Strategies of coronary reperfusion in acute myocardial infarction for patients admitted to hospitals without angioplasty facilities

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Strategies of coronary reperfusion in acute myocardial infarction for patients admitted to hospitals without angioplasty facilities

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. dr. A.C. Nieuwenhuijzen Kruseman,
volgens het besluit van het College van Decanen,
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Aan mijn ouders*

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CHAPTER 1

Introduction

Our understanding of the pathophysiological mechanisms of acute myocardial infarction (AMI) and the treatment of this disease evolved considerably during the past two decades. Whereas in the seventies the treatment mainly was directed towards control of cardiac arrhythmias, in the eighties and thereafter the therapy of patients with acute myocardial infarction focussed more on reperfusion of the culprit coronary artery leading to limitation of infarct size and improved clinical outcome.

At present, two reperfusion techniques have proven their efficacy; 1) the administration of fibrinolytic agents and 2) mechanical reopening of the occluded vessel followed by percutaneous transluminal coronary angioplasty (PTCA). Rescue PTCA after failed thrombolysis is likely to be beneficial, but definite proof is not available. The purpose of this thesis is to compare three strategies of management of acute myocardial infarction; a) thrombolytic therapy, b) thrombolytic therapy followed by acute coronary angiography and (if indicated) rescue PTCA, and c) primary PTCA.

So far, angioplasty in acute myocardial infarction has primarily been studied and practiced in patients who were admitted directly to a PTCA center (Chapter 3). However, the majority of patients with an acute myocardial infarction present to hospitals without PTCA facilities. We first studied retrospectively the possible benefit of early transfer for rescue PTCA (Chapter 4). Based on these findings, a prospective randomised multicenter trial was started comparing the three above mentioned reperfusion strategies in patients who were initially admitted to a hospital without angioplasty facilities (Chapter 6). The feasibility and safety of such an approach was evaluated (Chapter 7) and the cost effectiveness of these reperfusion strategies is assessed in chapter 8.

In order to avoid unnecessary acute coronary angiography and subsequent angioplasty in patients with successful reperfusion, either spontaneously or after successful thrombolysis, the value of non-invasive parameters of reperfusion has to be evaluated. For that purpose simple and widely available non-invasive reperfusion parameters have been suggested. In chapter 5 presence or absence of these reperfusion markers was evaluated just before the first intracoronary injection of the infarct-related vessel and correlated to coronary flow allowing evaluation of the reliability of these markers.

In chapter 9 conclusions are given.

Therefore, this thesis aims to answer the following questions:

1. Are there differences in clinical and angiographic outcome between rescue or primary PTCA? (Chapter 3)

2. Can unnecessary acute coronary angiography and subsequent angioplasty be avoided by accurate and simple reperfusion parameters? (Chapter 5)
3. Do patients with acute myocardial infarction initially admitted to a hospital without angioplasty facilities benefit from early transfer to an angioplasty center for emergency angioplasty? (Chapters 4,6,7)
4. What is the cost-effectiveness ratio of three different reperfusion strategies in patients with acute myocardial infarction admitted to a hospital without angioplasty facilities? (Chapter 8)

CHAPTER 2

Historic overview

'THROMBOLYTIC ERA'

Findings at autopsy indicate that approximately 90% of patients dying from acute myocardial infarction have a thrombotic coronary artery occlusion, frequently caused by local rupture of the intima of the atherosclerotic vessel wall (1). Since it became clear that thrombosis plays an important role in the pathophysiology of acute myocardial infarction, interest was directed towards drug therapy that could dissolve the coronary clot. Already in 1933, fibrinolytic activity of beta-hemolytic streptococci was described by Tillet and Garner (2). This observation led to the first therapeutic attempt to dissolve a fibrinous pleural effusion by Tillet and Sherry in 1948 (3). In the late sixties, dose finding studies with streptokinase were conducted (4,5), but results were variable and therefore streptokinase was not used widely thereafter.

In the early eighties large randomised studies confirmed the value of thrombolytic therapy in acute myocardial infarction. Initially thrombolytic therapy was directly given into the infarct-related artery, resulting in reperfusion and reduction of mortality of approximately 30 % if patients were treated within 4 hours (6). This approach was complex, time consuming, expensive and resulted not uncommonly in bleeding complications at the puncture site. In contrast to the initial expectation, a systemic thrombolytic effect was observed. This was reason to switch to the intravenous administration of the drug, which resulted in an acceptable benefit/risk ratio (7-11). As shown angiographically, reperfusion of the culprit artery resulted, as defined in the Thrombolysis In acute Myocardial Infarction (TIMI) study, in 50-90% at 90 minutes after the start of therapy and myocardial salvage was documented (11-27).

The GISSI trial was the first large trial of thrombolytic therapy. In 11,806 patients with acute myocardial infarction this study demonstrated that intravenous thrombolytic therapy was effective, although less than with the intracoronary route, saving approximately 20/1000 patients (7). Randomised studies demonstrated a clear correlation between infarct related vessel patency, mortality and preservation of left ventricular function. Even in case of late reperfusion the incidence of malignant arrhythmias decreased, and fatal embolic intracerebral stroke due to thrombus formation in the left ventricle was seen less frequently. The price to pay was more bleeding complications of which the intracerebral haemorrhage was feared most. Time delay between onset of AMI and thrombolytic therapy showed to be of significant importance. In the GISSI trial a reduction in mortality was only observed in patients who presented with acute myocardial infarction within 3 hours of the onset

of chest pain (7). This finding was confirmed by three more recently published trials, using prehospital thrombolysis (28-30). The earlier this therapy is given, the greater the benefit. The European Myocardial Infarction Project (EMIP) enrolled approximately 6000 patients who were randomised and treated with prehospital thrombolysis or with thrombolysis after admission to a hospital (29). When compared to the pre-hospital thrombolysis group, a median time delay of 55 minutes of the administration of a thrombolytic agent was observed in the hospital thrombolysis group. Adverse events like ventricular fibrillation, shock, symptomatic hypotension and bradycardia were seen more often in the prehospital thrombolysis group. These events usually occurred during the period before hospitalization. However, with the exception of symptomatic hypotension, the overall incidence of these events when including the hospital phase were similar for both groups. Thirteen percent further reduction in mortality of the prehospital thrombolysis group underlines the value of early administration of thrombolytic agents. The EMIP investigators concluded that prehospital thrombolytic therapy for patients with suspected myocardial infarction is both feasible and safe when administered by well-equipped and well-trained mobile emergency staff and results in a better clinical outcome.

FINE TUNING OF THROMBOLYTIC AGENTS

At present, several thrombolytic agents are available. There are some differences in speed and completeness of reperfusion as well as in side effects. To improve reperfusion, attention is also given to concomitant medication. The ISIS-2 study assessed the separate and combined effects of intravenous streptokinase and oral aspirin (8). In a randomised study of 17,187 patients it was concluded that the combination of streptokinase and aspirin in suspected myocardial infarction is beneficial in clinical outcome in terms of mortality and reinfarction rate. However even with the most aggressive thrombolytic agent alteplase combined with aspirin and intravenous heparin, complete (TIMI grade 3) reperfusion is achieved in only 54 % of all patients treated within 6 hours after the onset of pain (23). Newer thrombolytic agents result in higher patency rates. When combined with IIB/IIIA glycoprotein receptor antagonists further improvement is expected.

Risks of thrombolytic therapy, especially bleeding, have been reported in several studies (31). Since thrombolytic agents do not discriminate between an intracoronary thrombus and a clot at a potential bleeding site, hemorrhages can occur. Most bleeding complications consist of prolonged bleeding at the puncture site. When cardiac catheterization is performed, bleeding complications are seen in 20-40% of patients. Life-threatening intracerebral bleedings have been reported. The International Study Group investigated the clinical course in 20,891 patients with AMI randomized to alteplase or streptokinase with and without heparin (32). The risk of stroke was 1.3% with rt-PA as compared to 1% with streptokinase,

however the cause of stroke could not be established in all cases. For patients with contraindications to thrombolytic therapy (mainly patients with enhanced risk of bleeding) mechanical reopening by PTCA was found to be a good alternative. Later this approach was also evaluated for patients without contraindications to thrombolytic therapy.

CORONARY ANGIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

DeWood and coworkers in 1980 were the first to show that coronary angiography is feasible in acute myocardial infarction (33). In 126 patients they demonstrated that within 4 hours of symptom onset 87% of infarct related vessels were occluded. They also showed the safety of such a procedure with only little increased risk from the procedure itself as compared to elective coronary angiography. Later, acute coronary angiography became common practice in thrombolysis trials to determine infarct related vessel patency.

THROMBOLYSIS AND IMMEDIATE PTCA

The combination of thrombolytic therapy with immediate PTCA independent of the reperfusion status of the vessel was investigated in the past (34,35). The assumption was that the two-step process of fibrin dissolvment and plaque compression would be superior to only attacking thrombus formation. However, it was found that immediate PTCA after thrombolysis, independent of reperfusion status, did not improve cardiac function and led to a higher complication rate. The TIMI II A study showed that the 24 hour complication rate using the immediate invasive strategy was significantly higher (8.5%) than a delayed invasive strategy (4.6%) in case of persisting or recurrent ischemia (35). This negative outcome was considered to be the result of the "sick artery", conceptualized as an infarct vessel with a destabilized plaque, marked platelet aggregation and residual thrombus after thrombolytic therapy. Under such conditions PTCA did not show to be favorable (36). The SWIFT (Should We Intervene Following Thrombolysis) trial compared an invasive strategy with a conservative approach after thrombolytic therapy. The invasive strategy was early elective angioplasty (within 48 hours). Patients in the conservative group had angiography only if they had recurrent ischemic symptoms or positive results on exercise tests. At three months, mortality rates were not significantly different between the conservative (3.2%) and the invasive group (4.8%); the mean left ventricular ejection fraction was also similar. Thus, the results of the SWIFT trial were in line with other studies (37). However, in the TAMI-5 study an aggressive strategy of immediate catheterization and angioplasty for failed thrombolysis was better when compared to a strategy of deferred predischarge catheterization on days 5-10 (24,38). The strategy of immediate catheterization and angioplasty was associated with improved regional wall motion in the infarct region

($p=0.004$) and fewer adverse outcomes ($p=0.004$). When more and more study results became available the concept of “watchful waiting” was preferred in the patients treated with a thrombolytic agent, as indicated in 1990 by Meier (39).

RESCUE PTCA

From the randomized clinical trials, it became clear that patients with reperfused coronary arteries have a better clinical outcome than patients with failed thrombolysis. This observation led to the concept of rescue PTCA, a strategy using a mechanical approach immediately following failed thrombolysis. In 1992 Belenkie et al. reported a small randomized study in 29 patients between conservative therapy and rescue PTCA without significant difference in clinical outcome (40). In 1994 Ellis et al. published the results of the RESCUE study evaluating PTCA after failed thrombolysis for patients with acute anterior myocardial infarction (41). In this study one hundred fifty-one patients with first anterior AMI, treated with intravenous thrombolytic therapy and an angiographically demonstrated occluded infarct vessel, were randomised to either conventional treatment or acute balloon angioplasty. In the latter group, angioplasty was technically successful (final TIMI flow grade 3 and percent stenosis $< 50\%$) in 92%. This study demonstrated a limited reduction in mortality and heart failure as well as improved left ventricular function on exercise at 30 days follow-up, favoring rescue PTCA. However, this study consisted of a selected group of patients. Patients could be included up to eight hours after the onset of chest pain. A patient log showed that a strong investigator bias had been present. Patients presenting early in the course of their infarction or patients with extensive ischaemia usually were not included in the study. Possibly, this bias and the wide-open inclusion time window led to inclusion of patients with only a limited amount of salvagable tissue. In the RESCUE study 151 patients were included in three years with recruitment from 20 centers. Many angioplasty centers did not participate because potential investigators considered it unethical to refrain at the end of the acute coronary angiography from mechanical intervention after failed thrombolysis. A meta-analysis of studies with rescue PTCA by Ellis showed success rates in achieving infarct related artery patency ranging from 71% to 92% (42). There was little beneficial effect as to recovery of left ventricular function at the time of hospital discharge. However, patients with successful angioplasty had a considerably lower mortality rate than patients with unsuccessful coronary angioplasty (43-46). It should be stressed that in many patients rescue PTCA was done many hours after the start of thrombolytic therapy. Secondly, the decision to perform rescue PTCA was frequently taken in case of further deterioration of the clinical situation of the patient. These factors influenced the outcome of such therapy in a negative way.

Reocclusion rates after successful rescue angioplasty have been reported to be as high as 29%, but appear to be considerably lower when streptokinase, which induces

low fibrinogen levels during 24 to 48 hours ("general lytic state") is used (24,47-48). In a retrospective study comparing rescue and primary PTCA during acute myocardial infarction Bär et al. showed much lower reocclusion rates, 3% versus 3.9% for rescue and primary PTCA, respectively (49). Until today, only small randomised and observational studies have been published. As a consequence of this, the general application of rescue PTCA has not yet been accepted as a proven beneficial strategy.

PRIMARY PTCA

Direct or primary coronary angioplasty was first introduced by Hartzler et al. in 1983 (44). Patients with acute myocardial infarction are catheterized as soon as possible, the occluded artery is opened by PTCA. The use of a guide wire and angioplasty balloon seemed to result in more rapid reperfusion than thrombolysis. At present, five randomised clinical trials have been conducted comparing thrombolytic agents and primary PTCA in acute myocardial infarction (50-54). These trials demonstrated lower death and non-fatal reinfarction rates during hospital stay and after 6 month-follow up in the patients treated with primary PTCA. The Zwolle group and Gibbons et al. showed also an improvement of left ventricular function (52,54). In these studies primary angioplasty resulted in a higher acute and late patency rate of the infarct related vessel, in a smaller infarct size as evident from cumulative enzymatic release and left ventricular ejection fraction measurements, and in a better immediate and long term clinical outcome. Moreover, a shorter hospital stay, lower mortality, less reinfarction and fewer readmissions were observed.

Thus, under ideal circumstances primary PTCA leads to a faster and more complete vessel patency and avoids the need of a thrombolytic agent thereby limiting the risk of bleeding complications and paradoxical thrombin generation. Clearly these results can only be achieved in the patients with acute myocardial infarction who are admitted to an experienced PTCA center. Larger scale studies show that primary PTCA in the "real world" does result in no or minimal differences in clinical outcome when compared to thrombolytic therapy (55). The prolonged benefit of primary PTCA might among other reasons be the result of less residual coronary artery stenosis when compared to thrombolytic therapy only. A high residual coronary artery stenosis may be a risk factor for future reocclusion (51).

Although meta-analyses suggest that primary PTCA may be more beneficial than thrombolytic therapy in AMI, these data have to be interpreted cautiously until confirmed by larger studies (55).

PTCA FACILITIES IN THE NETHERLANDS

Since Andreas Gruntzig performed the first PTCA in 1977 surgical standby has been an important companion of coronary angioplasty (56). Among his first 50 patients 14% required emergency bypass surgery because of acute ischemia. In 1988

Guidelines for Percutaneous Transluminal Coronary Angioplasty by the joint ACC/AHA Task Force stated that “an experienced cardiac surgical team should be available within the institution for emergency surgery for all angioplasty procedures” (58). Basically, these guidelines were followed by the Dutch government and the Dutch Working group of Interventional Cardiology. Only 13 centers (less than 10% of all hospitals in the Netherlands) have permission to perform PTCA-procedures. In the United States approximately 20% of hospitals do have PTCA facilities. The others are not equipped to perform such interventions. Thus for acute PTCA they have to depend on the services of PTCA centers. Many of these centers do not accept such patients or they are not able to perform PTCA as a 24 hour service. In view of the reports on the beneficial outcome of primary and possibly also rescue PTCA, the treating physician in a non-PTCA center is faced with the issue whether or not his patient with acute myocardial infarction should be transferred for emergency angioplasty elsewhere. The decision to transfer a patient for PTCA will depend on timedelays, extent and localisation of the acute myocardial infarction, transport, PTCA center and pretreatment with a thrombolytic agent (59).

LOGISTICAL PROBLEMS ARISING WITH PATIENT TRANSFER BETWEEN HOSPITALS WITH AND WITHOUT PTCA FACILITIES

The current reports on the beneficial outcome of primary PTCA are encouraging, but still too small to draw general conclusions with respect to the optimal treatment of patients admitted with AMI. Recently, Zijlstra et al. showed that primary PTCA resulted in a better clinical outcome at 6 months compared to thrombolysis even in a low risk patient (60). One should keep in mind that this was found in patients directly admitted to a PTCA center. In the Netherlands approximately 27,000 patients are admitted with AMI per year (61). A substantial number of these patients are treated with thrombolytic agents, and no further action is taken. Of these 27,000 only approximately 3000 patients are admitted to centers with PTCA facilities. If primary or rescue PTCA is the most effective treatment in patients with AMI admitted in PTCA centers, it is still unclear whether the large proportion of patients admitted to hospitals without PTCA facilities can also profit from such intervention. It has to be considered that the time interval between onset of complaints and possible interventional treatment will lengthen because these patients need transport from one to another hospital. The logical question therefore then will be, “is emergency PTCA elsewhere useful in AMI patients who are admitted to a hospital without PTCA facilities”? Due to the expected time delays of transport and its potential risks, it is unclear whether thrombolytic therapy alone in such patients would be inferior to transport followed by either primary PTCA or rescue PTCA if indicated.

CORONARY ARTERY BYPASS SURGERY FOR ACUTE MYOCARDIAL INFARCTION

In the acute phase of myocardial infarction coronary artery bypass grafting (CABG) can limit myocardial necrosis (62,63). However, CABG has a very limited place in the management of the acute phase of myocardial infarction. It may be indicated in 2% to 5% of patients initially referred for PTCA, either because PTCA has failed, or PTCA is not feasible (62). Furthermore, it is limited to patients who are not eligible for thrombolytic treatment or who have failed thrombolysis within 4 to 6 hours after the onset of acute myocardial infarction (64). The intraoperative use of aprotinin after thrombolytic treatment may reduce haemorrhage related to the use of thrombolytic agents (65). Deferred CABG 3 to 7 days after myocardial infarction may be carried out with operative mortality approaching that for elective CABG (66-68).

STENTING IN ACUTE MYOCARDIAL INFARCTION

Although intracoronary stent implantation is an effective technique for the treatment of selected de novo lesions and for the management of abrupt closure, the use of stents in patients with acute myocardial infarction was not commonly accepted because of concerns regarding stent thrombosis (69-71). Non-randomised observational studies reported use of intracoronary stents to treat both suboptimal results and complications occurring in patients undergoing primary PTCA during AMI. Due to the thrombogenic nature of intracoronary stenting, combined antiplatelet therapy is recommended after stent placement in patients with acute myocardial infarction (72). Recently, two trials comparing primary PTCA and primary stenting in AMI have shown less mortality, angina and re-interventions after intracoronary stenting (73,74).

NON INVASIVE REPERFUSION MARKERS IN ACUTE MYOCARDIAL INFARCTION

If rescue PTCA is considered indicated in case of failed thrombolysis, unnecessary coronary angiography can be avoided if non-invasive signs of reperfusion are of value to select the patient who is (no) candidate for acute coronary angiography. Several tests have been proposed to diagnose reperfusion, all having limited specificity and sensitivity (75-77). To date no thrombolytic agent or combination of agents has consistently achieved reperfusion rates in excess of 75% to 80% when evaluated at up to 90 minutes after administration. Establishing successful thrombolysis is important. In recent years much research has been directed towards development of sensitive non-invasive reperfusion markers (75-77).

A rapid and complete resolution of ST-segment elevation correlates most accurately with reperfusion. This was found to occur in only 6% of patients with AMI (76). Partial reduction of ST-segment deviation to $\geq 50\%$ of the initial level of

ST-segment elevation occurs more frequently and has, especially in combination with other ECG criteria, also, important predictive value with respect to reperfusion and prognosis (76,78). Other clinical indicators (decrease of chest pain) or electrocardiographic signs (development of terminal negative T-wave in infarct leads, accelerated idioventricular rhythm (AIVR), restoration of atrioventricular conduction, increase in ventricular arrhythmia's) have either a low sensitivity or a low specificity to predict infarct vessel patency (79,80). Many small sized studies evaluating the value of reperfusion parameters have been conducted. The limited number of patients, the variable interval between non-invasive evaluation and angiographic validation of reperfusion status, and the frequently retrospective nature of these studies indicate the need to find new ways to obtain rapid and reliable non-invasive parameters of reperfusion.

FUTURE DEVELOPMENTS

One of our largest problems is that even aggressive therapy for myocardial infarction can prevent only 5% of the total number deaths from acute myocardial infarction, because most patients will die suddenly before any type of treatment can be initiated (81). Swift hospitalization, fast therapy (prehospital thrombolysis) will certainly be beneficial in reducing total death. However the majority of the patients do not experience cardiac complaints before the onset of acute myocardial infarction and therefore cannot be recognized beforehand.

Considerable effort and large sums of money are spent on constructing a risk profile for sudden death in the myocardial infarction survivor at the time of discharge from hospital. However the majority of sudden death victims cannot be identified before the event (81,82).

Future developments might influence the outcome of the treatment strategies performed in the three treatment groups as discussed previously. Newer thrombolytic agents with different points of action resulting in higher patency will soon be available (83,84). Newer thrombin inhibitors might replace heparin, and platelet aggregation inhibitors like glycoprotein IIb/IIIa receptor antagonists added to heparin can lead to higher sustained patency and lower reocclusion rates (85-90). This development can improve the outcome of patients treated with thrombolytic therapy and might decrease the need for rescue PTCA. On the other hand the implementation of new indications of coronary stenting may positively influence success rate of both primary and rescue PTCA (74,91). The net effect of these changes will have to be demonstrated in future studies.

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CHAPTER 3

Rescue PTCA following failed thrombolysis and primary PTCA

A retrospective study of angiographic and clinical outcome

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ABSTRACT

Background: Evidence is increasing that a patent culprit artery improves the prognosis of patients with acute myocardial infarction (AMI). Primary PTCA has shown to be more effective than thrombolytic therapy alone. How effective is rescue PTCA after failed thrombolytic treatment?

Methods: In a retrospective analysis, 176 consecutive patients with AMI and TIMI 0 or 1 perfusion grade were included. Patients had either rescue PTCA after failed thrombolysis (100 patients) or primary PTCA (76 patients). Angiographic data and in-hospital and one year outcome were analyzed.

Results: Comparison of baseline data of the two groups showed a higher proportion of long standing angina and use of nitrates and aspirin in the primary PTCA group, also the delay between onset of pain and PTCA was not significantly different: rescue PTCA mean 222 minutes, primary PTCA mean 245 minutes ($p=0.52$).

The angiographic outcome in the rescue PTCA group and the primary PTCA group was identical: the intervention was successful (TIMI 3 flow and residual stenosis $< 50\%$) in 86.0% and 85.5% respectively. Complication rates of the procedure were also similar except for bleeding complications. Blood transfusion was only needed after rescue PTCA: 3.0% vs 0.0% in primary PTCA patients. Clinical outcome during hospital stay in terms of death rate (4.0% and 6.6%), re-infarction (6.0% and 3.9%), recurrent angina (16.0% and 11.8%), and repeat interventions were comparable as was the first year outcome. Failed PTCA was the most important predictor of a poor one year outcome: 28.0% died after failed PTCA versus 4.6% after successful PTCA ($p < 0.001$).

Conclusion: In this retrospective analysis with 176 AMI patients, angiographic and clinical outcome, including a one year follow-up in patients who had rescue PTCA after failed thrombolysis were of the same magnitude of patients in whom primary PTCA was performed. These findings suggest that in this subset the outcome of patients with rescue PTCA because of failed thrombolysis is good and comparable to patients who underwent primary PTCA.

INTRODUCTION

In recent years it has become clear that re-opening of the occluded coronary artery in acute myocardial infarction (AMI) is a key factor determining clinical outcome (1). Because thrombosis is the most common cause for the obstruction, thrombolysis has become the therapy of choice. This type of treatment has shown to be reasonably effective: patency (TIMI 2-3) of the culprit vessel can be achieved in 50-90% at 90 minutes after the start of therapy, but drawbacks of thrombolytic therapy are severe bleeding complications like intracranial hemorrhage (2-22).

Therefore, primary PTCA was advocated as a safe, fast, but also as a more successful alternative (19). After primary PTCA, patency rates above 90% and a low incidence of complications were reported (23-29). In addition, three studies have been published indicating that also in randomized trials primary PTCA is more effective than thrombolytic therapy (30-32).

The value of rescue PTCA in addition to failed thrombolysis has so far inadequately been studied. The RESCUE study (33,34) and the TAMI V study (23) suggest that thrombolysis and rescue PTCA if indicated might be better than thrombolytic therapy only.

One of the questions remaining is, how effective is rescue PTCA after failed thrombolysis when compared with primary PTCA. To study safety and efficacy of both strategies, a retrospective analysis was performed of patients with AMI. All patients admitted between 1986 and 1992 who had PTCA in the acute phase of AMI were included. One hundred patients had rescue PTCA and 76 patients in whom thrombolytic therapy was withheld primary PTCA was done. Not only on the clinical outcome, but also on the complications of the angiography and PTCA will be reported because conflicting data have been published on the angiographic outcome of immediate PTCA after thrombolysis (19,30,33-54).

METHODS

In our hospital, patients with typical clinical and electrocardiographic signs of an AMI are treated with thrombolytic therapy if the chest pain lasts for ≥ 30 minutes. Initially, only patients ≤ 70 years were treated with thrombolytic therapy in case treatment delay was ≤ 4 hours. At later stage, the upper age criterium increased to 85 years and the delay to 6 hours. Electrocardiographic criteria for an intervention were: ST-segment elevation ≥ 1 mm in at least two extremity leads and ST-segment elevation ≥ 2 mm in at least two precordial leads. Most of the patients in this retrospective analysis were included in thrombolysis studies (16,17,48). AMI patients, who had a contra-indication for thrombolysis or in whom this therapy was withheld for other reasons, had primary PTCA in case the ECG was suggestive for a moderate to large AMI.

