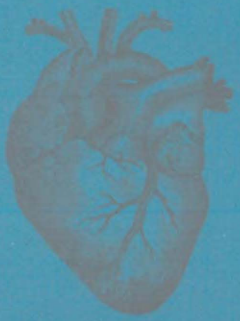
Intracoronary therapies and myocardial reperfusion in acute myocardial infarction

Gu, You Lan



Intracoronary therapies & myocardial reperfusion in acute myocardial infarction

You Lan Gu

INTRACORONARY THERAPIES AND MYOCARDIAL REPERFUSION IN ACUTE MYOCARDIAL INFARCTION

You Lan Gu

STELLINGEN

behorende bij het proefschrift

Intracoronary therapies and myocardial reperfusion in acute myocardial infarction

door You Lan Gu

1. Bij patiënten met een ST-segment elevatie myocardinfarct leidt manuele trombusaspiratie tijdens primaire percutane coronaire interventie (PCI) tot betere klinische uitkomsten dan conventionele PCI | dit proefschrift.

2. Niet-manuele trombusaspiratie en distale protectie dienen niet routinematig toegepast te worden bij een ST-segment elevatie myocardinfarct | dit proefschrift.

3. Intracoronaire toediening van abciximab tijdens primaire coronaire interventie leidt niet overtuigend tot verbeterde myocardperfusie vergeleken met intraveneuze toediening, maar ook niet tot meer bloedingscomplicaties | dit proefschrift.

4. Kwantitatieve meting van de myocardperfusie na primaire coronaire interventie middels de Quantitative Blush Evaluator is praktisch toepasbaar en gerelateerd aan andere parameters van myocardperfusie en functionele uitkomsten na een ST-segment elevatie myocardinfarct | dit proefschrift.

5. Een negatieve studie betekent niet per definitie dat het concept erachter niet klopt | dit proefschrift.

6. Mortaliteit is in studies noch in het leven het ultieme eindpunt.

7. Durven is even de grond onder je voeten verliezen; niet durven is jezelf verliezen | Søren Kierkegaard.

8. Geluk is een seconde die eeuwigheid wil zijn | Gerrit Komrij.

9. Volgzaamheid is in de huidige maatschappij enkel voor een danseres een groot compliment.

10. There is no fun in doing nothing when you have nothing to do | Jerome K. Jerome.

11. Hoe meer je leert, des te meer je merkt hoeveel je bent vergeten | vrij naar Peppermint Patty (Peanuts).

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Gu, You Lan

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Proefschrift

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To my parents

TABLE OF CONTENTS

Chapter 1 | General Introduction

Coronary heart diseases are a major cause of death in the Western world[1,2]. Acute myocardial infarction is a major contributor, which is estimated to affect 33,000 persons per year in the Netherlands[3]. A specific form of acute myocardial infarction that highly benefits from acute intervention presents with ST-segment elevation on the electrocardiogram[4]. ST-segment elevation myocardial infarction (STEMI) is mainly caused by rupture of a coronary atherosclerotic plaque[5], a highly thrombogenic event that induces platelet aggregation and thrombus formation, ultimately resulting in total coronary occlusion. If occlusion persists, the area of ischemic myocardium becomes irreversibly damaged.

To minimize myocardial damage in patients with STEMI, a timely diagnosis and initiation of reperfusion therapy are essential[6,7]. The treatment of STEMI has been based on restoring flow in the infarct-related artery by dissolving the thrombotic occlusion with pharmacological interventions, bypassing the occlusion with surgical interventions, or compressing the occlusion with a percutaneous catheter-based approach. Currently, the preferred reperfusion strategy for patients presenting within 12 hours of symptom onset is primary percutaneous coronary intervention (PCI)[8-10]. In primary PCI, flow through the infarct-related artery is restored by advancing a catheter through the femoral or radial artery, crossing and dilating the occluded artery with a balloon catheter, and supporting the reperfused artery with a stent. With adoption of contemporary evidence-based treatment strategies, mortality rates have been markedly reduced compared to the pre-reperfusion era to below 10%[11,12].

Primary PCI successfully restores flow through the epicardial coronary artery in over 90% of patients[9]. Yet, successful epicardial reperfusion does not always result in reperfusion of the myocardium itself. Reports illustrate that myocardial reperfusion is still impaired in up to 50% of patients with successful epicardial reperfusion[13,14]. Impaired myocardial reperfusion, also known as microvascular obstruction or the no-reflow phenomenon, is one of the most important determinants of poor left ventricular function and increased long-term mortality[14-16]. An important cause of impaired myocardial reperfusion is embolization of atherothrombotic material from the intracoronary thrombus or the ruptured plaque into the distal circulation[17]. To further improve myocardial reperfusion in STEMI patients, adjunctive mechanical and pharmacological therapies have been developed.

Intracoronary thrombus aspiration

The presence of intracoronary thrombus in STEMI was first demonstrated invasively more than 3 decades ago, when thrombus was retrieved from the coronary arteries of STEMI patients with but also those without angiographic features of thombus[18]. Re-

newed interest in the last decade has resulted in the development of several devices to remove this atherothrombotic material. One of these devices is a thrombus aspiration, or thrombectomy, catheter, which can be used as the first step during primary PCI to restore flow in the infarct-related artery by manual suction of atherothrombotic material. Several small-sized studies investigating aspiration catheters have indicated that manual thrombus aspiration improves myocardial reperfusion and reduces microvascular obstruction. In the largest randomized trial to date, 1071 STEMI patients were randomized to either manual thrombus aspiration or conventional primary PCI[19]. Compared to conventional PCI, thrombus aspiration consistently improved various electrocardiographic and angiographic measures of myocardial reperfusion. Moreover, clinical follow-up at 1 year showed improved clinical outcomes in patients randomized to thrombus aspiration compared to conventional PCI[20]. However, the issue remained controversial, as no large (multi-center) clinical trials or meta-analyses were available that were powered on clinical endpoints.

Intracoronary antiplatelet therapy

In patients with STEMI, mechanical reperfusion therapy is limited by its inability to prevent microvascular obstruction that has occurred before PCI or has been induced by mechanical manipulation itself during primary PCI. Therefore, several adjunctive pharmacological agents support mechanical therapy. A combination of antiplatelet and anticoagulant agents is currently used in clinical practice, including aspirin, an ADP-receptor blocker, heparin, and a glycoprotein (GP) IIb/IIIa inhibitor[8]. The GP IIb/IIIa inhibitor abciximab acts as a potent platelet inhibitor by competitive binding to the GP IIb/IIIa receptor on the surface of activated platelets, which prevents the binding of fibrinogen and von Willebrand factor, thereby inhibiting the final pathway for platelet aggregation. The clinical effectiveness of intravenous administration of abciximab during primary PCI has been established in several trials and meta-analyses[21,22]. More recently, experimental studies have reported that higher local concentrations of abciximab exert additional antiplatelet and antithrombotic effects, including disaggregation of newly formed thrombus[23]. A retrospective clinical study suggested that intracoronary administration of abciximab was associated with a 50% reduction of clinical events in patients with acute coronary syndromes[24]. In small-scale prospective studies, subsequently, intracoronary administration during primary PCI had beneficial effects on myocardial reperfusion, microvascular obstruction, infarct size, and recovery of left ventricular function[25,26]. To investigate the effects of intracoronary administration of abciximab during primary PCI on myocardial reperfusion in a larger randomized trial, we initiated the Comparison of IntraCoronary versus intravenous abciximab adminis-

tration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial.

Quantitative assessment of myocardial reperfusion

Several techniques are available to assess myocardial perfusion after primary PCI, including assessment of microvascular obstruction on cardiac magnetic resonance (CMR) imaging and myocardial contrast echocardiography, ST-segment resolution and residual ST-segment deviation on the electrocardiogram, and myocardial blush grade on the coronary angiogram[27]. Originally developed for further risk stratification in patients after primary PCI, ST-segment resolution and myocardial blush grade are currently widely used as surrogate endpoints in intervention trials. Assessment of myocardial blush grade is based on the contrast density in the infarcted myocardium after primary PCI, allowing a semi-quantitative grading of myocardial reperfusion. A novel technique to quantify myocardial reperfusion on the coronary angiogram is computer-assisted analysis of the myocardial blush grade with the Quantitative Blush Evaluator (QuBE). This open source software program provides a more operator-independent score by calculating the increase and decrease of myocardial contrast density in the area of interest. In over 1000 STEMI patients undergoing primary PCI, the QuBE program was applicable in a large majority of coronary angiograms and and showed high intra- and interobserver agreement. Furthermore, the QuBE score was associated with functional outcome such as electrocardiographic and angiographic measures of myocardial reperfusion, infarct size, and 1-year mortality[28]. Although QuBE has shown to be practical and feasible in a large number of patients with STEMI undergoing primary PCI at our center, QuBE has not yet been verified on reperfusion outcomes of primary PCI patients treated in other catheterization laboratories.

Aims of thesis

Aim of this thesis is to investigate aspects of adjunctive intracoronary therapy with thrombus aspiration and abciximab during primary PCI in patients with STEMI and to explore a novel technique to quantify myocardial reperfusion after primary PCI.

Part 1 of this thesis focuses on the relationship between intracoronary thrombus aspiration and long-term clinical outcome. Chapter 2 comments on the role of thrombus aspiration in STEMI and, more specifically, on recent findings that the presence of older thrombus in aspirated material of patients with STEMI was an independent predictor of long-term clinical outcome. Chapter 3 presents the results of a meta-analysis investigating the impact of thrombus aspiration during primary PCI on long-term clinical outcome based on individual patient data of 11 thrombus aspiration studies. Chapter 4

provides an overview of several devices designed to extract thrombus during primary PCI and reviews the up-to-date evidence for their use. Chapter 5 investigates the impact of the amount of angiographically observed thrombus on outcome after primary PCI in STEMI patients who were treated with or without thrombus aspiration.

Part 2 studies the effects of intracoronary administration of abciximab on myocardial reperfusion and clinical outcome in a randomized clinical trial. Chapter 6 provides the rationale and study design of the CICERO trial. In Chapter 7, the overall results of the CICERO trial are presented and discussed.

Part 3 investigates the application of the QuBE program on angiograms from patients undergoing primary PCI. Chapter 8 reports on the feasibility and applicability of quantitative assessment of myocardial reperfusion with the QuBE in STEMI patients after primary PCI at external catheterization laboratories. Chapter 9 assesses whether the QuBE scores relate to functional and contrast-enhanced CMR outcomes of STEMI patients at 4-6 months after primary PCI.

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Part 1 | Intracoronary thrombus aspiration

Chapter 2| The emerging role of thrombus aspiration in the management of acute myocardial infarction

Y.L. Gu
M.L. Fokkema
F. Zijlstra

Circulation 2008;118:1780-2

An acute thrombotic event resulting in total occlusion of a coronary artery is considered the principal mechanism of ST-segment elevation myocardial infarction (STEMI). De Wood et al[1] were the first to show that total coronary occlusion was visible on the coronary angiogram in a large majority of patients presenting during the early hours of STEMI. Thrombus could be retrieved in 52 of 59 patients with angiographic, and in 5 of 20 patients without, features of thrombus, suggesting that thrombus formation plays a major role in the pathophysiology of total occlusion and subsequent infarction. Total coronary artery occlusion has also been described, though less frequently, in a range of nonthrombotic events such as intraplaque hemorrhage, vasospasm, spontaneous coronary artery dissection, coronary emboli, coronary arteritis, and compression by myocardial bridging[2,3].

Acute coronary thrombosis is caused primarily by the rupture of a coronary atherosclerotic plaque, responsible for approximately 75% of all coronary thrombi leading to myocardial infarction or death[4], or by plaque erosion or calcified nodules. After rupture of the fibrous cap covering the atherosclerotic plaque, fragments of the lipid-rich core are exposed to the arterial lumen. This highly thrombogenic material causes platelet aggregation within the lipid core and on the ruptured fibrous cap, forming a mural thrombus consisting mainly of platelets, resulting in early coronary obstruction[3]. In this early stage of thrombus formation, intermittent flow is often present, because the platelet aggregates are unstable and embolize into the microcirculation[4,5]. As a consequence of a balance between thrombotic and thrombolytic factors, episodic growth of thrombus may take place that results in layered thrombus material of different ages. As platelet aggregation continues, the formation of a fibrin network causes stabilization of the white platelet-rich thrombus until eventually the whole lumen is occluded. Persistent obstruction of flow at the site of plaque rupture results in blood coagulation proximally and distally to the occlusion and causes red thrombus formation, consisting mainly of erythrocytes and inflammatory cells entrapped by a fibrin network[2].

Recently, adjunctive mechanical devices have been developed to retrieve thrombus from the infarct-related lesion during primary percutaneous coronary intervention (PCI) in patients with STEMI[6–9]. Favorable results have been reported with distal protection devices including distal occlusion devices and distal embolic filters, as well as with anterograde approaches with manual thrombus aspiration catheters or technically more complex mechanical thrombectomy catheters. Currently, the inexpensive and user-friendly manual thrombus aspiration devices seem to hold most promise[6]. With these devices, thrombotic material can be obtained in 73 to 89% of patients[8,9]. Several studies have reported that thrombus aspiration improves myocardial perfusion and reduces microvascular obstruction in patients with STEMI compared with conven-

tional balloon angioplasty[7–9], although the trial results show considerable variability in part due to patient and device selection. Because a strong relation has been established between improved myocardial perfusion, as assessed by angiography or electrocardiography, and lower long-term cardiac mortality[10,11], it can be hypothesized that thrombus aspiration will provide clinical benefits. This expectation is confirmed in recent reports showing that thrombus aspiration is associated with a reduction in short- and long-term mortality in patients treated with primary PCI[12,13]. The major limitation of thrombus aspiration is its inability to limit microvascular obstruction that has occurred before PCI. Adjunctive pharmacological therapies are therefore still needed to optimize myocardial perfusion. Therapy targeting platelets, for example, a major component in microvascular obstruction[5], has proven to reduce mortality and reinfarction in patients undergoing primary PCI[14].

Along with the clinical benefits of thrombus aspiration, retrieval of atherothrombotic material provides us with new possibilities to study the pathophysiology of thrombus formation, and thrombus characteristics may become of value in predicting outcome. In this issue of Circulation, Kramer et al[15] identify the age of aspirated thrombus as a predictor of long-term mortality in patients with STEMI treated with thrombus aspiration during primary PCI. Previously, these investigators have reported that in many STEMI patients who underwent thrombus aspiration during primary PCI within 6 hours of symptom onset, at least part of the thrombotic material was older than 1 day[16]. Thrombus that was present in the aspirated material of 211 STEMI patients contained older thrombus with lytic (1 to 5 days) or organized (>5 days) changes in 51%, and fresh thrombus (<1 day old) in 49%. These findings show that plaque rupture and thrombus formation are often initiated days before the development of a total coronary occlusion.

In the current study, Kramer et al have sought to investigate the relation between thrombus age and long-term mortality in 1315 STEMI patients in whom thrombus aspiration was performed during primary PCI[15]. Fresh thrombus was present in 60% of patients and older thrombus in 40%. In patients with older thrombus, the total ischemic time was longer (4.1±4.3 hours versus 3.3±2.4 hours, $P<0.001$) and the incidence of distal embolization was higher (18 versus 12%, $P=0.01$) than in those with fresh thrombus. No differences were observed for postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow and enzymatic infarct size as assessed by peak creatine kinase-MB. At 4 years follow up, all-cause mortality was 2-fold higher in patients with older thrombus compared with patients with fresh thrombus (16.0% versus 7.4%, hazard ratio 1.82, 95% confidence interval 1.17 to 2.85, $P=0.008$). In a landmark survival analysis, this higher mortality rate of patients with older thrombus versus those with

fresh thrombus was apparent during the first 14 days (5.7% versus 2.4%, P=0.009) but not after 14 days (11% versus 5.2%, P=0.20). In multivariate Cox regression analysis, the presence of older thrombus was an independent predictor of all-cause mortality at 4 years (hazard ratio 1.83, 95% confidence interval 1.14 to 2.93, P=0.01) next to well known risk factors such as female gender, age >60 years, diabetes mellitus, previous coronary artery bypass grafting, cardiogenic shock, and poor postprocedural TIMI flow.

This observation is pivotal because it is the first to show a relationship between thrombus composition and mortality. A plausible mechanism that explains why older thrombus is associated with higher mortality is that patients with older thrombus experience a longer period of nonocclusive thrombus formation. During this phase, the platelet-rich thrombus is unstable and prone to embolize into the distal microcirculation[4], a phenomenon known to be associated with higher long-term mortality[17]. This hypothesis is supported by the angiographic data, showing a higher incidence of distal embolization in patients with older thrombus. What remains unclear from the data presented here is whether this effect of the presence of older thrombus was also mediated through poor myocardial perfusion, increased microvascular obstruction, or both, and further studies should elucidate the impact of the presence of older thrombus on these parameters.

Further study should also assess whether retrieval of the thrombus was complete. Incomplete retrieval may have led to thrombus being unclassifiable, together with explanations that also account for the inability to retrieve any thrombotic material from 25% of patients, such as dissolution of the thrombus before aspiration, embolization into the distal vessel, disintegration of organized thrombus, or absence of a thrombotic cause of occlusion. More significantly, although the classification of older thrombus has a high specificity, fresh thrombus could have been misclassified if only thrombus of younger age superimposed on older thrombus was aspirated, thereby confusing the reported findings. Data on the size and composition of the aspirated material and on the angiographic thrombus score after thrombus aspiration might help us in judging whether all thrombus was aspirated. Coronary angiography is largely used to study the presence or absence of thrombus in the coronary system, although it is probably not very reliable, given that thrombotic material was still retrieved in a considerable proportion of patients without angiographic evidence of thrombus[1,9]. Catheter-based imaging modalities such as optical coherence tomography (OCT) may be better instruments to assess the presence of intracoronary thrombus[18,19]. OCT may also be able to identify a nonthrombotic event as the pathophysiological mechanism leading to coronary occlusion in patients in whom thrombus aspiration does not result in restoration of brisk anterograde flow in the infarct-related coronary artery.

Some limitations of this study have to be acknowledged. The study was performed retrospectively, and patient selection bias may play a role in the principal findings as well as in the choice to perform regression analysis at 4 years of follow-up. First, it is unclear whether criteria such as angiographic evidence of thrombus or total occlusion of the infarct-related artery were applied for performing thrombus aspiration. Second, the indications for the use of specific devices as well as of concomitant pharmacological treatment were at the discretion of the operator, and it is not reported whether differences were observed in retrieval rates and angiographic and procedural characteristics of different devices. Furthermore, causes of death are not reported, and follow-up at 4 years was incomplete.

Thrombus aspiration now enables the histopathological analysis of platelets, erythrocytes, inflammatory cells, and plaque components in living patients. Characterization of these components may contribute to the current understanding of the pathophysiology of atherosclerosis and myocardial infarction. In addition, ongoing research will elucidate mechanistic relationships between thrombus composition and parameters of myocardial perfusion and microvascular obstruction. This may provide further support in clinical risk assessment, currently based on angiographic, electrocardiographic, and biochemical markers and, very recently, the promising field of genetic markers. In plaque material obtained from carotid atherosclerotic plaques, Hellings et al[20] have already demonstrated that the macrophage infiltration rate and lipid core size are associated with restenosis. Ultimately, thrombus characterization may provide us with new information directing us in further development of pharmacological and mechanical therapies.

In conclusion, thrombus aspiration is emerging as an integral component of the interventional approach of acute myocardial infarction, enabling new insights into thrombus composition. It holds great therapeutic as well as diagnostic promise and leads us into a new era of mechanistic and pathophysiological studies.

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Chapter 3| Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials

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ABSTRACT

Aims

Thrombectomy in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) is associated to better myocardial reperfusion. However, no single trial was adequately powered to asses the impact of thrombectomy on long-term clinical outcome and to identify patients at higher benefit. Thus, we sought to assess these issues in a collaborative individual patient-data pooled analysis of randomized studies (study acronym: ATTEMPT, number of registration: NCT00766740).

Methods and results

Individual data of 2686 patients enrolled in 11 trials entered the pooled analysis. Primary endpoint of the study was all-cause mortality. Major adverse cardiac events (MACE) were considered as the occurrence of all-cause death and/or target lesion/vessel revascularization and/or myocardial infarction (MI). Subgroups analysis was planned according to type of thrombectomy device (manual or non-manual), diabetic status, IIb/IIIa-inhibitor therapy, ischaemic time, infarct-related artery, pre-PCI TIMI flow. Clinical follow-up was available in 2674 (99.6%) patients at a median of 365 days. Kaplan–Meier analysis showed that allocation to thrombectomy was associated with significantly lower all-cause mortality (P = 0.049). Thrombectomy was also associated with significantly reduced MACE (P = 0.011) and death + MI rate during the follow-up (P = 0.015). Subgroups analysis showed that thrombectomy is associated to improved survival in patients treated with IIb/IIIa-inhibitors (P = 0.045) and that the survival benefit is confined to patients treated in manual thrombectomy trials (P = 0.011).

Conclusion

The present large pooled analysis of randomized trials suggests that thrombectomy (in particular manual thrombectomy) significantly improves the clinical outcome in patients with STEMI undergoing mechanical reperfusion and that its effect may be additional to that of IIb/IIIa-inhibitors.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has been shown to provide mortality benefit compared with thrombolysis, mainly because of better and sustained optimal coronary perfusion[1]. However, despite epicardial recanalization with TIMI 3 flow, myocardial reperfusion is not achieved in a relevant percentage of ST-elevation myocardial infarction (STEMI) patients, with a significant impact on long-term survival[2–4]. Accordingly, a series of adjunctive devices with different design and mechanism of action have been developed and tested in clinical studies with conflicting results[5]. A meta-analysis of prospective randomized trials[6] suggested that the use of thrombectomy devices, but not of distal protection devices, is associated with a significant reduction of angiographically evident distal embolization and no-reflow (as assessed by post-procedural myocardial blush grade (MBG) and ST-segment resolution). As angiographic and electrocardiographic markers of myocardial reperfusion are well-known predictors of late clinical events[3,7–10], the use of thrombectomy may also translate into improved clinical outcome. Unfortunately, no published study was specifically designed and adequately powered to asses long-term clinical outcome. Yet, recent data from a large single-centre trial showed an advantage of thrombus-aspiration use in terms of mortality at 1 year follow-up[11] and a recent meta-analysis of nine randomized trials showed an advantage of thrombus-aspiration in terms of early (up to 30 days) mortality[12]. As such promising observations deserve further evaluations[13], we have designed and performed a pooled analysis of the individual patient data of prospective randomized trials comparing standard PCI with or without thrombectomy to evaluate the impact of thrombectomy use on clinical outcome.

METHODS

The study protocol has been registered in the clinicaltrials.gov website (number of registration: NCT00766740), has been drafted and submitted for publication before the first analysis was undertaken and has been published in details in a study design manuscript[14]. A systematic MEDLINE database search (www.ncbi.nlm.nih.gov) for studies comparing PCI with thrombectomy with standard PCI was conducted according to a modified Robinson and Dickersin strategy[15]. Keywords were 'STEMI', 'randomized', 'thrombus aspiration', and 'thrombectomy'. Furthermore, the TCT (http://www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (http://www.americaheart.org), and ESC (www.escardio.org) websites were searched for pertinent abstracts and expert slides presentations between October 2003 and February 2008. No language restriction was applied. Inclusion criteria for selected studies were: (i) comparison of thrombectomy with standard PCI in patients with STEMI; (ii) randomized treatment

allocation. Exclusion criteria were: (i) equivocal treatment allocation processes. Fifteen studies were published as full papers[16–30] and two additional studies[31–32] were reported as abstract[31] or expert slides presentation[32]. The 15 principal investigators of these 17 identified studies were contacted by mail or by fax to participate into the ATTEMPT study (pooled Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data). The study flowchart is depicted in Figure 1. Each principal investigator who agreed to participate into the study was asked to complete a structured patient-level database including a series of key baseline clinical and angiographic data as well as the longest available clinical outcome data of each patient previously enrolled in the corresponding trial. The modality of follow-up update was not defined in the study protocol.

The requested dataset included: sex (male or female), age (years), diabetes (yes or no), rescue PCI (yes or no), usage of IIb/IIIa-inhibitors (yes or no), infarct-related artery [left anterior descending artery (LAD), left circumflex artery (LCX), or right coronary artery (RCA)], multivessel disease (yes or no), baseline TIMI flow 0 or 1 (yes or no), time from symptoms to balloon/cath-lab (minutes), thrombectomy device used (name of the device), device efficacy (device able to reach and treat the culprit lesion), and long-term clinical follow-up [death for any cause, time to death, myocardial infarction

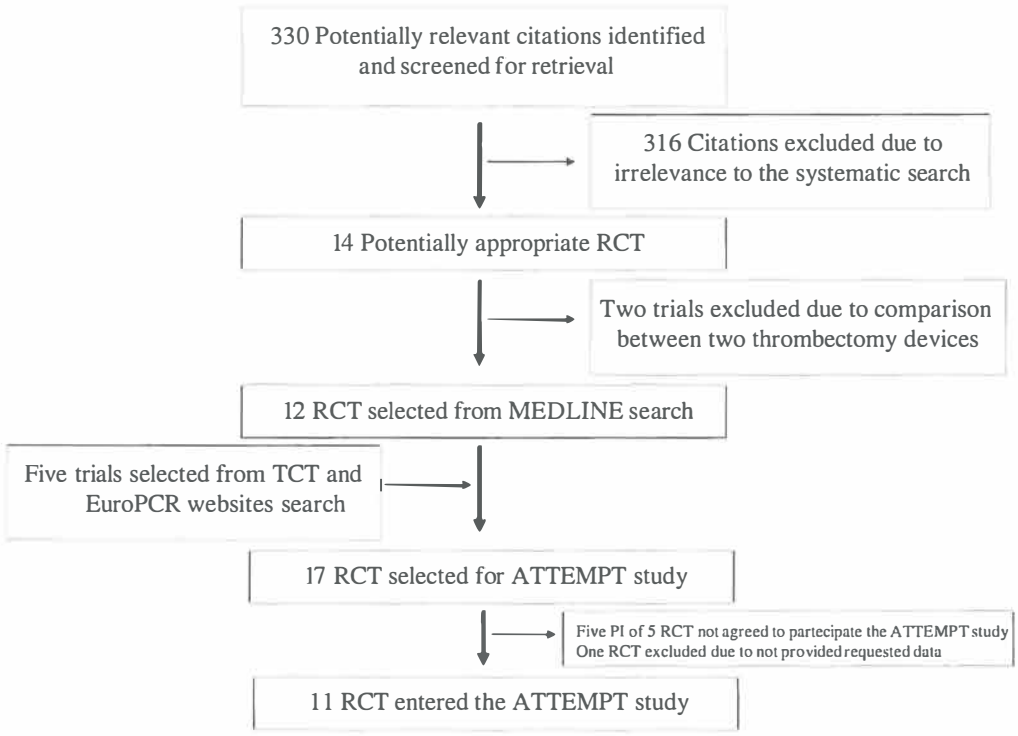


Fig. 1 Flow-chart of the systematic search process (RCT, randomized controlled trials; PI, principal investigator).

(MI), time to MI, target lesion/vessel revascularization (TLR/TVR), time to TLR/TVR]. Such individual patient data have been sent to the study coordinator (M.D.V.) who was responsible for data consistency checking (matching against previous publication of the trials as well as coherence controls) and for final pooling in a single database. A statistical expert in the field of meta-analysis (G.B.Z.) was responsible for statistical analyses.

Sample size calculation

A meta-analysis of randomized trials comparing thrombectomy with standard PCI in patients with STEMI[6] showed a rate of post-procedural MBG 3 significantly higher in the thrombectomy group with an OR estimate of 2.3. Moreover, van't Hof et al. demonstrated that post-PCI MBG is a strong predictor of long-term mortality in patients with STEMI treated with primary PCI. In particular, they reported a long-term total mortality rate of 3% in patients with post-PCI MBG 3 and of 29% in patients with post-PCI MBG<33. Considering these results, we anticipated a sample size of 1350 patients (675 for each randomization arm) to demonstrate, with an alpha risk of 5% and a beta risk of 20%, a survival advantage at 1 year using thrombectomy compared with standard PCI.

Primary endpoint

The primary endpoint of the study was the comparison of all-cause mortality between patients randomized to thrombectomy or standard PCI.

Secondary endpoints

Secondary endpoints of the study were survival free from MI, TLR or TVR, major adverse coronary events (MACE: death + MI + TLR/TVR) and death + MI between patients randomized to thrombectomy or standard PCI.

Pre-defined subgroup analyses

The comparison of all-cause mortality between patients randomized to thrombectomy and standard PCI was performed according to the following pre-defined subgroups[14]:

1. treated by manual thrombectomy devices or non-manual thrombectomy devices
2. with or without diabetes mellitus
3. undergoing primary PCI or rescue PCI (after failed thrombolysis)
4. treated or not treated with IIb/IIIa-inhibitors
5. different ischaemic time (pre-defined time intervals: ≤3, >3 ≤ 6, >6 h)
6. infarct-related artery (LAD, LCX, or RCA)
7. pre-PCI TIMI flow (TIMI 0–1 or TIMI 2–3)

Table 1 Key characteristics of the trials entered the ATTEMPT study and ATTEMPT FU length

Study	Design	Thrombectomy device	Timing of randomization	Angiographic inclusion criteria	Main exclusion criteria	Number of patients	Stenting rate	Complications of thrombectomy device use	Longest published clinical FU (days)	FU length (days) for ATTEMPT study (median, 1st–3rd quartiles)	
						SP	T				
Antoniucci et al[18]	Single centre	Non-manual T (Angiojet)	After coronary angiography	IRA diameter≥2.5 mm	Ischaemic time >12 h Previous MI Rescue PCI	50	50	98%	Not reported	30	180 (180 –180)
REMEDIA[20]	Single centre	Manual T (Diver CE)	Before coronary angiography	None	Ischaemic time >12 h	49	50	100%	None	30	371 (212 –516)
X-AMINE ST[21]	Multicentre	Non-manual T (X-Sizer)	After coronary angiography	De novo lesion Single V disease baseline TIMI flow 0 – 1 Thrombus containing lesion IRA diameter≥2.5 mm Absence of tortuosity or severe calcification in IRA	Ischaemic time >12 h Previous PCI in IRA Rescue PCI Killip class ≥3	101	100	99%	one case of coronary arterio-venous fistola at angio-FL	180	180 (180 –180)
Noel et al[31]	Single centre	Manual T (Export)	After coronary angiography	Baseline TIMI flow <3	Ischaemic time >12 h	26	24	100%	Not reported	In hospital	6 (6–6)
DEAR-MI[22]	Single centre	Manual T (Pronto)	Before coronary angiography	None	Ischaemic time >12 h Cardiogenic shock Previous MI Contraindication to Gp IIb/IIIa inhibitors	74	74	98%	Not reported	In hospital	657 (429 –862)
VAMPIRE[28]	Multicentre	Non-manual T (TVAC)	Before coronary angiography	Absence of LM disease IRA diameter≥2.5 and ≤5 mm	Ischaemic time >24 h Rescue PCI Cardiogenic shock Previous CABG LM disease	175	180	94%	Not reported	240	895 (239 –1192)
Kaltoft et al[23]	Single centre	Non-manual T (Rescue)	After coronary angiography	Absence of LM disease IRA suitable for thrombectomy according to treating physician	Ischaemic time >12 h Previous CABG Rescue PCI LM disease Cardiogenic shock	107	108	96%	None	30	365 (365 –365)
De Luca et al[24]	Single centre	Manual T (Diver CE)	After coronary angiography	Identifiable thrombus on IRA Culprit vessel LAD 3 V disease Baseline TIMI flow 0 –1	Ischaemic time >12 h Previous MI Previous CABG Severe valvular heart disease	38	38	100%	One case of coronary dissection	180	468 (384 –520)
PIHRATE[32]	Multicentre	Manual T (Diver CE)	After coronary angiography	Baseline TIMI flow 0–1	Ischaemic time >6 h ST -elevation >3 mm in one lead	96	100	98%	Not reported	180	180 (180 –180)

EXPIRA[30]	Single centre	Manual T (export)	After coronary angiography	IRA diameter >2.5 mm TS>3 Baseline TIMI flow 0 –1 De novo lesion Absence of LM or 3 V disease	Ischaemic time >12 h Previous MI Previous CABG Rescue PCI LM/3 V disease Cardiogenic shock Contraindication to Gp IIb/IIIa inhibitors Severe valvular heart disease	87	88	100%	Not reported	270	270 (270 –270)
TAPAS trial[27]	Single centre	Manual T (Export)	Before coronary angiography	None	Ischaemic time >12 h Rescue PCI Life expectancy <6 month	536	535	92%	None	365	365 (365 –365)
ATTEMPT study population	–	–	–	–	–	1339	1347	–		–	365 (232 –365)

Statistical analysis

Continuous variables are reported as mean ± standard deviation or median (first to third quartiles) and categorical variables as n (%), unless otherwise stated. Statistical pooling has been performed with the Peto fixed effect method for patient-level analysis (according to event counts reported at the longest available follow-up) as well as with a random effect method with generic inverse variance weighting (according to risk estimates obtained with Cox proportional hazard analysis). Thus, we have been able to compute pooled odds ratios (OR) with their corresponding 95% confidence intervals. Kaplan–Meier curves have been computed for survival and event-free survival analyses, both crude and stratified by study, with statistical testing based on log-rank test. A two-tailed P-value of 0.05 was chosen as cut-off for statistical significance at hypothesis testing, whereas statistical inconsistency was appraised by means of I2, with values more than 50% identifying subsets with at least moderate heterogeneity. The internal validity and quality of the individual studies entering the pooled analysis have been performed according to the Cochrane collaboration's tool for risk of bias assessment[33]. Publication bias has been appraised by means of funnel plot inspection and Egger test[34].

