Risk Stratification and Risk Modification
in Patients with Acute Coronary Syndromes

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Risk Stratification and Risk Modification
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Risico Stratificatie en Risico Modificatie
in Patienten met Acute Coronaire Syndromen

Thesis

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op gezag van de rector magnificus

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Aan Annemieke,
Dimitri en Anouschka

DATA forever !!!

Ter nagedachtenis aan mijn moeder

Contents

General introduction and outline

An epidemiological burden?!

Despite declining numbers of hospital admissions of patients with cardiovascular disease as initial diagnosis in the Netherlands and the declining mortality rate of those patients during the last ten years, cardiovascular diseases remain an important cause of death[1]. Additionally, limitation of resources, with expenses on health care risen to almost 10% of the nationals' gross income spend each year led to an extensive national debate on reorganizing and financing the health security system leading to a substantial reconstitution in 2006.

By identifying risk factors and developing risk models it might be possible to modify and reduce the risk for future events and subsequently lower financial costs. It is therefore important to identify between those patients hospitalised the patients that will have the greatest risk for developing a new event and subsequently try to decrease this risk.

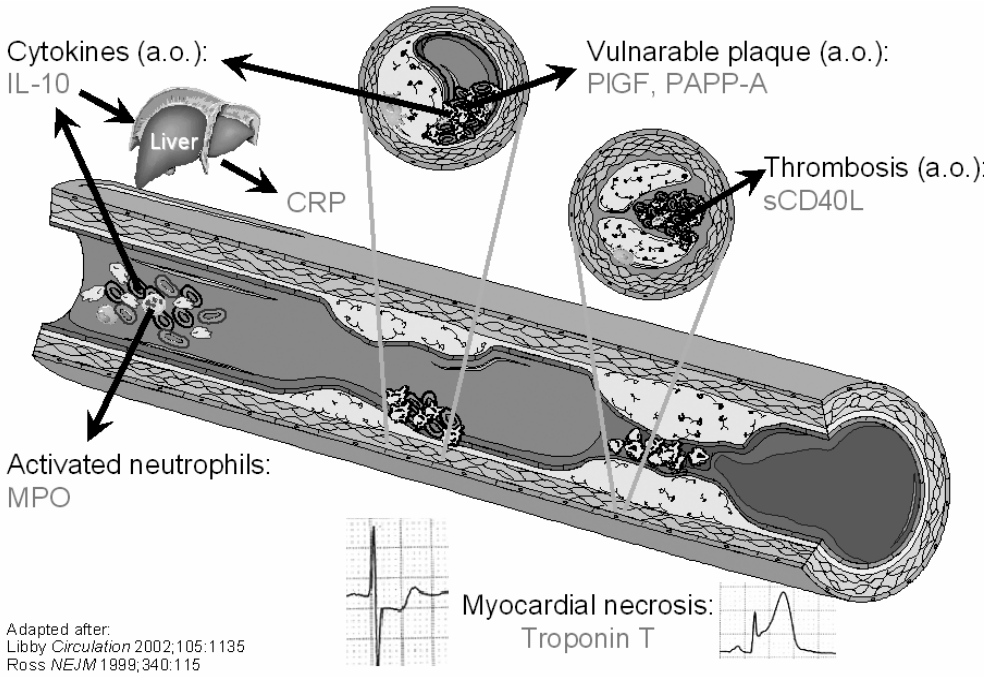

Figure 1

Acute Coronary Syndromes

Acute coronary syndromes (ACS) accounts for about 30% of the hospital admissions of patients diagnosed with cardiovascular diseases and about a third of the patients in this population will die due to an ACS[2]. Acute coronary syndrome encompasses a spectrum of events with different clinical severity based on a partial or complete occlusion of the coronary artery. This is predominantly due to thrombosis on a disrupted plaque in the vessel wall. The plaque, caused by an inflammatory process, stimulates the hemostatic cascade when the protective endothelial cells of the vessel wall are gone[3,4] (see Figure 1). Diagnosis of ACS is based on a group of signs and symptoms of cardiac ischemia, an electrocardiogram showing ST-segment elevation or depression or abnormalities of the T-wave and a typical increase and decrease in biochemical markers of cardiac necrosis. Final diagnosis as unstable angina pectoris (UAP) or myocardial infarction (NSTE MI or STE MI) is based on the level of cardiac markers as measured in blood samples[4-6] (see Figure 2). Therapeutic strategies for patients with NSTE MI / UAP and STE MI are complex and consist of oral, intravenous and / or interventional treatment modalities[4,5,8]. During the last 15 to 20 years considerable developments have taken place in understanding the pathophysiologic background, risk assessment and treatment. The Thoraxcentre

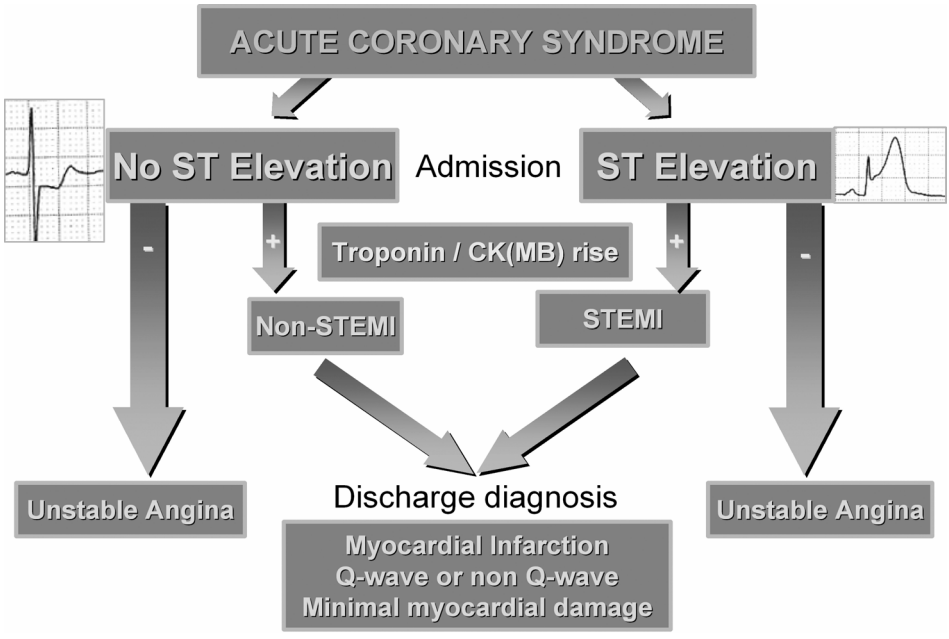

Figure 2

Rotterdam and its clinical trial organisation (Cardialysis) were closely involved in these developments. Part of this thesis is based on work done by the writer while he was working at Cardialysis as a coordinator of studies for new therapeutical interventions.

This thesis aims at making a contribution to the above mentioned developments. It will address long term mortality and risk stratification [1], with special attention to the use of biochemical markers of inflammation and myocardial necrosis [2] and also to the elderly [3]. Additionally long-term risk stratification at discharge will be assessed [4]. The bleeding risk of new anti-platelet treatment combined with older anti-platelet and anti-coagulant drugs will be assessed [5]. Risk modification questions addressed are: is there a newer better anti-coagulant therapy available [6] and is it possible to reduce mortality in ACS by giving statins very early [7].

Risk stratification and risk modification

Risk stratification of acute coronary syndromes allows for appropriate assessment whether patients should be hospitalised or not and could facilitate in optimizing treatment if they are hospitalised. Several risk models are developed for the different ACS patient groups[9-13]. These models predict short-term (30 day to 6 month) outcome by using variables including the cardiovascular history of the patient, the clinical situation at hospitalisation and elevation of a biochemical marker of necrosis. However, no models are available for long-term (more than one year) risk prediction in patients with ACS. Additionally, the last few years newer biochemical markers which can be used for risk assessment have become available. In the first three chapters of this thesis long-term risk stratification based on newer biochemical markers is described. In *chapter 1* we describe 4-year follow-up in patients with refractory unstable angina pectoris treated with the glycoprotein IIb/IIIa receptor antagonist abciximab (CAPTURE study) and we investigate the predictive value of baseline troponin T and high sensitivity C-reactive protein (hsCRP) for long-term cardiovascular events. In *chapter 2* a novel biomarker: placental growth factor is studied as predictor of long-term mortality and cardiovascular morbidity and is compared to hsCRP. In *chapter 3* we present a simple model predicting long-term mortality in CAPTURE patients combining several biochemical markers involved in the inflammatory process of plaque formation.

Unfortunately, in our effort to reduce new thrombotic events the counterpart of using more aggressive therapy like the combination of anti-platelet and anti-coagulant therapy will lead to a higher risk of bleeding. In *chapter 4* we describe risk factors for bleeding when patients with an acute coronary syndrome without ST-segment elevation are treated with the glycoprotein IIb/IIIa receptor antagonist abciximab (the GUSTO IV-ACS study).

Today's patients are getting older. The widely used TIMI10 and GUSTO9 risk evaluation models to estimate the risk of 30-day mortality after admission for STEMI however were developed in (study) databases consisting of

patients generally younger than those encountered in the emergency room these days. In *chapter 5* we describe the development of a mortality risk prediction model for patients older than 75 years of age having their first ST-elevation myocardial infarction and we evaluate to what extent the TIMI and GUSTO models can be used to adequately estimate mortality risk in these patients.

The earlier described models use data collected at the time of hospitalisation. Considering the therapeutic steps a physician takes during hospitalisation the risk of a patient is consequently modified, so risk for future events based on data collected at discharge seems more obvious. In *chapter 6* a model predicting 5 year mortality is described that also includes variables obtained shortly before discharge in patients with a myocardial infarction treated with placebo, recombinant tissue plasminogen activator (rTPA), or rTPA with additional immediate PTCA.

Statins effectively reduce cholesterol levels and thus provide secondary prevention in cardiovascular disease. They also have anti-inflammatory effects, which have been suggested to help reducing mortality, especially when given early. However, randomized trials of very early statin therapy are missing; therefore we performed an analysis in a large dataset of consecutive patients with an acute coronary syndrome. In *chapter 7* we studied whether statins should be initiated without delay after hospitalisation

Anti-coagulant therapy is proven to reduce mortality in ACS. In search for a better option than existing therapy like unfractionated heparin a new synthetic direct thrombin inhibitor, efegatran, was developed by Eli Lilly. It was expected that directly binding to thrombin and inactivating both circulating and clot-bound thrombin would prevent thrombotic blockage of the coronary artery and lead to better anti-ischemic effect and lesser bleeding events. In *chapter 8* we describe a phase II / III trial in which different dose levels of efegatran is compared to unfractionated heparin in patients with unstable angina pectoris.

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Chapter 1

Elevated troponin T and C-reactive protein predict impaired outcome for 4 years in patients with refractory unstable angina, and troponin T predicts benefit of treatment with abciximab in combination with PTCA

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Abstract

Aims

Treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab before and during coronary intervention in refractory unstable angina improves early outcome. We collected 4-year follow-up data to assess whether this benefit is sustained. Additionally, we investigated the predictive value of baseline troponin T and CRP for long-term cardiovascular events.

Methods and Results

Of 1265 patients enrolled in the CAPTURE trial follow-up was available in 94% of the patients alive after 6 months (median 48 months). Survival was similar in both groups. Both elevated troponin T and CRP were associated with impaired outcome, independently of other established risk factors, but with a different time course. Elevated troponin was associated with increased procedure related risk, and elevated CRP with increased risk for subsequent events. Lower rates of the composite end-point of death or myocardial infarction with abciximab vs. placebo were sustained during long-term follow up: 15.7% vs. 17.2% at 4 years (P = ns), particularly in patients with elevated troponin T: 16.9% with abciximab vs. 28.4% with placebo: P = 0.015. Elevated CRP was not associated with specific benefit of abciximab.

Conclusion

Troponin T as a marker of thrombosis and CRP as a marker of inflammation are independent predictors of impaired outcome at 4 years follow-up. The initial benefit from abciximab with regard to death and myocardial infarction was preserved at 4 years. No specific benefit with abciximab was observed for patients with elevated CRP, suggesting that a chronic inflammatory process is not affected by abciximab. In contrast the benefit of treatment in patients with elevated troponin T implies that the acute thrombotic process in refractory unstable angina is treated effectively.

Introduction

Acute coronary syndromes have been associated with inflammation and thrombosis. Markers for inflammation, such as C-reactive protein (CRP)[1,2] or interleukin-6[3] are associated with impaired outcome in patients with coronary heart disease. Cardiac troponin T (TnT) and troponin I are very sensitive and specific markers of myocardial necrosis in patients with acute coronary syndromes and identify patients at high risk for subsequent events.[4–6] Small amounts of necrosis detected by elevated troponin levels are probably caused by micro-emboli from thrombus at the site of unstable plaques. Accordingly elevated cardiac troponin levels may be considered markers of active thrombosis. In the CAPTURE trial[7] of patients with refractory unstable angina, undergoing percutaneous coronary intervention (PCI), elevated CRP and TnT were both associated with impaired outcome at 6 months. Treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab in CAPTURE did reduce the risk of early thrombotic complications (death or MI) particularly in patients with elevated troponin.[8] Also in several other studies treatment with abciximab and other glycoprotein IIb/IIIa receptor antagonists resulted in improved outcome in patients with acute coronary syndromes without persistent ST-segment elevation. [9,10] However, to date only one trial has reported long-term results of treatment with a glycoprotein IIb/IIIa receptor antagonist [11], while another study reported longterm predictive value of baseline troponin T and CRP for cardiovascular events.[12] In the latter study, however, no relationship of these markers to the treatment was reported. We collected follow-up data of patients enrolled in the CAPTURE study with a median follow-up of 4 years, and studied the effect of treatment with abciximab and the association with high troponin T and CRP levels.

Methods

Patients and treatment

The CAPTURE protocol has been described in detail.[7] Briefly, patients were eligible if they had refractory unstable angina, defined as chest pain at rest with concomitant ECG abnormalities compatible with myocardial ischemia (ST-depression, ST-elevation or T-wave inversion), and one or more episodes of typical chest pain or ECG abnormalities during at least 2 hour treatment with i.v. heparin and nitrates. The most recent ischemic episode should have occurred within 48h before enrolment, corresponding to Braunwald class III unstable angina. All patients had undergone coronary angiography, and percutaneous coronary intervention (PCI) was scheduled within 18–24h after the start of the study medication. After informed consent, patients were randomly assigned to abciximab (ReoPro, Centocor B.V., Leiden, The Netherlands; 0.25 mg . kg^{-1} bolus plus 10 µg .

min^{-1} continuous infusion) or placebo. Study medication was started within 2h of randomization and continued until 1 hour after the procedure. All patients received aspirin, heparin and nitrates, whereas β-blockers, calcium channel antagonists, and other cardiovascular drugs were given at the discretion of the investigator. Serum samples drawn at the time of randomization were available for determination of troponin T and CRP. Troponin T was measured using a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010, Boehringer Mannheim, Germany). The lower detection limit of this assay was 0.01 mg . l^{-1}, and the diagnostic threshold level was 0.10 mg . l^{-1} (i.e. patients with troponin T > 0.1 μg . l^{-1} were considered troponin-positive). Patients with postinfarction angina were not included in the troponin T analysis. C-reactive protein was measured by N Latex CRP Mono tests, performed on a Behring BN II Nephelometer (Dade Behring Inc., Deerfield, Illinois, USA) using polystyrene microbeads coated with monoclonal mouse antibodies. The detection limit of the assay was 0.2 mg . l^{-1}. Patients with CRP levels >10 mg . l^{-1} were considered as CRP positive.

End-points

The primary end-point of CAPTURE was a composite of 30-day all-cause mortality, myocardial infarction (MI) or an urgent intervention for treatment of recurrent ischemia. Follow-up at 6 months was part of the study protocol. MI during the index hospitalization was defined by CK-MB or CK levels exceeding three times the upper limit of normal in two samples and increased by 50% over the previous value or an ECG with new significant Q waves in two or more contiguous leads. Myocardial infarction after discharge was defined by CK-MB or CK levels exceeding twice the upper limit of normal, or new significant Q waves in two or more contiguous ECG leads. A clinical end-point committee adjudicated these events. Survival status and information on myocardial infarction and coronary revascularization procedures were collected for all 1234 patients who were alive 6 months after randomization. Follow-up was obtained from the treating physician, the patient or municipal registries and was not adjudicated.

Data analysis

Data were analysed according to the intention to treat principle. Continuous variables were summarized by median values with corresponding 25th and 75th percentiles. Discrete variables were summarized in terms of frequencies and percentages. Differences between abciximab and placebo were evaluated by Fisher's exact or Wilcoxon tests. Kaplan–Meier analyses were performed to evaluate the occurrence of events over time (obviously the 6% of patients without information beyond the 6 month period contribute to the time-to-event analysis only up to 6 months). Log-rank tests were applied to evaluate differences between abciximab and placebo. Multivariable Cox proportional hazards regression analyses were applied to evaluate the relation between troponin T, CRP and long-term outcome, adjusted for

known clinical determinants of adverse outcome in acute coronary syndromes. P values were two-sided, with P≤0.05 being considered significant.

Results

Baseline characteristics and clinical outcome

A total of 1265 patients were enrolled in the CAPTURE trial. Mortality during the first 6 months of follow-up was 2.5%. Of the remaining 1234 patients, follow-up information was obtained in 1157 patients (94%) (Table 1). Sixty-four patients did not respond on (repeated) requests for information; one patient withdrew his informed consent, while no information of their current address was available in 12 patients. The numbers of patients without follow-up were equally distributed over the two treatment arms (6.0% in both the placebo group and the abciximab group). Median follow-up since randomization was 48 months (inter-quartile range: 38 to 55 months). Patients with extended follow-up, were 4 years older (62 vs. 58 years; P<0.05, Table 1), but there were no other major differences between patients with and without extended follow-up.

Table 1

Baseline characteristics of 1234 patients alive at 6 months.

	Extended follow-up (N=1157)	No extended follow-up (N=77)
Age, years	62 (54, 69)*	58 (52, 66)
Male gender	73	74
Hypertension	41	50
Diabetes mellitus	14	13
Hypercholesterolemia	41	52
Current or recent smoker (quit in last year)	39	47
Angina	49	53
MI	39	40
CHF	2	5
Stroke	2	1
PVD	8	5
CABG	3	0
PCI	14	16
Any vascular history	66	70

Data presented are median (25th, 75th percentiles) or percentages. CABG: coronary bypass surgery; CHF: congestive heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.
*: P<0.05

The rate of death or myocardial infarction was consistently lower over 4 years in patients randomized to abciximab (Table 2), although statistical

significance was not maintained (Figure 1). Four-year mortality rates were similar: 6.4% in patients randomized to abciximab and 6.0% for placebo.

Table 2
Cardiac events during follow-up of all patients randomised at baseline.

	Abciximab N=630	Placebo N=635	HR (95% CI)
6 months post randomisation			
Death	17 (2.7)	14 (2.2)	1,22 (0,60-2,48)
MI	41 (6.5)	59 (9.3)	0,70 (0,47-1,04)
Death or MI	56 (8.9)	69 (10.9)	0,82 (0,58-1,16)
CABG	33 (5.2)	44 (6.9)	0,76 (0,48-1,19)
PCI	131 (20.8)	127 (20.0)	1,04 (0,82-1,33)
Any of above	193 (30.6)	193 (30.4)	0,96 (0,79-1,18)
1 year post randomisation			
Death	22 (3.5)	18 (2.8)	1,29 (0,70-2,39)
Myocardial infarction	44 (7.0)	62 (9.8)	0,72 (0,49-1,05)
Death or MI	66 (10,5)	76 (12.0)	0,85 (0,61-1,18)
CABG	43 (6.8)	52 (8.2)	0,84 (0,57-1,25)
PCI	151 (24.0)	146 (23.0)	1,03 (0,82-1,29)
Any of above	230 (36.5)	221 (34.8)	1,01 (0,83-1,21)
4 years post randomisation			
Death	40 (6.4)	38 (6.0)	1,01 (0,63-1,62)
Myocardial infarction	68 (10.8)	79 (12.4)	0,84 (0,61-1,17)
Death or MI	99 (15.7)	107 (16.9)	0,88 (0,66-1,16)
CABG	54 (8.6)	71 (11.2)	0,76 (0,53-1,08)
PCI	194 (30.8)	175 (27.6)	1,12 (0,91-1,37)
Any of above	288 (45.7)	271 (42.7)	1,04 (0,88-1,23)

Data presented are absolute numbers (percentages of the number of patients randomised). All p-values are not significant. For myocardial infarction at 6-month and 1-year post randomisation p-values were between 0.05 and 0.10. HR (95% CI): Hazard ratio with 95% confidence interval, other abbreviations as in Table 1.

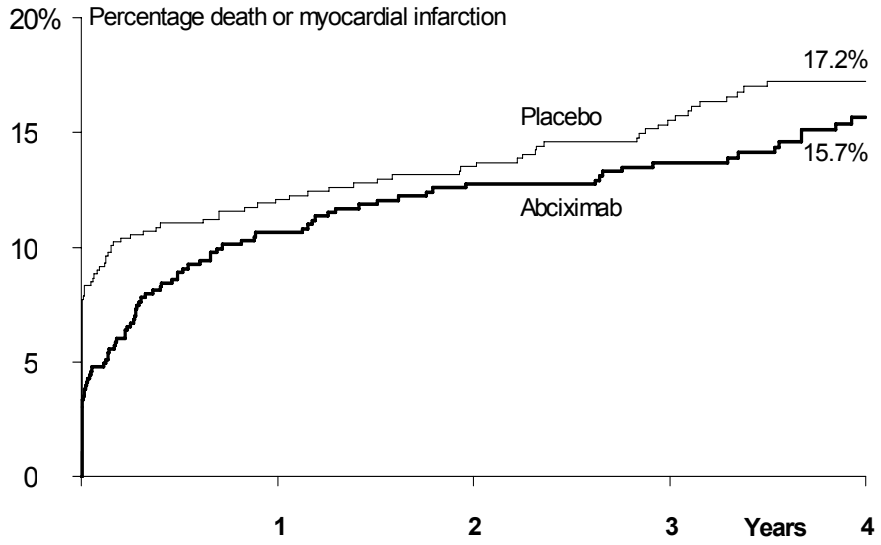

Figure 1
Kaplan–Meier curves of death or myocardial infarction during 4-year follow-up for all patients enrolled treated with abciximab or placebo (P = 0.36).

Troponin T

The initial large and significant difference in death or MI favouring abciximab among patients with troponin T > 0.1 μg . l^{-1} at randomisation was maintained throughout follow-up. At 4 years, death or myocardial infarction in patients with a positive troponin T occurred in 16.9% for those receiving abciximab and in 28.4% for those receiving placebo (P = 0.015). Four-year mortality rates were 8.7% and 11.7% (P = ns) in troponin T-positive patients randomized to abciximab and placebo, respectively (Table 3). Initially abciximab reduced event rates after randomization as compared to placebo in both troponin-positive and troponin-negative patients, while the absolute event reduction was most pronounced in the troponin-positive cohort. However, during follow-up the initial (modest) benefit of abciximab was further reduced in the troponin negative patients. In fact, the long-term incidence of death or MI among troponin-positive patients randomized to abciximab was similar to the troponin-negative patients, regardless of the treatment allocation in this latter group (Figure 2). With regard to the composite end-point (death, myocardial infarction or any revascularization – PTCA, CABG) some evidence of a differential treatment effect between troponin T-positive and negative patients was found (P = 0.065). In the troponin T-positive patients an event occurred in 42.7% with abciximab and

in 50.5% with placebo (P = 0.094). In the troponin T-negative patients these event rates were 48.7% and 43.6% (P = 0.44), respectively.

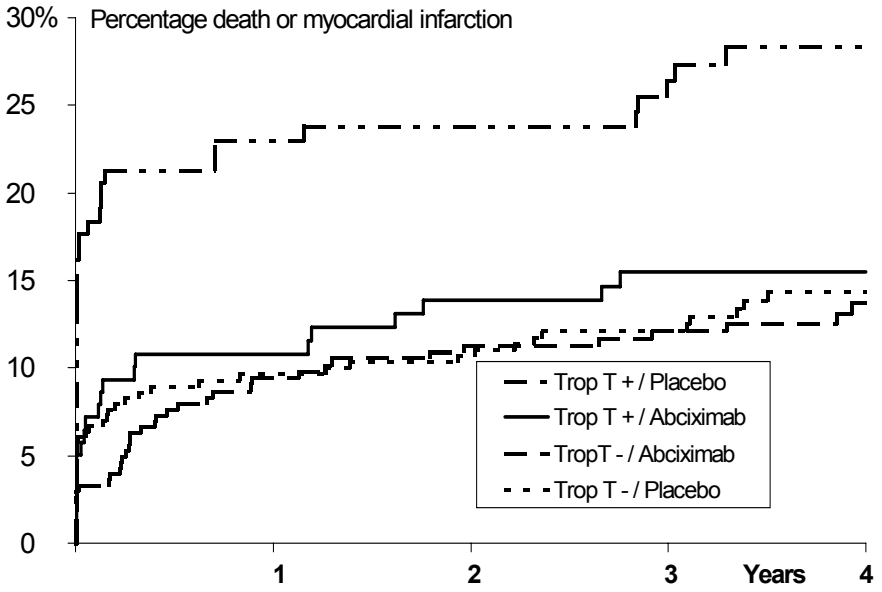

Figure 2
Kaplan–Meier curves of death and/or myocardial infarction according to troponin T status and treatment received. Significantly (P = 0.015) more events occurred in patients with positive troponin T and receiving placebo.

C-reactive protein

CRP upon admission was also a determinant of long-term outcome, as patients with a high CRP (>10 mg . l^{-1}) had a significantly higher incidence of death or MI than those with normal CRP (23.0% vs. 15.3%; P = 0.011) (Figure 3). Mortality at 4 years was 9.2% for patients with high CRP and 3.9% for patients with low CRP (P = 0.001). However, in contrast to troponin, the risk reduction by abciximab was not related to CRP status (differential treatment effect: P = 0.56). Death or a myocardial infarction at 4 years occurred in 18.9% of the patients with high CRP receiving abciximab and in 23.0% (P = 0.29) for patients having a high CRP receiving placebo. For a low CRP it was 11.4% and 15.3% (P = 0.16) respectively (Table 4). In the CRP-positive patients at 4 year death, myocardial infarction or revascularization occurred in 57.6% with abciximab and in 50.0% with placebo (P = 0.56). In the CRP-negative patients this was 47.0% and 42.7% (P = 0.79) respectively.

Table 3

Cardiac events during follow-up according to troponin T status.

Troponin T	Positive				Negative		
	Abciximab (N=139)		Placebo (N=136)		Abciximab (N=302)		Placebo (N=313)
6 months post randomisation		HR (95% CI)				HR (95% CI)	
Death	6 (4,3%)	0,98 (0,32-3,03)	6 (4,4)		6 (2,0)	1,04 (0,33-3,21)	6 (1,9)
MI	10 (7,2)	0,39 (0,19-0,82)	25 (18,4)		18 (6,0)	0,81 (0,44-1,50)	23 (7,3)
Death or MI	15 (10,8)	0,52 (0,28-0,98)	28 (20,6)	#	23 (7,6)	0,85 (0,49-1,48)	28 (8,9)
CABG	6 (4,3)	1,17 (0,36-3,85)	5 (3,7)		21 (7,0)	0,84 (0,47-1,49)	26 (8,3)
PCI	30 (21,6)	1,05 (0,63-1,75)	28 (20,6)		64 (21,2)	1,02 (0,72-1,44)	65 (20,8)
Any of above	42 (30,2)	0,80 (0,53-1,21)	50 (36,8)		96 (31,8)	0,99 (0,75-1,32)	95 (30,4)
1 year post randomisation							
Death	6 (4,3)	0,73 (0,26-2,12)	8 (5,9)	*	10 (3,3)	1,48 (0,56-3,89)	7 (2,2)
Myocardial infarction	10 (7,2)	0,38 (0,18-0,78)	26 (19,1)	*	20 (6,6)	0,86 (0,48-1,56)	24 (7,7)
Death or MI	15 (10,8)	0,47 (0,26-0,88)	31 (22,8)	$	28 (9,3)	0,97 (0,58-1,62)	30 (9,6)
CABG	10 (7,2)	1,21 (0,48-3,06)	8 (5,9)		25 (8,3)	0,81 (0,48-1,37)	32 (10,2)
PCI	33 (23,7)	0,98 (0,60-1,58)	33 (24,3)		75 (24,8)	0,99 (0,72-1,35)	79 (25,2)
Any of above	47 (33,8)	0,82 (0,55-1,21)	55 (40,4)		112 (37,1)	1,01 (0,78-1,31)	109 (34,8)
4 years post randomisation							
Death	11 (7,9)	1,54 (1,54-1,54)	15 (11,0)		13 (4,3)	1,05 (0,47-2,33)	12 (3,8)
Myocardial infarction	13 (9,4)	0,85 (0,23-0,85)	27 (19,9)	#	31 (10,3)	0,93 (0,57-1,51)	34 (10,9)
Death or MI	22 (15,8)	0,53 (0,31-0,90)	37 (27,2)	#	38 (12,6)	0,93 (0,60-1,44)	42 (13,4)
CABG	12 (8,6)	1,03 (0,45-2,33)	11 (8,1)		31 (10,3)	0,84 (0,52-1,35)	38 (12,1)
PCI	41 (29,5)	1,01 (0,65-1,58)	38 (27,9)		95 (31,5)	1,11 (0,83-1,49)	89 (28,4)
Any of above	57 (41,0)	0,74 (0,52-1,06)	66 (48,5)		138 (45,7)	1,10 (0,87-1,40)	130 (41,5)

Data presented are absolute numbers. In brackets percentages of events relative to the absolute number of patients stratified according to that arm (NB in the text Kaplan-Meier estimates are given). *: $p<0.01$ and # p is 0.01 and 0.05, otherwise p=NS. Abbreviations as in Table 1.

