombolytic therapy, and a totally occluded infarct related vessel before the administration of the thrombolytic agent (62). Routine angioplasty after thrombolysis with the aim to obtain a larger luminal diameter of the infarct related vessel and therefore to prevent reocclusion did not result in a better outcome (16, 19). A recent study showed that late angioplasty or surgical revascularisation is beneficial in selected patients with inducible ischemia shortly after thrombolysis (63). This emphasises that PTCA after thrombolysis should only be performed when clinically indicated. The reasons why a persistently patent infarct related vessel might give additional years of life to a patient are threefold: it results in enhanced infarct healing (56), with prevention of left ventricular remodelling (64), electrical stability (65-70) and it may serve as a collateral conduit in patients with multivessel disease.

Resistance to thrombolysis

From trials in which the thrombolytic agent was given directly into the coronary artery it became evident that not all acute occlusive coronary artery disease is the consequence of an obstructing thrombus (8,9). In about 20 to 30% of patients antegrade flow cannot be accomplished by lytic therapy. This may have different causes. Either the thrombus is too old, or platelet rich (71,72), or there is a mechanical obstruction such as plaque rupture, intramural hematomas, or profound vasospasm (73). Inadequate fibrinolysis might be another reason for failure of therapy (74). A recent study showed that the extent of decrease in fibrinogen was related to patency of the infarct related vessel and clinical outcome (75). Another explanation might be the fact that thrombolytic therapy induces platelet activation by way of enhanced thrombin activity and clot formation, which may counterbalance its positive lytic effects (76,77).

Cardiogenic Shock

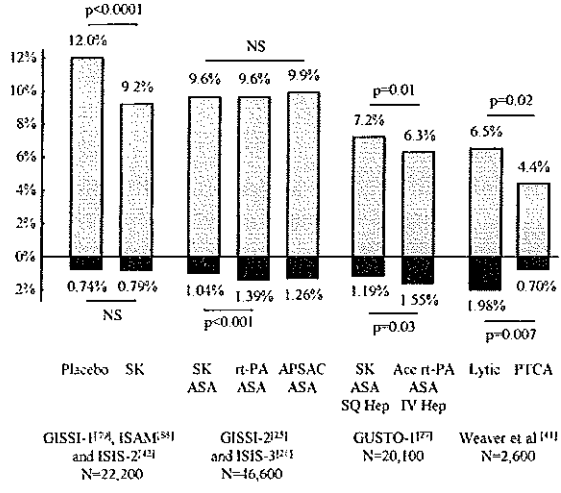
There is no convincing evidence that thrombolysis is effective in patients with cardiogenic

shock. Although subanalyses of randomised trials have shown that thrombolytic therapy is of the same or even greater benefit in patients with low blood pressure or tachycardia on admission (78), the overall mortality rate in patients with severe heart failure or cardiogenic shock remains unacceptable high (Killip III: 30-50%, Killip IV: 65-80%), despite treatment with lytic agents. The only trial which included patients with cardiogenic shock was the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto myocardico) phase 1 trial and showed no benefit of thrombolysis in patients with cardiogenic shock (79). In an overview of data, it was concluded that it is unclear whether thrombolytic therapy has reduced mortality due to cardiogenic shock (80). A possible explanation for the lack of efficacy of thrombolyic therapy in patients with cardiogenic shock might be coronary hypoperfusion (74).

Which patients benefit most from reperfusion therapy?

The first trials comparing thrombolytic therapy with placebo in patients with acute myocardial infarction included relative low risk patients (9,10,42,79). A recent article showed that only 13 to 52% of patients with a final diagnosis of acute myocardial infarction receive thrombolytic therapy (81). The remaining non-candidates for lytic therapy, either arrive too late (> 12 hours after symptom onset), or the diagnosis of acute myocardial infarction is not evident on arrival of the patient or there are contraindications for thrombolytic therapy. Mortality in patients considered ineligible for thrombolysis is up to five times higher than among those who receive treatment (82). More and more data suggest that reperfusion therapy, and especially TIMI grade 3 flow in the infarct related vessel, is beneficial in those patients who were previously excluded from thrombolytic therapy, i.e. patients over 75 years of age. (83). Failure to achieve early and complete reperfusion in these high risk infarct patients is associated with a very high mortality. These patients might especially benefit from rtPA and primary angioplasty compared to streptokinase. (84,85). However, in contrast to rtPA, primary coronary angioplasty is associated with a decreased risk of stroke (Figure 3) and should therefore be considered as primary therapy in high risk patients and in patients with contraindications for thrombolytic therapy (86,87).

Figure 3



One-month mortality and stroke rates after thrombolytic therapy or immediate angioplasty in patients with suspected myocardial infarction treated within 0-6 h of onset of symptoms. Reprinted with permission (89, Boersma H,PhD Thesis, 1998).SK = streptokinase, APSAC = anisoylated plasminogen streptokinase activator, rtPA = recombinat tissue typeplasminogen activator, PTCA = percutaneous transluminal coronary angioplasty; ASA = aspirin, Hep = heparin

Time to start of thrombolytic therapy

The Fibrinolytic Therapies Trialists (FTT) overview, which is a pooled-analysis of large randomised thrombolytic trials, showed convincingly that time to start of thrombolytic therapy is an important predictor of outcome (12). Whether this relationship is linear or non-linear is not certain (90, 91). Starting treatment within this first "golden hour" often results in considerable myocardial salvage (92) and is therefore associated with a better outcome. The exact influence of time on outcome however is difficult to assess. Patients who present early are different from patients presenting late (93-96). For instance, the latter are more often female and more often have diabetes. Therefore groups with different times to treatment are not comparable.

Pre-Hospital Thrombolysis

The proper method to study the influence of time to therapy on outcome without disturbing confounders is to compare pre-hospital thrombolysis with in-hospital therapy. These trials do not unequivocally show a mortality reduction in pre-hospital treated patients (97-99). The time gained by pre-hospital treatment varied from 33 to 130 minutes. The only study with a large sample size was the European Myocardial Infarction Project (EMIP) trial, which was intended to enrol 10,000 patients (99). However, this trial was halted after enrolment of 5300 patients because of lack of funds. A meta-analysis of all randomised trials showed a significantly lower mortality for patients treated in the pre-hospital phase (100). Patients included in the randomised trials were highly selected. Only 4-5% of eligible patients actually received the study drug either in the ambulance or at the hospital. The meta analysis of all randomised trials showed that pre-hospital thrombolytic therapy resulted in the saving of 16-21 lives saved per thousand patients treated per hour (100). From data of the Grampian Region Early Anistreplase Trial (GREAT), the benefit of pre-hospital thrombolysis, measured at 5 year follow-up, was estimated to vary between 6 lives saved per 1000 per hour to about 20 lives saved per 1000 per hour (101). If pre-hospital thrombolysis is given within the first hour after symptom onset it may even be 30 or more lives saved per 1000 per hour.

Late thrombolytic Therapy

On the other side of the spectrum the question remained whether late thrombolytic therapy (given later than 6 hours after symptom onset) is beneficial. Rentrop showed that, in the presence of collateral circulation, thrombolytic therapy results in myocardial salvage even when given relatively late (mean of 6.3 hours after symptom onset)(102). A substudy of the ISIS-2 trial previously had shown that thrombolytic therapy given late (between 6 and 24 hours) resulted in a mortality reduction (42), however, this trial was not specifically designed for late entry patients. Two large scale randomised thrombolytic trials tried to answer this question. The Late Assessment of Thrombolytic Efficacy (LATE) study (103) used alteplase and the Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS) Collaborative Group (104) used streptokinase, and both showed beneficial effects in patients who presented up to 12 hours after onset of symptoms, although the results of the latter were not conclusive. The mechanisms by which reperfusion therapy established beyond the time of myocardial salvage is beneficial are threefold: it results in improved infarct healing with prevention of infarct expansion, it promotes electrical stability and the open artery might serve as a conduit for perfusion of non-infarct related regions in the presence of multi-vessel disease (105). In a substantial subset of patients the moment of coronary occlusion remains uncertain. These patients with a intermittent coronary occlusion (106) may especially benefit from reperfusion therapy, despite the fact that the beginning of symptoms was more than 6 to 12 hours ago.

In summary thrombolytic trials have shown that optimal reperfusion therapy should result in early and sustained patency of the infarct related vessel with a low grade residual stenosis. Lincoff (50) showed in 1993, Verheugt in 1996 (58) and White and Van de Werf in 1998 (107) that this occurs only in a minority of patients given thrombolytic therapy and that the "ideal" thrombolytic agent has not yet been developed. Despite a continuing search for better thrombolytic drugs and more effective additional therapy, results have not improved dramatically so far (78,108) (Table 1).

Table 1

Rate of TIMI grade 3 flow 90 minutes after intravenous thrombolytic therapy

1988 - 1994		(ref:109)
standard tPA	50%	
accelerated tPA	63%	
streptokinase	32%	
APSAC	50%	
>1994		
reteplase	60%	(ref: 110)
streptokinase + high dose hirudin	48%	(ref: 111)
streptokinase + r-hirudin	41%	(ref: 112).
TNK tPA high dose	66%	(ref: 113)
accelarated tPA + high dose argatroban	58%	(ref: 114)
streptokinase + high dose argatroban	44%	(ref: 115)
accelarated tPA + high dose integrilin	66%	(ref: 116)
low dose tPA + abciximab + heparin	79%	(ref: 117)
streptokinase + high dose eptifibatide	52%	(ref: 118)
streptokinase + low dose integrilin	53%	(ref: 119)
60 minutes alteplase after 20 mg bolus	80%	(ref: 120)

tPA=tissue type Plasminogen Activator, APSAC=Anisoylated Plasminogen Streptokinase Activator Complex, TNK is a tPA molecule which is altered at 3 sites (T, N, K amino acid substitutions)

Lessons learned from primary coronary angioplasty trials

The Zwolle trial

The Zwolle trial demonstrated that by using primary angioplasty, it was possible to achieve TIMI grade 3 flow through the infarct related vessel in more than 90% of patients with acute myocardial infarction within 120 minutes after hospital admission (31). Treatment with primary angioplasty compared to streptokinase resulted in a smaller infarct size, a better left ventricular ejec-

tion fraction and a lower hospital mortality (2% vs 7%, p=0.024) (121). At follow-up recurrent ischemia and reinfarction were also significantly reduced in this patient group. Primary angioplasty was most beneficial in patients with anterior myocardial infarction and in patients treated early after symptom onset (within 2 hours). Quantitative coronary angiography showed that patients treated with angioplasty had a less severe residual diameter stenosis and a wider minimal luminal diameter at follow up coronary angiography compared to patients treated with streptokinase. Patency rates were 95% for patients in the angioplasty group compared to 66% for patients treated with streptokinase (122). At 31 months follow-up, the combined risk of death or non-fatal reinfarction was 4.6 times (95% confidence intervals: 2.2 - 8.3, p<0.001) higher in these patients (123). Both at 12 and at 31 months follow-up total costs for both treatments were analysed. The higher costs during first admission associated with primary angioplasty were compensated by a reduced need for pharmacological and other medical therapy during follow-up (123, 124). When costs were assessed in relation to event-free survival, treating patients with streptokinase was associated with higher costs compared to patients who underwent primary angioplasty (p<0.001). This has been confirmed later by other centres (125,126), provided that primary angioplasty is performed in high volume centres (>150 infarctions annually).

Mechanisms of benefit of primary angioplasty

One of the mechanisms by which primary angioplasty results in a lower mortality compared to thrombolytic treatment is the prevention of myocardial rupture. Patients with persistent occlusion of the infarct related vessel are at increased risk for rupture of the myocardial wall (127). Pathological findings in these patients frequently showed severe haemorrhage of the infarcted myocardium and suggested that this occurred more often in patients treated with thrombolytic therapy compared to patients who had reperfusion therapy without antecedent lytic treatment (128). The recent findings of the Primary Angioplasty in Myocardial Infarction (PAMI) group confirmed these findings (129). Primary angioplasty gives another advantage over thrombolytic therapy. Immediate coronary angiography in patients with suspected acute myocardial infarction gives the opportunity for risk stratifying patients and tailoring therapy to the needs of the individual patient. Patients without significant coronary artery lesions can be treated conservatively without the unnecessary risk of exposure to thrombolytic therapy. On the other hand, 2 to 4% of patients in the Zwolle trial underwent primary coronary bypass surgery within several hours after symptom onset, because of severe left main or critical triple vessel disease. Although it is not proven, the facility to perform immediate bypass surgery in very high risk patients, 24 hours a day, might attribute to the good results achieved in the total population (130).

Limitations of primary coronary angioplasty

Primary coronary angioplasty cannot be performed in every hospital. In contrast, thrombolytic therapy is widely available, and can even be administered by ambulance personnel or general practitioners in a pre-hospital setting. Its effect is not operator dependent. However, the outcome of primary angioplasty varies per centre (131). In a recent study, the rate of TIMI 3 flow of the infarct related vessel varied between 71% and 94%. The success of primary angioplasty depends on laboratory angioplasty volume as well (132). Cost-effectiveness also increases with the number of angioplasties performed yearly (126). For the abovementioned reasons, it is unwise to extend the facility to perform angioplasty to every hospital with angiography facilities. A recent study from the PAMI-investigators, however, suggested that performing primary angioplasty at hospitals with no-surgery on-site is safe and effective in high-risk patients. Only 1.4% of patients needed emergent transfer for performing coronary bypass surgery (133).

What makes angioplasty after thrombolytic therapy less attractive?

There are various reports that thrombolytic therapy has deleterious effects on reperfused myocardium (76) and consequently results in a low percentage of patients with TIMI 3 flow and evidence of tissue perfusion. A recent report, using myocardial contrast echocardiography, showed that primary angioplasty resulted in a significantly higher percentage of patients with evidence of myocardial reflow compared to patients receiving rtPA (134). Thrombolytic therapy has also a procoagulant effect (135,136). A recent study using coronary angioscopy suggested that thrombolysis exposes ulcerated plaques when the overlying thrombus has been resolved, possibly resulting in increased instability of the plaque (137). Routinely dilating the infarct related vessel after successful thrombolytic therapy therefore might do more harm than good as was found in previous trials (16-18). Rescue angioplasty after failed thrombolysis has not proven to be beneficial (138). However, when combined with aggressive antiplatelet therapy, it might be of value in certain subsets of patients as was found in a substudy of the GUSTO-III trial (139).

Impaired-reflow after direct coronary angioplasty

In patients treated with primary angioplasty, impaired flow after direct PTCA has been reported in 2 to 34% of patients (140). This state of impaired flow after successful opening of the epicardial infarct-related vessel has been called the "no-reflow" phenomenon, and may vary from an absence of any flow to slow flow in the dilated vessel, and is associated with a worse clinical outcome (141). The pathofysiologic mechanism of no-reflow has been studied in humans as well as in the animal laboratory and is based on extensive damage to the microcirculation of the myocardium (142). Prolonged ischemia leads to cell death, the release of several vasoactive substances and neutrophils that results in vasospasm and plugging of the small arterioles (143,144). This is not only caused by ischemia but may also be related to the relief of ischemia , the reperfusion itself, so-called reperfusion injury (145-151), although this has mainly been studied in animal models. Myocardial contrast echocardiography performed during and shortly after the primary coronary angioplasty procedure confirmed that in some patients, with TIMI 3 flow of the infarct related vessel, the myocardium is not perfused after intracoronary injection of sonicated microbubbles (152). Echocardiographic evidence of impaired myocardial reflow after successful primary angioplasty was associated with increased left ventricular dilatation and a worse outcome (153-157). This led to the opinion that not only epicardial flow is important (represented by TIMI flow grading) but that the extent of myocardial reperfusion also plays a role and that optimal reperfusion therapy should be aimed at both restoring epicardial and myocardial flow. Monitoring myocardial flow however, is difficult and the current methods are not applicable in routine clinical practice.

Time to reperfusion

Primary angioplasty offers the unique opportunity to document the exact moment of reperfusion. Therefore a more accurate estimation of total ischemic time (time from symptom onset to the first balloon inflation) is possible, compared to patients treated with thrombolytic therapy. It is known that ischemic time is related to infarct size (158-161) and a recent study suggested that a longer ischemic time results in more haemorrhagic infarction (162). Total ischemic time consists of at least two time intervals: the time from onset of symptoms until arrival of the patient at the hospital (presentation delay), and the time from hospital arrival until reperfusion (treatment delay or "door to balloon time").

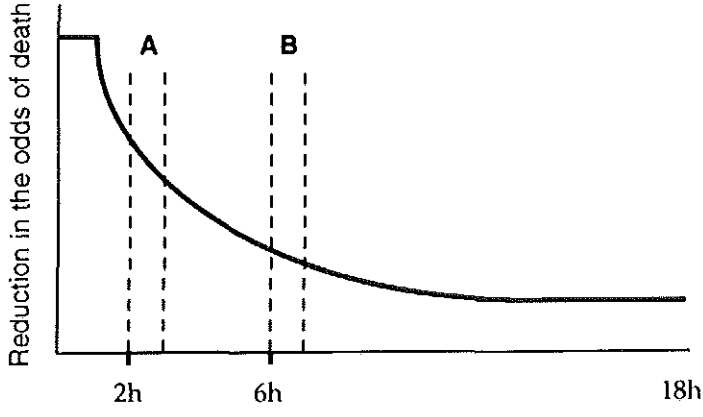
Presentation Delay

Presentation delay is patient related and difficult to influence (163), although it has recently been shown that a media and education campaign in a 90.000 inhabitants region in Switzerland resulted in an impressive reduction in presentation delay (2 hours and 30 minutes vs 4 hours and 10 minutes) and a better clinical outcome (164). Another study, also performed in Switzerland, showed a reduction in median presentation delay from 180 to 155 minutes as a result of a 12 months multimedia public campaign. (165).

Treatment Delay

Treatment delay, however, is easier to influence, but requires the co-operation of all personnel involved in logistics and treatment of patients with acute myocardial infarction. The delay may vary substantially from centre to centre. The pre-hospital thrombolysis studies showed that treatment delay was significantly shorter for study patients compared to non-study patients (97-99) and in the recently (1997) completed GUSTO-III, treatment delay was significantly shorter compared to GUSTO-I (initiated 1990)(0.8 vs 1.1 hours, $p<0.0001$) (166). This suggests that further streamlining of the organisation may help and that minimising time delay for every patient presenting with an acute myocardial infarction should be aimed at. For patients who are transported from other hospitals with an established diagnosis of infarction, treatment delay can be further reduced by preparing the catheterisation room or CCU unit in advance of arrival of the patient (167), or by other procedural changes (168,169). The exact influence of an additional delay on outcome after primary angioplasty is not known. Recently, a careful time analysis of the GUSTO-IIb data showed that hospital delay in performing primary angioplasty was a major determinant of outcome, and may partly explain the little difference between thrombolysis and angioplasty treated patients (170). The consequence of extra delay further depends on the type of patient and the time from symptom onset to the beginning of the delay: a delay of 60 minutes of a relatively low risk patient who already has chest pain for 4 hours has less consequences than a 60 minute delay in a high risk candidate for primary angioplasty who presented at a referring hospital one hour after symptom onset (Figure 4).

Figure 4



Time dependence of the value of shortening delay to reperfusion therapy. A 1-hour time saving at A is likely to produce a greater benefit than a similar reduction in delay at B.

Primary Angioplasty after 6 hours

Although the benefit of early reperfusion therapy has been shown convincingly, the benefit of late angioplasty after acute myocardial infarction is controver-sial. It is possible to achieve infarct vessel recanalisation in the majority of late entry patients with angiop-lasty. However, in these patients a higher rate of reocclusion has been reported (171). Accordingly, late reperfusion results in a somewhat lower rate of sustained patency. Data on infarct vessel patency have been reported in two studies (172, 173). Topol et al found a patency rate of 59% in late entry patients (6h - 24 h), who were either treated with thrombolytic therapy or angioplasty or both. In a study from Dzavik et al, only 43 % of patients, who had angioplasty for an occluded infarct-related vessel 2 days to 6 weeks after the infarction, had a patent artery at 4 months follow-up angiography. A recent study showed that additional intracoronary stenting may help in keeping the infarct related artery open, compared to balloon angioplasty alone (174). Late reperfusion may have the greatest benefit in patients with continued viability of myocardium, which has been described by many authors (175-178). Sabia et al. reported that delayed mechanical reopening of the infarct related vessel, even days to weeks after infarction in selected patients with demon-strated collateral blood flow, may significantly improve left ventricular function (179).

Aims of the Thesis

Monitoring reperfusion

Simple and reliable angiographic and electrocardiographic parameters are useful for monitoring myocardial reperfusion and for risk-stratifying patients at a very early stage after reperfusion therapy. High risk patients might be candidates for additional therapy, aimed at improving myocardial reperfusion or for aggressive left ventricular unloading to prevent remodelling. Low risk patients can be discharged early (180). We assessed the value of ST segment recovery on the 12-lead electrocardiogram after successful primary angioplasty to predict left ventricular function and clinical outcome in one study. Another study evaluated, whether blush of contrast of jeopardised myocardium (a marker of myocardial reperfusion) on routine angiography after angioplasty may have additional prognostic value compared to TIMI flow alone (a marker of epicardial reperfusion).

Primary Angioplasty for whom?

Previous studies suggested that high risk infarct patients have the greatest advantage when treated with primary angioplasty (89). The effect of primary angioplasty compared to thrombolytic therapy in low risk patients is unknown. Therefore acute infarct patients with low risk characteristics, i.e. inferior myocardial infarction, without haemodynamic instability were randomised to either treatment with streptokinase or primary angioplasty. If angioplasty would turn out to be better for low risk patients as well, this may result in a marked increase in patients who are transported to hospitals with angioplasty facilities. Therefore we studied the safety and logistic consequences of transportation of patients with an acute myocardial infarction.

Additional therapy

Although the majority of patients treated with primary angioplasty have a good prognosis, there remains a substantial minority at risk for adverse events. These patients might be candidates for additional therapy. Intra-aortic balloon pumping results in increased diastolic coronary flow and in afterload reduction of the left ventricle and might therefore improve coronary reflow after reperfusion therapy and could be an attractive additional therapy after primary angioplasty in high risk patients.

Stenting has dramatically changed the practice of interventional cardiology over the last years (181,182). However, randomised trials in the setting of acute myocardial infarction have not yet been reported. Therefore we randomly assigned patients without contra-indications for intracoronary stenting to either primary stenting or primary balloon angioplasty with the aim to improve clinical outcome and to reduce restenosis and reocclusion.

Influence of ischemic time on outcome

In patients treated with primary coronary angioplasty the exact time and success of reperfusion is known. This gives the opportunity to assess the influence of ischemic time (time from symptom onset to first balloon inflation) on outcome more accurately compared to patients treated with thrombolytic therapy. As increasing numbers of patients with acute myocardial infarction are transported to centres with angioplasty facilities, it is important to know the effect of this extra time delay on infarct size and outcome.

Restenosis and Reocclusion

Restenosis after elective coronary angioplasty occurs in about 30 to 40% of patients within 6 months. The incidence of restenosis after primary angioplasty for acute myocardial infarction however, is less well studied. We assessed restenosis, using quantitative coronary angiography, in a large cohort of patients successfully treated with primary angioplasty and determined which angiographic or clinical characteristics are predictive of restenosis.

References

1. Tillet WS, Sherry S. The effects in patients of streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease on fibrous, purulent or sanguineous pleural exudations. J Clin Invest 1949;28:173-90.
2. Fletcher AP, Alkjaersig N, Smyrniotis FE, Sherry S. Treatment of patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. Tran Assoc Am Physicians 1958;71:287-96.
3. Chasov EI, Mateeva LS, Mazaev AV, Sargin KE, Sadovskaia GV. Intracoronary administration of fibrinoysin in acute myocardial infarction. Ter Arkh 1976;48:8-19.
4. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang H. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897-902.
5. DeWood MA, Spores J, Hensley GR, Simpson CS, Eugster GS, Sutherland KI, Grunwald RP, Shields JP. Coronary arteriographic findings in acute transmural myocardial infarction. Circulation 1983;68:I-39-49.
6. Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. Br Heart J 1976;38:659-64.
7. Davies MJ, Fulton WFM, Robertson WB. The relation of coronary thrombosis to ischemic myocardial necrosis. J Path 1979;127:99-110.
8. Rentrop KP, Blanke H, Karsch KR, Wiegand V, Köstering H, Oster H, Leitz K. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. Clin Cardiol 1979;2:354-63.
9. Khaja F, Walton JA, Brymer JF, Lo E, Osterberger L, O' Neill WW, Colfer HT, Weiss R, Lee T, Kurian T, Goldberg D, Pitt B, Goldstein S. Intracoronary fibrinolytic therapy in acute myocardial infarction: report of a prospective randomized trial. N Engl J Med 1983;308: 1305-11.
10. Anderson JL, Marshall HW, Bray BE, Lutz JR, Frederick PR, Yanowitz FG, Datz FL, Klausner SC, Hagan AD. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983;308:1312-18.
11. Simoons ML, Brand van den M, de Zwaan C, Verheugt FWA, Serruys PW, Remme WJ, Bar F, Res J, Krauss XH, Vermeer F, Lubsen J. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in the Netherlands. Lancet 1985;ii:578-82.
12. 'Fibrinolytic Therapy Trialists' (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.
13. Meyer J, Merx W, Dorr R, Lambertz H, Bethge C, Effert S. Succesful treatment of acute myocardial infarction shock by combined percutaneous transluminal coronary recanalization and percutaneous transluminal coronary angioplasty. Am Heart J 1982;103:132-38.
14. Hartzler GO, Rutherford BD, McConnay DR, Johnson WL, McCallister BD, Gura GM, Conn RC, Crocket JE. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. Am Heart J 1983;106: 965-73.
15. Erbel R, Pop T, Henrichs KJ, Rupprecht HJ, Steuernagel C, Meyer J. Percutaneous transluminal coronary angioplasty after thrombolytic therapy: a prospective controlled randomized trial. J Am Coll Cardiol 1986;8:485-95.

16. Suryapranata H, Serruys PW, Vermeer F, de Feyter PJ, van den Brand M, Simoons ML, Bär FW, Res J, van der Laarse A, van Domburg R, Beatt K, Lubsen J, Hugenholtz PG. Value of immediate coronary angioplasty following intracoronary thrombolysis in acute myocardial infarction. Cathet Cardiovasc Diagn 1987;13:223-32.
17. Suryapranata H, Serruys PW, de Feyter PJ, van den Brand M, Beatt K, van Domburg R, Kint PP, Hugenholtz PG. Coronary angioplasty immediately after thrombolysis in 115 consecutive patients with acute myocardial infarction. Am Heart J 1988;115:519-29.
18. Simoons ML, Arnold AER, Betriu A, de Bono DP, Col J, Dougherty FC, von Essen FR, Lambertz H, Lubsen J, Meier B, Michel PL, Raynaud P, Rutsch W, Sanz GA, Schmidt W, Serruys PW, Thery C, Uebis R, Vahanian A, Van de Werf F, Willems GM, Wood D, Verstraete M. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. Lancet 1988;I:197-203.
19. TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI 2A results. JAMA 1988;260:2849-58.
20. Rogers WJ, Baim DS, Gore JM, Brown BG, Roberts R, Williams DO, Chesebro JH, Babb JD, Sheehan FH, Wackers FJT, Zaret BL, Robertson TL, Passamani ER, Ross R, Knatterud GL, Braunwald E. Comparison of immediate invasive, delayed invasive, and conservative strategies after tissue-type plasminogen activator. results of the Thrombolysis in Myocardial Infarction (TIMI) phase II-A trial. Circulation 1990;81:1457-76.
21. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial. N Engl J Med 1989;320:618-27.
22. SWIFT (Should We Intervene Following Thrombolysis) trial study group. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. Br Med J 1991;302:555-60.
23. Barbash GI, Roth A, Hod H, Modan M, Miller HI, Rath S, Zahav YH, Keren G, Motro M, Shachar A, Basan S, Agranat O, Rabinowitz B, Laniado S, Kaplinsky E. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. Am J Cardiol 1990;66:538-45.
24. Ellis SG, Ribeiro da Silva E, Heyndrickx GR, Talley JD, Cernigliaro C, Steg G, Spaulding C, Nobuyoshi M, Erbel R, Vassanelli C, Topol EJ for the RESCUE investigators. Randomized comparison of RESCUE angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994;90;2280-84.
25. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12490 patients with acute myocardial infarction. Lancet 1990;336:65-71.
26. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. Lancet 1992;339:753-70.
27. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
28. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis HK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, RossA, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis In Myocardial Infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76:723-5.

29. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival, after acute myocardial infarction. N Engl J Med 1993;329:1615-22.
30. Meier B. Balloon angioplasty for acute myocardial infarction. Was it buried alive? Circulation 1990; 82:2243-5.
31. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
32. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, Vlietstra RE, Strzelecki M, Puchrowicz-Ochocki S, O'Neill WW. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
33. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685-91.
34. Boyle RM. Immediate angioplasty in the United Kingdom. The time has not yet come. Britisch Heart J 1995;73:413-14.
35. Brooks N. Primary PTCA in the UK: if not for all, then for whom? Heart 1997;78:16-17.
36. The Global Use of Strategies to Open Occluded coronary arteries in Acute Coronary Syndromes (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;336:1621-8.
37. Stone GW, Grines CL, O'Neill. Primary coronary angioplasty versus thrombolysis. N Engl J Med 1997;337:1168-69.
38. Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD, for the myocardial infarction triage and intervention investigators. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. N Engl J Med 1996;335:1253-60.
39. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction. A report from the second national registry of myocardial infarction (NRMI-2). J Am Coll Cardiol 1998;31:1240-5.
40. Zahn R, Vogt A, Neuhaus K-L, Schuster S, Senges J for the ALKK study group. Angioplasty in acute myocardial infarction in clinical practice: results in 4625 patients from the ALKK angioplasty registry. J Am Coll Cariol 1997;29:15A.
41. Weaver DW, Simes JR, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfield L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction. A quantitative overview. JAMA 1997;278:2093-98.
42. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. Lancet 1988;2:349-60.
43. 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.
44. Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel BJ, O'Russell E, Smith III EE, WeaverWD. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary. A report of the

American College of Cardiology/American Heart Association task force on practice guidelines (committee on management of acute myocardial infarction). Circulation 1996;94:2341-50.
45. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL, for the TEAM-3 investigators. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for acute myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 study. Circulation 1993;87:1829-39.
46. Lincoff AM, Topol EJ. Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation 1993;87:1792-1805.
47. Simes RJ, Topol EJ, Holmes DR, White HD, Rutsch WR, Vahanian A, Simoons ML, Morris D, Betriu A, Califf RM, Ross AM, for the GUSTO Investigators. Link between the angiographic substudy and mortality outcome in a large randomized trial of myocardial reperfusion: import of early and complete infarct artery reperfusion. Circulation 1995;91:1923-28.
48. Ross AM, Coyne KS, Moreyra E, Reiner JS, Greenhouse SW, Walker PL, Simoons ML, Draoui YC, Califf RM, Topol EJ, Van de Werf F, Lundergan CF. Extended mortality benefit of early postinfarction reperfusion. Circulation 1998;97:1549-56.
49. Lenderink T, Simoons M, Es van G, Werf van de F, Verstraete M, Arnold AE, for the European Cooperative Study Group. Benefit of thrombolytic therapy is sustained throughout five years and is related to TIMI perfusion grade 3 but not grade 2 flow at discharge, Circulation 1995;92:1110-16.
50. Lincoff AM, Topol EJ, Califf RM, Sigmon KN, Lee KL, Ohman EM, Rosenschein U, Ellis SG, for the Thrombolysis and Angioplasty in Myocardial Infarction study group. Significance of a coronary artery with thrombolysis in myocardial infarction grade 2 flow "patency" (outcome in the thrombolysis and angioplasty in myocardial infarction trials). Am J Cardiol 1995;75:871-76.
51. Anderson JL, Karagounis LA, Califf RM. Meta-analysis of five reported studies on the relation of early coronary patency grades with mortality and oucomes after acute myocardial infarction. Am J Cardiol 1996;78:1-8.
52. Leung WH, Lau C. Effects of severity of the residual stenosis of the infarct-related coronary artery on left ventricular dilatation and function after acute myocardial infarction. J Am Coll Cardiol 1992;20:307-13.
53. Miyazaki S, Nakao K, Daikoku S, Itoh A, Miyao Y, Goto Y, Nonogi H. Correlation of residual stenosis immediately after coronary angioplasty with long-term prognosis. Cathet Cardiovasc Diagn 1998;43:262-70.
54. Simoons ML, Vos J, Tijssen JGP, Vermeer F, Verheugt FWA, Krauss XH, Manger Cats V. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989; 14:1609-15.
55. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? Circulation 1989;79:441-4.
56. White HD, Cross DB, Elliott JM, Norris RM, Yee TW. Long-term prognostic importance of patency of the infarct-related coronary artery after thrombolytic therapy for acute myocardial infarction. Circulation 1994;89:61-7.
57. Brouwer MA, Bôncke JR, Veen G, Meijer A, Eenige van MJ, Verheugt FWA. Adverse long term effects of reocclusion after coronary thrombolysis. J Am Coll Cardiol 1995;26:1440-4.
58. Verheugt F, Meijer A, Lagrand WK, Eenige van MJ. Reocclusion: the flip side of coronary thrombolysis. J Am Coll Cardiol 1996;27:766-73.
59. Veen G, Meijer A, Verheugt FWA, Werter CJ, Swart de H, Lie KI, Pol van der JM, Michels HR, Eenige MJ. Culprit lesion morphology and stenosis severity in the prediction of reocclusion

after successful coronary thrombolysis: angiographic results of the APRICOT study. J Am Coll Cardiol 1993;22:1755-62.

60. White HD, French JK, Hamer AW, Brown MA, Williams BF, Ormiston JA, Cross DB. Frequent reocclusion of patent infarct-related arteries between four weeks and one year: effects of antiplatelet therapy. J Am Coll Cardiol 1995;25:218-23.
61. Gibson CM, Cannon CP, Piana RN, Breall JA, Sharaf B, Flatley M, Alexander B, Diver DJ, McCabe C, Flaker GC, Baim DS, Braunwald E. Angiographic predictors of reocclusion after thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. J Am Coll Cardiol 1995;25:582-9.
62. Serruys PW, Simoons ML, Suryapranata H, Vermeer F, Wijns W, van den Brand M, Bär F, de Zwaan C, Krauss XH, Remme WJ, Res J, Verheugt FWA, van Domburg R, Lubsen J, Hugenholtz PG. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1986;7:729-42.
63. Madsen JK, Grande P, Saunamaki K, Thayssen P, Kassis U, Rasmussen K, Haunso S, Nielsen T, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen, Andersen L, on behalf of the DANAMI study group. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). Circulation 1997;96:748-55.
64. Danchin N, Angioni M, Cador R, Tricoche O, Dibon O, Juilieres Y, Cuilliere M, Cherrier F. Effect of late percutaneous angioplastic recanalization of total coronary artery occlusion on left ventricular remodelling, ejection fraction, and regional wall motion. Am J Cardiol 1996; 78:729-35.
65. Solomon SD, Ridker PM, Antman EM. Ventricular arrhythmias in trials of thrombolytic therapy for acute myocardial infarction. A meta-analysis. Circulation 1993;88:2575-81.
66. Moreno FLL, Karagounis L, Marshall H, Menlove RL, Ipsen S, Anderson JL. Thrombolysis-related early patency reduces ECG late potentials after acute myocardial infarction. Am Heart J 1992;124:557-64.
67. Aguirre FV, Kern MJ, Hsia J, Serota H, Janosik D, Greenwalt T, Ross AH, Chaitman BR. Importance of myocardial infarct artery patency on the prevalence of ventricular arrhythmia and late potentials after thrombolysis in acute myocardial infarction. Am J Cardiol 1991;68:1410-16.
68. Zimmerman M, Adamec R, Ciaroni S. Reduction in the frequency of ventricular late potentials after acute myocardial infarction by early thrombolytic therapy. Am J Cardiol 1991;67:697-703.
69. de Chillou C, Rodriguez LM, Doevendans P, Loutsides K, van den Dool A, Metzger J, Bär F, Smeets M. Effects on the signal-averaged electrocardiogram of opening the coronary artery by thrombolytic therapy or percutaneous transluminal coronary angioplasty during acute myocardial infarction. Am J Cardiol 1993;71:805-9.
70. Bourke JP, Richards DAB, Ross DL, Wallace EM, McGuire MA, Uther JB. Routine programmed electrical stimulation in survivors of acute myocardial infarction for prediction of spontaneous ventricular tachyarrhythmias during follow-up: results, optimal stimulation protocol and cost-effective screening. J Am Coll Cardiol 1991;18:780-8.
71. Jang I-K, Gold HK, Ziskind AA, Fallon JT, Holt RE, Leinbach RC, May JW, Collen D. Diffferential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi to lysis with recombinant tissue-type plasminogen activator: a possible explanation for resistance to coronary thrombolysis. Circulation 1989;79:920-28.
72. Coller BS. Platelets and thrombolytic therapy. N Engl J Med 1990;322:33-42.
73. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. Circulation 1996;95:2013-20.

74. Anderson JL. Why does thrombolysis fail? Breaking through the reperfusion ceiling. Am J Cardiol 1997;80:1588-90.
75. Tracy RP, Kleiman NS, Thompson B, Cannon CP, Bovill EG, Brown G, Collen D, Mahan E, Mann KG, Rogers WJ, Sopko G, Stump DC, Williams DO, Zaret BL, for the TIMI II investigators. Relation of coagulation parameters to patency and recurrent ischemia in the thrombolysis in myocardial infarction (TIMI) phase II trial. Am Heart J 1998;135:29-37.
76. Ohnishi Y, Butterfield MC, Salfitz JE, Sobel BE, Corr PB, Goldstein JA. Deleterious effects of a systemic lytic state on reperfused myocardium. Minimization of reperfusion injury and enhanced recovery of myocardial function by direct angioplasty. Circulation 1995;92:500-10.
77. Topol EJ. Toward a new frontier in myocardial reperfusion therapy. Emerging platelet preeminence. Circulation 1998;97:211-18.
78. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997;336:847-60.
79. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397-402.
80. Bates ER, Topol EJ. Limitations of thrombolytic therapy for acute myocardial infarction complicated by congestive heart failure and cardiogenic shock. J Am Coll Cardiol 1991;18:1077-84.
81. European Secondary Prevention Study group. Translation of clinical trials into practice: a European population-based study of the use of thrombolysis for acute myocardial infarction. Lancet 1996;347:1203-7.
82. Cragg DR, Friedmann HZ, Bonema JD, Jaiyesima I, Ramos RG, Timmis GC, O'Neill WW, Schreiber TL. Outcome of patients with myocardial infarction who are ineligible for thrombolytic therapy. Ann Intern Med 1991;115:173-7.
83. Brodie BR, Weintraub RA, Stickey TD, Le Bauer EJ, Katz JD, Kelly TA, Hansen CJ. Outcomes of direct angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. Am J Cardiol 1991;67:7-12.
84. Califf RM, Woodlief LH, Harrell FE, Lee KL, White HD, Guerci A,Barbash GI, Simes J, Weaver WD, Simoons ML, Topol EJ, for the GUSTO-I Investigators. Selection of thrombolytic therapy for individual patients: development of a clinical model. Am Heart J 1997;133:630-9.
85. Boersma E, Simoons MA. Reperfusion strategies in acute myocardial infarction. Eur Heart J 1997;18:1703-11.
86. Stone GW, Grines C, Browne KF, Marco J, Rothbaum D, O'Keefe JH, Hartzler G, Overlie P, Donohue B, Chelliah N, Vlietstra R, Puchrowicz-Ochocki S, O'Neill WW, for the Primary Angioplasty in Myocardial Infarction (PAMI) investigators. Outcome of different reperfusion strategies in patients with former contraindications to thrombolytic therapy: a comparison of primary angioplasty and tissue plasminogen activator. Cath Cardiovasc Diagn 1996;39:333-39.
87. Kahn JK. Why we get out of bed to do infarct PTCA. Cath Cardiovasc Diagn 1996;39:350.
88. The I.S.A.M. Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). Mortality, morbidity, and infarct size at 21 days. N Engl J Med 1986;314:1465-71.
89. Boersma H. Tailored reperfusion therapy of patients with evolving myocardial infarction: models to guide clinical decision making. PhDThesis 1998.
90. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5.
91. Califf RM, Newby K. How much do we gain by reducing time to reperfusion therapy. Am J Cardiol 1996;78[suppl 12A]:8-15.

92. Hermens W Th, Willems GM, Nijssen KM, Simoons ML, for the European Cooperative Study Group. Effect of thrombolytic treatment delay on myocardial infarct size. Lancet 1992;340:1297.
93. Newby LK, Rutsch WR, Califf RM, Simoons ML, Aylward PE, Armstrong PW, Woodlief LH, Lee KL, Topol EJ, van de Werf F, for the GUSTO-I investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996;27:1646-55.
94. Ottesen MM, Kober L, Jorgensen S, Torp-Pederson C. Determinants of delay between symptoms and hospital admission in 5978 patients with acute myocardial infarction. Eur Heart J 1996,17:429-37.
95. GISSI-avoidable delay study group. Epidemiology of avoidable delay in the care of patients with acute myocardial infarction in Italy. Arch Intern Med 1995;155:1491-88.
96. Weaver DW. Time to thrombolytic treatment: factors affecting delay and their influence on outcome. J Am Coll Cardiol 1995;25[suppl]:3S-9S.
97. Weaver DW, Cerqueira M, Hallstrom AP, Littwin PE, Martin JS, Kudenchuck PJ, Eisenberg M, for the Myocardial Infarction Triage and Intervention Project Group. Pre-hospital-initiated vs hospital-initiated thrombolytic therapy. The myocardial infarction triage and intervention trial. JAMA 1993;270:1211-6.
98. GREAT Goup. Feasability, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampion region early anistreplase trial. BMJ 1992;305:548-53.
99. The European Myocardial Infarction Project group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med 1993;329:383-9.
100. Fath-Ordoubadi F, Al-Mohammad A, Huehns TY, Beatt KJ. Meta-analysis of randomised trials of pre-hospital versus hospital thrombolysis. Circulation 1994;90:I-325.
101. Rawles JM. Quantification of the benefit from earlier thrombolytic therapy: the Grampion Regional Anistreplase Trial (GREAT). J Am Coll Cardiol 1997;30:1181-6.
102. Rentrop KP, Feit F, Sherman W, Stecy P, Hosat S, Cohen M, Rey M, Ambrose J, Nachamie M, Schwartz W, Cole W, Perdoncin R, Thornton JC. Late thrombolytic therapy preserves left ventricular function in patients with collateralized coronary occlusion: primary end point findings of the second Mount Sinai-New York university reperfusion trial. J Am Coll Cardiol 1989;14:58-64.
103. LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6-24 hours after onset of myocardial infarction. Lancet 1993;342:759-66.
104. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. Lancet 1993;342:767-72.
105. Kim CB, Braunwald. Potential benefits of late reperfusion of infarcted myocardium. The open artery hypothesis. Circulation 1993;88:2426-36.
106. Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction. N Engl J Med 1987;317:1055-9.
107. White HD, Van de Werf FJJ. Thrombolysis for acute myocardial infarction. Circulation 1998;97;1632-46.
108. The global use of strategies to open occluded coronary arteries (GUSTO III) investigators. A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997;337:1118-23.
109. Barbagelata NA, Granger CB, Oqueli E, Suarez LD, Borruel M, Topol EJ, Califf RM. TIMI grade 3 flow and reocclusion after intravenous thrombolytic therapy: a pooled analysis. Am Heart J 1997;133:273-82.

110. Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, Chernoff R, Christie LG, Feldman RL, Seals AA, Weaver WD, for the RAPID II investigators. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. Circulation 1996;94: 891-98.
111. White HD, Aylward PE, Frey MJ, Adgery AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B, on behalf of the Hirulog Early Reperfusion/ Occlusion (HERO) Trial investigators. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Circulation 1997;96:2155-61.
112. Neuhaus KL. Results of the HIT-4 study. Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.
113. Cannon CP. Results of the TIMI 10B trial. Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.
114. Van de Werf F. Results of the MINT study. Presented at the XIX congress of the European Society of Cardiology, Stockholm, Sweden, August 24-28, 1997.
115. AMI (Argatroban in Myocardial Infarction). Ferguson JJ. Meeting highlights. 46th Annual Scientific Sessions of the American College of Cardiology. Circulation 1997;96:367-71.
116. Ohman EM, Kleiman NS, Gacioch G, Worley SJ, Navetta FI, Talley JD, Anderson V, Ellis SG, Cohen MD, Spriggs D, Miller M, Kereiakes D, Yakubov S, Kitt MM, Sigmon KN, Califf RM, Krucoff MW, Topol EJ, for the IMPACT-AMI investigators. Combined accelarated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. Circulation 1997;95:846-54.
117. Antman EM, Giugliano RP, McCabe CH, Gibson M, Adgey AJJ, Ghali M, Coussement P, Anderson KM, Scherer J, van de Werf F, Braunwald E, for the TIMI 14 investigators. Abciximab (ReoPro) potentiates thrombolysis in ST elevation myocardial infarction: results of the TIMI 14 trial. J Am Coll Cardiol 1998;31:191A.
118. Simoons ML. Eptifibatide as adjunct to streptokinase in acute myocardial infarction. Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.
119. Ronner E, van Kestern HAM, Zijnen P, Tebbe V. Molhoek P, Cuffie C, Velti E, Lorenz T, Neuhaus K, Simoons ML. Combined therapy with streptokinase and integrilin. J Am Coll Cardiol 1998;31:191A.
120. Gulba DC, Tanswell P, Dechend R, Sosada M, Weis A, Waigand J, Uhlich F, Hauck S, Jost S, Rafflenbeul W, Lichtlen PR, Dietz R. Sixty-minute alteplase protocol: a new accelerated recombinant tissue-type plasminogen activator regimen for thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1997;30:1611-17.
121. de Boer MJ, Suryapranata H, Hoorntje JCA, Reiffers S, Liem AL, Miedema K, Hermens W Th, Brand van den M, Zijlstra F. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-61.
122. de Boer MJ, Reiber JHC, Suryapranata H, van den Brand M, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16:1347-55.