In our institution, catheterization service is available on a 24-hour basis.

MEDICATION

Routine treatment of our infarct population was as follows: patients were given intravenous nitroglycerin, heparin as a bolus of 5,000 U before thrombolytic therapy, followed by an intravenous heparin drip titrated according to the activated partial thromboplastin time (2-2.5 times normal value). Since 1988, patients were also pretreated with aspirin. Thrombolysis patients received one of the following thrombolytic agents: streptokinase, alteplase, APSAC or saruplase in the recommended dosages. In approximately 20% of the thrombolysis patients admitted to our hospital rescue PTCA was performed in the period analyzed.

CARDIAC CATHETERIZATION

All patients had cardiac catheterization within 90 minutes after admission. At that time, another 5000 U of heparin was given. If thrombolytic therapy was withheld or if this treatment failed, PTCA was performed routinely when the TIMI perfusion grade was 0 or 1. Patients with higher perfusion grades were not considered to be candidates for acute PTCA because of the results of the TIMI 2 Trial and the European Cooperative Study (34,35) PTCA was also not performed if it appeared unlikely that the patient would benefit from PTCA because of a small area perfused by the occluded artery. In patients with significant main stem disease bypass surgery was recommended. Rescue PTCA was performed 90 minutes after the start of thrombolytic therapy, primary PTCA as soon as possible.

Successful PTCA was defined as good flow (TIMI 3) and a residual stenosis of <50% 10 minutes after the last balloon inflation. After successful PTCA, an additional bolus of 15,000 U heparin and 300 mg iv aspirin was given.

CLINICAL FOLLOW-UP

All patients were followed during the first year after myocardial infarction in the out patient clinic. Data on outcome during admission and the period thereafter during the first year will be given separately. Follow-up angiography was only done when clinically indicated.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean $\pm$ SD and are compared by use of Student's *t* test. Non-continuous variables were compared by use of the chi square test. A *p* value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the 176 patients are given in table 1. The reasons to withhold thrombolytic treatment and to perform primary PTCA are listed in table 2. Patients with primary PTCA had more frequent long standing angina and, as a consequence, more medication. Due to the presence of long standing angina, 17 patients had a recent catheterization. The decision to perform primary PTCA in these 17 patients was partially based on the higher risk of a bleeding complication in the groin, but also because coronary anatomy was already known. Their outcome was similar to the total group. Time delay between onset of chest pain and admission was significantly longer in the patients with primary PTCA, mainly due to the 8 patients with a long delay (> 6 hours) between onset of chest pain and admission. All 8 patients still had signs of ongoing ischemia. The mean delay between pain and start of PTCA for the rescue PTCA patients was 222 minutes ($\pm$ 124 minutes) and 245 minutes ($\pm$ 282 minutes) for primary PTCA patients ($p=0.52$).

ANGIOGRAPHIC OUTCOME

The angiographic outcome in the two PTCA groups was comparable (Table 3). We were able to open more than 90% of the occluded arteries. However, not uncommonly such thrombotic or dissected lesions had a tendency to reocclude. Therefore, final patency at the end of the procedure was slightly lower: approximately 86% for both groups. Complication rates during this procedure were also similar.

CLINICAL AND ONE YEAR OUTCOME

During hospital stay, 3 patients, all treated with a thrombolytic agent, had a severe bleeding complication and needed blood transfusion (Table 4). Other clinical events were equally distributed between both groups. None of the patients suffered a cerebrovascular accident. In the patients who were offered rescue PTCA, 4 patients had re-PTCA because of recurrent myocardial infarction 2 other patients had re-PTCA because of recurrent angina; in the primary PTCA group 3 patients had re-PTCA all 3 because of re-infarction. Coronary artery bypass surgery was performed on an elective basis in one patient in each group because of failed PTCA and in 4 patients (1 rescue PTCA and 3 primary PTCA patients) on an emergency basis, because of acute recurrent ischemia without Q-wave infarction. Total in-hospital mortality was low (5.1%) and there were no significant differences between the two groups. In the first year after discharge, clinical outcome was also comparable between both groups. Interestingly, in the first year total mortality was slightly lower in patients treated with rescue PTCA: 5 patients (5.0%), versus 9 primary PTCA patients (11.8%) ($p=0.17$).

Table 1. Demographic, clinical, and angiographic data of the 176 myocardial infarction patients having acute PTCA with or without thrombolytic therapy

	Rescue PTCA		Primary PTCA		P-value
	N	[%]	N	[%]	
All patients	100	[100]	76	[100]	
Mean age (years $\pm$ SD)	58	[± 11]	57	[± 12]	0.56
Males	80	[80.0]	62	[81.6]	0.94
Previous MI >1 month	26	[26.0]	26	[34.2]	0.31
Long-standing angina	41	[0.41]	47	[61.8]	0.01
Recent-onset angina	6	[6.0]	5	[6.6]	0.87
Dyspnea	5	[5.0]	8	[10.5]	0.27
Medication before admission					
Nitrate	18	[18.0]	29	[38.2]	0.005
Calcium antagonist	21	[21.0]	21	[27.6]	0.39
Beta-blocker	23	[23.0]	25	[32.9]	0.19
Aspirin	10	[10.0]	20	[26.3]	0.008
No medication	57	[57.0]	35	[46.0]	0.19
Infarct location					
Anterior	52	[52.0]	42	[55.2]	0.78
Inferior	48	[48.0]	34	[44.7]	
Delays					
Pain-admission (mean $\pm$ SD)	100	± 98	175	± 280	0.03
Pain-admission (median)	60		90		0.03
Pain-thrombolysis (mean $\pm$ SD)	132	± 110	not performed		
Pain-PTCA (mean $\pm$ SD)	222	± 124	245	± 282	0.52
Pain-PTCA (median)	190		155		0.52
Culprit vessel					
RCA	34	[34.0]	22	[28.9]	
LAD	47	[47.0]	40	[52.6]	
CX	12	[12.0]	13	[17.1]	0.53
Graft	7	[7.0]	1	[1.3]	

RCA=right coronary artery; LAD=left anterior descending artery; CX=circumflex artery; PTCA=percutaneous transluminal coronary angioplasty.

Table 2. Reasons to withhold thrombolytic therapy in the 76 myocardial infarction patients who underwent primary PTCA

	N	[%]
Recent catheterization	17	[22.4]
Recent gastro-intestinal bleeding	17	[22.4]
Prolonged resuscitation	12	[15.8]
Delay pain-admission >6 hours	8	[10.5]
Recent cerebro vascular accident	4	[5.3]
Indury due to collaps	4	[5.3]
Recent surgery	1	[1.3]
Possible aortic dissection	1	[1.3]
Personal preference	12	[15.8]

Table 3. Angiographic results of acute PTCA in the 176 myocardial infarction patients with or without thrombolytic therapy

	Rescue PTCA		Immediate PTCA		P-value
	N	[%]	N	[%]	
All	100	[100]	76	[100]	
Initial success	92	[92.0]	70	[92.1]	0.79
Final success*	86	[86.0]	65	[85.5]	0.89
Diameter stenosis last view ($\pm$ SD)	38.2	$\pm$ 29	38.3	$\pm$ 30	0.98
Severe dissection	5	[5.0]	3	[3.9]	0.97
Reocclusion	3	[3.0]	3	[3.9]	0.93
Coronary embolus	3	[3.0]	5	[6.6]	0.44

*TIMI flow 3 and stenosis <50%.

PREDICTORS FOR ONE YEAR MORTALITY

Fourteen of 176 patients (8.0%) who underwent PTCA died during the first year after myocardial infarction (Table 5). In this limited group of patients failed PTCA was the only predictor for death: 7 of 25 patients (28.0%) with an unsuccessful procedure died versus only 7 of 151 patients (4.6%) with a successful PTCA. Other well known factors influencing mortality, like anterior wall AMI, PTCA of a graft, and recurrent infarction were of insufficient power to predict mortality, indicating the overwhelming influence of failed PTCA on mortality.

Table 4. Clinical outcome of acute PTCA in the 176 myocardial infarction patients with or without thrombolytic therapy

	Rescue PTCA		Primary PTCA		P-value
	N	[%]	N	[%]	
All	100	[100]	76	[100]	
During admission					
Death	4	[4.0]	5	[6.6]	0.67
Recurrent myocardial infarction	6	[6.0]	3	[3.9]	0.79
Recurrent angina	16	[16.0]	9	[11.8]	0.57
CABG or (re)-PTCA	8	[8.0]	7	[9.2]	0.99
Blood transfusion	3	[3.0]	0	[0.0]	0.35
Alive at discharge	96	[100]	71	[100]	
Death	1	[1.0]	4	[5.6]	0.20
Recurrent myocardial infarction	3	[3.1]	2	[2.8]	0.73
Recurrent angina	24	[25.0]	13	[18.3]	0.40
CABG or re-PTCA	10	[10.4]	5	[7.0]	0.63

CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty.

Table 5. Predictors for one year mortality of the 176 patients who underwent acute PTCA with or without thrombolytic therapy

		Survivors		Non-survivors		P-value
		N	[%]	N	[%]	
Previous MI	Yes	45	[86.5]	7	[13.5]	0.14
	No	117	[94.3]	7	[5.7]	
Thrombolysis	Yes	95	[95.0]	5	[5.0]	0.16
	No	67	[88.2]	9	[11.8]	
Anterior myocardial infarction		86	[91.5]	8	[8.5]	0.99
Inferior myocardial infarction		76	[92.7]	6	[6.3]	
Single vessel disease		84	[88.4]	11	[11.6]	0.10
Multi vessel disease		78	[96.3]	3	[3.7]	
PTCA succesful		144	[95.4]	7	[4.6]	0.001
PTCA unsuccessful		18	[72.0]	7	[28.0]	
Maximal ASAT in U/L (SD)		381	[±251]	440	[±468]	0.44
Age in years (SD)		57	[±11]	62	[±11]	0.10
Delay pain-PTCA in min (SD)		238	[±211]	160	[±100]	0.17

MI=myocardial infarction; PTCA=percuaneous transluminal coronary angioplasty; ASAT=aspartate aminotransferase.

DISCUSSION

Michels and Yusuf (55) performed a meta-analysis of randomized clinical trials on the value of PTCA in AMI. They concluded that primary PTCA might be more beneficial than thrombolytic therapy. However, this strategy has to be confirmed by larger studies. Various other strategies of PTCA to thrombolytic therapy do not convincingly indicate an improved outcome than if more conservative strategy is followed after thrombolytic treatment like immediate PTCA (at 6-24 hours) or subacute PTCA (at 4-12 days). Only if PTCA is used when clinically indicated, like rescue PTCA in extensive anterior AMI, effects might be observed.

As seen in the Study in Europe with Saruplase and Alteplase in Myocardial infarction (SESAM trial), a vessel opened by rescue PTCA carries a higher risk of reocclusion compared to a vessel which is successfully opened by thrombolysis and then left untouched (17). This finding suggests that PTCA of an already open artery probably increases the risk of reocclusion. For the present analysis, the reocclusion rate is not known because the patients did not systematically have a repeated angiography.

The angiographic data from the present study indicate that successful PTCA was independent of previous thrombolytic therapy: over 90% of the culprit lesions could initially be opened. However, the complexity of such a procedure in AMI is underlined by early reocclusions at the end of the catheterization in 6.8%. An additional 8% of patients had clinical signs of reocclusion during hospital stay.

No major differences were found in the feasibility and safety of the PTCA procedures between the two groups. This contrasts with the findings of others, who have suggested a deleterious outcome after rescue PTCA when compared with primary PTCA (45,46).

CLINICAL OUTCOME

Although thrombolytic therapy alone probably is inferior to primary PTCA (30-32), debate continues about the clinical value of rescue PTCA if thrombolytic therapy alone fails to reopen the infarct related artery (19,54,55). In the present retrospective analysis, patients with rescue PTCA had a good clinical outcome. One has to keep in mind that in this study rescue PTCA was performed in the group of patients in whom the highest complication rates could be expected. They received thrombolytics which failed and then had PTCA because a large area was still at risk. Also most patients of the primary PTCA group were at higher risk, for example, because they had contra-indications to thrombolytic agents. These patients also had a large area at risk. The outcome of the rescue PTCA was clinically comparable to the patients who underwent primary PTCA. One has to keep in mind, that there was a selection bias between the two groups.

A high mortality rate after failed acute PTCA (28.0%) is well known, death rates of 24%-40% are reported in the literature (36-41). The delay between onset of pain and PTCA was longer in the survivors (median 238 min) than in the non-survivors (median 160 min) ($p=0.17$). Unexpectedly, this difference in delay did not result in an improved outcome. The explanation might be, that non-survivors had more extensive AMI and therefore more complaints resulting in an earlier admission. Recurrences of ischemia were not uncommon but comparable in both groups. The diagnosis of recurrent ischemia was not only diagnosed by spontaneous chest pain but also by the outcome of exercise testing, which was performed before discharge. This explains why recurrences of ischemia were more frequent in our study population than in some other studies (30-32).

ONE YEAR OUTCOME

All surviving patients had were followed in the outpatient clinic during the first year after myocardial infarction. One year outcome (table 4) was not statistically different between the two groups, although total death rate at one year was higher in the primary PTCA group (11.8%) than in the rescue PTCA group (5.0%) ($p=0.17$). This difference is probably explained by the different patient groups in both treatment allocations. This is also the case for the differences in morbidity during the one year follow-up. In that year respectively 6.6% and 7.0% had recurrent myocardial infarction; 27.6% and 40% ($p=0.12$) recurrent angina; and 15.8% and 18.0% ($p=0.85$) re-PTCA or CABG.

STUDY LIMITATIONS

Several factors limit the value of this study. It was a retrospective, non-randomized, single center study in a limited group of patients, which probably created an important bias. The study includes the period between 1986 to 1992 indicating that increasing experience and changes of techniques might influence the outcome in the present period. Candidates for primary PTCA usually were patients in whom thrombolytic therapy was contra-indicated. They tended to be more clinically ill because they had a contra-indication to thrombolytic therapy. The patients undergoing rescue PTCA were also a selection, because thrombolytic therapy failed. They are not representative for the total group of patients with AMI treated with a thrombolytic agent. In randomized trials where primary PTCA is one of the treatment allocations, in approximately 10% of the patients PTCA is not feasible for anatomical reasons or because of the finding of a patent artery during angiography. In the present study, due to the protocol, all PTCA patients had an occluded artery. PTCA was performed only if the operator felt that the procedure was useful, which varied from doctor to doctor. The complexity of the lesion was no argument to remain conservative if the ischemic area was extensive. On the other hand, patients with a

small occluded artery were not dilated and therefore were not included in this analysis. This selection bias indicates that the clinical results of the PTCA groups would probably have been better if in all patients such intervention had been attempted.

POSSIBLE IMPLICATIONS

During the daytime, primary PTCA is probably the best option in centers where PTCA is available, especially in patients with extensive ischemia (51,56,58). However, only 18% of the hospitals in the United States and 10% of the hospitals in the Netherlands do have the capability to perform angioplasty, and fewer can do this on a round the clock basis (59). Logistical problems, especially during out of office hours, will cause a time delay before PTCA can be offered. This delay can be used meaningfully when the combined strategy of thrombolytic therapy and rescue PTCA, if indicated, is chosen. Using this approach, the need for acute angiography and intervention can be limited in case of reperfusion (59,60). At the moment a randomized study (the Limburg Myocardial Infarction Study) is in progress to investigate prospectively safety and feasibility of three treatment modalities: rescue PTCA after failed thrombolysis; primary PTCA; and thrombolysis only in patients with extensive AMI admitted to a hospital without PTCA facilities. This pilot study will later be followed by a large scale efficacy study (Holland Myocardial Infarction Study).

In conclusion, the present study shows that in patients with AMI reopening of the culprit lesion either by rescue PTCA or primary PTCA was safe and effective. It is still unclear how the present data should be extrapolated to the management of patients with AMI. Currently, the use of angioplasty is primarily limited by logistic problems. In centers in which angioplasty can be routinely applied, primary PTCA appears to be an attractive alternative to thrombolytic therapy. The question is whether this form of therapy should also be applied to patients primarily admitted to non-PTCA centers. Hopefully this last question will be answered by the Holland Myocardial Infarction Study.

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CHAPTER 4

Early referral for intentional rescue PTCA after initiation of thrombolytic therapy in patients admitted to a community hospital because of a large acute myocardial infarction

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ABSTRACT

Introduction: If no in-house PTCA facilities are present, thrombolytic therapy is the treatment of choice in acute myocardial infarction (AMI). A few studies showed benefit from rescue PTCA (RPTCA) in patients directly admitted to centers with PTCA facilities. The obvious question arises whether patients with AMI initially admitted to a community hospital (CH) can benefit from early transfer for intentional RPTCA.

Methods: One hundred sixty five patients were transferred early for intentional RPTCA from a CH at 20 miles distance. On arrival at the angioplasty center bedside markers were used to determine reperfusion. In case of obvious reperfusion no invasive procedure was done, otherwise coronary angiography and RPTCA, if necessary, was performed.

Results: During transfer 1 patient (1%) died and 15 patients (9%) suffered arrhythmic or haemodynamic problems. Median time delay between onset of chest pain and arrival at the community hospital and the PTCA center was 61 (range 0-413) minutes and 150 (range 28-472), respectively. In 66 patients (40%) reperfusion was diagnosed by non-invasive reperfusion criteria on arrival at the PTCA center (group 1). Ninety-eight patients (59%) without evident non-invasive criteria of reperfusion underwent angiography 187 median minutes after the onset of chest pain. Forty-one patients (25%) had TIMI-3 flow and no further intervention was performed (group 2). In the remaining 57 patients (35%), RPTCA was performed, which was successful in 96% (group 3). In-hospital mortality was lowest in group 1 compared to the other 2 groups (0% vs. 7% vs. 11%; $p < 0.05$). Re-infarction was highest in group 1 compared to the other groups (17% vs. 5% vs. 2%; $p < 0.01$). No significant differences were found in CABG, stroke or bleeding complications. The one-year follow-up data showed low revascularization rates and 2 (1%) patients died after discharge.

Conclusion: Early transfer of patients with large AMI for intentional RPTCA, can be done with acceptable safety and is feasible within therapeutically acceptable time limits and results in additional early reperfusion in 33% of patients. A large randomised multicenter trial is needed to compare efficacy of intravenous thrombolytic treatment in a CH versus early referral for either rescue or primary PTCA.

INTRODUCTION

Successful reperfusion in acute myocardial infarction (AMI) by either thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), or both improves clinical outcome (1-3). Early restoration of patency of the infarct related artery results in the largest benefit (4-6). Studies showing a beneficial effect of thrombolytic agents have been conducted in hospitals with and without PTCA facilities. However, trials showing the value of primary or rescue PTCA in AMI usually involve patients who are directly admitted to a PTCA center (3,7-12). However, the majority of patients with AMI, are admitted to community hospitals where angioplasty facilities are not available. The obvious question arises whether patients initially admitted to a community hospital, especially those with a large ischemic area, benefit from early transfer for rescue PTCA, when needed, after the initiation of thrombolytic therapy. Since the magnitude of the reduction in myocardial damage is strongly influenced by the rapidity of reperfusion, thrombolytic therapy should be given before transfer to accelerate the speed of reperfusion of the infarct-related artery. In case of reperfusion this may abolish the need for subsequent coronary angiography or rescue PTCA in the referral center in contrast to the strategy of transfer without thrombolytic therapy, for primary PTCA (12-13). Since many hospitals have no PTCA facilities we decided to study safety, feasibility and clinical outcome of patients with acute myocardial infarction initially treated with a thrombolytic agent in a community hospital with early referral to a PTCA center for rescue PTCA, when needed.

METHODS

One hundred sixty-five out of 1265 consecutive patients suffering from AMI, were transferred early from the community Maasland Hospital, Sittard, to the University Hospital Maastricht, Maastricht, for intentional rescue PTCA. The Maasland Hospital is a 580 bed community hospital located at 20 miles from the University Hospital Maastricht, a 720 bed tertiary care hospital with PTCA facilities and cardiac surgery. Transportation of patients from the community hospital to our center was done by the district ambulance service. The PTCA procedures were performed by 5 experienced interventional cardiologists with an individual patient load exceeding 200 cases yearly.

INDICATIONS FOR TRANSFER TO THE PTCA CENTER

In the referring community hospital, thrombolysis is the first choice reperfusion therapy for acute myocardial infarction. Predefined indications for early referral for intentional rescue PTCA were: electrocardiographic evidence of large AMI (sum of ST-segment deviation > 1.5 mV); Killip class 3-4 and or severe hypotension (systolic

blood pressure < 90 mmHg); electrocardiographic evidence of right ventricular involvement suggested by the presence of ST-segment elevation in lead V4R (14). The attending cardiologist in the Maasland Hospital, called the University Hospital Maastricht announcing that a patient with a large acute myocardial infarction would be transferred by ambulance after initiation of thrombolytic therapy (Fig. 1). Patients with the predefined indication for early intentional rescue PTCA were considered for transferral. Thrombolytic therapy given, was either intravenous streptokinase (1,500,000 units) or recombinant tissue-plasminogen activator (rt-PA). All patients were accepted for emergency evaluation. The ambulance was staffed with experienced paramedics and fully equipped to transfer critically ill patients, including continuous ECG monitoring, a defibrillator and equipment for mechanical ventilation. Expeditious transfer was facilitated by traffic light interrogation and a special high-way exit for the PTCA center.

During office hours, the first available room of the catheterization laboratory, (having two catheterization rooms), was used when indicated. Outside office hours, the catheterization personnel and the interventional cardiologist on duty were called. They always arrived before the patient and usually started the catheterization procedure within 1 hour after initial notification.

ADMISSION PTCA CENTER

On arrival at the University Hospital Maastricht, reperfusion status was evaluated by comparing the admission ECG of the community hospital and the ECG on arrival at the PTCA center and the severity of chest pain (15). Reperfusion was considered to be present in case of 1) a sudden decrease of chest pain and 2) a $\geq 50\%$ resolution of ST-segment elevation (15). In the case that non-invasive signs of reperfusion were absent, or non-conclusive, the patient was immediately transported to the catheterization laboratory for coronary angiography, and rescue PTCA when needed.

RESCUE PTCA

Catheterization and coronary angioplasty were performed using standard technique (16). All patients received a bolus of 10,000 units of heparin immediately after arterial entry. This was continued as a continuous infusion at approximately 900 units/hr to maintain the activated partial thromboplastin time at 1.5 fold normal or greater than normal for 48-72 hours. Rescue PTCA of the infarct related coronary artery was attempted in all cases with no flow or impaired flow according to the Thrombolysis In acute Myocardial Infarction (TIMI) grading system (TIMI 0-2) (17). If TIMI 3 flow was present no further intervention was done. PTCA was defined as being successful in case of persistent TIMI 3 flow and a residual stenosis < 50% at the end of the procedure. Other procedures, like intra-aortic balloon counterpulsation or stent implantation, were left to the discretion of the operator.

Figure 1. Flow chart

All patients received Acetyl Salicylic Acid (80 mg/d), intravenous nitrates for at least 24 hours and intravenous heparin as mentioned. The coronary angiograms were analyzed by two independent observers.

RETURN TO THE REFERRING HOSPITAL

When non-invasive signs of reperfusion were present on presentation to the PTCA center the patient returned to the referring hospital by the same ambulance when clinically stable.

After coronary angiography or rescue angioplasty, clinically stable patients returned to the Maasland Hospital, after an observation period of approximately 2 hours. Otherwise, patients were admitted to the University Hospital Maastricht until the clinical condition had sufficiently improved to ensure a safe return to the Maasland Hospital (Fig. 1).

BASELINE AND OUTCOME VARIABLES

The hospital records of all patients were examined and the clinical data were collected on a standard data acquisition form. The following outcome variables were collected: in-hospital death, recurrent AMI (chestpain with new ST-segment elevation and enzymatic evidence of myocardial necrosis (ASAT > 40 mmol/L)), recurrent anginal complaints according to the NYHA classification (18), repeat-PTCA, coronary artery bypass grafting, stroke (defined as a new neurological deficit) and bleeding complications requiring blood transfusion. One year follow-up data were also obtained from clinical and outpatient records.

The records of the district ambulance service were reviewed and information on complications during transport and time data of transfer, were collected.

The electrocardiograms were scored as to the sum of ST-segment deviation at the J-point using the 12-lead ECG, and the number of patients with a sum of ST-segment deviation ≥ 15 mm (1.5mV) was determined.

STATISTICAL ANALYSIS

Data were expressed as median (range) or mean ($\pm$ SD) for continuous variables or as rates (percentage) for categorical variables. Proportions of categorical variables were compared using the chi-square test. All results with a p-value < 0.05 were considered to be statistically significant.

RESULTS

PATIENT CHARACTERISTICS

In the three and a half-year observational period, 165 consecutive patients with large acute myocardial infarction were transferred early for intentional rescue angioplasty. This is approximately 13% of the infarct population in the community hospital.

Baseline clinical and angiographic data for the total patient group and the 3 subgroups are given in Table 1. The infarction was located anteriorly in 57% and inferiorly in 43%. Seventy-nine percent of the patients transferred early for intentional rescue PTCA had evidence of electrocardiographic extensive myocardial infarction (sum of total ST-segment deviation > 1.5 mV). Severe hypotension and or Killip class 3 or 4 was present in 22% of the patients. Twenty-four percent had electrocardiographic evidence of right ventricular involvement.

Table 1. Base-line characteristics of the 165 AMI patients referred for rescue PTCA

	All		Group 1		Group 2		Group 3	
	N	[%]	N	[%]	N	[%]	N	[%]
All patients	165	[100]	67	[100]	41	[100]	57	[100]
Age ($\pm$ SD) (years)	59 $\pm$ 11		59 $\pm$ 11		58 $\pm$ 11		60 $\pm$ 10	
Male sex	141	[85]	56	[84]	36	[88]	49	[86]
Anterior Myocardial								
Infarction	94	[57]	35	[52]	25	[61]	34	[60]
Thrombolytic therapy	165	[100]	67	[100]	41	[100]	57	[100]
Coronary angiography	98	[100]	NA		41	[100]	57	[100]
- single vessel disease	53	[54]	NA		22	[54]	31	[54]
- multi vessel disease	45	[46]	NA		19	[46]	26	[46]
Infarct related artery	98	[100]	NA		41	[100]	57	[100]
- Left anterior descending	59	[60]	NA		25	[61]	34	[60]
- Left circumflex artery	10	[10]	NA		4	[10]	6	[11]
- Right coronary artery	29	[30]	NA		12	[29]	17	[30]

Group 1= Patients with noninvasive reperfusion; Group 2= Patients with angiographic reperfusion; Group 3= Patients with rescue PTCA; AMI=acute myocardial infarction; RVI=right ventricular involvement; NA=non- applicable.