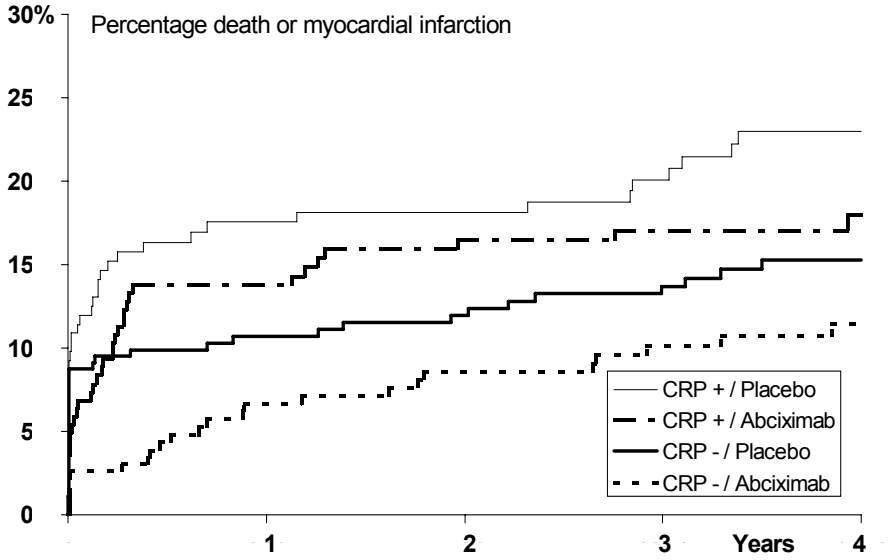

Figure 3
Kaplan–Meier curves of death and/or myocardial infarction according to CRP status and treatment received. There was no significant difference between the groups.

Troponin T and C-reactive protein

Troponin T and CRP had independent prognostic value (Figure 4). Patients with both elevated troponin T and CRP had the highest 4-year event rate (death or MI: 16.8%), whereas patients with a low CRP and negative troponin had the lowest event rate (3.9%; P<0.001). Both troponin T (hazard ratio 1.7 (1.1–2.5), P = 0.009) and elevated CRP (hazard ratio 1.6 (1.1–2.4), P = 0.013) remained independently significant determinants of long-term cardiac outcome after correction by multivariable analysis for other established risk factors: age, sex, diabetes, hypertension, smoking, hypercholesterolemia, previous cardiovascular disease i.e. myocardial infarction, heart failure, PTCA, CABG or stroke- and peripheral vascular disease. The long-term risk reduction with abciximab was most pronounced in troponin T-positive patients regardless of CRP value (hazard ratio 0.44 vs. 0.92, abciximab vs. placebo respectively; P = 0.073).

Table 4

Cardiac events during follow-up of according to CRP status.

CRP	Positive			Negative			
	Abciximab (N=203)		Placebo (N=184)	Abciximab (N=230)		Placebo (N=263)	
6 months post randomisation		HR (95% CI)			HR (95% CI)		
Death	10 (4,9)	0,82 (0,35-1,94)	11 (6,0)	2 (0,9)	2,29 (0,21-25,2)	1 (0,4)	
MI	20 (9,9)	0,86 (0,47-1,59)	21 (11,4)	8 (3,5)	0,35 (0,16-0,78)	26 (9,9)	*
Death or MI	28 (13,8)	0,88 (0,52-1,47)	29 (15,8)	10 (4,3)	0,44 (0,21-0,91)	26 (9,9)	#
CABG	12 (5,9)	0,84 (0,38-1,83)	13 (7,1)	15 (6,5)	0,95 (0,48-1,89)	18 (6,8)	
PCI	47 (23,2)	1,15 (0,75-1,77)	37 (20,1)	46 (20,0)	0,94 (0,64-1,39)	56 (21,3)	
Any of above	75 (36,9)	1,03 (0,74-1,43)	64 (34,8)	62 (27,0)	0,84 (0,60-1,17)	80 (30,4)	
1 year post randomisation							
Death	10 (4,9)	0,70 (0,31-1,59)	13 (7,1)	6 (2,6)	3,43 (0,69-17,0)	2 (0,8)	
Myocardial infarction	20 (9,9)	0,79 (0,48-1,32)	22 (12,0)	10 (4,3)	0,42 (0,21-0,88)	27 (10,3)	#
Death or MI	28 (13,8)	0,82 (0,45-1,51)	32 (17,4)	15 (6,5)	0,61 (0,33-1,15)	28 (10,6)	
CABG	15 (7,4)	0,85 (0,42-1,72)	16 (8,7)	20 (8,7)	0,95 (0,53-1,72)	24 (9,1)	
PCI	54 (26,6)	1,04 (0,70-1,54)	47 (25,5)	53 (23,0)	0,93 (0,65-1,34)	56 (21,3)	
Any of above	81 (39,9)	0,97 (0,71-1,33)	73 (39,7)	77 (33,5)	0,93 (0,69-1,26)	90 (34,2)	
4 years post randomisation							
Death	13 (6,4)	0,58 (0,29-1,17)	20 (10,9)	11 (4,8)	1,66 (0,63-4,37)	7 (2,7)	
Myocardial infarction	27 (13,3)	0,94 (0,54-1,62)	25 (13,6)	17 (7,4)	0,53 (0,30-0,95)	35 (13,3)	#
Death or MI	36 (17,7)	0,79 (0,50-1,23)	40 (21,7)	24 (10,4)	0,70 (0,42-1,16)	38 (14,4)	
CABG	17 (8,4)	0,65 (0,35-1,22)	23 (12,5)	26 (11,3)	1,14 (0,66-1,97)	26 (9,9)	
PCI	60 (29,6)	1,04 (0,72-1,52)	51 (27,7)	75 (32,6)	1,13 (0,82-1,55)	76 (28,9)	
Any of above	92 (45,3)	0,92 (0,68-1,23)	87 (47,3)	102 (44,3)	1,04 (0,79-1,36)	108 (41,1)	

Data presented are absolute numbers. In brackets percentages of events relative to the absolute number of patients stratified according to that arm (NB in the text Kaplan-Meier estimates are given). *: p <0.01 and #: p is 0.01 and 0.05, otherwise p=NS. Abbreviations as in Table 1.

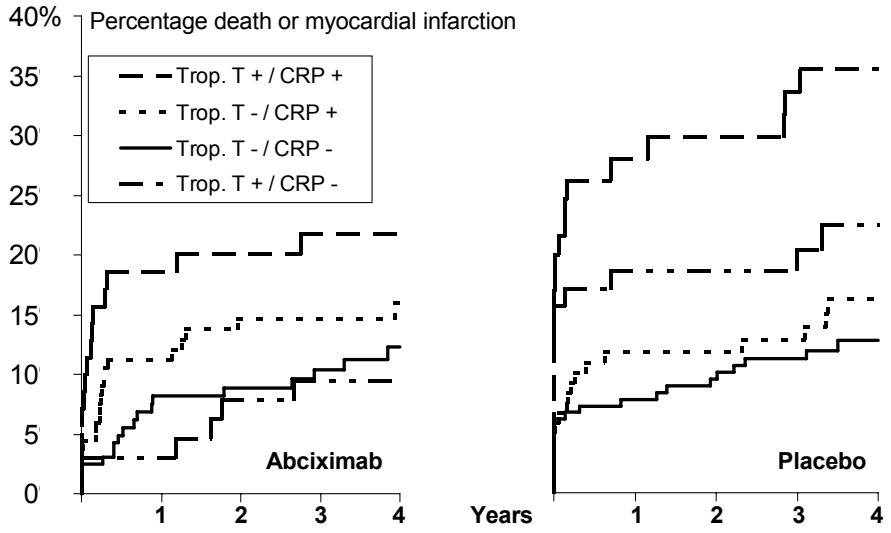

Figure 4
Kaplan–Meier curves of death and/or myocardial infarction according to CRP and troponin T status and treatment received.

Discussion

Abciximab was the first glycoprotein IIb/IIIa receptor blocker to demonstrate improved outcome at 30-days in patients with acute coronary syndromes scheduled to undergo percutaneous coronary intervention (PCI). These findings from CAPTURE7 are consistent with those from all other trials with abciximab in patients undergoing PCI, for stable or unstable angina or myocardial infarction, with balloon angioplasty, stent or other devices.[11,13–16] A combined analysis of all studies revealed a significant reduction of mortality at follow-up in patients receiving abciximab at the time of PCI, in addition to the reduction in death and myocardial infarction and urgent reintervention.[17] Patients in CAPTURE with a high troponin T value at enrolment, and patients having an elevated CRP were at increased risk for death or myocardial infarction during follow-up. A positive CRP became predictive as of 6 months follow-up. These results confirm those of the FRISC II study [12], in which the prognostic value of troponin T and CRP was studied in unstable angina patients treated with dalteparin. In both studies elevated levels of troponin T and CRP were strongly and independently related to the long-term risk of death from cardiac causes. A unique finding in CAPTURE is the marked acute and long-term treatment benefit with abciximab in patients with elevated troponin T irrespective of the CRP level (Figure 4). The present findings support the concept that the pathophysiology of atherosclerosis in acute coronary syndromes is multifactorial,

with a chronic (inflammatory) basis [18] and an acute thrombotic exacerbation.[19–21] Inflammation may result in plaque instability, fissuring or rupture, with resulting local thrombosis and micro-embolisation. This results in distal thrombotic occlusion and myocardial necrosis as detected by elevated cardiac troponin T. These local thrombotic events are in fact ameliorated by PCI, as is evident from the myocardial infarction event curves in CAPTURE and in other studies. Abciximab and other glycoprotein IIb/IIIa receptor antagonists inhibit platelet aggregation and thus reduce thrombotic complications associated with percutaneous coronary intervention, when started early before PCI [22], particularly in patients with elevated cardiac troponin T. In contrast, elevated CRP is a marker of a chronic inflammatory process in the coronary wall [23] resulting in repetitive occurrences of cardiovascular events.[2,24,25] In patients undergoing coronary angioplasty cardiac events at 1 year and beyond are predicted by high preprocedural levels of CRP.[26] Short-term therapy with abciximab provides no protection against these events. Although abciximab has demonstrated anti-inflammatory effects, which may ameliorate the acute inflammatory process [27] and lower CRP caused by PCI [28] it apparently does not control the underlying inflammatory process as a cause of elevated CRP that is associated with long-term risk. Also, prolonged treatment with an oral glycoprotein IIb/IIIa receptor antagonist provides no benefit.[29] In fact mortality was increased in five studies with these latter agents, possibly as a result of a pro-aggregating effect of glycoprotein IIb/IIIa receptor antagonists at the low doses which were given.[29]

Limitations to this study

The follow-up data was obtained either from the physicians, the municipal registries or directly from the patient. The clinical event committee did not adjudicate the follow-up data, accordingly criteria for myocardial infarction might differ between investigators and some events may have been missed. Seventy-seven patients were lost to follow up. They were significantly younger, which could explain their mobility and tendency not to reply. Yet missing data were evenly distributed and thus are unlikely to be biased. Patients with possible chronic infections of different origin resulting in elevated CRP at baseline were not specifically recorded and could not be removed from this analysis. However, as in most clinical trials patients with 'significant non-cardiac disease' were excluded. In the analyses, arbitrarily cut-off values for troponin T (>0.1 μg . l^{-1}) and CRP (>10 mg . l^{-1}) were applied. A more detailed subgroup analysis of troponin T and CRP revealed similar results (Figure 5).

Conclusion

This study confirms the value of abciximab in patients undergoing percutaneous intervention for refractory unstable angina pectoris and supports the recommendations in the European and other guidelines for routine troponin T testing in patients presenting with chest pain in an emergency department.[30–32] Both troponin T and CRP are independent predictors of

impaired long-term outcome. Troponin T is a powerful indicator for a treatment benefit with abciximab in patients with refractory angina undergoing PCI. If troponin T is positive and there are no contra-indications, abciximab or another glycoprotein IIb/IIIa receptor blocker should be given, and a percutaneous intervention should follow with at least 1 h, but preferably 12h of infusion.[17,22,33] Future studies with anti-inflammatory therapy that is more potent than aspirin should assess a potential additional long-term benefit in patients with unstable angina. The baseline CRP level may serve as an indicator for use of such anti-inflammatory therapy.

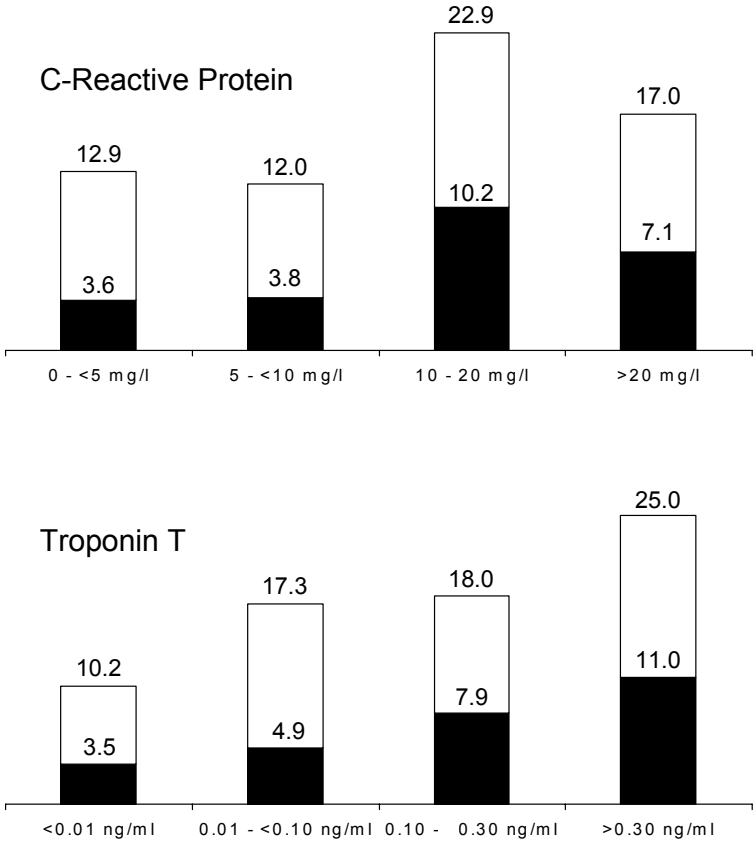

Figure 5

Incidence of death or myocardial infarction at 4 years according to CRP and troponin T status. Cut-off values used were: for troponin T: <0.01 ng/ml; 0.01–<0.10 ng/ml; 0.10–<0.30 ng/ml and >0.30 ng/ml. For CRP: <5 mg/1, 5–<10 mg/l, 10–20 mg/l and >20 mg/l. The numbers are percentages per subgroup:

■ = deaths; □ = total of death and myocardial infarcts.

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Chapter Two

Elevated placental growth factor levels are associated with adverse outcome at four year follow-up in patients with acute coronary syndromes

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Abstract

Objective

To evaluate the predictive value of baseline placental growth factor (PlGF) for long-term cardiovascular events in acute coronary syndromes.

Background

PlGF, a biomarker of vascular inflammation, is identified as powerful predictor for short-term outcome in patients with ACS.

Methods

In 544 patients who were enrolled in the placebo arm of the CAPTURE trial, PlGF levels were determined as well as markers of myocardial necrosis (troponin TTnT), general inflammation (high sensitivity CRPhsCRP), and platelet activation (soluble CD40 ligandsCD40L). Cox' proportional hazard regression analyses were applied to evaluate the relation between biomarkers and the occurrence of all-cause death or non-fatal myocardial infarction during a median follow-up period of 4 years.

Results

Patients with PlGF levels in the fourth and fifth quintile (>27 ng/L) had higher mortality than those with lower levels (10.8% versus 3.2%; hazard ratio 3.3 and 95% CI 1.6 to 7.1), as well as higher incidence of the composite endpoint death or myocardial infarction (27.6% vs. 11.3% events; hazard ratio 2.6 and 95%CI 1.7 to 3.9). The relation between PlGF and the composite endpoint remained significant after adjustment for TnT, sCD40L, and hsCRP (adjusted hazard ratio 3.3 and 95% CI 2.0 to 5.4).

Conclusions

In patients with ACS, elevated plasma levels of PlGF are associated with adverse cardiac outcome during long-term follow-up. These data suggest that PlGF as a more specific marker of vascular inflammation should be considered for risk stratification of patients with ACS rather than general markers of inflammation.

Introduction

Vascular inflammation is now believed to play an important role in atherosclerosis [1]. Markers of general inflammation such as high sensitivity C reactive protein (hsCRP)[2], interleukin-6 [3], and serum amyloid [4] are associated with adverse outcome in patients with coronary heart disease. However, placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family, was recently shown to be strongly up regulated in early and advanced atherosclerotic lesions. Increasing evidence suggests that PlGF acts as a primary inflammatory instigator of atherosclerotic plaque instability [5]. Indeed, recently it was demonstrated that PlGF is an independent biomarker of short-term adverse outcome in patients with chest pain suspicious of an acute coronary syndrome (ACS)[6].

Inflammatory processes of atherosclerosis are sustained after acute interventional or medical treatment, and trigger cardiovascular events during long-term follow-up[7,8]. Therefore, we studied the relation between baseline levels of PlGF and the incidence of all-cause mortality or non-fatal myocardial infarction during four year follow-up in ACS patients who enrolled the CAPTURE trial. We related our findings to other markers like one of general inflammation such as high-sensitivity CRP (hsCRP) and soluble CD40 ligand (sCD40L).

Methods

Patients and treatment.

The CAPTURE protocol has been described in detail [9]. Briefly, patients were eligible if they had refractory unstable angina, defined as chest pain at rest with concomitant ECG abnormalities compatible with myocardial ischemia (ST-depression, ST-elevation or T-wave inversion), and one or more episodes of typical chest pain or ECG abnormalities during at least 2h of treatment with i.v. heparin and nitrates. The most recent ischemic episode should have occurred within 48h before enrolment, corresponding to Braunwald class III unstable angina. All patients had undergone coronary angiography and percutaneous coronary intervention (PCI) was scheduled within 18-24h after the start of the study medication. After informed consent patients were randomly assigned to abciximab (ReoPro, Centocor B.V., Leiden, The Netherlands; 0.25 mg/kg bolus plus 10 μg/min continuous infusion) or placebo. Study medication was started within 2h of randomization and continued until 1 hour after the procedure. All patients received aspirin, heparin and nitrates, whereas β-blockers, calcium channel antagonists. Other cardiovascular drugs were given at the discretion of the investigator.

Analytical techniques.

Plasma samples drawn at the time of randomization were available for determination of troponin T (TnT), hsCRP, sCD40L, and PlGF. Because TnT[10,11] and sCD40L[12] have been shown to interact with the treatment effect of abciximab, the present analysis was restricted to the 544 patients receiving placebo in whom blood samples were available (86% of patients receiving placebo). Blood samples were collected a mean of 8.7 (SD, 4.9) hours after onset of symptoms, but prior to PCI and prior to the incidence of adverse events. Measurement of cardiac marker levels was performed blinded to the patients' histories. Levels of PlGF and sCD40L were measured by enzyme-linked immunosorbent assay (both from R&D Systems, Wiesbaden, Germany). Total imprecision (expressed as coefficient of variation) for PlGF was 7.3%. For sCD40L, a diagnostic threshold level of 5.0 µg/L was used. Levels of TnT were determined using a 1-step enzyme immunoassay based on electrochemiluminescence technology (Roche Diagnostics, Mannheim, Germany). A diagnostic threshold value of 0.01 µ/L was used. Levels of hsCRP were measured using the Behring BN II Nephelometer (Dade Behring, Deerfield, Ill). A diagnostic threshold value of 10 mg/L was used.

A cut-off value for PlGF of 27 ng/L. was used in this study based on the difference of number of events between the 3rd and 4th quintile (see results section), which was almost equal to the 25 ng/L. based on additional ROC analyses and looking at the maximal sum of sensitivity and specificity per ng/L.

Study endpoints.

Endpoints of the present analysis were all-cause mortality and the composite of all-cause mortality and non-fatal myocardial infarction. Follow-up at 6 months was part of the study protocol. Myocardial infarction during the index hospitalization was defined by CK-MB or CK levels exceeding 3 times the upper limit of normal in 2 samples and an increase by 50% over the previous value, or an ECG with new significant Q waves in 2 or more contiguous leads. Myocardial infarction after discharge was defined by CK-MB or CK levels exceeding 2 times the upper limit of normal or new significant Q waves in 2 or more contiguous leads. A clinical endpoint committee adjudicated these events. Survival status and information on myocardial infarction were collected for the patients who were alive 6 months after randomization. Follow-up data was obtained from the treating physician, the general practitioner, the patient or municipal registries and was not adjudicated.

Data analysis.

Continuous variables were summarized by median values with corresponding 25th and 75th percentiles. Discrete variables were summarized in terms of frequencies and percentages. Kaplan-Meier analyses were per-

formed to evaluate the incidence of events over time. Univariable and multivariable Cox proportional hazards regression analyses were applied to evaluate the relation between PlGF and long-term outcome. We adjusted for age, gender, history of diabetes and ST-depression on the qualifying ECG and the biomarkers sCD40L, hsCRP and troponin T (thresholds were: >5.0 µg/L., >10 mg/L. and >0.01 µg/L. respectively). P values were two-sided, with $p \leq 0.05$ being considered significant.

The main results are presented for 544 patients who entered the trial. Additional analyses were performed in the subgroup of patients who survived the first six months, with events counted after this period.

Results

Patients with PlGF levels above 27 ng/L had significantly higher levels of hsCRP than those with lower PlGF levels (64.7 vs. 26.2%, $p<0.0001$). Also, patients with elevated PlGF more often had a history of smoking (47.9 vs. 37.5%; $p=0.02$). Other established risk factors were evenly distributed over the two PlGF groups.

The median follow-up duration was 48 months (25th and 75th percentile: 38, 55) with 46 (38, 54) months of follow-up beyond 30 days. During follow-up, 31 patients had died and 60 experienced nonfatal MI. A total of 21 deaths and 21 non-fatal myocardial infarctions occurred after 30 days.

Analyses based on quintiles showed a noticeably higher calculated annual incidence of death and non-fatal myocardial infarction in the fourth and fifth quintile (Figure 1). Long-term mortality of patients with elevated PlGF levels was 10.8% as compared to 3.2% in those without elevated PlGF levels (crude hazard ratio 3.3 and 95%CI: 1.6 to 7.1; $p=0.002$; Figure 2). The composite endpoint of death and non-fatal myocardial infarction occurred in 27.6% and 11.3% patients (crude hazard ratio 2.6 and 95%CI: 1.7 to 3.9; $p<0.001$; Figure 3).

In the patients who survived the first 30 days, the incidence of all-cause mortality during extended follow-up was 8.7% in those with elevated baseline PlGF and 2.6% in those without elevated PlGF (crude hazard ratio 3.2 and 95%CI: 1.4 to 7.6; $p=0.007$). The composite endpoint occurred in 16.2% of patients with elevated PlGF levels and in 5.7% of patients without elevated PlGF (crude hazard ratio 2.9 and 95%CI: 1.5 to 5.3; $p=0.001$).

After adjustment for multiple baseline characteristics and troponin T, sCD40L and hsCRP PlGF remained a significant predictor for the incidence of death or myocardial infarction during 4 years after admission (adjusted hazard ratio 3.0 and 95%CI: 1.1 to 7.9, $p=0.026$, Table 1), as well as during long-term follow-up in 6 months survivors (adjusted hazard ratio 3.3 and 95%CI: 2.0 to 5.4, $p<0.001$, Table 1).

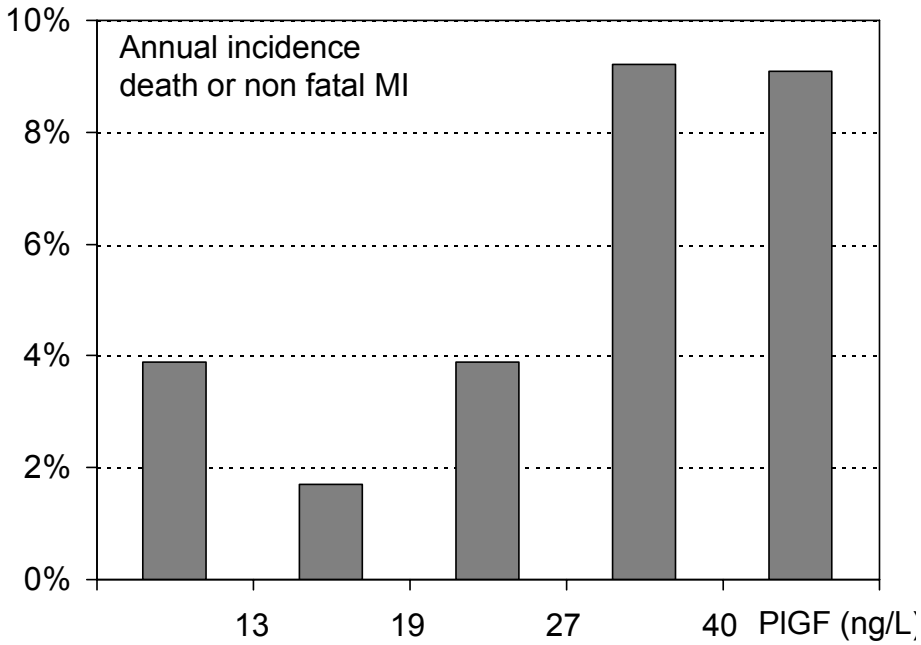

Figure 1

Bar graphs of the calculated annual incidence of death or non-myocardial infarction according to placental growth factor (PlGF) status grouped in quintiles.

Table 1.

Multivariable adjusted hazard ratios for the incidence of death or myocardial infarction during long-term follow-up.

	Total events (n=91) * in all patients (n=544)			Long-term events (n=30) † in MI-free survivors at 6 months (n=472)		
Variable	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Age (per year)	1.04	(1.01-1.06)	0.004	1.04	(1.0- 1.1)	0.06
Placental growth factor > 27 ng/L	3.3	(2.0-5.4)	<0.001	3.0	(1.4- 6.7)	0.006
sCD40-ligand > 5.0 µg/L	1.6	(1.0-2.5)	0.05	1.1	(0.5-2.2)	0.9
hsCRP > 10 mg/L	0.9	(0.5-1.5)	0.6	1.1	(0.5-2.3)	0.9
Troponin T > 0.01 µg/L	1.7	(1.0-2.9)	0.04	1.8	(0.8-4.0)	0.1
Male gender	0.6	(0.4-1.1)	0.08	0.6	(0.3-1.5)	0.3
History of diabetes	1.1	(0.6-2.1)	0.7	1.3	(0.5-3.3)	0.5
ST-depression on qualifying ECG	1.1	(0.7-1.7)	0.8	0.8	(0.4-1.6)	0.6

* Events were counted from randomization until the end of follow-up in all patients; † Long-term events were counted from 30 days following the index ACS in MI-free survivors at 30 days follow-up

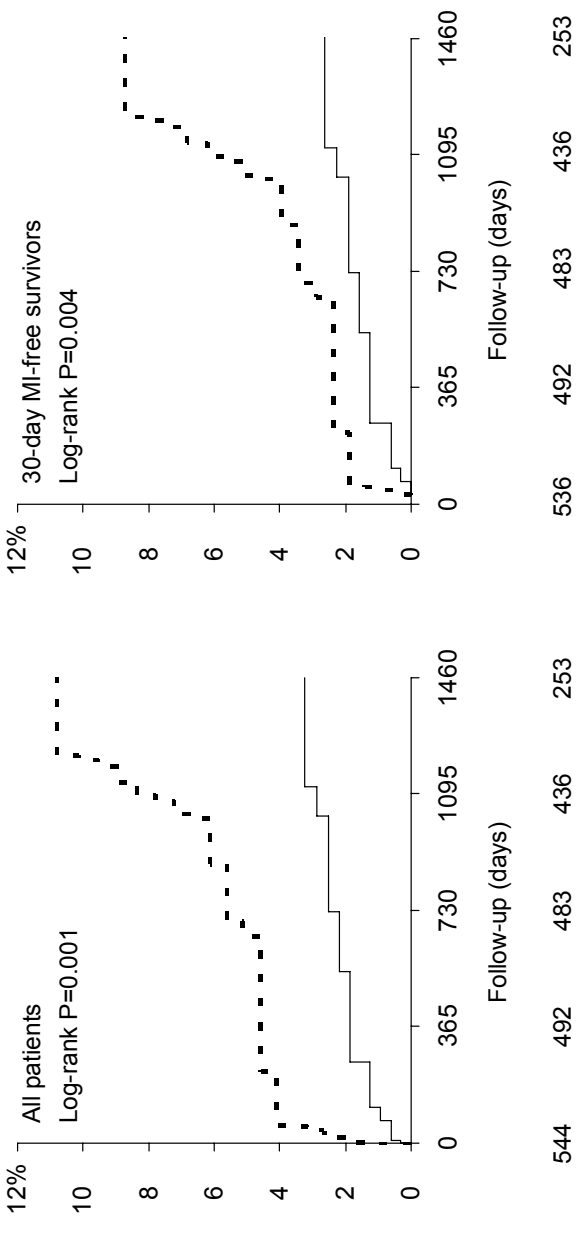

Figure 2
Kaplan-Meier curves of death during 4-year follow-up according to placental growth factor status.

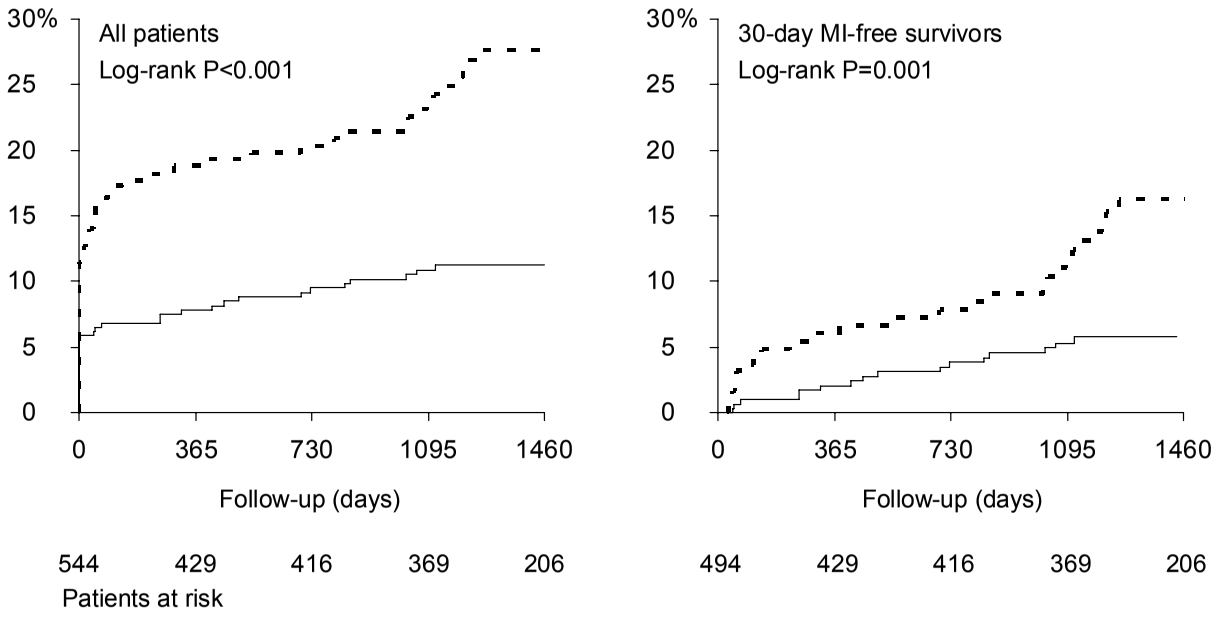

Figure 3

Kaplan-Meier curves of death or myocardial infarction (MI) during four-year follow-up according to placental growth factor status. In the right panel, 49 patients who died or experienced MI before the 30-day follow-up were excluded. Dotted line: placental growth factor >27 ng.

