PRIMARY CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION

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PRIMARY CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION

Primaire Coronaria-Angioplastiek als Behandeling van het Acute Hartinfarct

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To the front-cover:
Lithography by Kees de Goede (who is acknowledged for his kind permission to reproduce his art-work). Steendrukkerij Amsterdam, Rento Brattinga.

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Another option is, this catheter has a balloon in it somehow that they inflate when it's inside the plugged-up artery. It cracks the plaque. That's what they call it, plaque. I thought a plaque was what you got for winning the championship.

John Updike, Rabbit at rest

Ter nagedachtenis aan mijn vader
Cornelis de Boer (1904 - 1989)

Voor mijn moeder

CONTENTS

Chapter 1

Introduction

Introduction

1.1 Reperfusion therapy for myocardial infarction

Until 1980, coronary arteriography was considered to be contraindicated in patients in the early stages of myocardial infarction. The pioneering work of DeWood and colleagues established that emergency cardiac catheterization in patients with acute myocardial infarction (AMI), who were considered to be candidates for a therapeutic intervention, was feasible, relatively safe and that a high incidence of complete obstruction of the infarct-related vessel (IRV) existed in the early hours of a myocardial infarction [1,2]. Histopathologic, clinical and postmortem observations confirmed the role of thrombi as the cause of sudden occlusion. Such thrombi develop mostly at the site of a fissured and unstable atherosclerotic plaque [3-8]. Although Herrick in 1912 already proposed that AMI was caused by intracoronary thrombosis [9], it was suggested by "antagonists" that these two were not constantly or causally related and even that coronary thrombosis might be a complication of AMI [10,11]. The study by DeWood et al. [1,2] however, ended this controversy and opened a new approach to the treatment of myocardial infarction. It was appreciated that spontaneous recanalization occurs in a considerable amount of patients within the first 24 hours after myocardial infarction, but such reperfusion usually occurs too late, after the damage has been done. Accordingly several ways of restoring blood flow through occluded arteries have been proposed. Cardiosurgical coronary artery bypass grafting (CABG) was the only generally accepted revascularization therapy in the seventies. However, although data from small studies suggested promising results of early reperfusion by means of CABG [12-16], this approach was never tested in large scale studies.

In the late seventies Andreas Grüntzig and Peter Rentrop reported revolutionary developments in the treatment of coronary artery disease: coronary angioplasty or PTCA (Percutaneous Transluminal Coronary Angioplasty) and thrombolytic therapy [17,18]. Coronary angioplasty was introduced in the Netherlands in 1980 by Sjef Ernst from the St. Antonius Hospital [19] and some of the first trials on reperfusion therapy were conducted in the Netherlands [20-22]. Reperfusion of the occluded IRV in myocardial infarction can be achieved by thrombolytic agents either given intracoronary or intravenously [23-27], by mechanical intervention (PTCA) [28,29] or by a combination of these approaches [28, 30-35]. Subsequently a series of medium size and large trials have been conducted to assess the clinical value and the risk of different reperfusion strategies.

Initially attention was focused on the intracoronary administration of thrombolytic

agents but the fact that most hospitals do not have cardiac-catheterization laboratories stimulated evaluation of the effects of intravenous thrombolytic therapy. Several large studies established and defined the role of intravenous fibrinolytic therapy in patients with acute myocardial infarction:

* the "Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico" trials: GISSI-1 and 2 [26,36]
* the International Studies of Infarct Survival: ISIS-2 and 3 [27,37]
* the APSAC (Anisoylated Plasminogen Streptokinase Activator Complex) Intervention Mortality Study: AIMS [38]
* the Anglo-Scandinavian Study of Early Thrombolysis: ASSET [39]
* the Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries study: GUSTO [40,41]

These studies included approximately 134.000 patients, randomized to receive different thrombolytic regimens. The estimated average reduction of early mortality after myocardial infarction, attributed to thrombolytic therapy, is between 20 and 30 % [20,26,27,42]. Besides this, the possible benefit of acetylsalicylic acid (aspirin) and heparin became subject of interest and initiated studies to establish the role of these agents for the treatment of myocardial infarction [27,40,43-45].

Thrombolytic therapy became the treatment of choice for patients with myocardial infarction but concern was raised about the potentially deleterious impact of the residual stenosis remaining after thrombolytic therapy. Furthermore, intravenous thrombolytic therapy is limited by modest reperfusion rates (Table 2 and 3), the risk of bleeding [46], significant residual stenosis of the IRV in the majority of patients and a relatively high risk of reocclusion [40-42,47-54]. This initiated trials to assess the role of angioplasty immediately, early or late after thrombolytic therapy. The disappointing results from studies on the effects of coronary angioplasty, whether performed immediately, early or late after thrombolytic therapy, are summarized in Table 4 [47,55-60].

Restoring myocardial perfusion by means of primary or direct percutaneous transluminal coronary angioplasty, without antecedent administration of a thrombolytic agent, as first described by Hartzler [28], has a high primary success rate but never became widely accepted and angioplasty was only considered as a treatment option if there were contraindications for thrombolysis, when failure of infarct-related artery recanalization after thrombolytic therapy was suspected ("salvage" or "rescue" PTCA) or when optimal conditions for angioplasty were present (often depending on the experience and enthusiasm of the cardiologist on duty) [60-62]. In fact, PTCA was regarded as the "step-child" in the management of acute myocardial infarction. Still,

some people insisted on evaluation of primary angioplasty treatment [61,64]. The rationale for employing immediate coronary angiography and primary coronary angioplasty as a primary therapy in AMI is based on the following:

First, immediate angiography gives pivotal information for treatment stratification. Patients who may benefit from early cardiac surgery, for instance those with severe left main coronary artery stenosis, can be identified, whereas in patients with a patent or small IRV no aggressive therapy will be applied thus avoiding unnecessary exposure to thrombolysis. Second, primary angioplasty achieves a higher success rate of recanalization of occluded infarct-related vessels compared with thrombolytic therapy (approximately 90-95% versus 75-80% respectively) and avoids the significant bleeding risk associated with thrombolytics. Third, primary angioplasty may not turn an ischemic infarction into a hemorrhagic infarction [65]. Fourth, primary angioplasty can be used where thrombolytic therapy is contraindicated. Fifth, primary angioplasty can relieve ischemia by achieving reperfusion more rapidly than thrombolytic therapy. Last, primary angioplasty results in a less severe residual stenotic lesion than thrombolytic therapy and has the potential to reduce recurrent infarction, recurrent ischemia and reocclusion which are seen in approximately 15-30 % of the patients after thrombolytic therapy [42,45,66].

The general considerations mentioned above will be discussed in more detail.

1.2 The importance of an open infarct-related vessel

The human heart is dependent on an uninterrupted supply of substrates. These substrates cannot be stored in the myocardium and for this reason the heart cannot tolerate prolonged ischemia. Accordingly obstruction of a coronary artery is usually followed by cell death. The heart is the victim and not the perpetrator in the pathogenesis of ischemic heart disease [67].

Early and effective flow through the IRV results in limitation of infarct size and a better left ventricular function [51,68,69]. Left ventricular function in patients with coronary artery disease is a predictor of survival [70-74] and follow-up data of the Interuniversity Cardiology Institute of the Netherlands trial demonstrated a good prognosis after myocardial infarction in patients with a left ventricular ejection fraction at discharge of more than 40%, whereas short-term and long-term survival declined progressively as ejection fraction decreased [72].

Reopening of the IRV, limitation of infarct size, and time delay:

Recovery of left ventricular function after thrombolytic therapy is determined (among others) by the time between onset of symptoms and achievement of full reperfusion. This time window for myocardial salvage is however restricted to a few hours

[36,68,69,75] and after acute occlusion of a coronary artery irreversible ischemic myocardial injury develops in a time related wave front from subendocardial to subepicardial layers [76]. Reperfusion on the other hand, may have deleterious effects on myocardial tissue, often referred to as reperfusion injury. In the animal model, oxygen derived free radical activity and calcium overload after prolonged episodes of ischemia have been hypothesized as causes for this event. Whether this reperfusion injury is of clinical importance in humans remains controversial [77,78]. Free radical-scavenging drugs may play a role in cardioprotective therapy but studies in this field are lacking [78,79]. Reperfusion strategies should thus be aimed at the briefest time of ischemia. For the clinician however, this "time window" is a hazardous tool to in- or exclude patients for reperfusion therapy and his or her perception of time from the onset of infarction in the individual patient may be wrong. An advantage of thrombolytic therapy is, that it can be started by general practitioners and paramedical ambulance staff before the patients reach the hospital which may result in a reduction of time to start of treatment [80-82]. Coronary occlusion can be a dynamic process and intermittent occlusion with alternate reperfusion occurs frequently in the early hours after myocardial infarction [83,84]. There also is a strong variability in collateral blood flow to the ischemic myocardium between individual patients [85]. The presence of collateral vessels or residual antegrade blood flow to the infarct zone may extend the "time window" for myocardial salvage [85,86]. Patients with fluctuating symptoms and/or ST segments are likely to have residual flow to the infarct zone and effective reperfusion may improve their left ventricular function [84]. Another study demonstrated successful infarct vessel recanalization in the majority of late-entry patients (6-24 hours) with thrombolysis and/or angioplasty, and favorable effects on left ventricular remodeling [87]. "Late" reperfusion (after 6-24h) of occluded infarct-related vessels has the ability to prevent left ventricular dilation independent of infarct size [88]. The Second International Study of Infarct Survival (ISIS 2) showed a reduction of mortality in patients treated relative late (between six and 24 hours from the onset of symptoms) with the combination of streptokinase and aspirin [27]. Finally the LATE (Late Assessment of Thrombolytic Efficacy) study and the EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) Collaborative Group indicated beneficial effects of tPA and streptokinase respectively, until 12 h after symptom onset and maybe beyond this time-window, although the latter study was not conclusive [89,90].

Recanalization over time (24 hours), the so called "catch-up" phenomenon, reduces differences in patency after administration of different thrombolytic agents but early patency is important with regard to survival and left ventricular function [40,41,50,54].

In addition, a lot of "circumstantial evidence" has been gathered for the theory that an open infarct-related vessel gives additional years to the patient after having suffered from a myocardial infarction even when reopening of the IRV is accomplished beyond the time window wherein direct myocardial salvage may be expected [71-74,91]. This suggests that besides limitation of infarct size other mechanisms then early myocardial reperfusion play an important role:

First, enhanced infarct-healing. The frequency of myocardial rupture (including tamponade), formation of mural thrombus, acute mitral regurgitation, rupture of the intraventricular septum and formation of left ventricular aneurysm will be reduced. Recovery of the left ventricular function will be better in the presence of an open IRV, with less dilatation and remodeling. [74,87,91,86,92,93]

Second, electrical stability. Several studies demonstrated enhanced electrical stability as reflected by a reduction of the prevalence of ventricular premature complexes, inducible ventricular tachyarrhythmias and late potentials in patients with a patent IRV after thrombolysis for myocardial infarction [94-97]. All have been recognized as significant and independent adverse prognostic factors for survival. [94,96,99]

Third, collateral circulation. In an analysis of 250 consecutive patients, treated with primary angioplasty the incidence of multi-vessel coronary artery disease was 57% [100]. An open infarct-related artery may serve as an alternative coronary conduit to other myocardial zones in the acute phase, as well as in the later phase of myocardial infarction in patients with multi-vessel coronary artery disease. In these patients collateral circulation may serve as an important safety-mechanism.

1.3 Problems associated with thrombolytic therapy

1.3.1 The problem of resistance to reperfusion therapy

The primary goal and the cornerstone of treatment of patients with AMI is the achievement of early and optimal reperfusion of the IRV. The Thrombolysis in Myocardial Infarction (TIMI) Study Group, established by the National Heart, Lung, and Blood Institute in 1983, suggested an angiographic definition of perfusion of coronary vessels (Table 5) based on the assumption, that grades 0 and 1 are markers of occlusion and grades 2 and 3 of reperfusion [101]. Recently the clinical importance of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow has been recognized in several studies and an IRV with TIMI grade 2 flow, although until recently considered to be patent, does not lead to optimal myocardial salvage [40,41,48-54]. These studies stressed the importance of TIMI grade 3 flow. TIMI grade 2 flow is associated with a

greater risk for development of recurrent ischemia, congestive heart failure, diminished left ventricular function and a trend towards a higher mortality. What remains unclear is whether TIMI grade 2 is a cause or a marker of adverse outcome, and diminished flow may in fact represent a relative no-reflow phenomenon [102].

Data for patency after intravenous thrombolytic therapy are given in Table 2(TIMI 2 and 3) and Table 3 (TIMI 3). The incidence of normal, TIMI grade 3 flow through the IRV and its relation to clinical sequelae is reported from the GUSTO study, the TEAM (Trial of Eminase (anistreplase) in Acute Myocardial Infarction) 2 and 3 trials and from four German multicenter trials [40,41,48-51,54]. Early TIMI 3 patency rates were also reported from the TAMI (Thrombolysis and Angioplasty in Myocardial Infarction) 5 trial [53]. The majority of studies however, do not report on TIMI grade 3 flow through the IRV. As is clear from these studies, in 20 to 30 % of the patients some kind of antegrade blood flow is not accomplished. The resistance of coronary artery occlusion to thrombolysis may either be due to obstruction of the lumen by a mechanical, nonthrombotic mechanism or by intrinsic resistance of thrombus to dissolution. Considerable evidence exists, that platelet-rich thrombi are particularly resistant to thrombolytic therapy and at least in some patients, who fail to get reperfusion of the infarct-related vessel, this phenomenon may be the underlying mechanism [103,104]. Furthermore thrombolytic therapy can result in activation of platelets by the generation of thrombin, a potent platelet activator, and a stimulus for the proaggregatory thromboxane A_2 production [105]. This activation of platelets has been demonstrated in patients with myocardial infarction who received streptokinase as well as t-PA and may limit the therapeutic effectiveness of fibrinolytic agents [106-108]. All these factors can contribute to failure of reaching adequate reperfusion by means of thrombolysis alone or in combination with coronary angioplasty. The GUSTO trial suggests that tissue-type plasminogen activator (t-PA) given in an accelerated dosing schedule with intravenous heparin results in the highest early and optimal patency of the IRV (TIMI grade 3), and in a better in-hospital survival when compared with other thrombolytic strategies [40,41].

It was demonstrated that reperfusion therapy and its clinical impact can be improved by using "rescue" angioplasty to open infarct-related arteries that fail to open in response to thrombolytic therapy, but the clinical outcome of patients who fail to have an open IRV after such a combined approach is poor [53,109-111]. Data from the TAMI-5 trial support the potential value of an aggressive catheterization strategy for patients with evolving myocardial infarction and individual treatment decisions can be made without a significantly increased risk of the catheterization procedure itself [53]. In all patients with signs of hemodynamic compromise (Killip class ≥ 2) immediate coronary

arteriography should be considered. However, recently a randomized study, comparing the effects of rescue angioplasty or conventional treatment on clinical outcome in patients with anterior wall myocardial infarctions and failed thrombolysis, did *not* demonstrate additional benefits of rescue angioplasty [112].

Finally, there may be a particular resistance to thrombolytic therapy in patients presenting with cardiogenic shock: reduced coronary perfusion pressure and flow may be responsible for this phenomenon. This will be discussed in more detail in paragraph 1.6.

1.3.2 The problem of bleeding complications

The major adverse event associated with thrombolytic therapy is bleeding, ranging from minimal oozing to serious intracranial bleeding and death. Peripheral bleeding may be severe but is usually not associated with mortality or severe irreversible sequelae. Intracranial hemorrhage however is accompanied by a high mortality rate (35-40%) and often leads to persistent deficits. The estimated risk of intracranial hemorrhage is approximately 1% for the general population, receiving thrombolytic therapy for AMI [113-116]. Patients with the use of oral anticoagulants before admission, with a low body weight, with age > 65 years, with female gender, with hypertension and treated with high dose of thrombolytic for a given body weight, seem to be at higher risk. Initial enthusiasm for t-PA was based on presumed fibrin specificity and reduction of systemic bleeding complications because of reduction of the systemic fibrinolytic state, but the use of t-PA may be associated with a higher risk of intracranial bleeding compared to streptokinase therapy, although this effect seems to be dose-related [114,116]. In the Thrombolysis in Myocardial Infarction trial, patients who received 150 mg of t-PA had an incidence of 1.9 percent of intracranial hemorrhage and this number was reduced to 0.5 percent after the dose was lowered to 100 mg of t-PA [58,116]. In the GUSTO trial accelerated tPA produced a significant excess of intracranial hemorrhage but the beneficial effects on survival overwhelmed this adverse effect [40]. Because of the lower risk of intracranial bleeding the use of streptokinase may be the preferred thrombolytic treatment in patients at risk of stroke, those with small infarcts and in the elderly.

A model for individual risk assessment for intracranial hemorrhage during thrombolytic therapy was proposed by Simoons et al., derived from data from six large registries: the Netherlands registry of thrombolytic therapy, the European Cooperative Study Group trials, the GISSI-2 trial, the International Study Group trials, the TIMI II trials, the TAMI trials and the ISAM study. Four factors were identified as independent predictors of intracranial bleeding: age over 65 years (Odds Ratio [OR]: 2.2), body weight below 70 kg (OR: 2.1), hypertension on hospital admission (OR: 2.0) and

administration of alteplase (OR: 1.6). Patients without risk factors who receive streptokinase have a 0.26%, with one risk factor 0.96%, with two risk factors 1.32%, and with three risk factors a 2.17% probability of intracranial hemorrhage [46].

1.3.3 The problem of intramyocardial hemorrhage

After thrombolytic therapy and successful reperfusion, hemorrhagic myocardial infarction and extension of already infarcted tissue can occur and several reports have described extensive intramyocardial hemorrhage in post-mortem studies and even in survivors [65,117-127]. Whether reperfusion in a thrombolytic state induces additional myocardial necrosis remains the subject of debate but a study by Waller and co-workers gives some interesting information on the effects of thrombolytic agents on myocardial tissue. Their series of patients however, were small [65]. Although data from the large clinical trials of thrombolytic therapy have demonstrated benefit of the administration of thrombolytic agents late after onset of symptoms, as was already mentioned, this may increase the risk of cardiac rupture, usually accompanied by extensive hemorrhagic transformation of the infarcted tissue involved [123]. The puzzling observation of the excess of deaths early after thrombolytic therapy may in part be explained by the combination of reperfusion injury and myocardial hemorrhage [46]. Primary angioplasty may not have these deleterious effects and after primary angioplasty an "anemic infarction" was seen in a small group of patients [65]. Furthermore, intramural hemorrhage in the vessel wall, due to the thrombolytic state, may lead to abrupt closure of the initially reopened IRV [65]. Further clinical information on these phenomena is needed.

1.3.4 The problem of the residual stenosis

After successful thrombolytic therapy a high grade residual stenosis of the IRV may be of concern. Sometimes it is difficult to angiographically distinguish the underlying atherosclerotic plaque from residual thrombus, especially in the first few days after initially successful thrombolytic therapy [128-130]. If a high-grade residual stenosis persists after successful thrombolytic therapy, the incidence of reocclusion of the infarct-related vessel and reinfarction is increased, despite the use of additional therapy with heparin and aspirin [21,66,131,132]. Blood flow conditions act in concert with the involved platelets and the coagulation system. One study showed a close non-linear relation between the degree of residual stenosis of the IRV and the degree of left ventricular dilation 6 months and 12 months after first myocardial infarction [133] and reduction of the degree of residual stenosis of the IRV may be a very effective therapy for preventing topographic changes to the left ventricle (left ventricular remodeling) [92].

In a study to assess the degree of residual stenosis after streptokinase therapy for

AMI, 83% of the patients had a residual stenosis of 70 % or more and in most of these patients the culprit lesion was considered to be suitable for coronary angioplasty [129]. In the study by O'Neill and colleagues, comparing the effects of intracoronary streptokinase and primary angioplasty, the greatest improvement in global and infarct zone function was found in patients with lower residual stenosis of the IRV [134]. The residual coronary artery obstruction may limit the flow in the IRV after successful thrombolysis and result in continuing ischemia, delayed recovery and even ongoing necrosis of the myocardial tissue involved [101,135,136]. Coronary angioplasty has the potential advantage of relieving the degree of obstruction but few angiographic data are available: Holmes and coworkers reported a reduction of luminal stenosis of the IRV from 98% to 33% in a small series of patients who underwent primary angioplasty, without antecedent thrombolysis, for acute myocardial infarction [137]. The residual luminal stenosis of the IRV in the first randomized trial of primary angioplasty versus thrombolytic therapy by O'Neill et al. was reported to be 43% in the patients assigned to angioplasty, versus 83% in the patient group, treated with thrombolysis [134]. Clinical evidence indicates, that the residual stenosis after thrombolytic therapy is perhaps the most important determinant of the frequency of reocclusion and this concern initiated in fact the phase 2 of the TIMI trial where the role and timing of coronary angioplasty after thrombolysis were evaluated.

1.3.5 The problem of reocclusion

Reocclusion of the infarct-related vessel may result in death, reinfarction, and worsening of left ventricular function. [45,53,74,109] Evidence has accumulated that patency of the IRV at the time of discharge is of paramount importance for long-term survival, even independent of its influence on left ventricular function. In the Western Washington study, intracoronary streptokinase reduced the one-year mortality among patients with myocardial infarction, but this improvement occurred only among those in whom thrombolysis resulted in coronary artery patency [138]. Reocclusion of the IRV therefore is an important risk factor in patients who had initially successful reperfusion therapy [109]. Reocclusion after successful thrombolysis may occur early or late and may lead to severe clinical symptoms but may also occur "silently". In many studies on thrombolytic therapy for myocardial infarction the true incidence of reocclusion is not known. Angiographically documented reocclusion after successful reperfusion therapy occurred in 15 percent in the TAMI-1 study and in 24 percent of the patients in the TIMI-I study [101,139]. Ohman et al. reported a 12.4 % incidence of reocclusion after initially successful reperfusion therapy and 42% of these reocclusions occurred without symptoms [109]. Patients with reocclusion of the IRV at follow-up angiography had worse global as well as infarct-zone left ventricular function

compared to patients with sustained patency, regardless if the reocclusion was accompanied by symptoms or not. They also made the interesting observation that the right coronary artery seems to be more susceptible for reocclusion then other coronary vessels, an observation also made by others. [32,139].

The APRICOT (Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis) study demonstrated a high incidence of reocclusion of the IRV three months after initially successful thrombolysis with intravenous streptokinase (25-30% reocclusion). This study also suggested a deleterious effect of this phenomenon on left ventricular function [45].

Immediate addition of aspirin after thrombolytic therapy has some effect to prevent reocclusion and reinfarction after initially successful thrombolysis as was also demonstrated in the second International Study of Infarct Survival (ISIS-2) and the APRICOT study [27,45,140]. Long term follow-up data from the Western Washington Study suggested an improvement of early survival after streptokinase therapy for AMI when compared with placebo treatment, but after 3-8 years, this initial improvement was not seen anymore [141]. Reocclusion of the IRV over time could be an explanation for this observation.

Reocclusion at the site of the often critical residual coronary vessel stenosis within the following days after myocardial infarction led several cardiologists to perform percutaneous transluminal coronary angioplasty at varying intervals after thrombolysis and as early as 1982, Meyer et al. reported very encouraging results of this aggressive treatment [30,31,142] and others were soon to follow [21]. If reocclusion can be prevented, immediate angioplasty may be beneficial in selected patients [91]. However residual thrombus may obscure the true severity of the underlying atherosclerotic plaque (especially early after thrombolytic therapy) and may itself be activated in the "thrombolytic state" [128,143]. This may in part be the explanation of the disappointing results of routine angioplasty after initially successful thrombolytic therapy. An important problem to be solved is the identification of non-invasive markers of reperfusion after thrombolytic therapy. Time delay after failure of thrombolytic therapy may, as was already stated, results in further damage of myocardial tissue.

1.4 Combination of thrombolytic and angioplasty therapy

After the initial enthusiastic reports on successful angioplasty during, after or without thrombolytic therapy, several studies were designed to establish the role of coronary angioplasty in the treatment of myocardial infarction [28,30-33,35,47,55-60,134,144-146]. Table 4 summarizes the most important studies. The results of these

trials indicate, that routine angioplasty intended to correct the residual stenosis of the IRV, whether performed immediately or early after thrombolytic therapy, or days later is ineffective,, may be hazardous and is unnecessarily expensive. Possible explanations were mentioned before, namely activation of residual thrombotic material by intracoronary manipulation in a "thrombolytic state" and IRV intra-plaque hematoma formation both leading to an increased incidence of reocclusion. A pragmatic policy of conventional care with intervention only for clinical indications ("watchful waiting") was advocated. However, only about 60-70 % of the angioplasty assigned patients in the TAMI I, TIMI II A, TIMI IIB and SWIFT trials actually underwent the procedure and patients with an occluded IRV did *not* have a PTCA. These patients may have had considerable benefits of an open IRV. Recently O'Neill and colleagues evaluated possible differences in clinical outcome in patients treated with angioplasty with adjunctive thrombolytic therapy and primary coronary angioplasty as a stand alone procedure, and demonstrated clearly that intravenous streptokinase therapy should not be routinely given in patients with angioplasty treatment for myocardial infarction [146].

The incidence of bleeding complications is increased when cardiac catheterization or coronary angioplasty is performed in the setting of thrombolytic therapy [47,55,56] but one major advantage of immediate angiography and angioplasty above substantive intravenously administrated thrombolytic therapy is the ability to document successful reperfusion and coronary anatomy accurately. At least 25 % of all patients receiving thrombolytic therapy fail to have recanalization (TIMI grade 2 and 3), 90-120 minutes after start of therapy and emergency coronary angioplasty to achieve vessel patency has been termed "salvage" or "rescue" angioplasty. Successful angioplasty in this setting has a good prognosis, comparable to that of patients with patency of the IRV after thrombolysis, but failure of rescue PTCA is associated with a much higher mortality rate. [63,110] The role of rescue PTCA was only evaluated in one randomized study of patients with anterior wall involvement. In this study problems with including patients were encountered as interventional cardiologists from many centers who were invited to participate (including our hospital) felt it unethical to withhold a patient coronary angioplasty in case an occluded IRV was found [112]. None of all the above mentioned studies however was designed to investigate the possible role of stand-alone PTCA therapy.

1.5 Eligibility for thrombolysis and contraindications for this therapy

Possible contraindications for thrombolytic therapy are considered to be: gastrointestinal bleeding, prolonged resuscitation, recent surgery or trauma, recent stroke, recent vascular puncture, known bleeding disorder, uncontrolled hypertension despite vasopressor treatment, oral anticoagulant therapy and in premenopausal women (imminent) menstruation. Furthermore, thrombolytic agents are probably not being used so often in older patients because of their worse functional status before their infarctions, a higher frequency of co-existing illnesses, more time delay in presentation to the hospital, and more frequently non-diagnostic electrocardiograms often with less chest discomfort [147]. From the physicians point of view there is a reluctance because of the fear for a catastrophic intracerebral hemorrhage.

One study strongly suggested that prolonged (out-of-hospital) cardiopulmonary resuscitation by itself does not have to be a contraindication to thrombolytic therapy [148]. Earlier reports on thrombolysis have suggested that more than 70% of patients with AMI were not eligible for thrombolytic therapy with these strict criteria, many of them having more than one reason for exclusion [62,149]. However, the mortality without reperfusion therapy in this patient group was very high (19%). The in-hospital mortality of myocardial infarction is increased threefold in patients older than 70 years and may even exponentially increase with increments of age, in patients older than 75 years [147,149]. So the higher risk of intracranial hemorrhage in elderly patients seems to be less important than the gain to be expected from reperfusion therapy. Patients with bundle branch block were thought to be not eligible for thrombolytic therapy but recent data showed also beneficial effects in these patients, provided that they present with good clinical evidence for myocardial infarction [27].

The selection of patients with AMI, who should receive thrombolytic therapy, has gradually become broader as more data from trials were published and the majority of patients are candidates for this therapy nowadays The benefit in these subsets of patients will outweigh the risk. An overview of nine large trials demonstrated that thrombolytic therapy reduces mortality in a much wider range than is generally accepted at the present time, with clear benefits in patients presenting between 12 to 18 hours after symptom onset, irrespective of age, sex, blood pressure, heart rate, a history of previous myocardial infarction or diabetes [46]. Still, a considerable number of patients with AMI will have definite contraindications for thrombolytic therapy and are probably candidates for primary angioplasty [149-151].

1.6 Treatment of patients presenting with cardiogenic shock

About 5-10% of all patients, admitted to a hospital for acute myocardial infarction, develop cardiogenic shock [26,152]. This condition represents failure of the pumping action of the heart to provide adequate perfusion of the organs and tissue to meet resting metabolic demands. The mortality rate of this condition has remained in the range of 70-90% in many published studies [152]. Early treatment with inotropic agents and mechanical counterpulsation circulatory support (Intra-aortic Balloon Pumping; IABP), although important therapeutical improvements, cannot eliminate the cause of myocardial ischemia, namely occlusion of the IRV [153]. Massive cell death and permanent loss of function in large areas of the heart cannot be prevented without effective reperfusion of the IRV. After initially hopeful results of the use of the IABP during the course of myocardial infarction and signs of left ventricular failure, a randomized study failed to document a major impact on survival when used alone [154]. Thrombolysis can reduce the incidence of cardiogenic shock following AMI, but once the shock state has developed the effectiveness of this reperfusion regimen is disappointing [155-157]. It appears that thrombolytic treatment is relatively ineffective in these patients. Recent non-randomized studies showed improvement of survival of patients who developed cardiogenic shock in the course of myocardial infarction and were treated with primary coronary angioplasty, but large selection bias cannot be excluded. [144,158-161]

Prevention of reocclusion after initially successful reperfusion in patients with cardiogenic shock is clearly an essential factor in ultimate patient survival and by supporting the coronary circulation (increase of coronary blood flow) in the IRV and the other, often also compromised coronary arteries, the IABP can contribute to this goal. Further benefits of the IABP include: support of the post-ischemic "stunned" myocardium, reduction of the afterload of the left ventricle and enhancement of the collateral circulation. All patients with severe hemodynamic problems during the acute phase of myocardial infarction (even beyond the time window of 4 hours) should be considered candidates for primary coronary angioplasty with additional supportive measures and in community hospitals, transferal to hospitals with facilities for cardiac catheterization and interventional cardiology should be initiated to perform primary coronary angioplasty as soon as possible [157].

1.7 Primary or direct coronary angioplasty

Hartzler and colleagues were the first to report on the results of primary or direct coronary angioplasty (without antecedent or concomitant thrombolytic therapy) as a treatment modality for myocardial infarction [28]. The primary success rate of the procedure was very high for single vessel coronary artery disease (99%) as well as for multivessel-disease (90%) [100,162,163]; there were few procedural complications, the in-hospital mortality was low and at three-year follow-up the survival rate was 87% - 92%. In patients with previous coronary bypass surgery primary angioplasty appeared also to be effective and safe [164].

Gacioch and Topol have reported a high incidence of complications and death after angioplasty in patients with AMI and occlusion of the right coronary artery, attributed to a higher reocclusion rate, an exaggerated Bezold-Jarisch reflex, and reperfusion injury [165]. This could not be confirmed by another major study on complications of angioplasty in the setting of AMI, although minor catheterization related events were more common in patients presenting with an occlusion of the right coronary artery [100]. Combined results from nine, non-randomized, descriptive studies of primary coronary angioplasty with data from 2015 patients demonstrated an in-hospital mortality between 5 and 14%, probably reflecting the heterogeneity of the patient groups [166]. This stressed the need for randomized comparisons of thrombolytic therapy and primary angioplasty therapy for myocardial infarction.

The first trial that assigned patients to undergo primary PTCA or to receive thrombolytic therapy (intracoronary streptokinase) on a randomized, prospective base, was the study by O'Neill and colleagues (1986) [134] and demonstrated a more effective preservation of myocardial function and a less severe residual stenosis of the infarct-related coronary artery in patients treated with primary coronary angioplasty. Coronary reperfusion was established in 83% of the patients treated with angioplasty and in 85% of those treated with thrombolysis. The time from symptom onset to reperfusion was the same in both groups. Marco and co-workers also demonstrated the effectiveness, safety and beneficial effects on left ventricular function of primary coronary angioplasty in a non-randomized group of 43 patients with AMI [167].

An overview of reports on primary angioplasty is given in Table 6. Primary angioplasty is an effective means of complete recanalization in patients with acute myocardial infarction with reduction of the residual stenosis of the IRV and with the potential to eliminate thrombus ("squeezing the thrombus"). Bleeding complications, especially intracranial hemorrhage, may be significantly less than for thrombolytic therapy. Primary angioplasty may also be useful in patients beyond the traditional time window of 4-6 hours, especially when there are signs of ongoing ischemia [84,151].

1.8 Limitations of primary coronary angioplasty treatment for AMI

A limited number of hospitals have angioplasty facilities and in the United States only an estimated 10% of the hospitals is equipped to perform emergency angioplasty (Braunwald, comment: "This week in the New England Journal of Medicine", April 1993). In the Netherlands, coronary angioplasty is performed in 13 hospitals, all of them with on-site cardiac surgical support which, in the opinion of the Netherlands Society of Cardiology, is a prerequisite for performing coronary angioplasty [168]. The geographical distribution of these centers in the Netherlands is such that almost every community hospital is within 60 kilometers of a hospital with interventional cardiology facilities. Patients with large myocardial infarctions and hemodynamic compromise can be referred to these hospitals but the risk of serious complications during transportation should be kept in mind. Performance of primary coronary angioplasty for AMI in hospitals without interventional cardiology experience would probably result in a high incidence of adverse events, as was shown by Brodie and co-workers [149]. The risk of the angioplasty procedure is low in experienced hands but definitely not zero and serious unexpected problems with severe clinical implications can be encountered [55,100,165]. Emergency coronary artery bypass surgery after primary coronary angioplasty is indicated in approximately 5% of the patients versus 1% - 2% of patients undergoing elective PTCA [169].