123. Zijlstra F, de Boer MJ, Beukema WP, Liem AL, Reiffers S, Huysmans D, Hoorntje JC, Suryapranata H, Simoons ML. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial. Eur Heart J 1996;17:382-7.
124 de Boer MJ, Hout van B, Liem AL, Suryapranata H, Hoorntje JC, Zijlstra F. A cost-effective analysis of primary coronary angioplasty versus thrombolysis for acute myocardial infarction. Am J Cardiol 1995;76:830-33.
125. Stone GW, Grines CL, Rothbaum D, Browne KF, O'Keefe J, Overlie PA, Donohue BC, Chelliah N, Vlietstra R, Catlin T, O'Neill WW, for the PAMI Trial Investigators. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the primary angioplasty in myocardial infarction (PAMI) trial. J Am Coll Cardiol 1997;29:901-7.
126. Lieu TA, Gurley RJ, Lundstrom RJ, Ray GT, Fireman BH, Weinstein MC, Parmley WW. Projected cost-effectiveness of primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1997;30:1741-50.
127. Cherieux EC, Swart de H, Dijkman LW, Havenith MG, Maessen JG, Engelen DJ, Wellens HJJ. Myocardial rupture after myocardial infarction is related to the perfusion status of the infarct related coronary artery. Am Heart J 1995;129:644-50.
128. Waller BF, Rothbaum DA, Pinkerton CA, Cowley MJ, Linnemeier TJ, Orr C, Irons M, Helmuth RA, Wills ER, Aust C. Status of the myocardium and infarct-related coronary artery in 19 necropsy patients with acute recanalization using pharmacologic (streptokinase, r-tissue plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty), or combined types of reperfusion therapy. J Am Coll Cardiol 1987;9:785-801.
129. Kinn JW, O'Neill WW, Benzuly KH, Jones DE, Grines CL. Primary angioplasty reduces risk of myocardial rupture compared to thrombolysis for acute myocardial infarction. Cathet Cardiovasc Diagn 1997;42:151-57.
130. Zijlstra F, de Boer MJ. Chirurgische interventies bij het acute hartinfarct. Ned Tijdschr Geneeskd 1996;140:1933-35.
131. Christian TF, O'Keefe JH, DeWood MA, Spain MG, Grines CL, Berger PB, Gibbons RJ. Intercenter variability in outcome for patients treated with direct coronary angioplasty during acute myocardial infarction. Am Heart J 1998;135:310-17.
132. Grassman ED, Johnson SA, Krone RJ. Predictors of success and major complications for primary percutaneous transluminal coronaru angioplasty in acute myocardial infarction. An analysis of the 1990 to 1994 society for cardiac angiography and interventions registries. J Am Coll Cardiol 1997;30:201-8.
133. Wharton TP, Johnston JD, Turco MA, Souther TJ, Lew DC, Billnoski W, Singhi SK, Graham M, Grines L, Weaver WD, Grines CL. Primary angioplasty for acute myocardial infarction at hospitals with no-surgery on-site: the prospective multicentre PAMI-No SOS Registry. J Am Coll Cardiol 1998;31:210A.
134. Agati L, Voci P, Hickle P, Vizza DC, Autore C, Fedel F, Feinstein SB, Dagianti A. Tissue-type plasminogen activator therapy versus primary coronary angioplasty: impact on myocardial tissue perfusion and regional function 1 month after uncomplicated myocardial infarction. J Am Coll Cardiol 1998;31:338-43.
135. Eisenberg PR, Miletich JP, Sobel BE. Factors responsible for the differential procoagulant effects of diverse plasminogen activators in plasma. Fibrinolysis 1991;5:217-24.
136. Pederson OD, Gram J, Jespersen J. Plasma resistance to activated protein C regulates the activation of coagulation induced by thrombolysis in patients with ischaemic heart disease. Heart 1997;77:122-27.

137. Van Belle E, Lablanche JM, Bauters C, Renaud N, McFadden EP, Bertrand ME. Coronary angioscopic findings in the infarct related vessel within 1 month of acute myocardial infarction. Natural history and the effect of thrombolysis. Circulation 1998;97:26-33.
138. Rescue trial, Gibson CM, Cannon CP, Greene RM, Sequeira RF, Margorien RD, Leya F, Diver DJ, Baim DS, Braunwald E. Rescue angioplasty in the thrombolysis in myocardial infarction (TIMI) 4 trial. Am J Cardiol 1997;80:21-26.
139. Miller JM, Schildcrout JS, Smalling RW, Betriu A, Califf RM. Topol EJ. Survival benefit of abciximab administration during early rescue angioplasty: analysis of 387 patients from the GUSTO-III trial. J Am Coll Cardiol 1998;31:191A.
140. Marzilli M, Gliozheni E, Fedele S, Ungi I, Orsini E, Marraccini P. Prevalence and prediction of no-reflow after direct angioplasty in acute myocardial infarction. J Am Coll Cardiol 1997;29:90A.
141. Morishima I, Sone T, Mokuno S, Taga S, Shimauchi A, Oki Y, Kondo J, Tsuboi H, Sassa H. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. Am Heart J 1995;130:239-43.
142. Kloner RA, Ganote CE, Jennings RB. The "no reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496-1508.
143. Neumann F, Ott I, Gawaz M, Richardt G, Holzapfel, Jochum M, Schomig A. Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. Circulation 1995;92:748-55.
144. Hansen PR. Role of neutrophils in myocardial ischemia and reperfusion. Circulation 1995;91:1872-85.
145. Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion. Circulation 1984;70:513-21.
146. Kloner RA. Does reperfusion injury exist in humans?. J Am Coll Cardiol 1993;21:537-45.
147. Ferrari R. Metabolic disturbances during myocardial ischemia and reperfusion. Am J Cardiol 1995;76:17B-24B.
148. Cobbaert C, Hermens WT, Kint PP, Klootwijk PJ, Werf van de F, Simoons ML. Thrombolysis-induced coronary reperfusion causes acute and massive interstitial release of cardiac muscle cell proteins. Cardiovasc Res 1997;33:147-55.
149. Hansen PR. Myocardial reperfusion injury: experimental evidence and clinical relevance. Eur Heart J 1995;16:734-40.
150. Manche A, Edmondson SJ, Hearse DJ. Dynamics of early postischemic myocardial functional recovery, evidence of reperfusion-induced injury?. Circulation 1995;92:526-34.
151. Grech ED, Dodd NJ, Jackson MJ, Morrison WL, Faragher EB, Ramsdale DR. Evidence for free radical generation after primary percutaneous transluminal coronary angioplasty recanalisation in acute myocardial infarction. Am J Cardiol 1996;77:122-7.
152. Ito H, Okamura A, Iwakura K, Masuyama T, Hori M, Takiuchi S, Negoro S, Nakatsuchi Y, Taniyama Y, Higashino Y, Fujii K, Minamino T. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute myocardial infarction. Circulation 1996;93:1993-99.
153. Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K, Masuyama T, Kitabatahe A, Minanino T. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699-705.
154. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, Higashino Y, Fujii K, Minamino T. Clinical implications of the "no reflow" phenomenon. Circulation 1996;93:223-28.
155. Iliceto S, Marangelli V, Marchese A, Amico A, Galiuto L, Rizzon P. Myocardial contrast

echocardiography in acute myocardial infarction. Pathophysiological background and clinical applications. Eur Heart J 1996;17:344-53.
156. Kenner MD, Zajac EJ, Kondos GT, Dave MD, Winkelmann JW, Joftus J, Lancevilius A, Kybarskis A, Berukstis E, Urbonas A, Feinstein SB. Ability of the no-reflow phenomenon during acute myocardial infarction to predict left ventricular dysfunction at one month follow-up. Am J Cardiol 1995;76:861-68.
157. Kates MA, Meza MF, Barbee RW, Revall S, Moreno CA, Perry B, Murgo JP, Cheirif J. Potential clinical implications of abnormal perfusion patterns immediately after reperfusion in a canine model: a myocardial contrast echocardiography study. Am Heart J 1996;132:303-13.
158. Willerson JT, Watson JT, Hutton I, Templeton GH, Fixler DE. Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog. Circ Res 1975;36:771-81.
159. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I.Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786-94.
160. Hasche ET, Fernandes C, Freedman SB, Jeremy RW. Relation between ischemia time, infarct size, and left ventricular function in humans. Circulation 1995;92:710-9.
161. Raitt MH, Maynard C, Wagner GS, Cerqueirra, MD, Selvester RH, Weaver WD. Relation between symptom duration before thrombolytic therapy and final myocardial infarct size. Circulation 1996;93:48-53.
162. Pislaru SV, Barrios L, Stassen T, Jun L, Pislaru C, Werf van de F. Infarct size, myocardial hemorrhage and recovery of function after mechanical versus pharmacological reperfusion. Circulation 1997;96:659-66.
163. Blohm MB, Hartford M, Karlson BW, Luepker RV, Herlitz J. An evaluation of the results of media and educational campaigns designed to shorten the time taken by patients with acute myocardial infarction to decide to go to hospital. Heart 1996;76:430-34.
164. Saner H, Pfister R, Pirovino M, Castelli I, Gaspoz JM. Reduction of mortality by a media and education campaign in patients reporting chest pain. Eur Heart J 1997;18:124.
165. Gaspoz JM, Unger PF, Chevrolet JC, Rutishauser W, Lovis C, Goldman L, Heliot C, Sechaud L, Mischler S, Waldvogel FA. Impact of a public campaign on pre-hospital delay in patients reporting chest pain. Heart 1996;76:150-55.
166. Gibler WB, Gore JM, Weaver WD for the GUSTO-III investigators. Reduced time to thrombolytic delivery, but static time to presentation: the GUSTO experience from 1990 to 1997. Circulation 1997;96:I-201.
167. Miller-Craig MW, Joy AV, Adamowicz M, Furber R, Thomas B. Reduction in treatment delay by paramedic ECG diagnosis of myocardial infarction with direct CCU admission. Heart 1997;78:456-61.
168. Garot, P, Juliard JM, Benamer H, Steg PG. Are the results of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction different during the off-hours? Am J Cardiol 1997;79:1527-29.
169. Caputo RP, Ho KKL, Stoler RC, Sukin CA, Lopez JJ, Cohen DJ, Kuntz RE, Berman A, Carrozza JP, Baum DS. Effect of continuous quality improvement analysis on the delivery of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1997;79:1159-64.
170. Berger PB, Holmes DR, Califf RM, Criger DA. Hospital delay in achieving reperfusion with direct PTCA in GUSTO-IIb: relationship to 30-day mortality. Circulation 1997;96:I-531.
171. Ellis SG, O'Neill WW, Bates E, Walton JA, Nabel EG, Topol EJ. Coronary angioplasty as

primary therapy for acute myocardial infarction 6 to 48 hours after symptom onset: report of an initial experience. J Am Coll Cardiol 1989;13:1122-6.

172. Topol EJ, Califf RM, Vandormael M, Grines CL, George BS, Sanz ML, Wall T, O'Brian M, Schwaiger M, Aguirre FV, Young S, Popma JJ, Sigmon KN, Lee KL, Ellis SG, and the TAMI-6 Study Group. A rando-mized trial of late reperfusion therapy for acute myocar-dial infarction. Circulation 1992;85:2090-99.
173. Dzavik V, Beanlands DS, Davies RF, Leddy D, Marquis JF, Teo KK, Ruddy TD, Burton JR, Humen DP. Effects of late percutaneous coronary angioplasty of an occluded infarct-related coronary artery on left ventricular function in patients with a recent (<6 weeks) Q-wave acute myocardial infarction (Total occlusion post-myocardial infarction intervention study [TOMIIS]-a pilot study. Am J Cardiol 1994;73:856-61.
174. Bauters C, Lablanche J-M, Van Belle E, Niculescu R, Meurice T, Mc Fadden EP, Bertrand ME. Effects of coronary stenting on restenosis and occlusion after angioplasty of the culprit vessel in patients with recent myocardial infarction. Circulation 1997;96:2854-58.
175. Brodie BR, Stuckey TD, Hansen C, Muncy D, Weintraub RA, Lebauer J, Kelly TA, Katz JD, Berry JJ. Bene-fit of late coronary reperfusion in patients with acute myocardial infarction and persistent chest pain. Am J Cardiol 1994;74:538-43.
176. Eisenhauer AC, Matthes RV, Moore L. Late direct angioplasty in patients with myocardial infarction and fluctuating chest pain. Am Heart J 1992;123:553-59.
177. Rogers WJ, Hood WP, Mantle JA, Baxley WA, Kirklin JK, Zorn GL, Nath HP. Return of left ventricular function after reperfusion in patients with myocardial infarction: importance of subtotal stenoses or intact collaterals. Circulation 1984;69:-338-49.
178. Agati L, Voci P, Bilotta F,Luongo R, Autore C, Penco M, Iacoboni C, Fedele F, Diagianti A. Influence of residual perfusion within the infarct zone on the natural history of left ventricular dysfunction after acute myocardial infarction: a myocardial contrast echocardiographic study. J Am Coll Cardiol 1994;24:336-42.
179. Sabia PJ, Powers ER, Ragosta M, Sarembeck IJ, Burwell LR, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. N Engl J Med 1992;327:1825-31.
180. Grines CL, Marsalese DL, Brodie B, Griffin J, Donohue B, Constantini C, Balestrini C, Stone G, Wharton T, Esente P, Spain M, Moses J, Nobuyoshi M, Ayres M, Jones D, Mason D, Sachs D, Grines L, O'Neill W, 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.
181. Serruys PW, Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, GoY JJ, Heuvel van den P, Delcan J, Morel MA, for the BENESTENT study group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
182. Fishman DL, Leon MB, Baim DS, Schantz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Meuser R, Almond D, Teirstein PS, Fish RD, Columbo A, Brinker J, Moses J, Shaknovich A, Hirshfield J, Bailey S, Ellis S, Rake R, Goldberg S, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501.

CHAPTER 2

Part One

Clinical Value of 12-lead Electrocardiogram after Successful Reperfusion Therapy for Acute Myocardial Infarction

Arnoud WJ van 't Hof, Aylee Liem, Menko-Jan de Boer, Felix Zijlstra
on behalf of the Zwolle Myocardial Infarction Study Group

Ziekenhuis de Weezenlanden, Department of Cardiology
Zwolle,The Netherlands

Lancet 1997;350:615-19

Summary

Background A simple clinical method to stratify risk for patients who have had successful reperfusion therapy after myocardial infarction is attractive since it facilitates the tailoring of therapy.

Methods We investigated the clinical value of the 12-lead electrocardiogram (ECG), in 403 patients after successful reperfusion therapy by primary coronary angioplasty, in relation to infarct size measured by enzyme activity, left-ventricular function, and clinical outcome. ECGs were analysed to find the extent of the ST-segment-elevation resolution 1 h after reperfusion therapy.

Findings A normalised ST segment was seen in 51% of patients, a partly normalised ST segment in 34%, and 15% had no ST-segment-elevation resolution. Enzymatic infarct size and ejection fraction were related to the extent of the early resolution of the ST segment. The relative risk of death among patients with no resolution compared with patients with a normalised ST segment was 8.7 ((95% CI 3.7-20.1), and that among patients with partial resolution compared to patients with a normalised ST segment was 3.6 (1.6-8.3).

Interpretation Our findings suggest that ECG patterns reflect the effectiveness of myocardial reperfusion. Patients for whom reperfusion therapy by primary angioplasty was successful and who had normalised ST segments had limited damage to the myocardium and an excellent outlook during follow-up. Patients with persistent ST elevation after reperfusion therapy may need additional interventions since they have more extensive myocardial damage and have a higher mortality rate.

(Lancet 1997;350:615-619)

Introduction

Early and sustained patency of the infarct-related coronary artery has become the main goal in the care of patients with acute myocardial infarction (1-3). Several studies show that primary coronary angioplasty may offer more benefit than thrombolytic therapy (4,5). Favourable results for angiographic data, enzymatic infarct size, left ventricular function and clinical outcome have been described for angioplasty treated patients (6,7). Although clinical outcome after successful reperfusion therapy is good in most patients, a substantial minority are still at risk from adverse clinical events. A simple clinical method to assess the risk for these patients immediately after successful reperfusion therapy is, therefore, attractive since it would allow the tailoring of pharmacological interventions, such as additional antiplatelet therapy (8), mechanical support by stenting (9), or haemodynamic support by intra-aortic balloon pumping (10) in patients at high risk from adverse events.

Identification of low-risk patients can lead to early discharge and, therefore, a more cost-effective use of restricted medical resources. Electrocardiography is a good candidate for this role. The prognostic value of the 12-lead electrocardiogram (ECG) has been documented for patients given thrombolytic therapy (11,12). However, not all of these patients have early and sustained successful reperfusion of the infarct-related coronary artery.

In our published trials (4,6) and in continuing trials of therapies for acute myocardial infarction, all patients who present at or are referred to our hospital with ST-segment-elevation myocardial infarction are registered, and clinical and angiographic data are added to a database. We investigated the clinical value of the 12-lead ECG in a large cohort of these patients after successful reperfusion therapy by primary angioplasty, by enzymatic infarct size, left-ventricular function, and clinical outcome.

Patients and methods

Between August, 1990, and April, 1995, 725 patients with acute myocardial infarction and ST-segment-elevation of more than 0.1 mV in at least two contiguous ECG leads presented at or were referred to our institution. 205 patients received thrombolytic therapy as part of other randomised trials that compared primary angioplasty with thrombolytic therapy, and 520 patients were candidates for primary coronary angioplasty. Of these 520 patients, 485 (93.3%) had angioplasty. In 18 patients (3.5%), the infarct related coronary artery had reperfused spontaneously and there were no remaining signs or symptoms of ischaemia, these patients were managed conservatively. In 17 patients (3.3%) the coronary angiogram showed extensive triple-vessel coronary-artery disease or left main-coronary-artery disease that was judged to require immediate coronary-artery bypass surgery. Successful primary coronary angioplasty, defined as Thrombolysis In Myocardial Infarction 3 flow and a residual stenosis of the affected vessel by quantitative coronary angiography of less than 50%, was achieved in 455 (93.8%) of 485 patients. Adequate ECG data for this study, defined as available 12-lead ECGs that allowed assessment of the ST-segments, as described by Schröder and colleagues (11), before and 1 h after primary coronary angioplasty, were obtained in 403 (88.6%) of 455 patients. In 52 (11.4%) patients an ECG from before or after the intervention was missing or ST-segment resolution could not be interpreted, because of a new bundle-branch block, the use of a ventricular pacemaker or a sustained idioventricular rhythm. The data for the 403 patients with both ECGs were used for this report. Radionuclide measurements of the left-ventricular ejection fraction were obtained in 285 (70.7%) of the 403 patients before discharge from hospital. Enzymatic infarct size was calculated in 126 consecutive patients as part of our previously reported randomised trial.

Electrocardiography

ECGs were done on admission to hospital (first ECG), and in the coronary-care unit (second ECG), 1 h after the primary angioplasty, according to the protocol. Patients with right bundle-branch block who clearly had ST-segment-elevations were included in the analysis. All ECGs were analysed as pairs (the observer was aware of the order) and graded for ST-segment- elevation resolution by an investigator who was unaware of the clinical data, angiographic findings, and outcome data. Results were not clear for 23% of patients, and a second investigator, also unaware of the status of patients, assessed the extent of ST-segment resolution and consensus was reached in all cases. The sum of ST-segment-elevation was measured 20 ms after the end of the QRS complex in leads I, aVL and V1-V6 for anterior, and leads II, III, aVF and V5-V6 for non-anterior myocardial infarction. The findings from the coronary angiograms were used to confirm the infarct location. When the infarct-related artery was the left anterior descending coronary artery or one of its side branches, the infarct location was classed as anterior, and when the infarct-related coronary artery was the right or the circumflex coronary artery, the infarct location was judged to be non-anterior. The second ECGs were classified by comparison of the ST segments with those on the first ECGs.

Normalised ST segment was defined as no residual ST-segment elevation of 0.1 mV or more in any of the 12 leads (complete ST-segment-elevation resolution); improved ST segment was defined as residual ST-segment elevation of less than 70% of that on the first ECG (partial ST- segment-elevation resolution); unchanged ST segment was defined as a residual ST-segment elevation of 70% or more of that on the first ECG (no ST-segment-elevation resolution).

The reproducibility of the classification of the ECGs was assessed in two ways. The ECGs of all patients in the study born in January, February or March (n=105) were reanalysed in an identical manner. Agreement between first and seconds readings was found in 93 (89%) of 105 pairs of ECGs. Twelve patients had a one-grade difference between the two readings. The estimated weighted Kappa correlation coefficient was 0.90 (95% CI 0.84-0.95). The ECGs of the first 60 of these 105 patients were sent for outside review by an experienced clinical cardiologist not otherwise involved in our trial, and his reading was compared with our first and second reading. Agreement with our first and second readings was found in 53 (88%) of 60 patients and in 49 (82%) of 60 patients, respectively, with a one-grade difference in 7 and 11 patients. The weighted Kappa correlation coefficients between the independent readings and our first and second readings was: 0.92 (0.85- 0.98) and 0.83 (0.73- 0.93), respectively.

Enzymatic Infarct Size

We estimated infarct size by measurements of enzyme concentrations, with lactate dehydrogenase (LDH) as the reference enzyme. We used a two-compartment model, which has been validated in studies on the turnover of radio-labelled plasma proteins and circulating enzymes (13,14). Cumulative enzyme release was calculated from serial measurements up to 72 h after symptom onset. Samples were obtained at admission and every 12 h, to 72 h. From these measurements, an area under the curve was constructed, preferably from 7, but from at least 5 measurements. These measurements and calculations were done at the department of clinical chemistry, without access to clinical data. Further details of these methods have been published (6).

Left-Ventricular Function

We measured left-ventricular ejection fraction with a radio-nuclide technique (4) before hospital discharge. Measurement was done by the multiple-gated equilibrium method after labelling of red blood cells had been with [99mTc] pertechnetate. A gamma camera (General Electric Milwaukee, WI, USA) with a low-energy, all purpose, parallel-hole collimator was used. The global ejection fraction was calculated on computer (Star View, General-Electric), with the PAGE ™ program, version 2.3. Specialists in nuclear medicine who were unaware of the clinical data, gathered data on ejection fractions.

Mortality

Follow-up information was obtained for all patients. Records of 66% of patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patient's general physician. We were able to confirm that patients for whom we had not received written confirmation of death were alive. For patients who died during follow-up, hospital records and necropsy data were reviewed. No patient was lost to follow-up. All deaths were taken to be from cardiovascular causes, except for those from necropsy-confirmed malignant disorders.

Statistical Analysis

We did chi-square analysis to test differences between proportions, with calculation of relative risks and 95% CIs. Diffe-rences were signifi-cant if the two-sided p value was <0.05. We did time-to-event analysis to describe survival from the date when the patient was admitted to the hospital with SAS for Windows, version 6.11. Survival was represented by Kaplan-Meier curves. We did multivariate analysis with adjustments for age, sex, previous myocardial infarction and infarct location, (16) and trend analyses, as described by Schlesselman (17).

Table 1.

Baseline characteristics for total study population and patients for whom enzymatic infarct size or ejection fraction were available

Group of patients	Extent of resolution of ST-segment elevation			
Total study population (n=403)	Complete (N=204, 51%)	Partial (N=139, 34%)	No (N=60, 15%)	P
Age in years (SD)	58 (11)	60 (11)	64 (12)	0.002
Male/female	164 (80%)/ 40 (20%)	112 (81%)/ 27 (19%)	39 (64%)/ 21 (35%)	0.03
Anterior infarction	71 (35%)	70 (50%)	36 (60%)	<0.001
Previous infarction	35 (17%)	26 (19%)	15 (25%)	0.21
Triple-Vessel Disease	52 (26%)	38 (27%)	20 (33%)	0.26
Diabetes	14 (7%)	10 (7%)	4 (7%)	0.96
Ischaemic time* (SD)	226 (172)	278 (219)	338 (291)	0.005
Enzymatic infarct size known (n=126)	Complete N=64 (51%)	Partial N=47 (37%)	No N=15 (12%)	P
Age in years (SD)	57 (10)	61 (9)	61 (10)	0.07
Male/female	52 (81%)/ 12 (19%)	40 (85%)/ 7 (15%)	11 (73%)/ 4 (27%)	0.75
Anterior infarction	20 (31%)	23 (49%)	11 (73%)	0.002
Previous infarction	5 (8%)	7 (15%)	3 (20%)	0.13
Triple-Vessel Disease	14 (22%)	12 (26%)	4 (27%)	0.61
Diabetes	6 (9%)	3 (6%)	1 (7%)	0.60
Ischaemic time* (SD)	208 (152)	266 (230)	250 (177)	0.06
Left-ventricular ejection fraction known (n=285)	Complete N=138 (48%)	Partial N=110 (39%)	No N=37 (13%)	P
Age in years (SD)	58 (11)	59 (10)	62 (11)	0.05
Male/female	117 (85%)/ 21 (15%)	92 (84%)/ 18 (16%)	25 (68%)/ 12 (32%)	0.05
Anterior infarction	52 (38%)	57 (52%)	23 (62%)	0.003
Previous infarction	15 (11%)	17 (15%)	7 (19%)	0.15
Triple-Vessel Disease	29 (21%)	27 (25%)	10 (27%)	0.38
Diabetes	13 (9%)	9 (8%)	3 (8%)	0.73
Ischaemic time* (SD)	219 (160)	279 (221)	360 (311)	0.001

*Ischaemic time is defined as time from symptom onset until the first balloon inflation

Results

The patients were classified into 3 categories by results of the 12-lead ECG. Baseline clinical characteristics of the 3 groups are shown in table 1. Complete ST-segment-elevation resolution was present in 204 (51%) patients. Partial ST-segment resolution was seen in 139 (34%) patients, and 60 (15%) patients had either no resolution or showed an increase of ST-segment-elevation on the ECG done after angioplasty. The second ECGs were recorded a mean of 144 (SD 85) min after the first ECG and 59 (37) min after primary angioplasty in the complete resolution group; 153 (79) min after the first ECG and 59 (28) min after primary angioplasty in the partial resolution group; and 154 (82) min after first ECG and 56 (31) min after primary angioplasty in the group with no resolution. Patients in the latter group were older, there was a high proportion of women, and more patients had an anterior infarction than in the other two groups. Ischaemic time, defined as the time from the onset of chest pain to primary angioplasty, was 226 (172) min among patients with complete resolution, 278 (219) min among patients with partial resolution, and 338 (291) min among patients with no resolution ($p<0.005$).
Compared to patients who had no ST-segment-elevation resolution, a normalised ST- segment was associated with a large reduction in infarct size of 60%, as shown by serial enzyme measurements. Patients with partial resolution had a reduction in infarct size of 28% compared with patients with no resolution (table 2).

Table 2.
Extent of myocardial infarction measured by enzymatic infarct size and left-ventricular ejection fraction

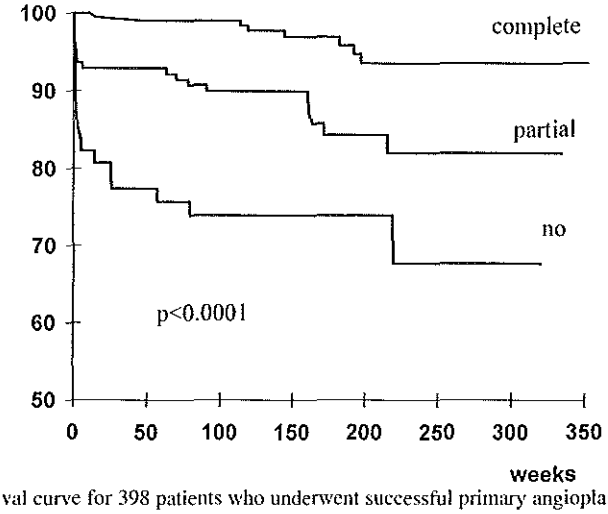
	Complete Resolution	Partial Resolution	No Resolution	P
Enzymatic infarct size (N=126) LDHQ72, U/l* (SD)	(N=65) 703 (511)	(N=46) 1274 (774)	(N=15) 1760 (1017)	<0.001
Ejection fraction (N=285) Before discharge from hospital (SD)	(N=138) 51 (9%)	(N=110) 44 (12%)	(N=37) 39 (13%)	<0.001

LDHQ72 indicates cumulative enzyme release from five to seven serial measurements up to 72 h after symptom onset.

Preservation of left-ventricular function, measured by radionuclide left-ventricular ejection fraction, was strongly related to the extent of ST-segment resolution. Patients with complete resolution of ST-segment elevation had a mean ejection fraction before discharge of 51% (SD 9), patients with partial resolution 44% (12), and patients with no resolution had an ejection fraction of 39% (13).
50 (12%) patients died during follow-up. Five patients died from a malignant illness -2 patients from lung cancer, 1 from an adrenal tumour, and 2 from carcinoma of the pancreas- and these were all excluded from the survival analysis. In hospital, there were no deaths among patients with a normalised ST-segment, but 6% of patients with partial ST-segment-elevation resolution and 13% of patients with no resolution died. At follow-up after 3.1 (1.6) years, the rate of death

was 4% among patients with a normalised ST-segment, 14% among patients with partial resolution, and 29% among patients with no resolution.

Figure 1



Kaplan-Meier survival curve for 398 patients who underwent successful primary angioplasty

The figure shows the survival curves for the 3 groups. The relative risk of death among patients with no ST-segment-elevation resolution compared with patients with a normalised ST- segment was 8.7 (CI 3.7-20.1). The relative risk of death among patients with partial ST- segment-elevation resolution compared with patients with a normalised ST-segment was 3.6 (1.6-8.3). We did multivariate analyses with adjustments for age, sex, infarct location, and previous infarction, but inclusion of these adjustments had little influence on the relative risks. The relative risk of death among patients with no resolution was 6.4 (2.7-15.3), and among those with partial resolution was 3.5 (1.5-8.0). In this model, only age and ECG classification were independent correlates of survival. None of the other baseline clinical variables changed the results significantly when we added them to this model.

Discussion

Our principle finding was that in a large cohort of patients with documented successful reperfusion therapy and TIMI 3 flow through the infarct-related coronary artery, the extent of ST-segment-elevation resolution on the 12-lead ECG is a strong predictor of clinical outcome. The clear relation between the ECG findings, enzymatic infarct size, and left-ventricular function show that the extent of ST-segment-elevation resolution reflects myocardial salvage.

Several studies have described the relation between changes of the ECG after the start of thrombolytic therapy and patency of the infarct-related vessel at follow-up coronary angiography (18,19). Although complete ST-segment resolution predicts an open infarct artery reasonably well, the absence of ST-segment-elevation resolution gives no information about patency (20). Our study shows that ECG will not predict infarct-vessel status in many patients with these criteria, since 49% of patients in our study had persistent ST-segment-elevation despite an open epicardial vessel with TIMI 3 flow. ST-segment changes after reperfusion therapy may, therefore, reflect myocardial flow rather than epicardial flow and predict clinical outcome better than epicardial vessel patency alone in patients treated with thrombolytic therapy (11,12).

Several techniques have been used to assess myocardial perfusion after reperfusion therapy. "No

reflow", which can be assessed with myocardial contrast echocardiography by intracoronary injection of sonicated microbubbles, is a predictor of clinical outcome and left- ventricular function after reperfusion therapy for acute anterior myocardial infarction (21-23). Positron emission tomography scans can show vascular integrity in the infarcted myocardium (24), which may help to select patients in whom additional interventions can improve recovery of left-ventricular function (25). However, these techniques are costly and time-consuming and not available in routine clinical practice. We found that 12-lead ECG reflects myocardial reperfusion and microvascular integrity rather than epicardial coronary-artery patency.

Complete ST-segment-elevation resolution is related to limited infarct size and preservation of left-ventricular function, whereas no resolution of ST-segment elevation is associated with extensive myocardial enzyme release, substantial impairment of left-ventricular function, and, consequently, a higher mortality. This mechanism is probably related to the extent of microvascular injury. Patients with no ST-segment resolution on ECG after angioplasty had a higher frequency of anterior-wall myocardial infarctions and presented late after symptom onset. Infarct location and ischaemic time are important determinants of infarct size (26-28). A large area at risk or an ischaemic time of more than 3 h results in oxidative stress, massive release of creatine phosphokinase from the myocardium, and a lack of recovery of aerobic metabolism; subsequent neutrophil plugging of capillaries and oedema results in an increased impedance to flow (29).

We found a strong relation between ischaemic time and the extent of ST-segment resolution. This relation has been assessed in studies of patients started on thrombolytic therapy (11,12,30). However, such investigations are confounded by the inability to assess the exact time of reperfusion in patients treated with thrombolytic therapy. Strong emphasis should be placed on methods (initial diagnosis, transportation and where patients are treated in hospital), that lead to shorter time from symptom onset to patency or myocardial reperfusion. Investigations of thrombolysis before admission to hospital have shown that patients taken part in studies have a substantially shorter delay from arrival in hospital to the start of thrombolytic therapy ("door to needle" time), than non-study patients, and that a long delay is associated with more depressed left-ventricular function and a worse clinical outcome (31,32). Further streamlining of the organisation may, therefore, lead to better outcome.

We assessed ST-segment resolution in a semiquantitative way, by comparison of two 12-lead ECGs. This approach might be less objective and accurate than continuous ST-segment tracking with automated analysis systems (18). Although these systems are attractive, they are not generally available, and whether they convey additional information has yet to be shown. Enzymatic infarct size and left-ventricular ejection fraction were not available for all our patients. Nevertheless, the samples were large enough to show s substantial difference between the groups with adequate statistical power. Our findings cannot be generalised to all patients presenting as emergencies with acute transmural infarction, since we describe patients with successful reperfusion by primary angioplasty. In particular, our data should not be extrapolated to patients in whom reperfusion therapy is not successful, those managed conservatively, or those who undergo urgent coronary-artery bypass surgery.

The extent of ST-segment-elevation resolution on the 12-lead ECG after successful reperfusion therapy for acute myocardial infarction is related to enzymatic infarct size and left-ventricular function and is related to clinical outcome. This relationship can be used to stratify patients for risk shortly after the acute event. Patients with normalised ST-segments have limited myocardial damage and an excellent long term clinical outcome. Additional therapeutic interventions should be considered for patients with persistent ST-segment elevation, despite a patent infarct-related vessel, since these patients have more extensive myocardial damage, can have depressed left-ventricular function, and have a higher mortality during long-term follow-up.

Appendix

Members of the Zwolle Myocardial Infarction Study Group are:

Department of Cardiology:
W.P. Beukema
M.R.F. Bloemers
M.J. de Boer
A.W.J. van 't Hof
J.C.A. Hoorntje
E.P. de Kluiver
A.C.M. van Nus
P.A.J. Remkes
H. Suryapranata
K. Thomas
F. Zijlstra

Data coordination:
L. v.d. Brink
T. Eenhuizen
A.L. Liem

Department of Nuclear Medicine:
J.D.C.S. Kuyvenhoven
S. Reiffers

Clinical Chemistry:
L.D. Dikkeschei
K. Miedema
E. van Voorst tot Voorst

Coronary Care Unit:
B. Benes
P. Santing
H. v.d. Wetering

Catheterization laboratory:
D. Dijkstra
H. Eenhuizen

Secretarial Assistance
V.R.C. Derks

Contributors

Arnoud WJ van 't Hof coordinated this project, and collated, checked and analysed the data, specific of this part of the Zwolle Myocardial Infarction Study. Aylee Liem assisted in data collection and analysis. Menko-Jan de Boer coordinated collection of angiographic and enzymatic infarct size data, and analysed them. The principle investigator was Felix Zijlstra who designed the study and advised on data analysis. All authors contributed to the writing of the paper.

Acknowledgments

Statistical analysis were done by W.K. Redekop, A.P. Haasdijk and Prof. Dr J.P.G. Tijssen, Department of Clinical Epidemiology & Biostatistics, Academic Medical Center, Amsterdam, The Netherlands.

The independent ECG review was done by Dr. P.E. Polak, St. Anna Hospital, Geldrop, The Netherlands.

References

1. Fibrinolytic Therapy Trialists' (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.
2. The GUSTO Angiographic Investigators. The effect of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival, after acute myocardial infarction. N Engl J Med 1993;329:1615-22.
3. Rentrop KP. Restoration of anterograde flow in acute myocardial infarction, the first 15 years. J Am Coll Cardiol 1995;25 (suppl):1S-2S.
4. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coro-nary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
5. Grines CL, Browne KF, Marco J, et al. for the Primary Angioplasty on Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
6. de Boer MJ, Suryapranata H, Hoorntje JCA, et al: Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-61.
7. de Boer MJ, Reiber JHC, Suryapranata H, van den Brand MJBM, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterisation laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16:1347-55.
8. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956-61.
9. Wong PHC, Wong CM. Intracoronary stenting in acute myocardial infarction. Cath Cardiovasc Diagn 1994;33:39-45.
10. Ohman EM, George BS, White CJ, et al. Use of aortic counterpulsation to improve sustained coronary patency during acute myocardial infarction. Results of a randomized trial. Circulation 1994;90:792-9.
11. 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.
12. Barbash GI, Roth A, Hod H, et al. Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli Study of early intervention in myocardial infarction. Br Heart J 1990;64:241-7.
13. van der Laarse A, Vermeer F, Hermens WT, et al. Effects of intracoronary streptokinase on infarct size estimated from cumulative enzyme release and on enzyme release rate: a randomised trial of 533 patients with acute myocardial infarction. Am Heart J 1986;112:672-81.
14. de Zwaan C, Willems GM, Vermeer F, et al. Enzyme tests in the evaluation of thrombolysis in acute myocardial infarction. Br Heart J 1988;59:175-83.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
16. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187-200.
17. Schlesselman JJ. Case-control studies, New York, Oxford Press 1982;203-6.
18. Klootwijk P, Langer A, Meij S, et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. Eur Heart J 1996;17:689-98.

19. Clemmensen P, Ohman M, Sevilla DC, et al. Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990;66:1407-11.
20. Califf RM, O'Neill W, Stack R, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988;108:658-62.
21. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699-705.
22. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the "no reflow" phenomenon. Circulation 1996;93:223-8.
23. Iliceto S, Galiuto L, Marchese A, et al. Analysis of microvascular integrity, contractile reserve, and myocardial viability after acute myocardial infarction by dobutamine echocardiography and myocardial contrast echocardiography. Am J Cardiol 1996;77:441-5.
24. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Limura O. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. Am J Cardiol 1996;77:25-30.
25. Maes A, Van de Werf F, Nuyts J, Bormans G, Desmet W, Mortelmans L. Impaired myocardial tissue perfusion early after successful thrombolysis. Impact on myocardial flow, metabolism, and function at late follow-up. Circulation 1995;92:2072-8.
26. Hasche ET, Fernandes C, Freedman SB, Jeremy RW. Relation between ischemia time, infarct size, and left ventricular function in humans. Circulation 1995;92:710-9.
27. Raitt MH, Maynard C, Wagner GS, Cerqueirra, MD, Selvester RH, Weaver WD. Relation between symptom duration before thrombolytic therapy and final myocardial infarct size. Circulation 1996;93:48-53.
28. Hermens W, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size. Lancet [letter] 1992;340:1297.
29. Ferrari R. Metabolic disturbances during myocardial ischemia and reperfusion. Am J Cardiol 1995;76:17B-24B.
30. Mauri F, Maggioni AP, Franzosi MP, et al. A simple electrocardiographic predictor of the outcome of patients with acute myocardial infarction treated with a thrombolytic agent. A GISSI-2-derived analysis. J Am Coll Cardiol 1994;24:600-7.
31. Weaver WD, Cerqueira M, Hallstrom AP, et al. Pre-hospital-initiated vs hospital-initiated thrombolytic therapy. The myocardial infarction triage and intervention trial. JAMA 1993;270:1211-6.
32. GREAT Goup. Feasability, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampion region early anistreplase trial. BMJ 1992;305:548-53.

CHAPTER 2

Part Two

Angiographic Assessment of Myocardial Reperfusion in Patients treated with Primary Angioplasty for Acute Myocardial Infarction Myocardial Blush Grade

Myocardial Reperfusion in Acute Infarction

Arnoud W.J. van 't Hof, MD; Aylee Liem, MD; Harry Suryapranata, MD; Jan C.A. Hoorntje, MD; Menko-Jan de Boer, MD; Felix Zijlstra, MD; on behalf of the Zwolle Myocardial Infarction Study Group.

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

Circulation, 1998:97:2302-2306

Summary

Background: The primary objective of reperfusion therapies for acute myocardial infarction is not only restoration of blood flow in the epicardial coronary artery but also complete and sustained reperfusion of the infarcted part of the myocardium.

Methods and Results: We studied 777 patients who underwent primary coronary angioplasty during a 6-year period and investigated the value of angiographic evidence of myocardial reperfusion (myocardial blush grade) in relation to the extent of ST-segment elevation resolution, enzymatic infarct size, left ventricular function, and long-term mortality. The myocardial blush immediately after the angioplasty procedure was graded by two experienced investigators, who were otherwise blinded to all clinical data: 0: no myocardial blush, 1: minimal myocardial blush, 2: moderate myocardial blush, and 3: normal myocardial blush. The myocardial blush was related to the extent of the early ST-segment elevation resolution on the 12-lead electrocardiogram. Patients with blush grades 3, 2 and 0/1 had enzymatic infarct sizes of 757, 1143 and 1623 ($P<0.0001$), respectively, and ejection fractions of 50%, 46% and 39%, respectively ($P<0.0001$). After a mean ±SD follow-up of 1.9±1.7 years, mortality rates of patients with myocardial blush grades, 3, 2 and 0/1 were 3%, 6% and 23% ($P<0.0001$), respectively. Multivariate analysis showed that the myocardial blush grade was a predictor of long-term mortality, independent of Killip class, Thrombolysis In Myocardial Infarction grade flow, left ventricular ejection fraction, and other clinical variables.

Conclusion: In patients after reperfusion therapy, the myocardial blush grade as seen on the coronary angiogram can be used to describe the effectiveness of myocardial reperfusion, and is an independent predictor of long term mortality.

(Circulation 1998;97:2302-2306)

Introduction

Over the past decades, great efforts have been made to improve the outcome of patients with acute myocardial infarction (1-7). Many trials have relied on mortality as the end point (1,2). The recent data from the Global Utilization of Streptokinase and Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) trial suggest that patency of the epicardial infarct -related coronary artery is an appropriate alternative end point (4). However, the primary objective of reperfusion therapies is not only restoration of blood flow in the epicardial coronary artery but also complete and sustained reperfusion of the infarcted myocardium. Echocardiographic assessment of myocardial perfusion after intracoronary injection of sonicated microbubbles is an investigational technique that has been used to describe myocardial reperfusion in patients with restored patency of the infarct-related coronary artery. The so-called "no-reflow" phenomenon, an open epicardial artery without flow into the myocardium, predicts complications and left ventricular dilation (8,9). A simple clinical tool that describes the effectiveness of myocardial reperfusion is lacking because noninvasive means so far have not been applicable in routine clinical practice and the widely used angiographic parameter, Thrombolysis In Myocardial Infarction (TIMI) flow grade, describes epicardial instead of myocardial blood flow (3,4). Therefore, we have introduced an angiographic parameter to describe the effectiveness of myocardial reperfusion: the myocardial blush grade. To validate this new tool we compared the myocardial blush grades with 12-lead ECG, enzymatic infarct size, left ventricular function, and clinical outcome in a cohort of patients after primary coronary angioplasty and assessed whether this new parameter might give additional prognostic value compared with that of TIMI flow grade.

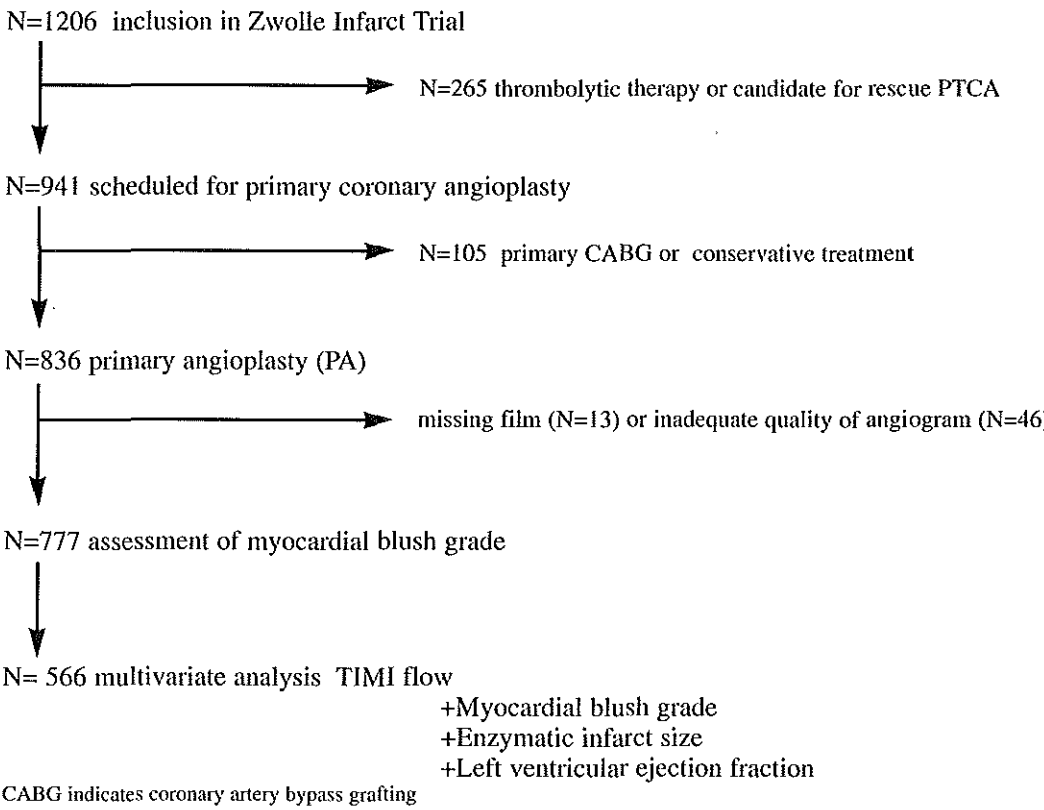
Methods

Patients

From August 1990 until April 1997, 1206 patients fulfilled the criteria for entry into one of our published or ongoing trials (6,10-12). Two hundred and sixty-five patients were treated with thrombolytic therapy. Forty-three patients underwent primary coronary bypass surgery because of severe left main or three-vessel disease, and 62 patients were treated conservatively because of nonsignificant disease and TIMI grade 3 flow of the infarct-related vessel. In 836 patients, primary angioplasty was performed. In 46 patients, the quality of the coronary angiogram did not allow adequate assessment of myocardial blush grade and for 13 patients, angiographic data were missing. The remaining 777 patients form the basis of this report (Figure 1).