Discussion

In this study we demonstrate that elevated baseline levels of PlGF, a more specific marker of vascular inflammation, are associated with adverse long-term outcome in patients with ACS. The predictive value of PlGF was independent of hsCRP, a biomarker of general inflammation. Interestingly, baseline PlGF was also associated with an increased risk of cardiovascular complications during extended follow-up in patients who survived the first six months.

These data add to the growing evidence that hsCRP as classic systemic acute-phase protein might not be specific enough for the inflammation process involved in vascular atherosclerosis [13]. Therefore, hsCRP levels collected in ACS patients appear to be less useful as a tool for cardiovascular risk stratification and patient management. In contrast, PlGF as a more specific marker of vascular inflammation providing independent predictive value for the short-term cardiovascular outcome is not hampered by the occurrence of an ACS[5,6]. We now demonstrate it's usefulness as a determinant of long-term outcome. It is important to note in this respect that the prognostic value of baseline PlGF was independent of biomarkers of platelet activation (soluble CD40-ligand) and myocardial necrosis (troponin T).

We observed both an early divergence of the curves shortly after onset of symptoms as well as an impressive late divergence of the curves after two years of follow up. These findings support the pathophysiological concept of a chronic (vascular) inflammatory basis of atherosclerosis with an acute superimposed process in the setting of an acute coronary syndrome [14]. The present data suggest that chronic inflammatory processes in the coronary vessel wall may indeed result in the repetitive occurrences of cardiovascular events during long-term follow-up[1,15,16]. In patients with acute coronary syndromes, early percutaneous coronary intervention, as performed in the present CAPTURE trial, obviously prevents adverse cardiac events during short-term (6 months) follow-up. Long-term events, however, apparently require a more effective and/or specific anti-inflammatory treatment such as blocking of the PlGF receptor or reducing the activity of circulating PlGF levels by administration of soluble VEGF receptor 1[17]. Future studies of anti-inflammatory therapies should assess a potential additional long-term benefit in patients with acute coronary syndromes. The baseline PlGF level may serve as a powerful indicator for the targeted use of anti-inflammatory therapy in patients at high risk for the rapid progression of coronary atherosclerosis. Follow-up PlGF levels could than be used as indicators for the effect of such therapy.

We acknowledge that this investigation has some limitations. First, the long-term follow-up data which were obtained from multiple sources were not adjudicated by an independent clinical event committee. Thus, the applied criteria for myocardial infarction might have differed between investigators and some events may actually have been missed. Second, no information is available on long-term medical treatment (such as statin or

ACE-inhibition therapy), which might have influenced patients' outcome. Accordingly, we recognize that there was information bias in our data. However, it is rather unlikely that this would have resulted in a differential bias between patients with or without elevated PlGF levels. In this respect, it should be emphasized that the investigators who collected long-term follow-up (EB, TL) were blinded for any information on baseline data (including Biomarker levels). Importantly, between patients with high and low PlGF levels, there was no difference in the prevalence of hypercholesterolemia, which was the primary reason for the initiation of statin treatment at the time of the CAPTURE study. With think therefore that further prospective studies should be performed using this post-hoc defined criteria of PlGF elevation and preferably and more time intervals.

Conclusion

In patients with acute coronary syndromes, increased plasma levels of PlGF are associated with adverse cardiac outcome during long-term follow-up. PlGF as a marker of vascular inflammation should be considered for risk stratification in patients with acute coronary syndromes rather than general markers of inflammation such as hsCRP.

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Chapter Three

Biochemical markers of atherosclerotic vascular inflammation predict 4 year cardiovascular risk in patients with acute coronary syndromes

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Submitted

Abstract

Background

Inflammation plays an important role in atherosclerosis. Biochemical markers reflecting distinct pathophysiological aspects of vascular inflammation are associated with an increased risk of coronary events in patients with acute coronary syndromes. We studied the relation between a series of biomarkers and long term cardiovascular events.

Methods

In 1090 patients who were enrolled in the CAPTURE trial, blood levels of C-reactive protein (CRP), myeloperoxidase (MPO), pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), soluble CD40 ligand (sCD40L), interleukin-10 (IL-10), and troponin T (TnT) were determined. Cox' proportional hazard regression analyses were applied to evaluate the relation between biomarkers and the occurrence of all-cause death or non-fatal myocardial infarction during a median follow-up period of 4 years.

Results

Patients with abnormal marker levels had higher incidence of an event. Troponin-T >0.1 mg/L (adjusted hazard ratio 2.0), IL-10 <3.5 ng/L (1.6), MPO ≥350 µg/L (1.8), and PlGF >27 ng/L (2.5) were significant outcome determinants, independently of clinical variables. In a simple model counting the presence of detrimental biomarkers, 4 year event rates varied between 3.3% (all markers normal) and 40% (all abnormal).

Conclusions

In patients with ACS, biochemical markers characterizing distinct aspects of the underlying inflammatory atherosclerotic process and the myocardial damage of the initial cardiac event can assist in predicting long-term adverse cardiac outcome.

Introduction

It is now well accepted that inflammation plays an important role in atherosclerosis [1]. The prognostic value of C-reactive protein (CRP) in unstable angina for short-term [2] and long-term [3] outcome has been repeatedly described. More recently, a number of inflammatory markers reflecting distinct pathophysiological processes in the setting of an acute coronary syndrome have also been associated with clinical outcome. The prevalence of myeloperoxidase (MPO), a leucocytic enzyme which appears as part of host defense in inflammatory disorders, and also present in soft plaque, was associated with an increased risk of major adverse cardiac events in patients with documented acute coronary syndromes [4] or presenting with chest pain without evidence of myocardial necrosis [5]. Also expressed in ruptured and eroded plaques, but not in stable plaques, is the metalloproteinase pregnancy associated plasma protein A (PAPP-A) [6]. Placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family, is considered a primary inflammatory instigator in atherosclerotic lesions [7], and has prognostic value in patients with unstable angina pectoris[8]. In contrast, elevated levels of the anti-inflammatory cytokine IL-10 were associated with a lower risk of coronary events in patients with acute coronary syndromes and elevated CRP [9] emphasizing the importance of the inflammatory balance in the vascular wall. Finally, elevated levels of soluble CD40 ligand (sCD40L), which is primarily released from activated platelets[10], were associated with an increased cardiovascular risk in acute coronary syndromes [11].

The prognostic value of these biochemical markers for the incidence of cardiovascular complications was previously studied, either alone or in combination with one other marker, whereas the follow-up duration was often limited to the first 6 months after admission. However, atherosclerosis as an inflammatory process probably is sustained after acute interventional or medical treatment and may trigger cardiovascular events during long-term follow-up. Therefore, we studied the relation between baseline levels of all these markers, together with that of myocardial necrosis (troponin T – TnT), and the incidence of all-cause mortality or non-fatal myocardial infarction during an extended four year follow-up period in ACS patients who were enrolled in the CAPTURE trial.

Methods

Patients and treatment.

The CAPTURE protocol has been described in detail [12]. Briefly, patients were eligible if they had refractory unstable angina, defined as chest pain at rest with concomitant ECG abnormalities compatible with myocardial ischemia (ST-depression, ST-elevation or T-wave inversion), and one or

more episodes of typical chest pain or ECG abnormalities during at least 2h of treatment with i.v. heparin and nitrates. The most recent ischemic episode should have occurred within 48h before enrolment, corresponding to Braunwald class III unstable angina. All patients had undergone coronary angiography and percutaneous coronary intervention (PCI) was scheduled within 18-24h after the start of the study medication. After informed consent patients were randomly assigned to abciximab (ReoPro, Centocor B.V., Leiden, The Netherlands; 0.25 mg/kg bolus plus 10 μg/min continuous infusion) or placebo. Study medication was started within 2 hour of randomization and continued until 1 hour after the procedure. All patients received aspirin, heparin and nitrates, whereas β-blockers, calcium channel antagonists. Other cardiovascular drugs were given at the discretion of the investigator.

Analytical techniques.

Blood samples were drawn 8.7±4.9 hours after the last episode of chest pain for determination of troponin T (TnT), hsCRP, sCD40L, IL-10, MPO, PAPP-A, and PlGF. Based on earlier analyses regarding the six months outcome of the study, TnT[13,14] and sCD40L[11] have been shown to possibly interact with the treatment effect of abciximab. Therefore the analysis was performed both in patients receiving placebo and in the entire population separately, although formal testing did not show a significant interaction for the long-term follow up. Blood samples were collected a mean of 8.7 (SD, 4.9) hours after the last episode of chest pain, but prior to PCI and prior to the incidence of adverse events. Measurement of cardiac marker levels was performed blinded to the patients' histories. Levels of PlGF, sCD40L, and MPO were measured by enzyme-linked immunosorbent assay (PlGF and sCD40L from R&D Systems, Wiesbaden, Germany and MPO from Calbiochem, Merck KGaA, Darmstadt, Germany). Diagnostic thresholds were 5.0 μg/L for sCD40L 350 μg/L for MPO, and 27 ng/L for PlGF. Levels of TnT and PAPP-A were determined using a 1-step enzyme immunoassay based on electrochemiluminescence technology (Roche Diagnostics, Mannheim, Germany). A diagnostic threshold value of 0.01 μ/L was used for TnT and the diagnostic threshold levels for PAPP-A was 12.6 mIU/L. Levels of hsCRP were measured using the Behring BN II Nephelometer (Dade Behring, Deerfield, Ill). A diagnostic threshold value of 10 mg/L was used. All measurements were performed in heparin plasma.

Study endpoints.

Endpoints of the present analysis were all-cause mortality and the composite of all-cause mortality and non-fatal myocardial infarction during 4 year (median) follow-up. Follow-up at 6 months was part of the initial study protocol, and a clinical endpoint committee adjudicated these events. Myocardial infarction during the index hospitalization was defined by CK-MB or CK levels exceeding 3 times the upper limit of normal in 2 samples and an increase by 50% over the previous value, or an ECG with new significant Q

waves in 2 or more contiguous leads. Myocardial infarction after discharge was defined by CK-MB or CK levels exceeding 2 times the upper limit of normal or new significant Q waves in 2 or more contiguous leads. Survival status and information on myocardial infarction during extended follow-up (i.e. after 6 months after randomization) were obtained from the treating physician, the general practitioner, the patient or municipal registries. These events were not adjudicated.

Data analysis.

Continuous variables were summarized by median values with corresponding 25th and 75th percentiles. Discrete variables were summarized in terms of frequencies and percentages. Kaplan-Meier analyses were performed to evaluate the incidence of events over time. Univariable and multivariable Cox proportional hazards regression analyses were applied to evaluate the relation between all biomarkers and long-term outcome. We adjusted for age, gender, smoking, diabetes mellitus, hypertension, left ventricular ejection fraction, and hypercholesterolemia. History of: myocardial infarction, peripheral vascular disease chronic heart failure or previous PCI. ST-depression, ST-elevation or T-wave changes on the admittance ECG. P values were two-sided, with $p \leq 0.05$ being considered significant. Sensitivity, specificity and area under the receiver operating characteristic curve (ROC) values were calculated for the individual biomarkers with regard to death or myocardial infarction at 4 years. In case patients had more than one event (myocardial infarction or death) the first was counted.

In earlier analyses of the CAPTURE study, significant interactions were observed between biomarkers (troponin T and CD40 ligand) and allocated treatment with respect to the incidence of cardiovascular events during 6 month follow up.11,13,14 Formal statistical tests demonstrated that these interactions were no longer present with respect to the incidence of such events during long-term follow-up. Therefore, we decided to conduct all analyses on the patients allocated to placebo (N=544), as well as on the entire study population (placebo and abciximab combined; N=1090). Results of both sets of analyses are presented.

Results

Baseline characteristics and clinical variables of the 1090 patients (546 abciximab, 544 placebo) that were included in our analyses are provided in Table 1. The median follow-up duration was 47 months (25th and 75th percentile: 38, 55). During follow-up, 58 patients had died and 109 experienced nonfatal MI. Thus, the composite endpoint was reached in 167 (15.3%) patients.

Patients with elevated biomarkers of vascular inflammation had higher risk of death or nonfatal MI than the remaining patients (Figure 1 and Table 2), while elevated levels of IL-10 were associated with a better prognosis. In the complete patient population those with elevated TnT levels had a 20.3%

incidence of death or myocardial infarction at 4 years of follow-up versus 11.1% in those with low TnT levels (crude hazard ratio 2.1 and 95%CI: 1.4 to 3.0). In patients receiving placebo 4-year event rates were 23.5% and 11.6% in those with and without elevated TnT, respectively (crude hazard ratio 2.0 and 95%CI: 1.1 to 3.4; Table 2). The results for all (other) biomarkers are given in Table 2.

Table 1

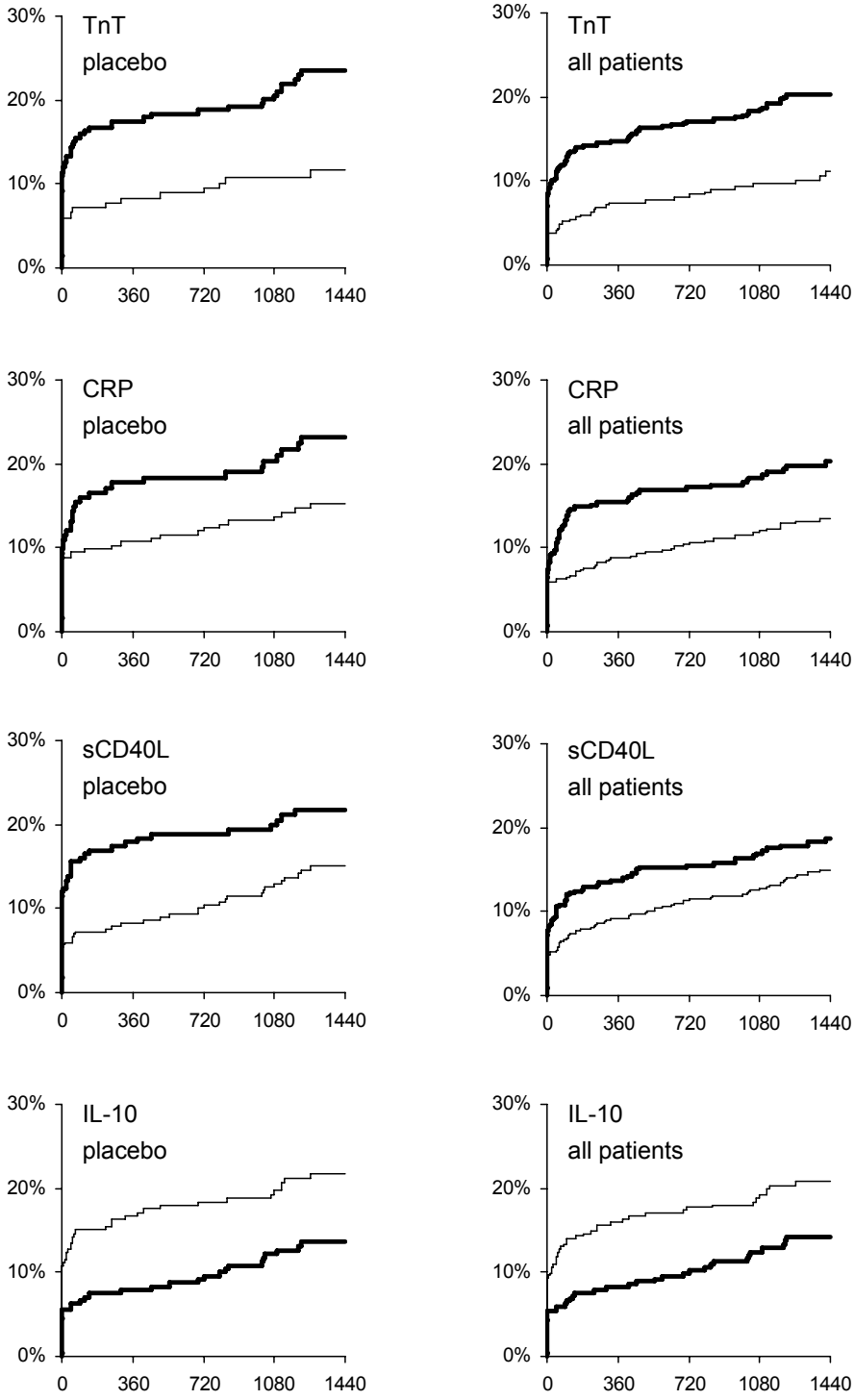
Baseline characteristics	
Age, years	62 (54, 69)
Male gender	73
Body mass index	26 (24, 28)
Diabetes Mellitus	14
Hypercholesterolemia	41
Current smoker or quit within 1 year prior	40
Prior angina	50
Prior myocardial infarction	39
Prior heart failure	2
Peripheral vascular disease	8
Coronary surgery	3
Percutaneous coronary intervention	13
History of any vascular disease	67
ST depression at presentation	43

After multivariable adjustment for clinical characteristics and other biomarkers TnT, IL-10, MPO, and PlGF remained significant predictors for the incidence of death or myocardial infarction in the entire study population and in patients receiving placebo (table 2). Consistent results were obtained for the entire study population (table 2). Only two clinical variables remained significant: age and ejection fraction (hazard ratio 1.03; 95%CI: 1.01 to 1.04 per year and HR 0.98; 95%CI: 0.96 to 0.99 per percentage point respectively; not given in Table 2)
Sensitivity, specificity and c-value of the ROC curve for the individual biomarkers with regard to death or myocardial infarction at 4 years are given in Table 3.

We created a simple risk model for 4 year mortality and non-fatal MI by counting the presence or absence of an abnormal biomarker that significantly predicted risk for an event. Four-year event rates varied between 6.0% (all markers normal) and 35.8% (all abnormal) in all patients, and between 3.3% and 38.6% in those receiving placebo (Figures 2 and 3).

Discussion

The results of the present study support the hypothesis that vascular inflammation might play a prognostically important role as part of the atherosclerotic process since several biomarkers of vascular inflammation


TnT
placebo
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CRP
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Figure 1

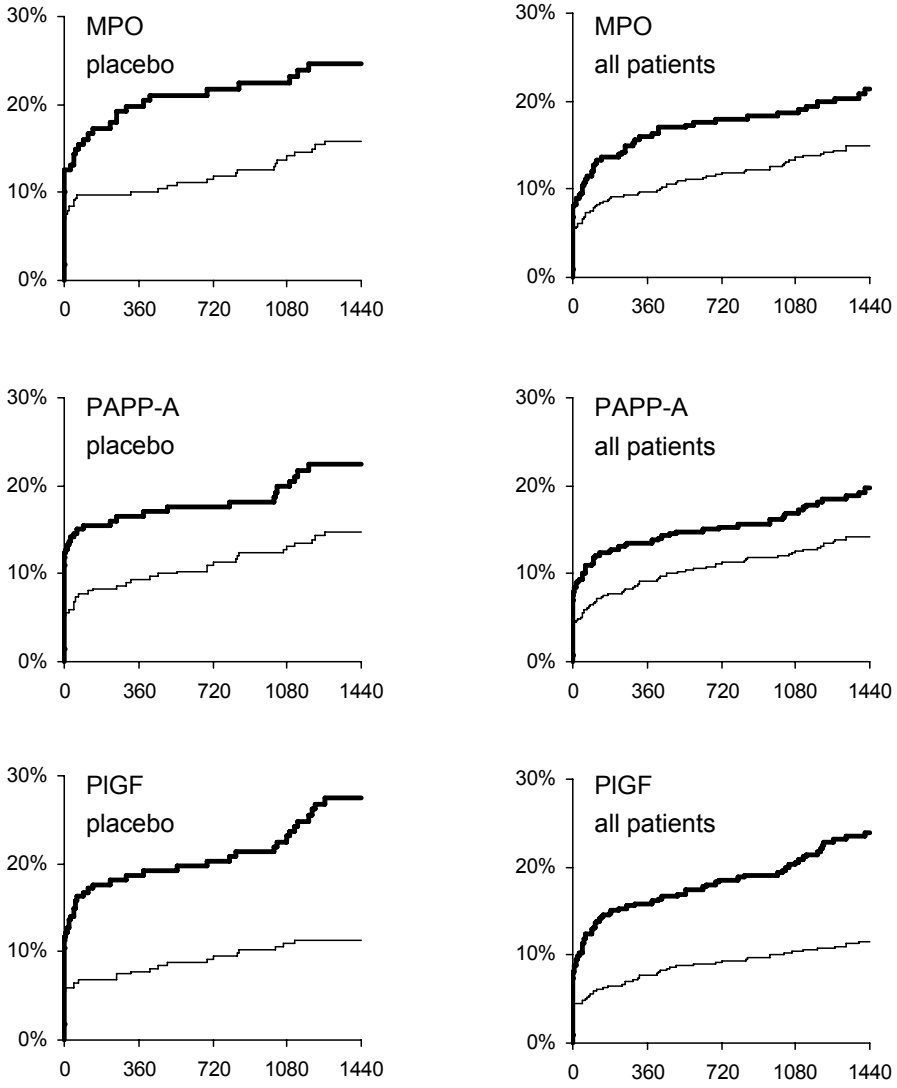

Figure 1(continued):

Kaplan-Meier curves of death or myocardial infarction during 4-year follow-up according to different markers for all patients and for placebo patients only. TnT =Troponin T (bold line is TnT > 0.1 mg/L.); CRP = high sensitive CRP (bold line is >10.0 mg/L.); sCD40L = serum CD40 Ligand (bold line is > 5.0 µg/L; IL-10 = interleukin 10 (bold line is <3.5ng/L); MPO = myeloperoxidase (bold line is >350µg/L); PAPP-A = pregnancy associated plasma protein A (bold line is >12.6 mIU/L); PlGF = placental growth factor (bold line is > 27 ng/L).

Table 2

Relation between biomarkers of (vascular) inflammation, myocardial necrosis, platelet-activation and adverse cardiac events during 4-year follow-up

				Hazard ratio and 95% CI					
				Patients receiving placebo (N=544)			All patients (N=1090)		
Biomarker	Result	Events at 4 year follow-up, % (Kaplan-Meier estimate) §		Unadjusted	Adjusted, for biomarkers only †	Adjusted, for biomarkers and clinical characteristics ‡	Unadjusted	Adjusted, for biomarkers only †	Adjusted, for biomarkers and clinical characteristics ‡
		Placebo	All pts						
TnT	>0.01 µg/L	23.5	20.3	2.2 (1.3, 3.6)	2.3 (1.4, 3.9)	2.0 (1.1, 3.6)	2.1 (1.4, 3.0)	2.1 (1.4, 3.0)	1.8 (1.2, 2.6)
	≤0.01 µg/L	11.6	11.1	1	1		1	1	
CRP	>10 mg/L	23.0	20.3	1.6 (1.0, 2.4)	NS	NS	1.6 (1.2, 2.3)	NS	NS
	≤10 mg/L	15.3	13.5	1			1		
sCD40L	>5.0 µg/L	21.8	18.7	1.6 (1.1, 2.4)	NS	NS	1.4 (1.0, 1.8)	NS	NS
	≤5.0 µg/L	15.1	15.0	1			1		
IL-10	<3.5 ng/L	21.7	20.8	1.7 (1.1, 2.6)	1.6 (1.1, 2.5)	1.7 (1.1, 2.7)	1.7 (1.1, 2.5)	1.6 (1.1, 2.5)	1.7 (1.1, 2.6)
	≥3.5 ng/L	13.7	14.2	1	1		1	1	1
MPO	≤350 µg/L	24.6	21.4	1.7 (1.1, 2.5)	1.8 (1.2, 2.9)	1.6 (1.0, 2.6)	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)
	>350 µg/L	15.9	14.9	1	1		1	1	1
PAPP-A	>12.6 mIU/L	22.4	19.7	1.6 (1.1, 2.5)	NS	NS	1.4 (1.1, 1.9)	NS	NS
	≤12.6 mIU/L	14.7	14.1	1			1		
PlGF	>27 ng/L	27.6	24.0	2.6 (1.7, 3.9)	2.4 (1.6, 3.7)	2.4 (1.4, 4.1)	2.2 (1.6, 3.0)	2.0 (1.4, 2.8)	1.9 (1.3, 2.8)
	<27 ng/L	11.3	11.5	1	1	1	1	1	1

TnT =Troponin T; CRP = high sensitive CRP; sCD40L = serum CD40 Ligand; IL-10 = interleukin 10; MPO = myeloperoxidase; PAPP-A = pregnancy-associated plasma protein A; PlGF = placental growth factor.

§ Events include all-cause mortality and non-fatal myocardial infarction † all biomarkers as presented in this table. ‡ all biomarkers as presented in this table, as well as age, gender, smoking, diabetes mellitus, hypertension, left ventricular ejection fraction and hypercholesterolemia. History of: myocardial infarction, peripheral vascular disease chronic heart failure or previous PCI. ST-depression, ST-elevation or T-wave changes on the admittance ECG.

Table 3

Sensitivity and specificity and c-value of the ROC curve for the individual biomarkers with regard to death or myocardial infarction at 4 years

	Placebo patients			Entire population		
	Sensitivity	Specificity	ROC c-value	Sensitivity	Specificity	ROC c-value
Troponin T	75	44	0.60	73	44	0.59
CRP	51	61	0.56	55	58	0.56
Serum CD40 Ligand	52	61	0.56	46	54	0.54
Interleukin-10	39	47	0.57	39	48	0.56
Myeloperoxidase	46	68	0.56	42	68	0.54
Pregnancy Associated Protein-P	51	62	0.56	49	60	0.54
Placental growth factor	62	63	0.63	57	63	0.60

independently predicted long-term risk of death and non-myocardial inflammation in patients with an acute coronary syndrome. Elevated baseline levels of placental growth factor, myeloperoxidase and low levels of the anti-inflammatory cytokine interleukin-10 are associated with adverse long-term outcome in patients with ACS. The divergence of the curves for placental growth factor at four year follow up was even significant in patients that were event free at one year.

These findings could support the pathophysiological concept of a chronic (vascular) inflammatory basis of atherosclerosis [15,16,17] with an acute superimposed process in the setting of an acute coronary syndrome1. The present data suggest that chronic inflammatory processes in the coronary vessel wall may indeed result in repetitive occurrences of cardiovascular events during long-term follow-up. These events occur on top of the myocardial injury experienced during the initial incident as expressed by the significance of troponin T as marker of myocardial necrosis in our multivariate analysis. The predictive value of the inflammatory markers was independent of clinical characteristics indicating a close relationship between the biomarkers and the ongoing process of atherosclerosis. We recognize the low sensitivity and specificity of the individual biomarkers for the prediction of 4 year mortality or myocardial infarction and therefore advice not to use the markers as single predictors, but in combination with other markers and clinical variables. In this line of argument risk for death or non-fatal myocardial infarction was calculated using simple risk stratification by counting the number of markers outside the normal range. We investigated the role of necrosis (troponin T) together with the instability of the plaque (PAPP-A), oxidative stress (myeloperoxidase), and the continuous "smouldering" inflammatory process (PlGF and IL-10) for developing a

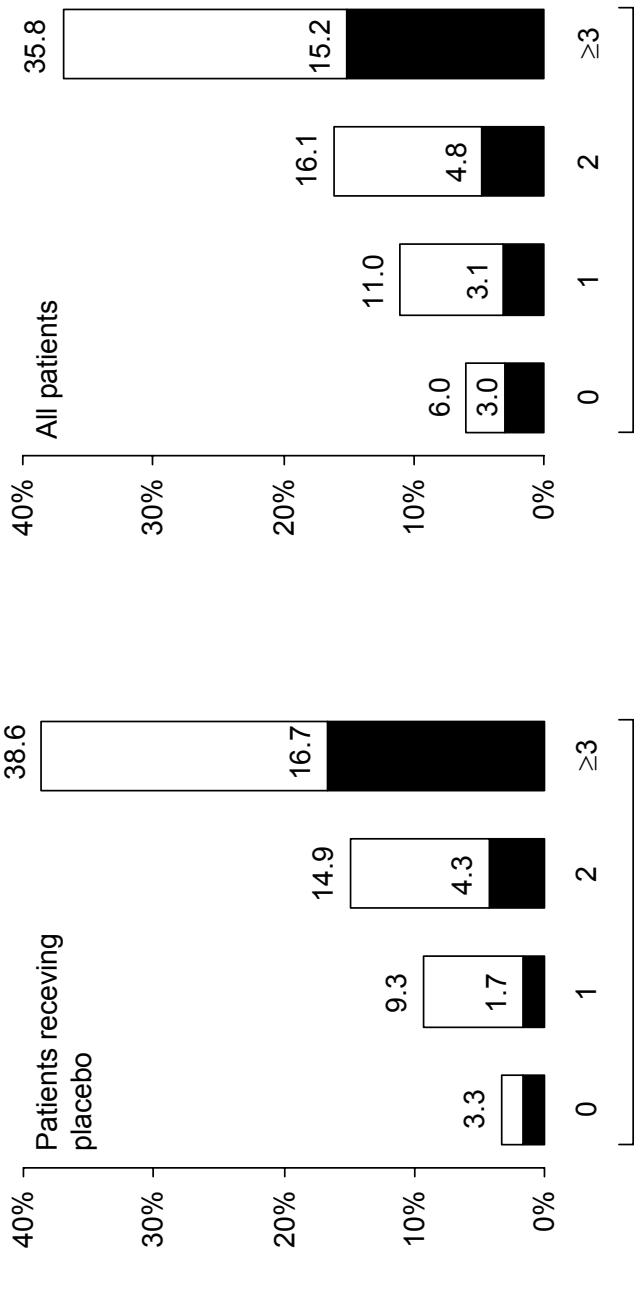

Figure 2

Predicted probability in patients treated with placebo (left panel) and in the entire study population (right panel) of death (black squares) or non-fatal myocardial infarction (white squares) at 4 years after counting the absence or presence of none, 1, 2, or ≥3 biomarkers with detrimental levels. Markers used are: troponin T, interleukin 10, myeloperoxidase, placental growth factor.