The costs of having a complete catheterization laboratory team available on a 24 hour base and the possible time-delay in mobilizing this team to establish rapid reperfusion of the IRV should be kept in mind and could be a drawback to perform primary angioplasty on a routine base, even in hospitals with all the facilities, mentioned above.

A biological obstacle of coronary angioplasty (often referred to as the "Achilles' heel") to be overcome remains the problem of restenosis after initially successful angioplasty procedures. After elective coronary angioplasty the incidence of restenosis is reported to be 20%-40% whereas this incidence is probably higher after angioplasty for unstable coronary syndromes [170-172]. The true incidence of restenosis and reocclusion after primary coronary angioplasty for AMI is unknown and may be higher than that reported for elective PTCA. It may be comparable to that in patients with unstable angina or recanalization of occluded coronary arteries [171]. In two studies the restenosis rate after primary coronary angioplasty was 31% and 36% and the reocclusion rate was 9%, but repeat angiography was performed only in approximately 70% of these patients [173,174]. Deposition and accumulation of platelets at the site of angioplasty is strongly related to restenosis and reocclusion and adequate antiplatelet therapy may be an important tool to prevent these phenomena [175,176].

Conclusion

Treatment of patients with acute myocardial infarction is changing and improving rapidly. Early reopening of the IRV with avoidance of subsequent reocclusion appears to be the cornerstone of therapy. Thrombolytic strategies for acute myocardial infarction have reached their "third generation" stage and combinations of already well known thrombolytic agents, newer drugs, accelerated dosing schedules and front-loading administration have recently been introduced and have shown to reduce mortality [40,177,178-181]. Potentially exciting new agents for antiplatelet therapy like the monoclonal antibody c7E3 Fab, an inhibitor of the glycoprotein IIb-IIIa receptors on the platelet surface, and potent thrombin inhibitors are under investigation. Ongoing clinical trials are examining modifications of these regimens [182]. The combined use of thrombolytic and angioplasty therapy for the treatment of AMI has been abandoned after disappointing study results. Advances in technique, equipment and development of new devices have expanded the use of coronary angioplasty, and coronary artery lesions only recently considered to be unsuitable for this non-surgical approach, are treated with a high rate of success. However, only an experienced team of operators with competent cardiosurgical support will achieve these excellent results [183]. The possibility that the results of angioplasty therapy for myocardial infarction may be worse *because* of the addition of thrombolytic therapy by the combination of intramyocardial hemorrhage, intra-plaque hemorrhage and activation of platelets by thrombolytic agents, has only recently been the subject of interest. One trial was designed to find out if thrombolytic therapy improved or deteriorated the outcome of angioplasty for AMI and these data demonstrated no beneficial effects on preservation of left ventricular function, no reduction of restenosis and a higher rate of complications in patients with adjunctive intravenous streptokinase therapy [146] However comparisons of primary angioplasty with other reperfusion strategies were lacking. This thesis tries to redefine the role of coronary angioplasty in acute myocardial infarction. During the completion of this work [184], results of two other prospective randomized studies with regard to primary angioplasty have been published and have given support to the conclusions drawn in this thesis [185,186].

Table 1: Questions, addressed in this thesis are indicated with a question mark.

	Thrombolysis	*Primary Angioplasty*
Success for achieving reperfusion	++	+++
Infarct size reduction	+	+?
Preservation LV function	+	?
Effect on survival	+	?
Long term effect on residual stenosis	±	?
Risk of reocclusion		
Early:	+	?
Late	+	?
Hemorrhagic changes		
Intramural	+	-?
Intraluminal	+	-
Risk of bleeding (non-cerebral)	+	-
Risk of stroke		
Intracranial bleeding	+	-
Ischemic	+	?
Availability	+++	+
Convenience	+++	-
Initial costs	+	+++
Long term costs	++	?

Table 2: Studies of intravenous thrombolytic therapy and reported angiographic patency rates (TIMI grade 2 and 3).

Time from start therapy	n	patency
60 min:		
Streptokinase:	224	48% (93/192)
tPA:	487	62% (241/425)
Accelerated tPA:	643	74% (401/545)
90 min:		
Streptokinase:	789	51% (411/799)
tPA:	1648	70% (1107/1585)
Accelerated tPA:	671	84% (533/632)
120 - 180 min:		
Streptokinase:	280	70% (189/270)
tPA:	147	73% (103/142)
Accelerated tPA:	-	
1 d:		
Streptokinase:	376	86% (294/344)
tPA:	1837	84% (1347/1606)
Accelerated tPA:	323	86% (253/293)
3-21 d:		
Streptokinase:	543	74% (324/438)
tPA:	2327	80% (1626/2042)
Accelerated tPA:	210	89% (158/177)

From: Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction. A review. Drugs 1992;44:293-325 [42]. With kind permission from the authors.

Table 3: Studies of intravenous thrombolytic therapy and TIMI grade 3 flow.

Time from start therapy	n	patency TIMI 3
90 min:		
Streptokinase + SC Heparin (GUSTO)	293	29% (85/293)
Streptokinase + IV Heparin (GUSTO)	283	32% (91/283)
Urokinase + heparin (TAMI 5)	95	40% (38/95)
tPA + Streptokinase (GUSTO)	299	38% (114/299)
tPA + Urokinase + heparin (TAMI 5)	97	61% (59/97)
tPA + heparin (TAMI 5)	95	56% (53/95)
Accelerated tPA (GUSTO)	292	54% (157/292)
120 min:		
Streptokinase (TEAM-2)	182	53% (93/176)
APSAC (TEAM-2)	188	60% (110/183)
180 min:		
Streptokinase + SC Heparin (GUSTO)	106	35% (37/106)
Streptokinase + IV Heparin (GUSTO)	97	41% (40/97)
tPA + Streptokinase (GUSTO)	91	53% (48/91)
Accelerated tPA (GUSTO)	93	43% (40/93)
1 d:		
Streptokinase + SC Heparin (GUSTO)	83	51% (42/83)
Streptokinase + IV Heparin (GUSTO)	92	41% (38/92)
APSAC (TEAM-3)	149	75% (112/149)
tPA + Streptokinase (GUSTO)	93	60% (56/93)
tPA (TEAM-3)	149	73% (109/149)
Accelerated tPA (GUSTO)	104	45% (47/104)
5-7 d:		
Streptokinase + SC Heparin (GUSTO)	93	51% (47/93)
Streptokinase + IV Heparin (GUSTO)	96	58% (56/96)
tPA + Streptokinase (GUSTO)	89	55% (49/89)
Accelerated tPA (GUSTO)	83	58% (48/83)

TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial; GUSTO = Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Study; TEAM = Trial of Eminase (anistreplase) in Acute Myocardial Infarction; tPA = tissue-type plasminogen activator; APSAC = Anisoylated plasminogen streptokinase activator complex.

Table 4: Mortality in the randomized studies of routine coronary angioplasty after thrombolytic therapy.

Study (year of publication and reference nr.)	n	Agent	time thrombolysis - angioplasty	early mortality C	A
Immediate angioplasty					
Erbel et al. (1986) [31]	162	SK	< 2 h	11%	7%
TAMI I (1987) * [47]	99	tPA	< 2 h	-	4%
TIMI IIA (1988) * [56]	195	tPA	< 2 h	-	7.2%
Simoons ECSG-5 (1988) [55]	367	tPA	< 3 h	3%	7%
Deferred - late angioplasty					
TIMI IIA (1988) * [56]	194	tPA	18 - 48 h	-	5.7%
TIMI IIB (1989) [58]	3262	tPA	18 - 48 h	4.7%	5.2%
SWIFT (1991) [59]	800	APSAC	24 h - 7 d	2.7%	3.3%
vd Brand (1992) [144]	218	tPA	48 h - 5 d	2.9%	0.9%
Barbash et al. (1990) [60]	201	tPA	5 d	4%	5%
TAMI I (1987) * [47]	98	tPA	7 - 10 d	-	1%
Ellis (1992) [187]	87	SK/tPA	4 - 14 d	0%	0%

* The TAMI I and TIMI IIA trials compared immediate and deferred angioplasty.
C = Conservative therapy, A = Angioplasty therapy (intention to treat). TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial; ECSG = European Cooperative Study Group; TIMI = Thrombolysis in Myocardial Infarction; SWIFT = Should We Intervene Following Thrombolysis; SK = streptokinase; tPA = tissue-type plasminogen activator; APSAC = Anisoylated plasminogen streptokinase activator complex.

Table 5: Definitions of perfusion in the TIMI trials

Grade 0	(no perfusion): There is no antegrade flow beyond the point of occlusion.
Grade 1	(penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence.
Grade 2	(partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel - e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
Grade 3	(complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Definition of the Thrombolysis in Myocardial Infarction (TIMI) study flow grades, used in Chapters 4 and 5.

Reference: Chesebro JH, Knatterud G, Roberts R et al.Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76:142-54.

Table 6: Studies of primary coronary angioplasty for acute myocardial infarction.

Study (First author, year of publication, reference nr.)	n	success	reocclusion #	restenosis	in-hospital death
Hartzler 1984 [188]†	78	90%	15%		8%
Kimura 1984 [189]	58	88%	16%		
O'Neill 1986 [133] *	29	83%	8.3%		6.8%
Rothbaum 1987 [177]	151	87%	9%	31%	7%
Marco 1987 [171]	43	95%	22%	30%	9.3%
Miller 1987 [178]	81	92%	7.9%	35%	7.8%
Flaker 1989 [190] ‡	93	78%	11%	34%	14%
DeWood 1989 [191] *	18				
O'Neill 1992 [149] *	63	93%	11%	37%	6.5%
Zijlstra 1993 [184] *	70	98%	9%	24%	2%
Grines 1993 [185] *	195	97%			2.6%
Gibbons 1993 [186] *	47	93%			4%
Ribeiro 1993 [192] *	40	90%	2.5%		6%
Saito 1994 [193]	198	93%	7.5%		8%
O'Keefe 1993 [194]	1000	94%	13%		8%
O'Neill 1994 [195]	271	92%			4%

#, indicates early or late reocclusion, depending on study design; * ,indicates if the study was a prospective randomized trial; †, some patients in the whole study group also received thrombolytic agents; ‡, only anterior wall infarcts were included.

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Chapter 2

A Comparison of Immediate Coronary Angioplasty with Intravenous Streptokinase in Acute Myocardial Infarction

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Abstract *Background.* Despite the widespread use of intravehous thrombolytic therapy and of immediate percutaneous transluminal coronary angioplasty for the treatment of acute myocardial infarction, randomized comparisons of the two approaches to reperfusion are lacking. We report the results of a prospective, randomized trial comparing immediate coronary angioplasty (without previous thrombolytic therapy) with intravenous streptokinase treatment.

Methods. A total of 142 patients with acute myocardial infarction were randomly assigned to receive one of the two treatments. The left ventricular ejection fraction was measured by radionuclide scanning before hospital discharge. Quantitative coronary angiography was performed to assess the degree of residual stenosis in the infarct-related arteries.

Results. A total of 72 patients were assigned to receive streptokinase and 70 patients to undergo immediate angioplasty. Angioplasty was technically successful in 64 of the 65 patients who underwent the procedure. Infarction recurred in nine patients assigned to receive streptokinase, but in none of those assigned to receive angioplasty ($P = 0.003$). Fourteen patients in the streptokinase group had unstable angina after their infarction, but only four in the angioplasty group ($P = 0.02$). The mean ($\pm$ SD) left ventricular ejection fraction as measured before discharge was 45 ± 12 percent in the streptokinase group and 51 ± 11 percent in the angioplasty group ($P = 0.004$). The infarct-related artery was patent in 68 percent of the patients in the streptokinase group and 91 percent of those in the angioplasty group ($P = 0.001$). Quantitative coronary angiography revealed stenosis of 36 ± 20 percent of the luminal diameter in the angioplasty group, as compared with 76 ± 19 percent in the streptokinase group ($P < 0.001$).

Conclusions. Immediate angioplasty after acute myocardial infarction was associated with a higher rate of patency of the infarct-related artery, a less severe residual stenotic lesion, better left ventricular function and less recurrent myocardial ischemia and infarction than was intravenous streptokinase.

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In 1980 De Wood et al. [1] showed that acute transmural myocardial infarction is usually associated with total coronary occlusion due to an intraluminal coronary thrombus superimposed on an atherosclerotic lesion. Over the past decade the efficacy of thrombolytic therapy and coronary angioplasty in restoring patency to the infarct-related coronary artery has been studied extensively [2-9]. Although "rescue" angioplasty may be advantageous in infarct-related arteries that fail to reperfuse after thrombolytic therapy [10], in general there is no additional benefit of routine angioplasty after thrombolytic therapy [7,8]. The results of recently published randomized trials indicate that the combination of streptokinase, aspirin and heparin is the generally accepted treatment for patients with acute myocardial infarction [11-13]. Immediate coronary angioplasty without previous thrombolytic therapy avoids the potentially adverse effects of myocardial and intraplaque hemorrhage that can occur after thrombolysis [14]. Immediate angioplasty is therefore advocated by some authors as the preferred treatment of acute myocardial infarction [9,15]. This approach has the additional advantage of reducing the hemodynamic importance of the underlying atherosclerotic lesion. One report suggested, however, that the incidence of complications is high after immediate angioplasty [16]. Except for a small randomized study comparing intracoronary streptokinase treatment with immediate angioplasty [17], comparisons of the two approaches are lacking. For that reason we performed a prospective, randomized trial comparing immediate angioplasty with intravenous streptokinase treatment in patients with acute myocardial infarction.

Methods

Patients

The research protocol was reviewed and approved by our institutional review board. The enrollment of patients began on August 20, 1990, and ended on February 10, 1992. Inclusion criteria were as follows: symptoms of acute myocardial infarction that persisted for more than 30 minutes, accompanied by an elevation of more than 1 mm (0,1 mV) in the ST segment in two or more contiguous electrocardiographic leads; presentation within 6 hours after the onset of symptoms (or between 6 and 24 hours, if there was evidence of continuing ischemia); an age of less than 76 years; and no contraindication to thrombolytic therapy, including previous stroke or other known intracranial disease, recent trauma or surgery, refractory hypertension, active bleeding or prolonged cardiopulmonary resuscitation. Previous coronary-artery bypass grafting, previous Q-wave or non-Q-wave infarction, and cardiogenic shock were not reasons for

exclusion. Before randomization we recorded each patient's age, sex, Killip class on admission [18], electrocardiographic site of infarction, history of infarction, heart rate, arterial pressure, time of onset of symptoms, and time of hospital admission.

Randomization and Treatment Protocol

After informed consent was obtained, the patients were randomly assigned to one of the two treatment groups by means of a closed-envelope system. All the patients received 300 mg of aspirin intravenously, followed by 300 mg of aspirin per day orally and intravenous nitroglycerin in a dose designed to maintain a systolic blood pressure of 110 mm Hg. Intravenous heparin was given in a dose designed to maintain the activated partial-thromboplastin time between two and three times the normal value for at least two days.This partial-thromboplastin time was measured twice a day. Although values more than three times the normal value occurred at least once in 57 percent of the patients, values less than two times the normal value were observed in only 13 percent. Drugs such as lidocaine, calcium-channel blockers, and ß-adrenergic blockers were given only at the discretion of the attending physicians. Fourteen percent of the patients in the streptokinase group and 16 percent of those in the angioplasty group received intravenous lidocaine; 31 percent and 41 percent, respectively, received calcium-channel blockers; and 39 percent and 27 percent received ß-adrenergic blockers. Patients assigned to streptokinase received 1.5 million units intravenously over a period of one hour. Patients assigned to undergo coronary angioplasty were moved to the catheterization laboratory as quickly as possible and underwent coronary angiography. Both coronary arteries were visualized; left ventriculography was not performed. The time from admission to the initiation of therapy was calculated as the time to the start of the streptokinase infusion or the first balloon inflation.

Study End Points

The variables we measured were the rate of recurrent ischemia before discharge, the left ventricular ejection fraction, and vessel patency. Recurrent ischemia before hospital discharge included the following: stable angina, defined as chest pain and a positive exercise test; unstable angina defined as chest pain and changes in the ST-T segment at rest; and recurrent myocardial infarction, defined as chest pain, changes in the ST-T segment, and a second increase in the creatine kinase level to more than two times the upper limit of normal, or an increase of >200 U per liter over the previous value if the level had not dropped below the upper limit of normal. All electrocardiograms and

laboratory results were reviewed for evidence of recurrent ischemia by two cardiologists blinded to assigned therapy. Electrocardiographic changes that were required for a diagnosis of ischemia were ST-segment depression or a new elevation of the ST-segment of at least 1 mm in two or more contiguous leads during chest pain; alternatively, unchanged or pseudonormal ST-segments had to be present during chest pain, with the T waves becoming inverted after the pain was relieved. These inverted T waves had to have a minimal depth of 2 mm and had to develop within three hours after the recurrence of chest pain. A symptom-limited bicycle exercise test was performed with the patient in the supine position, with increments of 10 W per minute. An exercise test indicating ischemia was defined as a test with an ST depression of more than 1 mm, measured 60 msec after the J point. In patients with base-line abnormalities in the ST-T wave, a depression of more than 1 mm in the ST segment was considered to indicate ischemia.

The left ventricular ejection fraction was measured with a radionuclide technique before hospital discharge [19-21]. The technique used in our hospital has been previously described [22]. Briefly, it involved the multiple-gated equilibrium method after the labeling of red blood cells with [^{99m}Tc] pertechnetate. A gamma camera (General Electric Milwaukee) with a low-energy, all-purpose, parallel-hole collimator was used. The global ejection fraction is calculated automatically by computer (Star View, General-Electric), with the PAGE program. The data on ejection fractions were gathered by a specialist in nuclear medicine who was blinded to the clinical data. This use of a software program whose results did not depend on the operator protected against possible bias. The reproducibility of the method is excellent, the mean (±SD) difference between duplicate measurements being 1.2 ± 1.1 percent [22].

Arterial patency, defined as a Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow in the infarct-related coronary artery [6], was assessed by coronary angiography. In the angioplasty group, angiography was repeated, preferably after three months, to assess the rate of restenosis [23]. Only the patient's name, date of birth, and electrocardiographic site of infarction were known during the assessment of the angiogram. All infarct-related vessels were analyzed quantitatively with a personal-computer-based-system of cardiovascular analysis (Cardiovascular Measurement System, Medis Medical Imaging Systems, Nuenen, the Netherlands) [24]. The basic algorithms have been described elsewhere [25]. The system uses a high-quality converter that allowed a selected cine frame to be projected onto a digital camera through a zoom lens. The video signal of the magnified region of interest was

subsequently digitized. For calibration, the boundaries of a nontapering part of the catheter were determined automatically over a length of approximately 2 cm. To determine the contours of the vessel the user had only to indicate the beginning and end of the coronary segment to be analyzed, after which a path was computed connecting these two points [26]. The contour procedure was then performed iteratively by resampling the image along scan lines perpendicular to the path computed in the first iteration. Next, a matrix of cost coefficients was computed that represented for each point in the resampled matrix the edge strength based on the weighted sum of the first and second derivative functions. The initial contours were found by the minimal-cost contour-detection technique applied to the cost-coefficient matrix [27]. In the second iteration, the contours determined in the first iteration functioned as models for the subsequent determination. The edge strengths were corrected for the limited resolution of the entire imaging chain, a procedure that is of particularly important for the accurate measurement of small vessels. From the final contours a new center line was computed. A diameter was determined in absolute terms (in millimeters) by computing along the vessel center line the shortest distances between the left and right contours. The reference diameter was defined as previously described [27].

Statistical analysis

All end points were analyzed according to the principle of intention to treat. Student's t-test was used to compare mean values. Comparisons of the rates of recurrent ischemia, vessel patency, and complications were made with a conventional chi-square test, but Fisher's exact test was used if there was an expected cell value of less than 5. All calculated P values are two-tailed. In our presentation of the data, continuous base-line and outcome variables are given as means ±SD, whereas discrete variables are given as absolute values and percentages.

Results

The patient's base-line clinical and angiographic characteristics are shown in Table 1. The mean time from admission to the start of the streptokinase infusion was 30 ± 15 minutes. All the patients assigned to angioplasty underwent emergency angiography. The infarct-related vessel showed a flow of TIMI grade 0 in 87 percent of the patients. Two patients with open vessels were treated conservatively. Three patients with severe multivessel disease or stenosis of the left main artery underwent emergency coronary-artery bypass grafting after the insertion of an intraaortic counterpulsation balloon. The

remaining 65 patients underwent immediate angioplasty of the infarct-related vessel, with success in 64 patients (98 percent). (The angioplasty was considered to be technically successful if there was residual stenosis of less than 50 percent on visual estimation and a flow of TIMI grade 2 or 3.) In one patient the infarct-related vessel could not be reopened: this patient underwent immediate coronary-artery bypass grafting. The time from admission to the first balloon inflation was 61 ± 22 minutes.

The creatine kinase level rose to 1327 ± 1304 U per liter in the streptokinase group and 1477 ± 1215 U per liter in the angioplasty group (P = 0.49). The normal value for creatine kinase is less than 100 U per liter in our hospital.

Complications and required procedures are shown in Table 2. Intercerebral bleeding and bleeding necessitating a blood transfusion were considered to be bleeding complications. There were fewer complications overall in the patients assigned to immediate angioplasty than is those assigned to streptokinase. In particular, death, bleeding, and heart failure occurred less frequently in the angioplasty group. Thirty-eight percent of the patients in the streptokinase group had recurrent ischemia, but only 9 percent of those in the angioplasty group (P < 0.001) (Table 3). The frequency of stable angina was similar in the two groups, but the incidence of recurrent myocardial infarction and unstable angina was higher in the patients who received streptokinase. Additional revascularization procedures were more often necessary in the streptokinase group (Table 3). Four patients assigned to angioplasty underwent bypass surgery within 24 hours after admission, three without having undergone angioplasty.Three patients had elective bypass surgery for anatomical reasons after successful angioplasty [6, 9, and 10 days after admission). Only one patient in the angioplasty group underwent emergency repeat angioplasty for threatened reocclusion. Two patients in the angioplasty group underwent elective angioplasty of non-infarct-related arteries (7 and 11 days after admission). In the streptokinase group, 2 patients had emergency bypass surgery, 6 had elective bypass surgery (13 ± 6 days after admission), 14 had emergency angioplasty, and 8 had elective angioplasty for recurrent ischemia (7 ± 5 days after admission).

The left ventricular ejection fraction at rest was measured in all 138 survivors; it was 45 ± 12 percent in the streptokinase group and 51 ± 11 percent in the angioplasty group (P = 0.004). Exercise testing was performed before discharge in 63 of the 72 patients in the streptokinase group (88 percent) and 67 of the 70 in the angioplasty group (96 percent), with exercise capacities of 87 ± 31 and 97 ± 30 W, respectively (P = 0.07). Angina was present during exercise in 10 of 63 who received streptokinase (16 percent)

and in 5 of 67 patients who underwent angioplasty (7 percent, P = 0.13). Significant ST-segment depression occurred in 41 percent of the streptokinase group (26 of 63 patients) and in 21 percent of the angioplasty group (14 of 67, P = 0.01). The ejection fraction measured during exercise was 46 ± 15 percent. Coronary angiography was performed after 21 ± 31 days in 68 of the 72 patients given streptokinase. Repeat angiography was performed after 82 ± 67 days in 63 of the 65 patients in the angioplasty group who actually underwent the procedure. The infarct-related vessel was patent in 68 percent of the patients who received streptokinase (49 of 72) and 91 percent of those assigned to angioplasty 64 of 70, P = 0.001). Among the patients assigned to angioplasty, only 7 percent had patent infarct-related arteries at base line, 47 percent had patent vessels 60 minutes after admission, 84 percent 90 minutes after admission, and 91 percent 120 minutes after admission and at follow-up. Quantitative angiographic analysis of the infarct-related vessels is shown in Table 4. Restenosis, defined as stenosis of more than 50 percent in the dilated vessel, was observed in 11 of 63 patients in the angioplasty group (17 percent). Although evidence has accumulated that the incidence of restenosis reaches a plateau at three months (23], the clinical implications of restenosis will become clear only after at least six months of follow-up. Excluding all angiography without evidence of restenosis performed within three months after angioplasty, we found the rate of restenosis to be 11 of 46, or 24 percent.

Discussion

Our study shows that in patients with acute myocardial infarction, direct angioplasty results in a higher rate of patency of the infarct-related coronary arteries, less severe residual stenotic lesions, better left ventricular ejection fraction, and a lower incidence of recurrent myocardial ischemia than intravenous streptokinase.

Over the past decade, great efforts have been made to assess the optimal approach to patients with acute myocardial infarction, with much attention being directed to large-scale trials in which mortality is the primary end point. However, the funds and numbers of patients needed to support multiple large trials are simply not available [28]. Left ventricular ejection fraction has been proposed [29], as well as rejected [28], as end point in trials of acute myocardial infarction. Long-term survival after reperfusion therapy is strongly related to the left ventricular ejection fraction [30], but one of the main objections to the use of the ejection fraction as an end point has been the problem of "missing values" and the consequent debate about imputating data because studies are unavailable or technically inadequate [28]. We therefore chose a radionuclide

technique that is easy to perform, requires only 10 to 15 minutes, and is not cumbersome for the patient. We were thus able to measure the ejection fraction in almost all patients. The difference between groups in the left ventricular ejection fraction (51 percent in the angioplasty group and 45 percent in the streptokinase group) is comparable to that reported by O'Neill et al [17].

The primary target of all reperfusion therapies is the reopening of occluded coronary arteries. Two characteristics of patency are important in this regard. The first is the time needed to reestablish flow in the infarct-related artery. The patients in our angioplasty group had rates of early patency that cannot be obtained with currently available thrombolytic agents. The second is the persistence of patency of the infarct-related artery, which is related to long-term survival [2]. The consequences of reocclusion after initially successful reperfusion are certainly a major concern [31]. However, the frequency of this phenomenon is low. The rate of patency in the patients who received streptokinase, assessed after a mean of 21 days, was 68 percent. The rate of patency in the angioplasty group was 91 percent, two hours after admission, and it was still 91 percent at follow-up angiography after a mean of 82 days. So, regardless of the timing of angiography for assessment, patients who undergo angioplasty have a higher rate of patency.

The third end point of our study was recurrent myocardial ischemia. Since the mortality from acute myocardial infarction has steadily declined recent years and is less than 10 percent in many recently published trials [8-11], morbidity in the survivors becomes the most relevant clinical end point. Immediate angioplasty, as compared with streptokinase treatment, reduces the incidence of recurrent myocardial ischemia drastically. A composite clinical end point has recently been proposed [28] and used [10]. It includes not only recurrent infarction or angina, but also death, stroke, reocclusion, and heart failure. Freedom from any of these adverse events can than be compared. Of the 72 patients in our study who were treated with streptokinase, 34 (47 percent) had one or more of these adverse events. Of the 70 patients assigned to angioplasty 13 (19 percent) had one or more of these adverse events. In the phase 5 of the Thrombolysis and Angioplasty in Myocardial Infarction trial [10], the group receiving urokinase followed by "delayed" coronary angiography had a rate of freedom from events of 55 percent, which is comparable to our streptokinase group (53 percent), whereas those who received a combination of tissue plasminogen activator and urokinase followed by "aggressive" catheterization had a rate of 72 percent. The patients in our angioplasty group had a rate of freedom from adverse events rate of 81

percent, significantly better than the rate in the streptokinase group (53 percent, P = 0.001).

The participation of a cardiac surgeon becomes important if coronary angiography is performed immediately after admission. A large majority of the patients randomly assigned to angioplasty had, on anatomical grounds, a clear-cut indication for angioplasty but there were exceptions. In our series, three patients had coronary anatomy that was highly unfavorable for angioplasty and therefore required emergency bypass surgery of all major coronary arteries, including the infarct-related vessel. Three other patients with extensive multivessel disease had direct angioplasty of the infarct-related vessel and subsequently underwent elective bypass surgery. Eight patients in the streptokinase group underwent bypass surgery for recurrent ischemia. Given that the coronary anatomy was known soon after admission in the angioplasty group, and not in the streptokinase group, clinical decision making was influenced by anatomical considerations. Finally, the implications of this study with respect to cost effectiveness require a formal analysis, which will be performed after one year of follow-up.

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Appendix

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Table 1. Base-line Clinical and Angiographic Characteristics of the Study Patients

	Streptokinase Group	Angioplasty Group
Characteristic	(N = 72)	(N = 70)
Age (yr)	61± 9	59 ± 10
Male - sex no. (%)	59 (82)	62 (89)
Anterior infarction - no. (%)	30 (42)	31 (44)
Previous infarction - no. (%)	10 (14)	13 (19)
Time from onset to admission (min)	162 ± 145	167 ± 165
Killip class on admission-no. (%)		
1	58 (81)	55 (78)
2	9 (13)	11 (16)
3	4 (6)	2 (3)
4	1 (1)	2 (3)
Diseased vessels - no. of patients (%)		
0 or 1	27 (37)	25 (36)
2	18 (25)	20 (29)
3	22 (31)	22 (31)
Left main artery	1 (1)	2 (3)
Unknown	4 (6)	0
Infarct-related artery - no. of patients (%)		
Left anterior descending	23 (32)	26 (37)
Left circumflex	11 (15)	12 (17)
Right coronary	30 (42)	30 (43)
Left main	1 (1)	1 (1)
Graft	3 (4)	1 (1)
Unknown	4 (6)	0

* Plus-minus values are means ± SD. Not all percentages sum to 100.

Table 2. Complications and Procedures in the Study Patients.

Variable	Streptokinase Group (N = 72)	Angioplasty Group (N = 70)	P Value
	no. (%)		
Death	4 (6)	0	0.13
Stroke	2 (3)	0	0.51
Bleeding	6 (8)	2 (3)	0.29
Mechanical ventilation	1 (1)	1 (1)	1.00
Femoral-artery repair	0	1 (1)	0.49
Heart Failure	8 (11)	4 (6)	0.25
Ventricular tachycardia and ventricular fibrillation	6 (8)	5 (7)	0.79
Bypass surgery *	2 (3)	4 (6)	0.44
Any of the above	19 (26)	10 (14)	0.07

* Coronary-artery bypass grafting was required within 24 hours after admission to the hospital.

Table 3. Recurrent Ischemia and Additional Procedures in the Study Patients *

	Streptokinase Group (N = 72)	Angioplasty Group (N = 70)	P Value
	no. (%)		
Recurrent ischemia	27 (38)	6 (9)	< 0.001
Stable angina	4 (6)	2 (3)	0.68
Unstable angina	14 (19)	4 (6)	0.02
Recurrent MI	9 (13)	0	0.003
Procedure			
Counterpulsation	9 (13)	8 (11)	0.84
PTCA	22 (31)	3 (4)	< 0.001
Bypass surgery	8 (11)	7 (10)	0.83

* MI denotes myocardial infarction, and PTCA percutaneous transluminal angioplasty.

Table 4: Quantitative Angiographic Data *

Variable	Angioplasty Group				Streptokinase Group
	Before	After	Follow-Up at 82 ± 67 Days		at 21 ± 31 Days
	(N = 70)	(N = 65)	(N = 63)	P Value	(N = 68)
Projections analyzed (no.)	2.0 ± 0.5	2.2 ± 0.6	2.2 ± 0.5	-	2.1 ± 0.6
Stenosis (%)	97 ± 10	29 ± 12	36 ± 20	< 0.001	76 ± 19
Minimal luminal diameter (mm)	0.11 ± 0.42	2.25 ± 0.62	2.04 ± 0.86	< 0.001	0.70 ± 0.58
Reference diameter (mm)†	-	3.17±0.66 (1.89-5.03)	3.15±0.64 (1.45-4.99)	0.244	3.02 ± 0.66 (1.72 - 4.82)
Largest balloon (mm)	2.98 ± 0.39	-	-	-	

* Plus-minus values are means ± SD. † By the interpolated method.

N Engl J Med 1993;328:680-84.

Beauchamp C, Westman EC, Govert JA. Treatment of acute myocardial infarction. Letter to the editor. N Engl J Med 1993;329:430.

To the Editor: "Referral filter" bias can affect the generalizability of the results of any clinical trial (1). The three clinical trials comparing angioplasty with thrombolytic therapy in the March 11 issue of the *Journal* did not mention the referral filter that led to the enrolled samples (2-4). Physicians have no way of knowing whether the study populations are similar to their own patients without a clinical description of the patients who were excluded. Could the authors comment on the number of patients excluded and the reasons for exclusion?

1. Sacket DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. 2nd ed. Boston: Little, Brown, 1991.
2. Grines CL, Browne KF, Marco J. et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-9.
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4. Gibbons RJ, Holmes DR, Reeder GS, Bayley KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685-91.

Zijlstra F, de Boer MJ, Suryapranata H. Treatment of acute myocardial infarction. Letter to the editor. N Engl J Med 1993;329:432.

The authors reply:

To the Editor: We agree with Beauchamp and colleagues that referral-filter bias can affect the generalizability of the results of a clinical trial. We registered all patients admitted to our hospital who fulfilled the inclusion criteria for our study, but were excluded for other reasons. During the study period, six eligible patients were not randomized. Two patients declined to participate, one died in the emergency room before randomization, and one who lived outside the Netherlands was not randomized because of anticipated problems with follow-up. In two cases the attending physicians did not wish to include the patient in the study.