Figure 1.

Flow chart of patients admitted with acute myocardial infarction and ST-segment elevation between August 1990 and April 1997



CABG indicates coronary artery bypass grafting

TIMI Flow Grades and Myocardial Blush Grades

TIMI flow grades were assessed as previously described (3,10). Both TIMI flow and myocardial blush were graded on the angiograms made immediately after the primary coronary angioplasty procedure, by two experienced investigators, who were blinded to all data apart from the coronary angiograms. Grading was done on cinefilm at 25 frames/s made in a Philips digital coronary imaging catheterization laboratory. In each patient, the best projection was chosen to assess the myocardial region of the infarct-related coronary artery, preferably without superpositioning of noninfarcted myocardium. Left anterior oblique or left lateral projections were used in 49%, right anterior oblique projections in 23%, both left anterior oblique or left lateral and right anterior oblique projections in 23%, and a cranial view in 5%. Angiographic runs had to be long enough to allow some filling of the venous coronary system, and back-flow of the contrast agent into the aorta (Hexabrix, 5-15 mL) had to be present to be certain of adequate contrast filling of the epicardial coronary artery. All angiograms were made with 7F or 8F guiding catheters in a standardized fashion after 400 mg nitroglycerin IC had been given immediately after the primary angioplasty procedures, and this procedure allowed quantitative coronary artery analysis (10). Myocardial blush grades were defined as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and 3, normal myocardial blush or contrast

density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush persisted ("staining"), this phenomenon suggested leakage of the contrast medium into the extravascular space (13), and was graded 0. Reproducibility and variabilities of the myocardial blush grades are shown in Table 1.

Table 1.

Reproducibility and Variabilities of Myocardial Blush Grades

			Difference	
	n	Agreement	1 grade	>1 grade
Reproducibility - 2 observers	71	60 (85%)	11 (15%)	0 (0%)
Variability - interobserver	30	27 (90%)	3 (10%)	0 (0%)
- intraobserver	30	29 (97%)	1 (3%)	0 (0%)

Reproducibility was assessed by reviewing a random sample of the coronary angiograms a second time by two observers. A random sample of 30 coronary angiograms was used to assess inter- and intra-observer variabilities.

ECG

ECGs were done on admission (first ECG), and shortly after arrival in the coronary care unit (second ECG) after the primary coronary angioplasty procedure. The sum of ST-segment elevations was measured 20 ms after the end of the QRS complex in leads I, aVL, and V1 to V6 for anterior and leads II, III, aVF, V5 and V6 for non-anterior myocardial infarction. The second ECGs were classified with regard to the ST segment in the same way as previously described (14): 1, normalized, defined as no residual ST-segment elevation; 2, improved, defined as a residual ST-segment elevation <70% of with that on the first ECG; and 3, unchanged, defined as a residual ST-segment elevation > 70% of that on the first ECG.

Enzymatic Infarct Size

The methodology for estimation of infarct size is equal to that obtained by the a-hydroxybutyrate dehydrogenase method and has been described previously (15). In brief, infarct size was estimated by measurements of enzyme activities by using lactate dehydrogenase as the reference enzyme. Cumulative enzyme release from five to seven serial measurements up to 72 hours after symptom onset was calculated. A two-compartment model was used, which has been validated in several studies with respect to the turnover of radio-labeled plasma proteins and circulating enzymes (16).

Left Ventricular Function

Before the patients were discharged, left ventricular ejection fraction was measured by radionuclide ventriculography. The multiple-gated equilibrium method was used after in vivo labeling of red blood cells of the patient with 99mTc-pertechnetate (6,17). A General Electric 300 g-camera with a low-energy, all-purpose, parallel-hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer and the fully automated PAGE program. Use of this software program protects against operator bias. The reproducibility of this method is excellent, with a mean difference (±SD) between first and second values of duplicate measurements of 1.2±1.1%.

Mortality

Mortality was assessed in August 1997. Records of patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patients general physician or by direct telephone interview with the patient. For patients who died during follow-up, hospital records and necropsy data were reviewed. No patient was lost to follow-up.

Statistical Analysis

Differences between group means were tested by two-tailed Student's t test. For comparison of rates of discrete outcome variables, a c2 test or Fisher's exact test was used. Trend analyses were done as described by Schlesselman (18). In our presentation of the data, continuous baseline and outcome variables are given as mean ±SD, whereas discrete variables are given as absolute values, percentages, or both. In 566 patients in whom TIMI flow as well as myocardial blush grading, enzymatic infarct size, and left ventricular ejection fraction (LVEF) were obtained, a multivariate logistic regression analysis was performed to determine independent predictors of long-term mortality. Continuous variables were divided into three categories, with the 25th and 75th percentiles as cutoff points. Odds ratios and 95% confidence intervals were calculated. Survival was represented by Kaplan-Meier curves. A log-rank test was done to assess significant differences in survival between patient subgroups.

Table 2.
Baseline Clinical and Angiographic Characteristics

	Myocardial Blush Grade			
	3 (n=148)	2 (n=393)	0/1 (n=236)	Trend P
Age, years	57±11	59±11	61±11	0.0001
Male	124 (84%)	319 (81%)	186 (79%)	0.22
MVD	79 (53%)	216 (55%)	143 (61%)	0.13
Previous MI	23 (16%)	43 (11%)	46 (20%)	0.01
Anterior MI	53 (36%)	216 (55%)	163 (69%)	<0.0001
Killip class 1	133 (90%)	346 (88%)	165 (70%)	<0.0001
Diabetes	12 (8%)	20 (5%)	26 (11%)	0.14
Ischemic time, min*	233±188	259±215	315±256	0.001
Infarct related artery				
-RCA	78 (53%)	138 (35%)	50 (21%)	<0.0001
-CX	21 (14%)	45 (11%)	24 (10%)	0.26
-LAD	49 (33%)	206 (53%)	156 (66%)	<0.0001
-Graft	0%	3 (1%)	4 (2%)	0.08
-Left Main	0%	1 (0.3%)	2 (1%)	0.17
Patency IRV before PTCA	43 (29%)	79 (20%)	24 (10%)	<0.0001

MVD indicates multivessel coronary artery disease; MI, myocardial infarction; RCA, right coronary artery; CX, circumflex artery; LAD, left anterior descending coronary artery. Patency of IRV before PTCA, infarct-related vessel with TIMI 2 or 3 flow before the angioplasty procedure (PTCA). *Ischemic time is the time from the first onset of symptoms to the first balloon inflation.

Results

Myocardial blush grades could be assessed in 777 of the 836 patients (93%). Baseline and angiographic characteristics of the patients classified by myocardial blush grade are shown in Table 2. Myocardial blush grades 0 and 1 were present in 5.8% and 24.6% of patients, respectively. In the presentation of the results, these two groups were combined. Patients with lower blush grades were older and more often presented in Killip class 2 or higher. There was a strong association between infarct location as well as infarct-related artery and myocardial blush grade. Furthermore, patients with higher blush grades had a higher incidence of antegrade flow into the infarct zone before the angioplasty procedure. There is an inverse relation between ischemic time and myocardial blush grade. TIMI flow of the infarct-related vessel could be assessed in all patients. Interpretable ECGs on admission as well as those performed after the primary coronary angioplasty procedure were available for 647 patients (83%). In 2% of the patients one or both ECGs did not allow an assessment of the ST-segments owing to rhythm or conduction abnormalities. The results of the TIMI flow classification and extent of ST-segment elevation resolution are shown in Table 3. TIMI flow, and LVEF were no longer independent predictors of mortality after inclusion of myocardial blush grade into the multivariate model.

Table 3.

TIMI flow and ST Segments on the 12-lead ECG After Primary Coronary Angioplasty.

	Myocardial Blush Grade			
	3 (n=148)	2 (n=393)	0/1 (n=236)	Trend Analysis P
TIMI flow (n=777)				
3	99%	98%	67%	<0.0001
2	1%	1%	21%	<0.0001
0-1	0%	1%	12%	<0.0001
ST-segment elevation (n=647)				
Normalized*	65%	54%	27%	<0.0001
Improved*	28%	34%	45%	0.002
Unchanged*	7%	12%	28%	<0.0001

* Defined as previously described in Reference 14.

Trend analysis revealed a distinct relation between TIMI flow, ST-segment recovery, and myocardial blush grades. Enzymatic infarct size, LVEF, and long-term mortality at 1.9±1.7 years after the event are shown in Table 4.

Table 4.

Enzymatic Infarct Size, LVEF, and Mortality

	Myocardial Blush Grade			
	3	2	0/1	Trend Analysis P
LDHQ72	757±582	1143±879	1623±1147	<0.0001
LVEF, %	50±10	46±11	39±12	<0.0001
Mortality, %	3	6	23	<0.0001

LDHQ72 indicates enzymatic infarct size from serial lactate dehydrogenase measurements up to 72 hours after angioplasty. LVEF was measured by predischarge radionuclide ventriculography; total mortality was assessed after a follow-up of 1.9 ± 1.7 years.

Enzymatic infarct size could be measured in 659 patients (85%). LVEF measurements were obtained for 584 patients (75%). There was a relation between myocardial blush grade, infarct size, and LVEF: the higher the blush grade, the lower the infarct size and the better the LVEF. During follow-up, 81 patients died (10%). There was also an inverse relation between myocardial blush grades and long-term mortality. In 566 patients, TIMI flow, myocardial blush grade, enzymatic infarct size, and LVEF were known. Multivariate analysis showed that the myocardial blush grade predicted mortality, independent of other-well known variables associated with long-term outcome after myocardial infarction, such as age and Killip class (Table 5).

Table 5.

Multivariate Analysis for 566 Patients With Available TIMI Flow, Myocardial Blush Grade, Enzymatic Infarct Size and LVEF

	Odds Ratio	95% CI	P
Age (per class)	2.6	1.4 - 5.4	0.003
Killip class (per class)	3.6	1.5 - 8.5	0.004
Myocardial blush grade (per class)	2.6	1.2 - 5.4	0.01
LDHQ72 (per class)	1.8	1.0 - 3.3	0.05
Multivessel disease	2.0	0.8 - 4.8	0.12
Anterior infarction	0.6	0.2 - 1.5	0.23
Female sex	1.8	0.7 - 4.5	0.24
TIMI flow before PA (per class)	1.7	0.6 - 5.1	0.33
LVEF (per class)	1.3	0.7 - 2.4	0.44
Diabetes	1.4	0.5 - 3.8	0.47
TIMI flow after PA (per class)	0.8	0.4 - 1.8	0.81
Ischemic time (per class)	1.1	0.6 - 1.8	0.81
Previous infarction	1.0	0.3 - 2.9	0.95

CI indicates confidence interval; LDHQ72, enzymatic infarct size from serial lactate dehydrogenase measurements up to 72 hours after angioplasty; and PA, primary coronary angioplasty. Ischemic time was measured from symptom onset to first balloon inflation.

Discussion

The principle finding of our study is, that in patients after primary angioplasty for acute infarction, myocardial perfusion, as described by the myocardial blush grade, is reflected by the resolution of ST-elevations on the 12-lead ECG; the extent of damage to the infarcted myocardium, as evident from enzymatic infarct size; and radionuclide ventriculography, and is independently related to long-term mortality. The myocardial blush grade can therefore be used as a predictor of clinical outcome.

Myocardial Perfusion

We previously described the relation between myocardial flow reserve assessed by densitometric analyses of contrast-medium passage in the infarcted myocardium, and left ventricular function (19). However, this semiquantitative method has several pitfalls and limitations and may not be applicable in routine clinical practice (20). Several studies have shown that myocardial perfusion can be assessed visually with intracoronary injection of sonicated microbubbles during echocardiography in the catheterization laboratory. This technique has been used to describe the effectiveness of myocardial reperfusion and predict clinical outcome (8,9). Myocardial contrast echocardiography can be used to categorize patients as having reflow or no-reflow, and it has been shown that even in the presence of TIMI 3 flow in the epicardial coronary artery, a patient may have no-reflow into the myocardium (21). Because the venous phase of the coronary angiogram is often clearly visible in patients with no-reflow, the echocardiographic or angiographic contrast agent passes from the arterial coronary vessels into the venous system by another route than the myocardial microcirculation in the infarct zone. We developed the angiographic myocardial blush grade based on the visually assessed contrast density in the infarcted myocardium after reperfusion therapy. The angiographic myocardial blush grades are analogous to the TIMI grades for flow in the epicardial infarct-related coronary artery. This information can be obtained during routine high- quality coronary angiography and can be used to describe the effectiveness of reperfusion therapies.

The pathophysiology of the no-reflow phenomenon

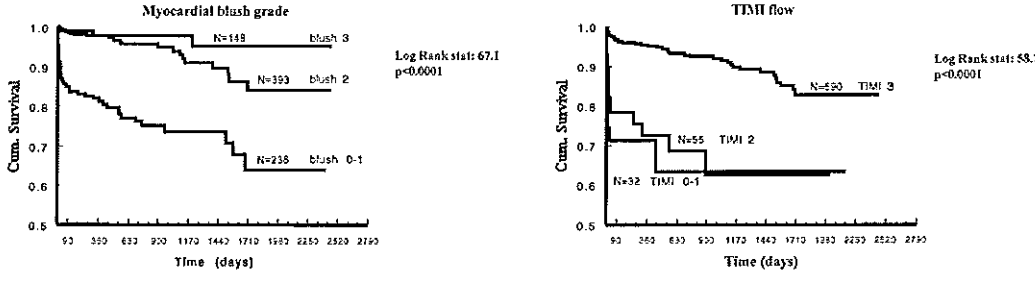
Coronary occlusion leads to cellular necrosis and myocardial damage. During a short period of occlusion, a variable amount of myocytes may become necrotic while the microvascular network is still intact. If coronary occlusion is prolonged, the microvasculature shows loss of its anatomic integrity (9,22). At the time of coronary reopening, myocardial reperfusion is achieved only in areas with anatomically preserved microvasculature, whereas reflow does not occur in myocardium with extensive microvascular damage. The no-reflow phenomenon is therefore associated with relatively more extensive necrosis and, as a consequence, is a predictor of poor regional and global contractile function (8,9). Contrariwise, adequate myocardial reflow shortly after epicardial coronary reperfusion is an accurate indication of microvascular integrity and consequently, of regional and overall functional recovery in patients with acute myocardial infarction (9,19).

Comparison of myocardial blush grades with TIMI flow grades

Myocardial blush grade was related to TIMI flow. However, from Table 3, it is clear that the majority of patients with myocardial blush grade < 2 had "normal" TIMI flow. The patients with TIMI 3 flow but low blush grades can be regarded as having no-reflow in a comparable way as patients who lack myocardial contrast on their echocardiogram after intracoronary injection of

sonicated microbubbles (8,9). A recent study from our group showed that a substantial number of patients with TIMI 3 flow have persistent ST-segment elevation on the post-angioplasty ECG, suggesting impairment of myocardial reperfusion (14). A further differentiation amongst patients with TIMI 3 flow is, therefore, needed and of clinical relevance. Multivariate logistic regression analyses showed that the myocardial blush grade was related to long-term mortality independent of TIMI flow. Therefore, an angiographic variable that takes the extent of myocardial reperfusion into account is of additional prognostic value. Figure 2 shows Kaplan-Meier curves and log-rank analysis for TIMI and myocardial blush grade, and it illustrates that survival in patients with TIMI 3 flow is not as high as survival in patients who have a high blush grade of the myocardium after primary angioplasty. Furthermore, it shows that myocardial blush grading might identify a much larger population at risk for adverse outcomes: n=236 (30%) with blush grades 0-1 versus n=87 (11%) with TIMI flow 0-2.

Figure 2.



Kaplan Meier survival curves for 777 patients with known TIMI flow and myocardial blush grades. Myocardial blush grade 0 or 1 indicates no or minimal blush or contrast density of myocardium supplied by infarct-related vessel on post angioplasty angiogram. Blush grade 2 indicates moderate blush or contrast density, and blush grade 3 indicates normal blush or contrast density, comparable with blush obtained during angiography of contralateral or ipsilateral non-infarct-related coronary artery. TIMI flow is defined as previously described (3). Cum. Survival indicates cumulative survival.

Limitations

The inter-observer and intra-observer variabilities associated with subjective angiographic assessments are certainly a limitation of the myocardial blush grades and are comparable with the variabilities in TIMI flow grades for epicardial coronary blood flow (3,23).

Implications

Early and sustained restoration of flow into the infarcted myocardium is the aim of reperfusion therapies for acute myocardial infarction. Angiographic studies of reperfusion therapies should assess myocardial perfusion as well as flow in the epicardial infarct-related coronary artery. A new standard for success of reperfusion therapy has been proposed: "90% TIMI 3 flow at 90 minutes" (24). We think that the future standard should include the phrase, "with evidence of adequate myocardial reperfusion".

References

1. Fibrinolytic Therapy Trialists' (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;343:311-322.
2. Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: a review. Drugs 1992;44:293-325.
3. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in myocardial infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76:142-154.
4. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival, after acute myocardial infarction. N Engl J Med 1993;329:1615-1622.
5. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, Vlietstra RE, Stezelecki M, Puchrowicz-Ochoki S, O'Neill WW for the Primary Angioplasty in Myocardial Infarction Study group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-679.
6. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-684.
7. Gibbons RJ, Holmes DR, Reeder GS, Bayley KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685-691.
8. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, Higashino Y, Fujii K, Minamino T. Clinical implications of the "no reflow" phenomenon. Circulation 1996;93: 223-228.
9. Iliceto S, Marangelli V, Marchese A, Amico A, Galiuto L, Rizzon P. Myocardial contrast echocardiography in acute myocardial infarction: pathophysiological background and clinical applications. Eur Heart J 1996;17:344-353.
10. de Boer MJ, Reiber JHC, Suryapranata H, van den Brand MJBM, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterisation laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16: 1347-1356.
11. Zijlstra F, Beukema WP, van 't Hof AWJ, Liem AL, Reiffers S, Hoorntje JCA, Suryapranata H, de Boer MJ. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction J Am Coll Cardiol 1997;29: 908-912.
12. Suryapranata H. Primary stenting in acute myocardial infarction. Main session, Birmingham, UK: 18th Congress of the European Society of Cardiology, August 29, 1996.
13. Little WC, Rogers EW. Angiographic evidence of hemorrhagic myocardial infarction after intracoronary thrombolysis with streptokinase. Am J Cardiol 1983;51:906-908.
14. van 't Hof AWJ, Liem AL, de Boer MJ, Zijlstra F, for the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-619.

15. van der Laarse A, Hermens WT, Hollaar L, Jol M, Willems GM, Lemmers HEAS, Liem AH, Souverijn JHM, Oudhof JH, De Hooge J, Buis B, Arntzenius AC. Assessment of myocardial damage in patients with acute myocardial infarction by serial measurement of serum a-hydroxybutyrate dehydrogenase levels. Am Heart J 1984;107:248-260.
16. Hermens WT, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size. Lancet 1992;340:1297 (Letter).
17. Zijlstra F, de Boer MJ, Beukema WP, Liem AL, Reiffers S, Huysmans D, Hoorntje JCA, Suryapranata H, Simoons ML. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. Eur Heart J 1996;17: 382-387.
18. Schlesselman JJ. Case-control studies. New York, NY: Oxford Press, 1982:203-06.
19 Suryapranata H, Zijlstra F, MacLeod DC, van den Brand M, de Feyter PJ, Serruys PW. Predictive value of reactive hyperemic response on reperfusion on recovery of regional myocardial function after coronary angioplasty in acute myocardial infarction. Circulation 1994;89:1109-1117.
20. Zijlstra F, Widimsky P, Suryapranata H. Possibilities and limitations of myocardial flow reserve. In: Reiber JHC, Serruys PW, eds. Progress in quantitative coronary arteriography. Dordrecht/Boston/London: Kluwer Academics Publishers; 1994:141-159.
21. Ito H, Okamura A, Iwakura K, Masuyama T, Hori M, Takiuchi S, Negoro S, Nakatsuchi Y, Taniyama Y, Higashino Y, Fujii K, Minamino T. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. Circulation 1996;93:1993-1999.
22. Kloner RA, Ganote CE, Jennings RB. The "no reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496-1508.
23. Gibson CM, Cannon CP, Daley WL, Dodge JT, Alexander B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole K, Braunwald E. TIMI Frame Count: A quantitative method of assessing coronary artery flow. Circulation 1996;93:879-888.
24. Forrester JS. New Standard for success of thrombolytic therapy. An earnest proposal. Circulation 1995;92:2026-2028.

CHAPTER 3

Part One

Randomized Comparison of Coronary Stenting with Balloon Angioplasty in Selected Patients with Acute Myocardial Infarction

Harry Suryapranata MD, PhD, Arnoud W.J. van 't Hof MD, Jan C.A. Hoorntje MD, PhD
Menko-Jan de Boer MD, PhD, Felix Zijlstra MD, PhD.

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

Circulation, 1998;97:2502-2505

Summary

Background: Although the benefits of primary angioplasty in acute myocardial infarction have been demonstrated, several areas for improvement still remain. Therefore, a prospective randomized trial comparing primary stenting with balloon angioplasty in patients with acute myocardial infarction was conducted.

Methods and Results: Patients with acute myocardial infarction were randomly assigned to undergo either primary stenting (n=112) or balloon angioplasty (n=115). The clinical endpoints were death, recurrent infarction, subsequent bypass surgery or repeat angioplasty of the infarct-related vessel. The overall mortality rate at 6 months was 2%. Recurrent infarction occurred in 8 patients (7%) after balloon angioplasty, and in one (1%) after stenting (p=0.036). Subsequent target vessel revascularization was necessary in 19 (17%) and 4 (4%) patients, respectively (p=0.0016). The cardiac event-free survival rate in the stent group was significantly higher than in the balloon angioplasty group (95% vs 80%; p=0.012).

Conclusion: In selected patients with acute myocardial infarction, primary stenting can be applied safely and effectively, resulting in a lower incidence of recurrent infarction and a significant reduction in the need for subsequent target vessel revascularization, when compared to balloon angioplasty.

(Circulation, 1998;97:2502-2505)

Introduction

Primary angioplasty in acute myocardial infarction (MI) has been shown to result in lower rates of mortality, recurrent MI and stroke, when compared to thrombolysis [1-3). However, recurrent ischemia and early reocclusion of the infarct-related vessel (IRV) occurs in 10 to 15%, after initially successful angioplasty. Whereas late restenosis (25 to 45%), requiring repeat revascularization in the first 6 months, remains disappointingly high (1-3). Although coronary stenting may potentially overcome some of major limitations of balloon angioplasty (4,5), currently available data on stenting in acute MI have been obtained from non-randomized trials or from retrospective analysis of patients undergoing stenting as a bail-out procedure (6-13). Therefore, a prospective randomized trial comparing stenting with balloon angioplasty in acute MI was conducted.

Methods

The protocol was approved by our institutional review board. The inclusion criteria were: patients with acute MI, presenting within 6 hours after symptom-onset, or between 6 and 24 hours if they had persisting symptoms with evidence of on-going ischemia, and in whom the culprit lesion was located in a native coronary artery that was considered suitable for stenting. The clinical exclusion criteria were: inability to give informed consent due to prolonged cardiopulmonary rescusitation or cardiogenic shock (Killip class 4 at admission requiring mechanical ventilation), participation in another study, life expectancy of less than one year, factors making follow-up unlikely, and known sensitivity to Aspirin, Ticlopidine, or Warfarin. History of previous coronary bypass surgery, coronary angioplasty, or previous MI were no reasons for exclusion. The decision to include a patient was made after the IRV was identified and reperfusion was achieved with a guidewire and a balloon. The angiographic exclusion criteria were: unprotected left main disease or severe triple vessel disease necessitating urgent bypass surgery, target lesion located in a bifurcation with a large side branch or located in a diffuse sclerotic IRV, excessive proximal vessel tortuosity, inability to cross the target lesion with a guide wire, the no-reflow phenomenon or extensive thrombus throughout the IRV. After informed consent, patients were randomized to undergo primary stenting or balloon angioplasty by means of a closed envelope system.

Bare Palmaz-Schatz stents (Cordis, a Johnson & Johnson company, Warren, NJ, USA) were mounted on the balloon used for predilatation. If necessary, high-pressure inflation was performed with a bigger sized balloon. Angiographic success, subacute occlusion, and bail-out stenting were defined as previously described (5). Prolonged inflation had to be attempted before bail-out stenting was considered. Bail-out stenting did not constitute an endpoint, as it is perceived as an integral part of an angioplasty strategy. Quantitative coronary angiography was analyzed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands), blinded to all clinical data and outcome.

The initial post-stenting regimen was as follows: Heparin infusion was started 2 hours after sheath removal and continued until the International Normalised Ratio values had reached the therapeutic levels. Coumadin was given for at least 3 months and Aspirin (80mg daily) indefinitely. However, as it became clear that Ticlopidine is more effective in preventing stent thrombosis (14), and the fact that anticoagulation therapy increases the risk of major bleeding complications (4,5), our post-stenting regimen protocol has been modified accordingly. From January 1996, only Ticlopidine (250mg daily for at least 2 weeks) and Aspirin were given after stenting, and Coumadin derivates were no longer used. Heparin infusion (1mg/kg/hour) or subcutaneous low molecular weight Heparin (0.6cc b.i.d.) was given for 48 hours after sheath removal in all patients, regardless of initial treatment allocation. Thrombolytic therapy, platelet glycoprotein

IIb/IIIa receptor-antagonists, or intravascular ultrasound were not used.
Clinical endpoints were: death of any cause, recurrent MI, subsequent bypass surgery or repeat angioplasty of the IRV. Recurrent MI was defined as previously described (1). The indication for a second intervention had to be substantiated by symptoms and/or by electrocardiographic or scintigraphic evidence of ischemia at rest or during exercise. Subsequent revascularization involving other coronary arteries did not constitute an endpoint. All events were reviewed by 2 cardiologists blinded to the treatment assignments.
Using an anticipated two-sided test for differences in independent binomial proportions at the 5% significance level with a power of 90%, 211 patients (105 in each group) were required to detect a reduction in a composite end point from 35% to 16%. Data were analyzed using a single comparison between the groups according to the intention-to-treat principle. Continuous variables were expressed as means ± SD and compared using the Student's t-test, whereas discrete variables were given as absolute values and percentages. The Chi-square test was used to compare proportions, or a Fisher's exact test when appropriate. The differences in event rates between the groups, during the follow-up period, were assessed by the Kaplan-Meier method using the log rank test. Multivariate analysis was performed using the Cox proportional hazard method, permitting calculation of odds ratios that may be interpreted as relative risks with 95% confidence intervals. All statistical tests were two-tailed.

Table 1.

Reasons for exclusion in candidates for primary angioplasty (n=225)

	n	%
Clinical exclusion criteria:		
Prolonged cardiopulmonary rescusitation or cardiogenic shock	19	8
Factors making follow-up unlikely	7	3
Life expectancy < 1 year	3	1
Angiographic exclusion criteria:		
Small IRV (< 3.0 mm)	77	34
Diffuse sclerotic IRV	47	21
Target lesion involving a major side branch	25	11
No-reflow phenomenon or extensive thrombus throughout IRV	17	8
Left main or severe 3-vessel disease necessitating subsequent surgery	13	6
Excessive proximal vessel tortuosity	12	5
Inability to cross target lesion with a guide wire	5	2

IRV = infarct-related vessel

Results

From June 1995 to March 1997, a total of 532 patients with acute MI have been admitted to our institution, of whom, 498 patients underwent immediate coronary angiography. One patient died before angiography could be performed; while in 12 patients, involved in another trial, and in 21 patients, presenting more than 24 hours after symptom-onset, coronary angiography was not performed. From those 498 patients undergoing coronary angiography, 25 patients with a small patent

IRV were treated conservatively, and 21 with severe triple vessel disease were referred for immediate bypass surgery. The remaining 452 patients did undergo primary angioplasty. Of these, 225 were excluded from the trial for various reasons (Table 1) and 227 eligible patients were randomized to undergo primary stenting (n=112) or balloon angioplasty (n=115). Most of randomized patients, 89 (79%) in the stent group and 92 (80%) in the balloon angioplasty group, were recruited in the trial after the protocol amendment and the modified post-stenting regimen was adopted. The baseline characteristics and in-hospital outcome are listed in Table 2, and are compared to those excluded from the trial.

Table 2.

Baseline characteristics and in-hospital events

	Randomized			
	Stent		Balloon	Excluded
	(n = 112)	P-value	(n = 115)	(n=225)
Age (yr)	59 ± 11	ns	57 ± 11	60 ± 12
Male	93 (83%)	ns	98 (85%)	173 (77%)
Previous infarction	15 (13%)	ns	15 (13%)	40 (18%)
Previous bypass surgery/angioplasty	17 (15%)	ns	13 (11%)	21 (9%)
Multivessel disease	49 (44%)	ns	51 (44%)	138 (61%)*
Killip class 4	3 (3%)	ns	2 (2%)	15 (7%)†
Symptom-onset to admission (min)	217 ± 222	ns	211 ± 242	236 ± 228
Admission to reperfusion (min)	62 ± 82	ns	62 ± 63	74 ± 122
IRV: - Left main or vein graft	0	ns	0	4 (2%)
- Left anterior descending	66 (59%)	ns	70 (61%)	116 (52%)
- Right coronary artery	34 (30%)	ns	35 (30%)	70 (31%)
- Circumflex	12 (11%)	ns	10 (9%)	35 (16%)
Mean balloon size (mm)	3.36 ± 0.34	0.011	3.25 ± 0.28	2.97 ± 0.48*
Mean balloon/artery ratio	1.08 ± 0.12	ns	1.09 ± 0.15	-
Maximal inflation pressure (atm)	13.2 ± 2.4	0.0001	11.6 ± 2.5	-
Angiographic success	110 (98%)	ns	110 (96%)	200 (89%)†
Subacute occlusion	1 (1%)	ns	5 (4%)	14 (6%)
Cross-over (Bail-out)	2 (2%)	0.0016	15 (13%)	17 (8%)
Intra-aortic balloon pumping	17 (15%)	ns	8 (7%)	64 (28%)*
Major bleeding complication	7 (6%)	ns	3 (3%)	12 (5%)
Peak creatine-kinase (U/L)	1880 ± 1752	ns	1743 ± 1495	1634 ± 1681
Radionuclide ejection fraction (%)	44 ± 10	ns	45 ± 11	44 ± 13
Mean hospital stay (day)	5.3 ± 3.9	ns	4.8 ± 4.4	8.9 ± 9.8*
In-hospital death	2 (2%)	ns	3 (3%)	16 (7%)†
Recurrent infarction	1 (1%)	ns	5 (4%)	15 (7%)†

IRV=infarct-related vessel; P-values are between the two randomized groups;*p<0.0002 and †p<0.05 between patients randomized and those excluded from the trial;Plus-minus values are means ± standard deviations.

Subacute occlusion occurred in 5 patients allocated to balloon angioplasty: at the same day of the initial procedure in 4 and at day 9 in one. Repeat angioplasty followed by stenting was performed in all patients, but 4 had a recurrent MI. Only one stent patient had subacute occlusion and recurrent MI at day 4, and underwent bypass surgery. Quantitative angiographic results are shown in Table 3.

Table 3.

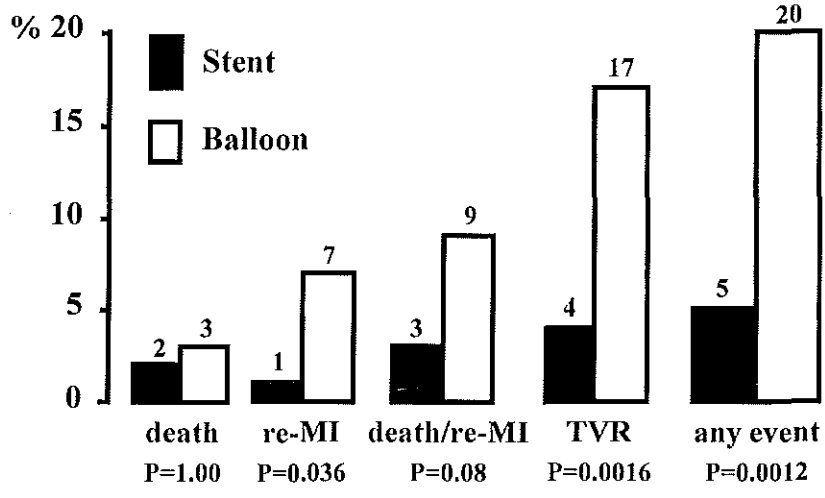
Quantitative angiographic results

		Stent (n = 112)	Balloon (n = 115)	P-value
Minimal luminal diameter (mm):	Pre	0.23 ± 0.45	0.35 ± 0.54	0.1
	Post	2.57 ± 0.37*	2.17 ± 0.45*	< 0.0001
Reference diameter (mm):	Pre	3.06 ± 0.56	3.05 ± 0.56	0.35
	Post	3.15 ± 0.46	3.14 ± 0.66	0.16
Diameter stenosis (%):	Pre	92.1 ± 15.1	88.6 ± 17.4	0.14
	Post	17.9 ± 6.8*	28.8 ± 9.1*	< 0.0001

*p < 0.0001 Post vs Pre procedure. Plus-minus values are means ± standard deviations.

Figure 1 shows the clinical outcome at 6 month. There were only 5 deaths (2%). Recurrent MI occurred in one patient after stenting and in 8 after balloon angioplasty (p=0.036). Subsequent target vessel revascularization was necessary in 4 and 19 patients, respectively (p=0.0016). Consequently, the cardiac event-free survival rate of 95% in the stent group was significantly higher than that of 80% in the balloon angioplasty group (p=0.0012).

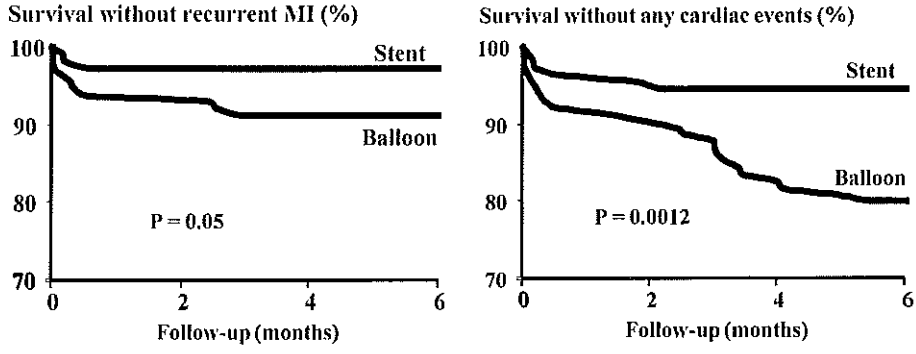
Figure 1.
Clinical outcome at 6 month in both study groups



re-MI = recurrent myocardial infarction; TVR = target vessel revascularization.

Figure 2 shows the Kaplan-Meier survival curves in both groups. No patient was lost during follow-up. Non-target vessel revascularization was performed in 6 (5%) and 4 (3%) patients, respectively.

Figure 2.



Kaplan-Meier cardiac event-free survival curves in both study groups during the 6 months follow-up period.The left panel represents patients without death or recurrent myocardial infarction (MI), and the right panel represents those without any-cardiac events (death, recurrent MI, or subsequent target vessel revascularization).

Table 4 shows the multivariate analysis of predictors of cardiac events in all patients, regardless of treatment allocation.

Table 4.

Multivariate analysis of predictors of adverse cardiac events

	Relative Risk	95% CI
Allocated to balloon angioplasty	3.2	1.2 - 8.5
Male gender	4.9	1.1 - 22.5
Age (per year)	1.03	0.99 - 1.07
Diabetes	1.4	0.3 - 6.6
Killip class >2 at admission	2.9	1.1 - 7.7
Left anterior descending artery	0.7	0.3 - 1.5
Residual minimal luminal diameter < 2mm	2.0	0.8 - 4.8
Reference diameter < 3mm	2.3	0.9 - 5.8

Cardiac event was defined as: any death, recurrent infarction, or subsequent target vessel revascularization; CI = confidence interval.

Discussion

The present trial indicates, for the first time in a prospective randomized manner, that primary stenting can be applied safely and effectively in selected patients with acute MI, resulting in a significant reduction in recurrent MI and subsequent target vessel revascularization, when compared to balloon angioplasty.

However, the major limitation of the present trial is the fact that the results were obtained from a single high-volume centre, involving a limited number of patients, and might be biased by the selection of those patients who were in relatively stable hemodynamic condition and in whom the IRV was considered to be technically and anatomically ideal for stenting. In fact, this limitation prevented at least half of patients, deemed suitable for primary angioplasty, from being

randomized. Therefore, the results may not be generalizable to all patients with acute MI. To address this limitation, in our currently on-going trial, all patients with acute MI are now randomized before coronary angiography.

Although the mortality rate (2%) was comparable to our previous trial (1), no difference could be observed between the groups. In fact, it would be unlikely that stenting could further reduce the low mortality rate achieved by balloon angioplasty. To determine the predictors of adverse events, multivariate analysis was performed by combining both study groups. Male gender, Killip class >2, and treatment with balloon angioplasty were associated with an increased risk of adverse cardiac event (Table 4). As most patients excluded from the trial had more complex coronary anatomy, multivessel disease, Killip class 4, and an intra-aortic balloon pump was more often needed, the initial success was lower when compared to the study population (Table 2). All of these may have contributed to the higher rates of death, recurrent MI, and subsequent target vessel revascularization, as well as a longer hospital stay. Despite this fact, the mortality rate in patients excluded from our study compares favorably with patients treated with thrombolytic therapy (1-3). Although the mean diameter stenosis after stenting of 17.9% seems to be relatively high for a low incidence of target vessel revascularization (4%), this is still lower than that of 22% reported in patients with stable angina (5). In addition, patients selected for this trial had a bigger vessel size, with post-stenting reference diameter of 3.15 mm, when compared to other randomized trials (4,5). Most of randomized patients (80%) were included after our post-stenting regimen was modified. This has led to less bleeding complications and a shorter hospital stay, when compared to earlier reports (4,5). In fact, all bleeding complications occurred in the beginning of our trial, before this strategy was adopted and aggressive anticoagulation was used. This protocol amendment was supported by studies reporting stenting in acute MI without conventional anticoagulation (6,7). Finally, the implications of the present study with respect to cost effectiveness require a formal analysis, which will be performed after one year of follow-up.

References

1. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-684.
2. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, Vlietstra R, Strzelecki M, Puchrowicz-Ochocki S, O'Neill WW. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-679.
3. De Boer MJ, Suryapranata H, Hoorntje JCA, Reiffers S, Liem AL, Miedema K, Hermens WTh, van den Brand MJBM, Zijlstra F. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-761.
4. Fischman DL, Leon MD, Baim D, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shaknovich A, Hirshfeld J, Bailey S, Ellis S, Rake R, Goldberg S. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501.
5. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel MA, for the Benestent Study Group. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-495.
6. Schömig A, Neumann FJ, Walter H, Schühlen H, Hadamitzky M, Zitzmann-Roth EM, Dirschinger J, Hausleiter J, Blasini R, Schmitt C, Alt E, Kastrati A. Coronary stent placement in patients with acute myocardial infarction: comparison of clinical and angiographic outcome after randomization to antiplatelet or anticoagulant therapy. J Am Coll Cardiol 1997;29:28-34.
7. Saito S, Hosokawa G, Kim K, Tanaka S, Miyake S. Primary stent implantation without coumadin in acute myocardial infarction. J Am Coll Cardiol 1996;28:74-81.
8. Antoniucci D, Valenti R, Buonamici P, Santoro GM, Leoncini M, Bolognese L, Fazzini PF. Direct angioplasty and stenting of the infarct-related artery in acute myocardial infarction. Am J Cardiol 1996;78:568-571.
9. Neumann FJ, Walter H, Richardt G, Schmitt C, Schömig A. Coronary Palmaz-Schatz stent implantation in acute myocardial infarction. Heart 1996;75:121-126.
10. Garcia-Cantu E, Spaulding C, Corcos T, Hamda KB, Roussel L, Favereau X, Guérin Y, Chalet Y, Souffrant G, Guérin F. Stent implantation in acute myocardial infarction. Am J Cardiol 1996;77:451-454.
11. Rodriguez AE, Fernandez M, Santaera O, Larribau M, Bernardi V, Castaño, Palacios IF. Coronary stenting in patients undergoing percutaneous transluminal coronary angioplasty during acute myocardial infarction. Am J Cardiol 1996;77:685-689.
12. Le May MR, Labinaz M, Beanlands RSB, Laramée LA, O'Brien ER, Marquis JF, Williams WL, Al-Sadoon K, Davies RF, Kearns SA, Johansen HL, Higginson LA. Usefulness of intracoronary stenting in acute myocardial infarction. Am J Cardiol 1996;78:148-152.
13. Steinhubl SR, Topol EJ. Stenting for acute myocardial infarction. Lancet 1997; 350: 532-33.
14. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. N Engl J Med 1996;334:1084-1089.

CHAPTER 3

Part Two

Costs of stenting for acute myocardial infarction

Arnoud WJ van 't Hof, MD; Harry Suryapranata, MD;
Menko-Jan de Boer, MD;Jan CA Hoorntje, MD and Felix Zijlstra, MD.

Hospital de Weezenlanden, Department of Cardiology
Zwolle, the Netherlands

Lancet 1998;351:1817(letter)

Sir- The role of stenting for acute myocardial infarction (AMI) has been investigated in randomised trials (1). Preliminary results seem promising, and stenting may overcome some of the limitations of primary angioplasty therapy for AMI (2). We have recently completed the initial phase of a randomised trial of stenting versus balloon angioplasty for AMI (3). On theoretical grounds, stenting may be cost-effective in various settings (4), but so far there are no published data available on the actual costs and cost-effectiveness of stenting for AMI.

Table 1.

Costs per patient (Dfl) of coronary stenting versus balloon angioplasty for acute myocardial infarction.

In-hospital costs	**Balloon** (N=115)	**Stent** (N=112)
Hospital stay	5000	5400
Angioplasties	9000	9000
Stents	365	2304
Additional balloons	104	161
IABP	196	349
Re-PTCA	500	103
CABG	157	161
Total costs	15322	17508
Follow-up at 1 year	**Balloon**	**Stent**
Re-MI	443	45
Follow-up angiogram	1739	2033
Re-PTCA	1607	412
CABG	2996	1420
Costs Follow-Up	6785	3910
Total costs at 1 year	**22107**	**21418**

re-MI=recurrent myocardial infarction, IABP=intra-aortic balloon pumping, PTCA=percutaneous coronary angioplasty, CABG=coronary bypass surgery. All costs are per patient.

We have now completed 12 months follow-up in our randomised trial, including initial in-hospital and follow-up costs. We calculated costs by counting the numbers of hospital days and procedures, as previously described (5). Results are shown in the table. Our data show that, at least in the setting of a Dutch (non-academic) hospital with an existing infrastructure for angioplasty and stenting, there is no difference in costs after 1 year between balloon angioplasty and stenting for AMI. Although the initial in-hospital costs of stenting are higher, this is compensated by the lower costs during follow-up which makes stenting a good investment.

References

1. Steinhubl SR, Topol EJ. Stenting for acute myocardial infarction. Lancet 1997;350:532-33.
2. 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; 278:2093-98.
3. Suryapranata H, van 't Hof AWJ, Hoorntje JCA, de Boer MJ, Zijlstra F. A randomized comparison of primary stenting with primary balloon angioplasty in acute myocardial infarction. Circulation, in press.
4. 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.
5. Zijlstra F, de Boer MJ, Beukema WP, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. Eur Heart J 1996;17:382-87.

CHAPTER 3

Part Three

A Randomised Comparison of Intra-Aortic Balloon Pumping after Primary Coronary Angioplasty in High Risk Patients with Acute Myocardial Infarction

AWJ van 't Hof, MD; AL Liem, MD; MJ de Boer, MD;
JCA Hoorntje, MD; H Suryapranata, MD; F Zijlstra, MD.

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

Submitted for publication

Summary

Aims. Intra-aortic balloon pumping (IABP) reduces afterload and may be effective in improving reperfusion in high risk infarct patients treated with primary angioplasty.

Methods. High risk infarct patients referred from other centres for primary PTCA were randomised to treatment with or without IABP. The primary end point consisted of the combination of death, non-fatal re-infarction, stroke or an ejection fraction < 30% at 6 month follow-up. A weighted unsatisfactory outcome score (as previously described by Braunwald), enzymatic infarct size and left ventricular ejection fraction were secondary end points.

Results. During a 3.5 year period, 238 patients were randomised, 118 to IABP therapy and 120 to no IABP therapy. Major complications occurred in 8% of patients who were treated with IABP. None of the outcome measures were significantly different between the treatment groups.

Conclusion. Systematic use of intra-aortic balloon pumping after primary angioplasty does not lead to myocardial salvage or to a better clinical outcome in high risk infarct patients. Use of intra-aortic balloon pumping after primary PTCA for acute myocardial infarction should be reserved for patients with severe hemodynamic compromise.

(Submitted for publication)

Introduction

Primary angioplasty has been shown to be an effective reperfusion strategy for patients with evolving myocardial infarction (1,2). TIMI 3 flow of the infarct-related vessel is obtained in the large majority of patients and the reocclusion rate is low compared to patients treated with thrombolytic therapy (3). However, in a substantial minority of patients ST-segment elevation persists after primary angioplasty, despite restored flow of the infarct-related epicardial vessel, suggesting impaired myocardial reflow (4). This occurs especially in patients with large anterior infarction, and in other high risk patients. Intra-aortic balloon pumping results in afterload reduction and an increase in diastolic coronary flow (5). Therefore, its use in the setting of acute myocardial infarction might be beneficial. Previous reports showed that intra-aortic balloon pumping after reperfusion therapy prevented reocclusion of the infarct vessel. However, it did not affect left ventricular function, and did not prevent hemodynamic deterioration (6-8). We conducted a randomised trial to evaluate the value of systematic use of intra-aortic balloon pumping in high risk myocardial infarct patients treated with primary coronary angioplasty.

