Primary percutaneous coronary intervention and the role of thrombus aspiration

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Stellingen

behorende bij het proefschrift

Primary percutaneous coronary intervention and the role of thrombus aspiration

1 De relevantie van een eenvoudig te gebruiken trombusaspiratiecatheter bij een hartcatheterisatie neemt toe in de setting van een acuut myocardinfarct.
Dit proefschrift

2 Primaire percutane coronaire interventie met implantatie van een intracoronaire stent leidt tot minder reocclusies in vergelijking met ballon angioplastiek.
Dit proefschrift

3 Angiografische 'myocardiale blush grade' als maat voor myocardiale reperfusie is een goede voorspeller van uitkomst na een acuut myocardinfarct.
Dit proefschrift

4 Manuele trombusaspiratie vóór intracoronaire stentplaatsing leidt tot een betere myocardiale reperfusie vergeleken met ballondilatatie als eerste stap bij een primaire percutane coronaire interventie.
Dit proefschrift

5 Trombusmateriaal kan door trombusaspiratie worden verkregen in rond 70% van patiënten met een acuut myocardinfarct ongeacht de aanwezigheid van pre-procedurele angiografisch zichtbare trombus.
Dit proefschrift

6 Indien trombusaspiratie resulteert in volledig herstel van epicardiale flow zonder significante restenose of angiografische aanwijzingen voor plaqueruptuur, is aanvullend gebruik van ballon of stent in de infarctgerelateerde laesie mogelijk niet nodig.
Dit proefschrift

7 'Our aspirations are our possibilities.'
Samuel Johnson en dit proefschrift

8 Het lange termijn resultaat van stofzuigen blijkt beter dan het vuil onder het kleed te vegen.
Huishoudelijk empirisme

9 'Alle priser utsikter fra fjellene, ingen snakker om alle de utsikter de ligger i veien for.'
[Iedereen prijst het uitzicht van de bergen, niemand heeft het over het uitzicht wat zij benemen.]
Nils Kjær

10 De meest gebrekkige bronvermelding in een proefschrift bevindt zich in de stellingensectie.

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Primary percutaneous coronary intervention and the role of thrombus aspiration

Proefschrift

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Chapters of the thesis

Chapter 1

General introduction and aims of the thesis

General introduction

Acute myocardial infarction (MI) is primarily caused by an acute thrombotic event resulting in total occlusion of a coronary artery. Cessation of antegrade flow to the myocardium will lead to ischemia and later necrosis of the myocardium, which is associated with left ventricular dysfunction and increased mortality. The 12-lead electrocardiogram (ECG) is an important tool to make an immediate diagnosis of acute MI. Based on ST-segment shift on the ECG, a difference is made between MI with ST-segment elevation (STEMI) and MI without ST-segment elevation (non-STEMI). Patients with complete occlusion of the coronary artery may manifest with STEMI if the lesion occludes an artery supplying a substantial volume of the myocardium. The clinical diagnosis of acute STEMI is defined and diagnosed by the presence of a clinical syndrome of new onset myocardial ischemia, together with electrocardiographic evidence of acute ischemic injury (ST-segment elevation), and elevated biomarkers for myocardial necrosis.[1]

Therapy for acute MI has been focusing on dissolving, compressing, and surgically bypassing the thrombotic occlusion, aiming at normalization of flow in the occluded epicardial artery. Primary percutaneous coronary intervention (PCI) has emerged as the preferred treatment of acute STEMI and is effective in obtaining patency of the infarct related artery.[2,3] Therapy targeting the thrombotic component of the occlusion and removal of atherothrombotic debris may further enhance reperfusion and outcome in primary PCI.

Pathophysiology of the acute thrombotic event

Probably the first report of a fatal coronary event linked to plaque disruption has been described in the Journal of Danish Medical Association in 1844 when the famous sculptor Thorvaldsen died suddenly in the Royal Theater of Copenhagen with at autopsy the finding of an atheromateus mass extruding the lumen of a significant coronary artery.[4] Herrick described the anatomic, pathologic, and clinical features of total coronary occlusions in 1912.[5] Coronary occlusions had first been first visualized röntgenographically in post-mortem injections of the coronaries by the German physicians Jamin and Merkel, who published the first rongenographic atlas of the human coronaries in 1907.[5,6] After the development of the technique of in vivo coronary angiography, DeWood draw attention to the pathophysiology of the acute coronary event in 1980, when he showed that a total coronary occlusion was visible on the coronary angiogram in 88% of patients presenting during the early hours of STEMI. He retrieved thrombi in 57 of 79 patients, suggesting that thrombus formation is responsible for a majority of total coronary occlusions.[7]

Acute coronary thrombosis is caused by the disruption of an atherosclerotic plaque.[8-10] The atheromatous component of the plaque is a core of lipid-rich material, which is separated from the arterial lumen by the sclerotic component, consisting of a fibrous cap of collagen tissue. The most frequent cause of acute coronary thrombosis is rupture of the fibrous cap, being responsible for 76% of all fatal infarctions.[11] The remaining causes are plaque erosion or calcified noduli. The lipid-rich core is highly thrombogenic, and when it is exposed to the arterial lumen, platelets are activated. This initiates the coagulation cascade from platelet activation to platelet aggregation to thrombin generation and activity, which leads to the formation of a mural thrombus.

The platelet aggregates are unstable and may allow intermittent flow or dissolve to emboli in the microcirculation. For the further stabilization of this platelet-rich thrombus, the subsequent formation of fibrin is necessary. In STEMI, the initial early and fragile platelet-rich thrombus (macroscopically white) at the site of the plaque disruption occludes the lumen totally. Following this event, the blood proximal and distal to the occlusion will stagnate and coagulate, giving rise to a secondarily formed stagnation thrombosis consisting mainly of red blood cells (macroscopically red).

Management

Until the late 1970's, the general management of acute MI was comforting presence at the bedside. DeWood's article in 1980 initiated a shift in the management of MI, focusing on early restoration and maintenance of coronary blood flow.[7] Initial strategies to restore flow included thrombolysis, with intravenous therapy becoming the mainstream approach as it was widely available, and documented by large randomized trials to reduce mortality compared with conservative therapy.[12] However, intravenous thrombolysis has limitations, and some patients have important contraindications. Failure to recanalize the infarct-related artery and reinfarction occurs in a substantial number of patients, and the risk of bleeding, particularly intracranial hemorrhage, remains a serious complication.[12] As a result, the intervention strategy of primary PCI developed as an alternative, and has become the preferred treatment for STEMI.[2,3] As primary PCI developed after thrombolysis was established, the effect of PCI in acute MI versus no treatment has not been compared in a randomized setting. While primary PCI in the late eighties only comprised balloon angioplasty, [2,3] resulting in better survival when compared to thrombolytic therapy, the introduction of intracoronary stents has shown improved outcome compared to balloon angioplasty only. This effect is based on a benefit in revascularization rates as stenting has failed to show a benefit in survival.[13]

In addition to mechanical intervention, pharmacological therapy is given targeting the thrombus in STEMI. In addition to the abnormalities in platelet function associated with acute STEMI, PCI and stent deployment result in further activation of the coagulation cascade. Pharmacological therapy given directly after diagnosing myocardial ischemia include aspirin acetylsalicylic acid), clopidogrel (a thienopyridine) and unfractionated heparin (UFH), which each act on different steps in the coagulation pathway. Aspirin (irreversibly inhibits platelet activation; Clopidogrel inhibits ADP induced platelet aggregation, and UFH binds to antithrombin and inhibits thrombin generation, and facilitates the inactivation of thrombin.

Timely initiation of therapy is essential in the treatment of STEMI patients for re-establishment of coronary blood flow. Early treatment enhances myocardial perfusion, reduces infarct size, attenuates left ventricular outcome, and improves mortality.[14-17] A timely establishment of the correct diagnosis is therefore essential. Pre-hospital confirmation of the diagnosis by 12-lead electrocardiogram, by either general practitioners or ambulance service, allows for direct transportation to a PCI hospital and for the catheterization laboratory to be prepared in advance, which reduces time to reperfusion.[18,19] Moreover, it makes possible initial pharmacological treatment with aspirin, clopidogrel, and heparin to be administrated already in the pre-hospital setting.[20,21]

However, successful and early restoration of the epicardial coronary artery after occlusion does not always lead to adequate reperfusion of the myocardium. Distal coronary microembolization of atherosclerotic debris of thrombotic material is thought to be responsible for a substantial part of microvascular obstruction.[22-25] Therefore, it is of interest to use additional therapies to reduce the thrombus load and prevent embolization of the thrombus and/or debris from the plaque. Pharmacological antithrombotic therapy with glycoprotein (GP) IIb/IIIa inhibitors has been evaluated as an adjunctive to PCI in STEMI. The use of GP IIb/IIIa inhibitors inhibits platelet aggregation at the site of plaque rupture and may create a better antithrombotic milieu and thereby further enhance initial reperfusion and less distal embolization.[26] Additional use of GP IIb/IIIa inhibitors during primary PCI results in better clinical outcome than after PCI alone.[27-30] In addition to pharmacological therapy, adjunctive mechanical thrombectomy devices have been developed and evaluated in clinical studies for their role in preventing distal embolization.

Thrombectomy catheters

DeWood gave the first report of the coronary application of a thrombectomy catheter.[2] This was the Fogarty catheter, which had been developed in 1963 by Thomas Fogarty, for the application in distal limb vessels. The catheter had a balloon at its tip which was inflated distal to the lesion, and when it was extracted, it dragged the blood clot with it.[31] Over the last years, several catheters have been developed for removal of thrombotic material, including systems for simultaneous fragmentation and aspiration of thrombus as well as devices for thrombus aspiration only, using vacuum or manual suction.[32-40] The manual thrombus aspiration devices seem to hold most promise, since they are relatively flexible and non-traumatic in use.[32]

Aims of thesis

The aim of this thesis is to give an overview of treatment modalities for STEMI and describe the emerging role of thrombus aspiration. The principle focus is on optimal infarct related vessel patency and myocardial reperfusion as these parameters are essential for preservation of myocardial function and survival in patients with STEMI.

Chapter 2 describes the contemporary practice of primary PCI, and facilitated PCI with platelet aggregation inhibitors. Chapter 2.1 is an editorial which provides a summary of the evidence for use of PCI in patients with contraindications for thrombolysis. It comments on a study giving a quantitative analysis of primary PCI versus placebo or untreated controls in patients eligible for, but with contraindications to, thrombolysis. Chapter 2.2 reports a systematic review of all randomized controlled trials comparing BMS (bare metal stenting) during PCI with balloon angioplasty in patients with acute STEMI, focusing on reocclusion rate. Reocclusion has shown to be a strong predictor of reduced left ventricular function and cardiovascular mortality.[41,42] The aim of the study was to examine coronary angiographic parameters of reocclusion as a different aspect of infarct related vessel patency than revascularization rate to support BMS placement in acute STEMI. Chapter 2.3 is an editorial summarizing the evidence for the use of

GP IIb/IIIa in primary PCI. It comments on the long-term results of the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) study examining the effect of the GP IIb/IIIa inhibitor abciximab in primary PCI for a follow-up duration beyond 1 year.

In Chapter 3 of this thesis, we describe the design and outcomes of the Thrombus Aspiration in Percutaneous coronary intervention in Acute. myocardial infarction Study (TAPAS) assessing whether manual thrombus aspiration is superior to conventional treatment during primary PCI. Chapter 3.1 describes the design of the TAPAS trial, and provides an overview of mechanical treatment strategies for optimal myocardial reperfusion and diagnostic measures for the assessment of reperfusion that can be applied in clinical practice. Chapter 3.2 aims to assess the effect of thrombus aspiration in terms of the primary endpoint of angiographic signs of myocardial reperfusion and the secondary outcomes of 30-day clinical outcome. In this chapter, the effectiveness of the thrombus aspiration catheter to retrieve atherothrombotic material is analyzed. In Chapter 3.3 the 1 year clinical outcome of cardiac death and reinfarction in the TAPAS trial is reported.

Chapter 4 assesses thrombus aspiration in clinical practice. Chapter 4.1 analyses the characteristics and outcome of five patients in whom thrombus aspiration was performed as a definitive mechanical intervention without additional angioplasty as treatment for STEMI. Chapter 4.2 aims to identify clinical and procedural predictors of two-year cardiac ischemic events in a contemporary STEMI population treated with thrombus aspiration, i.e. the patients enrolled in the TAPAS trial.

Finally, in Chapter 5, the results of this thesis are summarized and future perspectives are made.

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Chapter 2

Primary and facilitated PCI in clinical practice

Chapter 2.1

The benefit of an invasive approach in thrombolysis-ineligible patients with acute myocardial infarction

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Am J Med 2005;118:123-125.

Early and sustained patency of the infarct-related coronary artery is the principle goal of initial therapy in patients presenting with acute myocardial infarction. Intravenous thrombolysis, which is the most commonly used reperfusion therapy worldwide, is easy to apply, generally available, and documented by large randomized trials to reduce mortality benefit compared with conservative therapy.[1] However, the applicability of thrombolysis is limited because a considerable portion of patients with acute myocardial infarction are not candidates for thrombolysis due to the absence of a diagnostic electrocardiogram, presentation after the conventional reperfusion time window, or contraindications to thrombolysis.[2] An invasive strategy with acute coronary angiography as a prelude to primary angioplasty has emerged as a preferred alternative if logistically feasible. Randomized trials in the patients eligible for thrombolysis have shown that, compared with thrombolysis, primary angioplasty results in lower rates of stroke and reinfarction and improved survival during short- and long-term follow-up.[3,4] Intuitively, therefore, it makes sense to apply the invasive strategy to patients who are ineligible for thrombolysis. Yet, how strong is the evidence in favor of an invasive strategy in these patients?

Starting in the early 1980s, case series have reported the successful use of balloon angioplasty without concomitant administration of thrombolytic therapy in a wide range of clinical presentations of myocardial infarction, including patients in cardiogenic shock, patients who have had prior bypass surgery, and patients with contraindications to thrombolytic therapy.[5,6] In a post-hoc analysis of the Primary Angioplasty in Myocardial Infarction (PAMI) randomized trial, patients with relative contraindications to thrombolysis, such as late presentation, age >70 years, or prior bypass surgery, constituted a high risk group in whom both in-hospital (3% vs. 13%; P = 0.03) and 6-month mortality (3% vs. 16%; P = 0.01) were lower with primary angioplasty.[7] In the Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial, 201 patients who had suspected acute myocardial infarction and who were ineligible for thrombolysis were randomized to early triage angiography and subsequent therapies based on the angiogram versus conventional medical therapy. In the invasive group, 98% had angiography and 58% underwent revascularization; by comparison, in the conservative group, 60% subsequently underwent nonprotocol angiography, and 37% received revascularization. The primary endpoint of death or recurrent ischemic events favored the invasive group (13% vs. 34%; P = 0.0002). However, at a median follow-up of 21 months, no differences in late revascularization, reinfarction, or all-cause mortality were apparent.[8]

Patients with a non-diagnostic electrocardiogram

The relative merits of an invasive versus a conservative strategy in patients with non-ST elevation myocardial infarction were explored by the Myocardial Infarction Triage and Intervention (MITI) investigators. In a patient with suspected acute myocardial ischemia or infarction, a non-diagnostic electrocardiogram is usually followed by conservative therapy in hospitals that depend on thrombolysis as their reperfusion therapy. If clinical suspicion is high, a non-diagnostic electrocardiogram (no ST elevation) may be followed by triage angiography in hospitals with an active primary angioplasty program. In this MITI cohort of 1635 consecutive patients with symptoms of acute myocardial infarction without ST elevation, 308 patients presented to hospitals in which the initial strategy favored early angiography and intervention, whereas 1327 similar patients presented

to hospitals in which a conservative initial approach was favored. Triage angiography occurred in 59% versus 8% (P <0.001), and angioplasty was performed in 45% versus 6% (P <0.001). The early invasive strategy resulted in a lower 30-day (5.5% vs. 9.5%; P = 0.026) and 4-year mortality (20% vs. 37%; P <0.001). Multivariate analysis showed a significantly lower long-term mortality, with a hazard ratio of 0.61 (95% confidence interval [CI]: 0.47 to 0.80), in patients admitted to hospitals favoring an invasive strategy.[9] In another randomized comparison of early invasive versus early conservative strategies in patients with unstable coronary syndromes, 833 (39%) of 2220 patients without ST elevation presented with enzymatic evidence of acute myocardial infarction. The benefit of an invasive approach was most pronounced in the large subgroup that presented with acute myocardial infarction and a "non-diagnostic electrocardiogram".[10]

Presentation after the conventional reperfusion time window

Late presentation may be a reason to withhold reperfusion therapy, in particular thrombolysis. In the Treatment with Enoxapam and Tirofiban in Acute Myocardial Infarction (TETAMI) registry and randomized trial, 2737 patients presented with ST elevation or a new left bundle branch block, including 1654 (60%) who presented at ≤12 hours after the onset of symptoms. Reperfusion therapy was given to 1196 (72%) of these 1654 patients, whereas 458 (28%) were deemed "ineligible" for reperfusion, mostly because of contraindications to thrombolysis. From the entire cohort, 1083 (40%) presented >12 hours after the onset of symptoms, and only 34 (3%) received reperfusion therapy.[11] In response to these rather sobering facts, it is clear that we should intensify our efforts to provide initial diagnosis and therapy for acute myocardial infarction in the early hours after onset of symptoms. Furthermore, primary angioplasty may be a viable option for patients who present late after the onset of symptoms because the results of primary angioplasty may be less time-dependent than those of thrombolysis.[12,13]

Patients with contraindications for thrombolysis

Of 5869 patients with acute myocardial infarction registered by the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) trial, 337 (6%) patients had at least one strong contraindication for thrombolysis. Of those patients, 46 (14%) were treated with primary angioplasty, and 276 (86%) were treated conservatively. Hospital mortality was significantly lower in patients who received primary angioplasty (2% vs. 25%; P = 0.001), with an odds ratio for death after multivariate analysis of 0.46 (P = 0.02).[14] The clinical outcome after conservative management of patients with acute ST segment elevation myocardial infarction in patients with contraindications to thrombolysis has been described in the 1,799,704 patients enrolled between June 1994 and January 2003 in the National Registry of Myocardial Infarction. Of 19,917 patients who had contraindications to thrombolysis and were potential candidates for triage angiography and immediate revascularization, the in-hospital mortality rate in nonrevascularized patients was 31%, which confirmed the very high-risk nature of this clinical condition. By comparison, the in-hospital mortality with revascularization was 11%, a risk reduction of 64%. This treatment effect remained significant after propensity analysis and following a second logistic model (odds ratio [OR] = 0.64; 95% CI: 0.56 to 0.75).[15]

Given this abundance of circumstantial evidence, it may seem clear that an invasive approach must be strongly recommended in a broad spectrum of patients who present

with suspected acute myocardial infarction, especially in patients who are ineligible for thrombolysis. In a recent randomized trial that compared balloon angioplasty with stenting, myocardial salvage was calculated from paired scintigraphic studies[16] in 611 patients who did not have ST-elevation (40%), presented late after the onset of symptoms (>12 hours, 40%), or had contraindications to thrombolysis (20%). Both "plain old balloon angioplasty" and stenting resulted in substantial salvage of myocardium at risk. Unfortunately, there is no large randomized trial with mortality as the primary end-point to provide unequivocal proof of this concept, and it is very unlikely that such a trial will be performed. In this issue of The American Journal of Medicine, Massel describes an elegant attempt to circumvent this problem, using sophisticated statistical techniques to estimate quantitatively the benefits of primary angioplasty in the setting of ST-elevation myocardial infarction in comparison to conservative therapy. Calculated from 30 trials,[1,3] the synthesised odds ratio for mortality for primary angioplasty versus control was 0.56 (95% CI: 0.46 to 0.68). In a high-risk group of otherwise eligible patients who have contraindications to thrombolysis, the absolute benefit was 93/1000 (95% CI: 53 to 132). Furthermore, compared with conservative therapy, primary angioplasty also reduced the risk of stroke (OR = 0.45; 95% CI: 0.29 to 0.69; P = 0.001).[17] This analysis confirms that an invasive approach to acute myocardial infarction is of life-saving importance in patients who are ineligible for thrombolysis. Improvements in the quality of prehospital care, including electrocardiography and transportation to hospitals with active invasive cardiology programs, are essential steps to implement these important findings.

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Chapter 2.2

A quantitative estimate of bare-metal stenting compared with balloon angioplasty in patients with acute myocardial infarction: angiographic measures in relation to clinical outcome

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Heart 2007;93:792-800.

ABSTRACT

We performed a systematic review of all randomised controlled trials (RCTs) from the pre-drug-eluting-stent era comparing bare-metal stenting (BMS) with balloon angioplasty in patients with acute myocardial infarction (MI) to examine coronary angiographic parameters of infarct-related vessel patency and to relate the angiographic measures to clinical outcome.

The search was restricted to published RCTs in humans. 10 RCTs, (6192 patients) were analysed. Compared with balloon angioplasty, BMS was associated with reduced rates of reocclusion (6.7% vs 10.1%, OR 0.62, 95% CI 0.40 to 0.96, $p=0.03$) and restenosis (23.9% vs 39.3%, OR 0.45, 95% CI 0.34 to 0.59, $p<0.001$), but not with reduced rates of subacute thrombosis (1.7% in both groups). BMS showed a reduction in target vessel revascularisation (TVR; 12.2% vs 19.2%, OR 0.50, 95% CI 0.37 to 0.69, $p<0.001$), but not in mortality (5.3% vs 5.1%) or reinfarction (3.9% vs 4%). The findings of this study support BMS placement in acute MI. The discrepancy between angiographic and clinical parameters has important implications for future studies investigating further technical improvements in mechanical reperfusion therapy.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has emerged as the preferred treatment of acute myocardial infarction (MI) and has been proven to be a very effective method to obtain patency of the infarct-related vessel.[1-3] Although the outcome of patients with acute MI has clearly improved with primary PCI, abrupt vessel closure in the hours to days after the PCI procedure, as well as restenosis and reocclusion in the months after the procedure, are still limitations of this treatment modality. To address these limitations, intracoronary bare-metal stent (BMS) placement in addition to balloon angioplasty has been introduced. During the past decade, BMS implantation during PCI in the treatment of acute MI has become a common practice, and is included as a class Ia recommendation in the guidelines for PCIs of the European Society of Cardiology.[3] The potential benefits of BMS compared with balloon angioplasty during PCI in acute MI have been studied in several trials[4-16] and meta-analyses of randomised controlled trials (RCTs).[17-21] These studies have been focusing on clinical end points and in general have shown that routine use of BMS reduces the need for revascularisation of the infarct-related vessel, but does not convincingly improve 1-year survival or lower the risk of reinfarction. With the introduction and ongoing investigation of the benefit of drug-eluting stents during PCI, it is unlikely that prospective studies to address the question of mortality and reinfarction after BMS placement compared with balloon angioplasty will be performed, and current practice is mainly based on a beneficial effect of BMS on subsequent revascularisation rates as a measure of infarct-related vessel patency. Previous analyses have been inconclusive on angiographic measures of infarct-related vessel patency, in particular on rates of reocclusion and subacute thrombosis. The ischaemia-driven revascularisations used in most of the analysed trials do not necessarily reflect the real rates of reocclusion and restenosis as these events may occur silently – that is, without ischaemic symptoms.[22] The parameters of infarct-related vessel patency are of importance because reocclusion of the infarct-related vessel in the first months after the PCI procedure has been shown to be a predictor of reduced left ventricular function and cardiovascular mortality in up to 8 years of follow-up.[23-27] We believe that an analysis of angiographic parameters of infarct-related vessel patency will give more evidence to the use of BMS in primary PCI. Also, we consider an overview of these parameters important for future trials investigating further improvements in mechanical reperfusion therapy.

We performed a systematic review to quantify the treatment effect of BMS in primary PCI on angiographic measures of infarct-related artery patency in relation to clinical outcomes. We analysed all RCTs comparing BMS implantation to balloon angioplasty in the treatment of patients with acute MI.

METHODS

Study identification

We sought to identify all relevant published randomised trials comparing BMS with balloon angioplasty in the treatment of patients with acute MI. A literature search of MEDLINE and EMBASE from 1990 to February 2006 and the Cochrane Library (2005, Issue 2) was

performed. Search terms included a combination of index terms (myocardial infarction/therapy; myocardial revascularisation; stents; angioplasty; percutaneous transluminal coronary; balloon dilatation) and free text words or word stems (myocardial infarct*; stent*; balloon; dilatat*; angioplasty). The search was restricted to studies conducted in humans and classified as RCTs. No language restriction was used. In addition, we examined relevant reviews and reference lists of retrieved studies.

Study selection

Two investigators (IvdH and TS) independently evaluated studies for eligibility. Criteria for inclusion were: (1) randomised treatment allocation; (2) inclusion of patients with objectively diagnosed acute MI; (3) comparison of primary BMS with primary balloon angioplasty; and (4) available core-laboratory data on quantitative angiographic analysis and clinical outcomes at follow-up. Exclusion criteria were: (1) rescue angioplasty; (2) intervention >48 h after onset of symptoms; (3) exclusive inclusion of patients with cardiogenic shock; (4) coronary artery bypass grafts/small vessels; (5) use of drug-eluting stents or thrombectomy device; (6) no useful outcome data; and (7) reviews. Any disagreements were resolved by consensus.

Data abstraction and validity assessment

All data were abstracted independently by two investigators (FZ and TS) in duplicate using a prespecified reporting form. We extracted information on trial characteristics, including randomisation sequence, and outcome parameters (see below). Only outcome measures reported on an intention-to-treat basis were used in the analysis. Authors were contacted for additional and missing information. Discrepancies were resolved by consensus.

We chose not to use quality scoring that weighed the contribution of each study to the meta-analysis. The main criticism of incorporating quality scoring weights into meta-analyses is that there are no validated measures of quality and the use of subjective rating scales may lead to bias.[28] We considered the use of core-laboratory analysis of such importance for the quality of the study that we decided to make this a separate inclusion criterion. Angiographic follow-up results of <6 months after the acute event were not included in the pooled analysis. Descriptive follow-up data of <6 months were included with a remark.

Outcomes, definitions and data analysis

Primary angiographic outcomes of interest were the rates of reocclusion, restenosis and subacute thrombosis at angiographic follow-up. The examined secondary angiographic outcomes included thrombolysis in myocardial infarction (TIMI) flow 3 after coronary intervention as a measure of successful infarct-related artery reperfusion, and quantitative coronary angiographic parameters after coronary intervention and at follow-up. In addition, we examined crossover rates in both groups. We used the definition of restenosis as a stenosis of >50% and reocclusion as a totally occluded lesion. For subacute thrombosis, we have made use of the data reported in the trials. If rates of subacute thrombosis were not given, but if information was available on patients with angiographically documented reocclusion and reinfarction in the 30-day follow-up period, we included this as subacute thrombosis.

The clinical outcomes at the longest available follow-up investigated were rates of: all-cause mortality, myocardial reinfarction, target vessel revascularisation, emergency coronary artery bypass grafting (CABG) and bleeding complications. Myocardial reinfarction was defined as recurrent chest pain with new ST segment elevation and recurrent increase of cardiac enzymes. Target vessel revascularisation (TVR) was defined as percutaneous or surgical revascularisation of the infarct-related artery. For bleeding complications, we included bleeding requiring transfusion or surgical repair and intracerebral haemorrhage.

Data from all studies reporting on identical end points were pooled using Review Manager (RevMan) V.4.2 for Windows of the Cochrane Collaboration (www.cochrane.org). Dichotomous variables are reported as proportions and percentages, and continuous variables as mean values. Binary outcomes from individual studies were to be combined with both the Mantel Haenzel fixed effect model[29] and the random effects model.[30,31] The odds ratio (OR) and 95% CI were used as summary statistics for the comparison of dichotomous variables between BMS and balloon angioplasty. Reported values were two tailed, and results were considered statistically significant at $p<0.05$. For testing heterogeneity, statistical significance was accepted at a probability value of 0.10. This study was performed in compliance with the Quality of Reporting of Meta-Analyses guidelines.[32]

RESULTS

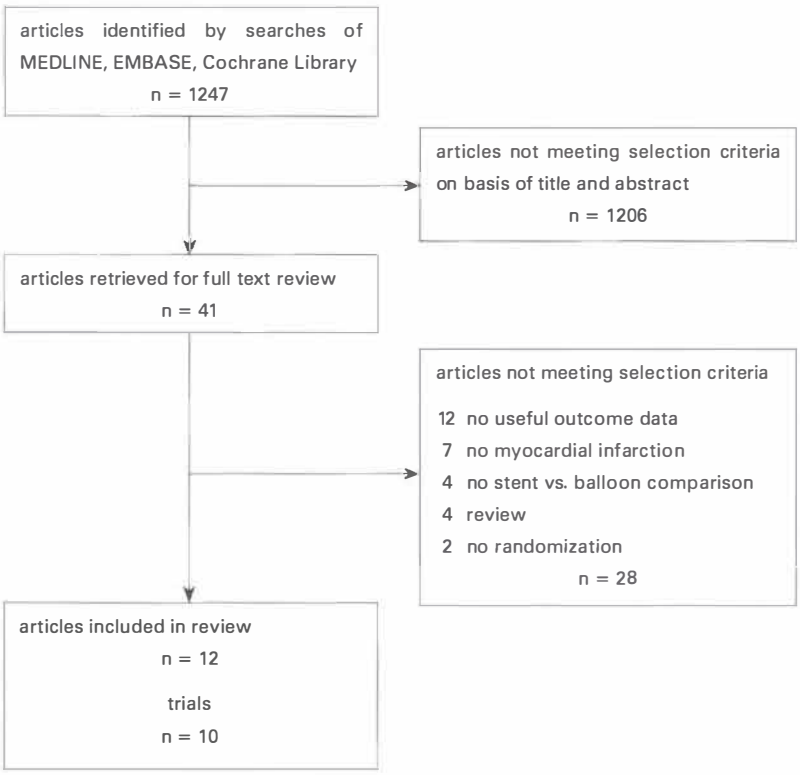
Study selection and trial characteristics

A flow diagram of the literature search is shown in **Figure 1**. Our search yielded 12 studies out of 10 trials: FRESCO,[5] GRAMI,[6] ZWOLLE I,[7,15] Stent PAMI,[8,16] PASTA,[9] STENTIM-2,[10] PSAAMI,[11] CADILLAC,[12] STOPAMI-3[13] and ZWOLLE II.[14] Two trials (ZWOLLE I and Stent-PAMI) were referred to by two citations of which both provided useful information on outcomes and follow-up results. Three trials were excluded because the information had only been presented as an abstract and the reported data were insufficient for our analysis. These were among the articles that did not meet the selection criteria after retrieval of more information (**Figure 1**).