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Menko Jan de Boer, M.D.
Harry Suryapranata, M.D., Ph.D.

Chapter 3

Immediate Coronary Angioplasty versus Intravenous Streptokinase in Acute Myocardial Infarction: Left Ventricular Ejection Fraction, Hospital Mortality and Reinfarction.

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This study was supported by Grant No. 321 from The Netherlands Heart Foundation.

the Journal of the American College of Cardiology 1994;23:1004-8.

Objectives: The purpose of the present study was to compare intravenous streptokinase with immediate coronary angioplasty without antecedent thrombolytic therapy with regard to left ventricular function and hospital mortality and reinfarction.

Background: Despite the widespread use of intravenous thrombolytic therapy and immediate percutaneous transluminal coronary angioplasty, these two strategies to treat patients with an acute myocardial infarction have only recently been compared in randomized trials. Coronary angioplasty has been shown to result in a higher patency rate of the infarct-related coronary artery, with a less severe residual stenotic lesion, compared with streptokinase therapy, but whether this more favorable coronary anatomy results in clinical benefit remains to be established.

Methods: We studied 301 patients with acute myocardial infarction randomly assigned to undergo immediate coronary angioplasty without antecedent thrombolytic therapy or to receive intravenous streptokinase therapy. Before discharge left ventricular ejection fraction was measured by radionuclide scanning.

Results: The in-hospital mortality rate in the streptokinase group was 7% (11 of 149 patients) compared with 2% (3 of 152) in the angioplasty group ($p = 0.024$). In the streptokinase group recurrent myocardial infarction occurred in 15 patients (10%) versus in 2 (1%) in the angioplasty group ($p < 0.001$). Either death or nonfatal reinfarction occurred in 23 patients (15%) in the streptokinase group and in 5 patients (3%) in the angioplasty group ($p = 0.001$). Left ventricular ejection fraction was $44 \pm 11\%$ (mean $\pm$ SD) in streptokinase group versus $50 \pm 11\%$ in the angioplasty group ($p < 0.001$).

Conclusions: These findings indicate that immediate coronary angioplasty without antecedent thrombolytic therapy results in better left ventricular function and lower risk of death and recurrent myocardial infarction than treatment with intravenous streptokinase.

(J Am Coll Cardiol 1994;23:1004-8)

During the past decade the efficacy of thrombolytic therapy and coronary angioplasty in restoring patency of the infarct-related coronary artery has been studied extensively [1-11]. Currently, the combination of streptokinase, aspirin and heparin is one of the generally accepted treatment strategies in patients with acute myocardial infarction [8-10]. Direct coronary angioplasty without antecedent thrombolytic therapy avoids the potentially adverse effects of myocardial and intraplaque hemorrhage that can be observed after thrombolytic therapy [12] and may be an appropriate alternative therapy [7,13-15]. In a previous report we showed that direct coronary angioplasty is associated with a higher patency rate, a less severe residual stenotic lesion in the infarct-related vessel, better preserved left ventricular function as well as less recurrent ischemia before hospital discharge compared with intravenous streptokinase therapy [13]. However, several important questions are still to be answered before direct angioplasty can be accepted as the therapy of choice in patients with acute myocardial infarction. In particular, does the superior coronary anatomy result in a more favorable clinical outcome? Although the results of the Primary Angioplasty In Myocardial Infarction trial [14] showed a strong trend toward survival benefit and lower rate of reinfarction with angioplasty versus intravenous tissue plasminogen activator, additional data are needed before definitive conclusions can be drawn. We therefore extended our trial to investigate differences in mortality, recurrent myocardial infarction and left ventricular ejection fraction before hospital discharge.

Methods

The research protocol was reviewed and approved by the institutional review board. The enrollment of patients began on August 20, 1990 and ended on April 26, 1993. Inclusion criteria were: 1) symptoms of acute myocardial infarction persisting > 30 min, accompanied by an electrocardiogram (ECG) with > 1-mm (0,1 mV) ST segment elevation in two or more contiguous leads; 2) presentation within 6 h after symptom onset or between 6 and 24 h, if there was evidence of continuing ischemia; 3) age < 76 years; 4) no contraindication to thrombolytic intervention. Before randomization the following variables were recorded: age, gender, Killip class on admission [16], ECG site of infarction, history of previous infarction, time of symptom onset and time of hospital admission.

Randomization and Treatment.

After informed consent was obtained, patients were randomly assigned to one of the two treatment modalities by means of a closed-envelope system. All patients

received aspirin and heparin. Heparin was given intravenously and titrated to a dose that resulted in an activated partial thromboplastin time of two to three times the normal value. Patients assigned to streptokinase therapy received 1.5 million U intravenously in 1 h. Patients assigned to undergo coronary angioplasty were immediately transported to the catheterization laboratory for coronary angiography. If the coronary anatomy was suitable for angioplasty, this procedure was performed immediately using standard techniques.

End points.

The study end points were the following: 1) death before hospital discharge. 2) Recurrent myocardial infarction before hospital discharge, defined as chest pain accompanied by changes in ST-T waves or new Q waves, and a second increase in creatine kinase of more than two times the upper limit of normal or an increase of this magnitude over the previous value if the level had not decreased below the upper limit of normal [13]. 3) Left ventricular ejection fraction was measured with a radionuclide technique before hospital discharge. The technique used in our hospital has been described elsewhere [13].

Statistical analysis.

Statistical analysis was performed with an SPSS personal computer, version 4.01, 1990. All end points were analyzed according to the principle of intention to treat. Differences between group means were tested by a two-tailed Student t test. A chi-square method was used to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals [17]. Patients randomized to undergo angioplasty were defined as the reference group. The Fisher exact test was used if there was an expected cell value < 5. Statistical significance was defined as a p value < 0.05. Multivariate analysis was performed by fitting a logistic regression model, permitting calculation of odds ratios that could be interpreted as relative risk and their 95% confidence interval (CI). All baseline characteristics that could have had an effect on the occurrence of in-hospital death or recurrent infarction were incorporated into the model to estimate the proper treatment effect. In the multivariate analysis, adjustments were made for differences in age (continuous variable), gender, infarct location (anterior versus nonanterior), Killip class on admission, time from onset of symptoms to admission and previous myocardial infarction. In the presentation of the data, continuous variables are given as mean value ±SD, whereas discrete variables are given as absolute values and percents.

Results

The 301 patients in this study include the 142 patients evaluated previously [13]. During the enrollment period, 301 patients were randomized to undergo either streptokinase therapy (149 patients) or coronary angioplasty (152 patients). All patients assigned to the angioplasty group underwent immediate coronary angiography, with one exception: One patient died of cardiogenic shock immediately after randomization. Five patients had an open infarct-related artery and were treated conservatively. Six patients with extensive coronary artery disease not suitable for angioplasty underwent primary coronary artery bypass grafting. Angioplasty was performed in 140 patients, and the procedure was successful in 136 (97%). In four patients angioplasty failed to reopen the infarct-related vessel. Three of them underwent emergency coronary artery bypass grafting, and one patient was treated conservatively. Of the 136 patients with successful angioplasty, 7 underwent elective coronary artery bypass grafting for left main coronary artery or extensive three-vessel coronary artery disease. All patients assigned to therapy with intravenous streptokinase were treated accordingly, with one exception: One patient died of cardiogenic shock immediately after randomization. Another 16 patients with hemodynamic compromise and signs of ongoing ischemia within 24 h after admission underwent rescue angioplasty, with procedural success in 15 patients. Emergency coronary artery bypass grafting was performed in one patient. Sixteen patients underwent emergency coronary angioplasty because of signs of recurrent ischemia, with emergency coronary artery bypass grafting in 1 patient, and procedural success in 15 patients. Nine patients underwent elective angioplasty, and 13 patients underwent elective coronary artery bypass grafting for exercise-induced signs of myocardial ischemia. The remaining 94 patients were treated conservatively. Coronary angiography was performed in 141 of the 149 patients assigned to receive streptokinase (95%). Baseline characteristics are shown in table 1, and additional clinical data are shown in Table 2.

End points.

Death: A total of 14 patients (5%) died, 11 (7%) in the streptokinase group and 3 (2%) in the angioplasty group ($p = 0.024$). The cause of death is shown in Table 3. If patients in cardiogenic shock were excluded, there was still a significantly lower mortality in the patients randomized to undergo angioplasty (2 of 144 versus 10 of 146, $p = 0.03$).

Recurrent myocardial infarction. A total of 17 patients (6%) had a recurrent myocardial infarction, 15 (10%) in the streptokinase group and 2 (1%) in the angioplasty group $p < 0.001$). Death or a nonfatal recurrent infarction occurred in 23 patients (15%) in the streptokinase group and in 5 patients (3%) in the angioplasty group ($p = 0.001$). The results of the univariate analysis are shown in Table 3.

Age was associated with mortality. Non-survivors were 66 ± 9.8 years old and survivors were 59 ± 5.5 years old ($p = 0.01$). After multivariate analysis, age, Killip class on admission, previous myocardial infarction and treatment with streptokinase were associated with the endpoints of death and recurrent myocardial infarction, as well as the combination of death and nonfatal recurrent infarction. Patients with a previous myocardial infarction had an increased risk of recurrent infarction (relative risk 4.5, 95% CI 1.4 to 14.5). Killip class on admission was associated with an increased risk of death (relative risk 3.6 per step, 95% CI 2.0 to 6.6). After adjustments were made for differences in age, gender, previous myocardial infarction, time from onset of symptoms to admission, location of the infarction and Killip class on admission, the relative risk of reinfarction in the streptokinase group was 9.7 (95% CI 2.1 to 45.1) compared with the angioplasty group, and the relative risk of death was 8.5 (95% CI 1.7 to 41.7) in the streptokinase group compared with the angioplasty group.

Left ventricular ejection fraction. Left ventricular ejection fraction was measured in 140 patients (94%) in the streptokinase group and in 149 patients (98%) in the angioplasty group. Patients in the streptokinase group had an ejection fraction of 44±11% and those in the angioplasty group had an ejection fraction of 50 ± 11% ($p < 0.001$). A previous myocardial infarction, the location of the infarction and the time from symptom onset to admission were related to ejection fraction, as shown in Table 4. Before discharge 260 (86%) of the 301 patients performed a symptom-limited exercise stress test. The results are shown in Table 5.

Discussion

Although thrombolytic therapy is one of the major advances in the care of patients with an acute myocardial infarction [1-4,6,9,10], reperfusion of the occluded infarct-related artery is not obtained in 20% to 32% of patients [8,11,13]. Recent trials have shown that immediate coronary angioplasty without antecedent thrombolytic therapy results in a reperfusion rate > 90% [7,13,14]. Furthermore, signs of recurrent myocardial ischemia that occur often in patients after thrombolytic therapy and result in reinfarction, as well as subsequent in-hospital interventions [5], seem to be reduced

after immediate angioplasty [13, 14]. We therefore extended our previous trial [13] to investigate whether these differences in coronary patency and recurrent ischemia would result in differences in mortality and the incidence of recurrent myocardial infarction. Our data support this hypothesis.

Myocardial salvage and left ventricular ejection fraction.

Left ventricular ejection fraction has been proposed [18], as well as rejected [19], as an end point in trials of acute myocardial infarction. Long-term survival is strongly related to left ventricular ejection fraction [6], but one of the main objections to the use of ejection fraction as an end point has been the problem of "missing values", and the consequent debate about imputing data because studies are unavailable or technically inadequate [19]. We therefore chose a radionuclide technique that is easy to perform, requires only 10 to 15 min and is not cumbersome for the patient [13]. We were thus able to measure ejection fraction in nearly all of our patients (289 [96%] of 301). Our results show (Table 4) that immediate angioplasty salvages more myocardium than thrombolytic therapy, especially in patients with an infarction of the anterior wall, and in patients with a short interval between symptom onset and hospital admission.

Impact of coronary angiography immediately after hospital admission.

All but one patient randomized to undergo angioplasty underwent immediate coronary angiography. Therefore, in patients randomized to undergo angioplasty coronary anatomy was known at an early stage as opposed to patients randomized to receive streptokinase. This knowledge of the coronary anatomy certainly played a role in the subsequent therapeutic strategy because it allowed emergency surgical intervention in patients with a high risk coronary anatomy. In patients randomized to receive streptokinase, revascularization procedures were performed only on clinical indication. "Rescue" angioplasty for failed thrombolysis was performed in 11% of patients, and angioplasty or bypass surgery for recurrent ischemia was performed in 26% of patients randomized to streptokinase. The difference in results between the two groups might therefore not only be due to differences in initial treatment but, possibly, to subsequent different management as well.

Which patients with acute myocardial infarction should have primary angioplasty?

If immediate angioplasty were offered to all patients with an acute myocardial infarction, a tremendous logistic burden would result and be impossible to organize at the present time [15]. However, this may not be necessary. A substantial number of patients fare very well with thrombolytic therapy. The most important task for the

coming years will therefore be to identify on admission those patients that will do well with thrombolytic therapy and to apply immediate angioplasty without antecedent thrombolytic therapy in subgroups of patients who are likely to gain the most benefit from this procedure [15]. This policy of "tailored" angioplasty and thrombolytic therapy in patients with a low risk of death or other complications should be based on easily obtainable clinical data that are available immediately after hospital admission.

Study Limitations

Given the limited number of patients in our study it is impossible to conclude exactly which subgroups do benefit most from angioplasty, the only easy applicable criterion being Killip class $\geq$ II on admission. Also the magnitude of the effect of angioplasty on the risks of reinfarction and death should be viewed with caution because of the wide confidence intervals.

Conclusion.

Our results show that immediate coronary angioplasty without antecedent administration of a thrombolytic agent results in better left ventricular function and a lower in-hospital incidence of recurrent infarction and death than treatment with intravenous streptokinase.

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Table 1: Baseline Characteristics of the Patients

	Streptokinase (N = 149)	p Value	Angioplasty (N = 152)
Age (years)	61 ± 9	0.06	59 ± 10
Male sex	121 (81%)	0.59	127 (84%)
Anterior infarction	68 (46%)	0.27	79 (52%)
Previous infarction	21 (14%)	0.11	32 (21%)
Time onset-admission (min)*	176 ± 172	0.43	195 ± 227
Killip class on admission: I.	122 (82%)	0.22	116 (76%)
II.	15 (10%)	0.26	22 (14%)
III.	9 (6%)	0.41	6 (4%)
IV.	3 (2%)	0.14	8 (5%)
Multivessel disease	88 (59%)	0.63	95 (63%)

* From onset of symptoms of myocardial infarction to hospital admission (the moment the ambulance drives through the door). Values presented are mean value ± SD or number (%)

Table 2: Clinical Data

	Streptokinase Group (N= 149)	p Value	Angioplasty Group (N= 152)
Hospital stay	14.4 ± 6.8	0.003	12.3 ± 5.3
Stroke	3 (2%)	0.37	1 (1%)
Vascular repair	0 (0%)	1.0	1 (1%)
Mechanical ventilation	3 (2%)	0.68	2 (1%)
Heart failure	17 (11%)	0.03	7 (5%)
Bleeding	9 (6%)	0.97	8 (5%)
IABP	12 (8%)	0.28	19 (13%)
Peak CK	1,403 ± 1,276	0.33	1,268 ± 1,088

Values presented are mean value ± SD or number (%). Bleeding = bleeding requiring a blood transfusion or intracranial bleeding; CK = creatine kinase; Heart failure = signs of heart failure requiring therapy with diuretic agents and angiotensin-converting enzyme inhibitors < 24 hours after admission; IABP = intraaortic balloon pump; Vascular repair = surgical repair of the femoral artery.

Table 3: Comparison of Outcome Between 149 Patients Assigned to Streptokinase Therapy and 152 Patients Assigned to Coronary Angioplasty (Univariate analysis)

	Streptokinase	Angioplasty	p-value	RR	95% CI
Death	11	3	0.024	3.96	1.01 - 22.5
Cardiogenic shock	5	2			
Cardiac rupture	2	0			
Sudden death	3	1			
Stroke	1	0			
Recurrent infarction	15	2	0.001	8.40	1.89 - 76
Death or recurrent infarction	23	5	0.0003	5.40	1.91 - 81

CI = Confidence Interval; pts = patients; RR = Relative Risk of outcome of streptokinase-treated patients compared to angioplasty-treated patients.

Table 4. Left Ventricular Ejection Fraction

	Streptokinase Group (n = 149)		Angioplasty Group (n = 152)		
	% (mean ±SD)	No.	% (mean ±SD)	No.	p value
All pts	44 ± 11	140	50 ± 11	149	< 0.001
Anterior infarction	38 ± 12	61	47 ± 12	76	< 0.001
No anterior infarction	48 ± 9	79	52 ± 9	73	0.006
Previous infarction	37 ± 12	18	43 ± 14	31	0.136
No previous infarction	45 ± 11	122	51 ± 9	118	< 0.001
> 120-min from onset to admission	44 ± 12	63	49 ± 9	48	0.01
< 120-min from onset to admission	46 ± 10	59	53 ± 8	71	< 0.001
< 60-min from onset to admission	44 ± 13	20	57 ± 6	15	0.002

	Difference	
	Absolute (%)	Relative (%)
All pts	6	12
Anterior infarction	9	19
No anterior infarction	4	8
Previous infarction	6	14
No previous infarction	6	12
> 120-min from onset to admission	5	10
< 120-min from onset to admission	7	13
< 60-min from onset to admission	13	23

pts = patients

8. The basic instinct that seduces the angioplaster to dilate a non-culprit lesion in patients with unstable coronary syndromes often turns out to be fatal attraction.

9. "Onderdilatatie", dat wil zeggen coronaria-angioplastiek uitgevoerd met een ballon die in verhouding te klein is voor de te dilateren kransslagader, is een belangrijke oorzaak van re-stenose.

10. Zo er al een mortaliteitsreductie van het cholesterolverlagend effect van het eten van een tot twee teentjes knoflook per dag bestaat, zal die teniet worden gedaan door de toename van geweldsdelicten tegen mensen die deze therapie volgen.

11. Als over tien jaar de parlementaire enquete over de teloorgang van de Nederlandse gezondheidszorg gehouden wordt, zullen de huidige verantwoordelijke politici beweren, dat de regelgeving en wetten op zich juist waren, maar dat de uitvoering door medici sterk te wensen over heeft gelaten.

12. Om het promoveren op rijpere leeftijd te bevorderen dient een "Old Investigator's Award" ingesteld te worden.

13. Een homeopathisch afslankmiddel, mits voldoende verdund, heeft het voordeel dat men er nauwelijks dikker van wordt.

14. De systematische evaluatie van de therapeutische effectiviteit van nieuwe medische behandelingsmethoden is niet uitsluitend een universitaire of wetenschappelijke taak maar moet een integraal deel van de gezondheidszorg zijn, waarbij de behandelaar, de ziektekostenverzekeraar, de overheid en ook de patiënt dienen mee te werken.

15. Zonder bemiddeling van Ivan Vaughan zou de historische ontmoeting tussen J.W. Lennon en J.P. MacCartney op Zaterdag 6 Juli 1957 tijdens een tuinfeest bij de St. Peter's Church te Woolton, Liverpool, nooit hebben plaatsgevonden. *(P.M. MacCartney, persoonlijke mededeling)*

Rotterdam, 21 September 1994
M.J. de Boer

Stellingen

1. Het gunstige effect van primaire coronaria-angioplastiek wordt voornamelijk bepaald door vroege, effectieve en blijvende doorgankelijkheid van het met het hartinfarct samenhangende vat.
   (dit proefschrift)

2. Infarct angioplastiek heeft zoveel verraderlijke aspecten dat een nuttig effect alleen te verwachten valt indien dit, met cardiochirurgische standby, door geoefende handen wordt uitgevoerd.
   (dit proefschrift)

3. Primaire coronaria-angioplastiek kan de sterfte aan een voorwandinfarct en een onderwandinfarct reduceren in een mate waardoor het onderlinge verschil in ziekenhuissterfte, zoals gezien wordt bij conventionele behandeling, vrijwel verdwijnt.
   (dit proefschrift en N Engl J Med 1993;328:673-679)

4. Prehospitale trombolyse ontneemt de patiënt met een hartinfarct de kans op behandeling met primaire coronaria-angioplastiek.

5. Blokkade van de thrombocyten glycoproteine IIb/IIIa receptor door het chimerisch 7E3 (c7E3) monoclonaal antilichaam Fab fragment geeft een aanzienlijke vermindering van complicaties voor, tijdens en na coronaria-angioplastiek wegens onstabiele angina pectoris.
   (Circulation 1994;89:596-603)

6. Vroege TIMI (Thrombolysis in Myocardial Infarction) graad 3 perfusie van de met het infarct samenhangende kransslagader kan opnieuw worden gebruikt als een alternatief eindpunt in studies naar nieuwe behandelingsmethoden van het acute hartinfarct.
   (dit proefschrift en N Engl J Med 1993;329:1615-1622)

7. Enerzijds beschermt NO door vasodilatatie de vaatwand tegen shear-stress schade, echter anderzijds vormt het een ernstige bedreiging voor het endotheel in de vorm van het toxische peroxynitriet ($ONOO^-$: het product van NO en O_2^-), waardoor het mogelijk een rol speelt in de pathogenese van atherosclerose.
   (J Biol Chem 1991;266:4244-4250 en Biol Chem 1994;375:81-88)

Table 5: Bicycle exercise test before discharge

	Streptokinase Group (N = 122)	p Value	Angioplasty Group (N = 138)
Angina	17 (14%)	0.04	9 (7%)
>1 mm ST depression	49 (40%)	< 0.001	30 (22%)
Maximal workload (Watt)	90 ± 30	0.03	98 ± 30

Values presented are mean value ± SD or number (%).

Chapter 4

Limitation of Infarct Size and Preservation of Left Ventricular Function After Primary Coronary Angioplasty Compared With Intravenous Streptokinase in Acute Myocardial Infarction.

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Background

Early and effective flow through the infarct-related vessel is probably of paramount importance for limitation of infarct size and preservation of left ventricular function in patients with acute myocardial infarction. Primary coronary angioplasty may offer advantages in these respects compared with thrombolytic therapy. The purpose of the present study was to assess the effects on estimated enzymatic infarct size and left ventricular function in patients with acute myocardial infarction randomly assigned to undergo primary angioplasty or to receive intravenous streptokinase.

Methods and results

We evaluated 301 patients with signs of acute myocardial infarction and without contraindications for thrombolysis who presented within 6 hours after onset of symptoms or between 6 and 24 hours if there was evidence of ongoing ischemia. One hundred fifty-two patients were randomly assigned to undergo primary angioplasty, and 149 patients were assigned to receive treatment with streptokinase, (1.5 million U IV). Infarct size was estimated from enzyme release. Global left ventricular ejection fraction and regional wall motion, if possible in combination with exercise testing, were evaluated by radionuclide ventriculography before discharge. Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 through the infarct-related vessel within 120 minutes after admission was achieved in 92 % of all patients assigned to receive primary angioplasty therapy. Myocardial infarct size was 23 % smaller in the angioplasty group compared with patients assigned to receive streptokinase (1003±784 U/L versus 1310±1198 U/L, $P = .012$). Global left ventricular ejection fraction (50±9% versus 45±11%, $P < .001$) and regional wall motion in the infarct-related zones (42±14% versus 34±13%, $P < .001$) were better in the angioplasty group, which could mainly be contributed to myocardial salvage in the infarct-related areas. The observed differences were more pronounced in patients with an anterior wall myocardial infarction, although patients with a nonanterior infarct location also showed a beneficial effect of primary coronary angioplasty on left ventricular function compared with streptokinase therapy. Furthermore, the observed differences appeared to be more pronounced in patients presenting relatively early (within 2 hours) after onset of symptoms.

Conclusions

In patients with acute myocardial infarction, primary angioplasty results in a smaller infarct size and a better preserved myocardial function compared with patients randomized to receive treatment with intravenous streptokinase. This is probably due to

early and optimal blood flow through the infarct-related vessel, as can be accomplished in a very high percentage of patients undergoing primary coronary angioplasty.

Key Words * myocardial infarction * angioplasty * thrombolysis * left ventricle * infarcts

In patients with acute myocardial infarction, early treatment resulting in restoration of adequate blood flow through the infarct-related vessel results in limitation of infarct size, preservation of left ventricular function and reduction of mortality [1-8]. Several large clinical trials have established that thrombolytic therapy reduces mortality, and thrombolysis is the treatment of choice in patients with acute myocardial infarction [4,6-8]. Recently we demonstrated a higher patency rate of the infarct-related coronary vessels, a reduction of the severity of the residual stenotic lesions, and a lower incidence of recurrent myocardial ischemia in patients with acute myocardial infarction who underwent primary (or direct) coronary angioplasty compared with those who received intravenous streptokinase. Furthermore, global left ventricular ejection fraction, as measured with a quantitative radionuclide method, was better in the patients assigned to undergo primary angioplasty [9,10]. After completion of this initial series of 142 patients [9], the randomized study was extended to a total of 301 patients to achieve greater certainty about the benefit of primary coronary angioplasty. Previous studies of percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction did not yield additional benefit in patients pretreated with thrombolytic agents. [11-15]. This lack of benefit has been attributed to activation of coagulation during thrombolytic therapy but could also be related to hemorrhage in the wall of the infarct-related artery or in the infarcted myocardium. [16,17]. Primary coronary angioplasty without pretreatment with thrombolytic agents may be advantageous since these deleterious phenomena are avoided. [9, 17,18].

This report describes the results of the full cohort of 301 patients with special emphasis on infarct size as measured from enzyme release and on global and regional left ventricular function.

Methods

Patient Selection

The research protocol was approved by the institutional review board of the Weezenlanden Hospital. Enrollment began on August 20, 1990, and ended on April 26, 1993. Inclusion criteria were: (1) symptoms compatible with acute myocardial infarction persisting for more than 30 minutes accompanied by an ECG with more than 0.1-mV ST-segment elevation in two or more contiguous leads; (2) all patients presenting within 6 hours after symptom onset, as well as those presenting between 6 and 24 hours if they had evidence of continuing ischemia; (3) age less than 76 years and (4) no

contraindication to thrombolytic therapy, including prior stroke or other known intracranial diseases, recent trauma or surgery, refractory hypertension, active bleeding, or prolonged cardiopulmonary resuscitation. Prior coronary artery bypass grafting, prior Q-wave or non-Q-wave infarction, and cardiogenic shock were no reasons to exclude a patient. After informed consent was obtained, patients were randomly assigned to one of the two treatment modalities using a closed envelope system.

Treatment Protocol

All patients received 300 mg aspirin IV followed by 300 mg/d PO and IV nitroglycerin in a dosage aimed at a systolic blood pressure of 110 mm Hg. Intravenous heparin was given in a bolus of 10 000 U and thereafter as a continuous infusion adjusted to maintain the activated partial thromboplastin time between two and three times the normal value for at least 2 days. Other drugs such as ß-adrenergic blockers, lidocaine, or calcium antagonists were given on indication only. Patients randomized to streptokinase received 1.5 million U IV in 1 hour. Patients randomized to coronary angioplasty were immediately transported to the catheterization laboratory and underwent coronary angiography followed by immediate coronary angioplasty if indicated. Both coronary arteries were visualized, and left ventriculography was not performed. Time from admission to therapy was calculated as time from admission to the first balloon inflation or to start of the streptokinase infusion.

Enzyme Measurements and Infarct Size

Creatine kinase (CK) and lactate dehydrogenase (LDH) were determined enzymatically on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 30°C [20]. Reference values for LDH are <320 U/L (adults) and for CK are <110 U/L (females) and <130 U/L (males). Infarct size was estimated by measurements of enzyme activities using LDH as the reference enzyme. This method is equal to estimation of infarct size from α-hydroxybutyrate dehydrogenase (HBDH) and has been described in detail [2,20]. Cumulative enzyme release from five to seven serial measurements up to 72 hours after symptom onset (LDH Q_{72}) was calculated by the Cardiovascular Research Institute Maastricht (W.Th.H.) with blinding to all data other then hospital registration number and date of birth.

A two-compartment model was used, which has been validated in several studies on the turnover of radio-labeled plasma proteins and circulating tissue enzymes [2,20-22]. The plasma activity of enzyme C at time t is determined by input of enzyme from the

heart and elimination of enzyme determined by a fractional catabolic rate constant (FCR_{LDH}). In addition, there is extravasation of enzyme, determined by a fractional transcapillary escape rate constant (TER), and return to plasma from the extravascular pool E(t) determined by a fractional extravascular return rate constant (ERR). Cumulative release of enzyme per liter of plasma from zero time up to time *t* is given by:

$$(1) \qquad Q(t) = C(t) + E(t) + {}_0\int^t FCR_{LDH}.C(\tau)\, d\tau$$

where C(t) and E(t) are the activities still present in the intravascular and extravascular spaces and the integral term encompasses eliminated activity. A value of FCR_{LDH} = 0.015 h^{-1} was used. The extravascular pool E(t) is determined by the time-dependent plasma activity and TER and ERR:

$$(2) \qquad E(t) = TER.exp\,(-ERR.t).\ {}_0\int^t exp\,(ERR.\tau)\, C\,(\tau)\, d\tau$$

Values of C(t) in Equations 1 and 2 were obtained by subtraction of the normal activities in plasma from the actual activities measured at time *t*. Individual values of these normal activities were estimated from the first sample of each patient when this sample was obtained within 3 hours after first symptoms. Otherwise, a fixed mean normal value of 175 U/L was used. Fixed values of TER = 0.014 h^{-1} and ERR = 0.018 h^{-1} were used.

Radionuclide Ventriculography

Left ventricular ejection fraction was measured before discharge by radionuclide ventriculography using the multiple gated equilibrium method following the labeling of red blood cells of the patient with ^{99m}Tc-pertechnetate [23]. A General Electric 300 gamma camera with a low-energy all-purpose parallel- hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer using the fully automatic PAGE program. The use of this software program protects against operator bias. The reproducibility of this method is excellent, with a mean difference (±SD) between first and second values of duplicate measurements of 1.2±1.1% [23]. The left anterior oblique projection with some degree of cranial angulation to separate the right and the left ventricle, was used to analyze regional wall motion. The left ventricle was

divided into five zones corresponding to the posterolateral, inferolateral, inferoapical, basoseptal, and anteroseptal regions. The area involving the valve planes was excluded. Regional wall motion was calculated from maximal and minimal counts in all regions and was expressed in percentages. Infarct- and non-infarct-related segments were indicated by two investigators using the ECG site of infarction and coronary anatomy as references, without further knowledge of clinical data. A symptom-limited bicycle exercise test was performed with participants in the supine position at increments of 10 W/min, only in patients without contraindications to exercise. An exercise test indicating ischemia was defined as a test with an ST-segment depression of more than 1 mm measured 60 milliseconds after the J point. In patients with baseline abnormalities in the ST-T wave, an additional downward shift of more than 1 mm in the ST segment was considered to indicate ischemia.

Angiography and Angioplasty Data

Data of the coronary angiography and angioplasty procedures were collected and judged by two of the investigators. Because blinding to angioplasty procedures was not possible, all angiograms were subsequently reviewed by an independent and highly experienced investigator (M.v.d.B.) who was not involved in other aspects of the trial. Consensus on collateral flow, procedural success, Thrombolysis in Myocardial Infarction (TIMI) graded flow before and after the angioplasty procedure, and extent of coronary artery disease was reached in all cases. Collaterals to the infarct-related vessel were classified as proposed by Rentrop et al [24].

Statistical Analysis

Differences between group mean values were tested by two-tailed Student's *t* test with a separate variance estimate if the F distribution of variances was significant at the two-sided 5% level. For comparison of rates of discrete outcome variables, a conventional χ^2 test was used. Fisher's exact test was used if there was an expected cell value of less than 5. Simple linear regression analysis was used for correlation of ejection fraction and enzymatic infarct size. In our presentation of the data, continuous baseline and outcome variables are given as mean ± 1 SD, whereas discrete variables are given as absolute values and percentages.

Results

Baseline and Clinical Data

A total of 301 patients were included in the study: 152 patients were randomly assigned to undergo primary coronary angioplasty and 149 patients to receive intravenous streptokinase therapy. Baseline characteristics of the two groups were similar (Table 1). One hundred fifty-one patients assigned to angioplasty underwent emergency coronary angiography; one patient died before angiography could be performed. The infarct-related vessel showed TIMI grade 0 or 1 flow in 124 of the 151 patients (82%). Coronary angioplasty was performed in 140 patients. Five patients with an open or small infarct-related artery were treated conservatively. Six patients with severe multivessel disease or left main stenosis had emergency coronary artery bypass grafting after insertion of an intra-aortic counterpulsation balloon. The time between admission to start of therapy defined as the first balloon inflation was 64 ± 26 minutes. In 4 patients, the infarct-related vessel could not be reopened. Three of these patients underwent immediate coronary artery bypass grafting; 1 was treated conservatively.

Of the 149 patients assigned to streptokinase therapy, 1 died before infusion could be started. The time from admission to start of infusion was 29 ± 16 minutes. Sixteen patients underwent a rescue coronary angioplasty because there was clinical evidence of failed reperfusion or hemodynamic collapse. In 15 patients, this procedure was successful; 1 underwent emergency coronary artery bypass grafting and was discharged after an uneventful in-hospital stay.