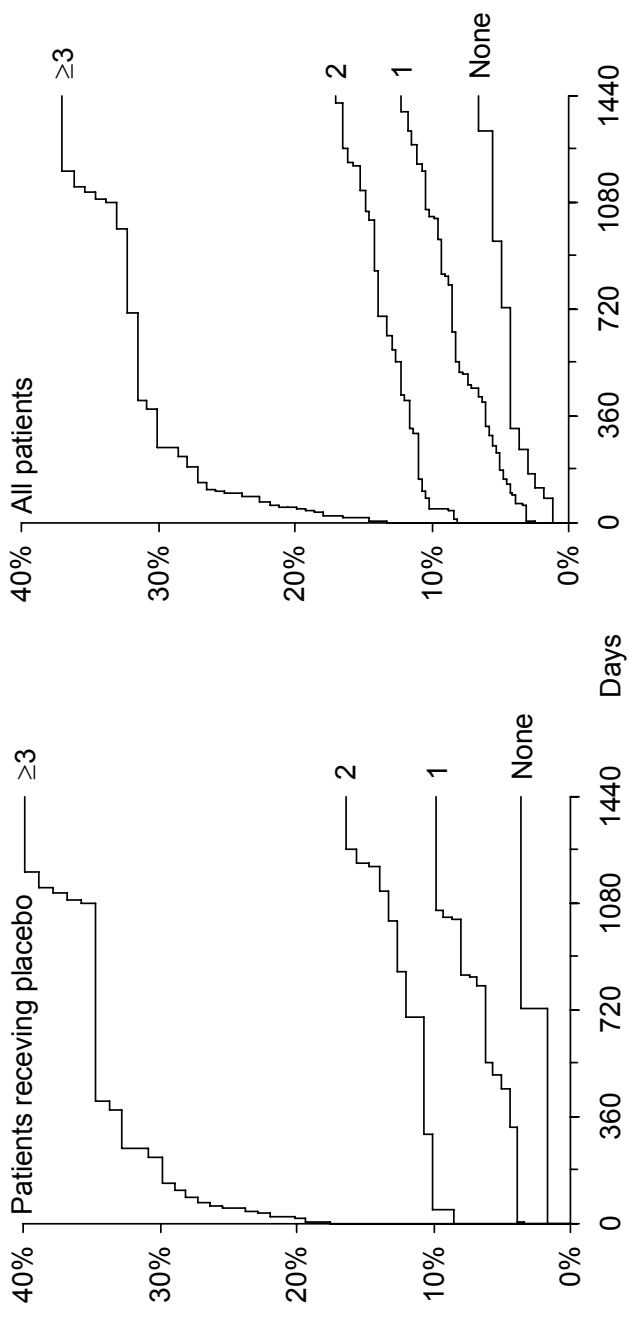

Figure 3

Kaplan-Meier curves of death or myocardial infarction during 4-year follow-up for patients treated with placebo (left panel) and for the entire study population (right panel) with none, 1, 2, or ≥3 biomarkers with detrimental levels. Markers used here are: Troponin T, interleukin-10, myeloperoxidase and placental growth factor.

cardiovascular event. Since there was indeed an important increase in risk if patients showed abnormal values for all these biomarkers (Figures 2 and 3), this simple stratification might aid to adjust and intensify treatment in patients with these biomarkers in the abnormal range.

For instance, a more aggressive therapeutic strategy might be useful not only in treating the current acute event, but also to prevent later events. This strategy could include in the future a more effective and/or specific anti-inflammatory treatment such as blocking of the PlGF receptor or reducing the activity of circulating PlGF levels by administration of soluble VEGF receptor 1[18].

Previous studies have shown interaction between allocated treatment and levels of biomarkers for short-term follow-up[11,13,14] Although formal testing did not show a significant interaction between the biomarkers and treatment with abciximab with respect to long-term event rates, we performed separate analyses for the placebo group and the entire study population. Since the obtained data consistently indicate that TnT, IL-10, MPO, and PlGF are independent predictors for the long-term outcome of the patients, we conclude that our findings have general applicability if confirmed in other trials including more heterogeneous study populations of patients with chest pain.

We acknowledge that this investigation has some limitations. First, the long-term follow-up data which were obtained from multiple sources were not adjudicated by an independent clinical event committee. Thus, the applied criteria for myocardial infarction might have differed between investigators and some events may actually have been missed. Second, no information is available on long-term medical treatment such as statin therapy or ACE-inhibition with their suggested anti-inflammatory effect[19,20] which might have influenced patients' outcome. Accordingly, we recognize that there was information bias in our data. However, it is rather unlikely that this would have resulted in a differential bias between patients with or without elevated biomarker levels. In this respect, it should be emphasized that the investigators who collected long-term follow-up (EB, TL) were blinded for any information on baseline data (including biomarker levels).

Using such a simple risk model with dichotomized biomarker data, quantitative information might be lost as higher levels for one or another biomarker could correspond with different individual risk. However, by using simple cut-off values, physicians might be able to calculate more easily the patients' risk. With the help of this model in conjunction with other biomarkers such as NT-proBNP, biomarkers of neurohumoral activation and clinical variables, we might be able to provide tailored treatment for the individual patient not only at the time hospitalization but also following discharge of patients. The threshold levels of the markers are based on exploratory analysis illustrated in previous publications. Naturally, if possible, prospective validation should be performed. Finally, it remains to be determined if assessment of these biomarkers at discharge or at even later time points in stabilized patients, might demonstrate an even closer

relationship between abnormal biomarker levels and the risk for future cardiovascular events.

Conclusion

In patients with acute coronary syndromes, long-term adverse cardiac outcome can be predicted using biochemical markers characterizing distinct processes of the underlying inflammatory pathophysiology in atherosclerotic lesions which are independent of the myocardial damage during the initial cardiac event.

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Chapter Four

Bleeding events with abciximab in acute coronary syndromes without early revascularization, an analysis of GUSTO IV–ACS

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Abstract

Background

The glycoprotein IIb/IIIa receptor antagonist abciximab reduces the risk of thrombotic complications with percutaneous coronary intervention, but also has been associated with higher bleeding rates.

Methods

In GUSTO IV–ACS abciximab, either a 24 hour or 48 hour infusion, was compared to placebo in 7800 patients with an acute coronary syndrome. During study drug administration 2% of the patients underwent a revascularization procedure.

Results

In 1507 patients (19.3%) bleeding according to the TIMI classification was observed in hospital or within 7 days. Eighty-nine patients (1.2%) had a major bleed, including 8 intracranial hemorrhages. In 215 patients (2.8%) a minor bleed and in 1194 (15.3%) an insignificant bleed was reported. Bleeding was more frequent in patients receiving 48 hour of abciximab. Spontaneous bleeding was seen in 911 patients (11.7%). The other 596 patients had a bleeding event in conjunction with a procedure. The most significant predictors for bleeding by multivariable analysis were: use of LMWH, duration of abciximab infusion, region of hospitalization, performance of CABG or PCI, advanced age and female gender. For major bleeding the predictors were performance of CABG or PCI, long duration of abciximab administration and advanced age.

Conclusion

Treatment with abciximab in NSTE ACS patients is safe since major bleedings and stroke are rare and the majority is clinically manageable or has little clinical consequences. Guidelines for use of abciximab in combination with other antithrombotic agents developed for PCI should also be respected in ACS. Specific dosing guidelines for combination with LMWH must be developed for patients who subsequently will undergo a PCI.

Introduction

The process of fissuring of an atherosclerotic plaque with subsequent thrombosis due to platelet aggregation is the most frequent cause of acute coronary syndromes (ACS) [1,2]. Aspirin has an important role in treatment of ACS [3,4]. However its overall antithrombotic activity is relatively modest. The glycoprotein IIb/IIIa blockers, which inhibit the final common pathway of platelet aggregation, provide more selective potent antithrombotic therapy. Based on the available evidence this class of drugs, and particularly abciximab, should be considered for use in all patients undergoing percutaneous coronary intervention (PCI) [5,6]. However the evidence for use in patients with ACS not undergoing PCI is less conclusive [7,8] especially since GUSTO IV-ACS did not show any benefit of abciximab in such patients [9]. Furthermore in GUSTO IV-ACS as in other ACS trials treatment with a glycoprotein IIb/IIIa receptor blocker was associated with modest but increased bleeding risk. In this report we present a detailed analysis of bleeding as observed in GUSTO IV-ACS, emphasizing those patient characteristics associated with an increased risk for spontaneous and/or procedure related bleeding.

Methods

Patients and treatment

The GUSTO IV-ACS study has been described in detail [9]. Briefly, 7800 patients with an acute coronary syndrome without persistent ST-segment elevation were recruited. They had one or more episodes of angina at rest within the preceding 24 hours, with either a positive cardiac troponin T or I test and/or at least 0.5 mm of transient or persistent ST-segment depression. This episode should be distinct from any recent acute myocardial infarction. Excluded were patients who underwent percutaneous coronary intervention within the previous 14 days; patients with planned percutaneous coronary intervention or coronary bypass surgery within 30 days after enrolment; and patients having a (risk for) active internal -, or cerebral bleeding. Other exclusion criteria were allergy to abciximab or other murine proteins or body weight over 120 kg. The medical ethics committees of the participating hospitals approved the protocol and the patients gave written informed consent.

Patients were randomly assigned to one of three treatment groups: abciximab 0•25 mg/kg bolus followed by a 24 hour infusion of 0.125 µg/kg per min up to a maximum of 10 µg/min followed by 24h of placebo infusion, the same bolus and infusion of abciximab for a total duration of 48h; or matching placebo bolus and 48h infusion. All patients were to receive aspirin, unfractionated heparin as a 70 IU/kg bolus (max. 5000 IU) followed by a continuous infusion of 10 IU/kg/hour (max. 800 IU/hour) to maintain

APPT between 50 and 70 seconds. Low molecular weight heparin (Daltaparin) was given to approximately 1000 patients in a substudy in a fixed dose of 120 IU/kg to a maximum of 10.000 IU 10. Daltaparin or placebo was given for 5–7 days, or until a revascularization procedure or discharge. Patients were analyzed based on their treatment during these first days (UFH or LMWH). Concomitant therapy with β-blockers was strongly recommended. Use of all other cardiac medications was left to the discretion of the investigator.

Coronary angiography was not recommended within 12h after the completion of study-agent infusion unless driven by refractory ischemia. If PCI was required masked crossover from placebo to active therapy with abciximab was provided at selected study sites that had facilities for such interventions. In all other sites, study drug was to be discontinued.

Bleeding was classified as major, minor, or insignificant by the thrombolysis in myocardial infarction (TIMI) criteria11. Spontaneous or procedure-unrelated bleeding events and bleeding events during cardiac catheterization without and with PCI or CABG were considered separately. An independent neurologist who was not aware of treatment assignment adjudicated all suspected occurrences of stroke or intracranial hemorrhage.

Data analysis

Data were analyzed according to actually treatment received. Continuous variables were summarized by median values with corresponding 25th and 75th percentiles. Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics between the treatment groups were evaluated by Fisher's exact tests. Kaplan-Meier analyses were performed to evaluate the incidence of events over time. Logistic regression modelling was applied to evaluate the relation between a number of clinical characteristics and the incidence of bleeding events. All relevant variables were included in the multivariable analysis irrespective of the result of the univariable analysis. The multivariable models were constructed by backward deletion of the least significant characteristics, while applying a threshold of significance of p= 0.10. Results are presented as odds ratios and corresponding 95% confidence intervals.

Results

A total of 7800 patients were enrolled in GUSTO IV–ACS, 2599 patients (33.3%) actually received placebo, 2588 patients (33.2%) a bolus and 24h infusion and 2613 (33.5%) a bolus and 48h infusion of abciximab. Eight patients did not receive their assigned medication. Two patients allocated to placebo received a 24 hour and a 48 hour infusion, 3 patients allocated to 24 hour infusion received 48 hour infusion in stead and 3 patients allocated to 48 hour infusion received placebo. Of these 8 patients only one receiving placebo had a major bleed. Any bleeding was reported in 1507 patients (19.3%). In the placebo group, the 24h and the 48h infusion group

bleeding rates were 10.3%, 21.3% and 26.4% patients respectively (p<0.001). Most bleedings were judged insignificant. A major bleeding event occurred in 98 patients (1.2%): 48 (1.8%) with 48 hours of abciximab, 26 (1.0%) with 24 hours of abciximab and 24 (0.9%) with placebo (p<0.0001, for 48 hour infusion against placebo; Figure 1).

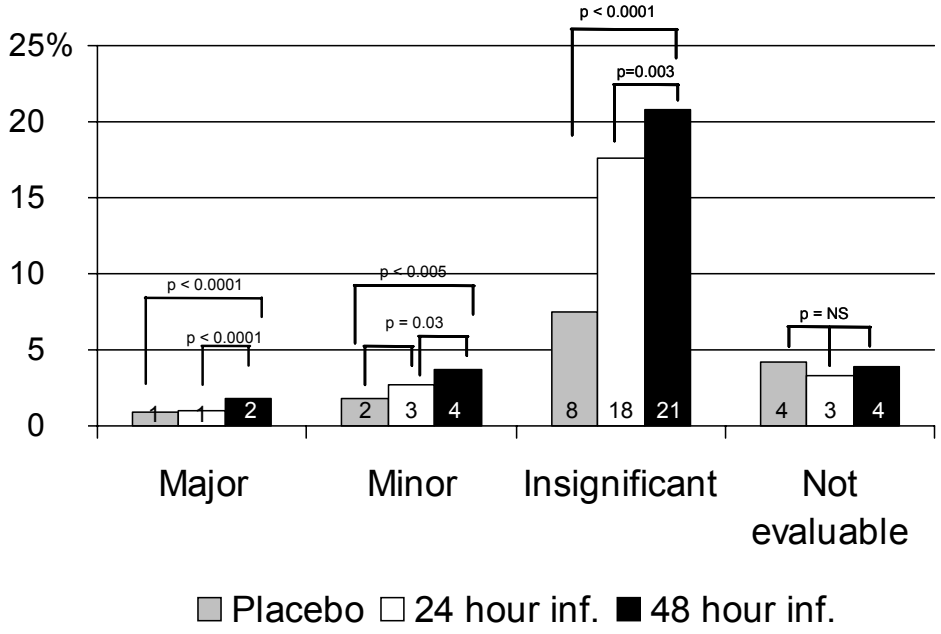

Figure 1
Percent bleeding events that occurred during hospitalization or the first 7 days after randomization according to TIMI classification severity and treatment received.

Forty-nine major bleeding events were CABG related (17 in the placebo group, 10 in the 24 hour abciximab and 22 in the 48 hour abciximab group, see Table 1) and a similar number was spontaneous. Ninety percent of all major bleedings occurred more than 60 hours after randomization and 70% more than 144 hours after randomization, thus several days after discontinuation of study medication. Yet these relatively late bleedings were more frequent in patients previously receiving a bolus and 48 hour infusion of abciximab. Eighteen patients died because of a bleeding event: 7 in placebo group and 5 and 6 in the 24h and 48h infusion group respectively. Eight patients had an intracranial hemorrhage: 1 in the placebo group, 4 in the 24h and 3 in the 48h infusion group. Minor and insignificant bleeding occurred in 1.8% and 7.5% in the placebo group, in 2.7% and 17.6% in the 24h infusion group and in 3.8% and 20.8% in the 48h infusion group respectively (Figure 1; p<0.005 for minor bleed and p<0.0001 for insignificant bleeding). In 297 patients (3.8%) TIMI score was not available. This was evenly distributed over the three treatment groups (Figure 1).

Table 1

Bleeding events in subgroups of patients according to procedure

	Major	Minor	Insignificant	Total bleeds	Not evaluable	Total per group
CABG and PCI	5	0	2	7	0	11
CABG	46	21	29	96	9	232
PCI	9	29	178	216	42	825
Catheterization only	6	35	236	277	69	1324
Patients not undergoing cath, PCI or CABG	32	130	749	911	177	5408
Total per group	98	215	1194	1507	297	

Data presented are absolute numbers

Most bleeding was spontaneous, however major and minor bleeding were more frequently associated with procedures (Figure 2), particularly with PCI or CABG (Figure 3). In 256 patients (3.3%) one or more units of packed cells or platelets were transfused. In the placebo group in 2.4% and in the 24h and 48h infusion group this was 3.3% and 4.2% respectively (p = 0.04 for placebo vs. 24h infusion, and p=NS between active treatment groups). Of the 98 patients with a major bleeding 77 (78.6%) received a transfusion and in the minor or insignificant bleeding group this was 23.7% and 5.3% respectively. Patients without documented bleeding received a transfusion in 0.9%.

Analysis for all bleeding events

Significantly more bleeding was seen in female and elderly patients. Other descriptive variables associated with bleeding events were prior heart failure (OR: 1.5; 95% CI: 1.2-1.8), history of stroke or TIA (OR: 1.5; 95% CI: 1.1-1.9), history of revascularization (OR: 1.2; 95% CI: 1.0-1.4), ST-segment depression of more than 0.5 mm (OR: 1.2; 95% CI: 1.1-1.4), positive troponin T (OR: 1.2; 95% CI: 1.1-1.4) or an evolving myocardial infarction at enrolment (OR: 1.1; 95% CI: 1.0-1.3) as well as black race (OR: 3.0; 95% CI: 1.8-4.8 in a small group of 64 patients). The duration of abciximab infusion was related to a higher bleeding risk as were other antithrombotic drugs before or during hospitalization like prior aspirin use (OR: 1.4; 95% CI: 1.2-1.6), prior use of oral anticoagulants (OR: 2.7; 95% CI: 1.4-5.0), use of the ADP-inhibitors ticlopidine or clopidogrel and concomitant use of low molecular weight heparin (LMWH) or dextran. Similarly, patients receiving inotropics or intravenous nitrates during hospitalization had a higher bleeding risk. Patients with a high creatinine level (> 130 µmol/l in female, and > 160 µmol/l in male patients) had 2.3 times higher risk of bleeding (95% CI: 1.8-3.0). Finally, higher bleeding risk was observed in patients from North America or Australia, while lowest bleeding rates occurred in Israel and Eastern Europe.

Patients with lower body weight (less than 50 kilograms) did not show a significantly higher risk of bleeding (OR: 1.29; 95% CI: 0.84-1.96). Interestingly patients who were smoking had fewer bleeding events.

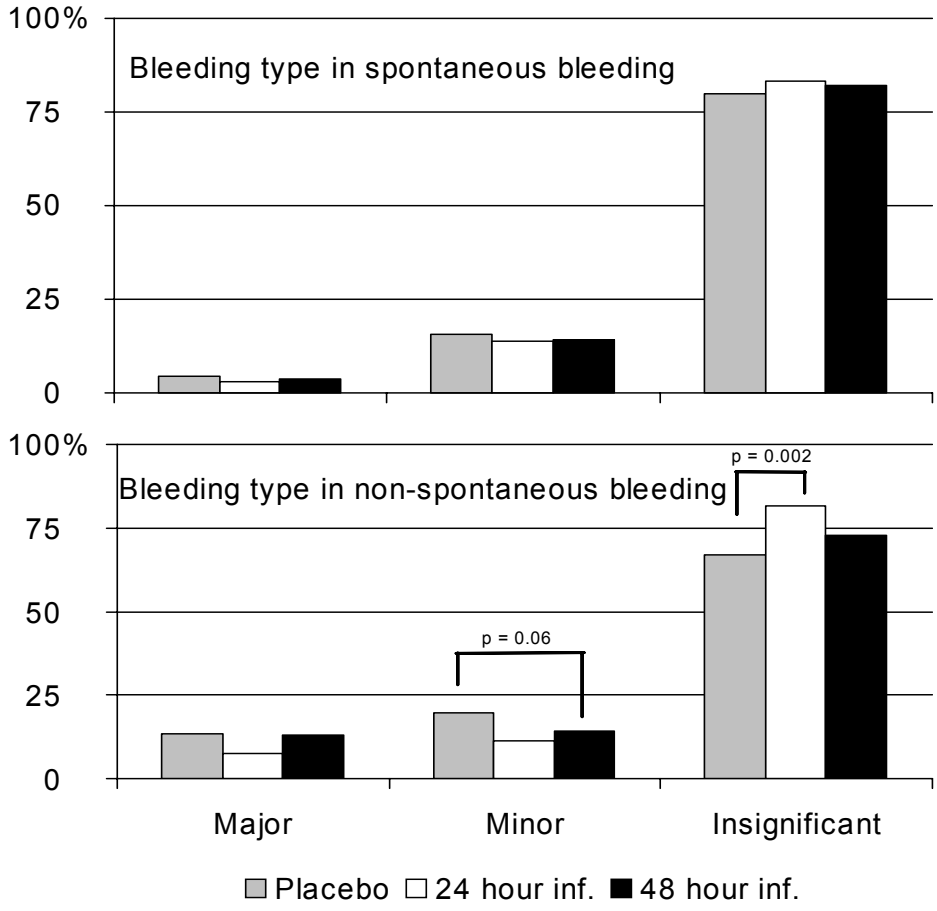

Figure 2
Percent bleeding events that occurred during hospitalization or the first 7 days after randomization according to TIMI classification severity and treatment received in patients with spontaneous and non-spontaneous bleeding

Multivariable analysis revealed administration of LMWH as the strongest predictor of bleeding (OR: 5.1; 95% CI: 4.3-6.1; X^2: 314). Patients randomized to 48 hour infusion of abciximab had a 3.9 time (95% CI: 3.3 – 4.6; X^2: 282) higher risk for bleeding as compared to patients receiving placebo, while in patients receiving 24 hour infusion this risk was 2.8. Also the region of hospitalization was associated with increased bleeding risk (X^2: 250). Patients hospitalized in North America or Australia had a 4.8 time greater risk (95% CI: 3.9 – 5.8) of bleeding as compared to patients admitted in Israel or Eastern Europe. Again weight was not a significant risk factor for bleeding (OR: 0.7; 95% CI: 0.5-1.3). Cardiac catheterization without intervention was eliminated as risk factor after adjustment in the multivariable model.

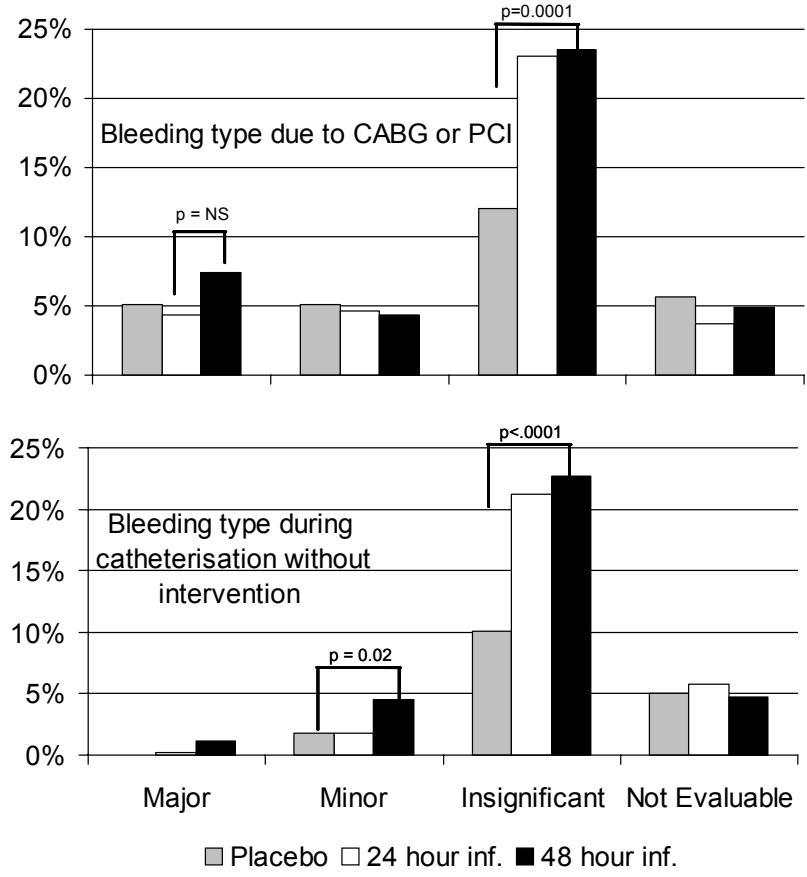

Figure 3

Percent bleeding events that occurred during hospitalization or the first 7 days after randomization according to TIMI classification severity and treatment received in patients that underwent catheterization only or underwent PCI or CABG.

Analysis for patients receiving any transfusion.

Transfusions were given particularly in elderly patients, patients with a history of heart failure or diabetes and in patients hospitalized in North America or Israel. Elevated creatinine was the most important risk factor for transfusion in the multivariable analysis (OR: 5.1 95% CI: 3.2-8.0) (table 2). With regard to the concomitant medication the most important predictor in the multivariable analysis was the use of low molecular weight heparin (OR: 2.7; 95% CI: 1.6-4.3), also significant were use of aspirin, use of dextran and i.v. nitrates. Only the longest duration of abciximab infusion was related with a significant higher transfusion risk in the univariable analysis. By multivariable analysis however both 24 hour as well as 48 hour duration of infusion were significant (table2)

Table 2

Unadjusted and adjusted odds ratio's for need for any transfusion in patients not undergoing any invasive procedure

		Patients	Bleeding rate	Unadj. OR	(95% CI)	Adj. OR	(95% CI)	$\chi 2$
Baseline Characteristics		(%)	(%)					
Age	≥ 70 yrs.	57.4	4.3	3.7	2.5 - 5.4	2.8	1.8 - 4.2	23.6
	< 70 yrs.	42.6	1.2					
Creatinine elevated	(Y)	4.5	14.2	8.3	5.5 - 12.5	5.1	3.2 - 8.0	47.6
	(N)	95.5	2.0					
Diabetes	(Y)	22.6	4.4	2.3	1.6 - 3.3	1.6	1.1 - 2.3	5.2
	(N)	77.4	1.9					
Heart failure	(Y)	8.8	6.8	3.5	2.3 - 5.2	1.9	1.2 - 3.1	8.4
	(N)	91.2	2.0					
USA or Israel		12.7	4.2	1.9	1.3 - 2.9	2.1	1.3 - 3.4	8.6
Rest of the world		87.3	2.2					
Treatment								14.0
Placebo		33.0	1.6	1		1		
24 hour inf.		33.2	2.7	1.2	0.8 - 1.6	2.1	1.3 - 3.4	
48 hour inf.		33.8	3.2	1.5	1.1 - 2.1	2.3	1.4 - 3.8	
Concomitant medication After randomization								
Aspirin	(Y)	97.2	2.4	0.4	0.2 - 0.8	0.4	0.2 - 0.8	5.9
	(N)	2.8	6.0					
Dextran	(Y)	0.1	28.6	15.8	3.0 - 82.4	18.0	2.4 - 133.5	8.0
	(N)	99.9	2.5					
Nitrates i.v.	(Y)	59.9	3.0	1.8	1.2 - 2.6	2.0	1.3 - 3.0	11.1
	(N)	40.4	1.7					
LMWH	(Y)	11.4	4.4	2.0	1.3 - 3.1	2.7	1.7 - 4.3	16.7
	(N)	88.6	2.3					

* : > 130 µmol/l in female, and > 160 µmol/l in male patients

Multivariable analysis for spontaneous (major or minor) bleeding events

After adjustment the most important risk factor for any spontaneous bleeding was concomitant therapy with low molecular weight heparin (OR 6.6; 95% CI: 5.3 – 8.4, X^2 :261) followed by long infusion of abciximab (table 3). The most important risk factors for spontaneous major or minor bleeding were age and treatment with abciximab (table 4). Patients who were 70 years or older had a 3.1 time greater risk of major or minor bleeding (95% CI: 2.2 – 4.5) than younger patients. For patients receiving abciximab for 48 hours the risk was 3.2 times higher (95% CI: 2.0 – 5.0) compared to placebo.

Table 3.