TRANSPORTATION AND TIME DELAYS

In general, transport to the angioplasty center was rarely accompanied by severe complications. Only 1 patient, who was already in severe cardiogenic shock, died during transport. This patient suffered an extensive anterior AMI complicated by right bundle branch block and left anterior hemiblock. The patient died the moment he was put into the ambulance. Another 8 patients (5%) had severe ventricular arrhythmia's necessitating defibrillation (which was successful in every case). Three patients (2%) had complete AV-block and in addition another 4 patients (2%) required fluid expansion because of the development of severe hypotension during transport. No bleeding complications were recorded in that period. No other adverse events occurred during or as a result of transportation. During transport in the reverse direction (from Maastricht to Sittard) no complications were observed.

Median delay between onset of chest pain and arrival in Maastricht was 150 (range 28-472) minutes (Table 2). The delay decreased considerably during the study period due to a shorter time delay between admission and transfer at the community hospital. Growing familiarity with the logistics of transfer may have accounted for this reduction (Fig. 2). No statistical significant relationship between time delays and mortality could be demonstrated but there was a tendency towards increased mortality with a longer time delay (Table 3).

Table 2. Time delays of the 165 patients referred for rescue PTCA

Time delay in minutes	Median	Percentile
All patients (N=165)		25th-75th
Onset chest pain-admission at NPC	61	30-114
Admission at NPC-departure to PC	53	43-82
Ambulance transport	16	15-18
Onset chest pain-arrival at PC	150	110-210
Patients with angiography (N=98)		
Arrival at PC-arrival cath lab	36	27-45
Onset chest pain-cath lab	187	146-255

NPC=non-PTCA center; PC=PTCA center; Cath lab=catheterization laboratory.

Table 3. Time delays between onset of chest pain and arrival at PTCA center in relation to mortality (N=165)

Minutes	N	Mortality	[%]	P-value
0-120	53	1	[2]	NS
120-240	81	5	[6]	NS
>240	31	4	[13]	NS

Table 4. Status of coronary reperfusion of the 164 patients on arrival at the PTCA center*

	N	[%]
Non-invasive signs of reperfusion**	66	[40]
Angiographic evidence of reperfusion	41	[25]
Noninvasive or invasive signs of reperfusion	107	[65]
No angiographic evidence of reperfusion	57	[35]

*One patient died in the ambulance. **Resolution of ST-segment elevation $\geq 50\%$ and sudden decrease in chest pain.

NON-INVASIVE CRITERIA FOR REPERFUSION

The non-invasive reperfusion criteria, as described in the methods section, showed that 66 patients (40%) (group 1) had evident signs of reperfusion (Table 4). In these patients coronary angiography was not performed. All but 4 of the 66 patients returned immediately to the community hospital, usually with the same ambulance (Fig. 1).

Figure 2. Time delays are given for the last 11 months of the year 1992, the full year 1993 and 1994 and the first 8 months of 1995. The vertical bar indicates the median delay in minutes between admission in the community hospital and arrival at the PTCA center.

CORONARY ANGIOGRAPHY AND PTCA

The 98 patients (60%) without obvious non-invasive signs of reperfusion underwent coronary angiography, showing complete restoration of flow in 41 patients (25%) (group 2). In the remaining 57 patients (35%) (group 3) having no or impaired flow acute PTCA was successful in 55 patients (96%). In 2 of these patients a stent was implanted because of recurrent occlusion. In 10 of the 98 patients (10%) an intra-aortic counterpulsation device was inserted.

CLINICAL OUTCOME

The data were analyzed for the total patient group and subsequently for three subgroups consisting of patients with 1) non-invasively determined reperfusion (group 1), 2) angiographically demonstrated TIMI 3 flow of the infarct-related coronary artery (group 2) and 3) rescue PTCA (group 3). The in-hospital mortality of the total group of 165 patients was 6% (10 patients), including the patient who died in the ambulance. Major bleeding complications were low. These and other clinical complications are listed in Table 5. There were no in-hospital deaths in group 1 ($p < 0.05$). Of the 14 patients (8%) who suffered recurrent AMI in-hospital, 11 patients (17%) belonged to the group of the 66 patients with non-invasive signs of reperfusion (group 1). The incidence of in-hospital re-infarction was significantly higher in this group as compared to the other 2 groups ($p < 0.01$).

ONE YEAR FOLLOW-UP AFTER DISCHARGE

Of the 165 patients included in the study one patient died during transfer and 9 patients died during hospital admission. In 3 of the remaining 155 patients follow-up data were incomplete in each group 1 patient but the patients were known to be alive (Table 6). Only 2 of the 155 patients died during the first year. One patient died due to left-sided heart failure and one patient experienced sudden cardiac death. There were no significant differences between the 3 patient groups concerning recurrent AMI, PTCA and coronary artery bypass grafting.

Table 5. In-hospital clinical outcome of the 165* patients referred for intentional rescue PTCA

	All		Group 1		Group 2		Group 3		p
	N	[%]	N	[%]	N	[%]	N	[%]	
Number of patients	165	[100]	66	[100]	41	[100]	57	[100]	
Death	10	[6]	0	[0]	3	[7]	6	[11]	<0.05
Recurrent MI	14	[8]	11	[17]	2	[5]	1	[2]	<0.01
Emergency PTCA	12	[7]	9	[14]	2	[5]	1	[2]	<0.05
Elective PTCA	5	[3]	3	[5]	2	[5]	0	[0]	NS
CABG	6	[4]	3	[5]	3	[7]	0	[0]	NS
Stroke	0	[0]	0	[0]	0	[0]	0	[0]	NS
Bleeding complication									
-Transfusion	5	[3]	2	[3]	2	[5]	1	[2]	NS

Group 1,2,3 = see Table 1; AMI= acute myocardial infarction; PTCA= percutaneous transluminal coronary angioplasty; CABG= coronary artery bypass graft. *One patient died during ambulance transport.

Table 6. One year follow-up in patients who were discharged alive* (N=155)

	All		Group 1		Group 2		Group 3	
	N	[%]	N	[%]	N	[%]	N	[%]
Number of patients	152	[100]	65	[100]	37	[100]	50	[100]
Death	2	[1]	1	[2]	1	[3]	0	[0]
Recurrent AMI	7	[5]	3	[5]	2	[5]	2	[4]
PTCA	8	[5]	6	[9]	0	[0]	2	[4]
CABG	8	[5]	2	[3]	4	[11]	2	[4]
Angina NYHA 2-4	40	[26]	17	[26]	10	[27]	13	[26]

Group 1,2,3 = see Table 1; AMI = acute myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; * In 3 patients (one in every group) follow-up data were incomplete, but the patients were known to be alive. There were no statistically significant differences between the three groups.

DISCUSSION

Most patients with acute myocardial infarction present to community hospitals where angioplasty is not available. The main purpose of this study, was to assess the feasibility, safety, and clinical outcome of early transfer of patients during the first hours of an electrocardiographic or clinically large myocardial infarction, from a

hospital without PTCA facilities, to a PTCA center for intentional rescue PTCA after thrombolytic therapy had been initiated.

PATIENT SELECTION

Patients with clinical or electrocardiographic evidence of large acute myocardial infarction were selected by the referring cardiologist. Previous reports indicated a good correlation between the sum of ST-segment deviation and the extent of the ischaemic area in patients admitted because of an AMI (19). It has also been shown that patients with large AMI profit most from reperfusion (19,20). Although, the majority of patients had anterior wall myocardial infarction, 43% of the patients had inferior AMI. The rather high contribution of inferior infarctions may have been caused by the extent of ST-segment deviation created by posterior wall ischemia.

During the study, the time interval before transfer of the patients changed. In 1993, the patients were transferred after completion of thrombolytic therapy. Later, the patients were transferred as soon as possible after initiation of thrombolytic therapy. This attitude resulted in a considerable decrease in time delays as reflected in fig.2.

SAFETY OF TRANSPORTATION

The present study indicates that transport of patients with a large AMI, pretreated with a thrombolytic agent, was relatively safe. Safety during transport is dependent on the quality of the ambulance personnel and equipment available. The low complication rate during transport is not an unexpected finding. In trials studying pre-hospital thrombolysis in patients with AMI, similar observations have been made (21,22).

The change to earlier referral did not lead to higher complication rates during ambulance transport.

As indicated by the absence of complications, also early return of patients to the referring hospital was safe. Only 36 patients (22%) were kept in the PTCA center for some time.

NON-INVASIVE REPERFUSION PARAMETERS

Coronary angiography remains the golden standard to determine patency of the infarct-related artery ever since DeWood et al. demonstrated safety and feasibility of acute coronary angiography in AMI (23). However, this diagnostic procedure has disadvantages. Logistic problems may arise if this has to be done in every patient with AMI. Apart from the costs, acute coronary angiography may have adverse events such as bleeding at the puncture site especially after the administration of thrombolytic agents. Thus, especially after thrombolytic treatment effective

non-invasive detection of reperfusion will diminish the need for acute coronary angiography. Sudden resolution of chest pain, one of the 2 parameters used for the non-invasive detection of coronary reperfusion in this study is a subjective finding during AMI and is dependent of the state of ischemia and of the moment of evaluation. The correlation between sudden resolution of chest pain and coronary artery patency has been documented previously (15,24). Resolution of ST-segment elevation the other non-invasive reperfusion parameter has been shown to be most valuable in determining coronary reperfusion but the predictive value (15,24,25,26) is limited. The validity of the clinical criteria for reperfusion is still a matter of debate.

DIAGNOSIS OF REPERFUSION

By applying the electrocardiographic and clinical reperfusion criteria, approximately one third of the patients were diagnosed to have reperfusion at the time of arrival in the angioplasty center (Group 1). In these patients, no coronary angiography was performed as is advocated in previous studies (27,28). They usually returned to the referring hospital by the same ambulance. Interestingly, none of these patients died in-hospital, however 11 of the 66 patients (17%) suffered re-infarction during hospital admission ($p < 0.01$) possibly due to a high-grade residual stenosis.

Another one fourth showed to have TIMI-3 flow at the time of coronary angiography (group 2). Based upon the results from previous studies, no angioplasty was attempted in those patients (27,28). Only 2 (5%) of these 41 patients developed re-infarction and 3 patients (7%) died in hospital. The 7% in-hospital mortality rate in patients with angiographically documented TIMI 3 flow seems high but may be explained by the small number of patients and the extent of the area at risk (57% anterior AMI).

Clinical or angiographic reperfusion was achieved in 107 of 165 (65%) patients. This is higher than expected with thrombolytic therapy. In part this may be explained by possible overestimation of the degree of reperfusion by the use of non-invasive criteria for reperfusion. Another explanation may be the beneficial effect of the ballistics of transport on the rapidity of reperfusion.

PTCA

In most countries, angioplasty facilities are limited to tertiary centers with cardiosurgical backup. In the Netherlands, only 10% of the hospitals are licensed and equipped for coronary angioplasty. At this time their patient load varies between 500 and 1600 patients yearly. This approach has certain advantages: to perform rescue angioplasty in AMI safely, high operator skills are required. Usually, only high-volume angioplasty centers meet these requirements and can guarantee 24 hours service.

Of the 98 patients who underwent coronary angiography, 57 patients (58%) were found to have incomplete restoration of coronary blood flow. Successful angioplasty was performed in 96% of cases, which is similar to the success rates reported in primary angioplasty (9-12). In 10 patients an intra-aortic balloon pump was inserted prior to the angioplasty procedure because of a poor haemodynamic condition of the patient. The low number of stents used reflects the years in which these patients were studied.

CLINICAL OUTCOME

In view of the selection of patients, the short and long-term clinical outcome in the present study appear to be acceptable. However, the lack of a control group, does not allow an estimation of the true value of the approach described above.

In comparing our data to the GUSTO-IIb trial (29), in which also smaller AMI's were included, overall mortality was similar, 6.1% and 6.3%, respectively. Of the 55 patients with successful rescue PTCA 4 patients died (7%) during admission; both patients with unsuccessful rescue PTCA died. This is in line with the findings of others: the prognosis in patients with failed rescue PTCA is poor (30-36). This might suggest that failed rescue angioplasty is in fact harmful, and is worse than no rescue attempt at all. Mckendall et al. showed a 7% mortality rate in the no rescue group, a 12% mortality rate in the group with successful rescue PTCA, and a 33% mortality rate in the group with failed rescue PTCA (37). However, especially patients doing poorly after failed thrombolysis are subjects for rescue PTCA, indicating the higher risk if this procedure is unsuccessful.

The number of severe bleeding complications requiring blood transfusion (3%) is low compared with other studies (38).

LIMITATIONS

Conclusions that can be drawn from this study apply especially for the subset of patients with large acute myocardial infarctions based on clinical or electrocardiographic grounds. Their value is limited, by the retrospective nature of our data and the lack of matched controls. The use of non-invasive criteria to establish presence of coronary reperfusion may have overestimated the degree of reperfusion. However we tried to create a practical approach in which we investigated the indication for coronary angioplasty in patients with early transfer for rescue PTCA, when needed. Prospective randomised studies analyzing this approach have not yet been performed but the results of this study justify a randomised study comparing thrombolytic therapy versus primary and rescue PTCA in patients with large acute myocardial infarction initially admitted to a community hospital without PTCA facilities.

CONCLUSIONS

This study of 165 consecutive patients with the electrocardiographic or clinical suggestion of a large AMI shows that early transfer after treatment with a thrombolytic agent from a community hospital to a PTCA center for intentional rescue PTCA is feasible and safe with respect to complications during transport. It can be considered in patients presenting with a large AMI. In the Maastricht area, transfer can be done within therapeutically acceptable time limits and leads to additional successful early reperfusion in 33% of patients. The use of non-invasive reperfusion criteria as a guide to coronary angioplasty and further therapy allowed recognition of patients with a very low mortality risk and was of value to reduce the work-load in the PTCA center. Those patients, however, had an increased incidence of in-hospital reinfarction. Recurrent AMI and late PTCA were significantly less frequent in the patients treated by rescue PTCA, but in-hospital mortality was higher, especially in those patients who failed rescue PTCA. Early return of stable patients did not result in complications during transport. The long term clinical outcome utilizing this reperfusion strategy of early transfer for intentional rescue PTCA was excellent.

In the absence of a control group, the true value of our approach cannot be evaluated. However, the outcome with regard to safety and feasibility, and a recently published study on transferring patients with AMI for primary PTCA (39), with favorable results, should be a reason to start a large scale multi-center prospective randomized trial comparing three treatment modalities in patients admitted with a large acute myocardial infarction to a non-PTCA hospital: 1) thrombolytic therapy in the admitting hospital without transport, 2) thrombolytic therapy followed by immediate transport and rescue PTCA if indicated, and 3) no pretreatment with a thrombolytic agent, immediate transport, and primary PTCA.

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CHAPTER 5

Angiographic assessment of prospectively determined non-invasive reperfusion parameters in acute myocardial infarction

Can the number of acute coronary angiography and subsequent angioplasty be reduced?

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ABSTRACT

Objective: Patients with acute myocardial infarction can benefit from coronary angiography and subsequent coronary angioplasty in case of no or insufficient reperfusion. The present study in 230 patients investigates the value of 7 non-invasive reperfusion parameters with respect to Thrombolysis in Myocardial (TIMI) flow, by avoiding the possible need for acute coronary angiography and subsequent angioplasty.

Design: In a prospective angiographic study, the value of 7 potential electrocardiographic or clinical markers of reperfusion was analysed in 230 patients with AMI. In all patients two 12-lead ECG's were used: the ECG on admission and the ECG immediately before coronary angiography. Non-invasive markers of reperfusion determined just before coronary angiography were prospectively correlated to TIMI flow. Data analysis was conducted correlating these non-invasive parameters to coronary flow (analysis A: TIMI 2-3 versus TIMI 0-1 flow; analysis B: TIMI 3 versus TIMI 0-2 flow).

Results: Sudden decrease in chest pain was the most common sign of reperfusion (36%), followed by resolution of ST-segment elevation $\geq 50\%$ in 30%, and the development of a terminal negative T-wave (20%) in the lead with highest ST-segment elevation. Resolution of ST-segment elevation $\geq 50\%$ and appearance of an accelerated idioventricular rhythm (AIVR) had the highest positive predictive value (PPV) for reperfusion. For analysis A and B the PPV was 85% and 66% for resolution of ST-segment elevation, and 94% and 59% for AIVR, respectively. The presence of 3 or more non-invasive markers of reperfusion predicted TIMI 3 flow accurately in 80% of cases.

Conclusions: The prospective use of non-invasive parameters of reperfusion is simple, practical, and can be of value to assess coronary patency in patients admitted with AMI. Using these parameters, discrimination between TIMI 0-1 and TIMI 2-3 flow can be done with good accuracy. However, TIMI 3 flow cannot reliably be determined. Depending on the goal of reperfusion the non-invasive parameters of reperfusion can be used accordingly.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
ECG	= electrocardiogram
AIVR	= accelerated idioventricular rhythm
PTCA	= percutaneous transluminal coronary angioplasty
CAG	= coronary angiography
SD	= standard deviation
PPV	= positive predictive value
NPV	= negative predictive value

INTRODUCTION

Several studies have shown the value of non-invasive reperfusion parameters in acute myocardial infarction (AMI) (1)(2)(3)(4). A number of non-invasive parameters were useful to determine coronary reperfusion like resolution of ST-segment elevation, change in chest pain and the occurrence of certain arrhythmia's. Most of these studies were done in a small number of patients and the interval between the non-invasive evaluation and the angiographic validation of reperfusion was variable. Many of these studies were retrospective. The prospective value of non-invasive parameters of reperfusion is still not clear.

Determination of the presence of coronary reperfusion through simple non-invasive tools is of obvious value to establish successful thrombolysis and to identify spontaneous reperfusion in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Acute intervention in the presence of reperfusion has not shown to improve clinical outcome and coronary angiography should be withheld in case non-invasive markers of reperfusion are of sufficient predictive value. (5)(6) When coronary blood flow has not been restored, emergency PTCA is likely to be helpful (7)(8)(9)(10). The value of intracoronary intervention in patients with Thrombolysis in Myocardial Infarction (TIMI) 2 flow is still a matter of debate. Anderson et al showed a better prognosis in patients with TIMI 3 flow in comparison to TIMI 2 flow (11). Other investigators could not confirm these results. (12)(13) In case the findings of Anderson et al are correct it would be of importance to discriminate non-invasively between patients with TIMI 0-2 and patients with TIMI 3 flow of the infarct-related artery. Otherwise, only differentiation is needed between TIMI 0-1 and TIMI 2-3 flow of the infarct-related artery. The aim of this angiographically controlled study was to determine the prospective value of seven reperfusion parameters. If non-invasive reperfusion parameters can reliably predict adequate restoration of flow, the costly, possible hazardous and oftentimes logistically difficult acute coronary angiography can be avoided.

METHODS

STUDY PATIENTS

Two-hundred thirty consecutive patients with acute coronary angiography were enrolled in this study. All patients were admitted within the first 6 hours of AMI. Entry in the study required chest pain for at least 30 minutes not responding to nitroglycerin, associated with more than 0.1mV (1mm) ST-segment elevation in two or more limb leads and at least 0.2 mV in two or more contiguous precordial leads according to normal standards for thrombolytic treatment. Thrombolytic therapy (streptokinase, saruplase, alteplase) was administered in-hospital, usually at the emergency department. The reasons for acute coronary angiography were: primary PTCA, coronary angiography after thrombolytic therapy in the setting of a study protocol, and possible rescue PTCA.

HISTORY

Careful attention was paid to chest pain evolution. Before coronary angiography, each patient was asked to rate the severity of chest pain to indicate whether sudden changes in chest pain had occurred. Chest pain was then classified as unchanged or as a sudden decrease or a sudden increase between admission and start of coronary angiography.

ELECTROCARDIOGRAPHY

A 12-lead electrocardiogram recording was made on admission and just prior to coronary angiography (Figure 1). These two ECG's were compared and used for the presence of reperfusion parameters. The criteria for reperfusion as listed in Table 1 were checked by the angiographer just prior to the angiographic procedure and documented in the patient record form. Using these criteria, the angiographer additionally predicted presence or absence of patency of the infarct related artery before the start of coronary angiography.

CORONARY ANGIOGRAPHY

All patients underwent coronary angiography in the acute phase of the AMI usually within 73 median minutes after admission at the Academic Hospital of Maastricht (Table 2). Coronary angiography was performed using the Seldinger technique. The first intracoronary injection was used to determine coronary flow. Reperfusion of the infarct-related artery was determined according to the TIMI criteria (6). In case of infero-posterior infarction combined with multi-vessel disease, right precordial leads and the aspect on coronary angiography were used to differentiate between circumflex and right coronary artery as the infarct related artery (14).

Figure 1. Example of the resolution of ST-segment elevation and development of terminal negative T-waves as a sign of reperfusion. Patient with extensive anterior wall myocardial infarction treated with a thrombolytic agent.

Panel A: Admission ECG showing ST-segment elevation in anterior leads (most prominent in lead V4). **Panel B:** ECG just prior to first intracoronary contrast injection showing TIMI 3 flow. Resolution of ST-segment elevation $\geq 50\%$ and development of terminal negative T-wave in lead V4. This patient also had a sudden decrease of chest pain.

STATISTICAL ANALYSIS

The data were stored in a computer and analysed by SPSS/7.0. Data were expressed as mean $\pm$ SD for continuous variables or as rates for categorical variables. For categorical variables the Chi-square test, or when applicable, Fisher's exact test was used. A p(robability) value <0.05 was considered statistically significant.

RESULTS

The characteristics of the 230 patients are listed in Table 2. One hundred sixty-five patients (72%) had received thrombolytic therapy. Coronary angiography data are shown in Table 3. Fifty-seven percent of the patients had TIMI 0 or 1 and 29% showed TIMI 3 coronary flow at the first intracoronary injection. One-year mortality was lowest in the patients with TIMI 3 flow at first injection (Table 3). The frequency of the individual non-invasive reperfusion parameters is shown in

Table 1. Definitions of the parameters of reperfusion

ST-segment resolution $\geq 50\%$:	Reduction of $\geq 50\%$ of ST-segment elevation in the infarct-lead showing the highest ST-segment elevation measured from the J-point between admission ECG and ECG just prior to coronary angiography (CAG).
Sudden decrease chest pain:	Sudden decrease of chest discomfort in the period between admission ECG and CAG as indicated by the patient.
Sudden increase chest pain:	Sudden increase of chest discomfort in the period between admission ECG and CAG as indicated by the patient.
Accelerated Idio-Ventricular Rhythm:	Run of > 4 consecutive non-premature ventricular complexes at a rate between 80-125 beats/min present at ECG in the period between admission ECG and CAG.
Ventricular fibrillation:	Episode of ventricular fibrillation requiring defibrillation between admission ECG and CAG.
Ventricular ectopy:	Premature ventricular complexes present on admission ECG or ECG just prior to CAG.
Terminal negative T-wave:	The development of terminal negative T-wave ≥ 0.1 mV (≥ 1 mm) in the infarct lead with highest ST-segment elevation on the ECG just prior to CAG.

Table 2. Patient characteristics of the 230 patients

	N	[%]
All patients	230	[100]
Age (mean $\pm$ SD in years)	59 $\pm$ 11	
Male	176	[77]
Previous infarction	29	[13]
Patients with anterior infarction	119	[52]
Thrombolytic therapy	165	[72]
Referred for primary PTCA	65	[28]
Hospital admission-CAG (min) median*	73	[34 ;102]
Maximal ASAT (U/L) median*	241	[132;340]

* Range [25th percentile ; 75th percentile].

Table 3. Angiographic data of the 230 patients

	N	[%]	1-y mortality*	
			N	[%]
All patients	230	[100]	15	[6.5]
<i>Infarct related artery</i>				
LAD	119	[51.7]	9	[7.5]
CX	14	[6.1]	0	[0]
RCA	96	[41.8]	6	[6.2]
Graft	1	[0.4]	0	[0]
<i>TIMI flow first injection</i>				
TIMI 0	106	[46.1]	8	[7.5]
TIMI 1	25	[10.9]	3	[12]
TIMI 2	32	[13.9]	2	[6.2]
TIMI 3	67	[29.1]	2	[3.0]
<i>Vessel disease</i>				
-One	134	[58.3]	8	[5.9]
-Two	45	[19.5]	1	[2.2]
-Three	51	[22.2]	6	[11.7]
PTCA	143	[62.2]	8	[5.5]

*3 patients were lost to follow-up.

Table 4. The frequencies of non-invasive parameters of reperfusion were not significantly different between the patients with or without thrombolytic therapy (Table 4). A sudden decrease in chest pain had the highest incidence (36%), followed by resolution of ST-segment elevation (30%). The average degree of ST-segment elevation in the most prominent infarct lead on the admission ECG was $4.7\text{ mm} \pm 3.4\text{ mm}$ (range 1-23mm). Just prior to coronary angiography mean ST-segment elevation in the same lead was $4.1\text{ mm} \pm 3.6\text{ mm}$ (range 0-30 mm). Thirteen patients (6%) had a sudden increase of chest pain after admission but prior to coronary angiography. The non-invasive reperfusion parameters were correlated to the TIMI flow at the first angiographic view of the infarct-related artery: analysis A: TIMI 2-3 versus TIMI 0-1 flow (Table 5); analysis B: TIMI 3 versus TIMI 0-2 flow (Table 6). Except for the sudden increase in chest pain and ventricular fibrillation, all parameters correlated well with TIMI flow. Table 7 shows the specificity, sensitivity and positive- and negative predictive value of the number of reperfusion parameters required to be present to determine TIMI 2-3 or TIMI 3 flow of the infarct-related artery. The presence of more than three parameters of reperfusion is highly specific for the presence of TIMI 3 flow of the infarct-related artery (99%).