The 10 included trials were published between 1998 and 2005 and involved 6192 patients, of which 3093 had been randomised to the BMS group and 3099 to the balloon group. **Table 1** shows the characteristics of the trials. In general, the included lesions in the trials were in medium-calibre vessels. Crossover rates to BMS implantation in the balloon groups varied from 0 to 36%, and cross-over rates to balloon angioplasty in the BMS groups varied from 0% to 13%.

Depending on the study design, the use of concomitant pharmacotherapy varied somewhat between the trials with respect to antiplatelet treatment and use of abciximab. In most trials, antiplatelet treatment with ticlodipine was administered for 4 weeks after PCI in the BMS group. In two of the earlier trials, the duration of administration was 2 months (both BMS and balloon groups)[5] and 4 months.[8] In one of the early trials,[7] anticoagulation with coumadines was used in some patients receiving a BMS instead of dual antiplatelet treatment. In most trials, abciximab was used in <5% of the patients, in two trials abciximab was used in half of the patients,[11,12] and in one trial Abciximab was used in most patients (90%).[13]

Figure 1. Flow diagram trial selection



n = number

The number of patients undergoing repeat angiography was specified in all trials, with the exception of two trials.[10,13] The rates of repeat angiography were roughly the same in both treatment groups of each of the trials. In two trials, the time of angiographic follow-up was 7 days[6] and 1 month[13] and the pooled angiographic data regarding restenosis and reocclusion rates of these trials were not included in the analysis. In all other trials, angiographic follow-up was performed at approximately 6 months (**Table 1**).

We measured significant statistical heterogeneity between trials in the assessment of postprocedural TIMI flow 3 ($p=0.03$), restenosis ($p=0.05$), reinfarction ($p=0.09$), and TVR ($p<0.001$), and we chose to present the results by the random effects model.

Table 1. Description of trials

Trial	Year	Sites	Patients	Patients BMS	Patients B	Time from s.o.	Vessel size	Cross-over BMS	Cross-over B	Clinical	Angiographic
		n	n	n	n	hours	mm	n (%)	n (%)	months	months
Fresco[5]	1998	1	150	75	75	< 6 (6-24*)	> 2.5	0 (0)	0 (0)	6	6
Grami[6]	1998	8	104	52	52	< 24	> 2.5	0 (0)	13 (25)	12	7 days
Zwolle I[7]	1998	1	227	112	115	< 6 (6-24*)	> 3.0	2 (2)	15 (13)	24	6
Stent Pami[8]	1999	62	900	452	448	< 12	3.0 - 4.5	7 (2)	67 (15)	12	6
Pasta[9]	1999	6	136	67	69	< 12	> 2.5	1 (1)	7 (10)	12	6
Stentim-2[10]	2000	17	211	101	110	< 12	> 3.0	3 (3)	33 (36)	12	6
Psaami[11]	2001	1	88	44	44	< 6 (6-24*)	> 3.0	1(2)	12 (27)	24	6
Cadillac[12]	2002	76	2082	1036	1046	< 12	2.5 - 4.5	22 (1)	168 (18)	6	7
Stopami 3[13]	2004	611	611	305	306	< 48	all	14 (5)	93 (30)	6	1
Zwolle II[14]	2005	1	1683	849	834	< 6 (6-24*)	all	109 (13)	214 (26)	12	6
Total			6192	3093	3099			159 (5.1)	622 (20.1)		

Year = year of publication, Sites = number of centers involved in trial, s.o. = symptom onset, BMS = bare metal stent group, B = balloon group, * for continuing myocardial ischemia

Table 2. Procedural data

Trial	PCI performed		MVD		PreTIMI 0/1		PostTIMI 3		CABG		Bleeding	
	BMS	B	BMS	B	BMS	B	BMS	B	BMS	B	BMS	B
	n		n (%)		n (%)		n (%)		n (%)		n (%)	
Fresco[5]	75	75	34	33	n.a.	n.a.	74	75	n.a.	n.a.	3	3
Grami[6]	52	52	n.a.	n.a.	41	42	50	43	0	1	1	1
Zwolle I[7]	112	115	49	51	n.a.	n.a.	110	110	2	1	7	3
Stent Pami[8]	452	448	208	297	n.a.	n.a.	404	415	1	1	23	17
Pasta[9]	67	69	25	31	62	65	66	67	n.a.	n.a.	1	1
Stentim-2[10]	101	110	31	36	101	110	85	75	n.a.	n.a.	n.a.	n.a.
Psaami[11]	44	44	10*	10*	44†	44†	41	39	n.a.	n.a.	4	6
Cadillac[12]	1036	1046	514	502	694	720	992	998	n.a.	n.a.	5	5
Stopami 3[13]	305	306	205	200	192	208	295	292	8	11	4	6
Zwolle II[14]	785	763	458	453	558	576	745	732	27	25	n.a.	n.a.
Total	3029	3028	1534 (52)	1513 (51)	1692 (71)	1765 (74)	2862 (94)	2846 (93)	38 (2)‡	39 (2)‡	48 (2)‡	42 (2)‡

PCI = percutaneous coronary intervention, MVD = multivessel disease, i.e. > 1 coronary vessel diseased, TIMI = thrombolysis in myocardial infarction, CABG = coronary artery bypass graft, pre TIMI 0/1 = pre-procedural TIMI grade 0/1, post TIMI 3 = post-procedural TIMI grade 3, BMS = bare metal stent group, B = balloon group, * 3 vessel disease, † TIMI 0/1/2, ‡ number of PCI performed based on studies with available data.

Procedural and angiographic data

Table 2 summarises the procedural and angiographic data. There were no differences between the BMS and the balloon groups in the rates of multivessel disease (52% vs 51%), TIMI flow 0/1 before angioplasty (71% vs 74%), TIMI flow 3 after angioplasty (94% vs 93%), emergency CABG (2% vs 2%) or bleeding complications (2% vs 2%).

Table 3 presents the quantitative coronary angiographic data after the initial procedure and at follow-up. Reference diameters of the BMS and the balloon groups were comparable. The BMS groups had larger luminal diameters and a lower percentage residual diameter stenosis after the initial procedure and at follow-up.

Table 3. Angiographic data post intervention and at follow-up

Trial	Post-procedure						Follow-up							
	RD		MLD		DS		patients		RD		MLD		DS	
	BMS	B	BMS	B	BMS	B	BMS	B	BMS	B	BMS	B	BMS	B
	mm		mm		mm		n		mm		mm		mm	
Fresco[5]	n.a.	n.a.	3.3	3.0	-4.0	5.0	68	56	n.a.	n.a.	2.4	2.0	n.a.	n.a.
Grami[6*]	3.0	3.1	2.7	2.3	10.0	27.6	50	50	3.0	3.1	2.7	2.0	10.8	36.2
Zwolle I[7]	3.2	3.1	2.6	2.2	17.9	28.8	101	96	3.1	3.1	2.0	1.6	33.4	47.3
Stent Pami[8]	2.9	2.8	2.6	2.1	11.1	25.1	348	348	2.8	2.9	1.8	1.6	35.6	44.7
Pasta[9]	3.1	3.1	2.9	2.5	9.8	18.9	64	64	3.1	3.0	2.2	1.7	26.8	42.8
Stentim-2[10]	3.0	3.0	2.4	2.1	19.4	28.5	101	110	2.9	2.8	1.7	1.5	42.5	46.8
Psaami[11]	n.a.	n.a.	3.1	2.6	n.a.	n.a.	37	33	n.a.	n.a.	2.2	1.5	n.a.	n.a.
Cadillac[12]	3.0	3.0	2.7	2.2	11.0	25.0	325	311	3.0	3.0	2.7	2.2	11.0	25.0
Stopami 3[13**]	2.9	2.9	2.8	2.3	n.a.	n.a.	305	306	2.8	2.9	1.8	1.6	34.5	43.7
Zwolle II[14†]	3.1	3.0	2.5	2.2	17.6	27.3	306	323	3.1	3.0	1.6	1.5	44.5	48.3

RD = reference diameter, MLD = minial lumen diameter, DS = diameter stenosis, BMS = bare metal stent group, B = balloon group, * follow-up 7d, ** follow-up 1 month, † RD post-procedure and follow-up.

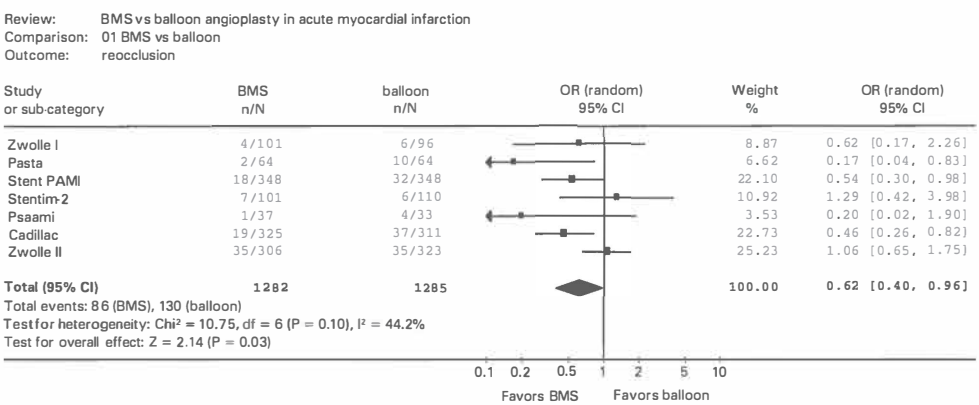
Table 4. Angiographic data at follow-up

Trial	Patients		RO		RS		SAT	
	BMS	B	BMS	B	BMS	B	BMS	B
	n		n (%)		n (%)		n (%)	
Fresco[5]	68	56	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Zwolle I[7]	101	96	4	6	12	33	1	5
Stent Pami[8]	348	348	18	32	71	117	4	5
Pasta[9]	64	64	2	10	11	24	2	3
Stentim-2[10]	101	110	7	6	26	44	n.a.	n.a.
Psaami[11]	37	33	1	4	9	20	n.a.	n.a.
Cadillac[12]	325	311	19	37	72	130	5	14
Stopami 3[13]	305	306	n.a.	n.a.	n.a.	n.a.	6	4
Zwolle II[14]	306	323	35	35	105	137	29	18
Total			86/1282 (6.7)	134/1285 (10.1)	306/1282 (23.9)	505/1285 (39.3)	47/2821 (1.7)	49/2818 (1.7)

RD = residual diameter, MLD = minial lumen diameter, RS = restenosis, RO = reocclusion, SAT = subacute thrombosis, BMS = bare metal stent group, B = balloon group.

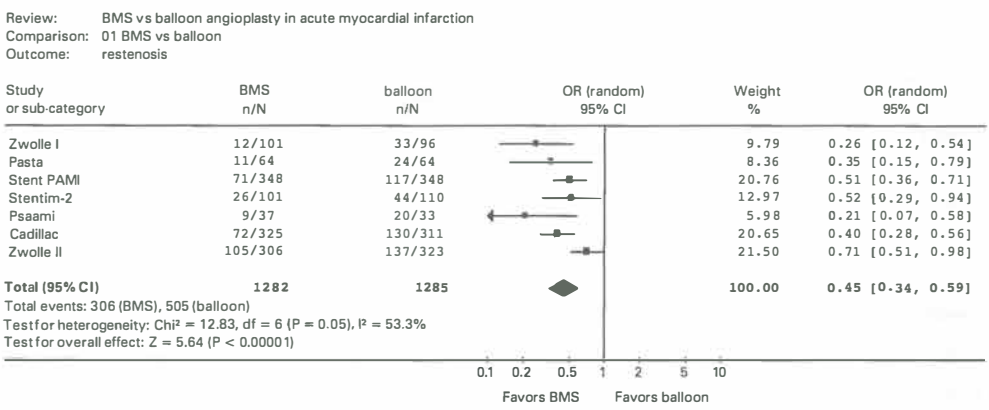
Table 4 presents the rates of reocclusion, restenosis and subacute thrombosis. Reocclusion was less frequent after BMS implantation compared with balloon angioplasty (6.7% vs 10.1%, OR 0.62, 95% CI 0.40 to 0.96, p=0.03) (**Figure 2**).

Figure 2. Reocclusion



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

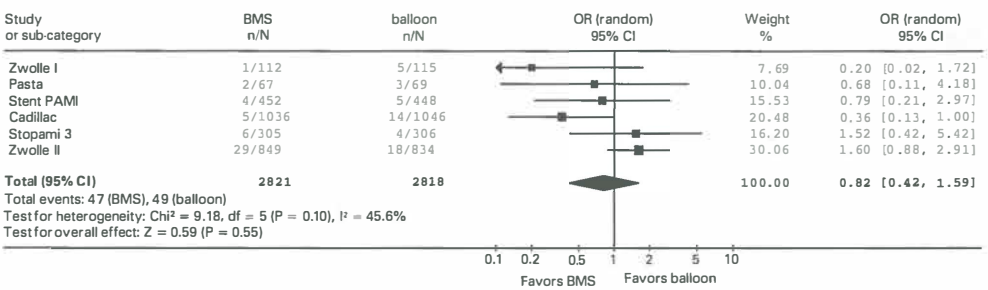
Figure 3. Restenosis



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

Also, restenosis was less frequent after BMS implantation compared with balloon angioplasty (23.9% vs 39.3%, OR 0.45, 95% CI 0.34 to 0.59, p<0.001) (**Figure 3**). Six trials reported rates of subacute thrombosis.[7-9,12-14] There was no difference in the rate of subacute thrombosis between the two groups (1.7% in both groups, OR 0.82, 95% CI 0.42 to 1.59, p=0.55) (**Figure 4**).

Figure 4. Subacute thrombosis



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

Clinical outcome

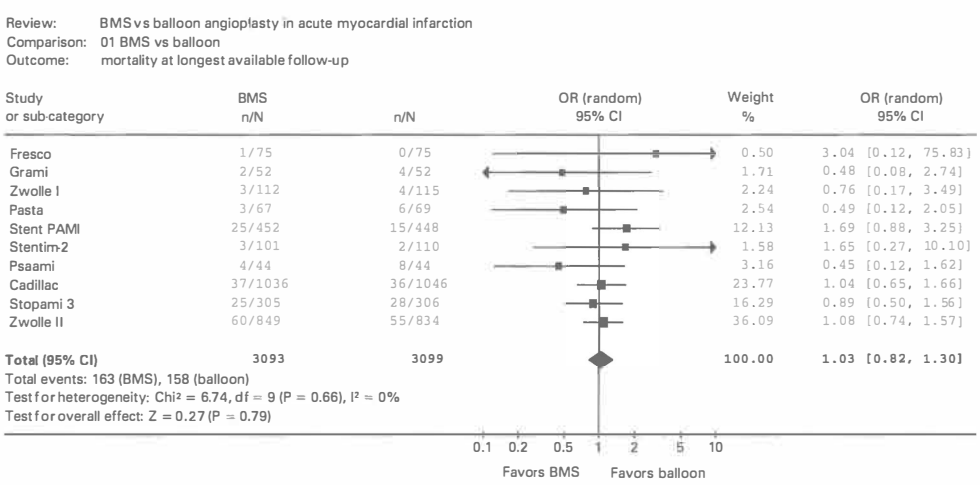
Table 5 presents clinical outcome. All trials reported all-cause mortality. There was no difference in mortality between the BMS and the balloon groups at the end of follow-up (**Figure 5**).

Table 5. Clinical data at follow-up

Trial	Randomization		Mortality		ReMI		TVR	
	BMS	B	BMS	B	BMS	B	BMS	B
	n		n (%)		n (%)		n (%)	
Fresco[5]	75	75	1	0	1	2	5	19
Grami[6]*	52	52	2	4	0	4	7	10
Zwolle I[7]	112	115	3	4	1	10	15	39
Stent Pami[8]	452	448	25	15	16	11	47	93
Pasta[9]	67	69	3	6	0	4	12	24
Stentim-2[10]	101	110	3	2	4	5	17	25
Psaami[11]	44	44	4	8	1	4	7	15
Cadillac[12]	1036	1046	37	36	20	23	76	166
Stopami 3[13]	305	306	25	28	7	4	25	32
Zwolle II[14]	849	834	60	55	71	57	166	173
Total	3093	3099	163 (5.3)	158 (5.1)	121 (3.9)	124 (4.0)	377 (12.2)	596 (19.2)

ReMI = reinfarction, TVR = target vessel revascularization, BMS = bare metal stent group, B = balloon group, * Mortality and ReMI at 30 days.

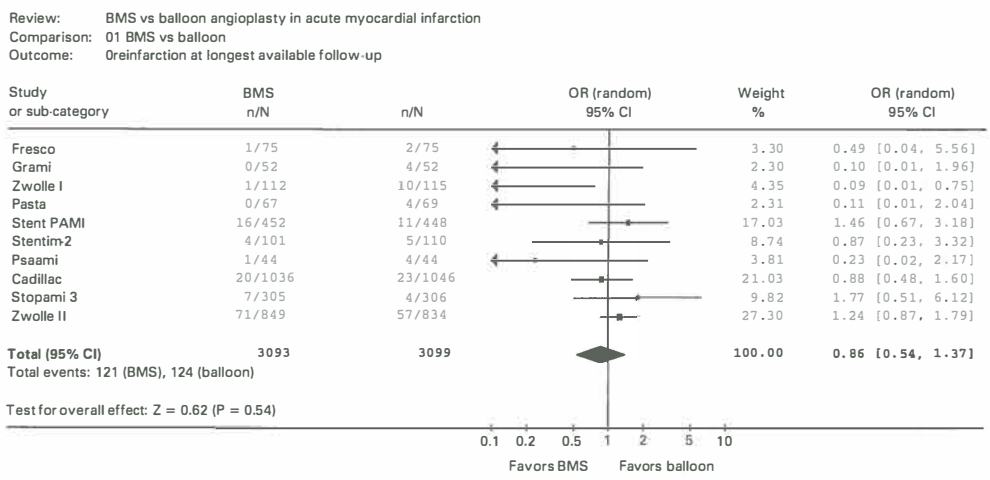
Figure 5. Mortality at longest available follow-up



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

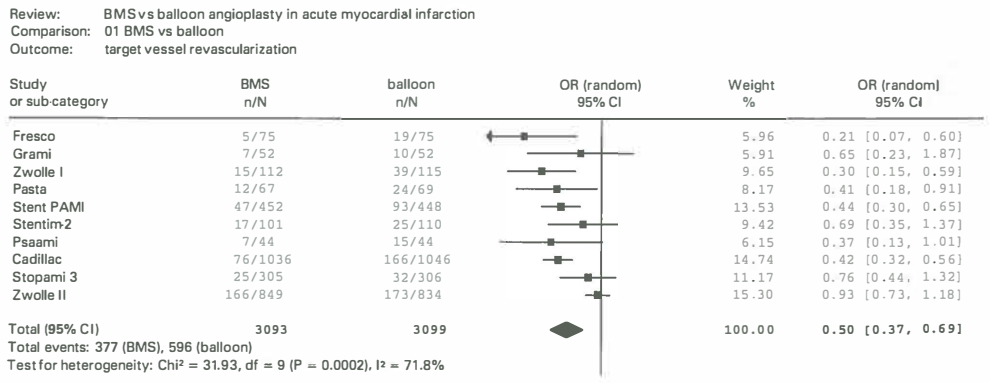
There was no difference in reinfarction rate (**Figure 6**). Rates of non-fatal MI were not given separately in some of the trials, so our reported rates of MI probably include a fraction of fatal cases. For repeat revascularisation, five trials specified the requirement for ischaemic symptoms in order to perform TVR,[5,7,8,10,12] which suggests that in some cases revascularisation has certainly been protocol-driven by the mandatory follow-up angiograms. TVR rates were performed in 12.2% in the BMS group compared with 19.2% in the balloon group, OR 0.50 (95% CI 0.37 to 0.69, p<0.001) (**Figure 7**).

Figure 6. Reinfarction at longest available follow-up



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

Figure 7. Target vessel revascularization



BMS = bare metal stent, OR = odds ratio, CI = confidence interval, n = number

DISCUSSION

The objective of our systematic review was to quantify the treatment effect of the use of BMS compared with balloon angioplasty in primary PCI on angiographic measures of infarct vessel patency, and to relate these angiographic measures to clinical outcome in patients with acute MI. We found an important reduction in the rates of reocclusion and restenosis with BMS implantation compared with balloon angioplasty. BMS implantation did not influence the rate of subacute thrombosis. As confirmed by previous studies, our data show that BMS implantation reduces the need for TVR compared with balloon angioplasty. The pooled data showed no clear impact on reduced reocclusion or restenosis rates on mortality or reinfarction rate with BMS implantation compared with balloon angioplasty in patients presenting with acute MI. There were no differences between BMS and balloon angioplasty in the rates of successful reperfusion measured by TIMI flow 3 after the procedure or in the need for emergency CABG. We did not observe a higher rate of bleeding complications with BMS.

The outcome of reocclusion shows a similar pattern as the results of one previously published analysis examining the frequency of reocclusion after balloon angioplasty, BMS placement and thrombolytic therapy in acute MI, which showed lower reocclusion rates after BMS placement than after balloon angioplasty alone (OR 0.28, 95% CI 0.65 to 1.75, $p<0.001$).[33] However, the study was not based on randomised comparisons of the two treatment modalities, which may have been an important source of bias in the analysis.

Although reocclusion has been associated with depressed left ventricular function and a poor outcome, both after thrombolytic treatment[23,24] as well as after PCI,[24–26] the difference in reocclusion rates in our pooled analysis did not seem to translate into a difference between the BMS and the balloon groups in mortality at 1 year of follow-up. One explanation for this finding could be that a reoccluded infarct-related artery and depressed left ventricular function may require a longer follow-up duration than 1 year to become clinically apparent.[1,23–26] Indeed, a mortality benefit of BMS placement seems to be less obvious in trials with a shorter follow-up period. An exception is the Stent PAMI trial in which a higher mortality rate in the BMS group despite a reduced reocclusion rate could be related to lesser number of patients with post-procedural TIMI 3 flow in the BMS group compared with the balloon group. Another possible explanation could be the timing of follow-up angiography at 6 months, which is mainly based on analyses with balloon angioplasty showing that the majority of restenosis occurs within the first 3 months after the procedure.[34] With coronary BMS opposing early elastic recoil of the vascular lumen as well as late vascular remodelling and thereby increasing luminal diameter, the time course of restenosis and reocclusion due to neointimal hyperplasia could be delayed. Hence, some patients in the BMS group may develop restenosis or reocclusion beyond the time of angiographic follow-up as compared with the balloon angioplasty group. This may lead to an underestimation of these rates in the BMS group.

Despite lower overall rates of reocclusion and restenosis with BMS, there were no significant differences between the BMS and the balloon angioplasty groups in terms of subacute thrombosis. One explanation for this finding is that the rates of subacute thrombosis in the individual trials are low and more data may be needed to show a

significant difference between the groups. An alternative explanation is that the pathophysiological mechanisms for restenosis and subacute thrombosis may differ. A beneficial effect of BMS on luminal diameter on the longer term may initially be opposed by the increased risk of thrombus formation before neointimal stabilisation of the stent.

The ZWOLLE II trial,[14] with 1683 of 6192 (27.2%) patients in our analysis, randomised consecutive patients in a single centre. Interestingly, this trial shows no benefits of coronary BMS compared with angioplasty in terms of reocclusion, restenosis and TVR. The study enrolled patients before coronary angiography, thereby decreasing the bias of preselecting patients. However, the study design resulted in high crossover rates, both from balloon to BMS as well as from BMS to balloon. As a consequence, the intention-to-treat analysis and the per-protocol analysis of this trial show different results. This trial shows that coronary BMS can be applied in 85–90% of patients with ST-elevation MI.

There seems to be an association between timing of randomisation with respect to coronary angiography and cross-over rates. The mentioned ZWOLLE II trial[14] was the only trial with randomisation of patients before coronary angiography. A total of 3232 of 6192 (52.2%) patients were enrolled in six trials[6,9–13] with randomisation after coronary angiography, but before initial reperfusion was obtained with wire and balloon. These trials are characterised by a lower crossover rate from balloon to BMS implantation than in the ZWOLLE II trial as a result of the used coronary angiographic inclusion and exclusion criteria. Three trials[5,7,8] enrolled patients (1277 of 6192, 20.6%) after coronary angiography and reperfusion with wire and balloon. Cross-over rates in these three trials were low and varied somewhat according to study design.

In primary PCI, as in elective PCI, it has been difficult to show that BMS placement reduces rates of mortality and reinfarction. With the introduction and ongoing investigation of the benefit of drug-eluting stents during PCI, it is unlikely that prospective studies to address the question of mortality and reinfarction after BMS placement compared with balloon angioplasty will be performed. As reocclusion, restenosis and TVR are the major differences in outcome after BMS compared with balloon angioplasty, it can be expected that technical improvements in mechanical reperfusion therapy will further enhance the benefits of stent implantation in terms of these outcome parameters.

LIMITATIONS

We performed our search and selection of trials in accordance with the Quality of Reporting of Meta-Analyses guidelines.[32] Nevertheless, this procedure does not give full protection against the consequences of publication bias. Significant results are more likely to get published than non-significant ones. Some of the other meta-analyses have included data from additional non-published trials of BMS implantation compared with balloon angioplasty. We have chosen not to include the data from these trials as methodology, patient selection, endpoint definitions and the use of core laboratory angiographic analysis are available only in a published, peer-reviewed manuscript. Another limitation of our approach is that we did not have access to the data of individual patients. Subgroup analyses according to specific clinical or angiographic

characteristics would certainly provide important additional clinical insights. Moreover, the effect of crossover on the results cannot be determined. Also, the results are not directly applicable to the treatment of small coronary vessels.

Further limitations are the sources of clinical heterogeneity between the trials. Firstly, some of the studies were designed to randomise the patients after successfull balloon angioplasty,[5,7,8] which might have resulted in an underestimation of the true effect of BMS. Furthermore, even though angiographic results are partially standardised by the use of angiographic core laboratories, we cannot exclude unmeasured differences in the outcomes across the studies. Finally, changing trends in the use of concomitant pharmacotherapy and the remarkable progress in stent technology has resulted in pharmacological and technical differences between the early trials and the more recent studies, which may also have influenced the results.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Intracoronary stent implantation has become the principal reperfusion technique after initial recanalisation with wire and balloon in patients with ST-elevation MI. Compared with balloon angioplasty supported by provisional stenting, routine BMS implantation results in an impressive benefit in terms of reocclusion and restenosis. There was no difference in the rate of subacute thrombosis between the two groups. As confirmed by previous studies, there are benefits from BMS compared with balloon angioplasty in terms of TVR. These findings do not seem to translate into a mortality benefit or a lower rate of reinfarction in the pooled data, but a longer follow-up period may be needed to detect a deleterious effect of a reocclusion of the infarct-related vessel. As current practice is mainly based on a beneficial effect of BMS on revascularisation rate as a measure of infarct-related vessel patency, we believe our angiographic findings support BMS placement in acute MI. Moreover, the discrepancy between angiographic and clinical outcome measures has important implications for future studies investigating further technical improvements in mechanical reperfusion therapy, such as the use of drug-eluting stents and devices for distal protection of the infarct-related vessel.

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Chapter 2.3

The role of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention for ST elevation myocardial infarction

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The administration of glycoprotein IIb/IIIa inhibitors is considered to provide additional benefit to mechanical reperfusion in the treatment of patients with ST elevation myocardial infarction and is included as a class-IIa recommendation in the Guidelines for Percutaneous Coronary Intervention of the European Society of Cardiology.[1] Glycoprotein IIb/IIIa inhibitors block the surface receptor, which is a member of the integrin superfamily of membrane-bound adhesion molecules. Binding to the major adhesive proteins, fibrinogen and von Willebrand, occurs due to a conformational change of the glycoprotein IIb/IIIa receptor. This final step in platelet aggregation is blocked by the glycoprotein IIb/IIIa inhibitors. Other effects of the glycoprotein IIb/IIIa receptor are interference with thrombus formation, including induction of platelet disaggregation, and reduced clot retraction. Inhibitors developed and used in routine clinical practice include abciximab, the Fab fragment of the chimeric monoclonal antibody, 7E3, and synthetic intravenous administered competitive integrin blocking agents, such as tirofiban and eptifibatide.

Effects on clinical outcome of adding glycoprotein IIb/IIIa to primary percutaneous coronary intervention (PCI) in patients with ST elevation myocardial infarction have been evaluated in a randomized fashion primarily for abciximab, whereas the clinical effects of tirofiban and epitifibatide are less well investigated. A pooled analysis of 3949 patients from five larger and three smaller randomized controlled trials found that the addition of abciximab to primary PCI reduced 30-day mortality from 3.4 to 2.4% ($P=0.047$) and 6–12-month mortality from 6.2 to 4.4% ($P=0.01$).[2] With a risk reduction of 1% at 30 days, the estimated number needed to treat to prevent one death was 100, and the risk reduction of 1.8% at 6–12-month follow-up corresponds to an estimated number needed to treat 56 patients. Abciximab was also associated with a significant reduction in 30-day re-infarction rate from 1.9 to 1.0% ($P=0.03$), corresponding to a number needed to treat 111 patients to prevent one re-infarction. With regard to safety, this pooled analysis reconfirms that abciximab was not associated with a higher incidence of intracranial bleeding.

To assess the equivalency of the different glycoprotein IIb/IIIa inhibitors, a systematic review of all 12 randomized placebo-controlled trials of glycoprotein IIb/IIIa inhibitor facilitation in patients undergoing urgent or elective PCI has been published recently.[3] Using three complementary methods (Bayesian analysis, Bayesian analysis incorporating prior information, and indirect comparisons via hierarchical Bayesian meta-analysis), Brophy and Joseph showed a reasonable probability of equal effect. The clinically obtained arguments in favour of equivalency of the three inhibitors are in line with similar levels of inhibition of platelet aggregation and with a similar reduction in the platelet–monocyte interaction that were observed when the inhibitors were compared given in standard dose.[4] In a trial of 112 patients with ST elevation myocardial infarction undergoing PCI, Ernst et al.[5] investigated the effect of abciximab, tirofiban, high-dose tirofiban, or no glycoprotein IIb/IIIa inhibitors on the extent of platelet aggregation. The direct comparison of standard dose abciximab with standard dose tirofiban yielded non-significant results.[5] However, it was observed that high-dose tirofiban induced a mean periprocedural platelet aggregation inhibition of 84% compared with 46 and 59% in patients treated with standard dose abciximab and tirofiban, respectively.