RESULTS

Study population

Ten principal investigators who authored 11 of 17 eligible randomized studies agreed to participate into the study and provided the requested data for each patient enrolled in the corresponding trial. A total of 2686 patients entered the present pooled analysis: 1347 (50.1%) subjects randomized to PCI with thrombectomy device use and 1339 (49.9%) randomized to standard PCI. The key protocol characteristics of the 11 randomized studies are summarized in Table 1. As shown in Table 1, the updated clinical

follow-up available for the present analysis was significantly extended compared with that previously published for the majority of the studies. As a result, from a total of 2686 patients clinical follow-up was available in 2674 (99.6%) patients at a median of 365 days (first to third quartiles 232–365; mean 380 ± 272 days; follow-up time interval: 6–1594 days). In particular, clinical follow-up was available in 2470 patients at 6 months, in 1896 patients at 9 months, in 1685 patients at 12 months, in 374 patients at 18 months, in 296 patients at 24 months, and in 281 patients at more than 24 months. The clinical and angiographic data collected in the pooled ATTEMPT population were similar between patients randomized to thrombectomy or standard PCI (Table 2). The assessment of internal validity and quality for each study included in the analysis is reported in Table 3.

Primary endpoint

Kaplan–Meier analysis at the longest available follow-up, either crude (Figure 2) or stratified by study (which provided similar results for direction and magnitude of statistical significance), showed that allocation to thrombectomy was associated with reduced all-cause mortality (log-rank P = 0.049). A similar result was provided by Peto fixed effect analysis, showing that thrombectomy was associated with significantly fewer deaths (OR = 0.71, 95% CI 0.49–1.00; P = 0.05) when compared with standard PCI. Notably, no evidence of heterogeneity (P for heterogeneity >0.10), statistical inconsistency (I2 < 50%), or small study bias (Egger test >0.05) was evident (Figure 3). The result was similar in the analysis performed excluding the two studies not yet published as full paper.

Table 2 Baseline key clinical and angiographic characteristics of the ATTEMPT study population

	ATTEMPT thrombectomy (n = 1347)	ATTEMPT standard PCI (n = 1339)	P-value
Age (mean ± SD)	63 ± 12	63 ± 12	1.0
Sex (M), n (%)	891 (66%)	894 (67%)	0.73
Diab etes, n (%)	183 (13%)	185 (14%)	0.86
Failed TL, n (%)	16 (1%)	14 (1%)	0.72
IIb/IIIa-inhibitors, n (%)	907 (67%)	880 (66%)	0.37
Time to reperfusion (min) (mean ± SD)	269 ± 184	281 ± 212	0.09
MVD, n (%)	555 (41%)	566 (42%)	0.57
Baseline TIMI flow 0–1, n (%)	944 (70%)	968 (72%)	0.20
Culprit vessel			
LAD, n(%)	578 (43%)	600 (45%)	0.32
LCX, n (%)	181 (13%)	167 (12%)	0.45
RCA, n (%)	462 (34%)	461 (34%)	0.94
Crossover	105 (7.7%)	29 (2.2%)	
FU length (median; 1st –3rd quartiles) (mean ± SD)	365 (197 –365) 384 ± 275	365 (180 –365) 376 ± 269	0.43

PCI, percutaneous coronary intervention; SD, standard deviation; TL, thrombolysis; MVD, multi-vessels disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; FU, follow-up.

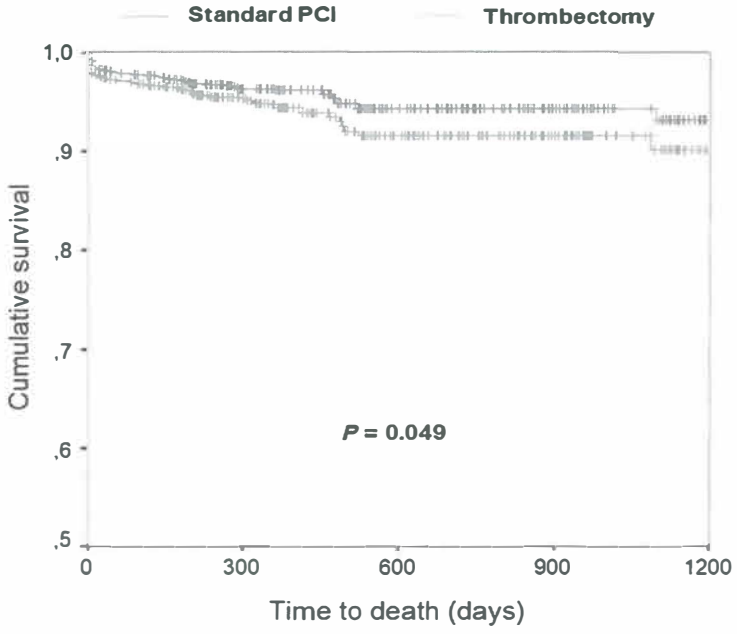
Secondary endpoints

Kaplan–Meier analyses at the longest follow-up available, either crude or stratified by study (which provided similar results for direction and magnitude of statistical significance), showed that allocation to thrombectomy was associated with significantly fewer MACE (log-rank P = 0.011) (Figure 4) and death + MI (log-rank P = 0.015), but non-significant differences in MI (log-rank P = 0.126) or in TLR/TVR (log-rank P = 0.126). Similar results were provided by Peto fixed effect analysis, showing that thrombectomy was associated with significantly fewer MACE (OR = 0.80, 95% CI 0.65–0.98; P = 0.03) and death + MI (OR = 0.70, 95% CI 0.52–0.93; P = 0.02) when compared with standard PCI, whereas there were non-significant differences in MI (OR = 0.72, 95% CI 0.47–1.10; P = 0.13) or TLR/TVR (OR = 0.87, 95% CI 0.67–1.12; P = 0.27). No evidence of heterogeneity (all P for heterogeneity >0.10), statistical inconsistency (all I2 < 50%), or small study bias (all P at Egger test >0.05) was evident in any of the analyses.

Subgroups Analysis

Type of thrombectomy device

The ATTEMPT study population was divided into two groups considering the type of thrombectomy device used: manual thrombectomy group (1815 patients enrolled in tri-



Patients at risk					
Standard PCI	1333	857	167	97	37
PCI with thrombectomy	1339	864	164	101	48

Fig. 2 Kaplan–Meier curves for cumulative survival; log-rank P = 0.049

Table 3 Appraisal of internal validity and quality of included studies

Study	Adequate sequence generation	Allocation concealment used	Blinding	Incomplete outcome data addressed in the published FU	Incomplete outcome data addressed in the extended FU	Losses to follow-up <10% in published and extended FU	Uniform and explicit outcome definitions	Free of selective published outcome reporting	Free of selective extended outcome reporting	Free of other bias	Overall risk of bias
Antoniucciet al[18]	Yes (computer generated)	Yes (sealed envelopes)	Yes (angiogram, EKG, SPECT and clinical outcome assessors)	No	Yes (1 patient lost to FU)	Yes	Yes	Yes	Unclear	Yes	Low
REMEDIA[20]	Yes (computer generated)	Yes	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (two patients lost to FU)	Yes	Yes	Yes	Yes	Yes	Low
X-AMINE - ST[21]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Moderate
Noel et al[31]	Unclear	Unclear	Unclear	No	Yes	Yes	No	Unclear	Unclear	Unclear	High
DEAR-MI[22]	Unclear	Unclear	Yes (angiogram, and EKG assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Moderate
VAMPIRE[28]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (eight patients lost to FU)	Yes	Yes	Yes	Unclear	Yes	Moderate
Kaltoft et al[23]	Yes (computer generated)	Yes (external personnel)	Yes (angiogram, EKG, SPECT and clinical outcome assessors)	No	No	Yes	No	Unclear	Unclear	Yes	Moderate
De Luca et al[24]	Unclear	Unclear	Yes (angiogram, EKG, echo and clinical outcome assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Low
PIHRATE[32]	Yes (computer generated)	Yes (sealed envelopes)	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (1 patient lost to FU)	Yes	Yes	Unclear	Unclear	Yes	Low
EXPIRA[30]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Yes	Yes	Low
TAPAS[27]	Yes (computer generated)	Yes (computerized voice–response system)	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Yes	Yes	Low

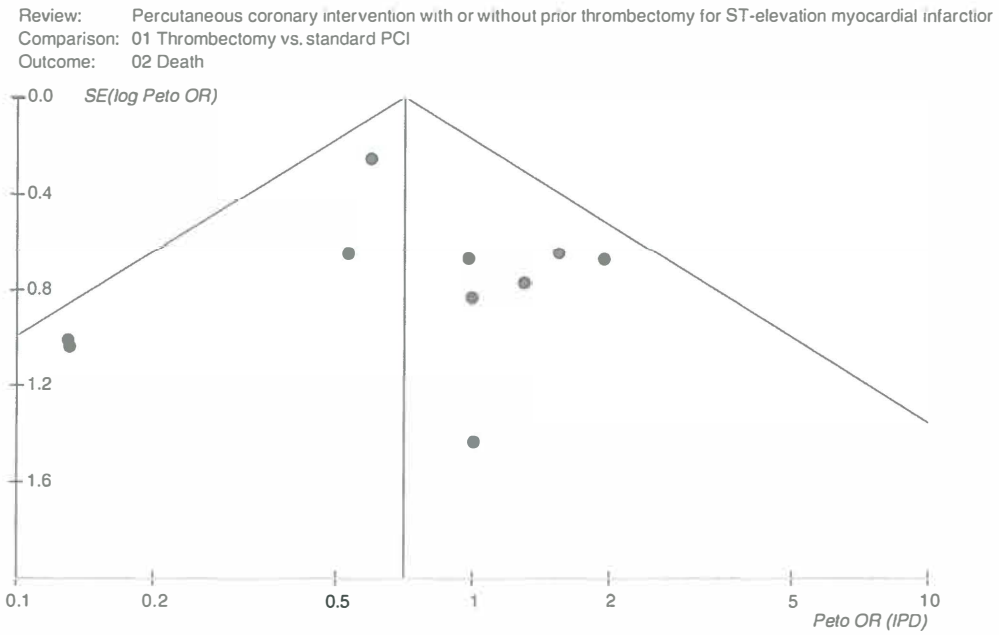


Fig. 3 Funnel plot graph for mortality.

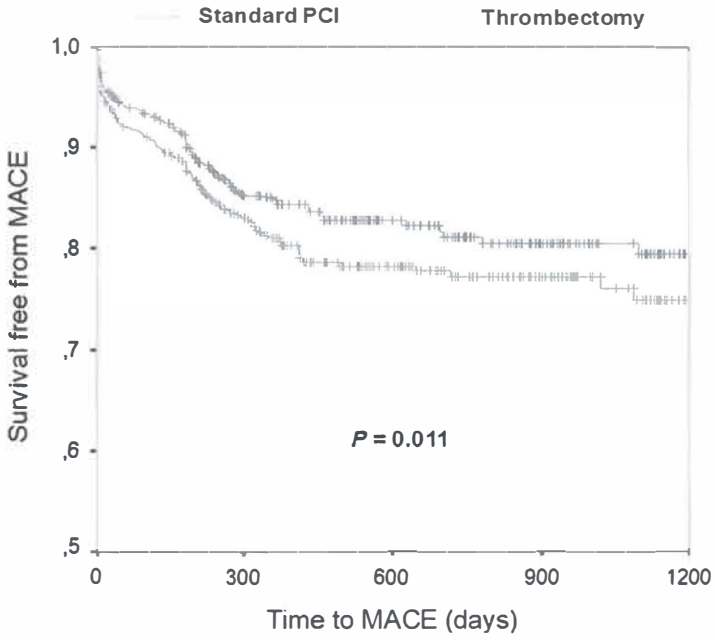
als with use of Diver CE, Pronto, and Export catheters) and non-manual thrombectomy group (871 patients enrolled in trials with use of X-Sizer, Angiojet, Rescue, and TVAC devices). In the manual thrombectomy group, Kaplan–Meier analyses at the longest follow-up available showed that allocation to thrombectomy was associated with significantly fewer deaths (log-rank P = 0.011) (Figure 5A), whereas in the non-manual thrombectomy group, the allocation to thrombectomy was associated to similar mortality compared with standard PCI (log-rank P = 0.481) (Figure 5B).

Clinical and angiographic subgroups

There was no qualitative difference in mortality when splitting the study population according to the presence or absence of diabetes, to shorter, intermediate or longer time-to-reperfusion, to type of culprit artery (left anterior descending or circumflex artery or RCA) and to pre-PCI TIMI flow (0–1 or 2–3). Conversely, subgroup analysis according to administration of IIb/IIIa-inhibitors showed that randomization to thrombectomy was associated to a survival benefit in the subgroup of patients treated with IIb/IIIa-inhibitors (1787 patients; log-rank P = 0.045; HR 0.61, 95% CI 0.38–0.90) and not in those not receiving this drugs (899 patients; log-rank P = 0.843; HR 0.93, 95% CI 0.48–1.80).

DISCUSSION

The failure to achieve myocardial tissue reperfusion is known to be the main complication limiting the early and long-term clinical benefit of mechanical reperfusion in pa-



Patients at risk					
Standard PCI	1333	768	164	96	37
PCI with thrombectomy	1339	777	159	99	48

Fig. 4 Kaplan–Meier curves for MACE-free survival; log-rank P = 0.011.

tients with STEMI. Among the different strategies to limit the 'no reflow phenomenon', reducing distal embolization by thrombectomy devices use is a promising one[13]. The present pooled analysis on 2686 individual patients data (from 11 randomized trials) shows that the adjunct of thrombectomy during mechanical reperfusion is associated to a detectable improvement of survival at follow-up with an estimated number needed to treat to prevent one death at 1 year of 62. Moreover, we found that the survival advantage of thrombectomy is confined to patients treated by simple manual thrombectomy catheters with an estimated number needed to treat to prevent one death at 1 year of 34.

Such findings extend the recently published single-centre TAPAS trial results[11] which showed a significantly lower cardiac mortality at 12 months in the group of patients treated with manual thrombectomy. However, the TAPAS trial was not specifically designed and powered to assess the difference between thrombectomy and standard PCI at the long-term clinical follow-up[35]. In the absence of large, multicentre trials adequately powered to assess long-term outcome in patients with STEMI treated with PCI and thrombectomy, the best way to evaluate the role of this treatment is pooling individual patient data collected by different investigators in different randomized studies of standard PCI vs. PCI with thrombectomy. Indeed, pooled analyses of randomized trials using individual patient data are known to provide more accurate results compared

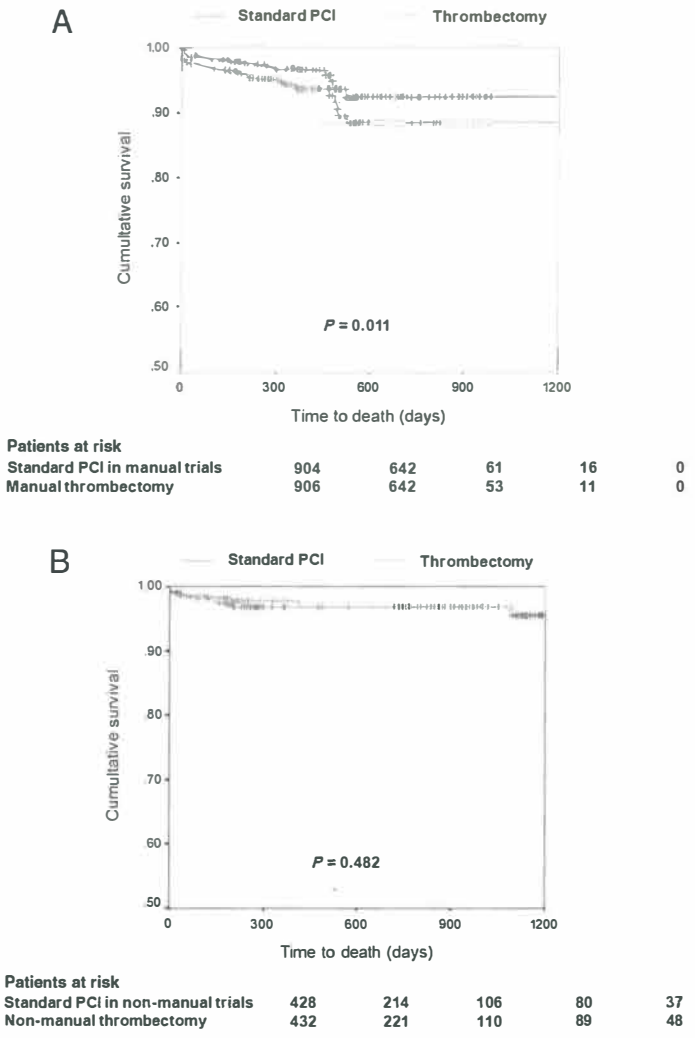


Fig. 5 (A) Kaplan–Meier curves for cumulative survival in the manual thrombectomy group and corresponding control group; log-rank P = 0.011. (B) Kaplan–Meier curves for cumulative survival in the non-manual thrombectomy group and corresponding control group; log-rank P = 0.481.

with simple meta-analyses[36], so that they have been used to answer the key questions in the field of cardiovascular medicine like the benefit of prolonged anti-platelet therapy[37], the benefit of beta-blockade after MI[38], the impact of mechanical over pharmacological reperfusion in STEMI[39] and the safety of drug-eluting stents in selected patients with coronary artery disease[40]. Thus, we designed and carried out this collaborative study, which allowed not only to collect a large number of patients, pooling the majority of available randomized trials, but also to significantly extend the clinical follow-up of some of the studies previously published with a short clinical follow-up. As a consequence, the number of patients with at least 1 year follow-up (i.e. 1685) was larger than the calculated sample size for a reliable assessment of the primary endpoint. Moreover,

as the very late outcome of patients treated by thrombectomy was not previously investigated, the present study provides novel information on a subgroup of patients with follow-up extended beyond 1 year. In keeping with the hypothesis of a long-lasting thrombectomy-induced benefit, the survival curves of thrombectomy-treated patients continued to differ from that of control patients throughout the study period.

Large studies are also needed to assess if subgroups of patients have more to gain from the application of this novel treatment. Thus, we planned to collect data allowing a series of pre-defined clinical and angiographic subgroup analyses. Interestingly, the benefit of thrombectomy was more evident in patients who received IIb/IIIa-inhibitors thus suggesting a possible additive benefit of thrombectomy in patients treated with IIb/IIIa-inhibitors. It might be speculated that pharmacological and mechanical thrombus remodelling are synergic to obtain the best myocardial reperfusion and, consequently, the best clinical outcome. Indeed, in the ATTEMPT study, patients treated by both thrombectomy and IIb/IIIa-inhibitors had the lower mortality rate, those who had none of these treatments had the higher mortality rate, patients receiving only one of these therapies exhibiting intermediate outcome (Figure 6). Accordingly, such observations seem to support the last release of the ESC guidelines on the management of patients with STEMI which recommends the use of both IIb/IIIa-inhibitors and thrombus-aspiration to prevent no-reflow[41].

Finally, once the use of thrombectomy to reduce distal embolization is accepted, the issue of device selection emerges. More complex (non-manual) devices are probably more effective than manual thrombus-aspiration catheters in extracting athero-thrombotic particles from the coronary arteries. Yet, they are bulky, require longer learning curves and selected coronary anatomies. Conversely, manual thrombus-aspirating catheters are user-friendly, not associated with specific complications, and suitable for most coronary anatomies. In the absence of large studies comparing the simple manual thrombectomy catheters with the more complex non-manual thrombectomy devices, the present study does not support the routine use of non-manual thrombectomy. Possible benefits of complex non-manual thrombectomy devices might be confined to selected subgroups of patients with larger thrombus burden and device-favourable coronary anatomy and need to be tested in ad hoc prospective studies.

Study limitations

The results obtained in the present study may have been influenced by the quality of each original trial. In particular, no further quality control has been performed nor any restriction in trial size, publication status, and updated clinical follow-up length or modality of assessment have been applied. All these limitations were anticipated[14] and

have been accepted in the effort to achieve the goal to collect in a single database the largest number of patients randomized in thrombectomy trials. Moreover, the validated statistical analyses applied allowed to show no evidence of heterogeneity, statistical inconsistency, or small study bias in any of the analyses.

Another limitation of the present study is the exclusion of six eligible trials (accounting for 1019 patients) due to lack of agreement by the principal investigators to participate the study. As a consequence, the participation was unbalanced in favour of manual thrombectomy trials (indeed 88% of studies testing manual thrombectomy were included when compared with 44% of studies testing non-manual thrombectomy). Thus, the hypothesis that the overall positive result may have been driven by manual thrombectomy studies cannot be discarded.

The subgroup analysis generated small subgroups of patients so that the survival analyses were underpowered. Yet, as no large assessment of clinical benefit of thrombectomy according to the key angiographic and clinical parameters has previously been conducted, the present results should be considered as hypothesis-generating and deserve further evaluations.

Finally, the different endpoint definitions for MI, TVR, or TLR adopted in the trials included may have limited the strength of the secondary endpoints analysis. However, the presence of such possible heterogeneity cannot have influenced the primary endpoint which was the unequivocal all-cause mortality.

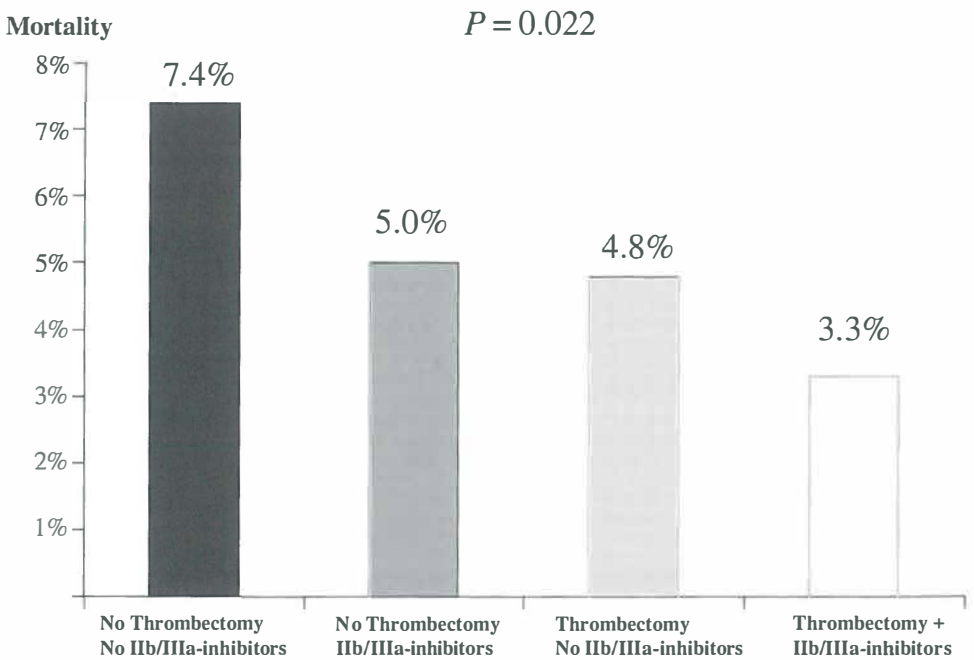


Fig. 6 Mortality rates observed in the ATTEMPT database according to thrombectomy and to administration of IIb/IIIa-inhibitors. Comparison between four treatment subgroups performed by Fisher test.

Conclusions

The pooled analysis of patients with STEMI enrolled in 11 randomized trials showed that the adjunct of thrombectomy (in particular manual thrombectomy) during mechanical reperfusion improves late clinical outcome and that this benefit is evident in patients receiving IIb/IIIa-inhibitors.

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Chapter 4 | Thrombus extraction in the contemporary management of ST-segment elevation myocardial infarction

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BACKGROUND AND INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is primarily caused by an acute thrombotic event resulting in total occlusion of a coronary artery. The precipitating factor for acute thrombosis is generally the rupture of a coronary atherosclerotic plaque, responsible for approximately 75% of all coronary thrombi leading to myocardial infarction (MI) or death[1]. After rupture of the atherosclerotic plaque, fragments of its lipid-rich core are exposed to the arterial lumen. This highly thrombogenic material induces local platelet aggregation, resulting in an early mural thrombus that partially occludes the artery. In time, the formation of a fibrin network causes consolidation of the thrombus. This can be followed by stabilization of the plaque without clinical sequelae, but additional thrombus formation may progress until eventually the whole lumen can be occluded. If occlusion continues for several hours, the ischemic myocardium becomes irreversibly damaged. The longer this coronary occlusion persists, the worse the clinical outcomes are[2].

Historically, treatment of STEMI has focused on restoring flow in the infarct-related artery by dissolving, compressing, or surgically bypassing the occlusion. In recent years, it is widely accepted that primary percutaneous coronary intervention (PCI) consisting of coronary stenting with or without balloon angioplasty is the preferred reperfusion strategy for STEMI patients[2]. This approach is able to restore flow through the epicardial artery in over 90% of patients and is associated with favourable short- and long-term survival[3].

However, reperfusion of the myocardium still remains impaired in over 50% of patients after successful primary PCI, which is a strong predictor of long-term mortality[4,5]. Therefore, these suboptimal results of the conventional primary PCI strategy have spurred the development of adjunctive approaches to reperfuse the occluded artery.

One of the causes of impaired myocardial perfusion is the occurrence of embolization of atherothrombotic material from the intracoronary thrombus or the ruptured plaque into the distal circulation. Embolization can occur both spontaneously during plaque rupture or thrombus formation as well as during reperfusion, induced by the intracoronary therapy of balloon angioplasty and stenting, leading to obstruction of the distal microcirculation and impaired reperfusion and myocardial salvage[6]. In accordance, angiographically visible embolization of atherothrombotic debris into the distal circulation after primary PCI is present in up to 16% of patients and is associated with impaired myocardial perfusion, larger infarct size, reduced left ventricular function and an increased mortality[7]. Furthermore, the incidence of distal embolisation is related to the presence and severity of angiographically visible thrombus[8,9].

In recognition of the clinical impact of atherothrombotic embolization, it be-

came attractive to develop mechanical interventions to reduce its occurrence. These devices remove atherothrombotic debris not by compressing but by extracting or entrapping the atherothrombotic material. In the latest guidelines on the management of patients presenting with STEMI, the use of these devices are recommended as adjunctive therapy to primary PCI to improve myocardial perfusion[2].

This chapter focuses on the role of devices to extract thrombus during primary PCI in patients with STEMI. The first section will discuss methods to evaluate thrombus, including visual assessment on coronary angiography, intracoronary imaging modalities, and histopathological analysis. Second, an overview of the types of extraction devices will be provided, divided into distal protection devices, non-manual thrombus aspiration devices, and manual thrombus aspiration catheters. In the following section, the clinical role of these devices will be evaluated in the current strategy of primary PCI in patients with STEMI. Finally, two clinical cases will be presented of patients with STEMI, illustrating the pivotal role of thrombus extraction in the contemporary percutaneous management of STEMI patients. It is neither the scope of this chapter to review the use of mechanical devices in indications other than STEMI such as in non-ST-segment elevation acute coronary syndromes nor to review its use in other interventions such as vein grafts and peripheral arteries.

THROMBUS CHARACTERIZATION

Intracoronary imaging

The presence of intracoronary thrombus was first demonstrated invasively by De Wood and colleagues[10], who retrieved thrombus using a Fogarty catheter from the coronary artery of STEMI patients with and without angiographic features of thrombus. Angiographic criteria for the presence of thrombus in a coronary artery were defined by Mabin and colleagues[11] as: 1) the presence of an intraluminal central filling defect or lucency surrounded by contrast material that is seen in multiple projections; 2) absence of calcium within the defect; and 3) persistence of contrast material within the lumen. To assess the severity of the thrombotic lesion, the TIMI (Thrombolysis in Myocardial Infarction) thrombus score is widely adopted in clinical practice and clinical trials[12]. This score ranges from grade 0, representing no presence of angiographic thrombus, to grade 5, representing total occlusion (Table 1).

Despite these clear definitions and their use in many important trials assessing intracoronary interventions, these visual estimations underestimate the incidence of thrombus as illustrated by the high retrieval rate of atherothrombotic material when thrombus aspiration is performed[13,14]. In addition, it is impossible to assess thrombus

Table 1 TIMI thrombus grading score

TIMI thrombus grade	Definition
0	No angiographic characteristics of thrombus
1	Possible thrombus present, angiographic characteristics such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus
2	Definitive thrombus, greatest dimensions≤1/2 vessel diameter
3	Definitive thrombus, greatest dimensions >1/2 but <2 vessel diameter
4	Definitive thrombus, greatest dimensions≥2 vessel diameter
5	Total occlusion

burden on the coronary angiogram in patients presenting with total occlusion of the infarct-related artery. In recent years, several technical advancements have enabled a more objective assessment of thrombus presence and size. These intracoronary imaging modalities include angioscopy, intravascular ultrasound, and optical coherence tomography (OCT). Of these modalities, OCT seems to be most promising, being superior in characterizing the coronary atherosclerotic plaque as well as in identifying thrombus in STEMI patients[15,16]. At least, all of these techniques are better able to identify presence of thrombus in STEMI patients than coronary angiography.

Histopathological analysis

As discussed earlier, the actual rate of retrieved atherothrombotic material by aspiration devices is far higher than can be assessed visually by coronary angiography of the culprit lesion. Similarly, the retrieval rate by distal protection devices is much higher than the incidence of angiographically visible distal embolization[7-9,17].

Atherothrombotic material consists of platelets, erythrocytes, and components of atherosclerotic plaque such as vessel wall fragments, cholesterol crystals, inflammatory cells, and collagen tissue. When platelet aggregation occurs, caused by atherosclerotic plaque rupture, a mural white thrombus is formed first consisting mainly of platelets. During this early phase with intermittent coronary flow, the white thrombus is unstable and easily embolizes into the distal circulation[1,6]. As platelet aggregation continues, the formation of a fibrin network causes stabilization of the white platelet-rich thrombus, which may result in total coronary occlusion. When obstruction of coronary flow persists, blood coagulates proximal and distal to the occlusion and causes red thrombus formation, consisting mainly of erythrocytes and inflammatory cells entrapped by a fibrin network[18].

Several studies have reported histopathological features of retrieved atherothrombotic material. Macroscopically, the distinction between white and red thrombus can be made on the retrieved atherothrombotic debris (Fig. 1), while plaque is only identified on histopathological analysis. Fig. 2 shows histopathological examples of white and red thrombus. In a study with manually aspirated atherothrombotic material, the majority consisted of platelets only (68%), mostly smaller than 0.5mm in size, while 15% contained organised layers of erythrocytes that were generally larger (>2.0mm)[14]. In 17%, plaque components were identified. In patients with angiographically visible distal embolization after PCI, the histopathological specimens contain erythrocytes more often and are generally larger compared to the specimens of patients without embolisation[8]. Another feature that has been studied is the age of aspirated atherothrombotic debris. In STEMI patients presenting within 6 hours of symptom onset, the aspirated atherothrombotic material was at least in part older than 1 day in 51%[19], emphasizing that the

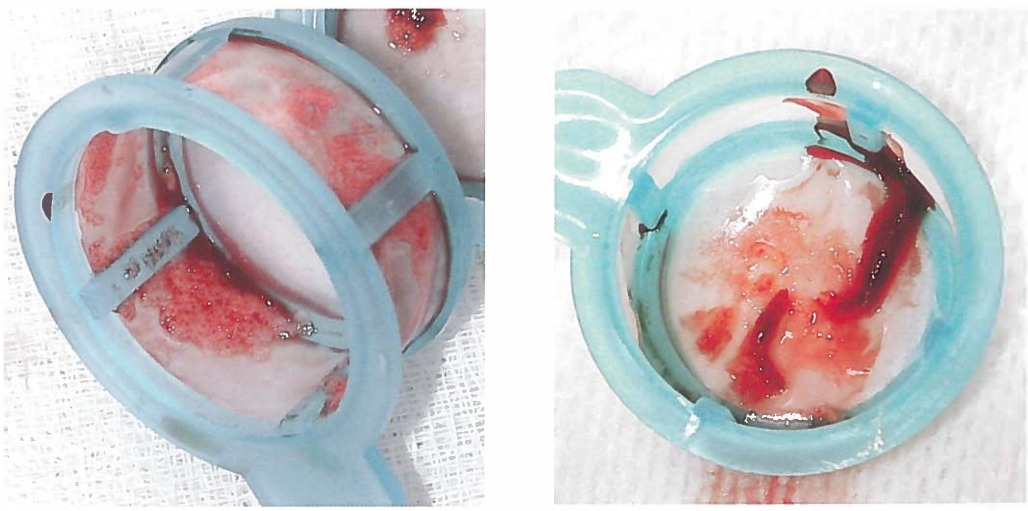


Figure 1 Macroscopical image of retrieved atherothrombotic material showing white (a) and red (b) thrombus.