Additional procedures during the in-hospital stay were infrequent in the angioplasty assigned patients: 3 patients had an additional angioplasty procedure of a non-infarct-related vessel and 7 underwent coronary artery bypass grafting. In the streptokinase assigned patients, 24 underwent an angioplasty procedure and 14 patients had coronary artery bypass grafting before discharge.

The in-hospital mortality was 2% (3 patients) in the angioplasty-assigned patient group and 7% (11 patients) in the streptokinase group. ($P = .024$)

Angiographic Data

Baseline angiographic data of all patients assigned to receive primary coronary angioplasty are given in Table 2. Three of the angioplasty-assigned patients (2%) had no significant coronary artery disease, 54 (36%) had one-vessel disease and 95 (62%) had multivessel disease. Not all patients had angiography of the non-infarct-related vessel before a coronary angioplasty was done; thus, classification of collaterals to the

infarct-related vessel could be assessed only in 141 patients (Table 2). Patency rates and TIMI flow rates before therapy are given for all patients undergoing angiography. The angioplasty was considered to be technically successful if there was a residual stenosis of less than 50 % and a flow of TIMI grade 2 or 3 at the end of the angioplasty procedure. Primary angioplasty of the infarct-related vessel was successful in 136 patients (97 %). A TIMI grade 3 flow was observed in 131 of these patients (96%) with a successful procedure. The relation between time from hospital admission to successful reperfusion is also given in Table 2. Patients who underwent immediate coronary angiography followed by emergency coronary artery bypass surgery were considered to have had restoration of adequate blood flow 120 minutes after admission (3 additional patients). In 4 patients, the infarct-related vessel was opened successfully more than 120 minutes after admission.

Enzymatic Infarct Size

Values for peak creatine kinase and LDH estimated infarct size (LDH Q_{72}) are given in Table 3. Peak CK values tended to be lower in the angioplasty treated patient group but this difference was not statistically significant. Cumulative enzyme release during the first 72 hours, with sufficient data from the sequential measurements and accurate timing of symptom onset, could be calculated in 92% of all patients, and the data are given in Table 3. For 10 patients in the angioplasty group and for 7 patients in the streptokinase group, data were insufficient for adequate analysis. Eight patients died within the first 48 hours, before serial enzyme release could be determined. Estimated infarct size using LDH Q_{72} was lower in the angioplasty-assigned patients compared with patients assigned to receive streptokinase, representing a reduction of estimated infarct size of 23% (95% confidence interval [CI] 13% to 32%). The difference of the LDH Q_{72} value between the two groups was greater in patients with anterior wall myocardial infarction than in patients with a nonanterior wall infarction.

The relation between time from onset of symptoms to reperfusion therapy and LDH Q_{72} is also shown in Table 3. In patients admitted to the hospital within 2 hours after the onset of symptoms, an even more pronounced difference was seen: LDH Q_{72} was 967 ± 730 U/L in the angioplasty group versus 1403 ± 1157 U/L in the streptokinase group (P = .010), representing a reduction of estimated infarct size of 31% (95% CI, 20% to 43 %).

Left Ventricular Function

In 149 patients in the angioplasty group (98 %) and 140 patients in the streptokinase group (94%) resting ejection fraction values were obtained. Three patients in the angioplasty-treated group and 9 patients in the streptokinase-treated group died before nuclear studies were performed. Global ejection fraction was measured in all 289 survivors, whereas regional wall motion could be obtained in 273 patients (91%). The interval between acute myocardial infarction and time of nuclear study was less in the angioplasty group than in the streptokinase group (14 ± 13 days and 17 ± 21 days respectively; $P = .04$). In all subgroups studied, resting global ejection fraction was significantly greater in patients assigned to primary angioplasty than in patients assigned to streptokinase therapy (Table 4). This difference was mostly due to better wall motion in the infarct-related region, although a relatively small but significant difference for non-infarct-related areas was also found between the two groups. There was a clear correlation between left ventricular ejection fraction and enzymatic infarct size in patients with a first myocardial infarction as shown in figure 1. Patients who had angioplasty for first nonanterior wall infarction had very well preserved left ventricular ejection fraction, and no regression line could be drawn.

One hundred twenty-three patients in the angioplasty-treated group and 118 in the streptokinase-treated group could perform an exercise test with radionuclide ventriculography before discharge. In both groups, there was a remarkably flat response of left ventricular ejection fraction during exercise with small, but significant improvement after exercise when compared with baseline (Table 5). This "pattern" was observed in patients with anterior wall infarction as well as in those with nonanterior infarctions. However, patients assigned to receive primary angioplasty therapy had less frequently significant ST-segment depression or angina during exercise than patients who received streptokinase (33 versus 49, $P = .02$). Finally, exercise tolerance of the patients assigned to angioplasty therapy was higher than of those assigned to streptokinase therapy, (98 ± 30 versus 90 ± 29 W, $P = .03$).

Discussion

The aim of the present study was to compare the effects of primary coronary angioplasty and thrombolysis as primary reperfusion strategy. Infarct size and left ventricular function improved after primary angioplasty. The sample size was not designed to examine mortality as an end point, although in-hospital mortality in this

study was significantly lower in the patients assigned to undergo primary coronary angioplasty than in those who received intravenous streptokinase (3 versus 11, P = .024) [10]. In all subgroups, a good relation was observed between the degree of reduction of infarct size and preserved left ventricular function.

Infarct Size

Due to the very slow elimination of LDH from plasma, this enzyme allows calculation of cumulative release over 72 hours from only five to seven plasma samples. Although reperfusion causes earlier enzyme release, which is also observed for LDH [20], infarct size can be calculated accurately from LDH because a single measurement after 6 to 8 hours represents approximately the total release over that period. By that time, less than 10 % of total release has been eliminated from plasma. It has been demonstrated that relation between global ejection fraction and LDH infarct size is maintained, regardless of whether or not thrombolytic therapy is given [25]. Similarly, in this study, regression lines relating infarct size and left ventricular function were the same in patients treated with primary coronary angioplasty or streptokinase (Fig 1).

In patients assigned to angioplasty, infarct size (LDH Q_{72}) was 23% (95% CI, 13% to 32%) lower than in those assigned to receive streptokinase (P = .012). Half of the patients in our study presented within 2 hours after onset of symptoms. In this subgroup, the limitation of infarct size by primary angioplasty was even larger: 31%. Beyond this "time window" of 2 hours, the reduction of infarct size by primary angioplasty was smaller and did not reach the level of statistical significance. This time-related phenomenon had also been demonstrated in patients receiving thrombolysis compared with those treated with placebo [1,22,26].

Myocardial Salvage by Primary Coronary Angioplasty.

Data from animal studies have demonstrated that myocardial salvage occurs primarily in the first 3 to 4 hours after coronary artery occlusion [27-29] and therefore that very early reperfusion is important to limit infarct size. This will result in better left ventricular function and as a consequence may lead to better rate of survival [30]. Early complete perfusion (TIMI grade 3) of the infarct-related vessel is the key to myocardial salvage. Often, incomplete perfusion (TIMI grade 2) is also considered to represent successful therapy, but recent studies revealed that patients with grade 2 flow of the infarct-related artery have in fact indexes of myocardial infarction similar to those of patients with occluded coronary arteries (TIMI 0 and 1) [31-33]. Primary PTCA has the potential to achieve more rapid and effective reperfusion, defined as TIMI grade 3 flow,

compared with thrombolytic therapy. In fact, TIMI grade 3 flow at 90 minutes or at 3 hours was achieved in only 54% to 60% of patients who received the best available thrombolytic regimen in the GUSTO study and the TEAM-2 study [33,34]. Rapid complete reperfusion is, in our perception, the reason for the significant additional salvage by primary angioplasty. Our study shows that in patients who undergo primary coronary angioplasty, effective restoration of blood flow through the infarct-related artery can be accomplished in 51% of patients by 60 minutes after admission, 81% by 90 minutes after admission, and in 92% by 120 minutes after admission.

Left Ventricular Function

Both global and regional left ventricular function were better preserved after primary angioplasty compared with after intravenous streptokinase in the present study (Table 3). Similarly, O'Neill and co-workers [35] reported a more effective preservation of ventricular function in patients who underwent primary coronary angioplasty compared with those who received intracoronary streptokinase, and Erbel et al [36] found improved left ventricular wall motion and patency after a combined medical and mechanical approach, a finding supported by data from a subgroup of the Dutch Interuniversity trial and a report by Belenkie and coworkers [37,38].

In one report, primary coronary angioplasty and tissue-type plasminogen activator therapy salvaged similar amounts of myocardium, as assessed by tomographic imaging with ^{99m}Tc-sestamibi, and additional left ventricular studies at discharge and after 6 weeks failed to show a significant difference between the two patient groups. However, the time from onset of symptoms to start of therapy in this study was longer, and the percentage of anterior wall myocardial infarctions was lower (36%) than in our study population (49%) [9,39]. Furthermore, the Primary Angioplasty in Myocardial Infarction (PAMI) study [18] failed to demonstrate any differences in left ventricular function, as measured with a radionuclide technique, between two groups, randomized to receive coronary angioplasty or tissue plasminogen activator therapy. This contrast with our results may be caused by selection bias. These data were obtained in only 62% of patients whereas in our study these data could be obtained in 96% of patients. Although patients in our trial were allowed to enter the study between 12 and 24 hours (these patients were not included in the PAMI trial), the mean times from symptom onset to randomization (PAMI, 189 minutes) or admission (the present study, 185 minutes) were not strikingly different. Furthermore, about half of the patients in our study presented within 2 hours after symptom onset. This may have influenced the results.

Mechanisms

In studies comparing thrombolytic therapy and placebo treatment, the differences in ejection fraction remained small although the greatest improvement was observed in the patients with an angiographically documented patent infarct-related artery [40,41]. Different mechanisms have to be considered to explain the remarkable differences between the two patient groups in the present study.

First, patency of the infarct-related coronary artery is established in approximately 70% to 80% of patients treated with thrombolytic therapy, whereas angioplasty results in patency rates of more than 90% [9,10,18,39,42].

Second, by rapid restoration of TIMI grade 3 flow and reduction of the residual stenosis in the infarct-related vessel in 92% of the patients in our study, who underwent primary angioplasty, recovery from ischemia is initiated rapidly, probably resulting in improvement of wall motion and better healing of the infarct zone. A recent study showed a close nonlinear relation between the degree of residual stenosis of the infarct-related artery and the degree of left ventricular dilation at both 6 months and 12 months after the first myocardial infarction, which is also in accordance with our (in-hospital) findings [43]. The residual coronary artery obstruction may thus limit the flow through the infarct-related artery after successful thrombolysis and result in continuing ischemia, delayed recovery, and even ongoing necrosis of the myocardial tissue involved [44,45].

Third, half of our patients presented early after symptom onset and were treated rapidly, with a mean time interval from admission to first balloon inflation of 64 minutes in the angioplasty-assigned group. Several studies have shown that restoration of antegrade blood flow in the infarct-related vessel within 2 hours after symptom onset results in the highest probability of myocardial salvage [22,26].

Fourth, the preservation of left ventricular function after primary angioplasty compared with thrombolytic therapy may be different because of hemorrhagic extension to noninfarcted areas of myocardial tissue after thrombolytic therapy and subsequent delayed healing of myocardium. After primary angioplasty, an "anemic infarction" was seen in a small group of patients [17]. However, these phenomena are speculative and need further clinical information.

Fifth, in patients with severe or diffuse three-vessel disease, enhancement of collateral flow to non-infarct-related areas of the myocardium may also contribute to improvement of left ventricular function, and the remodeling process may be reduced. The high incidence of sustained patency of the infarct-related coronary artery in the

angioplasty-treated patients may therefore be an important factor in this process [9].

Last, the avoidance of stimulation of platelet aggregation in patients without thrombolytic therapy could be responsible for the low incidence of reocclusion in patients undergoing primary angioplasty [46,47]. However, reocclusion remains a major problem after thrombolytic therapy as it results in increased mortality and impaired left ventricular function [38,48,49]. The reocclusion rate after initially successful thrombolytic therapy may be as high as 25% to 30% whereas reocclusion occurs only in 3% to 15% after primary coronary angioplasty [9,42,46,47,50,51].

Study Limitations

This report is based on data from a single center with an experienced group of interventional cardiologists and optimal 24-hour coverage of interventional cardiology and cardiac surgical standby. Accordingly, the results cannot necessarily be transferred to the treatment of patients with acute myocardial infarction in general practice.

It is unavoidable that measurement of infarct size and/or left ventricular function is missing for some of the patients. Still, it is unlikely that this has biassed our results because the data were very consistent and measurements were complete in at least 90% of the patients. Serial enzyme measurements were not available or were insufficient for adequate analysis for some patients (8%), but most of them also were "early" nonsurvivors, and these patients are likely to have had the largest infarcts. Because only 3 patients died in the angioplasty group versus 11 patients in the streptokinase group, the observed difference in LDH Q_{72} may have been underestimated. Missing data were distributed evenly over the two groups, and imputation for missing values would have strengthened rather than weakened the differences between the two treatment groups.

Data derived from the nuclear technique used for measurement of regional wall motion may be suboptimal because limited information on certain segments of the left ventricular wall is available with the use of a single view. This radionuclide technique is based on measurements of volume and changes of volume, and it gives only an approximation of the actual regional wallmotion. Delineation of the apical and inferolateral segments is especially difficult, and overlap is likely to occur in patients with anterior wall myocardial infarction. This may be the explanation for the observed differences in non-infarction-related segments between the two groups.

Evaluation of left ventricular function after myocardial infarction preferably should be done 2 to 3 weeks after the acute ischemic episode because "stunning" of the myocardium takes time to resolve [52,53]. Delayed recovery of left ventricular function,

however, may be observed much longer afterwards [54]. The small difference in time (3 days) between the two groups therefore is not likely to have influenced our study results.

Finally, our observations on left ventricular function were made before or at hospital discharge. No statements about the persistence of the observed differences can be made.

Conclusion

Primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction results in a reduction in enzymatic infarct size and in better preserved left ventricular myocardium, especially in the infarct-related zones, compared with patients initially treated with intravenous streptokinase. This resulted in markedly improved in-hospital survival. Rapid restoration of optimal blood-flow (TIMI grade 3), adequate reduction of the underlying stenosis in the infarct-related coronary vessel, and reduction of reocclusion probably are all related to the favorable results in patients with acute myocardial infarction treated with primary coronary angioplasty compared with therapy with intravenous streptokinase.

Clinical Implications

Because of the beneficial effects of primary coronary angioplasty on left ventricular myocardium, this procedure should be considered as the treatment of choice in all patients presenting with acute myocardial infarction and signs of involvement of a large amount of myocardial tissue. Primary coronary angioplasty will be particularly beneficial in patients with increased risk for intracranial bleeding or other severe bleeding during thrombolytic therapy [55]. Triage on admission should be able to identify which patients might benefit most from primary coronary angioplasty. A moderate time delay should not be a drawback to transportation of these patients to a hospital with experience and equipment for interventional cardiology, provided that transportation can be carried out safely. A study on the feasibility of such a policy will be of great importance for the optimal management of patients with acute myocardial infarction.

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Figure 1A

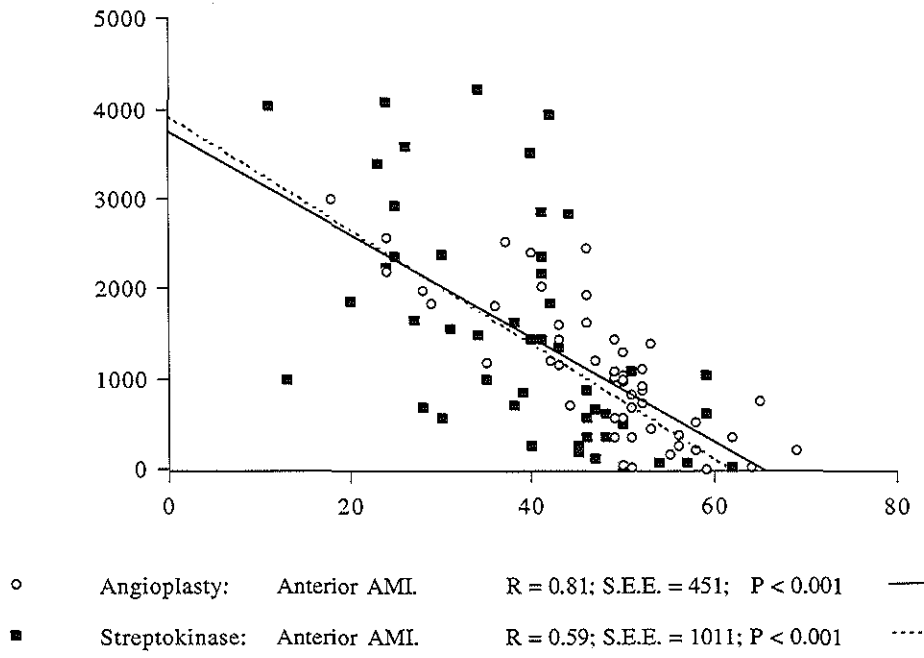


Figure 1A: Plot showing correlation between global left ventricular ejection fraction in percent (*x* - axis) and LDH Q_{72} (*y* - axis) in units per liter for patients with first acute anterior wall myocardial infarction (AMI) (both treatment arms).

Figure 1B

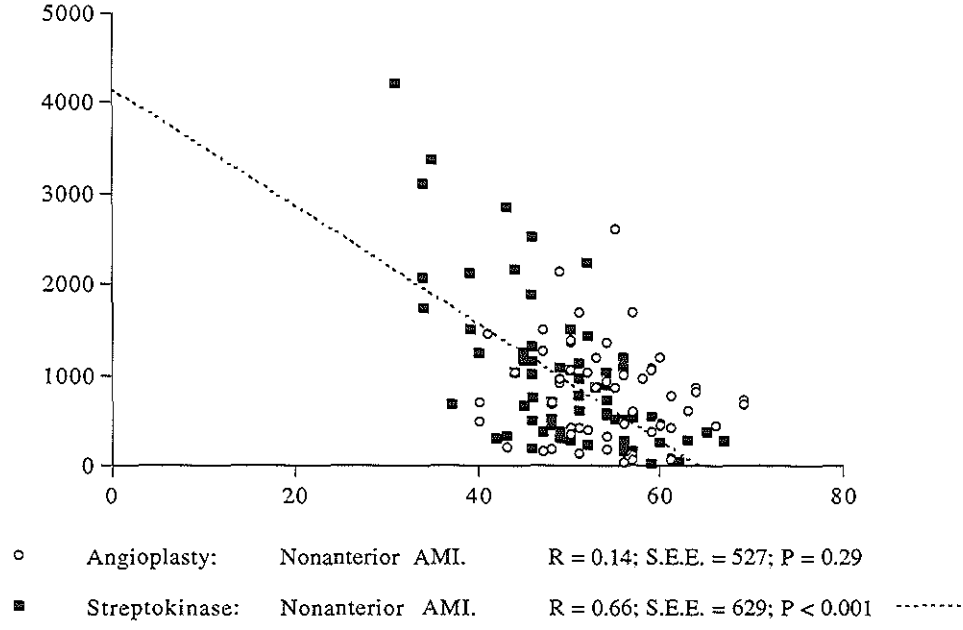


Figure 1B: Plot showing correlation between global left ventricular ejection fraction in percent (x - axis) and LDH Q_{72} (y - axis) in units per liter for patients with first acute nonanterior wall myocardial infarction (AMI) (both treatment arms).

Table 1: Baseline Characteristics and Clinical Course.

	Angioplasty n = 152	*P*	Streptokinase n = 149
Age, years	59 ± 10	.06	61 ± 9
Male sex, n (%)	127 (84)	.59	121 (81)
Previous MI, n (%)	32 (21)	.11	21 (14)
Anterior MI, n (%)	79 (52)	.27	68 (46)
Killip class III or IV, n (%)	14 (9)	.88	12 (8)
Time onset -> admission, min.	195 (20 - 1440)	.43	176 (25 - 975)
Time admission -> therapy, min.	64 ± 26	----	29 ± 16
Multivessel disease, n (%)	95 (63)	.63	88 (59)
Mortality in hospital, n (%)	3 (2)	.024	11 (7)
Recurrent MI, n (%)	2 (1)	< .001	15 (10)
"Late" PTCA, n (%)	3 (2)	< .001	24 (16)
"Late" CABG, n (%)	7 (5)	.16	14 (9)

MI indicates Myocardial Infarction; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass grafting.

Table 2: Angiographic Data of the Patients assigned to Primary Coronary Angioplasty.

	Grade	Baseline	60 min.	90 min.	120 min.
Collaterals *	0	85 (60%)			
(n = 141)	1	45 (32%)			
	2	11 (8%)			
	3	0			
TIMI †	0	109 (72%)	56 (37%)	19 (13%)	7 (5%)‡
(n = 151)	1	15 (10%)	11 (7%)	3 (2%)	1 (1%)
	2	17 (11%)	7 (5%)	7 (5%)	4 (3%)
	3	10 (7%)	77 (51%)	122 (81%)	139 (92%)

* : Collateral classification: grade 0, no visible filling of any collateral channels; grade 1, filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel; grade 2, partial filling via collateral channels of the epicardial segment of the vessel; grade 3, complete filling of the vessel.

† : Thrombolysis in Myocardial Infarction (TIMI) grade is flow grade through the infarct-related vessel according to the TIMI study flow classification (min indicates minutes after admission).

‡ : In four patients, the infarct-related vessel was opened successfully more than 120 minutes after admission.

Table 3: Enzyme Measurements and Estimated Infarct Size Expressed as LDH Q_{72}; Relation of Enzyme Measurements to Infarct Location and Interval From Onset of Symptoms to Admission.

	Angioplasty	*P*	Streptokinase
	(n = 141)		(n = 135)
Peak CK U/L	1268 ± 1088	.37	1404 ± 1276
LDH Q_{72} All infarcts U/L	1003 ± 784	.012	1310 ± 1198
LDH Q_{72} Anterior MI (U/L)	1158 ± 918 (n = 71)	.022	1606 ± 1264 (n = 62)
LDH Q_{72} Nonanterior MI (U/L)	853 ± 580 (n = 70)	.135	1060 ± 1085 (n = 73)
Time from symptom onset to admission:			
< 2 hours: LDH Q_{72}, U/L	967 ± 730 (n = 81)	.01	1403 ± 1157 (n = 65)
> 2 hours: LDH Q_{72}, U/L	1052 ± 855 (n = 60)	.36	1224 ± 1237 (n = 70)

Table 4: Global Ejection Fraction and Regional Wall Motion (%)

	Angioplasty	P	Streptokinase
EF (all patients)	50 ± 9 (n = 149)	< .001	45 ± 11 (n = 140)
IR wall motion (all patients)	42 ± 14	< .001	34 ± 13
NIR wall motion (all patients)	55 ± 11	.005	51 ± 12
EF anterior MI	46 ± 12	.002	39 ± 12
EF nonanterior MI	53 ± 9	.02	49 ± 9
EF one-vessel disease	51 ± 8 (n = 57)	.002	46 ± 10 (n = 59)
EF multivessel disease	48 ± 12 (n = 92)	.002	43 ± 12 (n = 81)
Time from symptom onset to admission:			
< 2 hours:EF, %	51 ± 10 (n = 83)	< .001	45 ± 11 (n = 70)
> 2 hours:EF, %	48 ± 12 (n = 66)	.04	44 ± 12 (n = 70)

EF indicates ejection fraction; IR, infarct-related; NIR, non-infarct-related; MI, Myocardial Infarction.

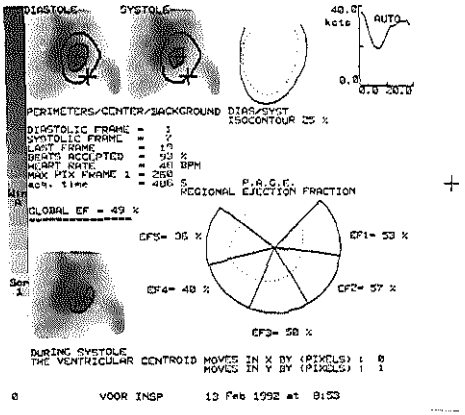
Table 5: Global Ejection Fraction at rest, during exercise and post-exercise in the two treatment groups.

	EF at rest, %	EF exercise, %	EF post-exercise, %	*P*
All patients				
Primary angioplasty (n = 123)	50 ± 10	50 ± 13	52 ± 12	< .001
Streptokinase (n = 118)	45 ± 11	45 ± 14	47 ± 13	< .001
Anterior MI				
Primary angioplasty (n = 64)	46 ± 11	46 ± 14	48 ± 13	.05
Streptokinase (n = 53)	40 ± 11	39 ± 14	42 ± 14	.02
Nonanterior MI				
Primary angioplasty (n =59)	54 ± 8	55 ± 9	57 ± 7	< .001
Streptokinase (n = 65)	50 ± 10	49 ± 11	52 ± 10	< .001

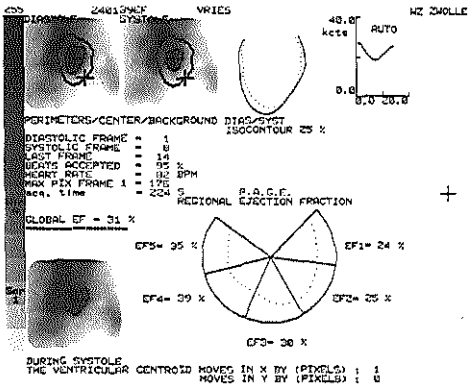
EF indicates ejection fraction and MI myocardial infarction.

* *P* value for comparison of EF at rest and EF after exercise.

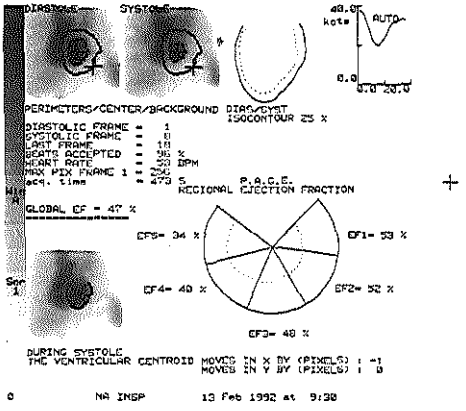
A.


DIASTOLE
SYSTOLE
AUTO
PERIMETERS/CENTER/BACKGROUND DIAS/SYST
ISOCONTOUR 25 %
DIASTOLIC FRAME = 1
SYSTOLIC FRAME = 7
LAST FRAME = 13
BEATS ACCEPTED = 93 %
HEART RATE = 48 BPM
MAX PIX FRAME 1 = 268
acq. time = 406 S
P.A.C.E.
REGIONAL EJECTION FRACTION
GLOBAL EF = 49 %
EF5= 36 %
EF1= 53 %
EF4= 48 %
EF2= 57 %
EF3= 58 %
DURING SYSTOLE
THE VENTRICULAR CENTROID MOVES IN X BY (PIXELS) : 0
MOVES IN Y BY (PIXELS) : 1
0 VOOR INSP 13 Feb 1992 at 8:53

B.


AUTO
PERIMETERS/CENTER/BACKGROUND DIAS/SYST
ISOCONTOUR 25 %
DIASTOLIC FRAME = 1
SYSTOLIC FRAME = 8
LAST FRAME = 14
BEATS ACCEPTED = 95 %
HEART RATE = 82 BPM
MAX PIX FRAME 1 = 176
acq. time = 224 S
P.A.C.E.
REGIONAL EJECTION FRACTION
GLOBAL EF = 31 %
EF5= 35 %
EF1= 24 %
EF4= 39 %
EF2= 25 %
EF3= 38 %
DURING SYSTOLE
THE VENTRICULAR CENTROID MOVED IN X BY (PIXELS) : 1
MOVES IN Y BY (PIXELS) : 0

C.


AUTO
PERIMETERS/CENTER/BACKGROUND DIAS/SYST
ISOCONTOUR 25 %
DIASTOLIC FRAME = 1
SYSTOLIC FRAME = 8
LAST FRAME = 18
BEATS ACCEPTED = 96 %
HEART RATE = 59 BPM
MAX PIX FRAME 1 = 256
acq. time = 473 S
P.A.C.E.
REGIONAL EJECTION FRACTION
GLOBAL EF = 47 %
EF5= 34 %
EF1= 53 %
EF4= 49 %
EF2= 52 %
EF3= 48 %
DURING SYSTOLE
THE VENTRICULAR CENTROID MOVED IN X BY (PIXELS) : -1
MOVES IN Y BY (PIXELS) : 0
0 NA INSP 13 Feb 1992 at 9:38

Page 108: Example of radionuclide ventriculography in combination with an exercise test, using the PAGE program. This technique uses the multiple gated equilibrium method following the labeling of red blood cells of the patient with ^{99m}Tc-pertechnetate. This method was applied in Chapters 2 to 4.
Before exercise the global left ventricular ejection fraction is 49% (A), whereas during exercise this value drops to 31% (B). This can be attributed to ischemia and subsequent diminished systolic function of the posterolateral, inferolateral and inferoapical regions. After exercise these regions recover their previous function and the global ejection fraction is 47% (C).

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Chapter 5

Angiographic Findings and Catheterization Laboratory Events in Patients with Primary Coronary Angioplasty or Streptokinase Therapy for Acute Myocardial Infarction.

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Abstract

Background.

The purpose of this study was to evaluate catheterization laboratory events and angiographic findings in patients randomly assigned to undergo primary coronary angioplasty or to receive intravenous streptokinase for acute myocardial infarction.

Methods.

We studied 301 patients with acute myocardial infarction randomly assigned to undergo primary coronary angioplasty without antecedent thrombolytic therapy or to receive intravenous streptokinase therapy. Follow-up coronary angiography was preferably performed after three months. All angiograms were analyzed with a quantitative coronary analysis system.

Results.

Of the 152 patients assigned to angioplasty treatment, 140 actually underwent this procedure with a success rate of 97%, a residual diameter stenosis of the infarct-related vessel (IRV) immediately after angioplasty of 27±15% and major events in the catheterization-laboratory in 14% of the patients. At follow-up angiography after a mean interval of 92 days in the angioplasty assigned patients, a diameter stenosis of 35±22% was observed in this group. The restenosis rate was 28% and the reocclusion rate 5%. A Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow immediately after angioplasty was predictive for reocclusion at follow-up ($P = 0.001$). In the streptokinase assigned patients (149) the IRV was patent at follow-up angiography after a mean of 22 days in 66% of the patients with a mean residual diameter stenosis of 77±20%.

Conclusion.

Primary coronary angioplasty is a highly effective and safe reperfusion modality for patients with acute myocardial infarction. Furthermore,TIMI grade 2 flow through the IRV immediately after angioplasty is a predictor of reocclusion.

Introduction

Primary coronary angioplasty without antecedent administration of thrombolytic agents as a treatment modality for patients with acute myocardial infarction (AMI) has only recently been rediscovered [1-4]. Two studies have demonstrated a high primary success rate, a reduced rate of recurrent ischemia and reinfarction, and better in-hospital survival in patients with AMI treated with primary coronary angioplasty when compared with patients treated with thrombolytic therapy [1,2,4]. In a previous paper, we have reported that the left ventricular function as measured with a radionuclide technique in patients assigned to angioplasty treatment is better compared with those assigned to streptokinase treatment. This is probably related to early restoration of flow through the infarct-related vessel (IRV) in a high percentage of patients [1,4]. The incidence of restenosis and reocclusion after primary coronary angioplasty for AMI is unknown and may be higher than that reported for elective coronary artery angioplasty. It could be comparable to that in patients with unstable angina or recanalization of occluded coronary arteries but no pertinent data are available [5,6] .

Several questions remain to be answered:
First, how safe is the primary coronary angioplasty procedure; second, what is the incidence of reocclusion and does the better coronary anatomy, observed immediately after primary coronary angioplasty protect against reocclusion, which is a major problem after initially successful thrombolysis,[7,8] and third, what is the incidence of restenosis after initially successful primary coronary angioplasty?

Methods

Our study group consisted of all patients admitted to the Zwolle trial between August 20,1990 and April 23,1993. The research protocol and initial results have been described previously [1,4]. In brief, all consenting patients <76 years of age with more than 30 minutes of symptoms characteristic of myocardial ischemia, diagnostic electrocardiographic ST segment elevation, presentation within six hours of symptom onset, and without contraindications to thrombolytic therapy were randomly assigned to coronary angioplasty or treatment with streptokinase, 1,5 million units given intravenously in 1 hour. If there was evidence of continuing ischemia between 6 and 24 hours after symptom onset patients were included in the study. Randomization was performed by means of a closed-envelope system. All patients were treated with acetylsalicylic acid 300 mg intravenously and nitroglycerin intravenously in a dose designed to maintain a systolic blood pressure of 110 mm Hg. Intravenous heparin was given in a bolus of 10000 U and thereafter in a continuous infusion in a dosage to keep the activated partial thromboplastin time between 2 and 3 times the normal value for at

least 2 days. The time from admission to the initiation of therapy was calculated as the time to the first balloon inflation or to the start of the streptokinase infusion.

Coronary angiography and angioplasty.

All patients in the angioplasty assigned group were transferred immediately to the catheterization laboratory and underwent angioplasty if their coronary anatomy was deemed suitable by coronary angiography. Only lesions of the IRV were dilated as we feel that it is hazardous to dilate lesions of non-infarct related vessels in the primary coronary angioplasty procedure. The angioplasty was considered to be technically successful if there was a residual stenosis of less than 50% on visual estimation and a flow of TIMI grade 2 or 3. Left ventricular angiography in the acute phase of myocardial infarction was not performed in the majority of patients because of time-delay, possible adverse reactions and the limited clinical value.