The benefits of the use of glycoprotein IIb/IIIa inhibitors in patients with ST elevation myocardial infarction treated with PCI have raised the question whether early treatment

with these inhibitors, with the aim to improve initial patency before intervention, may further improve outcome. The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) study was the first randomized controlled trial in which a subset of patients were treated with abciximab in the ambulance or in the emergency department prior to arrival at the catheterization laboratory.[6] Patients treated before arrival in the catheterization laboratory had a higher patency rate, a better left ventricular function, and a lower rate of death and myocardial infarction when compared with patients receiving placebo. In a systematic review including 931 patients from six randomized trials (three with abciximab and three with tirofiban) of early (prior to transfer to the catheterization laboratory) vs. late (at the time of PCI) administration of a glycoprotein IIb/IIIa inhibitor, early administration appeared to improve coronary patency and resulted in favourable trends for clinical outcomes.[7] Another pooled analysis, presented at the Scientific Sessions of the American College of Cardiology, Orlando, 2005, evaluated the use of abciximab on the basis of data from 602 individual patients. These data suggest that a beneficial effect of pre-treatment with abciximab is, in particular, present when the delay from symptom onset to therapy is <3 h.[8]

To test the hypothesis of the benefit of pre-treatment generated by the retrospective analyses of the early treated patients in the ADMIRAL trial, some randomized controlled trials have been completed and published recently.[9–11] A pilot trial with tirofiban given in the emergency room suggested the safety, feasability, and angiographic effectiveness of this approach.[9] The Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) trial was designed to evaluate the effect of tirofiban pre-treatment on initial TIMI flow of the infarct-related vessel in patients transported for primary PCI.[10] The combined TIMI flow 2 or 3 was present in 43% in the early group and in 34% in the late group ($P=0.04$). Despite this better patency, no beneficial effect on post-PCI angiographic or clinical outcome was found when compared with the initiation of tirofiban in the catheterization laboratory. For eptifibatide, results of a randomized pilot study with 102 patients showed that treatment 45 min before angiography was related to TIMI flow 3 patency before PCI in 34 vs. 10% in patients who received no eptifibatide or eptifibatide after PCI ($P=0.01$).[11]

Montalescot and co-workers[12] report the 3-year results of the ADMIRAL study. This is the first demonstration of a persistent benefit of abciximab for a follow-up duration beyond 1 year. The long-term results of 288 patients (96% of the initially included patients) showed a favourable trend in all-cause mortality and the composite endpoint of death, recurrent myocardial infarction, and urgent target vessel revascularization, albeit not significant. However, the initial difference observed at 30 days seemed to be preserved over the entire period. After an even longer follow-up period, the benefit brought by abciximab will be negated by underlying risk factors of poor clinical outcome. This may explain why the 5-year follow-up of 373 (96%) patients in the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) trial, in contrast to the follow-up data from the ADMIRAL trial, did not show sustained clinical benefit with the use of abciximab.[13]

Several issues related to glycoprotein IIb/IIIa inhibitors facilitated PCI in patients with ST elevation myocardial infarction remain to be clarified. First, it has to be proven whether glycoprotein IIb/IIIa inhibitors in addition to aspirin, heparine, and clopidogrel in ST elevation myocardial infarction patients treated with PCI still have an additive

benefit, as most trials have enrolled patients not treated with clopidogrel. Secondly, it remains to be determined whether glycoprotein IIb/IIIa inhibitors are associated with an increased risk of non-intracranial bleeding. Most data do not suggest an increased risk of major bleeding complications.[2] However, more information is needed to establish the relationship between the glycoprotein IIb/IIIa inhibitors and the risk of minor bleeding complications, e.g. at the femoral puncture site. Thirdly, the optimal dose of the inhibitors is unknown, higher doses may induce a more favourable effect on initial TIMI flow but potentially have a higher risk of bleeding.

In conclusion, when we review the data from the individual randomized controlled trials and meta-analyses, it is clear that glycoprotein IIb/IIIa inhibitors play a pivotal role in the management of patients treated with primary PCI. These drugs are most beneficial with early, pre-hospital treatment of patients in the first hours of acute ST elevation myocardial infarction.

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Chapter 3

Design and outcomes of the Trombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)

Chapter 3.1

Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) – Study design

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ABSTRACT

Background and Objective

Embolization of atherothrombotic material is common during percutaneous coronary intervention (PCI) in acute myocardial infarction (MI). This may lead to distal vessel occlusion resulting in impaired myocardial perfusion, which is associated with larger infarct size and increased mortality. Adjunctive devices for PCI to protect the microcirculation have been developed. We intend to determine whether aspiration of thrombotic material before stent implantation of the infarct-related coronary artery results in improved myocardial perfusion compared with conventional primary PCI.

Study Design

TAPAS is a single-center, prospective, randomized trial with a planned inclusion of 1080 patients with ST-elevation MI. Patients are assigned to treatment with thrombus aspiration with the 6F Export Aspiration Catheter (Medtronic Corporation, Santa Rosa, Calif) or to balloon angioplasty before stent implantation in the infarct-related artery. All patients will be treated medically according to current international guidelines including glycoprotein IIb/IIIa inhibitors before PCI. Randomization will be performed before coronary angiography. The primary end point is angiographic myocardial blush grade of <2. Secondary end points are enzymatic infarct size, ST-segment elevation resolution and persistent ST-segment elevation, postprocedural distal embolization, and Major Adverse Cardiac Events at 30 days and 1 year.

Implications

If thrombus aspiration significantly improves myocardial perfusion, it will lend support to the use of this treatment as part of the standard approach in patients with acute MI.

Acute myocardial infarction (MI) is considered to be related primarily to the rupture or erosion of a coronary atherosclerotic plaque, initiating intraluminal thrombus superimposed on the ruptured plaque, which leads to total or subtotal occlusion of an epicardial vessel.[1-3] Following coronary angiographic studies showing that thrombotic occlusion of the epicardial artery causes MI,[4] reperfusion therapy has been focusing on dissolving, compressing, or surgically bypassing thrombi, aiming at normalization of flow in the epicardial infarct-related artery. Optimal outcome of reperfusion treatment has in recent years been redefined to include not only sustained epicardial patency, but also reperfusion of the myocardium subtended by the affected coronary artery.[5-11] Primary percutaneous coronary intervention (PCI) has emerged as the preferred treatment of acute MI if logistically feasible and has been proven to be a very effective method to obtain patency of the infarct-related artery.[12-14] However, microvascular dysfunction with diminished myocardial perfusion is seen in a significant proportion of patients with a patent epicardial vessel after primary PCI and has been associated with larger infarct size, less recovery of left ventricular ejection fraction, and increased mortality.[8,10]

Two major impediments to normalization of microvascular function are considered to be reperfusion injury and microvascular obstruction. Reperfusion injury refers to the inability to reperfuse myocardium that is already necrotic through ischemic cell death.[15] Microvascular obstruction is believed to be caused by the embolization of soft plaque gruel (atheroembolization) and/or thrombotic material (thromboembolization) in the downstream bed of the infarct-related artery.[16,17] The embolization may occur spontaneously after plaque rupture, but recent studies emphasize mechanical crushing and fragmentation of the culprit lesion during PCI as the major cause.[8,18,19] Distal embolization induced by PCI therefore potentially results in further myonecrosis.

Several diagnostic testing strategies have evolved to evaluate the adequacy of reperfusion in the treatment of acute MI. The coronary angiogram can be used to obtain diagnostic information of epicardial as well as myocardial perfusion. Epicardial flow can be described according to the angiographic TIMI grading system[20] and quantitatively assessed by the corrected TIMI frame count.[21] Coronary angiographic techniques for the assessment of microvascular function and myocardial tissue perfusion include the visualization of distal embolization[8] and the evaluation of myocardial blush grade (MBG).[7] These angiographic methods are valuable in risk stratification after reperfusion therapy as they have been shown to correlate directly with mortality.[7,22] The angiographic characterization of reperfusion may be complemented by other surrogate markers of tissue level perfusion.[6,23-30] Of these, the most applicable for routine assessment of perfusion include the electrocardiographic (ECG) analysis of ST-segment resolution for evaluation of the efficacy of myocardial tissue reperfusion[6,23,24] and cardiac marker release patterns for determination of the amount of myocardial damage as measure of infarct size.[25,26]

The frequent suboptimal myocardial reperfusion after primary PCI has resulted in the development of adjunctive devices for PCI to protect the microcirculation, which include devices for use distal as well as proximal to the lesion. Distal embolic protection devices consist of occlusion balloons or filters in combination with aspiration devices. Occlusion balloons serve to obstruct the target vessel distal from the site of revascularization, thereby blocking the outflow of debris. The debris is then aspirated out of the vessel by an export catheter before the balloon is deflated. Filtering devices are attached to

guidewires and serve as a basket to trap embolic material downstream from the lesion. Aspiration has been attempted with devices such as over the wire balloons or the angiography catheter itself. These techniques have some limitations. The lumen of an over the wire balloon system is just large enough to allow passage of 0.014-in wire, which may not allow rapid aspiration. Use of the angiography catheter as an aspiration tool is limited by the inability to manipulate it deeply enough into the infarct-related artery to approach the culprit lesion, with the risk of damage. In two published randomized trials, the PROMISE trial (filterwire, FilterWire-Ex)[31] and the EMERALD trial (distal balloon and aspiration system, GuardWire),[32] the distal protection system did not result in improved reperfusion, reduced infarct size, or improved clinical outcome, despite a high procedural success rate in both trials (**Table 1**).

Embolic protection with intracoronary thrombectomy devices without a distal protection component may be useful in the setting of acute MI.[33] A few randomized trials have shown some advantage of these devices in acute coronary syndromes (**Table 1**).[34-38] In one large randomized trial, the AIMI trial, the patients treated with the AngioJet showed larger infarct sizes as compared with control patients.[39] The use of an aspiration catheter may be beneficial for embolic protection.[36,40,41] In the REMEDIA trial, manual thrombus aspiration with the Diver CE in patients with acute ST elevation MI resulted in improved angiographic and ECG myocardial reperfusion rates (**Table 1**).[42]

The 6F Export Aspiration Catheter (Medtronic Corporation, Santa Rosa, California) may be practical in the setting of primary PCI because its size allows access to the lesion over a routine wire and maneuvering into tortuous and distal coronary arteries. In this trial, we intend to evaluate the usefulness of this aspiration catheter in the improvement of myocardial perfusion during primary PCI in patients with acute ST-elevation MI. If thrombus aspiration significantly improves myocardial perfusion, it will lend support to the use of this treatment as part of the standard approach in patients with acute MI.

Table 1. Randomized trials in protection of distal embolization in ACS

Year of publication	First author	Procedure	Device	Category	No. of pts	C	D	Successful n (%)	TIMI 3 C/D (%)	cTFC C/D (mean)	MBG C/D (%)	ST resolution C/D (%)
2002	Beran[34]	Thrombectomy	X-sizer	ACS	66	31	30	31 (91)	84/90	25/18*	1.6/1.8†	52/83*
2003	Napadano[35]	Thrombectomy	X-sizer	ACS	92	46	46	40 (87)	96/94	NA	37/72*	52/83*
2005	Lefèvre[38]	Thrombectomy	X-sizer	STEMI	201	101	100	87 (87)	89/96	25/23	30/31	53/68*
2004	Antoniucci[37]	Thrombectomy	AngioJet	STEMI	100	50	50	48 (96)	NA	23/18*	NA	72/90*
2005	Ali[39]	Thrombectomy	AngioJet	STEMI	480	240	240	228 (95)	97/92	29/32	37/31	68/60
2004	Dudek[36]	Thrombectomy	RESCUE	STEMI	72	32	40	35 (87)	86/85	19/21	38/54	25/68
2005	Burzotta[42]	Thrombectomy	DiverCE	STEMI	100	50	49	44 (88)	NA	26/23	68/45‡	58/37
2005	Stone[32]	Distal Protection	GuardWire	STEMI	501	249	252	193 (79)	89/92	20/18	53/61	62/63
2005	Gick[31]	Distal Protection	FilterWireEx	AMI	200	100	100	95 (95)	93/93	NA	67/64*‡	NA

Category, Patients included in study, that is, patients with ST elevation myocardial infarction (STEMI), acute coronary syndrome (ACS), and acute myocardial infarction (AMI); C, control group; D, device group; No. of pts, number of patients included in study; Successful, number of interventions in the treatment group that were successful according to definition in respective trials; TIMI 3, Thrombolysis in Myocardial Infarction flow 3 after the procedure; cTFC, corrected TIMI frame count at the end of the procedure; MBG, myocardial blush grade 3 after the procedure; ST resolution, percentage of patients with ST-segment elevation resolution after the procedure according to definition in respective trials; NA, not available. *P < .05.† Mean MBG.‡ MBG 2/3.

Study objectives

The primary objective is to evaluate whether thrombus aspiration compared with balloon inflation before stent implantation of the infarct-related artery results in improved myocardial perfusion in the treatment of patients with acute MI. We hypothesize that aspiration will reduce the occurrence of MBG of <2 by a quarter (from 30% in the control group to 22.5% in the intervention group). Secondary objectives include investigating whether thrombus aspiration improves enzymatic infarct size, ST-segment elevation resolution and the incidence of persistent ST-segment elevation, postprocedural distal embolization, and Major Adverse Cardiac Events at 30 days and 1 year.

We will examine our primary and secondary objectives for the total population and according to two main prespecified subgroups defined by angiographic evidence of thrombus on the initial angiogram and successful thrombus aspiration.

Study design

This is a single-center, prospective, randomized, open trial with blinded evaluation of end points. Patient recruitment will start in 2005 and inclusion continues until 1080 patients with an acute MI have been randomized. Patients will be randomly assigned to one of two arms: treatment with intracoronary thrombus aspiration device followed by stenting, or balloon angioplasty followed by stenting. The study has been approved by the institutional review board. The study will take place at the University Medical Center of Groningen, a center with experience in primary PCI of patients with acute MI and with access to emergency cardiac surgery.

Patient selection and randomization

All patients with acute MI and candidates for primary PCI admitted to a single university center are considered for participation in the study.

Inclusion and exclusion criteria

The inclusion criterion is a diagnosis of acute MI defined by chest pain suggestive for myocardial ischemia for at least 30 minutes, with a time from onset of symptoms of <12 hours before hospital admission, and an ECG with ST-segment elevation of >0.1 mV in ≥2 leads. Exclusion criteria are rescue PCI after thrombolytic therapy, inability to obtain informed consent, and known existence of a life-threatening disease with a life expectancy of <6 months.

Randomization

After informed consent, eligible patients are randomized 1:1 to a strategy of thrombus aspiration followed by stenting of the infarct-related artery or to balloon angioplasty followed by stenting of the infarct-related artery. Randomization will be performed at the catheterization laboratory before coronary angiography, by means of a computerized voice response system. The invasive cardiologist contacts the randomization center and states his or her own code and the date of birth of the patient. The computer program is operating in blocks of 3 to 6 patients and is stratified by the invasive cardiologist to achieve a balanced allocation for therapy as well as for the cardiologist performing the procedure. The randomization computer discloses the treatment assignment of the patient and records the date and time of randomization. The cardiologist records the randomization outcome on the dedicated Case Report Form.

Treatment

Medication

Before PCI, the patient is treated with the following medical therapy:

- aspirin (a bolus of 300 mg if not already being taken, followed by 80-100 mg/24 hours);
- intravenous heparin/low-molecular-weight heparin;
- clopidogrel (600 mg followed by 75 mg/24 hours);
- glycoprotein IIb/IIIa inhibitor: abciximab, unless contraindicated.

Additional standard treatment consists of nitroglycerin intravenously. During PCI, 5000 to 10,000 IU heparin is administered guided by ACT measurements. In patients with atrial fibrillation, a large dyskinetic area of the left ventricle, and in immobile patients, low-molecular-weight heparin is given for 1 to 3 days after sheath removal. Standard therapies after PCI include aspirin 80 mg, clopidogrel 75 mg, ß-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, according to current international guidelines.[14]

Study device

The Export Aspiration Catheter (Medtronic Corporation) is a 6F thrombus aspiration catheter. The total usable length is 145 cm. The catheter has an oblique aspiration tip design, with an aspiration lumen of 0.041 in and a crossing profile of 0.068 in. A radiopaque marker is sited 2 mm from the distal tip. Suction is provided by hand with a lockable 20-mL syringe, which allows for a suction rate of 1 mL/s.

Clinical data and definitions

Baseline demographic and clinical characteristics

Baseline characteristics that will be collected include age, sex, time of symptom onset, time of admission, history of coronary artery bypass grafting, previous PCI, stroke and MI, positive family history for cardiovascular diseases, existence of diabetes mellitus, hypertension, smoking status, heart rate, systolic and diastolic blood pressure, weight, length, and the findings of cardiac and pulmonary auscultation. Major Adverse Cardiac Events are defined as the combination of death, reinfarction, and ischemia driven target vessel revascularization and will be recorded at 30 days and at 1 year. Follow-up information will be obtained from hospital records as well as by telephone interviews with the patient.

Coronary angiography

A coronary angiogram will be obtained at baseline, that is, before the PCI procedure, and after the procedure, i.e., after stent placement. Intravenously administered nitroglycerine will be given after the procedure and before the last angiogram in all patients. TIMI flow grades will be estimated as previously described.[20] The evaluation of MBG will be performed as described by van 't Hof et al[7]: 0, no myocardial blush; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. Persisting myocardial blush ("staining") suggests leakage

of contrast medium into the extravascular space and is graded 0. Distal embolization will be considered to have occurred if new circumscribed filling defects and/or abrupt cutoff of the vessel distal to the target lesion appears.[8] Thrombus is assessed according to the criteria summarized by Mabin et al.[43] These criteria include the presence of an intraluminal central filling defect or lucency surrounded by contrast material that is seen in multiple projections; the absence of calcium within the defect; and persistence of contrast material within the lumen. TIMI flow grade, the MBG, distal embolization, and thrombus load will be evaluated at baseline and after the PCI procedure.

The coronary angiograms will be analyzed by an independent core laboratory. Evaluations will be performed on spliced films without information regarding device use during the procedure.

Electrocardiography

A standard 12-lead ECG is acquired at the time of presentation, at 30 to 60 minutes, and at 3-6-9-12 hours after the end of procedure. Mean time interval between pre- and post-intervention will be registered. The magnitude of ST-segment elevation is measured 60 milliseconds from J point. ST-segment score is calculated as the sum of ST-segment elevation >0.1 mV for leads V_1 through V_6 and I, II, and aVL in anterior infarction and I, II, aVF, V_5, and V_6 in nonanterior infarction. The first post-intervention ECG will be classified by comparison of the ST segments with those of the ECG at presentation. The percentage ST-segment elevation resolution will be categorized as complete (>70%), partial (30%-70%), or absent (<30%).[6] Also, an analysis of persistent ST-segment elevation will be performed. Two observers blinded to study randomization and angiographic findings will analyze all ECG recordings.

Infarct size

Infarct size will be estimated by serial measurements of cardiac markers in serum, including creatinine kinase (CK), MB fraction of CK (CK-MB), lactate dehydrogenase (LDH), and troponin I. The first measurement is taken as soon as possible after admission. Thereafter, frequent marker determinations are performed according to a schedule that calls for 4 to 6 measurements in the first 24 to 36 hours. To accommodate the problem in practice that exact predefined times for blood sampling are not always followed, the actual times of sampling, expressed as minutes after the moment of randomization, are recorded. To allow optimal comparison of the time courses of marker levels and to best approximate the area under the marker level curves, we use a dedicated algorithm.[26,44] Per patient, the algorithm interpolates the marker levels based on the precise time of measurement. Next, it determines for each of the predefined intervals if an actual measurement has been performed in that interval. Marker levels are determined on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry recommendation, at 30°C. A peak marker release above the 75% percentile (ie, the highest quartile) is defined as high enzyme release. Time to peak release is also determined.

Histopathologic analysis

All aspirated material will be processed for histological analysis. After thrombosuction, the aspirated material is placed in formalin and fixed for 24 hours. Cell blocks for

paraffin embedding will be prepared. Histological sections will be cut and stained with hematoxylin-eosin for examination with a light microscope. To optimize visualization of smooth muscle cells and macrophage foam cells, additional immunostaining will be performed when applicable.

End point assessment

Primary end point

The primary end point is defined as the frequency of an MBG of <2. We expect this to be 30% in the control group, based on previously published data.[7,22] We hypothesize a reduction of this primary end point to ≤22.5% in the experimental group.

Secondary end points

Secondary end points are as follows:

- postprocedural distal embolization;
- postprocedural TIMI flow;
- ST-segment elevation resolution and persistent ST-segment elevation at 30 to 60 minutes after the procedure;
- infarct size as measured by cardiac enzymatic markers (CK, CK-MB, LDH) and troponin I;
- Major Adverse Cardiac Events at 30 days and 1 year.

Subgroups

The primary and secondary end points will be analyzed in prespecified subgroups defined by the following:

1. angiographic evidence of thrombus on the initial pre-PCI coronary angiogram;
2. successful thrombus aspiration defined as the presence of macroscopic or microscopic thrombus in the aspirate confirmed by histopathologic examination.

Additional subgroup analyses will be performed according to age, sex, preinfarction angina, time from symptom onset, infarct-related segment and vessel, and TIMI flow at baseline.

Statistical analysis

Statistical methods

Analyses will be performed according to the intention-to-treat principle for the whole population and in the specified subgroups. An analysis per protocol will also be performed. Differences between group means will be assessed with the 2-tailed Student t test. χ^2 Analysis or Fisher exact test is used to test differences between proportions. Survival will be calculated by the Kaplan-Meier product-limit method. The Mantel-Cox (or log-rank) test will be used to evaluate differences in survival between the two treatment groups. The Cox proportional hazards regression model will be used to calculate relative risks and to adjust for differences in baseline characteristics. Statistical significance is considered as a 2-tailed $P < 0.05$. The Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL) version 11.0.1 will be used for all statistical analysis.

Calculation of sample size
A sample size to detect differences between treatment groups has been calculated by a logistic regression binary response variable on a binary independent variable. Based on the estimated reduction in the primary end point, we have selected a target sample size of 1080 subjects. This sample size will provide 80% power at 0.05 significance level to detect anticipated differences and will offer some protection if accrual is lower, losses are greater, or effect sizes are smaller than anticipated.

Interim analysis
We will perform an interim analysis using Snapinn's method after the inclusion of approximately 200 patients.[45] This method describes a conditional probability procedure that attempts to maintain the overall significance level by balancing the probabilities of false early rejection and false early acceptance. At the time of the interim analysis, we will consider to include more patients when the incidence of the primary end point is <25% in both groups combined.

Study records

For each randomized patient, a Case Report Form (CRF) for data recording is provided. Case Report Forms are numbered and should be used in ascending numerical order. All data will be recorded in a dedicated database.

The investigator will ensure that patient anonymity is maintained. On CRFs or other documents, patients are not identified by their names but by the CRF code. The investigator will keep a separate log of patient codes, names, and addresses.

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Chapter 3.2

Thrombus aspiration during primary percutaneous coronary intervention

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ABSTRACT

Background
Primary percutaneous coronary intervention (PCI) is effective in opening the infarct-related artery in patients with myocardial infarction with ST-segment elevation. However, the embolization of atherothrombotic debris induces microvascular obstruction and diminishes myocardial reperfusion.

Methods
We performed a randomized trial assessing whether manual aspiration was superior to conventional treatment during primary PCI. A total of 1071 patients were randomly assigned to the thrombus-aspiration group or the conventional-PCI group before undergoing coronary angiography. Aspiration was considered to be successful if there was histopathological evidence of atherothrombotic material. We assessed angiographic and electrocardiographic signs of myocardial reperfusion, as well as clinical outcome. The primary end point was a myocardial blush grade of 0 or 1 (defined as absent or minimal myocardial reperfusion, respectively).

Results
A myocardial blush grade of 0 or 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional-PCI group ($P<0.001$). Complete resolution of ST-segment elevation occurred in 56.6% and 44.2% of patients, respectively ($P<0.001$). The benefit did not show heterogeneity among the baseline levels of the prespecified covariates. At 30 days, the rate of death in patients with a myocardial blush grade of 0 or 1, 2, and 3 was 5.2%, 2.9%, and 1.0%, respectively ($P=0.003$), and the rate of adverse events was 14.1%, 8.8%, and 4.2%, respectively ($P<0.001$). Histopathological examination confirmed successful aspiration in 72.9% of patients.

Conclusions
Thrombus aspiration is applicable in a large majority of patients with myocardial infarction with ST-segment elevation, and it results in better reperfusion and clinical outcomes than conventional PCI, irrespective of clinical and angiographic characteristics at baseline. (Current Controlled Trials number, ISRCTN16716833.)

INTRODUCTION

Acute myocardial infarction with ST-segment elevation is caused by the rupture or erosion of an atherosclerotic plaque, initiating intraluminal thrombosis resulting in partial or complete occlusion of a coronary artery.[1-3] Primary percutaneous coronary intervention (PCI) is the preferred treatment for myocardial infarction with ST-segment elevation and is effective in opening the infarct-related artery.[4-6] However, microvascular obstruction with diminished myocardial perfusion occurs in a large proportion of patients with a patent epicardial vessel after primary PCI, and this event is associated with an increased infarct size, reduced recovery of ventricular function, and increased mortality.[7-11]

Microvascular obstruction is related to the embolization of plaque or thrombotic material downstream in the infarct-related artery.[12,13] Embolization can occur spontaneously or by means of mechanical fragmentation during PCI.[12-15] One coronary angiographic technique used to assess perfusion in the myocardial tissue is myocardial blush grading.[7,9] In clinical practice, electrocardiographic (ECG) analysis of the degree of resolution of ST-segment elevation after PCI is often used.[8,10]

The high frequency of suboptimal myocardial reperfusion after primary PCI has resulted in the development of various devices to protect the microcirculation.[16-24] A 6-French–compatible manual-aspiration catheter is practical for this purpose, since it is relatively flexible and nontraumatic in use. Many previous trials have used findings on coronary angiography as selection criteria and have not performed a systematic analysis of the material retrieved during aspiration. We therefore evaluated the use of a manual-aspiration catheter to improve myocardial perfusion during primary PCI in patients with myocardial infarction with ST-segment elevation. Our patients were randomly assigned to a treatment group before coronary angiography was performed and therefore without consideration of angiographic selection criteria (such as the presence of a visible thrombus on angiography), and we conducted a histopathological analysis of the retrieved material as an additional evaluation of procedural efficacy.[25]

METHODS

Study Design and Population

The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) was a single-center, prospective, randomized, open trial involving the blinded evaluation of end points.[25] The institutional review board of the University Medical Center Groningen (Groningen, the Netherlands) approved the study. All patients provided written informed consent.

All consecutive patients presenting to the University Medical Center Groningen with a possible myocardial infarction with ST-segment elevation between January 2005 and December 2006 were considered eligible for participation. The inclusion criteria were symptoms suggesting acute myocardial ischemia lasting more than 30 minutes, the onset of symptoms less than 12 hours previously, and ST-segment elevation of more than 0.1 mV in two or more leads on the ECG. The exclusion criteria were the performance of a rescue PCI after thrombolysis, the known existence of a disease resulting in a life expectancy of less than 6 months, and the lack of informed consent.

Randomization and Treatment

Before diagnostic angiography was performed, patients were randomly assigned to undergo thrombus aspiration during PCI or conventional PCI, with the use of a computerized voice-response system. The randomization code was developed by means of a number generator used to select randomly permuted blocks of three to six patients, which were then stratified by the interventional cardiologist to achieve a balanced group assignment with regard to both the treatment group and the cardiologist performing the procedure.[25]

For all patients, the first procedural step was the passing of a floppy, steerable guidewire through the target lesion. In patients in the conventional-PCI group, this step was followed by balloon dilation to establish antegrade flow. In patients in the thrombus-aspiration group, this step was followed by the advancing of the 6-French Export Aspiration Catheter (Medtronic; crossing profile, 0.068 in.) into the target coronary segment during continuous aspiration; when necessary for stent delivery, balloon dilation was performed before stenting. In all patients, after the restoration of antegrade flow, intracoronary nitrates were given to ensure maximal epicardial vasodilation, in order to determine the size and length of the stent and to facilitate stent placement. All placed stents were bare-metal stents.

Pharmacologic treatment before PCI included the administration of aspirin (a loading dose of 500 mg), heparin (5000 IU), and clopidogrel (a loading dose of 600 mg). Patients also received the glycoprotein IIb/IIIa inhibitor abciximab, with the dose based on body weight, unless contraindicated, and additional heparin, with the dose based on the activated clotting time. Standard therapies after PCI included aspirin, clopidogrel, beta-blockers, lipid-lowering agents, and angiotensin-converting–enzyme inhibitors or angiotensin-II–receptor blockers, according to current guidelines.[6]

End Points, Assessment of Outcomes, and Definitions

The primary end point was the postprocedural frequency of a myocardial blush grade of 0 or 1 as detailed below.[25] Secondary end points were the postprocedural frequencies of a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 3, complete resolution of ST-segment elevation, the absence of persistent ST-segment deviation, target-vessel revascularization, reinfarction, death, and the combination of major adverse cardiac events by 30 days after randomization.

Coronary angiography was performed before and after the PCI. TIMI flow grades were assessed as previously described.[26] Myocardial blush grades were assigned as previously described by Van 't Hof et al.[7]: 0, no myocardial blush; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3, normal myocardial blush or contrast density, similar to that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. Persistent myocardial blush suggests leakage of contrast medium into the extravascular space and is given a grade of 0. Angiographic evidence of a thrombus was assessed according to the criteria summarized by Mabin et al.[27] Data from the coronary angiogram were analyzed at an independent core laboratory (Cordinamo).[25]

A 12-lead ECG was acquired at presentation and 30 to 60 minutes after PCI, and the ST-segments on the postprocedural ECG were compared with those on the ECG

at presentation. The degree of resolution of ST-segment elevation was categorized as complete (>70%), partial (30 to 70%), or none (<30%).[8] Persistent ST-segment deviation, defined as the sum of the ST-segment depression and the ST-segment elevation, was categorized as less than 2 mm, 2 to 10 mm, and more than 10 mm. The presence or absence of pathologic Q waves was also recorded.