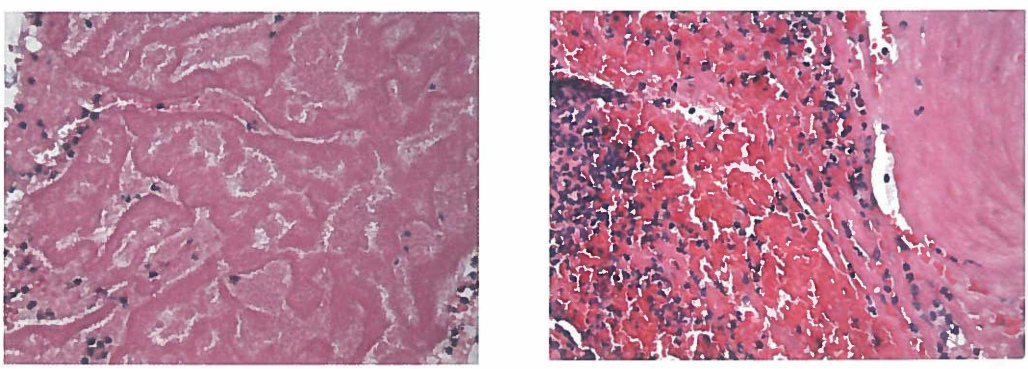


Figure 2 Histopathological images of atherothrombotic material containing platelets only (white thrombus, a) and erythrocytes (red thrombus, b).

process of thrombus formation can be initiated long before clinical symptoms occur.

Not only have studies on thrombus characterization provided insights into the pathophysiology of infarction, but these characteristics may also be useful in the prediction of clinical risk and outcome[20,21]: the age of aspirated thrombus is an independent predictor of long-term mortality in STEMI patients undergoing primary PCI[21].

TYPES OF THROMBUS EXTRACTION DEVICES

Thrombus extraction devices are classified into distal protection devices, non-manual thrombus aspiration devices, and manual thrombus aspiration catheters. An overview of efficacy studies investigating these devices is shown in Tables 2 – 4.

Distal protection devices

These devices have an occlusive balloon or non-occlusive filter that is placed distally to the lesion in order to retrieve atherothrombotic material that would otherwise embolize into the distal circulation. The Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial randomized 501 patients to PCI with or without the GuardWire Plus® System (Medtronic Inc., Santa Rosa, USA), an occlusive balloon device. Distal protection neither reduced infarct size as measured by technetium (Tc) 99m sestamibi imaging, nor did it improve the incidence of complete ST-segment resolution[17]. A Japanese trial confirmed the negative results with the use of an occlusive device[22]. Similar negative results were reported in trials investigating distal filter systems in STEMI patients. The FilterWire-EX® (Boston Scientific Corp., Natick, USA) showed no improvement of coronary flow velocity or infarct size as assessed by magnetic resonance imaging (MRI)[23]. Likewise, the SpideRX® protection device (ev-3, Minneapolis, USA) did not demonstrate improvement of ST-segment resolution as compared to conventional primary PCI[24]. The Drug Elution and Distal Protection in ST-

Table 2 Trials performed with distal protection devices in patients with ST-segment elevation myocardial infarction

Author	Acronym	Year*	No.	Device	Design	Angiography	Primary endpoint	Outcome	FU (days)
Stone[17]	EMERALD	2005	501	GuardWire Plus	Multi-centre	-	STR, infarct size	-	180
Gick[23]	PROMISE	2005	200	FilterWire -Ex	Single- centre	Thrombus present, IRA ≥3mm	Flow velocity	-	30
Cura[24]	PREMIAR	2007	140	SpideRX	Multi-centre	TIMI <3, IRA≥2,5mm	STR	-	180
Muramatsu[22]	ASPARAGUS	2007	341	GuardWire Plus	Multi-centre	IRA≥2,5mm	TIMI flow, cTFC, MBG	+/-	30
Kelbaek[25]	DEDICATION	2008	626	FilterWire-Ex	Multi-centre	-	STR	-	30

* Year of publication as full article.
cTFC, corrected TIMI frame count; FU, follow-up; IRA, infarct-related artery; MBG, myocardial blush grade; No., number of patients; TIMI, Thrombolysis in Myocardial Infarction; STR, ST-segment resolution.

Elevation Myocardial Infarction (DEDICATION) trial, the largest distal protection trial (n=626) did not show improvement of myocardial perfusion as assessed by ST-segment resolution in patients randomized to the FilterWire-EX® or SpideRX® device[25].

Non-manual thrombus aspiration devices

Non-manual aspiration devices are characterized by fragmentation of atherothrombotic material prior to aspiration or aspiration by means of an external mechanical pump. The X-Sizer® catheter (ev-3, White Bear Lake, USA) is a dual-lumen over-the-wire system that has a helical-shaped cutter at the distal tip of the inner lumen. Driven by a hand-held control unit, this system rotates at 2100 rpm once activated, fragmenting and collecting the atherothrombotic debris in a vacuum bottle through the outer lumen. Small- to medium-sized randomized clinical trials have shown that the X-Sizer® system improves electrocardiographic markers of myocardial perfusion and reduces the incidence of angiographically visible distal embolization in comparison to conventional PCI in patients with STEMI[26-28].

A different approach to fragmenting thrombus is used in rheolytic thrombectomy with the AngioJet® catheter (Possis Medical, Inc., Minneapolis, USA). Based on Bernoulli's principle, a piston pump produces a high-pressure saline jet that is ejected against a loop in the distal tip, creating a local low-pressure zone. At the tip, atherothrombotic material is aspirated, fragmented, and removed. Compared with conventional PCI, rheolytic thrombectomy led to a higher rate of ST-segment resolution, better coronary flow, and a smaller infarct size as assessed by Tc 99m sestamibi scintigraphy

Table 3 Trials performed with non-manual thrombus aspiration devices in patients with ST-segment elevation myocardial infarction

Author	Acronym	Year*	No.	Device	Design	Angiography	Primary endpoint	Outcome	FU (days)
Beran[28]		2002	66	X-Sizer	Single-centre	Vessel occlusion / intraluminal filling defect	cTFC	+	30
Napodano[27]		2003	92	X-Sizer	Single-centre	TIMI ≤2, TS≥2, and/or≥70% stenosis, IRA≥2.5 mm	MBG	+	30
Antoniucci[29]		2004	100	AngioJet	Single-centre	IRA≥2.5 mm	STR	+	30
Lefevre[26]	X AMINE ST	2005	201	X-Sizer	Multi-centre	TIMI 0/1, thrombus present, IRA ≥2.5 mm	STR	+	180
Ikari[53]	VAMPIRE	2008	355	TVAC	Multi-centre	IRA 2.5-5mm	Slow/no reflow	+/-	240
Kaltoft[54]		2006	215	Rescue	Single-centre	-	Myocardial salvage	-	30
Ali[30]	AIMI	2006	480	AngioJet	Multi-centre	IRA >2.0 mm	Infarct size	-	30

* Year of publication as full article.
cTFC, corrected TIMI frame count; FU, follow-up; IRA, infarct-related artery; MBG, myocardial blush grade; No., number of patients; TIMI, Thrombolysis in Myocardial Infarction; STR, ST-segment resolution.

at 1 month[29]. However, these positive results could not be reproduced in the larger AngioJet Rheolytic Thrombectomy In Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AIMI) trial in 480 patients, showing no differences in myocardial perfusion as assessed by myocardial blush grade (MBG) and ST-segment resolution[30]. Instead, in patients randomized to rheolytic thrombectomy, infarct size as measured by Tc 99m sestamibi imaging at 14 – 28 days was even larger (12.5±12.13 vs. 9.8±10.92, p=0.03). Furthermore, the occurrence of major adverse cardiac events (MACE) at 30 days was higher (6.7 vs. 1.7%, p=0.01), due to a higher mortality rate in patients treated with the AngioJet® system (4.6 vs. 0.8%, p=0.02), although no death was directly attributed to the device.

Third, non-manual aspiration catheters aspirate atherothrombotic material through continuous suction of an external vacuum pump. Medium-scaled trials investigating these non-manual aspiration catheters have reported conflicting results in unselected STEMI patients. In 355 patients with STEMI, the TransVascular Aspiration Catheter® (TVAC®, Nipro, Osaka, Japan) was associated with a higher rate of post-procedural MBG 3 in the STEMI group compared to the conventional PCI group (46.0 vs. 20.5%, p<0.001) as well as a reduction in MACE at 8 months (12.9 vs. 20.9%, p<0.05), primarily driven by a reduction in target lesion revascularization. However, a clinical trial in 215 patients using the Rescue® thrombus management system (Boston Scientific Corp./Scimed, Maple Grove, USA) did not report better myocardial salvage estimated by Tc 99m sestamibi imaging in STEMI patients randomized to the Rescue® catheter (13 vs. 18%, p=0.12). Furthermore, final infarct size was increased in the aspiration versus the conventional group (15 vs. 8%, p=0.004).

Manual thrombus aspiration catheters

These rapid-exchange manual aspiration catheters have the following common features: 1) they contain two lumens, a smaller guidewire lumen, and a larger one to aspirate atherothrombotic debris; 2) the distal end has a flexible atraumatic tip with one or multiple entry ports; and 3) the larger lumen is connected proximally to a syringe to allow manual suction. Manual thrombus aspiration catheters include the Diver Clot Extraction® (CE) catheter (ev3 Inc, Plymouth, USA), the Pronto® extraction catheter (Vascular Solutions, Minneapolis, USA), the QuickCat Extraction Catheter® (Spectranetics, Colorado Springs, USA) and the Export® aspiration catheter (Medtronic Inc., Santa Rosa, USA).

Several small- to medium-sized trials have demonstrated improvement of myocardial perfusion in STEMI patients randomized to manual thrombus aspiration[13,31-33]. In addition, substudies have reported a reduction of microvascular obstruction as as-

sessed by contrast-enhanced MRI with the Export® aspiration catheter[33] and as assessed by myocardial contrast echocardiography with the Diver CE® catheter[34]. Furthermore, De Luca and colleagues[35] have reported a lower incidence of left ventricular remodelling in patients with anterior STEMI successfully treated with the Diver CE® catheter.

In concert, improvement of myocardial perfusion was found in the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS), the largest trial to date investigating the effect of an adjunctive manual aspiration catheter to the conventional primary PCI strategy[14]. This study was designed to enroll an unselected population of STEMI patients without angiographic in- or exclusion criteria. Therefore, this study randomized 1071 consecutive STEMI patients to treatment with the Export® aspiration catheter or to conventional primary PCI before coronary angiography was performed. In the aspiration group, the catheter was advanced into the infarct-related segment under continuous aspiration to restore antegrade flow prior to stenting. In the conventional PCI group, antegrade flow was established by balloon dilatation. Thrombus aspiration was applicable in 89%. In 73% of these patients, thrombus aspiration resulted in retrieval of atherothrombotic material. Compared to conventional PCI, post-procedural myocardial perfusion was improved in patients randomized to thrombus aspiration as assessed by the occurrence of MBG 0/1 (17.1% vs. 26.3%, RR 0.65, 95% CI 0.51 – 0.83, p<0.001), complete ST-segment resolution (56.5% vs. 44.2%, RR 1.28, 95% CI 1.13 – 1.45, p<0.001), as well as absence of persistent ST-segment deviation (53.1% vs. 40.5%, RR 1.31, 95% CI 1.14 – 1.50, p<0.001). Furthermore, analysis on pre-specified subgroups consistently showed improvement in myocardial perfusion in the aspiration group compared to conventional PCI in all major categories of STEMI patients including gender, age, total ischaemic time, infarct-related vessel, infarct-related segment, pre-procedural TIMI flow, as well as angiographic

Table 4 Trials performed with manual thrombus aspiration devices in patients with ST-segment elevation myocardial infarction

Author	Acronym	Year*	No.	Device	Design	Angiography	Primary endpoint	Outcome	FU (days)
Burzotta[31]	REMEDIA	2005	99	Diver CE	Single-centre	-	MBG, STR	+	30
De Luca[35]		2006	76	Diver CE	Single - centre	TIMI 0/1, thrombus present, successful PCI	LV remodelling	+	180
Silva -Orrego[13]	DEAR - MI	2006	148	Pronto	Single-centre	-	MBG + STR	+	in-hospital
Svilaas[14]	TAPAS	2008	1071	Export	Single-centre	-	MBG	+	30
Chevalier[32]		2008	249	Export	Multi-centre	TIMI 0/1	MBG + STR	+	30
Sardella[33]	EXPIRA	2009	175	Export	Single-centre	TIMI ≤1, TS ≥3, IRA ≥2.5mm	MBG, STR	+	270

* Year of publication as full article.
FU, follow-up; IRA, infarct-related artery; LV, left ventricular; MBG, myocardial blush grade; No., number of patients; TIMI, Thrombolysis in Myocardial Infarction; STR, ST-segment resolution.

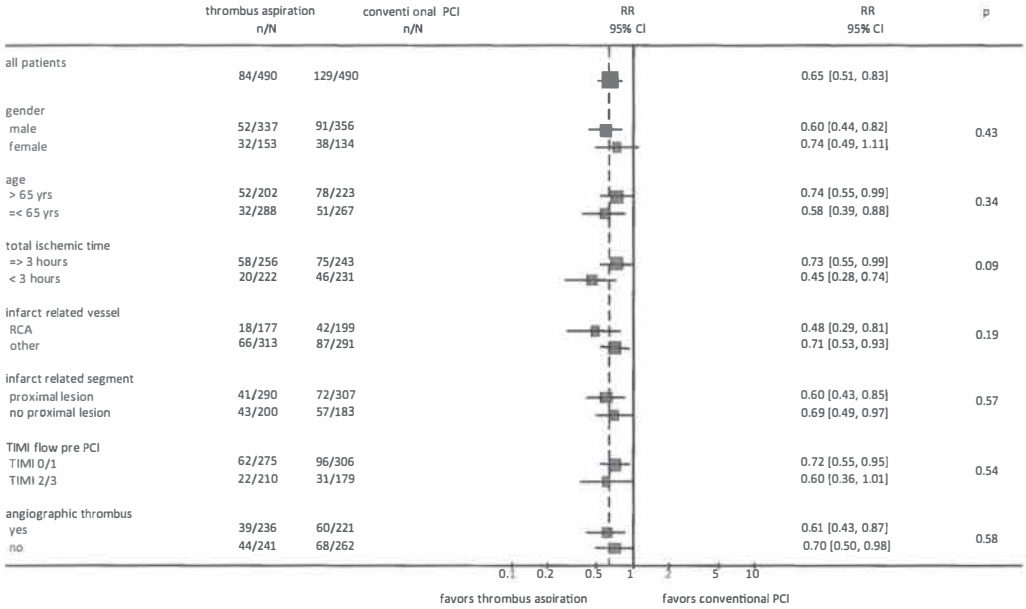


Figure 3 TAPAS subanalysis on pre-specified subgroups: given are risk ratios for the primary endpoint of occurrence of myocardial blush grade 0/1 in the aspiration versus the conventional PCI group. From Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358(6):557-67.

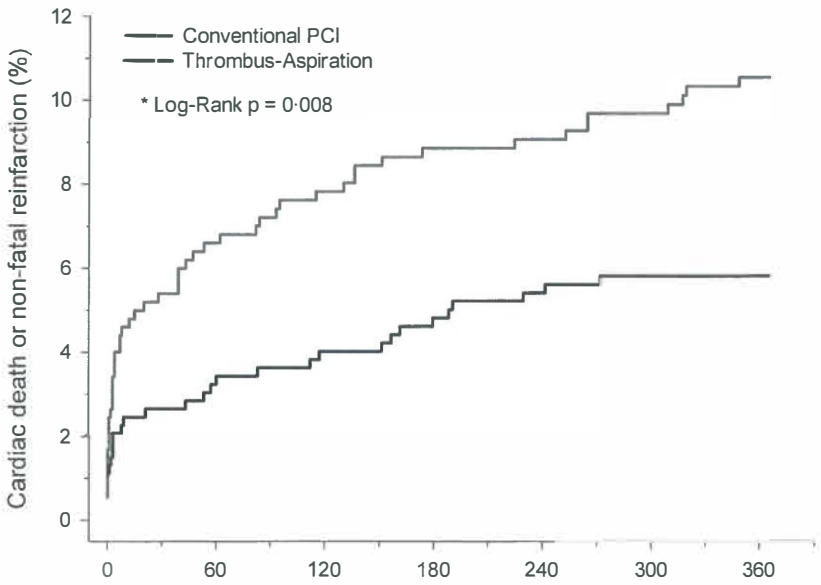
evidence of thrombus (Fig. 3). In contrast to these positive findings, the incidence of angiographically visible distal embolization was not significantly reduced in the thrombus aspiration compared to the conventional PCI group (6.7 vs. 6.0%, p=NS)[8]. Clinical follow-up at 30 days showed no differences between both groups. At 1 year, however, assignment to thrombus aspiration was associated with a reduction of cardiac mortality (3.6% vs. 6.7%, HR 1.93, 95% CI 1.11 – 3.37, p=0.020) and the combined endpoint of cardiac mortality or non-fatal reinfarction (5.6% vs. 9.9%, HR 1.81, 95% CI 1.16 – 2.84, p=0.009) compared to conventional PCI[36]. The Kaplan-Meier curve for the combined endpoint of cardiac mortality or non-fatal reinfarction is illustrated in Fig.4.

One limitation of this study is the use of functional or surrogate endpoints and the limited statistical power to estimate the magnitude of the clinical benefits. Although TAPAS was not primarily designed to detect differences in clinical outcome, the angiographic and electrocardiographic endpoints used are well accepted and widely used markers of myocardial perfusion in infarction studies that are strongly associated with mortality and MACE. Second, TAPAS represents a single-centre experience. Third, the use of balloon dilatation prior to stenting was left at the operator's discretion as this study was not designed to investigate the impact of predilatation. Therefore, the precise role of predilatation versus direct stenting on myocardial perfusion outcomes is still to be elucidated.

THE ROLE OF ADJUNCTIVE THROMBUS EXTRACTION DURING PRIMARY PCI

From the late 1990s, case reports and studies on small patient series showed that thrombus extraction devices were feasible and safe during primary PCI in STEMI patients. Larger efficacy studies followed, reporting mostly positive but also several negative results (see Tables 2 – 4). Although these studies were not powered to detect differences in clinical outcomes, they generally used accepted surrogate endpoints to assess myocardial perfusion. Myocardial perfusion can be measured in several ways, of which MBG and ST-segment resolution are widely used and practical methods. These classifications have proven to correlate well with long-term cardiac mortality after primary PCI[4,5]. Therefore, in studies using these surrogate endpoints, improvement in myocardial perfusion is expected to translate into clinical benefits.

Early meta-analyses on thrombus extraction devices did not report improvement of clinical outcomes at 30 days, although these devices were associated with improved epicardial and myocardial perfusion and a lower incidence of distal embolization[37-39]. However, more recent meta-analyses demonstrated that manual thrombus



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

Figure 4 Kaplan-Meier curve for the combined endpoint of cardiac mortality or non-fatal reinfarction at 1-year follow-up in aspiration versus conventional PCI patients in TAPAS. From Vlaar PJ, Svilaas T, van der Horst IC, et al. 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. Lancet 2008;371(9628):1915-20.

aspiration was associated with a reduction of mortality compared to conventional PCI at 30 days (1.7 vs. 3.1%, OR 0.58, 95% CI 0.34 – 0.98, p=0.04)[40] and at a mean follow-up of 6.2 months (2.7 vs. 4.4%, RR 0.63, 95% CI 0.43 – 0.93, p=0.018)[41]. At present, a beneficial effect of manual thrombus aspiration has been reported on 1-year clinical outcomes in the TAPAS trial as mentioned earlier[36]. Furthermore, the very recent pooled Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data (ATTEMPT) has reported similarly that manual thrombus aspiration in particular is associated with improved long-term survival and clinical outcome[42]. While heterogeneity among the individual trials should be acknowledged (inclusion criteria, devices, and definitions), there is convincing evidence that manual thrombus aspiration is associated with improved angiographic, electrocardiographic, as well as clinical outcomes.

In contrast to the positive results of manual thrombus aspiration, the other devices do not share the same clinical benefit. While manual thrombus aspiration was associated with a reduction in mortality compared to conventional PCI, non-manual thrombus aspiration was associated with an increased (5.3 vs. 2.8%, RR 1.93, 95% CI 1.00 – 3.72, p=0.050) and distal protection devices with a neutral effect on mortality (3.1 vs. 3.4%, RR 0.92, 95% CI 0.60 – 1.40, p=0.69)[41].

Table 5 summarizes the published meta-analyses on thrombus extraction devices. While filter systems have the theoretical advantage of maintaining antegrade flow through the culprit coronary artery, efficacy studies on neither distal occlusive devices nor filter systems could demonstrate improvement of myocardial perfusion or infarct size. Therefore, there is currently no evidence to recommend the routine use of non-manual thrombus aspiration devices or distal protection devices during primary

Table 5 Meta-analyses of mechanical adjunctive devices in patients with ST-segment elevation myocardial infarction

Author	Year*	Search period	Included trials (n)	No.	Device	Endp oints	Outcome	FU
Kunadian[38]	2007	Sep 2000 – Oct 2005	14	2630	all	Mortality/reinfarction	-	30 days
De Luca[37]	2007	Jan 1990 – Oct 2006	21	3721	all	TIMI flow	+	30 days
						MBG	+	
						DE	+	
						Mortality	-	
Burzotta[39]	2008	Oct 2003 – Jun 2006	18	3180	all	Mortality/reinfarction	-	≤30 days
						DE	+	
						TIMI flow	+	
						MBG	+	
						STR	+ (for TA)	
De Luca[40]	2008	Jan 1990 – May 2008	9	2417	TA	TIMI flow	+	30 days
						MBG	+	
						DE	+	
						Mortality/reinfarction	+	
Bavry[41]	2008	Jan 1996 – Jun 2008	30	6415	TA(47%)	Mortality	+	6.2 months**
					NTA (15%)	Mortality	-	4.6 months**
					DPD (38%)	Mortality	-	3.7 months**
Burzotta[42]	2009	Oct 2003 – Feb 2008	11	2686	TA(68%) NTA (32%)	Mortality	+	365 days**

* Year of publication as full article.
**Mean follow-up duration within the subgroup.
DE, distal embolization; DPD, distal protection device; FU, follow-up; MBG, myocardial blush grade; No., number of patients; NTA, non-manual thrombus aspiration; TIMI, Thrombolysis in Myocardial Infarction; STR, ST-segment resolution; TA, manual thrombus aspiration.

PCI in STEMI patients. For non-manual devices, the results of a European multi-centre study are still to be expected. In this trial, 500 STEMI patients are randomized to primary PCI with or without aspiration with the AngioJet® system and may provide additional insights into the role of non-manual aspiration in STEMI patients[43]. While distal protection devices are not recommended during primary PCI, they have a class Ia recommendation for use as adjunctive devices during elective PCI of vein grafts[44].

Although the exact patient population in which thrombus aspiration should be performed in clinical practice is not clearly defined, it seems reasonable to attempt aspiration in all patients presenting with STEMI. Angiographic evidence of thrombus should not be a selection criterion for the use of a manual aspiration catheter, as demonstrated in TAPAS. In this study, the benefit of thrombus aspiration on myocardial perfusion was irrespective of angiographic presence of thrombus.

Next to its benefit on clinical outcome, manual thrombus aspiration has several practical advantages. First, these aspiration catheters are effective in crossing, even small, target lesions. On the contrary, the other devices require a more permissive coronary anatomy as non-manual devices can usually target only larger vessels and distal protection devices need a distal landing zone. Second, the clinical applicability of manual aspiration catheters is high. Its use is easy and it does not require much practice to gain clinical experience. Third, manual aspiration catheters are safe, with no clinically manifest major complications reported. An additional advantage is that these catheters are inexpensive, being available in the same price range as balloon catheters. In most cases, thrombus aspiration has resulted in restoration of brisk antegrade flow and predilatation with a balloon catheter is not needed. Although formally it has not been investigated whether the use of thrombus aspiration catheters is cost-effective, it seems clear that their use does not lead to increased costs of the primary PCI strategy. In contrast, the more sophisticated and complex other approaches involve more expenditure, in increased costs of either disposables or additional equipment. These features of the three types of mechanical devices are summarized in Table 6.

Several factors may explain why the published studies have produced heterogeneous results. First of all, there is a clear group distinction between the manual aspiration catheters and non-manual and distal protection devices in their clinical performance in routine practice. Although the latter were able to retrieve atherothrombotic debris, this did not unequivocally translate into improvement of myocardial perfusion, infarct size, or clinical outcome. On the contrary, non-manual devices as well as distal protection systems may result in longer and more complex PCI procedures[30] and even major complications such as coronary dissection[28] or an AV fistula[26], negating a possible beneficial effect. Another reason why some studies were negative could be that the

devices studied are not fully able to prevent device-induced embolization when wire and/or device cross the lesion. In addition, technical details may influence this risk of embolization. For instance, it is believed that embolization is more easily induced by thrombus aspiration if a distal-to proximal approach is applied, in which aspiration is started after crossing the lesion, than if a proximal-to-distal approach is used, in which the catheter is advanced into the lesion during continuous active aspiration[45]. As the first approach was used in 52% of patients enrolled in the AIMI trial, this may have confounded the results.

Finally, the large negative studies investigating non-manual aspiration devices did not require angiographic selection criteria. While manual aspiration catheters are effective in all patients, these more complex devices may only benefit STEMI patients with a high thrombus burden. Unfortunately, their role in this subset of patients is not well investigated. Therefore, non-manual devices may be indicated in STEMI patients with a large thrombus load in case residual, more organised, thrombus remains after performance of manual thrombus aspiration.

Future perspectives

At present, there is convincing evidence for the superiority of adjunctive manual thrombus aspiration during primary PCI over conventional PCI in removing the source of embolization and in improving myocardial perfusion. Its benefit on clinical outcomes is derived from the 1-year results of the TAPAS trial and from several meta-analyses. Comparisons between individual devices have been sparingly performed[46], with a small-sized study reporting improved angiographic outcomes with the Export® compared to the Diver® catheter[47]. Further research should clarify this issue. In addition, more objective imaging techniques will be adopted in clinical practice to characterize

Table 6 Comparison of features of manual thrombus aspiration, non-manual thrombus aspiration, and distal protection devices

Feature	Manual thrombus aspiration	Non-manual thrombus aspiration	Distal protection
Ability to reach target lesion	++	+	+
Effective retrieval	+	+	+
Technical complexity	-	+	+
Complications	-	+	+
Costs	-	++	+(+)

and grade thrombus load. These techniques may also illustrate the other components of the multiple mechanisms by which vessels can become occluded.

Before retrieval of atherothrombotic material was performed in STEMI patients, histopathological analysis could only be performed in post-mortem studies. The knowledge largely derived from these studies, evidently suffering from a selection bias, is expected to be supplemented by analysis of aspiration samples.

An important limitation of thrombus aspiration is its inability to prevent distal embolization that has occurred spontaneously before PCI. Furthermore, distal embolization itself is only one of the causes of impaired myocardial perfusion in patients with STEMI. Several other mechanisms account for this phenomenon, including myocardial reperfusion injury, tissue oedema, capillary leakage, and endothelial dysfunction[48,49]. Therefore, although thrombus aspiration has proven to reduce the risk of atherothrombotic embolization, it neither compensates for these additional mechanisms that impair myocardial perfusion, nor for distal embolization that has occurred prior to intervention. These insights, together with the current knowledge of the histopathology and pathophysiology of thrombotic occlusions, should stimulate the development of adjunctive pharmacological therapies to target these pathways.

Last but not least, time to reperfusion remains one of the major predictors of clinical outcome in STEMI. Therefore, efforts to reduce ischaemic time in patients with STEMI are of paramount importance.

CLINICAL CASE STUDIES

Case 1

A 61-year old male smoker was referred to the catheterization laboratory within 2h after symptom onset with electrocardiographic evidence of an anterior infarction. Although antegrade flow was present on initial coronary angiography of the left coronary system, subtotal occlusion was observed of the mid left anterior descending (LAD) artery with a large thrombus burden grade 4 (Fig. 5a). Coronary angiography of the right coronary system was normal. The initial treatment step was thrombus aspiration in the mid LAD (Fig. 5b), leading to aspiration of macroscopically visible white thrombus. On angiography, TIMI 3 flow was restored through the culprit artery and the thrombus burden was successfully reduced to grade 1 (Fig. 5c). Finally, after stent deployment (Biotronik PRO-kinetic®, 3.5 x 15 mm, Fig. 5d), no thrombus was visible (Fig. 5e). At the end of procedure, a dedicated run (30° right anterior oblique view) was performed to allow assessment of TIMI flow and myocardial perfusion, measured both visually using the

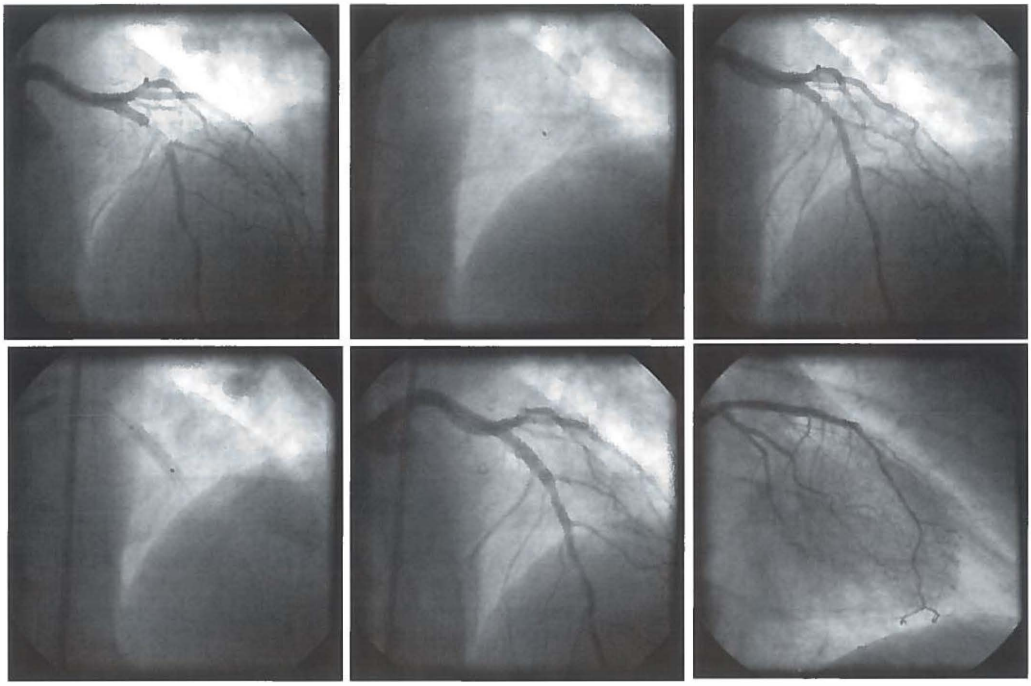


Figure 5 Primary PCI in a patient with subtotal occlusion of the left anterior descending artery with a high thrombus burden.

MBG as well as computerized using the Quantitative Blush Evaluator (QuBE, Fig 5f)[50]. In this patient, optimal reperfusion of both the epicardial artery as well as the myocardium was obtained.

Case 2

An 83-year-old woman was admitted after a sudden onset of chest pain for six hours. The initial coronary angiogram showed single-vessel disease with a distal site of total occlusion in the right coronary artery (RCA) as identified by staining from the test injection (Fig. 6a). Thrombus aspiration (Fig. 6b) resulted in removal of macroscopically red thrombus. Afterwards, brisk antegrade flow was restored through the culprit lesion without angiographically visible thrombus or a residual stenosis that required stenting. However, distal embolization was visible in the posterolateral branch (Fig. 6c). Additional thrombus aspiration was performed in this lesion (Fig. 6d), which led to restoration of TIMI 3 flow through the entire, large, RCA (Fig. 6e). Without further coronary intervention, optimal myocardial perfusion was achieved (Fig. 6f). Thrombus aspiration has been described as a safe and effective definitive treatment in STEMI patients[51,52].