Table 4. Frequency of non-invasive parameters of reperfusion in the 230 patients

	All (n=230)		Thrombolysis (n=165)		No Thrombolysis (n=65)		P-value
	N	[%]	N	[%]	N	[%]	
Chest pain							
Sudden decrease	83	[36]	65	[39]	18	[28]	0.070
Sudden increase	13	[6]	7	[4]	6	[9]	0.257
Resolution ST-segment elevation $\geq 50\%$	68	[30]	51	[31]	17	[26]	0.657
AIVR	17	[7]	15	[9]	2	[3]	0.194
Ventricular fibrillation	13	[6]	10	[6]	3	[5]	0.904
Ventricular ectopy	33	[14]	23	[14]	10	[15]	0.956
Development terminal negative T-wave	46	[20]	34	[21]	12	[18]	0.880

AIVR=accelerated idioventricular rhythm.

Table 5. Correlation non-invasive reperfusion parameters and TIMI 2-3 flow in the 230 patients

	TIMI 0-1		TIMI 2-3		PPV		NPV	P-value
	N	[%]	N	[%]	%	%		
All patients	131	[100]	99	[100]				
ST-segment resolution $\geq 50\%$	10	[7.6]	58	[58.6]	85	75		0.001
Sudden decrease chest pain	8	[6.1]	65	[65.7]	89	78		0.001
Sudden increase chest pain	7	[5.3]	6	[6.1]	46	57		0.83
AIVR	1	[0.8]	16	[16.2]	94	61		0.001
Ventricular fibrillation	5	[3.8]	8	[8.1]	62	58		0.17
Ventricular ectopy	9	[6.9]	24	[24.2]	73	62		0.001
Negative T-wave	11	[8.4]	35	[35.4]	76	65		0.001

PPV=positive predictive value (%); NPV=negative predictive value (%); AIVR=accelerated idioventricular rhythm.

Before the start of the procedure the invasive cardiologist predicted reperfusion: TIMI 2-3 flow of the infarct-related artery was accurately predicted in 88%. However, TIMI 3 coronary flow prediction could only be made in 67 % of cases. In case of prediction of improved flow by the invasive cardiologist the clinical outcome with respect to one-year mortality appeared to be excellent (0%).

Table 6. Correlation non-invasive reperfusion parameters and TIMI 3 flow in the 230 patients

	TIMI 0-2		TIMI 3		PPV	NPV	P-value
	N	[%]	N	[%]	%	%	
All patients	163	[100]	67	[100]			
ST-segment resolution $\geq 50\%$	23	[14.1]	45	[67.2]	66	86	0.001
Sudden decrease chest pain	36	[22.1]	47	[70.1]	57	86	0.001
Sudden increase chest pain	9	[5.5]	4	[6.0]	31	71	0.92
AIVR	7	[4.3]	10	[14.9]	59	73	0.005
Ventricular fibrillation	7	[4.3]	6	[9.0]	46	72	0.17
Ventricular ectopy	18	[11.0]	15	[22.4]	45	74	0.03
Negative T-wave	18	[11.7]	28	[41.8]	61	79	0.001

PPV=positive predictive value (%); NPV=negative predictive value (%); AIVR=accelerated idioventricular rhythm.

Table 7. The value of the total number of non-invasive parameters of reperfusion present in predicting either TIMI 2-3 or TIMI 3 flow of the infarct related artery

No. of parameters	Sens	Spec.	PPV	NPV
TIMI 2-3				
>0	85	71	69	86
>1	72	87	81	80
>2	46	95	88	70
>3	10	100	100	60
TIMI 3				
>0	88	61	48	93
>1	78	78	59	89
>2	54	90	69	83
>3	12	99	80	73

PPV= positive predictive value (%); NPV= negative predictive value (%); Sens.= sensitivity; Spec.= specificity.

DISCUSSION

The treatment of AMI is directed towards limitation of infarct size, to reduce complications and to prolong longevity (15)(16). Patients promptly treated after the onset of symptoms by restoring patency of the infarct-related artery will have the largest benefit. Patients with complete reperfusion of the infarct related artery will have a better prognosis than patients with no or incomplete restoration of flow (11). The one-year mortality is 5% in patients with TIMI 3 as compared to 27% in patients with TIMI 0/1 flow (17)(18). Therefore, the value of (non-invasive) detection of adequate reperfusion is of great importance. In case non-invasive reperfusion parameters point towards insufficient coronary flow, acute coronary angiography followed by PTCA if indicated, may alter the prognosis in a positive way.

STUDY POPULATION

The reason to perform acute coronary angiography in this group of 230 patients varied, as described in the methods section with 72% having received thrombolytic therapy. TIMI 0-1 flow was present in 57% (Table 3) which is rather high. It is in part explained by the contribution of patients referred for primary PTCA.

TIMI FLOW

Coronary angiography remains the golden standard to determine patency of the infarct related artery ever since DeWood et al demonstrated safety and feasibility of acute coronary angiography in AMI (19). However, this diagnostic procedure has disadvantages. Logistic problems may arise if this has to be done in every patient with AMI. Apart from the costs, acute coronary angiography may have adverse effects such as bleeding at the puncture site especially after the administration of thrombolytic agents. Thus, especially after thrombolytic treatment effective non-invasive detection of reperfusion will diminish the need for acute coronary angiography. The present prospective study documents the value of the 7 non-invasive parameters of reperfusion as a predictor for coronary reperfusion enabling differentiation between TIMI 0-1 and TIMI 2-3 flow of the infarct-related artery. The obvious advantage of the use of these non-invasive parameters of reperfusion is that they are simple, cheap and patient-friendly.

WHAT IS THE GOAL OF REPERFUSION; TIMI 2 FLOW OR TIMI 3 FLOW?

As stated earlier, the discussion on pursuing either TIMI 2 flow or TIMI 3 flow of the infarct-related artery is still ongoing but favours achievement of TIMI 3 flow. The non-invasive discrimination between TIMI 0-2 flow and TIMI 3 flow is important if the outcome of patients with TIMI 3 flow of the infarct-related artery is

considered to be superior to TIMI 2 flow. If TIMI 2 flow is considered to be more or less equal to TIMI 3 flow with respect to clinical outcome it is more important to discriminate between TIMI 0-1 and TIMI 2-3 flow. Limitations in budget, manpower, access to coronary angioplasty and the distance of travel to an angioplasty facility may intervene with the goal of reperfusion and definitions of treatment goals will depend on local and personal circumstances.

The issue of TIMI 3 flow or TIMI 2-3 flow may in fact be important in community hospitals without PTCA facilities who consider transfer of patients with AMI for emergency PTCA. This scenario is frequently the case in many European countries where angioplasty facilities are limited and the distance to tertiary PTCA centers is considerable. We recently published a study showing that early referral for intentional rescue angioplasty can be beneficial. In that study it was shown that patients with noninvasive signs of reperfusion in whom acute coronary angiography was refrained had a very good prognosis (20).

INCIDENCE AND VALUE OF THE DIFFERENT NON-INVASIVE PARAMETERS

ST-segment resolution $\geq 50\%$ had an incidence of 30% in this study population with good positive and negative predictive value to identify patients with reperfusion. In 85% of patients TIMI 2-3 flow was correctly predicted. However the positive predictive value of this non-invasive reperfusion parameter drops to 66% when it is used to predict TIMI 3 flow. Thus, using this non-invasive parameter only, it would lead to 15% of patients being falsely identified as having TIMI 2-3 flow and 34% of patients incorrectly considered to have TIMI 3 flow.

The weak prediction of complete restoration of flow (TIMI 3 flow) questions the value of this single reperfusion parameter. It is clear that there is considerable overlap in ST-segment behaviour in the patients with TIMI 2 or TIMI 3 flow of the infarct-related artery. Our findings are comparable to those of Kircher et al who found qualitative ST-segment improvement in 33% of patients with AMI associated with 88% probability of reperfusion (21). Clemmensen et al indicated that a decrease of 20% of the sum of ST-segment elevation was an useful non-invasive predictor of TIMI 2-3 flow of the infarct related artery (PPV 88%; NPV 80%) (22). In a small test population, Hogg and co-workers using the lead with maximal ST-segment deviation on the standard 12-lead ECG found that a 50% reduction in ST-elevation was 67% specific and 93% sensitive, however perfusion criteria were not given (23). Many other studies have been reported using a different percentage of ST-segment resolution usually in small patient groups and with a wide variety in time between the ECG recording and the determination of the state of reperfusion. The strength of our study lies in its prospective nature, in the simplicity of using only the ECG lead with the highest ST-segment elevation, the immediate coronary angiography after the second ECG giving the correct perfusion status, and the rather large patient population with a 43% coronary artery patency.

SUDDEN CHANGE IN CHESTPAIN

Increase or relief of chest pain is a subjective finding during AMI, and dependent on the state of ischemia and the moment of evaluation. Kircher et al showed the relation between sudden resolution of chest pain and coronary artery patency (21). However, extensive and long lasting myonecrosis can be accompanied by a gradual decrease in symptoms (the natural course of myocardial infarction). The duration between onset of pain and assessment of severity of complaints was rather short (<7.5 hours) in our study. During this time interval symptoms usually are still present. Pain-relieving medication and the administration of anti-ischemic agents can contribute to a decrease in symptoms and may partially have influenced assessment of chest pain (24)(25). Also cyclic changes of coronary perfusion and coronary tonus can contribute to changes in chest pain. Finally, an increase in chest pain can be experienced just after reperfusion of the infarct-related artery and could be caused by wash out of toxic metabolites. Like in other studies, the predictive value of sudden decrease or increase of chest pain had only limited predictive value (3) (26).

ARRHYTHMOGENECITY OF REPERFUSION

Due to the washout phenomenon during reperfusion of the infarct related artery, a sudden change in electrolytes, free radicals, fatty acids and other factors, can result in electrical instability and tissue heterogeneity of the reperfused myocardium. This is considered to be the ideal substrate for the occurrence of arrhythmias such as accelerated idioventricular rhythm (AIVR), increased ventricular ectopy, and ventricular fibrillation (27). Gressin et al have previously shown that AIVR and other ventricular arrhythmias can be observed in patients with an occluded artery but more than 5 hours after the onset of AMI (28). These ventricular rhythm disturbances will be observed during the first hour after reperfusion and fits well within our timing of coronary angiography. As shown in Table 4, AIVR has a high (94%) positive predictive value to discriminate between TIMI 0-1 and TIMI 2-3 flow of the infarct related artery, but the incidence of AIVR is low. It's positive predictive value drops to 59% if TIMI 3 flow has to be discriminated from TIMI 0-2 flow. It seems likely that the arrhythmia's are the result of reperfusion of the infarct related artery and not of the intensity of flow. Similar observations have been done with respect to ventricular fibrillation and the occurrence of ventricular ectopy during this study.

DEVELOPMENT OF TERMINAL NEGATIVE T-WAVE

Myocardial ischemia is a clinical condition associated with primary T-wave changes (3) (29). In the present study the early occurrence of a terminal negative T-wave more than 0.1 mV (1mm) in the most outspoken infarct lead, showed to be a sign of coronary reperfusion ($p < 0.001$). Although the positive predictive value of this

parameter in determining TIMI 2-3 flow is reasonably good, it drops to poor values in predicting TIMI 3 flow. It must be stated that for this parameter as for the other parameters considerable overlap in presentation exists.

PROSPECTIVE PREDICTION OF REPERFUSION BY THE INVASIVE CARDIOLOGIST

Prior to the start of the procedure, the invasive cardiologist was asked to write down his prediction about reperfusion. As previously mentioned, the invasive cardiologist was free to use the reperfusion parameters at his own discretion. He was able to predict reperfusion defined by TIMI 2-3 flow correctly in 88% of the patients and reperfusion defined as TIMI 3 flow in 66%. Prediction of complete restoration of flow by the invasive cardiologist correlated with excellent clinical outcome with respect to one-year mortality.

STUDY LIMITATIONS

The conclusions that can be derived from this study have to be placed against the rather heterogeneous group of patients referred for coronary angiography because of research protocols, possible rescue PTCA or primary PTCA. Because also patients were referred for primary PTCA, the overall patency rate at the first intracoronary injection was only 43%. We believe, however, that the patients used in the study population reflect all-day cardiology. The use of only the infarct-lead with highest ST-segment elevation to determine $\geq 50\%$ resolution and development of T-wave negativity were chosen to increase simplicity. The fact that only two moments of ECG evaluation have been used, does not take into account that ST-segment elevation frequently and significantly can fluctuate in the acute setting of AMI. However, the decision to perform acute coronary angiography has to be made promptly and cannot await long lasting analysis.

The evaluation of chest pain is a subjective measurement, but in our experience sudden changes in chest pain are well recognised by the patients. Complete avoidance of anti-ischemic agents might allow a more accurate determination of reperfusion with respect to chest pain, however it does not seem ethical not to give medication that potentially can limit infarct-size.

CONCLUSIONS

Using acute coronary angiography as the gold standard for the perfusion grade of the infarct related artery in 230 patients with acute myocardial infarction we confirmed that non-invasive parameters (especially the ST-segment) are of value in discriminating between TIMI 0-1 and TIMI 2-3 flow of the infarct related artery. The inability of non-invasive parameters of reperfusion to differentiate between patients

with TIMI 3 flow and TIMI 2 flow with great accuracy is a limitation because TIMI 3 flow of the infarct-related artery might be associated with better prognosis than TIMI 2 flow with respect to mortality and ventricular function. In case it is believed that TIMI 2 flow will have a poor prognosis, acute coronary angiography should be recommended to facilitate further treatment. The ability to do so will depend on the belief in that only TIMI 3 flow should be accepted and on the local circumstances. Especially in the European countries where access to angioplasty facilities is limited, and the manpower and healthcare budget is restricted, choices with respect to the (optimal) goal of treatment will have to be made. From the present data it becomes clear that a perfectly correct non-invasive confirmation of re-established infarct related coronary artery blood flow within therapeutically acceptable time limits, is not available at this moment.

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CHAPTER 6

Background and protocol of the Limburg myocardial infarction (LIMI) study

Participating centers:

Hospital Brunssum

Hospital Heerlen

Hospital Kerkrade

Hospital Roermond

Hospital Sittard

University Hospital Maastricht

INTRODUCTION

In recent years it has become clear that re-opening of the occluded coronary artery in acute myocardial infarction is the key factor determining clinical outcome (1). Because thrombosis is the most common cause for the obstruction, thrombolysis has become the therapy of choice in most institutions. This type of treatment has shown to be effective: patency of the culprit vessel can be achieved in 50-90% at 90 minutes after the start of therapy, but drawbacks of thrombolytic therapy are severe bleeding complications like intracranial hemorrhage (2-22). Therefore, primary PTCA (i.e. percutaneous transluminal coronary angioplasty, or balloon dilatation performed without previous administration of thrombolytic therapy) was advocated as a safe, fast, and also as a more successful alternative (19). After primary PTCA, patency rates above 90% and a low incidence of complications were reported (23-29). Recently, several studies have been published indicating that also in randomised trials primary PTCA is more effective than thrombolytic therapy (30-32). However, none of these studies had a treatment arm in which rescue PTCA (i.e. PTCA performed after administration of thrombolytic therapy that did not result in reperfusion of the infarct related vessel) was offered systematically to patients after failed thrombolysis. The RESCUE study, as commented in an editorial review, shows the controversies on rescue PTCA after failed thrombolysis (33). The question, therefore, remains if the efficacy and safety of the combined therapy of thrombolysis and rescue PTCA when needed, is different from that of primary PTCA. To study safety and efficacy of rescue PTCA after failed thrombolysis, a retrospective analysis was performed of patients with acute myocardial infarction. Patients with rescue PTCA were compared to patients in whom thrombolytic therapy was withheld and primary PTCA offered. In total 176 consecutive acute myocardial infarction patients admitted to the Academic Hospital Maastricht between 1986 and 1992 were reviewed: 100 patients had rescue PTCA after failed thrombolysis and 76 patients had primary PTCA (34). Procedural complications were compared and showed to be identical. This contrasts to other data which were published on the angiographic outcome of rescue PTCA after failed thrombolysis when compared to primary PTCA (19,30,33,35-55). In addition, in our study no significant differences were seen in the clinical outcome during admission and the outcome during the first year after the event.

Data of a consecutive subgroup of patients in which thrombolysis was successful, indicates that such patients also had an excellent prognosis. However, these findings were retrieved from a retrospective analysis in which the patient groups were not completely comparable. A retrospective study in 165 patients who were referred from a community hospital to a PTCA center for intentional PTCA showed that transport was safe and feasible within therapeutically acceptable time limits. So far, no prospective study has been published on the outcome of a three-armed strategy study of patients randomised to either thrombolysis only, to thrombolysis and rescue

PTCA if indicated, or to primary PTCA. The outcome of earlier trials however, makes it probably unethical to conduct such a study in patients directly admitted to a PTCA center. Reason is that the group of patients having thrombolysis only without further intervention has proven to have a worse outcome than the other two treatment modalities, if they are admitted in such centers. However, it is unclear whether thrombolytic treatment in patients admitted in non-PTCA centers is also inferior to the other two treatment forms. Negative effects of transport and time delays might be so important that the final outcome of "thrombolysis only" is identical to or even better than one of the two other regimes. Therefore, a study has been designed comparing 3 groups of myocardial infarction patients admitted in non-PTCA centers: Group 1: treated locally with thrombolytic therapy. Group 2: thrombolytic therapy and immediate transport to a PTCA center and rescue PTCA in case of persistent occlusion of the culprit artery. Group 3: Immediate transport to a PTCA center without thrombolytic therapy and primary PTCA in case of an occluded culprit artery. Inclusion in the trial will be limited to patients with large infarcts. The minimal requirements in ST segment elevation will lead to inclusion of the majority of patients with anterior myocardial infarction, but will limit the inclusion of patients with inferior myocardial infarction to those with extensive ischemia and a large area at risk. Clinical and angiographic follow-up will be done. Furthermore, a cost effectiveness analysis will be performed. All patients admitted to the cardiology department of non-PTCA centers in Limburg will enter the study in case they meet the inclusion criteria.

Feasibility: In the last three years more than 150 patients with acute myocardial infarction were sent to our institution for acute intervention, either rescue PTCA or primary PTCA.

Possible consequences: The outcome of the study might have important consequences for the treatment of acute myocardial infarction for patients who are admitted in non-PTCA centers and might influence the policies of the "Dutch Health Care" system.

REFERENCES AT THE END OF THE CHAPTER

OBJECTIVES

The aim of this trial is to evaluate three therapeutic regimens in the treatment of acute myocardial infarction: thrombolytic therapy, thrombolytic therapy followed by acute angiography and (if indicated) rescue PTCA, and primary PTCA. All patients are admitted to centers that do not have facilities for PTCA. All patients allocated to thrombolytic therapy followed by acute angiography and all patients allocated to primary PTCA have to be transported by ambulance to the University

Hospital Maastricht in the acute phase of the myocardial infarction. The patients allocated to thrombolytic therapy will stay in the hospital where they have been admitted. After the second angiogram (24 to 36 hours after the start of the study medication) the patient will be transferred back to the local hospital.

Primary endpoint of the study: Death and recurrent myocardial infarction during the first 42 days.

Secondary endpoints:

- One year mortality.
- NYHA functional class at one year.
- Reinfarction during the first 42 days.
- CABG.
- (Re)PTCA.
- ECG infarct score.
- Bleeding complications.
- Adverse events.
- Coronary patency at acute angiography.
- Complications due to the transport to and from Maastricht.
- Differences in delay to the start of therapy, especially delay related to the transport to and from Maastricht.
- Relation treatment delay and clinical parameters.

Technical:

- Estimation of enzymatic infarct size by cumulative enzyme release. The "Unsatisfactory Outcome Endpoint Score" according to Braunwald (56, see appendix).
- Echocardiographic assessments, assessing the development of left ventricular function and remodeling by serial echocardiography.
- Angiography analysis, assessing coronary patency and left ventricular function, at the acute stage (group 2 and 3 only) and after six months.
- Risk effectiveness analysis and cost effectiveness analysis, assessing the risks and costs involved with the different strategies in the various treatment arms, with special attention to the risks and costs involved with the transport by ambulance to and from Maastricht.
- Stratification of baseline risk, using a risk stratification score.

DESIGN

The study is an open randomised trial with three groups.

Group 1: Patients allocated to thrombolytic therapy without transport to Maastricht.

Group 2: Patients allocated to thrombolytic therapy followed by acute angiography (in Maastricht).

Group 3: Patients allocated to primary PTCA (in Maastricht).

From all eligible patients a fax of the ECG of the patient with the patient's initials and date of birth is sent to the CCU in Maastricht. After receipt of the fax the patient will be allocated to one of the treatment groups. The fax directly sent from Maastricht back to the local center with the allocated treatment number is considered to be the irrevocable entry in the study. Patients allocated to group 2 nad 3 will be transported to the University Hospital Maastricht in the acute phase. After the second angiogram (24 to 36 hours after inclusion in the study) transport back to the local center will be scheduled.

STEERING COMMITTEE AND POLICY ADVISORY BOARD

The steering committee will consist of the principal investigators of the participating centers, the study coordinators and the study monitors. A policy advisory board will be formed and will consist of three members not involved in the trial. The policy advisory board will be informed about the progress of the study, and the overall incidence of adverse events. The policy advisory board will (upon request) have access to the unblinded data at any time.

INFORMED CONSENT AND ETHICAL COMMITTEES

The nature and purpose of this study, including effects and possible side-effects of the treatment will be explained to each subject by the investigator according to the declaration of Helsinki and according to local requirements. Informed consent will be obtained from all patients, in the form of oral consent obtained in the presence of a witness. This protocol will be presented for approval to the ethical committee of the University Hospital Maastricht, and to the ethical committees of the trial centers. All patients will receive written information about the nature of the study (the day) after the acute phase of the study.

PATIENTS

Inclusion criteria:

- Age less than 80 years.
- First or recurrent myocardial infarction.
- Chest pain lasting for at least 30 minutes, not responding to nitrates.
- Onset of chest pain less than six hours before start of treatment.
- ST segment deviation (elevation in at least one lead + depression) of at least 15mm (1.5mV) or ST-segement deviation > 10 mm but < 15 mm and at least 2 of the 3 following criteria.

- Previous MI or
- Anterior wall MI or
- Signs of hemodynamic instability (HR > 100/min, or systolic bloodpressure < 100 mmHg).

Exclusion criteria:

- Severe hypertension unresponsive to nitrate therapy, remaining despite treatment > 180/110 mmHg.
- Known bleeding disorder or enhanced risk of bleeding.
- Active internal bleeding.
- Previous stroke in the last 12 months.
- Overt cardiogenic shock.
- Severe concomittant disease affecting life expectancy.
- A priori known logistic problems inevitable for transport or cath lab facilities (e.g. transport to Maastricht must be feasible within approximately 60 minutes after allocation)
- No informed consent.
- Incomplete follow-up anticipated (e.g. patients living abroad).

MEDICATION

Study medication:

- Group 1: alteplase.
- Group 2: alteplase.
- Group 3: no thrombolytic therapy.

Co-medication:

Heparin: heparin is to be given as a bolus of 5000 U i.v. before the administration of the thrombolytic agent (group 1 and 2) or as a bolus of 10.000U iv for patients allocated to primary PTCA. A second bolus of 5000 U of heparin is given at the start of the acute angiogram (group 2 and 3), and a third bolus of 5000 U of heparin is given after completion of the PTCA procedure (if applicable). After the infusion of the thrombolytic agent (group 1), or after the acute angiography (group 2 and 3), a heparin infusion is to be started with the dosage titrated against aPTT (2-2.5 X normal value for at least 24 hours.

Aspirin: Acetylsalicylic acid is to be given before the administration of the thrombolytic agent, either intravenously (dosage 300 mg) or orally (minimum dosage 160 mg), followed by a minimum dosage of 80 mg of aspirin daily, unless contraindicated. Note that other thrombotic agents should not be given unless the clinical situation requires such therapy.

Nitrates: If not contraindicated, a nitrate infusion (starting with 0,1 ug/kg/min and titrated against the blood pressure will be given on admission and will be continued for approximately 24 hours.

Other medication: All other medication is given on indication.

GENERAL GUIDELINES FOR ANGIOGRAPHY AND PTCA

- Start with angiography of the non-ischemic vessel to evaluate severity of coronary artery disease and presence of collaterals. At least 3 views of the left system and 2 views of the right system have to be made.
- An attempt of PTCA should be performed of the culprit lesion only.
- Do not undersize the angiography balloon.
- In all cases of TIMI 0/1 flow PTCA should be attempted unless the angiographic findings favour acute CABG.
- A final stenosis grade of < 50% and TIMI 3 flow should be reached. Local haziness after PTCA is a normal finding and should be accepted.
- In case of TIMI 2 flow the decision to perform PTCA will be made by the angiographer.
- In case of TIMI 3 flow PTCA should not be performed unless the clinical situation of the patient requires such procedure.
- In case of recurrent occluding dissection other technics than PTCA can be done.

ASSESSMENTS

The following assessments are scheduled:

Baseline/acute phase:

- Medical history.
- Physical examination.
- ECG.
- Delay (and reasons for delay) of transport by ambulance to and from Maastricht (group 2 and 3).
- Complications during or related to the transport to and from Maastricht (group 2 and 3).
- Angiography at 90 minutes followed by PTCA (in case of an occluded infarct related artery; group 2 and 3).
- Second coronary angiography at 24 to 36 hours (group 2 and 3).

In hospital phase:

- Adverse events.
- Follow-up ECG's.
- Cumulative enzyme release.
- Laboratory investigations (local routine).
- Echocardiogram (day 2 to 6; locally).
- Exercise test (day 5 to 10; locally).
- Coronary angiography (on clinical indication only).