Methods

Randomisation and stratification

All high risk patients who were transferred to the Weezenlanden hospital for treatment with primary or rescue angioplasty were considered for entry into the study. Specific inclusion criteria were: 1) arrival in the hospital within 3 hours after start of symptoms, 2) age younger than 70 years, 3) anterior infarct location or non-anterior infarction with cumulative ST-segment deviation of more than 20 mm. Patients were randomised prior to angiography and angioplasty and were allocated to either intra-aortic balloon pumping or no intra-aortic balloon pumping. For patients who were allocated to standard treatment but who had signs of cardiogenic shock (pulmonary wedge pressure > 18 mm Hg, systolic hypotension < 90 mm Hg and/or mixed venous blood oxygen saturation < 65%), cross-over to balloon pumping was prespecified.

Coronary angiography and coronary angioplasty

All patients were treated with 300 mg intravenous acetylsalicylic acid and intravenous nitroglycerin in a dose to maintain a systolic blood pressure of around 110 mm Hg. Intravenous heparin was given in a bolus of 10000 U and thereafter in a continuous infusion in a dosage to keep the activated partial thromboplastin time between 2 and 3 times the normal value for at least 2 days. Coronary angiography and angioplasty was performed using standard techniques. Flow through the infarct-related vessel was scored according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Data of the coronary angiography and angioplasty procedures were collected and graded by two of the investigators. Consensus on collateral flow, procedural success, TIMI flow before and after the angioplasty procedure, identification of the infarct-related vessel, and extent of coronary artery disease was reached in all cases. TIMI flow before angioplasty was judged at first injection of contrast agent.

Definitions

Successful PTCA was defined as a visually assessed <50% residual stenosis and TIMI grade 3 flow. Recurrent myocardial infarction was defined as chest pain, changes in the ST-T segment at rest, and a second increase in the creati-ne kinase level to more than two times the upper limit of normal, or an increase of more than 200 U per litre over the previous value if the level had not dropped below the upper limit of normal. Major bleeding was defined as requirement of blood transfusion during hospitalisation. Heart failure was defined as Killip class 2 to 4 heart failure.

Intra-aortic balloon pumping

The intra-aortic balloon pump (Datascope) was inserted via the femoral route after replacement of the 7 or 8 French sheath, used for angiography or PTCA, by a 12 French sheath. Aortic counterpulsation was continued for 48 hours. In case of limb ischemia or major hemorrhage at the access site the IABP was removed earlier.

Statistical analysis

The primary end point was defined as the combined incidence of death, reinfarction, stroke or an ejection fraction less than 30% at 6 months follow-up. The trial was designed to detect a reduction in the primary end point from 30% to 15%. With 80% power and a=.05 it was estimated that 266 patients were required. Differences between group means were tested by a two-tailed Student t test. A chi-square method was used to test differences between proportions. The Fisher exact test was used if there was an expected cell value < 5. Statistical significance was defined as a P value < 0.05. In the presentation of the data, continuous variables are given as mean value ± SD, whereas discrete variables are given as absolute values and percentages. Analysis was performed on an intention-to-treat basis. A secondary end point was the weighted unsatisfactory outcome score of different clinical and angiographic end points, previously described by Braunwald (9). Each patient is assigned a score that represents the single most serious outcome. This score included death, stroke, heart failure, ejection fraction <30%, reinfarction, reocclusion of the infarct related vessel, or major hemorrhage. Additional secondary endpoints were enzymatic infarct size and left ventricular ejection fraction at 6 month follow-up.

Enzymatic Infarct Size

The methodology for estimation of infarct size has been described previously (10). In brief, infarct size was estimated by measurements of enzyme activities using lactate dehydrogenase (LDH) as the reference enzyme. Cumulative enzyme release from five to seven serial measurements up to 72 hours after symptom onset (LDHQ72) was calculated. A two-compartment model was used, which has been validated in several studies on the turnover of radio-labelled plasma proteins and circulating enzymes (11).

Left Ventricular Function

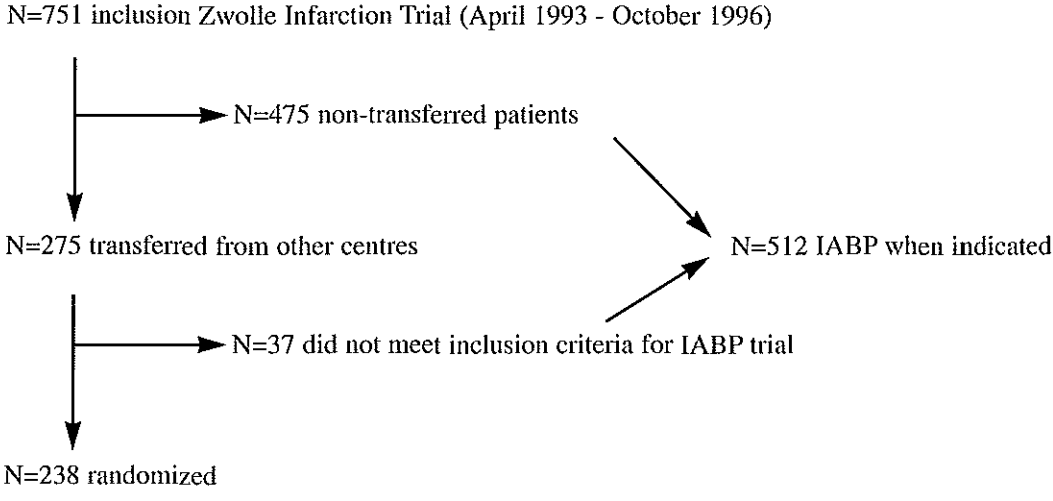
Left ventricular ejection fraction was measu-red with a radio-nuclide technique at 6 month follow-up. The technique used in our hospital has been des-cri-bed previ-ously (4). Briefly, it involved the multiple-gated equilibrium method after the labelling of red blood cells with (99mTc) pertechnetate. A gamma camera (General Electric, Milwaukee) with a low-energy, all purpose, parallel-hole collimator was used. The global ejection fraction is calculated automatically by computer (Star View, General-Electric), with the PAGE ™ program. The data on ejection fractions were gathered by a specialist in nuclear medicine, who was blinded to the clinical data.

Results

In October 1996, after evaluation of the in-hospital results of 238 included patients, the trial was stopped. Our results, in combination with the results of a similar randomised trial (12), made it very unlikely that a clinically relevant difference would be obtained in favourr of intra-aortic balloon pumping. Patient recruitment for the trial is described in Figure 1.

Figure 1.

Flow chart



Between April 1993 and October 1996, 751 patients were candidates for performing primary angioplasty according to the inclusion criteria of the Zwolle Infarction Trial (1). Two hundred and seventy-five patients (37%) were transferred from other centres. From these, 37 patients (13%) did not meet inclusion criteria for entry into the IABP trial. These patients had non-anterior infarctions and less than 20 mm of cumulative ST segment elevation and were transferred because of contra-indication(s) for thrombolytic therapy. The remaining 238 patients form the basis of this report.

Table 1.

Baseline and angiographic characteristics

	IABP (N=118)	P value	No IABP (N=120)
Age	59±10	0.04	56±11
Male gender	99 (84%)	0.95	101 (84%)
Anterior infarction	102 (86%)	0.96	104 (87%)
Killip class			
1	88 (75%)		90 (75%)
2	16 (14%)		15 (13%)
3	5 (4%)		5 (4%)
4	9 (8%)	0.89	10 (8%)
Diabetes	12 (10%)	0.47	9 (8%)
Previous infarction	17 (14%)	0.81	16 (13%)
Multi vessel disease	70 (59%)	0.35	64 (53%)
IRV			
LAD	100 (85%)		99 (83%)
CX	3 (2%)		4 (3%)
RCA	12 (10%)		15 (13%)
graft	1 (1%)		1 (1%)
Left Main	2 (2%)	0.82	1 (1%)
Primary CABG	3 (3%)		7 (6%)
Conservative therapy	4 (3%)		9 (8%)
Rescue angioplasty	16 (14%)		23 (19%)
Primary angioplasty	95 (81%)	0.15	81 (68%)
Successful angioplasty	103 (87%)	0.61	102 (85%)

IABP = Intraaortic balloon pump, IRV = Infarct related vessel, LAD = Left anterior descending artery, CX = Circumflex artery, RCA = Right coronary artery, CABG = Coronary artery bypass surgery, TIMI = Thrombolysis In Myocardial Infarction

One hundred and eighteen patients were allocated to IABP and 120 to standard therapy. The baseline clinical and angiographic characteristics are described in Table 1 and were not different between the 2 groups, apart from a higher age of patients in the IABP group. Fifty patients (21%) had received previous thrombolytic therapy in the referring hospital. After immediate angiography 13 patients (5%) were treated conservatively because of non-significant stenosis of the infarct related vessel and TIMI 3 flow. Ten patients (4%) underwent primary coronary bypass surgery because of significant left main disease or severe triple vessel disease. Cross-over occurred in both treatment arms. In the no-IABP group, 37 patients (31%) did receive an IABP. Fourteen patients had severe left main or 3-vessel disease, 2 patients had inadequate reflow after angioplasty, and in 21 patients hemodynamic instability was the reason for cross-over. In the

group assigned to IABP 30 patients (25%) did not receive an IABP, because of peripheral vessel disease (8), IABP device unavailability (9), patient refusal (2), physician preference (4), or relative contraindications for the device (7).
The primary end point, the combination of death, recurrent myocardial infarction, stroke or an ejection fraction less than 40% at 6 month follow-up, occurred in 31 (26%) patients assigned to IABP and in 31 (26%) patients assigned to the no-IABP group (p=0.94)(Table 2). Calculation of LDHQ72 was performed in 163 (68%) patients and was not significantly different between both groups. The left ventricular ejection fraction was measured at discharge in 127 (53%) patients and at 6 months follow-up in 168 patients (80% of patients alive). No difference in ejection fraction was found in both groups of patients.

Table 2.

Enzymatic infarct size, left ventricular function and clinical outcome

	IABP (N=118)	P value	No IABP (N=120)
IABP	89 (75%)		37 (31%)
LDHQ72 (N=163)	1616 (1148)	0.96	1608 (1163)
EF pre discharge (N=127)	39 (12)	0.21	36 (13)
EF Follow Up (N=168)	42 (13)	0.51	40 (14)
re-PTCA	24 (20%	0.70	22 (18%)
CABG	17 (14%)	0.63	20 (17%)
re-MI	7 (6%)	0.16	3 (3%)
stroke	1 (1%)	1.00	1 (1%)
major bleeding*	10 (8%)	0.78	9 (8%)
heart failure	10 (8%)	0.41	14 (12%)
death	12 (10%)	0.47	9 (8%)
primary end point**	31 (26%)	0.94	31 (26%)
WUO-score=	0.23 (0.36)	0.79	0.24 (0.36)

IABP = Intra-aortic balloon pump, LDHQ72 = Enzymatic infarct size, calculated as release of Lactate Dehydrogenase in 72 hours, EF = Ejection Fraction, PTCA = Percutaneous transluminal coronary angioplasty, CABG = Coronary artery bypass grafting, MI = Myocardial infarction, IRV = Infarct related vessel, *bleeding during admission requiring transfusion, ** combination of death, non-fatal reinfarction, stroke or an ejction fraction<30% at 6 months follow-up. =WUO: Weighted Unsatisfactory Outcome score as defined by Braunwald (9)

The results of the weighted unsatisfactory-outcome score are described in Table 3. Patients assigned to IABP had a score of 0.23 (0.36). This was 0.24 (0.36) for patients assigned to the no-IABP group (p=0.79).

Table 3.

Weighted Unsatisfactory-Outcome end point, 6 months after randomization

Event	Score	IABP (N=118)	No IABP (N=120)
1. Death	1.0	12	9
2. Intracranial hemorrhage with severe permanent nuerological deficit	1.0	1	0
3. Development of severe, sustained CHF or cardiogenic shock	0.8	2	10
4. Ejection fraction < 30% *	0.6	16	13
5. Reinfarction	0.5	2	2
6. Occlusion or reocclusion of IRV at FU angiography	0.4	1	2
7. Major hemorrhage requiring blood transfusion or intracranial hemorrhage without severe or permanent neurological deficit	0.3	3	4
None of the above	0.0	81	80

IABP = Intra-Aortic Balloon Pumping, CHF = Congestive Heart Failure, IRV = Infarct Related Vessel, FU = Follow Up, * determined by radionuclide technique at 6 months follow-up. The mean score of IABP assigned patients was 0.23 (0.36). The mean score of patients not assigned to IABP was 0.24 (0.36), p=0.79.

Complications of IABP

A total of 126 patients were treated with intra-aortic balloon pumping. The mean duration of intra-aortic balloon pumping was 56 hours (range 14-216). Serious complications occurred in 10 patients (8%). In 4 patients the device had to be removed within 48 hours because of limb ischemia or hemorrhagic complications. Another 2 patients developed a large groin hematoma after removal of the sheath for which surgical intervention was necessary. Four patients had symptoms of infection at 52, 96, 126 and 192 hours (with positive tip and blood cultures) for which the device was removed.

Discussion

In this study frequent use of intra-aortic balloon pumping in high risk myocardial infarct patients (70% of patients) did not lead to salvage of myocardium or to a better clinical outcome when compared to elective use in 30% of patients. Enzymatic infarct size and left ventricular ejection fraction did not differ between both patient groups. Only patients, in whom the time between onset of symptoms and arrival in our hospital was less than 3 hours, were included, because it was hypothesised that insertion of an IABP might lead to myocardial salvage in this group of high risk infarct patients who presented early. However, this was not found. Although a number of other studies have addressed the value of intra-aortic balloon pumping in high risk infarct patients, no improvement in clinical outcome has consistently been found. Most of these studies were non-randomised (5-8), however. Two randomised trials have been published. One study in 182 consecutive infarct patients, found a higher patency rate of the infarct-related vessel in the IABP group at 5- to 10-day follow-up angiography (92% vs 79% TIMI 2/3 flow, $p<0.05$), toget-

her with a significant reduction in the composite clinical end point of death, stroke, reinfarction, recurrent ischemia or repeat revascularization (13). A recent study showed that only thrombolytic treated patients benefit from intra-aortic balloon pumping, compared to patients treated with primary angioplasty (14). As the study of Ohman et al (13) mainly included patients who had undergone rescue PTCA for failed thrombolysis, this may be the explanation for the beneficial results for patients allocated to IABP therapy in this study. A more recently conducted randomised trial, comprising 437 high risk patients, all treated with primary coronary angioplasty, did not find a reduction in the primary end point of death, stroke, recurrent infarction, reocclusion or heart failure (15). The current trial confirmed these results and found no benefit of prophylactic intra-aortic balloon pumping after primary angioplasty for acute myocardial infarction in high risk patients. The primary end point was not different between patients allocated and not allocated to the device. Moreover 8% of patients had complications due to the insertion of the IABP. This complication rate is lower compared to a report of 1993 from our group, in which serious complications occurred in 16% of 200 consecutive patients treated with IABP (16). However, these patients had different clinical characteristics.
During the study period, 512 patients were not eligible for the study (Figure 1). From these, 95 patients (21%) were treated with intra-aortic balloon pumping because of severe left main or triple vessel disease, failed reperfusion or cardiogenic shock. Baseline characteristics and outcome are described in Table 4.

Table 4.

Comparison of baseline characteristics and outcome of patients who received an intra-aortic balloon pump on indication compared to patients randomised to IABP.

	IABP on indication (N=95)	P value	Randomized to IABP (N=118)
Age	61 (11)	0.14	59 (10)
Male gender	74 (78%)	0.26	99 (84%)
Multi vessel disease	66 (69%)	0.13	70 (59%)
Anterior infarction	52 (55%)	<0.0001	102 (86%)
Killip class 1	56 (59%)	0.02	88 (75%)
Open IRV before A	3 (3%)	0.003	18 (15%)
Primary angioplasty	80 (84%)	0.48	95 (81%)
TIMI 3 flow	78 (80%)	0.19	103 (87%)
re-PTCA	11 (12%)	0.09	24 (20%)
CABG	30 (32%)	0.003	17 (14%)
re-MI	4 (4%)	0.57	7 (6%)
stroke	1 (1%)	0.88	1 (1%)
major bleeding*	15 (16%)	0.10	10 (8%)
death	12 (13%)	0.57	12 (10%)

IRV = Infarct related vessel , A = Angioplasty, LDHQ72 = Enzymatic infarct size, calculated as release of Lactate Dehydrogenase in 72 hours, EF = Ejection Fraction, PTCA = Percutaneous transluminal coronary angioplasty, CABG = Coronary artery bypass grafting, MI = Myocardial infarction, *bleeding during admission requiring transfusion

The patients who received an IABP after the angioplasty procedure on indication, were of a higher risk category compared to the patients who were part of the randomised trial (systematic IABP use based on clinical high risk criteria): they were older, were in a higher Killip class on admission, less often had a successful angioplasty procedure and had a higher rate of bleeding complications. Despite this, mortality at 6 months follow-up (13%) was not significantly higher and compares favourable to previous reports in similar patients, with mortality rates of 15% and 40% (8,14,17). This low mortality might be attributed to the intra-aortic balloon pump, which has been shown to be of value in patients with cardiogenic shock (15), but might also be related to the high rate of repeat revascularization within 6 months. In 49% of IABP treated patients (41/83 patients alive) a second revascularization procedure was performed within 6 months, either a re-PTCA because of restenosis or an additional revascularization becuase of severe triple vessel disease and inducible ischemia.

Limitations

The main limitation of this randomised study is the fact that in a substantial minority (25%) of patients assigned to IABP therapy, the device was not inserted. This might be related to the fact that randomisation was done prior to angiography and therefore the operator was not informed about the coronary and peripheral vessel status of the patient. Also it shows that in clinical practice, a number of patients, in which an intra-aortic balloon pump is indicated on hemodynamic grounds, might not receive the device, mainly because of peripheral vessel disease and device unavailability.

The older age in the patients allocated to IABP therapy may underestimate the effect of IABP therapy, however, it is unlikely that this influenced outcome in a significant manner.

This study was designed to include 266 patients. After inclusion of 90% of the patients, the study was stopped. However, it is unlikely that the primary or secondary end point would be beneficial for IABP treated patients after inclusion of all 266 patients.

Conclusion

The systematic use of intra-aortic balloon pumping after primary angioplasty for acute myocardial infarction in high risk patients does not affect infarct size or left ventricular function and does not lead to a better clinical outcome when compared to elective use of the IABP.

The use of an intra-aortic balloon pump in patients after primary angioplasty should be reserved for patients with hemodynamic instability.

References

1. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coro-nary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
2. The Global Use of Strategies to Open Occluded coronary arteries in Acute Coronary Syndromes (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;336:1621-8.
3. de Boer MJ, Reiber JH, Suryapranata H, van den Brand MJ, Hoorntje, Zijlstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16:1347-55.
4. van 't Hof AWJ, Liem AL, de Boer MJ, Zijlstra F, for the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-619.
5. Kern MJ, Acuirre F, Bach R, Donohue T, Siegel R, Segal J. Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. Circulation 1993;87:500-511.
6. Ishihara M, Sato H, Tateishi H, Uchida T, Dote K. Intraaortic balloon pumping as the postangioplasty strategy in acute myocardial infarction. Am Heart J 1991;122:385-9.
7. Kono T, Morita H, Nishina T, et al. Aortic counterpulsation may improve late patency of the occluded coronary artery in patients with early failure of thrombolytic therapy. J Am Coll Cardiol 1996;28:876-81.
8. Ohman EM, Califf RM, George B, et al. The use of intraaortic balloon pumping as an adjunct to reperfusion therapy in acute myocardial infarction. Am Heart J 1991;121:895-901.
9. Braunwald E, Cannon CP, McCabe CH. An approach to evaluating thrombolytic therapy in acute myocardial infarction. The "unsatisfactory outcome " end point. Circulation 1992;86:683-687.
10. van der Laarse A, Hermens WT, Hollaar L, et al. Assessment of myocardial damage in patients with acute myocardial infarction by serial measurement of serum a-hydroxybutyrate dehydrogenase levels. Am Heart J 1984;107:248-260.
11. Hermens WT, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size. Lancet 1992;340:1297 (Letter).
12. Grines CL, Brodie BR, Griffin JJ, et al. Prophylactic intraaortic balloon pumping for acute myocardial infarction does not improve left ventricular function. J Am Coll Cardiol 1996;27 (suppl A):167.
13. Ohman ME, George B, White CJ, et al. Use of aortic counterpulation to improve sustained coronary patency during acute myocardial infarction. Circulation 1994;90:792-799.
14. Barron HV, Pirzada SR, Lomnitz DJ, Every NR, Gore JM, Chou TM. Use of intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock. J Am Coll Cardiol 1998;31:135A.
15. Stone GW, Marsalese D, Brodie BR, et al. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1997;29;1459-67.
16. Ottervanger JP, Steendijk CB, Zijlstra F, de Boer MJ, Hoorntje JCA. Complications of intra-aortic balloon pumping in 200 consecutive patients. Neth J Cardiol 1993;1:32-35.
17. Kovack, PJ, Rasak MA, Bates ER, Ohman EM, Stomel RJ. Thrombolysis plus aortic counterpulsation: improved survival in patients who present to community hospitals with cardiogenic shock. J Am Coll Cardiol 1997;29:1454-8.

CHAPTER 4

Part One

A Randomized Comparision of Primary Coronary Angioplasty with Thrombolytic Therapy in Low Risk patients with an Acute Myocardial Infarction

Felix Zijlstra, MD (1), Willem P. Beukema, MD (1),
Arnoud W.J. van 't Hof, MD (1), Aylee Liem, MD (1),
Stoffer Reiffers, PhD (2), Jan C.A. Hoorntje, MD (1),
Harry Suryapranata, MD (1), Menko-Jan de Boer, MD (1).

Department of Cardiology (1) and Department of Nuclear Medicine (2)
Hospital De Weezenlanden, Zwolle, the Netherlands

This work was partly supported by grant 1992:321 of the Netherlands Heart Foundation.

J Am Coll Cardiol 1997;29:908-12

Summary

Objectives. We sought to compare primary coronary angioplasty and thrombolysis as treatment for low risk patients with an acute myocardial infarction.

Background. Primary coronary angioplasty is the most effective reperfusion therapy for patients with acute myocardial infarction; however, intravenous thrombolysis is easier to apply, more widely available and possible more appropriate in low risk patients.

Methods. We stratified 240 patients with acute myocardial infarction at admission according to risk. Low risk patients (n=95) were randomized to primary angioplasty or thrombolytic therapy. The primary end point was death, nonfatal stroke or reinfarction during 6 months of follow-up. Left ventricular ejection fraction and medical charges were secondary end points. High risk patients (n=145) were treated with primary angioplasty.

Results. In low risk patients, the incidence of the primary clinical end point (4% vs. 20%, $p < 0.02$) was lower in the group with primary coronary angioplasty than in the group with thrombolysis, because of a higher rate of reinfarction in the latter group. Mortality and stroke rates were low in both treatment groups. There were no differences in left ventricular ejection fraction or total medical charges. High risk patients had a 14% incidence rate of the primary clinical end point.

Conclusions. Simple clinical data can be used to risk-stratify patients during the initial admission for myocardial infarction. Even in low risk patients, primary coronary angioplasty results in a better clinical outcome at 6 months than does thrombolysis and does not increase total medical charges.

(J Am Coll Cardiol 1997;29:908-12)

Introduction

Primary angioplasty, defined as angioplasty for acute myocardial infarction without prior or concomitant thrombolytic therapy, results in a higher patency rate of the infarct-related vessel, smaller enzymatic infarct size, better preserved left ventricular function and better clinical outcome when compared with intravenous thrombolytic therapy (1-4). However, the logistic burden of offering primary angioplasty to all patients with acute myocardial infarction is considerable (5-12). Previous studies (1,7,13) have shown that the increased benefit of primary angioplasty over that of thrombolytic therapy has been found in particular in high risk patients but is less certain in low risk patients. Therefore, we randomized patients at low risk to thrombolytic therapy or primary angioplasty. Several retrospective analyses (1,7,14-17) have shown that simple clinical and electrocardiographic (ECG) variables, assessed during initial presentation, can be used to stratify patients with acute myocardial infarction according to risk. We describe the clinical outcome and cost-effectiveness of primary angioplasty versus thrombolysis in low risk patients and compare these findings with those in a concomitant series of patients at high risk of untoward events.

Methods

Study patients: Inclusion criteria were symptoms of myocardial infarction for > 30 min, within 6 h of symptom onset or between 6 and 24 h if there were signs and symptoms of ongoing ischemia with > 0.1 mV ST segment elevation in more than two leads. No specific exclusion criteria were used. Only patients with a life expectancy of < 6 months or conditions resulting in severe impairment of quality of life were excluded. Oral informed consent was obtained from all patients. The trial was approved by the committee on ethics and research at our institute. During the enrollment period, 17 patients who fulfilled the entry criteria did not participate in the study because of patient refusal or preference of the patient or physician, or both, for a specific therapy. Sample size: Assuming an incidence rate of death and nonfatal stroke of 3% and nonfatal reinfarction of 12% after 6 months of follow-up (17-22) for low risk patients treated with thrombolytic therapy, and a 0.4 relative risk of the primary clinical end point (death, nonfatal stroke or reinfarction), a sample size of 296 low risk patients was calculated (one-sided alpha level of 0.05, and a power of 80%), with an expected total of > 500 patients in the trial. Interim analysis was planned after inclusion of 150 patients.

Statistical analysis

All end points were analyzed according to the intention to treat principle. Results are expressed as absolute numbers and mean values + SD. Differences between group means were tested by unpaired Student's t-test. A chi-square method or Fisher exact test was used to test differences between proportions. Statistical significance was defined as a p value < 0.05.

Randomization and stratification

Between May 1993 and April 1995, 240 patients were considered for this trial. All patients were classified as at high or low risk. Patients were regarded as at high risk if one of the following criteria were present: 1. contraindications for thrombolytic therapy (14,16), 2. Killip class > 2 (1,13), 3. ECG evidence of anterior wall infarction or evidence of extensive nonanterior infarction defined as eight or more leads with > 0.1 mVolt ST elevation or depression. or both (1,13,17). All high risk patients underwent immediate coronary angiography and were treated with primary angioplasty if the coronary anatomy was suitable. The low risk patients were randomly allocated by telephone to either primary angioplasty or intravenous streptokinase, after they gave informed consent.

Treatment

All patients received heparin intravenously and aspirin. Beta-adrenergic blocking agents were given unless contraindicated. All patients with clinical signs of heart failure or a left ventricular ejection fraction < 40% received angiotensin-converting enzyme inhibitors. Angioplasty was performed by standard techniques. Angioplasty success was defined as a residual lesion of < 50% in the infarct-related vessel, with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Thrombolytic therapy consisted of 1.5 million IU of streptokinase. Patients given thrombolytic therapy had coronary angiography between day 3 and day 7, or immediately if symptoms and signs of recurrent ischemia appeared. Patients treated with primary angioplasty underwent follow-up coronary angiography 3 and 6 months after angioplasty. Additional revascularization procedures were performed for left main and extensive triple-vessel coronary artery disease depending on coronary anatomy. In patients with less extensive coronary artery disease, revascularization during follow-up depended on angina and noninvasive evidence of myocardial ischemia.

Primary end point

This was defined as death, nonfatal stroke or reinfarction at 6 months. All patients with possible or suspected stroke were reviewed by a neurologist and underwent a computed tomography scan. Reinfarction was defined as a second episode of chest pain of > 30 min with a second creatine kinase (CK) rise to more than two times the upper limit of normal, or an increase of > 200 U/liter over the previous value if the level had not dropped below the upper limit of normal, and either concomitant ST-T wave changes or new Q-waves (3).

Secondary end points

The two secondary end points were left ventricular ejection fraction and total medical charges at 6 months. 1. Left ventricular ejection fraction was measured with a radionuclide technique at day 5 and at 6 months. The multigated equilibrium method was used after in vivo labeling of red cells with 99m-Tc-pertechnetate (3) using a gamma camera (General Electric) with a low energy, all purpose, parallel-hole collimator. Global ejection fraction was calculated automatically by computer (Star View, General Electric) with the PAGE™ program. The data on ejection fraction were analyzed by a nuclear medicine specialist who had no knowledge of the clinical data.
2. Total medical charges at 6 months were calculated by using estimates of unit costs concerning all aspects of medical care, as previous described (23-25). In the Dutch medical system the patient pays the charges of the hospital and those of independent physicians and the pharmacy; health insurance covers almost all of these expenses. Charges were considered from the perspective of the patient. This methodology has been described (25).

Results

After complete evaluation of the first 150 patients (26), and after consultation with the institute's committee on ethics and research, a decision was made to stop the trial. Of these 150 patients, 73 were at low risk and were randomized to primary angioplasty or streptokinase. The interim results indicated that primary coronary angioplasty in low risk patients facilitated early discharge and did not result in higher medical charges (27). Subsequently, a general policy of primary coronary angioplasty was adopted. At completion of the trial a total of 240 patients had been enrolled.

Table 1.

Baseline Clinical and Angiographic Characteristics

	Low Risk Group (n = 95)		High Risk Group
	Angioplasty (n=45)	Thrombolysis (n=50)	(n = 145)
Age (years)	63+11	59+12	62+12
Male	80%	74%	74%
Previous MI	18%	20%	15%
Anterior MI	0%	0%	63%
Killip class > 2	0%	0%	28%
C.I. for thrombolysis	0%	0%	8%
Infarct related vessel			
LMCA	0%	0%	3%
LAD	0%	0%	54%
RCA	85%	92%	30%
LCx	13%	8%	10%
Graft	2%	0%	2%
Multivessel disease	71%	50%	57%

C.I. = contraindications, multivessel disease was defined as at least one 50% lesion in a major noninfarct-related coronary artery. Data are presented as mean value + SD or percent of patients. LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; LMCA=left main coronary artery; MI=myocardial infarction; RCA=right coronary artery.

Baseline clinical and angiographic characteristics are shown in Table 1. In the low risk group randomized to angioplasty the proportion of patients with multivessel disease was higher than in the thrombolysis group; otherwise, the patient groups were well matched. The design of the trial resulted in a high proportion of low risk patients with the right coronary artery as the infarct-related vessel, whereas the left anterior descending coronary artery was usually the infarct-related vessel in the high risk patients.

Of the total of 240 patients, 95 (39%) were considered at low risk; 50 of the 95 patients were randomized to thrombolytic therapy and received this treatment. The time from hospital admission to start of the streptokinase infusion was 29±17 min. Forty-five patients were randomized to primary coronary angioplasty, and all underwent immediate coronary angiography that was followed by primary angioplasty in 92% with procedural success in 93%. The time from hospital admission to the first balloon inflation was 68±21 min. In three patients a conservative initial strategy was followed as spontaneous reperfusion of the infarct-related vessel was evident on the angiogram; one patient with left main coronary artery disease had emergency coronary artery bypass grafting. During the 6-month follow-up period, 13% of the low risk patients underwent bypass grafting for triple- vessel or left main coronary artery disease.

Of the total of 240 patients, 145 (61%) had one or more of the high risk characteristics. High risk patients with one high risk characteristic (n=111) had a 10% incidence of the primary clinical

end point; those with more than one high risk characteristic (n=34) had a 29% incidence. Additional revascularization procedures and clinical outcome at 6 months are shown in Table 2.

Table 2.
Results at 6 months

	Low Risk Group (n = 95)			High Risk Group
	Angioplasty (n=45)	Thrombolysis p-value*	(n=50)	(n = 145)
Revascularization Procedures				
CABG	6 (13%)	1	7 (14%)	23 (16%)
(re)PTCA	9 (20%)	<0.001	30 (60)%	20 (14%)
Clinical Outcome				
Death	1 (2%)	0.47	0 (0%)	16 (11%)
Stroke	1 (2%)	1	2 (4%)	0 (0%)
Reinfarction	0 (0%)	<0.01	8 (16%)	4 (3%)
Primary End point**	2 (4%)	<0.02	10 (20%)	20 (14%)

*Comparing the angioplasty and thrombolysis low risk group. **Defined as death, nonfatal stroke or reinfarction within 6 months. Data are presented as number (%) of patients. CABG=coronary artery bypass grafting; (re)PTCA= initial or repeat percutaneous transluminal coronary angioplasty.

Primary end point: The primary end point of death, nonfatal stroke or reinfarction was reached in 4% of low risk patients randomized to angioplasty in contrast to 20% in low risk patients randomized to thrombolytic therapy (relative risk 0.19, 95% confidence interval 0.04-0.90, $p < 0.02$). Only one low risk patient (1%) died from cardiac rupture (at the age of 75 years, 5 days after failed primary coronary angioplasty). Three patients had an ischemic stroke, 5, 7 and 14 days, respectively, after the acute event, and none of these strokes were related to the initial therapy. There were no strokes due to intracerebral hemorrhage. Eight of the low risk patients randomized to streptokinase had a reinfarction. All of these patients were readmitted to the coronary care unit, had ST-T abnormalities and CK elevation, and six of these eight had new Q waves. Five of the eight reinfarctions occurred within the 1st week after randomization. There were no reinfarctions in low risk patients randomized to primary angioplasty. The incidence of the primary clinical end point is lower in high risk patients treated with primary angioplasty (14%) than in the low risk patients assigned to thrombolysis, primarily because of a lower reinfarction rate in the high risk group.

Secondary end points: Left ventricular ejection fraction was measured in 93 (98%) of the 95 low risk patients and in 116 (80%) of the 145 high risk patients. At 6 months left ventricular ejection fraction in the low risk angioplasty group was $51\pm9\%$ and $48\pm10\%$ in the thrombolysis group ($p=0.11$). It was lower in the high risk group ($43\pm11\%$).

Total medical charges at 6 months were lower in the low than in the high risk group. There was

no difference in total charges/patient or total charges/survivor between the two low risk groups, although the charges/ event-free survivor were lower in the angioplasty group (Table 3).

Table 3.
Total Medical Charges in Dutch Guilders

	Low Risk Group (n = 95)		High Risk Group
	Angioplasty (n=45)	Thrombolysis (n=50)	(n = 145)
All patients	22.808	22.437	29.467
Survivors	23.327	22.895	33.122
Event-free survivors	23.869	28.765	34.182

Charges were calculated as previously described (23-25).

Discussion

Previous studies (1-7) have shown that primary coronary angioplasty offers certain advantages over thrombolytic therapy. High risk patients treated with primary angioplasty have a lower mortality rate and a lower risk of intracranial hemorrhage. Our study shows that low risk patients benefit in terms of a lower risk of reinfarction, without an increase in total medical charges. During long-term follow-up, nonfatal reinfarction has been shown (28) to have independent prognostic information.

Streptokinase The Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) data (29,30) have shown that thrombolytic therapy with front-loaded tissue plasminogen activator is more effective than therapy with streptokinase, with a higher 90-min patency rate and a lower mortality rate. However, in low risk patients the cost-effectiveness of tissue plasminogen activator is less than that of streptokinase (31,32). The main advantage of primary angioplasty over thrombolysis in low risk patients is the lesser risk of reinfarction. In this regard the choice of thrombolytic agent is irrelevant. A detailed analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II (GISSI-2) working group has illustrated the difficulties in predicting reinfarction, but they did not find a difference between these two thrombolytic agents in the rate of reinfarction (33). There is a small difference in the risk of stroke between these two drugs in favor of streptokinase (34). Finally, the benefits of primary angioplasty over thrombolytic therapy exceed the survival advantage of one thrombolytic agent over the other by an order of magnitude.

Risk stratification Many retrospective analyses (13-17) have shown that patients with acute myocardial infarction can be stratified with regard to risk on the basis of clinical and ECG data available on initial presentation. Our data confirm that patients classified as low risk do have a low risk for untoward events up to 6 months, with a mortality rate of only 1%. With our criteria only 40% of patients were considered to be at low risk, a lower proportion than we anticipated. In particular, patients with contraindications for thrombolytic therapy and patients in higher Killip classes are often excluded from reperfusion trials, whereas in our trial almost all patients with acute ST segment elevation myocardial infarction were included. The most important limitation of risk stratification during acute myocardial infarction is the inability to predict recurrent

myocardial infarction (7,33). Angiographic studies have documented a reocclusion rate of the infarct-related coronary artery in up to 30% of the patients after successful thrombolytic therapy (19,20), whereas reocclusion following primary angioplasty is rare (4,35). A recent overview (22) confirms that recurrent myocardial ischemia and reinfarction are less frequent after primary angioplasty than after thrombolytic therapy.

Study limitations Only a limited number of patients were included in our trial. It is therefore possible that certain less pronounced differences between angioplasty and thrombolytic therapy in low risk patients do not show up in our results, and the confidence intervals of the relative risk reduction are wide. Therefore, although we found that the risk of reinfarction is lower after primary angioplasty, the magnitude of this effect is not clear. The diagnosis of reinfarction can be difficult early after reperfusion therapy for acute myocardial infarction. For this reason we required a second episode of chest pain with ST-T segment changes and enzymatic confirmation before this diagnosis was made, and most of these patients had new Q waves. Although another strategy may also prevent recurrent infarction -thrombolysis followed by angiography and intervention a few days later, as has recently been suggested by the DANish Trial in Acute Myocardial Infarction (DANAMI) study (36)- many reinfarctions occur early and can therefore not be prevented by this approach.

Conclusions and clinical implications Simple clinical data, readily available during the 1st 15 min of hospital admission for acute myocardial infarction, can be used to stratify patients according to risk, and the results can be incorporated in the therapeutic strategy. Even in patients with a low risk of adverse events, primary coronary angioplasty results in a better clinical outcome, in particular a lower reinfarction rate, at 6 months than does thrombolytic therapyand it does not cause an increase in total medical charges. In hospitals with an existing infrastructure for interventional cardiology all patients with symptoms of acute myocardial infarction and ST segment elevation should be offered immediate coronary angiography and primary coronary angioplasty.

References

1. Grines CL, Browne KF, Marco J, et al, for the Primary Angioplasty in Myocardial Infarction Study group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
2. de Boer MJ, Suryapranata H, Hoorntje JCA, et al. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-61.
3. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
4. de Boer MJ, Reiber JHC, Suryapranata H, van den Brand MJBM, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterisation laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16:1347-55.
5. Kligfield P. Primary angioplasty in myocardial infarction. Br Heart J 1995;73:403.
6. Zijlstra F. Primary Angioplasty: the most effective therapy for patients with an acute myocardial infarction. Br Heart J 1995;73:403-4.
7. Grines CL, O'Neill WW. Primary angioplasty. Br Heart J 1995;73:405-6.
8. De Jaegere PP, Simoons ML. Immediate angioplasty: a conservative view from Europe. Br Heart J 1995;73:407-8.
9. Vaitkus PT. Limitations of primary angioplasty in acute myocardial infarction. Br Heart J 1995;73:409-10.
10. Brodie BR. Primary angioplasty in a community hospital in the USA. Br Heart J 1995;73:411-2.
11. Boyle RM. Immediate angioplasty in the United Kingdom. Br Heart J 1995;73:413-4.
12. Ramsdale DR, Grech ED. Experience of primary angioplasty in the United Kingdom. Br Heart J 1995;73:414-6.
13. de Boer MJ, Hoorntje JCA, Ottervanger JP, Reiffers S, Suryapranata H, Zijlstra F. Immediate coronary angioplasty versus intravenous streptokinase in acute myocardial infarction: Left ventricular ejection fraction, hospital mortality and reinfarction. J Am Coll Cardiol 1994;23: 1004-8.
14. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. Ann Intern Med 1991;115:173-7.
15. Hillis LD, Forman S, Braunwald E, et al. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. J Am Coll Cardiol 1990;16:313-5.
16. Brodie BR, Weintraub RA, Stuckey TD, et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. Am J Cardiol 1991;67:7-12.
17. Simoons ML, Arnold AER. Tailored thrombolytic therapy. A perspective. Circulation 1993;88:2556-64.
18. Gill JB, Cairns JA, Roberts RS. Prognostic importance of myocardial ischemia detected by ambulatory monitoring early after acute myocardial infarction. N Engl J Med 1996;334:65-70.
19. Meijer A, Verheugt FWA, Werter CJPJ, Lie KI, van der Pol JMJ, van Eenige MJ. Asperin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT study. Circulation 1993;87:1524-30.
20. White HD, French JK, Hamer AW, et al. Frequent reocclusion of patent infarct-related arteries between 4 weeks and 1 year: effects of antiplatelet therapy. J Am Coll Cardiol 1995;25:218-23.

21. Barbagelata A, Granger CB, Topol EJ, et al. Frequency, significance, and cost of recurrent ischemia after thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1995; 76:1007-13.
22. Lieu TA, Gurley J, Lundstrom RJ, Parmley WW. Primary angioplasty and thrombolysis for acute myocardial infarction: an evidence summary. J Am Coll Cardiol 1996;27:737-50.
23. de Boer MJ, van Hout BA, Liem AL, Suryapranata H, Hoorntje JCA, Zijlstra F. A cost-effective analysis of primary angioplasty versus thrombolysis for acute myocardial infarction. Am J Cardiol 1995;76:830-3.
24. Zijlstra F, de Boer MJ, Beukema WP, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. Eur Heart J 1996;17:382-7.
25. van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and C/E ratios alongside a clinical trial. Health Econ 1994;3:309-19.
26. Zijlstra F, Beukema WP, Liem AL, Suryapranata H, Hoorntje JCA, de Boer MJ. Results of the pilot phase of an ongoing randomized trial to evaluate a strategy of primary angioplasty for high risk and thrombolysis for low risk patients with acute myocardial infarction. Circulation 1994;90:I-168 (abstr.).
27. Brodie B, Grines CL, Spain M, et al. A prospective, randomised trial evaluating early discharge (day 3) without non-invasive risk stratification in low risk patients with acute myocardial infarction: PAMI-2. J Am Coll Cardiol 1995;25:5A (abstr.).
28. Mueller HS, Forman SA, Menegus MA, Cohen LS, Knatterud GL, Braunwald E. Prognostic significance of nonfatal reinfarction during 3-year follow-up: Results of the thrombolysis in myocardial infarction (TIMI) phase 2 clinical trial. J Am Coll Cardiol 1995;26:900-7.
29. The GUSTO angiographic investigators. The effect of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-22.
30. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
31. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med 1995;332:1418-24.
32. Arnold AER, Simoons ML. Thrombolytic therapy for evolving myocardial infarction needs an approach that integrates benefit and risk. Eur Heart J 1995;16:1502-9.
33. Volpi A, DeVita C, Franzosi MG, et al. Predictors of nonfatal reinfarction in survivors of myocardial infarction after thrombolysis. Results of the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI-2) Data Base. J Am Coll Cardiol 1994; 24:608-15.
34. Gore JM, Granger CB, Simoons ML, et al. Stroke after thrombolysis. Mortality and functional outcomes in the Gusto-I trial. Circulation 1995;92:2811-8.
35. Brodie BR, Grines CL, Ivanhoe R, et al. Six-month clinical and angiographic follow-up after direct angioplasty for acute myocardial infarction. Circulation 1994;25:156-62.
36. Grande P, Kyst Madsen J, Saunamäki K, et al. The Danish multicentre randomized study of invasive versus conservative treatment in patients with inducible ischaemia following thrombolysis in acute myocardial infarction (DANAMI). Eur Heart J 1996;17:A:559 (abstr.).

CHAPTER 4

Part Two

Transferring Patients for Primary Angioplasty

A Retrospective Analysis of 104 Selected High Risk Patients with Acute Myocardial Infarction

Felix Zijlstra, Arnoud W.J. van 't Hof, Ay Lee Liem,
Jan CA Hoorntje, Harry Suryapranata, Menko-Jan de Boer.

Department of Cardiology, Hospital De Weezenlanden
Zwolle, the Netherlands

Heart 1997;78:333-336

Abstract

Objective - To investigated the feasibility of primary coronary angioplasty as a treatment option in patients with acute myocardial infarction after initial diagnosis in a local community hospital.

Setting - Referral centre for interventional treatment of coronary artery disease.

Methods - During a five year period, 520 candidates for primary coronary angioplasty were treated in our institution, 104 after transfer from a community hospital. The transferred and the non-transferred patients (N=416) were compared with regard to baseline clinical characteristics, time intervals from symptom onset to treatment, and clinical outcome at six months.

Results - In this setting, the influence of transportation on total ischaemic time was limited, and there was no difference in clinical outcome between the transferred and the non-transferred patients. Clinical outcome was mainly dependent on the indication for transfer.

Conclusions - Safe and expedient transportation may facilitate the more widespread use of primary angioplasty in patients with acute myocardial infarction. A large randomised multicentre trial is needed to compare the relative merits of intravenous thrombolytic treatment in a local hospital with primary angioplasty after transfer in selected high risk patients with acute myocardial infarction.

(Heart 1997;78:333-336)

Introduction

Several randomised trials have recently shown that primary coronary angioplasty -defined as angioplasty performed on the infarct related vessel - during the early hours of acute myocardial infarction, without the use of thrombolytic agents, offers certain advantages over intravenous thrombolytic therapy (1-4). Rapid and sustained patency of the infarct related vessel is obtained in most patients, resulting in a lower mortality and less reinfarction without exposing them to the bleeding risks associated with thrombolytic treatment (5). The major limitation of primary angioplasty as first line treatment of acute myocardial infarction is its restricted availability. Even in Europe and North America, most hospitals do not have facilities for coronary angioplasty. For patients admitted to a hospital without angioplasty facilities this implies transportation to a hospital with interventional cardiology services. The time loss and the risks associated with transportation might negate (part of) the benefits of primary angioplasty compared to thrombolytic treatment. To compare intravenous thrombolytic treatment in a local facility with primary coronary angioplasty after transportation to a referral centre for interventional treatment of coronary artery disease, a multicentre randomised trial is currently planned in The Netherlands. This trial will enroll selected high risk patients with acute myocardial infarction with a substantial risk of adverse clinical events.