Conclusion

In patients with STEMI, adjunctive manual thrombus aspiration devices during prima-

ry PCI are able to protect the distal coronary microvasculature from atherothrombotic embolization and lead to better restoration of myocardial perfusion compared to conventional primary PCI. At present, there is increasing evidence that the use of manual thrombus aspiration is associated with improved long-term survival. Manual thrombus aspiration is safe and easily applicable in a large majority of patients presenting with STEMI. In contradistinction, the routine use of non-manual aspiration and distal protection devices is not recommended.

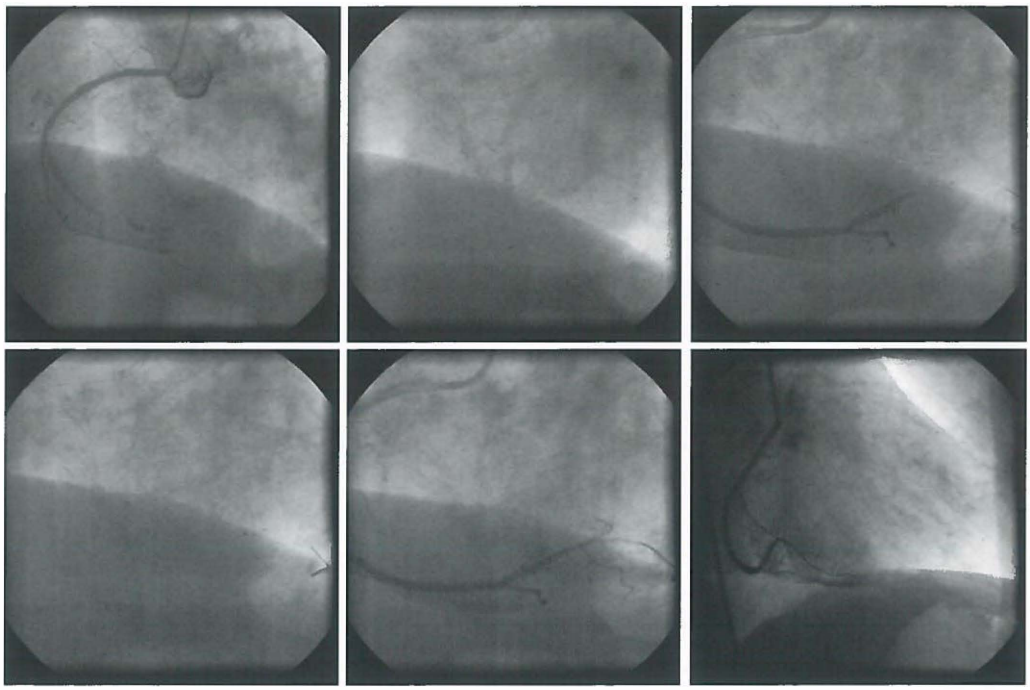


Figure 6 Primary PCI in a patient with total occlusion of the right coronary artery.

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Chapter 5| Impact of thrombus burden in ST-Elevation Myocardial Infarction patients treated with or without thrombus aspiration

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ABSTRACT

Aims

There are limited data regarding the impact of angiographically observed thrombus burden on outcome in patients with ST-Elevation Myocardial Infarction (STEMI) treated with or without thrombus aspiration. We evaluated whether thrombus burden is associated with impaired myocardial perfusion and 1-year all-cause mortality. Furthermore, we analyzed the effect of thrombus aspiration in patients with large and with small thrombus burden on these outcomes.

Methods and Results

We analyzed all consecutive STEMI patients treated with primary percutaneous coronary intervention between January 2004 and April 2010. Of the 2969 patients, 68% had large (Thrombolysis In Myocardial Infarction thrombus score 4 or 5) and 32% had small thrombus burden. Both myocardial blush grade (MBG) 0 or 1 and 1-year mortality were higher in patients with large compared to patients with small thrombus burden (34% vs. 21% $p<0.001$ and 9.0% vs. 6.6% $p=0.021$). Thrombus aspiration as first intervention was performed in up to 60% of patients in both groups. MBG 0 or 1 was lower when thrombus aspiration was performed in the patients, irrespective of whether the observed thrombus burden was large (31% vs. 38%, $p=0.001$) or small (18% vs. 25%, $p=0.017$). In addition, the use of thrombus aspiration was associated with lower 1-year mortality, irrespective of large (6.4% vs. 12.7%, $p<0.001$) or small observed thrombus burden (4.2% vs. 9.6%, $p=0.001$).

Conclusions

Large thrombus burden is associated with impaired myocardial perfusion and 1-year mortality in STEMI patients. Irrespective of thrombus burden observed on angiography, thrombus aspiration is related to improved outcomes.

INTRODUCTION

A large proportion of patients with ST-Elevation Myocardial Infarction (STEMI) has impaired myocardial perfusion despite a patent epicardial vessel after primary percutaneous coronary intervention (PCI).[1,2] Impaired myocardial perfusion is considered to be most likely caused by microvascular obstruction due to embolization of atherothrombotic particles.[3] However, the relatively low incidence of angiographically observed distal embolization[4,5] cannot fully explain impaired myocardial perfusion. Therefore, angiographically undetectable microembolization is suspected to occur.[3,6] The distal embolization observed during angiography is associated with large thrombus burden.[4,7] Meanwhile, limited data are available regarding the impact of angiographically observed thrombus burden on myocardial perfusion and outcome.[8]

Thrombus aspiration reduces the thrombus burden and improves myocardial perfusion and clinical outcome.[9,10] Therefore, this intervention is recommended in current guidelines for STEMI patients.[11,12] However, the question remains whether there is a difference in benefit of thrombus aspiration in large and in small thrombus burden as defined by angiography that can support selective use of thrombus aspiration. In this study, we used a large unselected consecutive STEMI cohort to evaluate whether thrombus burden is associated with impaired myocardial perfusion and 1-year all-cause mortality. Furthermore, we evaluated whether the use of thrombus aspiration improves these outcomes irrespective of large or small thrombus burden.

METHODS

Study population and design

All consecutive STEMI patients treated with primary PCI at the University Medical Center Groningen in The Netherlands were included in our database. For this retrospective study, we analyzed data of STEMI patients admitted from January 2004 to April 2010. The criteria for STEMI were the following; ST-segment elevation of >0.1mV in ≥2 leads on the electrocardiogram, and onset of symptoms less than 12 hours or less than 24 hours with persisting symptoms due to ongoing ischemia. The criterion for primary PCI was successful crossing of the culprit lesion with a guidewire. From January 2004 until December 2004, STEMI patients were treated with conventional PCI (mainly balloon angioplasty followed by stent implantation). From January 2005 until December 2006, conventional PCI and thrombus aspiration followed by stent implantation were randomly performed in the context of TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study).[10,13] Manual thrombus aspiration became the preferred treatment since December 2006, but the choice of pro-

cedure was left to the discretion of the operator. Acute pharmacotherapy was according to current international guidelines, including heparin, aspirin, clopidogrel and the glycoprotein IIb/IIa inhibitor abciximab.[14] All coronary angiograms were analyzed by either an independent core laboratory or by two experienced observers blinded to all clinical data.

Thrombus burden

Patients were included when thrombus burden was assessable on the angiogram before PCI. Thrombus burden was graded from 0 to 5 according to the Thrombolysis In Myocardial Infarction (TIMI) thrombus grade.[15] The definitions are as follows; TIMI thrombus grade 0, no angiographic characteristics of thrombus; grade 1, possible thrombus with reduced contrast density, haziness, irregular lesion contour or smooth convex 'meniscus' at the site of total occlusion suggestive but not diagnostic of thrombus; grade 2, definitive thrombus with greatest dimension ≤1/2 vessel diameter; grade 3, definitive thrombus with greatest dimension >1/2 but <2 vessel diameters; grade 4, definitive thrombus with greatest dimension ≥2 vessel diameters and grade 5, total occlusion. In this study, small thrombus burden was defined as TIMI thrombus grade ≤3 and large thrombus burden as TIMI thrombus grade ≥4. When assessable, thrombus burden was also graded after the first intervention: thrombus aspiration or balloon angioplasty.

Endpoints and Definitions

The primary endpoint of this study was impaired myocardial perfusion, defined as Myocardial blush Grade (MBG) 0 or 1. Secondary endpoints were angiographic and electrocardiographic outcome and 1-year all-cause mortality. The MBG was determined by the contrast density of the myocardial region of the infarct-related artery compared to the myocardial regions of non-infarct-related arteries. MBG was classified as MBG 0, no myocardial blush or persisting blush (staining); MBG 1, minimal myocardial blush; MBG 2, moderate myocardial blush or MBG 3, normal myocardial blush.[16] TIMI flow grade was classified as previously described.[17] Distal embolization was defined as angiographically visible filling defect and/or abrupt cut-off of the vessel distal to the culprit lesion.[6] Complete ST-segment resolution was defined as more than 70% resolution of the ST-segment deviation on the electrocardiogram at presentation compared to the electrocardiogram at 30 to 60 minutes after primary PCI.[18] Thrombus aspiration was classified as effective when macroscopic atherothrombotic material was identified in the retrieved aspirate. Histopathological analysis of aspirate was performed as part of our randomized clinical trials.[10,19] In November 2010 mortality data was collected using the municipal civil registry, which contains completeness of vital status of all residents

registered in The Netherlands.

Statistical analysis

Normally distributed continuous variables are presented as mean with standard deviation (SD) and were compared using a two-tailed Student's t-test. Skewed distributed continuous variables are presented as median with interquartile range (IQR) and were compared using a Mann Whitney U test. Categorical variables are presented as number and percentage and were compared using the $\chi 2$ test or Fisher's exact test. Kaplan Meier curves were used to determine 1 year survival and differences were analyzed using the log-rank test. Statistical significance was defined as a two-sided p-value of less than 0.05. Statistical analysis was performed using SPSS software version 16.0 (Chicago, USA).

RESULTS

Large versus small thrombus burden

A total of 2991 STEMI patients were treated with primary PCI in our hospital in the 6.3 year period. Of the 2969 patients in whom the thrombus burden could be assessed on coronary angiogram, 2023 (68%) patients had large thrombus burden and 946 (32%) patients had small thrombus burden (figure 1). At baseline, patients with large thrombus burden had less diabetes mellitus, slightly longer median ischemic time, more often the

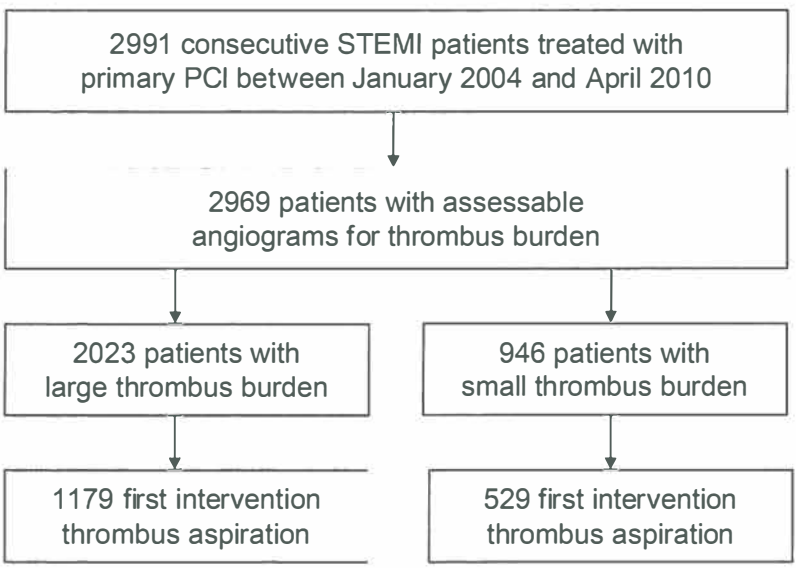

Figure 1 Flow chart. STEMI patients were classified based on their thrombus burden observed angiographically and whether they were treated with thrombus aspiration as first intervention. STEMI= ST-elevation Myocardial Infarction

right coronary artery as culprit and more often an impaired TIMI flow (table 1).

The impact of large and small thrombus burden was assessed on angiographic, electrocardiographic and clinical outcome. MBG could be assessed in 2775 (93%) patients. The primary endpoint, MBG 0 or 1, was significantly higher in patients with large versus patients with small thrombus burden (34% versus 21%, p<0.001) (table 2 and figure 2). Secondly, TIMI flow grade 3 after PCI was lower in patients with large thrombus burden. In patients with TIMI flow grade 3 after PCI, the incidence of MBG 0 or 1 was still higher in patients with large thrombus burden (22% vs. 16%, p<0.001). In addition, angiographically observed distal embolization after PCI was seen more often in patients with large thrombus burden. Furthermore, the incidence of complete ST-segment resolution was lower in patients with large thrombus burden. Finally, 1-year all-cause mortality was also higher in patients with large versus small thrombus burden (9.0% versus 6.6%, p=0.021) (figure 3).

Impact of thrombus aspiration

The effect of thrombus aspiration on outcome was evaluated in patients with large and small thrombus burden. Thrombus aspiration as first intervention was performed in 1179 (58%) and 529 (56%) patients with large and with small thrombus burden, respec-

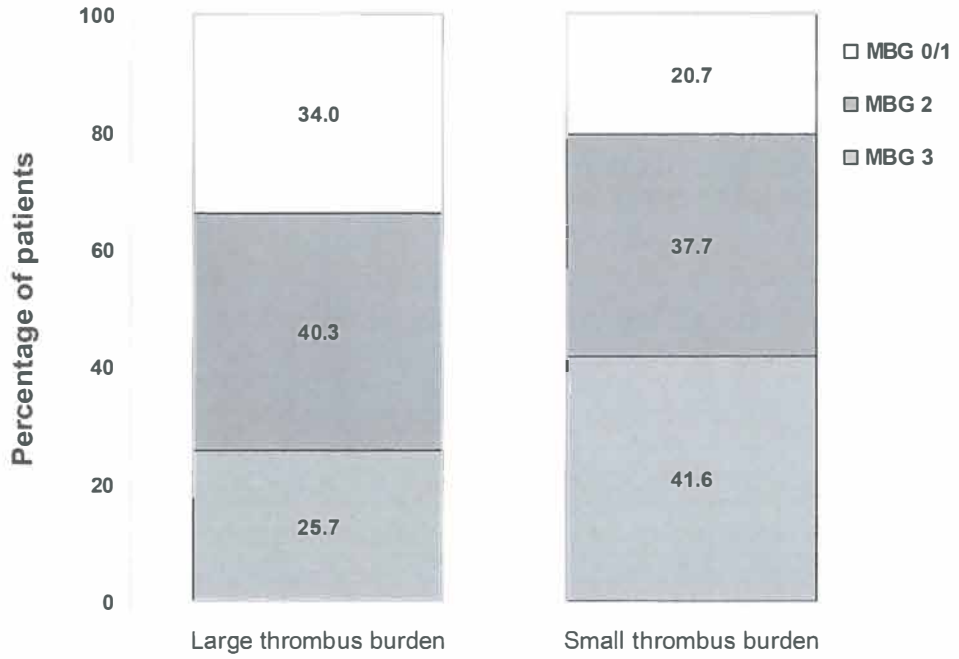

Figure 2 MBG related to large and small thrombus burden. MBG 0 or 1 was significantly higher in patients with large thrombus burden versus patients with small thrombus burden (p<0.001). MBG= Myocardial Blush Grade

tively (table 1). The incidence of MBG 0 or 1 was significantly lower when thrombus aspiration was performed compared to when no thrombus aspiration was performed. This result held true for both patients with large thrombus burden (31% versus 38%, p=0.001) and in patients with small thrombus burden (18% versus 25%, p=0.017) (figure 4). TIMI flow grade 3 after PCI was also more often seen when thrombus aspiration was performed compared to when no thrombus aspiration was performed in patients with large thrombus burden (85% versus 72%, p<0.001). A non-significant difference was seen in patients with small thrombus burden (93% versus 90%, p=0.130). There was no impact of thrombus aspiration on angiographically observed distal embolization compared to no thrombus aspiration as first intervention (in large thrombus burden 14% versus 16%, p=0.142, in small thrombus burden 6% versus 3% p=0.100). In 1535 patients, thrombus burden was prospectively scored before and after the first intervention. In the 1408 (92%) patients with thrombus observed before PCI, reduction of thrombus burden

Table 1 Baseline characteristics of patients with large versus with small thrombus burden in STEMI cohort

	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
General			
Age, years	64±13	64±13	0.942
Male sex	1467 (73)	660 (70)	0.122
History			
Hypertension	723 (40)	333 (38)	0.358
Diabetes mellitus	219 (11)	129 (14)	0.032
Hypercholesterolemia	499 (30)	232 (28)	0.478
Myocardial infarction	181 (9)	97 (11)	0.308
PCI	161 (8)	71 (8)	0.650
CABG	56 (3)	28 (3)	0.779
Current smoking	883 (50)	430 (51)	0.472
Body mass index, kg/m^2	27.0±4	26.7±4	0.071
Cardiovascular disease in family	811 (46)	391 (45)	0.795
Ischemic time, minutes	190 (135-300)	180 (130-270)	0.010
Angiographic			
Infarct-related artery			<0.001
Left anterior descending	807 (40)	468 (50)	
Circumflex	303 (15)	163 (17)	
Right coronary artery	875 (43)	284 (30)	
Other	38 (2)	31 (3)	
TIMI flow grade			<0.001
0 or 1	1781 (88)	85 (9)	
2 or 3	241 (12)	857 (91)	
Multivessel disease	1266 (63)	566 (60)	0.173
Procedural			
Administration of glycoprotein IIb/IIIa inhibitor	1735 (86)	807 (85)	0.741
Thrombus aspiration	1179 (58)	529 (56)	0.225

Data are presented as mean±SD, median (IQR) or as number (%).
PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, TIMI: Thrombolysis In Myocardial Infarction

Table 2 Outcome characteristics in STEMI cohort

	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
Post procedural			
MBG			<0.001
0 or 1	646 (34)	181 (21)	
2 or 3	1252 (66)	696 (79)	
TIMI flow grade			<0.001
<3	414 (21)	81 (9)	
3	1602 (79)	856 (91)	
Visible thrombus	117 (6)	17 (2)	<0.001
Distal embolization	276 (15)	41 (5)	<0.001
Side branch occlusion	42 (2)	14 (1)	0.261
Electrocardiographic			
Complete ST-segment resolution*	623 (52)	434 (68)	<0.001
Follow-up			
30 days mortality	135 (6.7)	36 (3.8)	0.002
1-year mortality	183 (9.0)	62 (6.6)	0.021

Data are presented as median (IQR) or as number (%). * Data were available in 1205 patients with large and 641 patients with small thrombus burden.
MBG: Myocardial Blush Grade, TIMI: Thrombolysis In Myocardial Infarction

with ≥1 TIMI thrombus grade was observed in 911 (87%) patients after thrombus aspiration and in 329 (90%) patients after balloon angioplasty as first intervention (p=0.211). Finally, 1-year all-cause mortality was significantly lower when thrombus aspiration was performed in patients with large thrombus burden (6.4% versus 12.7%, p<0.001) as well as in patients with small thrombus burden (4.2% versus 9.6%, p=0.001) (figure 5).

Retrieval of atherothrombotic burden

Retrieval of macroscopic aspirate was observed in 1241 of 1501 (83%) patients after thrombus aspiration as first intervention. Thrombus aspiration was effective in 880 (86%) patients with large thrombus burden. In patients with small thrombus burden, thrombus aspiration was effective in 361 (75%) patients, and in 150 (71%) patients with no angiographically observed thrombus. Histopathological analysis was performed in 369 patients. Patients with large thrombus burden had larger retrieved aspirate and more erythrocyte components in the aspirate than patients with small thrombus burden (Table 3).

DISCUSSION

This study shows that large thrombus burden defined by angiography is associated with impaired myocardial perfusion, less TIMI flow grade 3 after PCI, more angiographically observed distal embolization, less complete ST-segment resolution and higher 1-year all-cause mortality in a large unselected STEMI cohort. Furthermore, reducing the thrombus burden by thrombus aspiration is related to improved myocardial

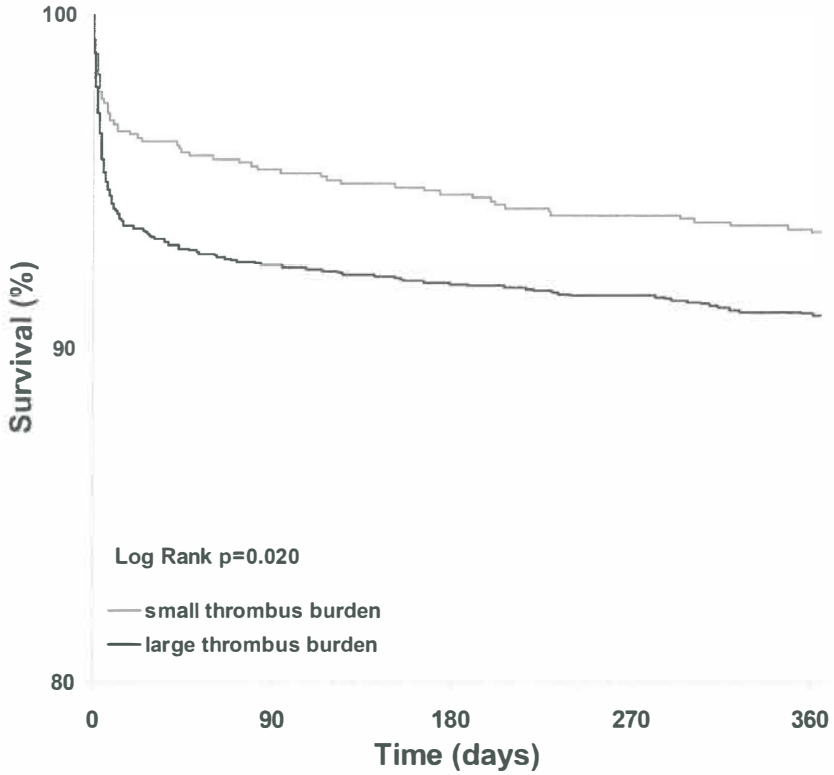

Figure 3 Survival related to large and small thrombus burden. One year mortality rate was significantly higher in patients with large thrombus burden versus patients with small thrombus burden (9.0% versus 6.6%, p=0.021).

perfusion and 1 year survival irrespective of large or small thrombus burden defined by angiography.

Large versus small thrombus burden

The probable explanation of the association between large thrombus burden and impaired myocardial perfusion lies in the embolization. Impaired myocardial perfusion is considered to be mainly caused by embolization of particles of the atherothrombotic burden or vessel wall into the microvasculature.[3, 20] This embolization can occur spontaneously or by iatrogenic manipulation as part of the PCI.[3, 20] Previous studies have suggested that large atherothrombotic burden before PCI increases the risk for embolization of atherothrombotic particles.[4, 5] In this study, we observed a higher incidence of distal embolization in patients with large thrombus burden. Since impaired myocardial perfusion is also observed in patients without distal embolization, angiographically undetectable microembolization is suspected to occur. The resulting microvascular obstruction causes microinfarcts impairing the myocardial perfusion.[3, 7, 20]

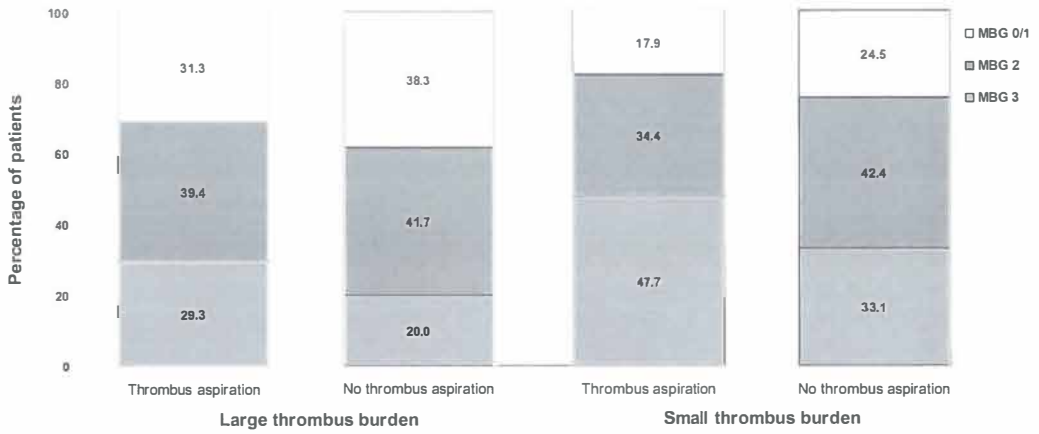

Figure 4 Impact of thrombus aspiration on MBG related to large and small thrombus burden. MBG 0 or 1 was significantly lower when thrombus aspiration was performed, irrespective of whether patients had large or low thrombus burden ($p<0.05$).

Consequently impaired myocardial perfusion is related to mortality, which may explain the relation between large thrombus burden and 1-year all-cause mortality.[16, 21] Another factor that may (partly) explain the higher mortality rate is that patients with a large thrombus burden had worse baseline characteristics, including more often worse TIMI flow. Third, a lower rate of TIMI flow grade 3 after PCI was observed in patients with large thrombus burden. Finally, residual thrombus burden at the site of the lesion, present in more patients with large than in small thrombus burden, is associated with restenosis and stent thrombosis as a response to its thrombogenic contents.[22, 23] Restenosis and stent thrombosis may increase the rate of reinfarction and target-vessel revascularization, which may further explain the higher mortality rate.

Impact of thrombus aspiration

By reducing the thrombus burden exposed to the lumen, thrombus aspiration is thought to decrease embolization of atherothrombotic material that otherwise could obstruct the distal (micro)vasculature. The current guidelines also recommend thrombus aspiration in STEMI patients based on several trials, a meta-analysis and an individual patient-data pooled analysis.[9-13, 24-25] However, the ACC/AHA guidelines add the comment that it is unknown whether a strategy of selective thrombus aspiration in patients with large thrombus burden might be superior to no thrombus aspiration or equivalent to routine thrombus aspiration.[11] While previous trials included only patients with (large) thrombus burden,[24, 26, 27] the largest trial to date consecutive STEMI patients were randomized to routine thrombus aspiration or to conventional PCI. This TAPAS trial demonstrated improved myocardial reperfusion after thrombus aspiration, irrespectively of angio-

graphically observed thrombus using the definition of Mabin et al.[10, 28]

To the best of our knowledge, this is the first study that analyzed the effect of thrombus aspiration in patients with large and with small thrombus burden on outcome. In the current study, thrombus aspiration was performed equally in patients with large and in patients with small thrombus burden. Irrespective of the thrombus burden observed on angiography, thrombus aspiration significantly improved MBG and 1 year survival in STEMI patients. This suggests that a strategy of routine manual thrombus aspiration is superior to selective thrombus aspiration as treatment for all STEMI patients.

Thrombus aspiration was not related to a decrease in the incidence of angiographically observed distal embolization. However, our study may have been underpowered to detect this. In addition, thrombus aspiration was just as effective as balloon angioplasty in reducing angiographically observed thrombus burden. One explanation may be that there is no visible difference angiographically between reduction of thrombus burden after thrombus aspiration and compression of the thrombus burden to the vessel wall after balloon angioplasty. However, as there is a difference in other outcome parameters, non-visible microembolization is suggested to occur that impairs the myocardial perfusion. Further evidence that thrombus burden is frequently inaccurately identified on angiography, is the high incidence of effective aspiration that was seen in patients with large as well as in patients with small thrombus burden. Nevertheless there was an association between size of the thrombus burden observed angiographically and size of the thrombus burden observed histopathologically.

Limitations

First, the observations seen in this retrospective study should be considered as hypothesis-generating. A randomized clinical trial should evaluate our observations by comparing manual thrombus aspiration to conventional PCI in STEMI patients with small thrombus burden. Secondly, in this study thrombus aspiration was performed by an

Table 3 Retrieval of atherothrombotic burden

	Large thrombus burden n=2023	Small thrombus burden n=946	p-value
Retrieved aspirate*	880 (86)	361 (75)	<0.001
Histopathological analysis	244	125	
Size <0.5mm	110 (45)	90 (72)	<0.001
0.5-2.0mm	72 (30)	25 (20)	
>2.0mm	62 (25)	10 (8)	
Erythrocyte component	75 (31)	4 (3)	<0.001

Data are presented as number (%). * Data were available in 1021 patients with large and 480 patients with small thrombus burden.

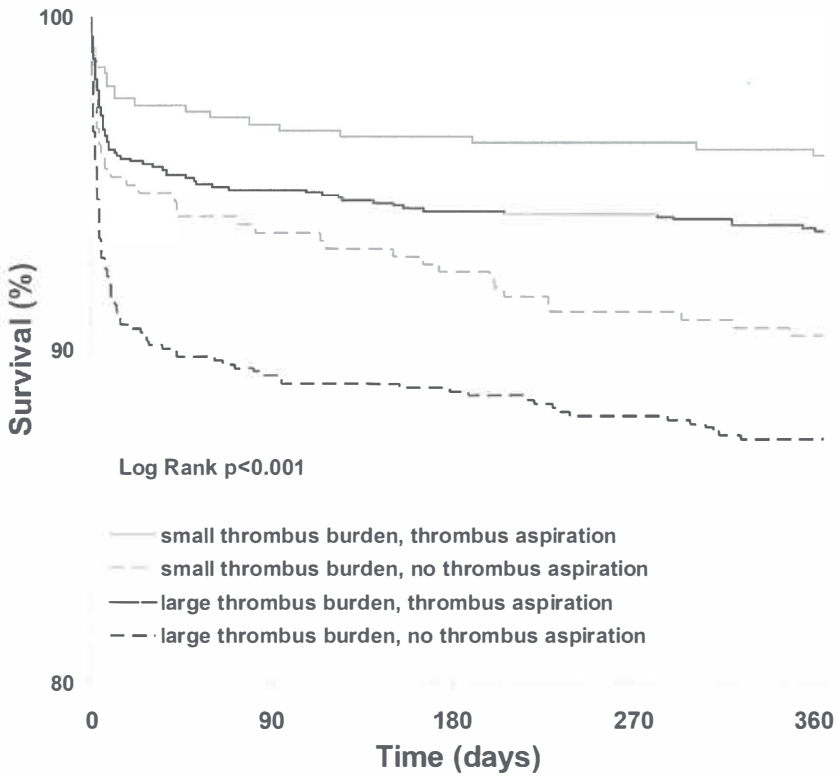

Figure 5 Impact of thrombus aspiration on survival related to large and small thrombus burden. One year mortality rate was significantly lower when thrombus aspiration was performed, in both patients with large thrombus burden (6.4% versus 12.7%, p<0.001) and patients with small thrombus burden (4.2% and 9.6%, p=0.001)

experienced group in a single-center setting. Therefore it is not clear whether these findings can be extrapolated to PCI centers in general. Finally, there were no data available on reinfarction or target-vessel revascularization. Despite this limitation, we did observe a difference in mortality in this large unselected consecutive STEMI cohort.

Conclusion

This large study confirms the general thought that large thrombus burden observed on angiography is associated with worse angiographic, electrocardiographic and clinical outcome in patients with STEMI. Reducing the thrombus burden by thrombus aspiration has beneficial effect on myocardial perfusion and 1-year survival irrespective of small or large thrombus burden. In conclusion, this retrospective study suggests that a strategy of routine manual thrombus aspiration is associated with better outcome than selective thrombus aspiration as treatment for all STEMI patients.

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Part 2 | Intracoronary antiplatelet therapy

Chapter 6 | Intracoronary versus intravenous abciximab in ST-segment elevation myocardial infarction: rationale and design of the CICERO trial in patients undergoing primary percutaneous coronary intervention with thrombus aspiration

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Trials 2009;10:90

ABSTRACT

Background

Administration of abciximab during primary percutaneous coronary intervention is an effective adjunctive therapy in the treatment of patients with ST-segment elevation myocardial infarction. Recent small-scaled studies have suggested that intracoronary administration of abciximab during primary percutaneous coronary intervention is superior to conventional intravenous administration. This study has been designed to investigate whether intracoronary bolus administration of abciximab is more effective than intravenous bolus administration in improving myocardial perfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration.

Methods/Design

The Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial is a single-center, prospective, randomized open-label trial with blinded evaluation of endpoints. A total of 530 patients with STEMI undergoing primary percutaneous coronary intervention are randomly assigned to either an intracoronary or intravenous bolus of weight-adjusted abciximab. The primary end point is the incidence of >70% ST-segment elevation resolution. Secondary end points consist of post-procedural residual ST-segment deviation, myocardial blush grade, distal embolization, enzymatic infarct size, in-hospital bleeding, and clinical outcome at 30 days and 1 year.

Discussion

The CICERO trial is the first clinical trial to date to verify the effect of intracoronary versus intravenous administration of abciximab on myocardial perfusion in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration.