Filtered, aspirated material was fixed in formalin for 24 hours. Histologic sections were cut and stained with hematoxylin and eosin for examination with a light microscope (magnification, ×100). Immunostaining was performed to optimize the visualization of smooth-muscle cells and macrophage foam cells. Aspiration was defined as effective or not effective on the basis of the presence of atherothrombotic material in the aspirate samples. The material was classified as from a thrombus containing only platelets, a thrombus with an erythrocyte component, or a thrombus with plaque, as well as according to length: small (<0.5 mm), moderate (0.5 to 2 mm), or large (>2 mm).

Follow-up data at 30 days were obtained from hospital records and through telephone interviews. Major bleeding was defined as symptomatic bleeding in a critical area or organ, bleeding causing a decrease in hemoglobin level of 2.0 mmol or more per liter, or bleeding that led to blood transfusion. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of the levels of cardiac markers to at least twice the upper limit of the normal range. Target-vessel revascularization was defined as ischemia-driven revascularization of the infarct-related artery, performed by means of PCI or surgery (e.g., coronary-artery bypass grafting) during the follow-up period. A major adverse cardiac event was defined as death, reinfarction, or target-vessel revascularization.

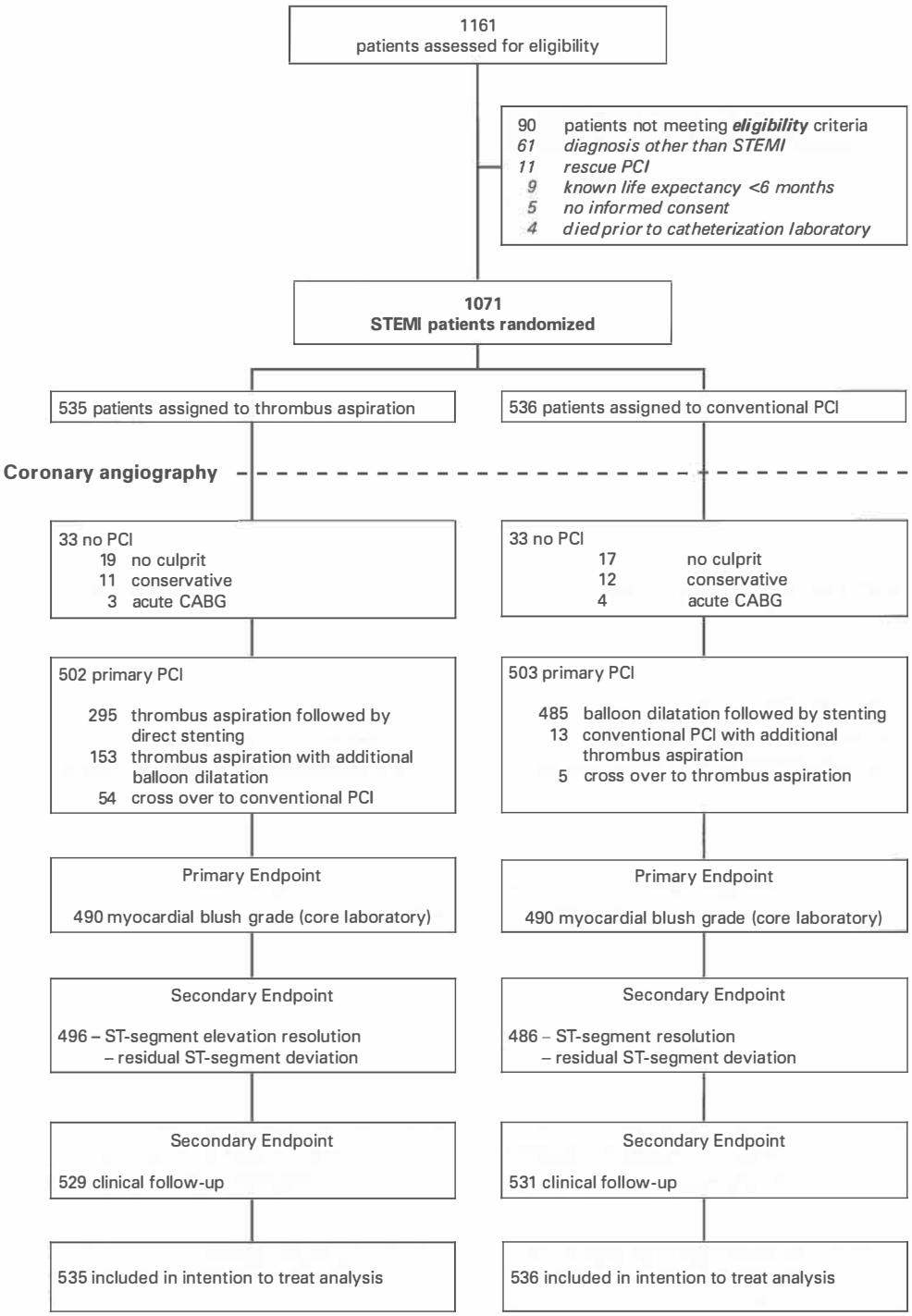
Statistical Analysis

We estimated that we would have to enroll 1080 patients to achieve a power of 80%, with a two-sided significance level of 0.05, to detect a 25% reduction in the primary end point in patients who underwent thrombus aspiration as compared with those who underwent conventional PCI, assuming a 30% rate of myocardial blush grade of 0 or 1 in the conventional-PCI group.[25] The study committee (see the Appendix) performed a planned interim analysis after 300 patients had been enrolled. The stopping limit was a difference of more than 25% in the primary end point between the two groups, with a P value of less than 0.01.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with the use of a two-tailed Student's t-test. Prespecified subgroup analyses were performed by means of logistic-regression analyses with formal tests for interaction.[28] We analyzed data for all patients who were randomly assigned to a treatment group and for whom outcome data were available. Exploratory analyses of the association between the surrogate and clinical end points were performed by means of logistic-regression analysis. Two-sided significance tests were used. P values of less than 0.05 were considered to indicate statistical significance. SPSS software, version 12.0.1, was used in all statistical analyses.

Data management and statistical analyses were performed by staff of the data coordinating center (see the Appendix) and the principal investigator, who vouches for the accuracy and completeness of the data.

Figure 1. Enrollment, group assignments, and follow-up of patients



Conservative treatment was treatment that did not include percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). STEMI=ST-segment elevation myocardial infarction.

RESULTS

Study Population

During the study period, 1161 patients were considered for inclusion, and 1071 patients were enrolled according to the eligibility criteria (**Figure 1**). Before coronary angiography, patients were randomly assigned to undergo either thrombus aspiration during PCI (535 patients) or conventional PCI (536 patients). The baseline clinical and angiographic characteristics were similar in the two groups (**Table 1**).

Procedural Data

On the basis of the initial angiographic findings, 33 patients (approximately 6%) in each group did not undergo PCI. In the thrombus-aspiration group, aspiration and direct stent implantation were performed in 295 patients (55.1%), balloon dilation was performed before stent implantation in 153 patients (28.6%), and conventional PCI was performed in 54 patients (10.1%) in whom the operator judged the target artery to be too small or too tortuous to permit use of the aspiration catheter (**Figure 1**).

Data about the procedures and intraprocedural complications are shown in **Table 1.** None of the complications were thought to be related to the aspiration device used. There were no intraprocedural deaths or strokes.

Myocardial Reperfusion

The postprocedural myocardial blush grade could be assessed in 980 (490 in each group) of the 1005 patients (97.5%) who underwent PCI. A myocardial blush grade of 0 or 1 occurred in 84 of the 490 patients (17.1%) in the thrombus-aspiration group and in 129 of the 490 patients (26.3%) in the conventional-PCI group (risk ratio, 0.65; 95% confidence interval [CI], 0.51 to 0.83; P<0.001) (**Figure 2a**).

The ECGs obtained at baseline and after the procedure were analyzed in 982 of the 1005 patients (97.7%) who underwent PCI. The median time from treatment to the postprocedural ECG was 44 minutes (interquartile range, 25 to 63) in the thrombus-aspiration group and 43 minutes (interquartile range, 25 to 61) in the conventional-PCI group (P=0.40). Complete ST-segment resolution occurred in 275 of the 486 patients (56.6%) in the thrombus-aspiration group and 219 of the 496 patients (44.2%) in the conventional-PCI group (risk ratio, 1.28; 95% CI, 1.13 to 1.45; P<0.001) (**Figure 2b**). Similarly, 258 of the 486 patients (53.1%) in the thrombus-aspiration group had no persistent ST-segment deviation, as compared with 201 of the 496 patients (40.5%) in the conventional-PCI group (risk ratio, 1.31; 95% CI, 1.14 to 1.50; P<0.001) (**Figure 2c**). In the thrombus-aspiration group, 119 of 486 patients (24.5%) did not have pathologic Q waves on the ECG, as compared with 79 of 496 patients (15.9%) in the conventional-PCI group (risk ratio, 1.54; 95% CI, 1.19 to 1.99; P=0.001).

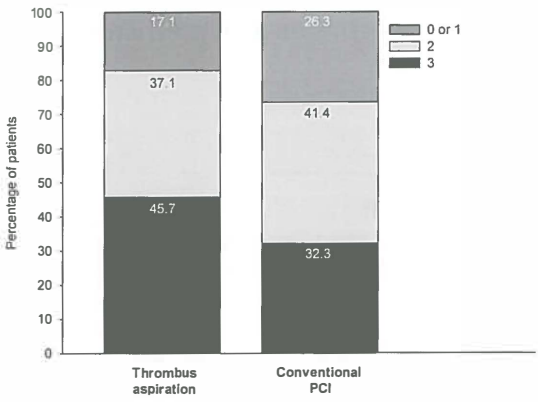
Table 1. Baseline demographic, clinical and angiographic characteristics

	thrombus aspiration (N=535)		conventional PCI (N=536)		p-value (2-tailed)
Baseline demographic and clinical data					
Age, years, mean (± SD)	63	(13)	63	(13)	0.36
Gender, male, N (%)	363/535	(67.9)	392/536	(73.1)	0.06
History, N (%)					
hypertension	171/517	(33.1)	195/526	(37.1)	0.18
diabetes mellitus	56/530	(10.6)	67/532	(12.6)	0.30
hypercholesterolemia	115/485	(23.7)	130/480	(27.1)	0.23
myocardial infarction	50/528	(9.5)	57/533	(10.7)	0.51
PCI	39/526	(7.4)	38/531	(7.2)	0.87
CABG	17/529	(3.2)	22/533	(4.1)	0.43
cerebrovascular disease	17/517	(3.3)	21/522	(4.0)	0.53
family	235/509	(46.2)	229/514	(44.6)	0.58
current smoking, N (%)	213/463	(46.0)	225/469	(48.0)	0.57
preinfarction angina	258/483	(53.4)	233/476	(48.9)	0.17
door-to-balloon time*, min, median (IQR)	28	(14-42)	26	(12-40)	0.92
total ischemic time, min, median (IQR)	190	(110-270)	185	(107-263)	0.61
body mass index	27	(4)	27	(4)	0.69
systolic blood pressure, mean (SD)	128	(26)	130	(26)	0.34
diastolic blood pressure, mean (SD)	74	(15)	75	(16)	0.65
pulse pressure, mean (SD)	78	(18)	78	(19)	0.98
Baseline angiographic data					
diseased vessels, N (%)	**(N=533)**		**(N=534)**		0.84
0	13/533	(2.4)	10/534	(1.9)	
1	166/533	(31.1)	157/534	(29.4)	
2	175/533	(32.8)	174/534	(32.6)	
3	178/533	(33.4)	193/534	(36.1)	
infarct related vessel, N (%)	**(N=515)**		**(N=517)**		0.62
left anterior descending artery	221/515	(42.9)	223/517	(43.1)	
left circumflex artery	93/515	(18.1)	79/517	(15.3)	
right coronary artery	189/515	(36.7)	204/517	(39.5)	
other	12/515	(2.3)	11/517	(2.1)	
TIMI flow, N (%)	**(N=526)**		**(N=531)**		0.23
0/1	288/526	(54.7)	316/531	(59.5)	
2	102/526	(19.4)	85/531	(16.0)	
3	136/526	(25.9)	130/531	(24.5)	
thrombus, N (%)	**(N=519)**		**(N=529)**		0.14
	252/519	(48.6)	233/529	(44.0)	

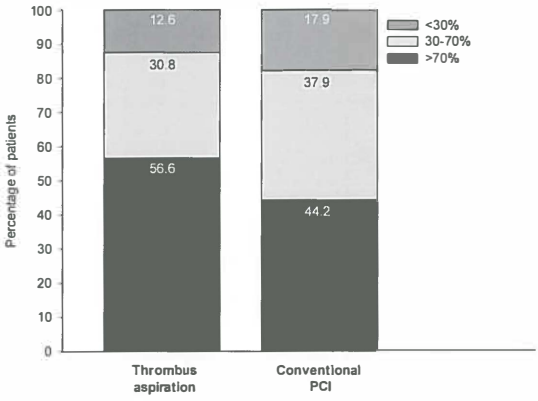
N = number, SD = standard deviation, IQR = interquartile range, PCI = percutaneous coronary intervention, CABG = coronary bypass grafting, min = minutes, TIMI = Thrombolysis In Myocardial Infraction, * door-to balloon time = door-to-first device time, i.e. time from entering the hospital unit to first balloon inflation or first aspiration

Figure 2. Myocardial reperfusion data on angiography and electrocardiography, according to treatment groups

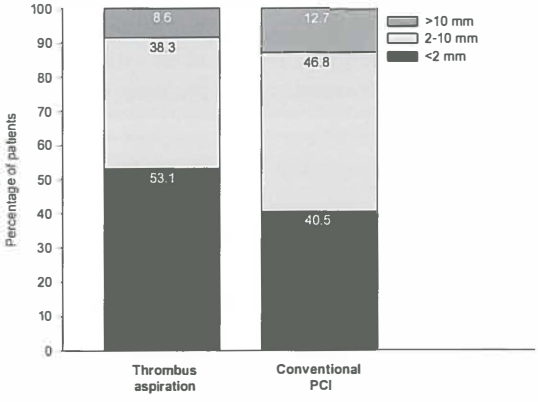
A Myocardial blush grade after the PCI procedure



B Resolution of ST-segment elevation



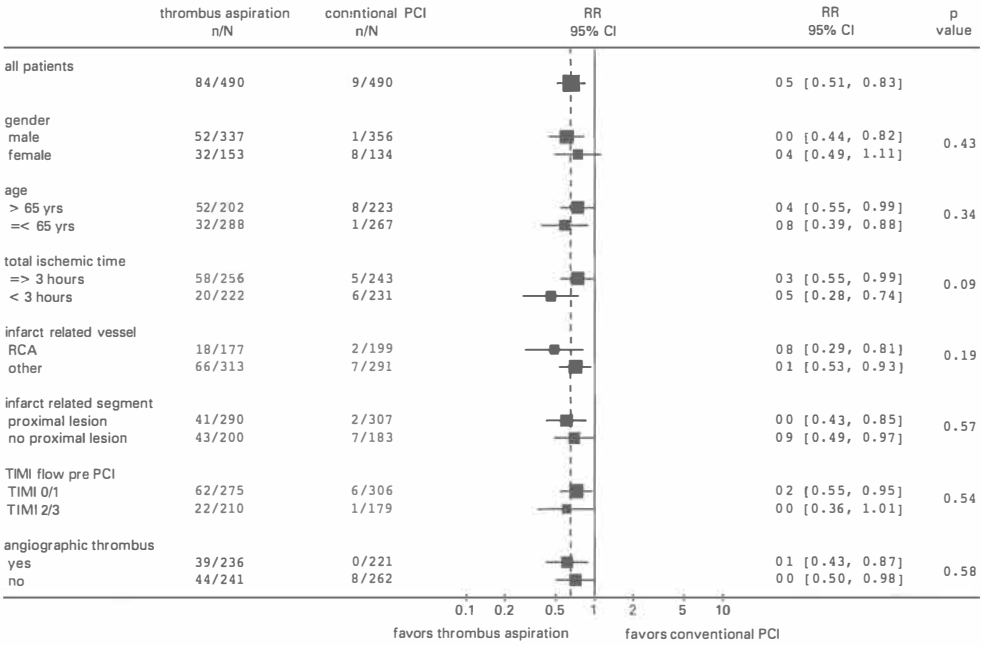
C Persistent ST-segment deviation



PCI=percutaneous coronary intervention.

There was no evidence that the benefit with regard to the primary end point was heterogeneous among the baseline levels of the prespecified covariates. There were no significant interactions for any subgroups (**Figure 3**).

Figure 3. Risk ratios for the primary end point, according to prespecified clinical or angiographic subgroup



Data are derived reported for the patients who had clinical and coronary angiographic data at baseline. RR=risk ratio, CI=confidence interval. PCI= percutaneous coronary intervention, RCA=right coronary artery, TIMI=thrombolysis in myocardial infarction.

Histopathological Features

Table 2 shows the rate of retrieval and the histopathological characteristics and size of the aspirate, according to initial angiographic findings in the patients who underwent aspiration. Histopathological examination was performed in 454 patients, which in 331 patients (72.9%) showed atherothrombotic material.

Table 2. Histopathologic characteristics of coronary artery thrombi from initial findings on coronary angiography in patients undergoing thrombus aspiration

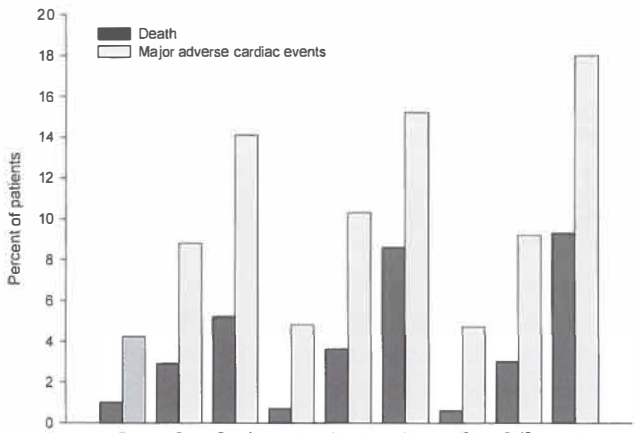
		total	infarct related vessel				TIMI flow		thrombus CAG	
			RCA	LCA	Cx	other	0/1	2/3	yes	no
aspiration group	patients, N	454	171	201	75	7	265	185	225	217
retrieved	material, N (%)	331 (72.9)	140 (81.9)	138 (68.7)	49 (65.3)	4 (57.1)	201 (75.8)	127 (68.6)	173 (76.9)	146 (67.3)
platelet	total, N (%)	224 (67.7)	88	101	33	2	120	101	116	100
	small, %	42.0	42.0	39.6	51.5	-	39.2	45.6	36.2	49.0
	moderate, %	52.6	54.6	54.5	39.4	100.0	56.6	47.5	60.3	44.0
	large, %	5.4	3.4	5.9	9.1	-	4.2	6.9	3.5	7.0
erythrocyte	total, N (%)	50 (15.1)	26	14	8	2	45	5	32	15
	small, %	-	-	-	-	-	-	-	-	-
	moderate, %	26.0	19.2	42.9	25.0	-	28.9	-	25.0	33.3
	large, %	74.0	80.8	57.1	75.0	100.0	71.1	100.0	75.0	66.7
plaque	total, N (%)	57 (17.2)	26	23	8	-	36	21	25	31
	small, %	7.0	7.7	8.7	-	-	8.3	4.8	8.0	6.4
	moderate, %	71.9	73.1	65.2	87.5	-	66.7	81.0	68.0	74.2
	arge, %	21.1	19.2	26.1	12.5	-	25.0	14.2	24.0	19.4

The 454 patients undergoing thrombus aspiration were 448 patients in the thrombus-aspiration group and 6 patients in the conventional percutaneous-coronary-intervention group. Data are reported for the patients who had coronary angiographic data at baseline. "Platelet" was defined as a thrombus composed only of platelets, "erythrocyte" as a thrombus with bands of erythrocytes, and "plaque" as a thrombus with any fragment of vessel wall, cholesterol crystals, inflammatory cells, or collagen tissue. N=number, Cx=left circumflex artery, LAD=left anterior descending artery, and RCA=right coronary artery, Small= < 0.05 mm, moderate= 0.5 – 2.0 mm, large= > 2.0mm. All millimeter measurements refer to length. TIMI=thrombolysis in myocardial infarction.

Clinical Outcome at 30 Days

In the thrombus-aspiration group and the conventional-PCI group, there was major bleeding in 20 of 529 patients (3.8%) and 18 of 531 patients (3.4%), respectively (risk ratio, 1.11; 95% CI, 0.60 to 2.08; P=0.11); death in 11 of 529 (2.1%) and 21 of 531 (4.0%) (risk ratio, 0.52; 95% CI, 0.26 to 1.07; P=0.07); reinfarction in 4 of 529 (0.8%) and 10 of 531 (1.9%) (risk ratio, 0.40; 95% CI, 0.13 to 1.27; P=0.11); target-vessel revascularization in 24 of 529 (4.5%) and 31 of 531 (5.8%) (risk ratio, 0.77; 95% CI, 0.46 to 1.30; P=0.34); and major adverse cardiac events at 30 days in 36 of 529 (6.8%) and 50 of 531 (9.4%) (risk ratio, 0.72; 95% CI, 0.48 to 1.08; P=0.12). The rates of death and major adverse cardiac events at 30 days were both significantly related to myocardial blush grade, resolution of ST-segment elevation, and ST-segment deviation (P=0.003 for the association between death and myocardial blush grade; P<0.001 for all other associations) (**Figure 4**).

Figure 4. Rates of death and major adverse cardiac events, according to myocardial blush grade and ST-segment variables



Rate of death (%)	1.0	2.9	5.2	0.7	3.6	8.6	0.6	3.0	9.3
Rate of major adverse cardiac events (%)	4.2	8.8	14.1	4.8	10.3	15.2	4.7	9.2	18.0

Rates are shown for the 968 patients for whom the data were available. P = 0.003 for the association between myocardial blush grade and death. P<0.001 for all other associations: that between myocardial blush grade and major adverse cardiac events, between ST-segment resolution and death, between ST-segment resolution and major adverse cardiac events, between persistent ST-segment deviation and death, and between persistent ST-segment deviation and major adverse cardiac events.

DISCUSSION

The results of our randomized trial show that effective manual aspiration of atherothrombotic material is feasible in a large majority of patients presenting with myocardial infarction with ST-segment elevation. As compared with balloon angioplasty as an initial step in primary PCI, aspiration before stenting results in improved myocardial reperfusion, documented by a clear improvement in the myocardial blush

grade, increased resolution of ST-segment elevation, and reduced residual ST-segment deviation. This beneficial effect of aspiration was consistently present in all patients, irrespective of baseline clinical or angiographic characteristics such as age, sex, infarct-related coronary artery, preprocedural TIMI flow, or visible thrombus on the angiogram. Atherothrombotic material was retrieved in 73% of the patients who underwent thrombus aspiration, and the main constituent of the retrieved material was platelets.

Our data confirm the prognostic value of the myocardial blush grade and degree of resolution of the ST-segment elevation after reperfusion therapy, since these variables were strongly related to the 30-day rates of death and major adverse cardiac events.[7,8] The trends we found for these rates were expected from the differences between the two groups in variables reflecting myocardial reperfusion. Since a larger proportion of patients in the thrombus-aspiration group than in the conventional-PCI group did not have pathologic Q waves on the postprocedural ECG, this benefit may be mediated, at least in part, by myocardial salvage.

The clinical importance of embolization of atherothrombotic material from unstable plaques in patients with myocardial infarction with ST-segment elevation has been recognized,[12,13] and embolic protection during PCI in such patients has been tested with various devices in small or medium-sized trials, with diverse results.[16-24] This variation in results may be in part related to the device used, since trials involving manual-aspiration devices have all shown favorable effects of aspiration on myocardial-perfusion variables.[20-22] Most of the previous trials have enrolled patients who were selected on the basis of angiographic features,[16-19,21-24] since it was assumed that patients with a large thrombotic burden are identified on angiography and will particularly benefit from the treatment. Our data show that angiographic variables such as TIMI flow or the presence of a visible thrombus are not predictors of patients in whom aspiration will be effective. Our findings therefore support the concept that the presence of a thrombus plays an important role in the pathophysiological characteristics of most patients with myocardial infarction with ST-segment elevation.

We powered our trial on the assumption of a 25% reduction in the frequency of myocardial blush grade of 0 or 1 in the thrombus-aspiration group. Our data confirm a benefit of this magnitude, albeit with a somewhat lower incidence of myocardial blush grade of 0 or 1 in the conventional-PCI group than expected: 26.4% instead of 30%. This may be explained by the administration of pharmacotherapy immediately after the diagnosis of myocardial infarction with ST-segment elevation was made, followed by the use of abciximab at the start of the PCI procedure.

Our trial provides a systematic analysis of the role of coronary thrombi in a representative, contemporary population with myocardial infarction with ST-segment elevation, since aspiration was performed soon after the onset of symptoms in a large cohort of patients who were not selected on the basis of angiographic characteristics and were randomly assigned to a treatment group. The rate of retrieval of atherothrombotic material (73%) is somewhat lower than that reported in smaller, nonrandomized pathological thrombectomy studies of patients who had myocardial infarction with ST-segment elevation,[13,29] possibly because of the selection of patients and angiographic characteristics or differences in the devices and antithrombotic regimens used.

Our histopathological findings confirm earlier observations that thrombi predominantly composed of platelets are common in patients who have myocardial infarction with

ST-segment elevation.[13,29] Platelets are thought to play an important role in embolization and microvascular dysfunction.[12,31] Mechanical removal of a thrombus before PCI reduces the existing source of embolization but does not address platelet aggregates generated after PCI. These can be abolished with the use of platelet inhibitors.[32] It is therefore possible that the combined use of aspiration and glycoprotein IIb/IIIa inhibitors will have a synergistic effect.

The platelet thrombi were mostly small or moderate in size, whereas the erythrocyte-rich thrombi were moderate or large in size. This may reflect the process whereby a platelet thrombus forms by means of the adherence and aggregation of platelets on a disrupted lesion, followed by the development of thrombus through the deposition of erythrocytes in the stagnant blood flow over the platelet thrombus.[1,33] The association between large erythrocyte-rich thrombi and a TIMI flow grade of 0 or 1 before PCI is consistent with this mechanism.

We could not identify atherothrombotic material in 27% of patients in whom aspiration was performed. This may be due to a variety of mechanisms. First, a thrombus may be dissolved by endogenic or pharmacologic antithrombotic or fibrinolytic agents. Second, a thrombus may break off and embolize before PCI or during PCI, owing to the guidewire or aspiration device. In some patients in our trial, mechanical resistance at the site of occlusion prevented passage of the aspiration device through the infarct-related segment. It seems likely that, in some patients who have myocardial infarction with ST-segment elevation, a high-grade, nonthrombotic, unstable atherosclerotic plaque causes the coronary obstruction (e.g., a plaque with hemorrhage).[33,34] The patients who did not have a response to aspiration might also not have shown reperfusion after thrombolytic therapy. Third, within hours after formation, a thrombus may be covered by mononuclear cells that stop the deposition of platelets.[35] Finally, fragile material may disintegrate while passing through the catheter or filter or in the collection bottle.

Our trial has several limitations. First, it represents a single-center experience using surrogate end points. However, the fact that the surrogate end points of myocardial blush grade and the electrocardiographic variables of reperfusion were clearly associated with the rates of death and major adverse cardiac events supports the validity of using such end points in studies of patients who have myocardial infarction with ST-segment elevation. Second, to prevent selection bias, we performed randomization before coronary angiography. As a consequence, some patients did not undergo PCI or received the alternative therapy. This may have diluted to some extent the positive effects of aspiration, but it makes our findings applicable to a general population with myocardial infarction with ST-segment elevation. Third, it cannot be ruled out that extractable thrombi differ from thrombi in situ. Finally, it has been suggested that primary stenting without balloon predilation in patients who have myocardial infarction with ST-segment elevation results in improved distal flow and reduced embolization. Our study was not designed to evaluate the effect of dilation before stenting. This issue needs further investigation in a randomized setting.

In conclusion, we found that manual thrombus aspiration can be performed in a large majority of patients presenting with myocardial infarction with ST-segment elevation, irrespective of their clinical and angiographic features (e.g., a visible thrombus on angiography) and results in improved myocardial reperfusion and clinical outcome as compared with conventional PCI. The significant relationship we found between

myocardial and electrocardiographic variables of reperfusion and the rates of death and major adverse cardiac events supports the validity of these reperfusion variables as surrogate end points in patients who have myocardial infarction with ST-segment elevation. The histopathological findings in the aspirate specimens underline the importance of antiplatelet therapy in improving the outcome after primary PCI.

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APPENDIX

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Chapter 3.3

Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study

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ABSTRACT

Background

Percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction can be complicated by spontaneous or angioplasty-induced embolisation of atherothrombotic material. Distal blockage induces microvascular obstruction and can result in less than optimum reperfusion of viable myocardium. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) found that thrombus aspiration resulted in improved myocardial reperfusion compared with conventional PCI, but whether this benefit improves clinical outcome is unknown. We aimed to investigate whether the early efficacy of thrombus aspiration seen in TAPAS translated into clinical benefit after 1 year.

Methods

Patients with ST-elevation myocardial infarction enrolled at the University Medical Centre Groningen were randomly assigned in a 1:1 ratio to either thrombus aspiration or conventional treatment, before undergoing initial coronary angiography. Exclusion criteria were rescue PCI after thrombolysis and known existence of a concomitant disease with life expectancy less than 6 months. Of the 1071 patients enrolled between January, 2005, and December, 2006, vital status at or beyond 1 year after randomisation was available for 1060 (99%). The primary endpoint was cardiac death or non-fatal reinfarction after 1 year, and analysis was by intention to treat. The TAPAS trial is registered with Current Controlled Trials number ISRCTN16716833.

Findings

Cardiac death at 1 year was 3.6% (19 of 535 patients) in the thrombus aspiration group and 6.7% (36 of 536) in the conventional PCI group (hazard ratio [HR] 1.93; 95% CI 1.11–3.37; p=0.020). 1-year cardiac death or non-fatal reinfarction occurred in 5.6% (30 of 535) of patients in the thrombus aspiration group and 9.9% (53 of 536) of patients in the conventional PCI group (HR 1.81; 95% CI 1.16–2.84; p=0.009).