Unadjusted and adjusted odds ratio's for spontaneous bleeding events

			Patients	Bleeding rate	Unadj. OR	(95% CI)	Adj. OR	(95% CI)	χ2
Baseline Characteristics			(%)	(%)					
Gender -	female		41.3	19.4	1.3	1.1 - 1.6	1.5	1.3 - 1.8	23
	male		58.7	16.0					
Age	≥ 70 yrs.		42.7	23.4	2.1	1.8 - 2.4	1.7	1.4 – 2.0	39
	< 70 yrs.		57.3	12.9					
Creatinine elevated*	(Y)		4.5	34.5	2.6	2.0 - 3.5	2.2	1.6 – 3.1	24
	(N)		95.5	16.7					
Region									101
	USA		9.7	29.8	2.2	1.8 - 2.7	3.7	2.9 – 4.8	
	W Europe		42.8	22.8	1.9	1.7 - 2.2	1.5	1.2 – 1.8	
	Rest world		46.5	9.0					
Treatment									226
Placebo			32.9	7.8	1		1		
24 hour inf.			33.4	19.2	1.2	1.0 - 1.4	3.2	2.6 – 4.1	
48 hour inf.			33.7	25.0	2.1	1.8 - 2.5	4.8	3.8 – 6.0	
Concomitant medication									
Before randomization									
ADP-inhibitors		(Y)	2.9	23.8	1.5	1.0 - 2.2	1.6	1.1 – 2.5	5
		(N)	97.1	17.2					
Anticoagulants		(Y)	0.6	41.4	3.3	1.6 - 7.1	3.4	1.4 – 8.2	7
		(N)	99.4	17.3					
After randomization									
LMWHeparin		(Y)	11.2	47.5	5.7	4.8 - 6.9	6.6	5.3 – 8.4	261
		(N)	88.8	13.6					
Dextran IV		(Y)	0.1	57.2	6.3	1.4 - 28.4	9.1	1.9 – 44.1	8
		(N)	99.9	17.4					
Inotropics		(Y)	1.9	36.0	2.7	1.8 - 4.1	2.1	1.3 - 3.4	10
		(N)	98.1	17.1					
β – blockers		(Y)	81.1	17.0	0.9	0.7 – 1.0	0.8	0.6 – 0.9	7
		(N)	18.9	19.3					

* : > 130 µmol/l in female, and > 160 µmol/l in male patients

Table 4

Adjusted and unadjusted odds ratio's for spontaneous major and minor bleeding events

		Patients	Bleeding rate	Unadj. OR	(95% CI)	Adj. OR	(95% CI)	$\chi 2$
Baseline Characteristics		(%)	(%)					
Age ≥ 70 yrs.		42.6	4.9	3.1	2.2 - 4.4	3.1	2.2 – 4.5	40
< 70 yrs.		57.4	1.6					
Creatinine elevated*	(Y)	4.5	2.8	2.8	1.7 - 4.7	1.9	1.1 – 3.2	5
	(N)	95.5	7.5					
Black	(Y)	0.6	15.6	6.1	2.3 - 16.2	5.0	1.7 – 14.7	9
	(N)	99.4	2.9					
Duration randomization	(Y)	39.3	2.3	0.7	0.5 - 0.9	0.6	0.4 – 0.8	8
to treatment> 6 hr.	(N)	60.7	3.5					
Region								
USA		10.0	5.9	2.3	1.5 - 3.4	2.0	1.3 – 3.1	10
Rest of world		90.0	2.7					
Treatment								28
Placebo		33.0	1.5	1		1		
24 hour inf.		33.2	3.1	1.1	0.8 - 1.5	2.2	1.4. – 3.5	
48 hour inf.		33.8	4.3	1.9	1.4 - 2.6	3.2	2.0 – 5.0	
Concomitant medication								
After randomization								
Inotropics	(Y)	2.0	12.7	5.1	2.8 - 9.1	3.6	1.9 – 6.6	16
	(N)	98.0	2.8					

* : > 130 µmol/l in female, and > 160 µmol/l in male patients

Multivariable analysis for major and minor bleeding events in patients undergoing invasive procedures

The strongest predictor of bleeding in this group of patients was the type of invasive procedure, with the highest risk in patients undergoing CABG, particularly when PCI preceded the CABG (11 patients). PCI or catheterization alone were not significant predictors of major or minor bleeding. Treatment allocation was not a strong predictor for procedure related bleeding. Patients receiving inotropics had a 9.4 times greater risk (95% CI: 5.3 – 16.9) of bleeding as compared to patients not receiving inotropics. Hyperlipedemia was a significant but protective risk factor for major or minor bleeding (OR 0.6; 95% CI: 0.4 – 0.9, X^2: 6 - Table 5).

Discussion

In this large trial of patients with ACS, major and significant minor bleeding were infrequent (1.3 and 2.8%), while bleeding judged to be clinical insignificant occurred in 15.3% of the patients. Administration of abciximab did increase bleeding risk, particularly when administrated for 48 hours. Bleeding occurred especially in patients undergoing coronary procedures and in patients receiving other antithrombotic medication. Furthermore bleeding risk was increased in elderly and female patients, in those with diabetes and in patients hospitalized in North America or Australia.

The rates of major bleeding or major and minor bleeding events were similar to the rates observed in other trials using other glycoprotein IIb/IIIa receptor blockers for ACS. For example major bleeding was reported in 1.1% of patients in PRISM-plus. In contrast, in PURSUIT 10.6% of patients suffered a major bleeding event, but in this trial investigators were not advised to delay catheterization. Stroke was infrequent in these trials and not significantly increased with abciximab or other glycoprotein IIb/IIIa receptor blocker. Similarly stroke risk was not significantly increased in patients receiving abciximab while undergoing percutaneous coronary intervention [12].

GUSTO IV-ACS was the first large trial using abciximab for periods longer than 24 hours. The 48 hour infusion lead to a significant higher bleeding rate (Figure 1) and was the second most significant predictor in the multivariable analysis for all bleeding events as well as for spontaneous bleeding (table 3). CABG with or without preceding PCI was associated with major or minor bleeding (table 4). Because the trial protocol allowed a "masked crossover" of placebo to active therapy bleeding in the context of PCI (alone) may be underestimated. Most major bleeding occurred after trial medication was stopped for more than 24 hours. In particular it is noteworthy that 48 hour administration of abciximab was associated with an increased risk for procedure related major and minor bleeding, while most procedures were done after discontinuation of study drug.

Table 5

Unadjusted and adjusted odds ratio's for major and minor bleeding events combined in patients undergoing any invasive procedure

			Patients	Bleeding rate	Unadj. OR	(95% CI)	Adj.OR	(95% CI)	$\chi 2$
Baseline Characteristics			(%)	(%)					
Age	≥ 70 yrs.		32.6	9.7	2.2	1.6 - 3.0	2.0	1.4 - 2.9	12
	< 70 yrs.		67.4	4.7					
Hyperlipedemia		(Y)	35.0	4.9	0.7	0.5 - 1.0	0.6	0.4 - 0.9	6
		(N)	65	6.9					
Region									
	USA		23.6	9.7	2.0	1.3 – 2.7	1.8	1.2 - 2.6	7
	Rest of the world		76.4	5.3					
Treatment									9
Placebo			34.0	5.4	1		1		
24 hour inf.			33.2	5.0	0.7	0.5 - 1.0	1.1	0.6 - 1.8	
48 hour inf.			32.8	8.6	1.7	1.2 - 2.4	2.0	1.3 - 3.2	
Concomitant medication									
After randomization									
	Inotropics	(Y)	3.1	52.0	21.3	13.0 - 34.9	9.4	5.3 - 16.9	55
		(N)	96.9	4.8					
	Nitrates IV	(Y)	65.5	7.7	2.1	1.4 - 3.2	1.8	1.2 - 2.9	7
		(N)	34.5	3.8					
Procedures									
Only cath done			55.4	1.7	1		1		
PCI			34.5	4.6	0.6	0.4 – 0.9	1.2	0.8 - 2.0	1
CABG, without cath or PCI			9.7	28.9	10.0	7.0 – 14.4	8.4	5.3 - 13.3	80
PCI and CABG			0.5	45.5	12.8	3.8 – 42.3	14.6	3.3 - 65.3	12

This is in agreement with the known prolonged effect of abciximab on platelet aggregation, which gradually weans over 1 to 2 weeks after administration[13, 14]. Thus in patients treated with abciximab in the preceding 2 weeks, monitoring of platelet function prior to revascularization procedures and appropriate adjustment of other antithrombotic medication should be considered. Nevertheless it should be appreciated that in patients treated with abciximab life threatening bleedings are rare and that bleeding can be managed with the administration of fresh platelets.

Concomitant therapy with other antithrombotic agents increased bleeding risk in the present trial as well as in previous trials. This has been appreciated by the investigators since EPIC, the first large trial with abciximab, in patients undergoing percutaneous coronary intervention[15]. The high rate of major bleeding in that trial (14%) led to reduction in dose of concomitant unfractionated heparin therapy. It also led to better care of vascular access sites, which resulted in less excess bleeding in subsequent trials[16, 17]. Bleeding was not increased in the recent EPISTENT[18] trial. Unfortunately clinicians have not yet sufficiently understood and adapted these recommendations in their practice as is evident from the increased bleeding rates with abciximab in GUSTO IV-ACS. For example excess bleeding was observed in a small number of patients receiving Dextran in the present study. This increased risk of combining abciximab and other glycoprotein IIb/IIIa receptor blockers with Dextran was recognized and use of Dextran was prohibited in the study protocol. Yet, apparently some investigators were not sufficiently aware of these facts.

Concomitant therapy with LMWH was associated with an increased bleeding risk, also after adjustment for confounding factors[10]. However LMWH was not associated with minor or major bleeding. Apparently most LMWH associated bleeding events were small or modest hematoma's caused by the subcutaneous injections of dalteparin. The NICE 4 trial examined the combination of abciximab and a reduced dose enoxaparin 0.75 mg/kg (another LMWH) during PCI. In this trial the reduced dose appeared to be associated with a lower incidence of bleeding as compared to the standard dose enoxaparin (1.0 mg/kg) that was given in the NICE 1 trial, although in the latter trial no abciximab was given[19]. In future studies and in clinical practice, adjusted low dosages of LMWH should be used in combination with glycoprotein IIb/IIIa receptor blockers similar to the reduced dose and APTT target for unfractionated heparin. Another reason for dose adjustment of low molecular weight heparin could be renal function as expressed by creatinine, since spontaneous bleeding was observed particularly in patients with a high creatinine level. This might be due to lower renal excretion rates of daltaparin. Reduction of the dose of antithrombotic agents should also be considered in elderly patients, similar to recommendations for thrombolytic regimens for patients having a myocardial infarction[20, 21].

In GUSTO IV-ACS no benefit was observed of abciximab in patients with ACS, not undergoing early revascularization. Accordingly such therapy, and especially an infusion for 48 hours, should not be recommended, unless

while preparing for coronary intervention in patients with documented coronary artery disease[15]. Nevertheless, this trial provides additional insight in bleeding risk in patients receiving a combination regimen of different antithrombotic drugs. The addition of more drugs with different modes of action in the future might further improve outcome in selected patient groups, but will most likely further increase bleeding risk[22].

Patients who were given inotropics had an increased bleeding risk for minor and major spontaneous bleeds as well as procedure related minor and major bleeding. This increased risk remained after adjustment. Inotropics were given significantly more in those patients undergoing a CABG but not in conjunction with catheterization or PCI. Therefore part of the higher bleeding risk associated with inotropics could be explained by surgery related complications, however not the spontaneous bleeding. Here a possible explanation could be the weak condition of the patient or the need of invasive monitoring or invasive support when in shock.

Bleeding and as mentioned thrombocytopenia may lead to transfusions of either packed cells or platelets. It should be noted that 5.3% of the patients received any transfusion. Age and use of LMWH were the main predictors for transfusion, which yield another argument for adjustment of LMWH dosages (table 2). Risks for hepatitis B, C or HIV infection are 1 per 63.000, 103.000 or 493.000 donations respectively[23]. So although the risk for infection is small, reduction in dose of some drugs used in combination regimens should be considered. Furthermore additional education of physicians and nurses about the benefits and risk of such combination regimens is required as well as careful adherence to established treatment guidelines.

The geographical difference in bleeding risk is a puzzling finding and cannot easily be explained since it remained highly significant even after correction for different variables. The excess of bleeding in some countries might be related to: the intervention rates, the experience of the interventional cardiologists, interpretation of hematoma size (for example, a similar hematoma might be considered minor in the US and insignificant in Eastern Europe), or the care for the groin and injecting dalteparin.

Conclusion

This study confirms that treatment with abciximab is safe with few major bleedings, although there is a high number of bleeding events, of which the majority has little clinical consequences and is clinically manageable. When additional interventions are performed careful attention with regard to the procedure and concomitant anti-thrombotic therapy may reduce the risk of bleeding events. Also special attention should be given to older and female patients.

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Chapter Five

Prediction of 30-day mortality in patients older than 75 years with their first acute myocardial infarction

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Abstract

Objectives

This study sought predictors of mortality in patients over 75 years experiencing their first ST elevation myocardial infarction and evaluated the validity of the GUSTO-I and TIMI risk models.

Background

The validity of the GUSTO-I and TIMI 30-day mortality risk models, created in clinical trial datasets, is unknown for elderly patients seen in common clinical practice.

Methods

Clinical variables, treatment and mortality data from 433 consecutive patients with a first STEMI were collected. Univariable and multivariable logistic regression analyses were applied to identify baseline factors associated with 30-day mortality. Subsequently a model predicting 30-day mortality was created and compared with the performance of the GUSTO-I and TIMI models.

Results

After adjustment, higher Killip class was the most important predictor (OR 16.1; 95% CI:5.7-45.6). Elevated heart rate, longer time delay until admission, hyperglycemia and older age were also associated with increased risk. Patients with hypercholesterolemia had a significant lower risk (OR 0.46; 95% CI:0.24-0.86). Discrimination (c-statistic: 0.79, 95% CI:0.75-0.84) and calibration (Hosmer-Lemeshow: 6, p=0.5) of our model were good. The GUSTO-I and TIMI risk scores produced adequate discrimination within our dataset (c-statistic: 0.76, 95% CI:0.71-0.81; and 0.77, 95% CI:0.72-0.82, respectively), but calibration was not satisfactory (HL 21.8, p=0.005 for GUSTO-I, and HL 20.6, p=0.008 for TIMI).

Conclusion

Thirty-day mortality in patients over 75 years old with their first STEMI depends on several factors, among which initial clinical and hemodynamic status are the most important. The GUSTO-I and TIMI models are insufficiently adequate for providing an exact estimate of 30-day mortality risk.

Introduction

Patients enrolled in clinical trials are usually not representative of the average patient population seen in clinical practice. The applicability of these trial results as well as their derived risk-evaluation models for patients seen in common clinical practice can be questioned. In clinical trials studying treatment strategies for patients presenting with ST-segment elevation myocardial infarction, including fibrinolysis or percutaneous intervention, average age is around 65 years [1–7]. Patient selection based on age is either dictated by explicit trial inclusion and exclusion criteria or by the decision of the treating physician, who usually avoid enrolling vulnerable elderly patients due to the concern of suspected high risk of side effects. In this study initially we sought predictors of mortality in patients over 75 years experiencing their first STEMI.

At the present time the GUSTO-I [8] and TIMI [9] risk evaluation models are widely used to estimate the risk of 30-day mortality after admission for STEMI. Secondly, we aimed to develop a 30-day mortality risk prediction model for consecutively admitted patients with a STEMI older than 75 years. We also evaluated to what extent these models, developed in clinical trial datasets, can be used to adequately estimate mortality risk in the elderly patient population.

Methods

Patients

The study population consisted of all 433 patients of 75 years or older, who were admitted consecutively from 1995 to 2000 to the coronary care unit of the Gregorio Maranon University Hospital, Madrid, Spain, with a definite diagnosis of first ST-segment elevation / left bundle branch block myocardial infarction. Patients were part of the PPRIMM75 (Pronóstico del PRimer Infarto de Miocardio en Mayores de 75 años, Prognosis of a first myocardial infarction in patients older than 75 years) registry, which is described in detail previously[10-12] Baseline characteristics were collected directly from clinical records. Patients were managed according to the discretion of the treating physician, and either received intravenous fibrinolysis, percutaneous coronary intervention, or no reperfusion therapy. Thirty-day mortality was assessed by hospital chart review and telephone calls for cases that were discharged alive.

Data analysis

Continuous data are presented as mean value and standard deviation (SD), whereas dichotomous data are presented as numbers and percentages. Differences in baseline characteristics between patients who died

within 30-day and those who survived were evaluated by unpaired Student's t-tests and Chi-square tests, as appropriate.

Univariable and multivariable logistic regression analyses were applied to identify baseline factors that were associated with 30-day mortality. We considered a broad range of patient demographic and clinical baseline characteristics, such as age, gender, medical history (hypertension, diabetes mellitus, hypercholesterolemia, smoking, prior angina, chronic heart failure, prior stroke, peripheral artery disease), delay of intervention, and clinical characteristics at admission (systolic blood pressure, heart rate, glucose levels, location of MI, number of leads with ST-segment elevation on the ECG, Killip class, and type of reperfusion therapy). For multivariable analysis, we entered variables associated with a p-value smaller than 0.2 in the univariable analysis. Significant variables in the multivariable analysis ($p<0.05$) remained in the final model. We report unadjusted as well as multivariable adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Because systolic blood pressure and heart rate were missing in about 20% of patients (91 for systolic blood pressure, and 90 for heart rate) and excluding patients with missing data could lead to biased risk estimates(13), we imputed these important predictors using the EM (estimated mean) procedure in SPSS. All multivariable analyses were performed on a dataset that included imputed variables.

The model created in our dataset was compared with two well-known predictive models of 30-day mortality in STEMI patients(8,9). Both in GUSTO-I and in the TIMI model average age was 62 years. In GUSTO-I model interquartile ranges were 52 to 70 years and in the TIMI model 13.7% of the patients were over 75 years. From the GUSTO model the 5 variables that explained 90% of the 30-day mortality incidence (age, Killip class, systolic blood pressure, heart rate, and location of MI) were available in our dataset and used for comparison. The remaining and less important variables prior angina, diabetes, hypertension smoking and previous stroke were also available in our dataset. The TIMI model used 10 variables (age, prior angina, Killip class, heart rate, anterior MI or left bundle branch block, systolic blood pressure, diabetes mellitus, history of hypertension, weight and timing of fibrinolytic treatment) to predict 30-day mortality. Patient weight and the time from onset to fibrinolytic treatment were not available (note that only part of the patients received fibrinolysis).

The performance of the multivariate models was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish mortality from survival. It was quantified by a measure of concordance, the c-statistic. For binary outcomes the c-statistic is identical to the area under the receiver operating characteristic (ROC) curve. The c-statistic lies between 0.5 and 1, and is better if closer to one(14). Calibration refers to whether the predicted risks of 30-day mortality agree with the observed risk frequencies. Calibration was measured with the Hosmer-Lemeshow (H-L) goodness-of-fit test(15).

To avoid overestimation of the performance measures, we internally validated the model created in our dataset, the GUSTO model, and the TIMI model with the use of bootstrapping. This method evaluates the performance of models in bootstrap samples, which were drawn with replacement from the original dataset, and have the same size as the original sample size. The procedure was repeated 100 times. Bootstrapping yields stable and nearly unbiased estimates of performance(12) In our analyses, the optimism was negligible and we presented the original estimates of performance. Analyses were performed in SPSS 10.0 and S-PLUS 2000 (Insightful Inc, Seattle WA, USA).

Results

Complete 30-day follow-up was obtained for all 433 patients. A total of 132 (31%) patients died. There were relevant differences in baseline characteristics between patients who died and those who survived (Table 1)

Univariable analysis

As compared to 30-day survivors, patients who died were older and more often men (Table 1). Patients who died presented later after onset of symptoms than survivors, had a higher heart rate, a lower blood pressure, and more often were in Killip class II to IV. Furthermore, patients who died less often had hypercholesterolemia, and less often were current or former smokers; also their glucose level at admission was higher. There was no relation between infarct location and 30-day mortality.

PPRIMM75 model

Baseline variables that remained significantly associated with mortality after multivariable adjustment included Killip class, glucose level at admission, delay to admission>24 hours , heart rate, age and hypercholesterolemia (Table 2). Killip class IV was highly associated with 30-day mortality (X2 = 29.5). The discrimination of our model was good (Figure 1a; c-statistic 0.79, 95% CI 0.75-0.84), and the calibration was adequate (Figure 1b; H-L test 6, p-value = 0.6)

Predictive accuracy of the GUSTO and TIMI models

Among the 5 variables that compose the core of the GUSTO model, Killip class IV was strongly associated with 30-day mortality (X2 = 29.0, Table 2), followed by older age and higher heart rate. Systolic blood pressure and infarct location were not significantly associated with 30-day mortality. The GUSTO model adequately discriminated between survivors and non-survivors in our study population of elderly patients (Figure 2a; c-statistic 0.76, 95% CI 0.71-0.81). However, the predicted 30-day mortality risks based on the GUSTO model did not agree with the observed risks.

Table 1

Distribution of clinical variables of patients according to survival status

	Died at day 30 (N=132)	Survived at day 30 (N=301)	Unadjusted OR (95% CI)	p-value	X2
Age (per year)	82.1† (5.1)	80.4† (4.8)	1.07 (1.03, 1.12)*	.001	11.2
Men (%)	38.6	55.8	2.0 (1.3, 3.1)	.001	11.1
Location ST-segment elevation (%)					
Other location	6.8	7.0	1		
Anterior	49.2	41.9	1.2 (0.5, 2.8)	0.7	0.2
Inferior	43.9	50.8	0.9 (0.4, 2.0)	0.8	0.1
Time delay first pain to admission (%)‡					
< 6hours	65.2	71.1	1		
6 to 12hours	12.9	13.0	1.1 (0.6, 2.0)	0.8	0.1
12 to 24hours	9.1	11.3	0.9 (0.4, 1.8)	0.7	0.1
24hours or more	9.8	4.0	2.6 (1.2, 6.1)	0.02	5.6
Type of reperfusion therapy (%)					
Thrombolysis	26.5	25.2	0.91 (0.55-1.52)	0.4	0.6
PCI	29.5	36.2	0.71 (0.44-1.15)	0.1	2.2
None	43.9	38.2	1		
Killip class (%)	(%)	(%)			
I	47.0	80.1	1		
II	15.9	12.3	2.2 (1.2, 4.0)	0.01	6.6
III	8.3	5.6	2.5 (1.1, 5.6)	0.03	5.0
IV	28.8	1.6	29.5 (11.1, 78.0)	<.001	46.5
Risk factors and medical history (%)					
Diabetes mellitus	34.1	29.6	1.2 (0.8, 1.8)	0.4	0.6
Glucose at admission (per mg/dl)	226† (98)	164† (69)	1.01 (1.01, 1.01)*	<.001	40.7
Hypertension	53.8	56.1	0.9 (0.6, 1.4)	0.6	0.2
Hypercholesterolemia	15.2	31.2	0.4 (0.2, 0.7)	.001	11.4
Current smoker	12.1	21.9	0.5 (0.3, 0.9)	.02	5.8
Previous Angina	27.3	22.3	1.2 (0.8, 2.0)	0.4	0.8
Congestive heart failure	7.6	3.7	2.1 (0.9, 5.1)	0.1	2.7
Previous stroke	11.6	12.6	1.1 (0.6, 2.0)	0.8	0.1
Peripheral artery disease	12.1	13.0	0.9 (0.5, 1.7)	0.8	0.3
Physical examination at hospitalisation					
Heart rate, per bpm	84.8† (18)	76.5† (15)	1.04 (1.02, 1.05)	<.001	23.6
Systolic blood pressure per mmHg	121.8† (30)	134.7† (25)	0.98 (0.97, 0.99)	<.001	19.2
Killip class (%)	(%)	(%)			
I	47.0	80.1	1		
II	15.9	12.3	2.2 (1.2, 4.0)	0.01	6.6
III	8.3	5.6	2.5 (1.1, 5.6)	0.03	5.0
IV	28.8	1.6	29.5 (11.1, 78.0)	<.001	46.5

Dichotomous data are presented as percentages. OR: Odds Ratio. *per unit of measurement;
† mean, SD; ‡ 4 dead and 1 alive missing

Table 2

Multivariable analysis for 30 day mortality in the PPRIMM75 cohort as compared to using predictors from the TIMI[9] and GUSTO[8] model

	PPRIMM75 Adjusted OR (95% CI)	X2	TIMI Adjusted OR (95% CI)	X2	GUSTO Adjusted OR (95% CI)	X2
Age	1.06 (1.01, 1.12)	6.1	1.07 (1.02, 1.13)	8.2	1.07 (1.02, 1.13)	8.2
Hypercholesterolemia	0.46 (0.24, 0.86)	5.8				
Hypertension	NS		1.2 (0.70, 1.9)	0.3		
Previous Angina	NS		1.4 (0.82, 2.4)	1.5		
Diabetes Mellitus	NS		1.1 (0.65, 1.8)	0.1		
Heart rate, per bpm	1.02 (1.01, 1.04)	6.3	1.03 (1.01, 1.04)	8.6	1.03 (1.01, 1.04)	8.7
Systolic blood pressure, (per mmHg)			0.99 (0.98, 1.00)	1.5	0.99 (0.98, 1.01)	1.2
Glucose at admission	1.01 (1.00, 1.01)	9.3				
Killip class						
I	1		1		1	
II	1.7 (0.86, 3.2)	2.2	1.6 (0.82, 3.0)	1.8	1.7 (0.88, 3.2)	2.5
III	1.3 (0.51, 3.1)	0.2	1.6 (0.68, 3.9)	1.1	1.8 (0.74, 4.2)	1.6
IV	16.1 (5.7, 45.6)	27.2	20.5 (6.9, 60.8)	29.5	20.4 (6.9, 60.0)	29.0
Time delay first pain to admission						
Less than 6h.	1					
6 to 12h.	1.1 (0.54, 2.2)	0.1				
12 to 24h.	0.74 (0.32, 1.7)	0.5				
24h. or more	3.5 (1.4, 8.9)	6.9				
Location	NS		1.4 (0.86, 2.2)	1.8		
ST-segment elevation						
Anterior					1.2 (0.46, 3.3)	0.2
Inferior					1.2 (0.45, 3.2)	0.1
Other location					1	

OR: Odds ratios, were adjusted for the given characteristics.

Discrepancy was especially observed in patients at suspected low risk (Figure2b; H-L test 21.8; p-value = 0.005). In the applied TIMI risk model, Killip class, age and heart rate were also the most significant variables. Similar to GUSTO, the TIMI model adequately discriminated between survivors and non-survivors (Figure 3a; c-statistic 0.77, 95% CI 0.72-0.82), but also failed to accurately predict the actual level of risk (Figure 3b; H-L test 20.6; p-value = 0.008).

Discussion

We found that the main determinants of 30-day mortality in patients over 75 years of age who presented with their first myocardial infarction included higher Killip class, hyperglycemia, elevated heart rate, longer time delay until admission, and older age. Our model had a good discrimination and calibration after correcting for overfitting. Known models derived from clinical trials including younger patients (GUSTO and TIMI) do not accurately predict the observed risk on this older population.

We found that after adjustment the Killip class is the strongest predictor. The most important predictor after Killip class however is a high glucose level at admission. A number of studies reported on the detrimental effect of hyperglycemia and the importance of glycemic control with insulin in patients admitted either to the ICU [16] or with a myocardial infarction [17,18]. This relation is also seen in the elderly [19]. Hyperglycemia may be the result of the stressful condition the patient is in or a sign of latent diabetes mellitus. There is however neither in our analysis nor in the aforementioned studies an interaction between diabetes and hyperglycemia at admission for higher risk of mortality. Stress hyperglycemia may be simply a marker of large infarcts, or of a complicated clinical course associated with a strong adrenergic response. Moreover, it can cause impairment in TIMI coronary flow as a result of the prothrombotic state or endothelial dysfunction [20].

The predictive weight of age for mortality was comparable to heart rate and the time delay between first occurrence of pain and admission. The relation between treatment delay and higher mortality risk is well known [21,22]. After 12 hours and certainly after 24 hours there is a higher relative and absolute mortality risk partly due to the increased risk of intracranial bleeding when given thrombolytic therapy, especially in the elderly [23,24]. The data in the referred meta-analysis however were collected in trials including largely a patient population younger than 65 years. In the elderly, thrombolysis may be associated with a higher mortality due to the increased risk of free wall rupture, particularly when treatment is initiated after the first six hours of symptom onset [12].

Patients with a history of hypercholesterolemia had a significant lower risk in the multivariable analysis. It is possible that when these patients were already treated for a longer period with statins that the not undisputed “pleiotropic effect” might have protected them [25-27].