Trial registration
ClinicalTrials.gov NCT00927615

BACKGROUND

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[1,2]. The preferred treatment strategy consists of prompt reperfusion therapy by means of primary percutaneous coronary intervention (PCI)[3-5]. However, despite optimal reperfusion of the infarct-related coronary artery, impaired myocardial perfusion is still present in a significant proportion of patients following successful PCI, which is associated with larger infarct size and increased long-term cardiac mortality[6,7].

One of the major causes of impaired myocardial reperfusion is embolization of atherothrombotic material including platelet aggregates into the distal microcirculation[8]. In recent years, the implementation of adjunctive mechanical and pharmacological therapies during primary PCI, including manual thrombus aspiration and glycoprotein (GP) IIb/IIIa inhibitors, has significantly reduced the occurrence of distal embolization and improved clinical outcome in STEMI patients[9-15]. Several trials and meta-analyses have demonstrated that manual thrombus aspiration improved myocardial reperfusion in patients presenting with STEMI and was associated with improved survival compared to conventional PCI at clinical follow-up up to 1 year[11,12,16-20]. However, 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 including thrombus aspiration itself. Adjunctive pharmacological therapies are therefore needed to target these sources of microvascular obstruction.

Anti-platelet therapy is an important cornerstone of modern STEMI management. During PCI, the use of GP IIb/IIIa inhibitors improves microvascular reperfusion[13,14]. In large randomized trials, intravenous (IV) administration of the GPIIb/IIIa inhibitor abciximab during PCI was associated with a significant reduction in short- and long-term mortality and reinfarction rates in patients with STEMI[9,10,15]. An alternative approach with the use of bivalirudin instead of the combination of unfractionated heparin and a GPIIb/IIIa inhibitor has been advocated and investigated[21]. Although this may result in a lower rate of bleeding complications, a major drawback seems to be the higher incidence of stent thrombosis.

Abciximab is the Fab fragment of the chimeric monoclonal antibody ^{7}E3, which acts as a potent platelet aggregation inhibitor mainly by binding to the GP IIb/IIIa receptor on the surface of activated human platelets. Hereby, abciximab inhibits the final common pathway for platelet aggregation by preventing the binding of fibrinogen and von Willebrand factor to activated platelets[22]. A receptor occupancy study reported that the absolute number of free GP IIb/IIIa receptors was decreased in patients with

successful restoration of myocardial perfusion who were treated with GP IIb/IIIa inhibitors[23]. Experimental studies have reported additional dose-dependent anti-platelet and anti-thrombotic effects of abciximab, which is not only able to prevent thrombus formation, but also to facilitate the dispersal of newly formed platelet aggregates by displacement of platelet bound fibrinogen with higher local drug concentration, and to inhibit platelet-induced thrombin generationd[22,24,25]. In contrast to other GP IIb/IIIa inhibitors, abciximab has also distinct non-GP IIb/IIIa-related properties that may reduce inflammatory pathways and reperfusion injury[26]. These dose-dependent anti-platelet, anti-thrombotic and anti-inflammatory features of abciximab suggest that a higher local platelet inhibitor concentration may translate into further clinical improvements. Higher local concentrations can be obtained by the direct administration of abciximab into the infarct-related artery.

Intracoronary (IC) administration of abciximab has been investigated in several case reports and clinical studies (Table 1)[27-35]. A retrospective study suggested a significant clinical benefit of IC administration, showing a 50% reduction of major adverse cardiac events (MACE) in patients with acute coronary syndromes treated with IC abciximab compared to IV abciximab[34]. A small prospective randomized trial showed a greater degree of myocardial salvage, better recovery of left ventricular function, and improved myocardial perfusion in patients with STEMI treated with IC abciximab[27]. Thiele et al[33] reported a reduced infarct size and extent of microvascular obstruction, and improved perfusion in patients treated with an IC bolus of abciximab. In addition, there was a trend towards a clinically relevant reduction in the incidence of MACE in patients treated with IC abciximab (5.2% vs. 15.6%, $p = 0.06$).

Given the limited number of patients included in these trials, a larger randomized clinical trial is required to verify the effect of IC abciximab administration in STEMI patients undergoing primary PCI. Furthermore, there is at the present time no information with regard to the combined strategy of thrombus aspiration and IC use of abciximab. Therefore, we intend to determine the effect of IC bolus administration of abciximab on post-procedural myocardial perfusion compared to IV bolus administration in STEMI patients undergoing primary PCI with thrombus aspiration.

METHODS/DESIGN

The CICERO trial is a single-center, prospective, randomized trial with blinded evaluation of endpoints (Figure 1). A total of 530 patients with STEMI undergoing primary PCI are randomly assigned to either an IC or IV bolus of weight-adjusted abciximab (0.25 mg/kg body weight, ReoPro 2 mg/ml, Centocor B.V., Leiden, the Netherlands). Randomization is performed by means of sealed envelopes at the catheterization labo-

Table I Studies comparing IC and IV administration of abciximab in patients with ST-segment elevation myocardial infarction

Author	Year*	Design	Patients	No	In favor of	Main results
Wohrle et al[34]	2003	retrospective	STEMI/NSTEACS	403	IC	reduced incidence of MACE at 30 days
Bellandi et al[27]	2004	prospective, randomized	STEMI	45	IC	higher salvage index and LV functional recovery (serial gated SPECT)
Romagnoli et al[32]	2005	prospective, matched	STEMI/NSTEACS	74	IC	increased coronary flow (cTFC)
Galache et al[29]	2006	prospective, randomized	STEMI/NSTEACS	137	neutral	no difference in the incidence of MACE at 1 year
Thiele et al[33]	2008	prospective, randomized	STEMI	154	IC	reduced infarct size and extent of MO (MRI at 2 days)
Dominguez-Rodriguez et al[28]	2009	prospective, randomized	STEMI	50	IC	larger reduction in soluble CD40 ligand

* Year of publication
cTFC: corrected TIMI frame count; IC: intracoronary; IV: intravenous; MACE: major adverse cardiac event; MO: microvascular obstruction; MRI: magnetic resonance imaging; No: number of patients; NSTEACS: non-ST-elevation acute coronary syndrome; SPECT: single photon emission computed tomography; STEMI: ST-segment elevation myocardial infarction

ratory when a decision to perform PCI is taken. The study takes place at a high-volume university hospital center providing 24-hours emergency cardiac care with 7 referral hospitals in a region with 750,000 inhabitants. The study was approved by the institutional committee on human research of the University Medical Center of Groningen and is in compliance with the declaration of Helsinki. The protocol of this trial has been registered at ClinicalTrials.gov (NCT00927615).

Study population

All consecutive STEMI patients who are candidates for primary PCI are considered eligible for participation. The inclusion criterion is a diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, time from onset of symptoms of less than 12 hours, and an ECG with new ST-segment elevation in 2 or more contiguous leads of ≥0.2 mV in leads V2-V3 and/or ≥0.1 mV in other leads or a new-onset left bundle branch block. Exclusion criteria are rescue PCI after thrombolytic therapy, need for emergency coronary artery bypass grafting, presence of cardiogenic shock, known existence of a life-threatening disease with a life expectancy of less than 6 months, inability to provide informed consent, age below 18 years, and contra-indications for the use of abciximab, which include active internal bleeding, history of stroke within 2 years, recent major surgery or intracranial or intraspinal trauma or surgery within 2 months, intracranial neoplasm, arteriovenous malformation or aneurysm, bleeding diathesis, severe uncontrolled hyperten-

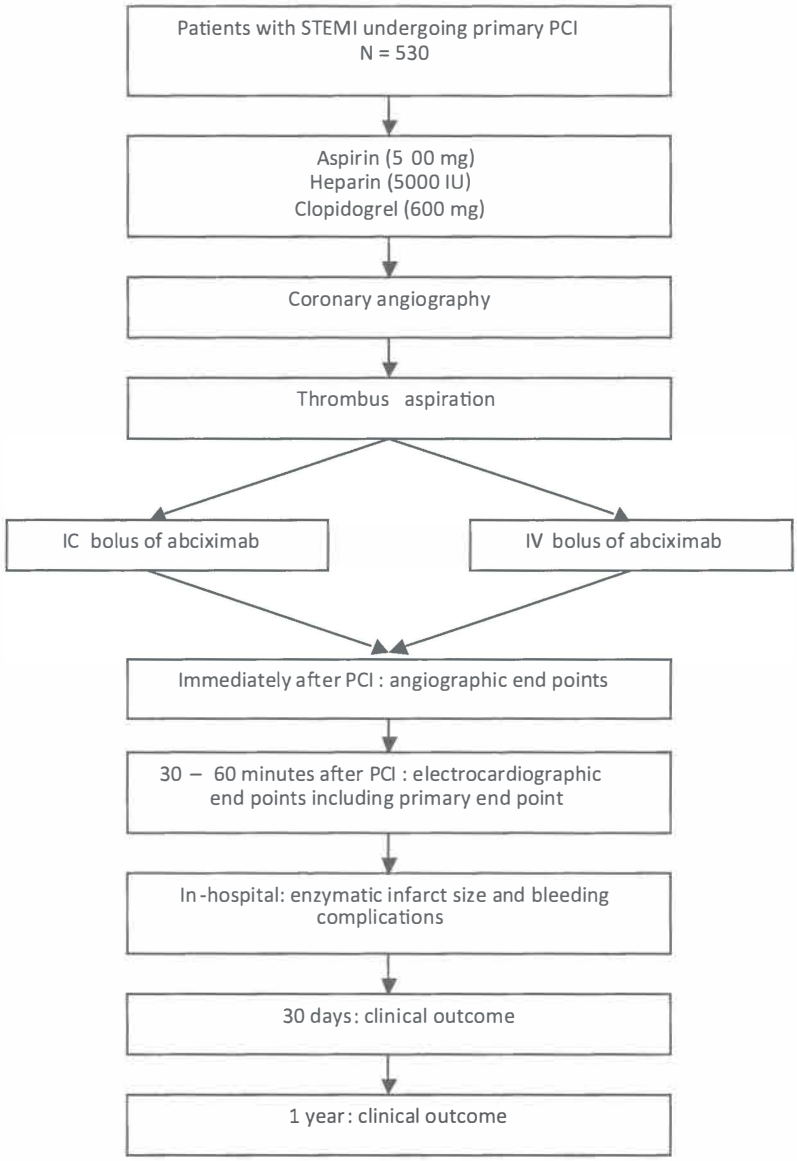

Fig. 1 The CICERO trial flow chart. IC: intracoronary; IV: intravenous; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

sion, thrombocytopenia, vasculitis, hypertensive or diabetic retinopathy, severe liver or kidney failure, and hypersensitivity to murine proteins.

Treatment

During PCI, the initial treatment step consists of manual thrombus aspiration whenever possible. Thrombus aspiration is performed with the Export aspiration catheter (Medtronic Inc., Santa Rosa, USA) as previously described[11]. Continuous manual suction is performed using a proximal-to-distal approach, which is defined as active aspi-

ration during initial passage of the lesion. In patients assigned to IC administration, a bolus of abciximab is administered through the guiding catheter proximal to the lesion in the infarct-related artery over a period of 1 minute after restoration of anterograde flow. As final step a stent is implanted. Additional pre- or postdilatation with a balloon may be required in certain patients.

Patients are pre-treated with aspirin (500 mg), heparin (5000 IU IV), and high-dose clopidogrel (600 mg orally) after electrocardiographic confirmation of STEMI, usually in the ambulance. IC administration of nitroglycerine (400 μg) is administered during the procedure at the operator's discretion. During PCI, additional low-dose weight-adjusted heparin is administered as guided by the activated clotting time (target: 200 - 250 seconds). Sheaths are removed immediately at the end of the PCI procedure using the Angio-Seal device (St. Jude Medical, Inc, St. Paul, MN, USA) or by manual compression after arrival at the coronary care unit. In the setting of STEMI, the femoral approach is preferred. The radial approach is reserved for patients without femoral access. In case of radial access, sheaths are removed immediately following the PCI procedure. 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 therapy after PCI includes aspirin (80 mg), clopidogrel (75 mg), beta-blockers, lipid lowering agents, and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, according to current international guidelines[36].

Electrocardiography

A standard 12-lead electrocardiogram (ECG) is acquired at the time of presentation and at 30 to 60 minutes after the end of procedure. Times of onset of symptoms, admission, first intracoronary intervention, end of PCI and ECG recordings are registered. The magnitude of ST-segment deviation is measured 60 ms from J-point. The first post-intervention ECG at 30 to 60 minutes is classified by comparison of the ST-segments with those of the ECG at presentation. ST-segment elevation resolution is categorized as complete (>70%), partial (30-70%), or absent (<30%)6. On the post-interventional ECG, residual ST-segment deviation is calculated as the sum of residual ST-segment elevation and depression in all leads[37]. New-onset of Q waves on the post-interventional ECG is defined as an initial negative deflection of the QRS complex of >0.1 mV and >40 ms in an ECG lead related to the myocardial area of infarction together with all pathological Q waves. All ECG recordings are analyzed by a physician blinded to treatment allocation and clinical data.

Coronary angiography

The following baseline, peri- and post-procedural angiographic features are recorded: the presence of thrombus and collaterals, Thrombolysis In Myocardial Infarction (TIMI) flow grades, myocardial blush grade (MBG), and the presence of angiographically visible distal embolization. TIMI flow grades are estimated as previously described[38]. Thrombus is assessed according to the criteria summarized by Mabin et al[39]. 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. Collaterals are assessed according to Rentrop's classification[40]: 0 = none, 1 = filling of side branches only, 2 = partial filling of the epicardial segment, 3 = complete filling of the epicardial segment. Evaluation of MBG is 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 contra- or ipsilateral non-infarct-related coronary artery, and 3 = normal myocardial blush or contrast density, comparable with that obtained during angiography of a contra- or ipsilateral non-infarct-related coronary artery. Persisting myocardial blush ("staining") suggests leakage of contrast medium into the extravascular space and is graded 0. In addition, MBG is quantified with the Quantitative Blush Evaluator (QuBE) as described by Vogelzang et al[41], which provides a computer-assisted and more operator-independent score by calculating the increase and decrease of myocardial contrast density in the myocardial area of interest. Distal embolization is considered to have occurred if new circumscribed filling defects and/or abrupt cutoff of the vessel distal to the target lesion appears[42,43]. The coronary angiograms are analyzed by a physician who is blinded to treatment allocation and clinical data.

Infarct size

Infarct size is estimated by serial measurements of cardiac markers including creatinine kinase (CK), myocardial band fraction of CK (CK-MB), lactate dehydrogenase (LDH), and troponin T. Blood is sampled at baseline and at 3, 6, 9, 12, 18, 24, and 48 hours after PCI. Peak release, time to peak release as well as area under the curve is determined. Marker levels are determined on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation.

End points assessment

The primary end point is the incidence of ST-segment resolution >70% as assessed on the ECG acquired 30 to 60 minutes after PCI compared to the ECG at presentation. Sec-

ondary end points include:

- Angiographic end points: post-procedural TIMI flow, MBG (by visual estimation and with the QuBE program) and angiographically visible distal embolization
- Electrocardiographic end points: residual ST-segment deviation 30 to 60 minutes after the procedure
- Enzymatic infarct size
- Mortality and Major Adverse Cardiac Events (MACE, a combined end point of target vessel revascularization, reinfarction, and cardiovascular mortality) at 30 days and 1 year. A safety endpoint consists of in-hospital bleeding complications. Furthermore, the primary and secondary endpoints are to be analyzed in pre-specified subgroups, which are defined as:
    1. Age (<65 versus >65 years)
    2. Gender
    3. Presence of diabetes
    4. Number of diseased vessels (multi-vessel versus single vessel)
    5. Infarct-related artery (left anterior descending artery (LAD) versus non-LAD)
    6. Ischemic time (<3 versus >3 hours)
    7. Angiographic presence of thrombus
    8. Pre-procedural TIMI flow
    9. Post-procedural TIMI flow
    10. Post-procedural myocardial blush grade

Clinical follow-up

Death, reinfarction, and ischemia driven target-vessel revascularization are to be registered at 30 days and 1 year. Follow-up information will be obtained from the central personal records database, hospital records as well as by telephone interviews with the patients and/or their general practitioners.

Statistical considerations

Sample size estimation

In previously published data, the incidence of our primary end point resolution of ST-segment elevation >70% has been reported to be 56.6% in patients with STEMI treated with thrombus aspiration[11]. We hypothesize that IC administration of abciximab during PCI increases the incidence of ST-segment resolution >70% by 25%. To detect a 25%

difference between the two treatment groups, 530 patients are required to reach a 5% significance level (two-sided) with 90% power.

Statistical analysis

All statistical analyses will be performed according to the intention-to-treat principle for the overall population as well as for the pre-specified subgroups. Statistical significance is considered as a two-tailed p value less than 0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.2 will be used for all statistical analyses. Differences between group means will be assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test will be used to test differences between proportions. Survival will be calculated by the Kaplan-Meier product-limit method. Chi-square analysis will be used to assess the relation between an individual variable and end points. 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.

DISCUSSION

The CICERO trial is a single-center, prospective, randomized trial to determine whether IC administration of abciximab during primary PCI is more effective than IV administration in improving myocardial perfusion in STEMI patients undergoing primary PCI with thrombus aspiration. This is the first large clinical trial to date to determine the effect of IC versus IV administration of abciximab in STEMI patients undergoing primary PCI with thrombus aspiration.

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Chapter 7.1 | Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: The Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial

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ABSTRACT

Background

Administration of the glycoprotein IIb/IIIa inhibitor abciximab is an effective adjunctive treatment strategy during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Although small-scale studies have suggested beneficial effects of intracoronary over intravenous administration of abciximab, this has not been investigated in a medium-scale randomized clinical trial.

Methods and Results

A total of 534 ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention with thrombus aspiration within 12 hours of symptom onset were randomized to either an intracoronary or an intravenous bolus of abciximab (0.25 mg/kg). Patients were pretreated with aspirin, heparin, and clopidogrel. The primary end point was the incidence of restored myocardial reperfusion, defined as complete ST-segment resolution. Secondary end points included myocardial reperfusion as assessed by myocardial blush grade, enzymatic infarct size, and major adverse cardiac events at 30 days. The incidence of complete ST-segment resolution was similar in the intracoronary and intravenous groups (64% versus 62%; P=0.562). However, the incidence of myocardial blush grade 2/3 was higher in the intracoronary group than in the intravenous group (76% versus 67%; P=0.022). Furthermore, enzymatic infarct size was smaller in the intracoronary than in the intravenous group (P=0.008). The incidence of major adverse cardiac events was similar in both groups (5.5% versus 6.1%; P=0.786).

Conclusions

In ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention with thrombus aspiration, intracoronary administration of abciximab compared with intravenous administration does not improve myocardial reperfusion as assessed by ST-segment resolution. However, intracoronary administration is associated with improved myocardial reperfusion as assessed by myocardial blush grade and a smaller enzymatic infarct size.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00927615.

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a clinical condition caused by rupture or erosion of an atherosclerotic plaque and subsequent platelet aggregation and thrombosis, resulting in acute occlusion of a coronary artery.[1,2] Prompt reperfusion therapy with primary percutaneous coronary intervention (PCI) has become the treatment strategy of choice.[3,4] Recently, the implementation of adjunctive mechanical and pharmacological therapies during primary PCI, including manual thrombus aspiration and glycoprotein (GP) IIb/IIIa inhibitors, has improved myocardial reperfusion and clinical outcome in STEMI patients.[5–9] In large randomized trials, intravenous administration of the GP IIb/IIIa inhibitor abciximab during primary PCI reduced short- and long-term mortality and reinfarction rates in patients with STEMI.[6,7] Recently, experimental studies have suggested that abciximab exerts additional antiplatelet, antithrombotic, and antiinflammatory effects when local drug concentrations are higher.[10] A recent study has reported that local GP IIb/IIIa receptor inhibition is higher with intracoronary administration of the GP IIb/IIIa inhibitor eptifibatide.[11] Therefore, a higher local drug concentration by intracoronary administration of abciximab is expected to further improve clinical outcome. Although small- to medium-scale registries and randomized clinical trials have suggested beneficial clinical effects of intracoronary administration,[12] this has not been investigated in a medium-scale randomized clinical trial with an adequate number of patients to assess myocardial reperfusion. Furthermore, there is no information at present with regard to the combined strategy of thrombus aspiration and intracoronary abciximab administration. Therefore, we investigated whether intracoronary administration of abciximab is superior to intravenous administration in improving myocardial reperfusion in STEMI patients undergoing primary PCI with thrombus aspiration.

METHODS

Study Design and Population

The Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial was a single-center, prospective, randomized, open-label trial with blinded evaluation of end points. The detailed study design has been published previously.[13] Between September 2008 and April 2010, consecutive STEMI patients undergoing primary PCI were randomly assigned to either an intracoronary or an intravenous bolus of abciximab (0.25 mg/kg body weight; ReoPro 2 mg/mL; Centocor BV, Leiden, the Netherlands). This study was performed at a high-volume university medical center providing 24-

hour emergency cardiac care with 7 referral hospitals in a region of 750 000 inhabitants. The study was approved by the Medical Ethics Review Committee of the University Medical Center of Groningen. All patients gave informed consent.

All STEMI patients who were candidates for primary PCI were considered eligible for participation. STEMI was defined as chest pain suggestive of myocardial ischemia for at least 30 minutes before hospital admission, time from symptom onset of <12 hours, and an ECG with new ST-segment elevation in 2 or more contiguous leads of ≥0.2 mV in leads V2 to V3 and/or ≥0.1 mV in other leads or a new-onset left bundle-branch block. Exclusion criteria were rescue PCI after thrombolytic therapy, need for emergency coronary artery bypass grafting, presence of cardiogenic shock, a life expectancy of <6 months, inability to provide informed consent, age <18 years, and contraindications for the use of abciximab, including active internal bleeding, history of stroke within 2 years, recent major surgery or trauma, intracranial neoplasm, arteriovenous malformation or aneurysm, bleeding diathesis, severe uncontrolled hypertension, thrombocytopenia, vasculitis, hypertensive or diabetic retinopathy, severe liver or kidney failure, and hypersensitivity to murine proteins.

Treatment

Patients were pretreated with aspirin (500 mg), heparin (5000 IU), and high-dose clopidogrel (600 mg), usually in the ambulance. When prasugrel became available in certain ambulances in 2010, use of prasugrel (60 mg) instead of clopidogrel was allowed. After diagnostic coronary angiography was performed, patients who met the eligibility criteria were randomized by means of sealed envelopes. After randomization, a bolus of abciximab was administered through the guiding catheter proximal to the lesion in the infarct-related artery over a period of 1 minute in patients assigned to intracoronary administration directly after first restoration of antegrade flow. The preferred initial treatment step to restore antegrade flow consisted of manual thrombus aspiration (Export Aspiration Catheter; Medtronic Inc, Santa Rosa, Calif) under continuous suction. In patients assigned to intravenous administration, abciximab was administered during PCI, but the exact timing of administration was not specified by protocol. Additional predilatation or postdilatation with a balloon and stent implantation were at the discretion of the operator. Intracoronary administration of nitroglycerine (400 μg) was administered periprocedurally at the operator's discretion. During PCI, additional low-dose weight-adjusted heparin was administered as guided by the activated clotting time (target, 200 to 250 seconds). No 12-hour infusion was initiated after PCI. Standard therapy after PCI included aspirin, clopidogrel, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, according

to current international guidelines.[14]

End Points

The primary end point was the incidence of restored myocardial reperfusion, defined as complete ST-segment resolution (STR). Secondary end points of myocardial reperfusion included myocardial blush grade (MBG) and residual ST-segment deviation. Other secondary end points included incidence of Q waves, postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow and angiographically visible distal embolization, enzymatic infarct size, all-cause mortality, and major adverse cardiac events (a combined end point of cardiac mortality, reinfarction, and target vessel revascularization) at 30 days. A safety end point consisted of in-hospital bleeding, defined according to the TIMI bleeding classification.[15]

ECG Analysis

For evaluation of the ECG end points, a 12-lead ECG was acquired at the time of presentation and at 30 to 60 minutes after primary PCI. The magnitude of ST-segment deviation was measured 60 ms from the J point. STR was assessed by comparing the ST-segment deviation in the infarct-related area on the ECG after PCI with the ECG at presentation and was categorized as complete (>70%), partial (30% to 70%), or absent (<30%), as previously described.[16] On the ECG after PCI, residual ST-segment deviation was categorized as <2, 2 to 5, 5 to 10, or >10 mm by summing the residual ST-segment deviation as previously described.[17] New-onset Q waves on the ECG after PCI were defined as an initial negative deflection of the QRS complex of >0.1 mV and >40 ms in an ECG lead related to the myocardial area of infarction together with all pathological Q waves.[18] All ECG recordings were analyzed by a physician blinded to treatment allocation and clinical data. When in doubt, the recordings were reviewed by 2 additional physicians until consensus was reached.

Angiographic Analysis

MBG was categorized as follows[19]: 0=no myocardial blush, or contrast density; 1=minimal myocardial blush; 2=moderate myocardial blush but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3=normal myocardial blush comparable to that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. In addition, MBG was measured with the quantitative blush evaluator, which provides a computer-assisted and continuous score.[20] TIMI flow was defined as previously described.[21] Distal embolization after PCI was defined as a new circumscribed filling defect and/or abrupt cutoff of the vessel distal to the target lesion.[22] Thrombus was assessed according to

the criteria of the TIMI group.[23] Coronary angiograms were analyzed by 2 physicians blinded to treatment allocation and clinical data until consensus was reached.

Infarct Size

Infarct size was estimated by serial measurements of cardiac markers, including creatine kinase, creatine kinase-MB, and cardiac troponin T. Blood was sampled at baseline and at 3, 6, 9, 12, 18, 24, and 48 hours after PCI in patients who were hospitalized in this

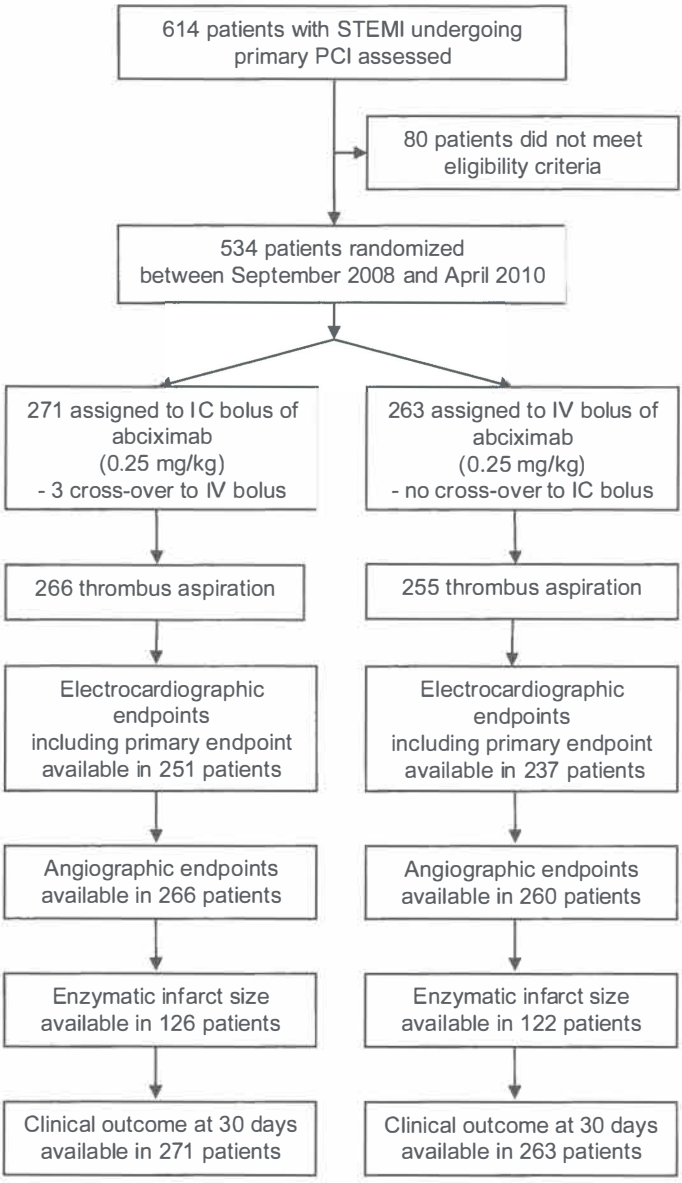

Fig. 1 Flowchart of patient enrollment. IC indicates intracoronary; IV, intravenous; STEMI, ST-segment elevation myocardial infarction; and PCI, percutaneous coronary intervention.

center after PCI. Peak release, time to peak release, and area under the curve over the first 48 hours were determined. If patients were observed for shorter periods, the area under the curve was estimated by multiplying the time-averaged mean level by 48 hours (adjusted values).

Clinical Follow-Up

Clinical follow-up was obtained from the central personal records database, hospital records, and interviews with the patients and/or their general practitioners. Mortality was considered cardiac unless an unequivocal noncardiac cause of death was established. Reinfarction was defined as recurrent symptoms suggestive of ischemia with new ST-segment elevation and/or elevation of the levels of cardiac markers.[24] Target vessel revascularization was defined as ischemia-driven revascularization of the infarct-related artery with PCI or coronary artery bypass grafting. Clinical events were adjudicated by a committee consisting of 3 physicians blinded to treatment allocation.

Sample Size and Statistical Analysis

In previously published data, complete STR was achieved in 56.6% of STEMI patients treated with thrombus aspiration.[8] To detect a 25% increase in the incidence of this primary end point in patients randomized to the intracoronary group, a total of 530 patients were required to achieve 90% power at a 5% significance level (2 sided), allowing 10% of ECGs to be not assessable for the primary end point. Statistical analyses were performed by intention to treat. Statistical significance was considered at a 2-tailed value of $P<0.05$. Differences between group means were assessed with the 2-tailed Student t test or Mann-Whitney U test if samples were not normally distributed. The $\chi 2$ or Fisher exact test was used to test differences between proportions. Statistical analyses were performed with the Statistical Package for the Social Sciences version 16.0.2 (SPSS Inc, Chicago, Ill). Investigators had full access to all primary data.

RESULTS

A total of 534 STEMI patients were randomly assigned to either intracoronary (n=271) or intravenous (n=263) abciximab administration (Figure 1). A total of 80 patients were excluded because of a contraindication for the use of abciximab (n=38), an inability to provide informed consent (n=2), cardiogenic shock (n=38), and need for emergency coronary artery bypass grafting (n=2). Baseline characteristics did not differ significantly between patients randomized to intracoronary or intravenous administration (Table 1). Clopidogrel was administered routinely before PCI in the prehospital setting either in the ambulance or at the referral hospital. In patients admitted through the

emergency department (9%), clopidogrel was administered before transportation for PCI. In 3%, clopidogrel was administered after PCI. Prasugrel was administered instead of clopidogrel in 2 patients randomized to intracoronary administration and 4 randomized to intravenous administration. Abciximab was administered after a median time of 3 minutes (interquartile range [IQR], 2 to 5 minutes) in the intracoronary group

Table 1 Baseline Characteristics of the 534 Patients Randomized to Intracoronary or Intravenous Administration of Abciximab

	Intracoronary (n=271)	Intravenous (n=263)	P
Clinical			
Age, y	64±13	64±13	0.940
Male gender, n (%)	208/271 (77)	187/263 (71)	0.137
Hypertension, n (%)	119/270 (44)	129/263 (49)	0.250
Hypercholesterolemia, n (%)	80/268 (30)	74/261 (28)	0.705
Diabetes mellitus, n (%)	36/271 (13)	29/263 (11)	0.425
Family history, n (%)	125/267 (47)	124/262 (47)	0.906
Cu rrent smoking, n (%)	116/270 (43)	127/263 (48)	0.217
Previous MI, n (%)	32/271 (12)	23/262 (9)	0.250
Previous PCI, n (%)	25/271 (9)	21/262 (8)	0.619
Previous CABG, n (%)	6/271 (2)	5/263 (2)	0.799
Previous stroke, n (%)	11/270 (4)	12/262 (5)	0.774
Preinfarction angina, n (%)	73/270 (27)	76/263 (29)	0.632
BMI, kg/m^2	27±4	27±5	0.929
Systolic blood pressure, mm Hg	131±27	129±25	0.319
Diastolic blood pressure, mmHg	76±15	74±13	0.231
Heart rate, bpm	76±20	78±18	0.196
Ischemic time, median (IQR), min	180 (120 −275)	179 (128 −275)	0.567
Angiographic, n (%)			
No. of diseased vessels			0.295
1	123/271 (45)	101/261 (39)	
2	78/271 (29)	84/261 (32)	
3	70/271 (26)	76/261 (29)	
Infarct-related artery			0.844
LAD	121/271 (45)	124/263 (47)	
Cx	33/271 (12)	34/263 (13)	
RCA	112/271 (41)	99/263 (38)	
Other	5/271 (2)	6/263 (2)	
TIMI flow grade, n (%)			0.050
0	125/271 (46)	145/263 (55)	
1	25/271 (9)	31/263 (12)	
2	64/271 (24)	49/263 (19)	
3	57/271 (21)	38/263 (14)	
Thrombus present, n (%)	236/270 (87)	242/263 (92)	0.080
Collaterals present, n (%)	52/266 (20)	48/256 (19)	0.817
Procedural, n (%)			
Thrombus aspiration	266/271 (98)	255/263 (97)	0.370
Balloon predilatation	119/271 (44)	126/263 (48)	0.354
Stent implantation	256/271 (95)	251/263 (95)	0.608
Postdilatation	32/271 (12)	25/263 (10)	0.389
IABP use	11/271 (4)	16/263 (6)	0.286

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; IQR, interquartile range; LAD, left anterior descending artery; Cx, circumflex artery; RCA, right coronary artery; and IABP, intra-aortic balloon pumping. Data are presented as mean±SD or No./total No. (%) as appropriate.

and 1 minute (IQR, 0–3 minutes) in the intravenous group from first intracoronary intervention (P<0.001). Crossovers occurred nonintentionally in 3 patients randomized to intracoronary administration.

