Platelet glycoprotein IIb/IIIa receptor blockers in clinical practice

ISBN 90-77017-089

Layout and cover design by Anna Bosselaar (anna@bonmot.nl) and Jorien Ronner-Schook

Printed by Optima Grafische Communicatie, Rotterdam

Platelet glycoprotein IIb/IIIa receptor blockers in clinical practice

Thrombocyten glycoproteïne IIb/IIIa receptor blokkers
in de klinische praktijk

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.ir. J.H. van Bemmel
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 31 oktober 2001 om 11.45 uur

door

Eelko Ronner

geboren te Leeuwarden.

Promotiecommissie

Promotor	:	Prof.dr. M.L. Simoons
Overige leden	:	Prof.dr. F.W.H.M. Bär Prof.dr. B. Löwenberg Prof.dr. J.R.T.C. Roelandt
Co-promotor	:	Dr. E. Boersma

Financial support by the Netherlands Heart Foundation and Cardialysis for the publication of this thesis is gratefully acknowledged.

Aan Jorien,
aan Lucas en aan Arthur.

Contents

1
Introduction

1.1 General introduction 3
1.2 IIb/IIIa receptor antagonists for failed rescue angioplasty 9

2
Acute coronary syndromes without persistent ST-segment elevation

2.1 Platelet glycoprotein IIb/IIIa receptor antagonists, an asset for treatment of unstable coronary syndromes and coronary intervention 15
2.2 Safety of abciximab drip-and-ship regimen while transferring unstable angina patients for PTCA by ground transportation 35
2.3 Patients with acute coronary syndromes without persistent ST-elevation undergoing percutaneous coronary intervention benefit most of early intervention with protection by a glycoprotein IIb/IIIa receptor blocker 45
2.4 Early angioplasty in acute coronary syndromes without persistent ST-elevation improves outcome, but increases need for 6 month repeat revascularization. An analysis of the PURSUIT-trial 59

3
Acute coronary syndromes with persistent ST-segment elevation

3.1 The use of platelet glycoprotein IIb/IIIa receptor antagonists during the acute phase of myocardial infarction 75
3.2 Safety and efficacy of eptifibatide versus placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction; a phase II dose escalation, randomized, double-blind study 83
3.3 Platelet GP IIb/IIIa receptor blockers for failed thrombolysis in acute myocardial infarction, alone or as adjunct to other rescue therapies. A single center retrospective analysis of 548 consecutive patients with acute myocardial infarction 95

4

Conclusion

4.1 Platelet GP IIb/IIIa receptor blockers in clinical practice 113
4.2 Samenvatting 139

Appendix: Trial acronyms 147

Dankwoord 149

Curriculum vitae 152

1 Introduction

1.1

General introduction

In this thesis, platelet glycoprotein (GP) IIb/IIIa receptor blockers are discussed for use in patients with acute coronary syndromes without persistent ST-segment elevation* (Chapter 2) but also for use in patients with overt myocardial infarction (Chapter 3). Furthermore, the role of intervention, and more specifically, the role of timing of percutaneous coronary intervention is described in patients with acute coronary syndromes without persistent ST-segment elevation incorporating use of platelet GP IIb/IIIa receptor antagonists.

Intracoronary thrombus (blood clot) formation can lead to myocardial infarction (MI) and death. Platelet GP receptor IIb/IIIa receptor blockers block the formation of thrombus in coronary arteries by blocking the platelet GP IIb/IIIa receptor. This receptor can be activated by numerous stimuli. Only specific stimuli are antagonized by other agents, but not all. Only platelet GP receptor IIb/IIIa receptor blockers block the receptor directly and thereby block the final common pathway of thrombocyte aggregation. The agents are therefore considered the most potent agents to prevent thrombus formation and have proven to reduce death and MI in various clinical settings (chapter 2.1, 4.1).

Convincing data are available to demonstrate the success of platelet GP IIb/IIIa receptor blockers, most notably in patients undergoing percutaneous coronary intervention. It was December 21st 1995 that the CAPTURE[1] study was stopped as a result of positive findings of the Safety and Efficacy Monitoring Committee. The EPILOG[2] and ESPRIT[3] trials were halted as well[3], due to a clear positive effect in the treated group. Moreover, the EPIC[4] data published in the New England Journal of Medicine in 1994 demonstrated impressive benefit of abciximab (a platelet GP IIb/IIIa receptor blocker) versus placebo[5]. CAPTURE, EPIC and EPILOG compared a platelet GP IIb/IIIa receptor blocker (abciximab) versus placebo in patients undergoing percutaneous coronary intervention (chapter 2.1, 4.1). In ESPRIT eptifibatide was compared with placebo in patients undergoing percutaneous coronary intervention.

In a review article (Chapter 2.1) the trials mentioned above, and other large randomized trials on platelet GP IIb/IIIa receptor blockers are discussed extensively. After this review-article of clinical trials, chapter 2.2 describes practical use of platelet GP IIb/IIIa receptor blockers in a non-interventional, non-trial setting in 168 patients with acute coronary syndromes without persistent ST-segment elevation. All patients on platelet GP IIb/IIIa receptor blockers are transferred for percutaneous coronary intervention elsewhere, and safety and efficacy is comparable to results from clinical trials.

* Unstable angina is now often referred to as "acute coronary syndromes without persistent ST-segment elevation".

In (especially high-risk) patients with acute coronary syndromes without persistent ST-segment elevation it is often advised to perform percutaneous coronary intervention. When to perform this percutaneous coronary intervention, and how this is influenced by platelet GP IIb/IIIa receptor blockers is addressed in the chapters 2.3 and 2.4. This issue of timing of intervention was explored using the PURSUIT database[6]. In the PURSUIT trial 9461 patients were enrolled with acute coronary syndromes without persistent ST-segment elevation. Interestingly, within the group of patients treated with percutaneous coronary intervention, large differences in outcome were noted with respect to timing of intervention.

Early intervention especially demonstrated to increase rates of procedural infarction and repeat revascularization. In chapter 2.3 we demonstrated that procedural risk of death or myocardial infarction is reduced considerably with platelet GP IIb/IIIa receptor blockers, to the point that acute intervention is associated with near similar peri-procedural events than later intervention. Later intervention however is associated with pre-procedural events. In chapter 2.4 the occurrence of repeat revascularization is compared in patients treated, acutely and later, with percutaneous coronary intervention. We observed a reduction of repeat revascularization in patients undergoing later percutaneous coronary intervention compared to those undergoing early intervention.

There seems to be a trade-off in patients with acute coronary syndromes without persistent ST-segment elevation treated with platelet GP IIb/IIIa receptor blockers with respect to timing of percutaneous coronary intervention. Early intervention (with these agents!) prevents infarction but restenosis increases. We hypothesize that in patients at high risk for death or MI early intervention under protection of a platelet GP IIb/IIIa receptor blocker is optimal treatment, in patients at lower risk however, intervention can best be withheld or deferred to reduce the need for repeat revascularization. The demonstrated retrospective findings with respect to timing of intervention are of interest for clinical decision making, randomized trials are needed to verify the findings.

The second part of the thesis addresses the role for platelet GP IIb/IIIa receptor blockers in patients with acute myocardial infarction (Chapter 3). The position of platelet GP IIb/IIIa receptor blockers in adjunct to current treatment of infarction is explored. The use of these agents when thrombolysis fails is described in chapter 2.3 and 1.2.

March 1996 a patient with acute infarction received thrombolysis in the Onze Lieve Vrouwe Gasthuis in Amsterdam and was catheterized ninety minutes later (according to a trial protocol). The catheterization demonstrated a large intracoronary thrombus and hampered coronary flow. Because severe chest pain and low blood pressure persisted despite thrombolytic therapy, rescue balloon angioplasty was performed to

enhance coronary perfusion. The feared complication of no-reflow developed: the vessel seemed patent, but not functional. Most of small distal branches were occluded by thrombotic debris. The patient seemed refractory to all treatment strategies (thrombolysis, balloon angioplasty and aortic balloon counterpulsation) and lost pulse; lost blood pressure and lost consciousness despite our extensive efforts. As a last resort, abciximab, the platelet GP IIb/IIIa antagonist from the EPIC and CAPTURE trial was administered, after which flow restored in approximately ten minutes. Our patient recovered, although large haematomas developed in the groins where catheters had been inserted. The infarction was limited and the haematomas recovered completely (Chapter 1.2, 3.3). We highly appreciate the inclusion of this case report in the well-established textbook, "Heart Disease" (Braunwald, Sixth edition).

Summer 1997 a trial commenced combining full dose thrombolysis (streptokinase) with intravenous platelet GP IIb/IIIa receptor blockers in patients with acute myocardial infarction. Unfortunately, serious bleeding risk was observed (Chapter 3.2). The most recent combinations of these two agents seems very promising, although the dosage regimens are revised, and switched to reduced (half) dose thrombolytic therapy in combination with (full dose) platelet GP IIb/IIIa receptor antagonists.

The use of these agents in acute myocardial infarction after thrombolysis fails, either alone, or in adjunct to rescue percutaneous intervention is explored in chapter 3.1. This chapter describes the safety of platelet GP IIb/IIIa receptor blockers after failed thrombolysis for acute myocardial infarction in 139 patients with failed thrombolysis in a single center setting.

Chapter 4.1, "Conclusion" describes the current applications of platelet GP IIb/IIIa receptor blockers, emphasizing results from most recent large clinical trials and findings from this thesis.

This thesis addresses the role of platelet GP IIb/IIIa receptor blockers in clinical cardiology. It aims

a) to identify the various indications for the agents in clinical cardiology;
b) to provide information on safe use and specific risks in various settings;
c) to describe the effect of timing of angioplasty in the era of platelet GP IIb/IIIa receptor blockers in patients with acute coronary syndromes without persistent ST-segment elevation.

References

1. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997; 349: 1429-1435.

2. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Eng J Med 1997; 336: 1689-1696.
3. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000; 356 : 2037-2044.
4. Ferguson JJ 3rd. EPILOG and CAPTURE trials halted because of positive interim results. Circulation 1996; 93: 637.
5. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
6. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.

1.2

IIb/IIIa receptor antagonists for failed rescue angioplasty

Eelko Ronner, L. Ron van der Wieken, Ton S. Slagboom, Gert-Jan Laarman and Ferdinand Kiemeij

Onze Lieve Vrouwe Gasthuis
Amsterdam
The Netherlands

Circulation 2000;101:214-215

Braunwald, *Heart Disease,* 6th ed., Harcourt Publishers Ltd 2001, ISBN 0808922580, chapter 'Myocardial Infarction'

A 46-year-old woman presented with three hours of severe chest pain, sweating, and nausea. The cardiac history included a small anterior wall infarction 8 years earlier, a slightly impaired left ventricle, and a successful balloon angioplasty of the left anterior descending and right coronary artery 11 months before presentation. Systolic blood pressure was 85 mm Hg, but further physical examination was normal. The electrocardiogram demonstrated an acute inferior wall infarction with extension to the right precordial leads without rhythm or conduction abnormalities.

The patient was included in the HIT-4 trial in which heparin was compared with hirudin in combination with streptokinase for acute myocardial infarction.

Treatment per protocol was started with streptokinase 1.5 million IU in 60 minutes, aspirin 300 mg, and heparin 12.500 IU SC. No signs of reperfusion were seen; sinus bradycardia developed, blood pressure was unchanged and diaphoresis was noted. Diuresis was absent.

Thirty minutes after streptokinase infusion, protocol angiography revealed a dominant right coronary artery with TIMI 2 flow (Thrombolysis in Myocardial Infarction flow grade 2 denotes partial perfusion) and a thrombus measuring ten millimeters in length (Figure 1). Because of persisting pain, hypotension, and bradycardia with hampered coronary flow, it was decided to perform balloon angioplasty.

After balloon inflation, cardiogenic shock worsened, despite intra aortic balloon pumping and inotropics. Total AV - block developed and shortly thereafter, ventricular fibrillation. Angiography showed that the thrombo-embolic mass was dislodged and the thrombotic mass occluded the distal artery, not amenable to angioplasty (Figure 2). Intracoronary verapamil gave no improvement.

As bailout, abciximab, a monoclonal platelet glycoprotein IIb/IIIa receptor blocker

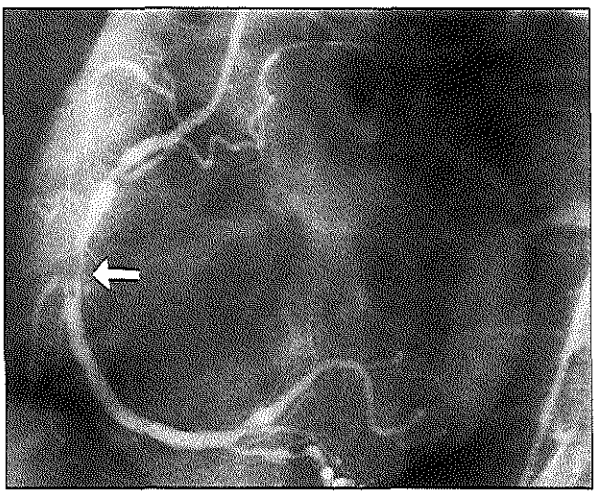


Figure 1. Before balloon angioplasty. Acute inferior myocardial infarction with hampered flow and cardiogenic shock. A thrombus is seen in the middle of the right coronary artery (arrow).

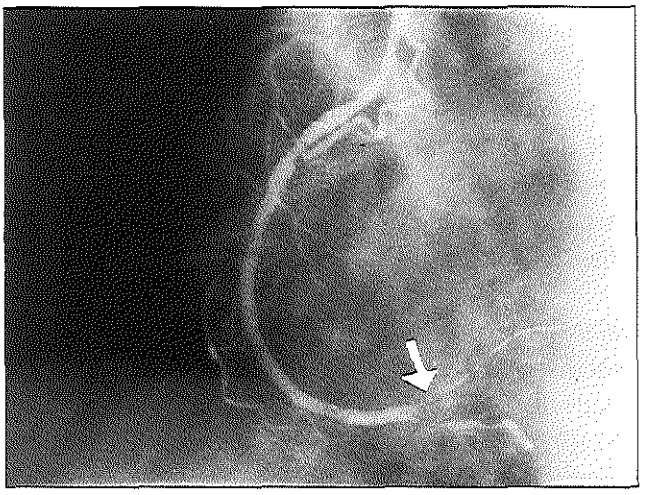


Figure 2. After balloon angioplasty, no reflow. Although the proximal coronary artery is patent, the smaller size distal vessels are occluded (arrow).

was started, with a 0.25 mg/kg bolus and a 10 μg/min infusion. In about 10 minutes TIMI 3 flow (complete perfusion) was restored (Figure 3), and pain subsided seven hours after chest pain had begun.

Bleeding developed in the groins. Heparin infusion was therefore stopped, but abciximab was given continuously up to 24 hours after balloon angioplasty. Cardiac recovery was uneventful. The myocardial fraction of creatinine kinase (CK-Mb) peaked at 90 U/L, and echocardiography showed a global good left ventricular function with a hypokinetic inferior wall. The massive left and right leg hematomas recovered without intervention or clinical sequelae. Hemoglobin decreased to 7.4 g/dL (4.6 mmol/L), a decrease of 6.4 g/dL (4.0 mmol/L). Seven units of packed cells were given. At 1-year follow-up, our patient is in good health without cardiac complaints.

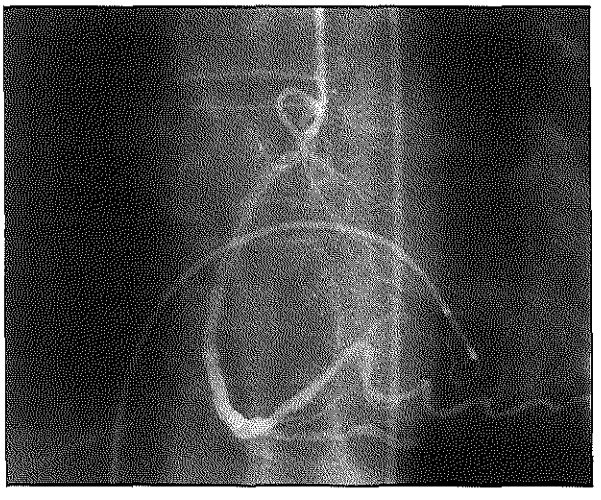


Figure 3. Approximately 10 minutes after abciximab administration (0.25 mg/kg bolus and a 10 μg/min infusion). Coronary artery flow is restored to TIMI 3 flow.

2 Acute coronary syndromes without persistent ST-segment elevation

2.1

Platelet glycoprotein IIb/IIIa receptor antagonists, an asset for treatment of unstable coronary syndromes and coronary intervention

Eelko Ronner[1], Yaroslav Dykun[2], Marcel J.B.M. van den Brand[3], L. Ron van der Wieken[1], Maarten L. Simoons[3]

[1] Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[2] Research Institute of Therapy, Kharkov, Ukraine
[3] Thoraxcenter, Rotterdam, The Netherlands

European Heart Journal 1998;19:1608-1614

Introduction

Platelet aggregation, at the site of an atherosclerotic plaque in the coronary arteries has been recognized as a crucial step in the pathogenesis of unstable angina and myocardial infarction. As part of current medical therapy in patients with unstable angina, evolving myocardial infarction and in patients undergoing coronary intervention, platelet aggregation is inhibited partly by administration of aspirin or ticlopidin[1,2]. In addition, heparin is administered in order to reduce thrombin activity. In spite of such combined antiplatelet and anticoagulant therapy, between 6% and 15% of patients with unstable angina progress to myocardial infarction or death within the first month[3,4]. Similarly, myocardial damage as assessed by periprocedural enzyme elevation has been reported in 4% - 14% of patients undergoing PTCA[5-11]. Follow up studies indicate that the larger, but also the smaller periprocedural enzyme elevations are associated with impaired long term outcome[12-14].

Major progress has been made by development of platelet glycoprotein (GP) IIb/IIIa receptor blockers, which block the final common pathway of platelet aggregation, the fibrinogen receptor on the thrombocytes[15]. In this review the clinical value

Table 1
List of available platelet GP IIb/IIIa receptor blockers

agent	form, type	company	trials	stage of development
Abciximab (c7E3,Reopro)	intravenous antibody	Centocor, Eli Lilly	PTCA, MI, UAP	FDA approved 1994, PTCA
Eptifibatide (integrilin)	intravenous peptide	Cor Therapeutics, Schering-Plough	PTCA, MI, UAP	FDA approved 1998, unstable angina and PTCA
tirofiban (aggrastat)	intravenous small molecule	Merck	PTCA, unstable angina	FDA approved 1998, unstable angina
lamifiban (Ro 44-9883)	intravenous small molecule	Hoffman LaRoche	PTCA, unstable angina	phase II/III
Fradafiban (BIBU 52)	intravenous nonpeptide, small molecule	Karl Thomae, Boehringer Ingelheim	PTCA	phase II
Xemilofiban (SC-54684A)	oral nonpeptide	Searle	PTCA, unstable angina	phase II
Sibrafiban (Ro 48-3657)	oral peptido-mimetic	Hoffman LaRoche, Genentech	acute coronary syndromes	phase III
Lefradafiban (BIBU-104xx)	oral pro-drug of fradafiban	Karl Thomae, Boehringer Ingelheim	PTCA, unstable angina	phase II

MI - myocardial infarction, UAP - unstable angina pectoris,
PTCA - percutaneous transluminal coronary angioplasty,
FDA – Food and Drug Administration

of treatment with platelet GP IIb/IIIa receptor blockers is assessed, based on data from medium size and large clinical trials in different groups of patients with unstable angina, evolving myocardial infarction and patients undergoing coronary intervention (table 1).

Different medical treatments of unstable angina

Medical treatment of patients with unstable angina and suspected myocardial infarction without ST segment elevation includes aspirin and heparin in addition to beta blockers[16], nitrates and in some patients calcium antagonists. Recent studies have assessed the value of different platelet GP IIb/IIIa receptor blockers on top of established medical therapy (tables 2 and 3).

Table 2
Trial characteristics

Trial	Disease	N	Drug	ASA	Heparin	treatment
PRISM	UAP	3231	tirofiban	+	or tirofiban	Rx
PARAGON	UAP	2282	lamifiban	+	or placebo	Rx
PURSUIT	UAP	10948	eptifibatide	+	at investigator	Rx
PRISM+	UAP/non Q	1915	tirofiban	+	+ (#)	Rx
CAPTURE	Refractory AP	1265	abciximab	+	+	ptca
EPIC	High risk PTCA	2099	abciximab	+	+	ptca
EPILOG	elective PTCA	2792	abciximab	+	+	ptca
IMPACT-II	elective PTCA	4010	eptifibatide	+	+	ptca
RESTORE	elective PTCA	2141	tirofiban	+	+	ptca
ERASER	stent	225	abciximab	+	+	stent
CAPTURE *	stent	112	abciximab	+	+	stent
EPILOG *	stent	326	abciximab	+	+	stent
EPI-STENT	stent	2399	abciximab	+	+	stent
EPIC - MI**	infarction	64	abciximab	+	+	ptca
RAPPORT	infarction	483	abciximab	+	+	ptca
INTEGRILIN AMI	infarction	171	eptifibatide	+	-	streptokinase
IMPACT AMI	infarction	160	eptifibatide	+	+	alteplase
TIMI 14 A	infarction	446***	abciximab	+	+	alteplase
SPEED	infarction	130***	abciximab	+	+	reteplase

UAP: unstable angina pectoris, MI: myocardial infarction, N.S.: not significant,
Rx: medical therapy, PTCA: percutaneous transluminal coronary angioplasty,
a third group of patients receives tirofiban without heparin,
*subgroup of stented patients,
** subgroup of patients with myocardial infarction at enrollment.
*** study ongoing

Table 3
Death and infarction at 30 days and 6 months

Trial	30 days			6 months		
	drug	placebo	P value	drug	placebo	P value
PRISM	5.8	7.1	0.11	n.a.		
PARAGON	10.3	11.7	0.668	12.6	17.9	0.025
PURSUIT	14.2	15.7	0.04	17.7	18.9	0.091
PRISM+	8.7	11.9	0.03	12.3	15.3	0.06
CAPTURE	4.8	9	0.003	9	10.9	0.19
EPIC	6.6	9.6	<0.05	9.4	12.6	<0.05
EPILOG	3.8	9.1	<0.001	6.1	11.6	<0.01
IMPACT-II	7.1	8.4	n.s.	10.3	11.6	0.19
RESTORE	5	6.4	n.s.	7.8	8.6	
ERASER	n.a.			8.1	15	n.s.
CAPTURE *	5.5	10.5		n.a.		
EPILOG *	better	n.a.	0.001	n.a.		
EPI-STENT	3.0	7.8	<0.05	n.a.		
EPIC-MI**	4.5	26.1	0.058	4.5	47.8	0.002
RAPPORT	4.6	5.8	0.38	6.9	12	0.079
INTEGRILIN-AMI	7.9	7.7	n.s.	n.a.		
IMPACT AMI	n.a.			n.a.		
TIMI 14	n.a.			n.a.		
SPEED	n.a.			n.a.		

UAP: unstable angina pectoris, (A)MI:myocardial infarction, n.s.: not significant, Rx: medical therapy, PTCA: percutaneous transluminal coronary angioplasty, n.a.: not available. *subgroup of stented patients, ** subgroup of patients with myocardial infarction at enrollment.

The PARAGON study enrolled 2282 patients who received placebo or low dose lamifiban (1 μg per minute) or high dose lamifiban (5 μg per minute)[17]. Patients receiving lamifiban were further randomized to receive either heparin or heparin placebo. At 30 day follow up no significant difference was apparent among the different treatment groups. Yet, in retrospect, the lowest event rate (death and myocardial infarction) was observed in patients receiving low dose lamifiban with heparin 10.6% in comparison with placebo 11.7% ($p = 0.668$). In fact, this difference was similar to the difference observed later in the PRISM and PURSUIT studies. At 6 months follow up patients receiving low dose lamifiban with heparin had a 30% relative reduction in death or myocardial infarction. This difference persisted at one year follow up. No good explanation has been offered for the increased difference between the placebo and low dose lamifiban groups between 1 and 6 month follow up. It is likely that this may have been a play of chance. Patients receiving high dose lamifiban with heparin had event rates

similar to the control group, while bleeding rates in this group were increased.

Tirofiban was investigated in the PRISM and PRISM+ studies[18]. PRISM enrolled 3232 patients with angina at rest within 24 hours before inclusion and either ECG changes indicating ischemia or a history of coronary artery disease[19]. All patients received aspirin and either heparin or tirofiban, 6 μg/kg/minute for 30 minutes followed by 0.15 μg/kg/minute for 48 hours. At 48 hours a significant reduction in death, myocardial infarction or refractory ischemia was observed. The reduction in death and myocardial infarction was still apparent at 30 days, although no longer statistically significant, showing an 18% reduction, from 7.1% for placebo to 5.8% for tirofiban-treated patients (P = 0.11).

The PRISM+ study enrolled patients at somewhat higher risk: all had symptoms of unstable angina with concomitant "ischemic" ECG changes within 12 hours prior to enrollment[20]. Three treatment arms were compared. Tirofiban in the same dose as in PRISM without heparin, was discontinued because of an increased mortality rate in the first 345 patients. At the time of the primary endpoint (7 days) patients receiving Tirofiban with heparin had a lower rate of death, myocardial infarction and refractory ischemia (12.9%) when compared to the heparin group (17.9%). Death and myocardial infarction at 30 day follow up were 8.7% for tirofiban treated patients, 11.9% for heparin treated patients (p = 0.03).

The largest trial in patients with unstable angina was PURSUIT[21]. 10,948 patients were randomized to receive eptifibatide bolus (180 μg/kg) followed by an infusion (1.3 or 2.0 μg/kg/minute) versus placebo. All groups received aspirin and heparin. The low dose group was discontinued since at interim analysis the high dose group appeared safe to continue. The primary endpoint was a reduction of death or myocardial infarction, as assessed by the clinical event committee, at 30 days follow up which was reduced from 15.7% in placebo treated patients to 14.2% in the eptifibatide group (p = 0.04).

The results of these studies are remarkably similar, showing a modest reduction in death or myocardial infarction ranging from 1.4 to 3.0 at 30 days per 100 patients treated. Yet a few differences between the trials should be appreciated. First, patient enrollment criteria in these trials were different (table 2), as were the definitions for myocardial infarction. In particular, a rise of CK or CK-MB exceeding twice the upper limit of normal was required to define an infarct in the PARAGON, PRISM and PRISM+ studies while any CK-MB above the upper limit of normal was labeled as an infarct by the PURSUIT clinical event committee. In fact, the investigators in PURSUIT called fewer infarcts. Using the investigator clinical approach a reduction in primary endpoint from 10.0% to 8.0% was reported by eptifibatide, at a rate similar to the other studies.

A further difference is the proportion of patients undergoing coronary intervention. In particular the larger treatment effect in the PRISM+ study may be due in

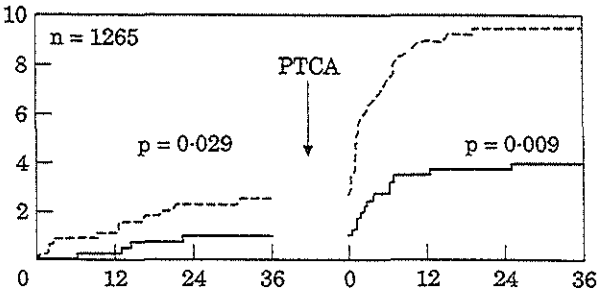


Figure 1. Development of myocardial infarction during treatment with abciximab or placebo, before and in association with PTCA; --- = placebo; — = abciximab. (Reprinted with permission from the Lancet, 1997; 349: 1429-35.)

part to the fact that all patients were scheduled to undergo coronary angiography after approximately 48 hours and a third of the patients subsequently underwent coronary intervention while receiving study drug. In contrast approximately 15% of patients in PURSUIT underwent PTCA while receiving study drug and very few patients in PRISM. Since treatment with a platelet GP IIb/IIIa receptor blocker in patients undergoing PTCA reduces periprocedural infarction (see below) the favorable outcome in the PRISM+ study reflects a combined effect of medical treatment and protection in patients undergoing early coronary intervention.

The double effect of platelet GP IIb/IIIa receptor blockers to prevent progression to myocardial infarction in patients with unstable angina and to avoid myocardial infarction at the time of coronary intervention was first shown in the CAPTURE study (figure 1), in which almost all patients underwent PTCA after 24 hours treatment with abciximab or placebo. A similar pattern has now been described in PRISM+ and in a subgroup of patients in the PURSUIT study. In view of the consistent findings in these studies treatment with a platelet GP IIb/IIIa receptor blocker will soon become standard in patients with unstable angina.

Medical treatment during coronary intervention

All studies with platelet GP IIb/IIIa receptor blockers in patients undergoing coronary intervention consistently show a reduction of death (which is infrequent) and myocardial infarction at 30 day follow up and beyond[22-26]. In three studies with abciximab a 50% reduction of death and myocardial infarction at 30 days was reported[27-35]. The magnitude of the benefit in the studies varies, reflecting differences in patient selection, differences in definition of myocardial infarction and possibly differences in the efficacy among various treatment regimens. In particular, the smaller effect observed in the IMPACT-II[36,37] study with eptifibatide when compared to the CAPTURE, EPIC and EPILOG studies with abciximab may be explained by the lesser degree of platelet inhibition as achieved by the rather low dose of eptifibatide used in IMPACT-II.

Treatment with abciximab or other platelet GP IIb/IIIa receptor blockers should be recommended for all patients undergoing PTCA, including those treated with direct atherectomy[38] and those receiving stents[39]! In fact platelet GP IIb/IIIa receptor blockers and stents have different complementary effects: the former improves procedural outcome by reduction of thrombotic complications as myocardial infarction and the latter by treatment of mechanical complications (large dissections) and reduction of restenosis[40,41].

There is no evidence from randomized trials on bail out use of abciximab in coronary intervention, although widely used[42].

PTCA in patients with unstable angina

Many patients with unstable angina admitted to a hospital will subsequently undergo coronary intervention or coronary bypass surgery. In some hospitals early coronary intervention may be offered to a majority of these patients although the superiority of such approach has not been established by randomized trials. In fact, a systematic strategy of early intervention was not superior to a strategy of watchful waiting in the TIMI IIIb study[43-45]. In recent studies in patients with unstable angina, intervention rates at 30 days with either PTCA or surgery were as high as 38% in PURSUIT to 54% in PRISM+. Major differences in intervention rates were observed among different regions in the world participating in PURSUIT. For example, percutaneous coronary intervention and bypass surgery were performed in 8% and 7% of patients respectively in eastern Europe, 25% and 14% in western Europe, compared to as many as 35% and 21% in North America.

If early coronary intervention is considered in patients with unstable angina or evolving myocardial infarction, current available data indicate that such patients will particularly benefit from treatment with a platelet GP IIb/IIIa receptor blocker[46] both before and during the interventional procedure, in addition to aspirin, heparin, beta blockers and nitrates. Troponin T levels can help to define a high risk subgroup likely to benefit most from the addition of platelet GP IIb/IIIa receptor blockers to standard therapy[47,48].

Direct PTCA in patients with evolving myocardial infarction

Patients with evolving myocardial infarction usually have a completely occluded coronary artery. Treatment with a platelet GP IIb/IIIa receptor blocker in this setting may result in opening of the artery through clot resolution[49]. Gold and coworkers observed opening of an occluded coronary artery in 7 (54%) out of 13 patients undergoing

angiography and treatment with abciximab in the early phase of myocardial infarction. These observations are supported by the GRAPE study in the Netherlands which documented a patent coronary artery in 24 (40%) out of 60 patients undergoing coronary angiography after receiving abciximab[50]. In studies without pretreatment with a platelet GP IIb/IIIa receptor blocker approximately 20% patent coronary arteries are reported[51,52]. In the RAPPORT trial TIMI flow rates 2 or 3 prior to angioplasty were higher (34.1%) in patients receiving abciximab compared to 25.5% in the placebo group, although this difference was not statistically significant[53].The combined primary endpoint at 6 month of death, re-infarction and urgent revascularization was reduced in the RAPPORT study from 17.8% in the placebo group to 11.6% for abciximab ($p = 0.062$) For those patients actually receiving study treatment and PTCA the reduction was from 12.0% to 4.6% ($p=0.005$).

The total body of randomized data in patients undergoing direct PTCA for myocardial infarction is rather limited. Yet, the findings are consistent with those reported in PTCA for stable or unstable angina as summarized above, and support the use of the platelet GP IIb/IIIa receptor blockers in this setting.

Platelet GP IIb/IIIa receptor blockers and thrombolytic therapy

Early animal experiments[54,55] reported enhanced thrombolytic activity when rtPA was administered with concomitant platelet GP IIb/IIIa receptor blockers. Yet, it remains uncertain whether this will translate into an improved clinical treatment regimen.

A pilot study with streptokinase and different dosages of eptifibatide in 171 patients did show improved coronary patency at 90 minute coronary angiography (65% versus 78%), but the differences in patency were not very large and combination therapy was associated with increased bleeding rates[56]. Similar improved patency rates were observed in patients receiving eptifibatide and rtPA as well as patients treated with abxicimab and a low dose of rtPA in the TIMI 14 study[57-59]. In the latter TIMI 3 flow was achieved in 79% of 34 patients treated with full dose abciximab combined with 50 mg. rtPA infused in one hour, while standard accelerated rtPA regime showed 58% TIMI 3 flow in 146 patients ($p < 0.001$). These initial results should be verified in larger patient series. Combination therapy with a thrombolytic agent and a platelet GP IIb/IIIa receptor blocker was associated with increased bleeding risk. It may be expected, or at least hoped, that further studies will allow development of an improved regimen for reperfusion therapy, through combination of carefully chosen doses of thrombolytics and platelet GP IIb/IIIa receptor blockers.

Oral platelet GP IIb/IIIa receptor blockers

The platelet inhibitory effect of eptifibatide and tirofiban rapidly disappears after discontinuation of the intravenous infusions while the effect of abciximab persists and gradually disappears during subsequent weeks[60-63]. Whether this difference in pharmacology has an impact on clinical outcome remains to be established. Yet, investigators realize that healing of the vessel wall in patients with unstable angina and myocardial infarction takes several weeks. Accordingly, treatment with antiplatelet agents during such period may be expected to be beneficial[64,65].

Oral platelet GP IIb/IIIa receptor blockers may provide such long term (weeks, perhaps months) treatment for patients with unstable angina or following acute myocardial infarction, to prevent early re-thrombosis. Different platelet GP IIb/IIIa receptor blockers which are acting after oral administration are currently being investigated, and a few phase II studies have been reported.

Twice daily administration of sibrafiban resulted in consistent platelet inhibition, defined as inhibition of over 50% of ADP-induced platelet aggregation more than 75% of the day. Major bleeding slightly increased, while muco-cutaneous bleeds were reported in one third of patients with the highest dose sibrafiban[66].

Xemilofiban is a nonpeptide pro-drug that inhibits platelet aggregation for more than 8 hours after a single oral dose[67,68]. Thirty patients with unstable angina who were undergoing PTCA were studied with placebo or xemilofiban orally three times a day for 30 days. Results show rapid, sustained and marked inhibition of platelet aggregation during this period, which was associated with increased major bleeding and particularly muco-cutaneous bleeding during chronic administration of the drug.

Lefradafiban is an oral prodrug of fradafiban, which can be administered intravenously[69,70]. In a study of patients undergoing PTCA, lefradafiban in appropriate dosage resulted in blockade of over 80% of fibrinogen (platelet GP IIb/IIIa) receptors on the thrombocyte. Bleeding of mucous membranes and gums were seen, but no serious bleeding complications occurred. The half life of 12 hours enables effective triple day dosage.

Further studies of these and similar drugs in different clinical settings are ongoing to address whether prolonged administration will help to reduce the incidence of coronary events, without an excessive risk for bleeding complications. Monitoring of the effect of platelet GP IIb/IIIa receptor blockade may be required for optimal safety and efficacy during long term treatment[71,72].

Platelet GP IIb/IIIa receptor blockers and bleeding risk

In the first larger trial with abxicimab a high rate of major bleeding complications

Table 4
Risk of stroke with abciximab – combined results of three large trials

	EPIC		CAPTURE		EPILOG		Total	
	placebo	drug	placebo	drug	placebo	drug	placebo	drug
No of patients	681	678	630	623	939	1853	2225	3112
Non-hemorragic	2	2	2	0	1	2	5	4
Hemorragic	2	2	1	0	1	2	4	4
Unknown	0	0	0	1	0	0	0	1
Any stroke	4	4	3	1	2	4	9	9

All p values>0.45; Unknown = unknown etiology

(14%) was observed in patients receiving abxicimab with concomitant aspirin and heparin[73]. Subsequent studies have shown that this bleeding excess is due to the combined therapy with heparin and may be avoided through reduction of the latter. With such modification in the EPILOG study, no excess of bleeding was observed in patients receiving abxicimab with low dose heparin (70 U per Kg, a maximal dose of 7000 U and additional bolus dosing to maintain an ACT of over 200 seconds)[73,74], while the efficacy to avoid thrombotic complications remained intact.

Yet, in the PRISM, PRISM+ and PURSUIT studies, bleeding rates were higher in patients receiving the respective platelet GP IIb/IIIa receptor blockers. Again this may have been related to the amount of heparin administered. In spite of the higher bleeding rates in PURSUIT, no excess intracranial hemorrhage or stroke was observed. In fact, intracranial hemorrhages were very rare, while embolic strokes were more common: 0.9% in the placebo group and 0.7% in the eptifibatide group. This difference was not statistically significant[75](table 4).