Interpretation

Compared with conventional PCI, thrombus aspiration before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for ST-elevation myocardial infarction.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion therapy for ST-elevation myocardial infarction. Spontaneous or PCI-induced embolisation of atherothrombotic material from the culprit lesion into the distal vasculature occurs in most patients. Distal blockage induces microvascular obstruction and can result in suboptimum reperfusion of viable myocardium.[1] In several randomised controlled trials, thrombus aspiration has improved myocardial reperfusion compared with conventional PCI.[2-6] The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)[2] found that thrombus aspiration resulted in improved myocardial reperfusion, indicated by the myocardial blush grade and ST-segment analysis on the 12-lead electrocardiogram (ECG), compared with conventional PCI. However, data from randomised trials that have assessed clinical outcomes are scarce, and several meta-analyses have shown conflicting results.[7,8] The aim of our study was to investigate whether the early efficacy of thrombus aspiration translates into clinical benefit after 1 year.

METHODS

The study design, methods, and first results of the TAPAS trial have been reported previously.[2,9] TAPAS investigated whether thrombus aspiration was better than conventional treatment of angioplasty without thrombus aspiration during primary PCI in patients with myocardial infarction. The trial was a single-centre, randomised open study with blinded assessment of endpoints.

Patients

1071 consecutive patients were enrolled at the University Medical Centre Groningen between January, 2005, and December, 2006. Inclusion criteria were symptoms suggesting acute myocardial ischaemia of more than 30 min, time from symptom onset of less than 12 h, and ST-segment elevation of more than 0.1 mV in two or more leads on the ECG. Exclusion criteria were rescue PCI after thrombolysis and known existence of a concomitant disease with life expectancy less than 6 months. The institutional review board approved the study and all patients included in the trial provided written informed consent.

Treatment

Before initial coronary angiography, patients were randomly assigned in a 1:1 ratio to either thrombus aspiration or conventional treatment. In patients randomly assigned to thrombus aspiration, the Export Aspiration Catheter (Medtronic Corporation, California, USA) was used to establish antegrade flow before stenting. When necessary for stent delivery, balloon dilation was done before stenting. In patients who received conventional treatment, balloon angioplasty was followed by stent placement (Figure 1). All patients were pretreated with aspirin (500 mg followed by 80–100 mg per day), heparin (5000 IU), and clopidogrel (loading dose of 600 mg followed by 75 mg per day), which was administrated directly after electrocardiographic confirmation of ST-elevation

myocardial infarction. Unless contraindicated, patients received weight-adjusted glycoprotein IIb/IIIa-inhibitor (abciximab) during the procedure and additional heparin guided by activated clotting time. Standard therapies after PCI included ß blockers, lipid-lowering agents, and angiotensin-converting-enzyme inhibitors or angiotensin-II receptor antagonists, according to current guidelines.[10]

Outcome measures and follow-up

The primary efficacy endpoint of TAPAS was post-procedural frequency of myocardial blush grade 0 or 1. Secondary endpoints included post-procedural Thrombolysis in Myocardial Infarction (TIMI)-flow 3, complete ST-segment elevation resolution, no persistent ST-segment deviation, and 30-day and 1-year major adverse cardiac events.[9]

Death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of cardiac markers to at least twice the upper limit of normal. Angiographically proven stent thrombosis was defined as a complete or partial occlusion within the stented segment, with evidence of thrombus and reduced antegrade flow (TIMI flow <3) with a concurrent acute clinical ischaemic event.[11] Distal embolisation after PCI was defined as a filling defect with abrupt cutoff in the vessel located distally of the culprit lesion.

Information on vital status, reinfarction, and coronary revascularisation procedures were assessed using hospital records, written questionnaires, and telephone interviews at or beyond 1 year after randomisation. Written questionnaires were also used to obtain information on medical therapy during follow-up. Vital status was also obtained from a central population registry. All major adverse cardiac events were assessed and classified by an interventional cardiologist who was unaware of the treatment allocation.

Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using a two-tailed Student's *t* test or Mann Whitney *U* test. Follow-up analysis was done using time-to-event data (for which patients were censored at the time of last follow-up). Hazard ratios and 95% CIs were estimated with a Cox's proportional hazard model, with treatment as the only covariate. 1-year clinical outcomes were displayed using Kaplan Meier methodology and were compared with log-rank test pooled over strata. The relation between reperfusion parameters (myocardial blush grade and ST-segment elevation resolution) and clinical outcome were calculated using χ^2 tests. Univariate and multivariate logistic-regression analyses were used for identifying risk factors for the combined endpoint of cardiac death or non-fatal reinfarction at 1 year follow-up. Baseline variables of the TIMI risk score[12] and treatment assignment were tested for their predictive value. These variables were age, diabetes, hypertension, systolic blood pressure at admission, heart rate at admission, weight, anterior myocardial infarction, total ischaemic time, and randomisation to thrombus aspiration. Significant variables at univariate analysis ($p<0.075$) were included in the multivariate model. Analyses were done according to the intention-to-treat principle. All p values were 2-tailed. Analyses were done with SPSS software version 14.0.2 (SPSS, Chicago, USA).

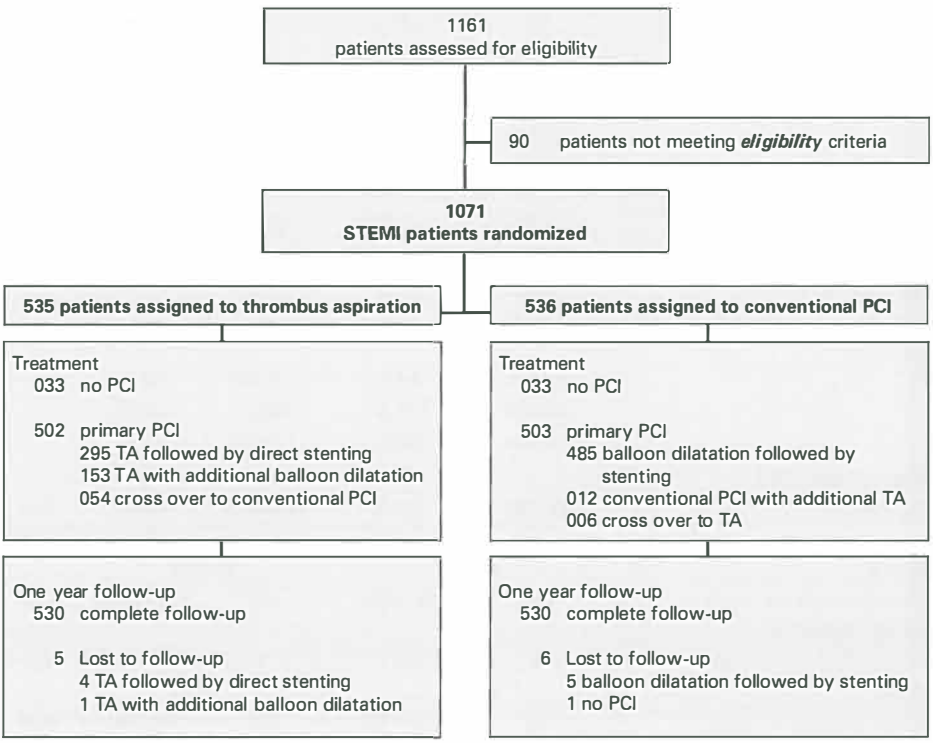
Role of funding source

The study was supported by an unrestricted grant from Medtronic (for angiographic analyses by the core laboratory). All other costs were covered by the Thorax Centre of the University Medical Centre Groningen. Medtronic had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Vital status 1 year after randomisation was available for 530 (99.1%) patients in the thrombus aspiration group and for 530 (98.9%) in the conventional PCI group (**Figure 1**). 54 patients (10%) in the thrombus aspiration group were crossed over to the conventional group because of a tortuous or distal infarct-related segment, and six patients (1%) in the conventional group were crossed over to thrombus aspiration because of angiographic evidence of thrombus. Baseline clinical and angiographic characteristics were well balanced between the treatment groups (**Table 1**).

Figure 1. Trial profile



STEMI=ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. TA=thrombus aspiration

Table 1. Baseline clinical and angiographic characteristics

	Thrombus aspiration (N=535)		Conventional PCI (N=536)		p-value
Clinical characteristics					
Age, years (mean ± SD)	63	(13)	63	(13)	
Male gender	363/535	(67.9)	392/536	(73.1)	
Risk factors					
Diabetes	56/530	(10.6)	67/532	(12.6)	
Hypertension	171/517	(33.1)	195/526	(37.1)	
Current smoking	213/463	(46.0)	225/469	(48.0)	
Hypercholesterolemia	115/485	(23.7)	130/480	(27.1)	
Previous MI	50/528	(9.5)	57/533	(10.7)	
Previous PCI	39/526	(7.4)	38/531	(7.2)	
Previous CABG	17/529	(3.2)	22/533	(4.1)	
Family history	235/509	(46.2)	229/514	(44.6)	
Body mass index (mean ± SD)	27	(4)	27	(4)	
Total ischemic time, min					
Median (Interquartile range)	190	(110-270)	185	(107-263)	
Hemodynamics pre-procedure					
Systolic blood pressure (mean ± SD)	128	(26)	130	(26)	
Diastolic blood pressure (mean ± SD)	74	(15)	75	(16)	
Heart rate, beats/min (mean ± SD)	78	(18)	78	(19)	
Diseased vessels					
0	13/533	(2.4)	10/534	(1.9)	
1	166/533	(31.1)	157/534	(29.4)	
2	175/533	(32.8)	174/534	(32.6)	
3	178/533	(33.4)	193/534	(36.1)	
Infarct related vessel					
Left anterior descending artery	221/515	(42.9)	223/517	(43.1)	
Left circumflex artery	93/515	(18.1)	79/517	(15.3)	
Right coronary artery	189/515	(36.7)	204/517	(39.5)	
Other	12/515	(2.3)	11/517	(2.1)	
Initial TIMI flow					
0/1	288/526	(54.7)	316/531	(59.5)	
2	102/526	(19.4)	85/531	(16.0)	
3	136/526	(25.9)	130/531	(24.5)	
Procedural characteristics					
Final TIMI flow 3	431/501	(86.0)	409/496	(82.5)	0.12
Visible distal embolization post PCI	25/446	(5.6)	25/434	(5.8)	0.92
Peak CK-total	N=421		N=418		
Median (Interquartile range)	565	(247-1506)	637	(291-1420)	0.24
Time to peak CK-total, hr					
Median (Interquartile range)	8	(5-12)	7	(5-12)	0.84
Peak CK-MB	N=406		N=405		
Median (Interquartile range)	58	(24-118)	63	(30-114)	0.46
Time to peak CK-MB, hr					
Median (Interquartile range)	7	(5-10)	7	(5 -10)	0.80

CABG = Coronary Artery Bypass Grafting, CK = Creatine kinase, IQR = Interquartile range, PCI = Percutaneous Coronary Intervention, SD = standard deviation, TIMI = Thrombolysis In Myocardial Infarction flow grade.

Written questionnaires to obtain information on vital status, hospital admissions, and current medical therapy were sent to 392 patients at 1 year or more after randomisation. In 289 (73.7%) cases the questionnaire was sent back with information on current medical therapy (**Table 2**).

Table 2. Medication at a median of 438 (402-486) days follow-up

	No (%)		p-value
	Thrombus aspiration	Conventional PCI	
Questionnaires send in total	199	193	
Information on medication	149/199 (74.9)	140/193 (72.5)	
Duration of follow-up, days (median, IQR)	443 (400-493)	431 (402-486)	0.54
No medication	1/149 (0.1)	0/140 (0.0)	0.94
Acetylsalicylic acid	126/149 (84.6)	117/140 (83.6)	0.82
Clopidogrel	13/149 (8.7)	21/140 (15.0)	0.10
Coumarine derivates	28/149 (18.8)	25/140 (17.9)	0.84
Statins	134/149 (89.9)	128/140 (91.4)	0.66
Beta-blocker	130/149 (87.9)	120/140 (85.7)	0.70
Metropolol	96/130 (73.8)	83/119 (69.7)	
Carvedilol	4/130 (3.1)	5/119 (4.2)	
Bisoprolol	25/130 (19.2)	28/119 (23.5)	
Sotalol	1/130 (0.8)	1/119 (0.8)	
Nebivolol	4/130 (3.1)	2/119 (1.7)	
Calcium channel blockers	23/149 (15.4)	21/140 (15.0)	0.92
Nitrates	11/149 (7.4)	10/140 (7.1)	0.94
Angiotensin-converting-enzyme inhibitor	77/149 (51.7)	80/140 (57.1)	0.35
Angiotensin-II receptor antagonists	30/149 (20.1)	29/140 (20.7)	0.90
Diuretics	37/149 (24.8)	32/140 (22.9)	0.90

IQR = Interquartile range.

66 patients died during 1-year follow-up. The number of deaths of cardiac origin was 55 (83.3%), of whom 30 died during the first 30 days and 25 between 30 days and 1 year. Of the 25 cardiac deaths after 30 days, ten occurred in the thrombus aspiration group and 15 in the conventional PCI group. Kaplan-Meier estimates for cardiac death after 30 days were 1.95% for thrombus aspiration and 3.00% for conventional PCI (log-rank p=0.284).

Causes of definite non-cardiac deaths were malignancy (n=8, including pulmonary cancer [3], hepatobiliary cancer [2], non-Hodgkin lymphoma [1], acute leukaemia [1], and prostate cancer [1]), septicaemia (n=1), trauma (n=1), and myelodysplastic syndrome (n=1). The Kaplan-Meier curves revealed a significant difference for 1-year all-cause mortality (log-rank p=0.040), cardiac death (log-rank p=0.018), and the combined endpoint of cardiac death or non-fatal reinfarction (log-rank p=0.008; **Figure 2**, **Figure 3**

and **Figure 4**). The hazard ratios of adverse clinical events at 1-year follow-up are shown in **Table 3**.

Figure 2. Kaplan-Meier curve for all-cause mortality at 1-year follow-up

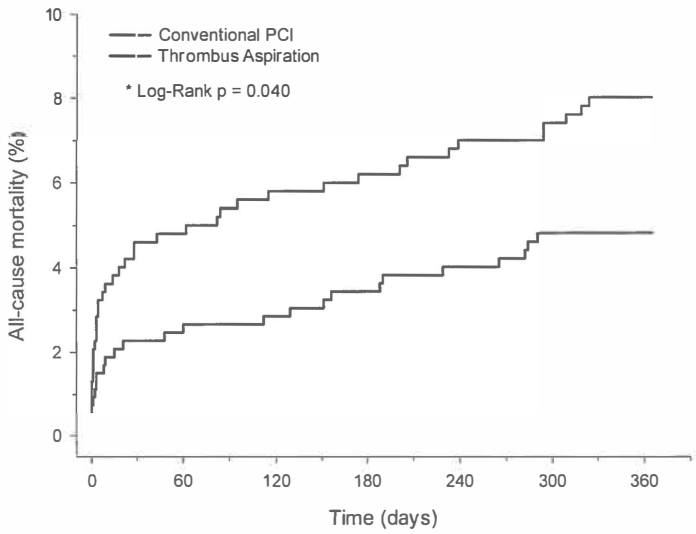


Figure 3. Kaplan-Meier curve for cardiac death at 1-year follow-up

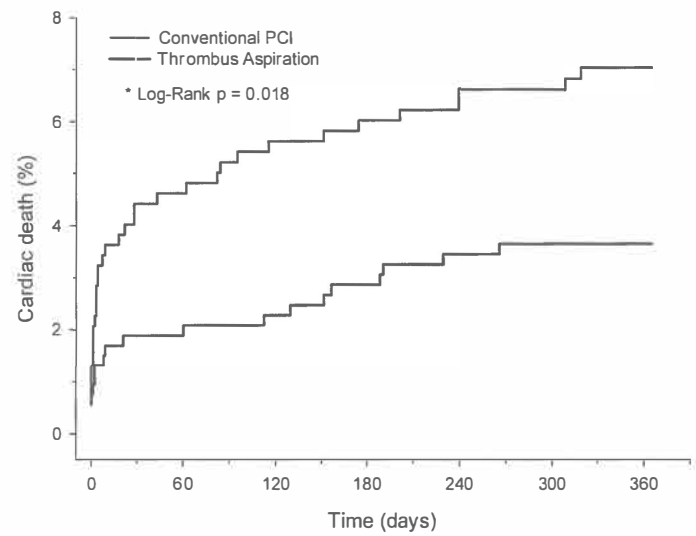
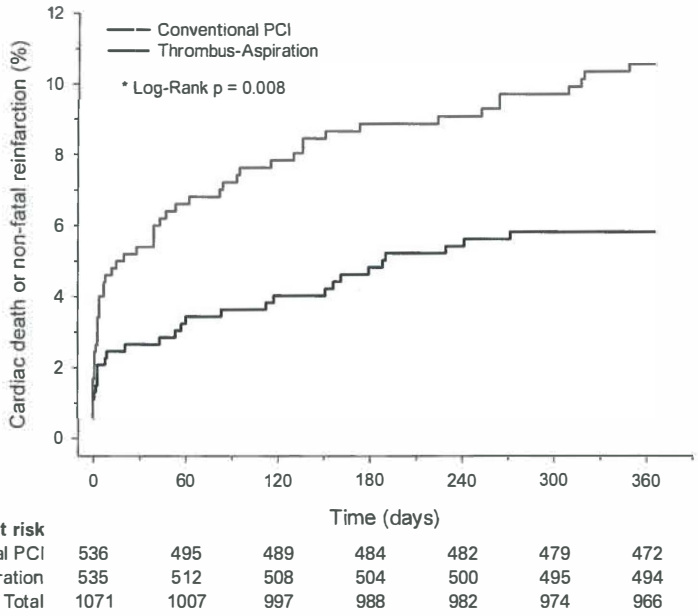


Figure 4. Kaplan-Meier curve for the combined end-point of cardiac death of non-fatal reinfarction at 1-year follow-up



Number at risk							
Conventional PCI	536	495	489	484	482	479	472
Thrombus aspiration	535	512	508	504	500	495	494
Total	1071	1007	997	988	982	974	966

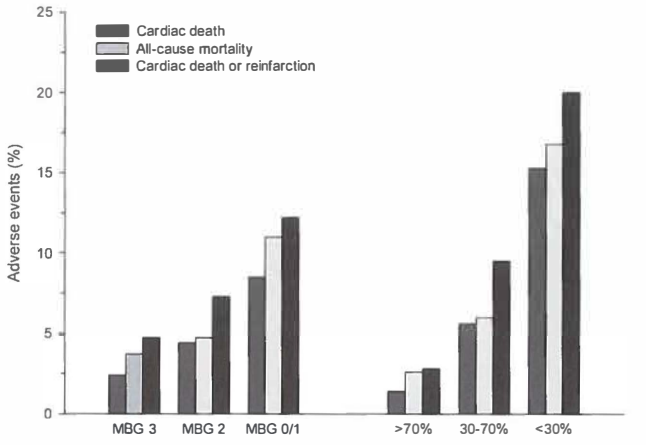
Table 3. Adverse clinical events at 1-year follow-up

	No (%)			
Endpoints	**Thrombus aspiration**	**Conventional PCI**	**Hazard Ratio (95% CI)**	**p-value**
All-cause mortality	25/535 (4.7)	41/536 (7.6)	1.67 (1.02 - 2.75)	0.042
Cardiac death	19/535 (3.6)	36/536 (6.7)	1.93 (1.11 - 3.37)	0.020
Reinfarction	12/535 (2.2)	23/536 (4.3)	1.97 (0.98 - 3.96)	0.05
Target vessel revascularization	60/535 (12.9)	69/536 (11.2)	1.19 (0.84 - 1.68)	0.34
RePCI target-vessel	37/535 (6.9)	51/536 (9.5)		
CABG target-vessel	25/535 (4.7)	20/536 (3.7)		
Cardiac death or Non-fatal reinfarction	30/535 (5.6)	53/536 (9.9)	1.81 (1.16 - 2.84)	0.009
Major Adverse Cardiac Events	89/535 (16.6)	109/536 (20.3)	1.26 (0.95 - 1.67)	0.10
Angiographically proven stent-thrombosis	6/535 (1.1)	12/536 (2.2)	2.05 (0.77 - 5.47)	0.15
Acute (24 hrs)	1/535 (0.2)	1/536 (0.2)		
Subacute (>1-30 days)	1/535 (0.2)	3/536 (0.6)		
Late (>30-365 days)	4/535 (0.7)	8/536 (1.5)		

CI=confidence interval, CABG=coronary artery bypass grafting, PCI=percutaneous coronary intervention

The primary endpoint of TAPAS was myocardial blush grade 0 or 1. Myocardial blush grade was associated with all-cause mortality (p=0.001), cardiac death (p=0.003), and the combined endpoint of cardiac death or non-fatal reinfarction (p=0.004) at 1-year follow-up. Moreover, the occurrence of clinical events at 1 year was also significantly related to ST-segment elevation resolution (p<0.0001 for all associations; **Figure 5**). Also, after exclusion of patients who died during the first 30 days, there was still a significant difference in distribution of cardiac death after 30 days according to myocardial blush grade: 4.4% (9 of 204) in myocardial blush grade 0 or 1, 1.6% (6 of 375) in grade 2, and 1.3% (5 of 377) in grade 3 (p=0.032).

Figure 5. Relation between parameters for myocardial reperfusion and total mortality, cardiac death, and the combined end-point of cardiac death of non-fatal reinfarction at 1-year follow-up



Rate of cardiac death (%)	2.4	4.4	8.5	p=0.003	1.4	5.6	15.3	p<0.0001
Rate of all-cause mortality (%)	3.7	4.7	11.0	p=0.001	2.6	6.0	16.8	p<0.0001
Rate of cardiac death or reinfarction (%)	4.7	7.3	12.2	p=0.004	2.8	9.5	20.0	p<0.0001

Treatment assignment and variables of the TIMI-risk score were tested for their univariate and multivariate predictive value (**Table 4**). Significant multivariate risk factors for cardiac death or nonfatal reinfarction were: assignment to thrombus aspiration (odds ratio 0.54; 95% CI 0.33–0.93; p=0.025); age (1.04; 1.02–1.06; p=0.001); diabetes (3.22; 1.80–5.74; p<0.0001); and heart rate at admission (1.02; 1.00–1.03; p=0.027).

Table 4. TIMI risk score variables of the combined endpoint of cardiac death or non-fatal reinfarction

TIMI risk score variables	Univariate analysis			Multivariate analysis*		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Thrombus-aspiration	0.54	0.34 - 0.86	0.010	0.54	0.33 - 0.93	0.025
Age (years)	1.05	1.03 - 1.07	<0.0001	1.04	1.02 - 1.06	0.001
Diabetes	3.62	2.15 - 6.07	<0.0001	3.22	1.80 - 5.74	<0.0001
Weight (kg)	0.98	0.96 - 0.99	0.010	0.98	0.96 - 1.00	0.07
Anterior MI	1.69	1.07 - 2.67	0.026	1.61	0.97 - 2.66	0.06
Heart rate at admission	1.01	1.00 - 1.03	0.021	1.02	1.00 - 1.03	0.027
Systolic Blood Pressure at admission	1.00	0.99 - 1.01	0.50	,	,	,
Hypertension	1.18	0.74 - 1.87	0.49	,	,	,
Total ischemic time (hrs)	1.04	0.97 - 1.11	0.32	,	,	,

* Multivariate analysis of significant univariate risk factors p<0.075. CI = Confidence Interval, MI = Myocardial Infarction

DISCUSSION

The main finding of this study is that a strategy of thrombus aspiration before stenting during primary PCI results in a lower cardiac mortality and a lower incidence of the combined endpoint of cardiac death or non-fatal reinfarction than does normal therapy alone.

Previous studies have reported that visually assessed myocardial blush is an important parameter for myocardial reperfusion after primary PCI and is strongly associated with infarct size, recovery of ventricular function, and mortality.[1, 13] Additionally, resolution of ST-segment elevation has proven to be an independent predictor of long-term mortality.[14] In line with these previous studies, we noted a strong association between these parameters for myocardial reperfusion and clinical events at both 30 days and 1 year in TAPAS. Also, after exclusion of patients who died during the first 30 days, there was still a significant association between cardiac death and myocardial blush grade. The benefit in improved parameters for myocardial reperfusion seen in the thrombus aspiration group resulted in less clinical events at 30 days.[2] Our study shows that this beneficial effect on reperfusion translates into a significant improvement of clinical outcome at 1 year.

The effect of manual thrombus aspiration on parameters for myocardial reperfusion has been widely investigated. However, randomised data for clinical outcome are scarce. Two small randomised trials have been published investigating the effect of thrombus aspiration on left ventricular remodelling. The myocardial contrast echocardiography substudy of the REMEDIA Trial[5] enrolled 50 patients randomly assigned to thrombus aspiration or standard PCI. Thrombus aspiration was associated with a significant reduction in severity and extent of myocardial obstruction at 24 h, which was sustained at 1 week and 6 months. Additionally, end-diastolic and end-systolic left ventricular volumes were slightly, but not significantly, smaller in patients undergoing thrombus

aspiration. De Luca and colleagues[6] showed that, in 76 patients with anterior myocardial infarction, thrombus aspiration was associated with significantly lower end-diastolic and end-systolic left ventricular volumes at 6 months than with conventional PCI. Although these trials show promising results, sample sizes were small and accuracy of echocardiography in assessing left ventricular function is relatively moderate compared with contrast-enhanced MRI.

In TAPAS, the mortality benefit and the reduced reinfarction rates in the thrombus aspiration group were probably associated with less thrombotic complications associated with the treatment. Less distal embolisation will result in improved myocardial perfusion[2-4] and left ventricular function,[5,6] and in a survival benefit at follow-up.[15] Thrombus aspiration reduced the source of distal embolisation by removing the clots as well as atherosclerotic plaque material exposed to the luminal surface after plaque rupture. Histopathological analysis of aspirated clots in TAPAS showed both so-called white clots, composed mainly of platelets, and red clots composed of fibrin and red blood cells.[2] Thrombus aspiration is therefore of additional value during primary PCI, since currently used antiplatelet agents mainly target white platelet clots. Furthermore, in TAPAS there were less reinfarctions in the thrombus aspiration group, contributing to the survival benefit. This lower reinfarction rate seems to be at least in part caused by a reduction in thrombotic complications, such as stent thrombosis, after thrombus aspiration. The presence of thrombus, in particular a large thrombus-load, has been associated with incomplete stent apposition,[16] reinfarction,[17] and stent-thrombosis at follow-up.[11] Therefore, a reduction in thrombus-load by thrombus aspiration could be expected to result in less reinfarction at follow-up.

Other elements contributing to the favourable outcome of manual thrombus aspiration are its simplicity (indicated by similar duration of fluoroscopy and door-to-balloon times as the control group) and safety (no flow-limiting dissections or other device-related complications occurred during the procedure).[2] 1-year target vessel revascularisation did not show an effect of thrombus aspiration on clinical recurrence. Therefore, our results do not indicate an effect of thrombus aspiration on neointima hyperplasia compared with conventional PCI.

TAPAS was designed to detect differences in myocardial reperfusion and – with 1071 patients, 66 deaths, and 35 reinfarctions – had limited power to investigate the magnitude of the effect of thrombus aspiration on clinical outcome. Another limitation of our study was that no systematic measurement of infarct size and left ventricular function was done. These data could have offered additional information on the mechanism behind the clinical benefit seen in the thrombus aspiration group.

In conclusion, compared with conventional PCI, thrombus aspiration before stenting of the infarct-related artery results in improved myocardial perfusion and seems to improve clinical outcome 1 year after PCI for ST-elevation myocardial infarction.

CONTRIBUTORS

All authors have read and finally approved the manuscript. All authors contributed to this paper. PJV had full access to all of the data in the study and has responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

ACKNOWLEDGEMENTS

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Chapter 4

Thrombus aspiration in clinical practice

Chapter 4.1

Thrombus aspiration as definitive mechanical intervention for ST-elevation myocardial infarction: a report of five cases

Fokkema ML, Vlaar PJ, Svilaas T

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INTRODUCTION

The primary goal of treatment in patients presenting with ST-elevation myocardial infarction (STEMI) is reperfusion of the infarcted myocardium. Percutaneous coronary intervention (PCI) has emerged as preferred reperfusion therapy for STEMI.[1] To protect the microcirculation against distal embolization during primary PCI, various mechanical devices have been developed. Randomized controlled trials have demonstrated that manual thrombus aspiration for STEMI is safe and results in improved myocardial perfusion when compared with conventional angioplasty.[2-4] In some patients, thrombus aspiration itself results in complete restoration of epicardial blood flow, without residual stenosis or angiographic signs of plaque rupture at the culprit lesion. It is currently unclear if additional angioplasty is also necessary in these patients. This case report describes 5 patients in whom thrombus aspiration was performed without additional angioplasty as treatment for STEMI.

METHODS

Population

Between January 2005 and March 2007, thrombus aspiration was performed to prepare the occluded vessel for stent implantation in 533 patients with acute STEMI.[5,6] We retrospectively analyzed procedural data and selected patients in whom only thrombus aspiration was performed. In 5 patients (0.9%), thrombus aspiration was used as definitive treatment without additional balloon angioplasty or stenting. These 5 patients all had total coronary occlusion (thrombolysis in myocardial infarction [TIMI] flow 0), which was observed in 249 (47%) of all thrombus aspiration patients.

Thrombus aspiration

The Export aspiration catheter (*Medtronic, Inc., Santa Rosa, California*) (Cases 1, 2, 4 and 5) or the Diver Clot Extraction catheter (*ev3, Inc., Plymouth, Minnesota*) (Case 3) was used for thrombus aspiration. The Export catheter has an aspiration lumen of 0.041 inches and contains a radiopaque marker located 2 mm from the distal tip. The aspiration lumen of the Diver catheter is 0.062 inches, and the radiopaque marker is located 1 mm from the aspiration tip. After passing the guidewire through the coronary occlusion, the thrombus aspiration catheter was advanced to the proximal side of the occlusion. Thrombus aspiration was performed by hand with a lockable 20 mL syringe that allowed for an aspiration rate of 1 mL/second. The thrombus aspiration catheter was advanced through the coronary occlusion several times, and at least 2 x 20 mL were aspirated to achieve maximal particle aspiration. The syringe was emptied in a filtering cup to separate the aspirated fragments from the blood.