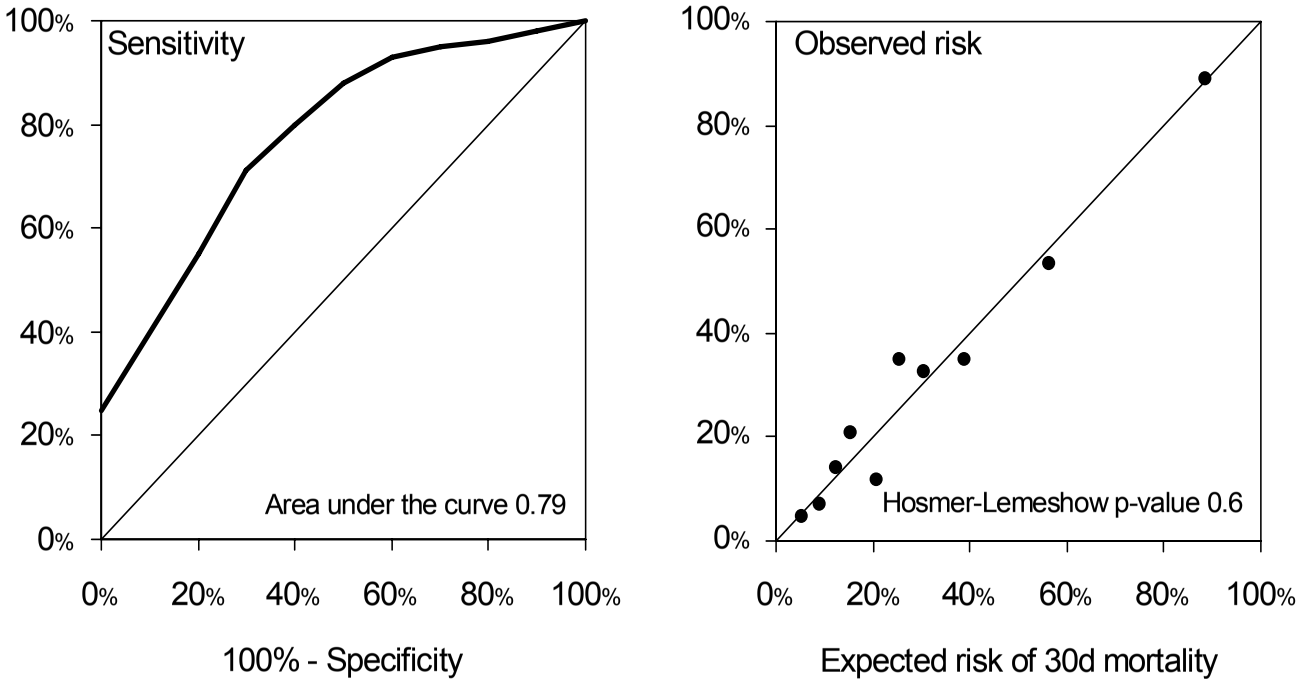

Figure 1

Receiver Operating Curve (left panel) demonstrating discrimination and a plot demonstrating calibration (right panel) of observed and predicted risk of 30 day mortality using the model created within PPRIMM75 dataset

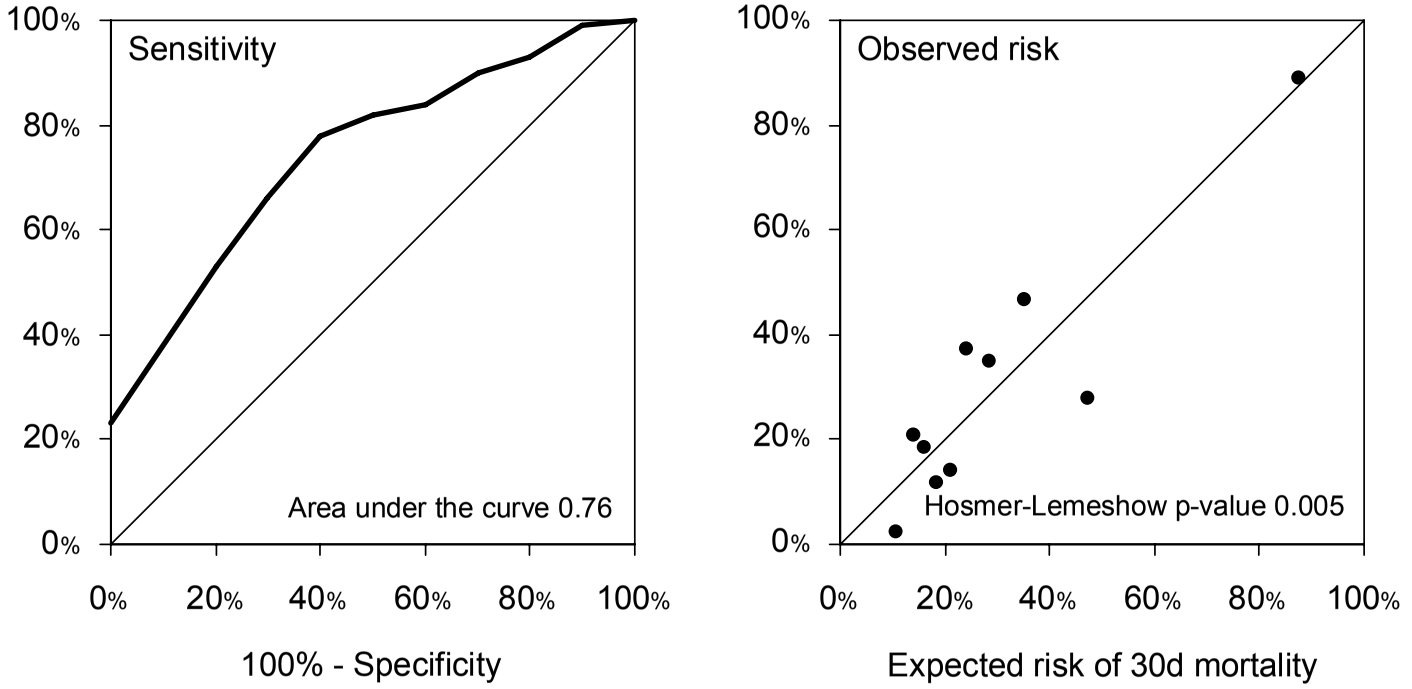

Figure 2

Receiver Operating Curve (left panel) demonstrating discrimination of the GUSTO[8] model in the PPRIMM75 dataset and a plot demonstrating calibration (right panel) of observed vs. predicted risk of 30 day mortality using the GUSTO model in the PPRIMM75 dataset

Unfortunately, previous use of statins was not recorded in this registry. Another possibility is that patients with higher cholesterol may have had a cardiovascular event at younger age, were more intensively managed and better protected by additional medical or invasive therapy.

The variables that significantly contributed to risk prediction for mortality in our model are comparable to the variables in the GUSTO and TIMI models. Killip class was the most significant in all models. Our model included hypercholesterolemia, for which lipid lowering therapy could be read in the TIMI model. Time delay between pain and admission was not used in the GUSTO and TIMI models because late comers were excluded of these trials addressing the effect of thrombolytic agents. An important difference is that infarct location is no longer a significant predictor in our model. Apparently in elderly patients infarct location plays no longer an important part in risk for survival. History of previous angina and hypertension (TIMI) did not show a significant impact on prognosis in our model. As PPRIMM75 is a dataset of first-time myocardial infarction, the effect of previous myocardial infarction (GUSTO) does not apply.

Based on the good discrimination obtained by the GUSTO and TIMI models in our dataset it appears that these models can be used in the elderly people to distinguish between high and low risk patients. For predicting a more exact risk of all cause mortality, especially in the lower risk population, the GUSTO and TIMI models are unsatisfactory. This is in accordance with Rathore et al., who also found a modest prognostic discrimination and calibration of the TIMI risk score for mortality at 30 days when applied to a large cohort of patients aged ≥65 years with STEMI enrolled in the Cooperative Cardiovascular Project [28].

This limitation may due to the differences in the populations from which the TIMI and GUSTO scores were created -in general consisting of younger and more homogeneous patients without contraindication for thrombolysis- compared with the unselected elderly population of a general clinical practice that PPRIMM75 represents. Therefore the observed risk in our dataset is higher than the calculated risk, and the calibration poor. We developed a new prediction model from this population with a good discrimination and calibration. This model may be used to calculate more precisely the risk of all-cause mortality at 30 days in older patients with their first STEMI.

Limitations

Developing risk models in a dataset based on consecutively admitted patients instead of data obtained in a study bares the risk of inaccuracy and incompleteness, and also for differences in treatment depending on the admitting hospital or physician. The patients were enrolled in one hospital and therefore treatment did not differ much between patients. Using data from “the real world” is also the strength of this analysis as there is no “study enrolment bias”. Unfortunately in about twenty percent of the patients heart rate and systolic blood pressure were missing. These data had to be imputed.

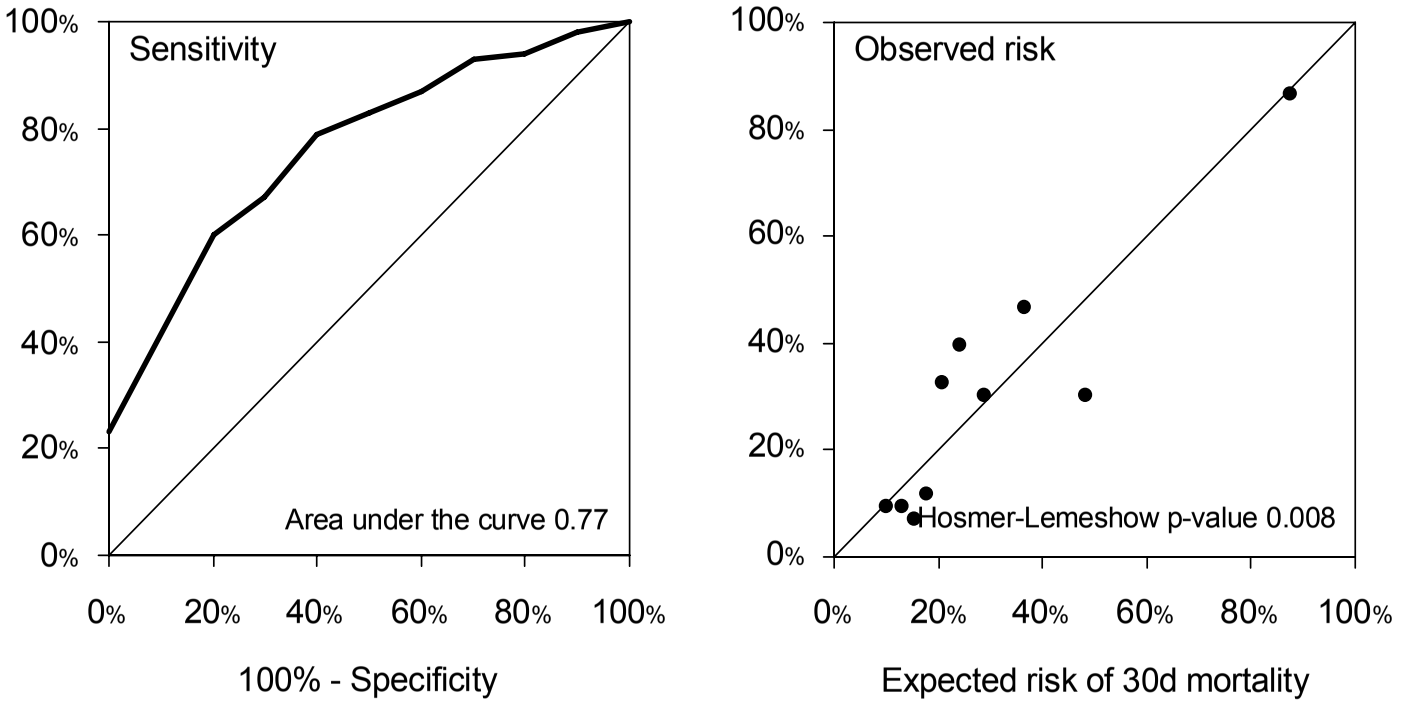

Figure 3

Receiver Operating Curve (left panel) demonstrating discrimination of the TIMI[9] model in the PPRIMM75 dataset and a plot demonstrating calibration (right panel) of observed vs. predicted risk of 30 day mortality using the TIMI model in the PPRIMM75 dataset

Because the data was collected during the period 1995 to 2000 a large number (see Table 1) of patients were not treated with primary PCI as current guidelines suggest. However, in our analysis patients treated with primary PCI did not show a significantly lower 30-day mortality risk than those treated with thrombolytics. Another drawback of the time period this dataset was build in, as in the GUSTO and TIMI dataset, is that biomarkers were not intensively used, so comparison with recent models using biomarkers is not possible. This is an interesting area for further research. Finally, the model we created has not been validated in another population. Further research on this aspect is warranted.

Conclusion

Thirty-day mortality in patients over 75 years having their first ST elevation myocardial infarction depends on several factors, among which initial hemodynamic status is the most important. Although the GUSTO and TIMI scores adequately discriminated patients who died from those who survived, both models are insufficiently adequate for providing an exact estimate of 30-day mortality risk. A better estimate can be obtained using our model, which is specifically calibrated for elderly patients.

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Chapter Six

Benefit of thrombolytic therapy is sustained throughout five years and is related to TIMI perfusion grade 3 but not grade 2 flow at discharge

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Abstract

Background

Long-term follow-up in patients treated with thrombolysis for acute myocardial infarction thus far has been reported in a few studies only, and no long-term follow-up is available for patients who underwent additional percutaneous transluminal coronary angioplasty (PTCA). This report describes 5-year survival as collected in patients who received placebo, recombinant tissue plasminogen activator (rTPA), or rTPA with additional immediate PTCA in two European Cooperative Study Group trials. Determinants for long-term survival were assessed in 1043 patients discharged alive.

Methods and Results

Five-year follow-up information on mortality was collected. Hospital mortality was lower after rTPA than placebo (2.5% versus 5.7%, P=.04) and higher after rTPA with immediate PTCA compared with rTPA without additional intervention (6.0% versus 2.2%, P=.07). Of the 1043 hospital survivors, data were available for 923 patients, of whom 109 died. In the placebo group, mortality after hospital discharge was 10.7% versus 11.0% in the comparative rTPA group. The patients treated with rTPA and immediate PTCA had a mortality rate of 10.5% versus 8.9% in the rTPA group without PTCA (all P=NS). Significant determinants of mortality in multivariate proportional hazards analysis were enzymatic infarct size, indicators of residual left ventricular function, number of diseased vessels and TIMI perfusion grade at discharge. Patients with TIMI grade 2 flow had mortality rates similar to those with TIMI flow grades 0 and 1, while prognosis was better in patients with TIMI flow grade 3.

Conclusions

The initial in-hospital benefit of thrombolysis with intravenous rTPA is maintained throughout 5 years, with no early or late beneficial effect of systematic immediate PTCA. Enzymatic infarct size, left ventricular function, and extent of coronary artery disease are predictors for long-term survival. TIMI perfusion grade 2 at discharge should be considered as an inadequate result of therapy.

Introduction

In patients with evolving myocardial infarction, thrombolytic therapy improves in-hospital survival and survival up to 1 or 2 years. [1-10] However, long-term follow-up data are scarce. The ISIS-2 study group recently reported that the improved survival in patients receiving intravenous streptokinase was sustained after 4 years [11], while the Interuniversity Cardiology Institute from the Netherlands reported further separation of survival curves up to 8 years after treatment with intracoronary streptokinase or conventional therapy.[12] In that study, the improved long-term survival after reperfusion therapy was explained by markedly improved left ventricular function at the time of hospital discharge.[13]

To assess which factors are associated with improved long-term survival after thrombolytic therapy with recombinant tissue plasminogen activator (rTPA), 5-year follow-up data were collected in 1043 hospital survivors of two studies performed by the European Cooperative Study Group.[5,14] The following questions were addressed. Is the improved 1-year survival after thrombolytic therapy with rTPA sustained or increased at 5-year follow-up? Is there a late benefit for patients who underwent systematic immediate percutaneous transluminal coronary angioplasty (PTCA), even though such intervention did not result in any benefit at hospital discharge or at 1 or 2 years of follow-up? [9,10,14-16] Which parameters available at hospital discharge predict 5-year survival, and are these the same as those factors predicting 1-year survival?

Methods

Between May 1986 and October 1987, the European Cooperative Study Group performed two randomized prospective clinical trials in patients with acute myocardial infarction: one to investigate the effect of rTPA (alteplase) versus placebo and one to investigate the additional effect of systematic immediate PTCA to thrombolytic therapy with rTPA. Detailed protocols and initial results have been published previously.[5,14] Briefly, a total of 1088 patients with electrocardiographic evidence of myocardial infarction were enrolled provided that thrombolytic therapy could be started within 5 hours after symptom onset. Seven hundred twenty-one patients were enrolled in the double-blind rTPA/placebo trial and 367 in the rTPA/PTCA trial. Patients were given an intravenous infusion of either 100 mg alteplase or placebo (in the rTPA/placebo trial) in 3 hours. All patients received 250 mg of acetyl salicylic acid and a bolus of 5000 IU of heparin intravenously, followed by a continuous infusion of heparin 1000 IU/h. The treatment strategies in the rTPA group of the rTPA/placebo trial and the noninvasive group of the rTPA/PTCA trial were identical. In the rTPA/PTCA trial, patients allocated to the invasive strategy underwent immediate coronary angiography and subsequently angioplasty if an occlusion or residual

stenosis exceeding 60% was present. Until hospital discharge, all patients were anticoagulated with heparin, which could be replaced by coumarin after 3 days, provided that full anticoagulation was maintained. In addition, 75 to 125 mg oral acetyl salicylic acid was given every other day until hospital discharge.

Clinical data were collected and blood samples were drawn for calculation of infarct size based on –hydroxy butyrate dehydrogenase. [17] Exercise testing, radionuclide ventriculography, coronary angiography, and left ventriculography were performed before hospital discharge. Before beginning the trial, each clinic participating in the study was assigned a specific time window for the performance of these examinations: 10 to 14, 12 to 16, 14 to 18, 16 to 20, or 18 to 22 days after allocation. β-Adrenergic blocking agents were to be prescribed unless contraindications were present. ECGs, infarct size, ventriculograms, and angiograms were centrally assessed.

There were 45 in-hospital deaths: 21, 9, 4, and 11 in the placebo, rTPA, rTPA without PTCA, and rTPA with PTCA treatment arms, respectively. Survival status was collected from all 1043 patients who were discharged alive (691 patients in the rTPA/placebo trial and 352 in the rTPA/PTCA trial). Follow-up was obtained from the treating physician, municipal registries, or the patient.

Data analysis

Survival curves for the different treatment groups and other variables were obtained as described by Kaplan and Meier. Variables were classified in four different groups. Group 1, clinical variables, were age; sex; sum of ST elevation at the J-point on different times during hospital stay; time from symptom onset to treatment allocation; previous myocardial infarction; site of infarction; Killip class at admission; angina at rest and during effort; clinical signs of heart failure, atrial fibrillation, or pericarditis; and use of ß-blockers, digitalis, diuretics, or a combination of the latter two between 24 hours and hospital discharge. A new variable was defined representing several clinical indices of impaired left ventricular function when the patient experienced one of the following: a period of systolic blood pressure below 90 mmHg or cardiogenic shock between 24 hours and hospital discharge, New York Heart Association class III or IV at discharge, use of diuretics and/or digitalis, and not giving ß-blockade to the patient. Patients in whom an exercise test was not performed on clinical grounds were also included in this variable. Group 2 variable was infarct size, as assessed from cardiac enzyme release.[17] Group 3 variables included exercise test results; systolic blood pressure rise from baseline to peak exercise; maximum heart rate during exercise; occurrence of angina; ST segment depression and elevation during exercise; and maximum workload and percentage of predicted workload achieved according to age and height. Group 4 variables included left ventricular ejection fraction from radionuclide ventriculography and variables obtained from coronary angiography and left ventriculography: TIMI perfusion grade of the infarct related vessel,

extent, and severity of coronary artery disease, and end-diastolic and end-systolic volumes. In the studies, left ventricular ejection fraction was measured both by radionuclide ventriculography and by contrast angiography. The former measurement was used in the analysis because this was obtained in a larger group of patients.

For all variables mentioned above, a univariate "crude" relative risk was calculated using data from those patients of whom survival status at 5 years was known. For continuous variables, patients were categorized into three subgroups of approximately equal size or dichotomized in clinically accepted groups, as indicated in Table 3. Subsequently, mortality was assessed in each subgroup. The category with the lowest expected risk was chosen as the reference group.

To obtain independent predictors for mortality, the Cox proportional hazards model was applied, which provides a conditional probability of death for every patient at each moment during follow-up, given a certain combination of risk factors.[18] In a stepwise procedure, variables were included in the models if the probability for inclusion was less than 0.10. A variable was removed if the associated probability exceeded 0.15. Clinical data, data of the exercise test, radionuclide angiography, and angiographic data were first analyzed in clusters; those retained in the various steps were combined in the final models. The 95% confidence interval for relative risk was derived from the natural antilogarithm of the coefficient ±1.96 times the standard error.

Multivariate analysis was used to develop a composite risk score based on patient characteristics related to 5-year mortality in the univariate analysis. Relative risk estimates were obtained with Cox multivariate regression analysis. Five risk functions were designed in which clinical (subjective) parameters were compared with or combined with objective parameters obtained at hospital discharge. One model consisted of clinical data only (model I). The next model consisted of clinical data combined with enzymatic infarct size (model II), and in the third model, exercise test results were added (model III). All parameters were combined in the last model (model IV). Treatment was forced into all the models. For each model, risk estimates were calculated for each patient and compared with the observed risk.

Results

A total of 1088 patients were enrolled in the two trials, of whom 45 died in hospital. Baseline characteristics have been described in detail. [5,14] Median age was 57 years (range, 37 to 69), 80% were men, 7% had a previous infarction, and 40% were admitted with an anterior infarction.

Complete 5-year mortality information could be obtained for 923 patients (Table 1). Median follow-up since discharge was 5.5 years, ranging from 1 day to 7.5 years. The 120 patients with incomplete follow-up (11.5%) were randomly distributed over the two studies and the four treatment groups.

Table 1

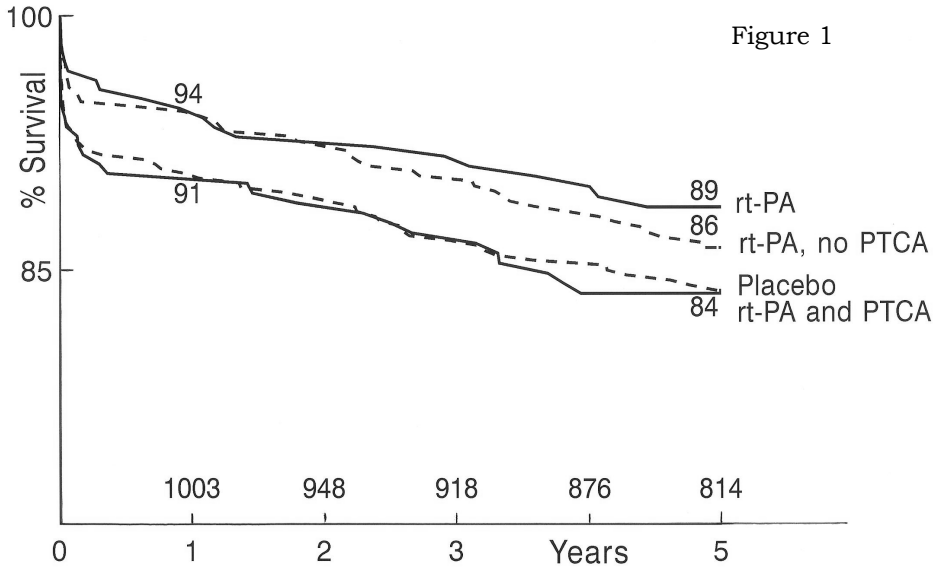
Follow-up data in the four treatment groups from the rTPA/Placebo and the rTPA/PTCA Study

	Random-ized	In-hospital death	P	Died since discharge	Alive ≥ 5 years	Alive < 5 years	Actuarial survival at 5 years
Total no. patients	1088	45		109	814	120	
Placebo	366	21		37 (10.7)	261	47	84 %
rTPA	355	9	.04	38 (11.0)	267	41	89 %
rTPA	184	4	.08	16 (8.9)	145	19	86 %
rTPA + PTCA	183	11	1	18 (10.5)	141	13	84 %

rTPA indicates recombinant tissue plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty. Hospital mortality was significantly lower in patients treated with rTPA vs. placebo in the rTPA/placebo trial (P=.04). Other differences were not significant. Mortality after discharge was similar in the four treatment groups. The survival difference in the rTPA/placebo trial was maintained at 5 years of follow-up (see Fig 1). Percentage of mortality in each group of patients is shown in parentheses.

Hospital mortality was 2.5% for alteplase versus 5.7% for patients receiving placebo and also 6.0% for patients allocated to additional immediate PTCA (Table 1). At 1 year and 5 years, this difference remained essentially unchanged (Figure 1). Five-year survival was similar in the two rTPA–only groups and better than either the placebo or rTPA–plus–PTCA group (P=.06). Five-year survival of patients discharged alive was 89%. Survival after discharge was similar in each treatment group, averaging 2.1% per year. At 5 years, as at 1 year, there was no additional beneficial effect for immediate PTCA.

Predictors for increased 5-year mortality risk after discharge angiography as obtained by univariate analysis (Table 2) were aged greater than 60 years; parameters representing residual left ventricular function: infarct size, remaining ST elevation at 6 hours, an increase of systolic blood pressure during exercise less than 30 mm Hg or inability to perform an exercise test, an ejection fraction below 40%, and the clinical index of impaired left ventricular function; as well as parameters representing the extent of coronary disease: a history of angina for more than 4 weeks, previous myocardial infarction, more than two diseased vessels, and a reduced perfusion (TIMI grade less than 3) of the infarct related artery. The relative mortality risk for incomplete perfusion (TIMI grade 2) was similar to that of TIMI grades 0 and 1, while this risk was reduced in patients with complete TIMI grade 3, flow (Figure 2).



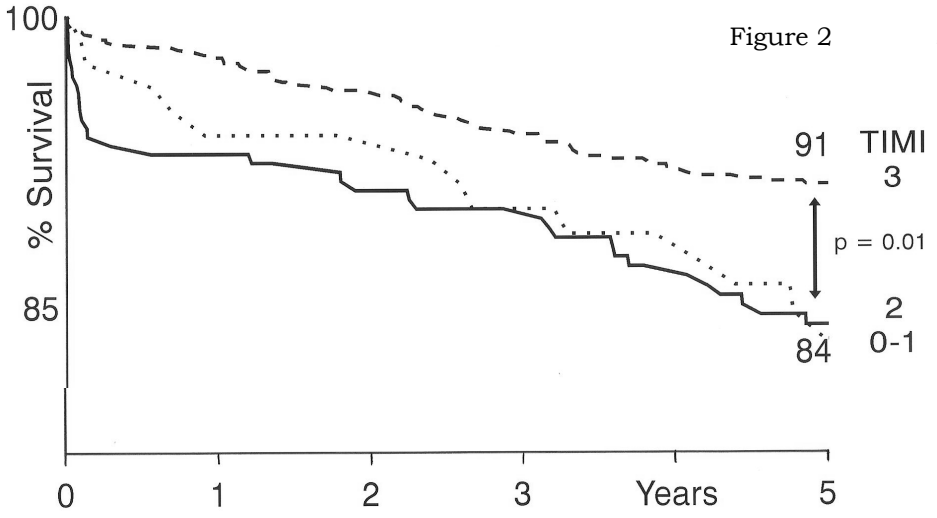


Figure 1
Survival curves after randomization of patients (n=1088) allocated to recombinant tissue plasminogen activator (rTPA) without immediate percutaneous transluminal coronary angioplasty (PTCA) or rTPA in the rTPA/placebo trial and patients allocated to conventional therapy (rTPA, no PTCA) or immediate PTCA in addition to rTPA in the rTPA/PTCA trial

Figure 2
Survival curves after hospital discharge with stratification for different TIMI perfusion grades obtained at discharge. Patients with TIMI grades 0 and 1 are combined (solid line). The difference between patients with complete perfusion (TIMI 3; 5-year survival, 95%) and those with TIMI grades 0 to 2 (survival, 84%) was significant (P=.01)

Table 2

Mortality within five years after hospital discharge in various subgroups of patients

	rTPA / Placebo trial		rTPA / PTCA trial			Risk Ratio
	Placebo	rTPA	rTPA	PTCA	Overall	(95% CI)
Age, y						
< 60	18/184	16/170	10/122	12/101	56/577	
≥ 60	19/114	22/135	6/39	6/58	53/346	1.6(1.1-2.2)
History of angina > 4 wk.						
No	30/251	25/242	10/122	9/114	74/729	
Yes	7/47	13/63	6/39	9/45	35/194	1.8(1.2-2.6)
History of infarction						
No	32/274	31/284	14/150	15/147	92/855	
Yes	5/24	7/21	2/11	3/12	17/68	1.3(1.0-1.6)
Clinical index of impaired left ventricular function†						
No	26/265	27/262	11/129	11/119	75/775	
Yes	11/33	11/43	5/32	7/40	34/148	2.3(1.7-3.4)
ST elevation ≥2 mV at 6h						
No	28/250	33/285	16/153	16/146	93/834	
Yes	7/33	3/6	0/3	1/6	11/48	2.0(1.2-3.6)
Missing	2/15	2/14	0/5	1/7	5/41	1.0(0.5-2.5)
Enzymatic infarctsize U/L.						
<1100	13/198	22/229	10/125	11/116	56/668	
≥1100	24/97	16/76	6/36	7/43	53/252	2.5(1.8-3.6)
Missing	0/3	-	-	-	0/3	
Blood pressure increase during exercise, mmHg						
≥30	14/180	17/203	12/126	12/119	55/628	
<30	19/103	16/81	3/22	3/27	41/233	2.0(1.4-2.9)
Missing	4/15	5/21	1/13	3/13	13/62	1.9(1.1-3.2)
Radionuclide ejection fraction, %						
≥40	18/197	19/205	11/120	5/108	53/630	
<40	17/90	18/91	5/34	11/44	51/259	2.3(1.6-3.3)
Missing	2/11	1/9	0/7	2/7	5/34	1.8(0.8-4.1)
No. of coronary vessels with ≥50% diameter stenosis						
<2	14/166	13/166	8/109	12/109	47/550	
≥2	22/126	23/129	8/47	4/39	57/341	2.0(1.4-2.8)
Missing	1/6	2/10	0/5	2/11	5/32	1.8(0.8-4.3)
TIMI flow grade at 10-22 days						
3	17/195	22/219	13/124	10/122	62/660	
2	8/32	3/26	1/10	1/3	13/71	2.0(1.1-3.4)
1	1/14	5/16	0/5	1/3	7/38	2.0(1.0-4.0)
0	9/50	6/33	1/12	4/20	20/115	1.9(1.2-2.9)
Missing	2/7	2/11	1/10	2/11	7/39	1.9(0.9-3.9)
Treament strategy						
Placebo	37/298					
rTPA		38/305				1.0(0.7-1.5)
rTPA*			16/161			.8 (0.5-1.4)
PTCA				18/159		.9 (0.5-1.6)
All					109/923	

Abbreviations as in Table 1. Number of deaths devided by the total number of patients in each subset of which complete follow-up at 5 years is shown. Risk ratios are unadjusted and obtained by univariate analysis. * rTPA given in the rTPA/PTCA study. † Included in the index are a period of systolic blood pressure below 90 mmHg or cardiogenic shock, New York Heart Association class III or IV, use of diuretics and/or digitalis, and not giving β-blockers to the patient. Patients with a missing exercise test are also included in this variable.

Not significant, among others, were treatment strategy, infarct location, and sex. As an example of the interaction between various parameters, figure 3 shows survival curves for patients subdivided on ejection fraction and the extent of coronary disease.

In Table 3, we present the relative risk of each risk factor conditional on the other factors in the four risk functions as obtained by multivariate analysis. In the risk function with clinical data, only four parameters were retained (in order of decreasing importance): the clinical index of the impaired left ventricular function, history of previous infarction, ST elevation of 2 mV or more at 6 hours, and age greater than or equal to 60 years. In addition to the clinical parameters, infarct size contributed strongly to the prediction of mortality at 5 years (model II). However, systolic blood pressure rise of less than 30 mm Hg during exercise testing did not contribute independently to mortality prediction (model III).In the final model (model IV), parameters representing left ventricular function and coronary anatomy were retained. A large infarct size and clinical findings related to an impaired ventricular function between 24 hours and discharge were associated with, respectively, 2.3- and 1.7-fold increases in mortality. Multivessel disease and TIMI perfusion grade below 3 also contributed to the risk (1.7- and 1.6-fold increases in mortality risk, respectively).