To investigate the feasibility, safety and logistic implications of the emergency transportation of these categories of patients we performed a retrospective analysis of all patients who underwent such a procedure in our institution. To put the clinical outcome of these transferred patients into perspective, we made a comparison with the primary angioplasty patients admitted directly to our hospital, although it is clear that the baseline characteristics of these two groups of patients are different. However, at present more appropriate data for comparison are not available.

Methods

The Weezenlanden Hospital is a referral centre for interventional treatment of cardiac diseases. Four interventional cardiologists perform 1600 coronary angioplasties per year and four thoracic surgeons perform 1400 cardiac surgical procedures per year. In our referral area, we and 14 other hospitals serve a population of 1.4 million. Transportation from most referral hospitals to our hospital is possible within 40 minutes, as the ambulance services are well organised and cooperative, and are used to working in close collaboration with coronary care units and catheterisation laboratories. Transportation of patients for elective and urgent coronary angioplasty procedures for stable and unstable angina are daily routine. Traffic congestion is rare in our part of The Netherlands. During the night and weekend an interventional cardiologist and catheterisation staff are on call. There are two catheterisation laboratories. There is 24 hours surgical backup. When a telephone call is received from a referring physician during the daily programme, it is always possible to have one of the two rooms prepared the moment the patient arrives in our hospital. The transported patients are accompanied by well trained paramedics of the ambulance services. In cases of marked haemodynamic or electrical instability, a physician from the referring hospital travels with the patient.

Patients

Between August 1990 and April 1995, 729 patients with symptoms of acute myocardial infarction and ST segment elevation on at least 2 contiguous electrocardiographic leads presented to or were referred to our institution. Of the patients who presented directly to our hospital, 87% participated in one of our trials (1,2,4,6). Thrombolytic treatment was given to 205 patients and 520 were candidates for primary angioplasty. Of these 520 patients, 416 presented directly to our

hospital, and 104 patients were initially admitted to another hospital without a catheterisation laboratory or angioplasty expertise and were transferred by ambulance for immediate angiography with a view to primary angioplasty after an initial diagnosis of acute myocardial infarction has been made at the local facility. When the decision to transfer was made, the patient was included in this analysis, irrespective of whether primary angioplasty was actually performed. None of the transported patients participated in one of our reported trials(1,2,4,6) as the decision to go for primary angioplasty had already been made and communicated to the patient as well as to relatives by the referring physician. Transferred patients were directed immediately towards the cardiac catheterisation laboratory to avoid additional delay resulting from a second assessment in an emergency room or coronary care unit.

Indications for transfer

In all the 14 hospitals that transferred these patients, thrombolysis is the first choice reperfusion therapy for acute myocardial infarction. Predefined indications for transfer for primary coronary angioplasty were: contraindications to thrombolytic treatment, with electrocardiographic evidence of a large myocardial territory at risk (31%); Killip class 3 or 4 (14%); and anterior wall infarctions with 2 mV cumulative ST segment elevation (67%).

Main Outcome Measures

Time of symptom onset, times of hospital admission, and transfer time, defined as time between first and second hospital admission, were recorded. Clinical end points, defined as previously described (1). and additional revascularisation procedures were assessed, at 6 months to compare the transferred and the non-transferred patients.

Statistics

Data are expressed as mean ±SD. Categorical data were analysed by Fisher's exact test or the Chi-Square test. Continuous variables were analysed by the unpaired Student's t-test. A p value of < 0.05 was considered statistically significant.

Results

Initial therapy and clinical characteristics

One patient with cardiogenic shock died during transportation and one patient in the non-transferred group died in the emergency room shortly after admission. Coronary angiography was performed in all other patients (n=518). Primary angioplasty was performed in 486 patients (94%) with a procedural success rate, defined as previously described (4) of 97%. A conservative approach was followed in 23 patients (4.4%) and 9 patients (1.7%) had emergency coronary artery bypass grafting without an attempt at angioplasty. Baseline characteristics of the 2 patients groups are shown in table 1.

Table 1.

Baseline characteristics and initial therapy

	Non-transferred (n = 416)	p	Transferred (n = 104)
Age (yr)	61 ± 11	NS	59 ±- 11
Male (%)	78	NS	77
Prior MI (%)	19	NS	22
Anterior MI (%)	42	<0.001	67
Killip class 3 or 4 (%)	6	<0.05	12
CI for thrombolysis (%)	13	<0.001	31
Multivessel disease (%)	60	NS	59
Initial treatment			
Primary angioplasty (%)	93	NS	98
Conservative approach (%)	4	NS	1
Emergency CABG (%)	3	NS	1

MI, myocardial infarction; CI, contraindication; CABG, coronary artery bypass grafting

Complications in the transferred patients during coronary angiography and angioplasty occurred in 15 (14.4%) cases. Two patients died during the procedure in cardiogenic shock, despite extensive resuscitation efforts. Six patients needed defibrillation and one needed a temporary pacemaker for third degree atrioventricular block. Major dissections occurred in 5 patients and were managed by bail-out stenting (3 patients) or, in the presence of severe triple vessel disease by coronary artery bypass grafting (2 patients). Two patients had allergic skin reactions and hypertension probably due to the contrast agent. In the transferred patients, hospital mortality was 6.7%, in-hospital reinfarction occurred in 2.9% of patients, and additional revascularisation procedures were performed in 17.3%. Four patients underwent a second angioplasty procedure -in 2 of them because of signs of reocclusion- and 14 patients had coronary artery bypass grafting for triple vessel or left main disease.

Transportation and time delays

One patient died during transportation (1%). This patient was already in profound cardiogenic shock before being transported. During transportation 10 patients (9.6%) were in cardiogenic shock. All were on inotropic support. One patient needed mechanical ventilation before transportation, and one additional patient was intubated during transport. In addition to the 14 patients who were in Killip class 3 or 4 before transportation, 2 patients required treatment for hypotension (fluid expansion and intravenous dobutamine). Ventricular tachycardia occurred in 1 patient and was treated with intravenous lidocaine. Two patients were defibrillated for ventricular fibrillation during transportation. No other adverse events occurred during or as a result of transportation. Travel distances of the transferred patients were < 25 km in 61%, between 25 and 50 km in 30%, and > 50 km in 9%. The time from symptom onset to first balloon inflation in the 2 groups of patients is shown in table 2.

Table 2.

Time between symptom-onset and first balloon inflation

	Non-transferred	Transferred
Hours	%	%
0-2	11	6
2-4	52	52
4-6	22	20
> 6	15	22

As patient delay (7) is the predominant determinant of time to treatment in patients treated after 6 hours, the detailed analysis of time delays shown in table 3 is restricted to patients treated within 6 hours. Differences in baseline characteristics (table 1) may be responsible for the shorter time from symptom onset to initial hospital presentation of the transferred patients (table 3), as sicker patients tend to call for help earlier after symptom onset.

Table 3.

Time delays of patients treated within 6 hours.

	Non-transferred (n = 416)	Transferred (n = 104)
symptom-onset to hospital admission	129 (± 69)	91 (± 60)
admission local community hospital-admission WZL		70 (± 27)
admission WZL-first balloon inflation of primary coronary angioplasty procedure	67 (± 28)	39 (± 31)
Total ischemic time	196 (± 74)	200 (± 62)

All times are in minutes (±SD); WZL, hospital De Weezenlanden.

An additional 28 minutes is gained back from the time lost during transfer by rapid in-hospital transfer to the catheterisation laboratory. As a result of these differences, the time delay between first and second hospital admission is not reflected in the comparable total ischaemic periods of 196 and 200 minutes in the two groups of patients, as shown in table 3.

Clinical Outcome

Clinical outcome at 6 months is shown in table 4. The high percentage of patients in the transferred group with baseline characteristics known to be associated with a higher risk of untoward events (8-10) results in a somewhat higher incidence of revascularisation procedures, non-fatal recurrent infarction, and death, although none of these differences reach statistical significance.

Table 4.

Clinical outcome at 6 months

	Non-transferred (n = 416) %	p	Transferred (n = 104) %
Re-PTCA	12.5	NS	12.5
CABG	13.7	NS	17.3
Re-MI	2.6	NS	3.8
Death	6.7	NS	8.7

Re-PTCA, repeated percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; Re-MI, recurrent myocardial infarction.

Discussion

Outcome after myocardial infarction can be improved by prompt reperfusion of the infarct related coronary artery. Primary coronary angioplasty and thrombolysis are complementary methods of reperfusion treatment and both strategies are still evolving. Angioplasty equipment and technique (stents?), improved dosing regimens and new drugs for thrombolysis, and improved adjunctive treatment such as antithrombin and antiplatelet agents for both types of treatment are ongoing developments that can be expected to improve outcome further, and will influence the balance between these methods of of treatment, along with economic and logistic issues. Emerging data support a role for primary coronary angioplasty, where it is available and accessible, but the extent and limitations of this role require further clarification (11-18) At this moment the large majority of patients with an acute myocardial infarction is admitted to hospitals without a catheterisation laboratory or angioplasty expertise, even in Europe and North America. This means that additional transportation, with inherent risks and time delay, will be necessary for many patients if a strategy of primary coronary angioplasty is introduced into clinical practice. Several trials are currently being prepared to compare optimal thrombolytic treatment at a local hospital, or even prehospital thrombolysis, with primary coronary angioplasty after transfer to a hospital with interventional cardiology. Although not yet based on evidence from randomised trials, transfer of selected patients may be appropriate if the benefits of primary angioplasty are likely to outweigh the risk of transportation and the negative impact of the additional time delay. Patients with contraindications for thrombolytic treatment and a large myocardial territory at risk, patients with extensive anterior wall infarctions and those with clear evidence of haemodynamic instability during the early hours of infarction may benefit from this approach. Emergency interhospital transport of patients during the early hours of acute myocardial infarction has been described to be feasible and safe (19,20). However, in these previous reports patients usually had thrombolytic treatment before transportation to a tertiary facility for coronary angiography. Mortality and morbidity during transportation were low but the additional time delay averaged more than 2 hours, resulting in arrival in the catheterisation laboratory around 6 hours after symptom onset. In particular, if myocardial salvage is one of the goals of the therapeutic strategy then the time to reperfusion is crucial. In contrast with these previous reports(19,20) in our setting a large proportion of patients is treated within the time frame that makes myocardial salvage possible, as 58% of transferred patients had a first balloon inflation

within 4 hours and 78% within 6 hours after symptom onset. As primary coronary angioplasty results in a patency rate -defined as TIMI 3 flow (4) - of more than 90%, in theory this would be better than thrombolytic treatment at a local facility (21) in particular if less than 1 hour is lost in transfer. This is a strong argument in favour of a large multicentre study.

Limitations

It should be recognised that the transferred patients were selected for this treatment by the referring physicians on the basis of limited available information, usually consisting of a (short) history, the most pertinent findings from physical examination, and a 12-lead electrocardiogram. Although no patients were transferred who did not fulfil one of our predefined indications, we do not know how many patients who fulfilled these criteria were not transferred, as we have no systematic data concerning all hospital admissions with myocardial infarction in the referring hospitals. In particular, we do not know how many patients were deemed too sick to transfer, although personal communication from the referring physicians suggests that this is rare. Although some referring hospitals have portable intra-aortic balloon pumps, they are used very seldom for this indication, as the additional delay resulting from the insertion procedure before transportation offsets the advantage of this support device.

Conclusions and Clinical Implications

Our data show, that at least in certain circumstances, primary coronary angioplasty after transportation to a referral centre for interventional treatment of cardiac disease, can be used in patients initially admitted to a hospital without angioplasty facilities. The risk of death due to transportation is low and the effect on total ischaemic time (time from symptom onset to balloon inflation) is small. A large randomised multicentre trial is needed to compare the relative merits of intravenous thrombolytic treatment in a local hospital with primary angioplasty after transfer in selected high risk patients with acute myocardial infarction.

References

1. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A compari son of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
2. De Boer MJ, Suryapranata H, Hoorntje JCA, Reiffers S, Liem AL, Miedema K, et al.Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction.Circulation 1994; 90:753-61.
3. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al, for the Primary Angioplasty in Myocardial Infarction Study group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
4. De Boer MJ, Reiber JHC, Suryapranata H, van den Brand MJBM, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. Eur Heart J 1995;16:1347-55.
5. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, et al. Stroke after thrombolysis. Mortality and functional outcomes in the Gusto-I trial. Circulation 1995;92:2811-8.
6. Zijlstra F, Beukema WP, Liem AL, Suryapranata H, Hoorntje JCA, de Boer MJ. Results of the pilot phase of an ongoing randomized trial to evaluate a strategy of primary angioplasty for high risk and thrombolysis for low risk patients with acute myocardial infarction (abstract). Circulation 1994;90:I-168
7. GISSI. Epidemiology of avoidable delay in the care of patients with acute myocardial infarction in Italy. Arch Intern Med 1995;155:1481-8.
8. Hillis LD, Forman S, Braunwald E and the TIMI phase 2 Co-investigators. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. J Am Coll Cardiol 1990;16:313-5.
9. Brodie BR, Weintraub RA, Stuckey TD, Le Bauer EJ, Katz JD, Kelly TA. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. Am J Cardiol 1991; 67:7-12.
10. Simoons ML, Arnold AER. Tailored thrombolytic therapy. A perspective. Circulation 1993; 88:2556-64.
11. Kligfield P. Primary angioplasty in myocardial infarction. Br Heart J 1995;73:403.
12. Zijlstra F. Primary Angioplasty: the most effective therapy for patients with an acute myocardial infarction. Br Heart J 1995;73:403-4.
13 Grines CL, O'Neill WW. Primary angioplasty. Br Heart J 1995;73:405-6.
14. De Jaegere PP, Simoons ML. Immediate angioplasy: a conservative view from Europe. Br Heart J 1995;73:407-8.
15. Vaitkus PT. Limitations of primary angioplasty in acute myocardial infarction. Br Heart J 1995;73:409-10.
16. Brodie BR. Primary angioplasty in a community hospital in the USA. Br Heart J 1995;73:411-2.
17. Boyle RM. Immediate angioplasty in the United Kingdom. Br Heart J 1995;73:
18. Ramsdale DR, Grech ED. Experience of primary angioplasty in the United Kingdom. Br Heart J 1995;73:414-6.
19. Bellinger RL, Califf RM, Mark DB, Weber RA, Collins P, Stone J, et al. Helicopter transport of patients during acute myocardial infarction. Am J Cardiol 1988;61:718-22.
20. Gore JM, Corrao JM, Goldberg RJ, Ball SP, Weiner BH, Aghababian RV, et al. Feasibility and safety of emergency interhospital transport of patients during early hours of acute myocardial infarction. Arch Intern Med 1989;149:353-5.
21. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-22

CHAPTER 5

Part One

Clinical Presentation and Outcome of Patients with Early, Intermediate and Late Reperfusion Therapy by Primary Coronary Angioplasty for Acute Myocardial Infarction

A.W.J. van 't Hof, A. Liem, H. Suryapranata, J.C.A. Hoorntje, M.-J de Boer, F. Zijlstra

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

Eur Heart J 1998;19:118-123

Abstract

Background: Reperfusion therapy by primary coronary angioplasty has been shown to be beneficial for patients who present themselves up to 12 h after the onset of symptoms. However, the relationship between outcome and ischaemic time for patients who present relatively late after the onset of symptoms is still uncertain. The aim of this study was to inves-tiga-te differences in patient characteristics, left ventricular function and clinical outcome between early (<3 h), intermediate (3-6 h) and late (6-24 h) treated patients.

Methods and Results: From August 1990 until December 1995, we studied 496 patients who underwent primary coronary angioplasty for acute myocardial infarction. Patients who underwent reperfusion therapy between 6 and 24 h were more often of female gender and more often had diabetes. Primary coronary angioplasty was less successful with later time to reperfusion. Patients who had reperfusion therapy within 6 h showed recovery of left ventricular function at 6 months follow-up, while the left ventricular function of patients treated late had deteriorated. Reocclusion of the infarct- related vessel at follow-up coronary angiography was highest for patients with an ischaemic time of more than 6 h. They more often suffered a repeat myocardial infarction and had a significantly higher 6 months mortality. After adjustment for age, heart rate at presentation, gender, and the presence of diabetes by multivariate analysis, ischaemic time remained an independent predictor of both left ventricular function recovery and 6 month mortality.

Conclusions: The time from symptom onset to reperfusion is related to some baseline clinical characteristics, procedural success rate, left ventricular function and clinical outcome.

(Eur Heart J 1998;19:118-123)

Introduction

It has been shown convincingly that reperfusion therapy for acute myocardial infarction started within 6 h after symptom onset results in an important mortality reduction (1,2), but there is no certainty about the relationship between the ischaemic time and clinical outcome. Although there is clear evidence that very early treatment, especially within the first "golden hour" results in a considerable mortality benefit (3,4), few studies have addressed the influence of time to treatment, including patients who are treated later than 6 h after the onset of symptoms. Most studies report on patients treated with thrombolytic therapy. In these patients it is not known whether reperfusion actually occurs, and if so, the time is uncertain. Therefore we compared patient characteristics and outcome of patients divided into 3 different groups according to time intervals between onset of symptoms and opening of the infarct-related vessel in a cohort of consecutive myocardial infarct patients treated with primary coronary angioplasty.

Patients and methods

From August 1990 to December 1995, 496 patients with symptoms of acute myocardial infarction persisting for more than 30 min and at least 1 mm ST segment elevation in two contiguous leads underwent primary coronary angioplasty at our institution, according to the protocol of the Zwolle Myocardial Infarction trial. Inclusion and exclusion criteria for this trial have previously been described (5). Patients who presented more than 6 h after symptom onset were only included if there was evidence of continuing ischae-mia, which was defined as the presence of persistent chest pain and ST segment elevation. Patients were transported to the catheterization laboratory immediate-ly after the diagnosis was made and corona-ry angioplasty was performed using standard techniques. Ischaemic time was defined as the time from symptom onset until the first balloon inflation. Flow through the in-farct-rela-ted vessel was scored accor-ding to the Thromboly-sis in Myocar-dial Infarc-tion (TIMI) classifi-cation (6). Primary angioplasty was considered successful if TIMI 3 flow was present after the procedure. Colla-terals to the infarct-rela-ted vessel were clas-si-fied as proposed by Rentrop et al (7). Grade 0: no visible filling of any collateral channels, grade 1: filling by means of collateral channels of side branches of the vessel but without any dye reaching the epi-cardial segment of that vessel, grade 2: partial filling via collateral channels of the epicardial segment of the vessel, grade 3: complete filling of the epicardial vessel. Follow-up coronary angiography was planned for all patients, with the exception of those who underwent early coronary artery bypass surgery or who had an unsuccessful angiop-lasty.
The left ventricular ejection fraction was measu-red before discharge and at 6 months follow-up, by radio-nuclide ventriculograp-hy using the multiple gated equilibrium method, as has been previously des-cri-bed (8). For patients in whom both an ejection fraction was measured before hospital discharge and at follow-up, the change of left ventricular function was defined as the difference between the two values (DEF).
Recurrent myocardial infarction was defined as the combination of chest pain, changes in the ST-T segment at rest, and a second increase in the creati-ne kinase level to more than twice the upper limit of normal, or an increase of more than 200 U per litre over the previous value if the level had not dropped below the upper limit of normal. Total mortality was assessed at 6 months follow-up.

Statistical Analysis

Differences between group means were tested by analysis of variance. A chi-square method or the Fischer exact test, adapted to analyse trends, were used to test differences between proportions. The Fi-scher exact test was used if there was an expected cell value < 5. Continuous baseline and outcome variables are given as means ± SD, with the exception of ischaemic time,

which is reported by median and percentiles 25 and 75 as this variable has a "non-Gaussian" distribution. Discrete variables are given as percentages. Diffe-rences were considered statistically signifi-cant if the two-sided P value was <0.05. The outcome measures were analysed irrespective of whether the angioplasty procedure was successful. A stepwise logistic regression procedure was used to determine independent predictors associated with mortality or left ventricular function. For this analysis, continuous variables were converted into binary variables, with the 75th percentile as the cut off point.

Results

The ischaemic time was recorded in 490 patients (98%). This was less than 3 h in 44% of patients, defined as the "EARLY" group. Thirty-eight percent of patients had an ischaemic time between 3 and 6 h, the "INTERMEDIATE" group and 18% of patients were treated between 6 and 24 h of symptom onset because of signs of continuing ischaemia. This latter group was classified as the "LATE" group. Median time from onset of symptoms to the first balloon inflation was 2.4 h, 4.1 h and 9.0 h for the three groups, respectively. Baseline characteristics are described in Table 1.

Table 1.

Baseline characteristics

	Ischaemic time			
	Early (n=215)	Intermediate (n=187)	Late (n=88)	Trend analysis P
Ischemic time (min) (25 perc-75 perc)	143 (118-160)	243 (210-287)	538 (420-838)	<0.0001
Male gender	86%	81%	67%	0.0003
Diabetes	3%	10%	12%	0.003
Successful PA	94%	87%	85%	0.006
Age (years)	59±11	61±12	61±11	0.14
Family history of CAD	44%	49%	34%	0.30
Previous angina	49%	45%	58%	0.31
Previous PTCA	7%	6%	5%	0.39
Hypertension	20%	23%	24%	0.36
Previous CABG	3%	2%	5%	0.78
Heart rate (beats/min)				
Killip 1(82%)	72±15	73±16	78±17	0.003
Killip 2 (12%)	89±29	87±25	90±19	0.89
Killip 3+4 (6%)	96±24	99±27	89±27	0.61
Smoking	51%	51%	51%	0.87
Multivessel disease	53%	58%	51%	0.89
Previous MI	13%	15%	12%	0.91
Anterior MI	51%	43%	58%	0.98

Ischaemic time=time from symptom onset to first balloon inflation; MI=myocardial infarction; CABG=coronary artery bypass surgery; PTCA= percutaneous transluminal coronary angioplasty; CAD=coronary artery disease. Successful is defined as TIMI 3 flow of the infarct-related artery; PA= primary angioplasty.

There was a significant trend towards a higher percentage of female patients and patients with diabetes and a longer ischaemic time. The other baseline characteristics were comparable in the three groups. The success rate of the primary angioplasty procedure, however, was highest in patients treated within 3 h. Results of the left ventricular ejection fraction for both in-hospital and at follow-up are described in Table 2. These measurements were available pre-discharge in 418 (85%) patients and at follow-up in 376 (82% of surviving patients). In patients with unsuccessful angioplasty the ejection fraction was measured in 33 patients (65%) pre-discharge and in 28 (78% of patients alive) at 6 months follow-up. Both pre-discharge and follow-up measurements (paired data) were available in 358 patients. Although there is a trend towards a lower ejection fraction with longer ischaemic time, this did not reach statistical significance. However, the change of left ventricular ejection fraction function between pre-discharge and 6 months follow-up was related to ischaemic time. Patients with an ischaemic time of less than 3 h showed an increase in ejection fraction of 1.6 %. For patients with an ischaemic time between 3 and 6 h the ejection fraction increased 1.3 %. In the patients who had their first balloon inflation after 6 h, the ejection fraction decreased by 1.9 %. After exclusion of patients with an occluded infarct-related vessel at follow-up angiography, these values for DEF were 1.5 %, 1.4%, and -1.5% respectively.

Table 2.
Left ventricular ejection fraction

	Ischaemic time			
	Early	Intermediate	Late	Trend analysis P
All patients				
LVEF pre discharge (n=418)	46±12	46±11	44±13	0.35
LVEF follow-up (n=376)	47±11	46±12	44±13	0.23
Patients with paired EF measurements				
LVEF pre discharge (n=358)	46±12	46±11	45±13	0.88
LVEF follow-up (n=358)	47±11	47±12	43±13	0.08
DEF (n=358)	+1.6±7.5	+1.3±7.3	-1.9±8.3	0.008
Patients who underwent successful PA				
DEF (n=326)	+1.6±7.7	+1.7±7.2	-2.1±8.1	0.007
Patients with a patent infarct-related vessel at follow-up				
DEF (n=343)	+1.5±7.6	+1.4±7.4	-1.5±8.2	0.03

LVEF=left ventricular ejection fraction measured by radionuclide ventriculography. DEF=difference between the ejection fraction predischarge and at follow-up. PA=primary angioplasty.

Clinical and angiographic outcome at follow-up is described in Table 3. In patients for whom a follow-up angiogram was planned, this procedure was performed in 162/183 (89%) of early , in 121/139 (87%) of the intermediate, and in 59/71 (83%) of the late-entry patients (P=0.27). No patient was lost to follow-up. Reinfarction, death and reocclusion of the infarct-related vessel at follow-up angiography were related to ischaemic time, with the best outcome for patients treated within 3 h, and the poorest outcome for patients treated after 6 h of symptom onset.

Table 3.

Reocclusion, reinfarction and death at 6 months follow-up

	Ischaemic Time			
	Early	Intermediate	Late	Trend P
Reocclusion	5%	8%	14%	0.04
Reinfarction	3 (1%)	6 (3%)	7 (8%)	0.01
Death	7 (3%)	16 (8%)	11 (13%)	0.003
Death (-failed PA)	5 (3%)	8 (5%)	3 (4%)	0.36

The results of the multivariate analysis are shown in Table 4. Ischaemic time was related to both 6-month mortality and change in ejection fraction independent of age, heart rate at presentation, gender or the presence of diabetes.

Table 4.

Multivariate analysis

End point: 6 month mortality			
	Odds ratio	95% CI	P-value
Age (>70 years)	4.38	(2.15 - 8.93)	0.00005
Heart rate > 70 beats/min	3.26	(1.68 - 6.34)	0.0005
Multivessel disease	2.41	(1.19 - 4.87)	0.01
Ischemic time (per class)	1.53	(1.01 - 2.32)	0.04
Diabetes	1.46	(0.87 - 2.46)	0.16
Female gender	1.59	(0.78 - 3.24)	0.20
Anterior infarction	1.27	(0.66 - 2.44)	0.48
Previous infarction	0.94	(0.39 - 2.24)	0.89
End point: DEF (Odds ratios for worsening of EF)			
	Odds ratio	95% CI	P-value
Anterior infarction	0.52	(0.33 - 0.80)	0.003
Ischemic time (per class)	1.43	(1.06 - 1.94)	0.02
Age (>70 years)	0.54	(0.28 - 1.02)	0.06
Heart rate > 75/min	0.67	(0.43 - 1.03)	0.07
Multivessel disease	1.50	(0.97 - 2.34)	0.07
Previous infarction	1.62	(0.84 - 3.13)	0.15
Diabetes	1.47	(0.71 - 3.05)	0.30
Female gender	0.91	(0.50 - 1.65)	0.75

CI= confidence interval, DEF=difference in left ventricular ejection fraction pre-discharge and at 6 month follow-up (n=358).

Discussion

Two previous studies of patients treated with primary coronary angioplasty for acute myocardial infarction suggested that the time delay to reperfusion, even after 6 h, did not affect outcome (9,10). However, this study shows that the time from symptom-onset to first balloon inflation is related to some baseline clinical characteristics, left ventricular functional recovery and clinical outcome.

Baseline Characteristics

The difference in baseline characteristics between the 3 groups of patients is consistent with the findings from other studies (11,12), who found female gender and diabetes to be independent variables for increasing patient delay. Ottesen et al (12) found that older age and pre-infarction angina were also a predictor for a long patient delay. Although our data show a trend in this direction, this was not significant. None of the other baseline characteristics were related to ischaemic time. Previous infarction, previous bypass surgery or hypertension, which were found

to be variables predictive of later time to presentation in the GUSTO trial (11), were equally distributed amongst the 3 groups in our study. This inability to detect some of these differences may be related to the relative small number of patients in our study.

Success of Primary Angioplasty

Our data show that the likelihood of achieving TIMI 3 flow of the infarct-related coronary artery is dependent on ischaemic time. Previous studies in patients treated with primary angioplasty did not find such a relationship (9,10). However, from a pathophysiological perspective, it is understandable that flow to a region with extensive necrosis due to prolonged occlusion of the infarct-related artery, may become less often normal. In patients with a longer ischaemic time, a higher incidence of impaired flow in the infarct-related vessel after reperfusion has been found by intracoronary Doppler measurements in humans as well as in an animal model (13,14).

Left Ventricular Function

Left ventricular ejection fraction of patients treated after 6 h was not significantly lower compared to patients treated within 6 h, although there was a trend in this direction. There was a significant difference in the extent of recovery of left ventricular function during follow-up between the three groups. After adjustment for differences in baseline characteristics by multivariate analysis, it was shown that ischaemic time independently predicted left ventricular function recovery (Table 4). This is consistent with the findings of Hassche et al (15), who found the same in patients treated with thrombolytic therapy. An explanation for this lack of recovery of left ventricular function for patients treated late might be related to a more extensive necrosis with absence of viable myocardium in the infarct region in late-treated patients. Studies using myocardial contrast echocardiography show that the left ventricular function in these patients benefit less from reperfusion therapy compared to patients who have evidence of continued viability (16,17). The lower success rate of the angioplasty procedure or the lower patency rate of patients treated late does not explain the lack of recovery of left ventricular function. After exclusion of patients with an unsuccessful procedure or an occluded infarct-related vessel at follow-up, the difference in extent of recovery of left ventricular function persisted (Table 2).

Clinical and Angiographic Outcome

Early treated patients have a better clinical and angiographic outcome at follow-up, compared to patients treated later. There is a substantial difference in mortality at follow-up. The difference in mortality is related to the difference in success rate of the angioplasty procedure between the three groups of patients. After exclusion of failed procedures, there is no longer a significant difference in 6 month mortality between the groups (Table 3). Although it was recently reported that diabetes is an independent predictor of mortality after myocardial infarction (18), the difference in incidence in diabetes between the groups does not explain the difference in mortality. Multivariate analysis showed that ischaemic time is an independent predictor of 6 month mortality, after adjustment for the differences in baseline characteristics between the groups (Table 4). Patients treated after 6 h more often had reocclusion of the infarct-related vessel. There is a wealth of information which shows that late patency of the infarct-related vessel is a strong predictor of long-term clinical outcome (19). However, this study reported on reocclusion rates and not patency rates, because follow-up angiography was performed in patients after a successful angioplasty procedure. If one assumes that the infarct-related vessel of the patients who underwent an unsuccessful procedure remained occluded (TIMI<3), patency rates at follow-up can be estimated. This is described in Table 5 and shows a significantly lower patency with later time to reperfusion. A lower patency rate at follow-up angiography for later-treated patients is in

accordance with a study performed by Simari et al in 1986, who showed that time to reperfusion was a determinant of early reocclusion after angioplasty for acute myocardial infarction (20). This may also explain the increased incidence of reinfarction in late treated patients.

Table 5.

Patency rates before and after primary angioplasty (PA) and at follow-up

	Early	Intermediate	Late	P-value
Before PA	11%	13%	12%	0.72
After PA	95%	87%	85%	0.006
Follow-up*	90%	82%	75%	0.002

*Assumption: infarct related vessel after non-successful angioplasty remains non-patent at follow-up.

Limitations of the study

We described a relatively small number of patients who underwent late reperfusion therapy. Baseline characteristics between the 3 groups were not similar for all variables: this probably reflects a true difference between patients treated early or late. Therefore this study is not merely a reflection of the effect of difference in time to treatment on outcome. This is a post-hoc analysis of the influence of ischaemic time on outcome in a large data-set of consecutive myocardial infarct patients treated with primary angioplasty. So far, the only studies in which the effect of time to reperfusion can be evaluated separately from confounding variables are those studies which randomize between pre-hospital and in-hospital thrombolysis (21-22).

Late entry patients were only treated with reperfusion therapy if there were signs of continuing ischaemia, i.e. chest pain and ST-segment elevation. This may have introduced a selection bias. Inclusion of all late entry patients, irrespective of signs of viable myocardium, would probably have resulted in different findings in this group, as reperfusion therapy seems most beneficial in patients with evidence of continued viability (23).

Conclusions

This study shows that in patients, undergoing primary coronary angioplasty for acute myocardial infarction, the time from symptom-onset to first balloon inflation is related to some baseline clinical characteristics, procedural success rate, left ventricular functional recovery and clinical outcome. In patients treated within 3 h or between 3 and 6 h there is an improvement of the left ventricular ejection fraction during follow-up. Patients treated after 6 h are more often female and have a higher incidence of diabetes and a poorer clinical outcome.

Acknowledgement

We wish to thank J.H. Dambrink, MD, PhD, Department of Cardiology, St Antonius Hospital, Nieuwegein, The Netherlands, for his advise concerning the multivariate analysis procedure.

References

1. Gruppo Italiano per lo studio della Streptochinasi nell'Infarcto miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;I:397-402.
2. Fibrinolytic Therapy Trialists' (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.
3. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5.
4. Hermens W, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size. Lancet [letter] 1992;340:129.
5. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coro-nary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
6. Chesebro JH, Knatterud G, Roberts R, et al: Throm-boly-sis in myocardial infarction (TIMI) trial, Phase I: a compa-rison between intravenous tissue plasminogeen activator and intravenous streptokinase: clinical findings through hospital dischar-ge. Circulation 1987;76:142-54.
7. Rentrop KP, Cohen M, Blanke H, et al: Changes in collateral filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587-92.
8. De Boer MJ, Suryapranata H, Hoorntje JCA, et al: Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-61.
9. Ellis SG, O'Neill WW, Bates E, Walton JA, Nabel EG, Topol EJ. Coronary angioplasty as primary therapy for acute myocardial infarction 6 to 48 h after symptom onset: report of an initial experience. J Am Coll Cardiol 1989;13:1122-6.
10. Stone GW, Brodie B, Griffin J, et al. Should the risk of delaying reperfusion prohibit inter-hospital transfer to perform primary PTCA in acute myocardial infarction (Abstr). Circulation 1996;94:I-331.
11. Newby LK, Rutsch WR, Califf RM, et al: Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996;27:1646-55.
12. Ottesen MM, Kober L, Jorgensen S, et al. Determinants of delay between symptoms and hospital admission in 5978 patients with acute myocardial infarction. Eur Heart J 1996,17:429-37.
13. Nakamura M, Tsunoda T, Wakatsuki T, Ui K, Degawa T, Yabuki S, Yamaguchi T. Distal coronay flow velocity immediately after direct angioplasty for acute myocardial infarction. Am Heart J 1996;132:251-7.
14. Willerson JT, Watson JT, Hutton I, Templeton GH, Fixler DE. Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog. Circ Res 1975;36:771-81.
15. Hasche ET, Fernandes C, Freedman SB, Jeremy RW. Relation between ischemia time, infarct size, and left ventricular function in humans. Circulation 1995;92:710-9.
16. Iliceto S, Galiuto L, Marchese A, et al. Analysis of microvascular integrity, contractile reserve, and myocardial viability after acute myocardial infarction by dobutamine echocar-diography and myocardial contrast echocardiography. Am J Cardiol 1996;77:441-5.
17. Agati L, Voci P, Bilotta F, et al: Influence of residual perfusion within the infarct zone on the natural history of left ventricular dysfunction after acute myocardial infarction: a myocardial contrast echocardio-graphic study. J Am Coll Cardiol 1994;24:336-42.

18. Woodfield SL, Lundergan CF, Reiner JS, et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol 1996;28:1661-9.
19. Lamas GA, Flaker GC, Mitchell G, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. Circulation 1995;92:1101-9.
20. Simari RD, Rutherford BD, Ligon RW, et al. PTCA in acute myocardial infarction: a multi variate analysis of predictors of early reocclusion. Circulation 1986; 74(Suppl):II-24.
21. Weaver WD, Cerqueira M, Hallstrom AP, et al. Pre-hospital-initiated vs hospital-initiated thrombolytic therapy. The myocardial infarction triage and intervention trial. JAMA 1993;270:1211-6.
22. GREAT Group. Feasability, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampion region early anistreplase trial. BMJ 1992;305:548-53.
23. Brodie BR, Stuckey TD, Hansen C, et al: Benefit of late coronary reperfusion in patients with acute myocardial infarction and persistent chest pain. Am J Cardiol 1994;74:538-43.

CHAPTER 5

Part Two

Influence of Treatment Delay on Infarct Size and Clinical Outcome in Patients with Acute Myocardial Infarction treated with Primary Angioplasty

Aylee L Liem, MD, Arnoud WJ van 't Hof, MD, Jan CA Hoorntje, MD,
Menko-Jan de Boer, MD, Harry Suryapranata, MD,
Felix Zijlstra, MD

Department of Cardiology, Hospital de Weezenlanden
Zwolle, The Netherlands

Journal of the American College of Cardiology, in press

Abstract

Objectives. The purpose of this analysis was to determine the influence of an additional treatment delay inherent in transfer to an angioplasty center for primary angioplasty of patients with acute myocardial infarction who are first admitted to hospitals without angioplasty facilities.

Background. Several randomized trials have demonstrated the benefits of primary angioplasty in acute myocardial infarction. In recent years increasing numbers of patients with myocardial infarction, initially admitted to hospitals without angioplasty facilities are transported to our hospital for primary angioplasty. However, the additional delay due to the transport may have a deleterious effect on infarct size and clinical outcome.

Methods. In a three year period (December 1993 - November 1996), 207 consecutive patients who were transferred for primary angioplasty were analyzed in a matched comparison with non-transferred patients. Matching criteria were age, sex, infarct location, presentation delay and Killip class.

Results. Patients who were transferred had an additional median delay of 43 minutes. This resulted in a larger enzymatic infarct size and a lower ejection fraction measured at 6 months. The rate of angioplasty success defined as TIMI grade 3 flow, and the 6 month mortality rate (7%) were comparable in both groups.

Conclusion. The additional delay had a deleterious effect on myocardial salvage, reflected by a larger infarct size and a lower left ventricular function. However the patency rate and 6 month clinical outcome were not affected by this delay.

(J Am Coll Cardiol, in press)

Abbreviations

CABG = Coronary artery bypass grafting
IRV = Infarct related vessel
IU = International units
LDH = Lactate dehydrogenase
LVEF = Left ventricular ejection fraction
MI = Myocardial infarction
PTCA = Percutaneus transluminal coronary angioplasty
TIMI = Thrombolysis in Myocardial Infarction

Introduction

The time related effect of treatment on survival and myocardial salvage in patients with acute myocardial infarction (MI) has been demonstrated in thrombolysis trials (1-6). Besides timing of treatment, the grade of flow achieved with reperfusion is important for the long term outcome (7-10). Primary angioplasty for patients with acute MI has been shown in randomized trials (11-14) to be a very effective reperfusion therapy, and high rates of complete and sustained patency have been reported. Achieving complete reperfusion as defined by Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow after reperfusion is an important factor in short and long term survival. In patients treated with thrombolytic therapy there is an inverse relationship between time to treatment and patency rate. This relationship is not so evident in patients treated with primary angioplasty (15,16). A previous study in infarct patients who were admitted directly to our hospital and treated with primary angioplasty did demonstrate differences in patency rates with increasing ischemic times, but also found important differences in patient characteristics related to the time from symptom onset to treatment (17). A registry study has shown that transferring patients for primary angioplasty to our hospital is safe and effective, and with an acceptable delay due to transportation (18). In this analysis an attempt is made to quantify the effect of an additional delay inherent in transfer to an angioplasty center.

Methods

Study patients.

The study was approved by the committee on ethics and research at our institution. For this analysis we retrospectively evaluated patients who were registered in our infarct database. We included patients with acute MI who were first admitted to a community hospital without angioplasty facilities and were transferred to our hospital for primary angioplasty. Only patients who underwent primary angioplasty were included in the analysis. They were compared to patients admitted directly to our hospital, who were also registered in our database for acute MI patients. In this database all consecutive patients with acute MI are prospectively registered. The transfer patients and the control patients are contemporaneous. The following definitions of the time intervals were used: the first part between symptom onset and hospital admission (for referral patients admission at the community hospital) is called presentation delay. The second part is called treatment delay, and is defined as time from hospital admission to first balloon inflation. The additional delay due to the inter-hospital transport is the subject of this analysis. Only patients who underwent primary angioplasty for acute MI were included to allow assessment of the time to reperfusion, defined as time to first balloon inflation. In addition, TIMI flow grade was assessed. To study the influence of treatment delay due to transportation, each of the transferred patients (n = 207) was matched to one non-transferred patient. Criteria for matching were: age, sex, infarct location, presentation delay and Killip class. Time intervals (onset of chestpain, presentation delay, transportation time, first balloon inflation) as well as all clinical and angiographic data have been prospectively recorded in our database. Transfer patients were transferred from 15 community hospitals to our hospital for primary angioplasty from December 1993 to November 1996. Our hospital serves as angioplasty center in the region with approximately 1.5 million inhabitants. Travel distances range from 2 to 43 miles.

Study design.

Acute MI was diagnosed if a patient had persistent symptoms of chestpain lasting more than 30 minutes and had ST segment elevation of ≥ 1 mm in at least 2 contiguous leads. The indications

for transfer were: electrocardiographic evidence of an anterior or large inferior infarction, contra-indications for thrombolytic therapy (relative or absolute) or hemodynamic instability (Killip class > 1). The cumulative sum of ST elevation was scored on the diagnostic electrocardiogram. The exclusion criteria were identical as previously described (11). All transfer patients underwent immediate coronary angiography followed by primary angioplasty if indicated; patients were not treated with primary angioplasty if they had severe multivessel coronary artery disease or involvement of the left main coronary artery which made subsequent urgent coronary bypass grafting (CABG) necessary. Patients with an open infarct related vessel (IRV) in whom no reperfusion therapy was indicated, were treated conservatively. After primary angioplasty, flow through the IRV was scored according to the TIMI classification. The angiograms were all read by two cardiologists blinded for group allocation and clinical data. Primary angioplasty was considered successful if the residual stenosis in the IRV was less than 50% and TIMI grade 3 flow was present after the procedure.

Enzymatic infarct size
Infarct size was determined by measurements of enzyme concentrations with lactate dehydrogenase as reference enzyme (LDH Q72). A two-compartment model was used, which has been validated in studies on the turnover of radio-labeled plasma proteins and circulating enzymes. Cumulative enzyme release was calculated from serial measurements up to 72 h after symptom onset. Samples were obtained on admission and every 12 h to 72 h thereafter. From these measurements, an area under the curve was calculated, from at least five measurements. Further details of this methods have been described before (11,13,19,20).

Left ventricular function
At 6 month follow up left ventricular ejection fraction (LVEF) was measured with a radionuclide technique as previously described (11,13). Measurements were done by the multiple-gated equilibrium method after labeling of red blood cells with technetium 99m pertechnetate. A g-camera (General Electric, Milwaukee, WI, USA) was used. The global LVEF was calculated with the PAGE program (version 2.3).

Clinical outcome
Follow-up information was obtained for all patients. Hospital records of patients who visited our outpatient clinic were reviewed. Information on transferred patients was obtained from referral cardiologists. If necessary, additional information was gathered by telephone contact with general physicians or patients.

Clinical parameters
In this analysis we compared the following clinical parameters: enzymatic infarct size (LDH Q72), LVEF and TIMI flow after primary angioplasty was scored. At 6 month follow up mortality (of all causes) and recurrent MI were evaluated in both groups. Recurrent MI was defined as the combination of chest pain, changes in the ST-T segment at rest, and a second increase in the creati-ne kinase level to more than two times the upper limit of normal, or an increase of more than 200 IU per liter over the previous value if the level had not dropped below the upper limit of normal (11). Recurrent infarction and mortality were assessed at 6 month follow-up.

Statistical methods
Time intervals are presented as medians with 25th and 75th percentiles. Data were analyzed as

a matched pairs study. The Wilcoxon signed rank test was used to compare means of continuous variables and the chi-square test or Fischer exact test for discrete variables. Two sided P-values < 0.05 were considered to be significant.

Results

During a three year period 236 patients with acute MI were transferred from referral hospitals. Of these, 213 patients were treated with primary angioplasty. Eight patients with severe multivessel coronary artery disease or involvement of the left main coronary artery underwent urgent CABG. In another 8 patients the IRV was open and no reperfusion therapy was indicated. Matching criteria were available for all of the patients who underwent primary angioplasty. No match could be found for 6 (3%) of the transferred patients, so 207 transfer patients were one to one matched to non transferred patients. The matching procedure resulted in an equal distribution of all matched baseline characteristics as shown in table 1.

Table 1.

Baseline characteristics

	Transfer group n = 207	Non transfer group n = 207
Age (years) (median, SD)	58 (11)	58 (10)
Male sex (%)	85	85
Anterior infarct location (%)	76	76
Heart rate (beats/min) (mean, SD)	79 (19)	76 (19)
Killip class 1-2 (%)	92	92
Killip class 3-4 (%)	8	8
Previous angina (%)	61	54
Contraindication for thrombolysis (%)	12	7
Median presentation delay (min)	90	100
(25th, 75th)	(60, 145)	(67, 180)
Cumulative sum of ST elevation (mm) (SD)	14 (10)	14 (11)
Previous MI (%)	11	14
Previous CABG (%)	1	0.5
Multivessel disease (%)	55	48
Diabetes (%)	5	7

CABG = coronary artery bypass surgery

There were more patients with a contraindication for thrombolysis and with multivessel disease in the transfer patients, but these differences were not significant. The cumulative sum of ST elevation showed no difference between the groups. Also the presence of other baseline characteristics such as previous infarction, previous CABG, multivessel disease and diabetes were equally divided. The transfer patients were slightly younger (58 years $\pm$ 11) than patients who were enrolled in our infarction trials in the past years, and a larger majority had an anterior infarct location (Table 1). For the 207 matched transfer patients the median treatment delay was 103 min compared to 60 minutes in the non transferred patients, so the transfer resulted in an additional delay in time to reperfusion of 43 minutes (Table 2).

Table 2.