Histopathological analysis

The aspirated material was collected for assessment of atherothrombotic characteristics. Aspirated fragments were histologically analyzed for thrombus type and classified as white or red thrombi. White thrombi consisted only of platelet aggregates and red thrombi contained layers of coagulated erythrocytes. In addition, thrombus size was measured and categorized into five groups: 1) residue of small, loosely cohesive platelets; 2) well-formed thrombi < 0.5 mm; 3) 0.5–1 mm; 4) 1–2 mm; and 5) thrombi > 2 mm.

Angiographic analysis

TIMI flow and myocardial blush grade (MBG) were evaluated after thrombus aspiration as previously described.[7,8] The percentage of residual stenosis was evaluated by quantitative coronary analysis (QCA). The guiding catheter was used as a reference measurement and residual stenosis was calculated by computerized analysis.

Pharmacologic treatment

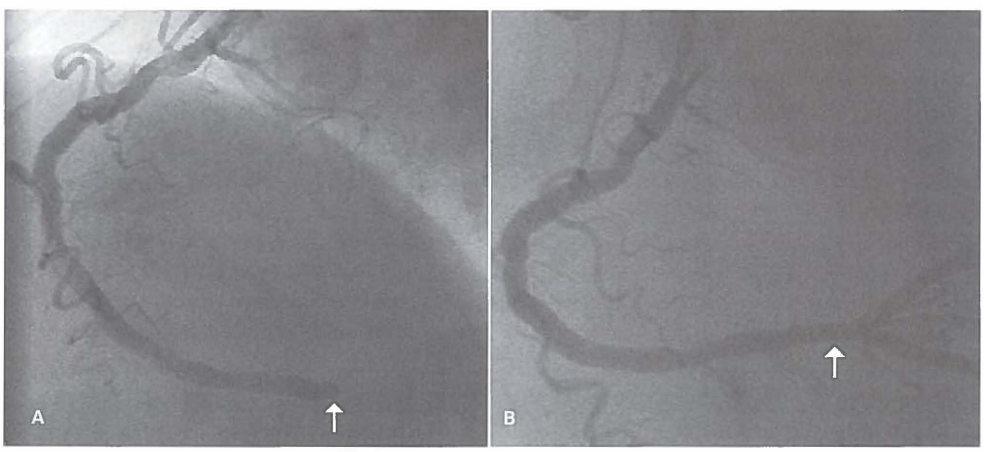
After electrocardiographic confirmation of STEMI, all patients received a bolus of acetylsalicylic acid (500 mg), intravenous heparin (5000–10,000 IU) and clopidogrel (600 mg). All patients were treated with abciximab after diagnostic coronary angiography. After sheath removal, low-molecular weight heparin was given. The standard medical therapy after PCI included acetylsalicylic acid (80–100 mg/24 hours), clopidogrel

(75 mg/24 hours for 1 month), lipid-lowering agents, ß-blockers and angiotensin-converting enzyme inhibitors.

Case 1. *An 85-year-old male with a history of 2 PCIs of the right coronary artery (RCA) more than 12 months before presentation was transferred to our hospital under suspicion of an acute myocardial infarction (AMI). He had diabetes, was a smoker and had a body mass index (BMI) of 28. Within 2 hours of symptomonset, coronary angiography was performed, and showed total occlusion of the distal RCA* ***(Figure 1a)****. Moderate lesion calcification was seen. The left main artery, left anterior descending artery (LAD) and circumflex artery (Cx) contained vessel stenoses up to 50%. Thrombus aspiration was performed in the RCA. Histopathological examination of the aspirated material showed multiple fragments of white thrombi without signs of erythrocytes or plaque material. The size of the aspirated fragments was < 0.5 mm.*

After thrombus aspiration, a stenosis of 30% remained in the culprit lesion, as measured by QCA ***(Figure 1b)****. No further balloon angioplasty or stenting was performed. TIMI 3 flow and MBG 3 were achieved. Partial ST-segment elevation resolution was seen on the electrocardiography (ECG) with a cumulative persistent ST-segment deviation of 0.5 mV on the first postinterventional ECG. The patient remained asymptomatic 1 year after treatment without any adverse events.*

Figure 1.
(A) Patient 1 presented with a total occlusion in the distal right coronary artery.
(B) After thrombus aspiration, 30% residual stenosis remained; TIMI 3 flow and myocardial blush grade 3 were restored. Please see digital version of this article for the moving coronary angiograms.

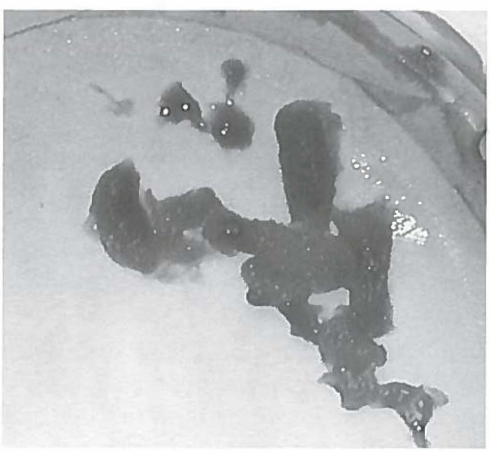


Case 2. *A 74-year-old female with no cardiac history or cardiovascular risk factors presented with symptoms of AMI. Her symptom duration was 3.5 hours at hospital admission. Based on the ECG, an apical MI was diagnosed. Angiography showed single-vessel disease with total occlusion in the distal LAD. Thrombus aspiration was performed and the aspirated material in this case contained white platelet aggregates*

without plaque material or erythrocytes. The size of the aspirated thrombus was > 2 mm. After thrombus aspiration, no additional balloon dilatation or stent implantation was performed. A < 20% stenosis remained and TIMI 3 flow was achieved. However, myocardial perfusion remained impaired after the procedure (MBG 1). The ECG showed partial ST-segment resolution with a cumulative persistent ST-segment deviation of 0.7 mV. Her symptoms rapidly disappeared after thrombus aspiration and the patient had an uneventful course at 1-year follow up.

Case 3. *An 87-year-old male with a BMI of 28 and no other cardiovascular risk factors or cardiac history was transferred to our hospital for acute anterior STEMI. His duration of symptoms was 1.5 hours. Angiography showed three-vessel disease with a total occlusion located in the proximal LAD. Thrombus aspiration was successfully performed in the proximal LAD and a stenosis of 35% remained. The aspirated thrombus material of > 2 mm contained layers of coagulated erythrocytes, but no plaque material* ***(Figure 2)****. No balloon angioplasty or stent placement was performed. TIMI 3 flow and MBG 1 were achieved. The ECG showed complete normalization of the ST segment. At 6-month follow up, the patient remained asymptomatic without additional coronary interventions or adverse cardiac events.*

Figure 2. Aspirated thrombus material containing coagulated erythrocytes.



Case 4. *A 54-year-old male with a BMI of 41 and a history of smoking presented to our hospital with acute anterior STEMI. He was known to have hypertension, hypercholesterolemia and a positive family history of cardiovascular disease. A small-cell bronchial carcinoma was diagnosed 1 month before presentation and was treated with chemotherapy. The patient's ischemic time was 5 hours. The angiogram showed a total occlusion in the proximal LAD with extensive thrombosis and ectatic diffuse coronary artery disease. Thrombus aspiration was performed in the LAD, resulting in 25% residual stenosis after the procedure. Multiple red thrombus fragments > 2 mm in size were aspirated. Examination of the aspirated thrombus showed only coagulated*

erythrocytes. After thrombus aspiration, no additional angioplasty or stenting was performed. TIMI 3 flow and MBG 1 were achieved. The ECG showed partial ST-segment elevation resolution with a residual cumulative ST deviation of 0.4 mV. No additional coronary interventions were performed at follow up. The patient died 10 months after thrombus aspiration from metastasized bronchus carcinoma.

Case 5. *A 50-year-old male smoker with a history of MI 5 years previously was transferred to our hospital under suspicion of inferior STEMI. He was known to have hypertension, hypercholesterolemia and a positive family history for cardiovascular disease. Symptom duration was 1.5 hours at hospital admission. Coronary angiography showed a 70% stenosis in the proximal LAD and vessel irregularities in the Cx, with moderate collateral filling. The RCA contained proximal aneurysms and a complete occlusion located distally. Thrombus aspiration was performed in the RCA. Aspirated material was > 2 mm in size, containing erythrocytes, but no plaque material at histopathological examination. A residual stenosis of 35% was measured. No additional balloon angioplasty or stenting was performed. TIMI 3 flow and MBG 3 were achieved and the patient's symptoms rapidly disappeared. The ECG showed complete normalization of the ST segments. The patient remained event-free 1 year after treatment.*

DISCUSSION

These cases demonstrate that when thrombus aspiration results in complete restoration of epicardial blood flow without significant residual stenosis or signs of plaque rupture, additional angioplasty with balloon or stent placement may not be necessary. At follow up, all patients remained event-free, indicating that thrombus aspiration as a standalone therapy was safe and effective in these patients. Thrombus aspiration without additional angioplasty has only been described before as therapy for coronary embolisms originating from outside the coronary arteries.[9,10] To our knowledge, this is the first report investigating the potential role of thrombus aspiration without additional angioplasty for STEMI caused by occlusive coronary artery disease.

Only 5 out of 249 patients with an acute total coronary occlusion underwent thrombus aspiration for definitive treatment of STEMI. Potentially, more than 5 patients could have been treated with thrombus aspiration as definitive therapy, but our data do not allow any conclusions with regard to how often this strategy can be applied. To gain greater clarity regarding the relevance of residual lesions and the necessity of performing additional PCI after thrombus aspiration, fractional flow reserve (FFR) or intravascular ultrasound (IVUS) measurements may be helpful.[11] Earlier studies have shown that elective patients with residual stenoses ≤ 30%[12,13] or ≤ 35% and FFR ≥ 0.9[14] after balloon angioplasty had favorable clinical outcomes at longterm follow up. This may suggest that in patients with minimal residual stenosis, no signs of plaque rupture on angiography and/or IVUS and almost normal FFR, thrombus aspiration alone may result in clinical outcomes comparable with those achieved after additional angioplasty or stenting. Furthermore, as thrombus aspiration is nontraumatic to the vessel wall, eventfree outcomes after thrombus aspiration without additional angioplasty may be

related to diminished vessel injury. During balloon angioplasty and stenting, platelet aggregation, inflammation and intimal proliferation are induced and these mechanisms may result in restenosis or reocclusion.[15]

We conclude from these 5 cases that the performance of thrombus aspiration alone, without the use of balloon or stenting in the culprit lesion, is safe and effective in selected patients.

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Chapter 4.2

Predictors of Long-term Cardiac Ischemic Events in Patients with Acute ST-segment elevation Myocardial Infarction: Results from the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)

Svilaas T for the TAPAS investigators

ABSTRACT

Background

The prognosis of patients with ST-segment elevation myocardial infarction (STEMI) has improved due to early invasive strategies and adjunctive pharmacologial treatment. A recent development is thrombus aspiration (TA). We sought to identify clinical and procedural predictors of long-term cardiac ischemic events in patients treated with primary percuteanous coronary intervention (PCI), both with and without TA.

Methods

The current subanalysis was based on all STEMI patients that underwent primary PCI after enrollment in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) randomized trial. Multivariate Cox regression analyses were performed to identify baseline predictors of the occurrence of composite cardiac ischemic events (cardiac death, non-fatal reinfarction, and target vessel revascularization) at long-term follow-up in all PCI treated patients as well as in the group of patients that underwent PCI with TA.

Results

Of the 1071 patients, 1005 patients (94%) underwent primary PCI, of which 2-year follow-up was available in 996 (99%) of patients. The 2-year incidence of composite cardiac ischemic events in all PCI treated patients was 205 (20.5%). The incidence of cardiac ischemic events in PCI with TA patients (n=452) was 69 (15.2%) vs 136 (24.6%) in PCI without TA patients (n=544). Predictors of cardiac ischemic events for all PCI patients were age, diabetes mellitus, history of myocardial infarction, angiographic infarct related segment in the left coronary artery. The use of TA was both associated with less cardiac ischemic events. In the TA patients, diabetes mellitus and pre-procedural angiographically visible thrombus were associated with cardiac ischemic events. Retrieval of atherothrombotic material was independently associated with reduced mortality at follow-up.

Conclusion

In a contemporary STEMI population, in addition to clinical risk factors of long-term outcome, such as age, diabetes mellitus and history of myocardial infarction, the use of PCI with TA was favorably associated with composite cardiac ischemic events. In PCI patients treated with TA, the retrieval of atherothrombotic material was associated with reduced mortality at follow-up. The findings lend support to the use of manual TA in primary PCI and to the concept that reduction of thrombus load is an important mechanism of a beneficial effect of TA.

INTRODUCTION

Prognosis of patients with ST-segment elevation myocardial infarction (STEMI) has improved the last decennia due to the strategies to restore epicardial coronary artery flow. Primary percutaneous coronary intervention (PCI) is the treatment of choice in STEMI patients.[1,2] Did primary PCI first consist of balloon angioplasty only, nowadays stenting with or without balloon predilation is the most favorable intervention. Also, adjunctive medical treatment with glycoprotein (GP) IIb/IIIa inhibitors is useful.[3,4] Recently, PCI with thrombus aspiration (TA) has shown to be of additional benefit for improvement of myocardial perfusion and therewith a reduction in short- and long-term mortalities.[5-7] Suggested explanations to the effect of TA are the reduction of thrombus load or the facilitation of stenting without balloon predilation, with thereby less manipulation of the infarct related lesion with less risk of embolization.[8-11] A synergistic effect with the concomitant use of a GP IIb/IIIa inhibitor has also been mentioned.[12,13]

Clinical predictors of long-term outcomes among STEMI patients have been well studied. Recently, it was found that baseline angiographic measures have predictive value in patients with acute coronary syndromes treated according contemporary practice.[14] Whether procedural factors such as TA on top of established baseline angiographic characterization and early invasive approach is not well defined. The predictors in patients treated with TA have not been established yet.

The aim of the present study was to examine the clinical and procedural factors that are independently associated with long-term cardiac ischemic events in STEMI patients treated with PCI with and without TA.

METHODS

Study design and population

In this substudy of the TAPAS trial all STEMI patients that underwent primary PCI were included. The study design, methods, and results up to 1 year of the TAPAS trial have been reported previously.[5,6,15] In short, the TAPAS trial was a single-center, prospective, randomized, open trial with blinded evaluation of endpoints investigating the effect of TA during primary PCI. All consecutive patients presenting to the University Medical Center Groningen with a possible STEMI between January 2005 and December 2006 were considered eligible for participation. Inclusion criteria were 1) symptoms suggesting acute myocardial ischemia >30 minutes, 2) time from symptom onset <12 hours, and 3) ST-segment elevation >0.1mV in 2 or more leads on the ECG. Exclusion criteria were rescue PCI after thrombolysis and known existence of a disease with life expectancy <6 months. In the trial, patients were randomized in a 1:1 ratio to PCI with TA or to PCI without TA before diagnostic angiography was performed. The institutional review board approved the study and all patients included in the trial provided written informed consent.

Treatment

In all patients, the first procedural step was passing a floppy steerable guidewire through the target lesion. In patients treated with PCI without TA, this was followed by balloon dilatation to establish antegrade flow. In PCI with TA patients, wire passage was followed by advancing the 6F Export Aspiration Catheter (Medtronic Corporation, California, USA, crossing profile 0.068inch) into the target coronary segment during continuous aspiration. When necessary for stent delivery, balloon dilatation was performed before stenting. In all patients, after restoration of antegrade flow, intracoronary nitrates were given to ensure maximal epicardial vasodilation and to determine stent size and length and facilitate stent placement. Stenting was performed with bare metal stents.

Pharmacologic treatment before PCI included aspirin (≥300mg followed by 80-100mg/day), heparin (5000 IU), and clopidogrel (loading dose of 600mg followed by 75mg/day). Unless contraindicated, patients received weight-adjusted GP IIb/IIIa-inhibitor (abciximab), and additional activated clotting time-guided heparin. Standard therapies after PCI was according to guidelines.[16]

Defintions, outcome assessment, and follow-up

The aim of this study was to evaluate the predictors of outcome after longer term follow-up in a group of STEMI patients treated with and without TA. The primary endpoint of this analysis was long-term outcome of combined cardiac ischemic events i.e. cardiac mortality, reinfarction and target vessel revascularization (TVR).

Death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and/or elevation of cardiac markers to at least twice the upper limit of normal. TVR was defined as ischemia-driven percutaneous or surgical revascularization of the infarct-related artery. Major adverse cardiac event (MACE) was defined as the combination of cardiac death, reinfarction, and TVR. Information on vital status, reinfarction, and coronary revascularization procedures was obtained using hospital records, written questionnaires, and telephone interviews at or beyond 2 years after randomization. Vital status was also obtained from a central population registry. Written questionnaires were used to obtain information on medical therapy during follow-up. All major adverse events were assessed and classified by two independent researchers who were unaware of the treatment allocation.

Coronary angiographic data were analyzed at an independent core laboratory (Cordinamo,Wezep,the Netherlands). A coronary angiogram was obtained before and after the PCI procedure. Thrombolysis in myocardial infarction (TIMI)-flow grades and myocardial blush grade were assessed as previously described.[17,18] Angiographic evidence of thrombus was assessed according to the criteria summarized by Mabin et al.[19] Distal embolization after PCI was defined as a filling defect with abrupt cutoff on antegrade flow in the vessel located distally of the culprit lesion. Stenting without predilation refers to no balloon dilatation before stenting.

The processing of filtered aspirated material has been described previously.[5,15] Samples were classified into effective or no effective aspiration based on the presence of atherothrombotic material based on pathohistological analysis. For the present study, identified material was classified by size: <0.5mm or >0.5mm.

Statistical methods and data management

The current analyses were based on all STEMI patients that underwent primary PCI after enrollment in the TAPAS trial with available outcome data. The endpoints were analysed for the total group of patients and for patients that actually underwent TA separately. All analyses were based per protocol. Categorical variables were compared with chi-square analysis or Fisher's exact test. Continuous variables were compared with the two-tailed Student's t-test or Mann Whitney U test.

Follow-up was censored at 25 months. Multivariate Cox regression analyses were performed to identify baseline predictors of the occurrence of composite cardiac ischemic events, all-cause mortality, cardiac death, and MI at follow-up. The following list of covariates was used to determine multivariable predictors: age, male sex, hypertension, diabetes, current smoking, previous MI, previous PCI, total ischemic time, number of diseased vessels, baseline TIMI-flow grade 0/1, baseline angiographically visible thrombus, collaterals, diameters score of the coronary lesion, stented length, treatment strategy of TA, treatment strategy of direct stenting, and GP IIb/IIIa inhibitor treatment. In the patients treated with TA, we examined the predictive effect of retrieved atherothrombotic material and of the size of material >0.5mm. The analysis was performed using backward stepwise selection with entry/stay criteria of 0.1/0.1. The probability values, hazard ratio's (HR's) and corresponding 95% confidence intervals (CI)s for predictors are presented. Two-sided significance tests were used. The Statistical Package for the Social Sciences (SPSS Inc.,Chicago,IL,USA) version 16.0 was used for all statistical analysis.

All authors contributed to data acquisition, revision, and final approval of the manuscript. There were no agreements concerning confidentiality of the data between the authors and crediting institutions.

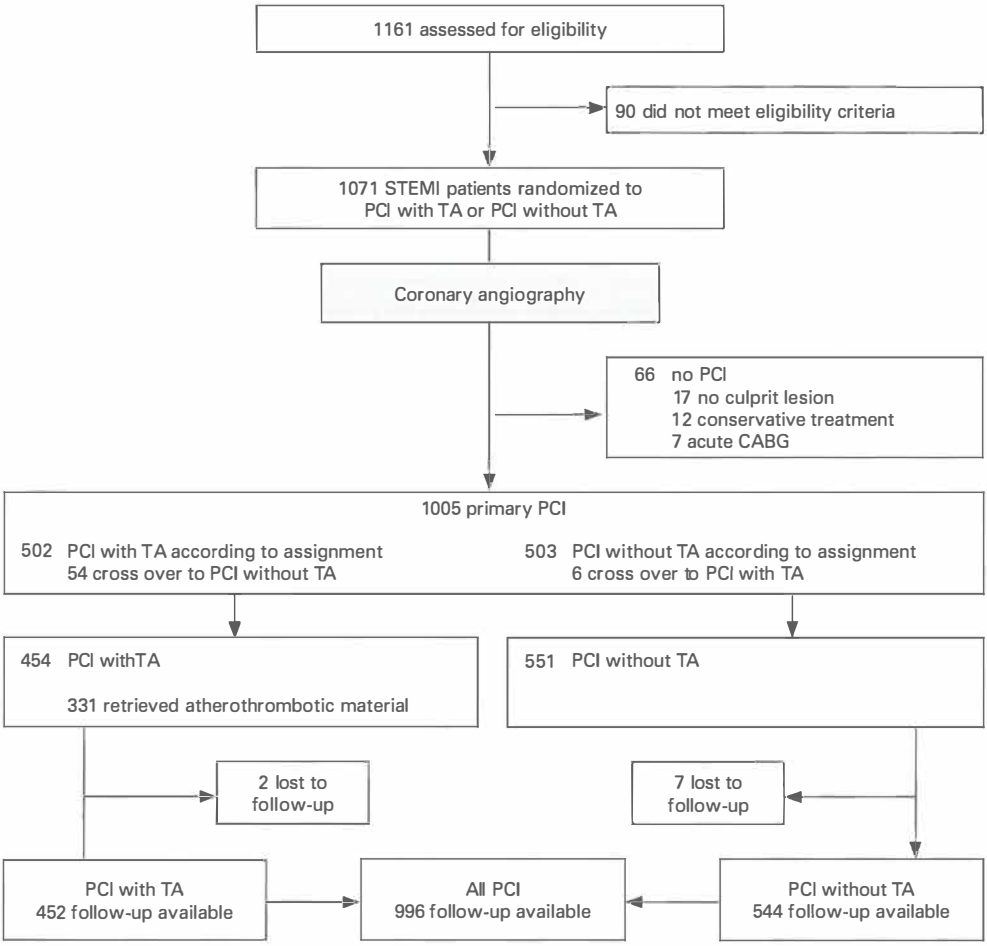
RESULTS

Study population

Figure 1 shows the flowchart of patients eventually included in this sub-study. After diagnostic coronary angiography, 66 (5.6%) out of 1071 patients did not undergo PCI. Of the 1005 (93.8%) patients who underwent PCI, 551 (54.8%) patients underwent PCI without TA and 454 (45.1%) patients underwent PCI with TA. Reasons for cross-over has been previously reported.[5 6] Of the TA patients, histopathological material was confirmed in 331 (72.9%) patients. Clinical follow-up was available in 996/1005 (99.1%) of all patients that underwent PCI at 25 months after intervention.

Baseline demographic, clinical and angiographic characteristics of patients according to treatment are outlined in **Table 1**. Comparing the patients who underwent PCI without TA and the patients treated with TA, more men underwent PCI alone (74.6% vs. 67.2%, p=0.01). Stenting without predilation was applied in 141 (25.6%) of patients treated with PCI without TA and in 274 (60.4%) of patients treated with TA (p<0.001). Use of GP IIb/IIIa inhibitors was more frequently applied in the TA patients (430 patients, 94.9%) than in the PCI without TA patients (487 patients, 88.4%), p<0.001.

Figure 1. Flow chart for enrollment



STEMI=ST segment elevation myocardial infarction, PCI=percutaneous coronary intervention, TA=thrombus aspiration

Table 1. Baseline clinical and angiographic characteristics according to treatment

	All PCI N=996		PCI without TA N=544		PCI with TA N=452	
Baseline demographic and clinical data						
Age, years, mean (± SD)	63	(13)	63	(13)	62	(13)
Gender, male, N (%)	709	(71.2)	405	(74.4)	304	(67.3)
History, N (%)						
hypertension	345/968	(28.8)	197/535	(36.8)	148/433	(32.7)
diabetes mellitus	111/987	(11.2)	61/540	(11.3)	50/447	(11.1)
myocardial infarction	96/986	(9.7)	64/541	(11.8)	32/445	(7.1)
PCI	81/983	(8.2)	44/539	(8.2)	27/444	(6.0)
CABG	34/987	(3.4)	22/541	(4.1)	12/446	(2.7)
Current smoking, N (%)	416/870	(47.8)	219/467	(46.9)	197/403	(43.6)
Total ischemic time, min, median (IQR*)	188	(138-292)	183	(135-285)	193	(140-298)
Angiographic and procedural data						
Number of diseased vessels, N (%)						
0	0	(0)	0	(0)	0	(0)
1	317/992	(32.0)	168/542	(31.0)	149/450	(33.1)
2	340/992	(34.3)	179/542	(33.0)	161/450	(35.7)
3	335/992	(33.8)	195/542	(35.9)	140/450	(31.1)
Infarct related vessel, N (%)						
Left anterior ascending artery	430/979	(43.9)	230/534	(43.1)	200/445	(44.9)
Left circumflex artery	169/979	(17.3)	94/534	(17.6)	75/445	(16.8)
Right coronary artery	380/979	(38.8)	210/534	(39.3)	170/445	(38.2)
Pre-procedural TIMI flow, N (%)						
TIMI flow 0 or 1	590/986	(17.7)	326/538	(58.9)	264/448	(58.4)
TIMI flow 2	177/986	(11.3)	86/538	(16.0)	91/448	(20.1)
TIMI flow 3	219/986	(71.0)	126/538	(23.4)	93/448	(20.6)
Pre-procedural thrombus, N (%)	466/975	(47.8)	241/535	(45.0)	225/440	(49.8)
Collaterals, N (%)	294/971	(30.3)	174/530	(32.8)	120/441	(26.5)
Stent diameter, mean (±SD)	3.1	(1.1)	3.0	(1.0)	3.1	(1.1)
Stent length, mean (±SD)	18.7	(8.7)	18.4	(9.0)	18.9	(8.4)
Stenting without predilation, N (%)	411/996	(41.3)	138/544	(25.4)	273/452	(60.4)
Glycoprotein IIb/IIIa inhibitors, N (%)	910/996	(91.4)	481/544	(88.4)	429/452	(94.9)
Retrieved thrombus					331/452	(73.2)
Initial procedural outcome						
Post-procedural TIMI flow 2/3, N (%)	958/988	(97.0)	518/537	(96.5)	440/451	(97.6)
Post-procedural distal embolization, N (%)	50/871	(5.7)	23/461	(5.0)	27/410	(6.6)
Post-procedural MBG 2/3, N (%)	758/971	(78.1)	385/527	(73.1)	373/444	(84.0)
CK MB, Ug/l, ln, mean (±SD)	3.77	(1.3)	3.72	(1.3)	3.81	(1.3)
ECG ST-segment resolution >70%, N (%)	467/925	(50.5)	221/503	(43.9)	246/422	(58.3)

N=number, SD= standard deviation, IQR=inter quartile range, PCI=percutaneous coronary intervention, TA=thrombus aspiration, CABG=coronary artery bypass grafting, TIMI=thrombolysis in myocardial infarction, MBG=myocardial blush grade, CKMB=creatinine kinase myocardial band fraction

Overall clinical outcomes

Of the 996 of all PCI patients in which follow-up was available, a total of 205 (20.5%) cardiac ischemic events had occurred, of which 88 (8.8%) deaths and 62 (6.2%) cardiac deaths. Non-fatal reinfarctions occurred in 42 (4.2%) patients and TVR in 134 (13.5%) of patients.

In the patients treated with PCI without TA, clinical follow-up was available in 544/551 (98.7%) of patients at 25 months after intervention. Cardiac ischemic events occurred in 136 (25.0%) of patients. There were a total of 54 (9.9%) deaths of which 42 (7.7%) cardiac deaths. Non-fatal reinfarctions occurred in 29 (5.3%) patients and TVR in 89 (16.4%). In the TA patients, clinical follow-up was available in 452/454 (99.7%) of patients at 25 months after intervention. Cardiac ischemic events occurred in 69 (15.3%) of patients. There were a total of 34 (7.5%) deaths of which 20 (4.4%) cardiac deaths. Non-fatal reinfarctions occurred in 13 (2.9%) patients and TVR in 45 (9.9%).

Baseline characteristics of patients with and without cardiac ischemic events

The relationship between baseline characteristics and the incidence of cardiac ischemic events for all PCI patients and the TA patients are shown in **Table 2a** and **2b** respectively. In all PCI treated patients, parameters associated with cardiac ischemic events were known risk factors as age, history of diabetes mellitus, history of cardiac ischemic events, multivessel disease, infarct related segment in the left coronary artery (LCA). Patients with cardiac ischemic events had smaller vessel diameter and shorter stent length, and were less often treated with thrombus aspiration, direct stenting, and GP IIb/IIIa inhibitors. In TA patients only, the same trend was seen as in the whole PCI population, but only multivessel disease was significantly associated with cardiac ischemic events. In this group, slightly more patients with cardiac ischemic events had undergone direct stenting.