In the angioplasty assigned patient group, all catheterization laboratory events were scored carefully during and immediately after the emergency procedure. Major and minor in-laboratory events were defined as new events not present before arrival in the catheterization room. Catheterization laboratory events with primary coronary angioplasty were assessed according to the classification as proposed by Kahn and colleagues [9].

Major catheterization laboratory events:

* death.
* cardiopulmonary resuscitation.
* ventricular fibrillation or tachycardia treated with electrical cardioversion.
* sustained hypotension defined as a systolic blood pressure $\leq$ 80 mm Hg requiring continuous intravenous vasopressor support, the insertion of an intra-aortic balloon pump or both.
* urgent surgery.

Minor catheterization laboratory events:

* transient hypotension defined as a systolic blood pressure $\leq$ 80 mm Hg requiring intravenous therapy.
* bradycardia or atrio-ventricular conduction abnormalities requiring bolus of intravenous therapy, a temporary pacemaker or both.

Flow through the IRV was scored according to the Thrombolysis in Myocardial Infarction (TIMI) classification [10]. Reocclusion was defined as a reduction in TIMI perfusion grade 2 or 3 to TIMI grades 0 and 1. To assess the restenosis rate and arterial patency in the angioplasty group, these patients preferably underwent repeat coronary angiography after 3 months [11,12]. Restenosis was defined as a more than 50%

diameter stenosis measured quantitatively, after an initially less than 50% stenosis after primary coronary angioplasty. Patients in the angioplasty assigned group, who underwent coronary artery bypass surgery, who had an unsuccessful angioplasty or no procedure at all, did not have a routine repeat angiography. Data of the coronary angiography and angioplasty procedures were collected and graded by two of the investigators. As blinding to angioplasty procedures was not possible, all angiograms were subsequently reviewed by an independent and highly experienced investigator (M.v.d.B.), not involved in other aspects of the trial. Consensus on collateral flow, procedural success, TIMI flow before and after the angioplasty procedure, identification of the IRV, and extent of coronary artery disease was reached in all cases. TIMI flow before angioplasty was judged at first injection of contrast material. Collaterals to the infarct-related vessel were classified as proposed by Rentrop et al. [13]. Grade 0: no visible filling of any collateral channels, grade 1: filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel, grade 2: partial filling via collateral channels of the epicardial segment of the vessel, grade 3: complete filling of the vessel.

Follow-up coronary angiography in the streptokinase assigned patient group was also preferably performed after 3 months. In both groups however, this procedure was allowed to be performed earlier or later at the discretion of the attending physicians.

Quantitative coronary angiography (QCA).

All infarct-related vessels were analyzed objectively with a personal-computer-based QCA system (CMS: Cardiovascular Measurement System, Software version 2.0, Medis Medical Imaging Systems, Nuenen, the Netherlands) [14]. The basic algorithms have been described elsewhere [14,15]. The system uses a high-quality cine-to-video converter that allowed a selected cine frame to be projected onto a digital video camera through an optical zoom lens. The video signal of the magnified region of interest was subsequently digitized. For calibration, the boundaries of a nontapering part of the catheter were determined automatically over a length of approximately 2 cm. To determine the contours of the vessel the user had only to indicate the beginning and end of the coronary segment to be analyzed, after which a path was computed connecting these two points [16]. The contour procedure was then performed iteratively by resampling the image along scan lines perpendicular to the path computed in the first iteration. Next, a matrix of cost coefficients was computed that represented for each point in the resampled matrix the edge strength based on the weighted sum of the first and second derivative functions. The initial contours were found by the minimal-cost contour-detection technique applied to the cost-coefficient matrix [17]. In the second iteration, the contours determined in the first iteration

functioned as models for the subsequent determination. The edge strengths were corrected for the limited resolution of the entire imaging chain, a procedure that is particularly important for the accurate measurement of small vessels. From the final contours a new center line was computed. A diameter was determined in absolute terms (in millimeters) by computing along the vessel center line the shortest distances between the left and right contours. The reference diameter was defined as previously described [17]. An example of QCA analysis with the CMS system is given in Figure 1.

Statistical analysis.

Differences between group means were tested by a two-tailed Student t test. A chi-square method was used to test differences between proportions, and if appropriate calculation of odds ratios and their 95% confidence interval (CI). The Fisher exact test was used if there was an expected cell value < 5. Statistical significance was defined as a P value < .05. In the presentation of the data, continuous variables are given as mean value ± SD, whereas discrete variables are given as absolute values and percents.

Results

Baseline clinical characteristics and clinical course are shown in Table 1 and were described in detail [4]. Baseline angiographic data are shown in Table 2. In the angioplasty assigned patient group immediate angiography was performed in 151 patients; one patient died before angiography could be performed. He had severe three vessel coronary artery disease at post-mortem examination. Four patients did not have significant coronary artery narrowing. Two of them, however, suffered a myocardial infarction, one of them showing residual thrombi in a large left circumflex artery. Coronary angioplasty was performed in 140 patients. Five patients with an open or small infarct-related artery were treated conservatively. Six patients with severe multivessel disease or left main stenosis had emergency coronary artery bypass grafting after insertion of an intra-aortic counterpulsation balloon. Primary angioplasty of the infarct-related vessel was successful in 136 patients (97%) resulting in a less than 50% residual stenosis and a TIMI grade 2 or 3 flow at the end of the procedure. In four patients the IRV could not be reopened. Three of these patients underwent immediate coronary artery bypass grafting; one was treated conservatively. All the in-laboratory events are summarized in Table 3.

Of the 149 patients assigned to streptokinase therapy, one died before infusion could be started. Sixteen patients underwent a "rescue" coronary angioplasty because there was clinical evidence of failed reperfusion or hemodynamic collapse. In 15 patients the procedure was successful, one underwent emergency coronary artery bypass grafting and was discharged alive after an otherwise uneventful in-hospital

stay. Further clinical and in-hospital events have been described elsewhere [4].

Technical characteristics of the actual primary angioplasty procedures are the following: one balloon was used in 97 patients, two balloons in 33 patients, three balloons in nine patients, and four balloons in one patient. The average number of balloons used per procedure thus was 1.41 whereas the mean number of balloons used in elective procedures in our institution is 1.28. The mean maximum balloon pressure was 9.9 atm. (range 3-16), the number of inflations 3.2 (range 1-10) with a mean total inflation time of 530 seconds (range 90 - 2400). After a successful procedure the attending interventional cardiologist described angiographic evidence of dissection in 29 patients (21%).

Coronary angiography was performed after 22±38 days (range 0 - 304) in 139 of the 149 patients assigned to streptokinase therapy. Eight patients died before coronary angiography was performed, two patients refused angiography. The results of the quantitative coronary angiography (QCA) analysis are depicted in Table 4. The minimal luminal diameter (MLD) of the IRV increased from 0.25±0.62 mm before, to 2.22±0.62 mm immediately after the primary angioplasty procedure. If all patients in the streptokinase group with an occlusion of the IRV were excluded, the mean diameter-stenosis of the IRV was 64±13% and the mean minimal luminal diameter was 1.05± 0.41 mm.

Repeat angiography was performed after 92±67 days (range 1 - 389) in 130 of the 136 patients in the angioplasty group who actually underwent a successful procedure. Reasons for not performing a repeat angiography were: death in two patients, early elective coronary artery bypass surgery because of concomitant left main coronary artery disease in two patients, malignancy detected after randomization in one patient and refusal in one patient.

The IRV was patent in 66% of the patients (92 of 139) who received streptokinase and 95% of those assigned to angioplasty therapy (123 of 130), ($P < 0.001$; Odds Ratio [OR]: 8.9, 95% Confidence Interval [CI] 3.7 to 23). In the angioplasty group seven patients (5%) had an occluded IRV at follow-up angiography: the right coronary artery in 3 patients, the left anterior descending artery and left circumflex artery both in 2 patients; of these seven patients three had a TIMI grade 2 flow immediately after the angioplasty procedure compared with two patients in the group with a patent IRV at follow-up angiography ($P = 0.001$).

Among the patients assigned to angioplasty therapy only 7% had patent infarct-related vessels (TIMI grade 3 flow) at baseline and 92% of the patients had patent vessels by 120 minutes after admission. As no early angiography was performed in the streptokinase assigned patient group, the data on TIMI grade 3 flow were compared

with the angiographic data from the GUSTO trial (Figure 2)[18]. QCA data of the infarct-related vessels in the angioplasty assigned patient group at repeat angiography are shown in Table 4. Restenosis, defined as stenosis of more than 50% in the dilated segment, was observed in 24 of 125 patients in the angioplasty group (20%). Although evidence has accumulated that the incidence of restenosis reaches a plateau at three months [11,12], the clinical implications of restenosis will become clear only after at least six months of follow-up. Excluding all angiography without evidence of restenosis performed within three months after angioplasty, the rate of restenosis was 28% (24 of 87).

Discussion

Our results are consistent with the findings from other studies and demonstrate that primary coronary angioplasty for acute myocardial infarction can be performed safely and without major persistent sequelae as a result from the procedure itself [9]. Major in-laboratory events were observed in 14% of the patients who actually had a primary coronary angioplasty and could be treated adequately in all patients. Although we found a significantly higher rate of minor complications in patients undergoing angioplasty of the right coronary artery these events could be anticipated and treated appropriately. The procedural success rate for angioplasty of the right coronary artery is high and sustained patency is as high as for angioplasty of other vessels. We could not confirm the findings by Gacioch and Topol who found a high major complication rate and in-hospital mortality for patients undergoing angioplasty of the right coronary artery [19]. Some kind of in-laboratory event (major plus minor) occurred in 32% of the patients.

The coronary angiographic findings of trials of acute myocardial infarction have so far been mostly assessed by visual interpretation of the angiograms irrespective of whether stenosis grades or flow grades have been used [9, 20-25]. Conventional visual interpretation of coronary angiograms has its limitations and more objective means should be developed to measure or assess the results of reperfusion therapies. In our study, quantitative coronary angiography (QCA) was used. Repeat angiography after successful coronary angioplasty should be performed after three months as this appears to be the optimal time interval to detect restenosis early [11,12].

The diameter stenosis of the IRV immediately after primary coronary angioplasty was 27±15% and 35±22% at repeat angiography after a mean of 92 days; Only seven patients had an occlusion at follow-up angiography and the patients with an angiographic restenosis (17) all had a normal (TIMI grade 3) flow through the IRV. The rate of restenosis (28%) is comparable to the restenosis rate reported for elective

angioplasty [26].

The diameter stenosis in the streptokinase assigned patients was 77±20% (including 47 patients with an occlusion) although angiography in these patients was performed after a mean of 22 days. Angiography in the streptokinase assigned patients was obviously more often performed before this time interval of three months. The high incidence of occlusion or reocclusion (25% to 30%) after streptokinase therapy was confirmed by the APRICOT (Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis) study, where patency of the IRV was associated with a better left ventricular function [7].

Assessment of coronary flow and vessel patency should preferably be done by two investigators to avoid interobserver variability and we therefore asked a highly experienced investigator in the field of myocardial infarction studies to review the data [27]. Recent studies stressed the importance of flow through the IRV: Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow, although until recently thought to represent effective recanalization, is associated with a greater risk for development of recurrent ischemia, congestive heart failure, diminished left ventricular function and a trend towards a higher mortality [18, 28-31]. What remains unclear is whether TIMI grade 2 is a cause or a marker of adverse outcome, and diminished flow may in fact represent a relative no-reflow phenomenon [32]. In our study TIMI grade 3 was accomplished within 120 minutes after hospital admission in 92% of the angioplasty assigned patients and this is a likely explanation for the better left ventricular function as measured with radionuclide ventriculography in the angioplasty group [1,4].

TIMI grade 2 flow immediately after the primary coronary angioplasty procedure, with adequate reduction of the IRV stenosis, although observed in only 4% of the patients (5 of 136), seems to be a strong predictor of occlusion of the IRV at follow-up angiography ($P = 0.001$). The reduced flow may be caused by distal embolization or ischemic changes in the distal coronary vascular bed.

Optimal balloon sizing in primary coronary angioplasty is probably a major determinant of early as well as late outcome. A small balloon will lead to underdilation and a more severe residual lesion whereas an oversized balloon will increase the endothelial disruption and damage, leading to more acute complications and possibly an increase of the incidence of restenosis [33]. In our study, the ratio of balloon-size and reference diameter of the IRV is almost one (2.93 versus 3.04 mm).

The study by Leung and Lau showed a close non-linear relation between the degree of residual stenosis of the infarct-related artery after thrombolytic therapy and the degree of left ventricular dilation 6 months and 12 months after first (anterior) myocardial infarction [34]. Patients with a stenosis diameter of more than 1.5 mm had a

smaller left ventricular end-diastolic volume and there was no further left ventricular enlargement after 1 year. Reducing the degree of residual stenosis of the infarct-related artery by coronary angioplasty may thus be an effective therapy for preventing topographic changes to the left ventricle (left ventricular remodeling) [35].

Holmes and coworkers reported a reduction of luminal stenosis of the IRV from 98% to 33% in a small series of patients who underwent primary angioplasty, without antecedent thrombolysis, for acute myocardial infarction [36].The residual luminal stenosis of the IRV in the first randomized trial of primary angioplasty versus thrombolytic therapy by O'Neill et al. was reported to be 43% in the patients assigned to angioplasty, versus 83% in the patient group, treated with thrombolysis [37]. Clinical evidence indicates, that the residual stenosis after thrombolysis is perhaps the most important determinant of the frequency of reocclusion [38-40].

Restenosis after primary coronary angioplasty.

The major biological obstacle of coronary angioplasty (often referred to as the "Achilles' heel") to be overcome remains the problem of restenosis after initially successful angioplasty procedures. After elective coronary angioplasty the incidence of restenosis is reported to be 20% to 40% whereas this incidence may be higher after angioplasty for unstable coronary syndromes [5,26]. In several studies the restenosis rate after primary coronary angioplasty was comparable to our findings namely between 27% and 37% and the reocclusion rate was 7.9% to 22%, but repeat angiography was performed only in approximately 70% of these patients [41-44]. Deposition and accumulation of platelets at the site of angioplasty is related to restenosis and reocclusion; adequate antiplatelet therapy may be an important tool in prevention of these phenomena [33,45]. No additional benefit of thrombolytic therapy may be expected in this setting and may even worsen the effects of angioplasty therapy [44].

Quantitative Coronary Angiography in this study.

Currently the QCA techniques have been developed to the point that the contour detection itself is quite robust and reproducible, thus requiring minimal editing of the contours by the user [15,17]. On the other hand, coronary arteriograms are only shadowgrams of the arterial tree, and therefore may be of limited value in the presentation of the actual morphology of the vessel, particularly in complex eccentric lesions as at post-coronary angioplasty. In this study several precautions were taken to minimize these limitations as much as possible. First of all, IRV was analyzed from at least two views (if possible orthogonal, but at least 60% apart). Each view was chosen such that the IRV was presented with minimal foreshortening, and parallel to the input screen of the image intensifier. Second, at follow-up angiography in the angioplasty

group, the views from the primary coronary angioplasty session were repeated as accurately as possible. Third, frame selection was done in a standardized manner: frames to be analyzed were selected in the end-diastolic phase. Under such a highly standardized aquisition procedure, it has been shown that the standard deviations for differences in repeat measurements for films 1 to 6 months apart is 0.24 mm for the minimal lumen diameter and 0.33 mm for the interpolated reference diameter [46]. The measured interpolated reference diameter between immediate post-angioplasty (3.04±0.62 mm) and at follow-up 92±67 days later (3.00±0.66 mm), as well as the fact that these values are at the average equal to the reference diameter values in the streptokinase group (3.00±0.56 mm) are supporting the theory that QCA is a reliable and objective method to assess coronary anatomy in studies on myocardial infarction.

Limitations of this study.

The results of this study should be seen in the light of the optimal conditions for performing primary coronary angioplasty in our hospital. This includes full cardiovascular surgical back-up and optimal support of the department of cardiovascular anesthesiology. Besides this, in our hospital coronary angioplasty is performed on a high volume basis (1400 procedures yearly) by 4 experienced interventional cardiologists (350 annual procedures per cardiologist) and a catheterization-laboratory team consisting of 10 well-trained persons. These results cannot be transferred to daily practice in community hospitals even if angiography facilities are available.

Repeat angiography in the angioplasty assigned patient group was performed after a mean of 92 days. However, a considerable amount of patients had a repeat angiography within three months. The restenosis rate may be higher because of restenosis occurring during further follow-up in the subgroup of patients who had angiography within three months. Furthermore, we do not know if the observed "plateau of angiographic restenosis" that is reached at three months after elective angioplasty procedures will have the same behavior in time after primary angioplasty. The true rate of restenosis may thus be higher but patients do seldom present with occlusion of the IRV at follow-up angiography as was demonstrated in the present study. The discrepancy between time to follow-up angiography between the two treatment groups (despite the intention to perform angiography at three months) was induced by the fact that the protocol permitted early angiography at the discretion of the attending physicians.

We did not routinely perform early angiography in the patients assigned to streptokinase therapy, but we do have the early angiographic data of patients treated with the same thrombolytic regimen in the GUSTO trial and there are no reasons to

assume that these data do not match the streptokinase-assigned patients in the present study [18]. As is shown in Figure 1, primary coronary angioplasty is far more effective in accomplishing early and optimal flow through the IRV than any regimen of thrombolytic therapy, available today.

Finally, the observations reported in this study were made in a selected group of patients namely patients also eligible for thrombolytic therapy. As primary coronary angioplasty is also a treatment modality for patients with contraindications for thrombolysis the results in this group may be different.

Conclusion.

We conclude that primary coronary angioplasty in AMI can be performed safely and leads to a more rapid and complete reperfusion than does intravenous streptokinase. This is a likely explanation for the better left ventricular function in angioplasty patients compared with patients treated with intravenous streptokinase. The favorable in-hospital as well as late outcome in patients after primary coronary angioplasty is probably related to the better coronary anatomy after this procedure when compared with streptokinase therapy, as was demonstrated in the present study. We were able to show that this favorable anatomy is sustained in the majority of the angioplasty patients and that the reocclusion rate is low (5%). The observed restenosis rate of 28% is comparable to that after elective PTCA. Although occurring only in about 4% of the patients undergoing primary coronary angioplasty for AMI, TIMI grade 2 flow through the IRV immediately after the procedure is a strong predictor of reocclusion at follow-up angiography even if the infarct-related stenosis is reduced adequately.

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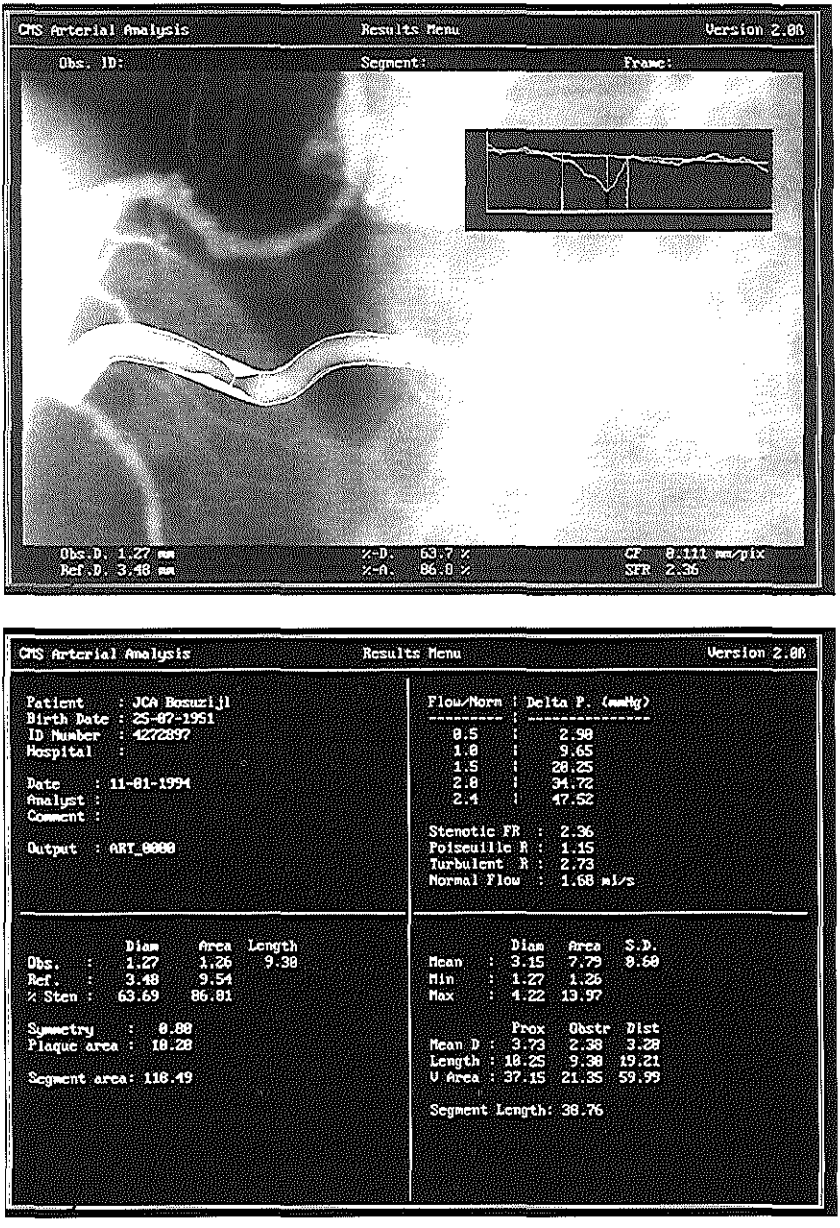

Figure 1: Print-out from the personal-computer-based QCA system (CMS: Cardiovascular Measurement System, Software version 2.0)

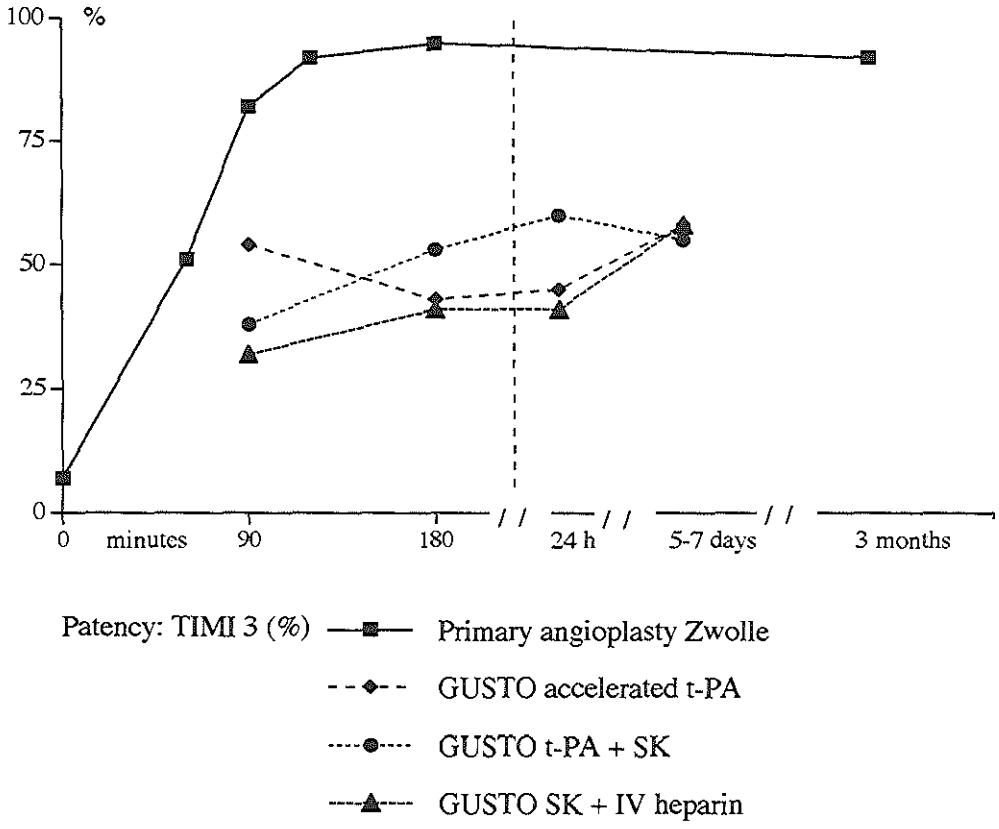

Figure 2: Graphic display of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow immediately after randomization: comparison of the angiographic results from the Zwolle and GUSTO trials. The data on TIMI flow in the GUSTO trial were gathered from different patients, who were randomly assigned to angiography at different time intervals after start of therapy. GUSTO indicates the Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded Coronary Arteries Study; tPA indicates tissue plasminogen activator; SK indicates Streptokinase.

Table 1: Baseline and Clinical Characteristics, Clinical Course.

	Angioplasty	P	Streptokinase
	(N=152)		(N=149)
Age (years)	59 ± 10	0.06	61 ± 9
Male sex	127 (84%)	0.59	121 (81%)
Anterior infarction	79 (52%)	0.27	68 (46%)
Previous infarction	32 (21%)	0.11	21 (14%)
Time onset -> admission (min)*	195 ± 227	0.43	176 ± 172
Time admission -> therapy (min)	64 ± 26		29 ± 16
Killip class III or IV on admission:	14 (9%)	0.73	12 (8%)
Mortality in hospital	3 (2%)	0.024	11 (7%)
Recurrent MI in-hospital	2 (1%)	< 0.001	15 (10%)
Hospital stay (first admission)	12.3 ± 5.3	0.003	14.4 ± 6.8
EF (%)	50 ± 9	< 0.001	45 ± 11
Recurrent ischemia first year	12 (8%)	< 0.001	55 (37%)
Mortality at one year	7 (5%)	0.15	13 (9%)

* From onset of symptoms of myocardial infarction to hospital admission. Values presented are mean ± SD or number (%). EF = Ejection Fraction before discharge measured with radionuclide ventriculography.

Table 2: Baseline Angiographic Characteristics.

		Angioplasty Group (N = 152)	Streptokinase Group (N = 149)
Diseased vessels			
None		3 (2%)	1 (1%)
One		54 (36%)	59 (40%)
Two		51 (34%)	37 (25%)
Three		37 (24%)	41 (28%)
Left main		6 (4%)	1 (1%)
Unknown		1 (1%)	10 (7%)
Infarct-related vessel			
Left anterior descending artery		60 (39%)	57 (39%)
Left circumflex artery		25 (16%)	21 (14%)
Right coronary artery		58 (38%)	58 (38%)
Left main coronary artery		2 (1%)	1 (1%)
Saphenous vein graft		3 (2%)	4 (3%)
Unknown		4 (3%)	10 (5%)
Collaterals (N=141) *	0	85 (60%)	
	1	45 (32%)	
	2	11 (8%)	

* Only patients who had visualization of the non-infarct related artery before the attempted angioplasty procedure are included.

Table 3: Catheterization-Laboratory Events in the Primary Coronary Angioplasty Group (N = 140)

	N	Percents
Major in-laboratory events:	20	(14%)
Involvement:		
Right coronary artery	8	(6%)
Left anterior descending artery	8	(6%)
Left circumflex artery	2	(1%)
Graft	1	(1%)
Left main coronary artery	1	(1%)
cardioversion	6	(4%)
cardiopulmonary resuscitation	6	(4%)
dopamine/adrenaline support	8	(6%)
intra-aortic balloon pump support for hypotension	6	(4%)
urgent surgery	3	(2%)
Minor in-laboratory events:	29	(18%)
Involvement:		
Right coronary artery	16	(11%) *
Left anterior descending artery	6	(4%)
Left circumflex artery	7	(5%)
brief bolus atropin or pressor	23	(16%)
temporary pacemaker	9	(6%)

* Risk of minor in-laboratory events of right coronary artery angioplasty significantly higher (P = 0.042) than for angioplasty of other vessels.

Table 4: Quantitative Angiographic Data *

Variable	Angioplasty Group				Streptokinase Group
	Before	After	Follow-Up at 92 ± 67 Days		at 22 ± 38 Days
	(N = 151)	(N = 140)	(N = 130)	P Value	(N = 139)
Projections analyzed (no.)	2.0 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	-	2.1 ± 0.5
Stenosis (%)	92 ± 19	27 ± 15	35 ± 22	< 0.001	77 ± 20
Minimal luminal diameter (mm)	0.25 ± 0.62	2.22 ± 0.62	1.99 ± 0.83	< 0.001	0.69 ± 0.60
Reference diameter (mm)†	-	3.04±0.62 (1.89-5.03)	3.00±0.66 (1.45-4.99)	0.924	3.00 ± 0.56 (1.72 - 4.82)
Largest balloon (mm)	2.93 ± 0.39	-	-	-	

* Plus-minus values are means ± SD. † By the interpolated method.

Chapter 6

Primary Coronary Angioplasty versus Intravenous Streptokinase in Acute Myocardial Infarction: Differences in Outcome during a mean Follow-up of 18 Months.

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Abstract

Background.

Intravenous streptokinase and primary coronary angioplasty are both considered effective treatment strategies for patients with acute myocardial infarction. Primary coronary angioplasty is associated with a high patency rate and a well preserved left ventricular function but whether it results in a more favorable clinical outcome has not yet been verified in randomized studies.

Methods.

Clinical data were obtained after a mean follow-up of 18 months (range 6-36 months) of 301 patients randomized to either primary coronary angioplasty (N=152) or intravenous streptokinase (N=149). The primary end-point includes cardiac death and non-fatal reinfarction. The secondary end-point is a weighted unsatisfactory outcome end-point which includes death, stroke, heart failure, shock, ejection fraction < 30%, reinfarction, reocclusion and bleeding complications. Furthermore, the need for revascularization procedures was recorded.

Results.

The relative risk of cardiac death and non-fatal reinfarction in the streptokinase group was 6.1 (95% confidence interval 2.9 - 12.7) as compared to the angioplasty group. There was a lower weighted unsatisfactory outcome score in patients randomized to angioplasty of 0.13 (median 0) compared to 0.34 (median 0.4) in patients randomized to streptokinase, ($P < 0.001$). Coronary angioplasty and/or coronary artery bypass grafting were more often performed in the streptokinase group, with a relative risk of 2.1 as compared to patients randomized to angioplasty, (95% confidence interval 1.5 - 3.2).

Conclusion.

Clinical outcome in patients with acute myocardial infarction after a mean follow-up of 18 months was more favorable in patients assigned to primary coronary angioplasty when compared with patients assigned to receive intravenous streptokinase.

Introduction

Over the last decade the value of thrombolytic therapy and/or coronary angioplasty to restore patency of the infarct-related coronary vessel has been established [1-16]. Primary coronary angioplasty without antecedent thrombolytic therapy avoids the potentially adverse effects of systemic bleeding or myocardial and intra-plaque hemorrhage that can be observed after thrombolytic therapy [8,12,13,16]. We previously reported a randomized trial comparing primary angioplasty with intravenous streptokinase in patients with acute myocardial infarction. A higher patency rate of the infarct-related vessel, smaller infarct size, preserved left ventricular function, less recurrent ischemia and a reduction of hospital mortality were observed in patients assigned to angioplasty compared to those, treated with intravenous streptokinase [13-15]. Another large multicenter trial confirmed these findings [16]. However, an important question still has to be answered before primary angioplasty can be accepted as the most efficacious therapy for patients with an acute myocardial infarction: do the superior coronary anatomy and ventricular function result in a more favorable clinical outcome during long-term follow-up?

Methods

The research protocol was reviewed and approved by the institutional review board. Enrollment began on August 20, 1990 and ended on April 26, 1993. Inclusion criteria were: 1. symptoms of acute myocardial infarction persisting for more than 30 minutes accompanied by an electrocardiogram with more than 1 mm (0,1 mV) ST segment elevation in two or more contiguous leads; 2. all patients presenting within 6 hours after symptom onset, as well as those presenting between 6 and 24 hours, if they had evidence of continuing ischemia; 3. age less than 76 years; 4. no contraindication to thrombolytic intervention [13]. Before randomization the following variables were recorded: age, sex, Killip class on admission [17], electrocardiographic site of infarction, history of prior infarction, time of symptom onset and time of hospital admission.

Randomization and Treatment

After informed consent was obtained, patients were randomly assigned to one of the two treatment modalities by means of a closed envelope system. All patients received aspirin and heparin [13]. Patients randomized to streptokinase received 1,5 million units intravenously in 1 hour. Patients randomized to coronary angioplasty were immediately transported to the catheterization laboratory and underwent coronary angiography. If the coronary anatomy was suitable for angioplasty this procedure was performed immediately using standard techniques.

End Points

1. Primary end point: the primary end point includes cardiac death, and non-fatal recurrent myocardial infarction, defined as previously described [13].
2. Secondary end point: a weighted unsatisfactory outcome end point, as proposed by Braunwald et al. [18] (see Table 1). Each patient is assigned a score that represents the single most serious outcome.
3. Revascularization procedures: coronary artery bypass grafting and/or coronary angioplasty (excluding the index infarct angioplasty).

Follow-up

Follow-up information was obtained in September 1993. All out-patient reports were reviewed, general practitioners as well as patients were contacted by telephone. For patients who died during follow-up hospital records and autopsy data were reviewed. No patient was lost to follow-up.