It should be appreciated that the measures to be taken, if a significant bleeding occurs, are different for the various groups of platelet GP IIb/IIIa receptor blockers. In all cases, the platelet GP IIb/IIIa receptor blockers should be stopped, as well as heparin and any other anticoagulant.

Patients receiving abxicimab can effectively be treated with an infusion of thrombocytes. When abxicimab is administered in the recommended dosages, almost all drug is bound to platelets and the concentration of circulating abxicimab is very low. Thus, the receptors on fresh platelets which are being administered will not be blocked and will remain available to induce platelet aggregation. Over time, some exchange of abxicimab will occur from "old" to "fresh" platelets, but the overall level of platelet inhibition will decrease after administration of fresh platelets.

The small molecule platelet GP IIb/IIIa receptor blockers which have been developed for intravenous administration (lamifiban, tirofiban, eptifibatide) are rapidly cleared from the body with a half life of a few hours. Thus, in patients developing

Table 5 Potential countermeasures for bleedings	
Drug	**method and time of effect**
abciximab	stop drug, rapid reversal when platelets given
eptifibatide	stop drug, several hours
lamifiban	stop drug, several hours
tirofiban	stop drug, several hours
oral compounds	stop drug, consider ultra filtration, empty stomach

major bleeding complications it suffices to discontinue drug administration and wait for the compound to clear (table 5). During drug administration plasma concentrations of these competitive antagonists to the platelet GP IIb/IIIa receptors are high. Accordingly it is not useful to administer platelets to counteract the drug effect in these patients.

The oral compounds which are currently under clinical investigation, have been selected for their long half-life. These are also competitive antagonists which require a relatively high plasma concentration. In patients developing bleeding complications while being treated with oral platelet GP IIb/IIIa receptor blockers it may be required to take measures which will help to remove the compound from the body including gastric emptying, forced diureses, and possibly ultra filtration. Treatment with fresh platelets will not be useful in the presence of high concentration of platelet receptor blockers.

Thrombocytopenia

Reversible thrombocytopenia has been reported in patients receiving platelet GP IIb/IIIa receptor blockers. The rate of such complications is low, varying from 0.5% of 744 patients described in a single center registry[76,77] to 1.6% in the CAPTURE population (platelets below 50.000 10^9/L). Rapid increase of thrombocytes is noted after cessation of the drug. A thrombocyte measurement after 12 hours of intravenous platelet GP IIb/IIIa receptor blocker is advised to detect thrombocytopenia early.

Antibodies to the monoclonal antibody abciximab

The early IgG murine monoclonal antibody, 7E3, consisted of a Fc and Fab fragment targeted against the GP IIb/IIIa receptor[78]. Especially the Fc fragment is expected to give a human antimurine response (HAMA) and subsequent removal of the IgG

bound platelets. The now-used monoclonal antibody abciximab is a human/chimeric version of the earlier antibody, of which the Fc portion has been removed before administration. The binding capacities of the 7E3 Fab fragment however remained intact, while antibody formation is minimized[79-81].

Preliminary data are being gathered on re-administration in the R3 Reopro Readministration Registry[82]. In 92 prospectively evaluated patients no increase in thrombocytopenia was seen (2.2% < 50.000 10^9/L) and no allergic reaction was observed. Clinical consequences of antibody formation seem limited, although data on re-administration are scarce.

Conclusion

More than 12,000 patients have been enrolled in large-scale trials in the setting of non-surgical percutaneous intervention, and the efficacy and safety of platelet GP IIb/IIIa receptor blockers is beyond dispute. These drugs markedly reduced the incidence of thrombotic and ischemic complications in patients with unstable angina and during PTCA. Trials presented here show benefit sustained to a follow up period of one month and show lasting effect up to three years and the majority meeting primary efficacy endpoints with statistical significance. Treatment with platelet GP IIb/IIIa receptor blockers is beneficial in all patients undergoing PTCA, both with and without stent implantation, provided the cost of treatment is acceptable. Primary PTCA for acute myocardial infarction should be performed under protection of platelet GP IIb/IIIa receptor blockers, just like other interventions.

In unstable angina treated with percutaneous intervention and platelet GP IIb/IIIa receptor blockers a dual effect is seen, consisting of a stabilization of the disease and prevention of myocardial infarction both before intervention and reduction of thrombotic events associated with the intervention. In patients with unstable angina and evolving myocardial infarction without ST segment elevation treated medically a modest reduction of early events is observed. Treatment with platelet GP IIb/IIIa receptor blockers is warranted as are aspirin, heparin (avoid excessive dosing) and beta-blockers and nitrates.

Trials in acute myocardial infarction with platelet GP IIb/IIIa receptor blocker alone or in adjunct with thrombolysis or intervention are currently underway. Dosing regimens of platelet GP IIb/IIIa receptor blockers as well as dosing of thrombolytics need to be clarified and tested for safety and efficacy. Available phase two data show improvement of TIMI 3 flow adding platelet GP IIb/IIIa receptor blockers to thrombolytics for treatment of acute infarction.

Trials with orally active platelet GP IIb/IIIa receptor blockers are conducted to establish their efficacy and safety. A future strategy might comprise three phases for

platelet GP IIb/IIIa receptor blockers in treatment of coronary disease. Initial treatment will include intravenous platelet GP IIb/IIIa receptor blockers with high levels of aggregation inhibition for patients during hospitalization for unstable angina, percutaneous intervention and perhaps infarction. Follow up treatment can include oral agents providing inhibition of platelet aggregation in a healing phase of the first weeks or months after hospitalization with either a high or medium level of inhibition of platelet aggregation. Third, secondary prevention with oral agents in a lower dosage may be appropriate.

The benefits for all platelet GP IIb/IIIa receptor blockers are offset by a bleeding risk in higher dosage groups. This bleeding is strongly related to the addition of high dose heparin. Careful titration of heparin during PTCA to ACT levels over 200 seconds in stead of earlier levels above 300 seconds has shown to lower bleeding risk to near placebo levels. For longer treatment with concomitant heparin, APTT's should be at most two times normal. Bleeding risk for combination therapy with thrombolytic regimens need further investigation, while safety and efficacy of oral agents is to be proven in phase III and IV trials.

The development of the new class of the platelet GP IIb/IIIa receptor blockers has been a breakthrough in antithrombotic therapy for patients with coronary artery disease.

References

1. Theroux P, Ouimet H, McCans J et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988; 319: 1105-1111.
2. Antiplatelet Trialist' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994; 308: 81-106.
3. The GUSTO IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. Circulation 1994; 90: 1631-1637.
4. The RISC group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990; 3376: 827-830.
5. Tenaglia AN, Fortin DF, Calif RM. et al. Predicting the risk of abrupt vessel closure after angioplasty in an individual patient. J Am Coll Cardiol 1994; 24: 1004-1011.
6. De Feyter PJ, de Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994; 127: 643-651.
7. Ellis SG. Percutaneous coronary intervention in the 1990s: results in patients with single or multivessel disease [review]. Herz 1992; 17: 18-26.
8. Mark DB, Lam LC, Kerry KL et al. Effects of coronary heart surgery, and medical therapy on employment in patients with coronary artery disease: a prospective comparison study. Ann Intern Med 1994; 120: 111-1117.
9. Altmann DB, Popma JJ, Hong MK et al. CPK-MB elevation after angioplasty of saphenous

vein grafts. J Am Coll Cardiol. 1993; 21: 232A. Abstract 903-7 1.
10. Braden GA, Applegate RJ, Young TM et al. ReoPro decreases creatinekinase elevation following rotationl atherectomy: evidence for a platelet dependent mechanism. Circulation 1996; 94 (suppl 1): I-248. Abstract 1452.
11. Buchbinder MA, Braden GA, Sharma SK et al. A pilot study of ReoPro with rotational atherectomy (RA) to reduce creatine kinase (CK) elevation post procedure. Circulation 1996; 94 (suppl 1): I-197. Abstract 1147.
12. Kong TQ Jr, Davidson CJ, Meyers SN et al. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. JAMA 1997; 277: 461-466.
13. Redwood SR, Popma JJ, Kent KM et al. "Minor" CPK-MB elevations are associated with increased late mortality following ablative new-device angioplasty in native coronary arteries. Circulation 1995; 92 (suppl 1): I-544.
14. Simoons M.L, Van den Brand MJ, Lincoff M, et al. Minimal myocardial damage during coronary intervention is associated with impaired outcome. Eur Heart J 1999; 20: 1112-1119.
15. Coller B.S., Peerschke E.I., Scudder L.E. et al. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelet produces a thrombastenic state in normal platelets and binds to glycoproteins IIb and/or IIIa. J Clin Invest 1983; 72: 325-338.
16. The Hint trial Group. Early treatment of unstable angina in the coronary care unit: A randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Br Heart J 1986; 56: 400-413.
17. The PARAGON investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa receptor inhibitor), heparin or both in unstable angina. Circulation 1998; 97: 2386-2395.
18. Chesebro JH, Badimon JJ. Platelet glycoprotein IIb/IIIa receptor blockade in unstable coronary disease. N Engl J Med 1998; 338: 1539-1540
19. The PRISM study investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-1505.
20. The PRISM-PLUS study investigators. Inhibibion of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. N Engl J Med 1998; 338: 1488-1497
21. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.
22. Topol EJ. Platelet glycoprotein IIb/IIIa receptor antagonists in coronary artery disease. Eur Heart J 1996; 17: 9-18.
23. Tcheng JE. Glycoprotein IIb/IIIa receptor inhibitors: putting the EPIC, IMPACT-II, RESTORE, and EPILOG trials into perspective. Am J Cardiol 1996; 78 (suppl. 3A): 35-40.
24. Lefkovits J., Topol E.J. Platelet glycoprotein IIb/IIIa receptor antagonist in coronary artery disease. Eur Heart J 1996; 17: 9-18.
25. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Engl J Med. 1995; 332: 1553-1559.
26. Verheugt FWA. In search of a superaspirin for the heart. Lancet 1997; 349: 1409-1410.
27. Simoons ML, de Boer MJ, van den Brand MJ et al. Randomized trial of a GP IIb/IIIa platelet receptor blocker in refractory unstable angina. European Cooperative Study Group. Circulation. 1994; 89: 596-603.
28. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-1435.

29. Van de Werf F. More evidence for a beneficial effect of platelet glycoprotein IIb/IIIa-blockade during coronary interventions. Latest results from the EPILOG and CAPTURE trials. Eur Heart J 1996; 17: 325-326.
30. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med. 1994; 330: 956-961.
31. Topol EJ, Califf RM, Weisman HF. et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC Investigators. Lancet 1994; 343: 881-886.
32. Topol EJ, Ferguson JJ, Weisman HF et al. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin P3 blockade with percutaneous coronary intervention. JAMA 1997; 278: 479-484.
33. Califf RM, Lincoff AM, Tcheng JE et al. An overview of the results of the EPIC trial. Eur Heart J 1995; 16 (Suppl) L: 43-9.
34. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularizatiom. N Eng J Med 1997; 336: 1689-1696.
35. Lincoff AM, Tcheng JE, Califf RM et al. Standard versus low dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3) during percutaneous coronary revascularization. Am J Cardiol 1997; 79: 286-291.
36. Tcheng JE, Harrington RA, Kottke-Marchant K. et al. Multicenter, randomized, double-blind, placebo-controlled trial of the platelet integrin glycoprotein IIb/IIIa blocker Integrelin in elective coronary intervention. IMPACT Investigators. Circulation 1995; 91: 2151-2157.
37. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349: 1422-1428.
38. Lefkovits J, Blankenship JC, Anderson KM et al. Increased risk of non-Q wave myocardial infarction after directional atherectomy is platelet dependent: evidence from the EPIC trial. J am Coll Cardiol 1996; 28: 849-855.
39. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
40. Serruys PW, De Jaegere P, Kiemeney F et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994: 331; 489-495.
41. Fischman DL, Leon MB, Baim DS et al.. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994: 331; 496-501.
42. Muhlestein JB, Karagounis LA, Treehan S et al. "Rescue" utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997: 30(7); 1729-1734.
43. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. Circulation 1994; 89:1545-1556.
44. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998; 338: 1785-1792.

45. Ferry DR, O'Rourke RA, Blaustein AS et al. Design and baseline characteristics of the Veterans Affairs Non-Q-Wave Infarction Strategies in-hospital (VANQWISH) trial. J Am Coll Cardiol 1998; 31(2): 312-320.
46. Umans VA, Kloeg PH, Bronzwaer J, et al. Safety and efficacy of Reo-Pro treatment for patients with unstable angina while awaiting PTCA in a referring clinic. Presented at the 19th Congress of the European Society of Cardiology; August 24-28, 1997; Stockholm, Sweden.
47. Hamm CW, Heeschen C, Goldman B et al. For the CAPTURE Investigators. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. N Engl J Med. 1999; 340: 1623-1629.
48. Hamm CW, Goldman BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or cardiac tropinin I. N Engl J Med 1997; 337: 1648-1653.
49. Gold HK, Garabedian HD, Dinsmore RE et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without erogenous plasminogen activators: observations in animals and humans. Circulation 1997; 95: 1755-1759.
50. van den Merkhof LF, Zijlstra F, Olsson H, Grip L, Veen G, Bar FW, van den Brand MJ, Simoons ML, Verheugt FW. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. Results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study. J Am Coll Cardiol. 1999; 33 : 1528-1532.
51. DeWood MA, Spores J, Notske R et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980; 303: 897- 902.
52. Timmis AD, Griffin B, Crick JCP et al. Anisoylated plasminogen streptokinase activator in acute myocardial infarction: a placebo-controlled arteriographic coronary recanalization study. J Am Coll Cardiol 1987; 10: 205-210.
53. Brener SJ, Barr LA, Burchenal JEB, Katz S, George BS, Jones AA, Cohen ED, Gainey PC et al, on behalf of the Reopro and primary PTCA organization and randomized trial (RAPPORT) investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734-741.
54. Roux SP, Tschopp TB, Kuhn H et al. Effects of heparin, aspirin and a synthetic platelet glycoprotein IIb-IIIa receptor antagonist (Ro 43-5054) on coronary artery reperfusion and reocclusion after thrombolysis with tissue-type plasminogen activator in the dog. J Pharmacol Exp Ther 1993; 264: 501-508.
55. Gold HK, Garabedian HD, Dinsmore RE et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without erogenous plasminogen activators: observations in animals and humans. Circulation 1997; 95: 1755-1759.
56. E. Ronner, H.A.M. van Kesteren, P. Zijnen, et al. Safety and efficacy of eptifibatide versus placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction. Eur Heart J 2000; 21: 1530-1536.
57. Ohman EM, Kleiman NS, Gacioch G et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. Circulation 1997; 95: 846-854.
58. Antman EM, Giugliano RP, Gibson MC, et al. for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolyis in myocardial infarc-

tion (TIMI) 14 trial. Circulation 1999; 99: 2720-2732.
59. Kleiman NS, Ohman EM, Califf RM et al. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy. Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 Pilot Study. J Am Coll Cardiol 1993; 22: 381-389.
60. Mascelli MA, Lance ET, Lakshmi Damaraju et al. Pharmacodynamic profile of short-term abciximab treatment demonstrates prolonged platelet inhibition with gradual recovery from GP IIb/IIIa receptor blockade. Circulation 1998; 97: 1680-1688.
61. Coller BS, Lang D, Scudder LE. Rapid and simple platelet function assay to assess glycoprotein IIb/IIIa receptor blockade. Circulation 1997; 95(4): 860-867.
62. Coller BS. Monitoring platelet GP IIb/IIIa antagonist therapy. Editorial. Circulation 1998; 97: 5-9.
63. Mascelli MA, Worley S, Veriabo NJ et al. Rapid assessment of platelet function with a modified whole-blood aggregometer in percutaneous transluminal coronary angioplasty patients receiving anti-GP IIb/IIIa therapy. Circulation 1997; 96: 3860-3866.
64. Fuster V, Badimon L, Badimon JJ, Chisibro JH: The Pathogenesis of Coronary Artery Disease and the Acute Coronary Syndromes. N Engl J Med 1992, 326: 242-250.
65. Fuster V, Badimon L, Badimon JJ, Chisibro JH: The Pathogenesis of Coronary Artery Disease and the Acute Coronary Syndromes. N Engl J Med 1992, 326: 310-318.
66. Cannon CP, McCabe CH, Borzak S et al. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome. Results of the TIMI 12 trial. Circulation 1998; 97: 340-349
67. Simpfendorfer C, Kottke-Marchant K, Topol EJ. First experience with chronic platelet GP IIb/IIIa blockade: a pilot study of Xemilofiban an orally active antagonist in unstable angina patients eligible for PTCA (abstr). J Am Coll Cardiol 1996; 27 (suppl A): 242.
68. Simpfendorfer C, Kottke-Marchant K, Lowrie M et al. First chronic platelet glycoprotein IIb/IIIa integrin blockade. A randomized, placebo-controlled pilot study of xemilofiban in unstable angina with percutaneous coronary interventions. Circulation 1997; 96: 76-81.
69. Van den Brand MJBM, Baardman T, Suryapranata et al. Initial experience with BIBU 104XX; a new, oral glycoprotein IIb/IIIa receptor blocker. Presented at the 19th Congress of the European Society of Cardiology; August 24-28, 1997; Stockholm, Sweden.
70. Muller TH, Weisenberger H, Brickl R. et al. Profound and sustained inhibition of platelet aggregation by fradafiban, a nonpeptide platelet glycoprotein IIb/IIIa antagonist, and its orally active prodrug, lefradafiban, in man. Circulation 1997;96:1130-38.
71. Kereiakes DJ, Runyon JP, Kleiman NS et al. Differential dose-response to oral Xemilofiban after antecedent intravenous abciximab. Circulation 1996; 94; 906-310.
72. Vorchheimer DA, Fuster V. Oral platelet glycoprotein IIb/IIIa receptor antagonists: the present challenge is safety. Circulation 1998; 97: 312-314.
73. Aguirre FV, Topol EJ, Ferguson JJ. et al. Bleeding complication with the chimeric antibody to platelet glycoprotein IIb/IIIa intergrin in patients undergoing percutaneous coronary intervention. Circulation 1995; 91: 2882-2890.
74. Blankenship JC, Helkamp AS, Demko SL et al. Vascular access site complications after percutaneous coronary intervention with glycoprotein IIb/IIIa inhibitor therapy in the EPIC trial. J Am Coll Cardiol 1997; 29: 278A. Abstract 993-10.
75. Deckers J, Califf P, Topol EJ et al. Use of abciximab (ReoPro) is not associated with an increase in the risk of stroke: overview of three randomized trials. J Am Coll Cardiol 1997; 29 (suppl A): 241A. Abstract 974-89.

76. Berkowitz SD, Harrington RA, Rund MM et al. Acute profound thrombocytopenia after c7E3 Fab (abciximab) therapy. Circulation 1997; 95: 809-13.
77. Kereiakes DJ, Essell JH, Abbottsmith CW et al. Abciximab associated profound thrombocytopenia: therapy with immunoglobulin and platelet transfusion. Am J Cardiol 1996; 78: 1161-63.
78. Coller BS. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet glycoprotein IIb/IIIa complex. J Clin Invest 1985; 76: 101-108.
79. Ellis GE, Tcheng JE, Navetta FI, et al. Safety and antiplatelet effect of murine monoclonal antibody 7E3 Fab directed against platelet glycoprotein IIb/IIIa in patients undergoing elective coronary angioplasty. Cor art dis 1993; 4: 167-175.
80. Jordan RE, Wagner CL, Mascelli MA, et al. Preclinical development of c7E3 Fab; a mouse/human chimeric monoclonal antibody fragment that inhibits platelet function by blockade of GPIIb/IIIa receptors with observations on the immunogenicity of c7E3 Fab in humans. In: Horton MA, ed. Adhesion Receptors as Therapeutic Targets. London: CRC Press, 1996: 281-305.
81. Knight DM, Wagner C, Jordan R, et al. The immunogenicity of the 7E3 murine monoclonal Fab antibody fragment variable region is dramatically reduced in humans by substitution of human for murine constant regions. Mol Immunol 1995; 32: 1271-1281.
82. Tcheng JE, Kereiakes DJ, George BS, et al. Safety of Readministration of Abciximab; Interim Results of the ReoPro Readministration Registry (R3). Presented at the 47th Annual Scientific Sessions of the American College of Cardiology; March 29 - April 1, 1998; Atlanta Georgia, USA.

2.2

Safety of abciximab drip-and-ship regimen while transferring unstable angina pectoris for PTCA by ground transportation

Doran Hilarius, Fons Windhausen, Eelko Ronner, Paul Kloeg, Stella Schrijver-van Velthoven, Jan-Hein Cornel, Victor A. Umans

Medical Center Alkmaar, Alkmaar, The Netherlands

Cardiologie 2000; 7: 273-277

Abstract

Background. *A pre-procedural regimen of abciximab, a monoclonal platelet glycoprotein IIb/IIIa receptor blocker, has been applied effectively in PTCA patients with unstable angina (UA), but its acceptance may be limited by safety concerns and economic constraints. The current trial investigated the safety aspects of the "drip-and-ship" protocol for unstable patients awaiting transfer between two hospitals.*

Methods. *From April 1996 through December 1998, 168 consecutive patients with refractory UA (Braunwald class I [3%] or II [49%] or III [48%] received abciximab prospectively at the Medical Center Alkmaar before undergoing angioplasty. The following drip-and-ship protocol was used: an 0.25 mg/kg bolus of abciximab followed by 10 μg/min intravenously for 16 hours, in addition to intravenous nitrates, heparin and aspirin therapy. Patients were then transferred to one of the Amsterdam interventional clinics by high-speed ambulance transport. All interventions were performed while abciximab was given.*

Results. *All but one patient received the full scheduled dose of abciximab; in that patient, the infusion was stopped after three hours because of an episode of severe thrombocytopenia. No patient required transfer for emergency PTCA. No specific alterations of routine transfer protocol were needed. No major bleeding complications occurred during pretreatment or transport to and from the site of intervention. The in-hospital clinical success rate (angiographic success without major complications) was 98%. No major bleeding complications occurred during the abciximab pre-treatment or post-treatment period.*

Conclusions. *Abciximab was administered safely to angioplasty patients with refractory UA awaiting transfer from a non-interventional setting to the site of PTCA. These results extend the current knowledge that has been established in randomized trials performed in interventional centers. This study protocol may serve as a preamble for the upcoming ICTUS trial in which an abciximab "drip-and-ship" regimen will be tested throughout the country.*

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) has taken on an important role in the management of patients with refractory unstable angina (UA)[1-9]. Unfortunately, PTCA in this setting remains limited by the peri-procedural complication of abrupt coronary artery occlusion secondary to thrombus formation, which increases the risk of acute myocardial infarction (MI) and urgent bypass surgery.

Thrombotic complications of PTCA can partly be prevented by platelet glycoprotein (GP) IIb/IIIa receptor blockers, a class of potent antiplatelet drugs. They have been used to advantage in patients with UA or evolving MI without persistent ST elevation undergoing PTCA[10-13]. Platelet aggregation at the site of intracoronary plaque rupture is believed to dominate the pathophysiology of both UA and the thrombotic complications of angioplasty[10-11]. Prophylactic use of platelet GP IIb/IIIa receptor blockers is an attractive strategy indeed for managing refractory UA. So far only limited experience exists with using this novel drug class when administered during transportation to and from a PTCA setting.

We therefore investigated a "drip-and-ship" protocol which, if proven safe, effective and practical would safely allow expanded use of prophylactic therapy with abciximab in UA patients awaiting transfer from a non-interventional referring hospital to a site with interventional capabilities.

Patients and methods

From April 1996 through December 1998, a total of 168 consecutive patients were treated with abciximab while awaiting transfer from the Medical Center Alkmaar for angioplasty. This cohort represented 24% of all stable and unstable patients referred for PTCA from Alkmaar during that period. Patients were eligible for abciximab treatment if they had refractory UA documented by electrocardiography (ECG) (one episode of ST-segment depression or elevation, or development of new persistent T-wave inversions) during treatment with intravenous heparin, nitroglycerin, or both. All patients had undergone angiography prior to abciximab treatment and had at least one major lesion suitable for coronary angioplasty. Demographic, clinical, procedural and follow-up data were collected prospectively.

Abciximab regimen and transfer protocol

Initially, our prophylactic regimen with abciximab differed somewhat from the regimen of the CAPTURE trial[10,14]. In the CAPTURE trial, patients received a randomly

assigned infusion of abciximab or placebo for 18-24 h before PTCA, continuing until 1 h afterwards, the intravenous dose was an 0.25 mg/kg bolus followed by a continuous infusion of 10 μg/min. In the interest of economic feasibility, we reduced the pre-PTCA infusion period to 16 hours, thereby saving one vial of abciximab (25% of the costs). Following the outcome of the EPIC and EPILOG trials, we further reduced the pre-PTCA infusion period, allowing a 12-hour post-PTCA infusion period.

This regimen was chosen to achieve adequate inhibition of platelet aggregation at the time of transportation and to lead to steady-state plasma concentrations of abciximab at the time of angioplasty[10,15]. The heparin regimen was adjusted according to the guidelines for low-dose, weight adjusted heparin established by the EPILOG trial (70 U/kg, maximum 7000 U, followed by additional boluses as needed to achieve an activated clotting time of 200 sec, and stopped immediately after PTCA)[13]. All patients also received aspirin.

The patients were transported to the catheterization laboratory in Amsterdam by ambulance. The distance between the Medical Center Alkmaar and the Amsterdam interventional clinic is 40 kilometers. On average, transportation took 25 min. The ambulance crew included intensive-care-trained nurses. No special adaptation of the transportation protocol was necessary. All patients were transported with their arterial femoral sheath in place. Following successful intervention, the patients were returned to Alkmaar by ambulance. During transport back to Alkmaar, careful attention was paid to the groin and the patients were kept in a horizontal position.

Coronary angioplasty

Angioplasty was performed using standard techniques. Balloon catheters and stents were deployed at the discretion of the operator, and a balloon to artery ratio of 1:1 was sought. After the procedure, heparin was continued at the discretion of the operator. Abciximab was continued until the full scheduled dose was given. All successfully treated patients received the pre-specified dose; none of the patients required an additional or extended abciximab regimen. The vascular sheath was removed at least 4 hours after termination of heparin treatment. Aspirin was continued in all cases. Routine CK measurements were obtained at six hours after angioplasty.

Results

Patient characteristics

Demographic and clinical data for the 168 UA patients enrolled in the study, 72%

Table 1
Demographic and clinical characteristics of the study population (n=168)

Characteristics	%
Sex (male)	72
Age (years)	58 ±11
Multivessel disease	46
Braunwald I	3
Braunwald II	49
Braunwald III	48
Hypertension	36
Hypercholesterolaemia	68
Smokers	32
Family history	48
Previous PCI	9
Previous CABG	8
Previous myocardial infarction	53

PCI = percutaneous coronary intervention
CABG = Coronary artery bypass grafting

Table 2
Angiographic characteristics of the study population

Characteristics	%
Lesion location	
LAD	44
LCX	15
RCA	35
Graft	6
AHA/ACC lesion type	
A	5
B1	17
B2	67
C	11
Thrombus containing lesion	41
Eccentric lesion	76
Lesion length	
< 10 mm	22
10 - 20 mm	67
> 20 mm	11
Side branch presence	22
TIMI flow	
1	8
2	2
3	15
Calcified lesion	3

LAD = Left anterior descending coronary artery
LCX = Left circumflex coronary artery
RCA = Right coronary artery

of whom were males, are presented in Table 1; 46% of the patients had multivessel coronary artery disease, 68% had hypercholesterolaemia, and 53% had experienced a prior MI. About 48% were treated for post-infarction UA.

Angiographic characteristics

The 168 patients underwent a total of 175 PTCA procedures. Angiographic characteristics at the time of diagnostic catheterization are described in Table 2. Almost all procedures were performed in native vessels (94% of patients), and lesions were most often localized in the left anterior descending coronary artery (44%). In 41% of the patients, some degree of intralesional thrombus was noted; in 75% of cases, however, normal (TIMI grade 3) coronary artery flow was present.

Procedural characteristics

In the initial phase of the protocol, a strict time frame was taken into account to comply with the CAPTURE trial infusion period. Characteristically, the abciximab infusion was started at 23.00 h in the night before the intervention to allow a sufficient pretreatment period in order to optimally stabilize the patient. Following the release

of the EPILOG trial, we would typically start the drip-and-ship regimen around 8.00 h in the morning before the scheduled PTCA. Before starting the abciximab infusion, a routine thrombocyte count was performed in order to prevent treating patients with thrombocytopenia. By protocol, the thrombocyte count was repeated after two hours of abciximab infusion. Subsequently all but one patient received the full dose of abciximab; in that patient, the infusion was stopped after three hours because of an episode of severe thrombocytopenia. No patient required transfer for emergency PTCA. No major bleeding complications occurred during pretreatment or transport to and from the site of intervention.

Primary stenting was used to treat the lesion in 52% of patients. All stented lesions were covered with one stent. The procedural success rate was 98% overall, and 98% in the balloon and stent recipients as separate groups. There were no cases of distal embolisation, procedural MI, or the no-reflow phenomenon. All but one patient left the angioplasty suite with a patent coronary artery and normal antegrade flow.

In-hospital clinical results

All patients successfully dilated had an uneventful in-hospital clinical course. There were no major bleeding complications. No patient had a subacute vessel occlusion or required urgent balloon angioplasty. No patient had a Q-wave infarction. Two patients required emergency bypass surgery after a failed angioplasty procedure. In addition, two patients had a small non-Q-wave MI (increase in CK and/or CK-MB > 3 times normal and no ECG changes). After the sheaths were removed, one patient had groin bleeding necessitating transfusion of two units of packed cells. None of the patients required peripheral vascular surgery. In one patient, groin ultrasound showed signs of a pseudoaneurysm that was effectively treated with the FemoStop (USCI Division of C.R. Bard Inc., Billerica, Mass., USA) cross-clamp device. None of the patients who returned without sheath had bleeding problems during their hospital stay. Furthermore, patients who were transported back to Alkmaar after sheath removal had a significantly shorter post-angioplasty in-hospital stay compared to those returning with the sheath still in place. For the whole population, including those treated for post-infarction UA, the mean post-PTCA in-hospital stay was 2.3 $\pm$ 1.6 days including a 0.8 $\pm$ 1.2 days stay at the coronary care unit. Currently, however, all patients are immediately transferred to the cardiology ward for completion of the abciximab treatment and further mobilization after sheath removal.

Discussion

This observational study confirms that abciximab can be safely and effectively administered at a referral hospital to patients with refractory UA who are being transferred

for coronary angioplasty. The study extends the findings on prophylactic use of abciximab to pacify unstable plaque and avert thrombosis while awaiting PTCA. Furthermore, these results may serve as a pilot experience for a nationwide application of the drip-and-ship regimen of platelet GP IIb/IIIa receptor blockers in unstable patients being transferred to PTCA centers.

Acute coronary syndrome and timing of platelet GP IIb/IIIa receptor blocker therapy

An emerging strategy with UA patients is to integrate treatment with platelet GP IIb/IIIa receptor blockers into conventional drug therapy of UA. Both the lamifiban[16] and eptifibatide trial[17] and the tirofiban trials[18,19] demonstrated significant reductions in ischemic events and deaths associated with infusion of platelet GP IIb/IIIa receptor blockers over several days. However, despite the proven efficacy of this strategy, still 25% of the patients are subsequently being sent for a PTCA. Recent data from the PURSUIT trial have confirmed the beneficial effect of eptifibatide in the pacification of the unstable thrombus-plaque interaction allowing a safe and early PTCA without an increase in thrombotic complications[20]. Introducing platelet GP IIb/IIIa receptor blockers into the treatment of UA may therefore call for a more expedite approach once a patient is about to be sent for PTCA.

The optimal choice of a platelet GP IIb/IIIa receptor blocker in conjunction with PTCA remains undefined. Given the data from three major randomized trials - The EPIC trial, the EPILOG trial and the CAPTURE trial - indicating that abciximab is effective in preventing ischemic complications during PTCA, we chose to use abciximab in a drip-and-ship regimen[10,12,13,21,22].

Drip-and-ship regimen

We initially chose an early treatment strategy, similar to that of CAPTURE, to stabilize activated plaque and adequately inhibit platelet aggregation in UA patients awaiting intervention[10,14]. Using this approach we anticipated a similar beneficial effect of abciximab on ischemia and thrombus burden reduction as observed in the CAPTURE trial. After release of the EPIC data, showing a comparable reduction of clinical endpoints as the CAPTURE regimen but with a more favorable long-term outcome, we reduced the pre-PTCA abciximab infusion period in our patients, still well in advance, however, of the PTCA procedure to allow a 12-hour post-PTCA infusion period. Our data show that UA patients can be safely transported to and from an interventional clinic while being treated with a platelet GP IIb/IIIa receptor blocker. They also underscore the concept of starting abciximab at the referral hospital right before transportation in order to fully benefit from its platelet-inhibitory action at the time of PTCA. This drip-and-ship strategy, therefore, allows the effects of abciximab to be exerted on the activated platelets well in advance of PTCA.

Expedite care and abciximab therapy

Despite the appeal of pretreatment with abciximab, the costs of this strategy may be prohibitive. Cost-effectiveness analyses showed that potential cost savings can be achieved by reducing ischemic events with abciximab[23,24]. An important and attractive way to reduce costs may be an approach of expedite care, thereby reducing the duration of hospital stay at the coronary care unit (CCU). By reducing the stay at the CCU both before and after PTCA, almost half the costs can be saved. More recently our group has described the potential advantage of internet technology in reducing the waiting time in interventional cardiology. The use of internet technology may thus facilitate expedite medical care for these critically ill cardiac patients[25]. Also, early sheath removal and ambulation of PTCA patients has been shown feasible in the setting of interventional cardiology and has reduced the duration of hospital stay. Finally, appropriate patient selection for abciximab treatment may lead to more favorable economics[26,27].

Conclusions

Abciximab was administered safely to angioplasty patients with refractory UA awaiting transfer from a non-interventional setting to the site of PTCA. These results extend the current knowledge that has been established through randomized trials performed in interventional centers. This study protocol may serve as a preamble for the upcoming ICTUS trial in which an abciximab drip-and-ship regimen will be tested throughout the country.

References

1. Domburg RT van, Miltenburg-van Zijl AJ van, Veerhoek RJ, Simoons ML. Unstable angina: good long-term outcome after a complicated early course. J Am Coll Cardiol 1998: 31: 1534-1539.
2. Ellis SG. Percutaneous coronary intervention in the 199Os: results in patients with single or multivessel disease. Herz 1992; 17: 18-26.
3. Myler RK, Shaw RE, Stertzer SH et al. Unstable angina and coronary angioplasty. Circulation 1990; 82 (Suppl II): II88-95.
4. De Feyter PJ, Van den Brand M, Laarman GJ, van Domburg R, Serruys PW, Suryapranata H. Acute coronary artery occlusion during and after percutaneous transluminal coronary angioplasty. Frequency, prediction, clinical course, management and follow-up. Circulation 1991; 83: 927-936.
5. De Feyter PJ, Suryapranata H, Serruys PW, et al. Coronary Angioplasty for Unstable Angina: Immediate and Late Results in 200 Consecutive Patients With Identification of Risk Factors for Unfavorable Early and Late Outcome. J Am Coll Cardiol 1988; 12: 324-333.

6. Lincoff AM, Popma JJ, Ellis SG, Hacker JA, Topol EJ. Abrupt vessel closure complicating coronary angioplasty: clinical, angiographic and therapeutic profile. J Am Coll Cardiol 1992; 19: 926-935.
7. Tenaglia AN, Fortin DF, Calif RM. et al. Predicting the risk of abrupt vessel closure after angioplasty in an individual patient. J Am Coll Cardiol 1994; 24: 1004-1011.
8. Abdelmeguid AE, Whitlow PL, Sapp SK, Ellis SG, Topol EJ. Long-term outcome of transient, uncomplicated in-laboratory coronary artery closure. Circulation 1995; 91: 2733-2741.
9. De Feyter PJ, de Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. Am Heart J 1994; 127: 643-651.
10. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997; 349: 1429-1435.
11. Braunwald E, Maseri A, Armstrong et al. Rationale and clinical evidence for the use of GP IIb/IIIa inhibitors in acute coronary syndromes. Eur Heart J 1998; 19 (suppl D) D22-D30.
12. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
13. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularizatiom. N Eng J Med 1997; 336: 1689-1696.
14. Umans VA, Kloeg PH, Bronzwaer J. The CAPTURE trial [letter]. Lancet 1997; 350: 445.
15. Simoons ML, de Boer MJ, van den Brand MJ, et al. Randomized trial of a glycoprotein IIb/IIIa platelet receptor blocker in refractory unstable angina. European Cooperative Study Group. Circulation 1994; 89: 596-603.
16. Theroux P, Kouz S, Knudtson M et al. Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina. The Canadian Lamifiban Study. Circulation 1996; 94: 899-905.
17. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.
18. The PRISM study investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-1505.
19. The PRISM-PLUS study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. N Engl J Med 1998; 338: 1488-1497.
20. Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. Eur Heart J 1998; 19: 1608-1616.
21. Lincoff AM, Califf RM, Anderson K, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1997; 30: 149-156.
22. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
23. Hout BA van, Bowman L, Zelinger DJ, Simoons ML. Costs and effects in therapy for acute coronary syndromes: the case of abciximab in high-risk PTCA patients undergoing percutaneous transluminal coronary angioplasty in the EPIC trial. Am Heart J 1998; 135: S98-S106.
24. Hout BA van, Simoons ML. Costs and effects of c7E3 in high risk PTCA patients: an indirect

analysis for the Netherlands. Eur Heart J 1995; 16 (Suppl L): 81-85.
25. Umans VAWM, Kok W, Spruijt H, Bronzwaer J. Clinical feasibility of remote angiographic teleconsultation using a ISDN-30 communication network. J Telemed 1999; 5: 391-394.
26. Khan MM, Ellis SG, Aguirre FV, et al, for the EPIC Investigators. Does intracoronary thrombus influence the outcome of high risk percutaneous transluminal coronary angioplasty? Clinical and angiographic outcomes in a large multicenter trial. J Am Coll Cardiol 1998; 31: 31-36.
27. Hamm CW, Heeschen C, Goldman B et al. For the CAPTURE Investigators. Benefit of abcximab in patients with refractory unstable angina in relation to serum troponin T levels. N Engl J Med. 1999;340:1623-1629.