ECG End Points

The primary end point of complete STR was achieved in 64% of the intracoronary group and 62% of the intravenous group (P=0.562). STR could not be assessed in 20 of 271 patients (7.4%) in the intracoronary group and 26 of 263 patients (9.9%) of the

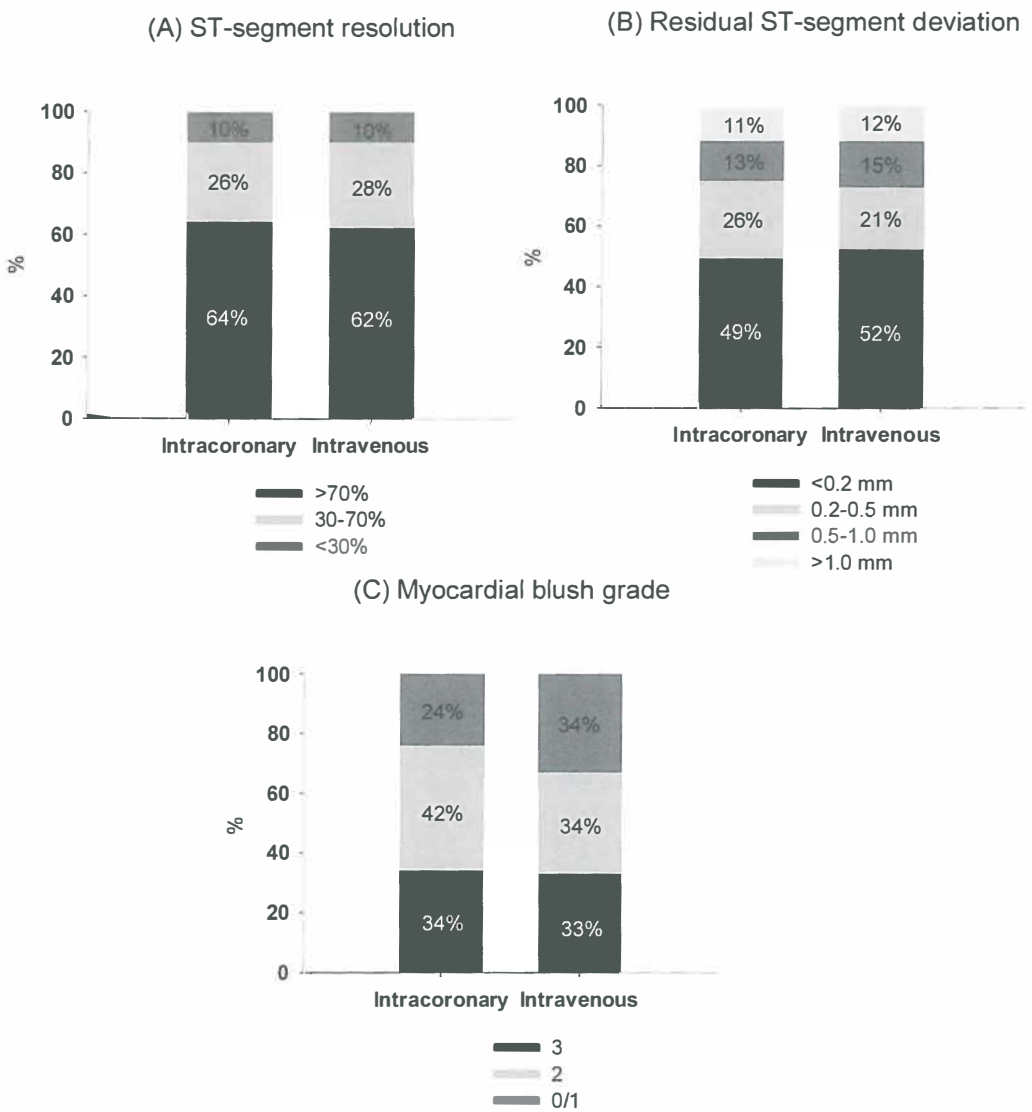

Fig. 2 Distribution of myocardial reperfusion as assessed by (A) ST-segment resolution (STR), (B) residual ST-segment deviation, and (C) myocardial blush grade (MBG) in patients randomized to intracoronary or intravenous administration of abciximab. Although the distribution of STR and residual ST-segment deviation was not different for both groups (P=0.844 and P=0.662, respectively), the distribution of MBG was borderline significant in favor of patients randomized to intracoronary administration (P=0.052).

intravenous group (P=0.302) because no pre-PCI ECG was available (n=11), no post-PCI ECG was available (n=24), or conduction abnormalities or arrhythmias were seen on the ECG (n=11). Patients without primary end-point analysis were slightly older, had a longer ischemic time, and more often had hypercholesterolemia, multivessel disease, and the left main, graft, or right coronary artery as the infarct-related artery. Concordantly, there were no differences in the distributions of residual ST-segment deviation between the intracoronary and intravenous groups (P=0.662; Figure 2). The incidence and number of Q waves on the postprocedural ECG were similar in both groups (77% versus 82%; P=0.143; median, 2 [IQR, 1 to 3] versus 2 [IQR, 1 to 4]; P=0.114). The median time from abciximab administration to the ECG after PCI was 4 minutes shorter for the intracoronary than for the intravenous group (38 minutes [IQR, 31 to 49 minutes] versus 42 minutes [IQR, 33 to 74 minutes]; P<0.001).

Angiographic End Points

Coronary angiograms were assessable in 526 of 534 patients (99%). In contrast to the distribution of ECG end points, the distribution of MBG was borderline significant in favor of patients randomized to intracoronary administration (P=0.052; Figure 2). Moreover, the incidence of MBG 2/3 was significantly higher in the intracoronary than in the intravenous group (76% versus 67%; P=0.022). When measured quantitatively with the quantitative blush evaluator (available in 75% of patients), myocardial reperfusion was slightly better in the intracoronary group than in the intravenous group, but this was not statistically significant (10.1±3.5 versus 9.7±3.6; P=0.269). After thrombus aspiration, assessable in 90% of patients, flow was restored (TIMI grade 2/3)

Table 2 Enzymatic Infarct Size in Patients With Complete In-Hospital Follow-Up

	Intracoronary (n=126)	Intravenous (n=122)	P
Peak CK, U/L	1214 (488 – 2184)	1746 (733 –3383)	0.008
Peak CK-MB, U/L	154 (62 –262)	232 (90 –400)	0.003
Peak cTnT, µg/L	3.03 (0.95 –5.81)	4.36 (1.43 –8.56)	0.008
Time to peak CK, h	7 (5 –11)	8 (5 –11)	0.991
Time to peak CK-MB, h	6 (5 –9)	6 (5 –9)	0.926
Time to peak cTnT, h	9 (6 –13)	9 (6 –12)	0.924
AUC_{48} CK	1134 (474 –1886)	1571 (612 –2597)	0.023
AUC_{48} CK-MB	117 (56 –219)	171 (80 –277)	0.006
AUC_{48} cTnT	2.92 (0.87 –5.35)	3.31 (1.39 –8.23)	0.032
AUC_{48} CK adjusted	1463 (600 –2841)	2206 (1002 –3781)	0.008
AUC_{48} CK-MB adjusted	172 (82 –305)	296 (122 –440)	0.001
AUC_{48} cTnT adjusted	4.00 (1.36 –7.41)	6.22 (2.08 –12.03)	0.004

CK indicates creatinine kinase; cTnT, cardiac troponin T; and AUC, area under the curve. Data are presented as median (interquartile range).

Table 3 Clinical Outcome at 30 Days in Patients Randomized to Intracoronary or Intravenous Administration of Abciximab

	Intracoronary (n=271), n (%)	Intravenous (n=263)	P
Mortality	5 (1.8)	7 (2.7)	0.524
Cardiac mortality	4 (1.5)	6 (2.3)	0.492
TVR	9 (3 .3)	10 (3.8)	0.764
Reinfarction	3 (1.1)	4 (1.5)	0.721
IST	1 (0.4)	3 (1.1)	0.366
MACEs	15 (5.5)	16 (6.1)	0.786

TVR indicates target vessel revascularization; IST, in-stent thrombosis; and MACEs, major adverse cardiac events.

in 211 of 235 patients (90%) in the intracoronary group and 201 of 232 patients (87%) in the intravenous group (P=0.291). Postprocedural TIMI grade 3 flow was achieved in 89% and 86% of the intracoronary and intravenous groups, respectively (P=0.261). Postprocedural distal embolization occurred a t similar frequencies between both groups (12% and 13%, respectively; P=0.635). The median time from abciximab administration to the angiographic run containing the blush sequence was 1 minute shorter for the intracoronary than for the intravenous group (8 minutes [IQR, 5 to 12 minutes] versus 9 minutes [IQR, 6 to 15 minutes]; P=0.006).

Infarct Size

Data on enzymatic infarct size could be assessed in 248 of 534 patients (46%). Infarct size was ≈30% smaller in the intracoronary group than in the intravenous group (1214 U/L [IQR, 488 to 2184 U/L] versus 1746 U/L [IQR, 733 to 3383 U/L] for creatine kinase, P=0.008; 154 U/L [IQR, 62 to 262 U/L] versus 232 U/L [IQR, 90 to 400 U/L] for creatinine kinase-MB, P=0.003; and 3.03 μg/L [IQR, 0.95 to 5.81 μg/L] versus 4.36 μg/L [IQR, 1.43 to 8.56 μg/L] for cardiac troponin T, P=0.008; Table 2).

Clinical Follow-Up

In total, 12 patients (2.2%) died within 30 days. All-cause mortality was 1.8% and 2.7% in the intracoronary and intravenous groups, respectively (P=0.524; Table 3). The incidence of major adverse cardiac events was low and not significantly different between the 2 groups (5.5% in the intracoronary group versus 6.1% in the intravenous group; P=0.786).

Safety

There were no adverse procedural events related to intracoronary abciximab administration. The incidence of in-hospital major and minor bleeding was low and similar between the intracoronary and intravenous groups (for major bleeding, 3.7% versus 3.4%, P=0.867; for minor bleeding, 7.7% versus 6.8%, P=0.688). In-hospital

thrombocytopenia <150×109/L developed in patients randomized to intracoronary and intravenous administration at similar frequencies (12% versus 13%; P=0.794).

DISCUSSION

This study indicates that intracoronary administration of the GP IIb/IIIa inhibitor abciximab during primary PCI with thrombus aspiration compared with intravenous administration does not improve myocardial reperfusion as assessed by STR. However, intracoronary administration is related to improved myocardial reperfusion as assessed by MBG, as well as in the subset of patients with evaluable infarct size, to a 30% smaller enzymatic infarct size. The CICERO trial is the largest clinical trial to date to determine the effect of intracoronary versus intravenous administration of abciximab in STEMI patients undergoing primary PCI. Moreover, this is the first medium-scale trial performed in a contemporary cohort of STEMI patients who were treated with manual thrombus aspiration.

Abciximab acts as a potent inhibitor of platelet aggregation mainly by competitively binding to the GP IIb/IIIa receptor on the surface of activated human platelets. As a result of a higher affinity to this receptor, abciximab prevents binding of fibrinogen and von Willebrand factor to activated platelets, blocking the final common pathway for platelet aggregation.10 Experimental studies have suggested that abciximab has additional dose-dependent antiplatelet, antithrombotic, and antiinflammatory features. Abciximab not only prevents platelet aggregation in vitro but also promotes thrombus disaggregation.[10] These findings suggest that a higher local concentration, achieved by intracoronary administration, results in improved outcome. Several small-scale studies have reported improved myocardial salvage, left ventricular functional recovery, and a smaller infarct size after intracoronary administration of abciximab.[12] In a randomized trial in 154 patients by Thiele et al,[25] STR as a continuous measure was higher in the intracoronary than in the intravenous group (77.8% versus 70.0%). However, this positive study was powered to detect differences in infarct size and extent of microvascular obstruction by MRI. In the present study, which was powered to detect a clinically relevant improvement in STR, we could not confirm the positive findings as previously suggested. In contrast, we did observe a clinically relevant improvement in myocardial reperfusion as assessed by MBG and, in the subset of patient with evaluable enzymatic infarct size, a reduction in infarct size in patients randomized to intracoronary administration, which are consistent with the effects reported previously.[25] Furthermore, the magnitude of the effect observed in this study was comparable.

Can the neutral findings on our primary end point be explained by differences between this and previous studies? In the positive study by Thiele et al,[25] the patient population appeared to be at a higher clinical risk than in our study: patients presented with an ≈60-minute-longer ischemic time and a higher incidence of TIMI grade 0/1 flow, diabetes mellitus, and anterior infarction. In subgroup analysis, the benefit was observed in patients treated after 4 hours of symptom onset. Furthermore, high-dose clopidogrel preloading was performed in a small proportion of patients, and the use of thrombus aspiration was not reported. Our patient population resembled a recent neutral study with a similar baseline risk, including similar ischemic time, frequent use of clopidogrel preloading, and use of thrombus aspiration in 40%.[26] Therefore, it is possible that the benefit of intracoronary administration on myocardial reperfusion was offset by a lower clinical risk and the routine use of thrombus aspiration in the present study.

The actual incidence of STR was higher than the estimated incidence used for sample size estimation. This estimation was based on data from the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) study performed in our center, which showed complete STR in 56.6% of patients randomized to thrombus aspiration.[8] In a more recent trial, ADenosine Administration during and after Primary percutaneous coronary intervention in acute myocardial infarction Trial (ADAPT), however, the rate of complete STR was considerably higher (66.3%) and more similar to that in this study.[17] It is therefore likely that the higher rate of STR is explained by differences in the rate of actual thrombus aspiration: TAPAS patients randomized to thrombus aspiration underwent thrombus aspiration in 84%, whereas 95% of patients in the ADAPT control group and 97% of CICERO patients underwent thrombus aspiration. Because the more recent STR data were not available during the design of CICERO, we could base our assumptions only on the TAPAS data. During the years after TAPAS, no significant changes took place that could explain the higher rates of STR.

We report an unexpected discrepancy between myocardial reperfusion as assessed by STR and by MBG; they are usually consistent in both positive and negative studies and in previous studies reporting on intracoronary abciximab.[8,17,25] Several reasons may account for this discrepancy. One possible reason is that STR and MBG represent different pathophysiological phenomena. MBG reflects mechanical patency of the microvasculature, whereas STR may reflect the functional status of the myocardial cells.[27] Although both markers are widely accepted as surrogate end points of clinical outcome,[16,19,28] restoration of myocardial reperfusion as defined by complete STR or MBG 2/3 is discordant in approximately one third of STEMI patients.[19,29] Nevertheless, both

markers are of independent prognostic value in predicting long-term mortality.[16,19,28,30] Recently, however, the prognostic value of STR has been debated in patients treated with primary PCI.[31] This discrepancy between both markers cannot be explained by the findings in this study and deserves further investigation. A second possible reason is that both markers are assessed at different time points after primary PCI: MBG directly after PCI and STR at 30 to 60 minutes after PCI. The beneficial effect of intracoronary administration on myocardial reperfusion may be present directly after PCI but not at 30 to 60 minutes after PCI. A discrepancy between myocardial reperfusion outcomes immediately after PCI and compared with later after PCI has been reported previously.[32] A third possible reason is that intracoronary administration itself instead of abciximab improves myocardial reperfusion directly after PCI but negates it during the first hour after PCI. Although there was no control group with intracoronary injection of saline, it is not likely that intracoronary administration itself would also result in the relevant reduction in enzymatic infarct size that was also observed in this study.

In contrast to previous studies that have suggested reductions to >50% of the incidence of major adverse cardiac events at 30 days in patients randomized to intracoronary administration,[12] we found no reduction or trend toward reduction. First of all, this study had insufficient power to detect differences in clinical events. Furthermore, this study was performed in patients receiving contemporary treatment, including prehospital administration of high-dose clopidogrel and thrombus aspiration. The absolute number of clinical events at 30 days was much lower in this trial than in these previous studies,12 making it even less likely to come to statistically significant improvements.

Although we observed conflicting results on myocardial reperfusion, the potential beneficial effects of intracoronary administration may become evident after 30 days. The reduction in enzymatic infarct size observed in a subset of patients may well translate into a better recovery of left ventricular function and improved clinical outcome at longer follow-up. Because this study was underpowered to detect possible differences in clinical events, larger randomized multicenter trials are needed to evaluate whether intracoronary administration during primary PCI improves clinical outcome. This is being investigated in an ongoing trial.[33] In addition, local delivery of abciximab with a dedicated infusion catheter is currently being investigated in 2 trials that randomize STEMI patients to intracoronary bolus versus intravenous bolus (IC-ClearLy)[34] and to intracoronary versus no bolus with or without thrombus aspiration in patients treated with bivalirudin (INFUSE AMI; http//www.ClinicalTrials.gov; unique identifier, NCT00976521).

Limitations

First, we performed an open-label study because blinding of the operator was not feasible. However, all end points were assessed in a blinded manner. Second, this study was powered on STR instead of a clinical end point. However, STR is strongly related to clinical outcomes and therefore is widely accepted as a surrogate marker. In addition, STR was measured in this study only as a categorization into 3 groups, thereby preventing direct comparison between this study and previous studies reporting on continuous STR. In general, categorization makes a measurement less sensitive to treatment differences. However, STR categorized into 3 groups is frequently used in medium-scale interventional trials to detect a clinically relevant improvement in STR. Third, we analyzed enzymatic infarct size in the subset of patients who were hospitalized in this center after PCI. However, the choice to stay in this center was based on geographical reasons and not biased by randomization. Fourth, all patients in this study received abciximab in a bolus-only strategy, which is not currently recommended.[14] Bolus-only use is supported by studies showing that bolus-only use reduces bleeding complications and is not inferior to abciximab bolus with subsequent 12-hour infusion in stable and moderate- to high-risk patients with acute coronary syndromes.[35,36] In this study, we did not compare the bolus-only strategy with the standard bolus with subsequent 12-hour infusion strategy. However, because infusion was not initiated in either randomization group, it has not influenced our comparison of intracoronary and intravenous administration. Finally, we did not investigate the effect of timing of intracoronary administration. Although previous studies have reported on intracoronary administration after wire passage but before restoration of epicardial flow, we chose to perform intracoronary administration after restoration of flow to have an optimal local concentration through the coronary artery both at the culprit site and in the distal microvasculature.

Conclusions

In STEMI patients undergoing primary PCI with thrombus aspiration, intracoronary administration of abciximab is not superior to intravenous administration in improving myocardial reperfusion assessed by STR as the primary end point. However, intracoronary administration is associated with improved myocardial reperfusion as assessed by MBG and, in the subset of patients with evaluable infarct size, a smaller enzymatic infarct size. Larger randomized multicenter trials are required to evaluate whether intracoronary administration reduces clinical adverse events.

Acknowledgments

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Chapter 7.2 | Response to Letter to the Editor

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We thank Niccoli et al for their letter, which interestingly suggested that intracoronary administration of abciximab may exert its action in patients with ST-segment elevation myocardial infarction through facilitation of reversible no-reflow. Our study was designed to detect a difference in electrocardiographic and angiographic measures of immediate myocardial reperfusion after primary percutaneous coronary intervention (PCI), markers which are frequently used in medium-sized randomized studies and show strong correlation with clinical outcome[1,2]. In this regard, we did not include recovery of myocardial perfusion at a later time point as a pre-specified endpoint. It is not our center's routine clinical practice to re-evaluate the initial angiographic result and recovery of myocardial perfusion in the infarct-related artery before discharge, either by repeat angiography or cardiac magnetic resonance (CMR) imaging. As only in highly selected cases the infarct-related artery may have been filmed in additional revascularization procedures, we believe that analysis of this small non-pre-specified subset of patients would not produce meaningful results. In fact, an early study has indicated that intracoronary administration of abciximab significantly reduced the primary endpoint of microvascular obstruction on CMR 2 days after primary PCI compared to intravenous administration[3]. Therefore, we agree with Niccoli et al that facilitation of reversible no-reflow is one of the plausible mechanisms of action of intracoronary abciximab, a hypothesis that may be further tested in ongoing randomized studies on intracoronary versus intravenous abciximab administration that include CMR endpoints[4,5].

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Part 3 | Quantitative assessment of myocardial reperfusion

Chapter 8| Feasibility and applicability of computer-assisted myocardial blush quantification after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

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ABSTRACT

Objectives

The aim of the study was to evaluate whether the "Quantitative Blush Evaluator" (QuBE) score is associated with measures of myocardial reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) treated in two hospitals with 24/7 coronary intervention facilities.

Background

QuBE is an open source computer program to quantify myocardial perfusion. Although QuBE has shown to be practical and feasible in the patients enrolled in the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS), QuBE has not yet been verified on reperfusion outcomes of primary percutaneous coronary intervention (PCI) patients treated in other catheterization laboratories.

Methods

Core lab adjudicated angiographic outcomes and QuBE values were assessed on angiograms of patients who were enrolled in the PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PREPARE) trial. ST-segment resolution immediately after PCI measured by continuous ST Holter monitoring was calculated by a blinded core lab.

Results

The QuBE score could be assessed on 229 of the 284 angiograms (81%) and was significantly associated with visually assessed myocardial blush grade ($P < 0.0001$). Patients with improved postprocedural Thrombolysis in Myocardial Infarction-graded flow, myocardial blush grade, ST-segment resolution immediately after PCI, or a small infarct size measured by peak CK-MB had a significant better QuBE score.

Conclusions

QuBE is feasible and applicable at angiograms of patients with STEMI recorded at other catheterization laboratories and is associated with measures of myocardial reperfusion.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred strategy for reperfusion in the treatment of ST-segment elevation myocardial infarction (STEMI), because it has been shown to produce superior clinical outcomes as compared with fibrinolytic therapy [1]. However, despite the presence of normal epicardial Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, impaired myocardial perfusion has been independently associated with increased mortality [2-4]. Several measures that assess the quality of myocardial reperfusion including myocardial blush grade and ST-segment resolution provide insight to the integrity of the microvasculature and myocardial metabolism and have also been shown to independently correlate with survival [2-5]. New therapies that may improve impaired myocardial perfusion are being developed, as are techniques to measure it [6, 7]. A new technique of measuring reperfusion after primary PCI is a computer-assisted analysis of the myocardial blush on the coronary angiogram (Fig. 1). Recently, Vogelzang et al. [7] have demonstrated that the Quantitative Blush Evaluator (QuBE), an open source software program, provides a practical, feasible and reproducible assessment of myocardial perfusion. Furthermore, high QuBE score was significantly associated with more ST-segment resolution, higher visually assessed myocardial blush grade, and a lower 1-year mortality in a single-center, prospective, randomized thrombus aspiration study [8]. Our study evaluated whether this computer-assisted myocardial blush quantification program could be used on coronary angiograms assessed in other catheterization laboratories and whether the QuBE score could be associated with other measures of myocardial reperfusion in patients with STEMI.

METHODS

Patients and Protocol

All patients included in this ancillary study were participants of the proximal embolic protection in acute myocardial infarction and resolution of ST-elevation (PREPARE) trial. In this two-centre, randomized, open trial, patients with STEMI were randomized to primary PCI with the Proxis system St. Jude Medical, St Paul, MN, (n = 141) or primary PCI alone (n = 143). Results from this randomized trial have been previously published[6]. In brief, patients were eligible for inclusion in the PREPARE trial if they experienced onset of symptoms of myocardial infarction less than 6 hours before presentation and had electrocardiographic evidence of persistent ST-segment elevation of at least 200 μV in two or more contiguous leads and TIMI flow grade 0 to 1 on diagnostic angiography. Exclusion criteria were: age younger than 18 years, any contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, coexistent condition associated

with a limited life expectancy, prior coronary artery bypass grafting or lytics, and recurrence of myocardial infarction in the same myocardial area. Primary end point of the PREPARE trial was ST-segment resolution assessed from continuous digital 12-lead ECG/Holter monitoring (Northeast Monitoring 180+ Natick, Mass) and analyzed at an independent core lab [9,10]. ST-segment resolution immediately after PCI was categorized as complete (≥70%) according to Schröder et al[11,12]. Also, major adverse cardiac and cerebral events at 30 days have been previously defined [6]. The present analysis included all patients with an angiogram suitable for core lab myocardial blush grade assessment and QuBE measurement. At two catheterization laboratories at the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands and Institut de Cardiology de Montréal, Montréal, Canada, coronary angiograms immediately after PCI were acquired by using digital technique (both Philips Medical Systems, Best, The Netherlands).

Quantitative Blush Evaluation and Core Lab Measurements

QuBE (available at http://QuBE.sf.net) has been developed and previously described by Vogelzang et al[7]. Briefly, the operator indicates a region of interest (polygonal shape) including the distal infarct-related area on the angiogram immediately after PCI. The computer program filters all large-scale structures, such as diaphragm and large blood

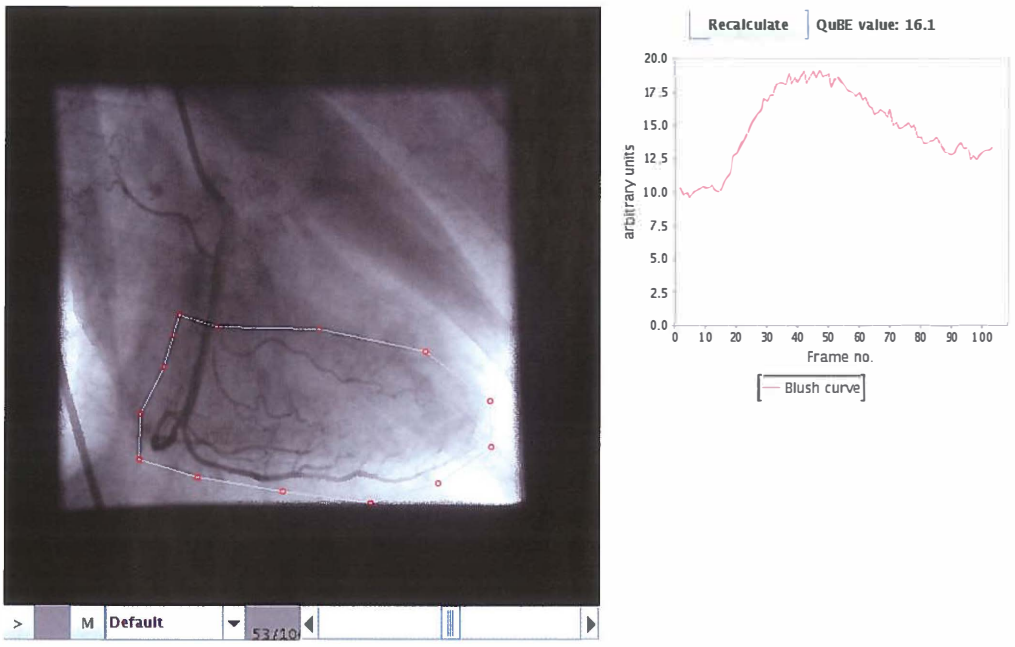

Fig. 1 The Quantitative Blush Evaluator program. Screenshot of a coronary angiogram of a right coronary artery with the indicated region of interest (left panel). The curve represents the quantified value in all frames and the Quantitative Blush Evaluator (QuBE) value equals the maximum increase (frame 14 to 47) plus the maximum decrease (frame 47 to 97) (right panel).

vessels, but not small size structures. All pixels in the polygon are divided in blocks and for each block the average of the darkest few pixels is used. The QuBE value is calculated as the average of the best 50% of pixel blocks. By summing the maximum increase and decrease in gray value the QuBE value (arbitrary units) reflects the myocardial contrast density in both the filling and emptying phase of the vessels. QuBE values were scored on angiograms immediately after PCI. Notably, adequate measurement of the QuBE score could be performed if data acquisition begins before the start of contrast injection and continues at least 10 seconds thereafter (12.5 frames per second). Furthermore, right anterior oblique view (RAO −30°) was used for assessment of the myocardial blush. For the left anterior descending artery, a left anterior oblique view (LAO −60° to 90°) was also suitable for QuBE measurement. Angiographic projections that deviated from those proposed up to 10° were allowed as well. The QuBE score was determined for all patients included in the present analysis by one experienced observer (YLG) blinded for all data. TIMI-graded coronary flow, myocardial blush grade, and angiographic signs of distal embolization as previously described were adjudicated by the core lab (YLG and FZ) [4, 13, 14].

Statistical Analysis

Values are reported as mean (SD) or median (25th to 75th percentile) for continuous var-

Table I Patient and Procedural Characteristics Divided by Tertiles of QuBE

	First QuBE tertile (n = 77)	Second QuBE tertile (n = 76)	Third QuBE tertile (n = 76)	P value
QuBE value	10.3 (8.0 −11.7)	15.4 (14.1 −16.4)	20.4 (18.8 −23.0)	
Age, yrs	63 (53 −71)	58 (48 −67)	60 (51 −67)	0.39
Male sex	55 (71%)	61 (80%)	63 (83%)	0.09
Symptom onset to balloon, min	163 (139 −221)	161 (129 −260)	146 (123 −214)	0.06
Maximal ST-segment deviation (μV)	572 (359 −762)	575 (331 −793)	490 (331 −750)	0.58
Body mass index	27.2 (25.2 −29.1)	26.3 (24.9 −29.3)	25.6 (23.8 −27.8)	0.009
Heart rate, bpm	75 (66 −90)	70 (58 −78)	66 (59 −81)	0.003
Systolic blood pressure, mm Hg	135 (120 −154)	126 (112 −154)	131 (117 −147)	0.44
Diastolic blood pressure, mm Hg	80 (67 −90)	76 (68 −86)	76 (70 −86)	0.41
Infarct-related vessel				<0.001
Left anterior descending artery	36 (47%)	23 (30%)	19 (25%)	
Left circumflex artery	10 (13%)	4 (5%)	3 (4%)	
Right coronary artery	31 (40%)	49 (65%)	54 (71%)	
Baseline TIMI-graded flow				0.92
0	68 (88%)	71 (93%)	67 (88%)	
1	6 (8%)	4 (5%)	7 (9%)	
2	3 (4%)	1 (1%)	2 (3%)	
Proxis system randomization	36 (47%)	41 (54%)	33 (43%)	0.69
GP IIb/IIIa receptor antagonists	32 (42%)	29 (38%)	26 (34%)	0.35

Data are expressed as median (interquartile range), or number of patients (percent).
GP, glycoprotein; TIMI, thrombolysis in myocardial infarction.

iables and as frequency with percentage for categorical variables. For the comparison of dichotomous or continuous variables, the Cochran-Armitage test or Jonckheere-Terpstra test was used to compare outcomes over ordered categories. To identify parameters independently associated with the QuBE score, multivariable linear regression analysis with a forward selection procedure was used. Variables were entered if $P < 0.10$. The squared multiple correlation coefficient (R2) is reported and could be interpreted as proportion of variance explained by the model. All statistical tests were two-tailed, and a P-value of <0.05 was considered to be statistically significant. All calculations were generated by the Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS, Chicago, IL).