Statistical Analysis

All end points were analyzed according to the principle of intention to treat. Differences between group means were tested by the two tailed Student-t test. A chi-square method or the Fisher exact test was used to test differences between proportions. Differences in the unsatisfactory clinical outcome score were tested by the Mann-Whitney (or Wilcoxon's) rank sum test. Statistical significance was defined as a P-value of less than 0.05. Survival functions were calculated, using the Kaplan-Meier product limit method [19]. The Mantel-Cox (or log-rank) test was applied to evaluate the differences between survival functions. Multivariate analysis was performed by fitting Cox' proportional hazards model [20]. Odds ratios, that may be interpreted as relative risks with 95% confidence intervals, were calculated. In the multivariate analysis, adjustments were made for differences in age (continuous variable), gender, infarct location (anterior versus non-anterior), Killip class on admission, time from onset of symptoms to admission and previous myocardial infarction.

Results

During the enrollment period 301 patients were randomized, 152 to coronary angioplasty and 149 to streptokinase therapy. Baseline characteristics are shown in Table 1. None of these characteristics differed significantly between the two treatment groups. All patients assigned to angioplasty underwent immediate coronary angiography except one patient with cardiogenic shock who died immediately. Five patients had an open infarct-related artery and were treated conservatively. Six patients with extensive coronary artery disease considered not suitable for angioplasty underwent primary coronary artery bypass grafting. Angioplasty was performed in 140

patients, and the procedure was successful in 136 (97%). An intra-aortic balloon pump was inserted in 19 patients for hemodynamic support. Seven underwent elective coronary artery bypass grafting for left main coronary artery or extensive 3-vessel coronary artery disease. The mean time from admission to the first balloon inflation was 64 minutes. In 4 patients angioplasty failed to reopen the infarct-related artery, 3 of them underwent emergency coronary artery bypass grafting.

All patients assigned to therapy with intravenous streptokinase were treated accordingly, with one exception: 1 patient with cardiogenic shock died immediately following randomization. The mean time from admission to start of the streptokinase infusion was 29 minutes. Sixteen patients with hemodynamic compromise and signs of ongoing ischemia within 24 hours after admission underwent rescue angioplasty with procedural success in 15 patients, emergency coronary artery bypass grafting was performed in one patient. In 12 patients an intra-aortic balloon pump for hemodynamic support or as a bridge to cardiac surgery was inserted. Sixteen additional patients underwent emergency coronary angioplasty before hospital discharge because of signs of recurrent ischemia, with procedural success in 15 patients, and emergency coronary artery bypass grafting in one patient. Nine patients underwent elective angioplasty and 13 patients underwent elective coronary artery bypass grafting before hospital discharge for symptoms and signs of exercise induced myocardial ischemia. The remaining patients (94) did not undergo a revascularization procedure before hospital discharge. Follow-up coronary angiography was performed in 141 of the 149 patients assigned to receive streptokinase (95%).

The mean follow-up time was 18 months, with a maximum of 36 months. Follow-up time did not differ between the two treatment groups. During follow-up a total of 26 patients (8.6%) died, of whom in 24 patients the cause of death was cardiovascular. Two patients died due to malignant disease, which was demonstrated by autopsy. Causes of death are shown in Table 3. Recurrent myocardial infarction occurred in 34 patients (11.3%), during the follow-up period. Differences between the two treatment groups during the follow-up period are shown in Table 4. The patients who were treated with thrombolytic therapy had in particular a higher incidence of recurrent myocardial infarction. The combined incidence of cardiac death and non-fatal recurrent infarction is shown in Figure 1. The incidence of revascularization procedures during the follow-up, (coronary angioplasty and/or bypass surgery) was 88/149 = 59% in patients randomized to streptokinase compared to 44/152 = 29% ($P < 0.001$) in patients randomized to primary angioplasty, resulting in a relative risk of patients randomized to streptokinase for revascularization procedures of 2.1 (95% confidence interval 1.5 - 3.2). Event-free survival, that is survival without recurrent infarction, stroke or a

revascularization procedure is shown in Figure 2. Some clinical variables were strongly related to events during follow-up. Killip class on admission of ≥ 2 was associated with a relative risk of cardiac death of 2.2 (95% CI 1.4 - 3.5). Patients with multi-vessel disease had a relative risk of 1.7 (95% CI 1.2 - 2.4) to develop any of the end-points during the follow-up period.

Multivariate analysis showed that after adjusting for differences in age, gender, localization of infarction, Killip class, multi-vessel disease, time from onset of symptoms to admission and previous myocardial infarction, the patients who were randomized to thrombolytic therapy had a higher risk of cardiac death, recurrent myocardial infarction and the combination of cardiac death and recurrent infarction, compared to patients randomized to primary angioplasty. Results of the univariate and multivariate analysis are summarized in Table 5.

There was a marked difference in the combined primary clinical end point of cardiac death and non-fatal recurrent myocardial infarction of 6% versus 29% in angioplasty and streptokinase patients respectively ($P < 0.001$) (see Figure 1).
There was a lower weighted unsatisfactory outcome score, in patients randomized to primary angioplasty therapy, of 0.13 (median 0) compared with 0.34 (median 0.4) in patients randomized to receive streptokinase ($P < 0.001$) (see Table 2).

Revascularization procedures were more often necessary in patients randomized to streptokinase, with a relative risk of 2.1 (95% confidence interval 1.5 - 3.2) compared with patients randomized to coronary angioplasty.

Discussion

This study shows that primary coronary angioplasty in patients with an acute myocardial infarction is associated with a lower incidence of cardiac death and recurrent infarction in comparison with "standard" streptokinase therapy. Furthermore, there was a lower weighted unsatisfactory outcome score, and the incidence of revascularization procedures during follow-up was lower in patients randomized to angioplasty, as compared with streptokinase therapy. Over the last decade, great efforts have been made to assess the optimal treatment for patients with an acute myocardial infarction with attention focusing on large scale trials using mortality as the primary end point. However, the funds and patient numbers to support multiple "megatrials" to compare all theoretically attractive treatment strategies, are simply not available [18,21,22]. Left ventricular ejection fraction has been proposed [22] as well as rejected [21] as end point in trials in acute myocardial infarction. In a previous paper [14] we showed that primary angioplasty results in better preserved left ventricular ejection fraction when compared with intravenous streptokinase. Long term survival after

reperfusion therapy is related to left ventricular ejection fraction [6]. Recently, a composite clinical end point has been introduced [21,18] and this unsatisfactory outcome end point may serve as an approach to evaluate new therapeutic strategies in patients with an acute myocardial infarction. Therefore we haven chosen the unsatisfactory outcome score to assess whether the better preserved left ventricular function and the higher patency rate that result from primary angioplasty are indeed "translated" into clinical benefit during follow-up.

The primary target of all reperfusion therapies is the rapid and complete reopening of acutely occluded coronary arteries. Acute patency rates achieved with primary angioplasty are currently not obtainable with thrombolytic agents [7,13,14]. The results of the GUSTO trial (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) strongly supports the hypothesis that earlier reperfusion leads to improved survival. This observation, which bears on the mechanism by which reperfusion therapies confer clinical benefit, may be the most important message of the GUSTO trial [23-25]. Coronary patency, defined as the restoration of normal blood flow through the infarct-related vessel, results in myocardial salvage and improved survival. Our data certainly fit within this hypothesis: a higher patency rate (of angioplasty patients compared to streptokinase patients) results in a more preserved left ventricular ejection fraction [13,14] and improved survival (see Figure 1 and Tables 4 and 5). A slight improvement of short-term clinical outcome was observed in the GUSTO trial after a regimen of accelerated tissue-type plasminogen activator with intravenous heparin compared with streptokinase and intravenous heparin, as was used in our study. However, long-term outcome seems not to be related to selection of thrombolytic agent but rather to infarct-related artery patency and left ventricular function [26]. A second mechanism by which primary angioplasty results in a better long-term clinical outcome is the low incidence of reocclusion three months after successful angioplasty of 5% [13], compared to a reocclusion rate of about 30%, three months after successful reperfusion by thrombolytic agents [27].

Conclusion

Primary coronary angioplasty for acute myocardial infarction results in a more favorable clinical course, a reduction of recurrent infarction and a reduction of revascularization procedures during a longer follow-up period, when compared with intravenous streptokinase therapy. Long-term infarct-related vessel patency and a better preserved left ventricular function are a plausible explanation for this observation. Further research to determine the role of primary angioplasty in the treatment of patients with acute myocardial infarction, especially to investigate which

patients benefit most from this approach, are urgently needed.

Appendix

An interim survey of the most important endpoints death, recurrent infarction and the combination of death and recurrent infarction, in May 1994 gave the following results (univariate analysis) with relative risks and 95% confidence interval (CI) of patients assigned to streptokinase therapy compared with angioplasty treatment.

		A	S	P value	Relative Risk	95% CI
Death	:	10	16	0.28	1.7	0.8-3.9
Recurrent infarction	:	5	31	< 0.001	7.7	2.9-20.5
Death and recurrent infarction:		10	42	< 0.001	5.6	2.7-11.6

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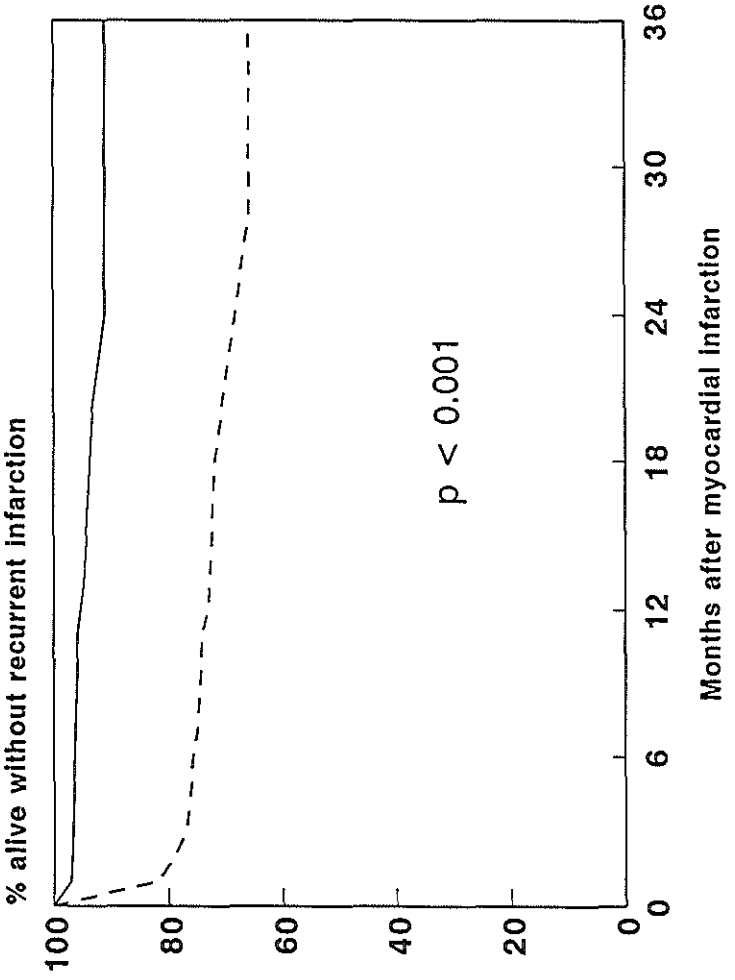

Figure 1: Survival without non-fatal recurrent myocardial infarction in 301 patients with acute myocardial infarction, randomized to treatment with thrombolysis (- - - -) or primary angioplasty (_____) ($P < 0.001$).

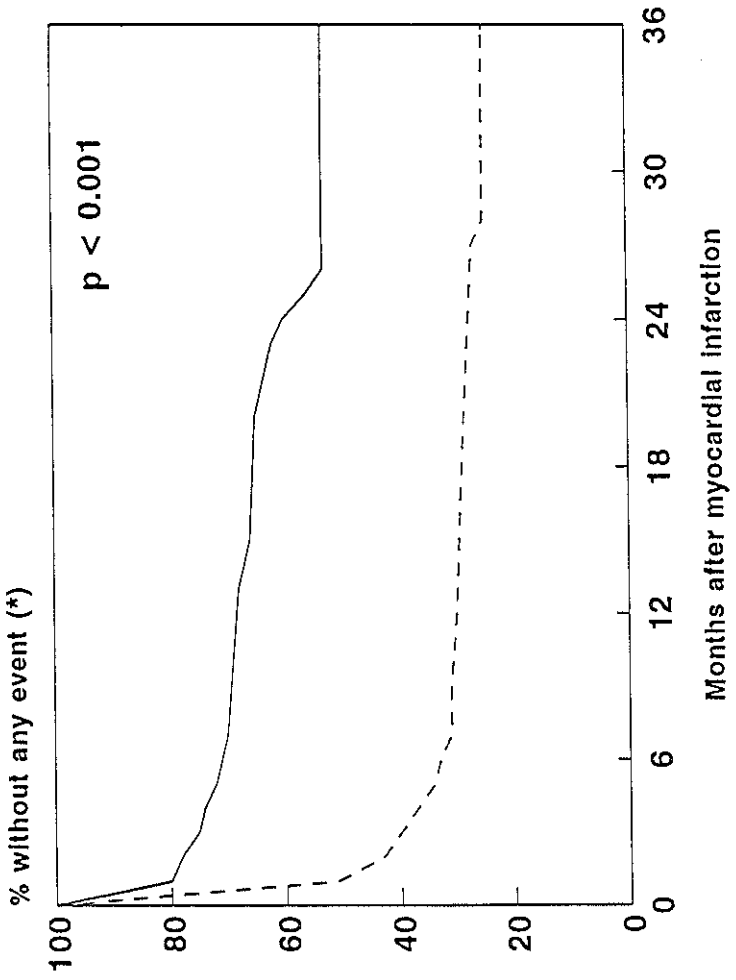

Figure 2: Survival without clinical events in 301 patients with acute myocardial infarction, randomized to treatment with thrombolysis (- - - -) or primary angioplasty (_____) (P < 0.001). An event was defined as cardiac death, recurrent myocardial infarction, stroke, coronary angioplasty or bypass grafting.

Table 1: Baseline Characteristics

	Angioplasty (N=152)	P	Streptokinase (N=149)
Age (years)	59 ± 10	0.06	61 ± 9
Male sex	127 (84%)	0.59	121 (81%)
Anterior infarction	79 (52%)	0.27	68 (46%)
Previous infarction	32 (21%)	0.11	21 (14%)
Time onset-admission (min)	195 ± 227	0.43	176 ± 172
Killip class on admission: I.	116 (76%)	0.22	122 (82%)
II.	22 (14%)	0.26	15 (10%)
III.	6 (4%)	0.41	9 (6%)
IV.	8 (5%)	0.14	3 (2%)
Multivessel disease	95 (63%)	0.63	88 (59%)

Table 2: Weighted Unsatisfactory-Outcome End Point, 18 months (range: 6-36 months) after randomization:

Event		Score	P (N=152)	S (N=149)
1.	Death	1.0	10	16
2.	Intracranial hemorrhage with severe permanent neurological deficit	1.0	0	0
3.	Development of severe, sustained CHF or cardiogenic shock	0.8	0	2
4.	Ejection fraction < 30% *	0.6	11	15
5.	Reinfarction	0.5	2	22
6.	Occlusion or reocclusion of IRV at F-U angiography	0.4	3	29
7.	Major hemorrhage requiring blood transfusion or intracranial hemorrhage without severe or permanent neurological deficit	0.3	4	4
8.	None of the above	0.0	122	61

P = primary angioplasty, S = streptokinase, CHF = Congestive Heart Failure, IRV = Infarct Related Vessel, F-U = Follow-Up, * determined by radionuclide technique before hospital discharge [12].

The mean score of Primary angioplasty patients was 0.13
(median = 0; 25 percentile = 0; 75 percentile = 0)

The mean score of Streptokinase patients was 0.34
(median = 0.4; 25 percentile = 0; 75 percentile = 0.5), $P < 0.001$.

Table 3: Causes of death in 152 patients assigned to angioplasty and 149 patients assigned to streptokinase

	Angioplasty	P	Streptokinase
Heart failure	4 (3%)	0.15	9 (6%)
Cardiac rupture	0	0.24	2 (1%)
Sudden death	2 (1%)	0.45	4 (3%)
Cardiac Death	6 (4%)	0.04	15 (10%)
Stroke	2 (1%)	1.0	1 (1%)
Malignancy	2 (1%)	0.50	0 (1%)
	10 (7%)	0.28	16 (11%)

Table 4: Comparison of outcome during a mean follow-up of 18 months between 152 patients assigned to primary angioplasty and 149 patients assigned to streptokinase therapy for acute myocardial infarction (univariate analysis)

	A	S	RR	95% CI
Number of patients	152	149		
Cardiac death	6	15	2.5	1.1 - 6.5
Recurrent myocardial infarction	4	30	8.3	2.9 - 23.5
Cardiac death or recurrent infarction	9	42	5.1	2.5 - 10.6

A = Angioplasty, S = Streptokinase, RR = Unadjusted Relative Risk of outcome, streptokinase compared with angioplasty, CI = Confidence Interval.

Table 5: Relative risks of outcomes during a mean follow-up period of 18 months in 152 patients assigned to primary angioplasty, compared to 149 patients assigned to streptokinase therapy *

Outcome	Relative Risk	95% Confidence interval
Cardiac death	3.5	1.3 - 9.3
Recurrent myocardial infarction	8.9	3.1 - 25.6
Cardiac death or non-fatal reinfarction	6.1	2.9 - 12.7

* adjusted for differences in age, gender, localization of infarction, Killip class, multivessel disease, time from onset of symptoms to admission, previous infarction.

Chapter 7

Is Primary Coronary Angioplasty more Expensive than Thrombolysis for Patients with Acute Myocardial Infarction? A Cost-Effectiveness Analysis.

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Introduction

In the Zwolle trial patients with acute myocardial infarction were randomly assigned to undergo primary coronary angioplasty or to receive intravenous streptokinase. A higher patency rate of the infarct-related vessel, smaller infarct size, preserved left ventricular function, less recurrent ischemia and a reduction of hospital mortality were observed in patients assigned to angioplasty compared to those, treated with intravenous streptokinase. [1,2,3]. Another multicenter trial confirmed these findings [4]. However, facilities for primary coronary angioplasty are restricted or not widely available, and the costs of the initial procedure are considerably higher than for thrombolytic therapy. Still the higher initial costs may be acceptable when these would be balanced against the additional benefits and when account is taken of the potential savings. In the short run, primary coronary angioplasty (i.e. angioplasty without concomitant thrombolytic therapy) leads to a decreased risk of bleeding and hemorrhagic stroke, implying lower costs. In the long run, additional savings might occur due to lower rates of recurrent ischemia and reinfarction [1,2,4]. The present study addresses the balance between costs and effects during the first year after initial treatment. The calculation of costs is based on total medical costs, including all hospital admissions, additional procedures and other medical events. Effects are defined as event free survival, including recurrent infarction, stroke and death as events. No patients were lost for follow-up.

Methods

Patient selection and treatment

Included were 301 patients with signs of acute myocardial infarction, with an age less than 76 years, without contra-indications for thrombolysis, and who presented within 6 hours after onset of symptoms. If there were signs of ongoing ischemia, patients could also be included up to 24 hours. After informed consent was obtained, 152 patients were randomly assigned to undergo primary angioplasty and 149 patients were assigned to treatment with streptokinase, 1.5 million units intravenously in 1 hour. Patients assigned to coronary angioplasty were immediately transported to the catheterization laboratory and underwent coronary angiography. If the coronary anatomy was deemed suitable for angioplasty, this procedure was performed immediately, using standard techniques.

Cost-Effectiveness Analysis

The question of efficiency was addressed by way of a cost-effectiveness (C/E) ratio, the difference in costs in the denominator, the difference in effects in the numerator. The estimates of costs concern the direct medical costs. They were estimated by multiplying volumes with estimates of unit costs. The volumes concern hospital days (distinguishing between normal care, coronary care and postoperative intensive care), procedures and medication (including the thrombolytic drugs given). All volumes were registered during the initial admission, during readmissions and during visits to the outpatient clinic. By general survey of patients (mostly by telephone interview) and of the referring physicians, readmissions to other hospitals could be traced and these data were added to the database. All patients were scheduled for follow-up angiography after three months and the costs of this procedure were included in the calculations. Data were collected for 12 to 14 months of follow-up after the index myocardial infarction.

Effects were measured in terms of event free survival after one year. Events in survivors include recurrent myocardial infarction and stroke. Coronary angioplasty or bypass grafting during follow-up were not included. However, they do effect the C/E ratio due to their effect on the costs. Information about mortality, morbidity and functional status (expressed in terms of the functional classification of the New York Heart Association, NYHA) was gathered during visits to our outpatient clinic and by telephone interview with referring physicians.

Unit costs for procedures and hospital days were calculated on the basis of hospital administration data of 1992. They included the professional charges and were corrected for the costs of procedures during the night or the weekend (One Dutch Guilder is approximately 0,53 U.S. Dollar). Costs applied for a diagnostic catheterization were Dfl. 1,500, for angioplasty Dfl. 8,000, for bypass surgery Dfl. 18,000, for 1 day in the coronary care unit Dfl. 1,550, for 1 day in the postoperative intensive care unit Dfl. 2,250, and for one day on a general ward Dfl. 500. Costs for streptokinase and tPA were Dfl. 400 and Dfl. 2,000 respectively. The costs for the radionuclide studies were not included in the analysis, since these studies were used in all patients for the determination of end-point data rather than for patient care. All costs were recorded and analysed according to the intention to treat principle.

Medication was classified using the main groups of cardiovascular drugs, and was obtained at discharge and after one year of follow-up. The costs of medical treatment was based on the average treatment costs of the different drugs according to their prices in 1992. This amount was calculated per month and includes costs for prescription and administration. The costs for oral anticoagulant therapy including hematological

monitoring were estimated on Dfl. 400 per year as was calculated for the Anticoagulants in the secondary prevention of events in coronary thrombosis (ASPECT) research group [5]. The groups of drugs and their costs were (per month): nitrates: Dfl. 20, aspirin Dfl. 10, coumadin Dfl. 33, β-blockers Dfl. 60, calcium-blockers Dfl. 70, diuretics Dfl. 30, Angiotensin Converting Enzyme -inhibitors Dfl. 105, antiarrhythmic agents Dfl. 35 and cholesterol lowering drugs Dfl. 135. Also the number of patients receiving thrombolytic therapy at readmission were registered.

Statistical analysis.

Differences between groups were tested by the Student t-test or the Mann-Whitney rank-sum test when appropriate. For comparison of rates of discrete outcome variables a conventional chi-square test was used. Relative risks with 95% confidence intervals were calculated. The Fisher exact test was used if there was an expected cell value of less than 5. A chi-squared test for trend was used for differences in functional status and medication. All P values are two-sided; a P-value of less than 0.05 was considered to indicate statistical significance. In our presentation of the data, continuous base-line and outcome variables are given as means ±1 SD, whereas discrete variables are given as absolute values and percentages. The uncertainty surrounding the C/E ratios was assessed using the methodology outlined by van Hout et al [6]. The basis for this methodology is that average costs and average effects approach a bivariate normal distribution. This allows for the calculation of a 95% confidence ellipse, i.e. a simultaneous confidence region for both costs and effects. Furthermore, P values can be calculated to indicate the probability that one treatment is more cost-effective than the other.

Results

Clinical course

Baseline characteristics and clinical course have been described elsewhere [2]. In-hospital mortality and reinfarction rate were lower, left ventricular ejection fraction was better and infarct size was smaller in the angioplasty-assigned patients compared with those, treated with intravenous streptokinase [2,3]. Seven patients (5%) in the angioplasty assigned group and 13 patients (9%) in the group assigned to receive streptokinase had died at one year (P = 0.15). The incidence of revascularization procedures (except procedures as treatment for the index infarction) in the first year was significantly reduced in the angioplasty assigned patients (49/152 versus 84/149, P = 0.04). Recurrent infarction, death or stroke at one year occurred in 11 patients in the angioplasty assigned group versus 39 patients in the streptokinase assigned group (P< 0.001).

In-hospital costs and costs during follow-up

Follow-up data could be collected in all patients. After 1 year, the functional status defined as NYHA class, was better in the angioplasty patients and 79% of these patients were in NYHA class 1 versus 62% of the patients in the streptokinase group (P value for trend 0.026; Table 1, Figure 1). This was also evident from costs for pharmacological therapy during the first year. The mean total costs of pharmacological therapy per patient after one year were Dfl. 1047 for the angioplasty assigned patients and Dfl. 1356 for the streptokinase patients (P = 0.01).

In-hospital costs, and costs during follow-up are presented in Table 2 together with the procedures performed. The calculated total costs of in-hospital treatment in both groups after 1 year of follow-up of all patients were Dfl. 26,355 per patient in the angioplasty assigned group and Dfl. 25,027 (P = 0.12) in the streptokinase assigned group. One patient in the angioplasty assigned group, a 75 year old woman who underwent coronary artery bypass surgery three months after the qualifying infarction, was responsible for 16% of all costs in this group during follow-up. She died after 50 days in the intensive-care unit. Excluding this patient, the average costs in the first year in the angioplasty group would amount to Dfl. 25,297. In Figure 2, the cumulative costs (in-hospital costs and costs of medication) during the first year are depicted. After one year the total costs per patient in both treatment groups are almost the same (Dfl. 27,354 for the angioplasty and Dfl. 26,264 for the streptokinase group, P = 0.22). The efficiency of both treatment modalities can be addressed by putting forward the average costs per event free survivor, where revascularization procedures were not considered to be events. The C/E ratios were Dfl. 29,280 for the patients assigned to angioplasty treatment and Dfl. 34,941 for those assigned to streptokinase therapy. The marginal C/E ratio (defined as additional costs per additional event free survivor: difference in costs of the two treatment groups divided by the difference in effects) were estimated at Dfl. 5,968. The reliability of this estimate is indicated in Figure 3 where change in costs (ΔC) and change in effects (ΔE) are depicted as a bivariate normal distribution. From this we may estimate the probability that treatment with primary angioplasty is more cost-effective than treatment with streptokinase to be 0.975 (thus representing a P value of 0.025). The results would be similar when coronary angioplasty and bypass grafting during follow-up were included in the measurement of effects (P < 0.001). Furthermore, changing all unit cost estimates with 20% did not effect the base line conclusion that treatment with angioplasty is more cost-effective than treatment with streptokinase.

Discussion

The present study indicates that primary coronary angioplasty is effective with regard to mortality, morbidity and functional status in the surviving patients. The concern that this new approach is far more expensive than "conservative" thrombolytic therapy was not confirmed.

Previously it was demonstrated that the combination of thrombolytic therapy and immediate angioplasty has no additional clinical benefit above "stand alone" thrombolytic therapy [7,8]. The rate of complications with this combined approach is considerable and the costs of emergency angiography and angioplasty are high, resulting in more costs during admission for the qualifying infarction without apparent benefit. Until recently however, it was unclear if, under optimal interventional cardiology covering, coronary angioplasty would be effective as a "stand alone" procedure. Furthermore the cost-effectiveness of this therapy was only subject of debate in one report, concluding that angioplasty was not more expensive than thrombolytic therapy [9].

In the present study, we examined resource consumption, the actual costs and functional status in 301 patients admitted for acute myocardial infarction, randomly assigned to treatment with primary coronary angioplasty or intravenous streptokinase, during the first year. Knowledge of the coronary anatomy as was obtained early in the angioplasty assigned patient group, will certainly influence the amount of revascularization procedures during the in-hospital stay. On the other hand, if recurrent ischemia is encountered more frequently in the thrombolysis treated patients this will increase the incidence of readmissions and revascularization procedures in this group during follow-up.

The better functional status of the angioplasty assigned patients in the present study, together with lower consumption of pharmacological and other sources compensated the higher costs on first admission associated with primary angioplasty. In view of the better clinical status at 1 year, the better left ventricular function and better coronary anatomy, compared with patients treated with intravenous streptokinase, it may be expected that primary angioplasty will have a more pronounced beneficial effect on health care costs in the following years, in favor of the angioplasty treated patients (Figure 1).

The present study was carried out in a hospital with the preexisting infrastructure for interventional cardiology (including a 24 hour cardiosurgical covering) and with a high case-load of 1400 angioplasty procedures per year. The data are not necessarily transferable to community hospitals without these facilities. Furthermore, it is unrealistic

to assume that all patients presenting with myocardial infarction can be treated with primary angioplasty because of limited availability and the enormous logistic burden for hospitals, doctors and ancillary personnel.

Conclusion

The present study demonstrates superior clinical outcome in patients after primary coronary angioplasty when compared with streptokinase therapy, at approximately the same costs per patient in the first year. When assessed in relation to survival without recurrent infarction or stroke, it was apparent that treatment of acute myocardial infarction with angioplasty is more efficient than streptokinase therapy. Additional savings of angioplasty treatment may be expected during longer follow-up.

The results of this study may help to encourage introduction of primary angioplasty as a treatment modality for patients with acute myocardial infarction in hospitals with existing interventional cardiology programs. Ongoing and future studies will further define which patients will benefit most from primary coronary angioplasty for acute myocardial infarction. Health care organizations and politicians, who feel that quality of care is as important as saving costs, should be aware of this new indication for coronary angioplasty.

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Table 1: Follow-up data at 1 year.

	Angioplasty *(N=152)*	P	Streptokinase *(N=149)*
NYHA			
1	120 (79%)		93 (62%)
2	23 (15%)		34 (23%)
3 + 4	2 (1%)		9 (6%)
Deceased	7 (5%)	0.15	13 (9%)
Trend analysis		0.0026 *	
Days alive (all patients)	353	0.51	335
Anterior	339	0.61	321
Non-anterior	365	0.50	345
Medication at 1 year	*N = 145*		*N = 136*
Aspirin	121(81%)	0.47	109 (80%)
Coumadin	16 (11%)	0.15	23 (17%)
Nitrates	12 (8%)	0.012 *	25 (18%)
β - blocker	34 (23%)	0.47	37 (27%)
Ca - blocker	42 (28%)	0.30	32 (24%)
Diuretics	13 (9%)	0.067	22 (16%)
ACE inhibitor	32 (21%)	0.09	42 (31%)
Antiarrhythmic drugs	9 (6%)	0.40	12 (9%)
Cholesterol -lowering drugs	4 (3%)	0.74	5 (4%)
Medication (aspirin excluded)			
0	52 (36%)		32 (24%)
1	61 (42%)		49 (36%)
≥2	32 (22%)		55 (40%)
Trend analysis		0.001*	

NYHA = New York Heart Association classification; ACE = Angiotensin Converting Enzyme; * P value significant.

Table 2: Total costs during the first year

	Angioplasty	Streptokinase
	N = 152	N = 149
Days CCU first admission	485 (3.23 ± 0.13)	590 (4.01 ± 2.52)
Days ICU first admission	64 (4.00 ± 4.37)	41 (2.93 ± 1.98)
Days general ward	1352 (9.07 ± 4.97)	1483 (10.90 ± 5.10)
Procedures first admission		
Angiography	49	79
Angioplasty	142	51
Bypass surgery	16	15
Thrombolysis	1	148
Costs first admission	Dfl. 3,014,800	Dfl. 2,570,450
Days CCU follow-up period	10	66
Days ICU follow-up period	73	40
Days general ward follow-up period	587	673
Procedures follow-up period		
Angiography	90	56
Angioplasty	21	23
Bypass surgery	10	20
Additional costs first year	Dfl. 956,250	Dfl. 1,156,800
Costs pharmacological treatment during the first year.	Dfl. 151,811	Dfl. 184,490
All costs per patient (intention to treat):	Dfl. 27,354	Dfl. 26,264

CCU = Coronary Care Unit (days); ICU = Intensive Care Unit (Postoperative) (days); CA = Coronary Angiography (no); P = Percutaneous Transluminal Coronary angioplasty (no); B = Bypass surgery (no).

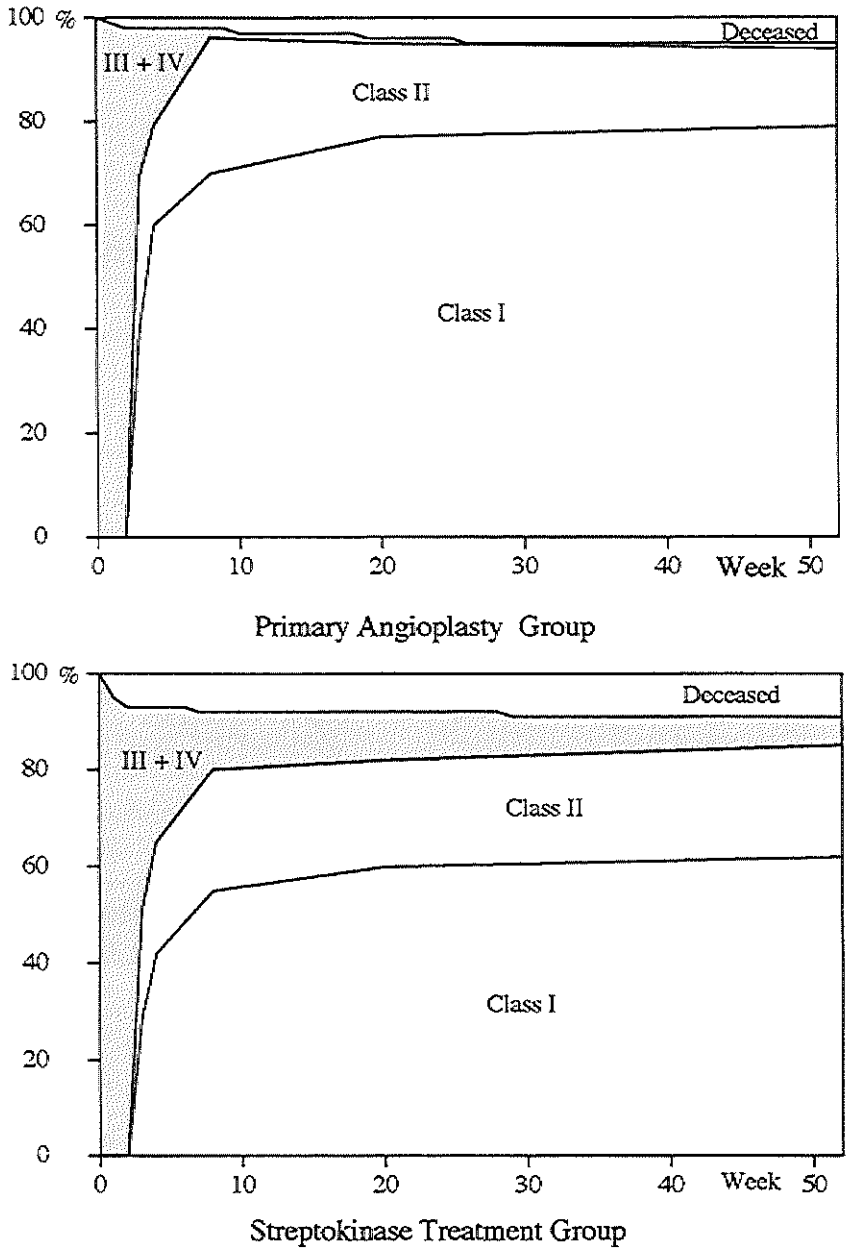

Figure 1: Graphic display of proportion of patients in each functional class during the first year in the two treatment arms. Class I - IV indicates functional class according to the New York Heart Association (NYHA) classification.