2.3

Patients with acute coronary syndromes without persistent ST-elevation undergoing percutaneous intervention benefit most of early intervention with protection by a glycoprotein IIb/IIIa receptor blocker

Eelko Ronner[1], Eric Boersma[1], K. Martijn Akkerhuis[1], Robert A Harrington[2], A. Michael Lincoff[3], Jaap W. Deckers[1], Karl Karsch[4], Neal S. Kleiman[5], Alec Vahanian[6], Eric J. Topol[3], Robert M. Califf[2], Maarten L. Simoons[1]

[1] University Hospital Rotterdam, Rotterdam, The Netherlands (ER, EB, KMA, JWD, MLS);
[2] Duke Clinical Research Institute, Durham, North Carolina, USA (RAH, RMC);
[3] Cleveland Clinic Foundation, Cleveland, Ohio, USA (AML, EJT);
[4] Bristol Heart Institute, Bristol, United Kingdom (KK);
[5] Baylor College of Medicine and the Methodist Hospital, Houston, Texas, USA (NSK);
[6] Tenon Hospital, Paris, France (AV)

European Heart Journal (in press)

PURSUIT was supported by COR Therapeutics, Inc., South San Francisco, California and the Schering-Plough Research Institute, Kenilworth, New Jersey

Abstract

Many patients with acute coronary syndromes are offered percutaneous coronary intervention. However, the appropriate indications for, and optimal timing of, such procedures are uncertain. We analysed timing of intervention and associated events (death and myocardial infarction) in the PURSUIT trial in which 9461 patients received a platelet glycoprotein IIb/IIIa inhibitor, eptifibatide or placebo for 72 hours. Other treatment was left to the investigators. 2430 patients underwent percutaneous coronary intervention within 30 days. Four groups were distinguished, who underwent percutaneous coronary intervention on day 1; at day 2 or 3; at 4 to 7 days; or between 8 until 30 days, for eptifibatide- and placebo-treated patients.

Results. *The four groups treated with placebo demonstrated total 30-day events of 15.9% for day 1 percutaneous coronary intervention, 17.7%, 15.0%, and 18.2%, respectively, for successive intervals of later intervention. Later intervention was associated with more pre-procedural events (2.2% up to 13.7%, $p = 0.001$) which was balanced by a decrease in procedure-related events (12.1 to 3.1%, $p = 0.001$), while the overall 30-day event rates were similar.*

Eptifibatide-treated patients with percutaneous coronary intervention on day 1 had the lowest rate of 30-day events (9.2%, $p < 0.05$ versus other groups). In this group, pre-procedural risk was only 0.3%, while percutaneous coronary intervention on eptifibatide was associated with low procedural risk (7.2%). The total 30-day event rate for later percutaneous coronary intervention in patients receiving eptifibatide was 14.0% on day 2 and 3, 15.0% for day 4 to 7 and 17.4% for days 7 to 30 respectively.

Conclusion. *Patients treated with a platelet glycoprotein IIb/IIIa receptor blocker, and early percutaneous coronary intervention (within 24 hours) had the lowest event rate in this post-hoc analysis. Thus "watchful waiting" may not be the optimal strategy. Rather an early invasive strategy with percutaneous coronary intervention under protection of a platelet glycoprotein IIb/IIIa receptor blocker should be considered in selected patients. Randomized trials are warranted to verify this issue.*

Introduction

A wide range of treatment strategies have been developed for patients with acute coronary syndromes without persistent ST-segment elevation. These strategies can be categorized as early invasive or conservative.[1,2,3] Recent randomised investigations did provide evidence of better outcome with an invasive strategy. Similar 30-day and 6-month complication rates were reported in some earlier trials.[4,5] In particular, the recent FRISC-II study reported favourable survival after an early invasive treatment strategy.[6] The TACTICS trial, incorporating platelet glycoprotein IIb/IIIa receptor blockers too, demonstrated benefit in invasive treated patients.[7] Yet, selection of the most suitable therapy in individual patients remains a challenge, and the early application of percutaneous interventions or coronary surgery and the timing of such intervention is largely dependent on local practice and facilities.[8,9]

Several registries of percutaneous coronary interventions (percutaneous coronary intervention) in acute coronary syndromes reported an increased risk of thrombotic complications during the procedure.[10,11] This risk was highest in patients treated during the acute phase, and lowest in patients who were stabilized for a few days or weeks by medical therapy. Accordingly, a strategy of 'watchful waiting' has been recommended. The recent introduction of platelet glycoprotein IIb/IIIa blockers, however, may change this paradigm, as these agents prevent thrombotic complications during medical treatment as well as during percutaneous coronary intervention.[12,13] We attempted to gain insight in the relationship between the timing of percutaneous coronary intervention, the use of glycoprotein IIb/IIIa inhibitors and patient outcome, by analysing data of the large Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of eptifibatide versus placebo in patients with non ST-elevation acute coronary syndromes.[14]

Methods

Patient population

The design and methods of the PURSUIT trial have been described in detail.[13] In summary, patients were eligible if they presented within 24h of an episode of ischaemic chest pain (>10 minutes), and had either transient ST-elevation (>0.5 mm), transient or persistent ST-depression (>0.5 mV), T-wave inversion (>0.1 mm), or elevation of the creatine kinase MB-fraction (CK-MB) above the upper limit of normal. Patients with persistent (>30 minutes) ST-elevation were excluded. There were no age restrictions. Eligible patients were randomly assigned to treatment with eptifibatide or placebo for 72 hours. Additional treatment, including percutaneous coronary intervention or coronary artery bypass grafting (CABG) was at the discretion of the treating

physician. If a percutaneous coronary intervention was performed during the first 72 hours, study medication could be continued for another 24 hours. The PURSUIT trial enrolled 9,461 patients.

Definition of myocardial infarction

The primary efficacy end-point of PURSUIT was a composite of death or non-fatal myocardial infarction at 30 days. Within 18 hours of enrolment myocardial infarction was diagnosed on the basis of ischaemic chest pain and new ST-segment elevation. After 18 hours, myocardial infarction was diagnosed on the basis of new Q waves, or new or repeated CK-MB elevations above the upper limit normal. For patients undergoing a percutaneous intervention, a CK-MB elevation above three times the upper limit of normal was required. End-points were adjudicated by a central Clinical Events Committee. A computerized algorithm was used to review the raw data. If a possible complication was identified, further documentation was collected and the case reviewed in detail. Local investigators also reported whether or not the patient had had an acute myocardial infarction. Discrepancies between the Clinical Events Committee opinion and that of the investigator have been investigated and discussed in detail.[15] This analysis presents data based on the Clinical Events Committee judgement. Differences with analyses based on the investigators' opinion are discussed, but data will not be shown.

Statistical analysis

There were 2,419 patients (26%) undergoing a percutaneous coronary intervention within 30 days of enrolment, without a prior CABG in this period. These patients were divided in four groups of approximately the same size according to the timing of the intervention: within 24 hours of randomization (day 1), within 24-72 hours (day 2-3), within 73-168 hours (day 4-7), and within 169-720 hours (day 8-30), respectively. These intervals were divided at complete days to enable comparison with clinical practice, choosing groups of roughly equal size. Chi-square tests, Student's T-tests and one-way analyses of variance were applied to investigate differences in baseline characteristics between these groups as well as between patients undergoing percutaneous coronary intervention and those not undergoing percutaneous coronary intervention. Results are compared between the four groups with and without eptifibatide. In addition the results are compared to patients treated conservatively.

Adverse cardiac complications (death or myocardial infarction) were separated as occurring during the period of initial medical management (i.e. among all patients, before a percutaneous coronary intervention or CABG, if any), within 48 hours after the start of a percutaneous coronary intervention procedure (peri-procedural complications), or in the period beyond 48 hours after the percutaneous coronary intervention procedure up to 30 days follow-up (post-procedural complications). The

complications were separated to enable detailed insight in procedure related events, which are likely to be influenced by timing of the percutaneous coronary intervention. Total 30-day event rate describes the percentage of patients with any event. As multiple events have occurred in certain patients, the sum of pre- peri and post-procedure events can be higher than the total 30-day (patients-with-) event rate. Complication rates in each of these periods are presented by percentages; the nominator is the number of patients with a complication during the target period, the denominator is the number of patients alive at the beginning of the period. Differences in complication rates between patient subgroups were evaluated by Chi-square tests. Kaplan-Meier complication curves were calculated for complications occurring during medical management. Log-rank tests were applied to evaluate subgroup differences. Univariable and multivariable logistic regression analyses were applied to describe the relation between the timing of percutaneous coronary intervention and the risk of death or myocardial infarction, corrected for patient characteristics that influence prognosis.[16] The statistical significance of all test was stated at the $P = 0.05$ level.

Results

In PURSUIT, 9461 patients were treated with eptifibatide or placebo on top of other antithrombotic and antiischaemic medication. Of these 9461 patients, 2430 underwent percutaneous coronary intervention within 30 days of enrolment. There were major differences in baseline characteristics between patients undergoing percutaneous coronary intervention within 30 days of enrolment and those not undergoing percutaneous coronary intervention. Of the patients who underwent percutaneous coronary intervention, 620 patients were treated within 24 hours of randomization (day 1), 624 within 24-72 hours (day 2-3), 614 within 73-168 hours (day 4-7), and 561 within 169-720 hours (day 8-30). The characteristics of the patient population according to the timing of percutaneous coronary intervention are described in Table 1. Patients undergoing percutaneous coronary intervention early after enrolment had a more favourable risk profile than those undergoing later percutaneous coronary intervention, as they were younger, less often than had peripheral vessel disease, less often ST-segment depression on admission, and a lower mean systolic blood pressure.

Complications during medical management

In the overall population, during medical therapy, including patients who subsequently underwent revascularization censored for intervention, the rate of death or infarction increased with time, with the steepest ascent occurring in the first 3 days (Figure 1). Complication rates preceding percutaneous coronary intervention in patients undergoing percutaneous coronary intervention were higher than in the

Table 1
Baseline characteristics

PCI * on day	1	2-3	4-7	8-30		All pts	Other	
Number of patients	620	624	614	561		2419	7042	
Hours (days) to PCI, median	11 (0.5)	46 (1.9)	110 (4.6)	305 (12.7)		72 (3.0)	—	
Mean age, years	59	59	61	62	§	61	64	§
Male gender, %	68	70	70	73		70	63	§
Hypertension, %	59	54	54	48	§	53	56	†
Diabetes mellitus, %	21	22	21	18		20	24	§
Current smoker, %	34	32	33	33		33	27	§
Previous MI, %	31	26	31	26		28	34	§
CCS class III or IV in previous 6 weeks	49	42	48	49		47	42	§
Previous heart failure	6	6	7	6		6	13	§
Previous CVA	2	4	2	4		3	4	†
Peripheral vessel disease, %	6	4	7	8	†	6	9	§
Previous CABG	15	15	13	12		14	11	‡
Previous PCI	25	21	19	13	§	20	10	§
Elevated cardiac enzymes at admission	45	48	49	46		47	45	
ST-depression at admission	38	39	45	49	§	43	53	§
Mean systolic blood pressure, mmHg	127	130	130	131	‡	130	132	§
Mean heart rate, bpm	71	72	72	71		71	74	§
Study medication eptifibatide	49	49	47	48		48	50	

* Patients undergoing a percutaneous coronary intervention within 30 days of enrollment, without a prior CABG in this period; † $P<0.05$; ‡ $P<0.01$; § $P<0.001$; bpm= beats per minute; CABG=coronary artery bypass grafting; CCS=Canadian Cardiovascular Society; CVA=cerebrovascular accident; MI=myocardial infarction; PCI=percutaneous coronary intervention.

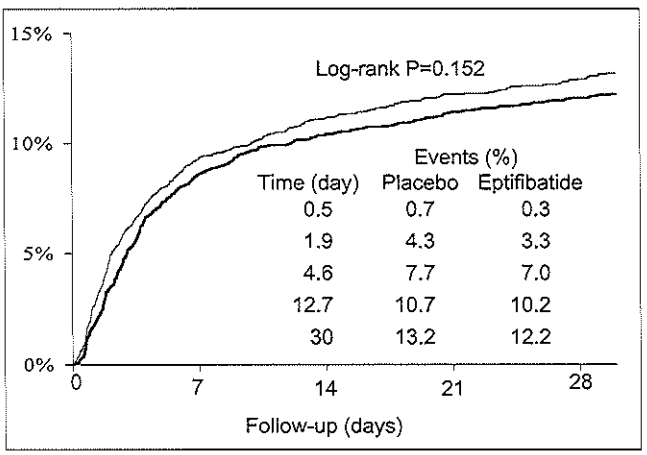


Figure 1. Kaplan-Meier curves showing the cumulative incidence of death or non-fatal myocardial infarction during the period of medical treatment alone, censored for percutaneous coronary intervention or bypass grafting if any, in patients randomly assigned to glycoprotein IIb/IIIa inhibition (bold line) or placebo for 72 hours.

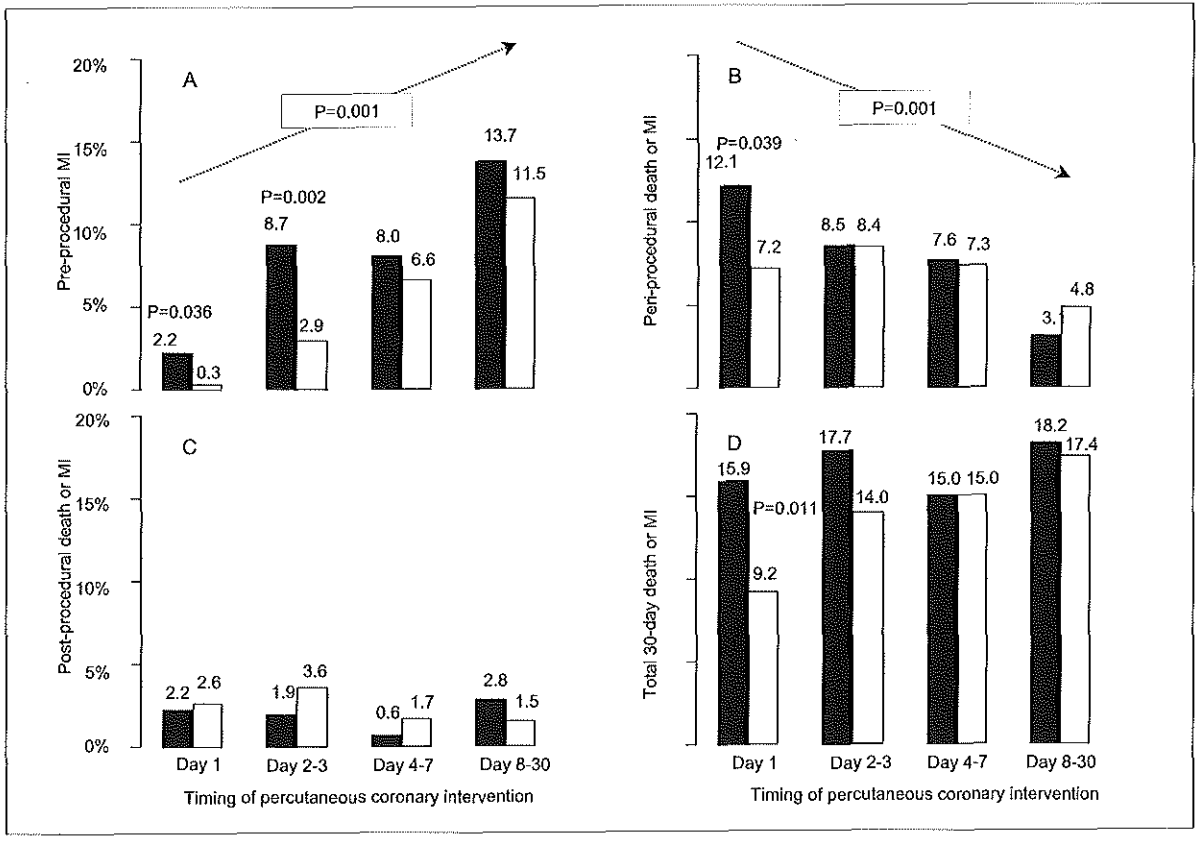


Figure 2. Percentage occurrence of cardiac complications in patients undergoing a percutaneous coronary intervention during days 0-30, randomly assigned to glycoprotein IIb/IIIa inhibition (white bars) or placebo for 72 hours. Cardiac complications were separated as occurring before the intervention, within 48 hours after the start of the procedure (peri-procedural complications), or in the period beyond 48 hours after the procedure up to 30 days follow-up (post-procedural complications). A patient could have had an event in all three of these periods, but in each period only one event is counted per patient. The overall 30-day complication rates could therefore be lower than the sum of the complication rates in the separate periods.

overall population, especially in patients who underwent intervention during day 0-3 and who were randomized to placebo. Complication rates on medical therapy on day 1 or until day 3 were only 0.7% and 4.3%. (Figure 1) While pre-procedural myocardial infarction occurred in 2.2% and 8.7% of placebo patients undergoing percutaneous coronary intervention on day 1 and days 2-3, respectively (Figure 2). Treatment with eptifibatide was associated with a reduction in end-points: there were 13.2% complications at 30 days in patients during medical treatment randomized to placebo, versus 12.2% in eptifibatide (log-rank $P=0.152$), excluding events associated with or occurring after percutaneous coronary intervention or CABG.

Peri- and post-procedural complications

A significant relation was observed between the timing of percutaneous coronary intervention and the rate of peri-procedural death or myocardial infarction (Figure 2), with the highest complication rate in the day 1 percutaneous coronary intervention cohort and the lowest complication rate in the days 8-30 cohort. The risk of peri-procedural complications in patients randomized to eptifibatide who underwent percutaneous coronary intervention at day 1 was significantly lower than in patients randomized to placebo (7.2% versus 12.1%; $P=0.001$). There were no significant differences in peri-procedural complication rates between eptifibatide and placebo in the other percutaneous coronary intervention subgroups (remember that the PURSUIT study medication was administered during the first 72 hours of enrolment only; see method section). Rates of death or myocardial infarction occurring beyond 48 hours after the percutaneous coronary intervention procedure were low, and neither were related with the timing of percutaneous coronary intervention, nor with the initial assignment to eptifibatide or placebo.

Timing of percutaneous coronary intervention, eptifibatide treatment and overall complications during the 30-day follow-up

Among all percutaneous coronary intervention patients, those undergoing percutaneous coronary intervention at day 1 who were randomized to eptifibatide had the lowest 30-day death or myocardial infarction rates (9.2%; Figure 2). This was significantly lower than patients undergoing percutaneous coronary intervention at day 1 who were randomized to placebo (15.9%; $P=0.011$). Eptifibatide therapy also reduced the 30-day complication rate in patients undergoing percutaneous coronary intervention at day 2-3 as compared to placebo, although the difference in event rates (14.0% versus 17.7%) did not reach statistical significance. The 30-day complication rate in all patients undergoing percutaneous coronary intervention during days 4-30 was 16.3%. This was significantly higher than the complication rate in patients undergoing early percutaneous coronary intervention under the protection of eptifibatide (9.2% in the day 1 cohort; $P=0.002$; and 13.1% in the combined day 1 and day 2-3 cohort; $P=0.007$).

There was, however, no evidence of a differential benefit of eptifibatide therapy over placebo between the day 1 and days 2-3 percutaneous coronary intervention cohort (Breslow-Day test of homogeneity of odds ratios: $P = 0.297$).

The 30-day death or myocardial infarction rate in patients continuing with medical management was higher (12.2%-13.2%, Figure 1) than in patients undergoing percutaneous coronary intervention at day 1 under the protection of eptifibatide. Results of logistic regression analyses, however, indicate that this difference can largely be explained by the favourable risk profile of those undergoing early percutaneous coronary intervention. After correction for all determinants of risk as mentioned in Table 1, percutaneous coronary intervention on day 1 under the protection of eptifibatide was associated with a similar outcome as 30-day medical management (corrected odds ratio and 95% CI: 1.0 [0.7-1.5]). The corrected odds ratios for percutaneous coronary intervention at day 1 plus eptifibatide treatment versus any other percutaneous coronary intervention subgroup were in the range 0.5-0.7. Differences in baseline characteristics as shown in Table 1 may have affected outcome among the early percutaneous coronary intervention cohorts. However, after correction for baseline characteristics by logistic regression, similar results were obtained in an analysis using investigator defined myocardial infarction as endpoint.

Discussion

The present analysis indicates that outcome is favourable in patients with acute coronary syndrome without persistent ST-segment elevation undergoing percutaneous coronary intervention when such a procedure is performed within 24 hours after admission under protection of a platelet glycoprotein IIb/IIIa receptor blocker. Thirty day rates of death or myocardial infarction were only 9.5% for those undergoing percutaneous coronary intervention within 24 hours, while treated with eptifibatide, compared with 14.3% to16.5% for later percutaneous coronary intervention, or 12.2% to 13.2% for no percutaneous coronary intervention.

Benefit of early revascularization

The recently reported FRISC-II study of an early invasive versus a non-invasive treatment strategy demonstrated a clear benefit of an early invasive strategy and revascularization when appropriate at 6 months and 12 months follow up.[6] Patients randomized to the early revascularization strategy in FRISC-II underwent coronary angiography, and subsequent revascularization if an obstruction of $\geq$70% of the diameter was observed in a major coronary artery. It should be noted that early percutaneous coronary intervention was performed at a median 4 days after admission, and surgery at 7 days. In FRISC-II non-invasive treatment advised coronary angiog-

raphy and revascularization when appropriate in patients with refractory or recurrent symptoms. By 10 days, 71% of patients in the invasive group had undergone coronary revascularization, versus 9% in patients allocated to continuing medical therapy. Complication rates (death or myocardial infarction) at 42 days were 8.6% and 11.8%, respectively ($P=0.009$). These findings were confirmed recently by the TACTICS study.[7] Earlier randomized investigations, such as TIMI-3b and VANQWISH, failed to demonstrate favourable results of an early invasive treatment strategy.[4,5] A sizeable proportion of patients in these trials, however, did not undergo early revascularization as assigned, while many patients allocated to a medical treatment strategy underwent an early intervention. It should also be noted, that these studies were performed in the pre-stent era and without platelet glycoprotein IIb/IIIa receptor blockers. In TACTICS all patients received a platelet glycoprotein IIb/IIIa receptor blocker, tirofiban, and most patients undergoing percutaneous coronary intervention received stents. In PURSUIT stents were used in 50% of all percutaneous coronary intervention procedures.

The present retrospective analysis does not confirm, nor refute a benefit for systematic early revascularization. The apparent benefit of revascularization was explained in part by differences in patient characteristics, and was no longer apparent by multivariable analysis. Patients were not randomized to undergo either an early invasive or conservative treatment strategy, but were managed according to the discretion of the treating physicians. The reasons for performing or not a specific intervention in a given patient were not recorded in PURSUIT. The indication for intervention in clinical practice should be based on recent guidelines as published by the European Society of Cardiology[17] and the American organisations[18], taking into account individual risk assessment, particularly elevated cardiac troponine levels and recurrent ischaemia.

Timing of intervention in patients scheduled for revascularization.

When a decision to perform a revascularization in a given patient is made, three factors which determine the optimal timing of revascularization should be taken into account: the risk of complications before the intervention, the procedure related risk and the risk after completion of the procedure.

The present analysis confirms earlier observations of the incremental risk of death and myocardial infarction while receiving medical therapy. This risk is particularly high early after admission, and gradually diminishes over time. Treatment with platelet glycoprotein IIb/IIIa receptor blockers and other antithrombotic therapy moderately reduces the risk under medical therapy as illustrated in Figure 1.[19,20,21] In patients subsequently scheduled for percutaneous coronary intervention, in the present study, the risk of pre-procedural complications did indeed increase over time both in patients receiving placebo as well as eptifibatide (Figure 2(a)). This risk was lower

in the latter group, particularly in the first 3 days when the drug was administered.

As in other studies procedure-related complications, particularly myocardial infarction, were most frequent in patients undergoing early percutaneous coronary intervention (Figure 2(b)).[10,11] This risk was significantly reduced by the platelet glycoprotein IIb/IIIa receptor blocker, particularly when procedures were performed on day 1. These findings are in agreement with other studies with platelet glycoprotein IIb/IIIa receptor blockers in patients undergoing percutaneous coronary intervention, which demonstrated a reduction of about 30 to 50% in peri-procedural thrombotic complications, both with balloon angioplasty and with stents[22-26], including patients with acute coronary syndrome without persistent ST-segment elevation.[22,25]

In all patient groups, events after the revascularization procedure were infrequent, and independent of the timing of such a procedure (Figure 2(c)). Again, this is in agreement with observations in many other studies of patients undergoing percutaneous coronary intervention, where most events occurred in association with the procedure.[22-26]

In the present study, the reduction of peri-procedural events (within 48 hours of percutaneous coronary intervention) was greater than the reduction of spontaneous events, pre-intervention. Overall outcome was superior in patients undergoing very early intervention, within 24 hours or at least within the first 3 days after enrolment, while receiving the platelet glycoprotein IIb/IIIa receptor blocker eptifibatide (Figure 2(d)).[6,22-26]

Limitations

This study is retrospective, and selection bias may have contributed to the observations as reported. However, in PURSUIT, the timing of intervention was determined mostly by local facilities and customs. Very early interventions were performed predominantly in the United States, and later interventions in Europe, independent of other patient characteristics (Table 1). In order to correct for differences in baseline characteristics of patients revascularized at different time intervals, a multivariable analysis was performed. In this analysis, the effect of timing of intervention on outcome remained statistically significant (odds ratio 0.0-0.7, $P=0.002$).

However, though the benefit of intervention by a glycoprotein IIb/IIIa receptor blocker within 24 hours would be less than reported in this study, there is no evidence that outcome would be worse with early intervention. Therefore it seems appropriate, once a decision has been made to perform a percutaneous intervention in a particular patient, to proceed as soon as feasible, and not opt for a prolonged period of stabilization.

It should also be appreciated that the precise timing of an event in relation to the start of a procedure (pre- or peri-percutaneous coronary intervention) is complex, particularly when only limited data are available to the clinical events committee. Peri-

procedural myocardial infarction was defined with a higher cut-off value for CK-MB than myocardial infarction in other intervals. This was chosen to adhere to the original PURSUIT protocol. Analysis with other cut-off values for myocardial infarction (three and five times the upper limit of normal, also for post-procedural myocardial infarction) did not influence results.

Furthermore, the more sensitive definition of spontaneous, not procedure related, myocardial infarction as applied by the clinical event committee (at least one CK-MB value above the upper limit of normal) may have prompted this committee to declare myocardial infarction already before the procedure, whereas during the procedure much higher enzyme elevations had occurred. This may explain the greater than expected benefit from pre-procedural events in patients undergoing percutaneous coronary intervention on days 2 and 3 and the smaller than expected benefit of eptifibatide in peri-procedural events on days 2 and 3. Thus the overall 30-day death and myocardial infarction rate will be more reliable than the rate recorded for pre- and post-procedure intervals. According to the opinion of the local investigators the difference in pre-procedural myocardial infarction rates between placebo and eptifibatide in the days 2-3 cohort was smaller (6.3% versus 2.9%; $P=0.043$), but the difference in peri-procedural complications larger (7.6% versus 3.6%; $P=0.029$). Using investigators' assessments, the reduction of peri-procedural myocardial infarction by eptifibatide was similar on day 1 and days 2 to 3. Furthermore, this analysis compared the improved outcome on 30-days for patients undergoing intervention at day 1, while receiving eptifibatide ($P=0.011$).

Conclusion

The present analysis of data from the PURSUIT study suggest that patients with acute coronary syndromes without persistent ST-segment elevation undergoing percutaneous coronary intervention benefit most from early intervention under protection by a glycoprotein IIb/IIIa receptor blocker. Deferral of percutaneous coronary intervention has no advantage once the decision has been made to perform angioplasty. If percutaneous coronary intervention is deferred for practical or logistic reasons, and is performed in a more stable setting, it will be useful to continue intensive antiplatelet therapy, or to restart such therapy at the time of the procedure (also beyond day 3).

These findings warrant confirmation by a prospective study, randomizing patients to very early or deferred intervention, while receiving intensive antithrombotic therapy before and during the intervention.

References

1. Braunwald E, Jones RH, Mark DB, et al. Diagnosing and managing unstable angina. Circulation 1994; 90: 613-622.
2. Hillis WS. The continuing debate: conservative or interventional therapy for unstable coronary artery disease. Am J Cardiol 1997; 80: 51E-54E.
3. Theroux P, Fuster V. Acute coronary syndromes. Unstable angina and non-Q myocardial infarction. Circulation 1998; 97: 1195-1206.
4. Theroux P, White H, David D, et al. for the TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. Circulation 1994; 89: 1545-1556.
5. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998; 338: 1785-1792.
6. The Fragmin and Fast Revascularization during Instability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: Frisc II prospective randomised multicentre study. Lancet: 1999; 354: 708-715.
7. Cannon CP, Weintraub WS, Demopoulos LA, et al. For the TACTICS-Thrombolysis in Myocardial Infarction 18 investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa receptor inhibitor tirofiban. N Engl J Med 2001; 334: 1879-1887.
8. Van Miltenburg-Van Zijl AJM, Simoons ML, Bossuyt PMM, Taylor TR, Veerhoek MJ. Variation in the use of coronary angiography in patients with unstable angina is related to differences in patient population and availability of angiography facilities, without affecting prognosis. Eur Heart J 1996; 17: 1828-1835.
9. Yusuf S, Flather M, Pogue J, et al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. Lancet 1998; 352: 507-514.
10. De Feyter PJ, Suryapranata H, Serruys PW, et al. Coronary Angioplasty for Unstable Angina: Immediate and Late Results in 200 Consecutive Patients With Identification of Risk Factors for Unfavorable Early and Late Outcome. J Am Coll Cardiol 1988; 12: 324-333.
11. Bentivoglio LG, Detre K, Yeh W, Williams DO, Kelsey SF, Faxon DP. Outcome of percutaneous transluminal coronary angioplasty in subsets of unstable angina pectoris. A report of the 1985-1986; National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. J Am Coll Cardiol 1994; 24: 1195-206.
12. Boersma E, Akkerhuis M, Theroux P. Platelet glycoprotein IIb/IIIa receptor inhibition in Non-ST-Elevation acute coronary syndromes. Early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 1999; 100: 2045-2048.
13. Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. Eur Heart J 1998; 19: 1608-1616.
14. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.

15. Harrington RA. Clinical trials in acute coronary syndromes: lessons from PURSUIT. Eur Heart J 1999;1(suppl. R):R28-R34.
16. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. Circulation in press.
17. Bertrand ME, Simoons ML, Fox KAA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST-segment elevation. Recommendations of the task force of the European Society of Cardiology. Eur Heart J 2000; 17: 1406-1432.
18. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the ACC/AHA task force on practice guidelines. Circulation 2000; 102: 1193-2009.
19. Cohen M, Demers C, Gurfinkel EP, et al, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group: A comparison of low-molecular weight heparin with unfractionated heparin for unstable coronary disease. N Engl J Med 1997; 337: 447-452
20. The FRISC Study Group (Fragmin during instability in coronary artery disease study group). Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996; 347: 561-568.
21. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q wave myocardial infarction. Circulation 1999; 100: 1593-1601
24. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-61.
25. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularizatiom. N Eng J Med 1997; 336: 1689-1696.
26. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled rial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
27. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997; 349: 1429-1435
28. The ESPRIT investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised placebo-controlled trial. Lancet 2000: 356: 2037-44.

2.4

Early angioplasty in acute coronary syndromes without persistent ST-elevation improves outcome, but increases need for repeat revascularization.

An analysis of the PURSUIT trial.

Eelko Ronner[1,2], Eric Boersma[1], Gert-Jan Laarman[2], G. Aernout Somsen[3], Robert A Harrington[4], Jaap W. Deckers[1], Eric J. Topol[5], Robert M. Califf[4], Maarten L. Simoons[1]

[1] University Hospital Rotterdam, Rotterdam, The Netherlands
[2] Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[3] Academic Medical Center, Amsterdam, The Netherlands
[4] Duke Clinical Research Institute, Durham, North Carolina, USA
[5] Cleveland Clinic Foundation, Cleveland, Ohio, USA (AML, EJT)

Submitted

PURSUIT was supported by COR Therapeutics, Inc., South San Francisco, California and the Schering-Plough Research Institute, Kenilworth, New Jersey

Abstract

Percutaneous coronary intervention (PCI) is widely used for treatment of acute coronary syndromes without persistent ST-segment elevation (ACS). Moreover, restenosis and subsequent revascularization after PCI are more frequent in ACS than in stable angina. The optimal timing of PCI in ACS without persistent ST-segment elevation is unknown.

Methods and results. *In the PURSUIT database patients were stratified to time of PCI. In PURSUIT 9461 patients received a platelet glycoprotein IIb/IIIa inhibitor, eptifibatide or placebo for 72 hours. Other treatment was left to the investigators. 2430 patients underwent PCI within 30 days. Death and myocardial infarction at 30 days was not influenced by timing of PCI significantly in placebo treated patients: 15.9%, 17.7%, 15.0% to 18.2% for successive PCI cohorts respectively. When eptifibatide was administered lowest mortality and 30 day infarction was noted in patients undergoing PCI within 24 hours (9.2%), compared with 14.0% (24-72 hours) to 15.0% (day 4-7) and 17.4% (day 8-30). Repeat revascularization (during 165 days) was notably higher for PCI within 24 hours of enrollment (19% of 620 patients), than within 24 to 72 hours (16.7%, $n=624$), within 3 to 7 days (13.2%, $n=614$) and 8 to 30 days (7.7%, $n=561$); $p<0.001$; irrespective of eptifibatide use. This gradual reduction of revascularization rate for later PCI was also observed after multivariable analysis correcting for baseline characteristics and with time as a continuous variable.*

Implications. *PCI within 24 is associated with improved outcome but more frequent restenosis. Prospective analysis are needed to test the hypothesis that rapid PCI in ACS with a platelet glycoprotein IIb/IIIa receptor antagonist reduces myocardial infarction (possibly death), and is therefore most suited for patients at highest risk of infarction, despite a higher need for repeat revascularization.*

Introduction

Percutaneous coronary intervention (PCI) under protection of a platelet glycoprotein (GP) IIb/IIIa receptor inhibitor is a widely adopted treatment strategy for acute coronary syndromes (ACS) without persistent ST-segment elevation. However, the optimal timing of PCI in these patients remains uncertain. The question remains to what extent the patient should be stabilized before the procedure. Especially in high-risk ACS-patients recent guidelines suggest to intervene relatively early[1,2], after various reports demonstrated reduction of myocardial infarction and possibly death for invasive versus conservative treated patients[3,4].

A consequence of PCI, however, is restenosis, and increased restenosis rates in unstable angina have been reported in comparison with stable angina[5-7], although others demonstrated no difference[8,9]. The exact relation between restenosis and the effect of timing of PCI in ACS is largely unknown. Therefore an analysis was performed of the PURSUIT[7] study *(Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy)* to verify the impact of timing of angioplasty on repeat revascularization and long term outcome in patients with acute coronary syndromes.

Methods

Patient population

The design and methods of PURSUIT have been described previously. In short: patients were enrolled within 24 hours of an episode of ischemic chest pain (>10 minutes) with transient ST-elevation (>0.5 mm), transient or persistent ST-depression (>0.5 mm), T-wave inversion (>0.1 mm), or elevation of the creatine kinase MB-fraction (CK-MB) above the upper limit of normal (ULN). There were no age-limits. Eptifibatide or placebo was administered for 72 hours, and up to 24 hours after PCI, to a maximum of 96 hours. Additional treatment, including interventions was left entirely to the investigators.

Four patient groups of approximately the same size were compared according to time of PCI. Comparing patients in whom PCI was performed within 24 hours, from 24 to 72 hours, between 3 and 7 days and from 8 days to 30 days. No systematic follow-up angiography for analysis of restenosis was performed. Subsequent revascularization was pragmatically defined as any repeat revascularization. In PURSUIT follow up after enrollment was 6 months. In the present analysis follow up after PCI was limited to 5.5 month (165 days) after first PCI to achieve similar length of follow up, for different groups of patients.

The primary efficacy endpoint of PURSUIT was a composite of death or nonfatal

myocardial (re)infarction (MI) at 30 days. Within 18 hours of enrolment MI was diagnosed on the basis of ischemic chest pain and new ST-segment elevation. After 18 hours, MI was diagnosed on the basis of new Q waves, or new or repeated CK-MB elevations above the ULN. For patients undergoing percutaneous intervention, CK-MB elevation above three times the ULN was required. Endpoints in this analysis were subsequent revascularization until 5.5 months after initial PCI and death and non-fatal MI. In addition, repeat revascularization was described at 30 day follow up and thereafter until 165 days after initial PCI.