Follow-up:

- Assessment at day 30 to 50 (including ECG and echo; locally).

- Assessment at 6 months (including ECG, echo, exercise test, coronary angiography and LV angiography; locally).
- Assessment after one year (including ECG; locally).

NUMBER OF PATIENTS

A total of 225 patients will be included in the trial (approximately 75 patients per treatment group). Patient recruitment is expected to be completed within two years after the start of the trial.

DATA ANALYSIS

The primary analysis will be on "intention to treat" basis. All patients allocated to one of the three treatment regimens in response to the fax received at the department of cardiology of the University Hospital Maastricht, will be included in the analysis. The mortality and reinfarction < 42 days will be used as the primary endpoint to assess the differences in safety and efficacy of the three treatment regimens. The differences in costs between the three treatment regimens will also be evaluated, especially the additional costs related to the acute transport to and from Maastricht. From the observed differences in efficacy, in safety, and in costs, a risk/effectiveness ratio, and a cost/effectiveness ratio will be computed.

SPECIAL ANALYSES

ESTIMATION OF ENZYMATIC INFARCT SIZE BY CUMULATIVE ENZYME RELEASE

Cumulative enzyme release is calculated from the total release of LDH in the first days after the onset of the myocardial infarction. LDH is measured twice daily during the first three days, and once daily during day 4 and 5. From the enzyme levels cumulative enzyme release is computed using the two compartment model (58).

ECHOCARDIOGRAPHIC ASSESSMENTS

Echocardiography is performed after 2 to 6 days, at the follow-up visit at day 30 to 50, and after six months. The echocardiograms will be made locally. The echocardiography analysis will be performed centrally. From the echocardiograms left ventricular function will be assessed, especially global and regional wall motion, the wall motion score, and the development of left ventricular volumes over time

(remodeling). Differences in diastolic function over time will also be analysed, as well as the development of mitral incompetence. The results of the echocardiography analysis will be compared to the results of the assessment of left ventricular function obtained by angiography.

ANGIOGRAPHY ANALYSIS

Coronary patency will be assessed at acute angiography and at the angiography performed after 24 to 36 hours for the patients in group 2 and 3, and angiography is performed in patients of all three groups after six months. At the angiogram performed after six months the status of the coronary anatomy is assessed, and global and regional wall motion is analysed. For the patients in group 2 and 3 these data can be compared to the data of the acute phase (angiography performed at the acute phase and after 24 to 36 hours). The data of the left ventricular wall motion will be compared with the echocardiographic data.

RISK EFFECTIVENESS AND COST EFFECTIVENESS ANALYSIS

A risk effectiveness analysis will be performed, as well as a cost effectiveness analysis. The effectiveness of the three different strategies is expressed as the outcome of the "Unsatisfactory Outcome Endpoint Score". The risks of the acute procedure, especially the acute transport (death, cardiopulmonary resuscitation, or artificial respiration during or related to the acute transport to Maastricht), will be weighted against the effectiveness of strategies in group 2 and 3. With regard to costs the following costs will be taken into account (if applicable):

- administration of the thrombolytic agent.
- transport by ambulance to and from Maastricht.
- coronary angiographies (acute phase, after 24 to 36 hours, after six months).
- acute PTCA (either primary PTCA or rescue PTCA).
- late interventions (additional angiographies, late PTCA or CABG).
- length of stay on CCU (in days).
- length of hospital stay (in days).
- costs involved with readmissions during follow-up.

From these data a cost effectiveness ratio will be computed. The costs per year of life gained will be calculated.

RISK STRATIFICATION

Baseline risk will be assessed for each patient. The baseline risk assessment will take into account the location of the infarct, the extent of the ischemic area (based on the total amount of ST segment elevation on the baseline ECG), the delay from onset of therapy to randomisation and to start of therapy, the age of the patient, the presence

of a previous myocardial infarction, and the presence of signs of heart failure (59). The baseline risk assessment score will be used as a predictor of the "Unsatisfactory Outcome Endpoint Score" in order to define the subsets of patients that benefit most of one of three treatment strategies as defined in this protocol.

Appendix. Unsatisfactory Outcome Endpoint Score

Event	Score
Death	100
Stroke with permanent deficit	100
LV pump failure (NYHA class III)	80
LVEF < 40% or infarct size > 20%	60
Stroke without permanent deficit	40
Reocclusion or reinfarction	40
Major "spontaneous" bleeding	30
No reperfusion of IRA	20
Major "catheter site" bleeding	10
None of the above	0

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CHAPTER 7

Prospective randomised comparison between thrombolysis, rescue PTCA and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities

The LIM1 study, a safety and feasibility study

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ABSTRACT

Objective: To assess the safety and feasibility of acute transport followed by rescue PTCA or primary PTCA in patients with acute myocardial infarction initially admitted to a hospital without PTCA facilities.

Design: In a multicenter randomised open trial, three regimens of treatment of acute large myocardial infarction were compared for patients admitted to hospitals without angioplasty facilities: thrombolytic therapy with alteplase (75 patients), alteplase followed by transfer to the PTCA center and (if indicated) rescue PTCA (74 patients), or transfer for primary PTCA (75 patients).

Results: Between 1995 and 1997 224 patients were included. Baseline characteristics were distributed evenly. Transport to the PTCA center was without severe complications in all patients. Mean delay from onset of symptoms to randomisation was 130 ± 75 minutes and from randomisation to angiography 90 ± 25 minutes. Clinical outcome: death or recurrent infarction within 42 days occurred respectively in 12 patients (thrombolysis group), 10 patients (rescue PTCA group), and 6 patients (primary PTCA group). These differences were statistically not significant.

Conclusions: Acute transfer for rescue PTCA or primary PTCA in patients with extensive myocardial infarction is feasible and safe. Efficacy of rescue PTCA or primary PTCA in this setting will have to be tested in larger series before this approach can be implemented as "routine therapy" for patients with extensive myocardial infarction.

INTRODUCTION

THE THROMBOLYTIC ERA

In the last decade it has become clear that reopening of the occluded coronary artery in acute myocardial infarction is the key factor determining clinical outcome (1). Because thrombosis is the most common cause for the obstruction, thrombolysis has become the therapy of choice. This treatment has shown to be reasonably effective: patency of the culprit vessel (TIMI 2 or 3 flow) can be achieved in 50-90% at 90 minutes after start of therapy. However, side effects of thrombolytic therapy are severe bleeding complications like intracranial haemorrhage (2-5).

PRIMARY PTCA

Primary PTCA (acute PTCA without previous administration of thrombolytic therapy) has shown to be a safe and successful alternative for thrombolytic therapy. After primary PTCA patency rates above 90% with low incidence of complications were reported (6-9). Recently, several randomised studies reported that primary PTCA is more effective than thrombolytic therapy (10-13). However, none of these studies included a treatment arm in which rescue PTCA (PTCA after failed thrombolysis) was part of the protocol.

RESCUE PTCA

So far, the published results of rescue PTCA (acute PTCA after failed thrombolysis) have been equivocal. A high complication rate was described in several retrospective studies (14-17). The RESCUE study prospectively evaluated rescue PTCA in patients with anterior infarction (18). The findings of the RESCUE study and several other studies support the suggestion that an invasive strategy in patients with acute myocardial infarction might contribute to an improved clinical outcome (19-21).

TRANSFER OF PATIENTS TO PTCA CENTER

The conclusions concerning PTCA as mentioned above are limited to the group of patients directly admitted to a hospital with PTCA facilities. The optimal strategy for patients initially admitted to a hospital without PTCA facilities remains unclear. The relative safety of transferring patients with acute myocardial infarction to a PTCA center for primary PTCA or for rescue PTCA has been described in retrospective studies (22,23), but prospective studies are lacking. The present study is the first study that compares prospectively the outcome of thrombolysis, primary PTCA, and thrombolysis followed by rescue PTCA (if indicated) for patients with

extensive myocardial infarction initially admitted to a hospital without PTCA facilities.

OBJECTIVES OF THE STUDY

The present study was designed as a pilot study with as main objective to test the safety and feasibility of acute transport to the nearest PTCA center for patients with acute myocardial infarction. For this reason the outcome of the patients who underwent or were allocated to immediate transport was compared to the outcome of the patients allocated to receive thrombolytic therapy without transport to the PTCA center.

METHODS

DESIGN

In this open randomised trial three therapeutic regimens in the treatment of acute myocardial infarction were compared: thrombolytic therapy, primary PTCA, and thrombolytic therapy followed by acute angiography and rescue PTCA (if indicated). All participating centers to which the patients were initially admitted had no PTCA facilities. Patients with extensive acute myocardial infarction were candidates for the study if they had no contraindications for thrombolytic therapy. From all eligible patients who gave informed consent a fax of the ECG with the patient's initials and date of birth was sent to the CCU of the PTCA center. Randomisation was done by computer. The fax from the PTCA center back to the referring center with the treatment allocation was considered to be the irrevocable entry in the study. Patients allocated to thrombolytic therapy received alteplase and stayed in the hospital where they were initially admitted. Patients allocated to primary or rescue PTCA underwent immediate transport to the PTCA center. The transport was operated by the ambulance services by well trained paramedic staff in ambulances equipped to transfer critically ill patients. A twenty-four hours service was available in the PTCA center for acute angiography with two catheterisation rooms. Patients were transferred back to the referring center the next day. If no bed was available, patients were transferred back after angiography as soon as their clinical situation had stabilised. Patient recruitment was completed within two years.

ENDPOINTS

The primary endpoint of this pilot study was to test the safety and feasibility of acute transport to a PTCA center for patients with acute myocardial infarction. The combined incidence of death and recurrent myocardial infarction within the first 42

days was considered to be a secondary endpoint and was used to compute the required sample size for a study to test the efficacy of these treatment strategies. Other endpoints were: mortality, recurrent infarction, thromboembolic and haemorrhagic stroke, recurrent interventions as PTCA or CABG, and recurrent ischemia during one year follow-up; coronary patency, bleeding complications, complications due to the transport to and from the PTCA center and differences in delay to start of therapy, especially delay related to the transport to the PTCA center. Recurrent infarction was defined as a new episode of chest pain occurring at least 48 hours after the initial infarction, accompanied by ECG changes and by a new rise in serum enzymes. The diagnosis of stroke was confirmed by the neurologist, the origin of the stroke was CT scan confirmed. Recurrent ischemia was defined as a new episode of chest pain at least 48 hours after the initial infarction with transient ECG changes and without enzyme rise.

PARTICIPATING CENTERS

Seven centers in Limburg, a province in the south of The Netherlands, participated in the study. The distance between the referring centers and the PTCA center (Maastricht) varied from 25 km (Sittard) to 50 km (Roermond).

PATIENT SELECTION

Inclusion criteria were: age less than 80 years, first or recurrent myocardial infarction, chest pain lasting for at least 30 minutes not responding to nitrates, and onset of chest pain less than six hours before randomisation. The following ECG criteria had to be fulfilled: ST segment deviation (elevation in at least one lead + depression) of at least 1.5 mV (=15 mm). Exclusion criteria were: severe hypertension unresponsive to acute therapy, enhanced risk of bleeding, previous stroke in the last 12 months, cardiogenic shock, severe concomitant disease affecting life expectancy, a priori known logistic problems for transport or angiography (transport to the PTCA center should be feasible within one hour after randomisation), no informed consent, incomplete follow-up anticipated.

MEDICATION

Alteplase (accelerated regimen) was given as thrombolytic agent. Alteplase was given immediately after randomisation. For the patients allocated to rescue PTCA the alteplase bolus was given and the alteplase infusion started prior to the ambulance transport. The alteplase infusion was continued during transport and upon arrival in the PTCA center. In the majority of cases the alteplase infusion was completed (at 90 minutes) before start of angiography. Heparin was given as bolus of 5000 U iv. before the administration of alteplase or as bolus of 10.000 U i.v. for patient allo-

cated to primary PTCA. A second bolus of 5000 U was given at the start of the acute coronary angiogram, and a third bolus of 5000 U was given after completion of the PTCA procedure (if applicable). After infusion of the thrombolytic agent or after acute coronary angiography a heparin infusion was started with the dosage titrated against the partial thromboplastin time (aPTT, prolongation 2 to 3 times) for 24 hours. Acetylsalicylic acid (300 mg intravenously or 160 mg orally) was administered before initiation of thrombolytic therapy, followed by 80 mg of oral aspirin daily unless contraindicated. A nitrate infusion titrated against blood pressure was started and continued for 24 hours. The patients were not treated with abciximab. All other medication was left at the discretion of the investigator.

PRIMARY PTCA

PTCA was performed of the culprit lesion only. In all cases of TIMI 0/1 flow PTCA was attempted unless the angiographic findings favoured acute CABG. In case of TIMI 2 flow the decision to perform PTCA was made by the angiographer. In case of TIMI 3 flow PTCA was not performed unless the clinical condition of the patient required such procedure. In case of a severe dissection or incomplete result of the PTCA a coronary stent was implanted. Successful PTCA was defined as TIMI 3 flow and stenosis < 50% at the end of the procedure.

RESCUE PTCA

In the patients allocated to rescue PTCA the same procedure was followed in the catheterisation laboratory as for the patients allocated to primary PTCA. The angiographer was not blinded to the treatment allocation. Rescue PTCA was defined as acute PTCA performed in patients with TIMI 0 or 1 flow at the angiogram performed (60 to appr. 120 minutes) after intravenous administration of the thrombolytic agent.

DATA ANALYSIS

The primary analysis was on intention to treat basis. All patients allocated to one of the three treatment regimens in response to the fax received in the PTCA center, were included in the analysis. If applicable, Fisher's exact test was used; two sided p values are reported.

Figure 1. Location of the participating hospitals. All participating centers are located in the province Limburg in The Netherlands, with on the west and south side the border with Belgium and on the east side the border with Germany.

RESULTS

BASELINE CHARACTERISTICS

Between September 1995 and August 1997 a total of 224 patients with acute myocardial infarction were included in the study; 75 patients were allocated to thrombolytic therapy, 74 patients to thrombolysis and rescue PTCA (if indicated), and 75 patients to primary PTCA. Inclusion was limited to the hospitals in the southern part of the province Limburg in The Netherlands (figure 1). Only patients with extensive ischemia (total ST segment elevation and depression at least 1.5 mV or 15 mm) were included. This resulted in a relatively large proportion of patients with anterior infarction. All baseline characteristics were distributed evenly over the three treatment groups (table 1).

TREATMENT DELAY

Mean interval from onset of symptoms to randomisation varied between 125 ± 80 minutes in the thrombolysis group to 140 ± 70 minutes in the rescue PTCA group. Mean interval between randomisation and start of angiography in the PTCA center was 85 ± 25 minutes in the primary PTCA group, and was slightly longer namely

Table 1. Baseline Characteristics

	Thrombolysis	Thrombolysis + rescue PTCA	Primary PTCA
Number of patients	75	74	75
Age (mean + sd; years)	59 ± 11	59 ± 12	58 ± 11
Male gender	56	57	54
Female gender	19	17	21
Anterior mi	36	37	34
Inferior mi	39	37	41
Previous mi	13	15	9
Previous PTCA/CABG	3	2	1
Previous angina	2	6	4

MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass graft.

100±30 minutes in the rescue PTCA group (figure 2). On average PTCA was started 15 minutes after start of coronary angiography. Patency of the infarct related coronary artery was in the majority of patients obtained within four hours after onset of symptoms. Hospital admission was on average 90 minutes after the onset of chest pain. In the thrombolysis group and in the rescue PTCA group the thrombolytic therapy was initiated on average 10 minutes after randomisation, i.e. on average 45 minutes after hospital admission. There were no significant differences in the treatment delays between the three treatment groups.

COMPLICATIONS DURING TRANSPORT

Immediately after randomisation, patients allocated to the primary PTCA or the rescue PTCA group were transferred to the PTCA center, located at a distance of 25 to 50 km from the referring hospital (figure 1), usually by the same ambulance that had taken care of the transfer of the patient to the hospital. Prior to the transfer all patients received aspirin, a heparin bolus, an infusion of nitroglycerin, and patients allocated to the rescue PTCA group also received a bolus and infusion of alteplase. Travel time in the ambulance lasted on average 20 minutes and did not exceed 30 minutes. There were no severe complications during transport. In the ambulance no patients died, two patients had to be cardioverted because of ventricular arrhythmias, two patients received atropine because of bradycardia, and the dosage of the nitroglycerin infusion had to be decreased in six patients because of hypotension. Acute transport was withheld in three patients. In one patient (rescue PTCA group) an echocardiogram was made because of suspicion of aortic dissection.

Figure 2. Treatment delays. Mean treatment delay in minutes from onset of chest pain to randomisation (lower part), and from randomisation to start of angiography for the rescue PTCA and the primary PTCA group (upper part).

At the end of the echocardiography (there were no signs of aortic dissection) the patient showed signs of reperfusion on the ECG. Because of the long delay and the ECG signs of reperfusion it was decided that acute transport was no longer indicated. In two patients allocated to primary PTCA the hemodynamic situation of the patient impeded acute transport, and thrombolytic therapy was given by the referring cardiologist. From the 146 patients who came to Maastricht, 143 underwent angiography. In 128 patients angiography took place without delay, in 15 patients there was a delay of 60 minutes or more from arrival at Maastricht till start of angiography (with a mean of 83 minutes), because at the time the patient arrived the catheterisation room was not immediately available. In three patients immediate angiography was not possible, and at the time the catheterisation laboratory was ready, immediate angiography was no longer considered indicated because of the time delay and the presence of non-invasive signs of reperfusion. The majority of patients was transferred back to the referring center the next day. Because of shortage of hospital beds in Maastricht, 33 patients had to be transferred back after coronary angiography as soon as their clinical situation had stabilised. The transport from the PTCA center back to the referring center was without complications in all cases.

ANGIOGRAPHY

Acute angiography was performed in 143 patients. In the rescue PTCA group TIMI 3 flow was seen at the first angiogram in 41 patients (57%), TIMI 2 flow was present in 10 patients (14%). This means that patency of the infarct related coronary artery (TIMI 2 or 3 flow) was obtained by alteplase in 51 patients (71%) at 90 minutes after initiation of the thrombolytic therapy. Rescue PTCA was performed in 14 of the 20 patients with TIMI 0 or 1 flow, and acute PTCA was performed in 5 of the 10 patients with TIMI 2 flow and in one patient with TIMI 3 flow. In the remaining seven patients with TIMI 0 or 1 flow PTCA was not performed for technical reasons, usually because of the small diameter of the infarct related vessel. Acute PTCA was successful in 18/20 patients (90%) with a stent implanted in three patients. At the end of the procedure TIMI 3 flow was obtained in 58 patients and TIMI 2 flow in 6 patients (figure 3). In the primary PTCA group the infarct related coronary artery appeared to be occluded (TIMI 0 or 1 flow) in 55 patients, and TIMI 2 flow was present in 8 patients. Primary PTCA was performed in 52 out of 55 patients with TIMI 0 or 1 flow, and in all patients with TIMI 2 flow. TIMI 3 flow was present from the beginning of the angiography in 9 patients, and PTCA was performed in two patients. PTCA was successful in 60/63 patients (95%) with a stent in 13 patients. At the end of the procedure TIMI 3 flow was obtained in 66 patients and TIMI 2 flow in 3 patients. Second angiography, scheduled 24 to 36 hours after inclusion, was done in 112 patients, with high patency rate in all groups (figure 3). Second angiography was not performed in 31 patients. The reasons not to perform second angiography were: patients transferred back immediately after the first angiogram (12 patients), no consent for second angiography (7 patients), sheath already removed (2 patients), angiography not possible or considered not indicated on clinical grounds (10 patients).

CLINICAL COURSE

There were no significant differences in the clinical course during the first 42 days between the three treatment groups (table 2). The clinical endpoint of the study (death or recurrent MI within 42 days) was reached in 12 patients (16%) in the thrombolysis group, in 10 patients (14%) in the rescue PTCA group, and in 6 patients (8%) in the primary PTCA group. A total of 7 patients suffered from stroke within 42 days, of which the stroke was of hemorrhagic origin in 3 patients. The incidence of recurrent ischemia and of late PTCA and CABG was the highest in the thrombolysis group, lower in the rescue PTCA group and lowest in the primary PTCA group (table 2). Severe bleeding complications were not observed, the incidence of minor bleeding complications was somewhat higher in the rescue PTCA group (21%), than in the other two groups (11%). Clinical course was uncomplicated in the majority of patients. Transient severe hypotension (4 patients) and signs

Figure 3. Angiography. TIMI flow at the begin of the acute angiography, at the end of the acute angiography, and at the second angiogram after 24 to 36 hours for patients allocated to rescue PTCA (left bars) and to primary PTCA (right bars).

of severe heart failure (8 patients) were observed only in a minority of the patients. The incidence of ventricular arrhythmia's was not different between the treatment groups, and of a magnitude as could be expected from a group of patients with extensive myocardial infarction.

ONE YEAR FOLLOW-UP

Results of one year follow-up are presented in table 2. Clinical course from 42 days up to one year follow-up was uneventful in the majority of patients. In the thrombolysis group any event (mortality, stroke, recurrent infarct, PTCA, CABG or recurrent ischemia) between 42 days and one year was observed in 15 patients, versus in 6 patients in the rescue PTCA group and in 11 patients in the primary PTCA group (differences not significant). In general, one-year mortality and morbidity was relatively low in these groups of patients who were admitted with extensive ischemia and suffered from large myocardial infarctions.

PATIENT LOG

A patient log was recorded in all participating hospitals. A total of 1267 patients with acute myocardial infarction were admitted at the participating centers during the period of patient recruitment. Reasons not to include patients were: no indication for thrombolytic therapy due to patient delay or absence of ECG abnormalities,

Table 2. Clinical course during one year follow-up.

	Thrombolysis	Thrombolysis + rescue PTCA	Primary PTCA
	N	N	N
Number of patients	75	74	75
Deceased	6 [5]	7 [6]	9 [5]
Thrombotic stroke	1 [1]	2 [1]	2 [2]
Haemorrhagic stroke	1 [1]	2 [2]	0 [0]
Recurrent infarction	9 [7]	5 [4]	4 [1]
Late PTCA/CABG	29 [23]	24 [17]	10 [6]
Recurrent ischemia only*	10 [6]	9 [5]	10 [6]
None of the above	33 [48]	38 [44]	47 [58]

Data are of one year follow-up. Between brackets data concerning 42 days follow-up. *Recurrent ischemia without infarction and not followed by intervention (PTCA/CABG).

contraindications for thrombolytic therapy, or absence of signs of extensive ischemia with total ST segment deviation not reaching 1.5 mV or 15 mm. In this latter group the patients were treated with thrombolytic therapy, if indicated, but acute transport to the PTCA center was not undertaken unless the clinical situation required such an action.

DISCUSSION

TREATMENT DELAY

Mean delay from onset of symptoms to hospital admission was somewhat on average 90 minutes, a delay that correlates well with results of other trials in patients with acute myocardial infarction in Europe (24,25), and compares favourably to the delay observed in GUSTO (13). This is of importance because the efficacy of reperfusion strategies is strongly dependent on total ischemia time. Mean delay from randomisation to start of angiography was 85 minutes in the primary PTCA group. On average, primary PTCA could be started 215 minutes after onset of symptoms, a finding similar to several primary PTCA studies in which the patient was directly admitted to the PTCA center (11-13). Delay from randomisation to start of angiography was slightly longer in the rescue PTCA group (on average 100 minutes). This was in part due to the time needed for the preparation of the bolus and infusion of the thrombolytic agent, but the fact that this was an open study might also have played a role. This bias could be avoided by giving a placebo instead

of the thrombolytic agent to the patients allocated to primary PTCA prior to the transport to the PTCA center.

LOCATION AND DISTANCE

The geographical location of the PTCA center in Maastricht limited the number of centers that could participate (see figure 1). In order to avoid excessive treatment delay participation of referral centers was limited to centers who were in the neighbourhood of the PTCA center and who were used to send unstable patients to Maastricht. In another study in The Netherlands, a retrospective study concerning acute transport for primary PTCA, transport was foreseen for distances up to 100 km with inevitably long treatment delay (22). This probably will influence the outcome of the patients, who undergo primary PTCA after a long treatment delay.

COMPLICATIONS DURING TRANSPORT

From the results of this trial it can be concluded that transfer of a patient with acute myocardial infarction to a PTCA center is probably feasible and safe. The incidence of complications during transport was low, and these complications could be handled well by the experienced ambulance personnel. These results are in accordance with the results of the retrospective studies, which were done in the same region in The Netherlands (23), and in a different region in The Netherlands (22).

ANGIOGRAPHY AND CLINICAL COURSE

The results of the angiograms and clinical course during follow-up show a similar pattern as reported from primary PTCA studies in which the patients were directly admitted to the PTCA center (11,21). In the rescue PTCA group 57% of the patients had TIMI 3 flow, and as a consequence acute PTCA was not necessary. This means that the costs and the workload were lower in the rescue PTCA group than in the primary PTCA group. With regard to clinical endpoints, there were no significant differences between the three treatment groups. However, a trend was visible towards a lower rate of recurrent infarction in the PTCA groups. The fact that after thrombolytic therapy a significant residual stenosis remains present in the majority of cases, might be the explanation for this finding. Total mortality and morbidity was low in this group of patients, moreover when it is taken into account that this was a patient group with extensive ischemia on the admission ECG, which reflects a large area at risk.

FUTURE STUDIES

This pilot study was designed as a safety and feasibility study, so conclusions about the efficacy of the three regimens are not possible, due to the low number of patients included. All centers in this region of The Netherlands (Limburg) participated in this study. This resulted in inclusion of 224 patients in two years. From the results of this study can be computed that a minimum of 600 patients per treatment group will be needed to discover relevant differences between thrombolytic therapy alone versus primary PTCA or rescue PTCA in this setting. In The Netherlands such a study is only feasible when done at a nation-wide level. Presently, a nation-wide study is planned. However, future developments might influence the outcome of these treatment strategies in all three treatment groups. Newer thrombolytic agents with high patency rates will soon be available (24,25). Thrombin inhibitors or glycoprotein IIb/IIIa receptor antagonists might either replace heparin or be added to heparin leading to higher patency and lower reocclusion rates (26,27). This will probably improve the outcome of patients treated with thrombolytic therapy, which will decrease the need for rescue PTCA. On the other hand, implementation of the new generation of stents will probably have a positive effect on the long term success rate of both primary and rescue PTCA (28,29). The net effect of these amelioration's will have to be awaited.