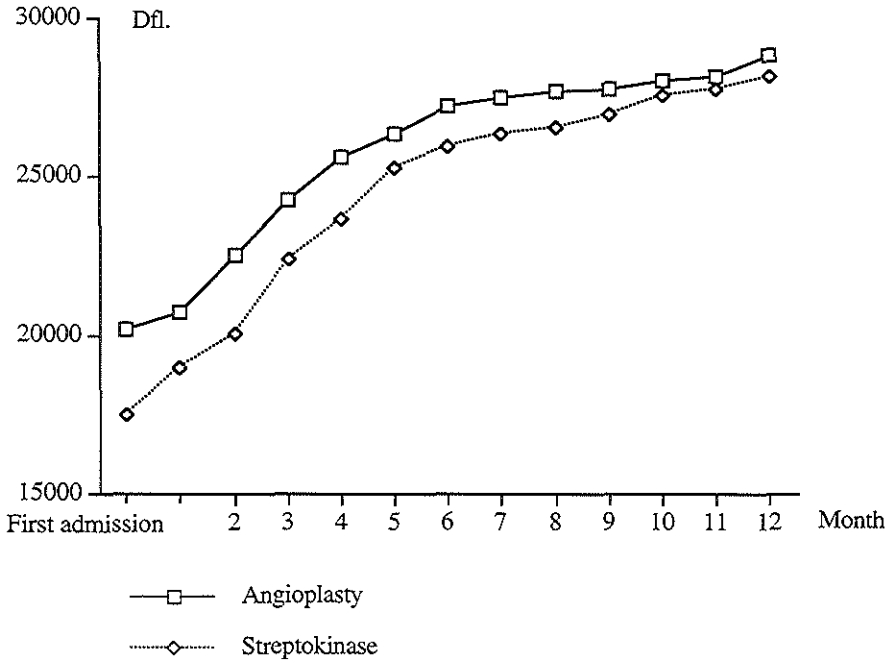

Figure 2: Total cumulative costs during the first year per patient, including in-hospital costs and costs of pharmacological treatment (in surviving patients) in both treatment arms. Dfl. = Dutch Guilders.

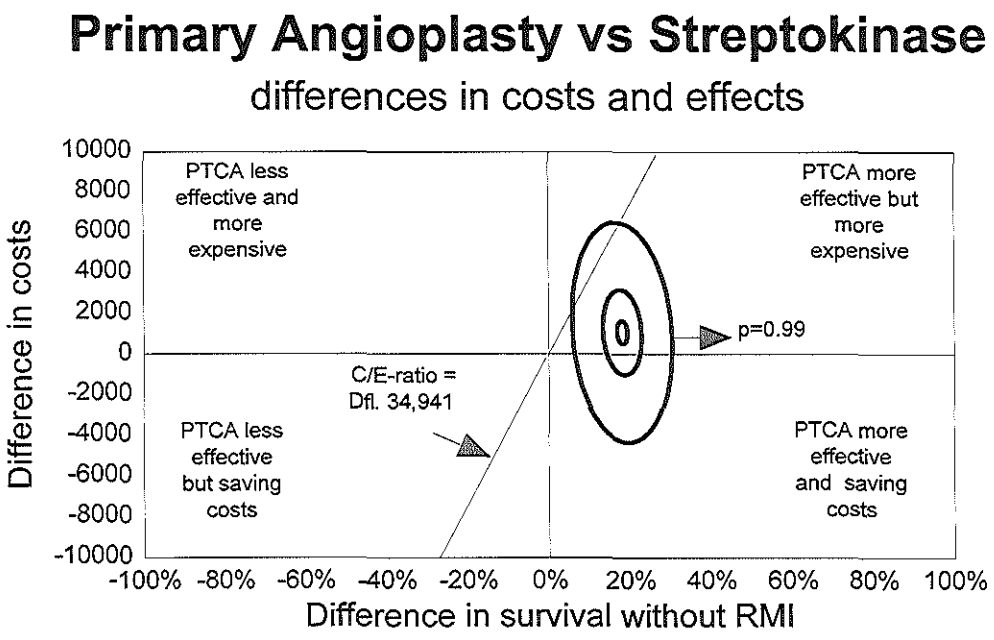

Figure 3: Bivariate normal distribution of cost and effects comparing primary coronary angioplasty and streptokinase treatment for acute myocardial infarction. A 99 % confidence ellipse, i.e. a simultaneous confidence region for both costs and effects is calculated. Differences in effects (x - axis) and costs (y - axis) are presented.

Chapter 8

Data from Three Prospective Randomized Clinical Trials of Thrombolytic versus Angioplasty Therapy of Acute Myocardial Infarction
Preliminary Results from a Pooled Analysis

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Introduction

Reperfusion therapy of acute myocardial infarction has revolutionized management of this illness. Mortality reduction has been demonstrated for both intracoronary [1,2] and intravenous thrombolytic therapy [3,4]. Recently the GUSTO (Global Utilisation of Streptokinase and Tissue plasminogen activator) trial [5] and the GUSTO angiographic sub-study [6] have confirmed the importance of early coronary patency after thrombolytic therapy. Both mortality reduction and preservation of systolic ventricular function depend on early, effective coronary artery recanalization.

The need for rapid arterial reperfusion has fuelled renewed interest in nonpharmacologic reperfusion therapy. Institutions with skilled operators and staff can achieve very high rates of arterial reperfusion with angioplasty therapy [7,8]. Pretreatment with intravenous thrombolytic therapy is unnecessary and may even have deleterious effects [9,10]. The potential advantages of angioplasty, including high rates of reperfusion, lesser residual stenosis and lower risk of stroke, might be negated by the potential time delay to treatment and potentially greater hospital costs incurred, compared to thrombolytic therapy. Three prospective clinical trials have been recently completed to attempt to resolve these issues [11,12,13].

However, none of these studies was large enough to answer the crucial question whether differences in mortality occurred after these greatly different treatment strategies. Furthermore, the individual studies did not allow definition of patientgroups with greatest benefit of primary angioplasty. Therefore the three groups have collaborated to combine the data, and to report the pooled outcome from these studies. Since access to primary data was allowed, detailed analysis of comparability to patient groups, subgroup analysis and multivariable regression analysis could be performed. In performing this pooled analysis, the role of angioplasty as an alternative reperfusion modality could be better clarified.

Methods

Protocol Design

The Primary Angioplasty in Myocardial Infarction (PAMI) study was conducted in 12 centers in the U.S.A. and France between June 1990 and July 1992. Patients presenting within 12 hours of symptom onset were randomized to angioplasty versus thrombolytic therapy. Thrombolytic therapy with tissue plasminogen activator (rt-PA, activase) at a dose of 100 mg over 3 hours (or 1,25 mg per kilogram of body weight for patients weighing less than 65 kilograms). The primary endpoint was freedom from either death or nonfatal reinfarction.

The Netherlands (Zwolle) study was a single-institution study in which 301 patients

presenting between August 1990 and April 1993 were recruited. Patients presenting with symptoms less than 6 hours duration or those presenting 6 to 24 hours after symptom onset with ongoing ischemia were randomized to angioplasty or thrombolytic therapy with intravenous streptokinase: 1.5 mega units over one hour. The primary endpoint of this study also was freedom from death or nonfatal reinfarction.

Finally, the Mayo Clinic study was a single-center study conducted between April 1989 and June 1991. Patients presenting within 12 hours of symptom onset were randomized to angioplasty or thrombolytic therapy. The thrombolytic agent was double-chain tissue plasminogen activator (duteplase). A total dose of 0.6 mega units per kilogram of body weight was administered over 4 hours. In the three studies in-hospital outcomes were reported.

Results

Comparability of Studies

Each of these three randomized clinical trials tested the strategy of immediate catheterization and angioplasty compared to intravenous thrombolytic therapy with "watchful waiting". For this reason, the major findings comparing the efficacy of these strategies can be pooled. Although the studies used three different thrombolytic agents, the use of heparin and aspirin was the same. Most importantly, the thrombolytic groups were treated without routine immediate catheterization so the principle of mechanical versus pharmacologic reperfusion was tested in each study. Baseline demographics were compared to sex and severity of illness of these patients in each study. Patients in the Zwolle study more often presented with anterior myocardial infarction compared to the PAMI or Mayo Clinic study. Also patients from the Zwolle study were more often male. Patients in the Mayo Clinic study less frequently had a history of previous MI and also less frequently underwent in-hospital bypass surgery. Patients presented earlier in the Zwolle study than in the PAMI trial and later in the Mayo Clinic study. In spite of these minor differences in baseline variables, there were no major differences in clinical outcome; overall mortality was similar as were the rates of reinfarction and rates of stroke. Recurrent ischemia was defined the same as in the PAMI and Zwolle study, and the outcome was similar for both studies. These data justify the pooling of outcomes for comparison.

In each study, careful analysis has been performed to assure that randomization was successful in segregating comparable treatment groups. When the data were pooled, severity of illness was identical for thrombolytic and angioplasty groups. In both groups, patients tended to have greater proportion of previous MI than other contempory thrombolytic trials [3,5].

While severity of illness was similar, the clinical outcome was dramatically different between the two groups. A mortality rate of 6.4% (26/405) was observed in the thrombolytic group, compared to a 2.6% mortality (10/394) for the angioplasty group, P = 0.008. This represents a ratio for risk reduction of 2.5 (95% Confidence Interval (CI) 1.21 to 5.55). Similarly, a 3.9 risk ratio reduction for reinfarction (2% versus 7.9%, P < 0.001, CI 1.8 to 8.4) for angioplasty treated patients was observed. Combining the two major adverse outcomes of death and/or reinfarction, angioplasty reduced the risk by a factor 3.0 (4.3% versus 13.1%, P < 0.00001, CI 1.8 to 5.1). Finally, angioplasty therapy resulted in a 9.7 risk ratio reduction (0.3% versus 2.5%, P = 0.007, CI 1.3 to 75.6) in the incidence of stroke. Freedom from any of these events was observed in 95% of patients treated with angioplasty compared to 85% of patients treated with thrombolytic therapy.

Subgroup analysis was performed to identify patients with greatest potential benefit from angioplasty therapy. Previously, the Thrombolysis in Myocardial Infarction (TIMI) study [14] had stratified patients in two groups: low risk versus those not at low risk, based on age, infarct location and admission heart rate. Mortality was equally low for thrombolytic therapy and angioplasty treated patients in the low risk group. The main mortality advantage occurred in the angioplasty treated patients at high risk. Risk of reinfarction or combined endpoint of death or reinfarction favored angioplasty whether the patients were at high risk or low risk. Risk of stroke was greater in the high risk patients treated with thrombolysis since by definition all elderly patients were considered high risk. In order to further determine which separate clinical variable incurred increased risk, an analysis was done of the impact of therapy on groups subdivided by age, infarct location or admission heart rate. Maximum benefit appears to accrue for patients with anterior infarction who are treated with angioplasty therapy.

Finally, all baseline variables and treatment variables were analyzed to determine which variables were associated with improved survival probability. Those variables with significant differences were then subject to multivariable linear regression analysis to determine variables independently associated with improved survival probability. The most potent independent predictor of improved survival was treatment with primary angioplasty. In addition, heart rate, less than 100 beats per minute and age less than 70 years were independently associated with improved survival. Of note: although women had a higher mortality than men (8.1% versus 3.4%, P = 0.008), gender was not associated with altered survival probability. Similarly, infarct location did not, of itself, independently predict survival probability in the multivariable analysis. These findings suggest that therapy with primary angioplasty has removed gender and infarct location as important baseline severity of illness discriminators.

Discussion

It is unrealistic to assume that mechanical reperfusion therapy is a viable worldwide treatment strategy for myocardial infarction. Logistics, the need for well-trained and dedicated personnel and catheterization laboratory makes this therapy impractical in remote areas and underdeveloped countries. In the developed Western and Pacific rim countries however, this therapy might be available on a larger scale. Even in institutions with facilities and personnel readily available this therapy is so specialized and personnel intensive, that compelling data must exist before many institutions will embark on this method of reperfusion therapy.

The three randomized trials have each shown encouraging trends towards benefit for angioplasty therapy. The PAMI trial and the Zwolle study showed a reduction in the combined endpoint of death or nonfatal reinfarction for angioplasty treated patients. Although the Mayo Clinic study showed no reduction in infarction size, the trend towards lower 6 month cost of therapy was present for angioplasty patients. None of these studies had sufficient sample size to show a mortality benefit with adequate power. Combining these three trials now does provide a compelling argument for mortality benefit from angioplasty therapy. In addition a striking reduction in the risk of stroke was observed for primary angioplasty therapy.

In an attempt to strengthen the confidence of this pooled analysis, we were provided full access to the prospectively collected databases. Thus, a more detailed analysis of the comparability of these studies could be performed. Although some differences in baseline variables occurred between the three studies, initial randomization successfully segregated comparable groups. Overall, therefore, the thrombolytic groups and the angioplasty groups had comparable severity of illness.

Two other studies were not included in the present analysis because of major differences in protocol design. The first thrombolytic versus angioplasty trial employed emergency catheterization on all patients [15]. It furthermore employed intracoronary streptokinase and did not routinely employ aspirin for angioplasty treated patients. The study of Ribeiro et al, [16] did not routinely employ aspirin therapy. More importantly, 8 patients in the angioplasty group were deemed not technically suitable for angioplasty, yet the procedure was still performed. Death occurred in 4/8 of these patients. Even with these deficiencies, if all of these studies were summarized, mortality occurred in 17 (3.5%) angioplasty treated patients and 29 (6.1%) thrombolytic treated patients (1.7 risk reduction ratio, CI 0.9 to 3.2).

Conclusion

These preliminary results from a pooled analysis of the three major trials comparing primary coronary angioplasty and thrombolytic therapy for acute myocardial infarction are the first to indicate that primary angioplasty is clinically the most effective reperfusion modality. The major drawbacks are availability and high initial costs. Furthermore, these are the combined results of very experienced interventional cardiology centers. The different thrombolytic regimens, used in the present studies had comparable effects on clinical outcome. However, the most effective non-mechanical reperfusion modality known today is a thrombolytic regimen with tPA in an accelerated dosing schedule [5,6]. Yet, the rate of early effective reperfusion with this regimen is much lower than that accomplished with primary angioplasty [11,12,13].

Patients who will benefit most from primary angioplasty are those considered to be at high risk (previous infarction, signs of anterior wall infarction, elderly patients, patients in Killip class $\geq$ 2) and those at increased risk of stroke. In these patients primary coronary angioplasty is the treatment of choice, provided that all the prerequisites for optimal interventional cardiology are available.

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General Discussion
&
Conclusions

General Discussion and Conclusions

The life saving effect of reperfusion therapy for myocardial infarction has been well established. In most patients thrombolytic agents are administered to achieve reperfusion of the occluded infarct-related vessel. Still, the major limitations of such thrombolytic therapy are failure to achieve initial reperfusion of the infarct-related vessel in 20% to 30% of all patients, combined early and late reocclusion of the infarct-related vessel despite aggressive regimens of heparin and aspirin in 10% to 30% of patients, intracranial bleeding in 1% of patients, and contraindications to this therapy in a considerable part of the patients (particularly related to the increased bleeding risk). Primary coronary angioplasty without adjunctive use of thrombolytic agents offers the possibility to overcome most of these problems. Major drawbacks of this treatment modality are limited availability and high initial costs. Several questions about primary angioplasty, that remained to be answered are raised in Table 1 of Chapter 1 and have been addressed in Chapters 2 to 8. The main conclusions, that can be drawn from these data, together comprising the most important results from the "Zwolle study", are summarized in this final chapter and remaining problems related to primary angioplasty are addressed.

1. Early and full perfusion i.e. Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, which is necessary to achieve maximal benefit of therapy, occurs in approximately half of all patients treated with fibrinolytic therapy and early reocclusion occurs in at least 6% to 15% of patients who initially achieve patency (Chapter 1)[1,2]. In the present study, TIMI grade 3 flow was accomplished in more than 90% of the patients treated with primary angioplasty, within 120 minutes after hospital admission. The ability of angioplasty to reduce residual coronary artery stenoses and to break up most thrombi seems to be the most important mechanism. There is no thrombolytic regimen that can match these results (Chapter 1, 2, 4 and 5).

Although in the early stage of myocardial infarction in more than 80% of the patients a total occlusion of the infarct-related vessel is found, the procedural success rate of angioplasty is very high (more than 90%). This is in contrast with the results obtained after angioplasty of chronically occluded vessels where success rates of less than 70% have been reported, depending on the "age" of the occlusion [3]. The material comprising the occlusion in patients with myocardial infarction is usually softer, making guide wire and balloon crossing easier than in chronic total occlusions.

2. The coronary anatomy as analyzed with quantitative coronary angiography is better, with sustained patency in 92% and a restenosis rate of 28% in the patients assigned to angioplasty (Chapter 5). TIMI grade 2 flow immediately after the angioplasty procedure, despite an adequate reduction of the stenotic lesion, is highly predictive for reocclusion. The ability to document the early result of reperfusion therapy is a major advantage of primary angioplasty above intravenous thrombolytic therapy. Finally, the application of a balloon to vessel reference diameter ratio of approximately one seems to be an adequate approach for dilation of the target lesion (Chapter 5).

3. Primary coronary angioplasty results in a reduction of infarct size (measured with serial enzyme release) and better left ventricular function (measured with radionuclide ventriculography), when compared with intravenous streptokinase therapy (Chapter 3 and 4). The most pronounced beneficial effects of primary coronary angioplasty are observed in patients with anterior wall infarction and patients who present within two hours after onset of symptoms. The relation between left ventricular ejection fraction and enzymatic infarct size in all patients, together with the very high early TIMI 3 flow rates for patients treated with primary angioplasty suggest that these effects are accomplished by rapid and effective restoration of blood flow through the infarct-related vessel (Chapter 4).

4. Primary coronary angioplasty in patients with acute myocardial infarction results in less recurrent ischemia, reinfarction, and a lower in-hospital mortality when compared with patients treated with intravenous streptokinase (Chapter 2,3 and 8). This is probably related to the better coronary anatomy and better left ventricular function after primary angioplasty (Chapter 3,4 and 5). The need for additional revascularization procedures during initial admission was reduced significantly in the angioplasty-assigned patients compared with patients assigned to streptokinase therapy.

5. The beneficial effects of primary coronary angioplasty are sustained throughout a follow-up period ranging from 6 to 36 months (Chapter 6).

6. The costs of primary angioplasty compared with the costs of intravenous streptokinase therapy at one year are approximately the same. The functional class is better and the need for pharmacological therapy at one year is less in the angioplasty treated patients. This makes primary coronary angioplasty a cost-effective therapy in hospitals with facilities for interventional cardiology and cardiac surgery (Chapter 7).

The results of Chapter 7 and the more favorable clinical outcome after primary angioplasty when compared with thrombolytic therapy, may help to encourage introduction of primary angioplasty as a treatment modality for patients with acute myocardial infarction in hospitals with existing interventional cardiology programs. Health-care organizations should be aware of this new indication for coronary angioplasty without fear of increasing costs.

Together with the initial results of our investigations [4], two other studies were published, both with results compatible with ours (the Primary Angioplasty in Myocardial Infarction (PAMI) study and the Mayo Clinic Study [5,6]. Another study did not show any benefit from primary angioplasty above streptokinase therapy but the design of this study was essentially different from the PAMI trial and the Zwolle study [7]. This study from the Sao Paulo Group, did not routinely employ aspirin therapy. More importantly, in patients in the angioplasty group, with a coronary anatomy deemed not suitable for angioplasty, the procedure was still performed.

However, all these studies indicate that success rate of primary coronary angioplasty is very high. The most important conclusion of the GUSTO (Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) study is that survival is determined by rapid restoration (90 minutes) of normal flow through the infarct-related vessel [1,8] and this stresses the potential benefits of primary coronary angioplasty (Chapter 4). An analysis of pooled data from the Zwolle, the PAMI, and the Mayo Clinic trials performed in May 1994, demonstrate a favorable outcome after primary coronary angioplasty compared with thrombolytic therapy and preliminary data from this analysis are presented in Chapter 8. Primary angioplasty for myocardial infarction has the ability to accomplish a reduction of mortality in patients considered to be at high risk and with an anterior wall infarction, a reduction of reinfarction, and a reduction of stroke. These data may have considerable impact on the treatment of patients with myocardial infarction in the future.

Questions that have to be addressed include:

1. Who should be offered coronary angioplasty for AMI?
Although data from this thesis and the PAMI study indicate that coronary angioplasty is a highly effective treatment, a large group of patients with AMI will fare well with thrombolytic therapy. Patients with large anterior wall infarctions, patients in cardiogenic shock and probably all patients in Killip class 2 or more, are candidates for primary coronary angioplasty (Chapter 3, 4 and 8) [9]. Easily obtainable parameters

for early decision making have to be identified and the ECG can be a of help. Two-dimensional doppler-echocardiography on admission is a technique that can provide useful information on extent of jeopardized myocardium, regional and global systolic wall motion and valvular function, without further discomfort for the patient, but skilful interpretation is required.

Simoons and Arnold have proposed a benefit/risk model for tailoring thrombolytic therapy [10] and new reperfusion modalities should also encompass primary coronary angioplasty. This new concept of "tailored reperfusion therapy" has to be tested in clinical models.

2. Is there an age-limit for patients that should be offered primary coronary angioplasty?

In our recent experience with primary angioplasty in very old patients (not included in this study) we encountered many problems ranging from difficult vascular access, massive bleeding at vascular puncture site and other vascular complications, to difficulties in decision making when severe coronary artery disease, not suitable for angioplasty, was found. The absolute gain in life years is lower and the burden for hospital organization and house-staff is high. However the elderly seem to benefit even more from primary angioplasty compared with thrombolytic therapy as was demonstrated by the results from the pooled analysis described in Chapter 8 and by the PAMI investigators [11]. In the very old but otherwise very fit patients, primary coronary angioplasty should not be denied if they present with large myocardial infarctions.

3. Where, when and who should perform primary coronary angioplasty?

We all need to examine our local logistic infrastructure to decide how primary angioplasty can be incorporated as a treatment option for patients with myocardial infarction. Although this is arguably the most important question, no definite answer may be expected from any study on primary angioplasty because extrapolation of study results to other operators in other settings is not justified. Primary coronary angioplasty, like elective angioplasty, is associated with an operator-dependent morbidity and mortality that varies with the skills and experience of the interventional cardiologist. Therefore, no general recommendations for application of primary angioplasty can be given. However, data from this thesis support the idea that primary angioplasty for myocardial infarction should strongly be considered in patients presenting early and when an experienced angioplasty team is available. Furthermore, emergency coronary artery bypass surgery is more often needed after primary coronary

angioplasty compared with elective angioplasty (Chapter 3). This was confirmed by data from the Primary Angioplasty Registry (PAR)[12]. In the Zwolle study, six (4%) of the angioplasty assigned patients underwent bypass surgery within the first few hours after admission for myocardial infarction and all these patients survived. On-site cardiosurgical standby is therefore in our view a prerequisite for safe performance of primary coronary angioplasty and data from the primary angioplasty studies cannot be extrapolated to hospitals without these facilities.

4. Is there a place for new devices in the treatment of myocardial infarction?
Recent reports gave promising results from DCA (Directional Coronary Atherectomy) and TEC (Transluminal extraction atherectomy) applied in smalls group of patients [13,14] but the skills and costs required for these techniques, the loss of time to achieve adequate flow through the infarct-related vessel due to technical preparations and the risk not to reach the culprit lesion, are major drawbacks. The excellent results of balloon angioplasty are difficult to beat. Stent placement at the culprit lesion site seems very unattractive because of the high thrombogenicity of both the device and the vascular trauma. Laser thrombolysis is a new and relatively unknown treatment modality but preliminary data are disappointing although it may have a role in the future [15]. A diverse array of drills, shavers, burrs and other exotic interventional devices have been proposed but not yet investigated in the setting of myocardial infarction. The use of an intra-aortic balloonpump (IABP) as an adjunct to reperfusion therapy has been evaluated in the TAMI trials and the benefits of this assist device were demonstrated in high-risk patients [16]. An increase in peak coronary blood flow velocity may prevent reocclusion and recurrent thrombus formation [17]. However further investigations are needed to define the role of IABP during and after primary coronary angioplasty for myocardial infarction.

5. Is primary angioplasty for AMI really safe?
Safety of the angioplasty procedures was addressed in this thesis and in several other studies. Patients may survive after a hemorrhagic stroke following thrombolytic therapy but major neurological deficits may be such a threat to the quality of life that the advantage of an open IRV is questionable. Little is known about the occurrence of adverse events in patients treated with primary coronary angioplasty although the results of the studies from experienced centers, together with data from Chapter 5 suggest that primary coronary angioplasty can be carried out safely.
However, we do not know if patients might even be harmed by primary angioplasty, but if this subgroup exists, it will probably be small. Finally, the pooled data from the

major trials on primary angioplasty (Chapter 8) give strong support to the theory that the incidence of stroke is greatly reduced with this approach [4,5,6].

6. How do we monitor patients after successful primary angioplasty?
Although data from Chapter 5 indicate that reocclusion is a relatively rare phenomenon after primary angioplasty, reocclusion is a serious threat for every patient after successful reperfusion therapy for myocardial infarction. The angioplasty-assigned patients in the present study comprises a selected group because they were also candidates for thrombolytic therapy and there was an age-limit for study inclusion. The small number of patients in Killip class 3 and 4 are probably more susceptible for reocclusion but no definite data are available. Assessment of initial reperfusion after intravenous thrombolytic therapy has its limitations [18], but primary angioplasty gives the unique opportunity to document patency angiographically, still regarded as the "gold standard". Noninvasive monitoring of markers that can indicate reocclusion after successful reperfusion include clinical signs (chest pain, hemodynamic deterioration), recurrence of ST elevation on the electrocardiogram, and monitoring of specific cardiac proteins in plasma [19]. A practical and a very promising approach for non-invasive monitoring is the Myocardial Infarction Diagnosis and Analysis (MIDA 1000 Ortivus Medical AB, Täby, Sweden) system, that is routinely used in our coronary care unit since 1992. [20]. This is a computerized system for on-line dynamic analysis of the QRS complex and ST segment changes using eight electrodes placed according to the Frank method. Three orthogonal leads X,Y and Z are continuously monitored and analyzed. Electrocardiac signals from the above mentioned electrodes compare the averaged complex to the initial complex and displays this information in trend graphs, that are continuously updated. The two most important parameters are the ST vector magnitude (ST-VM) which reflects the extent of ischemic tissue at risk and the QRS vector difference (QRS-VD) reflecting changes in the shape of the QRS complex. All these data can be stored on a computer internal hard-disk for further analysis; decision making by the physician in charge can be guided by the graphic display. An example of a MIDA scan during and after primary coronary angioplasty is depicted in Figure 1. However, more information is needed to define the sensitivity and selectivity of this monitoring technique in the prediction of reocclusion.

7. How do we measure the efficacy of new reperfusion strategies ?
The diversity of patients when we broaden our indications and eligibility for angioplasty treatment, the possible role of new agents as an adjunct to primary angioplasty (all in a time of restricted economical resources, cost containment and

logistical problems for centers that can offer an adequate cardiac interventional approach), and the simple fact that reduction of mortality is more difficult to measure against an already low mortality baseline, will force us to leave the concept of megatrials as the only way to evaluate new treatment strategies. Therefore the use of a composite unsatisfactory endpoint which measures failure of therapy together with adverse events ("net clinical benefit") [2], as was used in Chapter 6, seems to be a promising alternative. Infarct size as measured from enzyme release can also be used as a "marker of efficacy" as was demonstrated in Chapter 4. Thorough assessment of different combinations of reperfusion modalities will translate into treatment recommendations for myocardial infarction. A pragmatic strategy of "tailored angioplasty" as was proposed in the final paragraph of Chapter 3 with primary angioplasty for patients with large infarctions and/or signs of hemodynamic problems and thrombolytic therapy for other patients, is an example of a new approach that can be assessed with a composite unsatisfactory endpoint.

8. How do we convince health care organizations and politicians to give us the opportunity to treat our patients better?
In the future, continuous cost-efficacy and costs-utility assessment of the different treatment modalities will be part of our work and an attempt in this direction was made in Chapter 7. Recurrent ischemic events occur far less frequently and are even rare after angioplasty compared with thrombolytic therapy [21], as was demonstrated in this thesis and early discharge seems to be a reasonable approach (Chapter 2, 3 and 6). Early discharge of patients after infarcts treated with primary angioplasty was reported from two other studies [22,23] and readmissions for recurrent ischemia were reduced significantly (this thesis) resulting in substantial cost savings without additional risks.

9. What is the best treatment after myocardial infarction, regardless of the initial therapy?
Late angioplasty of occluded infarct-vessels after failed thrombolysis may have benefits with regard to left ventricular function and survival but early or "rescue PTCA" has a disappointing outcome [24,25,26]. However, coronary angiography and subsequent "tailored" therapy should be considered in all patients with severe problems after any kind of reperfusion approach. We do not know the optimal moment to perform angioplasty of an occluded infarct vessel late after failed reperfusion therapy and maybe it is appropriate to introduce a period of "cooling down" in asymptomatic patients, when angioplasty is considered. However, the reocclusion rate may be considerably higher than with primary coronary angioplasty [26].

Coronary artery restenosis in response to arterial injury is the Achilles' heel of angioplasty and prevention remains a clinical challenge after primary angioplasty especially because thrombus is thought to induce neointimal proliferation [27]. New pharmacological interventions may reduce the incidence of restenosis. Despite this limitation, in our experience, patients rarely present with an occluded vessel at follow-up angiography (Chapter 5) and repeat coronary angioplasty can be carried out safe if restenosis occurs.

It is highly desirable that patients, enrolled in the Zwolle, the PAMI and the Mayo Clinic trials, will not be lost for follow-up and that the endpoints death, recurrent infarction and need for revascularization are carefully recorded for the next ten years.

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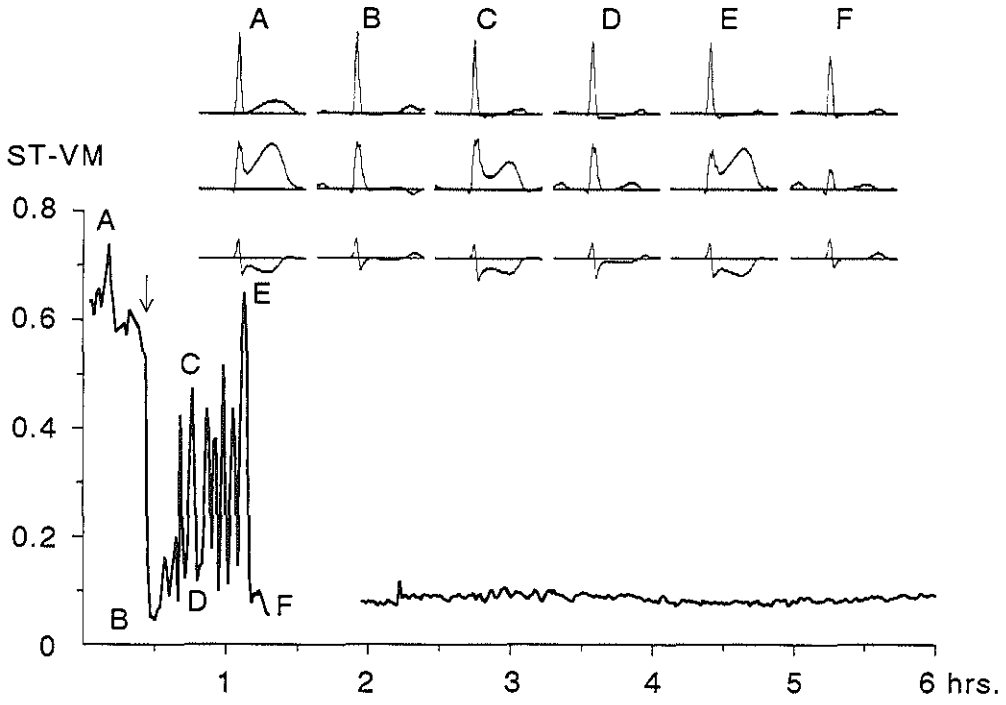

Figure 1: Continuous monitoring of six hours duration of ST vector magnitude (ST-VM) changes in a 59 year old patient with an acute infero-posterior infarction undergoing primary angioplasty of an occluded right coronary artery. The vector ECG leads X, Y and Z more or less resemble V5, II and V2. On arrival in the catheterization laboratory the sum of ST-segment deviation is 0.7 mV (A). The arrow indicates the first deflation of a 3.5 mm balloon and an immediate decrease of ST-segment deviation with subsequent relieve of chest pain and angiographic TIMI 3 flow (B). C and E indicate some of the multiple repeat balloon inflations and recovery of the ST-segments thereafter (D and F). During transportation of the patient to the coronary care unit (CCU) the registration was temporarily interrupted. On the CCU the ST level stabilizes and ischemic episodes remained absent. Accordingly, the QRS-vector difference (not presented here) did not indicate additional myocardial necrosis after successful reperfusion.