Statistical analysis

There were 2,419 patients in PURSUIT undergoing a PCI within 30 days of enrollment, constituting 26% of the 9,461 patients enrolled. These patients were stratified in four groups according to the time of intervention: within 24 hours of randomization, within 24 to 72 hours, within 3 to 7 days, and within 8 to 30 days, respectively. Chi-square tests, Student's t-tests and one-way analyses of variance were applied to investigate differences in baseline characteristics between these groups.

Outcomes were evaluated by Chi-square tests. Univariable and Cox multivariable logistic regression analyses were applied to describe the relation between timing of PCI and the risk of repeat revascularization. Characteristics that influence restenosis and prognosis as described in other models were included[10]. Statistical significance of all tests was stated at the $P = 0.05$ level.

Results

Patient population

PCI was performed in 620 patients within 24 hours, 624 after 24 to 72 hours, in 614 patients day 3 till day 7, and 561 from 8 days to 30 days (median 12 days) after enrollment. Significant differences were apparent among these patient groups (table 1). In particular, more North Americans received PCI within 24 hours (82% of all day 1 treated patients) (Table 1), and most day 8 to day 30 procedures were performed in Western European centers (69%). Hypertension was more frequent in earlier treated patients, as well as younger age and ST-depression at enrollment. Prior PCI was observed more frequently in earlier treated patients. More medication was used in earlier treated patients, a finding that reached significance for aspirin and nitrates. As demonstrated in Table 2 more TIMI 0 and 1 flow was observed at angiography before PCI in patients receiving PCI day 1 versus later PCI. In addition, the culprit lesions were more often not determined, when multiple lesions were present, in the late treated group.

Table 1
Baseline clinical characteristics

	Time from randomization to PCI								
	0 - 24h		>24 - 72h		>72 - 168h		>168 - 720h		P-value
	N	(%)	N	(%)	N	(%)	N	(%)	
Patients	620	(100)	624	(100)	614	(100)	561	(100)	
Demographics									
Mean age ± SD (years)	60 ± 11		60 ± 11		61 ± 11		62 ± 10		0.004
Male gender	423	(68)	437	(70)	432	(70)	408	(73)	0.410
Geographic region									
Western Europe	97	(16)	168	(27)	264	(43)	386	(69)	<0.001
Eastern Europe	11	(2)	20	(3)	30	(5)	53	(9)	
North America	507	(82)	424	(68)	294	(48)	95	(17)	
Latin America	5	(1)	11	(2)	26	(4)	27	(5)	
Risk factors and history									
Hypertension	363	(59)	334	(54)	332	(54)	262	(47)	<0.001
Diabetes mellitus	128	(21)	135	(22)	131	(21)	100	(18)	0.358
Current smoker	212	(34)	194	(31)	198	(33)	183	(33)	0.947
Hyperlipidaemia	289	(47)	288	(46)	285	(46)	257	(46)	0.993
PVD	37	(6)	24	(4)	44	(7)	45	(8)	0.017
Prior MI	188	(31)	161	(26)	187	(31)	143	(26)	0.072
Heart failure	38	(6)	35	(6)	46	(7)	36	(6)	0.587
Prior CVA	14	(2)	25	(4)	11	(2)	20	(4)	0.066
Prior PCI	153	(25)	130	(21)	118	(19)	75	(13)	<0.001
Prior CABG	90	(15)	92	(15)	80	(13)	69	(12)	0.560
Chronic medication									
Aspirin	459	(74)	447	(72)	427	(70)	336	(60)	<0.001
Beta-blocker	316	(51)	304	(49)	294	(48)	243	(43)	0.065
Calcium antagonist	195	(31)	210	(34)	187	(30)	158	(28)	0.230
Nitrates	476	(77)	457	(73)	445	(72)	327	(58)	<0.001
ACE inhibitors	125	(20)	116	(19)	123	(20)	105	(19)	0.846
Presenting characteristics									
MI at enrollment	282	(45)	300	(48)	298	(49)	260	(46)	0.643
ST-depression	237	(38)	241	(39)	277	(45)	277	(49)	<0.001
ST-elevation	120	(19)	116	(19)	93	(15)	94	(17)	0.207
T-wave inversion	342	(55)	330	(53)	325	(53)	285	(51)	0.521

ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CVA: cerebro-vascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vessel disease

Table 2
Baseline angiographic characteristics

	Time from randomization to PCI								P-value
	0 - 24h		>24 - 72h		>72 - 168h		>168 - 720h		
	N	(%)	N	(%)	N	(%)	N	(%)	
Patients	620	(100)	624	(100)	614	(100)	561	(100)	
Urgent intervention	217	(38)	125	(21)	109	(20)	98	(25)	
Culprit lesion location									
RCA	179	(29)	162	(26)	153	(25)	103	(18)	<0.001
LAD	227	(37)	219	(35)	245	(40)	201	(36)	
LCX	144	(23)	143	(23)	129	(21)	123	(22)	
LM	2	(0)	5	(1)	3	(0)	4	(1)	
Graft	39	(6)	43	(7)	31	(5)	13	(2)	
Not defined	29	(5)	52	(8)	53	(9)	117	(21)	
Mean ± SD DS (%) of culprit lesion	168	(34)	138	(30)	129	(26)	113	(27)	0.036
TIMI-flow grade 0 or 1 pre-PCI in culprit vessel									
Vessel disease §									
0 (i.e. DS < 50%)	14	(2)	12	(2)	25	(4)	96	(17)	<0.001
1	324	(52)	318	(51)	294	(48)	235	(42)	
2	183	(30)	183	(29)	184	(30)	141	(25)	
3	81	(13)	87	(14)	91	(15)	72	(13)	
LM	18	(3)	24	(4)	20	(3)	17	(3)	
Vessels dilated									
1	546	(88)	539	(86)	532	(87)	376	(67)	<0.001
2	26	(4)	36	(6)	34	(6)	28	(5)	
3	0	(0)	3	(0)	0	(0)	2	(0)	
Left Main	5	(1)	6	(1)	5	(1)	4	(1)	0.972
Graft lesion	51	(8)	42	(7)	32	(5)	16	(3)	<0.001
Stent used	313	(50)	312	(50)	311	(51)	198	(35)	<0.001
Procedural success #	582	(94)	591	(95)	572	(95)	402	(95)	0.815

DS: diameter stenosis; LAD: left anterior descending; LCX: left circumflex; LM: left main; RCA: right coronary artery; SD: standard deviation. Other abbreviations as in table 1. Percentages can demonstrate lower than expected from patients in the specific group due to occasional missing data. Vessels dilated 1, 2, and 3 are mentioned without left main and graft lesions.
§ Vessel disease: the number of vessels with at least one lesion ≥50% diameter stenosis
# Procedural success: <50% DS in all lesions treated

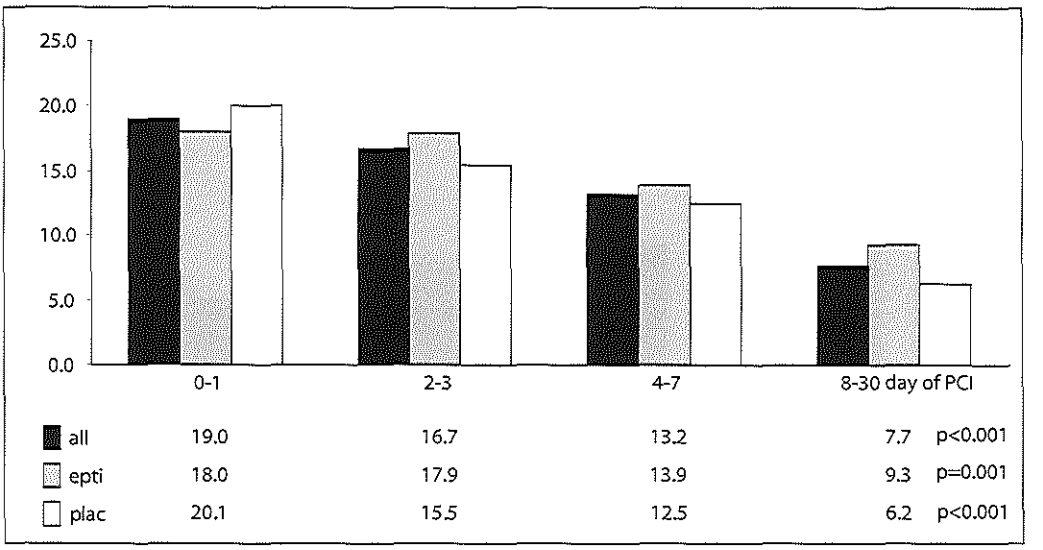


Figure 1 Total repeat revascularization (%) within 165 days of PCI in relation to timing of percutaneous coronary intervention in patients enrolled in the PURSUIT trial.

Repeat revascularization

Repeat revascularization was performed in 19.0% of patients who underwent initial PCI within 24 hours, 16.7% for patients treated day 2 and 3, and only 13.2% for PCI day 4 through 7 and 7.7% for PCI from day 7 to day 30 (Figure 1, $p = 0.001$).

Univariable and multivariable analysis confirmed the predictive value of timing of initial PCI on the frequency of repeat revascularization. Using timing of PCI either as a continuous or as a categorical variable, the p value in this analysis was < 0.0005. From figure 2 it is evident that most repeat revascularization occurred early. Geographic region was not related to repeat revascularization in multivariable analysis.

Early and late repeat revascularization

In separate analyses of repeat revascularization within or after 30 days, both early and late repeat revascularization were found to be related to the timing of initial PCI, independent of other baseline characteristics (Figures 2 and 3). In patients randomized to placebo, 30 day repeat revascularization was 13.7% when initial PCI was performed on day 1, 11.4% when initial PCI was performed day 2 or 3, 8.3% for PCI at day 4 to 7 and 5.2 % after 7 days of enrollment in PURSUIT ($p = 0.002$). For eptifibatide treated patients 30 day repeat revascularization did not demonstrate this highly significant trend. Repeat revascularization in eptifibatide treated patients was observed in 10.8% for day 1 PCI, 8.7% and 9.1 % for patients who underwent PCI day 2 to 3 or 4 to 7 respectively, and 6.3% for patients in whom initial PCI was performed after 7 days ($p = 0.304$).

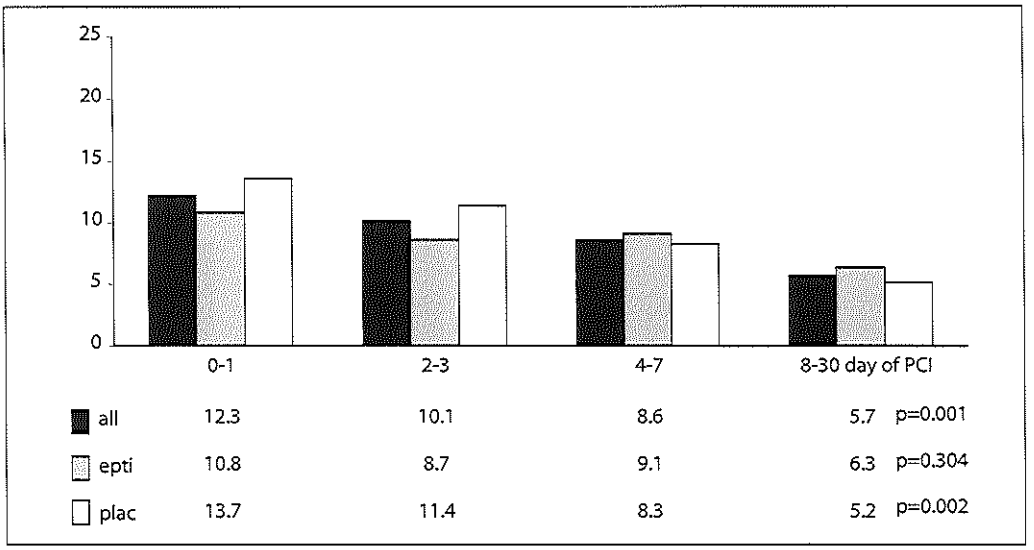


Figure 2 Repeat revascularization within 30 days (%) in relation to timing of percutaneous coronary intervention in patients enrolled in the PURSUIT trial.

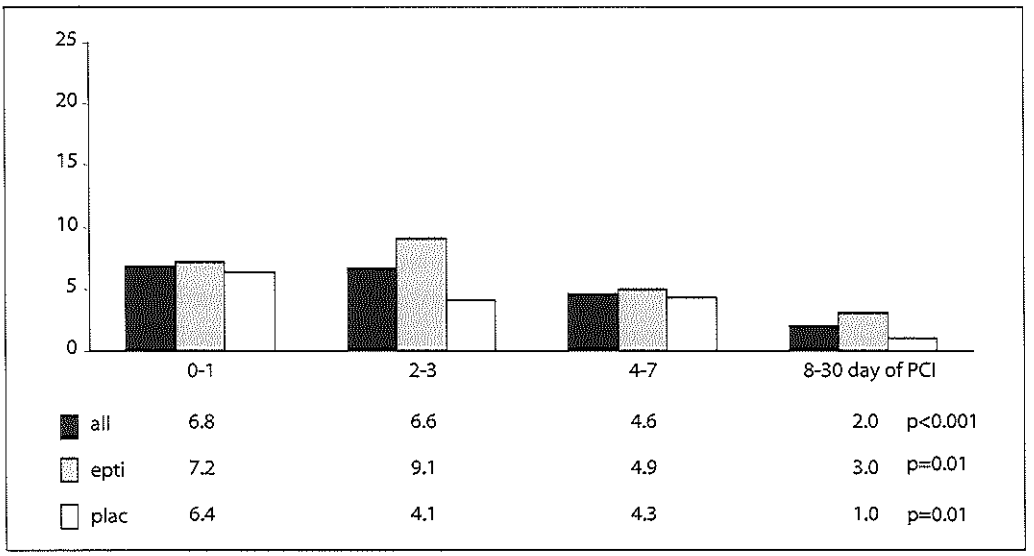


Figure 3 Repeat revascularization within 165 days (%), but after 30 days of PCI in relation to timing of percutaneous coronary intervention in patients enrolled in the PURSUIT trial.

"Late" repeat revascularization after one month of initial PCI up to 165 days of follow up was significantly dependent on time of initial PCI (Figure 3). This held true for both placebo and eptifibatide treated patients. There was a significant decrease in repeat revascularization when PCI was performed later. This difference was 6.8%

repeat revascularization for all patients who underwent PCI within a day of enrollment in PURSUIT, down to 2.0% for patients who had PCI after one week ($p < 0.001$). Especially patients undergoing PCI day 2 or 3 on eptifibatide demonstrated repeat revascularization in this retrospective analysis.

MI and mortality

The occurrence of MI and death was clearly influenced by timing of PCI in patients treated with eptifibatide as addressed in a separate report[11]. Especially PCI within 24 hours under protection of a platelet GP IIb/IIIa receptor antagonist demonstrated favorable 30 day outcome of 9.2% versus 14.0% to 17.4% for later PCI.

In placebo treated patients death and MI at 30 days ranged between 15.9% for PCI within 24 hours to 17.7% for PCI from 24 to 72 hours, 15.0% for PCI from day 4 to 7 and 17.4% for patients treated between day 8 to 30. In placebo treated patients no relation between timing of PCI and MI or mortality was apparent. Early procedures in placebo patients were associated with higher procedural event rates that balanced the reduction of subsequent post procedural death and MI.

Discussion

This retrospective analysis of PURSUIT demonstrated improved outcome (fewer MI) in patients undergoing PCI within 24 hours after enrollment but an increase of repeat revascularization when PCI is performed early. Revascularization rates were reduced from 27% (day 1 PCI) to 18% for PCI after 1 week (median day 12).

This observation held in uni- and multivariable analyses. To explain this finding, it is important to note that increased revascularization rates for patients undergoing early PCI are demonstrated for repeat revascularization occurring within a month as well as from 1 month up to 5.5 months.

Early (within one month of PCI) repeat revascularization is conceivably caused by mainly thrombotic complications alone or in combination with elastic recoil[12,13]. This thrombotic component of early revascularization is perhaps antagonized by eptifibatide. In patients receiving a platelet glycoprotein IIb/IIIa receptor blocker in acute MI in adjunct to primary PCI this reduction in urgent revascularization is well known[14].

In contrast to urgent revascularization, which is characterized by thrombus, in late restenosis intima hyperplasia is the key determinant. It is conceivable that intervention in a vessel after stabilization of disease and plaque stabilization leads to smaller inflammatory response with less intima proliferation and subsequent less development of restenosis and lower need for (late) repeat revascularization[15].

Indirect support for our finding comes from data on C-reactive protein and restenosis. Just as we demonstrated for time-of-PCI-since-presentation (in patients with ACS

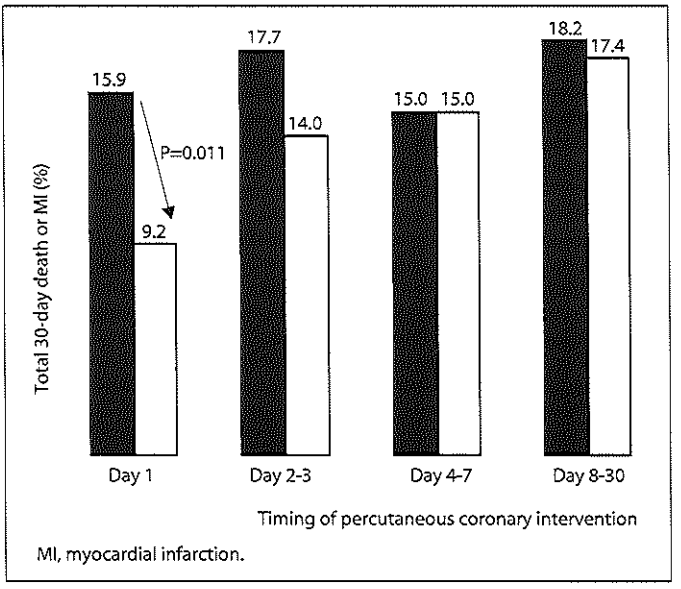


Figure 4 Death and myocardial infarction at 30 days according to time of percutaneous coronary intervention.

without persistent ST-segment elevation), elevated C-reactive protein proved a predictor for repeat revascularization[16]. This acute phase protein is a general inflammation marker, and is associated with progression of atherosclerosis and the severity of ACS without persistent ST-segment elevation as demonstrated in multiple large clinical trials like FRISC and CAPTURE[17,18,19]. Likewise, post-procedural C-reactive protein elevation after PCI demonstrated related to repeat revascularization as well. Another report demonstrated that patients with higher pre-procedural C-reactive protein react to PCI with higher procedural rise of C-reactive protein[20]. This suggests that state of disease, as represented by C-reactive protein, which is most likely related to time since acute complaints is strongly related to outcome.

Vessel pacification by deferring PCI seems therefore attractive with respect to repeat revascularization. However, "cooling down" of ACS before PCI may be unfavorable with respect to 30 day myocardial infarction and possibly death. In multiple recent trials and PURSUIT sub-analyses benefit of intervention over conservative treatment are demonstrated (Figure 4)[21,22,23]. For example, the recently published FRISC-2 trial demonstrated benefit for intervention versus conservative treatment. Intervention was performed at day 4 (median)[3]. Six month death and MI was 9.4% for intervention versus 12.1% in conservative treated patients ($p = 0.03$). In this trial, only 10% platelet GP IIb/IIIa receptor antagonists were administered in both the invasive and the conservative arm. Mean time of PCI was at day 4. Another recently reported trial, the TACTICS-TIMI 18 trial demonstrated benefit for early invasive strategy ($n = 1114$) compared to medical management ($n = 1106$) as well. Significantly less 30 day death

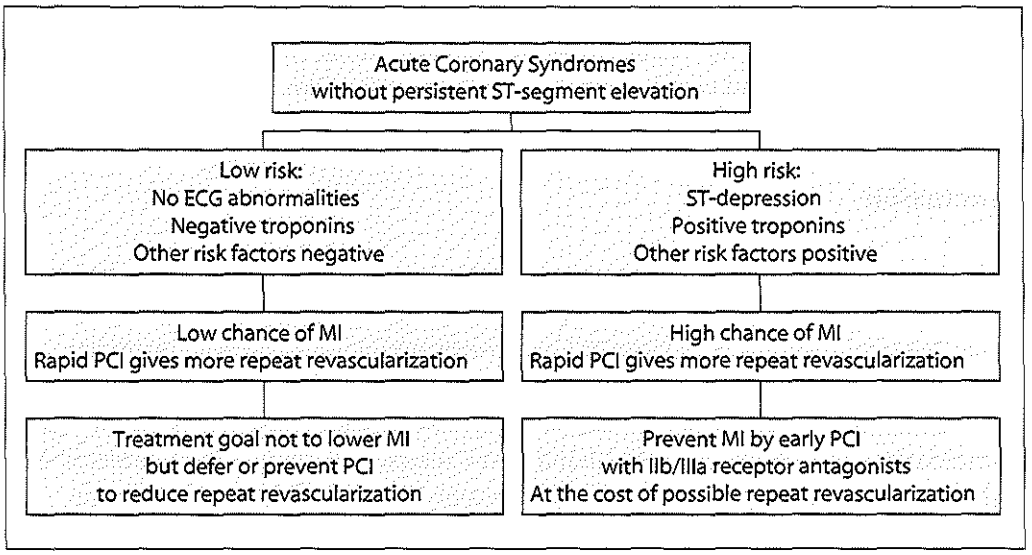


Figure 5 Different treatment goals in different patient categories.

and MI was observed in the early invasive arm (4.7%) compared with conservative treated patients (7.0%)[24].

Not surprisingly, current European and American guidelines for treatment of ACS recommend rapid PCI under protection of a platelet GP IIb/IIIa receptor antagonist in high risk patients[1,2]. How rapid this should be is however not stated in either guideline. Our recent PURSUIT report on timing of PCI demonstrated 9.2% 30 day death and MI for patients receiving day 1 PCI with eptifibatide versus 14.0 to 18.2 % events for other groups with and without PCI and eptifibatide ($p < 0.001$)[11].

Our finding counterweighs the benefit of reduction of MI seen with rapid PCI, does in our opinion not influence treatment of highest risk patients. It seems rational to treat highest risk patients with rapid PCI, to prevent MI, at the possible cost of more revascularization. Low risk patients may be better of with "watchful waiting", as infarcts are unlikely to occur and repeat revascularization can be avoided (Figure 5).

Limitations

It is emphasized that retrospective analysis of data can be misleading. A particular limitation for this specific analysis is the lack of detailed angiographic data in the PURSUIT trial. Most notably, lesion characteristics that predict restenosis, like length, calcification and tortuositas of the lesion were not recorded. It is possible that adverse angiographic revascularization predictors were not evenly spread throughout groups. Of interest in this respect is the fact that use of stents (approximately 50% throughout groups) was not related to repeat revascularization rates. This may be explained

by selection of angiographic lesions with high risk of revascularization in stented patients more than balloon treated patients. Elective versus bailout stenting was not specifically recorded and could constitute another explanation.

Conclusion

A clear inverse relation was demonstrated between time of PCI and subsequent need for 5.5 months repeat revascularization. Although retrospective, this decrease of repeat revascularization with later PCI was confirmed in multivariable analysis.

In treatment of ACS as seen in PURSUIT retrospectively, there seems to be a trade-off in timing of PCI. There is a benefit of deferred PCI with respect to need for repeat revascularization, but on the other hand there seems a negative effect deferred PCI with respect to myocardial infarction, and possibly death and costs of treatment.

Current recommendations to intervene early under protection of a platelet GP IIb/IIIa receptor antagonist are clear for high risk groups. For other groups the issue remains unresolved. If chances of developing MI are low, "watchful waiting" and performing PCI when symptoms or ischemia recurs seems attractive. It should be stressed however that prospective studies are needed to verify these findings.

References

1. Bertrand ME, Simoons ML, Fox KAA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST-segment elevation. Recommendations of the task force of the European Society of Cardiology. Eur Heart J 2000; 17: 1406-1432.
2. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the ACC/AHA task force on practice guidelines. Circulation 2000; 102: 1193-2009.
3. Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet; 2000, 356: 9-16.
4. Cannon CP, Weintraub WS, Demopoulos LA, et al. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial. Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis In Myocardial Infarction. Am J Cardiol 1998; 82: 731-736.
5. De Feyter PJ, Suryapranata H, Serruys PW, Beatt K, van Domburg R, van den Brand M, Tijssen JJ, Azar AJ, Hugenholtz PG: Coronary Angioplasty for Unstable Angina: Immediate and Late Results in 200 Consecutive Patients With Identification of Risk Factors for Unfavorable Early and Late Outcome. J Am Coll Cardiol 1988; 12: 324-333.

6. Hermans WR, Foley DP, Rensing BJ, et al. Morphologic changes during follow-up after successful percutaneous transluminal coronary balloon angioplasty: quantitative angiographic analysis in 778 lesions–further evidence for the restenosis paradox. MERCATOR Study Group (Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal Coronary Obstruction and Restenosis). Am Heart J 1994; 127: 483-494.
7. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.
8. Mintz GS, Popma JJ, Pichard AD, et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. J Am Coll Cardiol 1996; 27: 1678-1687.
9. Keelan ET, Nunez BD, Grill DE, et al. Comparison of immediate and long-term outcome of coronary angioplasty performed for unstable angina and rest pain in men and women. Mayo Clin Proc 1997; 72: 5-12.
10. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000; 101: 2557-2567.
11. Ronner E, Boersma E, Akkerhuis KM, et al. Patients with acute coronary syndromes without persistent ST-elevation undergoing percutaneous coronary intervention benefit most of early intervention with protection by a glycoprotein IIb/IIIa receptor blocker. Submitted.
12. Ellis SG, Roubin GS, King SB III, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988; 77: 372 - 379.
13. Mak KH, Belli G, Ellis SG, Moliterno DJ. Subacute stent thrombosis: evolving issues and current concepts. J Am Coll Cardiol 1996; 27: 494 - 503.
14. Brener SJ, Barr LA, Burchenal JEB, Katz S, George BS, Jones AA, Cohen ED, Gainey PC et al, on behalf of the Reopro and primary PTCA organization and randomized trial (RAPPORT) investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734-741.
15. Liuzzo G, Buffon A, Biasucci LM, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. Circulation 1998; 98: 2370-2376.
16. Heeschen C, Hamm CW, Bruemmer J, Simoons ML.Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. J Am Coll Cardiol 2000; 35:1535-1542.
17. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994; 331: 417-424.
18. Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. Circulation 1997; 96: 4204-4210.
19. Biasucci LM, Liuzzo G, Grillo RL, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation 1999; 99: 855-860.
20. Tomoda H, Aoki N. Instability of coronary lesions in unstable angina assessed by C-reactive protein values following coronary interventions. Am J Cardiol 2001; 87: 221-223.
21. Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. PURSUIT Investigators. Circulation 2000; 101: 751-757.
22. Marzocchi A, Piovaccari G, Marrozzini C, et al. Results of coronary stenting for unstable

versus stable angina pectoris. Am J Cardiol 1997; 79: 1314-1318.
23. Cannon CP, Weintraub WS, Demopoulos LA, Robertson DH, Gormley GJ, Braunwald E. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial. Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis In Myocardial Infarction. Am J Cardiol 1998; 82: 731-736.
24. Cannon CP, Weintraub WS, Demopoulos LA, et al. For the TACTICS investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa receptor inhibitor tirofiban. N Engl J Med 2001; 344: 1879-1887.

3 Acute coronary syndromes with persistent ST-segment elevation

3.1

The use of platelet glycoprotein IIb/IIIa receptor antagonists during the acute phase of myocardial infarction

Marcel van den Brand[1] and Eelko Ronner[2]

[1] Department of interventional cardiology, Thoraxcenter, University Hospital Dijkzigt, The Netherlands
[2] Thoraxcenter, University Hospital Dijkzigt, The Netherlands

Seminars of Interventional Cardiology 1999; 4: 85-87

Introduction

The era of thrombolysis in myocardial infarction started after the recognition that a myocardial infarction is caused by thrombus, overlying a ruptured or otherwise thrombogenic plaque[1]. The thrombolytic agents used today produce a substantial survival benefit, especially if instituted early after the occurrence of a myocardial infarction. Nevertheless full reperfusion of the infarcted area, as judged by the qualitatively analysed TIMI 3 epicardial coronary blood flow, is only achieved in 50% of patients, 90 minutes after administration of thrombolytic agents[2]. Primary angioplasty may achieve higher TIMI 3 grade coronary flow, but will by its interventional nature, continue to be confined to larger centres[3]. After successful opening of the culprit artery by intraveneous thrombolytic therapy, the effect of reperfusion is counteracted by a 10% reocclusion rate[2]. Fresh arterial thrombi are generally rich in platelets and are less susceptible to lysis by thrombolytic agents. The action of aspirin, although beneficial, by blocking the cyclo-oxygenase pathway, leading to inhibition of thromboxane A2 formation, is also weak[4]. Other platelet agonists can cause activation of the final common pathway of platelet aggregation by exposing the IIb/IIIa receptor through thromboxane A2 independent pathways[5].

Preclinical studies

Several studies have shown that GP IIb/IIIa receptor blockade could enhance thrombolysis with alteplase and prevent reocclusion in experimental coronary thrombosis[6-10]. Subgroup analysis of the EPIC study, administering the GP IIb/IIIa receptor blocker abciximab or placebo to high risk angioplasty patients, confirmed a clinical benefit in patients with an acute myocardial infarction, randomised to active treatment[11]. Angiographic data suggested a dethrombotic effect of abciximab, resulting in the disappearance of visible intracoronary thrombi, after treatment with abciximab[12]. Research in patients with acute myocardial infarction has centered around the application of GP IIb/IIIa receptor blockers as an adjunct to primary angioplasty, or to facilitate thrombolysis with thrombolytic agents.

Primary angioplasty

When dog coronary arteries were subjected to balloon injury, the pretreatment with abciximab, prevented coronary occlusion to a large extent[13]. The first clinical indication for a beneficial effect of abciximab as an adjunct to primary angioplasty, came from a subgroup analysis from EPIC[11]. In this study, enrolling high risk PTCA patients,

in retrospect 64 patients had been included with primary or rescue angioplasty. The results in the abciximab bolus plus infusion group were better than in comparable placebo patients. The same trends towards a better outcome for primary PTCA patients pretreated with GP IIb/IIIa receptor blockers came from a subgroup analysis of three other trials IMPACT II, RESTORE and Gusto III[14-16].

In the RAPPORT trial patients with an acute MI were randomised within 12 hours after onset of symptoms to abciximab or placebo, prior to primary angioplasty[17]. Non significant higher TIMI 2 and 3 flow rates were observed before angioplasty: 34.1% for abciximab and 25.5% for placebo patients. The primary combined endpoint at 6 months including death, reinfarction and any target vessel rerevascularisation, occurred in equal numbers: 28.1% in the placebo group and 28.2% in the abciximab group. When only patients were analysed who actually had both study drug infusion and underwent primary angioplasty, the reduction in the combined primary endpoint from 31.9% to 28.0% was also not significant. The additional treatment with abciximab which led to a modest reduction in primary endpoint events, in the actual treated patients, without a reduction when all patients were analysed, almost doubled the incidence of severe bleeding (16.6% vs 9.5%, $p = 0.02$).

The total amount of data of patients with acute myocardial infarction, undergoing primary angioplasty with GP IIb/IIIa receptor blockers, is limited, and needs further study.

Also the role of GP IIb/IIIa receptor blockers in patients with AMI and treated with primary stenting needs further evaluation. The first results from Munich show that patients suffering from AMI undergoing primary stenting and randomly treated with abciximab, have a higher peak flow velocity of the infarct related artery, a better left ventricular function and less clinical events, when compared to patients treated with standard therapy alone[18].

GP IIb/IIIa receptor blockade as adjunct to thrombolytic therapy

Animal experiments showed a better reperfusion when thrombolytic agents were combined with GP IIb/IIIa receptor blockers after induced coronary thrombosis[19-22].

Also the rate of reocclusion was lower when thrombolytic agents and antiplatelet IIb/IIIa receptor blockers were combined. After these animal experimental data had been confirmed in several studies, the cost and benefit in humans, particulary bleeding and clinical outcome, needed to be established.

In the first human study, TAMI 8, the interval between the administration of tPA and the murine antibody m7 E3 fab was progressively shortened from 15 hours to 3 hours. Also the bolus dose of the antibody was increased from 0.1mg/kg to 0.25 mg/kg, while aspirin was administered as early as possible. A full or reduced dose of heparin,

respectively 90 minutes, 4 hours and 5 hours after the start of tPA bolus (60 mg) and infusion (40 mg) for 2 hours was also administered. Both recurrent ischemia and TIMI grade 2 or 3 coronary flow were significantly improved, when m7 E3 fab and tPA were combined, however CABG related bleeding was higher in patients receiving combination therapy[23]. Another pilot study combined streptokinase and different doses of eptifibatide in 181 patients with AMI. Although there was an increased TIMI 2 and 3 flow at 90 minutes, (79% vs 62%) when patients were treated with the combination therapy, this result came at a cost of increased bleeding rates[24].

The combination of tPA and eptifibatide after AMI, together with aspirin and heparin, was subsequently evaluated in the IMPACT-AMI study[25]. Increasing doses of eptifibatide were administrated to 180 patients within 6 hours of AMI, directly after the administration of tPA. After an initial phase of open label eptifibatide administration or placebo in a 2:1 ratio, in phase II patients were randomised in a 3:1 ratio to the highest dose of eptifibatide. TIMI grade 3 flow at 90 minutes was present in 66% of eptifibatide treated patients, versus 39% of control patients (p = 0.006). An analysis of ST-segment recovery showed a shortening of this measure of reperfusion from 116 minutes in placebo patients to 65 minutes in patients receiving the highest dose of eptifibatide. In contrast with the previous SK - eptifibatide study, this beneficial result did not come at a price of severe bleeding events. The study was too small to detect any differences in clinical outcome.

Another study, PARADIGM, explored the combination of lamifiban and tPA or streptokinase in patients within 12 hours of AMI[26]. After an initial dose finding phase in order to achieve a 85% - 95% inhibition of ADP induced platelet aggregation, patients were in the second phase randomized to lamifiban bolus and infusion or placebo in a 2:1 ratio. Continuous ECG monitoring indicated a shorter time to steady state ST-segment resolution, and a higher patency rate at 90 minutes of 236 lamifiban treated patients, compared with 117 placebo patients. Although the study was underpowered to detect differences in clinical outcomes, an increased bleeding tendency in patients treated with lamifiban and either streptokinase or tPA was obvious. Two cerebral hemorrhages versus 0, and 5.6% gastro intestinal bleedings versus 0.9% were observed in the patients treated with lamifiban, and placebo respectively.

The largest and most complete study of the combination of lytic therapy and GP IIb/IIIa antagonists has recently been published by Antman et al.[27]. In this TIMI 14 study, 888 patients with ST-segment elevation MI, were enrolled within 12 hours of onset. All patients received aspirin and heparin, and one of four thrombolytic treatments: group 1 received 100 mg alteplase, group 2 abciximab 0.25 mg/kg as a bolus and 0.125 mg/kg/min as a 12 hours infusion, group 3 and 4 received the same dose of abciximab and various reduced doses of respectively streptokinase and alteplase. TIMI 3 flow at 90 minutes, the primary endpoint of the study, was observed in 57% of group 1, in 32% of group 2, in 34% - 80% of group 3 and in 38% - 76% of group 4. The

highest efficacy and safety was established with a regimen of aspirin, very low dose heparin (30 U/kg bolus plus 4 U/kg/hr infusion), full dose abciximab and alteplase 15 mg bolus and 35 mg infusion over 1 hour. The patency rate established at 90 minutes by means of angiography after the above mentioned regimen of alteplase and abciximab was 76%, which compares favourably with full patency rates of 57%, and 32% after alteplase or abciximab alone respectively. The GUSTO - I trial also demonstrated 54% complete patency after alteplase but only 32% after 1.5 x 106 U streptokinase[2].

The GRAPE - pilot study evaluated the effect of administering abciximab at hospital admission, before primary angioplasty after recent myocardial infarction. After a median time interval of 45 minutes between abciximab bolus administration and first injection for angiography, TIMI 3 flow in the infarct related artery was 29%[28], comparable with 32% at 90 minutes after abciximab alone in the TIMI 14 trial.

Conclusion

The main goals of reperfusion therapy are quick and complete restoration of blood flow after coronary occlusion, at an acceptable risk of complications. Whether this better can be achieved by primary PTCA, the mechanistic approach, or by medical therapy, the holistic approach, is at the moment undecided. In dedicated centres, providing a 24 hour service, primary angioplasty might be the better choice, while hospitals, not experienced in doing primary angioplasty, or hospitals without angioplasty facilities, have no choice between the two therapies. It is encouraging that the optimal medical reperfusion therapy in achieving the best 90 minutes TIMI 3 flow after infarction, at acceptable bleeding risk, has recently been established. Numerous studies will be needed to re-establish the relative advantages of primary angioplasty with or without GP IIb/IIIa blockers over combinations of alteplase (or other thrombolytic agents) and abciximab (or other GP IIb/IIIa receptor blockers). Other large studies will be needed to prove that the optimal lytic medication after infarction, not only leads to a high TIMI 3 flow, but translates into less events and a higher survival at longer term follow up. Finally different infarcts could lead to different treatments, not only governed by the absence of interventional facilities or the presence of a bleeding tendency, but by sound cost effectiveness calculations in different patient populations, presenting with different types of infarction.

References

1. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980; 303: 897-902.

2. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-1622.
3. The GUSTO IIb Angioplasty Substudy Investigators. An international randomized trial of 1138 patients comparing primary coronary angioplasty versus tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997; 336: 1621-1628.
4. The ISIS-2 collaborative group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17, 187 cases of suspected acute myocardial infarction: ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988; 2: 349-360
5. Coller BS. Antiplatelet agents in the prevention and therapy of thrombosis. Annu Rev Med 1992; 43: 171-180.
6. Yasuda T, Gold H, Leinbach RC, et al. Lysis of plasminogen activator-resistant platelet-rich coronary artery thrombus with combined bolus injection of recombinant tissue-type plasminogen activator and antiplatelet glycoprotein IIb/IIIa antibody. J Am Coll Cardiol 1990; 16: 1728-1735.
7. Gold HK, Garabedian HD, Dinsmore RE, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators: observations in animals and humans. Circulation 1997; 95: 1755-1759.
8. Yasuda T, Gold HK, Fallon JT, et al. Monoclonal antibody against the platelet glycoprotein (GP) IIb/IIIa receptor prevents coronary artery reocclusion after reperfusion with recombinant tissue-type plasminogen activator in dogs. J Clin Invest. 1988; 81: 1284-1291.
9. Jang IK, Gold HK, Ziskind AA, et al. Differential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi in lysis with recombinant tissue-type plasminogen activator: a possible explanation for resistence to coronary thrombolysis. Circulation 1989; 79: 920-928.
10. Kohmura C, Gold H, Yasuda T et al. A chimeric murine/human antibody Fab fragment directed against the platelet GPIIb/IIIa receptor enhances and sustains arterial thrombolysis with recombinant tissue-type plasminogen activator in baboons. Arterioscler Thromb 1993; 13: 1837-1842.
11. Lefkovits J, Ivanhoe RJ, Califf RM, et al. Effects of platelet glycoprotein IIb/IIIa receptor blockade by a chimeric monoclonal antibody (abciximab) on acute and six-month outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol. 1996; 77: 1045-1051.
12. Muhlestein, JB, Karagounis, LA, Treehan, S, et al. "Rescue" utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997; 30:1729-34.
13. Bates ER, McGillem MJ, Mickelson JK, Pitt B, Mancini GB. A monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor complex prevents platelet aggregation and thrombosis in a canine model of coronary angioplasty. Circulation 1991; 84: 2463-2469.
14. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. Lancet 1997; 349: 1422-1428.
15. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997; 96: 1445-1453.
16. Miller JM, Smalling R, Ohman EM, et al. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarc-

tion (results from the GUSTO-III trial). Global use of strategies to open occluded coronary arteries. A J Cardiol 1999; 84: 779-784.
17. Brener SJ, Barr LA, Burchenal JEB, Katz S, George BS, Jones AA, Cohen ED, Gainey PC et al, on behalf of the Reopro and primary PTCA organization and randomized trial (RAPPORT) investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734-741.
18. Neumann FJ, Blasini R, Dirschinger J, et al. Intracoronary stent implantation and antithrombotic regimen in acute myocardial infarction randomized placebo-controlled trial of the fibrinogen receptor antagonist abciximab. Circulation 1998; 98: 734-741,
19. Roux SP, Tschopp TB, Kuhn H, et al. Effects of heparin, aspirin and a synthetic platelet glycoprotein IIb-IIIa receptor antagonist (Ro 43-5054) on coronary artery reperfusion and reocclusion after thrombolysis with tissue-type plasminogen activator in the dog. J. Pharmacol. Exp. Ther. 1993; 264: 501-508.
20. Mickelson JK, Simpson PJ, Cronin M, et al. Antiplatelet antibody 7E3 F(ab)2 prevents rethrombosis after recombinant tissue-type plasminogen activator-induced coronary artery thrombosis in a canine model. Circulation 1990; 81: 617-627.
21. Yasuda T, Gold HK, Leinbach RC, et al. Kistrin, a polypeptide platelet GPIIb/IIIa receptor antagonist, enhances and sustains coronary arterial thrombolysis with recombinant tissue-type plasminogen activator in a canine preparation. Circulation 1991; 83: 1038-1047.
22. Gold HK, Garabedian HD, Dinsmore RE, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators: observations in animals and humans. Circulation 1997; 95: 1755-1759.
23. Kleiman NS, Ohman EM, Califf RM, et al. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy. Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 Pilot Study.J Am Coll Cardiol 1993; 22: 381-389.
24. E. Ronner, H.A.M. van Kesteren, P. Zijnen, et al. Safety and efficacy of eptifibatide versus placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction. Eur Heart J 2000; 21:1530-1536.
25. Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators.Circulation 1997; 95 (4): 846-854.
26. The PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial. J Am Coll Cardiol. 1998; 32: 2003-2010.
27. Antman EM, Giugliano RP, Gibson MC, et al. for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolyis in myocardial infarction (TIMI) 14 trial. Circulation 1999; 99: 2720-2732.
28. Lambert FM, Van den Merkhof LFM, Zijlstra F, et al. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous coronary angioplasty. J Am Coll Cardiol 1999; 33: 1528-1532.

3.2

Safety and efficacy of eptifibatide versus placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction; a phase II dose escalation, randomized, double blind study

Eelko Ronner[1], Henri A.M. van Kesteren[2], Piet Zijnen[3], Ernst Altmann[4], Peter G. Molhoek[5], L. Ron van der Wieken[6], Cynthia A. Cuffie-Jackson[7], Karl L. Neuhaus[8†], Maarten L. Simoons[9]

[1] Cardialysis, Rotterdam, The Netherlands
[2] Maria Ziekenhuis, Tilburg, The Netherlands
[3] St. Elisabeth Ziekenhuis, Tilburg, The Netherlands
[4] Krankenhaus Dresden-Friedrichstadt, Dresden, Germany
[5] Medisch Spectrum Twente, Enschede, the Netherlands
[6] Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands
[7] Schering-Plough Research, Kenilworth, USA
[8] Karl L. Neuhaus, Stadtische Kliniken Kassel, Germany
[9] Thoraxcenter, Rotterdam, The Netherlands
[†] Prof. Neuhaus died before publication of this paper.

European Heart Journal 2000; 21: 1530-1536.

Acknowledgements

The trial was supported by COR Therapeutics, Inc. (South San Francisco, CA, USA) and the Schering Plough Research Institute (Kenilworth, NJ, USA).

Participating centers by country, in order of recruitment:

The Netherlands
H.A.M. van Kesteren, Maria Ziekenhuis, Tilburg; P. Zijnen, St. Elisabeth Ziekenhuis, Tilburg; G.P. Molhoek, Medisch Spectrum Twente, Enschede; L.R. van der Wieken, Onze Lieve Vrouwe Gasthuis, Amsterdam; L.H.M. Bouwens, Deventer Ziekenhuizen, Deventer; A.E.R. Arnold, Medisch Centrum Alkmaar, Alkmaar; S. Strikwerda, Ziekenhuis "De Baronie", Breda; E.J. Muller, Spaarne Ziekenhuis, Heemstede; B.J.B. Hamer, Eemland Ziekenhuis, Amersfoort; M.L. Simoons, Dijkzigt Hospital, Rotterdam; J.H. Kingma, St. Antonius Ziekenhuis, Nieuwegijn; D. P. Hertzberger, Canisius-Wilhelmina Ziekenhuis, Nijmegen.

Germany
E. Altmann, Krankenhaus Dresden-Friedrichstadt, Dresden; F. Forycki, Krankenhaus Neuköln, Berlin; K. Haerten, Marien-Hospital, Wesel; F. Pratorius, Städtische Kliniken Offenbach, Offenbach; K.L Neuhaus, Städtische Kliniken Kassel, Kassel; W. Mauer, Klinikum Bayreuth, Bayreuth; U. Tebbe, Klinikum Lippe-Detmold, Detmold; A. Hepp, Vinzenzkrankenhaus, Hannover; M. Gotwick, Klinikum Süd der Stadt Nürnberg, Nürnberg; G. Berg, Unikliniken des Saarlandes, Homburg; T. Bonzel, Städtisches Klinikum Fulda, Fulda; K.R. Karsch, Eberhard-Karls-Universität, Tübingen

Abstract

Aims. Thrombolytic therapy restores coronary patency in patients with acute myocardial infarction, although normal perfusion (TIMI 3 flow) is not achieved in all patients. In an attempt to improve TIMI 3 flow, a combination of full-dose streptokinase, aspirin and escalating dosages of a platelet glycoprotein IIb/IIIa receptor blocker, eptifibatide, vs placebo was tested.

Methods and results. *A bolus of 180 $\mu g.kg^{-1}$ of eptifibatide was administered in each group, followed by a 72 hours continuous infusion of 0.75 (44 patients), 1.33 ($n=45$) and 2.00 $\mu g.kg^{-1}.min^{-1}$ ($n=30$); 62 patients received placebo. Normal perfusion (TIMI 3 flow) at ninety minutes was observed with 31% of placebo compared to 46, 42 and 45% in the ascending eptifibatide groups (44% for combined eptifibatide groups, $p=0.07$). Patency (TIMI 2 and 3 flow combined) increased from 61% (placebo) to 78% for the combined eptifibatide groups ($p=0.02$). Reocclusion was infrequent. No differences were observed in TIMI flow grades among eptifibatide groups. Major and minor bleeding was increased and occurred mainly at the arterial puncture site.*

Conclusion. *A combination of full dose streptokinase with different eptifibatide regimens enhanced coronary perfusion, but bleeding risk was excessive. Additional trials are needed with different dosage regimens to determine the optimal combination of fibrinolytic agents and platelet glycoprotein IIb/IIIa receptor blockers.*

Background

Coronary occlusion in acute myocardial infarction is caused by intracoronary platelet aggregation and fibrin formation which together forms an intracoronary thrombus. Fibrin can be dissolved by fibrinolytic therapy, while the final common pathway of platelet aggregation can be blocked with platelet glycoprotein (GP) IIb/IIIa receptor inhibitors[1,2]. Various agents have been tested in percutaneous coronary intervention, unstable angina and myocardial infarction[3-10]. Eptifibatide is a synthetic GP IIb/IIIa platelet receptor antagonist providing high levels of receptor blockade in vitro and in vivo. Such platelet receptor blockade may enhance thrombolytic therapy and improve clot resolution[11-14]. Indeed, a combination of eptifibatide with full-dose alteplase and heparin showed an improvement in TIMI 3 flow rates within 90 minutes from 39% with placebo to 66% in eptifibatide-treated patients[15].

Streptokinase is used widely for treatment of acute myocardial infarction. Since this therapy yields a 32-56% TIMI 3 flow at 90 minutes[16,17], this therapy may be improved by the addition of a platelet GP IIb/IIIa receptor inhibitor. Therefore combined therapy with streptokinase and eptifibatide was tested, focussing on early (90 minutes), as well as late (7 days) perfusion of the infarct related artery, and on the safety of various dose combinations.

Methods

Patients

Patients were enrolled if they had evolving myocardial infarction and onset of chest pain within 6 hours, ST-elevation of 0.1 mV in two or more standard leads or 0.2 mV in two or more precordial leads. Patients over 75 years of age had to weigh over 50 kg, to avoid the excessive risk of intracranial hemorrhage[18]. Exclusion criteria were previous cerebrovascular disease, previous coronary artery bypass graft operation (CABG), current anticoagulant therapy, as well as recent gastro-intestinal or urinary tract bleeding, severe trauma or major operation; known thrombocytopenia, known liver and kidney function abnormalities; and suspected streptokinase intolerance. The lower age limit was 18 years.

Witnessed oral informed consent was requested, confirmed by written consent at a later stage during hospitalization. The medical ethics committees of all participating hospitals gave approval for this trial.

Treatment

Treatment consisted of an aspirin loading dose of 250 - 500 mg, continued with at least 80 mg daily, and 1.5 million units of streptokinase given intravenously in 60 minutes.

Eptifibatide or placebo, randomized 2:1, was administered within 10 minutes but in no case later than 30 minutes after the start of streptokinase with a bolus dose of 180 $\mu g.kg^{-1}$ and escalating dosages of a continuous infusion for 72 hours: 0.75, 1.33 and 2.00 $\mu g.kg^{-1}.min^{-1}$. The lowest dosage of eptifibatide was similar to the optimal level found in a comparable dose-finding IMPACT-AMI trial with alteplase and eptifibatide[15]. The highest dose corresponded to the regimen tested in PURSUIT[19]. Following recommendations by the European Society of Cardiology[20], heparin was not given in the current trial, which is in contrast to IMPACT-AMI[15]. Other medication was left at the discretion of the investigator. Warfarin, abciximab and intravenous dextran were not to be combined with the study medication.

Endpoint analysis

TIMI criteria were used to assess bleeding during hospitalization[21]. Major bleeding was defined as intracranial hemorrhage or an Hb decrease of at least 5 $gr.dl^{-1}$ (3.1 $mmol.l^{-1}$) or an Ht decrease of 15% or more. Minor bleeding was described as spontaneous gross haematuria or haematemesis or an Hb decrease between 4 and 5 $gr.dl^{-1}$ (2.5 to 3.1 $mmol.l^{-1}$) or an Ht decrease of 10% to 15%. Angiography was performed after 90 minutes and repeated after approximately 7 days. TIMI flow grades were evaluated by the investigators and by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). TIMI 0 represents absence of flow antegrade of the occlusion. TIMI 1 denotes penetration of the contrast agent without perfusion, failing to opacify the entire coronary bed distal to the occlusion. TIMI 2 shows partial perfusion with a slower rate of entry or clearance of the coronary bed than in other comparable areas. TIMI 3 flow is defined by complete perfusion with antegrade flow as promptly as proximal to the obstruction and clearance as rapid as clearance from an uninvolved bed in the same or opposite coronary artery[17].

At 7 days coronary angiography was repeated and ventriculography was performed to assess left ventricular ejection fraction, except in patients who underwent rescue percutaneous transluminal coronary angioplasty (PTCA) or bypass surgery. TIMI flow grades of both angiograms were compared to determine re-occlusion.

ST-segment resolution was calculated from 12 lead ECGs, recorded immediately before and 3 hours after start of therapy. Resolution was expressed as complete (over 70%), partial (30 to 70%) and no ST-segment resolution (less than 30%)[22,23].

After approximately 42 evaluable patients in each dose, the Safety Review Committee assessed safety and efficacy and decided on possible dosage escalation.

Results

In 1996 and 1997 181 patients were enrolled in 24 hospitals in Germany and the

Table 1
Baseline characteristics; Killip class and infarct location on admission.

		Placebo (n=62)	180 bolus 0.75 infusion (n=44)	180 bolus 1.33 infusion (n=45)	180 bolus 2.00 infusion (n=30)	Eptifibatide combined (n=119)
Age (years)		58	63	60	62	62
Male	%	76	77	84	70	78
Hypertension	%	23	27	20	20	23
DM	%	16	7	18	3	10
Smoking	%	66	73	71	63	70
High chol	%	21	14	22	43	24
Previous infarct	%	5	5	16	7	9
PTCA	%	2	5	7	10	7
Killip class 1	%	94	84	93	93	90
Killip class 2	%	7	11	7	7	8
Killip class 3/4	%	0	5	0	0	1
Anterior	%	39	30	49	27	36
Inferior	%	57	64	47	70	59
Posterior	%	19	25	9	20	18
Lateral	%	23	25	20	30	24

DM=diabetes mellitus, High chol=hypercholesterolaemia, PTCA= Percutaneous transluminal coronary angioplasty. Class=Killip class: 1=no rales or third heart sound, 2=rales < 50% of the lungs and no third heart sound, 3=rales > 50% of the lungs, 4=cardiogenic shock and pulmonary edema.
Infarct location was classified according to the leads with ST segment elevation. Multiple locations may be present in one patient.

Netherlands. The highest dose group was discontinued after enrollment of 30 patients because of excess bleeding complications. Baseline characteristics were similar among the different treatment groups (Table 1). Two patients in the placebo group, one patient in the lowest dose group and two patients in the highest dose group did not receive full dose streptokinase. In the median dose group one patient was withdrawn by decision of a treating physician. These patients were retained in the analyses.

Mean duration of eptifibatide or placebo infusion was between 63 and 67 h (standard deviation 18 to 21 h). Study drug was discontinued because of bleeding complications in seven eptifibatide-treated patients and because of loss of haemoglobin without manifest bleeding in two other patients (in the median and high dose groups). In another 23 patients study-drug was prematurely discontinued due to various causes (cardiac events, nursing errors, incompatible co-medication), not different among treatment groups. In total, 15% of patients discontinued in the placebo group, and 21%, 18% and 20% in the ascending eptifibatide dose groups.

Major and minor bleeding increased with escalating dosages of eptifibatide ($p < 0.01$). In this trial 97 bleeding events emerged on study treatment (including pla-

Table 2
Bleeding, in percentage of patients, according to TIMI criteria

		Placebo	180 bolus 0.75 infusion	180 bolus 1.33 infusion	180 bolus 2.00 infusion	Eptifibatide combined	P-value
Major	%	0	7	18	17	14	
Minor	%	5	16	29	37	27	<0.001
Other	%	7	5	0	3	3	
None	%	89	73	53	43	59	
Transfusion	%	0	11	11	17	13	0.007

Major bleeding: intracranial hemorrhage or Hb decrease of at least 5 gr.dl^{-1} (3.1 mmol.l^{-1}) or Ht decrease of 15% or more. Minor bleeding: spontaneous and observed as gross hematuria or hematemesis. Or Hb decreases between 4 gr.dl^{-1} (2.5 mmol.l^{-1}) up to 5 gr.dl^{-1} (3.1 mmol.l^{-1}) or Ht decrease of more than 10%. P-value is calculated with a χ^2-test with the combined eptifibatide group and placebo.

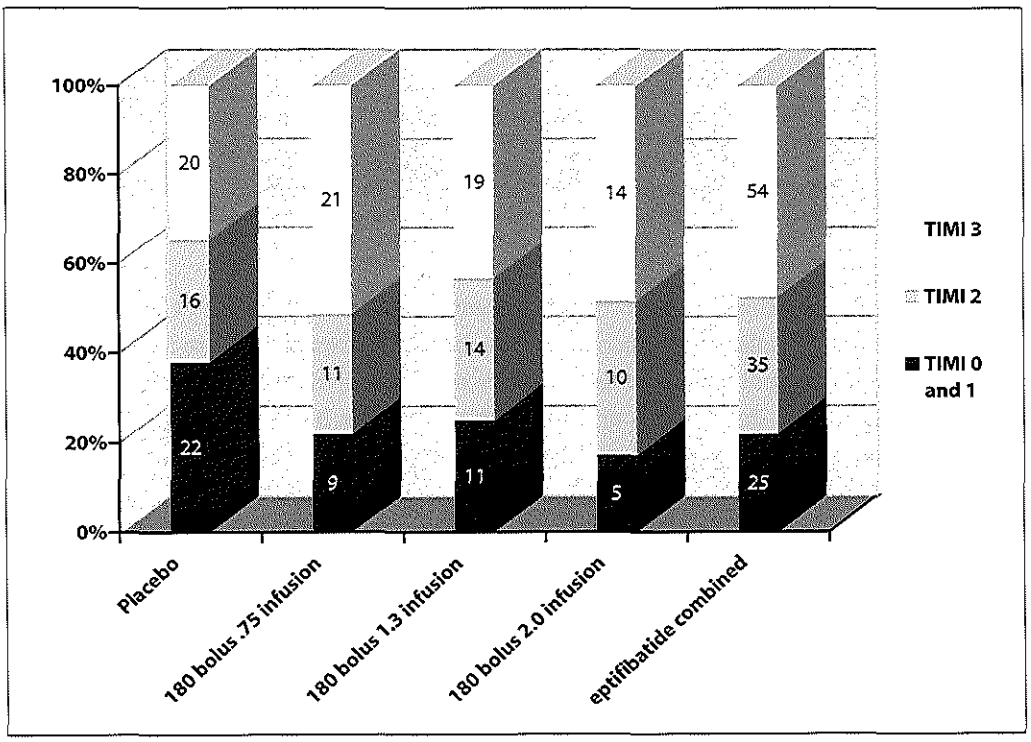


Figure 1. Patients treated with 1.5 million units of streptokinase in 60 minutes and aspirin plus placebo or eptifibatide for acute myocardial infarction. Inside the bars the number of patients with the specified TIMI flow at 90 minutes is given. Adjacent (left) to the bars the percentage of patients is given with the particular TIMI flow within the treatment group.

cebo), of which 50 were related to the catherization access site. No intracranial hemorrhage was observed (Table 2).

Of all eptifibatide-treated patients, 15 patients received transfusions, five in each group (Table 2). No patients on placebo needed transfusion ($p = 0.007$). Patients receiving transfusions included one patient in the lowest dose group undergoing CABG, while all other transfusions were required for manifest bleeding or Hb decrease.

The core laboratory reported TIMI 3 flow at 90 minutes in 46, 42 and 45% of patients receiving ascending doses of eptifibatide. In the combined eptifibatide groups TIMI 3 flow was more frequent than in the placebo group: 44 versus 31% although not statistically significant, $p = 0.07$ (Figure 1). Also patency defined as either TIMI 2 or TIMI 3 flow was more frequent with eptifibatide: 78% versus 61% with placebo, $p = 0.02$ (table 3). No difference was observed between the three eptifibatide infusion regimens (Figure 1).

Re-occlusion was not noted in either the placebo patients or the lowest dose eptifibatide patients, but occurred in two and three patients in the other eptifibatide groups. TIMI 3 flow at day seven revealed no significant differences between groups, ranging from 64% to 77%. Also patency rates (TIMI 2 or 3) were similar (Table 3).

Left ventricular function was assessed by angiography in 145 patients, and could be quantified by the Cardialysis core laboratory in 79 patients. Ejection fractions were not different among the groups (Table 4). Also ST-segment resolution patterns were similar. In placebo patients 49 % demonstrated complete ST-resolution, compared to 41, 38 and 55 % for the escalating eptifibatide groups (Table 4).

Table 3
TIMI flow rates both after 90 minutes and approximately 7 days. Percentages of patients in each group are given

		Placebo	180 bolus 0.75 infusion	180 bolus 1.33 infusion	180 bolus 2.00 infusion	Eptifibatide combined	P-value
90 minutes							
TIMI 0, 1	%	39	22	26	17	22	
TIMI 2, 3	%	61	78	74	83	87	0.02
Day 7							
TIMI 0, 1	%	11	8	11	13	11	
TIMI 2, 3	%	89	92	89	87	89	0.99
Re-occlusion	N=	47	37	35	28	100	
TIMI 3 to 0-2	%	0	0	6	0	2	0.33
TIMI 2-3 to 0-1	%	0	0	0	11	3	0.24

P-values are calculated with a χ^2-test for placebo and combined eptifibatide groups. N is the amount of patients in whom two angiograms were available for analysis of re-occlusion

Table 4
Left ventricular ejection fraction at approximately 7 days and ST-segment resolution on serial ECGs in percentages

		Placebo	180 bolus 0.75 infusion	180 bolus 1.33 infusion	180 bolus 2.00 infusion	Eptifibatide combined	P-value
Mean E.F.	%	57	56	60	60	59	n.s.
ST-Resolution							
Complete		49	41	38	55	43	
Partial		37	48	38	34	41	
No		14	11	24	10	16	n.s.

E.F.= left ventricular ejection fraction, standard deviation is 2.1.
Complete Resolution= Complete ST-segment resolution: more than 70% resolution. Partial resolution= between 30% and 70% ST-segment resolution. No resolution= less than 30% ST-segment resolution. P-values are calculated with a χ^2-test (combined eptifibatide group versus placebo).

Table 5
Adverse events till day 30 (actual number of patients). Multiple events may have occurred in individual patients

	Placebo	180 bolus 0.75 infusion	180 bolus 1.33 infusion	180 bolus 2.00 infusion	Eptifibatide combined
Death	4	1	2	2	5
IC Bleed	0	0	0	0	0
Stroke	0	0	1	1	2
Re-infarct	3	1	7	0	8
PTCA	8	2	4	0	6
Shock	6	5	1	1	7
Re-ischemia	7	7	6	3	16

Number of patients with each event throughout the 30 day follow up.

Clinical outcome was not affected by combination therapy in this limited series of patients. In particular, death, recurrent infarction and percutaneous coronary intervention were not significantly different between groups (Table 5). Nine patients died before the end of follow up. Four patients had been randomized to placebo, and one, two and two in the respective eptifibatide groups. One placebo treated patient was lost to follow up.

Discussion

Combination of fibrinolytic therapy (standard dose streptokinase) with ascending

doses of the platelet glycoprotein IIb/IIIa receptor blocker, eptifibatide, did result in improved coronary perfusion as assessed by angiography. These results confirm studies with other fibrinolytic-IIb/IIIa receptor blocker combinations[24]. However, at 90 minutes angiography no differences in patency between eptifibatide groups were seen. In fact, the actual dose administered at 90 minutes was similar among the eptifibatide groups, since the bolus was relatively large: 180 $\mu g.kg^{-1}$ in all three groups. This represents the major part of the total infused volume at 90 minutes. ST-resolution measurements, often used as surrogate marker for tissue perfusion, failed to demonstrate significant differences between groups.

The combination of streptokinase and eptifibatide appeared not superior to coronary patency as achieved with alteplase[16] and other tissue plasminogen activators[25,26,27], while bleeding rates and transfusion requirements in the current trial were excessive (table 2). Streptokinase is a non-fibrin specific thrombolytic and is therefore likely to interfere with normal haemostasis more than fibrin specific agents, such as tPA and other plasminogen activators, which may explain the excess of bleeding in this study.

A strategy of full dose fibrinolytic (alteplase) combined with a platelet glycoprotein IIb/IIIa receptor blocker (eptifibatide) was also tested in IMPACT-AMI[15]. Patency improved significantly, with 66% TIMI 3 flow for eptifibatide (180 $\mu g.kg^{-1}$ bolus, 0.75 $\mu g.kg^{-1}.min^{-1}$ infusion) compared to 39% for the placebo group ($p = 0.006$), while bleeding was not increased.

In the PARADIGM trial the platelet GP IIb/IIIa receptor inhibitor lamifiban was given in adjunct to full dose streptokinase (without heparin) or to alteplase (with heparin)[28]. An increase in bleeding was reported in patients treated with lamifiban in combination with full dose streptokinase: 16.1% of lamifiban and 10.3% of placebo treated patients received transfusions.

A different strategy was followed in the GUSTO-IV pilot or SPEED trial[29] and in the TIMI-14 trial[24]. In these trials full dose platelet glycoprotein IIb/IIIa receptor blocker (abciximab) was tested in combination with a reduced dose of a fibrinolytic agent (respectively reteplase and alteplase). Data on a combination of full-dose abciximab with a reduced dose of 35 mg of alteplase infused in 60 minutes demonstrated an encouraging 77% TIMI 3 flow at 90 minutes, compared to 62% for full dose alteplase alone ($p = 0.02$). In a small group of patients in this dose titration trial, abciximab with full dose streptokinase showed an unacceptable risk of bleeding complications and accordingly this regimen was not further investigated.

Throughout these trials a consistent improvement of TIMI 3 flow was achieved by a combination of fibrinolytic therapy and platelet glycoprotein IIb/IIIa receptor blockers. However, full dose fibrinolytic therapy with streptokinase and a platelet glycoprotein IIb/IIIa receptor blocker leads to an unacceptable bleeding risk. Due to this risk, and the fact that full dose streptokinase with a platelet glycoprotein IIb/IIIa receptor blocker results in TIMI 3 flow not superior to flow rates seen after standard tPA treat-

ment, this treatment strategy seems not to be of clinical benefit. In contrast, a strategy combining a fibrinolytic agent in a reduced dose with a platelet glycoprotein IIb/IIIa receptor blocker at a level which inhibits over 80% of platelet aggregation, seems promising[24]. Large randomized trials with clinical end-points are needed to assess the clinical benefit which may be expected from improvement of early TIMI 3 flow rates in relation to the possible increased bleeding risk.

While waiting for such large trials, we recommend avoiding streptokinase in patients who develop myocardial infarction while receiving eptifibatide or another platelet glycoprotein IIb/IIIa receptor blocker, and to treat such patients by either direct PTCA or with a reduced dose of alteplase or reteplase.

References

1. Kong DT, Calif RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998; 98: 2829-2835.
2. Ronner E, Dykun Y, Van den Brand MJBM, Van der Wieken LR, Simoons ML. Platelet glycoprotein IIb/IIIa receptor antagonists. An asset for treatment of unstable coronary syndromes and coronary intervention. Eur Heart J 1998; 19: 1608-1616.
3. Simoons ML, de Boer MJ, van den Brand MJ, et. al. Randomized trial of a glycoprotein IIb/IIIa platelet receptor blocker in refractory unstable angina. Circulation 1994; 89: 596-603.
4. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-1435.
5. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
6. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Eng J Med 1997; 336: 1689-1696.
7. Brener SJ, Barr LA, Burchenal JEB, et al, on behalf of the Reopro and primary PTCA organization and randomized trial (RAPPORT) investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734-741.
8. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
9. Gibson MC, Goel M, Cohen DJ, Piana RN, Deckelbaum LI, Harris KE, King III SB, for the RESTORE investigators. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. J Am Coll Cardiol 1998; 32: 28-34.
10. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349: 1422-1428.
11. Song A, Scarborough RM, Phillips DR, Adelman B, Strony J. Eptifibatide enhances fibrinoly-

sis and prevents acute arterial reoclusion following thrombolysis in a canine anodal current model with high-grade stenosis. Circulation; 1992: 86(suppl. 1) I - 410, abstract.
12. Gold HK, Coller BS, Yasuda T, et al. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet glycoprotein IIb/IIIa antibody in a canine preparation. Circulation 1988; 77: 670-677.
13. Yasuda T, Gold HK, Leinbach RC, et al. Lysis of plasminogen activator-resistant platelet-rich coronary artery thrombus with combined bolus injection of recombinant tissue-type plasminogen activator and antiplatelet glycoprotein IIb/IIIa antibody. J Am Coll Cardiol 1990; 16: 1728-1735.
14. Moliterno DJ, Topol EJ. Conjunctive use of platelet glycoprotein IIb/IIIa antagonists and thrombolytic therapy for acute myocardial infarction. Thromb Haemost 1997; 78: 214-219.
15. Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. Circulation 1997; 95: 846-854.
16. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-1622.
17. The TIMI study group. The thrombolysis in myocardial infarction (TIMI) trial. N Engl Med 1985; 312: 932-936.
18. Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. Lancet 1993; 342: 1523-8.
19. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-443.
20. The Task Force on the management of acute myocardial infarction of the European Society of Cardiology. Acute myocardial infarction: pre-hospital and in-hospital management. Eur Heart J 1996; 17: 43-63.
21. Rao Ak, Pratt C, Berke A, et al. Thrombolysis in myocardial infarction (TIMI) trial - phase 1: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988; 11: 1-11.
22. Schröder R, Dissman R, Brüggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994; 24: 389-91.
23. Van't Hof A.W.J, Liem A, De Boer MJ, Zijlstra F, for the Zwolle Myocardial Infarction Study. Clinical value of 12-lead electrocardiogram after succesfull reperfusion therapy for acute myocardial infarction. Lancet 1997; 350: 615-619.
24. Antman EM, Giugliano RP, Gibson MC, et al. for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolyis in myocardial infarction (TIMI) 14 trial. Circulation 1999; 99: 2720-2732.
25. Den Heier P, Vermeer F, Ambrosioni E, et al. Evaluation of a weight-adjusted single-bolus plasminogen activator in patients with myocardial infarction: a double-blind, randomized angiographic trial of lanoteplase versus alteplase. Circulation 1998; 98: 2117-2125.
26. Tebbe U, Michels R, Adgey AAJ, et al. Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. Comparison trial of saruplase and streptokinase (COMASS) investigators. J Am Coll Cardiol

1998; 31: 487-493.
27. Benedict CR, Refino CJ, Keyt BA, Pakala R, Paoni NF, Thomas GR, Bennet WF. New variant of human tissue plasminogen activator (TPA) with enhanced efficacy and lower incidence of bleeding compared with recombinant human TPA. Circulation 1995; 92: 3032-3040.
28. The PARADIGM investigators. Combining thrombolytics with the platelet glycoprotein IIb/IIIa inhibitor lamifiban; results of the platelet aggregation receptor antagonist dose investigation and reperfusion gain in myocardial infarction (PARADIGM trial). J Am Coll Cardiol 1998; 32: 2003-2010.
29. The SPEED investigators. Strategies for patency enhancement in the emergency department (SPEED) group. Trial of abciximab with and without low-dose reteplase for acute myocardial infartion. Circulation 2000; 101: 2788-2794.

3.3

Platelet GP IIb/IIIa receptor blockers for failed thrombolysis in acute myocardial infarction, alone or as adjunct to other rescue therapies.

A single center retrospective analysis of 548 consecutive patients with acute myocardial infarction.

Eelko Ronner, Ron T. van Domburg, Marcel J.B.M. van den Brand, Pim J. de Feyter, David P. Foley, Wim J. van der Giessen, Patrick W. Serruys, Maarten L. Simoons.

Erasmus Medical Center, Rotterdam, The Netherlands

Abstract

In order to study safety of "rescue" strategies to treat patients with failed thrombolysis, all 548 patients admitted with evolving myocardial infarction to the Thoraxcenter Rotterdam from January 1997 until April 1999 were reviewed.

Of these patients 49% had received thrombolysis. Patients treated with thrombolysis and not referred from other hospitals (n = 154) received rescue therapy for failed thrombolysis in 36%.

Three rescue therapies after failed thrombolysis were used; PCI (74%), retreatment with thrombolysis (39%) and platelet glycoprotein (GP) IIb/IIIa receptor blockers (53%), often in combinations. Platelet GP IIb/IIIa receptor blocker were administered in 53% of patients treated with rescue PCI.

Major bleeding occurred in 14% of all thrombolysis treated patients, but in 30% of patients who received multiple rescue therapies. Bleeding was related to heparin usage and platelet GP IIb/IIIa receptor blockers. Furthermore the insertion of catheters for PCI or intra-aortic balloon pumps was associated with bleeding.

Most major bleedings observed were one death due to a ruptured ventricle, one hemorrhagic stroke, and three cases of tamponade for which surgery was needed. Four of these patients had received combination rescue therapy.

Rescue therapy is a widely used strategy for failed thrombolysis, but associated with a high bleeding rate. Alternative reperfusion strategies to avoid failed thrombolysis should be considered in high risk patients.

Introduction

Thrombolysis has dramatically improved outcome in acute myocardial infarction (MI)[1]. In a considerable number of patients, however, this therapy fails to relieve symptoms, fails to achieve TIMI 3 flow or fails to restore ST-segment elevation while in other patients re-infarction occurs early, within 24 hours, or in subsequent days[2]. Various rescue therapies have been considered in so-called "failed thrombolysis"[3].

In particular, rescue percutaneous coronary intervention (rescue PCI)[4,5] and rescue lysis (readministration of thrombolytics)[6-8] are widely used to treat failed thrombolysis. Furthermore platelet glycoprotein (GP) IIb/IIIa blockers are often used in combination with rescue PCI and sometimes with rescue lysis[9,10].

Platelet GP IIb/IIIa receptor blockers reduce the risk of thrombotic complications in patients undergoing PCI[11-13]. These agents have demonstrated superior TIMI 3 flow 60 minutes after onset of therapy if administered simultaneously with reduced dose of thrombolytic agent in patients with MI. Moreover, this combination of medication proved superior to thrombolysis alone, with respect to death and myocardial infarction at seven days (secundary endpoint of GUSTO V, although the primary endpoint of 30 day mortality was not significant reduced.)[14] Rescue administration of platelet GP IIb/IIIa receptor blockers in patients with failed thrombolysis or administration of a second fibrinolytic agent combined with a platelet GP IIb/IIIa receptor blocker may therefore be an attractive strategy. However combination of fibrinolytics, antiplatelet agents and anticoagulation will increase bleeding risk and little is known about safety and efficacy of these rescue therapies. Therefore, in this retrospective analysis, the records of patients with acute MI admitted to the coronary care unit of the Thoraxcenter were reviewed focusing on patients receiving additional or "rescue" reperfusion therapy on top of thrombolysis. The incidence, results and bleeding complications of different rescue therapies are described.

Methods

All patients presenting with acute myocardial infarction in a large university hospital in The Netherlands (The Thoraxcenter, Erasmus Medical Center, Rotterdam) between January 1997 and April 1999 were included in this retrospective analysis. Computerized patient records from the catheterization laboratory and coronary care unit, as well as discharge letters were reviewed to identify these patients. This analysis includes patients treated with primary PCI, all patients treated with thrombolysis (also those without rescue therapy) and patients with a diagnosis of MI who did not receive reperfusion therapy are mentioned shortly. A considerable proportion of patients had been referred from other hospitals specifically for primary or rescue

PCI.

Acute MI was defined as chest pain or ECG-findings suggestive of acute MI with any CK rise above twice the upper limit of normal and elevated CK-Mb.

Major bleeding was defined as intra-cerebral bleeding, decrease of hemoglobin over 3.1 g/dL (2 mmol/L) as well as bleeding for which surgery was performed or transfusion was administered. Death at 30 days was checked at municipal registries for patients who did not visit the outpatient clinic at or after 30 days.

Failed thrombolysis was defined when rescue reperfusion treatment was given within 24 hours after the onset of infarction, consisting of rescue lysis, rescue PCI or platelet GP IIb/IIIa receptor blockers after primary thrombolysis, or any combination of such. Each treatment modality is described separately. Patients with either ongoing infarction despite thrombolysis or patients with early re-occlusion were analyzed in combination.

Incidence of rescue therapy for referred patients treated with thrombolysis is high at our institution, as many of these patients are specifically referred for rescue PCI. Therefore when figures are presented concerning incidence of rescue therapy, a distinction is made between referred and non-referred patients.