RESULTS

Patients

Of the 284 patients who participated in the PREPARE trial, 229 patients (81%) could be included in the current analysis. The flow chart of patients who entered this QuBE analysis is shown in Figure 2. The patient and procedural characteristics are summarized in Table I. All patients were divided into tertiles according to their scored QuBE arbitrary units [first tertile, 10.3 (8.0–11.7); second tertile, 15.4 (14.1–16.4); third tertile, 20.4 (18.8–23.0), Table I]. Patients in the lower QuBE tertiles had more often an anterior myocardial infarction, a higher body mass index, and an increased heart rate compared

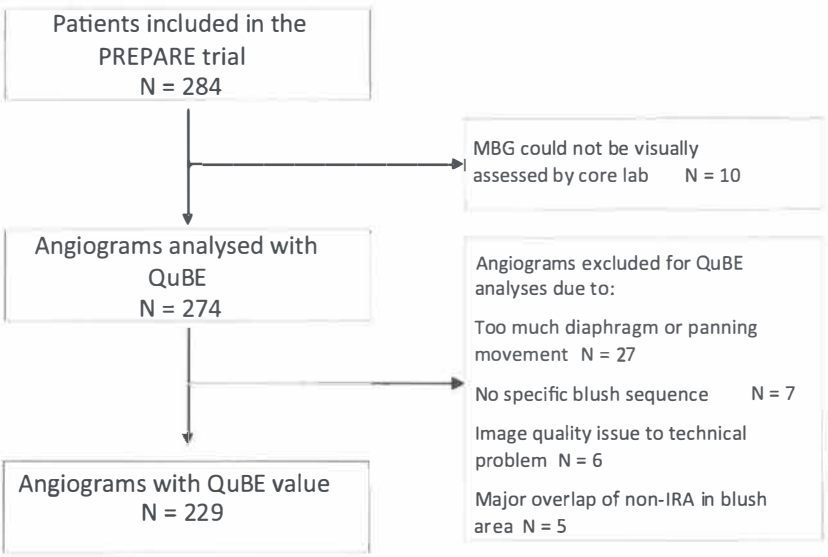

Figure 2 Flow chart of patients included in the analysis. MBG = myocardial blush grade; QuBE = quantitative blush evaluator; IRA = infarct related artery.

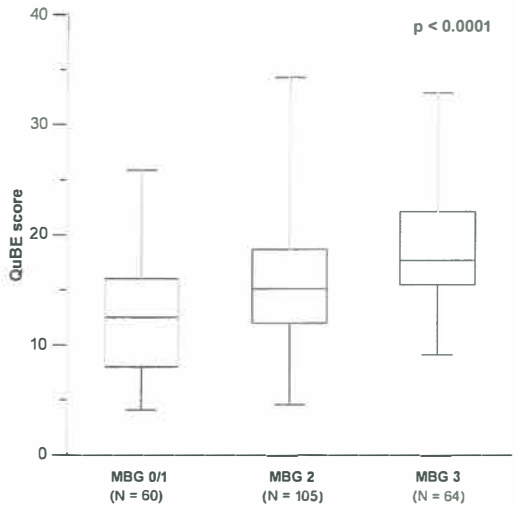

Fig. 3. Association of visually assessed myocardial blush grade with QuBE. MBG = myocardial blush grade; QuBE = quantitative blush evaluator. MBG 0/1 = no or minimal myocardial blush or contrast density; 2 = moderate blush or contrast density; 3 = normal blush (comparable with a noninfarct related artery).

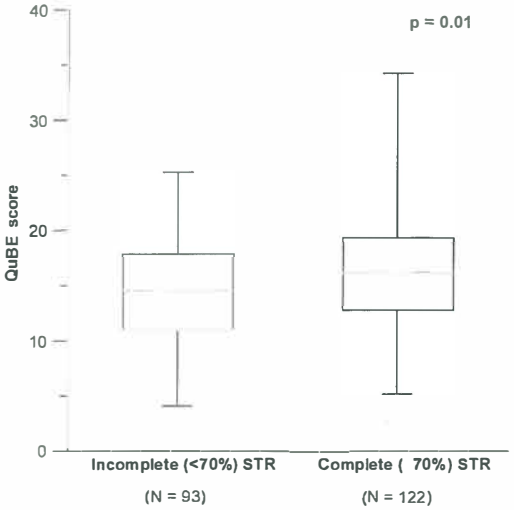

Fig. 4. Association of ST–segment resolution with QuBE. STR = ST-segment resolution ; QuBE = quantitative blush evaluator.

with the patients in the highest tertile (all $P < 0.009$, Table I). Forward multivariable linear regression analysis including univariable predictors of QuBE identified anterior myocardial infarction ($\beta = -3.5$; SE = 0.7; $P < 0.001$) and body mass index ($\beta = -0.2$; SE = 0.1; $P = 0.018$) as independent variables related to the QuBE score ($R2 = 0.11$).

QuBE and Measures of Reperfusion

Figure 3 presents a box plot of QuBE values for the three groups of patients with myocardial blush grade 0 to 1, myocardial blush grade 2, and myocardial blush grade 3. The difference among groups was significant ($P < 0.0001$). Patients with a myocardial blush grade 0 to 1 had mean (±SD) QuBE values of 12.3 ± 5.1, whereas those with myocardial blush grade 3 had QuBE values of 18.5 ± 5.1. The patients with myocardial blush grade 2 had a mean QuBE value of 15.4 ± 4.9.

Figure 4 shows QuBE values in relation to ST-segment resolution immediately after PCI. QuBE values differed significantly between incomplete (<70%) ST-segment resolution and complete (≥70%) ST-segment resolution ($P = 0.01$). The mean QuBE values were 14.2 ± 5.1 among patients with incomplete ST-segment resolution and 16.5 ± 5.5 among those with complete ST-segment resolution. The angiographic outcomes, ST-segment resolution immediately after PCI, and peak creatine-kinase myocardial band (CK-MB) in relation with the QuBE score are listed in Table II. Patients with improved postprocedural TIMI-graded flow, myocardial blush grade, ST-segment resolution im-

mediately after PCI, or a small infarct size measured by peak CK-MB had a significant better QuBE score. Although QuBE values tended to increase in patients without distal embolization, no significant differences were observed (15.7 ± 5.6 vs. 13.9 ± 4.5, P = 0.09, respectively, Table II). Table II shows also QuBE values in relation to infarct size measured by peak creatine kinase-myocardial band (CK-MB, μg/L). Patients with more than 50 times the upper limit of normal of the CK-MB level had a mean QuBE value of 14.0 ± 5.2, whereas those with less than 10 times the upper limit of normal of the CK-MB level had QuBE values of 16.7 ± 3.8. The patients with 10 to 50 times the upper limit of normal of the CK-MB level had a mean QuBE value of 15.7 ± 5.1. Overall major adverse cardiac and cerebral events (MACCE) within 30 days occurred in eleven patients. No significant differences in QuBE values were observed between patients with or without an overall MACCE rate at 30 days (15.3 ± 4.4 vs. 15.5 ± 5.5, P = 0.83, respectively).

DISCUSSION

The current study shows that computer-assisted quantitative blush evaluation is feasible and applicable at angiograms of patients with STEMI recorded at other catheterization laboratories. The QuBE score significantly correlates with the core lab-adjudicated myocardial blush grade and ST-segment resolution immediately after PCI. Quantitative blush evaluation could be performed in 81% of the angiograms immediately assessed after PCI of the patients included in the PREPARE trial, a rate which is similar to the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS). Notably, all angiograms were acquired at two catheterization laboratories with different acquisition machines and were not particularly performed for quantitative blush evaluation assessment. Furthermore, the QuBE values found in the PREPARE trial were comparable with the TAPAS trial [7].

Although the QuBE score significantly differs with ~2 units between incomplete and complete ST-segment resolution, the interquartile range indicate that there is a substantial overlap in QuBE values between both categories of ST-segment resolution. These findings implicate that there is a discrepancy between both measures of myocardial reperfusion. Although both measures have recently been correlated with clinical outcomes [2, 7], further validation of the QuBE score will lead us to understand its values and pathophysiological meanings.

Postprocedural TIMI 3 flow is established in most acute myocardial infarction patients undergoing primary PCI[5]. Nevertheless, selected patients within this group with successful PCI remain at high risk for adverse events. The QuBE program could identify high-risk subgroups with the greatest potential for myocardial salvage which could be a target population for novel protective therapies. The present study indicate

Table II QuBE Values by Measures of Reperfusion

	n	QuBE value	P value
Postprocedural TIMI-graded flow			0.004
0–1	1	7.4	
2	19	12.1 ± 6.3	
3	209	15.8 ± 5.3	
Myocardial Blush Grade			<0.0001
0–1	60	12.3 ± 5.1	
2	105	15.4 ± 4.9	
3	64	18.5 ± 5.1	
Angiographic signs of distal embolization			0.09
yes	28	13.9 ± 4.5	
no	199	15.7 ± 5.6	
ST -segment resolution immediately after PCI			0.01
Incomplete (<70%)	93	14.2 ± 5.1	
Complete (≥70%)	122	16.5 ± 5.5	
Peak CK - MB (µg/L)			0.04
>50 times ULN	49	14.0 ± 5.2	
10–50 times ULN	85	15.7 ± 5.1	
<10 times ULN	11	16.7 ± 3.8	

Data are expressed as number of patients and mean (±SD). Angiographic signs of distal embolization analyzable on 227 angiograms. Data of ST-segment resolution immediately after PCI available in 215 patients and peak CK-MB in 145, respectively. TIMI = Thrombolysis in Myocardial Infarction; CK-MB = creatine kinase-myocardial band; ULN = upper limit of normal (7.0 µg/L).

that identification of patients at continued high risk is possible immediately after PCI, before other modalities such as peak biomarker values, echo-assessed ejection fraction, or cardiac magnetic resonance obtained infarct size are available. The QuBE program requires only an angiogram recorded immediately after PCI. Quantitative blush evaluation is inexpensive, immediately available, and less time-consuming compared with advanced techniques, such as cardiovascular magnetic resonance. Moreover, quantitative blush evaluation limits intra- and inter-observer variability which is a typical phenomenon in visually assessed myocardial blush grading [4]. Quantitative blush evaluation may therefore also be suitable as risk assessment tool in daily clinical practice. With the relationship between the generally accepted markers of myocardial reperfusion shown in both the patients enrolled in the TAPAS trial and the PREPARE patients, the QuBE program could be used as a readily available surrogate end point reflecting myocardial reperfusion in clinical trials of interventional reperfusion modalities intended to enhance myocardial recovery and herewith reduce mortality.

Limitations

The QuBE score measurement has its own limitations. First, QuBE is dependent on action of the operator, such as the choice of angiographic view and determined region of interest of the infarct-related artery. Second, the settings of the coronary angiogram acquisition machines and the choice of type and volume of the contrast agent are not standardized. Third, the QuBE score could have been underestimated in patients with a high body mass index. However, in our cohort, this magnitude of effect of body mass

index on QuBE measurements was modest. Fourth, variation in the degree of infarcted myocardium in the region of interest is inevitable, as the QuBE value is based on two dimensional data of coronary angiograms. Computer-assisted myocardial blush quantification using three dimensional angiographic data could overcome this limitation. Yet, computer-assisted myocardial blush quantification using three dimensional angiographic data is not readily available. Furthermore, mainly due to the necessity of a "landing zone" for the Proxis system, patients with a myocardial infarction related to an ostial coronary artery occlusion were not included in the PREPARE trial. This resulted in more myocardial infarctions related to a right coronary artery (59%) compared with a "normal" STEMI population. With only two deaths and a MACCE rate of eleven, this study lacks adequate statistical power to examine relationships between the QuBE score and clinical end points at 30 days and to compare within subgroups of patients.

Conclusions

Computer-assisted myocardial blush quantification is feasible and applicable at angiograms of patients with STEMI recorded at other catheterization laboratories and is associated with measures of myocardial reperfusion.

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Chapter 9| Computer-assisted quantification of myocardial reperfusion after primary percutaneous coronary intervention predicts functional and contrast-enhanced cardiovascular magnetic resonance outcomes in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Objective

We investigated whether the Quantitative Blush Evaluator (QuBE) value predicts functional and contrast-enhanced cardiovascular magnetic resonance (CMR) outcomes at 4–6 months after primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). Background. QuBE is a computer-assisted open source program to quantify myocardial reperfusion. Although a higher QuBE value is associated with improved myocardial reperfusion measures and lower 1-year mortality, the association with intermediate functional parameters after STEMI has not yet been investigated.

Methods

QuBE values were quantified retrospectively on angiograms of patients enrolled in the ancillary CMR study of the proximal embolic protection in acute myocardial infarction and resolution of ST-elevation trial. QuBE en CMR outcomes were independently assessed by reviewers blinded to clinical data.

Results

A higher QuBE value was significantly associated with a smaller left ventricular (LV) end-diastolic and end-systolic volume, a higher LV ejection fraction and systolic wall thickening in the infarct area, and a smaller final infarct size and extent of transmural segments ($P \leq 0.008$). In a multivariable model, including age, gender, infarct location, time to treatment, history of myocardial infarction, and postprocedural thrombolysis in myocardial infarction flow grade, only the QuBE value and infarct location remained as independent predictors of LV ejection fraction ($P = 0.018$ for QuBE value).

Conclusion

Higher QuBE values are independently associated with improved functional and contrast-enhanced CMR outcomes including LV ejection fraction at 4–6 months after primary PCI and may therefore aid in identifying high-risk patients who benefit most from adjunctive therapies sustaining myocardial function after PCI.

INTRODUCTION

Reperfusion of the myocardial microvasculature is an important prognostic factor in the short- and long-term outcome of patients with ST-segment elevation myocardial infarction (STEMI) after successful primary percutaneous coronary intervention (PCI). In patients undergoing primary PCI, suboptimal myocardial reperfusion is associated with a larger enzymatic infarct size, a lower left ventricular (LV) ejection fraction before hospital discharge, and increased long-term cardiac mortality [1, 2].

The Quantitative Blush Evaluator (QuBE) is a computer-assisted quantification technique to measure myocardial reperfusion after primary PCI on the coronary angiogram in STEMI patients. We have previously reported that determination of the QuBE value using this freely available program is feasible and reproducible on angiograms from STEMI patients at various primary PCI centers [3, 4]. Furthermore, a higher QuBE value was strongly associated with improved angiographic and electrocardiographic markers of reperfusion, smaller enzymatic infarct size, and lower 1-year mortality. In this study, we investigated whether the QuBE value could predict intermediate functional outcomes as determined with the current golden standard cardiovascular magnetic resonance (CMR) in STEMI patients at 4–6 months after primary PCI.

METHODS

Patient Selection

We studied STEMI patients undergoing primary PCI who were enrolled in the ancillary CMR study of the proximal embolic protection in acute myocardial infarction and resolution of ST-elevation (PREPARE) trial [5, 6]. This was a two-center randomized clinical trial, in which patients with STEMI were assigned to primary PCI with combined proximal embolic protection and thrombus aspiration (Proxis, St. Jude Medical, St Paul, MN) or to primary PCI alone. The detailed study design and results have been published previously [5, 6]. In brief, patient inclusion criteria consisted of onset of symptoms less than 6 hr before presentation, electrocardiographic evidence of persistent ST-segment elevation of at least 0.2 mV in two or more contiguous leads, thrombolysis in myocardial infarction (TIMI) flow grade 0–1 on diagnostic angiography, and a coronary anatomy suitable for application of the Proxis system. Patient exclusion criteria included age under 18 years, contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, a coexistent condition associated with a limited life expectancy, prior coronary artery bypass grafting or thrombolytic therapy, previous myocardial infarction in the same myocardial area, and an ECG unsuitable for ST-segment resolution analysis. Angiographic exclusion criteria were left main occlusion or stenosis of more than 30%, severe proximal calcifications, an infarct-related artery <2.5 mm in

diameter, and a proximal lesion location resulting in an insufficient landing zone for the Proxis system.

Primary end point of the PREPARE trial was ST-segment resolution assessed from continuous digital 12-lead ECG/Holter monitoring at an independent core laboratory [7, 8]. As part of an ancillary study, patients underwent CMR at 4–6 months after the index procedure. CMR imaging was performed with a 1.5-T clinical scanner (Sonato/Avanto, Siemens, Erlangen, Germany). Functional assessment was studied with a standard cine steady-state free precession sequence. Late gadolinium enhancement (LGE) images were acquired after administration of a gadolinium-based contrast agent (0.2 mmol/kg, Magnevist, Schering AG, Berlin, Germany). All functional and LGE images were analyzed as described previously [5]. The CMR data were analyzed by a single experienced physician (JDEH) who was blinded to clinical and angiographic data using the MASS software (version 5.1, MEDIS Medical Imaging Systems, Leiden, The Netherlands). Clinical follow-up was performed at 6 months after the index event. All reported clinical end points have been previously defined [5]. Clinical end points included death, spontaneous or procedural myocardial infarction, stroke, and percutaneous or surgical target vessel revascularization. The current retrospective analysis included all patients who were enrolled in the ancillary CMR study with an angiogram suitable for QuBE.

Angiographic Analysis with the QuBE Program

The QuBE program (available as open-source software at http://qube.sf.net) has been developed and described previously by Vogelzang et al. [3]. In brief, the operator indicates a polygonal shape (the region of interest) that contains the infarct-related area on the angiogram acquired immediately after PCI (Fig. 1, left panel). Each frame is corrected for panning motions, and all pixels in the polygon are divided into blocks of 5 × 5 pixels. The value of each pixel block is proportional to the amount of darkening compared to a wider area around that block. This automatically marks larger structures such as the diaphragm and large vessels as part of the background. The value of a single frame is calculated as the average of the most darkened 50% of pixel blocks. The QuBE value is obtained by summing the maximum increase and decrease of the single frame values during the first 10 sec (125 frames in our configuration). This representation of the myocardial contrast density in the area of interest shows a typical curve (Fig. 1, right panel). Adequate measurement of the QuBE value could be performed if data acquisition begins before the start of contrast injection and continues at least 10 sec thereafter. A right anterior oblique (−30°) projection was used for the assessment of the myocardial blush. For the left anterior descending artery (LAD), a left anterior oblique (−60° to −90°) was also suitable for the QuBE measurement. Angiographic projections that deviated from those proposed up to 10° were allowed as well.

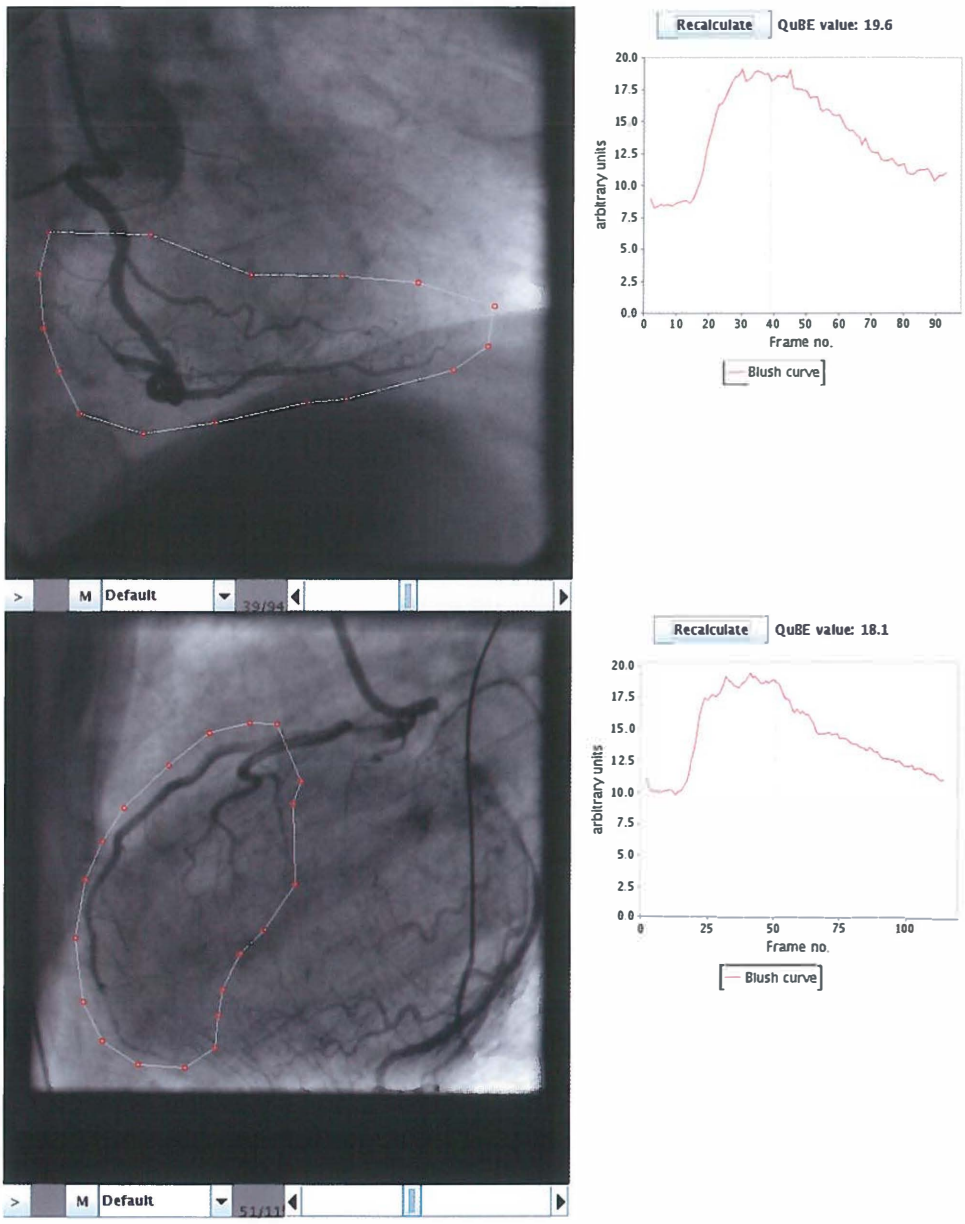

Figure 1 Screenshot of the QuBE program. Image showing coronary angiograms of a right coronary artery (upper) and left anterior descending artery (lower). On the left, a specific blush run is loaded into the QuBE program, and a polygonal shape is drawn containing the infarct-related area. The myocardial contrast density in the area indicated on this run in each single frame is represented graphically on the curve on the right, which shows a typical curve. The QuBE value is calculated as the sum of the maximum increase and maximal decrease of the single frame values during the first 125 frames. QuBE, Quantitative Blush Evaluator.

Coronary angiograms (Philips Medical Systems, Best, The Netherlands) were acquired at two catheterization laboratories (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and Institut de Cardiology de Montréal, Montréal, Canada). The QuBE value was measured by a single experienced physician (YLG) blinded to clinical and CMR data at the core laboratory (University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands).

Statistical Analysis

Values are expressed as mean (±standard deviation) or median (25th–75th percentile) for continuous data and as counts (percentage) for categorical variables. For the baseline characteristics, the QuBE values were divided into tertiles and treated as an ordinal variable. Outcomes over ordered categories were compared using the Jonckheere–Terpstra test for continuous data and the Cochran–Armitage test (P for trend) for categorical data. To investigate clinical predictors of the QuBE value, we performed multivariable linear regression analysis with a backward selection procedure including all significant variables as reported previously [3] and baseline variables of the current study if $P < 0.10$. Associations between the QuBE value and CMR outcomes were assessed with univariable linear regression analysis. To identify parameters independently associated with LV ejection fraction, we composed a multivariable linear regression model using a backward selection procedure that included the variables age, gender, infarct location, time to treatment, a history of myocardial infarction, and postprocedural TIMI flow as well as the QuBE value. Statistical significance was considered as a two-tailed P value less than 0.05. The Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 16.0.2 was used for all statistical analyses.

RESULTS

Of the 284 patients enrolled in the PREPARE trial, CMR imaging was performed in 200 patients (Fig. 2). In 35 patients, the angiogram was not assessable with the QuBE program due to excess movement of the diaphragm or panning motions, absence of a specific blush sequence, technical quality problems, or too much overlap of a noninfarct-related artery in the blush area of interest. The remaining 165 patients (83%) were included in this analysis.

Baseline Characteristics and Predictors of the QuBE Value

The baseline clinical and angiographic characteristics of these patients are summarized in Table I according to tertiles of QuBE values [first tertile 10.5 (range, 4.1–12.8), second tertile 15.4 (12.9–17.6), third tertile 20.1 (17.6–32.9)]. Patients with a lower QuBE value were more frequently women and had a slightly higher body mass index (BMI), higher heart rate, and a higher rate of infarction in the left coronary system. In a multivariable

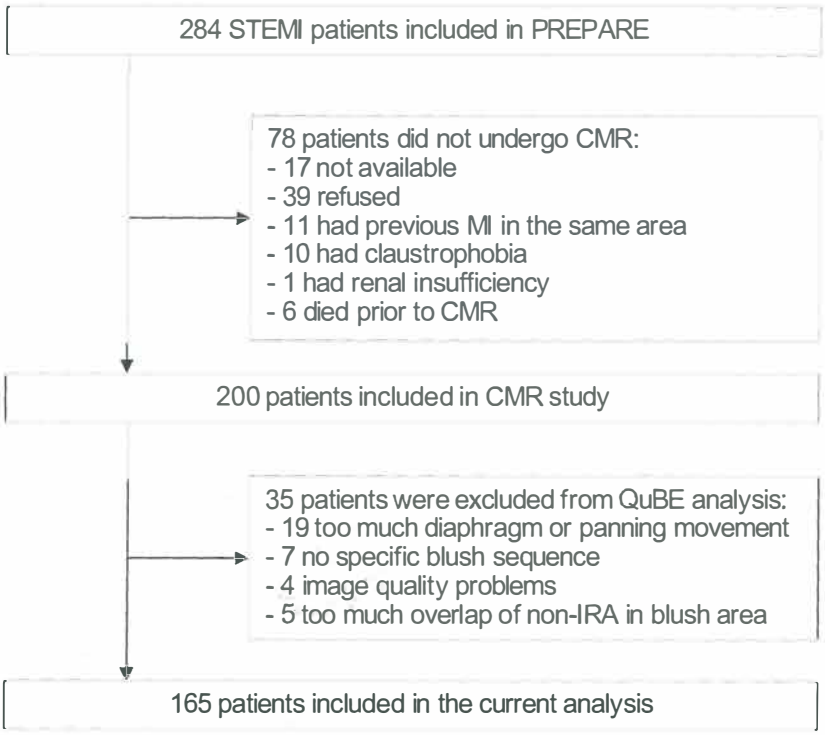

Figure 2 Flow chart of PREPARE patients. Of the total 284 patients included in the PREPARE trial, 200 patients were included in the ancillary CMR study. After exclusion of 35 patients who had a coronary angiogram not assessable with QuBE, the remaining 165 patients entered the current analysis. PREPARE, proximal embolic protection in acute myocardial infarction and resolution of ST-elevation; CMR, cardiovascular magnetic resonance; QuBE, Quantitative Blush Evaluator.

regression model including age, BMI, heart rate, baseline as well as postprocedural TIMI flow, and infarct location, the independent predictors of the QuBE value were BMI (coefficient = −3.5, SE 0.1, P = 0.002) and infarct location (coefficient = −2.2, SE 0.9, P = 0.012, r2 = 0.12).

Functional CMR Outcomes by QuBE Tertiles

A higher QUBE value was significantly associated with improved functional CMR outcomes at 4–6 months including LV end-diastolic and end-systolic volumes, LV ejection fraction, and systolic wall thickening in the infarct area (P ≤ 0.008, Table II). As illustrated in Table III, patients had a lower LV end-diastolic volume with increasing tertiles of QuBE (192 ± 59, 190 ± 46, and 170 ± 37 mL, respectively). Similarly, the LV end-systolic volume was lower for a higher QuBE tertile (102 ± 53, 97 ± 35, and 81 ± 28mL, respectively). Patients in the first QuBE tertile had an LV ejection fraction of 49% ± 13%, those in the second tertile 50% ± 9%, and those in the third tertile had an LV ejection fraction of 53% ± 9%. Patients in the third tertile had better systolic wall thickening in the infarct area compared to patients in the first and second tertile (1st QuBE tertile 1.8 ± 1.2 mm, 2nd QuBE tertile 2.1 ± 1.1 mm, and 3rd QuBE tertile, 2.6 ± 1.3 mm, respectively).

Table I Baseline Chararacteristics of the 165 PREPARE patients with QuBE and CMR data according to tertiles of QuBE

	1st QuBE tertile (n = 56)		2nd QuBE tertile (n = 54)		3rd QuBE tertile (n = 55)		
QuBE value (range)	10.5	(4.1 - 12.8)	15.4	(12.9 - 17.6)	20.1	(17.6 - 32.9)	p
Age, yrs	56	(49 - 67)	56	(46 - 61)	58	49 - 64)	0.785
Male sex	41	(73%)	49	(91%)	49	(89%)	0.022
History							
Diabetes mellitus	3	(5%)	7	(13%)	0	(0%)	0.244
Hypertension	12	(21%)	9	(17%)	15	(27%)	0.461
Hypercholesterolemia	4	(7%)	9	(17%)	6	(11%)	0.531
Myocardial infarction	2	(4%)	4	(7%)	0	(0%)	0.321
PCI	0	(0%)	4	(7%)	2	(4%)	0.303
Cerebrovascular disease	2	(4%)	2	(4%)	1	(2%)	0.592
Cardiovascular disease in family	19	(34%)	20	(37%)	27	(49%)	0.105
Smoking	5	(9%)	11	(20%)	6	(11%)	0.752
Current smoking	39	(70%)	32	(59%)	36	(66%)	0.641
Preinfarction angina	0	(0%)	5	(9%)	2	(4%)	0.338
Body mass index	27.2	(25.3 - 29.3)	26.3	(24.9 - 29.8)	25.6	(24.1 - 27.8)	0.010
Systolic blood pressure, mm Hg	136	(120 - 156)	121	(107 - 155)	131	(117 - 153)	0.472
Diastolic blood pressure, mm Hg	80	(68 - 92)	77	(70 - 89)	80	(70 - 88)	0.812
Heart rate, bpm	75	(65 - 91)	70	(58 - 78)	66	(56 - 83)	0.019
No. of diseased vessels							0.954
1	39	(70%)	38	(70%)	39	(71%)	
2	14	(25%)	14	(26%)	12	(22%)	
3	3	(5%)	2	(4%)	4	(7%)	
Infarct-related vessel							0.011
Left anterior descending artery	23	(41%)	17	(32%)	16	(29%)	
Left circumflex artery	7	(13%)	2	(4%)	2	(4%)	
Right coronary artery	26	(46%)	35	(65%)	37	(67%)	
Baseline TIMI flow							0.052
0	54	(96%)	51	(94%)	48	(87%)	
1	2	(4%)	2	(4%)	5	(9%)	
2	0	(0%)	1	(2%)	2	(4%)	
Symptom onset to balloon, min	163	(138 - 230)	160	(128 - 227)	150	(116 - 219)	0.087

Data are expressed as mean±SD, median (interquartile range), or number of patients (percent). Data for angiographic signs of distal embolization were available in 227/229 patients. GP = glycoprotein; TIMI = Thrombolysis in Myocardial Infarction; QuBE = Quantitative Blush Evaluator; CMR = cardiac magnetic resonance.

Contrast-Enhanced CMR Outcomes by QuBE Tertiles

LGE measurements were available in 161 of the 165 patients. A higher QuBE value was related to a smaller final infarct size and extent of transmural segments ($P \leq 0.003$, Table II). As shown in Table IV, patients in the first QuBE tertile had a mean final infarct size of 13.7 ± 11.6 g, whereas those in the third tertile had a final infarct size of 9.7 ± 8.1 g. The patients in the second tertile had a mean final infarct size of 11.3 ± 8.6 g. Segmental analysis of the contrast-enhanced CMR images showed that patients in the third tertile had less extent of transmural segments compared to patients in the first and second tertile (1st QuBE tertile 10.9% ± 13.4% of segments, 2nd QuBE tertile 7.6% ± 9.2% of segments, and 3rd QuBE tertile 5.1% ± 9.1% of segments, respectively).

Table II Univariable association of the QuBE value with functional and contrast-enhanced CMR characteristics

	QuBE Coefficient (SE)		p	R
Functional				
LV end-diastolic volume (ml)	-1.908	(0.692)	0.006	0.211
LV end-systolic volume (ml)	-1.984	(0.573)	0.001	0.262
LV ejection fraction (%)	0.490	(0.147)	0.001	0.252
Systolic wall thickening in infarct area (mm)	0.064	(0.023)	0.008	0.275
Late gadolinium enhancement				
Infarct size (g)	-0.411	(0.137)	0.003	0.231
Extent of transmural segments (% of segments)	-0.558	(0.156)	<0.001	0.274

Data are expressed as mean±SD. CMR = cardiovascular magnetic resonance; LV = left ventricular. QuBE= quantitative blush evaluator.

Predictors of LV Ejection Fraction

In a multivariable model, including age, gender, infarct location, time to treatment, history of myocardial infarction, and postprocedural TIMI flow grade as well as the QUBE value, the QuBE value remained an independent predictor of LV ejection fraction at 4–6 months (coefficient = 0.329 for every unit increase in QuBE, SE = 0.138, P = 0.018, r2 = 0.218) next to infarct location. The test for interaction between infarct location and the QuBE value was not significant (P = 0.252).

Clinical Follow-Up at 6 Months by QuBE Tertiles

At 6 months' follow-up, four patients died: two in the first tertile and one in each of the higher tertiles (P = 0.55). Major adverse cardiac en cerebral events occurred in 8 (10%) of the patients in the first tertile, 6 (5%) in the second, and 5 (7%) in the third tertile (P = 0.39).