Angioplasty or the art of infarct vessel maintenance

"Obstruction of a coronary artery or any of its large branches has long been regarded as a serious accident"
J.B. Herrick, 1912.

Primary coronary angioplasty is a highly effective intervention in patients with acute myocardial infarction. However, as a primary reperfusion strategy for all patients only centers with a large experience in performing coronary angioplasty will be able to match the results described in this thesis. The role of the staff of the catheterization laboratory, the coronary care and intensive care unit, the cardiovascular surgeons, and the cardiovascular anesthesiologists cannot be overemphasized. All recently published results should be seen in this light. Often the most difficult part of the emergency procedure is to identify the infarct-related vessel and serious complications can be induced by performing angioplasty of non-infarct-related vessels. If there is doubt about the "culprit" lesion, immediate consultation of other interventional cardiologists and cardiac surgeons is warranted. Maybe this is one of the most important reasons to perform primary angioplasty only in centers with a large experience in interventional cardiology and cardiovascular surgery.

Patients presenting with large infarcts, patients in cardiogenic shock and patients with contraindications to thrombolysis are probably best treated with primary coronary angioplasty. Referral of these patients from community hospitals to centers with experience in performing primary angioplasty should always be considered.

This thesis is not a guide or "cook-book" for cardiologists who are not familiar with the techniques used or described in different parts of this study. Every cardiologist facing a patient with an acute myocardial infarction should offer the best treatment available. Primary coronary angioplasty should be considered in all patients but thrombolysis is an effective and efficient treatment modality if *not* combined with coronary angioplasty. The American Heart Association/American College of Cardiology Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (committee on percutaneous transluminal coronary angioplasty) changed their appreciation of primary coronary angioplasty as a treatment option for acute myocardial infarction [1]. The degree of consensus of the committee members was graded as Class 1: "Conditions for which there is general agreement that coronary angioplasty is justified". It is worth while to cite the first paragraph on primary coronary angioplasty for evolving acute myocardial infarction:

Class 1: This category applies the dilation of a significant lesion in the infarct-related artery only in patients who can be managed in the *appropriate laboratory setting* and who

1. are within 0 to 6 hours of the onset of a myocardial infarction (the procedure is used as an alternative to thrombolytic therapy),
2. are within 6 to 12 hours of the onset of a myocardial infarction but who have continued symptoms of ongoing myocardial ischemia, or
3. are in cardiogenic shock with or without previous thrombolytic therapy and within 12 hours of the onset of symptoms".

Maybe the most important conclusion of this thesis is that primary coronary angioplasty as treatment for patients with acute myocardial infarction is here to stay. In our institution, primary coronary angioplasty is a practical and safe intervention for myocardial infarction, with improved patient outcome and without an increase in costs, when compared with conventional treatment. This was confirmed by other groups with the same attitude to interventional cardiology and reperfusion therapy for myocardial infarction. "The sigh of relief" uttered after rejection of angioplasty as additional approach after or during thrombolytic therapy [2] has to be changed to a "jump for joy" to welcome primary coronary angioplasty as a generally accepted treatment modality.

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Summary

Summary

This thesis addresses the value of primary coronary angioplasty, i.e. angioplasty without adjunctive thrombolytic therapy, as treatment for patients with acute myocardial infarction. In recent years, thrombolysis has been established as the treatment of choice for patients with evolving myocardial infarction. Reperfusion of ischemic myocardium through reopening of the occluded infarct-related vessel results in limitation of infarct size and reduction of morbidity and mortality. Coronary angioplasty or PTCA (Percutaneous Transluminal Coronary Angioplasty) was believed to be dangerous, expensive and ineffective and was only considered as an alternative when contraindications for thrombolytic treatment were present. However, several reports from a few large centers with extensive experience in performing coronary angioplasty, demonstrated the potential benefit of this approach. Until 1993 only data from one small randomized trial comparing thrombolysis and primary angioplasty were available. In that year the results of three major trials were published in one issue of the New England Journal of Medicine. One of these studies is described in detail in this thesis.

One problem of evaluating reperfusion therapy following AMI is the choice and definition of endpoints. Mortality is often considered to be the only relevant endpoint but mortality studies require enormous numbers of patients. Other endpoints have therefore been proposed to evaluate the efficacy of new treatment strategies for AMI:

1. Angiographic data, especially coronary artery patency and residual stenosis of the IRV, as was used in Chapter 2 and 5 of this thesis.
2. Infarct size, measured from enzyme release as was applied in Chapter 4.
3. Left ventricular function, as was used in Chapters 2,3 and 4 of this thesis.
4. A composite clinical endpoint combining mortality, stroke, reinfarction and other adverse outcome events. This approach was used in Chapter 6 of this thesis.

In addition in Chapter 7 an attempt was made to evaluate the cost-effectiveness of primary coronary angioplasty on the basis of data from all 301 patients included in this study. In Chapter 8 preliminary results from a pooled analysis of the three major studies on primary coronary angioplasty are presented.

Chapter 1: Introduction

An overview of thrombolytic therapy for myocardial infarction is given with emphasis on the risk-benefit-ratio of this therapy. The role of coronary angioplasty as an adjuvant to, or instead of thrombolytic therapy is discussed in detail and the inconsistent results of the different trials that evaluated coronary angioplasty in the setting of myocardial infarction are presented. It is concluded that more information is

required especially with regard to coronary angioplasty as a stand-alone procedure. Until 1993 only one small randomized trial addressed the possible role of this approach.

Chapter 2

In this chapter the results of the first 142 patients randomized in the Zwolle trial are presented, as published in 1993. This trial was designed to evaluate the role of primary coronary angioplasty (i.e. without previous or adjuvant thrombolytic therapy) as a treatment modality for patients with signs of acute myocardial infarction (AMI). This initial report presented the results in 70 patients with AMI randomly assigned to coronary angioplasty and 72 patients assigned to streptokinase therapy. Even in this relatively small group of patients remarkable differences between the two treatment arms were demonstrated. Primary coronary angioplasty after AMI was associated with a higher rate of patency of the infarct-related vessel, a less severe residual stenotic lesion, better left ventricular function and less recurrent myocardial ischemia and reinfarction compared with intravenous streptokinase.

Chapter 3

Primary coronary angioplasty was compared with intravenous streptokinase therapy with regard to hospital mortality, reinfarction and left ventricular function in a larger series of 301 patients admitted to the Zwolle trial. The in-hospital mortality rate in the angioplasty group was significantly lower than in the streptokinase group (2% versus 7% respectively, $P = 0.024$). Recurrent myocardial infarction occurred less frequently and left ventricular ejection fraction was better (50 versus 44%) in angioplasty patients compared with patients assigned to streptokinase therapy. From these data it is concluded that primary angioplasty results in a lower risk of death, recurrent myocardial infarction and a better left ventricular function.

Chapter 4

Primary coronary angioplasty and intravenous streptokinase treatment were compared with regard to infarct size measured with serial enzyme release and left ventricular ejection fraction measured with a radionuclide technique in more than 90% of the 301 patients enrolled in the Zwolle trial. Early effective blood flow through the infarct-related coronary vessel could be accomplished within 2 hours after hospital admission in 92% of all patients assigned to angioplasty which is a plausible explanation for the observed benefit of this therapy. Estimated infarct size was 23% smaller in patients assigned to primary coronary angioplasty. Global left ventricular function was better preserved, particularly in the angioplasty assigned patients

presenting within 2 hours after symptom onset or with anterior wall infarction. It is concluded that primary coronary angioplasty is the treatment of choice in these subgroups of patients, provided that this procedure can be carried out by an experienced interventional cardiology team.

Chapter 5

This chapter provides additional angiographic data and catheterization laboratory events during primary angioplasty procedures in the Zwolle trial. Patency of the infarct-related vessel in the streptokinase assigned patients was 66% and the residual stenosis was 77% ± 20% at follow-up angiography after a mean of 22 days. In contrast, the stenosis of the infarct-related vessel was reduced from 92% ± 19% to 27 ± 15% immediately after the angioplasty procedure. At follow-up angiography after a mean of 92 days the residual stenosis was 35% ± 22%, the incidence of restenosis was 28%, and the incidence of reocclusion was 5% in the angioplasty assigned patients. TIMI grade 2 flow immediately after the angioplasty procedure was a strong predictor for reocclusion at follow-up angiography and additional therapeutic measures are recommended in these patients. Major complications during primary angioplasty were observed in 14% of the patients.

Chapter 6

Follow-up data were obtained after 18 months (range 6-36 months) of all 301 patients in the Zwolle study. The relative risk of cardiac death and non-fatal reinfarction in the streptokinase group was 6.1 (95% confidence interval 2.9 - 12.7) as compared with the angioplasty group. Additional revascularization procedures during follow-up were more often performed in the streptokinase group, with a relative risk of 2.1 as compared to patients randomized to angioplasty, (95% confidence interval 1.5 - 3.2). It is concluded that primary coronary angioplasty for acute myocardial infarction results in a more favorable clinical course, a reduction of recurrent infarction and a reduction of revascularization procedures during a longer follow-up period, when compared with intravenous streptokinase therapy. Long-term infarct-related vessel patency and a better preserved left ventricular function are a likely explanation for this observation.

Chapter 7

In-hospital costs after the qualifying myocardial infarction, costs of all readmissions and additional procedures, and costs of pharmacological treatment during the first year were recorded. The accumulated costs for angioplasty treatment after one year were

not significantly higher compared with streptokinase treatment.

The functional status following the New York Heart Association classification was better in the angioplasty group and the average consumption of pharmacological therapy was less in the angioplasty-assigned group. After one year seven patients died in the angioplasty-assigned group and thirteen in the group assigned to streptokinase therapy (P = 0.15). The marginal cost-effectiveness ratio, defined as additional costs per additional event free survivor were estimated at Dfl. 5,968. From this it is concluded that treatment with primary angioplasty is more cost-effective than treatment with streptokinase.

Chapter 8

A pooled analysis of the three major studies on primary angioplasty for acute myocardial infarction, the Zwolle study, the Primary Angioplasty in Myocardial Infarction study, and the Mayo Clinic study was performed with full access to the prospectively collected databases. In spite of the differences in thrombolytic regimens and minor differences in clinical characteristics, overall rates of mortality, reinfarction and stroke were the same for the three studies. This justifies the pooling of outcomes for comparison. A mortality rate of 6.4% (26/405) was observed for the thrombolytic group, compared to a 2.6% mortality (10/394) for the angioplasty group, (P = 0.008). This represents a ratio for risk reduction of 2.5. Combining the two major adverse outcomes of death and/or reinfarction angioplasty reduced the risk by a factor 3.0 (4.3% versus 13.1%, P < 0.00001). The incidence of stroke was reduced in angioplasty treated patients: 9.7 risk ratio reduction (0.3% versus 2.5%, P = 0.007). Greatest benefit of angioplasty treatment was observed in patients at high risk (age > 70 years, heart rate on admission > 100 per minute) and those with anterior wall infarctions. It is concluded that in patients who are considered to be at high risk (previous infarction, signs of anterior wall infarction, elderly patients, patients in Killip class $\geq$ 2) and those at increased risk of stroke, primary angioplasty is the treatment of choice, provided that all the prerequisites for optimal interventional cardiology are available.

Samenvatting in het Nederlands

Samenvatting

Inleiding, hoofdstuk 1

De inzichten omtrent de behandeling van het acute hartinfarct zijn in het laatste decennium sterk gewijzigd. In 1980 toonden DeWood en medewerkers aan dat het acute hartinfarct doorgaans gepaard gaat met een trombotische afsluiting van een kransslagader, meestal gesuperponeerd op een atherosclerotische afwijking. Deze bevinding heeft ertoe geleid dat in de acute fase trombolyse (het oplossen van het trombotische materiaal door middel van thrombolytica) en ballondilatatie van de kransslagader (percutane transluminale coronaria-angioplastiek; PTCA) werden toegepast. De grote gerandomiseerde onderzoeken van de jaren tachtig tonen een belangrijke reductie van de sterfte aan het acute hartinfarct, namelijk van 13-15% in het pre-trombolyse-tijdperk tot ongeveer 7%-10% thans. Het is inmiddels onomstotelijk aangetoond dat dit gunstige effect terug te voeren is op het weer opengaan van de afgesloten kransslagader door het oplossen van het aanwezige stolsel. De grootte van het myocardinfarct is afhankelijk van het tijdstip van effectieve reperfusie. Van wezenlijk belang is het duurzaam open blijven van het met het infarct samenhangende vat (het open-arterie-concept). Hiervoor is aanvullende behandeling met acetylsalicylzuur (aspirine) en in de initiële fase met heparine van nut gebleken.

Het belang van reperfusie

In de eerste uren na het hartinfarct is de ischemische schade het grootst en sterven de meeste myocardcellen af; in het algemeen wordt aangenomen dat bij de meeste patiënten irreversibele beschadiging van de linker hartkamer binnen 4-6 uur tot stand gekomen is. Vroege en succesvolle trombolysetherapie beperkt de grootte van het infarct. Het is dan ook opmerkelijk dat steeds meer onderzoeken aantonen dat doorgankelijkheid van de met het infarct samenhangende kransslagader een voorwaarde is voor een gunstig beloop na een doorgemaakt hartinfarct en dat dit beloop zelfs voor een deel onafhankelijk is van de functie van de linker hartkamer en het tijdstip van reperfusie. Inmiddels zijn daarvoor verklaringen aangedragen, waarvan de belangrijkste hier kort worden genoemd.

Bevorderen van genezing. Het genezingsproces in het necrotische en ischemische myocardweefsel kan worden bevorderd door een adequate bloedvoorziening en daarvoor is een open kransslagader van belang. Dit zou kunnen betekenen dat de incidentie van myocardruptuur (met harttamponade), murale trombusvorming, acute mitralisklepinsufficiëntie, kamerseptumruptuur en aneurysma cordis kan worden teruggedrongen.

Beperken van ritmestoornissen. Rondom het geïnfarceerde hartspierweefsel bevindt zich een ischemische randzone waarin de electrische instabiliteit bij afsluiting van de betreffende kransslagader groter is dan bij een open kransslagader; dit zou vooral levensbedreigende ritmestoornissen tot gevolg kunnen hebben.

Collaterale circulatie. Een open kransslagader kan in de acute fase van het myocardinfarct, maar ook later, dienen als alternatieve bloedvoorziening bij meertaks-coronaria-aandoeningen (collaterale circulatie) en vormt op deze wijze een ingebouwd veiligheidsmechanisme, dat vooral op langere termijn van belang is.

Coronaria-angioplastiek met en zonder trombolyse

Een belangrijk nadeel van trombolyse behandeling is de kans op bloeding en beroerte: in de literatuur wordt de kans op een ernstige bloeding geschat op 1-2% en de kans op een beroerte 0,5-2%. Deze kans neemt toe naarmate de patiënt ouder is; ook is de kans groter als de patiënt andere aandoeningen in de anamnese heeft, waarbij speciaal gedacht moet worden aan gastro-intestinale aandoeningen, een beroerte, een recente chirurgische ingreep of een trauma. Tevens moet bij jonge vrouwen menstruatie of op korte termijn te verwachten menstruatie als een contra-indicatie worden beschouwd. Een ander nadeel is dat 20-30% van de kransslagaders niet open gaat na trombolytische therapie.

Indien ballondilatatie zonder trombolyse wordt toegepast, kunnen deze nadelen worden voorkomen; deze behandeling wordt wel directe of primaire coronaria-angioplastiek genoemd. Aanvankelijk werd deze benadering incidenteel gebruikt bij patiënten die niet in aanmerking kwamen voor trombolytische behandeling.

Dit proefschrift tracht de rol van primaire coronaria-angioplastiek als eerste behandeling van het acute myocardinfarct te definiëren aan de hand van de bevindingen in 301 patiënten. De resultaten, beschreven in genoemde hoofdstukken, worden tegenwoordig in de Angelsaksische literatuur vaak aangeduid als "the Zwolle trial". Tijdens de voltooiing van dit proefschrift is een Amerikaanse studie (de PAMI: Primary Angioplasty in Myocardial Infarction study) gepubliceerd die de resultaten van dit onderzoek ondersteunt.

In **hoofdstuk 2** worden de resultaten van de eerste 142 patiënten beschreven. De patiënten met een hartinfarct werden aselect verdeeld voor behandeling met primaire coronaria-angioplastiek of intraveneus toegediende streptokinase. Er werd een hoog succespercentage van coronaria-angioplastiek (98%) en een reductie van het optreden van hernieuwde ischemie gevonden. Tevens was de waarde voor de ejectiefractie van de linker hartkamer, gemeten met radionuclide-ventriculografie, belangrijk hoger in de patiëntengroep behandeld met angioplastiek. Uit het onderzoek blijkt verder dat de

rest-stenose van de met het infarct samenhangende kransslagader minder ernstig was na primaire coronaria-angioplastiek, hetgeen de resultaten op lange termijn kan beïnvloeden ten gunste van de met angioplastiek behandelde groep.

In **hoofdstuk 3** worden de resultaten van alle 301 garandomiseerde patiënten beschreven. De in hoofdstuk 2 beschreven verschillen ten gunste van de met primaire coronaria-angioplastiek behandelde patiënten werden ook gevonden in deze studie, die een uitbreiding is van het oorspronkelijke onderzoek. De mortaliteit in de eerste ziekenhuisfase in de met angioplastiek behandelde patiënten was 2%, tegenover 7% in de met streptokinase behandelde patiënten. In de streptokinase groep trad een recidief infarct op bij 10% van de patiënten terwijl dit slechts optrad bij 1% in de angioplastiek groep. De functie van de linker hartkamer, gemeten met radionuclide-ventriculografie, was belangrijk beter in patiënten die een primaire coronaria-angioplastiek hadden ondergaan (50% versus 44%).

In **hoofdstuk 4** wordt getracht, naar aanleiding van de resultaten van enzymatische infarct-grootte bepaling, de linkerkamer functie gemeten met radionuclide-ventriculografie en de coronair-angiografische gegevens een verklaring te vinden voor de opvallend betere resultaten, behaald na behandeling met primaire coronaria-angioplastiek. Dit hoofdstuk is de kern van het gehele onderzoek aangezien het een paradigma ondersteunt dat zeer waarschijnlijk de verklaring is voor de gerapporteerde resultaten. Het wordt aannemelijk gemaakt dat het bewerkstelligen van een snellere en meer effectieve reperfusie door toepassing van primaire coronaria-angioplastiek de verklaring is voor de goede resultaten. Vroege en effectieve doorstroming van het met het infarct samenhangende vat kon worden bereikt binnen twee uur na ziekenhuisopname, in 92% van de patiënten die werden gerandomiseerd voor primaire angioplastiek. De infarctgrootte, geschat door middel van enzymbepalingen, was gemiddeld 23% kleiner in de voor angioplastiek gerandomiseerde patiënten. Ook was de linkerkamer ejectiefractie, gemeten met radionuclide-ventriculografie significant beter, namelijk 50% versus 45%. Deze gunstige effecten van primaire angioplastiek werden met name gezien bij patiënten die zich vroeg (binnen 2 uur) na het begin van de klachten in het ziekenhuis melden en bij patiënten met een voorwand infarct.

In **hoofdstuk 5** worden de angiografische bevindingen en complicaties tijdens het verblijf in de hartcatheterisatie-kamer beschreven. De ernst van de stenose van het met het infarct samenhangende vat, gemeten met een quantitatieve angiografische methode werd door de primaire coronaria-angioplastiek procedure teruggebracht van gemiddeld

92% tot 27%. Belangrijke, maar goed te behandelen complicaties tijdens verblijf in de hartcatheterisatie-kamer werden gevonden bij 14% van de met angioplastiek behandelde patiënten.

Bij angiografisch na-onderzoek na gemiddeld 92 dagen bleek een groot deel van het initiële effect behouden te zijn en de rest-stenose was dan gemiddeld 35%. In 28% van deze patiënten wordt een stenose van meer dan 50% gevonden (re-stenose) en reocclusie van het met het infarct samenhangende vat werd bij slechts 5% van de met angioplastiek behandelde patiënten gevonden. Van deze 7 patiënten hadden drie een verminderde doorstroming door het vat, onmiddellijk na de procedure en dit bleek een goede voorspeller te zijn voor late reocclusie. Doorgankelijkheid van het met het infarct samenhangende vat werd bij na-onderzoek na gemiddeld 22 dagen gevonden bij slechts 66% van de met streptokinase behandelde patiënten, terwijl de quantitatief angiografische rest-stenose gemiddeld 77% was. Indien alleen de open vaten werden geanalyseerd bleek de rest-stenose 64% te zijn.

Hoofdstuk 6 beschrijft de data bij vervolg-onderzoek na gemiddeld 18 maanden van de patiënten in de Zwolle studie. Van alle patiënten konden vervolg-data worden verkregen. Het relatieve risico voor overlijden en een niet fataal recidief infarct was in de streptokinase groep 6,1 (95% betrouwbaarheidsintervallen 2,9 tot 12,7) indien vergeleken met patiënten behandeld met primaire coronaria-angioplastiek. Revascularisatieprocedures gedurende de vervolg-periode moesten vaker uitgevoerd worden na streptokinasebehandeling, met een relatief risico van 2.1 vergeleken met patiënten die aselect werden gekozen voor behandeling met angioplastiek (95% betrouwbaarheidsintervallen 1,5 tot 3,2).

Hoofdstuk 7 betreft een analyse van de kosten van de twee behandelingsmethoden gedurende het eerste jaar. De ziekenhuiskosten, gemaakt in de eerste fase, de kosten van alle daaropvolgende nieuwe opnames en additionele procedures, en de kosten van medicijngebruik tijdens het eerste jaar werden geregistreerd. De totale kosten van behandeling met coronaria-angioplastiek waren nauwelijks hoger dan die van behandeling met streptokinase.

De functionele klasse van de patienten volgens de indeling van de New York Heart Association was beter en de gemiddelde consumptie van medische middelen was lager in de voor primaire coronaria-angioplastiek aangewezen patiëntengroep.

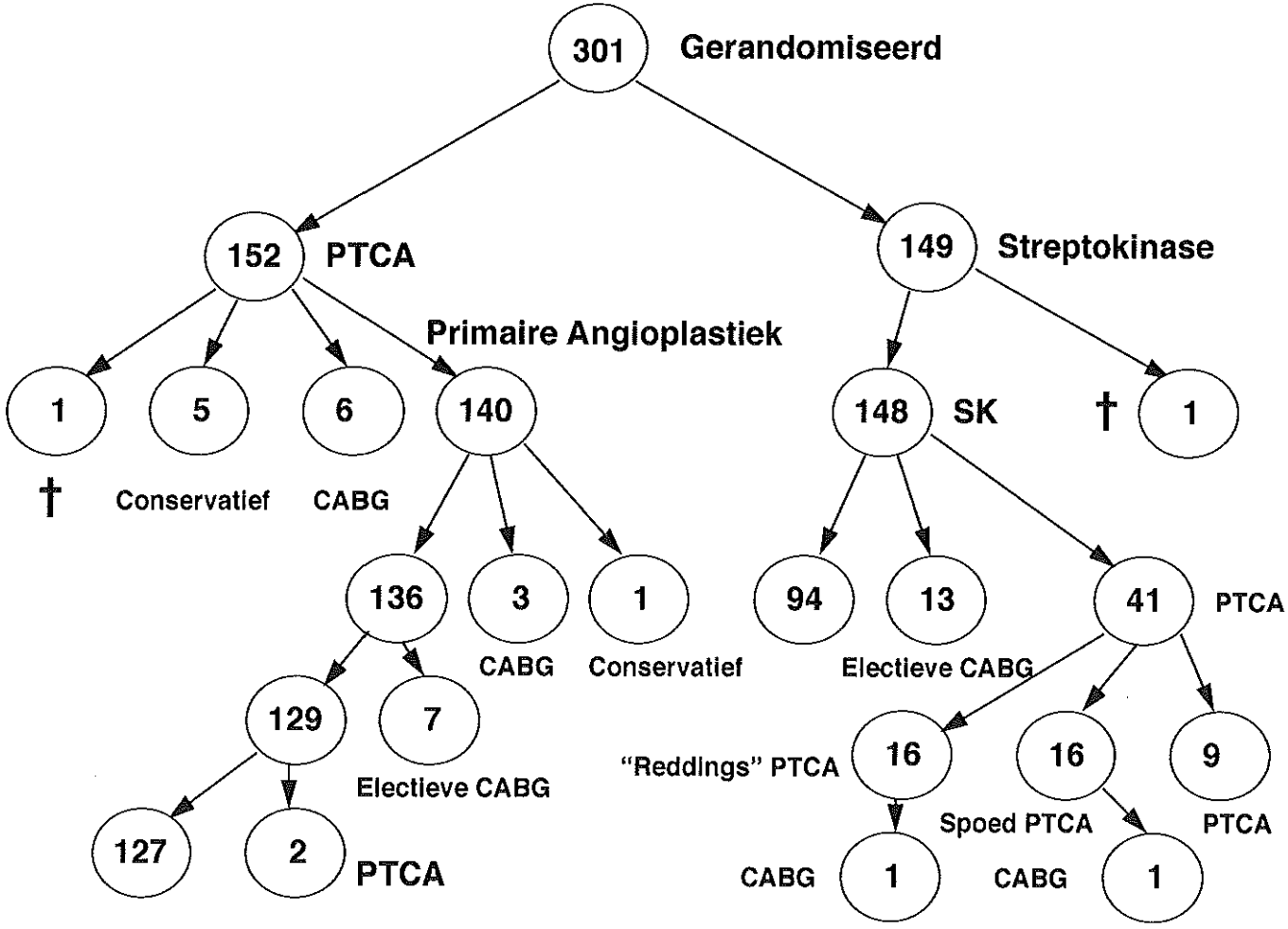
De raming van de additionele kosten per "gewonnen" patiënt, die het eerste jaar na het infarct overleeft zonder een hernieuwd infarct (de marginale kosten-effectiviteits-ratio) wordt geschat op fl. 5968,-. Op grond van deze gegevens kan worden

geconcludeerd dat behandeling van het acute hartinfarct met primaire coronaria-angioplastiek zeer kosten-effectief is, indien vergeleken met behandeling met streptokinase.

Hoofdstuk 8 is een voorlopige analyse van de drie belangrijkste onderzoeken naar de rol van primaire coronaria-angioplastiek bij het acute myocardinfarct: de Zwolle studie, de PAMI studie, en de studie van de Mayo Clinic. De analyse werd verricht met volledige toegang tot de gegevens. Ondanks verschillen in studieopzet en kleine verschillen in eigenschappen tussen de patiëntengroepen was de incidentie van totale sterfte, het hernieuwd optreden van een infarct, en het optreden van een beroerte gelijk voor de drie studies. Dit rechtvaardigt een overkoepelende analyse.

De sterfte in de trombolyse groep was 6,4% (26/405), vergeleken met 2,6% (10/394) in de met angioplastiek behandelde groep (P = 0.008). Dit betekent een reductie van het sterfterisico met een factor 2,5. Indien de twee belangrijkste eindpunten, overlijden en het optreden van een hernieuwd infarct, samen werden geanalyseerd was de risicoreductie een factor 3 (13,1% versus 4,3%) in het voordeel van de angioplastiek groep. Het risico voor een beroerte was aanzienlijk lager in de met angioplastiek behandelde patiënten namelijk een reductie van het risico met een factor 9,7 (2,5% versus 0,3%, P = 0.007). Patiënten met een hoog risicoprofiel (met een in het verleden doorgemaakt hartinfarct, met een voorwandinfarct, ouder dan 70 jaar, of met tekenen van pompfalen) hadden het meeste baat bij behandeling met angioplastiek. Geconcludeerd wordt, dat deze groep bij voorkeur behandeld dient te worden met primaire coronaria-angioplastiek, vooropgesteld dat aan alle voorwaarden voor optimale interventiecardiologie kan worden voldaan.

Figuur op pagina 199: Schematisch overzicht van randomisatie en daaropvolgende procedures in de Zwolle studie. Alleen de gebeurtenissen in de eerste fase na randomisatie (tot 30 dagen) zijn weergegeven. PTCA = percutane transluminale coronaria-angioplastiek, CABG = coronaire bypass chirurgie, SK = streptokinase, † = overleden.


301
Gerandomiseerd
152
PTCA
149
Streptokinase
Primaire Angioplastiek
1
†
5
Conservatief
6
CABG
140
148
SK
†
1
136
3
CABG
1
Conservatief
94
13
Electieve CABG
41
PTCA
129
7
Electieve CABG
"Reddings" PTCA
16
16
Spoed PTCA
9
PTCA
127
2
PTCA
CABG
1
CABG
1

Nawoord

Het onderzoek, beschreven in dit proefschrift, is niet uit de lucht komen vallen en heeft een voorgeschiedenis. In Januari 1988 werden in het Ziekenhuis de Weezenlanden in Zwolle hartchirurgie en PTCA (percutane transluminale coronaria-angioplastiek) geïntroduceerd na jarenlange voorbereiding. Tevens werd, na een goed verlopende aanloopfase, waarover al snel gerapporteerd werd [1,2,3], onderzoek geinitïeerd naar de mogelijkheden om diagnostische en therapeutische toepassingen van hartcatheterisatie te combineren in één procedure [4], naar de waarde van een aggressieve therapeutische benadering van patiënten met cardiogene shock als gevolg van een acuut hartinfarct [5], en de indicatiestelling voor coronaria-angioplastiek [6]. In 1989 en 1990 werd in het kader van The European Cooperative Study Group geparticipeerd in twee onderzoeken betreffende trombolyse en PTCA bij het acute myocardinfarct [7,8]. In het voorjaar van 1990 bestond er een "onderzoeksvacuum" waarin Felix Zijlstra, Jan Hoorntje en ik, naast reeds lopend eigen onderzoek, naarstig op zoek gingen naar aanluiting bij andere studies. Het daaropvolgend multicenter-onderzoek (the effects of a glycoprotein IIb/IIIa platelet receptor blocker on PTCA in unstable angina pilot study [8]) kon pas begin 1991 worden gestart. Jan Hoorntje en ik behandelden patiënten met een hartinfarct al incidenteel met primaire angioplastiek (tegen de toen algemeen gerespecteerde opvattingen in) en hadden daar goede ervaringen mee. Felix Zijlstra, die ons in 1988 kwam versterken verbaasde zich in hoge mate over de voortreffelijke resultaten van deze behandeling. Immers, uit het grote, vanuit het Thoraxcentrum Rotterdam geinitïeerde onderzoek naar PTCA verricht tijdens of onmiddellijk na trombolyse [9] was gebleken dat deze behandeling niet wenselijk of zelfs gevaarlijk was. De idee voor de Zwolle studie was toen geboren. Eind 1991 konden wij ons gelukkig prijzen met de komst van Harry Suryapranata. De unieke infrastructuur van het ziekenhuis de Weezenlanden, de goede intercollegiale verhoudingen en het grote aanbod van patiënten heeft het mogelijk gemaakt een onderzoek te initiëren dat inmiddels ook buiten Zwolle de aandacht heeft getrokken.

Met Professor Dr M.L.Simoons reizend naar Wenen (om precies te zijn op 8 mei 1992) werd de idee voor dit proefschrift geboren.

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Erkenning, dank of erkentelijkheid

Deze letterlijke vertaling van "acknowledg(e)ment" geeft drie betekenissen weer van het oorspronkelijke woord. Aan iedereen die hier vervolgens genoemd wordt laat ik de interpretatie van "acknowledgment".

Professor Dr M.L. Simoons, Maarten, je was "the fifth Beatle" of wel de George Martin van ons onderzoek. Een groter compliment kan ik je niet maken.

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Curriculum Vitae

Menko Jan de Boer

Born	Delfzijl, July 25, 1951
Nationality	Dutch
State	Married to Anna Maria Reuvers. They have two children: Cees Jan and Hilje
1963-	Beatle Fan
1968-1974	Medical Study, State University Groningen
1971-1973	Student Internship Histology, Immunology, State University Groningen. (Head of Department Professor Dr F.J. Keuning)
1974-75	Guest Internship: Internal Medicine and Nephrology: Veterans Administration Hospital. Miami Fla.U.S.A.(Head of Department Professor B.J. Materson)
1975-1976	Military Service: 11 Engineers Battalion, Ground Forces
1976-1978	Residency in Internal Medicine: de Weezenlanden Hospital Zwolle (Head of Department: Dr J.A. ten Bokkel Huinink)
1978-1981	Residency in Cardiology, St. Antonius Ziekenhuis Utrecht (Head of Department: Professor Dr A.V.G. Bruschke)
1981-	Practicing Cardiologist: de Weezenlanden Hospital Zwolle

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