The incidence and severity of bleeding events seen for patients with each rescue strategy was compared to corresponding events in other rescue strategies.

Results

548 patients were identified who experienced an acute MI, of whom 389 were primary admissions to the Thoraxcenter and 159 patients were acutely referred from other centers for primary PCI or rescue PCI (Table 1, Figure 1).

Use of rescue therapy

Rescue therapy was administered to 139 patients after initial treatment with thrombolysis. Of non-referred patients treated with thrombolysis (n = 154) 36% received rescue therapy. The most frequently used rescue therapy was PCI (74%), while rescue fibrinolysis was applied in 39%. 25 patients (18%) received a second dose of a thrombolytic drug as well as rescue PCI. Rescue PCI was combined with a platelet GP IIb/IIIa receptor blocker in 53% of the procedures (Figure 1).

Patient characteristics and outcome

Patients treated with rescue therapies were predominantly middle aged (56 years old on average) men (80%) who experienced an infarction of the anterior wall of the left ventricle (59%). The majority of these patients were referred from other hospitals (63%). A high 37% of patients were in Killip class 3 and 4, and mechanical ventila-

Table 1
Thrombolysis treated patients: in hospital mortality and major bleeding.

Initial treatment MI	Thrombolytic therapy			p-value (chi-square)
	All	Without	With rescue	
Number	268	129	139	
30 day mortality %	6.7	10.1	5.7	0.03
Major bleeding %	14.7	7.0	21.6	0.01

PCI; percutaneous coronary intervention.

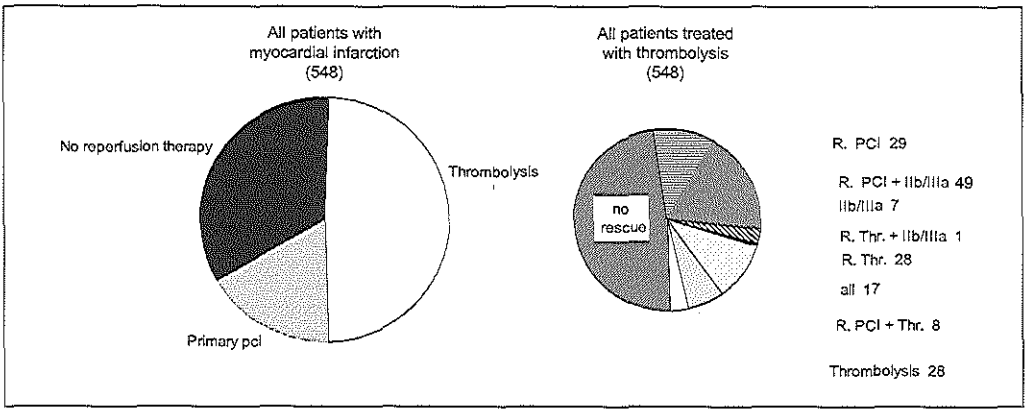


Figure 1 Treatment of myocardial infarction (left) and rescue treatment after thrombolysis (right). R. PCI; Rescue (R) Percutaneous Intervention (PCI), IIb/IIIa; Platelet Glycoprotein IIb/IIIa receptor antagonists, Thr; thrombolysis, All; the combination of R. PCI, R. Thr and IIb/IIIa. Numbers denote amount of patients.

tion was necessary in up 13.5% treated with rescue PCI (table 2). Patients in whom rescue PCI was performed as (part of) rescue therapy had significantly more cardiopulmonary resuscitation: 27%, versus 6.8% for rescue platelet GP IIb/IIIa receptor blockers and 11.1% for patients in whom repeat thrombolysis was administered (table 2, $p < 0.05$).

Bleeding complications

Rescue therapies were associated with bleeding in 21.6% of patients, versus 5.9% to 13.7% bleeding in patients treated without reperfusion therapy and primary PCI respectively (table 3, $p < 0.001$). In patients treated with thrombolysis without rescue therapies bleeding was observed in 7%.

A rescue strategy with readministration of tPA as sole rescue therapy caused bleed-

Table 2
Baseline characteristics of patients with specific additional reperfusion therapies.

	Re Administration	Rescue PCI	Platelet GP blockers
Number	54	103	74
Male	80%	80%	82%
Age (years)	55	56	58
DM	11.1	8.1	12.2
Previous MI	18.5	21.6	23.0
Hx PTCA	3.7	13.5	8.1
Hx CABG	5.6	8.1	6.8
Referred	61.1	66.7	60.8
Anterior MI	62.7	58.8	55.7
Inferior MI	31.4	35.3	37.7
Other MI	5.9	5.9	6.6
CPR	11.1	27.0*	6.8*
Killip class 3 or 4	35.2	37.8	39.2
Mechanical ventilation	9.3	13.5	6.8
IABP	11.1	21.6	17.6
First agent STK	52.9	30.6	26.2
First agent tPA	41.2	57.6	62.3
Agent unknown	5.9	11.8	11.5
Mean aPTT	91	94	98
ASA	20.4	18.9	23.0
OAC	22.2	5.4*	20.3

Of note: multiple strategies have been used in several patients (therefore percentages exceed 100%).
P-values (* < 0.05) compare the specific treatment versus patients without this treatment).
DM, diabetes; MI, myocardial infarction; Hx, history of; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CPR, cardiopulmonary resuscitation; ASA, acetyl salicylic acid; OAC, oral anticoagulant agents; STK, streptokinase; tPA, tissue plasminogen activator.

Table 3
Outcome of various rescue strategies. In some patients therapies have been combined.

ART	Re Administration	*p*	Rescue PCI	Platelet GP IIb/IIIa blockers	*p*
Number	54		103	74	
30 day mortality %	5.9		5.9	4.9	
Major bleeding %	21.6	*	29.4	36.1	*

ing in 10.7%, compared to 6.9% in patients with rescue PCI as sole rescue treatment (p = 0.627; table 4). Bleeding was seen in 3 out of 7 patients (43%) in the small group of patients treated with platelet GP IIb/IIIa receptor blockers as single rescue therapy (table 4).

Major bleeding was frequent in all combination rescue groups: 30% versus 12% for

Table 4
Additional reperfusion therapies alone or in combination related to major bleeding and death.

Re-administration		+	+	+	+	-	-	-	
Rescue PCI		+	+	-	-	+	+	-	**All**
IIb/IIIa blockers		+	-	+	-	+	-	+	
Number		17	8	1	28	49	29	7	139
Mortality	%	5.9	0	0	7.1	2.0	10.3	14.3	5.7
Major bleeding	%*	41.2	25.0	0	10.7	26.6	6.9	42.9	21.6

* Major bleeding was defined as intra-cerebral bleeding, decrease of hemoglobin over 3.1 g/dL (2 mmol/L) as well as bleeding for which surgery was performed or transfusion was administered.

"single" rescue therapy" ($p = 0.01$). Platelet GP IIb/IIIa receptor blockers were included in 53% of patients as part of a (single or combination) rescue strategy, and were associated with 31% bleeding versus 11% in rescue strategies without these agents; $p = 0.004$ (table 4). Bleeding for patients treated with the combination of a platelet GP IIb/IIIa receptor blocker, rescue lysis and rescue PCI was 41% versus 13% in patients treated with a platelet GP IIb/IIIa receptor blocker in combination with rescue PCI without fibrinolysis.

Heparin and IABP usage (intra aortic balloon counterpulsation) were related to bleeding as well. APTT measured 84 seconds in patients with rescue therapy without bleeds, compared to 114 seconds in patients with bleeding complications (n.s.). IABP was associated with 48% bleeding, versus 17% in patients without IABP ($p = 0.002$). IABP in combination with platelet GP IIb/IIIa receptor blockers or in combination with rescue lysis led to the highest bleeding rates: 62% and 67% respectively.

Most bleeding, albeit "major" because of the amount of blood lost, occurred at the site of arterial or venous access sites (70% of all major bleeding).

Life threatening bleeding events occurred in 5 of 139 patients receiving rescue therapy. One patient died of a ruptured wall of the left ventricle after combination therapy of rescue lysis, PCI and a platelet GP IIb/IIIa receptor blocker. Hemorrhagic stroke occurred in another patient treated with rescue PCI and a platelet GP blocker. Three cases of cardiac tamponade were drained surgically. Two of these patients had been treated with PCI and a platelet GP blocker, one of whom received this treatment on top of rescue lysis. The third tamponade patient had been treated with a thrombolytic and IABP.

All rescue strategy therapies were compared in a multivariable model, including patient characteristics, referral status and IABP usage. After adjustment for other factors, platelet GP blockers were related to the highest risk of bleeding, with an odds ratio of 7.5 ($p = 0.02$). Odds ratios were 3.7 for IABP ($p = 0.02$) and 2.6 for rescue lysis ($p = 0.1$).

Mortality

In all patients treated with thrombolysis (including "rescue" patients) death at 30 days occurred in 6.7%. For patients treated with primary PCI this was 10.5%, and 11.4% in patients without either therapy. Referred patients constituted a particular high risk group, with 30 day mortality of 12.5% versus 9.3% in non-referred patients.

Patients treated with IABP demonstrated a 19.1% death rate, compared to 3.4% in patients without ($p = 0.005$).

In patients receiving rescue therapy, mortality was 4.9% in patients with platelet GP IIb/IIIa receptor blockers as rescue therapy, 6.7% for the other failed thrombolysis groups. Mortality in patients in whom rescue PCI was the method of reperfusion was 4.9% (8.1% for all others).

Discussion

This retrospective analysis of patients admitted with acute MI reveals a high rate of major bleeding complications in patients receiving "rescue" therapy. In particular, one third of patients (23 of 74) in whom platelet GP IIb/IIIa receptor blockers were used as part of a rescue strategy suffered from major bleeding. Major bleeding was observed in 62% of patients when an IABP had been inserted in the course of rescue therapy.

High rates of major bleeding occurred in patients receiving full dose, and sometimes double dose, fibrinolytic therapy with an additional platelet GP IIb/IIIa receptor blocker. Such excessive bleeding risk has been reported in a few studies on such antithrombotic therapy, for example when eptifibatide in accelerating doses was added to full dose thrombolytic[15], but also when abciximab was combined with full dose streptokinase or tPA[16]. In contrast, bleeding rate was acceptable in studies when the thrombolytic agent was reduced and combined with a platelet GP IIb/IIIa receptor blocker[16,17].

A recent report from 4 Canadian tertiary care hospitals described 147 patients who underwent PCI within 48 hours of thrombolytic therapy (t-PA in 89%) for acute MI. Abciximab was administered in 39% of patients, and was associated with 12% major bleeding compared to 3% in patients with rescue/urgent PCI without abciximab after thrombolytic therapy[18].

Incidence of failed thrombolysis and rescue therapy

The current use of rescue strategies should not be underestimated, although the actual use of rescue therapy is not well known. Nevertheless, incomplete reperfusion after thrombolytic therapy is well recognized and is often considered an indication for rescue therapy. In GUSTO-1 for example approximately 70% of patients treated with streptokinase lack optimal reperfusion (TIMI 3 flow) at 90 minutes angiography, while 46% of patients treated with tPA do not achieve early TIMI 3 flow[1]. Moreover,

complete tissue perfusion, expressed indirectly by complete ST-segment resolution, was observed in only 45% of patients on serial ECG-recordings[19]. Complete ST resolution was associated with lower 21 day mortality (2.2%) versus 5.6% for incomplete ST-segment resolution, $p < 0.05$. Furthermore, recurrent ST deviations, observed between 6 and 24 hours in 33% of patients, were associated with adverse outcome[2]. Many of these patients with symptoms, electrocardiographic or angiographic signs of failed thrombolysis can be considered for rescue therapy.

We report 36% rescue therapy in non referred patients treated with thrombolysis. Another report from an interventional clinic with a large cohort of patients (n = 759) treated with early angioplasty was described by Bär et al.[20] In this series, rescue PCI was performed in 22% (n = 196) of patients treated with thrombolysis (excluding referred patients). Eight percent cardiac catheterization for failed thrombolysis was registered in the Euro Heart Survey. This survey included 4431 patients with acute myocardial infarction of whom 1556 received thrombolysis[21]. Unpublished data from the Swedish national registry (RIKS-HIA) report only 4% (1999) and 5% (2000) rescue PCI[22]. The data from the Euro Heart Survey and the RIKS-HIA database are based on data from all (also non-interventional) hospitals, and therefore much lower than our 36%, and the 22% from Bär.

Efficacy of rescue therapy

Despite extensive data on occurrence of failed thrombolysis[23], evidence for effective treatment of this condition is scarce. Several investigators have addressed the issue indirectly by description of results of rescue PCI after early per protocol angiography at a predefined moment after thrombolysis[24,25,26]. One of the exceptions is the randomized RESCUE trial[27]. In this trial 151 patients with TIMI 0 or 1 flow at a mean time of about 4.5 hours after thrombolysis for a first anterior wall infarction were randomized to no additional therapy versus rescue PCI. There was no rescue lysis and platelet GP IIb/IIIa blockers were not used. A trend towards lower mortality (5% versus 10%) and less severe congestive heart failure (1% versus 7%) was observed in the rescue PCI group. These combined results just reached statistical significance ($p = 0.05$). This trial clarifies safety and suggests efficacy, but efficacy in "real world" patients where most often rescue therapy is instigated by symptoms or ECG findings remains to be investigated. Moreover, possible benefit is offset by reported mortality rates of 33% to 39% described for failed rescue PCI[28,29].

In this retrospective cohort, a 5.7% 30 day mortality was demonstrated in patients in whom rescue strategies were applied, similar to the 5% mortality in selected patients in the RESCUE trial. It is important to note that mortality data from our single center experience are influenced by patient selection and cannot easily be compared with other patient series. Yet, the Gusto-1 trial and more recent trials on thrombolysis in acute myocardial infarction demonstrate near similar mortality with thrombol-

ysis alone, (6.3 and 6.2%)[1,30] while failed thrombolysis left untreated is associated with around 7 to 17% mortality[31,32,33]. The aforementioned retrospecive analysis Bär et al.[34] compared rescue PCI with primary PCI, and demonstrated no significant benefit of one treatment over the other. Death at one year was 2.7% (rescue PCI) vs 3.7% ($p = 0.63$; primary PCI)

A review article combining 9 randomized controlled clinical trials ($n = 1456$) with 4 registries ($n = 977$) demonstrated less severe heart failure (3.8% vs. 11.7%, $p = 0.04$) and improved 1 year survival (92% vs 87%, $p = 0.001$)[35] in patients in whom rescue PCI was performed (vs thrombolysis alone). It should be noted however that this was observed in patients with TIMI 0 and 1 flow only, no statistical significant benefit was observed in patients with TIMI 2 flow treated with rescue PCI. Benefit was furthermore limited to patients with moderate size to large infarcts.

Rescue therapy or direct PCI

The high bleeding rates observed with the different rescue strategies that appeared in clinical practice necessitate reconciliation of the concept of rescue therapy. Overall, the benefits of such rescue therapy have not been proven beyond doubt, while the risk of bleeding is significant as indicated in this report. Rescue therapy in our hospital, and in other practices is considered for patients with a relatively large evolving infarct, not responding to fibrinolytic therapy. It may be more appropriate to identify such patients up front, and to refer these for direct PCI, instead of thrombolytics. This is recommended especially in very large myocardial infarction[43,36], when failed thrombolysis is prone to seriously compromise the patient.

If rescue therapy is applied, for example when primary PCI is not available, measures to prevent bleeding should be stressed. In particular, combinations of different antithrombotic drugs and fibrinolytics as rescue therapy and/or the use of an intra-aortic balloon pump may lead to major bleed A large cohort of patients ($n = 759$) treated with early angioplasty was described by Bär et al.[37] Unlike trials discussed hereabove, this trial compared rescue PCI with primary PCI. Rescue PCI was performed in 21.8% ($n = 196$) of patients receiving thrombolysis.

Optimal combination regimens

Improved thrombolytic regimens are under intense investigation, encompassing more potent agents, as well as agents for single or double bolus administration to promote out of hospital start of therapy and avoid dosing errors. Other anticoagulant drugs like low molecular weight heparins are tested on safety and efficacy in adjunct to thrombolytic agents. For example, the low molecular weight heparin enoxaparin as adjunct to t-PA reduced reocclusion rates (3 versus 9%) and slightly improved early 90 minutes TIMI 3 flow (52 versus 48% for unfractionated heparin) in HART-2[38]. Enoxiparin added to streptokinase in another recent trial, compared with placebo, improved early ST-

segment resolution, subsequent coronary patency and improved clinical outcome[39]. Another low molecular weight heparin, daltaparin, in combination with streptokinase reduced left ventricular thrombus formation (14 versus 22% for placebo)[40].

Further improvement is expected from platelet GP IIb/IIIa receptor blockers. They demonstrated improved TIMI 3 flow in combination with reduced (half-dose) dose thrombolytic at 90 minutes[16]. Ninety minutes TIMI 3 flow increased from 62 to 77% ($p = 0.02$) for the combination of abciximab with tPA[16] and to a similarly high 78% for eptifibatide with tPA[17]. In the large scale GUSTO-V AMI trial[14], patients with acute MI were randomized to reteplase versus half dose reteplase with abciximab ($n = 16588$). At 30 days no statistical significant reduction of death was observed (primary endpoint), 5.9% (reteplase) vs 5.6% (half dose reteplase with abciximab). The secondary endpoint of 7 day death and non-fatal MI was 8.8% (reteplase) vs 7.4% ($p = 0.0011$; half dose reteplase with abciximab). The ASSENT III trial results (similar design, other agents) is expected shortly.

Sole therapy with platelet GP IIb/IIIa receptor blockers has not demonstrated improvement of TIMI 3 flow compared to thrombolytic strategies[16]. The combination of full dose thrombolysis with full dose platelet GP IIb/IIIa receptor blocker led to serious safety concerns and is therefore no serious alternative to other thrombolytic strategies[15,16].

In primary PCI the implantation of coronary stents has proven beneficial, demonstrating reduction of procedural complications and need for repeat revascularization. Co-medication like platelet GP IIb/IIIa receptor blockers before the procedure gained momentum after randomized trials demonstrated a benefit of this treatment with respect to less urgent revascularization.

Limitations and lessons

This analysis was retrospective and therefore patient selection and physician decisions are difficult to identify and to quantify. Moreover, there is no control group to compare the findings with, because patients with failed thrombolysis left untreated were not identified.

The exact time of specific treatments given was not always available, although such timing is likely to be of major influence on bleeding events, especially considering the short half life of tPA. More than 50% of tPA is cleared within 5 minutes after cessation of the infusion, and about 80% is cleared from the plasma within 10 minutes. In contrast, for streptokinase the fibrinolytic effects last a few hours, and the anticoagulant effects persist for 12-24 hours. It is conceivable that bleeding complications of successive antithrombotic or interventional treatment is highly dependent on time since thrombolysis. Finally true incidence of bleeding events may have been underes-

timated especially for patients transferred back to the referring clinic. Despite these limitations the data can form a valuable contribution to the very limited data available on rescue strategies.

Patients without thrombolytic therapy

Selection for primary PCI in our study was based on the clinical condition of the patients reserving such therapy for high risk patients[41,42], many of them after resuscitation (27%) and on mechanical ventilation (13.5%). As a consequence death rates in patients treated with primary PCI are higher than found in literature[43] and higher than in patients treated with fibrinolysis.

In our series of consecutive patients a high proportion (34%) of patients did not receive any reperfusion therapy at all. This group included patients not qualifying for reperfusion with small infarctions or patients arriving too late to expect benefit from reperfusion therapy. A few of these patients were already in extremis, many dying soon after presentation on the first aid department or on their way to the catherization laboratory.

Conclusion

Rescue therapy was offered on clinical grounds in 36% of non-referred patients initially treated with fibrinolytics in this single center retrospective analysis. Administration of platelet GP IIb/IIIa receptor blockers as part of rescue therapy was clearly related to bleeding risk. Lethal bleeding was observed once. Also a single intracranial bleed occurred. It remains unproven whether an efficacy benefit outweighs the bleeding risk in failed thrombolysis[44], although the excellent survival after rescue therapy supports the efficacy of such. More and preferably prospective randomized data on all three rescue therapies are clearly needed to guide therapy for failed thrombolysis.

The efficacy of early reperfusion therapy has been demonstrated beyond doubt. Yet, the choice of therapy in a given patient will depend on local facilities, budgets and physician preferences. We do recommend that regional protocols are developed to optimally use the available facilities. Such protocols should specify the criteria for administration of one of different fibrinolytic agents, and for direct PCI. Furthermore criteria for rescue procedures should be provided. In view of the excess of bleeding complications, we would recommend to provide direct PCI to all patients who might qualify for a rescue procedure if initial fibrinolytic therapy proves to be not effective. Such protocols would offer direct PCI to all patients with large evolving infarct and to medium size infarct with increased bleeding risk. Other patients should receive thrombolytic therapy. In such patients rescue procedures should rarely be indicated. A protocol of such design will be introduced in the Rotterdam region. In patients with

failed thrombolysis, rescue therapy might be offered. Physicians responsible for such therapy should be aware of the excessive bleeding risk as evident from this retrospective study.

References

1. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673 -682.
2. Langer, A, Krucoff, MW, Klootwijk, P, et al, for the GUSTO-I ECG Monitoring Substudy Group. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: The GUSTO-I ST segment monitoring substudy. J Am Coll Cardiol 1998; 31:783-789.
3. Davies CH, Ornerod OJM. Failed coronary thrombolysis. Lancet 1999; 351: 1191-1196
4. The CORAMI Study Group. Outcome of attempted rescue coronary angioplasty after failed thrombolysis for acute myocardial infarction. Cohort of Rescue Angioplasty in Myocardial Infarction. Am J Cardiol 1994; 74: 172-174
5. Baim, DS, Diver, DJ, Knatterud, GL, and the TIMI 2A Investigators. PTCA "salvage" for thrombolytic failures: implications from TIMI 2A. Circulation 1988; 78(Suppl II):II-112
6. White HD, Cross DB, Williams BF, Norris RM, Woo KS, Hamer AW, Elliott JM, Ormiston JA. "Rescue" thrombolysis with intracoronary tissue plasminogen activator for failed intravenous thrombolysis with streptokinase for acute myocardial infarction. Am J Cardiol 1995; 75: 172- 174
7. Becker RC Thrombolytic retreatment with tissue plasminogen activator for threatened reinfarction and thrombotic coronary reocclusion. Clin Cardiol 1994;17: 3-13.
8. Simoons ML, Arnout J, Van den Brand M, Nyssen K, Verstraete M. Retreatment with Alteplase for early signs of reoclusion after thrombolysis. The European Cooperative Study Group. Am J Cardiol 1993; 71: 524-528
9. Miller JM, Smalling R, Ohman EM, et al. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). Global use of strategies to open occluded coronary arteries. A J Cardiol 1999; 84: 779-784.
10. Muhlestein, JB, Karagounis, LA, Treehan, S, et al. "Rescue" utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997; 30:1729-1724
11. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Eng J Med 1997; 336: 1689-1696.
12. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-61.
13. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
14. The GUSTO V investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001; 357: 1905-1914.
15. Ronner E, Zijnen P, Altmann E, et al. Safety and efficacy of eptifibatide vs placebo in

patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction. A phase II dose escalation, randomized, double-blind study. Eur Heart J 2000; 18: 1530-1536.
16. Antman EM, Giugliano RP, Gibson MC, et al. for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolyis in myocardial infarction (TIMI) 14 trial. Circulation 1999; 99: 2720-2732
17. INTRO-AMI was presented at the 21st Congress of the European Society of Cardiology in Barcelona September 1999.
18. Jong P, Cohen EA, Batchelor W, Lazzam C, Kreatsoulas C, Natarajan MK, Strauss BH. Bleeding risks with abciximab after full-dose thrombolysis in rescue or urgent angioplasty for acute myocardial infarction. Am Heart J 2001; 141: 218-25.
19. Schröder R, Dissman R, Brüggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute AMI. J Am Coll Cardiol 1994; 24: 389-391.
20. Bär F, Vainer J, Stevenhagen J, et al. Ten-year experience with early angioplasty in 759 patients with acute myocardial infarction. J Am Coll Cardiol 2000; 36: 51-58.
21. Hasdai D, Batter A, Wood D, et al. Euro Heart Survey, Presented at the 23rd Congress of the European Society of Cardiology in Stockholm, 2001.
22. Stenestrand U, Wallentin L. Swedish national database; RIKS-HIA database. Data on file.
23. Simes RJ, Topol EJ, Holmes DR, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial perfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. Circulation 1995; 91:1905.
24. Ohman, EM, Califf, RM, Topol, EJ et al and the TAMI study group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990; 82:781-791.
25. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317: 581-588.
26. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group.SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. BMJ 1991; 302:555-560.
27. Ellis SG, De Silva RE, Heyndrickx G, et al. For the RESCUE investigators. Randomized comparison of rescue angioplasty with conservative management of patients with early failure thrombolysis for AMI. Circulation 1994; 90: 2280-2284.
28. Ross AM, Lundergan CF, Rohrbeck SC, et al. Rescue angioplasty after failed thrombolysis: technical and clinical outcomes in a large thrombolysis trial. GUSTO-1 Angiographic Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1998; 31: 1511-1517.
29. Gibson CM, Cannon CP, Greene RM, Sequeira RF, Margorien RD, Leya F, Diver DJ, Baim DS, Braunwald E. Rescue angioplasty in the thrombolysis in myocardial infarction (TIMI) 4 trial. Am J Cardiol 1997; 80: 21-16
30. Tebbe U, Michels R, Adgey AAJ, et al. Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. Comparison trial of saruplase and streptokinase (COMASS) investigators. J Am Coll Cardiol 1998; 31: 487-493
31. Schroder R, Wegscheider K, Schroder K, et al for the INJECT Trial Group. Extent of early ST segment elevation resolution: A strong predictor of outcome in patients with acute myo-

cardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) Trial. J Am Coll Cardiol 1996; 26:1657-1667
32. Betriu A, Califf RM, Bosch X, et al. Recurrent ischemia after thrombolysis: importance of associated clinical findings. Gusto-1 investigators. J Am Coll Cardiol 1998; 31: 94-102
33. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-1622
34. Bär F, Vainer J, Stevenhagen J, et al. Ten-year experience with early angioplasty in 759 patients with acute myocardial infarction. J Am Coll Cardiol 2000; 36: 51-58.
35. Ellis GE, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley D. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. Am Heart J 2000; 139: 1046-
36. Grines CL, Browne KF, Marco J, et al: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993: 328: 673-679
37. Bär F, Vainer J, Stevenhagen J, et al. Ten-year experience with early angioplasty in 759 patients with acute myocardial infarction. J Am Coll Cardiol 2000; 36: 51-58.
38. HART - 2 was presented at the 49th Annual Scientific Sessions of the American College of Cardiology, Anaheim, March 2000.
39. SK - AMI, submitted
40. Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. J Am Coll Cardiol 1997; 30: 962-969.
41. Simoons ML, Arnold AE. Tailored thrombolytic therapy. A perspective. Circulation 1993; 88: 2556-2564.
42. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343: 311-22.
43. Zijlstra F, de Boer MJ, Hoomtje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328: 680-684.
44. Abbottsmith, CW, Topol, EJ, George, BS, et al. Fate of patients with acute AMI with patency of the infarct-related vessel achieved with successful thrombolysis versus rescue angioplasty. J Am Coll Cardiol 1990; 16: 770-778.

4 Conclusion

4.1

Platelet GP IIb/IIIa receptor blockers in clinical practice

Eelko Ronner[1,2], Eric Boersma[1], G.J. Laarman[2],
L. Ron van der Wieken[2], Ferdinand Kiemeneij[2], Ton S. Slagboom[2],
Alf E.R. Arnold[3], Victor A.W.M. Umans[3], G. Aernout Somsen[4],
Maarten L. Simoons[1]

[1] University Hospital Rotterdam, Rotterdam, The Netherlands
[2] Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[3] Medical Center Alkmaar, Alkmaar, The Netherlands
[4] Academic Medical Center, Amsterdam, The Netherlands

Introduction

Inhibition of platelet aggregation by aspirin has unambiguously demonstrated to reduce mortality and morbidity in patients with coronary heart disease and especially in patients with acute coronary syndromes[1,2]. Compared to aspirin and other antiplatelet agents like clopidogrel, platelet GP IIb/IIIa receptor blockers are more potent since they block the final common pathway of platelet aggregation. Aspirin only inhibits platelet aggregation indirectly by blocking the cyclo-oxygenase pathway. From a theoretical point of view therefore platelet GP IIb/IIIa receptor blockers seem attractive to reduce thrombo-embolic complications in patients with coronary heart disease.

Multiple large randomized trials have indeed confirmed a highly beneficial effect of platelet GP IIb/IIIa receptor blockers together with a favourable safety profile. In patients treated with percutaneous coronary intervention (PCI), multiple trials were halted prematurely after interim-analyses demonstrated significant reduction of death and myocardial infarction (MI) in patients randomized to a platelet GP IIb/IIIa receptor blocker[3,4,5].

This review chapter describes efficacy and safety of different platelet GP IIb/IIIa receptor blockers in various clinical settings. This review aims to guide clinical application of these agents, not only when to use the agents, but also when to refrain. Findings from this thesis are incorporated, including the chapters on timing of PCI in patients with ACS without persistent ST-segment elevation in the era of platelet GP IIb/IIIa receptor blockers.

Platelet GP IIb/IIIa receptor blockers in patients undergoing PCI for stable angina

Platelet GP IIb/IIIa receptor antagonists have demonstrated highly beneficial in prevention of MI when used around PCI. Although the Holy Grail of interventional cardiology is undoubtedly the reduction of restenosis, the problem of procedural infarction is eminent. Myocardial infarction (MI), defined as CK-MB rise over twice the upper limit of normal, within 30 days is noted in 10% of patients after routine PCI if cardiac enzymes are collected routinely, even when excluding PCI in particular high risk patients[6].

Platelet GP IIb/IIIa receptor blockers have demonstrated reduction of MI after PCI irrespective of clinical and angiographic criteria, throughout trials with a large variety of trial exclusion and inclusion criteria. The reduction was consistent, statistical significant and lasting. Clinical relevance of reduction of even small MIs is increasingly recognized, because small MIs proved to be related to significantly more late events[7,8,9], although some demonstrated other results[10], most likely because cardiac

enzymes were not collected routinely. Mortality is reduced significantly at 48 hours, and at 30 days the odds ratio for mortality was 0.87 (95% confidence interval 0.74 to 1.02; P=0.08) in favour of platelet GP IIb/IIIa receptor blockers versus placebo (in PCI)[11,12,13].

In clinical practice however, platelet GP IIb/IIIa receptor blockers are prescribed in only a small proportion of patients undergoing PCI. Most likely, this relates to restricted health care resources, where patient selection is often a, perhaps unjustified, necessity despite the convincing relative reduction of MI related to PCI. It seems therefore important to identify patients at risk for procedural MI, in order to determine which group of patients is more likely to benefit from platelet GP IIb/IIIa receptor blockers. Patients at risk for procedural MI should be treated with the agents. On the other hand, if patients at lower risk can be identified, perhaps a subset of patients can be defined in whom platelet GP IIb/IIIa receptor blockers are not needed.

In a large group of patients, risk of developing procedural MI becomes apparent only during intervention. Risk of MI for example is strongly related to the appearance of complex coronary dissections during PCI[14,15]. But the risk of dissection is not reliable predicted by pre-procedural characteristics[16]. Although it is tempting to reduce development of MI in these cases, not recognized before the PCI, it is unknown if prevention of MIs is still feasible if preventive measures are started only during the procedure. Data on strategies with platelet GP IIb/IIIa receptor blockers started during PCI ("bailout") are limited to retrospective series and the ESPRIT trial which demonstrated worse outcome when bailout platelet GP IIb/IIIa receptor blockers were compared to standard treatment with platelet GP IIb/IIIa receptor blockers before the procedure[5,17]. The ESPRIT trial aimed to include low risk patients, more specifically it included patients who would otherwise not have received a platelet GP IIb/IIIa receptor blocker. In addition, treatment with eptifibatide was compared with placebo in combination with bailout eptifibatide[5]. At a pre-specified interim-analysis administration of the agent routinely proved highly efficacious after which the trial was halted. These results suggest to administer platelet GP IIb/IIIa receptor blockers to all patients undergoing PCI for stable angina or ACS without persistent ST-segment elevation.

Randomized trials too, did not identify a group in whom platelet GP IIb/IIIa receptor blockers around PCI were not beneficial. For example, we tried to identify low risk patients by selecting patients that underwent PCI for stable angina. Stable angina patients (among other patients!) were included in ESPRIT, EPILOG and EPISTENT. In EPIC too, stable angina patients were included, but only if adverse lesion characteristics were present. As expected, the relative treatment effect was clearly beneficial, with a reduction of death and MI at 30 days of 17% (IMPACT 2, p=n.s.) to 74% (EPILOG, p<0.05). Surprisingly, not only the relative benefit, but also the absolute benefit in this category of patients with stable angina is high. While despite the con-

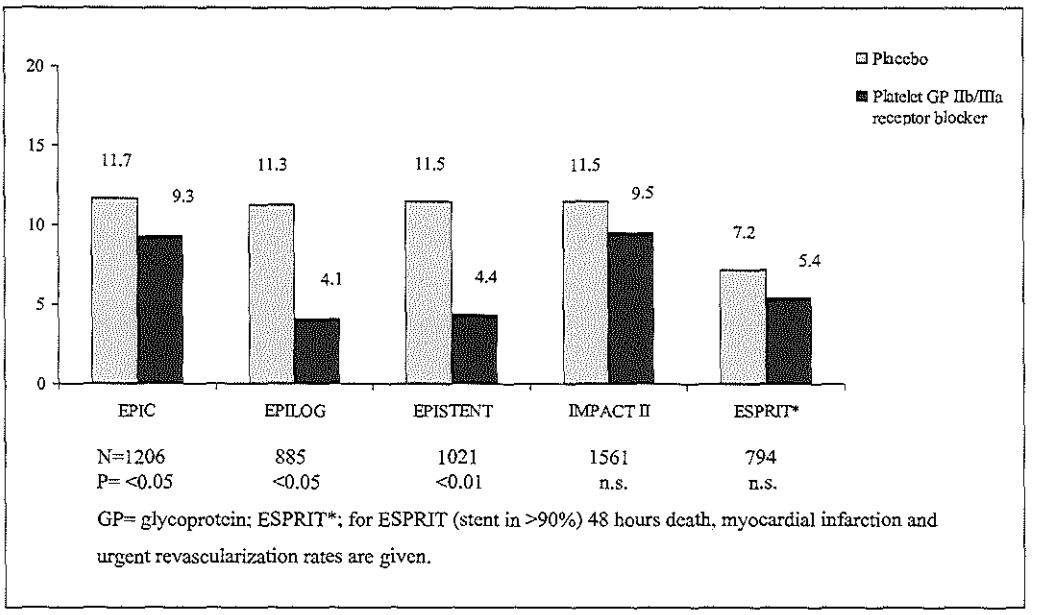


Figure 1 30-day death and myocardial infarction (%) in patients undergoing PCI for stable angina.

ceivable low risk of PCI in patients with stable angina, death and MI at 30 days in placebo treated patients was still around 11%, which is even comparable to historical event rates in patients undergoing PCI for ACS without persistent ST-segment elevation (Figure 1).

Although we recognize that patients with high risk can be identified; for example patients with ACS without persistent ST-segment elevation, patients with diabetes or previous infarction, or with elevated troponins or C-reactive protein[18], we recommend not to restrict administration of platelet GP IIb/IIIa receptor blockers to these patients. Neither should treatment be confined to patients at elevated risk for MI by adverse lesion characteristics, as visible thrombus at angiography preceding PCI, the occurrence of multiple lesions, lesion calcification and other adverse lesion characteristics[19,20]. Again, the platelet GP IIb/IIIa receptor blockers should be administered to patients without these risk factors too.

To our opinion, the only patients undergoing PCI not likely to benefit from platelet GP IIb/IIIa receptor blockers are patients with contra-indications to the agents as mentioned in the package inserts, as summarized in table 1. Most of the contra-indications refer to patients with increased bleeding risk. Others appoint to general issues, like previous hypersensitivity to the agents or thrombocytopenia.