CONCLUSIONS

Acute transport for rescue PTCA or primary PTCA in patients with extensive myocardial infarction is feasible and safe. Efficacy of rescue PTCA or primary PTCA in this setting will have to be tested in larger series. The results of these trials will have to be awaited before transfer of patients in the acute phase to a PTCA center can be implemented as "routine therapy" for patients with extensive myocardial infarction.

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CHAPTER 8

Cost-effectiveness analysis of the LIM1 protocol

A prospective comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with acute myocardial infarction initially admitted to a hospital without PTCA facilities

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ABSTRACT

Introduction: The Limburg Myocardial Infarction study (LIMI), a multicenter open randomized trial for patients admitted to hospitals without angioplasty facilities was designed to evaluate three strategies of reperfusion in the treatment of extensive acute myocardial infarction; 1) thrombolytic therapy with alteplase (T), 2) alteplase followed by immediate transfer to a PTCA center for acute coronary angiography and rescue PTCA, if indicated (RP) and 3) immediate transfer for primary PTCA (PP). Previously has been published, that acute transfer of patients for either rescue PTCA or primary PTCA was safe and feasible. Cost-effectiveness of the three strategies are assessed in this study.

Methods: Costs are limited to the direct medical costs and are calculated per patient after one year by multiplying volumes of resource utilization with estimates of unit costs. Effectiveness is expressed in terms of survival free of death, myocardial infarction (MI) and/or stroke; survival free of death, MI/Stroke and revascularisations (MACE-free survival), and in terms of the distribution of patients by functional class. The balance between costs and effects was addressed by cost effectiveness ratio's and by probability ellipses indicating the distribution of both costs and effects.

Results: 224 patients were randomised: 75 to thrombolytic therapy, 74 to rescue PTCA and 75 to primary PTCA. The percentage of patients with survival free of death, MI and or stroke after one year follow up was estimated at respectively 81% (T), 81% (RP) and 84% (PP). One-year-MACE-free survival was estimated at respectively 55% (thrombolysis) 58% (rescue PTCA) and 76% (primary PTCA) $p=0.021$. Costs per patient after 1 year were estimated at EUR 8,704 (thrombolysis); EUR 11,524 (rescue PTCA); and EUR 11,661 (primary PTCA). The additional costs per additional MACE free survivor in comparison to treatment with thrombolysis was EUR 81,928 for rescue PTCA and EUR 13,862 for primary PTCA.

Conclusion: Transferring patients to a PTCA center may improve clinical outcome but at significant costs. Moreover, the data raise serious doubts about whether transferring patients to a PTCA center is a cost efficient way to further improve health care, suggesting that thrombolytic therapy may be the best approach in the management of acute myocardial infarction for patients admitted to a hospital without angioplasty facilities in an environment of limited resources.

INTRODUCTION

Over the past decade, several reperfusion strategies in acute myocardial infarction (AMI) have been developed. The administration of thrombolytic therapy has reduced early mortality by 20-30% (1-2). Until now this treatment remains the most common mode of reperfusion in patients admitted with acute myocardial infarction. Previous randomized studies indicate that primary PTCA (angioplasty not preceded by the administration of thrombolytic therapy) is a safe and effective alternative for thrombolytic therapy (3-7). Also when patients are referred from another hospital the place of rescue PTCA (angioplasty after failed thrombolysis) has been less clear (8-12). The RESCUE study, a prospective study to evaluate rescue PTCA in patients with anterior myocardial infarction suggested that invasive treatment can improve clinical outcome (13). A recent analysis by Bär et al. suggested that the angiographic and clinical outcome of rescue PTCA and primary PTCA is similar in case rescue PTCA is performed early after failed thrombolysis (14). However, the conclusions concerning rescue PTCA or primary PTCA, as mentioned above, are mostly from patients directly admitted to a PTCA center.

The optimal strategy for patients admitted to a hospital without angioplasty facilities remains unclear and requires further clarification. The question can be asked whether certain patients with acute myocardial infarction admitted to a non-interventional hospital should be transported to a nearby PTCA center for rescue or primary PTCA with its inherent risks, costs and time delays. Transfer of selected patients may be appropriate if the benefits of rescue or primary PTCA outweigh the risk of inter-hospital patient transport, costs and the potentially negative effects of the additional time delay.

Vermeer et al. reported a prospective randomized multi-center study in patients with acute myocardial infarction who were initially admitted to a hospital without angioplasty facilities. In this Limburg Myocardial Infarction (LIMI) pilot study three strategies were compared 1) thrombolytic therapy without transfer, 2) thrombolytic therapy, immediate transport and early rescue PTCA, in case of failed thrombolysis and 3) transfer and primary PTCA (15). If referred angioplasty would be more effective than thrombolysis alone, valid reasons may exist to adopt either the strategy of immediate transfer to an angioplasty center with or without pretreatment with a thrombolytic agent, and to increase the number of hospitals with angioplasty facilities. Such an approach should however be also evaluated for additional (side)-effects and the costs.

METHODS

THE LIM1 STUDY

Briefly the primary aim of this open randomized multi-center study was to evaluate the safety and feasibility of transfer of patients with extensive acute myocardial infarction for acute intervention (15). All patients were admitted to five non-interventional hospitals in the mid and southern region of Limburg, a province in the southern part of the Netherlands with approximately 550.000 inhabitants. Patients allocated to thromolytic therapy only remained at the referring hospital. Patients allocated to primary or rescue PTCA had immediate transport to the PTCA center. Interventions were performed in the Academic Hospital of Maastricht. In general, patients were transferred back to the referring hospital after a 24-hour stay at the PTCA center. Time of discharge from the referring hospital was left to the discretion of the referring cardiologist and was dependent on the clinical condition of the patient.

PATIENT SELECTION

Inclusion criteria were: age less than 80 years, first or recurrent myocardial infarction, chest pain lasting for at least 30 minutes, not responsive to nitrates and onset of chest pain less than six hours before randomization. The following ECG criterium had to be fulfilled; ST-segment deviation (ST segment elevation in at least one lead + ST segment depression) of at least 1.5 mV (15 mm).

Exclusion criteria were contraindications for thrombolytic therapy like: severe hypertension unresponsive to acute therapy, enhanced risk of bleeding, previous stroke in the last 12 months. Patients were also excluded in case of overt cardiogenic shock, severe concomitant disease, logistical problems already known before randomization, no informed consent and incomplete follow-up to be expected.

THROMBOLYSIS AND ACUTE PTCA

Patients allocated to the thrombolysis regimen were treated with alteplase (accelerated dose) after a bolus of 5,000 U of heparin and a heparin infusion, and acetylsalicylic acid.

Patients allocated to rescue PTCA had the same treatment but were immediately thereafter transferred to the PTCA center by ambulance. Patients allocated to primary PTCA were immediately transferred to the PTCA center after receiving a bolus of 10,000 U of heparin intravenously and 300 milligram of acetylsalicylic acid.

In all cases of TIMI 0-1 flow, PTCA was attempted unless the angiographic findings favored acute CABG. In case of TIMI 2 flow the decision to perform PTCA was left to the discretion of the operator. In case of TIMI 3 flow, PTCA was not

performed. A stent was placed in case of a flow limiting dissection. PTCA was performed of the culprit lesion only.

FOLLOW-UP

All patients were followed at the outpatient clinic for at least one year. The following data were recorded:

- Functional class for angina at 42 days, 6 months and 12 months, according to the criteria of the New York Heart association (16).
- All hospital admissions, including length of admission and reason for admission.
- Date and cause of death.
- Recurrent myocardial infarction or cerebrovascular accident.
- All coronary interventions such as coronary angiography (CAG), PTCA or coronary artery bypass grafting (CABG).
- Drug therapy at 42 days, 6 months and 12 months.

COSTS

Costs were calculated per patient by multiplying volumes of resources with unit costs. The resources included length of hospital stay (distinguishing between ICU-CCU- and ward days), all major interventions (CAG, PTCA, CABG), cost of medication and costs associated with the transfer of the patients to and from the PTCA-center.

With respect to the cost of PTCA procedures a distinction was made between the costs of elective PTCA and those associated with rescue and primary PTCA. The latter being more expensive because of the unplanned character. All other unit costs were derived from previous analyses, calculated on the basis of hospital administration data (17).

EFFECTIVENESS

Effectiveness was measured in terms of the percentage of patients free of death, MI or stroke after 1 year (MI/Stroke free survival) and in terms of the percentage of patients free of death, myocardial infarction, stroke or any revascularisation (MACE-free survival). Additionally, effectiveness was measured by categorizing the patients according to their functional class at 1-year follow up.

COST EFFECTIVENESS

The balance between costs and effects is addressed by calculating the probabilities that transfer to a PTCA center is a) more effective and cost saving; b) more effective and more expensive; c) less effective and more expensive and d) less effective and cost

saving. Additionally, incremental cost effectiveness ratio's are calculated addressing 1) the additional costs per additional patient free of death, MI or stroke and 2) the additional costs per additional patient free of death, MI, stroke or revascularisation.

STATISTICAL ANALYSIS

All endpoints were analyzed according to the 'intention to treat' principle. Continuous variables are expressed as mean $\pm$ standard deviation (SD) or as median (range) depending on their distribution. If applicable Fisher's exact test was used; two sided p-values are reported. A p-value <0.05 was considered to be statistically significant. Uncertainties surrounding the estimates of the incremental CE ratios are expressed by probability ellipses using the methodology reported by van Hout et al (18), realizing that additional uncertainties surrounding the estimates of cost per event are neglected in calculating these estimates.

RESULTS

PATIENT CHARACTERISTICS

Between September 1995 and August 1997 a total of 224 patients with acute myocardial infarction were included in the study; 75 patients were allocated to thrombolytic therapy, 74 patients to thrombolysis and rescue PTCA (if indicated) and 75 patients to primary PTCA (Table 1). Only patients with extensive ischemia were included. This resulted in a relative large contribution of patients with anterior myocardial infarction. The difference in time of 15 minutes from randomization to the start of coronary angiography between rescue PTCA and primary PTCA can be explained by the time needed to administer the thrombolytic agent and the 10 minute longer delay between onset of complaints and admission.

Table 2 depicts the clinical course during one-year follow-up.

EVENTS

The first three columns of table 3 show the number of procedures as well as data concerning length of hospital stay in either group during index hospitalization, and during one-year followup. In the patients allocated to thrombolytic therapy without early transport for angioplasty, ambulance transport to the PTCA center was needed 17 times at later stage during the same admission. Coronary bypass surgery or PTCA after the initial treatment was performed for reasons of recurrent ischemia at rest or during exercise.

Table 1. Baseline characteristics of 224 patients of the LIM1 study stratified by reperfusion modality

	Thrombolysis PTCA		Rescue PTCA		Primary PTCA	
	N	[%]	N	[%]	N	[%]
Number of patients	75	[100]	74	[100]	75	[100]
Age (yr) mean $\pm$ SD	59	± 11	59	± 11	58	± 11
Anterior myocardial infarction	36	[48]	37	[50]	34	[45]
Inferior myocardial infarction	39	[52]	37	[50]	41	[55]
Men	56	[75]	57	[77]	54	[72]
Women	19	[25]	17	[23]	21	[28]
Previous myocardial infarction	13	[17]	15	[20]	9	[12]
Previous heart failure	0	[0]	1	[1]	0	[0]
Previous PTCA/CABG	3	[4]	2	[3]	1	[1]
Time pain-randomisation Mean min (SD)	125	± 85	140	± 70	130	± 75
Onset pain-Angiography Mean min (SD)	–		240	± 80	215	± 80

Table 2. Clinical course during one year follow up stratified by reperfusion modality

	Thrombolysis PTCA		Rescue PTCA		Primary PTCA	
	N	[%]	N	[%]	N	[%]
Number of patients	75	[100]	74	[100]	75	[100]
Deceased	6	[8]	7	[9]	9	[12]
Stroke	2	[3]	4	[5]	2	[3]
Recurrent AMI	9	[12]	5	[7]	4	[5]
Thrombolysis	7	[9]	1	[1]	2	[3]
Late PTCA/CABG	29	[39]	24	[32]	10	[13]

Table 3. Mean costs per patient after one year follow-up stratified by reperfusion modality in EURO

	Thrombolysis	Rescue PTCA	Primary PTCA	Unit Costs	Thrombolysis	Rescue PTCA	Primary PTCA
N	75	74	75				
<i>Initial treatment</i>							
Thrombolysis	75	74	2	900	900	900	24
Ambulance to PTCA center	0	73	73	450	0	444	438
CAG	0	71	72	700	0	672	672
PTCA	0	20	63	4000	0	1081	3360
Ambulance to non PTCA center	0	68	66	450	0	414	396
<i>Later treatment</i>							
Ambulance to PTCA center	17	0	0	450	102	0	0
CAG	15	1	1	700	140	9	9
Additional PTCA	12	11	3	3000	480	446	120
CABG	5	5	2	7000	467	473	187
Thrombolysis	1	1	1	900	12	12	12
<i>Admission</i>							
ICU (days)	9	10	4	1150	138	155	61
CCU (days)	241	320	344	700	2249	3027	3211
Ward (days)	614	627	455	225	1842	1906	1365
<i>Total costs index hospitalisation</i>							
					6330	9540	9855
<i>One-year follow Up</i>							
ICU (days)	13	8	8	1150	199	124	123
CCU (days)	22	16	16	700	205	151	149
Ward (days)	122	160	131	225	366	486	393
CAG	13	15	14	700	121	142	131
PTCA	5	4	1	3000	200	162	40
CABG	7	4	4	7000	653	378	373
Thrombolysis	6	0	1	900	72	0	12
Medication					557	540	585
<i>Follow up costs</i>							
					2374	1984	1806
<i>Total costs</i>							
					8704	11524	11661

Table 4. Effectiveness and cost effectiveness stratified by reperfusion modality in EURO

	Thrombolysis	Rescue PTCA	Primary PTCA
AP functional class 1	79.0%	76.0%	76.0%
AP functional class 2	9.0%	14.0%	12.0%
AP functional class 3-4	4.0%	0.0%	0.0%
Alive at 12 months	92.0%	90.5%	88.0%
No infarction	89.3%	93.2%	94.7%
No Stroke	97.3%	94.6%	97.3%
No CABG/PTCA	65.3%	70.3%	86.7%
Survival free of MI/Stroke	81.3%	81.1%	84.0%
Survival free of MI/Stroke/revascularisations	54.7%	58.1%	76.0%
Costs per MI/Stroke free survivor		-1,117,736	110,897
Costs per MI/Stroke/Revascularisation free survivor		81,928	13,862

In contrast to the protocol, acute transfer of patients to the PTCA center was withheld in 3 patients (1 rescue PTCA, 2 primary PTCA). In all but three patients transferred to the PTCA center acute coronary angiography was performed according to the protocol. In three patients (2 rescue PTCA, 1 primary PTCA), immediate angiography was logistically not possible, and at the time the catheterisation laboratory was ready, angiography was no longer considered useful because of the time delay and/or signs of reperfusion using non-invasive reperfusion criteria. Of the 74 patients assigned to the rescue PTCA group, an acute intervention was performed in 20 patients (27%). During the index hospitalisation another 11 patients (15%) in the rescue PTCA group underwent their angioplasty as a "second-step procedure".

Of the patients assigned to primary PTCA acute intervention was performed in 63 patients (84%). Due to the acute angioplasty, the amount of late revascularisation procedures during admission (3 patients (4%)) was significantly lower in the patient group randomized to primary PTCA compared to the other two strategies ($p=0.041$). The length of hospital stay was shortest for the patients allocated to primary PTCA.

COSTS

The results in terms of mean costs per patient are presented in the last three columns of table 3. The middle column presents the estimates of the unit costs in EUR currency. The costs are highest in both PTCA groups. These are related to the costs of the transport, the costs of thrombolysis, angiography and coronary angioplasty in

the rescue PTCA group and the costs of the initial coronary angiography and angioplasty in the primary PTCA group. The costs of the “thrombolysis only” strategy was significantly lower than the costs of the other two strategies ($p < 0.001$). However, during hospitalisation and during follow-up, part of the initial high costs of the primary PTCA group were compensated by a lower need for late revascularizations when compared to the other strategies.

EFFECTIVENESS

Table 4 presents the distribution of patients according to functional class at one year as well as survival, MI/Stroke free survival, and MACE-free survival. After one-year follow-up, there were no differences between thrombolysis and rescue PTCA in terms of MI/Stroke free survival; in both groups there were 15 patients with such an event. When revascularisations were included in the effectiveness measure there was a slight advantage of 4% for rescue PTCA, however this difference did not reach statistical significance.

When comparing primary PTCA with thrombolysis, a small non-significant advantage is found for primary PTCA in MI/stroke-free-survival and a significant advantage is found in terms of MACE-free-survival ($p = 0.021$). In terms of functional classes, again somewhat more favorable results are found for primary and rescue PTCA, the differences however not reaching statistical significance.

COST-EFFECTIVENESS RATIO AT ONE-YEAR FOLLOW-UP

Figure 1-4 show the results concerning the balance between costs and effects using two dimensional probability ellipses. In figure 1 and 2 the costs and effects are compared between rescue PTCA and thrombolysis, and in figure 3 and 4 between primary PTCA and thrombolysis. All results indicate that both rescue PTCA and primary PTCA are significantly more expensive than thrombolysis as all ellipses lie above the horizontal axis (of no difference in costs). The results with respect to MI/Stroke-free survival illustrate the lack of significant differences in effectiveness, both probability ellipses lie well over the vertical axes (of no difference in effects). A similar lack of statistical difference is seen when addressing the difference in MACE-free survival between rescue PTCA and thrombolysis. Here, the central cost effectiveness ratio is estimated at EUR 81,928. Only when comparing primary PTCA with thrombolysis an ellipse is found that is completely in the upper right quarter of the CE-plane. Here the central estimate of the additional costs per additional MACE free survivor is EUR 13,862 with an upper 95% limit of EUR 27,716.

Figure 1 to 4. Bivariate normal distribution of costs and effects using two dimensional probability ellipses. Differences in effects are depicted on the X-axis. Differences in costs are presented on the Y-axis. The C/E ratio is presented in the four separate figures. Outer ellipses define smallest area containing both costs and effects with 95% probability, middle ellipses define same area with 50% probability, inner ellipses with 5% probability.

Figure 1. compares the cost and effects between rescue PTCA and thrombolysis with respect to MI/Stroke free survival.

Figure 2. compares the cost and effects between rescue PTCA and thrombolysis with respect to MACE free survival.

Figure 3. compares the cost and effects between primary PTCA and thrombolysis with respect to MI/Stroke free survival.

Figure 4. compares the cost and effects between primary PTCA and thrombolysis with respect to MACE free survival.

DISCUSSION

The value of primary PTCA in comparison to thrombolytic therapy has been shown previously (3-7). De Boer et al. indicated that primary coronary angioplasty is effective with regard to mortality, morbidity, and functional status in patients with acute myocardial infarction. His cost-effectiveness study did not confirm the general concern that primary PTCA would be far more expensive than thrombolysis only (17). Also in the PAMI-trial the relative costs and effectiveness was determined for alteplase and primary PTCA in 395 patients. The authors concluded that reperfusion by primary PTCA compared with t-PA improved clinical outcome with similar or reduced costs (19). They proposed greater availability of primary PTCA in a cost-effective manner to patients presenting at hospitals without interventional facilities. Recently, the results of the Prague study with a comparable study design to our study, showed a significant better outcome for the combined outcome death, reinfarction or stroke in favour of primary PTCA ($p < 0.02$) (20).

A way to increase angioplasty availability to patients with acute myocardial infarction could be triage using ECG findings by the ambulance service with subsequent referral to regional angioplasty facilities minimizing treatment delay. Investing in new angioplasty facilities could be another option to increase wider availability of primary PTCA. Lieu et al. reported an analytic model comparing three policies: primary angioplasty, intravenous thrombolysis and no intervention (21). The authors concluded that primary PTCA performed in skilled high-volume centers with an existing cardiac catheterization laboratory would be cost-effective relative to other medical interventions. However, the procedure would be cost-ineffective at low volume or redundant laboratories (22). These findings favour regionalization of interventional facilities and transfer of patients to interventional facilities.

The LIM1 study was the first prospective randomised study to demonstrate the safety and feasibility of acute transport of patients with extensive acute myocardial infarction followed by a PTCA procedure (15). In contrast to other interventional studies, the patients in the LIM1 study had to be transported to a PTCA center and a treatment arm with rescue PTCA was included. All former studies more or less neglect the fact that the majority of patients with AMI are admitted to community hospitals where angioplasty facilities are not available. Only a minority of the hospitals are equipped with angioplasty facilities. In the United States 18% of the hospitals are able to perform angioplasty procedures on-site (23). In the Netherlands only 10% of hospitals are equipped with these facilities, mainly because of requirements concerning the numbers of procedures that a center needs to perform to guarantee a good quality level.

In a retrospective study, we previously demonstrated that early referral for intentional rescue PTCA after initiation of thrombolytic therapy in patients admitted to a community hospital because of a large acute myocardial infarction is feasible and safe and can be done within therapeutically acceptable time limits (24). Zijlstra et al. also

have retrospectively demonstrated safety and feasibility of such an approach with primary PTCA (25). Just recently, Schaumann et al showed the same in an observational study for primary PTCA in patients with high risk myocardial infarction (26). The option of rescue PTCA was included in the LIMI study after a retrospective analysis by Bär et al. showed that the angiographic and clinical outcome is similar in a large series of patients treated with early rescue PTCA or primary PTCA (12,14). Additionally, the administration of a thrombolytic agent before patient transfer may lead to reperfusion and abolish the need for acute angiography and subsequent rescue PTCA, thereby diminishing initial costs. Note that, the design of the LIMI study dictated acute coronary angiography in both PTCA groups. Previous studies indicate that acute coronary angiography may not be necessary in patients having non-invasive signs of reperfusion (24,27). Indeed, in the LIMI study we found a difference of 57% in initial angioplasty when rescue PTCA is indicated, in comparison to the strategy of primary PTCA. However, late PTCA in the rescue PTCA group (the majority was performed during the admission for the index myocardial infarction), was needed in 20% (especially in those who had no initial intervention). The paradoxical procoagulant effect of thrombolytic therapy and or persistence of the stenosis are probably responsible for this phenomenon (28,29).

The results, presented here, indicate better clinical outcome after PTCA. However, the only difference that reached statistical significance concerned the comparison between primary PTCA and thrombolysis and only in terms of MACE free survival. In our study, a later PTCA procedure was part of the MACE analysis. One should note that patients with primary PTCA had already an acute PTCA procedure, which was not counted as a major adverse cardiac outcome. This fully explains the differences in the analysis of MACE free survival between the treatment groups. With the limited number of observations one has to conclude that there is insufficient evidence to support large-scale transportation of patients to specialized PTCA centers. When considering the point estimates, and disregarding the uncertainties one might come to the conclusion that the benefits may not outweigh the costs. It was estimated that the additional costs per additional MACE free survivor are respectively EUR 81,928 and EUR 13,862 for rescue PTCA and primary PTCA. This figure of EUR 81,928 and 13,862 for rescue PTCA and primary PTCA respectively per additional MACE free survivor may be on or beyond the border of what is acceptable. Whether or not this is acceptable, is an economical and political issue.

Results presented here and the results of primary PTCA without transfer to a specialized center might create a more positive attitude towards creating more PTCA centers. However, one should realize that such a center is only sufficiently qualified if a certain caseload can be guaranteed. Although the incidence of myocardial infarction is high, it is clear even after regionalisation, that only a limited number of hospitals will meet these requirements. Costs per PTCA may increase considerably when PTCA procedures are performed in centers with a sub-optimal number of proce-

dures. The indirect costs for a 24-hour service have not been taken into account in our study. The lower the patient-load for rescue PTCA and primary PTCA, the higher the cost per patient. This again may change the balance between costs and effects in a less favourable way for PTCA.

Our study was conducted in a high volume PTCA center (800 PTCA procedures yearly, on 24-hour basis) in an urbanised area. The ambulance services were well acquainted with the procedures. Logistically it is a burden for the ambulance service, the interventionalists and their personnel to offer a 24-hour service for acute angioplasty for all patients with myocardial infarction in their region. Therefore it was decided to treat only patients with an electrocardiographically extensive infarction in this trial which was approximately 20% of all acute myocardial infarctions. Conclusions that can be drawn from this study only apply for the subset of patients with an electrocardiographic extensive myocardial infarction. They cannot be transferred to patients with small myocardial infarction, low-volume centers, longer travel distances or other countries with different circumstances in health care. Adequate assessment of indirect costs was not possible. The contribution of these costs will most certainly influence the conclusions from this study.

CONCLUSIONS

Acute transfer for rescue PTCA or primary PTCA in selected patients with electrocardiographic extensive myocardial infarction is feasible and safe. The data from the present analysis in a limited number of patients suggest that transfer to a PTCA center may improve clinical outcome and decrease late interventions but in contrast to findings of others at significant costs as compared to thrombolytic therapy only. When considering one-year MACE free survival as the outcome of interest, the cost-effectiveness ratio of treatment of patients with extensive acute myocardial infarction initially admitted to hospitals without angioplasty facilities is in favour of transfer for primary PTCA. These differences can be explained by the non-acute PTCA procedures in the thrombolysis group and the rescue PTCA group. In case these late PTCA procedures are seen as part of the strategy, thrombolysis only is by far the most cost-effective therapy.

The efficacy of transfer for rescue or primary PTCA has to be tested in larger randomized series. The results of these trials have to be awaited before transfer of patients in the acute phase to a PTCA center for acute intervention can be implemented as a "routine and cost-effective therapy" for patients with extensive myocardial infarction initially admitted to hospitals without angioplasty facilities.