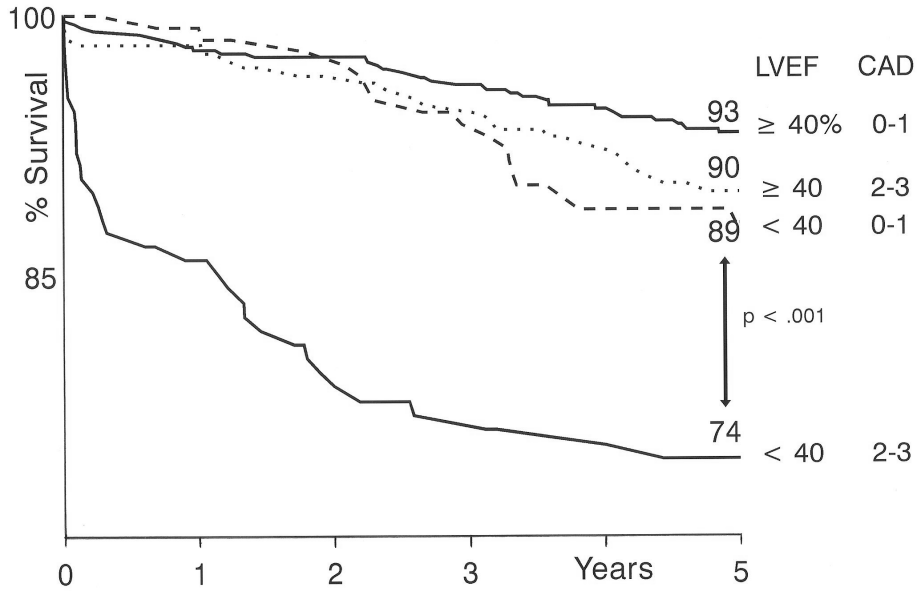


Figure 2

Survival curves after hospital discharge stratified for patients with left ventricular ejection fraction (LVEF) of 40% or greater or below 40% combined with none or one diseased vessel versus more than one diseased vessel (coronary artery diseaseCAD 0 to 1 or 2 to 3). Differences between the top three curves were not statistically significant, whereas patients discharged with impaired LVEF (<40%) and multivessel disease had worse prognoses (P<.001). Five-year survival rates are presented for each sub-group.

The information content of the models was compared by use of receiver operator characteristic (ROC) curves.[19] The areas under the ROC curves were almost equal in size. This implies that the predictive accuracy of the different models is similar. Thus simple clinical data suffice for long-term risk assessment after myocardial infarction.

Conclusions

Sustained survival benefit of thrombolysis for acute myocardial infarction was already demonstrated for intravenous and intracoronary streptokinase. [11-13] The present data demonstrate the sustained effect of thrombolysis with intravenous alteplase 5 years or more after randomization. The survival Figures at 5 years in these European Cooperative Study Group trials were higher than in the cited trials with streptokinase [11,13], both in the thrombolysis group and in the placebo group. This is probably due to patient selection and to improved adjunctive therapy in recent years, including the addition of acetyl salicylic acid to thrombolytic therapy, increased use of angiotensin-converting enzyme inhibitors, and possibly to the high number of interventions during the first year. [9] No further separation of the survival curves occurred after discharge. This is in agreement with reports from TIMI II at 2- and 3-year follow-up [10] and with preliminary ISIS-2 follow-up results, which also show a sustained, unchanged benefit at 4 years. [11] The earlier study by the Interuniversity Institute did show further segregation of survival curves during 8-year follow-up. This can be explained by the large difference in left ventricular ejection fraction between patients with and without reperfusion therapy in that study. [13] The predictors of mortality in the present study and in the Interuniversity Institute trial were similar.

Indicators for increased mortality risk during 5 years after hospital discharge can be grouped as parameters representing infarct size or residual left ventricular function (enzymatic infarct size, the amount of ST elevation, the clinical index of impaired left ventricular function, blood pressure increase during exercise, and left ventricular ejection fraction) and parameters representing the extent of coronary disease (history of angina, previous infarction, TIMI perfusion grade, and multivessel disease).

The indicators that were retained in the multivariate analysis were all interchangeable and appeared or disappeared in the model, depending on which variables were entered to represent left ventricular function or extent of coronary disease.

In particular, the strongest predictor of long-term mortality risk in the final analysis, enzymatic infarct size, might be replaced by left ventricular ejection fraction without loss of accuracy in the prediction, the latter being the consequence of a large area of nonfunctioning myocardium after extensive myocardial damage.

Table 3

Multivariate analysis and relative risks

Model		I	II	III	IV
Clinical data		+	+	+	+
Enzymes			+	+	+
Exercise test				+	+
RNA, LVEF					+
Angiogram					+
	%				
Age, y					
< 60	62.5				
≥ 60	37.5	1.4(1.0-2.1)	1.5(1.0-2.3)	1.5(1.0-2.3)	
History of angina > 4 wk.					
No	78.9				
Yes	21.1		1.6(1.0-2.4)	1.5(1.0-2.4)	
History of infarction					
No	93.2				
Yes	6.8	2.2(1.3-3.8)	2.2(1.3-3.8)	2.0(1.2-3.6)	
Clinical index of impaired left ventricular function†					
No	84.0				
Yes	16.0	2.4(1.6-3.7)	2.0(1.3-3.0)	1.9(1.2-3.0)	1.7(1.0-2.6)
ST elevation ≥2 mV at 6h					
No	90.2				
Yes	4.9	2.0(1.0-3.9)			
Missing	4.9				
Enzymatic infarctsize U/L.					
<1100	73.0				
≥1100	27.0		2.5(1.7-3.8)	2.4(1.6-3.6)	2.3(1.5-3.6)
No. of coronary vessels with ≥50% diameter stenosis					
<2	59.8				
≥2	36.2				
Missing	4.0				
TIMI flow grade at 10-22 days					
3	70.8				
0, 1, or 2	24.4				
Missing	4.9				
Treament strategy					
Placebo	33.0	1			
rTPA	33.2	1.0(0.6-1.7)	1.0(0.7-1.7)	1.1(0.7-1.8)	1.1(0.7-1.8)
rTPA*	17.3	0.9(0.5-1.6)	0.9(0.5-1.6)	0.9(0.5-1.8)	1.0(0.6-2.0)
PTCA	16.5	0.9(0.5-1.5)	0.9(0.5-1.6)	0.9(0.5-1.6)	1.1(0.7-1.8)
5 yr syurvival without any risk factor		0.939	0.947	0.947	0.940
Prevelance, % patients without risk factor		41.1	31.5	26.1	22.1

RNA LVEF indicates radionuclide left ventricular ejection fraction; other abbreviations as in Table 1. Different multivariate models tested and survival for patients 5 years after hospital discharge without any risk factor. Relative risk of each risk factor was obtained by Cox multivariate regression analysis. Treatment was forced into the models; 95% confidence intervals are shown in parentheses. † See Table 2.

Limitations of the analysis

It should be appreciated that data from two studies were combined in this analysis. [5,14] These studies were designed and conducted in parallel, with similar data collection methods. The actual treatment strategies did not contribute to the prediction of postdischarge mortality (Table 3), and similar results were obtained when the trials were analyzed separately, albeit with loss of statistical power.

Follow-up was less than 5 years in 120 patients, equally divided among the trials and patient groups (Table 1). Still, 1-year follow-up was complete in 99%. Thus, it is unlikely that the results are biased by incomplete follow-up.

In all clinical trials, actual treatment may vary, depending on the physician's preference. At 1 year, 25.5% of the patients in the noninvasive arm of the rTPA/PTCA trial had undergone PTCA or bypass surgery versus 15.6% to 18.5% in the three other groups. [9] A separate analysis was performed using actual treatment within 14 days after hospital admission. The results were very similar to the intention-to-treat analysis as presented in this report. Despite the higher intervention rate in patients allocated to rTPA in the rTPA/PTCA trial, 5-year survival was similar between the two rTPA groups (Fig 1). Thus, it is unlikely that the results have been influenced by subsequent unrecorded interventions after the first year.

Importance of complete coronary perfusion for short-term and long-term follow-up

It was remarkable, as demonstrated in Figure 2, that long-term prognosis for patients with incomplete perfusion, TIMI grade 2, appeared to be similar to patients with occluded (TIMI flow grades 0 or 1) vessels, while prognosis was superior in patients with complete, TIMI grade 3 flow. These observations are in concordance with other studies that reported greater myocardial salvage in patients with early complete reperfusion (TIMI grade 3) compared with those with incomplete perfusion or occlusion of the infarct related artery (TIMI grades 2, 1, or 0).20 Immediate PTCA during thrombolytic therapy was performed in some of the patients in an attempt to improve coronary reperfusion. However, at predischarge angiography, coronary perfusion was not better after PTCA compared with patients receiving alteplase only.14 In contrast, other studies have shown that patients undergoing direct PTCA without concomitant thrombolysis appeared to do better with a greater proportion of TIMI grade 3 flow, smaller infarct size, better preserved left ventricular function, and better survival.21,22 This supports the notion that early, complete reperfusion is the determinant of myocardial salvage, whereas both early and late (before hospital discharge) complete perfusion are determinants of long-term survival.

Conclusions

The salutary effect of reperfusion therapy with intravenous rTPA is maintained throughout 5 years of follow-up. There was no additional late beneficial effect of systematic immediate PTCA in patients treated with rTPA. Long-term prognosis for patients with myocardial infarction could be predicted from infarct size, residual left ventricular function, and the extent of coronary artery disease at discharge. TIMI perfusion grade 2 at discharge should be considered as a result of inadequate therapy.

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Chapter Seven

Patients using statin treatment within 24 hours after admission for ST-elevation acute coronary syndromes had lower mortality than non-users. A report from the first Euro Heart Survey on acute coronary syndromes

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Abstract

Aims

Statins provide effective secondary prevention in cardiovascular disease. However, it remains uncertain how soon statins should be started after an acute coronary syndrome (ACS). Recently published trials suggest starting before discharge. We hypothesize that statins should be initiated without delay.

Methods and results

Data from a large cohort of 10484 consecutive patients with an ACS were analysed. Of this cohort 1426 first time statin receivers and survivors of the first 24 hours were compared to 6771 first day survivors not receiving statin therapy. A propensity score for the likelihood of receiving statin therapy within 24h was developed and used with other established risk factors in a multivariable analysis. There was a significantly reduced all cause 7 day mortality in patients receiving early statin therapy (0.4% vs. 2.6%; unadjusted HR 0.16; 95% CI: 0.08-0.37, adjusted HR 0.34; 95% CI 0.15-0.79). Statistical significance was observed in patients presenting with STE-ACS (adjusted HR 0.17; 95%CI 0.04-0.70) and not in NSTE-ACS patients. However no statistical evidence of heterogeneity in treatment effect was observed between these groups.

Conclusion

These data suggest that very early statin therapy is associated with reduced mortality in patients presenting with STE-ACS, however, these findings have to be confirmed by prospective, randomised controlled trials before firm treatment recommendations can be given.

Introduction

Since publication of the landmark trials 4S, CARE and LIPID, HMG-coA reductase inhibitors (statins) are recognised effective treatment for secondary prevention of cardio-vascular events[1-3]. In these trials statin therapy was started late (months) after a coronary event, and the benefit became apparent only after long-term use. Beyond a favourable effect on serum lipids, statins may also directly stabilize coronary plaques[4,5]. Accordingly, in acute coronary syndrome (ACS) patients, presenting with (STE-ACS) or without (NSTE-ACS) ST-elevation, it might be advantageous to start statin therapy early after hospital admission. Two observational studies confirmed this hypothesis. In the Swedish myocardial infarction registry[6], and in the combined datasets of the GUSTO IIb and PURSUIT trials in ACS, patients who received statin therapy before hospital discharge had lower mortality than the remaining patients[7]. In contrast, in the SYMPHONY studies, statin therapy within 3 days after admission was not associated with improved outcome[8]

Randomised trials of early statin therapy versus control in ACS patients that are conducted so far showed mixed results. The MIRACL trial, which enrolled NSTE-ACS patients, reported a statistically significant 16% lower rate of death and nonfatal major cardiac events at 4 months follow-up in patients receiving 80 mg/d of atorvastatin compared with placebo[9]. In MIRACL, study medication was initiated within 24 to 96h after admission. In the small FLORIDA trial, which enrolled patients presenting with STE-ACS, fluvastatin therapy (80 mg/d) did not affect the incidence of major adverse cardiac events as compared with placebo. The median time to the initiation of study medication after the onset of symptoms was 8 days. The larger A to Z trial, which included NSTE-ACS as well as STE-ACS patients, showed a favourable, but statistically non-significant trend toward reduction of major cardiovascular events during 6 to 24 months follow-up in patients receiving an intensive simvastatin regimen (40 mg/d for 1 month followed by 80 mg/d thereafter) as compared to those receiving a less intensive regimen (placebo for 4 months followed by 20 mg/d of simvastatin)[10]. Study medication in the A to Z trial was started after patients were stabilized for at least 12h. A trend toward better outcome after early statin therapy (0.4 mg/d of cerivastatin) was also observed in the PRINCESS trial STE-ACS, but again statistical significance was not reached (data presented at the annual congress of the European Society of Cardioloy, august 2004). Study medication in the PRINCESS trial was initiated within 48h of symptom onset.

We suppose that the relative late start of statin treatment, especially in patients with ST-elevation, is one of the reasons for the lack of benefit in these trials, as the beneficial non lipid lowering effects might be optimal very early in the process of plaque destabilisation. Therefore, we postulate that statin therapy that is initiated within 24h after admission is associated with improved outcome in ACS patients. We studied this hypothesis in the

large cohort of patients who were enrolled in the first Euro Heart Survey on Acute Coronary Syndromes and were not receiving statins before hospitalisation.

Methods

Euro Heart Survey on ACS

The details of the Euro Heart Survey ACS have been previously described in detail[11]. The survey was performed in clusters composed of academic and non-academic hospitals and hospitals with and without cardiac catheterisation laboratories and cardiac surgery facilities. The enrolment period was planned from September 4 to December 31, 2000. Due to technical delays (primarily delays in approval by ethic committees in several countries), the Expert Committee decided to extend the duration of the survey to May 15, 2001.

All patients with suspected ACS, screened at the emergency room, chest pain units, catheterisation laboratory, or otherwise were registered on a screening log (after acquisition of written informed consent if required), but they were not enrolled until the diagnosis of ACS was confirmed. Patients who had been in another hospital for a short (<12 h) observation period and were transferred for diagnosis and management were also registered, and information from the referring hospital was sought. However, patients who were referred only for a specific treatment (i.e. cardiac catheterisation or coronary bypass surgery) were not included. For all logged patients, we recorded the tentative initial diagnosis made by the attending physicians based on the initial electrocardiographic pattern: ACS with ST elevation, ACS without ST elevation, and ACS with an undetermined electrocardiographic pattern. The full case report form was filled out for patients with a discharge diagnosis of unstable angina or myocardial infarction. The case report form included details regarding the demographic, clinical, and electrocardiographic characteristics of the patient, the diagnostic and treatment modalities, the in-hospital complications, and the discharge status. A total of 10484 patients were enrolled.

Study population

As chronic use before hospitalisation might influence its early effects, we excluded 2099 patients already receiving statin treatment before hospitalisation from this analysis. Because, this is not a randomised trial, and decisions regarding the initiation of early (statin) treatment might be influenced by the physician's anticipation of the patient's condition. Specifically, estimates of the effectiveness of early statin therapy might be biased by the fact that moribund patients are less likely to receive such early therapy than their thriving counterparts. In order to partly adjust for this phenomenon, we excluded the 188 (2.2%) patients who died within the first 24h after

admission. Thus, a total of 8197 patients who survived the first 24h were available for analysis.

Endpoint definition

The Euro Heart Survey ACS was designed to evaluate the application of treatment guidelines in patients with acute coronary syndromes during routine clinical practice. With regard to patient outcome, the Survey mainly focussed on major adverse cardiac events that occurred during hospital stay, including myocardial (re)infarction and death. Adverse events were reported by the local investigators, and not adjudicated by an independent endpoint committee. Furthermore, the Survey protocol did not mandate serial electrocardiograms, or blood sampling for determination of cardiac enzymes (as per design, it was the intention to minimise the impact of the Survey protocol on routine procedures). Since we realise the Survey design is susceptible to observer bias, especially with regard to ”soft” endpoints, we choose the incidence of all-cause mortality at 7 days and at 30 days after admission as the endpoints of this study.

Data analysis

Continuous data are presented as mean value and standard deviation (SD), whereas dichotomous data are presented as numbers and percentages. Differences in baseline characteristics between patients who received statin therapy within 24h after admission (statin users) and those who did not receive statin therapy within this time period (statin non-users) were evaluated by unpaired Student’s t-tests and Chi-square tests, as appropriate.

We developed a propensity score for the likelihood of receiving statin therapy within 24h. Multivariable logistic regression analysis was applied to identify baseline factors that were associated with such early statin use. We considered a broad range of patient baseline characteristics, including age, sex, diabetes, hypertension, dislipidemia, family history of CAD, smoking, history of myocardial infarction, history of heart failure, history of coronary artery bypass grafting, history of percutaneous coronary intervention, history of renal insufficiency, ST-segment changes at the qualifying ECG, Killip class at admission, heart rate at admission, systolic blood pressure at admission, reperfusion therapy within 24h, and the use of aspirin, heparin, ticlopidin, beta-blockers, ACE-inhibitors and glycoprotein IIb/IIIa inhibitors during the first 24h. Potential interactions between these variables were not considered. All variables entered the multivariable stage. In general, for the development of a propensity score, it is recommended to use an extensive model, to ensure that any predictors (true and chance) are accounted for. Hence, no model reduction procedures were applied. We report adjusted odds ratios and 95% confidence intervals (CI) of the variables that compose the final propensity model. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish statin users from non-users; it was quan-

tified by the c-statistic. Calibration refers to whether the predicted probability of statin use is in agreement with the observed probability; calibration was measured with the Hosmer-Lemeshow goodness-of-fit test. In an attempt to optimise the discriminatory power of the propensity model, first order interactions between the variables that compose the model were considered. Furthermore, second-order terms for continuous variables were considered. However, both attempts did not result in an improvement of the c-statistic. Therefore, we decided to apply the model without interaction terms and based on first-order terms for continuous variables.

The method of Kaplan-Meier was used to describe the incidence of death over time. Log-rank tests were applied to study differences in survival between statin users and nonusers. These relations were further evaluated by multivariable Cox' proportional hazards regression analyses, with adjustment for confounders. We considered a broad range of potential confounders, including the propensity for early statin use (the propensity of statin use was determined for each patient, based on the obtained regression formula; see above), age, sex, risk factors for coronary disease, medical history, ECG changes, hemodynamic condition, and medication use. The multivariable models were constructed by backward deletion of the least significant characteristics, while applying the Akaike information criterionthat is, the applied threshold of significance depended on the degrees of freedom (DF) associated with the variable at hand; if DF = 1, then $P \approx 0.157$[12]. We report crude and adjusted hazard ratios (HR) and corresponding 95% CI.

We speculated that treatment effects of statin therapy might be different in patients presenting with STE-ACS versus NSTE-ACS. In order to study a potential heterogeneity in treatment effect, we included the ECG changes*statin use interaction-term in the final multivariable model. No other interactions between statin use and clinical characteristics were studied.

Clinical variables were missing for 2702 patients (1689 -63%- had missing values for only one clinical variable and in 2214 patients -82%- values for two variables). This subset had higher 7-day (5.3% vs. 2.1%) and 30-day (8.8% vs. 3.8%) mortality than the patients with complete data. Excluding patients with missing data therefore could lead to biased risk estimates[13]. To partly correct for this, all multivariable analyses were performed on a dataset that included imputed predictive variables. A simple imputation algorithm was used, and missing variables were replaced with the mean value of the variable at hand, as observed in the dataset. (Dichotomous variables were coded as 0factor absent or 1factor present. Thus, the imputed value for patients with missing data corresponds with the prevalence of the factor in the patients with non-missing data).

Statistical significance of all tests was stated at the 0.05 probability level. All tests were two-sided.

Results

Propensity score for early statin use

A total of 1426 (17%) patients received statin therapy within 24 hours after admission. There were relevant differences in clinical baseline characteristics between the statin users and non-users (table 1). Statin users were younger and more often men than non-users. Patients receiving early statin therapy were more often diagnosed as NSTE-ACS and less often as STE-ACS, whereas the undetermined ECG pattern was equally distributed. Traditional risk factors for coronary artery disease, including diabetes mellitus, hypercholesterolemia, a family history of coronary disease, and cigarette smoking as well as a prior history of coronary disease (previous myocardial infarction or coronary intervention) were also more prevalent in the group of statin users. Patients receiving early statins more often received standard treatment for ACS within 24h after admission, including aspirin, heparin, and beta-blockers. Gender, diabetes, history of renal insufficiency, systolic blood pressure at admission, and the use of ticlopidin during the first 24h were not included in the propensity score because of a p-value >0.5. Variables that compose the propensity score for the likelihood of receiving statin therapy within 24h are presented in Table 1. The propensity score model adequately discriminated between early statin users and non-users (c-statistic 0.75), and the predicted frequencies agreed with the observed frequencies (Hosmer-Lemeshow p-value 0.75; Figure 1).

Statin use within 24h and early mortality

Seven-day follow-up was complete for 7696 (94%) patients, and 30-day follow-up was complete for 6899 (84%) patients. All cause mortality at 7 days was 1.3% in patients presenting with NSTE-ACS patients (Kaplan-Meier estimate; 52 events in 4021 patients), 2.8% in those presenting with STE-ACS (100/3583) and 5.1% in patients with an undetermined ECG (25 / 504). At 30 days these Figures were 3.3% (123/4021), 5.1% (174/3583) and 9.6% (45/504). All cause mortality at seven days was significantly lower in the group of patients receiving early statin therapy (0.4% versus 2.6% events; absolute difference 2.2%; unadjusted HR 0.16 and 95% CI: 0.08 to 0.37; adjusted HR 0.34 and 95% CI 0.15 to 0.79; Table2 and Figure 2) There was no statistical evidence of heterogeneity in treatment effect between subgroups of patients according to ST-segment changes on the presenting ECG (P-value for heterogeneity 0.11, based on the ECG changes * statin use interaction-term in the multivariable model). However, after adjustment for multiple confounders, early statin therapy was not associated with reduced mortality in patients presenting with NSTE-ACS. The propensity score for early statin use was a significant contributor in all multivariable models, indicating that it acted as an important confounder of the relation between statin use and clinical outcome.

Table 1

Relation between baseline characteristics and statin use within the first 24h after admission n patients not receiving any statin therapy before hospitalisation

	Statin therapy within 24h (N=1426)	Patients not receiving statin therapy within 24h (N=6771)	Adjusted OR (95% CI) for the association with statin therapy within 24h
Age, years	62 ± 12	67 ± 13	0.93 (0.88, 0.99) per 10 years
Men	71	67	1
Baseline ECG			
- ST-segment elevation	48	43	0.9 (0.7, 1.2)
- ST-segment depression	47	50	1.2 (0.9, 1.6)
- Undetermined pattern	11	7	1
Risk factors and medical history			
Diabetes mellitus	19	22	1
Hypertension	55	58	0.8 (0.7, 0.9)
Hypercholesterolemia	72	36	2.9 (2.5, 3.3)
Family history of CAD	33	25	1.3 (1.1, 1.5)
Current or former smoker	64	55	1.2 (1.1, 1.4)
Myocardial infarction	19	27	0.7 (0.6, 0.9)
Congestive heart failure	5	12	0.6 (0.4, 0.7)
Coronary bypass surgery	5	4	1.4 (1.0, 1.8)
PCI	6	7	1
Renal insufficiency	3	5	0.7 (0.5, 0.9)
Physical examination			
Heart rate, bpm	78 ± 18	81 ± 20	0.94 (0.91, 0.97) per 10 bpm
Systolic blood pressure, mmHg	143 ± 28	143 ± 29	
Killip class			
I	86	79	1
II	12	15	1
III	1	4	1
IV	1	1	1
Treatment within 24h after admission			
Reperfusion therapy	42	27	1.5 (1.3, 1.8)
Aspirin	93	83	1.7 (1.4, 2.2)
Heparin	89	78	1.6 (1.3, 1.9)
Beta-blocker	81	59	2.4 (2.1, 2.8)
ACE-inhibitor	52	42	1.7 (1.5, 1.9)
Glycoprotein IIb/IIIa inhibitor	21	8	2.0 (1.7, 2.4)
Ticlid	24	14	1

Continuous data are presented as mean value ± SD; dichotomous data are presented as percentages. Odds ratios are adjusted for the variables as presented in this Table.
PCI: Percutaneous coronary intervention

The absolute difference in all-cause mortality between early statin users and non-users observed at 7-days follow-up had increased at 30 days. Hence, at 30 days early statin therapy was still associated with reduced mortality, although statistical significance was not reached after adjustment for multiple confounders (unadjusted HR 0.44 and 95%CI 0.31 to 0.64; adjusted HR 0.90 and 95%CI 0.60 to 1.3). Statistical significance was observed in patients presenting with STE-ACS (adjusted HR 0.49 and 95%CI 0.25 to 0.95). There was statistical evidence of a heterogeneity in treatment effect between subgroups of patients according to ST-segment changes on the presenting ECG (P-value for heterogeneity 0.01, based on the ECG changes * statin use interaction-term in the multivariable model).

Table 2

Relation between statin use within 24 hours after admission and short-term mortality

	Patients receiving statin therapy within 24h (N=1426)	Patients not receiving statin therapy within 24h (N=6771)	Unadjusted HR (95% CI)	Adjusted * HR (95% CI)
7-day follow-up				
ST-elevation ACS	0.3%	3.4%	0.09 (0.02, 0.35)	0.17 (0.04, 0.70)
Non ST-elevation ACS	0.6%	1.5%	0.41 (0.15, 1.1)	1.0 (0.34, 2.9)
Undetermined ECG	0%	5.8%	NA †	NA †
All	0.4%	2.6%	0.16 (0.08, 0.37)	0.34 (0.15, 0.79)
30-day follow-up				
ST-elevation ACS	1.6%	5.9%	0.25 (0.13, 0.47)	0.49 (0.25, 0.95)
Non ST-elevation ACS	2.7%	3.5%	0.78 (0.47, 1.3)	1.6 (0.95, 2.8)
Undetermined ECG	5.6%	10.1%	0.52 (0.16, 1.7)	1.1 (0.32, 3.8)
All	2.3%	5.0%	0.44 (0.31, 0.64)	0.90 (0.60, 1.3)

* Hazard ratios were adjusted for the following characteristics: propensity score for statin use within 24h, Killip class, age, diabetes mellitus, heart failure, a history of PCI, renal insufficiency, heart rate, blood pressure, use of the following medication within 24h: aspirin, ticlopidin / clopidogrel, beta-blockers, ACE inhibitors, glycoprotein IIb/IIIa inhibitors.
† Cannot be determined, since there were to few events in this subgroup

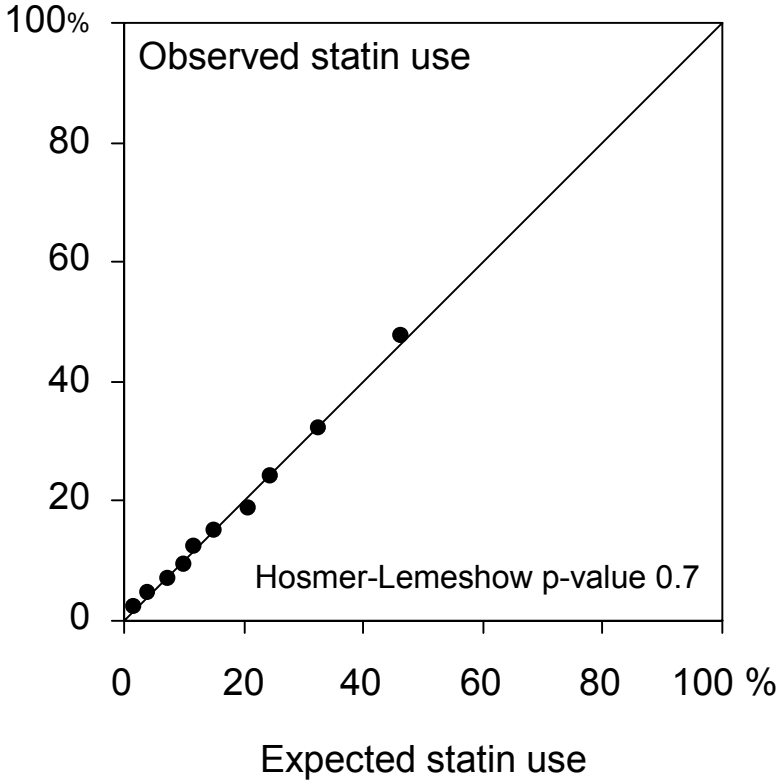

Figure 1
Plot demonstrating calibration of observed statin use versus statin use predicted by the propensity model.

Discussion

Statin therapy that is initiated within 24 hours after hospitalisation was associated with reduced short-term mortality in patients admitted with acute coronary syndromes. This treatment effect was already present after 7 days follow-up. The beneficial effects of early statin use were mainly observed in patients presenting with ST-segment elevation.

Several randomised clinical trials have demonstrated the effectiveness of long-term statin therapy in patients with established coronary disease. Statin therapy was associated with a 20% to 42% reduction in long-term mortality[1-3]. Hence, current treatment guidelines indicate that (life-long) statin therapy should be considered for secondary prevention in CAD patients[14,15]. Still, it should be appreciated that in these landmark trials patients were enrolled several months after CAD was diagnosed (the majority of patients were enrolled after they experienced a myocardial infarction), whereas the benefits of statin therapy only became apparent after the first

year of treatment. Recently published randomised trials in which patients are treated with statins before discharge as compared to placebo show an event reduction that became already apparent during the first 6 months [9,10]. Our data support the hypothesis that a much earlier start of statin therapy (i.e. within the first 24 hours after an acute coronary syndrome) may result in a mortality reduction within 7 days and confirm the results of the analysis done by the NRMI-4 investigators[16].