Table 2a. Baseline clinical, therapeutic and angiographic characteristics with and without cardiac ischemic event in all PCI patients

	Yes 203		No 793		p-value (2-tailed)
Baseline demographic and clinical data					
Age, years, mean (± SD)	66	(12)	62	(13)	0.00
Gender, male, N (%)	76	(37.4)	628	(79.2)	0.23
History, N (%)					
hypertension	72/200	(36.0)	273/768	(35.5)	0.91
diabetes mellitus	37/202	(18.3)	74/785	(9.4)	0.00
myocardial infarction	31/202	(15.3)	65/784	(8.3)	<0.01
PCI	25/202	(12.4)	46/781	(5.9)	<0.01
CABG	14/202	(6.9)	20/785	(2.5)	<0.01
Current smoking, N (%)	77/167	(46.1)	339/703	(48.2)	0.62
Total ischemic time, min, median (IQR)	185	(140-309)	186	(134-290)	0.87
Angiographic and procedural data					
Multivessel disease, N (%)	163/203	(80.3)	512/794	(64.5)	0.00
Infarct related vessel LCA, N (%)	102/192	(53.1)	328/787	(41.7)	<0.01
Pre-procedural TIMI flow 0/1, N (%)	129/202	(63.9)	461/784	(58.8)	0.19
Pre-procedural thrombus, N (%)	102/200	(51.0)	397/775	(51.2)	0.30
Collaterals, N (%)	63./198	(31.8)	231/773	(29.9)	0.60
Stent diameter, mm, mean (±SD)	2.8	(1.2)	3.1	(1.0)	0.00
Stent length, mm, mean (±SD)	17.3	(9.6)	19.1	(8.4)	<0.01
Thrombus aspiration	63/203	(31.0)	374/739	(50.6)	0.00
Stenting without predilation, N (%)	71/203	(35.0)	340/739	(46.0)	0.04
Glycoprotein IIb/IIIa inhibitors, N (%)	174/203	(85.7)	736/739	(99.6)	<0.01
Post-procedural outcome					
Post-procedural TIMI flow 2/3, N (%)	190/199	(95.5)	768/789	(97.3)	0.17
Post-procedural distal embolization, N (%)	9/165	(5.5)	41/706	(5.8)	0.86
Post-procedural MBG 2/3, N (%)	138/193	(71.5)	620/778	(79.7)	0.01
CKMB*, Ug/l, ln, mean (±SD)	3.83	(1.5)	3.77	(1.3)	0.20
ECG ST-segment resolution >70%, N (%)	69/189	(36.5)	398/736	(54.1)	0.00

N=number, SD= standard deviation, IQR=interquartile range, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, LCA=left coronary artery, TIMI=thrombolysis in myocardial infarction, CKMB=creatinine kinase myocardial band fraction

Table 2b. Baseline clinical, therapeutic and angiographic characteristics with and without cardiac ischemic event in patients receiving PCI with thrombus aspiration

	Yes 69		No 383		p-value (2-tailed)
Baseline demographic and clinical data					
Age, years, mean (± SD)	65	(12)	62	(13)	0.09
Gender, male, N (%)	52	(75.4)	252	(65.6)	0.12
History, N (%)					
hypertension	22/68	(32.4)	126/365	(34.5)	0.73
diabetes mellitus	12/69	(17.4)	38/378	(10.1)	0.08
myocardial infarction	6/69	(8.7)	26/376	(6.9)	0.60
PCI	6/69	(8.7)	21/375	(5.6)	0.32
CABG	5/69	(7.2)	7/377	(1.9)	0.01
Current smoking, N (%)	24/58	(41.4)	173/345	(50.1)	0.21
Total ischemic time, min, median (IQR)	180	(140-300)	191	(137-295)	0.28
Angiographic and procedural data					
Multivessel disease, N (%)	56/69	(81.2)	245/384	(64.0)	<0.01
Infarct related vessel LAD*, N (%)	33/65	(50.8)	167/380	(43.9)	0.31
Pre-procedural TIMI flow 0/1, N (%)	43/69	(62.3)	221/379	(58.3)	0.53
Pre-procedural thrombus, N (%)	37/68	(54.4)	188/372	(50.5)	0.56
Collaterals, N (%)	19/66	(26.9)	101/375	(26.9)	0.76
Stent diameter, mm, mean (±SD)	2.9	(1.1)	3.1	(1.0)	0.13
Stent length, mm, mean (±SD)	18.3	(8.8)	19.0	(8.3)	0.49
Stenting without predilation, N (%)	44/69	(63.8)	229/383	(59.8)	0.53
Glycoprotein IIb/IIIa inhibitors, N (%)	63/69	(91.3)	366/383	(95.6)	0.14
Atherothrombotic material					
Retrieved atherothrombotic material, N (%)	48/69	(69.6)	281/383	(73.4)	0.51
Material size >0.5mm, mm, N (%)	32/67	(47.8)	200/363	(55.1)	0.27
Post-procedural outcome					
Post-procedural TIMI flow 2/3, N (%)	1/69	(1.4)	10/382	(2.6)	0.56
Post-procedural distal embolization, N (%)	4/61	(6.6)	23/349	(6.6)	1.00
Post-procedural MBG 2/3, N (%)	8/68	(11.8)	63/376	(16.8)	0.30
CKMB*, Ug/l, ln, mean (±SD)	3.78	(1.4)	3.82	(1.2)	0.79
ECG ST-segment resolution >70%, N (%)	29/62	(46.8)	217/360	(60.3)	0.05

N=number, SD= standard deviation, IQR=interquartile range, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, LCA=left coronary artery, TIMI=thrombolysis in myocardial infarction, MBG=myocardial blush grade, CKMB=creatinine kinase myocardial band fraction

Predictors of cardiac ischemic events in all PCI patients

The multivariate impact of baseline characteristics on cardiac ischemic events, including all cause death, and cardiac death at follow-up for all PCI patients and the TA patients are shown in **Table 3**. Predictors of cardiac ischemic events for all PCI patients remained age, diabetes mellitus, history of myocardial infarction, angiographic infarct related segment in de LCA. The use of TA and GP IIb/IIIa inhibitors both remained predictors of less cardiac ischemic events. A test for a possible interaction between the positive effect of the use of GP IIb/IIIa inhibitors and TA was non-significant (p=0.92). The effect of TA on cardiac ischemic event was dictated mainly by an effect of TVR (Hazard ratio (HR) 0.59, 95% Confidence interval (CI) [0.41-0.85] p<0.01, not shown in Table), and also to some extent by cardiac mortality (**Table 3**). The use of GP IIb/IIIa inhibitors also showed a positive effect on all-cause death. There were no predictors of non-fatal reinfarction identifiable. TVR was predicted by gender (HR 0.61, 95% CI [0.39-0.95]), multivessel disease (HR 2.03, 95% CI [1.33-3.11]), and infarct related segment in the LCA (HR 1.60, 95% CI [1.13-2.28]).

Predictors of cardiac ischemic events in thrombus aspirated patients

Cardiac ischemic events in the TA patients were associated with diabetes mellitus and angiographically multivessel disease (**Table 3**). Predictors of all-cause mortality were similar to cardiac mortality. In this group of patients, pre-procedural thrombus was a predictor of mortality. In addition to the use of GP IIb/IIIa inhibitors, the retrieval of atherothrombotic material was associated with less mortality. As the presence of angiographically visible pre-procedural thrombus could influence the possibility for retrieval of material, an interaction term for these parameters was added to the final model. This interaction was non-significant (p=0.84). There were no predictors of reinfarction or TVR identifiable.

Table 3. Multivariate predictors of cardiac ischemic events in all PCI patients and PCI with thrombus aspiration patients at 2 years of follow-up

	All PCI						PCI with TA					
	Cardiac ischemic event		Death		Cardiac death		Cardiac ischemic event		Death		Cardiac death	
Predictors	**HR**	**[95% CI]**	**HR**	**[95% CI]**	**HR**	**[95% CI]**	**HR**	**[95% CI]**	**HR**	**[95% CI]**	**HR**	**[95% CI]**
Clinical factors												
Age >65 year	2.31	[1.42-3.74]	4.71	[2.56-8.66]	4.10	[1.92-8.75]		NS	2.50	[1.08-5.75]		NS
Diabetes mellitus	2.96	[1.77-4.96]	3.24	[1.91-5.49]	4.95	[2.75-8.90]	1.75	[0.94-3.26]	2.81	[1.17-6.78]	3.88	[1.47-10.23]
Previous myocardial infarction	2.43	[1.34-4.39]		NS		NS		NS		NS		NS
Angiographic and procedural factors												
Multivessel disease		NS		NS		NS	2.25	[1.23-4.12]		NS		NS
Infarct related vessel LCA	1.80	[1.13-2.86]		NS		NS		NS	1.80	[1.13-2.86]		NS
Pre-procedural thrombus		NS		NS		NS		NS	3.02	[1.25-7.32]	4.03	[1.41-11.55]
Thrombus aspiration	0.57	[0.35-0.93]		NS	0.53	[0.29-0.97]		-		-		-
Glycoprotein IIb/IIIa inhibitors	0.37	[0.19-0.70]	0.41	[0.20-0.83]	0.29	[0.14-0.61]		NS	0.37	[0.19-0.70]	0.19	[0.05-0.67]
Retrieved material		-		-		-		NS	0.41	[0.18-0.89]	0.33	[0.13-0.86]

PCI=percutaneous coronary intervention, TA=thrombus aspiration, HR= hazard ratio, CI=confidence interval, LCA=Left Coronary Artery, NS=non-significant

DISCUSSION

In this contemporary STEMI population treated with primary PCI including TA, and pharmacologically according to current guidelines, TA was associated with a lower risk of long-term composite cardiac ischemic events and cardiac death. The long-term incidence of composite cardiac ischemic events in all PCI treated patients was 20.5%. For TA patients, this incidence was 15.2%. Other factors associated with cardiac ischemic events and cardiac – as well as all-cause mortality included age and the presence of diabetes mellitus. In the TA patients in this analysis, age and diabetes mellitus and the presence of pre-procedural thrombus was independently associated with mortality. Retrieval of atherothrombotic material was on the contrary associated with a significantly lower risk of mortality.

A previous study of patients with an acute coronary syndrome have reported that the risk of adverse cardiac events was related to clinical factors, including age, female sex, diabetes mellitus, previous history of CAD, ECG changes on admission, and elevated CK-MB or cardiac troponin levels.[14] This study included angiographic characteristics and showed that these were independent predictors of adverse events, along with such clinical factors as a prior history of PCI, renal insufficiency, and age. However, the study included only 25% STEMI patients. A recent study in STEMI patients involving the use of different thrombus aspiration devices and unknown selection criteria focused on the predictive role of older thrombus on mortality, and identified similar clinical factors associated with long-term mortality as in the TA patients in our study. This study did not report on rates of angiographically visible pre-procedural thrombus or retrieval of atherothrombotic material.[20]

Angiographically visible thrombus being a known predictor of mortality in patients with acute coronary syndromes[14] intuitively suggests that removal of atherothrombotic material would improve outcome. Although TIMI flow 3 was achieved in 98% of our patients undergoing TA and thrombus aspiration studies show that a variety of atherothrombotic components are extractable,[5,20,21] there is still little evidence for how much of an intracoronary thrombus is actually retrieved during TA. Thrombus still in situ or having been embolized after TA have been reported.[22-24] To the best of our knowledge, this study is the first to relate thrombus removal with improved long-term mortality. A possible explanation could be that the presence of unresolved thrombus may lead to incomplete apposition with resulting impaired infarct related patency. However, in this analysis, retrieval of material was not reflected in improved TVR. This suggests that the benefit of retrieval of material is related to less microvascular obstruction and better myocardial reperfusion with a positive effect on left ventricular remodeling,[25] rather than decreased recurrent ischemia.

It has been suggested that the higher rate of stenting without predilation with TA has influenced the positive effect of this treatment modality. Stenting without predilation in patients not treated with TA has shown to improve myocardial reperfusion,[26,27] and has in a recent meta-analysis has demonstrated to improve outcome, primarily by reducing the incidence of myocardial infarction at six months follow-up.[28] Suggested mechanisms of the effect of stenting without predilation has been decreased invasiveness during PCI, with less repeat balloon dilations and vessel wall injury, which may also be considered a

dominant risk factor for embolization. Because stenting without predilation is more likely done when antegrade coronary flow is visible on coronary angiography allowing for identification of the culprit lesion and, in turn, calibration to the appropriate stent length, another possible explanation is selection bias of patients with better antegrade flow at baseline and with consequently better perfusion and outcome than patients presenting without flow. As removal of thrombus increases the antegrade coronary flow, stenting without predilation is more frequently applied in patients undergoing TA. In this study, stenting without predilation yields no benefit in terms of long-term outcome. This may be due to a limited number of patients or to potential embolization during the crossing attempt of the infarct related lesion with a stent.

TA is not able to prevent microvascular obstruction that has occurred prior to PCI or that has been induced by primary PCI.[29,30] Therefore, adjunctive pharmacological therapies seem to be needed to target these sources of microvascular obstruction. Platelets have been found to form the main constituent of thrombus aspirated from the epicardial arteries of patients with STEMI. The antagonism of platelet aggregation with GP IIb/IIIa inhibitors has been shown to enhance the recovery of microvascular perfusion with a concomitant recovery of contractile function of ischemic myocardium,[31] and to improve short- and long-term outcome after primary PCI.[32,33] Theoretically, addressing platelet aggregates that have already accumulated in the microcirculation, the use of GP IIb/IIIa inhibitors would add to the effect of TA. In this analysis we found that GP IIb/IIIa inhibitors and TA were associated with favourable long-term outcome independently of the respective other therapy. These findings are consistent with a subanalysis from the Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data (ATTEMPT) study showing that patients treated with both thrombectomy and GP IIb/IIIa inhibitors had a lower mortality rate than patients receiving only one of these therapies.[7] Treatment with GP IIb/IIIa inhibitors were however not based upon randomization in our and the other studies, and in the present study, the thrombus aspirated patients received slightly more frequently GP IIb/IIIa inhibitors compared to the PCI patients treated without TA, which might be related to selection bias. Therefore, the suggestion that GP IIb/IIIa inhibitors would add to the effect of TA is hypothesis generating.

Limitations

Several limitations can be addressed. First, the predictors of long-term outcome only apply to the patients studied within the TAPAS trial that actually underwent primary PCI. On the other hand, broad inclusion criteria as in the TAPAS trial make the results still be translatable to a large amount of STEMI patients. We recorded the reasons for a different treatment behavior in order to define the population to which the results are applicable. In the TA patients, the data are implementable to patients in which TA was intended, but technically not possible due to lesion characteristics as turtuosity and distal vessels. Furthermore, in the line of the present study being a substudy, the results should be considered exploratory and hypothesis generating. Especially, the relative effect of the procedural factors that are prone to selection bias, like direct stenting and the use of GP IIb/IIIa inhibitors, should be analyzed in a randomized setting. Finally, the outcome of cardiac ischemic events should be viewed with caution given its composite nature.

However, we believe that reporting the different components of this endpoint brings transparency to the data.

CONCLUSION

In a contemporary STEMI population treated with primary PCI, in addition to clinical risk factors of long-term outcome, such as age, diabetes mellitus and history of myocardial infarction, the use of TA was favorably associated with long-term composite cardiac ischemic events. With the use of TA, cardiac adverse events still occur, and factors as age, diabetes mellitus, and angiographically visible pre-procedural thrombus remain predictors of outcome. Retrieval of atherothrombotic material was associated with reduced mortality in long-term follow-up. The findings lend support to the use of manual TA in patients treated with primary PCI and to the concept that reduction of thrombus load is an important mechanism of its beneficial effect.

TAPAS INVESTIGATORS

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Chapter 5

Summary of results and future perspectives

SUMMARY AND GENERAL DISCUSSION

ST-segment elevation myocardial infarction (STEMI) is generally caused by rupture or erosion of atherosclerotic plaque and subsequent platelet aggregation and thrombosis, resulting in acute occlusion of a coronary artery. Cessation of antegrade flow to the myocardium will lead to ischemia and later necrosis of the myocardium, which is associated with left ventricular dysfunction and increased mortality. Timely restoration of flow and perfusion of the myocardium are key factors in the treatment of STEMI.[1,2] Primary percutaneous coronary intervention (PCI) has emerged as the preferred therapy for STEMI.[3,4] The strategy of primary PCI developed in the 1980's after thrombolysis was established. While primary PCI in the late eighties comprised balloon angioplasty resulting in better survival when compared to thrombolytic therapy, the introduction of intracoronary stents has showed even better short- and long-term results in terms of a benefit in revascularization rates. To further improve the outcome of STEMI patients, additional interventions have to be investigated. This thesis focus on the role of removing atherothrombotic material with thrombus aspiration in primary PCI. In addition, general aspects of the invasive and pharmacological management of STEMI are described.

The **First part** of the thesis outlines a historical perspective of developments in the understanding of the pathophysiology and management of STEMI.

The **Second part** of the thesis focuses on the components of primary PCI, including stents and adjunctive pharmacological therapy. **Chapter 2.1** is a response to an article of David Massel addressing a hypothetical evaluation of the effect of PCI in acute myocardial infarction versus no treatment.[5] Using data from 30 trials and sophisticated statistical techniques, the author showed a synthesized odds ratio for mortality for primary PCI versus placebo/untreated controls of 0.56, consistent with a hypothetical reduction in short-term risk of death by 44%. We commented that the study confirms the importance of an invasive approach in patients who would receive no treatment when ineligible for thrombolysis, i.e. patients with a non-diagnostic electrocardiogram, presentation after the conventional reperfusion time window, and patients with contra-indications for thrombolysis.

The use of stents during primary PCI are based on a benefit in revascularization rates, but has failed to show a benefit is survival so far. Reocclusion as a parameter of infarct-related vessel patency has shown to be a stronger predictor of reduced left ventricular function and cardiovascular mortality than revascularization rates.[6,7] Therefore, we analyzed the effect of bare metal stenting (BMS) in rates of reocclusion, restenosis, and subacute thrombosis in **Chapter 2.2**. Analyzing 10 RCTs including 6192 patients, comparing BMS implantation with balloon angioplasty we found an impressive reduction in rates of reocclusion (6.7% vs 10.1%, $p=0.03$) and restenosis (23.9% vs 39.3%, $p<0.001$), but no reduction in rates of subacute thrombosis (1.7% in both groups). We believe that these findings support BMS placement in STEMI.

The administration of glycoprotein (GP) IIb/IIIa inhibitors is considered to provide additional benefit to mechanical reperfusion in the treatment of patients with STEMI.[8,9] In **Chapter 2.3** we comment on the study of Montalescot and co-workers reporting the 3-year results of the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) study, which is the

first demonstration of a persistent benefit of the GP IIb/IIIa inhibitor Abciximab for a follow-up duration beyond 1 year.[10] The long-term results of 288 patients showed a favorable trend in all-cause mortality and the composite endpoint of death, recurrent myocardial infarction, and urgent target vessel revascularization, albeit not significant. In our editorial, we gave a view of the data from the individual randomized controlled trials and meta-analyses at the time the editorial was written and conclude that GP IIb/IIIa inhibitors play an important role in the management of patients treated with primary PCI. We noted that most benefit is seen with early, pre-hospital treatment in the first hours of acute STEMI, and that it's additive effect in relation to clopidogrel and the optimal dose needs to be investigated in new studies. After our editorial on the use GP IIb/IIIa inhibitors in STEMI, a large amount of new data has been published.[11-16] An example is the ON-TIME 2 trial, in which pre-hospital initiation of high-dose tirofiban in association with aspirin, clopidogrel (600mg), and heparin improved ST-segment resolution without an increase in major bleeding, but was not associated with more patency of the infarct related vessel or a significant clinical benefit compared with placebo.[14]

Although results of primary PCI are improved with additional stenting and adjunctive pharmacological therapy, myocardial reperfusion is often limited by microvascular obstruction by embolization of thrombus from the infarct related lesion with occlusion of distal vessels, contributing to increased infarct size and reduced survival.[17] In recent years, thrombectomy devices have been evaluated for their role in preventing distal embolization. In the **Third part** of the thesis, we describe the design, primary and secondary outcomes of the Trombus Aspiration in Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) assessing whether manual thrombus aspiration was superior to conventional PCI with balloondilatation during primary PCI. In **Chapter 3.1** we showed the design of the study, which was a single-center, prospective, randomized trial with a planned inclusion of 1080 patients with STEMI. Patients were assigned to treatment with thrombus aspiration with the 6F Export Aspiration Catheter (Medtronic Corporation, Santa Rosa, California) or to balloon angioplasty before stent implantation in the infarct-related artery. Pharmacological treatment were according to current international guidelines including GP IIb/IIIa inhibitors before PCI. Randomization was performed before coronary angiography. The primary end point was angiographic myocardial blush grade (MBG) of 0 or 1 as marker of impaired myocardial perfusion. Secondary end points were enzymatic infarct size, ST-segment elevation resolution and persistent ST-segment elevation, post-procedural distal embolization, and major adverse cardiac events at 30 days and 1 year.

The primary study results are outlined in **Chapter 3.2** and showed that thrombus aspiration improved myocardial reperfusion.[18] A MBG of 0 or 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional-PCI group ($P<0.001$). Complete resolution of ST-segment elevation occurred in 56.6% and 44.2% of patients, respectively ($P<0.001$). This beneficial effect of aspiration was consistently present in all patients, irrespective of baseline clinical or angiographic characteristics such as age, sex, total ischemic time, infarct-related coronary artery, pre-procedural TIMI flow, or visible thrombus on the angiogram. There was an improvement in the clinical outcome, although not significant at 30 days. The rate of death in patients with a MBG of 0 or 1, 2, and 3 was 5.2%, 2.9%, and 1.0%, respectively ($P=0.003$), and the

rate of major cardiac adverse events was 14.1%, 8.8%, and 4.2%, respectively (P<0.001). Histopathological examination confirmed successful aspiration in 72.9% of patients. Therefore, we concluded that thrombus aspiration is applicable in a large majority of patients with myocardial infarction with ST-segment elevation, and it results in better myocardial reperfusion and clinical outcomes than conventional PCI, irrespective of clinical and angiographic characteristics at baseline. Why this trial showed favorable results in contrast to many previous trials with thrombectomy devices[19-22] is thought to be the simplicity of the device used, which relevance is amplified in the setting of acute myocardial infarction, when PCI is often performed out-of-hours, with reduced staffing capabilities and higher rates of procedural complications.[23] Moreover, the study size, broad inclusion criteria, and adjunctive pharmacologic treatment according to current guidelines make the data in the trial implementable to a contemporary STEMI population.

The benefits in restoration of myocardial reperfusion in thrombus aspiration was probably seen in terms of a positive effect on left ventricular remodeling,[24] with an effect on the late clinical outcome.[25] Data on 1-year mortality and reinfarction reported in **Chapter 3.3** did show a significant benefit with thrombus aspiration.[26] Cardiac death at 1 year was 3.6% (19 of 535 patients) in the thrombus aspiration group and 6.7% (36 of 536) in the conventional PCI group (hazard ratio [HR] 1.93; 95% confidence interval [CI] 1.11–3.37; p=0.020). 1-year cardiac death or non-fatal reinfarction occurred in 5.6% (30 of 535) of patients in the thrombus aspiration group and 9.9% (53 of 536) of patients in the conventional PCI group (HR 1.81; 95% CI 1.16–2.84; p=0.009). We concluded that compared with conventional PCI, thrombus aspiration before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for STEMI. A recent meta-analysis on individual patient data has confirmed the 1-year improvement in clinical outcome.[27] Recently, thrombectomy devices have been increasingly applied to prevent distal embolization.[28-30] Thrombus aspiration is now classified in the European Guidelines as a IIa A indication for treatment.[31]

As the TAPAS trial provided important support for thrombus aspiration as the preferred initial step in PCI in a general STEMI population, the **Fourth part** of this thesis focuses on role of thrombus aspiration in clinical practice regarding the relative role with other treatment components in PCI and the possible mechanisms of its effect. Suggested explanations to the effect of thrombus aspiration other than the reduction of thrombus load is the facilitation of stenting without predilation, with thereby less manipulation of the infarct related lesion with less risk of embolization,[32-35] and a synergistic effect with the concomitant use of a GP IIb/IIIa inhibitor.[36,37] In **Chapter 4.1** five cases of patients with an acute total coronary occlusion are demonstrated in which only thrombus aspiration as a definite treatment of STEMI resulted in complete restoration of epicardial blood flow without significant residual stenosis or signs of plaque rupture. At follow up, ranging from 6 months to 1 year, all patients remained event-free, indicating that thrombus aspiration as a standalone therapy without additional angioplasty with balloon or stent placement was safe and effective in these five patients. **Chapter 4.2** shows predictors of long-term cardiac ischemic events in STEMI patients treated with PCI including thrombus aspiration in the TAPAS trial. In a contemporary STEMI population predictors of long-term composite cardiac ischemic events were age, diabetes mellitus, history of myocardial

infarction, and culprit in the left coronary artery. The use of thrombus aspiration was favorably associated with long-term composite cardiac ischemic events. With the use of thrombus aspiration, factors as age, diabetes mellitus, and angiographically visible pre-procedural thrombus remained associated with outcome. In addition, retrieval of atherothrombotic material was associated with reduced mortality in long-term follow-up. These findings lend support to the use of manual thrombus aspiration in primary PCI and to the concept that reduction of thrombus load is an important mechanism of a beneficial effect of thrombus aspiration.

FUTURE PERSPECTIVES

Improvements in treatment options for STEMI patients have changed the prognosis of these patients. The number of major adverse cardiac events has decreased with thereby increased limitation in power to show effect of an intervention on clinical outcome. Therefore, the evaluation of new treatment strategies for myocardial infarction either has to be done in a large group of patients, for which a meta-analysis can be a helpful instrument, or the primary outcome has to be a surrogate of or a combination of major adverse cardiac events. This trend is reflected in this thesis. With over 1000 patients included in the TAPAS-trial, a primary surrogate endpoint and also a combination of major adverse cardiac events are used for the evaluation of an effect. As previously shown,[38] this trial found a very strong relationship between the MBG 0 or 1 and ST-segment elevation resolution as markers of reperfusion with clinical outcome, and it may be suggested that future trials would selectively focus on these surrogate endpoints for effect evaluation.

Despite the use of thrombus aspiration, distal embolization of atherothrombotic material occurs, and there is room forfurther improvement. A major limitation of thrombus aspiration is its inability to prevent microvascular obstruction that has occurred prior to PCI or that has been induced by primary PCI.[39] Adjunctive pharmacological therapies seem to be needed to target these sources of microvascular obstruction beyond the present antiplatelet therapy include acetylsalicylzuur, clopidogrel, GP IIb/IIIa antagoinists, and heparin. The role of GP IIb/IIIa inihibitors administered as an intracoronary bolus has shown to be beneficial in a restricted amount of patients.[40,41] The local application may target distal embolization more effectively, with less bleeding complications. Currently, the Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial is aiming to include 530 patients to evaluate the effect of intracoronary weight-adjusted abciximab on angiographic and clinical outcome.[42] Recently, prasugrel, a next generation thienopyridine, has shown to work faster and more efficient than clopidogrel.[43-44]

In addition to therapy targeting the thrombus, current research is directed towards improving myocardial function and preserving left ventricular function. One of the strategies is to investigate the the role of stem-cells and progenitor cells through stimulating angiogensis. These therapies have so far not shown improvement in left-ventricular function, but the use of erythropoetin was related to less major adverse cardiovascular events.[45,46]

Retrieved thrombus provides material for further investigation of the pathophysiology of atherosclerosis, thrombus formation, and the mechanism of plaque rupture.[47,48] Thrombus aspiration enables the histopathological analysis of platelets, erythrocytes, inflammatory cells, and plaque components. The role of genetic markers is in addition an interesting field of further research.[49] By finding relationships between thrombus composition and outcome such as vessel patency and myocardial perfusion, thrombus characteristics may become of value in clinical risk assessment[47,50] and therewith provide information for improving reperfusion therapies in acute STEMI.

CONCLUSION

Prognosis of STEMI patients has improved the last decennia due to the invasive and pharmacological strategies targeting the occluding thrombus to restore epicardial coronary artery flow. Epicardial reperfusion does not always lead to adequate myocardial reperfusion, which for a substantial part is due to distal embolization of atherothrombotic material. Although no therapy has yet 'solved' the problem of distal embolization in patients undergoing primary PCI for STEMI, this thesis shows a favorable effect of thrombus aspiration in improving myocardial reperfusion and long-term clinical outcome. Thrombus aspiration also holds diagnostic promise as thrombus characterization provides us with material for pathophysiological studies and clinical risk assessment. This may subsequently provide us with information for further improvement of pharmacological and mechanical therapies.

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Samenvatting en discussie

Sammendrag og diskusjon

SAMENVATTING EN DISCUSSIE

ST-segment elevatie myocardinfarct (STEMI) wordt meestal veroorzaakt door een ruptuur van een atherosclerotische plaque gevolgd door plaatjesaggregatie en trombosevorming, wat leidt tot een acute afsluiting van een coronairarterie. Hierdoor wordt de toevoer van bloed naar het myocardweefsel beperkt en treedt ischemie en later necrose van het myocard op. Dit is geassocieerd met linker ventrikel dysfunctie en verhoogde mortaliteit. Vroeg herstel van de doorbloeding van de coronairarterie en perfusie van het myocard is daarom essentieel in de behandeling van STEMI.[1,2] Primaire percutane coronaire interventie (PCI) is de voorkeursbehandeling voor STEMI.[3,4] Deze behandelingsstrategie werd ontwikkeld in de jaren 1980 toen patiënten met een myocardinfarct in de regel behandeld werden met trombolyse. Primaire PCI in de tachtiger jaren omvatte ballonangioplastiek en resulteerde in betere overleving vergeleken met trombolyse. Later werd de angioplastiek gecombineerd met het achterlaten van een intracoronaire stent die een vermindering van het aantal revascularisaties van de infarctgerelateerde coronairarterie liet zien vergeleken met angioplastiek plaatsing van een stent. Vervolgens werden aanvullende interventies gericht op het verbeteren van de prognose van STEMI-patiënten onderzocht, zoals optimale farmacologische behandeling. Dit proefschrift richt zich met name op de rol van het weghalen van atherotrombotisch materiaal met behulp van aspiratie gedurende PCI. Daarnaast worden algemene aspecten van de invasieve en aanvullende farmacologische behandeling van STEMI-patiënten onderzocht.

Het **Eerste deel** van het proefschrift geeft de ontwikkeling in de kennis over de pathofysiologie en behandeling van STEMI-patiënten kort weer.

Het **Tweede deel** van het proefschrift is gericht op de componenten van primaire PCI met betrekking tot aanvullende farmacologische behandeling en intracoronaire stents. **Hoofdstuk 2.1** is een reactie op een publicatie van David Massel, waarin een evaluatie van het effect van PCI vergeleken met geen reperfusiebehandeling voor een acuut myocardinfarct wordt gegeven.[5] Deze vergelijking heeft nooit in een gerandomiseerde setting plaatsgevonden aangezien primaire PCI werd ontwikkeld nadat trombolyse een geaccepteerde behandelingsvorm was. Met data van 30 studies en geavanceerde statistische technieken laat de auteur een gesynthetiseerde odds ratio voor mortaliteit met primaire PCI vergeleken met onbehandelde controles zien van 0.56, wat overeenkomt met een theoretische afname van korte-termijn risico op overlijden van 44%. We merken op dat deze studie het belang benadrukt van een invasieve benadering bij patiënten met een contra-indicatie voor trombolyse, een niet-diagnostisch electrocardiogram, of een presentatie buiten het afgesproken reperfusietijdsinterval,

Het gebruik van stents gedurende primaire PCI is gebaseerd op een vermindering van het aantal revascularisaties, maar heeft geen voordeel laten zien ten aanzien van mortaliteit vergeleken met PCI zonder stentplaatsing. Reocclusie wordt beschouwd als een betere voorspeller voor gereduceerde linker ventrikel functie en cardiovasculaire mortaliteit dan het aantal revascularisaties.[6,7] In **Hoofdstuk 2.2** hebben we daarom het effect onderzocht van het plaatsen van een "bare metal stent" (BMS) op reocclusie, restenose en subacute trombose. Door het samenvoegen van de resultaten van in totaal 6192 patiënten in 10 gerandomiseerde studies die BMS implantatie vergelijken met ballondilatatie, werd een indrukwekkende reductie gevonden in het aantal

reocclusies (6.7% vs 10.1%, p=0.03) en restenoses (23.9% vs 39.3%, p<0.001), maar geen vermindering in het aantal subacute tromboses (1.7% in beide groepen). Deze bevindingen ondersteunen het gebruik van BMS in STEMI.