DISCUSSION

The principal finding of this study is that higher QuBE values quantified after primary PCI are associated with improved functional as well as contrast-enhanced CMR outcomes at 4–6 months. In the STEMI patients studied, a higher QuBE value was linearly associated with smaller LV end-diastolic and end-systolic volumes, a higher LV ejection fraction and systolic wall thickening in the infarct area, and a smaller final infarct size and extent of transmural segments. After correction for known predictors of LV function and infarct size including age, gender, infarct location, time to treatment, a history of myocardial infarction, and postprocedural TIMI flow grade, a higher QuBE value remained independently associated with improved LV ejection fraction at 4–6 months.

Table III Functional CMR outcomes by QuBE tertiles

	LV end-diastolic volume (mL)	LV end-systolic volume (mL)	LV ejection fraction (%)	Systolic wall thickening in infarct area (mm)
QuBE value				
1st tertile	192 ± 59	102 ± 53	49 ± 13	1.8 ± 1.2
2nd tertile	190 ± 46	97 ± 35	50 ± 9	2.1 ± 1.1
3rd tertile	170 ± 37	81 ± 28	53 ± 9	2.6 ± 1.3

Data are expressed as mean (±SD). LV=left ventricular; CMR= cardiovascular magnetic resonance; QuBE=quantitative blush evaluator.

Myocardial reperfusion after primary PCI is an important prognostic factor in STEMI patients and is associated with enzymatic infarct size, LV ejection fraction before hospital discharge, and long-term survival[1, 2, 9, 10]. For these reasons, the myocardial blush grade is used as a surrogate or functional end point in randomized clinical trials. However, visual grading is subjective and operator-dependent and results in a rough classification into four groups. We have previously reported that myocardial blush quantification with the QuBE program is feasible and applicable on angiograms of patients enrolled in the thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study (TAPAS) and achieved excellent intra and interobserver agreement rates of 99.7% and 97.7%, respectively [3]. In these unselected STEMI patients, the QuBE value was associated with conventional measures of myocardial reperfusion including visually scored myocardial blush grade and ST-segment resolution, in-hospital enzymatic infarct size, and mortality at 1 year. Its discriminating power with respect to 1-year mortality was also present in the subset of patients with successful and optimal reperfusion therapy (TIMI 3 flow and myocardial blush grades 2 or 3). More recently, we have reported that the QuBE program is also feasible on angiograms from patients included in the PREPARE trial that were acquired at other catheterization laboratories and confirmed the association of the QuBE value with conventional measures of myocardial reperfusion [4]. The findings of this study add

Table IV Contrast-enhanced CMR outcomes by QuBE tertiles

	Final infarct size (g)	Extent of transmural segments (%)
QuBE value		
1st tertile	13.7 ± 11.6	10.9 ± 13.4
2nd tertile	11.3 ± 8.6	7.6 ± 9.2
3rd tertile	9.7 ± 8.1	5.1 ± 9.1

Data are expressed as mean (±SD). CMR=cardiovascular magnetic resonance; QuBE=quantitative blush evaluator.

to this knowledge by reporting the value of QuBE in predicting intermediate functional outcomes.

CMR imaging is considered the golden standard in the assessment of the combination of LV ejection fraction and final infarct size [11–13], both of which are related to long-term mortality. However, this comprehensive technique is technically demanding, time-consuming, and expensive. In contrast, QuBE is a readily available simple computer program that can be used in the catheterization laboratory by anyone with knowledge of the coronary anatomy and usually requires no longer than a minute to assess. In this study, the QuBE program was applicable in 83%, a rate almost similar to that reported in the TAPAS trial [3], whereas these angiograms were acquired at two different PCI sites and were also not specifically recorded for quantitative analysis. To further improve its clinical applicability, several issues should be taken into account. First, diaphragm or panning movement, accounting for more than half of the excluded angiograms, can be put to a minimum by instructing the patient to hold his breath and by keeping the table still. Second, dedicated blush sequences should be recorded in all patients. Finally, overlap of a noninfarct-related artery into the area of interest can usually be minimized by choosing a different projection. Therefore, it is expected that, with these efforts, a QuBE value can be obtained from almost all patients.

The relationships between QuBE and functional and contrast-enhanced CMR parameters observed in this study could have been weakened as a result of the PREPARE inclusion criteria, requiring a landing zone for the Proxis system. Patients with a myocardial infarction related to an ostial coronary artery occlusion were therefore not included. This resulted in more myocardial infarctions related to a right coronary artery (RCA) (60%) compared to a general STEMI population and led to exclusion of very proximal infarct-related LAD artery and left circumflex artery (LCx) lesions. The RCA typically perfuses a much smaller amount of LV myocardium and as such is associated with much smaller final infarct size. Also, patients with a nonproximal LAD- or LCx-related lesion have a much smaller LV myocardium at risk. Nevertheless, the QuBE value was highly associated with several functional CMR outcomes in this cohort with a relatively low variability in functional outcomes.

Considering the deleterious effect of impaired myocardial perfusion on infarct size, LV function, and long-term clinical outcome, its clinical course may be improved by identifying high-risk patients as early as possible and developing and intensifying specific treatment regimens in this subgroup. The QuBE program can be adopted easily in the catheterization laboratory and enables quantitative risk assessment in clinical practice. Next to being readily available, once implemented, the QuBE value provides a risk indicator (long) before other indicators including enzymatic infarct size during hospital stay and functional recovery at follow-up can be determined. QuBE may not replace more technically sophisticated techniques, but may serve as a practical

marker for myocardial perfusion and as a surrogate end point in clinical trials, where a functional or surrogate end point is necessary that is able to detect a difference between treatment groups [14], especially with small numbers of patients.

Further investigations should be directed at the reproducibility of these findings in other centers, validation of the prognostic utility in larger-scaled studies, and cut-off values that assist in interpretation in clinical practice.

Study Limitations

First, as quantitative analysis with the QuBE program was not available when this clinical trial was designed, this analysis was not prespecified. Nevertheless, QuBE was still applicable in the majority of these angiograms that were not specifically made for quantitative analysis. Second, any quantification tool suffers from some level of subjectivity. QuBE is dependent on several actions of the operator, such as the choice of angiographic view and determined region of interest of the infarct-related artery. However, excellent intra and interobserver agreement has been reported with the QuBE program [3]. Furthermore, several operator- and site-specific parameters are not standardized that may influence the QuBE value including type and volume of the contrast agent, speed of injection, and specific settings on the acquisition machines. Third, with the low number of clinical events at follow-up, there was inadequate power to compare the clinical outcome of patients between the QuBE tertiles. Finally, the QuBE tertiles generated in this population are not representative to a general STEMI population as this study included patients presenting with TIMI flow grade 0/1 and excluded patients with an ostial lesion [5, 6].

Conclusions

Higher QuBE values are independently associated with improved functional and contrast-enhanced CMR outcomes including LV ejection fraction at 4–6 months after primary PCI in STEMI patients. Early identification of high-risk patients may select those who can benefit from adjunctive therapies targeted at sustaining myocardial function after PCI.

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Chapter 10 | Summary & future perspectives

Although recent advances in primary percutaneous coronary intervention (PCI) have markedly reduced mortality in patients with ST-segment elevation myocardial infarction (STEMI), myocardial perfusion is not optimally restored in a substantial number of patients. To further improve myocardial perfusion after primary PCI, intracoronary therapies have been explored to limit embolization of atherothrombotic material into the distal microcirculation, an important cause of unsuccessful myocardial reperfusion. This thesis focuses on the role of adjunctive intracoronary therapy with thrombus aspiration and abciximab during primary PCI for STEMI for this purpose and explores a novel technique to quantify myocardial reperfusion after primary PCI.

Part 1 | Intracoronary thrombus aspiration

Thrombus aspiration facilitates restoration of flow during primary PCI by aspirating atherothrombotic material from the infarct-related artery. Part 1 of this thesis investigates the relationship between thrombus aspiration and long-term clinical outcome.

Chapter 2 is an editorial, which comments on the role of thrombus aspiration in STEMI and, more specifically, on recent findings that the age of aspirated atherothrombotic material in patients with STEMI was an independent predictor of long-term mortality. In 1315 patients treated with thrombus aspiration, the presence of older thrombus (>1 day) was independently associated with a 2-fold higher mortality at 4 years compared to fresh thrombus (<1 day). It is hypothesized that the underlying mechanism leading to a higher mortality is explained by a higher burden of atherothrombotic embolization in patients with older thrombus. The results of such studies on thrombus characteristics may provide new insights into the pathophysiology of myocardial infarction, clinical risk assessment, and direct further targets for therapy.

Chapter 3 describes the results of a meta-analysis investigating the impact of thrombus aspiration during primary PCI on long-term clinical outcome. In this pooled Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data (ATTEMPT) study, long-term clinical outcome was calculated on individual patient data of 11 studies investigating aspiration devices with a total of 2686 patients. Allocation to thrombus aspiration was associated with a 29% lower rate of the primary endpoint of all-cause mortality, next to lower rates of major adverse cardiac events and mortality plus reinfarction during a median follow-up of 1 year. When stratified into type of device, the clinical benefit was present only in the patients randomized to manual thrombus aspiration and not in non-manual devices. In an additional subgroup analysis, the benefit was only seen in those receiving glycoprotein (GP) IIb/IIIa inhibitors as well, suggesting that there is a synergistic effect of mechanical and pharmacological intervention. While meta-analyses are limited by heterogeneous

inclusion criteria, devices, and definitions of the individual studies, in the absence of studies powered on clinical endpoints, this study adds to the growing evidence in favor of manual thrombus aspiration.

Chapter 4 is a book chapter, which reviews the role of the available devices for extraction of atherothrombotic material. These devices include [1] distal protection devices, which place an occlusive balloon or a non-occlusive filter distally to the infarct-related lesion,[2] non-manual thrombus aspiration devices, which extract the atherothrombotic material after fragmentation or with a mechanical pump, and [3] manual thrombus aspiration catheters, which allow manual suction of atherothrombotic material with a syringe. There is increasing evidence that application of manual thrombus aspiration is able to improve myocardial reperfusion during primary PCI and that it is associated with improved long-term survival. Based on published randomized studies and meta-analyses, it seems reasonable to attempt manual aspiration in all patients presenting with STEMI. However, there is no evidence to support the routine use of non-manual thrombus aspiration devices or distal protection devices during primary PCI.

Chapter 5 investigates whether angiographically observed thrombus burden was associated with angiographic and electrocardiographic outcome variables and 1-year all-cause mortality in 2969 consecutive STEMI patients treated with primary PCI with or without manual thrombus aspiration. A larger thrombus burden was associated with impaired myocardial perfusion as measured by myocardial blush grade and ST-segment resolution and with higher 1-year mortality. Furthermore, application of thrombus aspiration as the first step during primary PCI was related to improved myocardial reperfusion and lower 1-year mortality in both patients with large and small thrombus burden. These results suggest that a strategy of routine manual thrombus aspiration is justified in patients with STEMI.

Part 2 I Intracoronary antiplatelet therapy

Part 2 discusses the potential of intracoronary administration of abciximab on improving myocardial reperfusion and clinical outcome.

During PCI, mechanical reperfusion therapy alone is limited by its inability to prevent microvascular obstruction by atherothrombotic material that has occurred before PCI or has been induced by mechanical manipulation during primary PCI. Adjunctive pharmacological antiplatelet therapy is therefore frequently used in clinical practice, including the GP IIb/IIIa inhibitor abciximab. While platelet inhibition with abciximab improves myocardial reperfusion and is associated with improved clinical outcomes, experimental studies have suggested that higher local abciximab concentrations may have additional antiplatelet and antithrombotic effects. Based on recent

findings from small-scale studies suggesting beneficial effects of direct intracoronary over intravenous administration of abciximab, we investigated whether intracoronary bolus administration of abciximab is more effective than intravenous bolus administration in improving myocardial perfusion in a larger number of patients with STEMI. Hereto, we designed and initiated the Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction (CICERO) trial (**Chapter 6**). In this single-center, prospective, randomized open-label trial with blinded evaluation of endpoints, 534 STEMI patients were randomized within 12 hours of symptom onset to either an intracoronary or an intravenous bolus of weight-adjusted abciximab during primary PCI. Patients were pretreated with aspirin, heparin, and high-dose clopidogrel. Manual thrombus aspiration was performed in almost all patients.

The results of this study are presented in **Chapter 7**. Intracoronary administration of abciximab, compared with intravenous administration, did not improve the primary endpoint of this trial, which was restored myocardial reperfusion, defined as >70% ST-segment. In accordance, intracoronary administration did not improve the secondary electrocardiographic endpoint of residual ST-segment deviation. However, intracoronary administration was associated with a significantly higher rate of restored myocardial reperfusion as assessed by myocardial blush grade compared to intravenous administration. Furthermore, enzymatic infarct size was smaller in the intracoronary group, although infarct size was only evaluable in nearly half of patients. With regard to safety, bleeding complications occurred at similar frequencies between both treatment groups. All-cause mortality and MACE at 30 days occurred at low and similar frequencies between the both groups. This trial could therefore not fully confirm the beneficial effects suggested by previous smaller studies but did not exclude any clinically relevant potential benefits of intracoronary administration.

Part 3 I Quantitative assessment of myocardial reperfusion

Part 3 evaluates the application of the Quantitative Blush Evaluator (QuBE), a novel open source computer program to quantify myocardial perfusion, on coronary angiograms after primary PCI. In a previous study, the QuBE was applicable in a large majority of coronary angiograms performed at our center in patients with STEMI and correlated with several outcome variables. In **Chapter 8**, we investigated whether quantitative assessment of myocardial reperfusion with the QuBE is feasible and applicable after primary PCI on coronary angiograms from external catheterization laboratories. In 284 STEMI patients who were enrolled in the two-centre, randomized PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PRE-

PARE) trial, a QuBE score could be measured in 81% of patients. Concurrent with the previous study, a higher QuBE score was associated with improved conventional measures of epicardial and myocardial reperfusion, including visually assessed myocardial blush grade and ST-segment resolution immediately after PCI, and a smaller enzymatic infarct size. In **Chapter 9**, we determined whether the QuBE score was related to intermediate functional outcomes. In the patients from the PREPARE ancillary cardiac magnetic resonance (CMR) substudy, a higher QuBE score was associated with improved functional and contrast-enhanced CMR outcomes, including a higher left ventricular (LV) ejection fraction and smaller infarct size. When corrected for other determinants of LV ejection fraction, the QuBE score was still independently associated.

Other investigators have also reported that the QuBE score was strongly associated with infarct size and microvascular obstruction on CMR performed early after STEMI[1]. These findings suggest that the QuBE program may aid in early identification of high-risk patients who benefit most from adjunctive therapies during and after PCI. Since the QuBE is a readily available computer program that only requires an angiogram recorded immediately after PCI, it can be applied in the catheterization laboratory by anyone with knowledge of the coronary anatomy and usually requires no longer than a minute to measure in contrast to more sophisticated techniques, such as CMR, which are technically demanding, time-consuming, and expensive. QuBE may not replace such technically more advanced techniques, but may serve as a practical angiographic marker of myocardial reperfusion immediately after PCI.

Future perspectives

In the last few years, additional studies and meta-analyses have shed more light on the intracoronary therapies described in this thesis. For thrombus aspiration, several additional meta-analyses have confirmed that manual thrombus aspiration results in improved myocardial perfusion and fewer adverse events in patients with STEMI[2-5]. In the most recent meta-analysis including 5534 patients from 25 randomized trials[2], manual thrombus aspiration improved myocardial perfusion and, at 6 months' follow up, was associated with a 29% reduction in all-cause mortality and 24% reduction in major adverse cardiac events. However, this benefit was not seen in non-manual thrombus aspiration, in line with previous observations, while there was even a trend towards a higher incidence of stroke, which was not observed in the manual aspiration studies. Two large multi-center trials have been initiated that are powered on clinical endpoints. In the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial, of which the results are presented at the European Society of Cardiology Congress in September 2013, 7243 patients with STEMI from three Scandinavian countries were

randomized to either manual thrombus aspiration or conventional PCI and followed for the primary endpoint of all-cause mortality at 30 days[6]. The international routine aspiration ThrOmbecTomy with PCI versus PCI ALone (TOTAL) study, with a planned inclusion of 6000 patients with STEMI, aims to determine whether manual thrombus aspiration reduces the primary composite endpoint of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or new or worsening heart failure at a longer duration of 6 months. Currently, there is solid evidence that manual thrombus aspiration improves myocardial perfusion and is associated with a clinically relevant reduction in clinical events. In the largest randomized trial published so far in 1071 patients[7], manual thrombus aspiration resulted in an approximately 30% improvement in markers of myocardial reperfusion, consistent with the effect size observed in meta-analyses. At 1 year, this improvement translated into a considerably lower mortality rate in the aspiration group than in the conventional PCI group[8]. Although the effect size may be surprisingly large and the trial was not powered to detect a difference in clinical outcome, numerous reports have consistently demonstrated that myocardial perfusion such as measured by myocardial blush grade is strongly related to short and long term clinical events[7-9]. For example, data from INFUSE-AMI show that 30-day mortality was 1.7% in those with myocardial blush grade 2/3 versus 8.3% in those with myocardial blush grade 0/1 after primary PCI[9]. Given this numerically relevant difference in clinical events between patients with successful versus impaired myocardial perfusion, a clinically meaningful improvement in myocardial perfusion of approximately 30% is expected to result into at least some clinical benefit.

For intracoronary administration of abciximab, several meta-analyses have suggested improvement in clinical endpoints in addition to improvement in myocardial perfusion[10-13]. In a meta-analysis including 4 randomized trials with a total of 1148 patients[10], intracoronary abciximab was associated with a 56% reduction in early mortality. However, this clinical effect could not be confirmed in the most recent and largest trial on intracoronary versus intravenous administration of abciximab to date. The Abciximab Intracoronary versus intravenously Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) trial randomized 2065 patients with STEMI from several PCI centers in Germany who were treated with dual antiplatelet therapy to either intracoronary or intravenous administration of abciximab with subsequent 12-hour infusion[14]. There was no difference on the primary composite endpoint of all-cause mortality, reinfarction, or new congestive heart failure within 90 days. In addition, there were no differences in early ST-segment resolution. While fewer patients in the intracoronary group developed new heart failure within 90 days, this effect was not statistically significant at 1 year[15]. The international multi-center study INFUSE-AMI (Intracoronary

Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) tested whether intracoronary abciximab, manual thrombus aspiration, or the combination, reduced infarct size in 452 patients with STEMI presenting within 4 hours with an anterior infarction and who were treated with bivalirudin anticoagulation[16]. Abciximab was delivered to the site of the infarct-related lesion through a novel drug delivery catheter, the Clearway RX, and tested against placebo. After 30 days, a significant but modest reduction in infarct size was observed in the intracoronary abciximab versus no intracoronary abciximab group but not in the thrombus aspiration versus no aspiration group. No differences were observed in early indicators of myocardial reperfusion (myocardial blush grade and ST-segment resolution) or clinical outcomes at 30 days. With respect to safety, both studies did not show more bleeding complications in patients treated with intracoronary administration of abciximab. Therefore, intracoronary abciximab appears safe but its efficacy is still unproven. Several issues are open for discussion.

Have we facilitated optimal conditions in these studies? For intracoronary administration of abciximab, small-sized studies suggest that a dedicated perfusion catheter such as the one used in INFUSE-AMI could be a better option to deliver abciximab. This catheter achieves high local drug concentrations at the infarct-related lesion by reducing loss of agent in the aorta and washout by coronary flow. When compared to intracoronary administration through the guiding catheter, infusion through the Clearway catheter resulted in a reduction of thrombus burden as assessed by optical coherence tomography and improvement of myocardial perfusion[17]. Such dedicated perfusion catheters could be promising to achieve high local concentrations of pharmacological agents at the infarct-related lesion in general[18].

There is also indirect evidence from the ATTEMPT and INFUSE-AMI trials suggesting an additional effect of thrombus aspiration and abciximab. This hypothesis is currently tested in a mechanistic study, which aims to determine whether intracoronary abciximab with a drug delivery catheter, manual thrombus aspiration, or both, results in reduction of intra-stent thrombus as assessed with optical coherence tomography after stent implantation in 128 patients with STEMI presenting with angiographically visible thrombus[19].

It was surprising that manual aspiration did not result in reduction of infarct size in INFUSE-AMI. This brings into question how effective aspiration was in patients treated with thrombus aspiration, as no data are available on what was retrieved from the infarct-related site. For a mechanical study, effective aspiration using good technique and operator experience are important features that determine successful aspiration. This could also be one of the reasons that attempts with non-manual aspiration

devices have not been very successful, as they are more complex to operate and take longer to become experienced with.

Have we selected the right patients? It has been suggested that thrombus aspiration, intracoronary abciximab, or both, may be especially beneficial in certain high-risk patients, such as those with high thrombus burden. To date, there are no randomized studies investigating routine versus selective thrombus aspiration. For intracoronary abciximab, it is not clear, if there is an actual effect, which patients benefit most from its application. For intravenous abciximab, there are data suggesting that abciximab is mainly beneficial in high-risk patients[20]. The neutral results of AIDA STEMI could be explained by inclusion of a large number of low-risk patients. Future studies in general should focus on high-risk patients, such as those with high thrombus burden or with poor myocardial perfusion after primary PCI as they are most likely to develop clinical events and benefit most from additional therapies.

Were studies adequately powered? From studies such as AIDA STEMI we can learn that the actual primary endpoint rate (7.6% in the control group) was much lower than the expected rate used for power analysis (12%). Considering that an even larger number of patients would then have been required, it is possible that a significant difference between groups was not detected with this sample size. It will be interesting to see whether the TASTE and TOTAL studies are adequately powered. Furthermore, AIDA STEMI was powered on a 33% reduction in clinical events, which is a highly ambitious expectation for a trial comparing two routes of administration of the same drug. In general, it is not expected that with contemporary treatment of patients with STEMI, any treatment would have such a large effect size.

Do we always need mortality as the endpoint? It can be questioned whether mortality is always the ultimate endpoint. With current mortality rates of as low as 3 – 5% at 30 days in STEMI trials, it is not realistic to always demand trials powered on a clinical endpoint. This is especially true as investigator-driven studies on clinical endpoints are not only difficult to initiate as they involve a very large number of patients but also as they are difficult to fund. Instead, a surrogate endpoint such as myocardial perfusion seems to be the only alternative to a hard clinical endpoint. Moreover, trials on a surrogate endpoint are very valuable for proof-of concept studies, when the question whether there is some effect of a certain therapy can be evaluated without including a large number of patients.

Is there a true effect of intracoronary therapy? Novel mechanical and pharmacological therapies have changed the landscape of treatment in STEMI patients rapidly. It is possible that in STEMI patients who are treated with dual antiplatelet therapy with newer and more potent oral antiplatelet agents, such as prasugrel and ticagrelor, the

effects are diminished. Or it may be that the anti-platelet, anti-thrombotic, and anti-inflammatory effects of abciximab observed in experimental studies are too small to translate into relevant clinical effects. Nevertheless, it seems biologically plausible to treat intracoronary thrombus, the cause of coronary occlusion leading to STEMI, with locally acting devices and high local concentrations of a therapeutic agent. Intracoronary administration of diverse agents continues to be investigated, of which some are promising[18,21].

In conclusion, there is convincing evidence that manual thrombus aspiration results in improved myocardial perfusion and reduced clinical events in patients with STEMI undergoing primary PCI. It is reasonable to attempt manual thrombus aspiration as the first step during primary PCI in all patients with STEMI based on the current literature on effectiveness, safety, and clinical applicability. For intracoronary administration of abciximab, the current evidence is conflicting. However, intracoronary administration is safe and does not result in increased bleeding complications compared to intravenous administration. Therefore, considering the theoretical advantages of intracoronary administration, this route can be considered and may be promising with newer delivery catheters that can achieve higher local drug concentrations.

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NEDERLANDSE SAMENVATTING

Hartziekten van de kransslagvaten vormen een van de belangrijkste oorzaken van sterfte in de Westerse wereld. Het acuut hartinfarct draagt hier in grote mate aan bij, waarbij geschat wordt dat circa 33.000 personen jaarlijks in Nederland een hartinfarct doormaken. Een acuut hartinfarct wordt veroorzaakt door ruptuur van atherosclerotisch weefsel in een kransslagvat. Dit veroorzaakt op zijn beurt een cascade van reacties met als gevolg de vorming van een bloedstolsel. Bij het ST-segment elevatie myocardinfarct (STEMI, genoemd naar specifieke afwijkingen op het elektrocardiogram) wordt hierdoor uiteindelijk het gehele kransslagvat afgesloten. Als deze afsluiting te lang aanwezig is, zal het hartspierweefsel, dat van bloedvoorziening uit dit vat afhankelijk is, onherstelbaar beschadigd raken. Vroegtijdige behandeling is daarom van essentieel belang. In de acute behandeling van het STEMI zijn de afgelopen jaren grote vooruitgangen geboekt, vooral door het gebruik van dotteren, ook wel primaire percutane coronaire interventie (PCI) genoemd, en aanvullende medicatie tijdens deze procedure. Toch is in een substantieel aantal patiënten de doorbloeding van het hartspierweefsel na behandeling niet hersteld, wat gepaard gaat met een verminderde hartfunctie en hogere sterfte. In dit promotieonderzoek werden twee veelbelovende aanvullende behandelingen onderzocht die direct in het aangedane kransslagvat worden toegepast tijdens PCI bij patiënten met een STEMI en daarnaast een nieuwe manier om de doorbloeding van het hartspierweefsel na de acute behandeling te meten.

In het eerste deel van dit proefschrift wordt trombusaspiratie, oftewel het opzuigen van het bloedstolsel in het aangedane bloedvat, onderzocht. Met deze techniek wordt de afsluiting in het aangedane kransslagvat niet op de conventionele manier met een ballon opgerekt om de bloedvoorziening te herstellen, maar wordt het stolsel dat de vernauwing veroorzaakt opgezogen. In **hoofdstuk 2** wordt een publicatie becommentarieerd, die een relatie toont tussen de 'leeftijd' van het geaspireerde stolsel bij patiënten met een STEMI en hun overleving op langere termijn. De resultaten van studies naar karakteristieken van trombus kunnen in de toekomst nieuwe inzichten geven in de pathofysiologie van het acuut myocardinfarct en bijdragen aan klinische risicostratificatie en nieuwe behandelingen. **Hoofdstuk 3** beschrijft de resultaten van een synthese van gerandomiseerde studies, een meta-analyse, naar de effecten van trombusaspiratie tijdens primaire PCI op de lange termijn. Voor deze studie werden individuele patiëntdata gebruikt van 11 gerandomiseerde studies die trombusaspiratie onderzochten met in totaal 2686 patiënten. In de groep patiënten met trombusaspiratie werd onder andere een 29% lager mortaliteitscijfer gevonden vergeleken met de groep zonder trombusaspiratie bij een mediane follow-up van 1 jaar. Wanneer de methode van aspiratie

werd vergeleken, was het klinische voordeel enkel aanwezig in de patiënten die waren gerandomiseerd naar manuele trombusaspiratie, waarbij het opzuigen met de hand wordt verricht via een spuit. **Hoofdstuk 4** geeft een beschouwing van diverse aanwezige methoden om bij patiënten met een STEMI het bloedstolsel te verwijderen. De beschikbare studies die worden besproken suggereren dat vooral manuele trombusaspiratie de doorbloeding van het hartspierweefsel verbetert en de langetermijnoverleving kan verbeteren. In **hoofdstuk 5** werd onderzocht of de uitgebreidheid van het bloedstolsel dat zichtbaar is tijdens primaire PCI samenhangt met uitkomsten in doorbloeding van het hartspierweefsel na primaire PCI en op overleving in 2969 patiënten met STEMI. De aanwezigheid van meer stolsel was geassocieerd met gestoorde doorbloeding van het hartspierweefsel en met een hogere 1-jaarsmortaliteit. Bovendien werd in patiënten die met trombusaspiratie werden behandeld een betere doorbloeding van het hartspierweefsel en een lagere 1-jaarsmortaliteit gevonden, zowel in patiënten bij wie veel als bij wie weinig stolsel werd gezien tijdens primaire PCI. De resultaten van deze hoofdstukken dragen bij aan het bewijs ten gunste van manuele trombusaspiratie en suggereren dat routinematig gebruik van trombusaspiratie bij patiënten met een STEMI gerechtvaardigd is.

Tijdens primaire PCI wordt het gebruik van mechanische therapie, zoals trombusaspiratie, aangevuld met medicamenteuze therapie om de doorbloeding van het bloedvat en hartspierweefsel te bewerkstelligen. Een van de medicijnen die vaak wordt gebruikt tijdens primaire PCI is abciximab, een middel dat een vroeg onderdeel van de stolselvorming remt. Het tweede deel van dit proefschrift richt zich op een specifieke toediening van dit middel direct in het aangedane bloedvat. In experimentele studies wordt gesuggereerd dat hogere lokale concentraties van abciximab leiden tot aanvullende klinische voordelen. In kleine studies bij patiënten lijkt directe toediening van abciximab in het aangedane bloedvat (in plaats van op de gebruikelijke manier door een infuus) te leiden tot onder andere verbeterde doorbloeding van het hartspierweefsel. Gebaseerd op deze veelbelovende bevindingen werd in dit promotieonderzoek onderzocht of deze intracoronaire manier van toediening effectiever is dan toediening door een infuus op het verbeteren van de doorbloeding van het hartspierweefsel in een groter aantal patiënten. De opzet van deze gerandomiseerde studie wordt besproken in **hoofdstuk 6** en de resultaten in **hoofdstuk 7**. In deze studie bij 534 patiënten was het bewijs voor de effectiviteit tegenstrijdig, omdat intracoronaire toediening van abciximab niet tot verbeterde doorbloeding van het hartspierweefsel leidde op enkele uitkomstparameters. De resultaten suggereerden echter ook dat er in de intracoronaire groep wel een verschil was in andere uitkomstparameters van doorbloeding en dat er een positief effect was op de omvang van het infarct. Deze studie kon daarom niet de

positieve effecten bevestigen van eerdere kleinere studies, maar ook niet mogelijke relevante voordelen van deze manier van toediening uitsluiten.

In het derde deel wordt de Quantitative Blush Evaluator (QuBE) geëvalueerd, een vrij toegankelijk computerprogramma, dat op een relatief simpele manier de doorbloeding van het hartspierweefsel kan meten na primaire PCI. Uit een eerdere studie bleek dat de QuBE toepasbaar was in een merendeel van patiënten met STEMI en samenhang vertoonde met diverse uitkomstparameters. In **hoofdstuk 8** werd onderzocht of dit ook gold voor patiënten uit een extern hartkatheterisatiecentrum. In 284 patiënten uit een gerandomiseerde studie kon een QuBE-score inderdaad bij 81% worden beoordeeld en werd de samenhang met diverse uitkomstparameters van doorbloeding van het hartspierweefsel bevestigd. In **hoofdstuk 9** werd bovendien aangetoond dat de QuBE-score ook samenhangt met functionele uitkomsten na 4 tot 6 maanden na een STEMI. Een hogere QuBE-score was gerelateerd aan een verbeterde hartspierfunctie en een kleinere omvang van het infarct. Deze bevindingen suggereren dat het QuBE-programma ondersteuning biedt in het tijdig identificeren van hoog-risico patiënten met een suboptimale doorbloeding van het hartspierweefsel die het meest baat kunnen hebben van aanvullende behandelingen tijdens en na PCI.

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CURRICULUM VITAE

Youlan Gu was born on 29 March 1984 in Shanghai, China. After relocating to Groningen, the Netherlands, in 1989, she finished primary school at the Groningse Schoolvereniging (1989 – 1996) and secondary school at the Willem Lodewijk Gymnasium (1996 – 2002, cum laude). In 2001, she obtained the second prize at an international contest translating from Latin and commenting on the work of Roman lawyer, politician, and philosopher Marcus Tullius Cicero. After a start in both medicine and international and European law at the University of Groningen, she continued in medicine. Her interest in scientific research started with the Scientific Research Week of the Junior Scientific Masterclass. During her studies, she commenced on several research projects at the department of cardiology of the University Medical Center Groningen (UMCG), University of Groningen. After graduating in medicine and receiving her medical doctor (MD) degree (2002 – 2008, cum laude for propaedeutic, doctoraal, and MD examinations), she continued her scientific research, which resulted in this thesis under supervision of her promotor prof.dr. F. Kuipers and copromotores dr. B.J.G.L. de Smet and dr. I.C.C. van der Horst. In October 2011, she started her cardiology specialty training at the UMCG (supervisor prof.dr. M.P. van den Berg / dr. P.P. van Geel) with a two-year core medical training at the department of internal medicine (supervisor prof.dr. R.O.B. Gans).

She has held positions in several committees at the Faculty of Medicine in the past, including as vice-chair of the Programme Committee Medicine and Secretary of the International Student Congress of Medical Sciences (ISCOMS). She currently serves as a board member of the Assistentenvereniging UMCG. In her free time, she enjoys singing and dancing (salsa).