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Summary and conclusions

Chapter 1

Introduction

The aim of the investigations, described in this thesis is to contribute to optimal treatment of patients who are admitted to community hospitals without angioplasty facilities. At present, two reperfusion techniques have proven their efficacy in the treatment of acute myocardial infarction; the administration of fibrinolytic agents and coronary angioplasty. The questions to be answered in this thesis were threefold. The first important question was whether the angiographic and clinical outcome differ between rescue and primary PTCA? Secondly, can noninvasive parameters of reperfusion help us in selecting patients for acute coronary angiography and subsequent coronary angioplasty?

Thirdly, most patients with acute myocardial infarction are initially admitted to community hospitals without direct access to angioplasty facilities. Can patients who are admitted to a center without PTCA facilities benefit from early transfer to a PTCA center for rescue angioplasty or primary angioplasty and can this be performed with a favourable relation between cost and effectiveness?

Chapter 2

Hystoric overview

In the eighties, a great deal of clinical research was directed towards safety and efficacy of thrombolytic agents in the treatment of acute myocardial infarction. The first steps were taken to perform early coronary angiography in acute myocardial infarction. The vast majority of the infarct related vessels showed to be occluded when coronary angiography was performed within 4 hours of symptom onset. At the same time, Hartzler was the first to introduce a mechanical approach to open occluded coronary vessels through coronary angioplasty. It lasted till the early nineties before coronary angioplasty in acute myocardial infarction was used widely. Early studies showed that immediate PTCA after thrombolysis, irrespective of the status of coronary reperfusion, was not beneficial. The results of rescue PTCA: coronary angioplasty after failed thrombolysis, were equivocal. However, primary PTCA showed to be a favourable treatment under ideal circumstances with respect to immediate and longterm outcome.

In the mid-nineties an explosive growth in the use of intracoronary stents was observed. Use of intracoronary stents together with antiplatelet therapy appeared to

be effective in the treatment of acute myocardial infarction especially with respect to the number of re-interventions. Mortality is not influenced.

Throughout the relative short history in the development of very effective tools in the treatment of acute myocardial infarction, it seemed to be forgotten that access to angioplasty facilities in the real-life situation is limited. Thus, the excellent results of mechanical intervention only account for those patients who are directly admitted to a hospital with angioplasty facilities. Only a few reports directed attention towards the possibility of transportation of patients with acute myocardial infarction to an angioplasty center for emergency angioplasty. The scarcity and the retrospective nature of these reports were the incentive for the theme of this thesis:

“Strategies of coronary reperfusion in acute myocardial infarction for patients admitted to hospitals without angioplasty facilities”.

Chapter 3

The angiographic and clinical outcome of rescue and primary PTCA is similar

Patency of the infarct related artery improves the prognosis of patients with myocardial infarction. Previous studies have shown that primary PTCA was more effective than thrombolysis alone. How effective is rescue PTCA after failed thrombolysis? A retrospective analysis was performed in 176 consecutive patients suffering from acute myocardial infarction with documented TIMI 0-1 flow during angiography. These patients underwent either rescue PTCA after failed thrombolysis (n=100) or primary PTCA (n=76). The angiographic outcome was similar; success could be obtained in 86% and 85.5% respectively. The clinical outcome in terms of mortality (4% versus 6.6%), reinfarction (6% versus 3.9%), and repeat interventions were comparable. This study confirmed that failed emergency PTCA was the most important predictor of mortality. Successful PTCA led to a one-year mortality of 4.6% versus 28% mortality for failed PTCA. It was concluded that the clinical and angiographic outcome of patients with rescue PTCA because of failed thrombolysis is good and comparable to patients who underwent primary PTCA.

Chapter 4

Early transfer for intentional rescue angioplasty

For patients admitted with acute myocardial infarction in a community hospital without angioplasty facilities, thrombolytic treatment is the treatment of choice. In this chapter the question was raised whether patients with acute myocardial infarction initially admitted to a community hospital can benefit from early transfer for intentional rescue PTCA after the administration of a thrombolytic agent. This study was performed in collaboration with the community hospital of Sittard, located approximately 35 kilometers from the angioplasty center. Transport of patients with ongoing myocardial infarction appeared to be safe and feasible, only 1 of the 165

transferred patients died and 9% suffered haemodynamic or arrhythmia problems during transport. The median time delay between onset of chest pain and arrival at the catheterisation laboratory was 187 minutes.

In this chapter also the use of non-invasive markers of reperfusion was introduced. Forty percent of the patients in this study were non-invasively identified to have successful reperfusion and acute coronary angiography was withheld. The patients identified as such appeared to have 0% in-hospital mortality versus 7% for the group with angiographic reperfusion and 11% for the group with rescue PTCA $p < 0.05$. However, re-infarction rate was highest in the group with non-invasively determined reperfusion. It was concluded that early transfer after treatment with a thrombolytic agent from a community hospital to a PTCA center for intentional rescue PTCA is safe with respect to complications during transport and that it can be done within therapeutically acceptable time limits. An additional 33% of patients could benefit from early reperfusion through rescue PTCA. Non-invasive reperfusion criteria allowed the recognition of patients with an excellent outcome in terms of mortality and is useful to reduce the workload of an angioplasty center. This was prospectively studied in the next chapter.

Chapter 5

Can myocardial reperfusion be diagnosed non-invasively?

A simple and reliable non-invasive method to identify patients with successful reperfusion is lacking. In this chapter we prospectively investigated the value of seven non-invasive reperfusion parameters. Previous studies have shown that immediate angioplasty, of open vessels is not beneficial. If reperfusion could be demonstrated through the use of these markers, acute coronary angiography for subsequent angioplasty is not necessary. In the community hospital situation without angioplasty facilities, the consideration to transport a patient with acute myocardial infarction to an angioplasty center for emergency angioplasty could be guided by these non-invasive reperfusion markers. Also the recipient angioplasty center can re-evaluate the perfusion status of the patient and refrain from acute coronary angiography if reperfusion is suspected. In an angiographically controlled study in 230 patients it appeared that TIMI 2-3 flow could be discriminated from TIMI 0-1 flow with good accuracy. In contrast, TIMI 3 flow could not reliably be discriminated from TIMI 2 flow. Depending on local circumstances the goal of acceptable reperfusion (TIMI 2-3 or TIMI 3 flow) might differ. The reperfusion parameters should be used accordingly.

Chapter 6

The LIMi protocol

Chapter 4 was the basis for a prospective multicenter randomised study addressing the question whether it is safe, feasible, and effective to transfer patients with an acute myocardial infarction to an angioplasty center for either rescue PTCA or primary PTCA.

Chapter 6 delineates the protocol of the Limburg Myocardial Infarction (LIMI) study. The aim of this prospective multicenter randomized pilot study was to evaluate prospectively the safety of transportation and feasibility of interventions in patients with extensive acute myocardial infarction referred for primary or rescue PTCA in case of failed thrombolysis. Three therapeutic regimens in the treatment of acute myocardial infarction in patients initially admitted to community hospitals without angioplasty facilities were evaluated: thrombolytic therapy, thrombolytic therapy followed by acute coronary angiography and rescue PTCA if indicated and primary PTCA. As secondary endpoints, clinical outcome and cost evaluations were planned.

Chapter 7

Acute transport for rescue PTCA or primary PTCA in patients with extensive myocardial infarction is feasible and safe

The benefits of primary angioplasty and some what equivocal those of rescue angioplasty have been demonstrated in the treatment of acute myocardial infarction. However, the promising results of the published papers on this subject accounted only for patients directly admitted to an angioplasty center. In most countries access to angioplasty is limited, for example in the Netherlands only 10% of hospitals do indeed have in-house angioplasty facilities. For this reason a prospective randomized multicenter pilot study was started comparing thrombolysis ($n=75$), thrombolysis with acute coronary angiography and (if indicated) rescue PTCA ($n=74$) and primary PTCA ($n=75$) in patients who were admitted with extensive myocardial infarction in one of the five community hospitals without angioplasty facilities in the province of Limburg, the Netherlands. None of the patients who were transferred for angioplasty died during transport. The time delays for rescue PTCA and primary PTCA were 240 ± 80 minutes and 215 ± 80 minutes respectively. There were no significant differences in the early (42 days) and one-year clinical outcome variables. The PTCA center was able to handle the additional patient load. One-year mortality was 8% in the thrombolysis group, 9% in the rescue PTCA group and 12% in the primary PTCA group. As expected, patients allocated to primary PTCA had the highest TIMI 3 flow rate and less late reinterventions than the other 2 groups. The limited number of patients, however, did not allow us to make conclusions in terms of efficacy.

It was concluded that in patients with extensive myocardial infarction acute transfer for rescue PTCA or primary PTCA is feasible and safe. The efficacy of these reperfusion strategies must be tested in a larger series of patients.

Chapter 8

Transfer for acute PTCA; Cost effectiveness ratio in favor of primary PTCA

In order to adapt new strategies of treatment in clinical practice, cost effectiveness is becoming more and more important to convince policy makers to either adapt the proposed treatment or to provide physicians with appropriate funding. From the LIMI trial as described in chapter 6 and 7 we learned that acute transfer for either rescue or primary PTCA is safe and feasible. In this study the cost for hospital admission procedures and medication were estimated by multiplying volumes with estimates of unit cost. After one-year follow-up the cost per patient for thrombolysis, rescue PTCA or primary PTCA were respectively EUR 8,704, EUR 11,524 and EUR 11,661 ($p < 0.001$). The efficiency of both invasive strategies for the treatment of acute myocardial infarction in patients initially admitted in hospitals without angioplasty facilities can be addressed by putting forward the incremental costs per event-free survivor. The clinical results presented in this study indicate better outcome after PTCA. However, the additional costs per additional MACE free survivor in comparison to treatment with thrombolysis was EUR 81,928 for rescue PTCA and EUR 13,682 in favour of primary PTCA. The acceptability of these considerable costs are subject to political debate. The data of this study suggest better clinical outcome after PTCA but at significant cost. The results of larger randomized trials are necessary before transfer of patients in the acute phase of extensive acute myocardial infarction for rescue PTCA or primary PTCA can be implemented as routine and cost-effective therapy.

Conclusions

1. The clinical and angiographic outcome for patients with acute myocardial infarction with angiographically proven inadequate coronary flow is similar for early rescue PTCA and primary PTCA.
2. Reperfusion parameters are of help in identifying patients with acute myocardial infarction with open coronary arteries in which subsequent angioplasty is not necessary. TIMI 3 flow cannot reliably be discriminated from TIMI 2 flow. However, the prognosis of patients with acute myocardial infarction with positive criteria of reperfusion is excellent
3. Acute transfer of patients with extensive acute myocardial infarction from a hospital without angioplasty facilities to a hospital with angioplasty facilities is safe and at least in our setting feasible and can be done in a therapeutically acceptable time window. Transferring patients to a PTCA center may improve clinical

outcome but at significant cost. The additional cost per additional MACE free survivor in comparison to thrombolytic treatment seems most favourable for primary PTCA. The treatment with "thrombolysis only" remains the best alternative in an environment of limited resources.

Where to go from here?

Every answer to a question raises new questions. In other words every thesis is the kick-off for the next one. Reperfusion strategies in acute myocardial infarction are in a continuous flux. The "optimal" treatment is guided by the resultant of continuous forces between the development of new techniques, local circumstances and health care budgets. Depending on the preference, capabilities and facilities of physicians, a certain strategy will be followed. At this moment it is assumed by many cardiologists that the clinical outcome in patients who are transferred for either rescue or primary PTCA is in favour of primary PTCA. Does this imply that every patient with an acute myocardial infarction should be transported to an angioplasty center for primary PTCA? In the Netherlands approximately 27,000 patients are admitted yearly with the diagnosis of myocardial infarction. Assuming that in 40% the electrocardiogram is not diagnostic for acute myocardial infarction, at least the remaining 60% of patients (approximately 16,000) are candidates for some sort of reperfusion treatment. In the Netherlands, approximately 10%-15% of these patients are immediately admitted to hospitals with an existing infrastructure for interventional cardiology where primary coronary angioplasty can be considered. The remaining patients (approximately 14,000) will be admitted to hospitals without angioplasty facilities. If indications would extend to transfer all these patients for primary PTCA an enormous logistic burden for the angioplasty centers will be the consequence. In the LIM1 trial, transfer of patients was limited to patients with electrocardiographic evidence of extensive myocardial infarction. Assuming that 20% of the patients will meet these criteria, approximately 2800 patients are candidates for transfer for primary PTCA. For the situation in the Netherlands, where 13 hospitals do have an interventional infrastructure, this means an additional caseload of approximately 210 emergency angioplasties for each center yearly. Are we willing to match this increase in caseload, or should we decrease the number of interventions by pre-transportation thrombolytic therapy? If this strategy is to be followed it will take off the steam of logistically difficult emergency angioplasties since reperfusion during transportation will limit the number of acute angioplasties with approximately 60%. The price to pay is a considerable number of late PTCA/CABG in this patient group. The third option is to accept that thrombolytic therapy is reasonably effective making it not worthwhile to transport the patient to a PTCA center. Also in the patients with open vessels after thrombolysis a considerable group of patients needs late interventions, but this can potentially be managed in a logistically more efficient way.

Implications for emergency PTCA

In order to implement around the clock angioplasty services, sufficient staff and facilities are needed. With an increasing workload of emergency angioplasty, it is required to train a sufficient amount of physicians with an interventional subspecialisation. Similarly, appropriate numbers of nursing staff, cardiac technicians and facilities are needed. Additional catheterisation rooms are necessary as well as hospital beds and CCU beds to receive an additional caseload of very ill patients who require a high level of care. Some patients may need ventilation, intra aortic balloon pumping or emergency CABG requiring support of an experienced and cooperative surgical team and a high quality nursing staff. Transferring patients with acute myocardial infarction requires a well-motivated ambulance service that can be responsible for safe and rapid interhospital transfer. Central ambulance units must have adequate capacity and staff to transfer critically ill patients prepared for full life support. More importantly is the establishment of protocols and guidelines for hospitals without angioplasty facilities who refer patients for emergency angioplasty. Protocols enhance the recognition of the appropriate patient in an efficient way thereby minimising time delays. Also protocols for the follow-up care in the hospitals without angioplasty facilities should be established especially in respect to sheath removal and the increasing use of drugs intervening with coagulation.

Where should infarct angioplasty be performed

If infarct angioplasty is limited to the current tertiary angioplasty centers, sufficient ambulance services are needed for rapid, safe and swift transfer to these centers. It has been shown that regionalization of angioplasty facilities is cost-effective in high volume centers. Infarct angioplasty is not easy, therefore transfer of infarct patients to a regional tertiary center implies an appropriate caseload of emergency angioplasty per individual operator thereby increasing chances of good outcome.

Another option is to provide around the clock angioplasty in every district hospital. Such a development is not likely to succeed because of the high costs in capital goods and human resources.

However, in areas where prehospital thrombolysis is implemented it would be interesting to triage patients with extensive myocardial infarction immediately to hospitals with angioplasty facilities with or without pre-transportation thrombolysis in order to reduce the time to reperfusion even further. Studies addressing this issue are currently being performed.

The results of a large multicenter trial are required before transfer of patients with extensive myocardial infarction in the acute phase to a PTCA center can be implemented as routine therapy. At this moment studies are ongoing trying to answer this important question.

Samenvatting en conclusies

Hoofdstuk 1

Introductie

Dit proefschrift heeft tot doel een bijdrage te leveren aan de verbetering van het inzicht in de behandeling van patiënten die initieel worden opgenomen in een ziekenhuis zonder mogelijkheden voor een percutane transluminale coronairangioplastiek (PTCA) ofwel dotterprocedure. Heden ten dage zijn er bij de behandeling van het acute hartinfarct twee technieken beschikbaar die kunnen leiden tot het opnieuw doorgankelijk maken van de geocludeerde kransslagader. De toediening van een stolseloplossend geneesmiddel of het verrichten van PTCA. Het merendeel van de patiënten met een acuut myocardinfarct wordt opgenomen in ziekenhuizen zonder PTCA faciliteiten. Derhalve werd in dit proefschrift tot doel gesteld een antwoord te geven op een drietal vragen. Allereerst werd onderzocht of dat de klinische en angiografische uitkomsten van rescue PTCA (dotterprocedure na het falen van een stolseloplossend middel) en primaire PTCA (dotterprocedure bij een geocludeerde kransslagader zonder voorbehandeling met een stolseloplossend middel) vergelijkbaar waren. Op de tweede plaats werd nagegaan of non-invasieve parameters waarmee we zonder hartcatheterisatie reperfusie (herstel van doorbloeding) kunnen aantonen van nut zouden kunnen zijn om patiënten met reperfusie te identificeren zodanig dat acute coronair angiografie gevolgd door eventuele PTCA niet nodig is. Op de derde plaats werd de vraag gesteld of het gunstig is, om patiënten met een uitgebreid myocardinfarct vroegtijdig te verwijzen naar een PTCA centrum voor een acute PTCA procedure al dan niet voorafgegaan door de behandeling met een stolseloplossend geneesmiddel. Tevens werd onderzocht of de cost-effect analyse van een dergelijke reperfusiestrategie acceptabel was.

Hoofdstuk 2

Historisch overzicht

In de jaren tachtig was een aanzienlijk deel van klinisch onderzoek gericht op de veiligheid en effectiviteit van stolseloplossende geneesmiddelen bij de behandeling van het acute myocardinfarct. Schoorvoetend werden er acute hartcatheterisaties verricht bij het acute myocardinfarct waarbij werd aangetoond dat het merendeel van de kransslagvaten waren afgesloten wanneer de hartcatheterisatie binnen 4 uur na de aanvang van de klachten werd verricht. De vroege jaren tachtig luidde dan ook het begin in van onderzoeken naar de waarde van PTCA, om het afgesloten kransslagvat te openen. Het heeft echter 10 jaar geduurd alvorens deze techniek bij het

myocardinfarct tot volle volwassendom is gekomen en een ruime toepassing ontstond. Enkele studies toonden aan, dat de stelselmatige toepassing van de PTCA techniek ongeacht de mate van doorbloeding van het infarctgerelateerde kransslagvat weinig zinvol was. De resultaten van rescue PTCA, waren niet eensluidend. Het bleek dat primaire PTCA, angioplastiek van het infarctgerelateerde coronairvat zonder voorbehandeling met een stolseloplossend geneesmiddel, onder ideale situaties leidt tot uitstekende resultaten zowel op korte als wel langere termijn, vergeleken met de behandeling met een stolseloplossend geneesmiddel. De midden jaren negentig werden gekenmerkt door een explosieve groei van het gebruik van intracoronaire stents (ijzeren veertje). Het gebruik van deze stents met gelijktijdig gebruik van plaatjesremmers bleek effectief bij de behandeling van het acute myocardinfarct, met name ten aanzien van het aantal re-interventies. Het gebruik van stents bij het acute infarct had geen invloed op de mortaliteit.

Gedurende de in feite korte tijdspanne waarin een aantal zeer effectief gebleken behandelingsstrategieën zich ontwikkelden werd vergeten dat de zeer bemoedigende resultaten voornamelijk van toepassing waren op patiënten die rechtstreeks in de ziekenhuizen met PTCA faciliteiten worden opgenomen. Het overgrote deel van de patiënten, wordt echter opgenomen in ziekenhuizen zonder PTCA faciliteiten. Er is slechts schaars onderzoek gedaan naar de mogelijkheid van transport van deze patiënten naar een PTCA centrum voor acute PTCA. Deze schaarste aan veelal retrospectieve data stond aan de wieg van dit proefschrift met als titel "Strategies of coronary reperfusion in acute myocardial infarction for patients admitted to hospitals without angioplasty facilities".

Hoofdstuk 3

De klinische en angiografische uitkomst van rescue en primaire PTCA is vergelijkbaar

De prognose van de patiënt met een acuut myocardinfarct wordt bepaald door de doorgängelijkheid van de infarctgerelateerde kransslagader. Enkele studies hebben laten zien dat primaire PTCA effectiever is, dan alleen de toediening van een stolseloplossend geneesmiddel. Hoe effectief is rescue PTCA vroeg na het falen van een dergelijke therapie in vergelijking met primaire PTCA? In een retrospectieve studie in 176 opeenvolgende patiënten met een hartinfarct en tijdens hartcatheterisatie bevestigde, slechte of zelfs afwezige doorbloeding van het kransslagvat (TIMI 0-1 flow) werden de resultaten vergeleken tussen patiënten behandeld middels rescue PTCA na thrombolysen ($n=100$) en patiënten behandeld middels primaire PTCA ($n=76$). Bij een PTCA procedure wordt succes gedefinieerd indien er een normale doorstroming van het kransslagvat is (TIMI 3 flow) en de restvernauwing minder is dan 50%. Deze was vergelijkbaar bij beide therapievormen, respectievelijk 86% en 85,5%. Mortaliteit (4% versus 6,6%), reinfarct (6% versus 3,9%) en re-interventies waren eveneens vergelijkbaar. Indien de PTCA procedure echter faalde, bleek de

mortaliteit sterk toe te nemen. De mortaliteit bedroeg 28% bij een mislukte PTCA procedure versus 4,6% na een geslaagde procedure. De uitkomsten van deze studie suggereren vergelijkbare klinische en angiografische resultaten bij patiënten die worden behandeld middels rescue of primaire PTCA.

Hoofdstuk 4

Vroege overplaatsing naar een PTCA centrum voor eventuele rescue PTCA

Voor patiënten met een hartinfarct die worden opgenomen in een ziekenhuis zonder PTCA faciliteiten is behandeling met een stolseloplossend geneesmiddel de behandeling van eerste keus. Bij het ontbreken van tekenen van herstel van doorbloeding (reperfusie) kan rescue PTCA overwogen worden. In dit hoofdstuk is de vraag aan de orde gekomen of het zinnig is om patiënten met een uitgebreid myocardiinfarct na behandeling met thrombolyse over te plaatsen naar een PTCA centrum voor eventuele rescue PTCA in de acute fase van het myocardiinfarct.

Deze studie heeft plaatsgevonden in samenwerking met het Maasland Ziekenhuis in Sittard gelegen op ongeveer 32 kilometer afstand van het Academisch Ziekenhuis Maastricht. Tijdens het transport waren de complicaties relatief laag (9%), terwijl 1 patiënt overleed bij aanvang van het transport. De tijd die nodig was tussen het begin van de klachten en aankomst op het catheterisatielaboratorium bedroeg mediaan 187 minuten.

In dit hoofdstuk werd tevens het gebruik geïntroduceerd van enkele niet invasieve criteria, voor het herstel van doorbloeding van het kransslagvat. Middels toepassing van deze criteria werd bij 40% van de patiënten dit herstel, op niet-invasieve wijze aannemelijk gemaakt. Hierdoor kon worden afgezien van acute hartcatheterisatie of PTCA procedure. Deze patiënten werden veelal met dezelfde ambulance terugverwezen naar het verwijzend centrum. Ze hadden in vergelijking tot de patiëntengroep waarbij de criteria onduidelijk waren, maar die bij hartcatheterisatie toch herstel van doorbloeding hadden en de patiëntengroep met rescue PTCA, een gunstige prognose; de mortaliteit was 0% versus 7% en 11% bij patiënten waar alsnog gedotterd moest worden wegens een afgesloten kransslagader ($p < 0,05$). Echter het aantal recidief infarcten was zoals verwacht het hoogst in deze groep. Concluderend kan worden gesteld dat vroege verwijzing voor eventuele rescue PTCA na behandeling met een stolseloplossend geneesmiddel in een ziekenhuis zonder PTCA faciliteiten veilig is en een haalbare therapie blijkt binnen een therapeutisch acceptabel tijdsbestek. Dankzij deze behandelingsstrategie kon toch nog in 33% van de patiënten vroeg herstel van doorbloeding worden bereikt middels rescue PTCA. Het gebruik van niet-invasieve criteria voor herstel van doorbloeding maakte het mogelijk een patiëntengroep te identificeren met een uitstekende prognose waarbij acute hartcatheterisatie niet noodzakelijk was. In de praktijk kan dit leiden tot een aanzienlijke reductie voor de werklust van het PTCA centrum. Dit werd prospectief onderzocht in het volgende hoofdstuk.

Hoofdstuk 5

Kan myocardreperfusie noninvasief worden vastgesteld?

Een simpele en betrouwbare methode voor de identificatie van patiënten met een geslaagd herstel van de doorbloeding (reperfusie) is nog niet geheel voorhanden. In dit hoofdstuk wordt onderzocht wat de individuele en gecombineerde waarde is van 7 niet-invasieve criteria voor reperfusie, samengesteld uit ECG gegevens en de klachten van de patiënt. Uit eerder onderzoek is gebleken dat het verrichten van een PTCA procedure bij een open kransslagvat na een voorbehandeling met een stolseloplossend geneesmiddel bij geslaagde reperfusie weinig zinvol is. Acute hartcatheterisatie is vermijdbaar indien herstel van doorbloeding door niet-invasieve criteria kan worden aangetoond. In ziekenhuizen zonder PTCA faciliteiten zou het besluit omtrent eventuele overplaatsing voor bijvoorbeeld rescue PTCA op grond van deze criteria kunnen worden genomen. Ook het ontvangend PTCA centrum kan nadat er door het transport tijd over heen is gegaan, nogmaals de patiënt evalueren op herstel van doorbloeding en zo nodig afzien van acute hartcatheterisatie. Uit middels hartcatheterisatie gecontroleerd onderzoek bij 230 patiënten bleek dat patiënten met trage doorbloeding (TIMI 2 flow) of normale doorbloeding (TIMI 3 flow) van het infarctgerelateerde kransslagvat goed kon worden onderscheiden van patiënten met geen of geringe doorbloeding (respectievelijk TIMI 0-1 flow). Echter TIMI 3 flow kan niet met grote betrouwbaarheid worden onderscheiden van TIMI 2 flow. Het accepteren van redelijke maar niet perfecte doorbloeding hangt af van lokale inzichten en mogelijkheden. Afhankelijk hiervan, kunnen de niet-invasieve criteria voor reperfusie al dan niet worden toegepast.