Het toedienen van glycoprotein (GP) IIb/IIIa remmers speelt een belangrijke rol naast de mechanische reperfusie bij patiënten met STEMI.[8,9] In **Hoofdstuk 2.3** reageren we op een artikel van Montalescot en collegae die de 3-jaar resultaten geven van de 'Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up' (ADMIRAL) studie, de eerste studie die een voordeel laat zien met de GP IIb/IIIa remmer abciximab bij een follow-up duur van langer dan 1 jaar.[10] De studie liet met 288 patiënten een trend zien in de afname van de mortaliteit en het gecombineerde eindpunt van dood, recidief van myocardinfarct, en spoedrevascularisaties van het infarctvat ('major adverse cardiac events', MACE). In ons commentaar lieten we data zien van enkele gerandomiseerde studies en meta-analyses die bekend waren toen het geschreven werd. Hieruit concludeerden we dat het gebruik van GP IIb/IIIa remmers van toegevoegde waarde is in de behandeling van patiënten met primaire PCI. We merkten op dat het meeste voordeel wordt gezien met vroege, prehospitale behandeling, en dat een aanvullend effect ten aanzien van clopidogrel en de optimale dosis onderzocht moeten worden in nieuwe studies. Later zijn veel data gepubliceerd over GP IIb/IIIa remmers in STEMI.[11-16] Een voorbeeld is de ON-TIME 2 studie, waarin prehospitale initiatie van een hoge dosis tirofiban samen met aspirine, clopidogrel (600mg), en heparine de ST-segment resolutie verbeterde zonder een toename van belangrijke bloedingscomplicaties, maar ook zonder significante verbetering in klinische eindpunten vergeleken met de controlegroep.[14]

Hoewel de resultaten met primaire PCI verbeterd zijn met stentplaatsing en aanvullende farmacologische therapie, wordt myocardiale reperfusie vaak beperkt door microvasculaire obstructie door embolisatie en occlusie van distale vaten, die bijdraagt tot toename van infarctgrootte en verminderde overleving.[17] In de laatste jaren zijn trombectomiecatheters geëvalueerd ter voorkoming van distale embolisatie. In het **Derde gedeelte** van dit proefschrift beschrijven we de opzet en de primaire - en secundaire eindpunten van de Thrombus Aspiration in Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) studie, die beoordeelt of manuele trombusaspiratie een betere microvasculaire reperfusie geeft vergeleken met conventionele PCI met ballondilatatie gedurende primaire PCI. In **Hoofdstuk 3.1** laten we de opzet zien van deze prospectieve en gerandomiseerde studie, met een geplande inclusie van 1080 patiënten met STEMI. Patiënten werden gerandomiseerd voor trombusaspiratie met de 6F Export Aspiration Catheter (Medtronic Corporation, Santa Rosa, California) of ballondilatatie voorafgaand aan het plaatsen van een intracoronaire stent. Farmacologische behandeling was conform de huidige internationale richtlijnen en bevatte GP IIb/IIIa remmers gevolgd door PCI. Randomisatie vond plaats voorafgaand aan het verrichten van een coronairangiogram. Het primaire eindpunt was de angiografisch myocardiale blush graad (MBG) van 0 of 1 als uiting van beperkte myocardiale perfusie. Secundaire eindpunten waren enzymatische infarct-grootte, resolutie van ST-segment elevatie, postprocedurele distale embolisatie, en het aandeel MACE na 30 dagen en 1 jaar.

De primaire resultaten van de studie zijn weergegeven in **Hoofdstuk 3.2** en lieten zien dat trombusaspiratie de myocardiale reperfusie verbeterde.[18] Een MBG van 0 of

1 was in 17.1% van de patiënten in de trombusaspiratie groep aanwezig en in 26.3% van de patiënten in de conventionele PCI groep (P<0.001). Complete resolutie van de ST-segment elevatie vond respectievelijk plaats in 56.6% en 44.2% van de patiënten (P<0.001). Dit gunstige effect van aspiratie was onafhankelijk van klinische of angiografische kenmerken zoals leeftijd, geslacht, totale ischemietijd, infarctgerelateerd coronairvat, preprocedurele "thrombolysis in myocardial infarction (TIMI) flow", of een zichtbare trombus op het angiogram. Een verbetering in klinische uitkomstparameters werd gezien, echter niet significant na 30 dagen. Het aantal doden bij patiënten met een MBG van 0 of 1, 2, en 3 was 5.2%, 2.9%, en 1.0% (P=0.003), en het aandeel MACE was 14.1%, 8.8%, en 4.2% (P<0.001). Histopathologisch onderzoek bevestigde succesvolle aspiratie bij 72.9% van patiënten. We concludeerden dat trombusaspiratie toepasbaar is in een grote meerderheid van patiënten met een acuut myocardinfarct, en leidt tot betere myocardiale reperfusie en klinische uitkomst dan conventionele PCI. Waarom deze studie gunstige resultaten liet zien vergeleken met eerdere studies met trombectomiecatheters[19-22] heeft mogelijk te maken met het feit dat de catheter eenvoudig in gebruik is. De relevantie daarvan is toegenomen in geval van een acuut MI, wanneer PCI wordt verricht buiten kantooruren en met minder personeel en hogere procedurele complicaties.[23] Verder maken de studiegrootte, brede inclusiecriteria, en aanvullende farmacologische behandeling volgens de huidige richtlijnen de bevindingen toepasbaar in een actuele populatie van patiënten met een STEMI.

De verbetering in myocardiale reperfusie heeft vermoedelijk een positief effect op linker ventrikel remodellering,[24] met een effect op late klinische uitkomstvariabelen.[25] De 1-jaars mortaliteit en reinfarct gegevens gerapporteerd in **Hoofdstuk 3.3** lieten inderdaad een positief effect zien van trombusaspiratie.[26] Cardiale dood na 1 jaar bedroeg 3.6% (19 van 535) van patiënten in de trombusaspiratie groep en 6.7% (36 van 536) in de conventionele PCI groep (hazard ratio [HR] 1.93; 95% confidence interval [CI] 1.11–3.37; p=0.020). Cardiale dood of niet-fataal reinfarct vond plaats in 5.6% (30 van 535) en 9.9% (53 van 536) (HR 1.81; 95% CI 1.16–2.84; p=0.009). We concludeerden dat trombusaspiratie de 1-jaars klinische uitkomsten na PCI voor STEMI verbeterden vergeleken met conventionele PCI. Een recente meta-analyse met individuele patiëntendata heeft het 1-jaars uitkomst bevestigd.[27] Catheters voor trombectomie zijn ook in recente studies beoordeeld op preventie van distale embolisatie.[28-30] Trombus aspiratie wordt nu omschreven in de Europese Richtlijnen als een IIa A behandelingsindicatie.[31]

Omdat de TAPAS studie het gebruik van trombusaspiratie als een eerste stap in PCI in een algemene STEMI-populatie ondersteunt, richt zich het **Vierde deel** van dit proefschrift op de rol van trombusaspiratie in de klinische praktijk met daarbij de relatieve rol van andere behandelingscomponenten van PCI en mogelijke mechanismen voor een effect. Mogelijke verklaringen voor een effect naast afname van de hoeveelheid trombus is het faciliteren van het aanbrengen van een stent zonder predilatatie met daarbij minder manipulatie van de aan het infarct gerelateerde laesie[32-35] en een synergetisch effect met gelijktijdig gebruik van GP IIb/IIIa remmers.[36,37] In **Hoofdstuk 4.1** worden vijf patiëntencasussen beschreven met een acute totale coronaire occlusie, waarin trombusaspiratie gebruikt werd als enige en definitieve behandeling voor STEMI. Na de procedure werd een volledig herstel van de coronaire bloedstroom gezien zonder reststenose of tekenen van plaqueruptuur. Bij follow-up, die varieerde tussen 6 maanden

en 1 jaar, had geen van deze patiënten een cardiovasculair incident gehad, wat erop wijst dat trombusaspiratie als enige behandeling zonder additionele angioplastiek met ballon of stentplaatsing veilig en effectief was bij deze vijf patiënten. **Hoofdstuk 4.2** laat voorspellers zien van lange-termijn cardiale gebeurtenissen bij STEMI-patiënten behandeld met PCI en trombusaspiratie in the TAPAS studie. In een huidige STEMI-populatie zijn voorspellers van lange termijn cardiale ischemische gebeurtenissen: leeftijd, diabetes mellitus, een voorgeschiedenis met myocardinfarct, en de aan het infarct gerelateerde afwijking in de linker coronairarterie. Trombusaspiratie was positief geassocieerd met het ontbreken van lange-termijn cardiale ischemische gebeurtenissen. In de trombusaspiratie groep waren de factoren leeftijd, diabetes mellitus, en een angiografisch zichtbare preprocedurele trombus geassocieerd met een slechtere uitkomst. Bovendien was het verkrijgen van atherotrombotisch materiaal gerelateerd aan een afname in mortaliteit bij lange-termijn follow-up. Deze bevindingen ondersteunen het gebruik van trombusaspiratie in primaire PCI en het concept dat afname van de hoeveelheid trombusmateriaal een belangrijk mechanisme is voor het gunstige effect van trombusaspiratie.

TOEKOMSTPERSPECTIEVEN

Verbetering in de behandeling van STEMI patiënten heeft de prognose van deze patiëntengroep verbeterd. Het aantal cardiovasculaire gebeurtenissen na behandeling van STEMI is gedaald met daarbij een beperkte mogelijkheid om een effect van een interventie op klinische uitkomstparameters te laten zien. Daarom moet een evaluatie van nieuwe behandelingsstrategieën voor een myocardinfarct uitgevoerd worden in een grote groep patiënten. Een meta-analyse kan hiervoor een een hulpmiddel kan zijn. Eventueel kan gekeken worden naar een zogenaamd surrogaat eindpunt, of een gecombineerd eindpunt van ernstige cardiale complicaties als klinische uitkomst. Deze trend wordt gereflecteerd in dit proefschrift. Zelfs met meer dan 1000 geïncludeerde patiënten in de TAPAS studie werd een primair surrogaateindpunt en ook een combinatie van ernstige cardiale complicaties gebruikt ter evaluatie van een effect. Zoals eerder aangetoond[38] toonde deze studie een sterk verband aan tussen MBG 0 of 1 en ST-segment elevatie resolutie als marker voor reperfusie en een gunstige klinische uitkomst, en kunnen toekomstige studies mogelijk selectief deze surrogaat eindpunten gebruiken voor effectevaluatie.

Ook met het gebruik van trombusaspiratie vindt distale embolisatie van atherotrombotisch materiaal plaats; trombusaspiratie kan microvasculaire obstructie die heeft plaatsgevonden voor PCI of geïnduceerd is door de PCI niet voorkomen.[39] Aanvullende farmacologische behandelingsvormen gericht op de trombus zijn noodzakelijk om deze bronnen van microvasculaire obstructie te voorkomen, naast de huidige plaatjesremmers met acetylsalicylzuur, clopidogrel, GP IIb/IIIa remmers, en heparine. GP IIb/IIIa remmers toegediend als intracoronaire bolus lijken een gunstig effect te hebben.[40,41] Een plaatselijke behandeling in het coronairvat kan een meer effectieve aanpak van de distale embolisatie zijn voor wat betreft minder bloedingscomplicaties. Momenteel evalueert de "Comparison of IntraCoronary versus intravenous abciximab

administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO)" studie het effect van intracoronaire administratie van abciximab op angiografische en klinische uitkomstvariabelen.[42] Recent heeft prasugrel, een thienopyridine van de volgende generatie, een sneller en meer efficiënt effect laten zien dan clopidogrel.[43-44]

Naast behandeling met focus op de trombus, is huidig onderzoek gericht op verbetering van myocardiale functie en verbetering van linker ventrikelfunctie. Een van de strategieën is het onderzoek naar het stimulerende effect van stam- en progenitorcellen op de angiogenese. Tot nu heeft het toedienen van stamcellen geen verbetering laten zien in linker ventrikelfunctie na STEMI, maar het gebruik van erytropoetine was wel verbonden met minder cardiovasculaire gebeurtenissen.[45,46]

Het verkrijgen van trombus geeft materiaal voor onderzoek naar de pathofysiologie van atherosclerose, trombusvorming, en het mechanisme van de plaqueruptuur.[47,48] Trombusaspiratie maakt een histopathologische analyse van plaatjes, erytrocyten, ontstekingscellen, en plakcomponenten mogelijk. De rol van genetische markers is hiernaast een interessant gebied van verder onderzoek.[49] Door het vinden van relaties tussen de samenstelling van de trombus en uitkomstvariabelen zoals een blijvend open coronairarterie na een interventie en myocardiale perfusie kunnen trombuskarakteristieken belangrijk worden bij klinische risicobeoordeling[47,50] en daarbij informatie geven voor verbetering van reperfusietherapie in het acute STEMI.

CONCLUSIE

De prognose van STEMI-patiënten is in de laatste decennia verbeterd door invasieve en farmacologische strategieën gericht op de occluderende trombus om zo de epicardiale flow door de coronairarterie te verbeteren. Epicardiale reperfusie leidt niet altijd tot adequate myocardiale reperfusie, die voor een belangrijk deel het gevolg is van distale embolisatie van atherothrombotisch materiaal. Hoewel geen behandeling het probleem van distale embolisatie heeft 'opgelost', laat dit proefschrift een gunstig effect zien van trombusaspiratie bij het verbeteren van myocardiale reperfusie en lange-termijn uitkomst. Trombusaspiratie biedt ook materiaal voor pathofysiologische studies en klinische risicoinschatting, die ons vervolgens informatie kunnen geven voor farmacologische en mechanische behandelingsvormen.

SAMMENDRAG OG DISKUSJON

Myokardinfarkt med elevasjon av ST-segment (STEMI) blir vanligvis forårsaket av en ruptur av et aterosklerotisk plaque, fulgt av aggregering av blodplater og trombosedannelse. Dette gir en akutt avstengning av en koronararterie. Blodtilførselen i myokardvevet blir redusert, og denne ischemi gir nekrose og derved venstre ventrikkeldysfunksjon og fare for død. Hurtig gjenopprettelse av gjennomblødningen i koronararterien og blodtilførsel av myokard er derfor essensielt i behandlingen av STEMI.[1,2] Primær perkutan koronar intervensjon (PCI) er den foretrukne behandling ved STEMI.[3,4] Denne metoden ble utviklet i 1980-årene, da pasientene med myocardinfarkt som regel ble gitt trombolyse. Til å begynne med ble det gjort ballongdilatasjon, og overlevelsen med denne teknikken var bedre enn med trombolyse. Senere ble denne angioplastikk kombinert med innleggelse av stent i koronararterien, og det medførte redusert behov for revaskularisering. For ytterligere å forbedre STEMI-pasientenes prognose, ble det søkt etter andre typer intervensjoner. Denne avhandling beskriver rollen til fjernelse av aterotrombotisk materiale ved hjelp av aspirasjon ved primær PCI. I tillegg undersøkes de generelle aspekter ved invasiv og farmakologisk behandling av STEMI-pasienter.

Avhandlingens **Første del** gjennomgår kort den historiske utviklingen av patofysiologi og behandling ved STEMI.

Avhandlingens **Annen del** dreier seg om metodeutvikling av primær PCI, stenter og adjuvant farmakologisk behandling. **Kapitel 2.1** er en omtale av en artikkel av David Massel, der det blir gjort en evaluering av effekten av PCI ved akutt myocardinfarkt versus ingen behandling.[5] Denne sammenligning er aldri undersøkt i randomiserte studier, siden primær PCI ble utviklet etter at trombolyse ble en akseptert behandlingsform. Forfatteren brukte data fra 30 studier og fant, ved hjelp av avanserte statistiske teknikker, en odds ratio for mortalitet med primær PCI sammenlignet med ubehandlede kontroller på 0.56, som tilsvarer en teoretisk reduksjon av korttids-risiko for død på 44%. Vi kommenterte at denne studien bekrefter viktigheten av invasiv tilnærming i de tilfeller der det ikke kan gis trombolyse, som for eksempel ved kontraindikasjon for trombolyse, et ikke-diagnostisk elektrokardiogram, og ankomst til sykehus for sent til behandling i følge det konvensjonelle reperfusjonsvindu.

Bruk av stent ved primær PCI er begrunnet med mindre behov for revaskularisering, men bedrer ikke mortalitet sammenlignet med PCI uten stenting. Reokklusjon blir ansett som en bedre prediktor på redusert venstre ventrikkelfunksjon og kardiovaskulær mortalitet enn antall revaskulariseringer.[6,7] I **Kapitel 2.2** beskriver vi effekten av en "bare metal stent" (BMS) på reokklusjon, restenose og subakutt trombose. Vi samlet resultatene fra i alt 6192 pasienter i 10 randomiserte studier som sammenlignet BMS-implantering med ballondilatatasjon og fant en imponerende reduksjon i antall reokklusjoner (6.7% vs 10.1%, $p=0.03$) og restenoser (23.9% vs 39.3%, $p<0.001$), men ikke redusert antall subakutt trombose (1.7% i begge grupper). Disse funn støtter bruk av BMS ved STEMI.

Administrering av glycoprotein (GP) IIb/IIIa-hemmere er viktig ved siden av den mekaniske reperfusjon hos pasienter med STEMI.[8,9] I **Kapitel 2.3** diskuterer vi en artikkel av Montalescot og medarbeidere som gir tre-års resultater av 'Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up' (ADMIRAL)-studien, som er den første som demonstrerer fordelen med GP

IIb/IIIa-hemmeren abciximab ved follow-up på mer enn ett år.[10] Denne studien med 288 pasienter viste en trend til redusert mortalitet i det kombinerte endepunkt død, residiv av myokardinfarkt, og akutt revaskularisering ved infarkt ('major adverse cardiac events', MACE). I vår lederartikkel viste vi data fra noen randomiserte studier og meta-analyser som var kjent på det tidspunkt. Ut fra dette konkluderte vi at bruk av GP IIb/IIIa-hemmere er verdifullt i behandlingen av pasienter med primær PCI, at det er viktig med tidlig pre-hospital behandling, og at optimal dose samt tilleggseffekt med clopidogrel må undersøkes i nye studier. Senere er det kommet mange data om GP IIb/IIIa-hemmere ved STEMI.[11-16] Et eksempel er "ON-TIME 2"-studien, der pre-hospital initiering av en høy dose tirofiban sammen met acetylsalisylsyre, clopidogrel (600mg) og heparin forbedret ST-segment-resolusjon uten økt blødningskomplikasjon, men også uten signifikant bedring av klinisk effekt sammenlignet med placebo.[14]

Selv om resultatene ved primær PCI er bedret med stenting og adjuvant medikasjon, blir reperfusjonen i myokardet ofte begrenset av mikrovaskulær obstruksjon på grunn av embolisering og okklusjon av distale kar, som bidrar til økt infarktstørrelse og redusert overlevelse.[17] I de seneste år er trombektomi-katetre evaluert for deres rolle i å forhindre distal embolisering. I den **Tredje del** av denne avhandling beskriver vi design og primære og sekundære endepunkter i "Thrombus Aspiration in Percutaneous coronary intervention in Acute myocardial infarction Study" (TAPAS), som vurderer om manuell trombusaspirasjon ved primær PCI gir bedre mikrovaskulær reperfusjon enn konvensjonell PCI med ballongdilatatasjon. I **Kapitel 3.1** beskriver vi protokollen til denne prospektive og randomiserte studien, med en planlagt inklusjon på 1080 pasienter med STEMI. Pasientene ble randomisert til trombusaspirasjon med 6F Export Aspiration Catheter (Medtronic Corporation, Santa Rosa, California) eller ballongdilatasjon, før plassering av en intrakoronar stent. Farmakologisk behandling var i henhold til de aktuelle internasjonale retningslinjer og besto av GP IIb/IIIa-hemmere fulgt av PCI. Randomisering ble gjort før koronar angiografi. Det primære endepunkt var den angiografiske myokardiale blush grad (MBG) på 0 eller 1, som uttrykk for redusert myokardial perfusjon. Sekundære endepunkter var enzymatisk infarktstørrelse, resolusjon av ST-segment- elevasjon, post-prosedyriell distal embolisering, og andel MACE etter 30 dager og etter ett år.

De primære resultatene i studien er gjengitt i **Kapitel 3.2** og viser at trombusaspirasjon bedret den myokardiale reperfusjon.[18] I pasientgruppen som fikk trombusaspirasjon hadde 17.1% MBG på 0 eller 1, mot 26.3% hos gruppen med konvensjonell PCI ($P<0.001$). Komplett resolusjon av ST-segment-elevasjon var på henholdsvis 56.6% og 44.2% ($P<0.001$). Denne gunstige effekt av aspirasjon var uavhengig av kliniske eller angiografiske karakteristika som alder, kjønn, total ischemitid, infarktrelatert koronarkar, pre-prosedyriell "thrombolysis in myocardial infarction (TIMI) flow", eller synlig trombe på angiogrammet. Vi så også en bedring av kliniske utfallsparametre etter 30 dager, dog ikke signifikant. Antall døde hos pasienter med MBG på 0 eller 1, 2 og 3 var henholdsvis 5.2%, 2.9% og 1.0% ($P=0.003$), og andel MACE var 14.1%, 8.8% og 4.2% ($P<0.001$). Histopatologisk undersøkelse bekreftet vellykket aspirasjon hos 72.9% av pasientene. Vi konkluderte med at trombusaspirasjon er anvendelig hos de fleste pasienter med akutt myokardinfarkt, og metoden resulterer i både bedre perfusjon av myokard og klinisk utfall enn med konvensjonell PCI. Hvorfor vår studie viste gunstige resultater sammenlignet

med tidligere studier med trombektomikatetere,[19-22] skyldes muligens at kateteret er enkelt i bruk. Dette er spesielt viktig ved akutt myokardinfarkt, når PCI ofte blir utført utenfor vanlig arbeidstid, med mindre assistanse og høyere prosedyrekomplikasjoner.[23] Videre gjør studiens størrelse, de brede inklusjonskriterieriene samt den anbefalte adjuvante farmakologiske behandling funnene anvendelige i en aktuell pasientpopulasjon med STEMI.

Den forbedrede myokardperfusjon har formodentlig en positiv effekt på remodellering av venstre ventrikkel,[24] og derved på senere klinisk utfall.[25] Ett års mortalitet og data på reinfarkt rapportert i **Kapitel 3.3** viser faktisk en positiv effekt av trombusaspirasjon.[26] Kardial død etter ett år var på 3.6% (19 av 535) i gruppen med trombusaspirasjon og 6.7% (36 av 536) i gruppen med konvensjonell PCI (hazard ratio [HR] 1.93; 95% confidence interval [CI] 1.11–3.37; p=0.020). Kardial død eller ikke-fatalt reinfarkt så vi hos henholdsvis 5.6% (30 av 535) og 9.9% (53 av 536) (HR 1.81; 95% CI 1.16–2.84; p=0.009). Vi fant at PCI ved STEMI med trombusaspirasjon forbedret ett-års klinisk resultat sammenlignet med konvensjonell PCI i tråd med en nylig publisert meta-analyse med individuelle pasientdata.[27] Katetre for trombektomi brukes i økende grad i forebyggelse av distal embolisering.[28-30] Trombusaspirasjon blir nå i de europeiske retningslinjene klassifisert som IIa A behandlingsindikasjon.[31]

Fordi TAPAS-studien gir viktig støtte til bruk av trombusaspirasjon som første steg i PCI i en vanlig STEMI-populasjon, handler **Fjerde del** i denne avhandling om denne metodens rolle i klinisk praksis og den relative rolle andre behandlingskomponenter i PCI har, samt mulige mekanismer for den dokumenterte effekt. I tillegg til reduksjon av trombusmengde er mulige forklaringer på den gunstige effekten en lettere anbringelse av stent i et kar som ikke på forhånd må dilateres og derved mindre manipulering av infarktlesjonen,[32-35] samt en synergi ved samtidig bruk av GP IIb/IIIa-hemmere.[36,37] I **Kapitel 4.1** beskrives fem pasientkasuistikker med total koronarokklusjon der trombusaspirasjon blir brukt som eneste behandling for STEMI. Etter inngrepet var den koronare blodstrøm fullstendig gjenopprettet, uten tegn til reststenose eller plaqueruptur. Ved follow-up, som varierte mellom seks måneder og ett år, hadde ingen av pasientene hatt noen kardiovaskulær hendelse. Dette viser at trombusaspirasjon som eneste behandling uten ekstra angioplastikk med ballong eller stenting var trygt og effektivt hos disse fem pasientene. **Kapitel 4.2** illustrerer prediktorer for langtids kardiale hendelser hos STEMI-pasienter behandlet med PCI og trombusaspirasjon i TAPAS-studien. I dagens STEMI-populasjon er disse prediktorer: alder, diabetes mellitus, tidligere myokardinfarkt samt trombe lokalisert til venstre koronararterie. Trombusaspirasjon var positivt assosiert med fravær av langtids kardiale ischemiske hendelser. I gruppen med trombusaspirasjon var faktorene alder, diabetes mellitus og angiografisk synlig pre-prosedyriell trombe forbundet med et dårligere utfall. Uthenting av aterotrombotisk materiale var relatert til reduksjon av mortalitet ved langtids follow-up. Disse funn støtter bruk av trombusaspirasjon i primær PCI, og konseptet at reduksjon av mengde trombusmateriale er en viktig mekanisme for den gunstige effekt av trombusaspirasjon.

FREMTIDSPERSPEKTIVER

Forbedret behandling ved STEMI endrer prognosen i denne pasientgruppe. Antall kardiovaskulære hendelser etter behandling av STEMI har gått ned, og det er vanskeligere å påvise klinisk effekt. Derfor må evaluering av nye behandlingsstrategier for myokardinfarkt gjøres på en stor pasientpopulasjon. En meta-analyse kan være nyttig i denne sammenheng, men man kan også se på primære surrogatendepunkter for, eller en kombinasjon av, alvorlige kliniske hendelser. Denne studieutvikling blir gjenspeilet i denne avhandlingen. Selv med de vel over 1000 inkluderte pasienter i TAPAS-studien ble det primære surrogatendepunkt MBG og også en kombinasjon av alvorlige kliniske hendelser brukt til evaluering av en behandlingseffekt. Som tidligere nevnt[38] viste denne studien en sterk sammenheng mellom MBG 0 eller 1 og resolusjon av ST-segment-elevasjon som markør for reperfusjon og et gunstig klinisk utfall. Fremtidige studier skulle derfor kunne bruke et slikt surrogatendepunkt selektivt for evaluering av effekt.

Selv ved bruk av trombusaspirasjon skjer distal embolisering av aterotrombotisk materiale. Trombusaspirasjon kan ikke hindre at mikrovaskulær obstruksjon opptrer før PCI, eller blir indusert av inngrepet.[39] Adjuvant farmakologisk behandling av tromben er nødvendig for å forhindre mikrovaskulær obstruksjon, i tillegg til den antitrombotiske medikasjon med acetylsalisylsyre, clopidogrel, GP IIb/IIIa-hemmere og heparin. GP IIb/IIIa-hemmere administrert som intrakoronar bolus synes til å ha en gunstig effekt.[40,41] Målrettet behandling i koronarkaret kan være mer effektivt, med færre blødningskomplikasjoner. "Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO)"-studien ser på effekten av intrakoronar administrering av abciximab på angiografiske og kliniske utfallvariabler.[42] Nylig har prasugrel, et neste generasjons thienopyridin, vist seg å virke raskere og være mer effektivt enn clopidogrel.[43-44]

I tillegg til trombebehandling er aktuell forskning rettet mot bedring av myokardfunksjon og bevaring av venstre ventrikkelfunksjon. En av strategiene er å undersøke den stimulerende effekt av stam- og progenitorceller på angiogenesen. Tilførsel av stamceller har så langt ikke vist noen forbedring av venstre ventrikkelfunksjon etter STEMI, men bruk av erytropoetin har vært forbundet med færre kardiovaskulære hendelser.[45,46]

Oppsamling av trombemateriale gir mulighet for undersøkelse av patofysiologi ved aterosklerose, trombusforming og mekanismen bak plaqueruptur.[47,48] Trombusaspirasjon gir mulighet for histopatologisk analyse av blodplater, erytrocytter, inflammasjonsceller og plaquekomponenter. Studier av den rolle genetiske markører spiller er dessuten interessant.[49] Finnes sammenhenger mellom sammensetningen av en trombe og utfallsvariabler som koronararteriens tilstand etter intervensjon og myokardperfusjon, kan trombuskarakteristika bli viktige i den kliniske risikobedømmelse.[47,50] Det kan også gi informasjon om forbedring av reperfusjonsbehandling ved akutt STEMI.

KONKLUSJON

Prognosen for STEMI-pasienter er i de siste decennier forbedret gjennom invasive og farmakologiske strategier rettet mot den okkluderte trombe, for derved å forbedre den epikardiale blodstrøm i koronararterien. Epikardial reperfusjon fører ikke alltid til en adekvat reperfusjon av myokard, som for en stor del skyldes distal embolisering av aterotrombotisk materiale. Selv om problemet med distal embolisering ikke er løst ennå, viser denne avhandling at trombusaspirasjon bedrer både myokardperfusjon og på lengre sikt den kliniske tilstand. Trombusaspirasjon gir også grunnlag for patofysiologiske studier og klinisk risikobedømmelse, som kan bidra til videreutvikling av farmakologiske og mekaniske behandlingsformer.

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