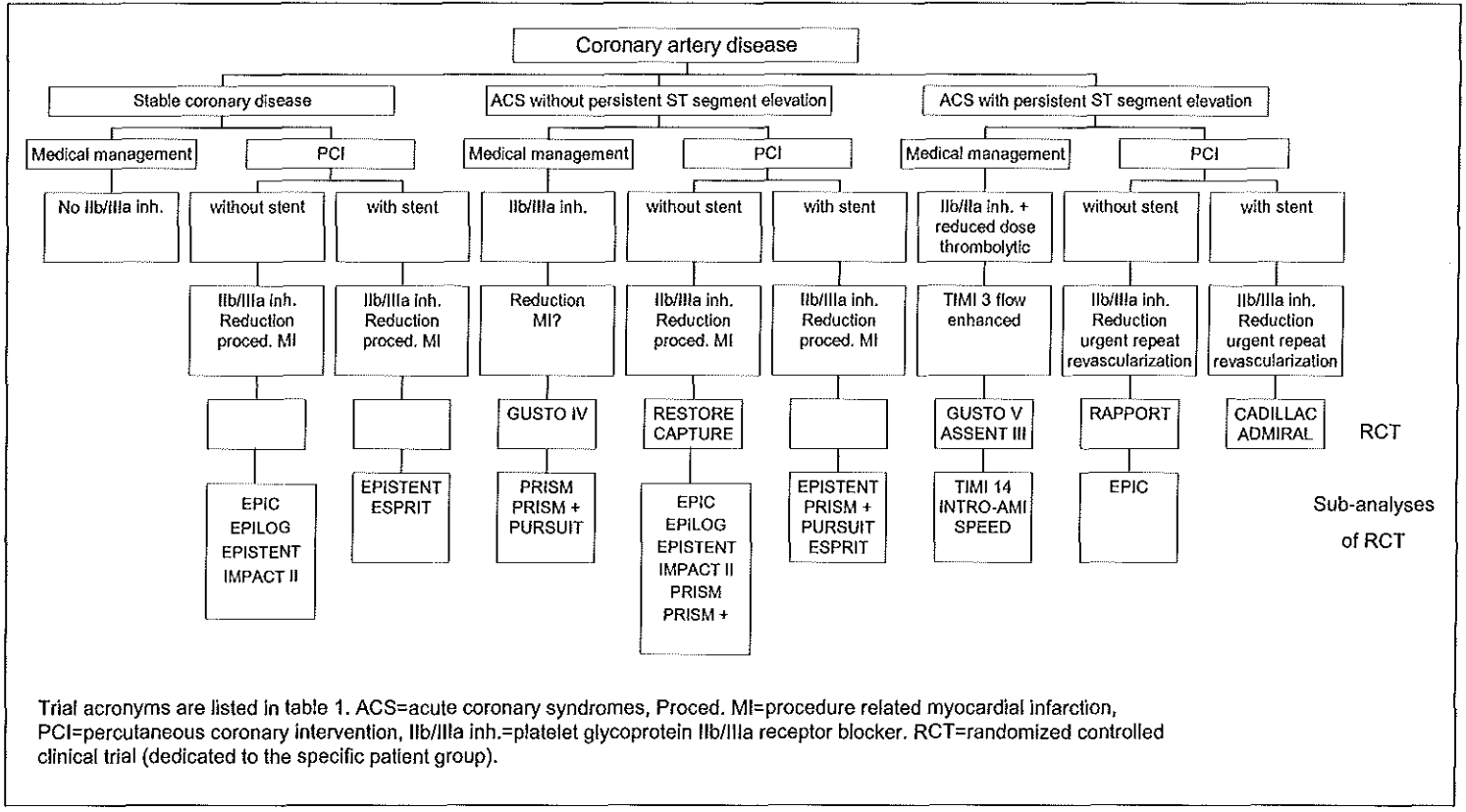
In summary, relative benefit of approximately 20 to even 40% reduction of MI have been demonstrated in trials. Although we recognize that benefit in absolute num-

Table 1
When to refrain from platelet GP IIb/IIIa receptor blockers according to prescription texts and suggested time frames to withold treatment.

	Abciximab	Eptifibatide	Tirofiban
Recent major surgery, large trauma	6 weeks	6 weeks	1 month
Non hemorrhagic stroke	2 years, or when sequelae	30 days	30 days
Hemorrhagic stroke	yes	yes	yes
Bleeding diathesis, large active bleeding	yes	yes, within 30 days	yes, within 30 days
Intracranial aneurysm, neopl, malf.	yes		Yes
Aortic dissection			if ever or suspected
Pericarditis			yes
Severe hypertension	if severe uncontrolled	over 200/110 despite Rx	over 180/110 mm.Hg
Thrombocytopenia	if below 100.000 mm^{-3}	yes	if previously with
Current or planned other iv IIb/IIIa Inh.	yes	yes	Yes
Creatinin clearance		below 4 $mg.dl^{-1}$	
Renal dialysis		yes	
Vasculitis	yes		
Hypersensitivity previously	yes	yes	Yes
Oral anticoagulant within 7 days	unless pt INR below 1.2		
Dextran	concomittant or planned		

Neopl, neoplasma; malf, malformation; iv IIb/IIIa inh, intravenous platelet glycoprotein IIb/IIIa receptor blocker; hypersensitivity, hypersensitivity during previous use of the specific agent; Rx, medication; INR, International Normalized Ratio.

bers will depend on the risk profile of the specific patient, it should be recognized that presumably low risk patients are hard to identify. Therefore it is recommended to administer platelet GP IIb/IIIa receptor blockers to all patients undergoing PCI for stable angina unless contra-indications are present. It should be noted however that no particular trial limited inclusion to patients with stable angina only (Figure 2).



Trial acronyms are listed in table 1. ACS=acute coronary syndromes, Proced. MI=procedure related myocardial infarction, PCI=percutaneous coronary intervention, IIb/IIIa inh.=platelet glycoprotein IIb/IIIa receptor blocker. RCT=randomized controlled clinical trial (dedicated to the specific patient group).

Figure 2 The diagram demonstrates the trials for specific clinical conditions

Platelet GP IIb/IIIa receptor blockers in patients with acute coronary syndromes without persistent ST-segment elevation

Invasive versus conservative treatment strategies in the era of platelet GP IIb/IIIa receptor blockers.

As a general principle, when in doubt, it is often advised to refrain from invasive treatment strategies (in dubio abstine). Doubt still surrounds the question whether to treat patients with ACS without persistent ST-segment elevation with medical management alone or with PCI.

Evidence to refrain from intervention, and treating with medical management alone is found in the older trials VANQWISH and TIMI IIIb trial[21,22]. It should be noted that cross-overs to interventional treatment occurred in a large proportion of patients in both trials. Other, more recent investigations like FRISC-2[23] and the OASIS registry[24] demonstrate a modest benefit for interventional over pharmacological treatment alone. Noteworthy, PCI was not performed within the first days, when the largest risk of death or MI is observed, and possibly largest risk reduction could have been obtained.

Our subanalysis of PURSUIT (see chapters 2.3 and 2.4 of this thesis) found a benefit in specifically very early PCI (within 24 hours) with a platelet GP IIb/IIIa receptor blocker in patients with ACS without persistent ST-segment elevation, for combined low and high-risk patients[25]. Mortality and MI at 30 days was observed in 9.2% of patients receiving day 1 PCI up to 17.7% for patients receiving later PCI ($p=0.011$). In 12.2% of patients 30 day death or MI occurred with medical management alone, (including eptifibatide randomized patients). However, without the platelet GP IIb/IIIa receptor blocker no benefit of early PCI (or later PCI) was observed over medical management alone. More support for invasive treatment comes from the recently reported TACTICS-TIMI 18 trial[26]. TACTICS-TIMI 18 demonstrated benefit of early PCI under protection of a platelet GP IIb/IIIa receptor blocker ($n=1114$) compared to medical management alone ($n=1106$). In this trial tirofiban was administered for 48 to 108 hours to patients with acute coronary syndromes without persistent ST-segment elevation. Patients were stratified to angiography (between 4 and 48 hours) and subsequent revascularization versus medical management alone. In the invasive arm PCI was performed in 41% during hospitalization, CABG in 19%. In the medical management group, cross-over to invasive treatment was allowed when specific conditions or criteria were met (like refractory angina after enrollment) that necessitated intervention, leading to crossover in many patients (PCI 24%, CABG 13%). Significantly less 30 day death and MI was observed in the early invasive arm (4.7%) compared with early conservative treated patients (7.0%).

Although the plea for invasive treatment seems to gain momentum[27] our PURSUIT analysis (see chapter 2.4 of this thesis) describes an increase of repeat revascularize-

tion after early intervention and we suggest to restrict early PCI to patients at highest risk[28]. In these high risk patients MI is prevented by PCI in combination with a platelet GP IIb/IIIa receptor blocker, whereas in others revascularization is a much more prominent problem than MI and should therefore be reduced by postponing or refraining from PCI. More information is needed to determine the optimal treatment for low risk patients. In the mean time it is advised to treat highest risk patients with invasive management, including pre-treatment with platelet GP IIb/IIIa receptor blockers and PCI while the patient is still on the drug. High risk patients are stratified with ST-deviation, troponin elevation but also clinical criteria[29,30]. If intervention is scheduled, early intervention seems to be optimal with respect to reduction of MI, but is possibly associated with higher revascularization rates.

In conclusion, with respect to treatment of patients with ACS without persistent ST-segment elevation, we advise to follow recent evidence, and perform PCI in high-risk patients with ACS without persistent ST-segment elevation, and to defer PCI in others. With respect to timing of PCI we recommend a tailored approach. In high risk patients intervention should be performed early (preferably within 24 hours) in order to reduce death and MI, in patients at lower risk for death or MI however, deferring PCI seems beneficial as this leads to less revascularization.

Platelet GP IIb/IIIa receptor blockers for patients with ACS without persistent ST-segment elevation treated with PCI

According to current guidelines, patients with ACS without persistent ST-segment elevation undergoing PCI should be treated with platelet GP IIb/IIIa receptor blockers[31,32]. This is unambiguously demonstrated in numerous trials. For example, EPIC[33] demonstrated a large treatment benefit in patients undergoing PCI with ACS without persistent ST-segment elevation, although inclusion encompassed patients with angiographical adverse characteristics as well. In CAPTURE patients were included with refractory ischemia despite optimal medical treatment and again they benefited clearly from abciximab before (18 to 24 hours) and after PCI (1 hour)[3].

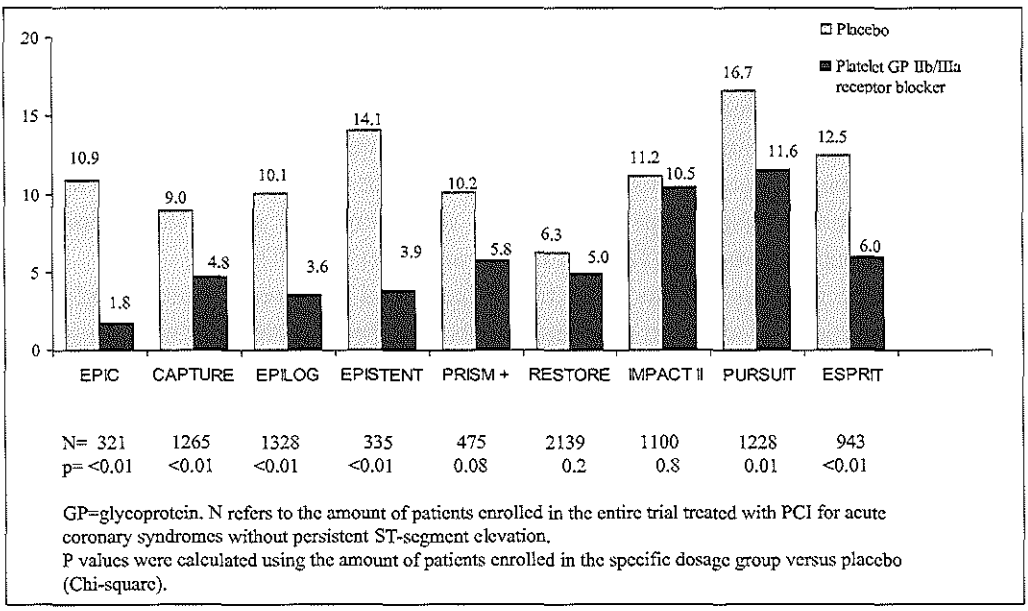
It should be recognized that most trials had broad inclusion criteria, including other patient groups as well. On one hand, trials have been performed including only patients with ACS without persistent ST-segment elevation, but including patients managed medically without PCI as well. On the other hand, trials have been conducted on PCI, with broad inclusion criteria encompassing patients undergoing PCI for stable coronary disease, and sometimes patients undergoing PCI for MI as well (figure 3). It is therefore necessary to resort to sub-analysis of these trials to estimate the effect of adding platelet GP IIb/IIIa receptor blockers to patients referred for PCI in the setting of ACS without persistent ST-segment elevation.

In but two trials inclusion was limited to patients undergoing PCI for ACS without persistent ST-segment elevation, the RESTORE and the CAPTURE trial.

In RESTORE (n = 2139) tirofiban was compared to placebo in patients with ACS within 72 hours of hospitalization[34]. Tirofiban was administered in a lower dose than customary in later trials; 10 μg/kg for 3 minutes followed by a 36 hours infusion of 0.15 $\mu g.kg^{-1}.min^{-1}$. This relatively low dose was a possible explanation for the modest reduction of mortality, MI, recurrent intervention or failed (initial) PCI observed at 30 days, 10.3% versus 12.2% in placebo (p = 0.160). The results cannot be extrapolated to clinical practice as the current dosages recommended for tirofiban are increased and therefore are likely to resort in different, most likely better, results.

The CAPTURE trial included patients with ACS without persistent ST-segment elevation only when proven refractory to oral or intravenous nitrates and intravenous heparin within 24 hours before inclusion[3]. Patients were all scheduled for PCI. Thirty day death and MI was reduced from 9.0% for placebo treated patients to 4.8% for patients randomized to abciximab (p = 0.003).

Interventional trials that included patients with, but also without ACS are EPIC, EPILOG and EPISTENT as well as ESPRIT[33,4,35,5]. All of these trials have proven benefit of platelet GP IIb/IIIa receptor blockers around PCI for the complete heterogeneous patient groups the trials included. The subgroups of patients with ACS without persistent ST-segment elevation within these trials demonstrate strongly beneficial results (Figure 3). In EPIC 489 patients demonstrated unstable angina (now often referred to as ACS without persistent ST-segment elevation) at inclusion. At 30 days, the primary



GP=glycoprotein. N refers to the amount of patients enrolled in the entire trial treated with PCI for acute coronary syndromes without persistent ST-segment elevation.
P values were calculated using the amount of patients enrolled in the specific dosage group versus placebo (Chi-square).

Figure 3 30-day death and myocardial infarction (%) in patients undergoing PCI for acute coronary syndromes without persistent ST-segment elevation.

endpoint of death, MI, or urgent repeat revascularization was reduced by 62 percent compared to placebo (4.8 versus 12.8 percent), primarily due to a decrease in death and MI.

Other information stems from trials selectively enrolling patients with ACS without persistent ST-segment elevation. PCI but also medical management was given. Patient characteristics but also local customs and physician preferences influenced treatment choice. Subanalysis of these trials are subject to bias, but unequivocally demonstrate a large treatment effect of platelet GP IIb/IIIa receptor blockers when administered around PCI.

There is an indication for platelet GP IIb/IIIa receptor blockers in patients undergoing PCI for ACS without persistent ST-segment elevation. According to recent analysis it seems particularly attractive to treat patients selected for PCI as soon as possible with the combination of PCI and platelet GP IIb/IIIa receptor blockers, it is advised to continue infusion for at least 12 hours after PCI, as customary in multiple trials. Timing of PCI seems to play a role in outcome, however, more evidence is needed to determine optimal timing of PCI in patients with ACS without persistent ST-segment elevation.

Platelet GP IIb/IIIa receptor blockers in patients managed medically for ACS without persistent ST-segment elevation

Before GUSTO IV ACS was reported, administration of platelet GP IIb/IIIa receptor blockers seemed an attractive option to stabilize patients with ACS without persistent ST-segment elevation. Sub-analyses of trials in whom patients were pre-treated with platelet GP IIb/IIIa receptor blockers before PCI were reported for the CAPTURE, PURSUIT as well as the PRISM PLUS trial. Data from CAPTURE, PURSUIT, and PRISM-PLUS (n = 12,296) demonstrated reduced death and MI during drug infusion for patients treated with platelet GP IIb/IIIa receptor blockers (2.5 versus 3.8 percent for placebo).

Clear pre-procedural stabilization was demonstrated by less pre-procedural ST-segment deviations and significantly less pre-procedural MI. It was expected that patients treated without PCI altogether would demonstrate similar event reduction in a randomized trial. Guidelines anticipated to this expected benefit and advised to start a GP IIb/IIIa receptor antagonist in ACS without persistent ST-segment elevation even if PCI was not scheduled.

Unexpectedly, in GUSTO IV this hypothesis could not be proved. Indeed, platelet GP IIb/IIIa receptor blockers did not reduce events in patients managed medically for ACS without persistent ST-segment elevation. In GUSTO-IV (n = 7800) patients were enrolled with high risk ACS without persistent ST-segment elevation, encompassing either minimally 0.5 mm ST-segment depression and/or elevated troponins[36].

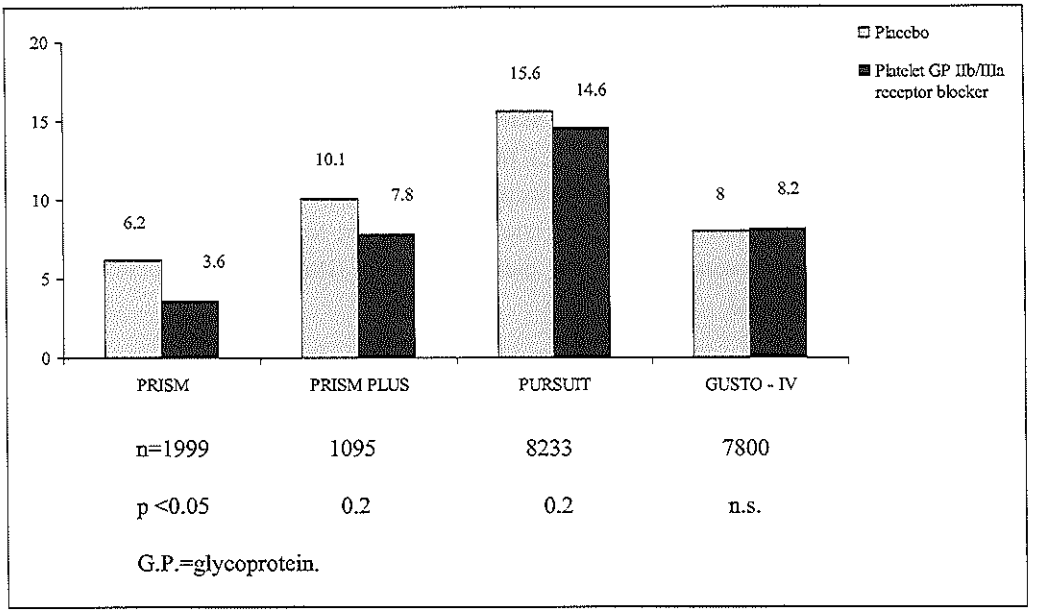


Figure 4 30-day death and myocardial infarction (%) in patients treated medically alone for acute coronary syndromes without persistent ST-segment elevation.

Thirty day mortality and MI was 8.0% in patients treated with placebo, versus 8.2% in patients treated with 24 hours of abciximab and 9.1% in patients treated for 48 hours of abciximab (p = n.s.). Abciximab demonstrated no benefit and no trend towards a benefit on other endpoints, including 6 month revascularization and combined or separate endpoints. Results of trials are summarized in figure 4. Reasons to explain this lack of efficacy of abciximab in GUSTO-IV are perhaps patient selection, a low event rate, the specific drug regimen, or a play of chance.

Combining the data from several trials of GP IIb/IIIa receptor antagonists in patients with ACS without persistent ST-segment elevation treated without PCI an overall modest but significant benefit of treatment is observed, as can be calculated with data from figure 4 (placebo 11% versus 10% events for platelet GP IIb/IIIa receptor blockers, n = 19127, p = 0.02). A formal meta-analysis will elucidate this issue further[29]. Given the heterogeneous results of platelet GP IIb/IIIa receptor blockers in patients with ACS without persistent ST-segment elevation in whom PCI is not to be performed within first days, the agents are likely to reduce events, but the effect is modest. It seems therefore reasonable to reserve this treatment to highest risk patients.

Platelet GP IIb/IIIa receptor blockers in persistent ST-segment elevation myocardial infarction

Invasive versus conservative treatment strategies

A continuous debate surrounds the issue of thrombolytic therapy versus PCI in acute ST-segment elevation MI that goes beyond the scope of this article[37-41]. The role of platelet GP IIb/IIIa receptor antagonists in adjunct to thrombolytic therapy and as bailout therapy after failed thrombolysis is described in this thesis, while the role of platelet GP IIb/IIIa receptor blockers in combination with PCI is addressed in this overview and chapter 2.1 and 3.1. Platelet GP IIb/IIIa receptor blockers as sole reperfusion therapy are not described separately as trials have not proven benefit of this therapy over conventional reperfusion therapies (primary PCI or thrombolysis).

Primary PCI; always with platelet GP IIb/IIIa receptor blockers?

Data from EPIC in acute MI (n=64) suggested a large treatment benefit of platelet GP IIb/IIIa receptor blockers in acute MI[42]. Multiple trials followed to explore the role of platelet GP IIb/IIIa receptor blockers in acute MI. Platelet GP IIb/IIIa receptor blockers in combination with PCI were randomly compared to PCI without a platelet GP IIb/IIIa receptor blocker in RAPPORT, ADMIRAL and CADILLAC.

In RAPPORT 483 patients were randomized to PCI with and without abciximab[43]. Thirty-day mortality, MI and repeat revascularization were reduced. Surprisingly the benefit was obtained largely by a reduction of repeat revascularization, in contrast to findings of abciximab in other clinical settings were mainly MI is reduced. An explanation is that the reduction encompassed mainly urgent, most likely thrombosis related repeat revascularization, and not scheduled repeat (restenosis-) revascularization. Major bleeding was observed in the abciximab group in 16.6% versus 9.5% in placebo treated patients.

In the ADMIRAL trial, stent or balloon angioplasty was performed in 300 patients randomized to abciximab or placebo before PCI[44]. 24 hours TIMI 3 flow was 86% for abciximab versus 78% for placebo. Thirty day mortality, recurrent MI and/or recurrent revascularization was improved in the abciximab group (10.7%) versus 20% for placebo. This effect again was most profoundly due to reduction of urgent repeat revascularization.

Finally the CADILLAC trial (n=1961) randomized balloon angioplasty versus angioplasty with stent implantation, and in each group abciximab versus placebo was given[45]. Again ischemia-driven repeat revascularization (before discharge) was decreased by abciximab in the angioplasty group (0.25 versus 2.3% for PTCA alone) as well as in the group treated with intracoronary stenting (0.2 versus 0.8%).

Platelet GP IIb/IIIa receptor blockers are highly efficacious in patients undergoing PCI, and these findings are consistent in patients treated with PCI for MI with

persistent ST-segment elevation. This is prospectively demonstrated in the aforementioned trials on acute MI. It is therefore recommended to treat patients with acute MI undergoing primary PCI with platelet GP IIb/IIIa receptor blockers unless contra-indications for this class of drugs are present.

Platelet GP IIb/IIIa receptor blockers and thrombolysis in acute MI

In TIMI 14 different combinations of abciximab and thrombolysis were explored in 888 patients with acute MI[46]. In one arm full dose abciximab alone was given, others received the combination of full dose abciximab in combination with full and reduced doses of either tPA or streptokinase. 32% of patients treated with abciximab alone had 90 minutes TIMI III flow. 57% TIMI 3 flow was observed in patients receiving full dose tPA alone. In patients randomized to reduced dose streptokinase with abciximab 34 to 46% TIMI 3 flow at 90 minutes was seen. In combination with tPA, full dose abciximab was associated with 61 to 76% TIMI 3 flow at 90 minutes.

Improvement of ST resolution was also noted in the reduced dose tPA plus abciximab group (59 versus 37%, $p < 0.0001$). Major hemorrhage was 6% in the combination group, compared to 7% for patients treated with tPA alone.

The benefit of combined therapy was confirmed in the SPEED trial. 304 patients were randomized to reduced dose rPA (retevase; optimal dose two times 5 units at 30 minutes apart) with abciximab versus abciximab alone[47]. TIMI 3 flow at 90 minutes was 60% versus 27% in patients receiving abciximab alone. Another 224 patients were randomized to the best combination therapy of SPEED versus rPA alone in the second phase of SPEED[48]. TIMI 3 flow was 47% of patients treated with rPA alone versus 51% for patients receiving rPA and abciximab. However, major bleeding was more frequent in patients treated with combination of rPA and abciximab (9.8 versus 3.7% for rPA alone).

INTRO-AMI was a trial similar in design and outcome as TIMI 14. In INTRO-AMI eptifibatide was combined with various dosages of tPA, and again, the combination of half dose tPA with eptifibatide demonstrated optimal TIMI 3 flow at 90 minutes (78% of patients).

Combination therapy of reduced (50%) dose thrombolysis with platelet GP IIb/IIIa receptor blockers enhances TIMI 3 flow at 90 minutes. Improved outcome is expected, but results of GUSTO-V[49] recently published demonstrated no significant reduction of the primary endpoint of 30 day mortality. In GUSTO V patients were randomised to reteplase versus half-dose reteplase ($n = 8260$) and full-dose abciximab ($N = 8328$).

There was a reduction in 30 day death and recurrent infarction in the combination group (8.8% for reteplase, versus 7.4% for the combination; $p = 0.0011$). Intracranial bleeding was not significantly different in patients treated with combination of reteplase and abciximab (1.0%) versus reteplase (0.9%; $p = 0.55$), although a trend towards more intracranial bleeding in patients over 75 years old was observed (2.1%

for combination versus 1.1% for reteplase only; p = 0.069).

In the ASSENT III trial, 6095 patients with acute MI of less than 6 hours were randomly assigned to either abciximab and half dose tenecteplase with unfractionated heparin (2017); or tenecteplase with unfractionated heparin (2038) or tenecteplase with enoxaparin (2040)[76]. The primary efficacy endpoint of 30-day mortality, in-hospital reinfarction or in-hospital refractory ischemia was 11.1% in patients receiving abciximab/ tenectaplase/ unfractionated heparin, 11.4% for the enoxaparin/tenecteplase arm, versus 15.4% in the treatment arm with tenecteplase and unfractionated heparin (p = 0.0001). Death at 30-days was observed in 6.6% abciximab/ enecteplase/ unfractionated heparin), 5.4% (tenecteplase/enoxaparin) and 6.0% (tenectaplase/unfractionated heparin), p = 0.25. In hospital intra-cranial bleeding was 0.9% in all three arms. Other major bleeding was noted in 4.3% of abciximab/ tenecteplase/ unfractionated heparin, 3.0% for patients treated with tenecteplase/ enoxaparin, and 2.2% for tenecteplase/ unfractionated heparin. Overall, the two novel strategies that included either enoxaparin or abciximab demonstrated improved results with respect to ischemic complications of MI, compared to tenecteplase and unfractionated heparin. Safety between these two arms is slightly superior in the enoxaparin arm. Enoxaparin, abciximab and half-dose tenecteplase has not been combined in this trial. Other trials on "combination therapies" for acute myocardial infarction are INTEGRITI (integrilin and tenecteplase, n = 400), and ENTIRE (TNK with or without abciximab, with or without low-molecular weight heparin).

Given current evidence, combination therapy with a platelet GP IIb/IIIa receptor blocker and half-dose thrombolytic seems promising, as better 90 minutes TIMI 3 flow has been demonstrated for abciximab and eptifibatide, and reduced 30 day death and MI has been observed (abciximab). Further trials are awaited to determine the indication for combination therapy among current reperfusion strategies with thrombolysis alone and primary PCI, but also to clearify optimal (co-) treatment with other agents like low-molecular weight heparins.

Rescue platelet GP IIb/IIIa receptor blockers for failed thrombolysis

Thrombolysis has improved outcome in acute myocardial infarction (MI)[50]. In a number of patients however this therapy fails to restore perfusion or infarction recurs early[51]. Persistent chest pain, haemodynamic compromise, lack of ST-segment resolution and/or inadequate TIMI flow at 90 minutes suggest failed reperfusion and can prompt additional reperfusion treatment. Currently rescue PCI, repeat thrombolysis and platelet GP IIb/IIIa receptor blockers are used to treat this condition of so-called "failed thrombolysis"[52-59].

The class of platelet GP IIb/IIIa receptor blockers is however not well documented for this indication. No randomized trials have been performed to our knowledge, besides incidental reports that unequivocally describe high bleeding risk. A recent

report (n=147) describes patients undergoing rescue PCI within 48 hours of thrombolysis (n=147) for acute MI. Abciximab was administered in 39% of patients and was associated with 12% major bleeding compared to 3% in patients with only rescue/urgent PCI after thrombolytic therapy[60].

In chapter 3.3 we describe 548 patients with evolving MI. Of these patients 49% had received thrombolysis. In 139 of thrombolysis treated patients, rescue therapies were used, PCI in 74%, retreatment with thrombolysis in 39% and a platelet GP IIb/IIIa receptor blocker in 53%, often in combinations. Platelet GP IIb/IIIa receptor blockers were used in 53% of patients treated with rescue PCI.

Major bleeding occurred in 14% of all thrombolysis treated patients, but in 30% of patients who received multiple rescue therapies. Bleeding was related to heparin usage and platelet GP IIb/IIIa receptor blockers. Furthermore the insertion of catheters for PCI or intra-aortic balloon pumps was associated with bleeding.

Most major bleedings observed were one death due to a ruptured ventricle, one hemorrhagic stroke, and three cases of tamponade for which surgery was needed. Four of these patients had received a combination of rescue therapies.

Decisions for treatment of acute MI should encorporate the risk of (treatment of) failed thrombolysis versus risk of bleeding[61]. Primary PCI should be strongly considered in patients in whom the risk of failed thrombolysis or rescue therapy is high.

General issues

Stents

In current interventional cardiology, stents are used in a large proportion of patients undergoing PCI. The addition of platelet GP IIb/IIIa receptor blockers to coronary stents proved beneficial in trials. The benefit is attributable to 30 day reduction of death and MI, from 7.8% for placebo treated patients to 3.0% for patients receiving stent and abciximab in the EPISTENT trial ($p=0.001$)[35]. It is noteworthy that balloon angioplasty with platelet GP IIb/IIIa receptor blockers proved superior to stenting alone with respect to 30 day death and MI (4.7% versus 7.8% for stenting alone, $p=0.01$). Other trials have included patients with stents, but did not stratify patients according to stenting. In these trials too, stenting and platelet GP IIb/IIIa receptor blockers proved safe and effective.

Often coronary stents are inserted to ascertain vessel patency when complications develop during PCI. However, data on coronary stenting learn that procedural infarction is hereby not clearly reduced, although the need for emergency cross-over to coronary artery bypass grafting is diminished. We recommend to administer platelet GP IIb/IIIa receptor blockers to all patients undergoing PCI, irrespective of stenting, except perhaps in patients undergoing primary PCI with stent (see the specific section

of this chapter).

Co-medication

Heparin use is strongly recommended with platelet GP IIb/IIIa receptor blockers. Heparin has been obligatory in adjunct to platelet GP IIb/IIIa receptor blocker in most clinical trials, and if left out has proven adversary in some cases[62]. Dosing however should be targeted at modest levels of ACT (about 200 seconds) or APTT (1.5 times the upper limit of normal) to prevent serious bleeding[63,4]. Data on conjunctive use of low-molecular weight heparins proved safety, although efficacy compared to intravenous heparin is unknown.

Aspirin is used in most trials, and is therefore recommended in adjunct to these agents. Moreover safety was contained when platelet GP IIb/IIIa receptor blockers were used in combination with ADP-antagonists like clopidogrel or ticlopidine as customary in coronary stenting.

Bleeding complications

Modest bleeding rates are reported throughout most trials, especially if moderate heparin doses are used. It is reassuring that bleeding is not higher than in placebo patients in some trials[64]. Fortunately, rates of both hemorrhagic and non hemorrhagic stroke are low[65]. Combination with full dose thrombolysis is associated with a serious risk of major bleeding and can therefore better be avoided as demonstrated in this thesis.

Pooled data from studies in which patients were receiving platelet GP IIb/IIIa receptor blockers prior to emergency CABG have demonstrated a tendency towards reduced peri-procedural MI, without increase in major bleeding[66]. However, it is strongly recommended however to antagonize abciximab by administration of platelets to avoid bleeding. This reduces the percentage of GP receptors blocked, and thereby reduces the effect of the agents to subtherapeutic levels. Eptifibatide and tirofiban treated patients can undergo CABG after 3 hours of cessation of therapy due to their short half lives.

Thrombocytopenia complications

According to a pooled report, thrombocytopenia occurs in 4.2% of patients as a complication of abciximab use, versus 2% for placebo[67]. To avoid clinical sequelae, it is recommended to determine platelet count within 24 hours after start of therapy with abciximab. Platelet transfusion can be necessary. It should be appreciated that pseudothrombocytopenia can be the cause of thrombocytopenia, which can be discovered by re-determining platelet count in citrate medium, instead of EDTA solvent. The occurrence of pseudothrombocytopenia should not be underestimated, as this was observed in 36% of patients with thrombocytopenia in a pooled report of trials with abciximab[68]. Other intravenous platelet GP IIb/IIIa receptor blockers have demonstrated about

1.5% thrombocytopenic reactions, defined as platelet counts below 100.000/mm^3.

In patients treated with abciximab as well as 300 mg of clopidogrel, thrombocytopenia is reported as high as 24%, of whom 4 (25%) needed blood transfusion in a small report[69]. In patients receiving abciximab and ticlopidine or clopidogrel (EPISTENT data) 2.2% major bleeding occurred and 2.2% transfusions were given. In ESPRIT, 97% of 1025 patients received the combination of eptifibatide and clopidogrel, 2 (0.2%) developed severe thrombocytopenia within 24 hours (platelet count below 20.000 mm^{-3}. Both recovered without transfusion hours after cessation of eptifibatide[5]. It is likely that the combination of abciximab and clopidogrel causes more thrombocytopenia than eptifibatide and tirofiban. Therefore assesment of platelet count within 24 hours of start of abciximab is advised.

Oral platelet GP IIb/IIIa receptor blockers

Various oral IIb/IIIa receptor blockers are under clinical investigation. The various agents share a high selectivity for the GP IIb/IIIa receptor, but they differ in their pharmacodynamic and pharmacokinetic profiles.

Large clinical experience was obtained with xemilofiban, an oral prodrug with high bioavailability and its protracted effect lasts for 8 to 10 hours. In ORBIT (n=549) a benefit of highest dose xemilofiban was observed in patients who received high dose xemilofiban for 4 weeks after PCI compared to low dose and placebo[70]. However, in the EXCITE study (n=7232) no benefit of xemilofiban was observed in patients undergoing PCI with respect to death, nonfatal MI and urgent revascularization at 6 months.

Comparable to xemilofiban is the prodrug orbofiban, although it has a longer half life (14 hours). In OPUS (TIMI 16) (n=10288) efficacy could not be demonstrated. This trial was prematurely halted after excess mortality was found in the orbofiban treated patients (2.3 versus 1.4 % for placebo)[71].

Sibrafiban, another prodrug, with a half-life of 10 to 12 hours failed to demonstrate benefit on any of the predetermined combined and individual endpoints (90 day death, MI, stroke or ischemia driven revascularization) in patients within 7 days of ACS stabilized for at least 12 hours (SYMPHONY 1)[72]. Results from the second SYMPHONY trial were disappointing too, (n=6637) again patients were enrolled suffering ACS without persistent ST-segment elevation but again they demonstrated no reduction of mortality, MI or severe recurrent angina when randomized to sibrafiban[73]. Indeed, in highest dose group an untoward effect on death and MI was observed.

In BRAVO, lotrafiban was associated with excess mortality, and subsequently the trial was halted (2.7 versus 2.0 %)[74,75].

Possible explanations for the lack of effect are relatively large differences in peak and through levels with the current agents . In contrast, the protracted effect with

more stable levels of receptor blockade seem undesirable with respect to safety. Another explanation for the lack of effect is the lower level of platelet aggregation than targeted with the intravenous agents. Intravenous agents are targeted at 80% inhibition of ADP dependent platelet aggregation versus around 50% at through levels for the oral agents (but sometimes over 80% at peak levels). Clearly, safety concerns prohibit higher inhibitory levels. Interestingly, it has been hypothesized that conformational changes of the platelet GP IIb/IIIa receptor occur with oral agents, eventually leading to paradoxical platelet activation. Another possibility is a partial agonist effect of oral agents on platelet aggregation. A reactive indirect stimulating effect of platelets on thrombin generation is not unlikely. Finally, it should be stated that in several trials on PCI or ACS, benefit of the oral agents may have been blunted by low event rates.

Over 30.000 patients have been enrolled in randomized placebo controlled trials with oral platelet GP IIb/IIIa agents, while over 20.000 patients received these agents. An overall 31% increase in death was observed (2.7% versus 2.1%), and major bleeding doubled in patients with ACS without persistent ST-segment elevations and treated with PCI oral platelet GP IIb/IIIa receptor blockers. As long as no clear explanation and no clear solutions are found for the high complication rate and lack of benefit, oral platelet GP IIb/IIIa receptor blockers are not indicated in patients with ACS without persistent ST-segment elevation and PCI.

Conclusion

Platelet GP IIb/IIIa receptor blockers have been extensively investigated in patients undergoing PCI and as medical treatment of ACS with and without persistent ST-segment elevation. Specific groups of patients were reviewed, those undergoing PCI for stable angina, and for ACS with and without persistent ST-segment elevation.

The role of platelet GP IIb/IIIa receptor blockers in treatment of ACS with persistent ST-segment elevation MI in combination with reduced dose thrombolysis is under investigation. The first randomized prospective trial demonstrated reduction of recurrent MI but no significant effect on mortality and an increased bleeding risk. In patients with ACS without persistent ST-segment elevation treated without PCI an estimated 10% reduction of events (approximately 11% versus 10%) was observed, when trial results are combined. In patients with ACS without persistent ST-segment elevation managed without (scheduled) PCI, a platelet GP IIb/IIIa receptor blocker should be considered, especially when a high risk of MI is present.

Intravenous platelet GP IIb/IIIa receptor blockers are indicated for PCI, irrespective of indication; low and high risk setting, with and without stent implantation, for patients suffering stable angina or ACS with and without persistent ST-segment eleva-

tion. Contra-indications are few, most markedly increased bleeding risk. The agents reduce peri-procedural MI in patients with stable angina and ACS without persistent ST-segment elevation with approximately 30%. Furthermore, in patients treated with primary PCI for acute MI these agents particularly reduce urgent, most likely thrombosis related, repeat revascularization.