Hoofdstuk 6

De LIM1 trial

Het retrospectieve onderzoek zoals beschreven in hoofdstuk 4 heeft de aanzet gegeven tot een prospectieve gerandomiseerde multicenter studie met de vraagstelling of het veilig en haalbaar is om patiënten met een uitgebreid acuut hartinfarct te verwijzen naar een PTCA centrum voor rescue PTCA of primaire PTCA.

Hoofdstuk 6 beschrijft het protocol van de Limburg Myocard Infarct (LIMI) trial. Deze studie heeft ten doel om drie handelingsstrategieën te evalueren voor de behandeling van een groot acuut hartinfarct bij patiënten die initieel worden opgenomen in ziekenhuizen zonder PTCA faciliteiten. In deze pilot studie worden patiënten prospectief gerandomiseerd tot een behandeling met een stolseloplossend geneesmiddel, tot behandeling met stolseloplossende medicatie en rescue PTCA indien noodzakelijk, of tot primaire PTCA. In deze studie is prospectief nagegaan of het vervoer vanuit niet-PTCA centra naar het Academisch Ziekenhuis Maastricht haalbaar en veilig was. Tevens is gekeken naar de effectiviteit en de kosten van de verschillende benaderingen.

Hoofdstuk 7

Acute overplaatsing voor rescue of primaire PTCA van patiënten met een uitgebreid myocardinfarct is veilig en haalbaar

Van de behandeling van het acute hartinfarct zijn in de literatuur gunstige resultaten beschreven van primaire PTCA, minder duidelijk is dit voor rescue PTCA. Echter, deze resultaten zijn in feite alleen van toepassing voor patiënten die rechtstreeks worden opgenomen in een ziekenhuis met PTCA faciliteiten. In de meeste westerse landen is de beschikbaarheid van PTCA faciliteiten beperkt. In Nederland beschikt slechts 10% van de ziekenhuizen over dergelijke faciliteiten. Dit was de reden voor het starten van het prospectief gerandomiseerd multicenter Limburg Myocardial Infarction onderzoek waarbij thrombolysie (stolseloplossend middel) zonder transport naar een dottercentrum ($n=75$) wordt vergeleken met thrombolysie met transport naar een dottercentrum voor rescue PTCA ($n=74$) en transport naar een dottercentrum voor primaire PTCA ($n=75$). Het betreft patiënten die werden opgenomen met een uitgebreid acuut hartinfarct in een van de 5 deelnemende ziekenhuizen zonder PTCA faciliteiten in de provincie Limburg. Geen van de patiënten overleed tijdens het transport. De tijd (gemiddeld) tussen het begin van de klachten en hartcatheterisatie bedroeg in de rescue PTCA groep 240 ± 80 minuten, en 215 ± 80 minuten in de primaire PTCA groep. Er werden geen significante verschillen gevonden in morbiditeit en mortaliteit tussen de 3 groepen gedurende de eerste 42 en na 1 jaar follow-up. De mortaliteit na een jaar was 8% in de groep die werd behandeld met een stolseloplossend geneesmiddel, 9% in de patiëntengroep met rescue PTCA en 12% in de groep met primaire PTCA. De één-jaars morbiditeit en mortaliteit was relatief laag in deze patiëntengroep met behandeling voor een uitgebreid myocardinfarct. De patiënten die werden behandeld middels primaire PTCA hadden gemiddeld al vroeg een betere doorbloeding van het kransslagvat en vertoonden daarom ook minder noodzaak tot latere interventies. Concluderend blijkt de behandeling middels rescue of primaire PTCA bij patiënten met een uitgebreid myocardinfarct na acuut transport goed uitvoerbaar en veilig. De omvang van deze studie was te klein om een ferme uitspraak te doen over de effectiviteit. Een grote multicenter studie is noodzakelijk om deze vraag te beantwoorden.

Hoofdstuk 8

Overplaatsing voor acute PTCA. Cost-effectiveness ratio meest gunstig voor primaire PTCA

Voor het implementeren van nieuwe behandelingsmethodieken en het verkrijgen van steun voor wetenschappelijk onderzoek zijn kosten-effectiviteit analyses van toenemend belang. Van de LIMI studie weten wij (hoofdstuk 7) dat overplaatsing voor rescue en primaire PTCA veilig en haalbaar is. In deze studie werden prospectief gegevens verzameld en werden de kosten voor opname, onderzoeken en medi-

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Hoofdstuk 8

Overplaatsing voor acute PTCA. Cost-effectiveness ratio meest gunstig voor primaire PTCA

Voor het implementeren van nieuwe behandelingsmethodieken en het verkrijgen van steun voor wetenschappelijk onderzoek zijn kosten-effectiviteits analyses van toenemend belang. Van de LIM1 studie weten wij (hoofdstuk 7) dat overplaatsing voor rescue en primaire PTCA veilig en haalbaar is. In deze studie werden prospectief gegevens verzameld en werden de kosten voor opname, onderzoeken en medi-

Hoofdstuk 5

Kan myocardeperfusie noninvasief worden vastgesteld?

Een simpele en betrouwbare methode voor de identificatie van patiënten met een geslaagd herstel van de doorbloeding (reperfusie) is nog niet geheel voorhanden. In dit hoofdstuk wordt onderzocht wat de individuele en gecombineerde waarde is van 7 niet-invasieve criteria voor reperfusie, samengesteld uit ECG gegevens en de klachten van de patiënt. Uit eerder onderzoek is gebleken dat het verrichten van een PTCA procedure bij een open kransslagvat na een voorbehandeling met een stolseloplossend geneesmiddel bij geslaagde reperfusie weinig zinvol is. Acute hartcatheterisatie is vermijdbaar indien herstel van doorbloeding door niet-invasieve criteria kan worden aangetoond. In ziekenhuizen zonder PTCA faciliteiten zou het besluit omtrent eventuele overplaatsing voor bijvoorbeeld rescue PTCA op grond van deze criteria kunnen worden genomen. Ook het ontvangend PTCA centrum kan nadat er door het transport tijd over heen is gegaan, nogmaals de patiënt evalueren op herstel van doorbloeding en zo nodig afzien van acute hartcatheterisatie. Uit middels hartcatheterisatie gecontroleerd onderzoek bij 230 patiënten bleek dat patiënten met trage doorbloeding (TIMI 2 flow) of normale doorbloeding (TIMI 3 flow) van het infarctgerelateerde kransslagvat goed kon worden onderscheiden van patiënten met geen of geringe doorbloeding (respectievelijk TIMI 0-1 flow). Echter TIMI 3 flow kan niet met grote betrouwbaarheid worden onderscheiden van TIMI 2 flow. Het accepteren van redelijke maar niet perfecte doorbloeding hangt af van lokale inzichten en mogelijkheden. Afhankelijk hiervan, kunnen de niet-invasieve criteria voor reperfusie al dan niet worden toegepast.

Hoofdstuk 6

De LIM1 trial

Het retrospectieve onderzoek zoals beschreven in hoofdstuk 4 heeft de aanzet gegeven tot een prospectieve gerandomiseerde multicenter studie met de vraagstelling of het veilig en haalbaar is om patiënten met een uitgebreid acuut hartinfarct te verwijzen naar een PTCA centrum voor rescue PTCA of primaire PTCA.

Hoofdstuk 6 beschrijft het protocol van de Limburg Myocard Infarct (LIMI) trial. Deze studie heeft ten doel om drie handelingsstrategieën te evalueren voor de behandeling van een groot acuut hartinfarct bij patiënten die initieel worden opgenomen in ziekenhuizen zonder PTCA faciliteiten. In deze pilot studie worden patiënten prospectief gerandomiseerd tot een behandeling met een stolseloplossend geneesmiddel, tot behandeling met stolseloplossende medicatie en rescue PTCA indien noodzakelijk, of tot primaire PTCA. In deze studie is prospectief nagegaan of het vervoer vanuit niet-PTCA centra naar het Academisch Ziekenhuis Maastricht haalbaar en veilig was. Tevens is gekeken naar de effectiviteit en de kosten van de verschillende benaderingen.

Hoofdstuk 7

Acute overplaatsing voor rescue of primaire PTCA van patiënten met een uitgebreid myocardinfarct is veilig en haalbaar

Van de behandeling van het acute hartinfarct zijn in de literatuur gunstige resultaten beschreven van primaire PTCA, minder duidelijk is dit voor rescue PTCA. Echter, deze resultaten zijn in feite alleen van toepassing voor patiënten die rechtstreeks worden opgenomen in een ziekenhuis met PTCA faciliteiten. In de meeste westerse landen is de beschikbaarheid van PTCA faciliteiten beperkt. In Nederland beschikt slechts 10% van de ziekenhuizen over dergelijke faciliteiten. Dit was de reden voor het starten van het prospectief gerandomiseerd multicenter Limburg Myocardial Infarction onderzoek waarbij thrombolysen (stolseloplossend middel) zonder transport naar een dottercentrum ($n=75$) wordt vergeleken met thrombolysen met transport naar een dottercentrum voor rescue PTCA ($n=74$) en transport naar een dottercentrum voor primaire PTCA ($n=75$). Het betreft patiënten die werden opgenomen met een uitgebreid acuut hartinfarct in een van de 5 deelnemende ziekenhuizen zonder PTCA faciliteiten in de provincie Limburg. Geen van de patiënten overleed tijdens het transport. De tijd (gemiddeld) tussen het begin van de klachten en hartcatheterisatie bedroeg in de rescue PTCA groep 240 ± 80 minuten, en 215 ± 80 minuten in de primaire PTCA groep. Er werden geen significante verschillen gevonden in morbiditeit en mortaliteit tussen de 3 groepen gedurende de eerste 42 en na 1 jaar follow-up. De mortaliteit na een jaar was 8% in de groep die werd behandeld met een stolseloplossend geneesmiddel, 9% in de patiëntengroep met rescue PTCA en 12% in de groep met primaire PTCA. De één-jaars morbiditeit en mortaliteit was relatief laag in deze patiëntengroep met behandeling voor een uitgebreid myocardinfarct. De patiënten die werden behandeld middels primaire PTCA hadden gemiddeld al vroeg een betere doorbloeding van het kransslagvat en vertoonden daarom ook minder noodzaak tot latere interventies. Concluderend blijkt de behandeling middels rescue of primaire PTCA bij patiënten met een uitgebreid myocardinfarct na acuut transport goed uitvoerbaar en veilig. De omvang van deze studie was te klein om een ferme uitspraak te doen over de effectiviteit. Een grote multicenter studie is noodzakelijk om deze vraag te beantwoorden.

Hoofdstuk 8

Overplaatsing voor acute PTCA. Cost-effectiveness ratio meest gunstig voor primaire PTCA

Voor het implementeren van nieuwe behandelingsmethodieken en het verkrijgen van steun voor wetenschappelijk onderzoek zijn kosten-effectiviteits analyses van toenemend belang. Van de LIMI studie weten wij (hoofdstuk 7) dat overplaatsing voor rescue en primaire PTCA veilig en haalbaar is. In deze studie werden prospectief gegevens verzameld en werden de kosten voor opname, onderzoeken en medi-

catie berekend door het gebruiksvolume te vermenigvuldigen met een unit kostprijs. Na een jaar follow-up bedroegen de kosten voor thrombolyse, rescue PTCA of primaire PTCA respectievelijk EUR 8.704, EUR 11.524 en EUR 11.661 ($p < 0,001$). De additionele kosten per additionele event-vrije overleving met inbegrip van alle revascularisaties was in vergelijking tot een behandeling met een stolseloplossend middel in het voordeel van primaire PTCA; EUR 13.682 versus EUR 81.928 voor de behandeling met rescue PTCA. In het algemeen kan gesteld worden, dat overplaatsing naar een PTCA centrum voor acute interventie leidt tot een verbetering van de klinische uitkomsten maar het gaat gepaard met aanzienlijke kosten. De bereidheid om deze kosten te accepteren lijkt een zaak voor politieke beschouwing. De resultaten van grote gerandomiseerde studies moeten worden afgewacht alvorens de strategie van het overplaatsen van een patiënt in de acute fase van het grote hartinfarct kan worden geïmplementeerd als zijnde een routine en kosten-effectieve behandeling.

Conclusies

1. Rescue PTCA en primaire PTCA leiden tot een vergelijkbare uitkomst met betrekking tot doorbloeding van de kransslagaderen en klinische resultaten bij patiënten met angiografisch aangetoonde afwezige of slechte doorbloeding (TIMI 0-1 flow) bij het acute myocardinfarct.
2. Niet-invasieve parameters voor het herstel van doorbloeding blijken nuttig ter identificering van patiënten met een open kransslagvat zodat acute hartcatheterisatie niet noodzakelijk is. Echter, normale doorbloeding (TIMI 3 flow) kan niet betrouwbaar worden onderscheiden van tragere doorbloeding van het kransslagvat (TIMI 0-2 flow).

De prognose van patiënten met positieve criteria voor het herstel van doorbloeding is uitstekend.

3. Acute verwijzing voor rescue of primaire PTCA vanuit een ziekenhuis zonder PTCA faciliteiten is veilig, haalbaar, en kan worden verricht binnen een therapeutisch acceptabel tijdsinterval.

Verwijzing van patiënten naar een PTCA centrum leidt tot een verbetering van klinische uitkomsten maar tegen aanzienlijke kosten. De additionele kosten per additionele MACE-free overleving, lijkt in het voordeel van primaire PTCA vergeleken met thrombolytische therapie. In een omgeving met beperkte financiële en logistieke middelen, blijft thrombolytische therapie het beste alternatief.

Toekomst verwachtingen

Elke vraag staat aan de basis van nieuwe vragen. Met andere woorden, een voltooid proefschrift behoort de aftrap voor een nieuw onderzoek te zijn. Strategieën voor het bewerkstelligen van goede doorbloeding van de kransslagaderen zijn voortdurend in

beweging. De behandeling die wordt toegepast is een resultante van krachten tussen de ontwikkeling van nieuwe technieken, lokale gebruiken en de budgettering in de gezondheidszorg. Afhankelijk van de voorkeur, bekwaamheid en de faciliteiten die ter beschikking staan van de behandelend cardioloog zal een bepaalde behandeling worden ingezet.

Dit proefschrift heeft laten zien dat het mogelijk is om patiënten met een uitgebreid hartinfarct over te plaatsen naar een PTCA centrum voor acute PTCA waarbij primaire PTCA, hoewel niet in alle opzichten significant, iets gunstiger lijkt. Betekent dit nu dat elke patiënt met een acuut hartinfarct in aanmerking komt voor overplaatsing voor een acute PTCA procedure? In Nederland worden jaarlijks 27.000 patiënten opgenomen onder de diagnose hartinfarct. Aangenomen dat het electrocardiogram in 40% van de patiënten onvoldoende reden is voor het toepassen van een stolseloplossend geneesmiddel of acute PTCA, dan heeft dit tot gevolg dat circa 16.000 patiënten in aanmerking komen voor een dergelijke behandeling. Primaire PTCA moet sterk overwogen in de patiënten (10-15%) die worden opgenomen in ziekenhuizen met mogelijkheden voor PTCA. Wat te doen bij de andere circa 14.000 patiënten die worden opgenomen in ziekenhuizen zonder PTCA faciliteiten? Het betekent een enorme belasting voor de PTCA centra indien de indicatiestelling voor het verrichten van primaire PTCA zou worden uitgebreid voor elk hartinfarct. In de LIMI studie werd overplaatsing beperkt tot de electrocardiografische uitgebreide hartinfarcten. Aangenomen dat in 20% er sprake is van een uitgebreid hartinfarct, dan blijven er bij benadering 2.800 patiënten over die in aanmerking komen voor primaire PTCA. In de Nederlandse situatie met 13 PTCA centra betekent dit een additionele last van ongeveer 210 acute PTCA's per jaar per centrum. Het is de vraag of fysiek aan deze vraag kan worden voldaan, of dat een strategie bestaande uit een stolseloplossend geneesmiddel voor transport met een vrijwel identieke uitkomst niet een praktischere oplossing is. Dit beperkt het aantal acute interventies met $\pm 60\%$. Een dergelijke benadering zou de logistieke druk van de PTCA-centra kunnen beperken door het herstel van doorbloeding die dankzij het stolseloplossend geneesmiddel gedurende het transport optreedt. De keerzijde van de medaille betekent in dat geval een toename in het aantal late PTCA procedures en CABG.

Implicaties van acute infarct PTCA

Voor de implementatie van een 24-uurs service voor infarct PTCA, zijn voldoende faciliteiten en mankracht noodzakelijk. Met het oog op een enorme toename in infarct angioplastiek is het vereist om goed gemotiveerde gesubspecialiseerde interventiecardiologen op te leiden. Gelijkerwijs, zijn extra faciliteiten noodzakelijk evenals uitbreiding van verplegend personeel en hartfunctielaboranten. Uitbreiding van het aantal catheterisatie laboratoria, verpleeg- en CCU-bedden is vereist om de toename van het aantal overplaatsingen van ernstig zieke patiënten het hoofd te bieden en om hoogwaardige zorg te leveren. Enkele patiënten zullen beademingsbe-

hoefdig zijn of vereisen het gebruik van een intra-aortale ballonpomp, of acute CABG waarvoor hoog gekwalificeerd verpleegkundig personeel een vereiste is evenals een coöperatieve cardiochirurgische staf. Ook de ambulancedienst krijgt te maken met een veranderend verwijspatroon. De ambulancedienst zal middels mankracht en faciliteit moeten kunnen inspelen op veilig en snel transport van ernstig zieke patiënten in ambulances die zijn geëquipt voor full-life support. Nog belangrijker is de implementatie van protocollen in de ziekenhuizen zonder faciliteiten voor PTCA. Onderlinge afstemming tussen deze centra en de PTCA centra omtrent overplaatsing van de patiënten voor infarctangioplastiek zal resulteren in een adequate verwijzing van patiënten met een minimum aan tijdsdelay. Ook de follow-up van de zorg van deze patiënten in de verwijzende ziekenhuizen zal in protocollen moeten worden geïmplementeerd met name ten aanzien van de know-how omtrent sheath verwijdering en de groeiende groep van anticoagulantia.

Localisatie van infarctangioplastiek

In het geval dat infarctangioplastiek gelimiteerd blijft tot de tertiaire PTCA centra is een goed gemotiveerde ambulancedienst cruciaal voor snel en veilig transport naar een PTCA centrum. Het is reeds eerder aangetoond dat regionalisatie van PTCA centra kosten-effectief is in de zogenaamde high-volume centra. Het dotteren bij een acuut hartinfarct is niet eenvoudig en vereist veel ervaring. Regionalisatie van PTCA centra heeft automatisch tot gevolg dat de individuele interventiecardioloog een grote individuele caseload heeft waardoor de kans op succes toeneemt.

Een andere mogelijkheid zou kunnen zijn om ieder streekziekenhuis toe te rusten met PTCA faciliteiten en deskundig personeel. Vanwege de hoge kosten van een dergelijke ontwikkeling in faciliteit en mankracht, heeft dit weinig kans van slagen.

Echter, in regio's waar prehospitala behandeling met een stolseloplossend geneesmiddel is geïmplementeerd zou het interessant zijn om alreeds via de ambulance triage van patiënten met een uitgebreid myocardiinfarct al dan niet na thrombolysen, naar een ziekenhuis met PTCA faciliteiten te laten plaatsvinden. Diverse studie protocollen met betrekking tot bovenstaande zijn momenteel in wording. Het resultaat van dergelijke reperfusiestrategieën zal kunnen leiden tot verdergaande reductie in de tijd tot (mechanische) reperfusie en een reductie van de kosten.

De resultaten van een grootschalig onderzoek zijn noodzakelijk om een definitieve uitspraak te kunnen doen betreffende de effectiviteit van de diverse therapieën alvorens de overplaatsing van patiënten met een uitgebreid hartinfarct naar een PTCA centrum voor acute PTCA kan worden geïmplementeerd als zijnde "standaard therapie". Tot die tijd moeten het stolseloplossend geneesmiddel, rescue PTCA en primaire PTCA worden gezien als zijnde symbiotische reperfusiestrategieën in plaats van op zichzelf staande therapievormen. Momenteel zijn er studies gaande die tot doel hebben meer helderheid te brengen in deze materie.

Dankwoord

En toen was er niets meer....

Een dergelijk gevoel zal menigeen hebben overmeesterd toen de definitieve goedkeuring voor zijn of haar proefschrift daar was. Vergeten zijn de vele uren achter de tekstverwerker, de besprekingen, onderzoeken, kritieken en momenten van voldoening als er weer een hoofdstuk af was of een veronderstelling juist bleek te zijn.

In gedachten ga ik terug naar het voorjaar van 1994 toen er een onderhoud plaatsvond in de ochtendbesprekingskamer van het Academisch Ziekenhuis Maastricht. Onder aanvoering van professor Bär en collegae Vermeer en van Ommen ontspon zich een levendig discussie omtrent een destijds al "routinematige" behandeling van patiënten met een acuut hartinfarct, die na voorbehandeling met een thrombolyticum vanuit het ziekenhuis in Sittard werden verwezen naar Maastricht voor eventuele acute interventie.

Het idee voor dit proefschrift was geboren en dankzij gezamenlijke inspanning kwam al spoedig een protocol tot stand.

Professor Frits Bär ben ik zeer dankbaar dat ik in de gelegenheid werd gesteld om ervaring op te doen in de interventionele technieken binnen de cardiologie en dat hij mij, na retrospectief voorwerk, het LIM1 project toe wees.

Een persoonlijkheid als professor Bär mag iedere promovendus zich wensen. Zijn kennis en kunde, snelle correcties, enthousiasme, maar ook donderpreken en het stellen van deadlines zijn een onmisbare stimulans bij het schrijven van een proefschrift.

Beste Frits, ik heb vakinhoudelijk zeer veel van je mogen leren. Je zin voor realiteit, pragmatie en oog voor menselijke problematiek maken je, naast een streng leermeester, op de eerste plaats een eerlijk en buitengewoon plezierig mens.

"How to get the right message, at the right time, at the right place, to be understood by the right people" is the greatest asset van mijn tweede promotor professor Hein Wellens.

Hein beoefent de cardiologie op een welhaast holistische wijze waarbij fenomenen als elektriciteit, coronairperfusie en contractiliteit als een legpuzzel in elkaar passen.

Waarde Hein, heel veel dank voor je gedegen opleiding, je gedachtegoed reikt verder in Nijmegen.

Een onmisbare eigenschap voor het welslagen van een onderzoek is systematiek en kennis van databeheer en organisatie. Zonder de hulp van Frank Vermeer, mijn co-promotor, had ik dit werk onmogelijk kunnen verrichten. Zijn systematische werkwijze en beschikking over enorme databestanden zullen nog vele promovendi van nut zijn.

De leden van de beoordelingscommissie te weten prof. dr. M.P. van Dieijen-Visser (voorzitter), prof. dr. A.P.W.M. Appels, prof. dr. M.J.A.P. Daemen, prof. dr. J.J. Piek en prof. dr. F.W.A. Verheugt wil ik graag bedanken voor de tijd en energie die zij hebben besteed aan het beoordelen van het manuscript.

Natuurlijk ben ik mijn ex-collegae uit Maastricht niet vergeten. Met name hen wil ik dankzeggen voor de vrijwillige medewerking aan het protocol. Vooral tijdens de onvermijdelijke nachtelijke momenten dat er weer eens met spoed een patiënt vanuit de periferie binnenkwam voor spoedeisende interventie. Hetzelfde geldt voor de "dotteraars" dr. Pieter Doevendans, dr. Ebo de Muinck, dr. Vincent van Ommen, drs. Hans de Swart en drs. Jindra Vainer; Zonder hen had ik onmogelijk al die dotters kunnen doen.

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Ik wil niet voorbijgaan aan de Rotterdamse econoom met veel verstand van angioplastiek, dr. Ben van Hout, de "Guru" van de kosteneffectiviteit, waar ik menig uurtje heb doorgebracht in ons beider geboortestad Rotterdam. Beste Ben, heel veel dank, ik heb veel van je geleerd en hoop dat wij in de toekomst nog veel gezamenlijke projecten krijgen

De wijze van databeheer was voortreffelijk. Aimée Lousberg, je bent onmiddellijk welkom in Nijmegen. Student-assistenten, het secretariaat in Maastricht en Nijmegen, met in het bijzonder Margriet Dirkx en Marion Hartog, de cardiologen van de participerende onderzoekscentra uit Heerlen, Brunssum, Kerkrade, Sittard en Roermond, alsmede ambulancediensten, de medewerkers van de hartfunctie, Eerste Hart Hulp, CCU en de verpleegafdelingen. Ook jullie bijdrage ben ik niet vergeten.

De maatschap Cardiologie van het Canisius-Wilhelmina Ziekenhuis heeft mij voortdurend aangespoord om te promoveren, hetgeen van onmiskenbare betekenis is geweest en zeker tot meer zal leiden. Met name mijn dottergenoot in de maatschap, tevens paranimf, BartJan Meursing heeft mijn betrokkenheid bij acute dotterinterventies alleen maar vergroot.

Een gezonde wedijver tussen de andere paranimf, broer en tevens vakbroeder Michèl Oude Ophuis en mijzelf, heeft de duur van deze promotie zeker bekort. Michèl, succes met jouw laatste loodjes.

Vanuit zijn bijzondere positie wil ik mijn vader bedanken voor zijn bijdrage aan dit proefschrift, zonder woorden weet hij wat ik daarmee bedoel.

Tenslotte mijn gezin,

Deze woorden vallen mij het zwaarst. Er waren tijden dat Bas en Sanne, lief en vrolijk als altijd, mij minder zagen dan hun fantastische oppasmoeder Narda van Rens. "Papa zat immers boven achter de computer", kinderen willen aandacht en spelen en hebben geen boodschap aan een proefschrift.

En dan “last but not least” Carole, ik hoor je nog zeggen bij het lezen van een dankwoord behorende bij een proefschrift vijf jaar geleden “wat een onzin al die lofuitingen aan de partners”. Inmiddels besef je dat dit zeker op zijn plaats is.

Lieve Carole (woppel), mijn geweldige vrouw, jouw steun, liefde en geduld zijn niet in een dankwoord als dit samen te vatten.

Curriculum vitae

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ABSTRACTS

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