In-hospital clinical outcome

	Transfer group n = 207	P-value	Non transfer group n = 207
Median treatment delay (min) (25th, 75th)	103 (80, 130)	<0.0001	60 (45, 80)
Non fatal reinfarction	4 (2%)	NS	5 (2%)
Non fatal ischemic stroke	1 (0.5%)	NS	0 (0%)
Death	10 (5%)	NS	7 (3%)
TIMI grade 3 flow after PTCA	178 (86%)	NS	186 (90%)
	n = 137		n = 137
Enzymatic infarct size (LDHQ72)	1536 IU	< 0.005	1235 IU

NS = not significant; TIMI = Thrombolysis in Myocardial Infarction; PTCA = percutaneous transluminal coronary angioplasty; LDH = lactate dehydrogenase

In-hospital clinical outcome

TIMI grade 3 flow was obtained in most patients; 86% in the transfer group and in 90% in the non transfer group (Table 2). During the hospital period 10 transfer patients (5%) died and 7 (3%) non transfer patients. Five patients died within the first 48 h, before serial enzyme release could be determined. Cumulative enzyme release during the first 72 h could be calculated in 145 (70%) of the transfer patients (mean enzyme release: 1544 IU, SD 1106 IU) and in 193 (93%) of the non transfer patients (mean enzyme release: 1196 IU, SD 1004 IU). This resulted in 137 matched pairs (66%) in whom enzyme release could be calculated and compared. For 49 (24%) patients in the transfer group and for 16 (8%) patients in the non transfer group, there were inadequate data for analysis. The enzymatic infarct size was 1536 IU in the transferred patients, compared to 1235 IU in the non transfer patients (P-value < 0.005) (Table 2).

Six month follow-up

At 6 month a total of 15 (7%) patients in the transfer group and 12 patients in the non transfer group (6%) had died. Reinfarction had occurred in 8 (4%) of the transfer patients and in 6 (3%) of the non transfer patients (Table 3). LVEF was measured at 6 month, in 139 matched pairs (72%) of the survivors. Non transfer patients had an ejection fraction of 47% vs 43% in the transfer patients (P = 0.003). In 27 (13%) patients in the transfer group and in 17 (8%) patients in the non transfer group a LVEF measurement was not available, in a small number of patients the test was performed but inconclusive due to an irregular heart rhythm (three patients in the transfer group and two in the non transfer group). Reasons for not performing this test were inability to return to our hospital (e.g. travel distance) or patients refusal.

Table 3.

Six months clinical outcome

	Transfer group n = 207	P-value	Non transfer group n = 207
Non fatal reinfarction	8 (4%)	NS	6 (3%)
Non fatal ischemic stroke	1 (0.5%)	NS	2 (1%)
Death	15 (7%)	NS	12 (6%)
	n = 139		n = 139
Ejection fraction	43%	0.003	47%

NS = not significant

Discussion

Treatment delay

In this study we analyzed the treatment delay in patients who were transferred from hospitals without angioplasty facilities to our center for primary angioplasty. In this setting patients who were transferred had an additional treatment delay of 43 minutes. Although the time delay had no effect on the patency rate after the angioplasty procedure, there was more extensive myocardial damage. As patency is the major determinant of survival, this results in a comparable 6 months clinical outcome of transferred patients compared to non-transferred patients. However, long term survival is yet unknown and LVEF may become more important over time. The analysis shows that in this cohort of patients the myocardial damage due to the additional delay inherent to transfer to an angioplasty center in high risk patients with acute MI may be outweighed by the high rate of early, sustained and complete reperfusion as a result of the primary angioplasty procedure. This high rate of successful angioplasty applies to patients with ischemic times up to 6 h, as most of the transfer patients had short presentation delays (median 90 min) and the additional delay caused by the transfer was limited. Few patients with longer presentation delays were transferred, but it may be expected that procedure success rates will be lower after 6 h (17).

Myocardial salvage

The effects of treatment delay could be measured in enzymatic infarct size as well as LVEF. However more factors may play a role in the degree of myocardial salvage. The presence or absence of collaterals, the size of the infarct area, history of previous infarction or previous angina, will be responsible for a wide range of outcomes in individual patients. Nevertheless, for these patient groups a difference in measured infarct size and LVEF was found in relation with a median treatment delay of 43 minutes.

Transfer for primary angioplasty

Only a limited number of hospitals have angioplasty facilities and most patients with acute MI will be admitted to hospitals without these facilities. Urgent transfer of infarct patients to angioplasty centers is an alternative option to treatment with thrombolysis administered at the community hospital. By evaluation of this cohort of patients who have been transferred for primary angioplasty to our hospital it is demonstrated that this treatment strategy is safe and can be done effectively. Inter-

hospital delays are minimized by timely referral by the physician at the referral hospital. On arrival at the angioplasty center the patient can be brought to the catheterization laboratory immediately. Measures to prepare the catheterization laboratory can be made during the patient transport.

Study limitations

This study population represents a selected group of patients, slightly younger than the usual infarct population and with a short presentation delay. Concerning the high percentage of anterior infarctions the transfer patients are a population at higher risk. This fact has probably contributed to the differences found in enzymatic infarct size and LVEF. In patients with non-anterior infarctions, the area at risk would be smaller, and differences expressed in infarct size and LVEF might not be measurable. Also the fact that the total delay before treatment for both groups was within the period of myocardial salvage may have contributed in the difference between the transported patients and matched controls. A bias might be introcuced by the fact that some of the clinically better patients did not return for the LVEF test, but only in 13% of the transported patients and in 8% of the matched controls LVEF measurement was not available. The large majority of patients had completed data for enzymatic infarct size and LVEF, but in a matched comparison the percentage of available results in patient pairs is obviously lower. This analysis does not answer the question whether it would be more beneficial to transfer a patient for primary angioplasty than to treat these patients immediately with thrombolysis. This comparison can only be made by means of a randomized trial.

Conclusions

This analysis demonstrates that the success of primary angioplasty in patients with acute MI is not influenced by an additional delay due to inter-hospital transfer. Analysis of time intervals showed that in our setting the additional delay is limited and only 43 minutes longer in patients transferred from community hospitals compared to patients admitted directly to the angioplasty center. Therefore total time from symptom onset to first balloon inflation is within a 6 h time window for most patients. The effect of the additional treatment delay on myocardial salvage measured in enzymatic infarct size and in LVEF at 6 month was estimated by a matched pair analysis. Although the additional delay was limited there was a measurable effect on myocardial salvage, which indicates the need to reduce time to treatment in patients treated with primary angioplasty. In this particular setting and infrastructure the transfer of patients for primary angioplasty is safe and can be done with a limited loss of time. The high success rate in the transfer patients is encouraging to apply this treatment strategy for patients with high risk features (contraindications for thrombolysis, anterior infarct location and/or hemodynamic instability). However, in each individual patient it should be clear that an additional delay during the first hours of acute MI results in more extensive myocardial damage. If transfer for primary angioplasty is the treatment strategy of choice then the rule "time is muscle" still holds good.

Clinical implications

The strategy to transfer patients with acute MI admitted to a community hospital without angioplasty facilities to an angioplasty center is safe and effective. If the time from symptom onset to treatment does not exceed the period in which myocardial salvage is possible, the results of primary angioplasty will be comparable to those obtained in patients directly admitted to an angioplasty center. Reductions in time to treatment can result in substantial additional myocardial salvage.

We appreciate the complementary advice and critical review by Freek Verheugt, MD, PhD. We thank the referral doctors from the 15 community hospitals in the region for their cooperation.

References

1. Fibrinolytic Therapy Trialistsí (FFT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311-22.
2. Gruppo Italiano per lo studio della streptochinasi nellí infarcto miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;I:397-402.
3. Hermens WT, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarction size. Lancet 1992;340:1297. Letter.
4. Lee KL, Woodlief LH,Topol EJ, et al, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from a international trial of 41 021 patients. Circulation 1995;91:1659-68.
5. Newby LK, Rutsch WR, Califf RM, et al, for the GUSTO-I Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996; 27:1646-55.
6. Califf RM, Newby LK. How much do we gain by reducing time to reperfusion therapy? Am J Cardiol 1996;78 (suppl 12A):8-15.
7. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-22. [Erratum N Engl J Med 1994;330:516.
8. Brodie BR, Stuckey TG, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1996;28:319-25.
9. Lamas GA, Flaker GC, Mitchell G, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. Circulation 1995;92:1101-9.
10. Simes RJ, Topol E, Holmes DR, et al; for the GUSTO-I Investigators. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. Circulation 1995; 91:1923-8.
11. Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coro-nary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-4.
12. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
13. De Boer MJ, Suryapranata H, Hoorntje JCA, et al. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intra venous streptoki-nase in acute myocardial infarction. Circulation 1994;90:753-61.
14. Zijlstra F, Beukema WP, van't Hof AWJ, et al. A randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with an acute myocardial infarction. J Am Coll Card 1997;29:908-12.
15. Ellis SG, OíNeill WW, Bates E, Walton JA, Nabel EG, Topol EJ. Coronary angioplasty as primary therapy for acute myocardial infarction 6 to 48 hours after symptom onset: report of an initial experience. J Am Coll Cardiol 1989;13:1122-6.
16. Stone GW, Brodie B, Griffin J, et al. Should the risk of delaying reperfusion prohibit inter-hospital transfer to perform primary PTCA in acute myocardial infarction? Circulation 1996 (Abstract);94:I-331.

17. Van't Hof AWJ, Liem AL, Suryapranata H, Hoorntje JCA, De Boer MJ, Zijlstra F. Clinical presentation and outcome of patients with early, intermediate and late reperfusion therapy by primary coronary angioplasty for acute myocardial infarction. Eur Heart J 1998;19:118-23.
18. Zijlstra F, van't Hof AWJ, Liem AL, Hoorntje JCA, Suryapranata H, de Boer MJ. Transferring patients for primary angioplasty: a retrospective analysis of 104 selected high risk patients with acute myocardial infarction. Heart 1997;78:333-6.
19. Van der Laarse A, Vermeer F, Hermens WT, et al. Effects of intracoronary streptokinase on infarct size estimated from cumulative enzyme release and on enzyme release rate: a randomized trial of 533 patients with acute myocardial infarction. Am Heart J 1986;112:672-8.
20. De Zwaan C, Willems GM, Vermeer F, et al. Enzyme tests in the evaluation of thrombolysis in acute myocardial infarction. Br Heart J 1988;59:175-83.

CHAPTER 6

Incidence and Predictors of Restenosis after Successful Primary Coronary Angioplasty for Acute Myocardial Infarction: The Importance of Age and Procedural Result

Arnoud W.J. van 't Hof, MD, Menko-Jan de Boer, MD, PhD,
Harry Suryapranata, MD, PhD, Jan C.A. Hoorntje, MD, PhD,
Felix Zijlstra, MD, PhD

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

American Heart Journal, in press

Abstract

Background: Previous studies have suggested that restenosis and reocclusion occur frequently in patients with acute coronary syndromes. This study was undertaken to assess the incidence and predictors of restenosis in a cohort of patients who underwent successful primary coronary angioplasty for acute myocardial infarction.

Methods: 312 patients, who underwent successful primary angioplasty of a native coronary vessel, were candidates for follow-up coronary angiography. This was performed in 284 patients (92%) at 3 or 6 months follow-up. Quantitative coronary angiography was performed using the CMS-system. Multivariate analysis was performed to determine independent predictors of restenosis

Results: Restenosis, defined as a diameter stenosis of more than 50%, occurred in 27% of patients at 3 months and in 37% of patients at 6 months follow-up. Reocclusion occurred in 4% and 6% respectively. Reference diameter (vessel size) was related to restenosis. Age and lumen diameter immediately after angioplasty were independent predictors of restenosis. Young patients (<50 years) and patients with a minimal luminal diameter of more than 2.5 mm, had restenosis rates of less than 25%. The radionuclide ejection fraction was 46% in patients with restenosis compared to 47% in patients without restenosis.

Conclusions: The incidence of restenosis after successful primary coronary angioplasty for acute myocardial infarction is comparable to the reported incidence after elective coronary angioplasty for stable angina. Restenosis is related to age and the lumen diameter after angioplasty and does not affect left ventricular function in this population.

(Am Heart J, in press)

Introduction

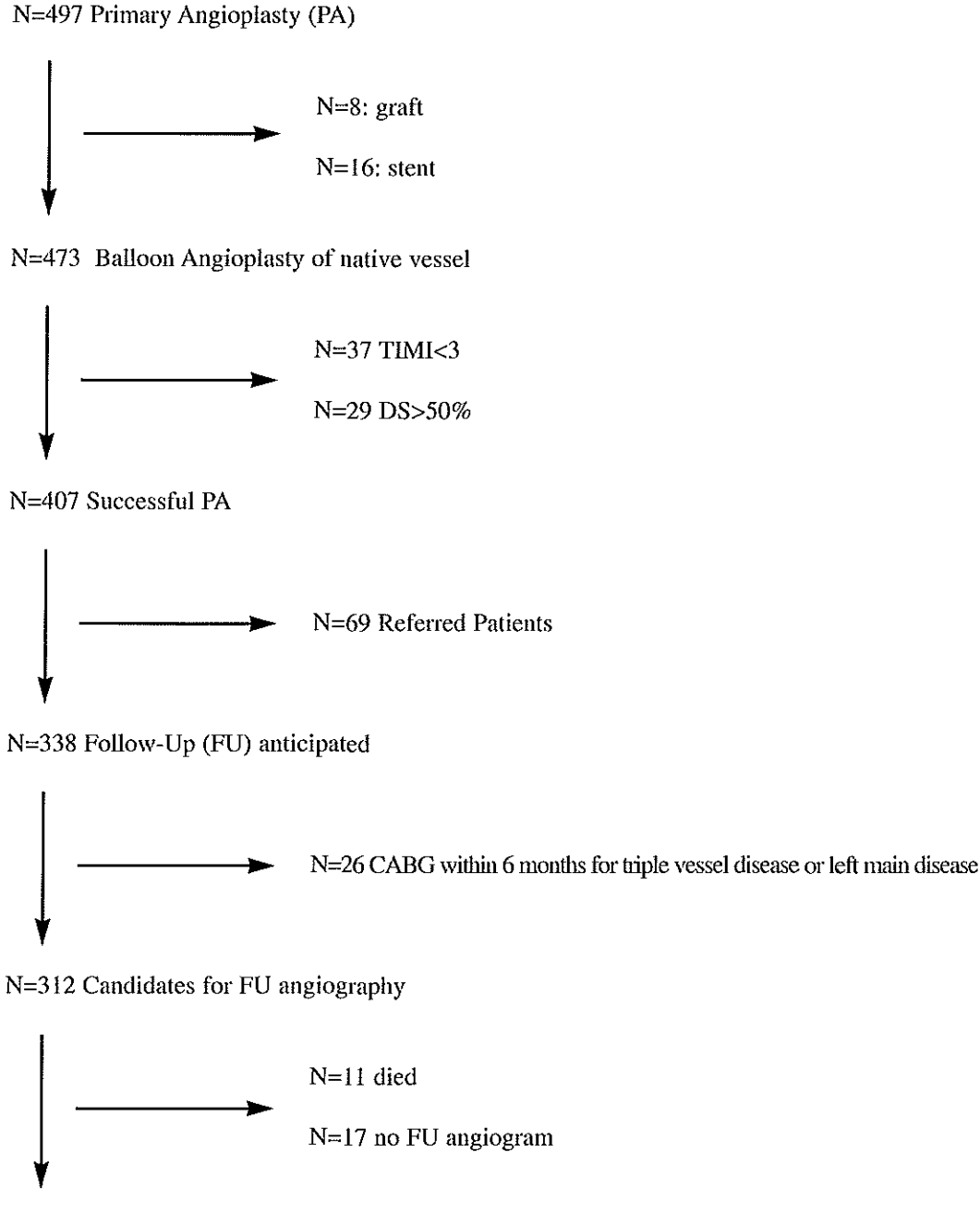
Primary coronary angioplasty has been shown to be an effective strategy in the treatment of patients with acute myocardial infarction. Beneficial immediate and longterm results have been described with regard to patency of the infarct-related vessel, preservation of left ventricular function and reduction of mortality (1-4). A number of studies have described late clinical outcome and found recurrent ischemia to occur in 10%-23% of patients (5-8). However, restenosis and reocclusion may occur without symptoms and therefore may be undetected. It has been suggested that restenosis in patients with acute myocardial infarction might be more prevalent compared to restenosis after angioplasty for stable coronary artery disease due to a high thrombus content of the lesion. This may predispose to restenosis and in particular to reocclusion in patients with unstable angina (9,10). A detailed quantitative description of restenosis and reocclusion after primary angioplasty in patients with acute myocardial infarction has not yet been performed. The aim of this study is to assess restenosis and reocclusion by quantitative coronary angiography (QCA) in a cohort of consecutive infarct patients successfully treated with primary angioplasty, and to describe the clinical and angiographic variables that are related to restenosis. As reocclusion may have an impact on left ventricular function and mortality in thrombolytic treated patients (11,12) and in patients treated with primary angioplasty (13,14), we also describe left ventricular function and clinical outcome.

Materials and Methods

Study population

From August 1990 until December 1995, 312 consecutive patients were included, who met the following criteria: 1) acute myocardial infarction characterized by symptoms that persisted more than 30 minutes, accompanied by ST elevations of more than 1 mm (0.1 mV) in two or more contiguous electrocardiographic leads; 2) an age less than 75 years; 3) presentation within 6 hours after symptom onset or between 6 and 24 hours if there was evidence of continuing ischemia; 4) a successful primary angioplasty procedure of a native infarct-related artery, defined as TIMI 3 flow of the infarct-related vessel and a diameter stenosis of less than 50%, measured by quantitative coronary angiography. Patient selection is described in Figure 1.

Figure 1.
Flow chart



Patients were excluded when follow-up in our hospital could not be anticipated (N=69), if primary stenting of the infarct related vessel was performed (N=16) or if patients underwent urgent

or semi-elective bypass surgery, based on the findings of the initial coronary angiogram (N=26). Of the 312 patients who met the inclusion criteria, 284 patients had repeat angiograms suitable for quantitative coronary angiography (92%). Eleven patients (3%) died before the follow-up angiogram was performed and from 17 patients (5%) no angiogram was available, because of either patient refusal or contraindications to follow-up-angiography. Of the total study population of 284 patients, A group of 115 patients (40%) had their follow-up angiograms planned at 3 months (112 days), according to the protocol of the first Zwolle trial (1). The other 169 patients (60%), part of the second Zwolle trial (15), were scheduled for recatheterization at 6 months. Patients who were reinvestigated before their appointed time because of evidence of recurrent ischemia were analyzed in their initially assigned follow-up group.

Coronary Angiography and Angioplasty.

All patients were treated with intravenous acetylsalicylic acid and intravenous nitroglycerin in a dose to maintain a systolic blood pressure of 110 mm Hg. Intravenous heparin was given in a bolus of 10,000 U and thereafter in a continuous infusion in a dosage to keep the activated partial thromboplastin time between 2 and 3 times the normal value for at least 2 days. Ischemic time was calculated as the time from symptom onset to the first balloon inflation. The angioplasty procedure was performed using standard techniques. Flow through the infarct-related vessel was scored according to the Thrombolysis in Myocardial Infarction (TIMI) classification (16). Data of the coronary angiography and angioplasty procedures were collected and graded by two of the investigators. Consensus on collateral flow, procedural success, TIMI flow before and after the angioplasty procedure, identification of the infarct-related vessel, and extent of coronary artery disease was reached in all cases. TIMI flow before angioplasty was judged at first injection of contrast material. Collaterals to the infarct-related vessel were classified as proposed by Rentrop et al (17). Grade 0: no visible filling of any collateral channels, grade 1: filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel, grade 2: partial filling via collateral channels of the epicardial segment of the vessel, grade 3: complete filling of the vessel. Restenosis was defined as the presence of a more than 50% diameter stenosis at follow-up angiography, including the vessels with reocclusion. Reocclusion was defined as a reduction in TIMI perfusion grade 3 to TIMI grades 0 or 1.

Quantitative Coronary Angiography (QCA).

A quantitative analysis of all infarct-related vessels was performed with a personal-computer-based QCA system, (CMS: Cardiovascular Measurement System, Software version 2.0, Medis Medical Imaging Systems, Nuenen, the Netherlands). This has been described previously (1,18). The system uses a high-quality cine-to-video converter that allowed a selected cine frame to be projected onto a digital video camera through an optical zoom lens. The video signal of the magnified region of interest was subsequently digitized. For calibration, the boundaries of a nontapering part of the catheter were determined automatically over a length of approximately 2 cm. To determine the contours of the vessel the user had only to indicate the beginning and end of the coronary segment to be analyzed, after which a path was computed connecting these two points. The contour procedure was then performed iteratively by resampling the image along scan lines perpendicular to the path computed in the first iteration. Next, a matrix of cost coefficients was computed that represented for each point in the resampled matrix the edge strength based on the weighted sum of the first and second derivative functions. The initial contours were found by the minimal-cost contour-detection technique applied to the cost-coefficient matrix. In

the second iteration, the contours determined in the first iteration functioned as models for the subsequent determination. The edge strengths were corrected for the limited resolution of the entire imaging chain, a procedure that is particularly important for the accurate measurement of small vessels. From the final contours a new center line was computed. A diameter was determined in absolute terms (in millimeters) by computing along the vessel center line the shortest distances between the left and right contours. The reference diameter was defined as previously described (19). As the computer algorithm is unable to measure total occlusions, a value of 0 mm was substituted for the MLD and a value of 100% for the percent diameter stenosis.

Left Ventricular Function

Left ventricular ejection fraction was measu-red with a radio-nuclide technique before hospital discharge and during follow-up. The technique used in our hospital has been previ-ously des-cribed (1). Briefly, it involved the multiple-gated equilibrium method after the labeling of red blood cells with [99mTc] pertechnetate. A gamma camera (General Electric Milwaukee) with a low-energy, all purpose, parallel-hole collimator was used. The global ejection fraction is calculated automatically by a computer (Star View, General-Electric), with the PAGE™ program. The data on ejection fractions were gathered by a specialist in nuclear medicine, who was blinded to the clinical data.

Statistical analysis.

Differences between group means were tested by a two-tailed Student t test. A chi-square method was used to test differences between proportions. The Fisher exact test was used if there was an expected cell value < 5. Statistical significance was defined as a P value < 0.05. Restenosis was the primary outcome variable and defined as a categoric variable. Univariate and multivariate predictors of restenosis were analyzed according to a model previously described by Hirshfeld et al (20). In brief: a two by two chi-square analysis was used to examine the relation of categoric variables to restenosis and for continuous variables both univariate logistic regression and 4 by 2 chi-square analysis was done after division of the variables into quartiles. A multivariate logistic regression analysis was performed to find independent variables related to restenosis. Only variables which were (borderline) significantly related to restenosis after univariate testing were included in the multivariate analysis.

Table 1.

Baseline and Angiographic characteristics of 284 patients with successful Primary Angioplasty

	3 months (N=115)	6 months (N=169)	P-value
Day of FU-angiogram	94 ± 64	135 ± 82	<0.001
Age	58 ± 10	57 ± 11	0.28
Male Gender	99 (86%)	134 (79%)	0.14
Anterior Infarction	59 (51%)	99 (59%)	0.23
Previous PTCA	6 (5%)	8 (5%)	0.85
Previous CABG	2 (2%)	2 (1%)	0.53
Previous Infarction	20 (18%)	13 (8%)	0.01
Preinfarction Angina	64/108 (59%)	85/169 (50%)	0.14
Hypertension	23 (20%)	31 (18%)	0.73
Smoking	54 (47%)	84 (50%)	0.65
Family History of CAD	49 (43%)	73 (43%)	0.92
Ischaemic Time (min)	254 ± 221	268 ± 215	0.61
multi-VD	66 (57%)	80 (47%)	0.10
IRV			
LAD	49 (43%)	97 (57%)	0.01
CX	16 (14%)	17 (10%)	0.24
RCA	48 (43%)	54 (32%)	0.09
QCA before PA			
DS (%)	95 ± 11	94 ± 14	0. 63
MLD (mm)	0.16 ± 0.39	0.19 ± 0.40	0.54
QCA after PA			
DS (%)	25 ± 9	31 ± 11	<0.0001
MLD (mm)	2.30 ± 0.49	2.12 ± 0.48	0.003
Ref Diam (mm)	3.07 ± 0.64	3.07 ± 0.54	0.92
Balloonsize (mm)	2.93 ± 0.40	3.01 ± 0.37	0.10
Balloon to Artery ratio	0.98 ± 0.15	0.99 ± 0.13	0.65
Any dissection (N=252)	30/111 (27%)	50/141 (36%)	0.16

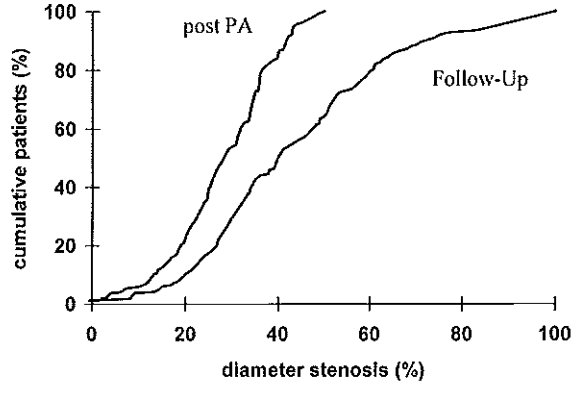
FU: follow-up, PTCA: Percutaneous Transluminal Coronary Angioplasty, CABG: Coronary Artery Bypass Grafting, CAD: Coronary Artery Disease, Ischaemic Time: time from symptom onset to the first balloon inflation, VD: Vessel Disease, IRV: Infarct-Related-Vessel, LAD: Left Anerior Descending Artery, CX: Circumflex Coronary Artery, RCA: Right Coronary Artery, QCA: Quantitative Coronary Angiography, PA: Primary Angioplasty, MLD: Minimal Luminal Diameter, Ref Diam: Reference Diameter

Results

Baseline characteristics of patients in the two groups are listed in Table 1. The mean time from angioplasty to follow-up angiography in the 3 and 6 months group was 94 days and 135 days respectively. Baseline characteristics were comparable between the two groups, apart from a lower percentage of patients with a previous myocardial infarction and a higher number of patients with an occluded left anterior descending artery in the patients, who were recatheteri-

zed at 6 months. These differences are due to the study design of the 2 consecutive Zwolle trials (1,15). The first Zwolle trial randomized all patients to thrombolytic therapy or primary angioplasty (1) wheras the second Zwolle trial randomized only low risk patients and treated all high risk patients with primary angioplasty (15). The results of the quantitative coronary angiography analysis in the 284 patients who had angiographic follow-up are shown in Table 2 and Figure 2.

Figure 2.



Graph showing cumulative distribution of percentage diameter stenosis immediately after primary coronary angioplasty and at follow-up. PA: Primary Angioplasty, DS: Diameter Stenosis

Patients in the 3 months group had a lower diameter stenosis and a higher minimal luminal diameter immediately after primary angioplasty. At follow-up angiography, a trend is present towards a more severe diameter stenosis and a smaller minimal luminal diameter with later follow-up angiography. The absolute change in diameter stenosis and minimal luminal diameter from post angioplasty to follow-up, is not different between the two groups.

Table 2.

Results of Quantitative Coronary Angiography at 3 and 6 months

	3 months (N=115)	6 months (N=169)	P-value
DS (%)			
Post PA	25 ± 11	31 ± 11	0.00003
FU	38 ± 23	46 ± 21	0.003
D DS	+13 ± 23	+15 ± 23	0.51
MLD (mm)			
Post PA	2.30 ± 0.49	2.12 ± 0.48	0.003
FU	1.76 ± 0.90	1.55 ± 0.90	0.06
D MLD	-0.54 ± 0.84	-0.57 ± 0.87	0.80
Ref Diam (mm)			
Post PA	3.07 ± 0.64	3.07 ± 0.54	0.93
FU	3.03 ± 0.67	3.16 ± 0.57	0.10
D Ref Diam	-0.05 ± 0.55	+0.07 ± 0.38	0.04

DS: Diameter Stenosis , PA: Primary Angioplasty, FU: Follow-Up, MLD: Minimal Luminal Diameter, Ref Diam: Reference Diameter, D: difference between Follow Up and Post Angioplasty measurements

Restenosis is present in 27% of patients at 3 months and in 37% at 6 months follow-up. Reocclusion occurs in 4% and 6% of patients respectively (Table 3).

Table 3.

Restenosis and Reocclusion at 3 and 6 months follow-up

	3 months (N=115)	P-value	6 months (N=169)
Restenosis*	27%	0.09	37%
Reocclusion**	4%	0.56	6%

*Restenosis is defined as a Diameter Stenosis of more than 50% by quantitative coronary angiography, **Reocclusion is defined as a reduction of TIMI 3 to TIMI 0 or 1 flow

Categoric and continuous variables related to restenosis by univariate analysis are described in Table 4A and 4B and C respectively. Age, as clinical variable and balloonsize, balloon to artery ratio, minimal luminal diameter and reference diameter after angioplasty as angiographic variables were significantly different in patients with and without restenosis. After multivariate analysis only age and minimal luminal diameter after angioplasty were independent predictors of restenosis (Table 5).

Table 4A.

Univariate Analysis: Categorical Variables

Variable	No Restenosis 67% (191)	Restenosis 33 % (93)	P value
Baseline			
Male Gender	159 (83%)	74 (80%)	0.45
Killip class 1	160/189 (85%)	83/92 (90%)	0.20
Anterior Infarct	102 (53%)	56 (60%)	0.21
Previous PTCA	7 (4%)	7 (8%)	0.16
Previous CABG	3 (2%)	1 (1%)	0.60
Previous Infarction	19 (10%)	14 (15%)	0.21
Previous Angina	94/184 (51%)	55/93 (59%)	0.20
Hypertension	33 (17%)	21 (23%)	0.29
Smoking	94 (49%)	44 (47%)	0.76
Family History of CAD	83 (44%)	39 (42%)	0.81
Diabetes	13/188 (7%)	7/93 (8%)	0.85
Preprocedure Related			
Multi-VD	96 (50%)	50 (54%)	0.58
IRV (%)			
LAD	95 (51%)	50 (54%)	0.55
CX	25 (13%)	8 (9%)	0.27
RCA	69 (36%)	33 (36%)	0.94
Collaterals Rentrop > 0*	61/178 (34%)	27/75 (36%)	0.78
Open IRV before PA **	32/188 (17%)	18/79 (23%)	0.27
Postprocedure Related			
Balloonsize > 3mm	51/188 (27%)	12/91 (13%)	0.01
Any Dissection	50/171 (29%)	30/81 (37%)	0.21
IABP treatment	41 (22%)	17 (18%)	0.53

PTCA: Percutaneous Transluminal Coronary Angioplasty, CABG: Coronary Artery Bypass Grafting, CAD: Coronary Artery Disease, VD: Vessel Disease, IRV: Infarct-Related-Vessel, LAD: Left Anerior Descending Artery, CX: Circumflex Coronary Artery, RCA: Right Coronary Artery, *: angiographic collaterals visible on the pre-treatment angiogram during injection of the contralateral coronary artery, **: TIMI 2 or 3 flow on the pre-treatment angiogram, IABP: Intra Aortic Balloon Pumping

Table 4B.

Univariate Chi-Square Analysis: Continuous Variables

Variable	Quartile 1 Range Rest/Total (%)	Quartile 2 Range Rest/Total (%)	Quartile 3 Range Rest/Total (%)	Quartile 4 Range Rest/Total (%)	Chi Square (P-value)
Baseline Variables					
Age (years)	30 to 50 17/76 22%	51 to 58 25/73 34%	59 to 66 25/67 37%	67 to 81 26/68 38%	5.36 (0.15)
Ischemic Time (min)	40 to 148 20/70 29%	149 to 185 26/71 37%	186 to 283 22/73 30%	248 to 1534 24/69 35%	1.39 (0.71)
Postprocedure Variables					
DS (%)	1 to 22 20/71 28%	23 to 28 24/72 33%	29 to 36 26/82 32%	37 to 50 23/59 39%	1.77 (0.69)
MLD (mm)	1.26 to 1.85 33/74 45%	1.86 to 2.14 23/70 33%	2.15 to 2.51 20/69 29%	2.52 to 4.03 17/71 24%	7.66 (0.05)
Ref Diam (mm)	1.89 to 2.64 23/71 32%	2.65 to 3.01 33/75 44%	3.02 to 3.40 21/68 31%	3.41 to 5.03 16/70 23%	7.53 (0.06)
Balloon to Artery ratio	0.63 to 0.89 21/71 30%	0.90 to 0.96 18/63 29%	0.97 to 1.09 26/75 35%	1.10 to 1.41 26/70 37%	1.56 (0.67)

Ischaemic Time: time from symptom onset to the first balloon inflation, DS: Diameter Stenosis, MLD: Minimal Luminal Diameter, Ref Diam: Reference Diameter

Table 4C.

Univariate Logistic Regression Analysis: Continuous variables

	P value
Baseline Variables	
Age	0.08
Ischemic Time	0.23
Preprocedure Variables	
DS (%)	0.73
MLD (mm)	1.00
Postprocedure Variables	
DS (%)	0.26
MLD (mm)	0.002
Ref Diam (mm)	0.02
Balloon to Artery ratio	0.95

Ischaemic Time is defined as time from sympton onset to the first balloon inflation, DS: Diameter Stenosis, MLD: Minimal Luminal Diameter, Ref Diam: Reference Diameter

A radionuclide ejection fraction measurement was available in 274 (95%) patients pre-discharge and in 251 (91%) of patients at follow-up. Left ventricular ejection fraction at follow-up was not significantly different between patients with and without restenosis or reocclusion (Table 6).

Table 6.

Clinical and Angiographic characteristics of patients with and without restenosis

	No Restenosis 67% (191)	P-value	Restenosis 33 % (93)
EF pre discharge (%)	47 ± 11	0.62	46 ± 12
EF Follow up (%)	48 ± 11	0.56	47 ± 11
re MI	1 (0.5%)	0.02	5 (5%)
re PTCA	24 (13%)	<0.0001	31 (33%)
CABG	11 (6%)	0.04	12 (13%)
Death	1 (0.5%)	0.60	1 (1%)
Collaterals*			
Rentrop 0 (%)	96	<0.0001	65
Rentrop 1 (%)	3	0.001	20
Rentrop 2 (%)	1	0.001	15

EF: Ejection Fraction, MI: Myocardial Infarction, PTCA: Percutaneous Transluminal Coronary Angioplasty, CABG: Coronary Artery Bypass Grafting, *: angiographic collaterals visible on the follow-up angiogram during injection of the contralateral coronary artery

During the follow-up period of 6 months, 6 patients (2%) suffered a non-fatal reinfarction, 55 patients (19%) had a repeat angioplasty procedure and 23 patients (8%) underwent coronary bypass surgery. Patients with restenosis or reocclusion had a higher incidence of recurrent myocardial infarction and coronary revascularization procedures. From the 93 patients with documented angiographic restenosis, 41 patients (44%) had either a second percutaneous coronary angioplasty procedure or underwent surgical revascularization. Patients with restenosis more often had visible collaterals on their follow-up angiogram compared to patients without restenosis. Table 7 summarizes the clinical consequences of reocclusion. At follow-up 84% of patients received Aspirin, 14% Coumadin, 13% Nitrates, 51% a b-blocker, 26% a Ca-antagonist, 12% Diuretics, and 26% of patients received an ACE-inhibitor.

Table 7.

Clinical consequences of reocclusion

Patient	age	gender	1/2/3 VD	day	IRV	collaterals*	symptoms	revascularization	QCA after PA (DS (%), Ref Diam (mm))
1	55	m	1	131	RCA		none	-	33, 2.70
2	52	m	2	118	RCA	2	none	-	34, 4.44
3	73	f	1	123	LAD	2	SA	PTCA	36, 2.26
4	51	m	2	5	CX	0	UA	PTCA	4, 2.65
5	64	m	1	108	CX	2	SA	-	28, 2.59
6	48	f	1	86	LAD	3	SA	CABG	31, 2.66
7	34	m	1	7	LAD	0	MI	PTCA	12, 2.75
8	64	f	3	104	CX		SA	CABG	35, 3.00
9	69	m	1	10	LAD		MI	PTCA	26, 2.73
10	56	m	3	1	RCA	0	MI	PTCA+stent	14, 2.82
11	34	f	1	165	RCA	2	none	-	10, 2.93
12	43	m	1	122	RCA	2	none	-	1, 3.12
13	59	m	1	176	CX	3	none	-	16, 3.21

VD: Vessel Disease, IRV: Infarct-Related-Vessel, LAD: Left Anerior Descending Artery, CX: Circumflex Coronary Artery, RCA: Right Coronary Artery, *: angiographic collaterals visible on the pre-treatment angiogram during injection of the contralateral coronary artery, QCA: Quantitative coronary angiography, PA: Primary Angioplasty, DS: Diameter Stenosis, MLD: Minimal Luminal Diameter, Ref Diam: Reference Diameter

Discussion

Restenosis

This study shows that restenosis after successful primary angioplasty for acute myocardial infarction occurs in 37% of patients 6 months after the index myocardial infarction. These findings are very similar compared to the results of conventional balloon angioplasty for stable angina patients (21) and compare favorably with the restenosis rate after elective angioplasty for chronic total occlusions or for patients with unstable angina pectoris (22,23).
Previous studies in patients who underwent primary angioplasty for acute myocardial infarction reported restenosis rates varying from 17% to 45% (1,6,8,24). Brodie et al (6) describes angio-

graphic restenosis, measured with a caliper technique in a subset of 65% of patients with a follow-up angiogram, and found restenosis to occur in 46 % of patients. This study included patients who had an unsuccessful primary angioplasty procedure as well. Nakagawa et al (24) recently reported a serial angiographic follow-up of a selected group of patients, who all had a 100% occluded infarct-related-vessel before intervention. They found a slightly higher restenosis rate at 4 months follow-up of 43%, mainly due to a higher rate of reocclusion.

Predictors of restenosis

Age was found to be an independent predictor of restenosis. This has also been described in studies of restenosis after elective PTCA for stable angina (25). In Table 4B it is shown that especially a young age (<50 years) is related to a low restenosis rate. No significant interaction between age and any baseline variable that might influence restenosis was found. A possible explanation might be the fact that in young patients an acute thrombotic occlusion occurs on a relative healthy coronary artery without much underlying coronary artery disease. Dilatation of the occlusion may mainly be matter of "thrombus squeezing". Other baseline characteristics, like diabetes and hypertension, which were found to be related to restenosis after angioplasty for stable or unstable angina (25), were not predictive in this cohort of infarct patients.
There was a strong relation between the occurrence of restenosis and the angiographic characteristics of the vessel after the angioplasty procedure. In Figure 2 it is shown that the follow-up diameter stenosis curve tends to diverge instead of making a parallel shift to the right. This shows that a wider lumen after the procedure is associated with less restenosis. This is confirmed by multivariate analysis in which the minimal luminal diameter after angioplasty is independently related to restenosis. The reference diameter of the vessel was related to restenosis as well. Patients with a reference diameter less than 3.0 mm had a significantly higher restenosis rate compared to patients who had a reference diameter greater than 3.0 mm (38% vs 27%, p=0.03). Reference diameter (vessel size) is related to lumen diameter after angioplasty, and therefore reference diameter was no longer predictive of restenosis after correction for minimal luminal diameter by multivariate analysis (Table 5).

Table 5.

Multivariate analysis

	Odds Ratio	95% CI	P-value
Baseline Variable			
Age (per quartile)	1.27	1.01 - 1.60	0.04
Postprocedure Variables			
MLD post (per quartile)	1.46	1.07 - 2.01	0.02
Ref Diam post (per quartile)	0.86	0.60 - 1.24	0.42
Balloon to Artery ratio (per quartile)	0.91	0.68 - 1.22	0.55
Balloon Diameter	1.10	0.52 - 2.34	0.81

MLD: minimal luminal diameter; Ref Diam: Reference Diameter

These findings are in accordance with previous studies, both in patients after elective angioplasty for stable angina as in myocardial infarct patients treated with either thrombolytic therapy

or primary angioplasty (24,26,27), who found the residual lumen diameter after reperfusion therapy to be strongly related to restenosis. This makes primary stenting, by which a large luminal diameter of the infarct-related vessel can be achieved, an attractive alternative therapy. Preliminary findings of this therapy indeed suggest superior angiographic and clinical results in patients with acute myocardial infarction, who are candidates for primary stenting (28).

Clinical consequences of restenosis

Patients with restenosis had a significantly higher rate of reinfarction and more often had repeat coronary revascularization procedures, compared to patient without restenosis. However, most patients with angiographic restenosis could be managed without a second intervention. Only patients with chest pain and non-invasive evidence of reversible ischemia were candidates for a second revascularization procedure. This is in accordance with recent findings of Brodie et al, and Nakagawa et al, who managed 55% and 51% of patients with angiographic restenosis without reintervention (6,24), and suggests that a strategy of watchful waiting in patients with restenosis after angioplasty for acute myocardial infarction is applicable (29).

Reocclusion

Reocclusion of the infarct-related vessel was seen in 5% of the study population. This is not higher than the reported reocclusion rate in a large patient cohort, who underwent elective balloon angioplasty for stable or unstable angina (9,10,30), and considerably lower than the reocclusion rate after successful thrombolytic therapy, in which rates varying between 10% and 35% have been described (11,31).

Influence of restenosis or reocclusion on left ventricular function

Recent reports state that reocclusion of the infarct related vessel has detrimental consequences for left ventricular function (11,12). Our data do not confirm these findings. Although there is a trend towards a lower left ventricular ejection fraction in patients with restenosis or reocclusion, this difference is not significant. This is probably related to the small number of patients with reocclusion, but might also be related to a concomitant increase in collateral circulation in patients with restenosis and reocclusion: patients without restenosis or reocclusion almost never had visible collaterals on their follow-up angiogram (Table 6). Patients with reocclusion had the highest grade of angiographic documented collaterals on their follow-up angiogram: 21% Rentrop class 1, 43% Rentrop class 2, and only 36% of patients with reocclusion did not have visible collaterals.

Time to follow up angiography

Studies performed in patients with stable angina showed that restenosis is a time related phenomenon with an increasing number of patients with restenosis with later time to follow-up angiography (32,33). This study was not designed to assess the influence of time to follow up angiography on restenosis. Comparison of the restenosis rate of the 2 groups who had angiography at different time intervals show that restenosis increases from 27% at 94 days to 37% at a mean of 135 days after angioplasty. However, the higher restenosis rate in the 6 months group might otherwise be explained by the smaller luminal diameter after angioplasty in this group, which has been shown to be an independent risk factor for development of restenosis.

Limitations of the study

This study describes restenosis in selected patients treated with primary angioplasty during a 5 year period and therefore results cannot be extrapolated to all patients treated with primary angioplasty. The excluded patients (N=213) were older (62 vs 58 years), more often had a previous myocardial infarction (21% vs 9%) and more often had multivessel disease (60% vs 50%). They had a significantly smaller minimal luminal diameter after primary angioplasty (1.97 vs 2.20 mm). Based on the findings of our study, it is to be expected that restenosis in this cohort of excluded patients might be higher compared to the study patients. Previous studies on restenosis after angioplasty for stable angina however, excluded the same kind of patients from follow up angiography (32,33). One might discuss the exclusion of referred patients from analysis. However, this patient group itself is a selected group of high risk infarct patients, and adding these patients to the study group might decrease the generalisability of the results.

Conclusion

Restenosis or reocclusion after successful primary coronary angioplasty for acute myocardial infarction occurred in 27% of the patients at 3 months and in 37% of patients at 6 months follow-up. Independent predictors of restenosis were age and lumen diameter immediately after angioplasty. Young patients (<50 years) and patients with a minimal luminal diameter of more than 2.5 mm had a restenosis rate less than 25%. A second revascularization procedure was performed in 44% of patients with restenosis. Although the incidence of reinfarction was higher in patients with restenosis, there was no significant difference in left ventricular ejection fraction between patients with and without restenosis.

Clinical Implications

This study, which shows that the minimal luminal diameter immediately after primary angioplasty is an independent predictor of restenosis, suggests that primary stenting or other interventions that improve the minimal luminal diameter after the angioplasty procedure, may reduce the restenosis rate and therefore reduce the need for subsequent re-interventions and hospital re-admissions.

Acknowledgments

The authors wish to thank Prof dr Ir J.H.C. Reiber from the Department of Diagnostic Radiology, Leiden University Hospital for critically reviewing the manuscript, Dr S. Reiffers for his work on the ejection fraction measurements, A.L. Liem for data management and V.R.C. Derks for secretarial assistance.