According to this thesis, the agents form an attractive treatment strategy for high-risk patients with ACS without persistent ST-segment elevation undergoing early PCI. In patients with ACS, without persistent ST-segment elevation, considered at low-risk for death or MI, PCI can best be deferred, as later PCI seems to lead to less repeat revascularization according to our sub-analysis, and platelet GP IIb/IIIa receptor blockers have only a modest effect. In patients with acute ST-elevation MI, the agents should not be combined with full dose thrombolysis, unless perhaps in a rescue PCI setting, because of an increased bleeding risk.

After a decade of intensive investigations, the place of platelet GP IIb/IIIa receptor blockers in patients undergoing PCI has been well established. As the value of PCI in ACS without persistent ST-segment elevation has been documented. Further studies are warranted to compare the value of very early PCI, within 24 hours of admission, in patients with ACS without persistent ST-segment elevation.

References

1. The Second International Study of Infarct Survival (ISIS-2) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 8607: 349-360.
2. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. Circulation 1993; 87: 659-675.
3. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997; 349: 1429-1435.
4. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularizatiom. N Eng J Med 1997; 336: 1689-1696.
5. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000; 356 : 2037-2044.
6. Klein LW, Kramer BL, Howard E, Lesch M. Incidence and clinical significance of transient creatine kinase elevations and the diagnosis of non-Q wave myocardial infarction associated with coronary angioplasty. J Am Coll Cardiol 1991; 17: 621-626.
7. Topol EJ, Ferguson JJ, Weisman HF, et al. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Preven-

tion of Ischemic Complications. JAMA 1997; 278: 479-484.
8. Tardiff BE, Califf RM, Tcheng JE, et al. Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. IMPACT-II Investigators. Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II. J Am Coll Cardiol 1999; 33: 88-96.
9. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998; 31: 241-251.
10. Kugelmass AD, Cohen DJ, Moscucci M, Piana RN, Senerchia C, Kuntz RE, Baim DS. Elevation of the creatine kinase myocardial isoform following otherwise successful directional coronary atherectomy and stenting. Am J Cardiol 1994; 74: 748-754.
11. Lincoff AM, Califf RM, Anderson K, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1997; 30: 149-156.
12. Bhatt DL, Marso SP, Lincoff AM, et al. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. J Am Coll Cardiol 2000; 35: 922-928.
13. Kong DT, Calif RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998; 98: 2829-2835.
14. Ellis SG, Roubin GS, King SB, Douglas JS Jr, Weintraub WS, Thomas RG, Cox WR. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988; 77: 372-379.
15. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 1991; 68: 467-71.
16. Athanasiadis A, Haase KK, Wullen B, et al. Lesion morphology assessed by pre-interventional intravascular ultrasound does not predict the incidence of severe coronary artery dissections. Eur Heart J 1998; 19: 870-878.
17. Haase KK, Mahrholdt H, Schroder S, et al. Frequency and efficacy of glycoprotein IIb/IIIa therapy for treatment of threatened or acute vessel closure in 1332 patients undergoing percutaneous transluminal coronary angioplasty. Am Heart J 1999; 137: 234-240.
18. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA. Predictive value of C-reactive protein in patients with unstable angina pectoris undergoing coronary artery stent implantation. Am J Cardiol 2000; 85: 92-95.
19. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Ellis SG, Vandormael MG, Cowley MJ, Di Sciascio G, Deligonul U, Topol EJ, Bulle TM. Circulation 1990; 82: 1193-202.
20. Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993; 22: 2033-2054.
21. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998; 338: 1785-1792.
22. Theroux P, White H, David D, et al. for the TIMI IIIB Investigators. Effects of tissue plasmin-

ogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. Circulation 1994; 89: 1545-1556.
23. The Fragmin and Fast Revascularization during Instability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: Frisc II prospective randomised multicentre study. Lancet: 1999; 354: 708-715.
24. Yusuf S, Flather M, Pogue J, et al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. Lancet 1998; 352: 507-514.
25. Ronner E, Boersma E, Akkerhuis KM et al. Patients with acute coronary syndromes without persistent ST-elevation undergoing percutaneous coronary intervention benefit most of early intervention with protection by a glycoprotein IIb/IIIa receptor blocker. European Heart Journal, in press.
26. Cannon CP, Weintraub WS, Demopoulos LA, et al. For the TACTICS-Thrombolysis in myocardial infarction 18 investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa receptor inhibitor tirofiban. N Engl J Med 2001; 334: 1879-1887.
27. Kereiakes D, McDonald M, Abbottsmith C, Broderick T. Cost efficient stenting: a multifacetted approach. J Am Coll Cardiol 1998; 31 (Suppl A): 598.
28. Ronner E, Boersma E, Laarman GJ, et al. Early angioplasty in acute coronary syndromes without persistent ST-elevation improves outcome, but increases need for 6 month repeat revascularization. An analysis of the PURSUIT-trial. Draft
29. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. Circulation in press
30. Antman AM, Cohen M, Bernink PJLM, et al. The TIMI Risk Score for unstable angina/Non-ST elevation MI. A method for prognostication and therapeutic decision making. JAMA 2000; 284: 835-842.
31. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation; recommendations of the Task Force of the European Society of Cardiology. Eur Heart J 2000; 21: 1406-1432.
32. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the ACC/AHA task force on practice guidelines. Circulation 2000; 102: 1193-2009.
33. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
34. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997; 96: 1445-1453.
35. The EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352: 87-92.
36. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascular-

sation: the GUSTO IV-ACS randomised trial. Lancet 2001; 357: 1915-1924.
37. Stone GW, Brodie BR, Griffin JJ, et al: for the PAMI stent pilot trial investigators. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction. The primary angioplasty in myocardial infarction (PAMI) stent pilot trial. Circulation 1999; 99: 1548-1554.
38. The PAMI Trial Investigators: Stone GW, Grines CL, Rothbaum D, et al for The PAMI Trial Investigators. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. J Am Coll Cardiol 1997; 29: 901-907.
39. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction N Engl J Med 1999; 341: 1413-1419.
40. Julian DG, Boissel JP, de Bono DP, et al.Task Force of the ESC Acute Myocardial Infarction: pre-hospital and in-hospital management. Eur Heart J 1996 ; 17: 43 - 63.
41. Braunwald E Ryan, TJ, Anderson, JL, Antman, EM, et al. ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practical Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1996; 94: 2341.
42. Lefkovits J, Ivanhoe RJ, Califf RM, et al. Effects of platelet glycoprotein IIb/IIIa receptor blockade by a chimeric monoclonal antibody (abciximab) on acute and six-month outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol. 1996; 77: 1045-1051.
43. Brener SJ, Barr LA, Burchenal JEB, Katz S, George BS, Jones AA, Cohen ED, Gainey PC et al, on behalf of the Reopro and primary PTCA organization and randomized trial (RAPPORT) investigators. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734-741.
44. Montalescot G, Barragan P, Wittenberg O, et al. Abciximab associated with primary angioplasty and stenting in acute myocardial infarction: the ADMIRAL study, 30-day final results. Circulation 1999; 100 (suppl I):1-87. Abstract 446.
45. Stone GW. Controlled abciximab and device investigation to lower late angioplasty complications (the CADILLAC trial). Presented at the 72nd Scientific Sessions of the American Heart Association 1999.
46. Antman EM, Giugliano RP, Gibson MC, et al. for the TIMI 14 investigators. Abciximab facilitates the rate and extent of thrombolysis. Results of the thrombolyis in myocardial infarction (TIMI) 14 trial. Circulation 1999; 99: 2720-2732.
47. The SPEED investigators. Strategies for patency enhancement in the emergency department (SPEED) group. Trial of abciximab with and without low-dose reteplase for acute myocardial infartion. Circulation 2000; 101: 2788-2794.
48. Herrmann HC, Moliterno DJ, Ohman EM, et al. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) Trial. J Am Coll Cardiol 2000; 36: 1489-1496.
49. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001; 357: 1905-1914
50. The GUSTO Investigators. An international randomized trial comparing four thrombolytic

strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673 -682.
51. Langer, A, Krucoff, MW, Klootwijk, P, et al, for the GUSTO-I ECG Monitoring Substudy Group. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: The GUSTO-I ST segment monitoring substudy. J Am Coll Cardiol 1998; 31:783-789.
52. Davies CH, Ornerod OJM. Failed coronary thrombolysis. Lancet 1999; 351: 1191-1196
53. The CORAMI Study Group. Outcome of attempted rescue coronary angioplasty after failed thrombolysis for acute myocardial infarction. Cohort of Rescue Angioplasty in Myocardial Infarction. Am J Cardiol 1994; 74: 172-174
54. Baim, DS, Diver, DJ, Knatterud, GL, and the TIMI 2A Investigators. PTCA "salvage" for thrombolytic failures: implications from TIMI 2A. Circulation 1988; 78(Suppl II):II-112
55. White HD, Cross DB, Williams BF, Norris RM, Woo KS, Hamer AW, Elliott JM, Ormiston JA. "Rescue" thrombolysis with intracoronary tissue plasminogen activator for failed intravenous thrombolysis with streptokinase for acute myocardial infarction. Am J Cardiol 1995; 75: 172- 174
56. Becker RC Thrombolytic retreatment with tissue plasminogen activator for threatened reinfarction and thrombotic coronary reocclusion. Clin Cardiol 1994;17: 3-13.
57. Simoons ML, Arnout J, Van den Brand M, Nyssen K, Verstraete M. Retreatment with alteplase for early signs of reocclusion after thrombolysis. The European Cooperative Study Group. Am J Cardiol 1993; 71: 524-528.
58. Miller JM, Smalling R, Ohman EM, et al. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). Global use of strategies to open occluded coronary arteries. A J Cardiol 1999; 84: 779-784.
59. Muhlestein, JB, Karagounis, LA, Treehan, S, et al. "Rescue" utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997; 30:1729-1724
60. Jong P, Cohen EA, Batchelor W, Lazzam C, Kreatsoulas C, Natarajan MK, Strauss BH. Bleeding risks with abciximab after full-dose thrombolysis in rescue or urgent angioplasty for acute myocardial infarction. Am Heart J 2001; 141: 218-25.
61. Abbottsmith, CW, Topol, EJ, George, BS, et al. Fate of patients with acute AMI with patency of the infarct-related vessel achieved with successful thrombolysis versus rescue angioplasty. J Am Coll Cardiol 1990; 16: 770-778.
62. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators.Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488-1497.
63. PROLOG investigators. Standard versus low-dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. Am J Cardiol 1997; 79 :286-291.
64. Kereiakes DJ, Lincoff AM, Miller DP, et al. Abciximab therapy and unplanned coronary stent deployment: favorable effects on stent use, clinical outcomes, and bleeding complications. EPILOG Trial Investigators. Circulation 1998; 97: 857-864.
65. Deckers J, Califf RM, Topol EJ, Lincoff AM, Tcheng JE, Simoons ML. Use of abciximab (ReoPro) is not associated with an increase in the risk of stroke: overview of three randomized trials. J Am Coll Cardiol 1997; 29: 974-989.
66. Boehrer JD, Kereiakes DJ, Navetta FI, Califf RM, Topol EJ. Effects of profound platelet inhi-

bition with c7E3 before coronary angioplasty on complications of coronary bypass surgery. Am J Cardiol. 1994; 74: 1166-1170.
67. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: A pooled analysis. Am Heart J 2000; 140: 206-211.
68. Sane DC, Damaraju LV, Topol EJ, et al. Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy. J Am Coll Cardiol 2000; 36: 75-83.
69. Dillon WC, Eckert GJ, Dillon JC, Ritchie ME. Incidence of thrombocytopenia following coronary stent placement using abciximab plus clopidogrel or ticlopidine. Catheter Cardiovasc Interv 2000; 50: 426-430.
70. Kereiakes DJ, Kleiman NS, Ferguson JJ, et al. Pharmacodynamic efficacy, clinical safety, and outcomes after prolonged platelet glycoprotein IIb/IIIa receptor blockade with oral xemilofiban: results of a multicenter, placebo-controlled, randomized trial. Circulation 1998; 98: 1268-1278.
71. Cannon CP, McCabe CH, Borzak S, et al. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. Thrombolysis in Myocardial Infarction. Circulation 1998; 97: 340-349.
72. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial.. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. Lancet 2000; 355: 337-345.
73. Second SYMPHONY investigators. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. Circulation 2001; 103: 1727-1733.
74. Harrington RA, Armstrong PW, Graffagnino C, et al. Dose-finding, safety, and tolerability study of an oral platelet glycoprotein IIb/IIIa inhibitor, lotrafiban, in patients with coronary or cerebral atherosclerotic disease. Circulation 2000; 102: 728-735.
75. SmithKline Beecham halts tests of lotrafiban, an oral glycoprotein IIb/IIIa inhibitor. Circulation 2001; 103: E9001-2.
76. The assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT) -III investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT III randomised trial in acute myocardial infarction. The assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT) -III investigators. Lancet 2001; 358: 605-613.

4.2

Samenvatting

In dit proefschrift wordt de rol van "thrombocyten glycoproteïne IIb/IIIa receptor blokkers" in de klinische praktijk beschreven. Alvorens tot een samenvatting van de verschillende hoofdstukken te komen, eerst een korte inleiding over thrombocyten glycoproteïne IIb/IIIa receptor blokkers.

Inleiding

Thrombocyten glycoproteïne IIb/IIIa receptor blokkers vormen een nieuwe klasse medicijnen, waarvan de eerste, abciximab, in Nederland is geregistreerd in 1996.

Thrombocyten glycoproteïne IIb/IIIa receptor blokkers zijn middelen die de bloedstolling tegengaan door hun werking op bloedplaatjes (thrombocyten). Bloedplaatjes zijn de cellen in het bloed, die verantwoordelijk zijn voor bloedstolling. Bloedstolling treedt op nadat bloedplaatjes zijn "geactiveerd", dat wil zeggen, wanneer de glycoproteïne IIb/IIIa receptor van het bloedplaatje is geactiveerd door een beschadigde vaatwand. Thrombocyten glycoproteïne IIb/IIIa receptor blokkers blokkeren deze receptor, waardoor de bloedplaatjes geen onderlinge verbindingen kunnen vormen (en hierdoor geen stolsel).

Juist de bloedstolling is van groot belang in de cardiologie, omdat stolselvorming in de aanvoerende bloedvaten van het hart (kransslagaders) kan leiden tot een hartinfarct of overlijden. In het bijzonder is stolselvorming in de bloedvaten van het hart een bedreiging voor patiënten met zowel onstabiele angina pectoris (ook wel onstabiele angina pectoris of "acuut coronair syndroom zonder blijvende ST-elevatie" genoemd), als een acuut hartinfarct, evenals voor patiënten die worden behandeld met een ballon-verwijding van een vernauwing van de kransslagaders (dotterbehandeling of PTCA; dit staat voor percutane transluminele cor-angioplastiek). Ook in deze patiënten ([dreigend] hartinfarct en/of PTCA) kan stolselvorming leiden tot een hartinfarct of overlijden.

Om de klasse medicatie voor klinisch gebruik te beschrijven is gebruik gemaakt van verschillende onderzoekstechnieken, zoals de beschrijving van een enkele patiëntencasus, de retrospectieve analyse, de sub-analyse van een grote database, het literatuuronderzoek en de multi-center gerandomiseerde en placebo-gecontroleerde studie.

Hoofdstuk één

In de inleiding (hoofdstuk één) komt naar voren dat het klinisch onderzoek naar thrombocyten glycoproteïne IIb/IIIa receptor blokkers een voorspoedige start kende; zo zijn meerdere PTCA-studies voortijdig gestopt vanwege gunstige studie-resultaten.

Deze eerste PTCA-studies, maar ook latere PTCA-studies, lieten een afname van de kans op een hartinfarct zien van omstreeks 30 - 40% (Hoofdstuk 1.1).

Ook is een patiënten-casus in de inleiding opgenomen. Dit betreft een illustratie van succesvol gebruik van thrombocyten glycoproteïne IIb/IIIa receptor blokkers bij een patiënt die levensbedreigend ziek was door een acuut hartinfarct. Haar kritieke toestand verbeterde niet ondanks behandeling met zeer sterke bloedverdunnende medicatie (streptokinase, aspirine, alsmede subcutane heparine) en PTCA. Pas na toediening van abciximab losten de stolsels in de kransslagaders op en knapte patiënt op, hoewel grote bloedingen in de liezen ontstonden (vanwege het feit dat in de liezen de PTCA catheter en aan de andere kant de catheter voor een tijdelijke "ballonpomp" werden ingebracht) (Hoofdstuk 1.2).

Zowel de gunstige studie-resultaten met deze klasse medicatie, alsmede de ervaring van dit middel bij de beschreven patiënt deden mij besluiten promotie-onderzoek te verrichten naar de klinische toepassingen van thrombocyten GP IIb/IIIa receptor blokkers.

Hoofdstuk twee

In hoofdstuk twee ligt de nadruk op de behandeling van patiënten met onstabiele angina pectoris. Deze behandeling bestaat uit medicatie, niet zelden in combinatie met PTCA.

In hoofdstuk 2.1 wordt een overzicht gegeven over verschillende aspecten rond klinisch gebruik van thrombocyten glycoproteïne IIb/IIIa receptor blokkers, waarbij wordt ingegaan op veiligheidsaspecten en er wordt ingegaan op de combinatie van thrombocyten GP IIb/IIIa receptor blokkers met andere medicatie die de bloedstolling beïnvloedt (zoals heparine). Verder komen de verschillende toepassingen voor gebruik aan de orde. Ook worden de verschillen tussen de diverse thrombocyten GP IIb/IIIa receptor blokkers toegelicht (Hoofdstuk 2.1).

In hoofdstuk 2.2 wordt er ingegaan op veilig en effectief gebruik van thrombocyten GP IIb/IIIa receptor blokkers in een perifeer ziekenhuis. Het betrof patiënten met onstabiele angina pectoris ondanks medicamenteuze behandeling, die wachten op PTCA in Medisch Centrum Alkmaar, toentertijd zonder PTCA-faciliteiten (de centra mét PTCA faciliteiten, deden als eerste ervaring op met deze medicatie).

Ook worden in dit hoofdstuk twee subanalyses gepresenteerd van de PURSUIT studie. In PURSUIT kregen wereldwijd 9461 patiënten met onstabiele angina pectoris óf placebo óf eptifibatide (een thrombocyten GP IIb/IIIa receptor blokker). Het bijzondere van de studie was verder dat de behandelende artsen geheel vrij waren in de verdere behandelstrategie.

Met de eerste subanalyse (Hoofdstuk 2.3) van PURSUIT wordt aangetoond dat zónder deze thrombocyten GP IIb/IIIa receptor blokkers, vroege PTCA (bijvoorbeeld binnen 72 uur) geen voordeel biedt boven late PTCA (bijvoorbeeld na een week), want de krachtige snelle behandeling kent ongeveer net zoveel procedure gerelateerde hartinfarcten als die op zouden treden tijdens wachten op een "veiligere" latere PTCA in een "afgekoelde" patiëntengroep. Maar, voor de groep patiënten die mét thrombocyten GP IIb/IIIa receptor blokkers worden behandeld, geldt dat bij snelle PTCA geen hoger risico van PTCA wordt gevonden dan bij latere PTCA, terwijl de wachtperiode op PTCA wordt vermeden, met een duidelijke reductie van de kans op een hartinfarct als gevolg. Ook na statistische correctie, voor verschillen tussen de groepen van vroege en late PTCA, blijft duidelijk dat vroege PTCA met een thrombocyten GP IIb/IIIa receptor blokker leidt tot de laagste kans op een hartinfarct. Dit geldt voor de patiënten opgenomen met onstabiele angina pectoris in de PURSUIT studie (Hoofdstuk 2.3).

Een tweede subanalyse (Hoofdstuk 2.4) gaat in op de kans van herhaalde PTCA binnen 5.5 maand na de eerste procedure. Er bleek namelijk dat hoe sneller de eerste PTCA, hoe meer kans op de noodzaak van een tweede procedure. Dit werd gevonden voor zowel patiënten die placebo kregen als degene die thrombocyten GP IIb/IIIa receptor blokkers kregen. We zagen dit effect niet alleen na 5.5 maand maar ook al na 1 maand en in de tijd tussen 1 en 5.5 maand. Dit onderscheid is van belang omdat de "vroege" herhaalde PTCA's vooral door stolselvorming veroorzaakt worden, terwijl de late herhaalde PTCA's meer gekenschetst worden door zogenaamde intima-proliferatie (littekenvorming in de vaatwand van de verwijde kransslagader). De verschillen in optreden van herhaalde PTCA bleken in op één na, alle groepen statistisch sterk significant, dus "hoe sneller PTCA, hoe meer herhaalde PTCA". Alleen in de patiëntengroep behandeld met eptifibatide bleek de specifieke vroege herhaalde PTCA (binnen 30 dagen) niet vaker verricht te zijn bij patiënten die vroege PTCA ondergingen dan bij patiënten die latere PTCA kregen. Het is aannemelijk dat dit effect gerelateerd is aan het toedienen van thrombocyten GP IIb/IIIa receptor blokkers. Evenals de resultaten van de eerste subanalyse, bleken de resultaten van de tweede subanalyse onverminderd statistisch significant aantoonbaar na multivariabele analyse (Hoofdstuk 2.4).

Het is van belang te benadrukken dat aan de twee subanalyses methodologische bezwaren kleven, omdat er immers achteraf niet altijd te zeggen is of de klinische setting de behandeling dicteerde of dat er daadwerkelijk een "toevallige" andere behandeling werd gekozen, bijvoorbeeld omdat deze meer gangbaar was in de betreffende kliniek of bij de betreffende behandelaar. In de analyses worden verschillen in uitgangssituatie (zg. "baseline characteristics") gecorrigeerd door multi-variabele analyse, zoals bijvoorbeeld voor overige medicatie en voor regio van behandeling (Noord-Amerika versus Europa bijvoorbeeld). Verder is in beide subanalysis uitgebreid gerefereerd

aan artikelen rond het betreffende thema, die onze theorieën ondersteunen.

Ten slotte wordt benadrukt dat het voornaamste doel van de subanalyses is, het aangeven van de noodzaak van meer onderzoek op dit vooralsnog braakliggende terrein van "timing van PTCA". Vooralsnog is onze opvatting betreffende het "timen" van PTCA: vroege PTCA bij een hoog risico-patiënt, om de kans op een hartinfarct of overlijden te beperken, en late (of geen) PTCA in de laag risico patiënt om de kans op de noodzaak van herhaalde PTCA door intima-proliferatie te beperken. Onderzoek naar deze hypothese lijkt gewenst, waarbij patiënten met onstabiele angina pectoris worden gerandomiseerd naar vroege (binnen 24 uur, evt. 72 uur) versus late PTCA (na 4 tot 7 dagen).

Hoofdstuk drie

In hoofdstuk drie worden de thrombocyten glycoproteïne IIb/IIIa receptor blokkers beschreven in de behandeling van patiënten met een acuut hartinfarct. Ter inleiding is er een kort overzichtsartikel opgenomen (Hoofdstuk 3.1). Verder is een multi-center dubbel blind gerandomiseerde studie verricht naar de combinatie van de standaard dosering van de sterke bloedverdunner streptokinase, een thrombolyticum, met verschillende doses eptifibatide. De verschillende combinaties bleken niet duidelijk superieur aan thrombolyse alleen, terwijl onacceptabel veel bloedingen werden gezien. Uit later onderzoek is inmiddels gebleken dat de combinatie van beide middelen veelbelovend is, onder de voorwaarde dat echter de dosis thrombolyticum wordt aangepast, in combinatie met volle dosis van een thrombocyten GP IIb/IIIa receptor blokker, in plaats van dosis-aanpassing van de thrombocyten GP IIb/IIIa receptor blokker, zoals in onze studie wordt beschreven (Hoofdstuk 3.2).

Een ander onderzoek werd verricht naar aanleiding van de in de inleiding beschreven casus van thrombocyten GP IIb/IIIa receptor blokkers na mislukte thrombolyse bij een acuut infarct. Er is in het Academisch Ziekenhuis Rotterdam Dijkzigt retrospectief geanalyseerd hoe vaak thrombocyten GP IIb/IIIa receptor blokkers zijn gegeven na onvoldoende effect van thrombolyse voor een acuut hartinfarct en in hoeverre dit heeft geleid tot bloedingen. Net als in de casus (Hoofdstuk 1.2) werden ernstige bloedingscomplicaties gezien, terwijl de mortaliteit in deze ernstig zieke patiëntengroep relatief beperkt bleef.

Het blijft aanlokkelijk in noodgevallen na mislukte thrombolyse terug te vallen op thrombocyten GP IIb/IIIa receptor blokkers. Het verdient echter de voorkeur mislukte thrombolyse te voorkomen door directe PTCA, danwel halve dosis van een thrombolyticum te geven in combinatie met thrombocyten GP IIb/IIIa receptor blokkers, zoals door de recente GUSTO V studie wordt ondersteund. (Hoofdstuk 3.3).

Hoofdstuk vier

Hoofdstuk vier vat één en ander (Engels- en Nederlandstalig) samen, waarbij de laatste studie-resultaten van internationale studies (tot en met juni 2001) worden besproken en een visie wordt gegeven op klinisch gebruik van thrombocyten GP IIb/IIIa receptor blokkers bij patiënten met zowel een acuut hartinfarct als onstabiele angina pectoris. Er wordt een poging gedaan, nu niet hoog- maar juist laag risico PTCA patiënten te identificeren. Hiermee wordt beoogd om een groep aan te wijzen die de middelen niet hoeven te krijgen. Dit bleek met de huidige data niet mogelijk: de gebruikte methode toonde een forse relatieve (omstreeks 30%), maar ook een duidelijke absolute reductie aan van optreden van hartinfarct in laag risico patiënten (stabiele angina pectoris subgroepen). Zodat gesteld kan worden dat iedereen rond PTCA thrombocyten GP IIb/IIIa receptor blokkers moet krijgen, tenzij contra-indicaties worden gevonden, zoals in de bijsluiterteksten aanwezig zijn (Hoofdstuk 4.1).

Concluderend biedt dit proefschrift een breed overzicht over het gebruik van thrombocyten GP IIb/IIIa receptor blokkers in de klinische praktijk, waarbij zowel effectiviteit als veiligheid uitgebreid aan de orde komen.

Er wordt beschreven hoe deze klasse medicatie veilig bij een acuut hartinfarct kan worden gegeven, waarbij wordt ingegaan op de combinatie met thrombolyse en als redmiddel na falen van thrombolyse.

Patiënten met onstabiele angina pectoris bij wie PTCA wordt verricht dienen, uitzonderingen daargelaten, thrombocyten IIb/IIIa receptor blokkers te krijgen. In dit proefschrift komt aan de orde wanneer voor de hóóg- en wanneer voor de láág-risico patiënten deze PTCA met thrombocyten GP IIb/IIIa receptor blokkers het beste plaats kan vinden.

Appendix: Trial acronyms

ADMIRAL	Abciximab before direct angioplasty and stenting in acute myocardial infarction recarding acute and long-term follow up
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic
BRAVO	blockade of the glycoprotein IIb/IIIa receptor to avoid vascular occlusion
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Compications
CARPORT	Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism
CAPTURE	cE3Fab antiplatelet therapy in unstable refractory angina
EPIC	Evaluation of 7E3 in preventing ischemic complications of percutaneous coronary intervention
EPILOG	Evaluation in PTCA to improve long-term outcome with abciximab GP IIb/IIIa blockade
EPISTENT	Evaluation of platelet IIb/IIIa inhibitor for stenting
ESPRIT	Eptifibatide in planned coronary stent implantation
EXCITE	Evaluation of Xemilofiban in Controlling Thrombotic Events
FRISC 2	The Fragmin and Fast Revascularization during Instability in Coronary artery disease
GRAPE	The glycoprotein receptor antagonist in myocardial infarction patency evaluation
GUSTO	Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries
IMPACT	Integrilin to minimise platelet aggregation and coronary thrombosis
IMPACT - AMI	Integrilin to minimise platelet aggregation and coronary thrombosis in acute myocardial infarction
INTRO - AMI	Integrilin and reduced dose of thrombolytic in acute myocardial infarction
OASIS	The Organisation to Assess Strategies for Ischemic Syndromes
PAMI	Primary Angioplasty in Myocardial Infarction
PARADIGM	Platelet aggregation receptor antagonist dose investigation and reperfusion gain in myocardial infarction
PARAGON	Platelet IIb/IIIa antagonism for the reduction of acute coronary syndrome events in a global organization network
PRISM	The platelet GP IIb/IIIa receptor blocker receptor inhibition in ischemic syndrome management
PRISM PLUS	The platelet GP IIb/IIIa receptor blocker receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RAPPORT	the Reopro and primary PTCA organization and randomized trial
RESTORE	Randomized efficacy study of tirofiban for outcomes and restenosis
SPEED	Strategies for patency enhancement in the emergency department
TACTICS-TIMI 18 Trial	Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy
TAMI	The thrombolysis and angioplasty in myocardial infarction
TIMI	The Thrombolysis in Myocardial Infarction
VANQWISH	Veterans Affairs Non-Q-Wave Infarction Strategies in-hospital

Dankwoord

Het was een voorrecht en genoegen samen te werken met mijn promotor, Professor Simoons. Professor Simoons, uw unieke combinatie van aandacht voor detail, maar ook voor de grote lijnen; uw pragmatiek en precisie; uw kennis van de cardiologie zullen mij altijd als voorbeeld dienen. Een artikel bespreken kon altijd: 's avonds bij u thuis, overdag vanuit de trein, ver weg op een congres, of via e-mail zelfs tijdens uw vakantie, dit heb ik zeer gewaardeerd.

De eerste onderzoekservaring deed ik op bij professor F.C. Visser. Beste Frans, na deze eerste positieve ervaringen heb ik nooit meer getwijfeld over de keuze voor cardiologie. Ik wil je bedanken voor de inspirerende begeleiding rond een aantal onderzoeksprojecten op het gebied van de nucleaire cardiologie. Het is achteraf bezien, een vorm van luxe geweest, niet bezig te zijn met artikelen schrijven en toch met uitgebreid onderzoek.

Jaap Deckers en Gerrit-Anne van Es wil ik bedanken voor de samenwerking bij Cardialysis. Zonder dit jaar bij Cardialysis was dit project zeker niet in 2001 voltooid. Het was een voorrecht analyses op de PURSUIT database te verrichten en te corresponderen met de meest vooraanstaande cardiologen van de "Steering Committee" van PURSUIT. Cardialysis heb ik als een zeer inspirerende en prettige werkomgeving ervaren.

Met gedeeld genoegen leerde ik bij Cardialysis statistiek bedrijven met SAS, een heuse beproeving, waarbij ik de hulp van de afdeling statistiek maar vooral van Eric Boersma (co-promotor) niet kon missen. Eric, je was altijd in staat mij, op uiterst sympathieke wijze, snel van gegevens te voorzien, ook al betekende dat niet zelden dat mijn SAS-programmatuur in een fractie van de tijd veel compacter werd herschreven.

Naast de cardiologen en arts-assistenten in het Onze Lieve Vrouwe Gasthuis in Amsterdam, wil ik met name GertJan Laarman en Ron van der Wieken bedanken, die de diverse stukken van schriftelijk en mondeling commentaar voorzagen. Gertjan, het was nuttig de verschillende manuscripten vanuit het perspectief van een interventiecardioloog te bezien. Ron, je stimuleerde mij me in de GP IIb/IIIa receptor blockers te storten. Jullie steun om opleiding met promotie te combineren heb ik als zeer positief ervaren.

Ook wil ik de cardiologen uit Medisch Centrum Alkmaar bedanken. Het was dankzij de arbeidsvoorwaarden in Medisch Centrum Alkmaar dat ik promotie en werk kon combineren, dit eerste, inspirerende, opleidingsjaar.

De vele arts-assistenten met wie ik in het Medisch Centrum Alkmaar, het OLVG in Amsterdam en in ziekenhuis Hilversum heb gewerkt, hebben mijn bezoekjes aan Rotterdam mogelijk gemaakt, ook als dit niet tijdens compensatie-uren kon. Dit waardeer ik zeer.

Anna Bosselaar, jou contracteren voor lay-out, de omslag en voor praktische adviezen was een gouden greep waar ik geen moment spijt van heb gehad. Ook de praktische adviezen en de steun die ik kreeg van Marianne Eichholtz en Yvonne Kalkman (secretariaat professor Simoons) waren onontbeerlijk.

Aernout Somsen, zwager/vak- en lotgenoot/co-auteur. Doctor Aernout, vooral je onbevangen blik als expert in geheel andere zaken, zetten mij terug op de rails wanneer ik woordblind werd voor mijn eigen teksten.

Peter-Paul en Jaap, paranimfen, jullie hulp, maar vooral jullie gezelligheid wanneer het bestaan achter de computer teveel werd, heb ik zeer gewaardeerd. Dit geldt natuurlijk ook voor de rest van de eens zou trouwe bezoekers aan "de Tap" in Amsterdam.

Graag bedank ik de Hartstichting voor de bijdrage in de drukkosten, maar ook Cardialysis en de farmaceutische bedrijven die deze promotie sponsoren: Schering-Plough; Merck, Sharp and Dohme; Eli Lilly; Asta Medica; Centocor en Aventis; Bayer; Bristol-Myers Squibb; Byk; GlaxoSmithKline; Leo Pharma; Novartis Pharma B.V. en Sanofi-Synthelabo.

Mijn ouders wil ik bedanken voor het vertrouwen dat zij van jongs af aan in mij stelden, dit vertrouwen gaf me uiteindelijk de kracht om door te gaan, ook als de uren van de week nauwelijks toereikend leken voor de geplande bezigheden. Jullie stimuleerden mij, niet als schreeuwende ouders langs het sportveld van hun kroost, maar meelevend en enthousiasmerend, met de soms zware combinatie van werk, werk, werk en privé.

Marlies, zus, het was altijd fijn te bellen, zonder uitzondering sprak je je steun uit en respect voor de vele uren werken, precies daarvoor verklaarden anderen mij voor gek, maar jou reactie was achteraf precies wat ik nodig had.

Heleen, zus, onze vele bezoekjes en telefoontjes waren ontspannen en vol humor,

hoe onze gemoedsrust ervoor ook was. Deze contacten vormden een fantastische uitlaatklep.

Lieve Jorien, mijn vrouw, hoe kan ik je bedanken. Je hebt mij onbaatzuchtig mijn gang laten gaan, die talloze weekenden en avonden, dat ik alleen achter de computer zat, of ver weg zat te congresseren of dichterbij verdween naar ziekenhuis of cursus. Dit is des te bijzonderder omdat er de laatste vier jaren al zo weinig tijd over was voor ons samen... Voor ons en ons gezin regelde jij ondertussen een fantastische bruiloft en een groot deel van de verhuizing. Maar bovenal verricht je wonderen thuis, voor Lucas en voor Arthur, onze tweelingzoontjes, die halverwege hoofdstuk twee geboren werden (december 1999). Ik wil je dan ook enorm bedanken voor de vele manieren van directe en indirecte steun!

Lieve Lucas, de onbevangenheid en vrolijkheid waarmee je de wereld verkent en je enthousiasme zijn vertederend. Het doorzettingsvermogen waarmee je de onbekende zee inloopt, hoevaak we je ook weer op het strand terugzetten, is bewonderenswaardig. Ondanks een pijnlijke val, of een zandbakgenootje dat je speelgoed afpakt, je laat je niet uit het veld slaan; je bent een voorbeeld voor een promovendus.

Lieve Arthur, alle viervoeters heten "auau" (miauw), alle vogels "uiui" (uil), ik hoop dat de wereld nog lang zo overzichtelijk mag blijven voor je. Het is aandoenlijk hoe jij soms een uur in je bedje stilletjes speelt of nieuwe geluidjes probeert te maken, terwijl je broertje allang slaapt, aan deze zelfredzaamheid en rust kan ik een voorbeeld nemen.

Curriculum vitae

Eelko Ronner was born November 27th 1966 in Leeuwarden. He attended Middle School in Bellingham, Washington, USA (1979-1980) and finished High School in Eindhoven in 1986.

He obtained his medical degree in 1994 at the Free University of Amsterdam. He was involved in research in nuclear cardiology (Prof. Dr. F.C. Visser, cardiology department of the Free University Hospital) and rural primary health care in Indonesia (Prof. Dr. I. Wolffers, primary health care, Free University) and followed a graduate course in management (Faculty of Economics, Free University).

Throughout his residencies he was involved in clinical research, including design, clinical implementation, conduct, and analysis of several large trials. His specific field of interest became platelet glycoprotein IIb/IIIa receptor blockers in acute coronary syndromes, leading to this thesis (promotor Prof. Dr. M.L. Simoons, Thoraxcenter Rotterdam). One year of work on this thesis was performed at Cardialysis and the Thoraxcenter, Rotterdam. Residencies in cardiology were followed at The Onze Lieve Vrouwe Gasthuis, Amsterdam; the Kennemer Gasthuis locatie Elisabeth, Haarlem and Medisch Centrum Alkmaar. In Ziekenhuis Hilversum, a residency in internal medicine was finished September 2001.

He participated as a member of the board of the Amsterdam Department of the Koninklijke Maatschappij ter bevordering der Geneeskunst (KNMG, somewhat comparable to the American Medical Association). He is married, and a father of twin boys. He will finish his cardiology training September 2003 at the Onze Lieve Vrouwe Gasthuis in Amsterdam