References

1. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocaridial infarction. N Eng J Med 1993;328:680-4.
2. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al, for the Primary Angioplasty on Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
3. de Boer MJ, Suryapranata H, Hoorntje JCA, Reiffers S, Liem AL, Miedema K, et al. Limitation of infarct size and preser-vation of left ventricular function after primary coronary angioplasty compared with intravenous streptoki-nase in acute myocardial infarction. Circulation 1994;90:753-61.
4. Simes JR, Weaver DW, Ellis SG, Grines CL. Overview of the randomized trials of primary PTCA and thrombolysis in acute myocardial infarction. Circulation 1996 [Abstract];94:I-331.
5. Zijlstra F, de Boer MJ, Beukema WP, Liem AL, Reiffers S, Huysmans D, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. Eur Heart J 1996;17:382-7.
6. Brodie BR, Grines CL, Ivanhoe R, Knopf W, Taylor G, O'Keefe J, et al. Six-months clinical and angiographic follow-up after direct angioplasty for acute myocardial infarction. Circulation 1994;25:156-62.
7. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, et al. Implications of recurrent ischemia after reperfusion therapy in acute myocardial infarction: a comparison of thrombolytic therapy and primary angioplasty. J Am Coll Cardiol 1995;26:66-72.
8. Nakae I, Fujita M, Fudo T, Iwase T, Tanaka T, Tamaki S, et al. Relation between preexistent coronary collateral circulation and the incidence of restenosis after successful primary coronary angioplasty for acute myocarial infarction. J Am Coll Cardiol 1996;27:1688-92.
9. Violaris A, Melkert R, Herrman JP, Serruys PW. Role of angiographically identifiable thrombus on long-term luminal renarrowing after coronary angioplasty. Circulation 1996;93:889-97.
10. Bauters C, Lablanche JM, McFadden EP, Hamon M, Bertrand ME. Relation of coronary angioscopic findings at coronary angioplasty to angiographic restenosis. Circulation 1995; 92:2473-9.
11. Brouwer MA, Bohncke JR, Veen G, Meijer A, van Eenige MJ, Verheugt FW. Adverse long-term effects of reocclusion after coronary thrombolysis. J Am Coll Cardiol 1995;26:1440-4.
12. Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. TAMI Study Group. Circulation 1990;82:781-91.
13. Brodie BR, Stuckey TD, Hansen CJ, Cooper TR, Weintraub RA, LeBauer J, et al. Importance of a patent infarct-related artery for hospital and late survival after direct coronary angioplasty for acute myocardial infarction. Am J Cardiol 1992;69:1113-9.
14. Brodie BR, Stuckey TD, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1996;28:319-25.
15. Zijlstra F, Beukema WP, van 't Hof AWJ, Liem AL, Reiffers S, Hoorntje JCA, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908-12.
16. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in myocardial infarction (TIMI) trial, Phase I: a comparison between intravenous tissue plasminogen activator and streptokinase. Circulation 1987;76:142-54.
17. Rentrop KP, Cohen M, Blanke H, Philips RA. Changes in collateral filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587-92

18. Reiber JHC, van der Zwet PMJ, von Land CD, Koning G, van Meurs B, Buis B, et al. Quantitative coronary arteriography: equipment and technical requirements. In Reiber JHC, Serruys PW, eds. Advances in quantitative coronary arteriography. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1992:75-111.
19. Reiber JHC, Schiemanck LR, van der Zwet PMJ, Goedhart B, Koning G, Lammertsma M, et al. State of the art in quantitative coronary arteriography as of 1996. In: Reiber JHC, van der Wall EE, eds. Cardiovascular Imaging. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1996:39-56.
20. Hirshfeld JW, Schwartz JS, Jugo R, Macdonald RG, Goldberg S, Savage MP, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. J Am Coll Cardiol 1991;18:647-56.
21. Serruys PW, de Jaegere P, Kiemeney F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
22. Violaris AG, Melkert R, Serruys PW. Long-term luminal renarrowing after successful elective coronary angioplasty of total occlusions. A quantitative angiographic analysis. Circulation 1995;91:2140-50.
23. Topol EJ, Califf RM, Weisman HF, Ellis SG, Tcheng JE, Worley S, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at 6 months. Lancet 1994;343:881-6.
24. Nakagawa Y, Iwasaki Y, Kimura T, Tamura T, Yokoi H, Yokoi H, et al. Serial angiographic follow-up after successful direct angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:980-4.
25. Weintraub WS, Kosinski AS, Brown CL III, King SB III. Can restenosis after coronary angioplasty be predicted from clinical variables? J Am Coll Cardiol 1993;21:6-14.
26. Kuntz RE, Gibson M, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993;21:15-25.
27. Beatt KJ, Serruys PW, Luijten HE, Rensing BJ, Suryapranata H, de Feyter PJ, et al. Restenosis after coronary angioplasty: the paradox of increased lumen diameter and restenosis. J Am Coll Cardiol 1992;19:258-66.
28. Hoorntje JCA, Suryapranata H, de Boer MJ, Zijlstra F, van 't Hof AWJ, van den Brink L. Escobar: Primary stenting for acute myocardial infarction: Preliminary findings of a randomized trial. Circulation 1996 [Abstract]; 94:I-570.
29. Ormiston JA, Stewart FM, Roche AHG, Webber BJ, Whitlock RML, Webster MWI. Late regression of the dilated site after coronary angioplasty: a 5 year quantitative angiographic study. Circulation 1997;96:468-74.
30. Preisack MB, Athanasidis A, Voelker W, Karsch KR. Early luminal deterioration following successful percutaneous transluminal coronary angioplasty. Frequency, predicton and clinical implications. Eur Heart J 1994;15:739-46.
31. Gibson CM, Cannon CP, Piana R, Breall JA, Shara JB, Flattery M, et al. Angiographic predictors of reocclusion after thrombolysis: results from the thrombolysis in myocardial infarction (TIMI) 4 trial. J Am Coll Cardiol 1995;25:582-9.
32. Serruys PW, Luyten HE, Beatt KJ, Geuskens R, de Feyter PJ, vd Brand M, et al. Incidence of restenosis after successful coronary angioplasty: a time related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1,2,3 and 4 months. Circulation 1988;2:361-71.
33. Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616-23.

CHAPTER 7

General Discussion and Closing Remarks

General Discussion

This thesis describes various aspects of primary coronary angioplasty in patients with acute myocardial infarction: reperfusion at the tissue level, additional stent or IABP therapy, treatment of low risk patients, the feasibility and safety of transporting infarct patients to a centre with PTCA facilities, the importance of ischemic time and transportation delay for outcome and restenosis and reocclusion of the infarct related vessel.

Monitoring Reperfusion

In the first trials which evaluated the efficacy of thrombolytic therapy, the agent was administered directly into the coronary artery. Reperfusion could be monitored by repeated injections of contrast into the infarct related artery. Later, when patients were treated with intravenous lytic agents, successful reperfusion was defined as a combination of electrocardiographic, biochemical and clinical features. This combination was excellent in risk stratifying patients shortly after the event, but was of limited value in the prediction of the patency status of the infarct related vessel (1). This thesis showed that this is due to limitations of TIMI flow for assessment of completeness of reperfusion. It was shown that, in part of the patients, persistent ST segment elevation was present, suggestive of impaired reperfusion, despite TIMI 3 flow in the infarct related artery. By means of 12-lead electrocardiography, important information was obtained about the success of reperfusion therapy. Thus it was possible to risk stratify patients at a very early stage after the acute event.

So far, no simple clinical parameter was available to obtain information about the extent of myocardial reperfusion. We have previously described the relation between myocardial flow reserve assessed by densitometric analyses of contrast medium passage in the infarcted myocardium and left ventricular function (2). However, this semiquantitative method has several pitfalls and limitations and is not applicable in routine clinical practice (3). Other available tools, like myocardial contrast echocardiography (4,5), dobutamine stress echocardiography (6,7), TIMI frame count (8), post angioplasty intracoronary flow measurements (9-12), Positron Emission Tomography (PET) scanning (13,14), or MRI (15) are also not readily available during the first hours after reperfusion therapy. Both the extent of ST segment elevation recovery on the 12-lead electrocardiogram and the myocardial blush on a routine angiogram can be used for risk stratification after primary angioplasty in patients with acute myocardial infarction.

Myocardial blush

The blush of myocardial tissue is the reflection of filling of the small arterioles of the myocardium with contrast (Figure 1). This blush is present on every diagnostic coronary angiogram and has been used in studies to calculate myocardial flow reserve (3). Decreased blushing of myocardial tissue suggests that some epicardial flow bypasses the microcirculation and shunts directly into one of the greater cardiac veins. It is therefore questionable whether "normal" TIMI flow and absent myocardial blush may coexist. As mentioned in the article in chapter 2, "normal" TIMI flow is probably not "normal" in these patients. In an article in which intracoronary flow measurements were performed in patients with acute myocardial infarction, TIMI 3 flow varied from 17 to 40 cm per second and considerable overlap existed in blood flow between patients with TIMI 2 and TIMI 3 flow (10,16). This highlight the limitation of TIMI flow assessment. In our opinion, qualifying not only epicardial but myocardial flow (blush) as well might reduce some of these limitations of TIMI flow grading.

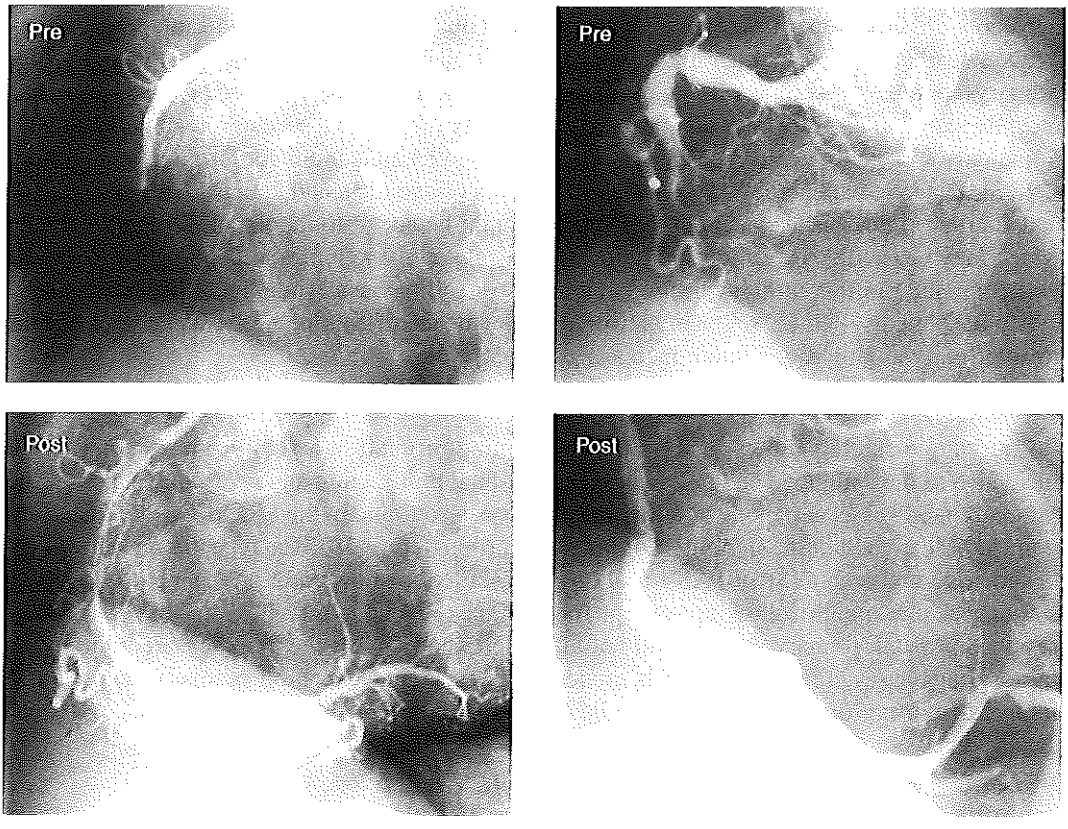


Figure 1 showing different blush grades after succesful opening of the infarct related vessel. The left panel shows adequate staining of reperfused myocardium with contrast. The right panel shows no staining of myocardium.

Primary Angioplasty for whom?

Previous studies showed that high risk patients benefit particularly from treatment with primary angioplasty, compared to thrombolytic therapy (17-19). This thesis shows that low risk patients, particular patients with inferior infarction, benefit from primary angioplasty as well, primarily because of a lower rate of reinfarction. This has been accomplished without an increase in total medical charges. It has been concluded that in hospitals with an existing infrastructure for interventional cardiology primary coronary angioplasty should be considered in **all** patients with symptoms of acute myocardial infarction and ST segment elevation. This study is the first to randomise low risk patients to different types of reperfusion therapy. A recent overview concluded that administering reperfusion therapy to low risk patients with inferior infarction (ST elevation in leads II, III, and AVF only) should be reconsidered, as baseline mortality risk in these patients is only 2-4% (20).
If the benefit of treating low risk infarct patients with primary angioplasty is only a reduction in reinfarctions, what price should be paid for prevention of reinfarction? Would it be cost-effective to put a low risk patient on transport to a tertiary centre with the aim to perform primary angioplasty to prevent reinfarction? A recent study presented a model for choosing different types of reperfusion therapy, based on risk estimation and gain in life-expectancy (21). In this model, primary angioplasty will only be considered if the expected gain in life expectancy would be more than 12 months or if an increased risk of intracranial haemorrhage is present. In hospitals without angioplasty facilities, this model may help the physician in deciding for the best and

most cost-effective reperfusion strategy and when to put a patient on transport to a tertiary centre. New patient groups are identified, which may especially benefit from reperfusion therapy by primary angioplasty compared to thrombolytic therapy. The European Society of Cardiology recently stated in its guidelines that primary angioplasty may have a special role in the treatment of patients with cardiogenic shock and in those with contra-indications for thrombolytic therapy (22,23). Diabetic patients (24), patients over 75 years of age (25), and patients with evidence of concomitant right ventricular infarction (26-28) might be added to the list of high risk patients which may be candidates for transportation to a hospital with angioplasty facilities. However, as was concluded in this thesis, whenever angioplasty facilities are available 24 hours round the clock, **all** patients with ST segment elevation and evidence of continuing ischemia may benefit from primary angioplasty without increasing costs.

Primary Stenting

In our single-centre study, primary coronary stenting resulted in a significant decrease in the incidence of the combined end point of death, non-fatal reinfarction and revascularisation of the infarct related vessel at 6 months follow-up. This was also found in the FRESCO (Florence Randomised Elective Stenting in Acute Coronary Occlusions) trial (29). The recently presented data of the large multicentre Stent-PAMI trial however, failed to show additional benefit of primary stenting at one month follow-up, except for a slight reduction in re-PTCA's (30). Our study results show that primary stenting did not affect left ventricular function, measured during the in-hospital phase , myocardial blush grades or ST segment elevation recovery nor reduced infarct size or pre-discharge left ventricular function (Table 1).

Table 1.

TIMI flow, Myocardial blush, ST segment elevation resolution, enzymatic infarct size and left ventricular function in patients randomised to primary stenting or balloon angioplasty.

	balloon (N=115)	stent (N=112)	P value
TIMI 3 flow (%)	94%	90%	0.35
Myocardial Blush (N=203)*			
normal (%)	28	23	0.31
moderate (%)	50	57	0.37
minimal or no (%)	23	24	0.98
ST recovery (N=183)*			
complete (%)	47	48	0.94
partial (%)	34	42	0.27
no (%)	19	10	0.08
Enzymatic Infarct size (N=147)**	1266 ± 1014	1317 ± 1052	0.22
Ejection Fraction (N=135)#	44 ± 11	43 ± 10	0.42

* as defined in chapter 2, ** LDHQ72 :calculated from at least 5 serial measurements of lactate dehydrogenase up to 72 hours after reperfusion. #: calculated with radionuclide angiography at 6 months follow-up

These results make it questionable whether every eligible patient should receive a stent. An important aspect is cost-effectiveness. We estimated total costs of primary coronary stenting compared to balloon angioplasty and showed that, although initial costs were higher for primary stenting, this was largely compensated by a reduced need for second revascularisation procedures during one year follow-up.

Intra-aortic Balloon Pumping

Our data show that there is no additional benefit of routine intra-aortic balloon pumping after primary angioplasty in high risk patients with acute myocardial infarction. This is consistent with the findings of a large randomised trial, who reported similar results (31). In patients in cardiogenic shock, however, insertion of an intra-aortic balloon pump may be indicated (32). The benefit of balloon pumping has been the prevention of (re)occlusion of the infarct related vessel (33,34). Before insertion of an intra-aortic balloon pump, the risk of 8 % major complications must be weighted against the scant evidence of a positive effect on clinical outcome in high risk infarct patients treated with reperfusion therapy. Especially in elderly patients (>75 years), the risk may outweigh the benefit (35).

Other additional therapies

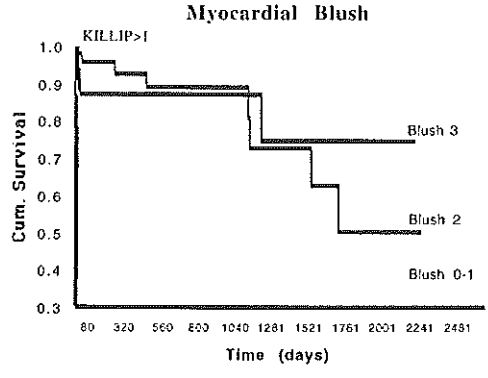
Studies are undertaken or ongoing on other adjunct or additional therapies in patients after primary angioplasty. Recently the efficacy and safety of glycoprotein IIb/IIIa receptor antagonists have shown its value in patients during and after elective coronary angioplasty (36-38). The aggressive blockade of thrombocyte aggregation is of great importance shortly after angioplasty to prevent recurrent ischemia and reocclusion, especially since it has been shown that the level of platelet activation is increased by primary angioplasty (39). The RAPPORT (ReoPro® in acute myocardial infarction and Primary PTCA Organisation and Randomisation Trial) trial has evaluated this drug in patients treated with primary angioplasty for acute infarction and found a lower occurrence of the combined incidence of death and reinfarction in this patient group (40). Recently two pilot studies have been performed with high dose heparin or abciximab, a glycoprotein IIb/IIIa receptor blocker, as pre-treatment of patients with acute myocardial infarction with the aim to increase patency before primary angioplasty. Patients with TIMI 3 flow of the infarct related vessel at acute angiography can be treated safely without intervention, have small infarctions and an excellent in-hospital outcome (41). It has been shown that both heparin and abciximab have thrombolytic potential (42,43) and may be indicated for patients before transportation to a hospital with angioplasty facilities. A pilot study showed a significantly higher patency rate of the infarct related vessel before angioplasty in patients who were pretreated with a megadose of intravenous heparin (either 20.000 or 30.000 IU as a bolus) compared to a matched population of patients who received the normal pretreatment of oral aspirin without the high dose heparin (TIMI 2 and 3 flow: 35% vs 12%, p=0.001, 44). However, preliminary results of a larger randomised trial failed to show a difference in patency rate before angioplasty between patients pre-treated with or without high-dose heparin (45). Abciximab, however, do seem to have lytic capacity. The GRAPE (Glycoprotein Receptor Antagonist in Early Patency trial) pilot study (46), the earlier mentioned RAPPORT study (40), and the recently presented TIMI 14 study (47), found a patency rate (TIMI 3 flow) of 18%, 22% and 32% respectively. The latter result is comparable to the rate of TIMI 3 flow achieved with intravenous streptokinase.

The importance of tissue reperfusion

As is shown in the first part of this thesis, a high degree of reperfusion at the myocardial, cellular level is of paramount importance for a good prognosis after primary angioplasty. This was

found especially for patients who presented in a higher Killip class. Despite reperfusion therapy, mortality remains unacceptably high in these patients. A recent study however, showed that, using an aggressive strategy of systematic and stent-supported direct angioplasty (which was successful in 85% of patients) in-hospital mortality could be reduced to 26% (48). Figure 2 shows that patients in Killip class 2 or higher with a high grade of myocardial blush (grade 2 or 3) after angioplasty have a good to excellent prognosis.

Figure 2.



Kaplan-Meier curve of 132 patients who underwent primary angioplasty and presented in Killip class 2 or higher

Future additional therapies should therefore be aimed at improvement of impaired myocardial reperfusion shortly after coronary angioplasty. Various agents, with different mechanisms of action, have shown beneficial results in this regard: A glycoprotein IIb/IIIa receptor antagonist (Abciximab,49,50), intracoronary Verapamil or Nifedipine (51-53), Glucose-Insulin-Potassium (GIK,54), Adenosine (55, 56), Nicorandil or Cromakalim (57,58), a Na+-H+ exchange inhibitor (59) or an anti-apoptotic agent (60). Although one agent, ReoThRx,, has shown beneficial effects as adjunct therapy in thrombolytic treated patients (61), the same agent proved not to be effective as adjunct in patients treated with primary angioplasty (62). However, as both recovery of ST segment elevation and myocardial blush grade were related to total ischemic time, the most effective "additional therapy" might be to keep the time from symptom onset to reperfusion as short as possible.

Transporting patients with acute myocardial infarction.

Transporting high risk patients with acute myocardial infarction to a centre with angioplasty facilities is feasible and safe, as is discussed in this thesis. However, these results were obtained in an area with excellent transportation facilities in a non-urbanised region and may therefore not be extrapolated to other regions in other countries. In highly urbanised areas (traffic jams), as well as in remote areas, as for example northern Scotland, the time needed to transport a patient to the nearest intervention centre, may be much longer than the 70 minutes from our study.
One must be aware of the logistic burden, which may be the consequence of the extension of indications for transportation of patients for performing primary angioplasty. Using the Rotterdam model (21), only 5% to 10% of all infarct patients are candidates for treatment with primary angioplasty. In 1997, 29.000 patients were hospitalised under the diagnosis of (acute) myocardial infarction in the Netherlands (63). Assuming that two third of these patients are candidates for reperfusion therapy, primary angioplasty should be considered in a total of 1900 patients

annually. The majority of these patients will be presented in hospitals without angioplasty facilities. Assuming that all 13 angioplasty centres will be equally involved, about 120 patients annually (2 to 3 patients weekly) are presented from elsewhere per centre. Extension of the indication for primary angioplasty to 20% of reperfusion eligible patients would double the number of patients with an indication for transportation to a tertiary centre. The annual number of patients transferred to our centre for performing primary angioplasty increased from 25 patients per year in the early nineties to more than 100 in recent years.

The price of transportation

Transportation of high risk patients to a centre with angioplasty facilities may be done, at the cost of an increase in infarct size, but without a negative influence on the success rate of primary angioplasty and 6 month mortality. This was found in a selected population of patients with large anterior infarctions who had a mean presentation delay of only 90 minutes. The study was a matched control study, and not a randomised comparison. The exact influence of extra time delay on outcome can only be determined by deliberately delaying time to reperfusion and this would be unethical . Furthermore, our study results are applicable for the Zwolle situation only. Tiefenbrunn and colleagues recently reported a significantly higher mortality in patients who had a 2.3 hours extra delay due to transportation in an observational study of more than 10.000 patients (64). The American College of Cardiology-American Heart Association Guidelines recommend performing primary angioplasty if it can be performed within 90 minutes of diagnosis (65). An alternative strategy is followed in the Limburg region of the Netherlands (66). During the delay, associated with transportation, patients were treated with thrombolytic therapy. In Baltimore, USA, thrombolysis before transfer is advised only if anticipated delay exceeds 120 minutes (67). A randomised trial between direct transportation and performing primary PTCA versus direct transportation after thrombolytic therapy and performing rescue angioplasty in case of failed thrombolysis, is ongoing in the Maastricht area. Results of the pilot study showed that there were no differences in outcome between the groups, although patients allocated to primary angioplasty had the highest rate of TIMI 3 flow and the lowest rate of second interventions (68). A large multicentre trial and perhaps the ongoing PACT (Plasminogen Activator-Angioplasty Compatibility Trial) (69) may answer the question whether transportation delay plays an essential role in patients treated with primary angioplasty, and if or when patients might benefit from additional pre-transportation fibrinolytic therapy.

Time to reperfusion

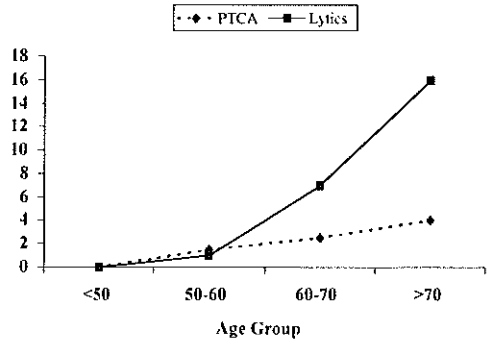
In patients treated with primary angioplasty the relationship between presentation delay and clinical outcome in patients with acute myocardial infarction was not evident, according to a recent report (70). No difference in mortality was found between patients treated early (<3 hours) or late (>3 hours). This thesis however, showed that ischemic time (time from symptom onset to first balloon inflation) in patients treated with primary angioplasty is an independent predictor of both mortality and left ventricular function recovery. Especially the finding that later mechanical opening of the infarct-related vessel led to a decreased rate of TIMI 3 flow has not previously been reported in patients treated with primary angioplasty. In 1987 this had already been shown for patients treated with thrombolytic therapy in the TIMI phase 1 trial (71), and this is probably one of the reasons why earlier thrombolytic therapy leads to a better outcome (72). The articles in chapter 1 show that myocardial reperfusion, as reflected by ST segment elevation recovery and myocardial blush grade, is correlated with ischemic time. The earlier the vessel is opened, the better the ST elevation recovery and the higher the blush grade.

Should late entry patients receive reperfusion therapy?

Although our study found that patients treated after 6 hours had the worst outcome, compared to patients treated earlier, it does not mean that reperfusion therapy in these patients should not be given. A rate of TIMI 3 flow of 83% in these patients is far higher than the spontaneous recanalisation rate in patients not given reperfusion therapy (which is about 20% 12 hours after symptom onset (73), and although reopening of the infarct related vessel in these patients probably does not directly lead to myocardial salvage, a patent vessel is beneficial possibly by greater infarct healing and electrical stability (74).

In our study it was found that female and elderly patients and patients with diabetes presented later after symptom onset. These patients are belonging to a high risk group (35,75), and therefore reperfusion therapy should be started instantaneously on arrival of these patients at the hospital, despite the fact that these patients arrive later than 6 hours after symptom onset. Especially in female patients and in patients who are older, considerable underutilisation of therapies is reported, while these patients might particular benefit from late opening of the infarct related vessel (24,25, 76, Figure 3). This will have consequences for the future as a large increase in the number of patients with myocardial infarction in the older age groups may be expected (77).

Figure 3.



The impact of age on mortality (y-axis). Patients under age 60 have a low mortality, regardless of treatment. The mortality reduction by primary angioplasty appears greatest for patients over age 70. Reprinted with permission (76).

Restenosis and Reocclusion

Restenosis or reocclusion of the infarct related vessel occurred in 37% of the patients after successful primary coronary angioplasty at 6 months follow-up. The 6% reocclusion rate is comparable to the reocclusion rate of patients after elective angioplasty for stable angina. Patients who were younger than 50 years of age and patients whose minimal luminal diameter after successful angioplasty exceeded 2.5 mm, had a restenosis rate of less than 25%. Therefore it is questionable whether these patients may benefit from additional stenting. There are more data which support the theory that in patients with a stent-like result, additional stenting is of limited value (78), although the recently published FRESCO trial showed superior outcome for stent treated patients compared to optimal balloon angioplasty (29). A recent perspective advised to use coronary stenting as an adjunct to balloon angioplasty and not as an alternative, mainly because of the difficult-to-treat problem of in-stent restenosis (79). Preserving stents for patients with the highest benefit may also be more cost-effective. Preliminary data of our randomised trial, described in chapter 2, showed that restenosis occurred in only 8% of patients treated with primary

stenting, compared to 36% for the angioplasty only group (80). However, one must be aware that these results are obtained in a selected population of patients with vessels over 3 mm in size.
A recent study (non-randomised, matched control) showed a restenosis rate of 27% for patients treated with bailout or primary stenting, compared to a restenosis rate of 52% for patients treated with primary angioplasty (38% restenosis, 14% reocclusion) (81). This high rate of restenosis was due to inclusion of patients who had unsuccessful angioplasty as well. The minimal luminal diameter after angioplasty of 1.97 mm recorded in this study is exactly the same compared to the minimal luminal diameter of our patients which were excluded from the trial (unsuccessful procedure, CABG< 6 months, death< 6 months). Assuming that these 213 excluded patients have a rate of restenosis comparable to the French group, the rate of restenosis in our total population of 497 consecutive patients who underwent primary angioplasty during a 6 year period, would be 41%.
The issue "the bigger the better" suggests that using more aggressive intervention techniques, like rotablator or coronary atherectomy, which maximise luminal diameter, would reduce restenosis. However, in one study, which used coronary atherectomy in patients with acute myocardial infarction, clinical outcome was not improved compared to plain old balloon angioplasty, mainly because of significant late loss of minimal luminal diameter at long term (90 days) follow-up (82).

Future research

This thesis addressed various questions about the role and effectiveness of primary coronary angioplasty in patients with acute myocardial infarction, but also showed its limitations. Therefore further research is necessary. The following questions might lead to a more optimal therapy for patients with acute coronary syndromes.

Question 1

According to the new definition of successful reperfusion (TIMI 3 flow with evidence of myocardial reperfusion), would it be possible to achieve this in more than 90 % of patients treated with primary angioplasty?
The GUSTO angiographic substudy has shown that early and complete reperfusion is the essential goal of reperfusion therapy, but this was achieved in only 35%-65% of patients (83). Primary angioplasty however, with early and successful opening of the infarct related vessel is possible in more than 90% of patients. Despite this high rate of epicardial reperfusion, only 60-70% of patients had evidence of myocardial reperfusion. Therefore future research should be aimed at improving myocardial reperfusion at the cellular level. ST segment recovery and angiographic myocardial blush may help in identifying high and low risk patients and monitoring the effect of treatment modalities.

Question 2

What should be indications for transfer of an infarct-patient to a tertiary centre?
Recently Pasceri suggested that future research on primary angioplasty should aim at finding subgroups of patients who have an adverse prognosis with standard treatment (84).
Preliminary data suggest that patients with diabetes (24), patients over 75 years of age (25), or with evidence of right ventricular infarction (26-28), may especially benefit from treatment with primary angioplasty compared to thrombolytic therapy.

Question 3

Is primary stenting for acute myocardial infarction cost-effective?

Although it was calculated that total costs were not higher for patients treated with primary stenting, the comparative cost-effectiveness needs to be established. To improve cost-effectiveness, further research should be aimed at finding subgroups of patients, which benefit most from primary stenting.

Question 4

How can treatment delay ("diagnosis to balloon" time) be further reduced?
Treatment delay for our patients is about 60 minutes, and did not further decrease since 1991. However, from the studies on pre-hospital thrombolysis it became evident that the diagnosis of acute myocardial infarction can be reliably made in the ambulance. A prehospital electrocardiogram resulted in further reduction of treatment delay and a higher number of patients who received of reperfusion therapy (85). Recent studies showed that an additional 20-50 minutes can be saved by preparation of the CCU unit or catheterisation laboratory (86,87). Outcome may be improved if these patients are pre-treated with agents like Aspirin (88), high dose heparin, or a glycoprotein IIb/IIIa receptor blocker (abciximab) during transportation (89). Furthermore, it should be evaluated if the decision, whether a patient is a candidate for primary angioplasty can be made in the ambulance. The Rotterdam model (21) might help in identifying these patients. By doing so, unnecessary admission in non-tertiary centres can be avoided. A feasibility study to test this hypothesis has been started in the Zwolle region with support from health care organisations and ambulance services.

Question 5

Can the risk of reocclusion and reinfarction after primary angioplasty be reduced by stenting, the use of a glycoprotein IIb/IIIa receptor blocker (Abciximab) or both?
Our data showed that reocclusion occurred in only 6% of patients after successful primary angioplasty. However, other centres report rates of 10-15%. Either coronary stenting (81) and the use of glycoprotein IIb/IIIa receptor antagonists (40), or both (90) have resulted in a reduction of recurrent ischemic events and reocclusion of the infarct related vessel. A recent report suggested that the combination of primary stenting and the use of a glycoprotein IIb/IIIa receptor antagonist (Abciximab (ReoPro,)) results in an increased procedural result and a better coronary flow (91). New studies should be aimed at identifying high risk patients for which additional stenting or pharmacological intervention or both is cost effective.

Question 6

Should immediate angiography be considered in patients with suspected myocardial infarction without ST segment elevation ?
Recent data showed that between 20% and 40% of patients with acute myocardial infarction are not candidates for reperfusion therapy because the electrocardiogram made on admission is not diagnostic (92, 93). Especially patients with acute posterior infarction are often excluded from reperfusion therapy, because the electrocardiogram only show ST segment depression or no repolarisation abnormalities at all. A recent perspective showed that many patients with non- ST segment elevation myocardial infarction do not receive even the most fundamental forms of therapy (94). Little or no ST segment elevation may be a sign of preserved flow (either antegrade or retrograde) to the infarcted myocardium and in 1989 Rentrop suggested that the time window of benefit for reperfusion therapy may be much wider in these patients (95). Furthermore, an immediate angiogram may be used as risk stratification in patients with a non-diagnostic ECG, as a proportion of them may have underlying severe triple vessel disease or even left main disease (96).

Question 7

How can fatality outside the hospital from acute coronary syndromes be reduced?
Two-thirds of deaths from acute coronary syndromes occur outside the hospital. This has not changed the last 25 years(97). This was found especially for patients under 55 years of age, in which a case fatality rate of 90% was reported (98). Therefore further large reductions in mortality can be accomplished only by primary prevention, secondary prevention or intervention before admission. This emphasises the need for better preventive programs, especially since the ongoing trend for increased smoking behaviour amongst young teenagers.

Closing Remarks

The final common pathway of the treatment of acute myocardial infarction is to open the infarct related vessel as good and as quick as possible. In a hospital without angioplasty facilities, the question remains whether to start the lytic (earlier, but less effective) or to wait for the balloon (later, but more effective), or both. With modern telecommunication, ambulance personnel and equipment, any patient with suspected acute myocardial infarction should receive the most optimal reperfusion strategy. This requires good co-operation between intervention and non-intervention centres.
O'Neill et al. concluded that all institutions committed to a mechanical reperfusion approach should pursue 90% patency rates or more, an emergency-room-to-cath-lab-time of less than 1 hour, and mortality rates of thrombolytic eligible patients and patients with cardiogenic shock of 3% and less than 50% respectively (76). These targets should not be restricted to patients undergoing primary angioplasty but should be aimed for every patient with an acute myocardial infarction, independent the centre he or she presents.

References

1. Califf RM, O'Neill W, Stack R, Aronson L, Mark DB, Mantell S, George BS, Landela RJ, Kereiakes DJ, Abbitsmith C. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988;108:658-62.
2. Suryapranata H, Zijlstra F, MacLeod DC, van den Brand M, de Feyter PJ, Serruys PW. Predictive value of reactive hyperemic response on reperfusion on recovery of regional myocardial function after coronary angioplasty in acute myocardial infarction. Circulation 1994;89:1109-1117.
3. Zijlstra F, Widimsky P, Suryapranata H. Possibilities and limitations of myocardial flow reserve, in "Progress in quantitative coronary arteriography", ed by JHC Reiber, PW Serruys, Kluwer Academics Publishers. Dordrecht/Boston/London 1994;141-159.
4. Firschke L, Lindner JR, Wei K, Goodman NC, Skyba D, Kaul S. Myocardial perfusion imaging in the setting of coronary artery stenosis and acute myocardial infarction using intravenous injection of a second-generation echocardiographic contrast agent. Circulation 1997;96:959-967.
5. Porter TR, Shouping L, Kricsfeld D, Armbruster RW. Detection of myocardial perfusion in multiple echocardiographic windows with one intravenous injection of microbubles using transient response second harmonic imaging. J Am Coll Cardiol 1997;29:791-799.
6. Iliceto S, Galiuto L, Marchese A, Cavallari D, Colonna P, Biasco G, Rizzon P. Analysis of microvascular integrity, contractile reserve, and myocardial viability after acute myocardial infarction by dobutamine echocardiography and myocardial contrast echocardiography. Am J Cardiol 1996;77:441-5.
7. Sklenar J, Camarano G, Goodman NC, Ismael S, Jayaweera A, Kaul S. Contractile versus microvascular reserve for the determination of the extent of myocardial salvage after reperfusion. The effect of residual coronary stenosis. Circulation 1996;94:1430-40.
8. Gibson CM, Cannon CP, Daley WL, Dodge JI, Alexander B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count. A quantitative method of assessing coronary artery flow. Circulation 1996;93:879-88.
9. Iwakura K, Ito H, Takiuchi S, Taniyama Y, Nakatsuchi Y, Negoro S, Higashino Y, Okamura A, Masuyama T, Hori M, Fujii K, Minamino T. Alteration in the coronary blood flow velocity pattern in patients with no reflow and reperfused acute myocardial infarction. Circulation 1996;94:1269-1275.
10. Kern MJ, Moore JA, Aquirre FA, Bach RG, Caracciolo EA, Wolford T, Khoury AF, Mechem C, Donohue TJ. Determination of angiographic (TIMI grade) blood flow by intra coronary doppler flow velocity during acute myocardial infarction. Circulation 1996;94:1545-1552.
11. Nakamura M, Tsunoda T, Wakatsuki T, Ki K, Degawa T, Yabuki S, Yamaguchi T. Distal coronary flow velocity immediately after direct angioplasty for acute myocardial infarction. Am Heart J 1996;132:251-7.
12. Sherman JR, Anwar A, Bret JR, Schreibfeder MM. Distal vessel pullback angiography and pressure gradient measurement: an innovative diagnostic approach to evaluate the no-reflow phenomenon. Cathet Cardiovasc Diagn 1996;39:1-6.
13. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Limura O. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. Am J Cardiol 1996;77:25-30.
14. Maes A, Van de Werf F, Nuyts J, Bormans G, Desmet W, Mortelmans L. Impaired myocardial tissue perfusion early after successful thrombolysis. Impact on myocardial flow, metabolism, and function at late follow-up. Circulation 1995;92:2072-8.

15. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JAC. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765-72.
16. Moynihan J, Ryan K, Kelley M, Rizzo M, Marble S, Cannon CP, McCabe C, Gibson M, for the TIMI10Aand B study group. The range of QCA velocities for TIMI grades 2 and 3 flow. J Am Coll Cardiol 1998;31:11A.
17. Boer de MJ, Hoorntje JCA, Ottervanger JP, Reiffers S, Suryapranata H, Zijlstra F. Immediate coronary angioplasty versus intravenous streptokinase in acute myocardial infarction: left ventricular ejection fraction, hospital mortality and reinfarction. J Am Coll Cardiol 1994; 23:1004-8.
18. Grines CL, O'Neill WW. Primary angioplasty. Br Heart J 1995;73:403-4.
19. The Reperfusion Therapy Consensus Group. Selection of reperfusion therapy for individual patients with evolving myocardial infarction. Eur Heart J 1997;18:1371-1381.
20. Bates E. Revisiting reperfusion therapy in inferior myocardial infarction. J Am Coll Cardiol 1997;30:334-342.
21. Boersma H, Vlugt van der MJ, Arnold AER, Deckers JW, Simoons ML. Estimated gain in life expectancy. A simple tool to select optimal reperfusion treatment in individual patients with evolving myocardial infarction. Eur Heart J 1996;17:64-75.
22. 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.
23. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe JH, Hartzler GO, Overlie P, Donohue B, Chelliah N, Vlietstra R, Puchrowicx-Ochocki S, O'NeillWW, for the primary angioplasty in myocardial infarction (PAMI) investigators. Outcome of different reperfusion strategies in patients with former contraindications to thrombolytic therapy: a comparison of primary angioplasty and tissue plasminogen activator. Cathet Cardiovasc Diagn 1996;39:333-9.
24. Srivatsa SS, Hasdai D, Criger DA, Vassanelli C, Kopecki SL, Garratt KN. Diabetic status and reperfusion strategy for acute myocardial infarction. Circulation 1997;96:I-399.
25. Berger AK, Breall JA, Johnson AE, Schulman KA, Oetgen WJ, Pirzada SR, Frederick PD, Every NR. Primary Angioplasty versus thrombolytic therapy in the elderly: the CCP experience. Circulation 1997;96:I-595.
26. Giannitsis E, Potratz J, Wiegand U, Stierle U, Dionlagic H, Sheikhzadek A. Impact of early accelerated dose tissue plasminogen activator on in-hospital patency of the infarct related vessel in patients with acute right ventricular infarction. Heart 1997;77:512-516.
27. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. N Engl J Med 1998; 338:933-40.
28. Rosales OR, Schroth GW, Thiessen M, Anderson HV, Fujise K, Smalling RW. Primary angioplasty improves outcome in right ventricular infarction. J Am Coll Cardiol 1998;31:233A.
29. Antoniucci D, Santoro GM, Bolognese L, Valenti R, Trapani M, Fazzini PF. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction. Results from the Florence Randomized Elective Stenting in acute COronary syndromes (FRESCO) trial. J Am Coll Cardiol 1998;31:1234-9.
30. Grines CL. Stent-PAMI: a randomized trial of primary PTCA versus heparin coated stent implantation for acute myocardial infarction. Presented at the American College of Cardiology Scientific Sessions 1998.

31. Stone GW, Marsalese D, Brodie BR, Griffin JJ, Donohue B, Constantini C, Ballestrini C, Wharton T, Esente P, Spain M, Moses J, Nobuyoshi M, Ayres M, Jones D, Mason D, Grines L, O'Neill WW, Grines CL. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1997;29:1459-67.
32. Kovack, PJ, Rasak MA, Bates ER, Ohman EM, Stomel RJ. Thrombolysis plus aortic counterpulsation: improved survival in patients who present to community hospitals with cardiogenic shock. J Am Coll Cardiol 1997;29:1454-8.
33. Ohman ME, George B, White CJ, Kern MJ, Gurbel PA, Freedman RJ, Lundergan C, Hartmann JR, Talley JD, Owens PM, Lee KL, Stack RS, Califf RM, for the randomized IABP study group. Use of aortic counterpulation to improve sustained coronary patency during acute myocardial infarction. Circulation 1994;90:792-799.
34. Kono T, Morita H, Nishina T, Fujita M, Ouaka H, Hirota Y, Kawamura K, Fujiwara A. Aortic counterpulsation may improve late patency of the occluded coronary artery in patients with early failure of thrombolytic therapy. J Am Coll Cardiol 1996;28:876-81.
35. Paul SD, O'Gara PT, Mahjoub ZA, DiSalvo TG, O'Donnell CJ, Newell JB, Villarreal-Levy G, Smith AJ, Kondo NI, Cararach M, Ferrer L, Eagle K. Geriatric patients with acute myocardial infarction: cardiac risk factor profiles, presentation, thrombolysis, coronary interventions, and prognosis. Am Heart J 1996;131:710-715.
36. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. N Engl J Med 1994;330:956-961.
37. EPILOG Investigators. Effect of the platelet glycoprotein IIb/IIIa receptor inhibitor abciximab with lower heparin dosages on ischemic complications of percutaneous coronary revascularization. N Engl J Med 1997;336:1689-96.
38. CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE trial. Lancet 1997;340:1429-35.
39. Gawaz M, Neumann F-J, Ott I, Schiessler A, Schomig A. Platelet function in acute myocardial infarction treated with primary angioplasty. Circulation 1996;93:229-37.
40. Brener SJ, Barr LA, Cohen ED, White HJ, Moliterno DJ, Cheek HB, Effron MB, Topol EJ. Abciximab reduces urgent target vessel revascularization at 30 days after primary angioplasty, independently of acute angiographic results. The RAPPORT trial. J Am Coll Cardiol 1998;31:54A.
41. Steg PG, Himbert D, Benamer H, Karillon G, Boccara A, Juliard JM. Conservative management of patients with acute myocardial infarction and spontaneous acute patency of the infarct-related artery. Am Heart J 1997;134:248-52.
42. Agnelli G, Borm J, Cosmi B, Levi M, Ten Cate JW. Effects of standard heparin and a low molecular heparin (Kabi 2165) on fibrinolysis. Thromb Haemost 1988;60:311-3.
43. Gold HK, Garabedian HD, Dinsmore RE, Geurrero LJ, Cigarroa JE, Palacios IF, Leinbach RC. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators. Circulation 1997;95:1755-59.
44. Verheugt FWA, Liem AL, Zijlstra F, Marsh RC, Veen G, Bronzwaer JGF. High dose bolus heparin as initial therapy before primary angioplasty for acute myocardial infarction: results of the Heparin in Early Patency (HEAP) pilot study. J Am Coll Cardiol 1998, 31:289-93.
45. Hoorntje JCA. Megadose of Heparin before primary PTCA. Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.

46. Verheugt FWA. Results of the Glycoprotein Receptor Antagonist in Early Patency Evaluation (GRAPE) pilot study. Presented at the XIX congress of the European Society of Cardiology, Stockholm, Sweden, August 24-28, 1997.
47. Antman EM, Giugliano RP, McCabe, Gibson M, Adgey AJJ, Ghali M, Coussement P, Anderson KM, Scherer J, Van de Werf F, Braunwald E. Abciximab (ReoPro) potentiates thrombolysis in ST elevation myocardial infarction: results of the TIMI 14 trial. J Am Coll Cardiol 1998;31:191A.
48. Antoniucci D, Valenti R, Santoro GM, Bolognese L, Trapani M, Moshi G, Fazzini PF. Systematic direct angioplasty and stent-supported direct angioplasty therapy for cardiogenic shock complicating acute myocardial infarction: in-hospital and long-term survival. J Am Coll Cardiol 1998;31:294-300.
49. Rawitscher D, Levin TN, Cohen I, Feldman T. Rapid reversal of no-reflow using abciximab after coronary device intervention. Cathet Cardiovasc Diagn 1997;42:187-90.
50. Kingma JG, Plante S, Bogati P. Blockade of the platelet glycoprotein IIb/IIIa receptor reduces infarct size in a canine model of myocardial infarction and reperfusion. J Am Coll Cardiol 1998;31:135A.
51. Taniyama Y, Hiroshi I, Iwakura K, Masuyama T, Hori M, Takiuchi S, Nishikawa N, Higashino Y, Fujii K, Minamino T. Beneficial effect of intracoronary verapamil on microvascular salvage in patients with acute myocardial infarction. J Am Coll Cardiol 1997;30:1193-9.
52. Przyklenk K, Ghafari GB, Eitzman DT, Kloner RA. Nifedipine administered after reperfusion ablates systolic contractile dysfunction of postischaemic "stunned" myocardium. J Am Coll Cardiol 1989;13:1176-83.
53. Lauerma K, Saeed M, Wendland MF, Derugin N, Yu KK, Higgins CB. Verapamil reduces the size of reperfused ischemically injured myocardium in hypertrofied rat hearts as assessed by MR Imaging. Am Heart J 1996;131:14-23.
54. Fath-Ordoubadi F, Beatt K. Glucose-Insulin-Potassium therapy for treatment of acute myocardial infarction. An overview of randomized placebo-controlled trials. Circulation 1997;96:1152-56.
55. Marzilli M, Gliozheni E, Fedel S, Ungi I, Orsini E, Marraccini P. Beneficial effects of adenosine in acute myocardial infarction. J Am Coll Cardiol 1997;29:133A.
56. Ferguson JJ. AMISTAD. Meeting Highlights. Highlights of the 70th scientific sessions of the American Heart Association. Circulation 1998;97:1217-20.
57. Sakata Y, Lim Y, Ishikura F, Hirayama A. Restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction by a K+-ATP channel opener, Nicorandil. J Am Coll Cardiol 1997;29:133A.
58. Shigematsu S, Sato T, Abe T, Saikawa T, Sakata T, Arita M. Pharmacological evidence for the persistent activation o f ATP sensitive K+ channels in the early phase of reperfusion and as protective role against myocardial stunning. Circulation 1995;92:2266-75.
59. Miura T, Ogawa T, Suzuki K, Goto M, Shimamoto K. Infarct size limitation by a new Na+-H+ exchange inhibitor, Hoe 642: difference from preconditioning in the role of protein kinase C. Circulation 1997;29:693-701.
60. Silver MJ, Chetcuti SP, Mukherjee DB, Malycky JL, Tomei DL, Umansky S, Nicolini FA. Use of a novel anti-apoptotic agent (LXR017) reduces infarct size following ischemia-reperfusion in the canine myocardium. J Am Coll Cardiol 1998;31:66A.
61. Schaer GL, Spaccavento LJ, Browne KF, Krueger KA, Krichbaum D, Phelan JM, Fletcher WO, Grines CL, Edwards S, Jolly MK, Gibbons RJ. Beneficial effects of RheothRx (poloxamer 188, N.F) in patients receiving thrombolytic therapy for acute myocardial infarction. Circulation 1996;94:298-307.

62. O'Keefe JH, Grines CL, DeWood MA, Schaer GL, Browne K, Magorien RD, Kalbfleisch JM, Fletcher WO, Bateman TM, Gibbons RJ. Poloxamer-188 as an adjunct to primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:747-50.
63. Hart- en Vaatziekten in Nederland 1997. Cijfers over ziekte en sterfte. Nederlandse Hartstichting. Den Haag 1997.
64. Tiefenbrunn AJ, Chandra NC, Every NR, French WJ, Gore JM, Rogers WJ. High mortality in patients with myocardial infarction transferred for primary angioplasty: a report from the national registry of myocardial infarction-2. Circulation 1997;96:I-531.
65. Committee on Practice Guidelines for the management of patients with acute myocardial infarction. J Am Coll Cardiol 1996;28:1328-1428.
66. Vermeer F, Werter C, van de Berg E, Boehmer T, Dassen W, Krijne R, van Ommen V, Oude Ophuis T, Bär F. Safety and feasibility of rescue PTCA or primary PTCA in patients with acute myocardial infarction admitted to a hospital without PTCA facilities. J Am Coll Cardiology 1997;29:390A.
67. Kahn JK, O'Neill WW. Acute myocardial infarction. In: Ellis SG, Holmes DR Jr, eds. Strategic approaches in coronary intervention, 1996:558-65.
68. Bär FWHM. Results of the Limburg Myocardial Infarction Study (LIMI). Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.
69. Ross AM. Results of the PACT (Plasminogen Activator-Angioplasty Compatibility Trial) trial. Presented at the 13th International Workshop on Thrombolysis and Interventional Therapy in acute myocardial infarction, Orlando USA, November 8, 1997.
70. Stone GW, O'Keefe, Brodie BR, O'Neill WW, Grines CL. Lack of relationship between the time to reperfusion and short-term mortality after primary infarct angioplasty. J Am Coll Cardiol 1998;31:271A.
71. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis HK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, RossA, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis In Myocardial Infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76:723-5.
72. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5.
73. Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. Am J Cardiol 1994;74:1220-28.
74. Kim CB, Braunwald. Potential benefits of late reperfusion of infarcted myocardium. The open artery hypothesis. Circulation 1993;88:2426-36.
75. Woodfield SL, Lundergan CF, Reiner JS, Thompson MA, Rohrbeck SC, Deychak Y, Smith JO, Burton JR, McCarthy WF, Califf RM, White HD, Weaver WD, Topol EJ, Ross AM. Gender and acute myocardial infarction: is there a different response to thrombolysis. J Am Coll Cardiol 1997;29:35-42.
76. O'Neill WW, de Boer MJ, Gibbons RJ, Holmes DR, Timmis GC, Sachs D, Grines CL, Zijlstra F. 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 Inv Card 1998 suppl A;10:4A-10A.
77. Pepine CI. Changing myocardial infarction population characteristics: reasons and implications. Am Heart J 1997;134:S1-S3.

78. Siegel RM, Bhaskaran A, Underwood PC, Barker B, Nuttall AW, Breisblatt W, Swayson D, Vermillion JC. Stenting versus optimal balloon angioplasty in direct infarct interventions. Eur Heart J 1997;18:125.
79. Narins CR, Holmes DR, Topol EJ. A call for provisional stenting. The balloon is back! Circulation 1998;97:1298-1305.
80. Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Randomized comparison of primary stenting with primary balloon angioplasty in acute myocardial infarction. J Am Coll Cardiol 1997;29:I-327.
81. Bauters C, Lablanche J-M, Van Belle E, Niculescu R, Meurice T, Mc Fadden EP, Bertrand ME. Effects of coronary stenting on restenosis and occlusion after angioplasty of the culprit vessel in patients with recent myocardial infarction. Circulation 1997;96:2854-58.
82. Saito S, Kim K, Hosokawa G, Tanaka S, Miyake S, Harada K, Hirobayashi K. Short- and long-term clinical effects of directional coronary atherectomy for acute myocardial infarction. Cathet Cardiovasc Diagn 1996;39:157-65.
83. Simes RJ, Topol EJ, Holmes DR, White HD, Rutsch WR, Vahanian A, Simoons ML, Morris D, Betriu A, Califf RM, Ross AM, for the GUSTO Investigators. Link between the angiographic substudy and mortality outcome in a large randomized trial of myocardial reperfusion: import of early and complete infarct artery reperfusion. Circulation 1995;91:1923-28.
84. Pasceri V. Primary coronary angioplasty versus thrombolysis. N Engl J Med 1997;337:1169.
85. Canto JG, Rogers WJ, Bowlby LJ, French WJ, Pearce DJ, Weaver WD. The pre-hospital electrocardiogram in acute myocardial infarction: is its full potential being realized? J Am Coll Cardiol 1997;29:498-505.
86. Prasad N, Wright A, Hogg KJ, Dunn FG. Direct admission to the coronary care unit by the ambulance service for patients with suspected myocardial infarction. Heart 1997;78:462-64.
87. Miller-Craig MW, Joy AV, Adamowicz M, Furber R, Thomas B. Reduction in treatment delay by paramedic ECG diagnosis of myocardial infarction with direct CCU admission. Heart 1997;78:456-61.
88. Prasad N, Srikanthan VS, Wright A, Dunn FG. Management of suspected myocardial infarction before admission: updated audit. BMJ 1998;316:353.
89. Glatt B, Guyon P, Chevalier B, Royer T, Jullien T, Hennequin B, Herlin C, Sebbah JL, Belotte F, Dambrin G. Pre-hospital treatment with abciximab in acute myocardial infarction with direct percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1998; 31:230A.
90. Murdock DK, Logemann T, Hoffmann MT, Olson KJ, Engelmeier RS. Coronary artery stenting for suboptimal PTCA results in acute myocardial infarction in patients treated with abciximab: early and six-month outcome. Cathet Cardiovasc Diagn 1997;42:173-79.
91. Neumann FJ, Blasini R, DirschingerJ, Schmitt C, Alt E, Gawaz MP, Fakhoury L, Huppmann R, Schomig A. Intracoronary stent implantation and antithrombotic regimen in acute myocardial infarction: randomized placebo-controlled trial of the fibrinogen receptor antagonist Abciximab. Circulation 1997;96:I-398.
92. European Secondary Prevention Study group. Translation of clinical trials into practice: a european population-based study of the use of thrombolysis for acute myocardial infarction. Lancet 1996;347:1203-7.
93. Barron HV, Bowlby LJ, Breen T, Rogers WJ, Canto JG, Zhang Y, Tiefenbrunn AJ, Weaver WD, for the National Registry of Myocardial Infarction 2 Investigators. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the national registry of myocardial infarction 2. Circulation 1998;97:1150-56.

94. Burns M, Becker RC, Every NR, Maynard C, Frederick P, Gore JM, Lambrew C, for the NRMI investigators. Current in-hospital management of patients with non-ST segment elevation myocardial infarction: the national registry of myocardial infarction perspective. J Am Coll Cardiol 1998;31:73A.
95. Rentrop KP, Feit F, Sherman W, Stecy P, Hosat S, Cohen M, Rey M, Ambrose J, Nachamie M, Schwartz W, Cole W, Perdoncin R, Thornton JC. Late thrombolytic therapy preserves left ventricular function in patients with collateralized coronary occlusion: primary end point findings of the second mount sinai-new york university reperfusion trial. J Am Coll Cardiol 1989;14:58-64.
96. Wharton TP, McNamara NS, Schmitz JM, Fedele FA, Jacobs MI, Gladstone AR, Funk EJ, Corbett P. Primary PTCA in patients with acute myocardial infarction without ST elevation: a community hospital experience. Circulation 1997;96:I-595.
97. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveier D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA registration project: registration procedures event rates and case fatality rates in 30 populations from 21 countries in 4 continents. Circulation 1994;90:583-612.
98. Norris RM on behalf of the United Kingdom Heart Attack Study Colaborative Group. Fatality outside hospital from acute coronary events in three british health districts, 1994-5. BMJ 1998;316:1065-70.

How to perform Primary Angioplasty?

10 commandments

1. In suspected myocardial infarction, initial assessment < 15 minutes:
   TIME = MUSCLE = LIVES

2. When diagnosis of myocardial infarction is confirmed before hospital arrival, go to cathetarization lab, and not to emergency room or CCU.

3. Do not forget aspirin, heparin, nitrates (Beta-blocker).

4. Visualise both coronary arteries.

5. Use a balloon and perhaps a stent, forget other techniques.

6. Consider conservative management and acute or elective CABG.

7. Be sure that somebody looks after the patient when you perform angiography and angioplasty.

8. Beware of and prepair for reperfusion arrhythmias, bradycardia and hypotension.

9. Do not undersize.

10. Stent the plague, not the vessel.

SUMMARY

Summary

Chapter 1

Introduction

Primary coronary angioplasty, i.e. angioplasty in patients with acute myocardial infarction without antecedent thrombolytic therapy, has been evaluated as a means of reperfusion therapy since the early nineteeneightees. The results of the first trials were promising, however, after the disappointing results of angioplasty after (failed) thrombolytic therapy, much of the initial enthusiasm was lost. In 1993, the publication of three trials, which randomly compared thrombolysis with primary angioplasty, resulted in a revival of primary angioplasty as an effective reperfusion modality in patients with acute myocardial infarction. In 1996, both the American and European Heart Association recommended primary angioplasty as a first treatment option, especially for patients in cardiogenic shock and for patients with contra-indications for thrombolytic therapy. This thesis addresses some aspects of patients treated with primary angioplasty.

Chapter 2

ST segment elevation resolution

A simple clinical method to stratify patients for risk who have had successful reperfusion therapy after myocardial infarction is lacking. We investigated the clinical value of the 12-lead electrocardiogram (ECG), in 403 patients after successful reperfusion therapy by primary coronary angioplasty, in relation to infarct size measured by enzyme activity, left-ventricular function, and clinical outcome. ECGs were analyzed to find the extent of the ST-segment-elevation resolution 1 h after reperfusion therapy. A normalized ST segment was seen in 51% of patients, a partly normalized ST segment in 34%, and 15% had no ST-segment-elevation resolution. Enzymatic infarct size and ejection fraction were related to the extent of the early resolution of the ST segment. The relative risk of death among patients with no resolution compared with patients with a normalized ST segment was 8.7 (95% CI 3.7-20.1), and that among patients with partial resolution compared to patients with a normalized ST segment was 3.6 (1.6-8.3). Our findings suggest that ECG patterns reflect the effectiveness of myocardial reperfusion. Patients for whom reperfusion therapy by primary angioplasty was successful and who had normalized ST segments had limited damage to the myocardium and an excellent outlook during follow-up. Patients with persistent ST elevation after reperfusion therapy may need additional interventions since they have more extensive myocardial damage and have a higher mortality rate.

Myocardial Blush

In the second part of chapter 2, we studied 777 patients who underwent primary coronary angioplasty during a 6 year period and investigated the value of angiographic evidence of myocardial reperfusion (myocardial blush grade) in relation to the extent of ST segment elevation resolution, enzymatic infarct size, left ventricular function and long term mortality. The myocardial blush immediately after the angioplasty procedure was graded by 2 experienced investigators, blinded to all clinical data: 0: no myocardial blush, 1: minimal myocardial blush, 2: moderate myocardial blush, 3: normal myocardial blush. The myocardial blush was related to the extent of the early ST-segment elevation resolution on the 12-lead electrocardiogram. Patients with blush grades 3, 2 and 0/1 had enzymatic infarct sizes of respectively 757, 1143 and 1623 ($P<0.0001$) and ejection fractions of 50%, 46% and 39%, ($P<0.0001$). After follow-up of 1.9 $\pm$

1.7 years, mortality rates of patients with myocardial blush grades, 3, 2 and 0/1 were 3%, 6% and 23% (P<0.0001) respectively. Multivariate analysis showed that the myocardial blush grade was a predictor of long term mortality, independent of Killip class, TIMI flow, left ventricular ejection fraction and other clinical variables. This chapter emphasizes that reperfusion therapy in patients with acute myocardial infarction should not only be aimed at opening the epicardial vessel, but also at achieving a high level of reperfusion at the myocardial, cellular level.

Chapter 3

Primary Stenting

Although the benefits of primary angioplasty in acute myocardial infarction have been demonstrated, several areas for improvement still remain. Therefore, a prospective randomized trial comparing primary stenting with balloon angioplasty in patients with acute myocardial infarction was conducted. Patients with acute myocardial infarction were randomly assigned to undergo either primary stenting (n=112) or balloon angioplasty (n=115). The clinical endpoints were death, recurrent infarction, subsequent bypass surgery or repeat angioplasty of the infarct-related vessel. The overall mortality rate at 6 months was 2%. Recurrent infarction occurred in 8 patients (7%) after balloon angioplasty, and in one (1%) after stenting (p=0.036). Subsequent target vessel revascularization was necessary in 19 (17%) and 4 (4%) patients, respectively (p=0.0016). The cardiac event-free survival rate in the stent group was significantly higher than in the balloon angioplasty group (95% vs 80%; p=0.012). It was concluded that in selected patients with acute myocardial infarction, primary stenting can be applied safely and effectively, resulting in a lower incidence of recurrent infarction and a significant reduction in the need for subsequent target vessel revascularization, when compared to balloon angioplasty.

Intra-aortic Balloon Pumping

Further improvement in outcome after primary angioplasty can be achieved by using intra-aortic balloon pumping. It may be effective in improving reperfusion and in achieving afterload reduction in high risk infarct patients treated with primary angioplasty. In the second part of chapter 3, high risk infarct patients referred from other centers for performing primary PTCA were randomized to treatment with or without IABP. The primary end point consisted of the combined incidence of death, non-fatal infarction, stroke or an ejection fraction < 30% at 6 month follow-up. A weighted unsatisfactory outcome score (as previously described by Braunwald), enzymatic infarct size and left ventricular ejection fraction were secondary end points. During a 3,5 year period, 238 patients were randomized, 118 to IABP therapy and 120 to no IABP-therapy. None of the outcome scores were significantly different between both groups. Major complications occurred in 8% of patients who were treated with IABP pumping. It was concluded that systematic use of intra-aortic balloon pumping after primary angioplasty does not lead to myocardial salvage or to a better clinical outcome in high risk infarct patients. The device should be reserved for patients with severe haemodynamic compromise.

Chapter 4

Primary Angioplasty in low risk patients?

Previous studies emphasized that especially high risk infarct patients benefit from treatment with primary angioplasty. In the first part of chapter 4, we sought to compare primary coronary angioplasty and thrombolysis as treatment for low risk patients with an acute myocardial infarction.

We stratified 240 patients with acute myocardial infarction at admission according to risk. Low risk patients (n=95) were randomized to primary angioplasty or thrombolytic therapy. The primary end point was death, nonfatal stroke or reinfarction during 6 months of follow-up. Left ventricular ejection fraction and medical charges were secondary end points. High risk patients (n=145) were treated with primary angioplasty. In low risk patients, the incidence of the primary clinical end point (4% vs. 20%, $p < 0.02$) was lower in the group with primary coronary angioplasty than in the group with thrombolysis, because of a higher rate of reinfarction in the latter group. Mortality and stroke rates were low in both treatment groups. There were no differences in left ventricular ejection fraction or total medical charges. High risk patients had a 14% incidence rate of the primary clinical end point. It was concluded that even in low risk patients, primary coronary angioplasty results in a better clinical outcome at 6 months than does thrombolysis and does not increase total medical charges.

Transfer of infarct patients

In the second part of chapter 4 we investigated the feasibility of primary coronary angioplasty as a treatment option in patients with acute myocardial infarction after initial diagnosis in a local community hospital. During a five year period, 520 candidates for primary coronary angioplasty were treated in our institution, 104 after transfer from a community hospital. The transferred and the non-transferred patients (N=416) were compared with regard to baseline clinical characteristics, time intervals from symptom onset to treatment, and clinical outcome at six months. In this setting, the influence of transportation on total ischaemic time was limited, and there was no difference in clinical outcome between the transferred and the non-transferred patients. Clinical outcome was mainly dependent on the indication for transfer. It was concluded that safe and expedient transportation may facilitate the more widespread use of primary angioplasty in patients with acute myocardial infarction and that a large randomized multicentre trial is needed to compare the relative merits of intravenous thrombolytic treatment in a local hospital with primary angioplasty after transfer in selected high risk patients with acute myocardial infarction.

Chapter 5

Time to Treatment

The relationship between outcome and ischemic time for patients who present relatively late after the onset of symptoms is uncertain. The aim of the described study was to inves-tiga-te differences in patient characteristics, left ventricular function and clinical outcome between early (<3 hours), intermediate (3-6 hours) and late (6-24 hours) treated patients. From August 1990 until December 1995, we studied 496 patients who underwent primary coronary angioplasty for acute myocardial infarction. Patients who underwent reperfusion therapy between 6 and 24 hours were more often of female gender and more often had diabetes. Primary coronary angioplasty was less successful with later time to reperfusion. Patients who had reperfusion therapy within 6 hours showed recovery of left ventricular function at 6 months follow-up, while the left ventricular function of patients treated late had deteriorated. Reocclusion of the infarct related vessel at follow-up coronary angiography was highest for patients with an ischemic time of more than 6 hours. They more often suffered a repeat myocardial infarction and had a significantly higher 6 months mortality. After adjustment for age, heart rate at presentation, gender, and the presence of diabetes by multivariate analysis, ischemic time remained an independent predictor of both left ventricular function recovery and 6 month mortality.

An increasing number of patients with acute myocardial infarction who present at a local hospi-

tal are transferred to a tertiary hospital with the aim to perform primary angioplasty. In the last part of chapter 5 we determined the influence of this extra treatment delay (due to transportation) in transferred patients. In a three year period (December 1993 - November 1996), 207 consecutive patients who were transferred for primary angioplasty were analyzed in a matched comparison with non-transferred patients. Matching criteria were age, sex, infarct location, presentation delay and Killip class. Patients who were transferred had an median additional delay of 43 minutes. This resulted in a more extensive enzymatic infarct size and a lower ejection fraction measured at 6 months. The rate of angioplasty success defined as TIMI grade 3 flow, and the 6 month mortality rate (7%) were comparable in both groups. It was concluded that the additional delay had a deleterious effect on myocardial salvage, reflected by a larger infarct size and a lower left ventricular function. However the patency rate and 6 month clinical outcome were not affected by this delay.

Chapter 6

Restenosis

Previous studies have suggested that restenosis and reocclusion occur frequently in patients with acute coronary syndromes. This study was undertaken to assess the incidence and predictors of restenosis in a cohort of patients who underwent successful primary coronary angioplasty for acute myocardial infarction. 312 patients, who underwent successful primary angioplasty of a native coronary vessel, were candidates for follow-up coronary angiography. This was performed in 284 patients (92%) at 3 or 6 months follow-up. Quantitative coronary angiography was performed using the CMS-system. Multivariate analysis was done to determine independent predictors of restenosis. Restenosis, defined as a diameter stenosis of more than 50%, occurred in 27% of patients at 3 months and in 37% of patients at 6 months follow-up. Reocclusion occurred in 4% and 6% respectively. Reference diameter (vessel size) was related to restenosis. Age and lumen diameter immediately after angioplasty were independent predictors of restenosis. Young patients (<50 years) and patients with a minimal luminal diameter of more than 2.5 mm, had restenosis rates of less than 25%. The radionuclide ejection fraction was 46% in patients with restenosis compared to 47% in patients without restenosis. It was concluded that the incidence of restenosis after successful primary coronary angioplasty for acute myocardial infarction is comparable to the reported incidence after elective coronary angioplasty for stable angina. Restenosis is related to age and the lumen diameter after angioplasty and does not affect left ventricular function in this population.

Chapter 7

General Discussion

This chapter discusses some of the issues of this thesis. How can tissue perfusion after primary angioplasty be ameliorated? Should low risk patients with acute myocardial infarction be transferred to a hospital to perform primary PTCA? What will be the consequences of transferring increasing numbers of patients? What is the additional value of primary stenting, except for a reduction in the rate of restenosis? How can treatment delay be further reduced and what additional therapies can be given during this delay? Further research should clarify some of these issues.

SAMENVATTING

in het nederlands

Samenvatting

Hoofdstuk 1

Introductie
Primaire ballonangioplastiek, oftewel het "dotteren" bij patiënten met een acuut hartinfarct, zonder dat hieraan voorafgaand trombolytische therapie is gegeven, is bekend vanaf het begin van de tachtiger jaren. De tegenvallende resultaten van "rescue"- en "deferred" angioplastiek, na thrombolyse, zorgden ervoor dat ook de primaire ballonangioplastiek naar de achtergrond verdween. In 1993 leidde de gelijktijdige publicatie van 3 gerandomiseerde onderzoeken tussen trombolyse en primaire PTCA in de "New England Journal of Medicine", tot een herwaardering van deze techniek als een zeer effectieve manier van het open maken van de bij het infarct afgesloten kransslagader. Drie jaar later stelden zowel de Europese als de Amerikaanse verenigingen voor Cardiologie primaire PTCA als een eerste keus behandeloptie, met name bij patiënten in shock en bij patiënten met contra-indicaties voor trombolytische therapie.

Hoofdstuk 2

ST elevatie resolutie na geslaagde reperfusie.
Tot voor kort bestond het belang van het ECG na reperfusie therapie uit het inschatten of de infarct-gerelateerde kransslagader open of dicht zou zijn. Dit gelukte maar ten dele, met name bleek dat persisterende ST segment elevatie niet altijd gerelateerd was aan een dichtzittend vat. In dit hoofdstuk wordt getoond waarom. Bij 403 patiënten, die succesvol waren behandeld met primaire PTCA werd het ECG vóór reperfusie vergeleken met het ECG erna. Ondanks het volledig open zijn van het vat (TIMI 3 flow) bleek bij 49% van de patiënten nog ST elevaties aanwezig op het post PTCA ECG, suggestief voor een nog niet geheel geslaagde reperfusie. Deze patiënten hadden een grotere enzymatische infarct grootte en een slechtere linker kamer restfunctie, vergeleken met de patiënten bij wie de ST elevaties volledig waren verdwenen. De mate van resolutie van ST elevatie na geslaagde reperfusie bleek, na leeftijd en Killip klasse, de belangrijkste voorspeller te zijn van overlijden tijdens een 3 jarige follow-up periode. Deze bevindingen laten zien dat persisterende ST elevatie heel goed kan optreden bij een volledig open infarct gerelateerd epicardiaal vat en dat dit waarschijnlijk een uiting is van een minder geslaagde reperfusie op myocardiaal niveau. Het al of niet geslaagd zijn van reperfusie is blijkbaar niet alleen door middel van het beoordelen van de doorstroming van het epicardiale vat (TIMI flow) te bepalen.

Myocardiale Blush
In het tweede deel van hoofdstuk 2 is gekeken of het angiogram ook informatie kan geven over het al of niet aanwezig zijn van myocardiale reperfusie. Dit werd gedaan door bij 777 patiënten de post- PTCA gemaakte angiogrammen te scoren op de mate van contrast-aankleuring (blush) van het tevoren geïnfarceerde myocardiale weefsel. Wanneer het geïnfarceerde myocard volledig aankleurde (blush graad 3) bleek dit samen te gaan met een beperkte enzymatische infarct grootte en een goede linker kamer functie. Daarentegen bleek dat bij 30% van de patiënten deze myocardiale aankleuring niet of nauwelijks aanwezig was en dat deze patiënten een gemiddeld 40% groter infarct en een matige linker kamer restfunctie hadden. De mate van myocardaankleuring bleek een belangrijke voorspeller van overlijden te zijn, onafhankelijk van TIMI flow. Deze bevindingen benadrukken dat niet alleen een open epicardiaal vat van belang is voor reper-

fusie, maar dat deze pas volledig geslaagde genoemd mag worden als er eveneens aanwijzingen zijn voor reperfusie op myocardiaal niveau.

Hoofdstuk 3

Primaire Stenting
De boven genoemde gegevens maken duidelijk dat verdere verbetering van de resultaten van reperfusie therapie nodig is. Daarom word gezocht naar aanvullende behandelingsvormen, zoals stenting en behandeling met een intra-aortale ballonpomp.
In het eerste gedeelte van hoofdstuk 3 worden de resultaten beschreven van een gerandomiseerd onderzoek naar de waarde van het primair stenten van het infarct-gerelateerd bloedvat. Bij de 112 patiënten, die door het lot een stent kregen toegewezen, bleek dat na 6 maanden minder reïnfarcten waren opgetreden en minder tweede revascularisaties (re-PTCA of CABG) waren gedaan vergeleken met de 115 patiënten die geen stent kregen. Het blijkt dus dat stentimplantatie veilig toepasbaar is en klinische voordelen biedt bij een geselecteerde patiënten populatie met een acuut hartinfarct.

Intra-aortale ballonpomp
In het tweede deel van hoofdstuk 3 wordt de waarde van de intra-aortale ballonpomp na primaire PTCA beschreven. Tijdens een periode van drie en een half jaar zijn 238 hoog risico infarct patiënten gerandomiseerd naar wel (N=118) of geen (N=120) ballonpomp-behandeling. Na 6 maanden follow-up bleek er tussen de 2 groepen geen verschil te bestaan in het gecombineerd voorkomen van overlijden, reïnfarcering, CVA of een ejectiefractie van minder dan 30%. Ook bleek behandeling met een intra-aortale ballonpomp niet te leiden tot vermindering van enzymatische infarctgrootte of een betere pompfunctie van het hart. Daarentegen trad bij 8% van de patiënten complicaties op ten gevolge van de ballonpomp. Systematisch gebruik van een intra-aortale ballonpomp bij hoog risico infarct patiënten is derhalve niet van voordeel.

Hoofdstuk 4

Primaire PTCA voor laag-risico patiënten
Uit eerder onderzoek kwam naar voren dat met name hoog risico infarct patiënten baat hebben van behandeling met primaire PTCA, maar of dit ook gold voor patiënten met bijvoorbeeld een onderwandinfarct was onbekend. Twee honderd veertig patiënten werden aan de hand van simpele klinische criteria onderverdeeld in hoog of laag risico patiënten. Alle 143 hoog risico patiënten werden behandeld met primaire PTCA, terwijl de 97 laag risico patiënten werden gerandomiseerd naar behandeling met streptokinase of primaire PTCA. Het gecombineerd voorkomen van overlijden, CVA of reïnfarcering was lager in de met primaire PTCA behandelde laag risico groep, met name door een minder voorkomen van reïnfarcten. Na 6 maanden bleken de kosten voor de behandeling met primaire PTCA niet hoger, met name door een geringer aantal heropnames, vergeleken met de patiënten die streptokinase hadden gehad. Het feit dat ook laag risico infarct patiënten baat hebben bij behandeling met primaire PTCA suggereert dat in een centrum waar PTCA faciliteiten voorhanden zijn **alle** patiënten met een acuut hartinfarct op deze manier behandeld dienen te worden.

Transport van infarct patiënten
Voor patiënten die een hartinfarct krijgen in een ziekenhuis waar geen PTCA kan worden

verricht bestaat de keuze tussen trombolytische therapie ter plekke of primaire PTCA na transport naar een PTCA centrum. In het tweede deel van hoofdstuk 4 wordt een onderzoek beschreven naar de veiligheid en haalbaarheid van transport van patiënten met een acuut hartinfarct. Honderdvier patiënten die van elders kwamen werden vergeleken met 416 patiënten die zich primair meldden in het PTCA centrum. De klinische uitkomst na 6 maanden werd met name bepaald door de indicatie van het transport en niet door het transport zelf. Verder bleek dat door de betere voorbereiding van de catheterisatiekamer de totale ischemische tijd (tijd van begin klachten tot balloninflatie) niet langer was in de groep die op transport was gesteld.

Hoofdstuk 5

Tijd tot reperfusie

Uit diverse studies bij patiënten die behandeld zijn met thrombolytica is duidelijk geworden dat het van groot belang is om een patiënt met een myocardinfarct zo vroeg mogelijk te behandelen. Behandeling met primaire PTCA geeft het voordeel dat de exacte tijd van reperfusie bekend is (het leeg laten lopen van het ballonnetje na de eerste balloninflatie). Om deze reden is bij dit soort patiënten goed vast te stellen wat de invloed is van ischemietijd op het uiteindelijke resultaat. Een groep van 496 patiënten werd op grond van totale ischemietijd ingedeeld in 3 groepen. De groep patiënten bij wie het vat binnen 3 uur na het begin van de klachten geopend werd bleken vaker een goede flow in dit vat te hebben en hadden een zeer lage mortaliteit na 6 maanden (3%). Ook bleek het herstel van linker kamer functie afhankelijk te zijn van de tijd tot reperfusie. Bij patiënten die behandeld waren binnen 6 uur na begin klachten trad verbetering op van de ejectiefractie na 6 maanden, terwijl de linker kamer functie gemiddeld genomen verslechterde in de groep die na 6 uur was behandeld. Dit bleek onafhankelijk van het hogere percentage patiënten met reocclusie in deze laat behandelde groep. Verder bleek dat oudere patiënten en patiënten met diabetes mellitus vaak laat (> 6 uur) behandeld worden, met name doordat ze zich pas laat presenteren met klachten. Na correctie voor dit verschil in basiskenmerken tussen de drie groepen bleef de tijd tot reperfusie een onafhankelijke voorspeller van herstel van linker kamerfunctie en overlijden na 6 maanden follow-up.

Het tweede deel van hoofdstuk 5 bekijkt wat het effect is van tijd, nodig voor transport van patiënten van elders, op het resultaat van de behandeling. Om te zorgen dat alleen het effect van tijd zich zou openbaren werd een groep van 207 getransporteerde patiënten gematched (op leeftijd, geslacht, infarctlocatie en Killip klasse) met een populatie van niet getransporteerde patiënten. Het bleek dat een additionele transporttijd van 43 minuten leidde tot een grotere enzymatische infarct grootte en een significant lagere linker kamer functie, ondanks een zelfde succespercentage van de behandeling. De mortaliteit na 6 maanden bleek in beide groepen niet te verschillen. Het transport van infarct patiënten naar een PTCA centrum heeft dus wel zijn prijs, maar beïnvloedde in deze studie niet de 6 maands overleving.

Hoofdstuk 6

Restenose

Er is lang gedacht dat restenose na PTCA bij patiënten met instabiele coronaire syndromen frequent optreedt. In dit hoofdstuk wordt het voorkomen van restenose bepaald in een populatie van 312 patiënten die succesvol waren behandeld met primaire PTCA in verband met een acuut hartinfarct. Restenose, gemeten met behulp van kwantitatieve coronairangiografie en gedefinieerd als een diameterstenose van meer dan 50%, trad op bij 27% van de patiënten na 3 maanden en bij

37% na 6 maanden follow-up. Reocclusie trad op in slechts 4 and 6% van de patienten respectievelijk. Leeftijd en diameter van het bloedvat na interventie bleken onafhankelijke voorspellende factoren voor het optreden van restenose. Patiënten jonger dan 50 jaar en patiënten met een diameter van het bloedvat na PTCA van meer dan 2,5 mm hadden een restenose percentage van minder dan 25%. Verder bleek dat restenose en reocclusie geen invloed hadden op linker kamer functie na 6 maanden. Het gevonden restenose percentage na PTCA vanwege een acuut hartinfarct blijkt dus niet hoger dan gerapporteerde cijfers bij patiënten die een PTCA ondergingen vanwege stabiele angina pectoris.

Hoofdstuk 7

Algemene Discussie

In dit hoofdstuk worden een aantal kanttekeningen geplaatst bij de gevonden resultaten. Het blijkt dat primaire stenting leidt tot een reductie van reïnterventies en reïnfarcten. Dit zorgt ervoor dat de initieel hogere kosten voor de stentimplantatie na 1 jaar ruimschoots worden terugverdiend. Stenting resulteert echter niet in een betere reperfusie of een reductie van enzymatische infarctgrootte of een betere linker kamerfunctie. Verder wordt in dit hoofdstuk besproken wat de gevolgen zijn van uitbreiding van de indicatiestelling voor behandeling met primaire PTCA. Het hoofdstuk word afgesloten met een aantal suggesties voor toekomstig onderzoek. Dit dient met name gericht te zijn op verbetering van myocardiale reperfusie en op verdere reductie van de tijd tot behandeling. Recent onderzoek laat zien dat nog steeds een groep patiënten met een acuut infarct geen vorm van reperfusietherapie krijgt. Thrombolytische therapie en primaire PTCA dienen in dit opzicht niet als rivalen op te treden, maar als elkaar aanvullende behandelingsvormen, waarbij het uiteindelijke doel is om zoveel mogelijk patiënten met een acuut hartinfarct zo vroeg mogelijk te behandelen.

Dankwoord

Dit proefschrift is opgezet en tot stand gekomen op de afdeling cardiologie in een perifeer ziekenhuis, dat in 10 jaar tijd is uitgegroeid tot een volwaardig regionaal hartcentrum met 1500 hartoperaties, 1800 PTCA's en 200 electrofysiologische procedures per jaar, en dat in 1995 de erkenning heeft gekregen van een A-opleiding. Dit is mogelijk gemaakt door de enorme drive en inzet van niet alleen de maatschapsleden cardiologie, maar ook van de specialisten en personeel van de afdeling thorachirurgie, de afdeling thoraxanaesthesiologie, en de ziekenhuisdirectie.

Professor dr M.L. Simoons, beste Maarten, wellicht dat jij een beetje van je gedrevenheid hebt overgedragen op de club hier, hartelijk dank voor je scherpe en opbouwende kritiek .

dr F. Zijlstra, beste Felix, het echte brein achter dit proefschrift. Ongelooflijk dat een idee op het Europese congres in Amsterdam, binnen 2 jaar heeft geleid tot een publikatie in de Lancet. Dit is typerend voor je manier van werken: hoog scoren door het simpel en praktisch te houden. Het feit, dat je méér arts-assistenten op de afdeling en publiceren belangrijker vindt dan je eigen inkomen, geeft al aan wat voor eigen-aardige cardioloog en gedreven onderzoeker je bent.

dr J. Hoorntje, beste Jan. Mijn eerste bezoek en kennismaking staat me nog helder voor ogen. Jij, met je pijp, wat onderuitgezakt in een stoel, zeer ontspannen verhalend over wat Zwolle voor kliniek is. Jouw brede interesse en aandacht voor het menselijke waardeer ik zeer. Ik weet zeker dat dit zijn vruchten zal afwerpen bij de generatie Zwolse cardiologen die jij hebt opgeleid en gaat opleiden.

dr M.J. de Boer, beste Menko-Jan. Dit is een vervolg op jouw proefschrift, wat precies 4 jaar geleden verscheen, waarmee in Nederland de toon werd gezet voor mechanische revascularisatie bij het acute hartinfarct. Ik hoop dat je er tevreden over bent en wie weet kan ik de fakkel overdragen aan een nieuwe Zwolse promovendus.

dr H. Suryapranata, beste Harry. Dank voor je suggesties over de opzet en inhoud van het proefschrift. Ik blijf erbij dat het acronym ESCOBAR (Emergency Stenting COmpared to Balloon Angioplasty Randomised study) het beter doet en ook beter onthouden wordt, met name in het buitenland, dan de ZIS (Zwolse Infarct Studie)-6 studie.

dr P.A.J. Remkes, beste Peter. Met alle respect, als iemand de old investigators award zou moeten winnen, dan ben jij het. Vorig jaar stond jij hier. Jouw boekje is erop gericht patientenstromen in te dammen, terwijl dit boekje misschien alleen maar meer patienten naar Zwolle zal aantrekken. Dank voor je nuttige tips en aanbevelingen. Ik hoop dat je nog lang onze club met je advies mag dienen.

Dank aan mijn collegae Willem Beukema, Rob Bloemers, Georges Gerritsen, Ed de KLuiver, Willem Jan Louridtz, Angela Maas, Ton van Nus, Henk Oude Luttikhuis, Anand Ramdat Misier, Peter Remkes en Karen Thomas voor de belangstelling voor mijn onderzoek.

Dank aan de leden van de kleine commisie, Prof Hermens, Prof Serruys en Prof Verheugt, voor het kritisch doorlezen van het manuscript.

Dank aan alle arts-assistenten, die bij nacht en ontij, even Amsterdam belden, om een volgende patient te includeren of te randomiseren en voor het invullen van de CRF's.

Dank voor de grote bijdrage van de afdeling klinische chemie, onder leiding van Kor Miedema, Bert Dikkeschei en Evelien van Voorst tot Voorst, en de afdeling Nucleaire Geneeskunde, onder leiding van Stoffer Reiffers en Jaap Kuyvenhoven. Al die buisjes bloed, die "even" opgehaald en verwerkt moesten worden en die rust ejectiefracties, die vóór overplaatsing van een patient nog "even" tussen het programma door gingen.

Dank aan alle leden van het hartcatheterisatieteam en CCU verpleegkundigen. Mede dankzij jullie is de tijd van aankomst van de patient tot eerste balloninflatie slechts 60 minuten, iets waar vele centra jaloers op zullen zijn.
Dank aan alle verpleegkundigen, functielaboranten, team leiders, en afdelingshoofden cardiologie die naast de zorg voor de patient, ook de zorg voor de wetenschap hoog in het vaandel hebben.
Dank aan de dames van het secretariaat cardiologie en de medische registratie, voor het opzoeken van honderden klinische en poliklinische statussen.
Dank aan Linda, Annemiek en Cocky voor het coördineren van alles wat met onderzoek te maken heeft.
Dank aan Vera Derks, voor het aanhoren van verhalen over niet slapen en lieve kinderen, maar met name dank voor het aanpassen van alle artikelen, dia's en voor die kleine dingen, die je voor me hebt gedaan, die maken dat publiceren in een perifeer ziekenhuis leuk blijft.
Dank aan Drs A.L. Liem, beste Ay Lee, voor het eindeloos gebruik van jouw database, voor de gezelligheid tijdens congresbezoek en voor het halen van heel veel blikjes cola.
Dank aan Rein van der Wal, medisch fotograaf, voor het maken en verfraaien van vele dia's, grafieken en plaatjes.
Dank aan Martijn Doeland voor het oplossen van computerproblemen.
Dank aan alle huisartsen in de regio en het ambulance personeel, die hun leven in de waagschaal stellen om de tijd tot reperfusie maar zo kort mogelijk te houden.
Natuurlijk veel dank aan alle Zwolse Infarct Studie (ZIS) patienten, zonders wiens medewerking dit proefschrift er nooit was geweest.
Dank aan de afdeling cardiologie van het St. Antonius Ziekenhuis te Nieuwegein, met name Carl Ascoop en Norbert van Hemel, voor de gedegen vooropleiding die ik bij hen heb genoten.
Professor I. Segal, dear Issidor. You were the one that made me enthusiastic for research and showed that doing research in South Africa is very special.
Dank aan Marianne Eichholz, voor de hartelijke ontvangsten in Rotterdam en de ondersteuning bij de voorbereiding van de promotie.
Gerard Metselaar en Ernesto de la Fuente, muchas gracias!
Ruurd Buitenhuis en Rob Barnasconi, paranymfen en oud-huisgenoten. Ik vind het echt geweldig, jullie tijdens de verdediging aan mijn zijde te hebben.
Dank aan mijn ouders, voor jaren van steun, stimulans, sponsoring en belangstelling.

Last, but not least, Karin, Marlou en Lasse, zonder jullie afleiding was "deze scriptie" maanden eerder klaar geweest, maar gelukkig bestaat het leven uit meer dan alleen een boekje maken.

Curriculum Vitae

Born	't Harde, June 19, 1963
Nationality	Dutch
State	Married to Karin Gilissen, General Practitioner. Two children:Marlou and Lasse
1975 - 1981	Secondary School, C.S.G. de "Heertganck" te Heerde
1981 - 1982	Propaedeuse, Forestry, Agricultural University Wageningen
1982 - 1989	Medicine, State University Utrecht
1984 - 1985	Student Internship Anatomy, State University Utrecht (Head: Prof.dr W.J. van Doorenmaalen)
1986 - 1987	Primary Healtcare projects, Salesian mission, Peru and Venezuela
1988	Internship Cardiology, State University Bern, Switserland (Head:Prof. H.P. Gurtner)
1989 - 1990	House Officer Internal Medicine, Elkerliek Hospital, Helmond
1990 - 1991	House Officer Cardiology, St. Antonius Hospital, Nieuwegein
1991 - 1993	Resident Internal Medicine, Eemland Hospital, Amersfoort (Head: dr R. Geerdink)
1993 - 1994	Resident Internal Medicine, Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa (Head: Prof. Huddle)
1994 - 1995	Resident Cardiology, St Antonius Hospital, Nieuwegein (Head: dr C.A.P.L. Ascoop, and Prof. dr N. van Hemel)
1995 - 1998	Resident Cardiology, de Weezenlanden Hospital, Zwolle (Head:dr J.C.A. Hoorntje)
1998 -	Practicing Cardiologist, Ziekenhuis de Weezenlanden, Zwolle

List of Pubications

1. Arnoud van 't Hof. Dringen in de Co-Schappen. Medisch Contact 1989 [letter], 44:1434.

2. Suttorp MJ, Polak PE, van 't Hof AWJ, Rasmussen HS, Dunselman PH, Kingma JH. Efficacy and safety of a new class III antiarrhythmic agent Dofetilide in patients with paroxysmal atrial fibrillation or atrial flutter, Am J Cardiol 1992;69:417-419

3. Suttorp MJ, Kingma JH, Koomen EM, van 't Hof AWJ, Tijssen JGP, Kingma JH. Recurrence of paroxysmal atrial fibrillation or flutter after succesful cardioversion in patients with normal left ventricular function. Am J Cardiol 1993;71:710-713.

4. Lie-A-Huen L, Suttorp MJ, van 't Hof AWJ, Hulst RM, Meyer DKF, Kingma JH. Is episodic treatment of paroxysmal atrial fibrillation feasible with an oral solution of flecainide? Thesis L. Lie-A-Huen, 1991.

5. van 't Hof A, Gilissen K, Cohen RJ, Taylor L, Haffajee Z, Thornley AL, Segal I. Colonic cell proliferation in two different ethnic groups with contrasting incidence of colon cancer: is there a difference in carcinogenesis? Gut 1995;36:691-5.

6. van 't Hof AWJ, Mosterd A, Suttorp MJ. Amiodarone for prevention of atrial fibrillation. Am J Cardiol [letter]1996;77:327.

7. van 't Hof AWJ, Zijlstra F, De Boer MJ, Liem AL, Hoorntje JCA, Suryapranata H. Patency and reinfarction in late-entry myocardial infarct patients treated with reperfusion therapy. Angiology 1997;48;215-22.

8. Zijlstra F, Beukema WP, van 't Hof AWJ, Liem AL, Reiffers S, Hoorntje JCA, Suryapranata H, de Boer MJ. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908-12.

9. van 't Hof AWJ, Liem AL, de Boer MJ, Zijlstra F, on behalf of the Zwolle myocardial infarction study group. The clinical value of the 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-19.

10. Zijlstra F, van 't Hof AWJ, Liem AL, Hoorntje JCA, de Boer MJ, Suryapranata H. Transferring patients for primary angioplasty. Heart 1997;78:333-336.

11. van 't Hof AWJ, Liem AL, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Clinical presentation and outcome of patients with early, intermediate and late reperfusion therapy by primary coronary angioplasty for acute myocardial infarction. Eur Heart J 1998;19:118-123.

12. van 't Hof A, F Leicher, C Schipper, JCA Hoorntje. Presentation of a pseudoaneurysm as a supravalvular aortic stenosis 20 years after aortic root reconstruction. Eur J Thor Surg 1998;13:481-483.

13. van 't Hof AWJ, Hoorntje JCA. Cardiogenic shock due to isolated right ventricular infarction. Rapid haemodynamic improvement after primary angioplasty. Cardiologie 1998; 5:189-192

14. van 't Hof AWJ, Suryapranata H, de Boer MJ, Hoorntje JCA, Zijlstra F. Costs of stenting for acute myocardial infarction. Lancet 1998;351:1817(letter)

15. van 't Hof AWJ, Liem AL, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F, on behalf of the Zwolle myocardial infarction study group. Angiographic Assessment of Myocardial Reperfusion in Patients treated with Primary Angioplasty for Acute Myocardial Infarction: Myocardial Blush Grade. Circulation 1998, 97:2302-2306.

16. Suryapranata H, van 't Hof AWJ, Hoorntje JCA, de Boer MJ, Zijlstra F. Randomized Comparison of Coronary Stenting with Balloon Angioplasty in Selected Patients with Acute Myocardial Infarction. Circulation, 1998; 97:2502-2505.

17. van 't Hof A, Schipper C, Reiffers S, Gerritsen G, Hoorntje JCA. Comparison of radionuclide ejection fraction with two echocardiographic parameters of left ventricular function in post myocardial infarct patients. Int J Cardiac Imaging, accepted for publication with minor revi sion.

18. Liem AL, van 't Hof AWJ, Hoorntje JCA, de Boer MJ, Suryapranata H, Zijlstra F. Influence of treatment delay on infarct size and clinical outcome in patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol, in press.

19. van 't Hof AWJ, de Boer, MJ, Suryapranata H, Hoorntje JCA, Zijlstra F. Incidence and Predictors of Restenosis after Primary Coronary Angioplasty for Acute Myocardial Infarction: The Importance of Age and Procedural Result. Am Heart J, in press.

20. Ottervanger JP, Liem AL, de Boer MJ, van 't Hof AWJ, Hoorntje JCA, Suryapranata H, Zijlstra F. Limitation of myocardial infaract size after primary angioplasty: is a higher patency the only mechanism? Am Heart J, in press.

Additional financial support by the following sponsors is gratefully acknowledged:

Cordis / Johnson & Johnson Nederland BV
Bard Benelux NV
Schneider Benelux
Bristol-Myers Squibb BV
Eli Lilly Nederland BV
Vitatron Nederland BV
Henry Schein Wigro van der Kuip BV