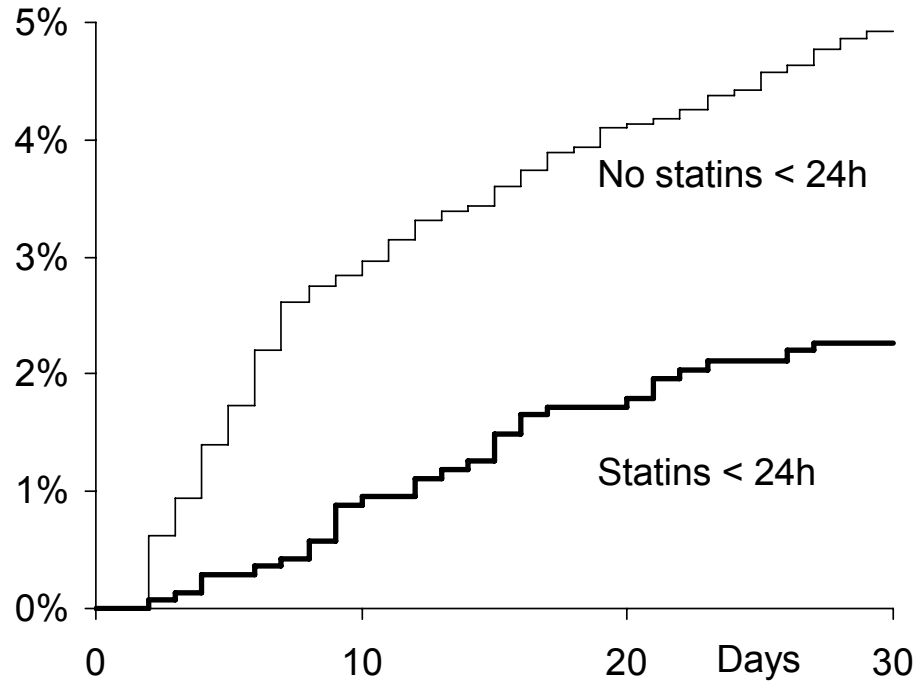

Figure 2
Kaplan Meier curves for mortality in all patients surviving the first 24 hours and stratified according to statin treatment within 24 hours after hospitalisation or not

The benefits of long-term statin treatment can largely be explained by it's cholesterol-lowering effects (especially the reduction of low-density lipoprotein cholesterol) and the associated retardation of the progression of atherosclerosis[5,17]. In contrast, the short-term benefits of statins are most likely due to the non-cholesterol-lowering vascular effects, like plaque stabilisation, improvement of endothelial function, inhibiting monocyte recruitment and decreasing the pro-thrombotic state, which have been demonstrated in vitro as well as in vivo studies[4,18]. Support for these vascular effects is provided by the recently published analysis from the PROVE-IT study in which patients with high levels of hsCRP had better clinical outcomes independent of LDL lowering[19]. Also reduction of periprocedural (not

a late effect) myocardial injury by statin therapy is demonstrated in patients undergoing PCI[20]. Finally a reduction of peri-operative mortality after statin therapy was also observed in patients undergoing non-cardiac vascular surgery[21].

We do not fully understand why the association between early statin therapy and reduced mortality was particularly observed in patients presenting with ST-elevation, while this association was absent in those presenting without ST-elevation. It is true that there was no (strong) statistical evidence for heterogeneity in treatment effect between subgroups according to abnormalities on the presenting ECG, and a chance effect cannot be excluded. At the other hand, statistical tests of heterogeneity often lack power to detect clinically relevant differences between subgroups. More importantly, such tests may also fail to reveal differences in the pathophysiologic processes underlying subgroups of patients with STE or NSTE-ACS, which could have been the case in our analysis. A proposed mechanism could be an effect of statins on the acute activated stage in ST-elevation coronary syndromes, where they might exert an anti-thrombogenic or plaque stabilizing effect reducing further thrombotic occlusion with subsequent myocardial damage and risk for death. This effect could be the result of the inhibition of plasminogen activator inhibitor I (PAI-I) or reduction of expression of procoagulant tissue factor[22]. Another mechanism could be a reduction in lethal arrhythmia's as was observed by Lorentz et al[23]. This might also be a reason why in the A to Z trial and in the SYMPHONY analysis, in which patients were included after stabilisation, these anti-thrombogenic effects of statins were no longer as strong as in the acute phase and statin therapy was less effective. Noteworthy, data from the A-Z trial also suggests a stronger effect of early statin therapy in patients presenting with STE-ACS as compared to NSTE-ACS. More research to address this issue however is needed. Finally the lower event rate in the NSTE-ACS group could also explain the absence of power to detect a difference in effect.

Our analysis has several limitations. Most importantly, this study was not designed as a randomised trial of statin therapy within 24h versus placebo or control therapy. In fact, our data were derived from an observational database of patients who were admitted for ACS, and we do not know why early statin therapy was initiated in some patients and withheld in others. The treating physician's perception of the patient's risk and clinical risk profiling likely played an important role in this respect. Indeed, important differences in clinical characteristics and medication use were observed between early statin users and non-users. We accounted for these differences by means of a propensity score for early statin use. It is known that the accuracy of this score is highly depended on the accuracy and the extent of the model that generates it. Therefore, in the regression analysis to develop the score, we applied the backward selection approach, and used a liberal threshold for statistical significance of the candidate components to remain in the model, as suggested by Akaike [12]. Still, although the use of a propensity score resembles randomisation, we realise that it cannot be

considered as good as randomisation. Thus, we cannot exclude the possibility that the estimate of treatment effect is still biased due to differential patient selection.

Conclusions and clinical implications

These data suggest that very early statin therapy is associated with reduced mortality in patients presenting with STE-ACS. It is true that our findings have to be confirmed by prospective, randomised controlled trials before firm treatment recommendations can be given. Still, based on our observational data and recently published randomised trials, we conclude that statin therapy should be started in patients admitted with (STE-) acute coronary syndromes, preferably as soon as possible, and regardless their lipid levels.

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Chapter Eight

Anticoagulant properties, clinical efficacy and safety of efegatran, a direct thrombin inhibitor, in patients with unstable angina

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Abstract

Aims

Thrombin plays a key role in the clinical syndrome of unstable angina. We investigated the safety and efficacy of five dose levels of efegatran sulphate, a direct thrombin inhibitor, compared to heparin in patients with unstable angina.

Methods

Four hundred and thirty-two patients with unstable angina were enrolled. Five dose levels of efegatran were studied sequentially, ranging from 0·105 mg/kg.h^{-1} to 1·2 mg/kg.h^{-1} over 48h. Safety was assessed clinically, with reference to bleeding and by measuring clinical laboratory parameters. Efficacy was assessed by the number of patients experiencing any episode of recurrent ischemia as measured by computer-assisted continuous ECG ischemia monitoring. Clinical end-points were: episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA or CABG), and death.

Results

Efegatran demonstrated dose dependent ex-vivo anticoagulant activity with the highest dose level of 1·2 mg/kg.h^{-1} resulting in steady state mean activated partial thromboplastin time values of approximately three times baseline. Thrombin time was also increased. None of the efegatran doses studied were able to suppress myocardial ischemia during continuous ECG ischemia monitoring to a greater extent than that seen with heparin. There were no statistically significant differences in clinical outcome or major bleeding between the efegatran and heparin groups. Minor bleeding and thrombophlebitis occurred more frequently in the efegatran treated patients.

Conclusion

Administration of efegatran sulphate at levels of at least 0·63 mg/kg.h^{-1} provided an antithrombotic effect which is at least comparable to an activated partial thromboplastin time adjusted heparin infusion. There was no excess of major bleeding. The level of thrombin inhibition by efegatran, as measured by activated partial thromboplastin time, appeared to be more stable than with heparin. Thus, like other thrombin inhibitors, efegatran sulphate is easier to administer than heparin. However, no clinical benefits of efegatran over heparin were apparent.

Introduction

Acute coronary ischemic syndromes are usually the result of a ruptured atherosclerotic plaque, followed by platelet aggregation, often in combination with increased vasomotor tone, leading to a sudden increase in the pre-existing stenosis [1,2]. This process may culminate in one or more episodes of impaired flow without myocardial necrosis and the syndrome of unstable angina [3], or progress into total coronary occlusion and myocardial infarction. Thrombin plays a key role in this process. It causes fibrin formation through proteolytic cleavage of plasma fibrinogen, and induces platelet activation and aggregation [4,5]. Thus, drugs which directly inhibit thrombin, such as efegatran sulphate, have been considered for the treatment of unstable angina, in order to prevent recurrent ischemic episodes and progression into myocardial infarction. Efegatran sulphate is a tripeptide, direct acting thrombin inhibitor. Unlike heparin it has the capacity to bind directly to thrombin, and to inactivate both circulating and clot-bound thrombin [6]. Efegatran sulphate also inhibits thrombin-induced platelet aggregation. The primary objective of the present study was to assess the safety and efficacy of different doses of efegatran sulphate compared to heparin in patients with unstable angina. Safety was assessed clinically with particular reference to bleeding occurrences and by measurement of laboratory parameters. Efficacy was assessed primarily by comparison of the number of patients experiencing any episode of recurrent ischemia, as measured by computer-assisted 48h continuous ECG ischemia monitoring during different treatment regimens. The latter technique has proven to be useful for detection and quantification of recurrent ischemia (related to clinical outcome) and for assessment of treatment efficacy in patients with refractory unstable angina who are treated with a platelet glycoprotein IIb-IIIa receptor blocker [7,8]. Clinical end-points were the incidences of recurrent angina, myocardial infarction or coronary intervention (PTCA or CABG) and death at 7 days and 30 days follow-up. The first stage of this study was a dose ranging programme to assess the ex-vivo anticoagulant and anti-thrombotic effect and the bleeding risk associated with administration of five dose regimens of efegatran sulphate in 132 patients with unstable angina, compared to heparin. These results were used for selection of two dose levels of efegatran sulphate which were compared to heparin in a subsequent study of 300 patients.

Patients and methods

Study patients

Patients between 21 years and 75 years old with a clinical diagnosis of unstable angina were eligible for the study. For inclusion, patients should exhibit at least one episode of angina at rest or minimal exertion and have

concomitant transient ST- and/or T-wave changes on their ECG, either at admission, or during observation in hospital. Patients were excluded for any of the following reasons: ECG abnormalities making ST-T segment interpretation unreliable, such as left bundle branch block, left ventricular hypertrophy or artificial pacemaker rhythm; suspected acute myocardial infarction or recent myocardial infarction (within the hospitalization period), unless creatine kinase had returned to less than twice the normal upper limit; heparin treatment since the most recent episode of ischemia prior to study enrolment; known aspirin allergy or other contraindication for aspirin; concurrent use of oral anticoagulants (coumarins) at the time of study entry, or anticipated need for oral anticoagulants during the study period; recent administration of a thrombolytic agent, unless fibrinogen values had returned to more than 50% of the normal lower limit; activated partial thromboplastin time and prothrombin time values exceeding the normal upper limits, within the 24h prior to study enrolment; active internal bleeding or peptic ulcer; bleeding risk factors such as recent surgery, major trauma, gastrointestinal or genito-urinary bleeding, puncture of noncompressible vessels or organ biopsy in the 3-month period prior to enrolment; a history of cerebrovascular accident, transient ischemic attack, cranial or intraspinal surgery; underlying medical conditions such as persistent hypertension despite treatment, a history of hemorrhagic diathesis, or a platelet count of less than $100*10^9$/L within the 24h prior to the study; known, or suspected major hepatic or renal disease and known hemostatic defects, including those secondary to hepatic or renal insufficiency, or a bleeding time ≥8 min (Ivy method), or ≥20 min (Simplate method) while receiving aspirin; women with childbearing potential.

Study design

A single, blind randomized multicentre comparison of different dose levels of efegatran sulphate vs. heparin was performed in patients with unstable angina. The study consisted of a dose ranging phase, where five doses of efegatran were assessed in a sequential manner. Based on the safety and efficacy findings of this dose ranging phase, two dose levels of efegatran were chosen by the Steering Committee for further evaluation in a parallel phase, in which two doses of efegatran were compared to heparin. In this second phase of the study, subjects were randomly assigned to receive either one dose level of efegatran or heparin and safety was assessed on an ongoing basis by the Steering Committee. Efficacy criteria were the number of patients experiencing any episode of recurrent ischemia as measured by computer-assisted 48h continuous ECG ischemia monitoring and the incidence of recurrent angina, myocardial infarction or coronary intervention (PTCA or CABG) and death at 7 days (dose ranging phase) and 30 days follow-up (parallel phase).

Study drug regimens

In the dose ranging phase, the patients of dosage groups 1–4 received efegatran sulphate as an initial loading i.v. bolus of 0·1 mg/kg over 15 min, followed by continuous infusion of either 0·105, 0·32, 0·63 or 0·84 mg/kg.h^{-1}. In the fifth dosage group, an i.v. loading bolus of 0·3 mg/kg over 1 min was given, followed by continuous infusion of 1·2 mg/kg.h^{-1}. The infusions were to be continued for 48±10h. The parallel design phase compared group 3 (loading dose of 0·1 mg/kg over 15 min followed by continuous infusion of 0·63 mg/kg.h^{-1}), and group 5 (loading dose of 0·3 mg/kg over 1 min followed by 1·2 mg/kg .h^{-1}) with heparin. Control patients were treated with a bolus injection of 5000 IU heparin, followed by a continuous infusion of 1000 IU .h-1 heparin for 48±10h. After this period, treatment could be continued with heparin at the discretion of the treating physician. Throughout any heparin infusion, the heparin dosage was adjusted to an activated partial thromboplastin time ratio of 2·0 to 2·5 times normal, based on local laboratory activated partial thromboplastin time values. Heparin treatment was not allowed before the start of the study, or during the infusion of efegatran sulphate. After termination of the efegatran sulphate infusion, heparin could be initiated for treatment of recurrent or continuing ischemia, at the discretion of the treating physician. All patients were concomitantly treated with aspirin. If the patient was on aspirin treatment prior to the start of study, aspirin was continued at a dose of 80 mg once daily for the first 4 days. If a patient was not on aspirin, the initial dose was a minimum of 250 mg chewed, or intravenously, followed by an oral dose of 80 mg aspirin once daily during the first 4 days. After day 4, aspirin was continued at the discretion of the physician. Nitroglycerin, beta-blockers, calcium channel blockers and other cardiovascular drugs were allowed.

Laboratory tests

The effect of efegatran sulphate and heparin on markers of thrombosis and haemostasis was assessed by measuring bleeding time (Ivy, Simplate, Surgicut and Duke method, local laboratory, dose-ranging part only), the activated partial thromboplastin time (local, and central laboratory), prothrombin time (local, and central laboratory) and fibrinogen levels (central laboratory). Levels of fibrinogen were measured using both the ACL and Clauss methods. Levels of activation markers of platelets (beta-thromboglobulin, platelet factor 4), coagulation (prothrombin fragment 1·2, fibrinopeptide A, thrombin–antithrombin complexes) and fibrinolysis (fibrin degradation products) were measured in the dose finding phase only (central laboratory). General hematology (local laboratory), chemistry (central laboratory) and urinanalysis (local laboratory) were also performed.

Efficacy criteria

The efficacy of efegatran sulphate as compared with heparin was assessed by its effect on the percentage of patients experiencing any episodes

of recurrent ischemia, measured by computer-assisted continuous ECG ischemia monitoring, as described below. Episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA with balloon or other devices, CABG) and death were also evaluated at 7 days (dose ranging phase) and 30 days follow-up (parallel phase). Definition of a myocardial infarction required either documentation of an increase in creatine kinase or creatine kinase-MB levels, or electrocardiographic changes. Creatine kinase or creatine kinase-MB levels should exceed twice the upper limit of normal (in two samples collected at different sampling times) and increase by at least 50% over the baseline value. If both creatine kinase and creatine kinase-MB values were available creatine kinase-MB took preference. Electrocardiographic changes were defined as new significant Q waves of ≥0·04s duration or with an amplitude of at least one-fourth of the corresponding R-wave amplitude in two or more contiguous leads. The onset of a myocardial infarction was derived from the occurrence of chest pain of at least 30 min duration. In the absence of chest pain, the time of measurement of the trough creatine kinase (-MB) level immediately preceding creatine kinase (-MB) rise was taken as the moment of onset of myocardial infarction, unless the time interval between these two samples was greater than 6h. Recurrent angina was defined as a re-occurrence of chest pain after the moment of randomization, with concomitant transient ST or T wave changes, not leading to a creatine kinase (or creatine kinase-MB) rise or to the development of new significant Q waves. Each patient was carefully observed for signs or symptoms of bleeding. Bleeding was classified as major, or minor. Major bleeding was defined as clinically overt, and accompanied by either transfusion of two or more units of blood, surgery for treatment of the bleeding, or intracranial location of the bleeding. Bleeding was defined as minor if it was clinically overt but did not meet the other criteria for major bleeding.

Computer-assisted continuous ECG ischemia monitoring

Continuous ECG monitoring was performed using the ELI-100 continuously updated 12-lead ECG monitoring system (Mortara Instruments, Milwaukee, U.S.A). ECG monitoring was started preferably before the start of the study drug and continued for at least 6h following termination of the study-drug infusion. The system was programmed to store median ECG complexes from the 12 ECG leads every 20 s if ≥100 μV ST segment shift was present in one lead relative to the baseline ECG of that patient, or if ≥50 μV ST shift was present in any two leads of the 12-lead ECG. If less or no ST change was present, a baseline median ECG was stored every 20 min. Median ECG complexes and ST trend data were stored on a removable hard disk or floppy disk. After completion of the recording, this disk was sent to the central ECG core-laboratory of Cardialysis Rotterdam, The Netherlands, for subsequent editing and analysis. ST changes were evaluated in a blinded fashion and considered indicative of ischemia if ≥100 μV for more than 1 min duration. The method of editing and analysis of the

recorded data has recently been described in detail 9. In brief, the onset of an ST episode was defined as a change of ST amplitude in one or more leads of at least ±100 μV from the baseline ST level, developing within a 10 min period and persisting for at least 1 min. The end was defined as a return of the ST level within ±100 μV of the baseline ST level, again lasting for at least 1 min. Episodes had to be separated from each other by at least 1 min. If ≥100 μV ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level. Postural ST changes were defined as a sudden change of the electrical axis or a sudden QRS amplitude shift in the precordial leads 9.

Statistical analysis and power calculation

Laboratory parameters were compared using analysis of variance and are expressed as medians and interquartile ranges (25th and 75th percentiles). Continuous nonparametric variables were compared using the Kruskal– Wallis test. Discrete variables are described with percentages and were compared using Fisher's exact test. A two-tailed P value was calculated in all instances. A P value of ≤0·05 was considered statistically significant. The Kaplan–Meier method was used for evaluation of event free survival and for evaluation of the time to the occurrence of a first ST episode or a recurrent ST episode, with censoring of data. Statistical difference was tested with the log rank test. Based on the data of the dose ranging group, we expected that approximately 75% of the heparin treated patients and 55% of the efegatran treated patients would exhibit ischemic episodes during the 48h continuous ECG ischemia monitoring. Power calculations indicated that approximately 100 patients per treatment group were needed to achieve a power of 80% (α=0·05).

Results

A total of 432 patients were included: 132 patients in the dose ranging phase and another 300 patients in the parallel phase. Baseline patient characteristics are summarized in Table 1. The mean age of the patients was 60 years, 70% were male, and almost all were Caucasian (98%). There were no differences in the prevalence of previous myocardial infarction, diabetes mellitus, hypertension or smoking history among the treatment groups. Fifty-eight patients (13·4%) were enrolled as having unstable angina, but actually had a myocardial infarction at presentation which became evident from subsequent creatine kinase elevation.

Table 1

Baseline data

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Male	5 (50%)	17 (68%)	83 (68%)	19 (79%)	100 (78%)	77 (63%)	301 (70%)
Mean (SD) age in years	60 (9)	60 (10)	62 (10)	59 (10)	60 (10)	61 (10)	61 (10)
Weight (kg, SD)	75 (9)	77 (12)	77 (12)	79 (10)	82 (13)	77 (12)	79 (12)
Height (cm, SD)	170 (11)	171 (10)	172 (9)	173 (7)	175 (9)	172 (9)	173 (9)
Number of patients with							
Previous MI	7 (70%)	10 (40%)	41 (34%)	11 (46%)	38 (30%)	43 (35%)	150 (35%)
PTCA	0 (0%)	0 (0%)	15 (13%)	0 (0%)	13 (10%)	14 (11%)	42 (10%)
CABG	0 (0%)	2 (8%)	15 (12%)	2 (8%)	13 (10%)	14 (11%)	46 (11%)
Risk factors							
Diabetes	0 (0%)	2 (8%)	12 (10%)	3 (13%)	14 (11%)	10 (8%)	41 (10%)
Hypercholestolaemia	5 (50%)	9 (36%)	45 (37%)	12 (50%)	56 (44%)	51 (42%)	178 (42%)
Hypertension	2 (20%)	1 (4%)	14 (12%)	0 (0%)	11 (9%)	12 (10%)	40 (9%)
Current smokers	4 (40%)	11 (44%)	42 (34%)	9 (38%)	58 (45%)	44 (36%)	168 (39%)

MI = myocardial infarction; Percentages only calculated for those patients in whom data were reported.

Markers of coagulation and bleeding time

Infusion of efegatran was associated with an increase in the activated partial thromboplastin time, the prothrombin time as well as the thrombin time, which rapidly resolved following cessation of therapy (Figure 1). The activated partial thromboplastin time increase appeared to be dose dependent. The increase in activated partial thromboplastin time associated with 1·2 mg/kg.h^{-1} efegatran was comparable to that observed with heparin (P=0·89). The activated partial thromboplastin time was more stable when using efegatran as compared to using heparin. With respect to the three major treatment groups, prothrombin time was mildly increased following administration of efegatran, with a significant difference between the 1·2 mg/kg.h^{-1} efegatran and heparin groups (P=0·006). Prothrombin time returned rapidly to normal after discontinuation of therapy (Figure 1b). Thrombin time was influenced in a strong and dose dependent manner by efegatran, while administration of heparin did not modify thrombin time (Figure 1c). Efegatran 0·63 mg/kg.h^{-1} was associated with an increase of thrombin time levels of approximately 40%, while thrombin time values doubled following the administration of efegatran 1·2 mg/kg .h-1. These differences were all highly significant (P=0·0007). Thrombin time levels returned to normal rapidly after cessation of efegatran. Fibrinogen levels decreased following administration of efegatran, and returned to baseline levels immediately following discontinuation of therapy (Figure 1d). The concentration of fibrinogen did not change under heparin. Different methods were employed to measure bleeding times. Local measurements were abnormal at baseline in 9·1% of the patients. The number of abnormal values increased slightly during infusion of heparin and efegatran, but no consistent pattern emerged across the different treatment groups.

Markers of coagulation activation

Levels of activation markers were measured in the dose finding phase group only and were therefore available in a limited number of patients. It should be appreciated that the concentrations of all these parameters, with the exception of the fibrin degradation products, could have been affected artificially as a result of a traumatic vein puncture, although attempts were made to avoid this. Levels of beta-thromboglobulin and platelet factor 4 showed wide variability at baseline, during treatment with heparin and efegatran, and following discontinuation of medication. No consistent changes were observed, and no differences between the treatment groups could be established. Also fibrinopeptide A, prothrombin fragment 1·2, thrombin-antithrombin complexes and fibrin degradation products did not change significantly during treatment with heparin or efegatran.

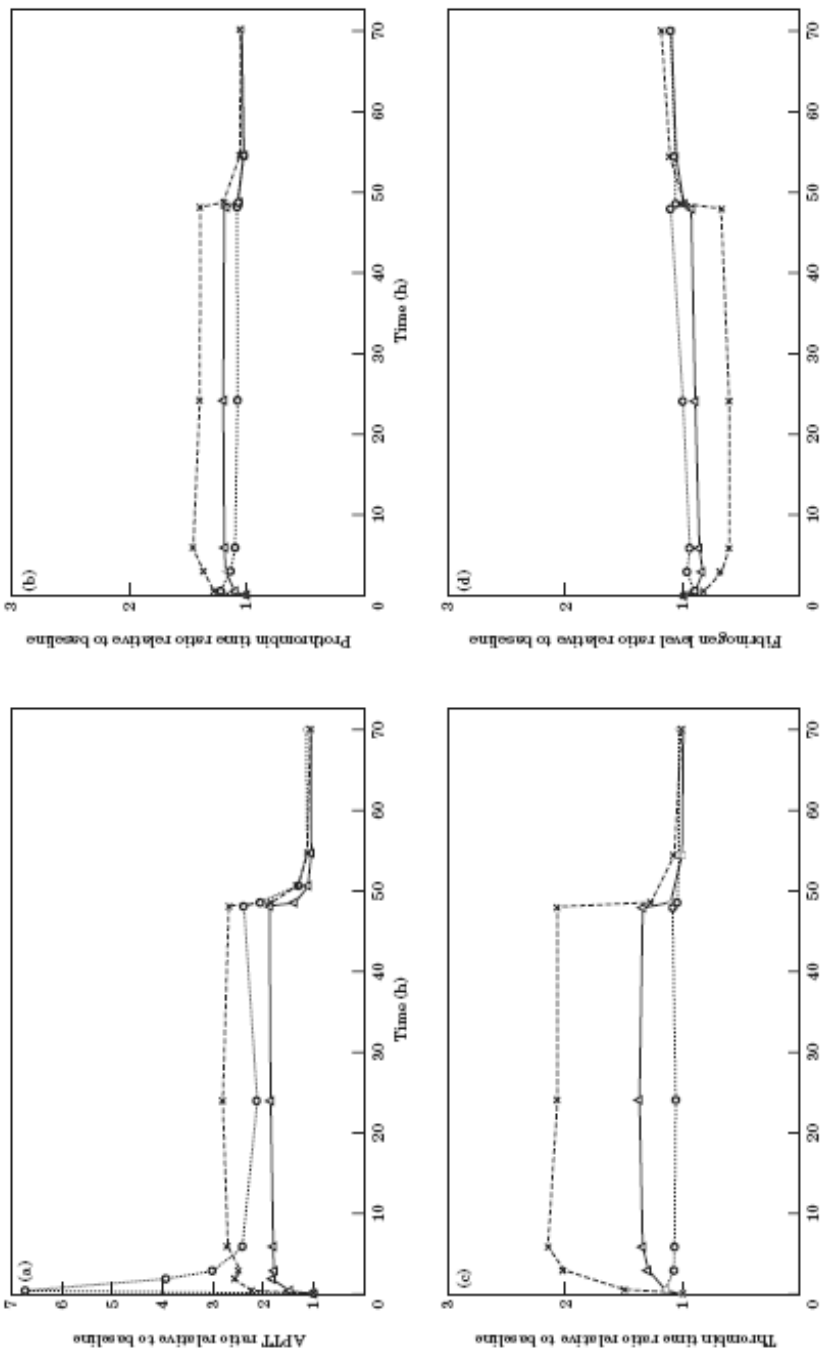

Figure 1 Activated partial thromboplastin times (APTT), prothrombin times, thrombin times and fibrinogen levels of the three major treatment groups. (a) Ratio of median activated partial thromboplastin times relative to baseline value; (b) ratio of median prothrombin times relative to baseline; (c) ratio of median thrombin times relative to baseline; (d) ratio of median fibrinogen levels relative to baseline levels. —x— = efegatran 1-2; —△— = efegatran 0-63; - -◇- - = heparin.

Recurrent ischemia during computer-assisted continuous ECG ischemia monitoring

Good quality ECG recordings were obtained in 405 patients (93%). One hundred and fourteen patients were randomized to one of the six treatment groups in the dose finding phase, and 291 to one of the three treatment groups of the parallel design phase. For all patients, the median (25–75 percentiles) total ECG monitoring time from the start of study drug until the end of monitoring was 51 (46–54)h. Total analysable ECG monitoring time was 46 (39–50)h and did not differ across treatment groups. The median ECG recording data loss was 6% (2–6). Recurrent ischemic episodes were observed in 64% of all patients. Symptomatic episodes occurred in 14% of patients. The median number of episodes (25–75 percentiles) per patient (normalized to 24 h) was 0·6 (0–3·4) and the total duration of ischemic episodes per patient in those patients with ischemia was 10 (4–17) min (Table 2). Ischemia of ≥30 min duration was present in 27% of all patients. There was no significant difference between the number of patients with recurrent ischemia or the number or duration of ischemic episodes among the treatment groups, although there was a trend towards less prolonged ischemia with the higher doses of efegatran compared to heparin (P=0·068). Figure 2 demonstrates Kaplan–Meier estimates of the probability of remaining free of recurrent ischemia during the course of the monitoring period for the three largest groups. Overall, the median time to the first episode in patients with recurrent ischemia was 9·2h. The risk of a first, second or third recurrent ischemic episode was comparable among the three treatment groups. There was no evidence of a rebound of ischemia following cessation of efegatran or heparin administration (data not shown).

Clinical outcomes

Recurrent angina was frequent in all groups, but only 2·1% and 0·5% of patients experienced a myocardial infarction or death at 7 days follow-up, respectively (Table 3). The percentage of patients that reached the composite end-point (recurrent angina, myocardial infarction, ischemia driven coronary intervention or death) at 7 days ranged from 52% to 71% in the efegatran treatment groups and was 71% in patients treated with heparin. Although the need for percutaneous interventions in the efegatran treated patients was slightly higher than in the heparin group (9%, vs. 4% in the heparin treated patients), no significant differences were observed among the treatment groups. At 30 days follow-up, the percentage of patients that reached the composite end-point was 73% and 81% in the efegatran treatment groups, and 81% in those treated with heparin. Only 3·2% and 2·1% of patients experienced a myocardial infarction or death at 30 days follow-up, respectively (Figure 3). The relationship of ischemic episodes during treatment with subsequent death and myocardial infarction was explored but the number of these complications was too low for a meaningful assessment of such an association.

Table 2

Number and duration of ischaemic episodes during continuous ECG ischaemia monitoring

	Efegatran 0·105	Efegatran 0·32	Efegatran 0·63	Efegatran 0·84	Efegatran 1·2	Heparin	All
Patients	7	21	115	18	124	120	405
Ischaemic episodes*							
≥1 ST episode	5 (71%)	17 (81%)	68 (59%)	10 (56%)	80 (65%)	77 (64%)	257 (64%)
≥2 ST episodes	4 (57%)	10 (48%)	53 (46%)	7 (39%)	55 (44%)	55 (46%)	184 (45%)
≥3 ST episodes	2 (29%)	7 (33%)	37 (32%)	5 (28%)	34 (27%)	34 (28%)	130 (32%)
Patients with ≥30 min ischaemia*	2 (29%)	7 (33%)	31 (27%)	2 (11%)	28 (23%)	39 (33%)	109 (27%)
Total duration/pt (min)*, **	11 (6, 14)	11 (4, 16)	8 (3, 16)	11 (3, 13)	8 (3, 16)	12 (5, 20)	10 (4, 17)
Time to first episode (h)**	13·7 (2·1, 22·1)	9·2 (4·0, 37·5)	9·1 (1·8, 21·5)	9·0 (2·9, 20·6)	10·9 (2·3, 20·4)	7·5 (1·9, 21·6)	9·2 (2·2, 21·3)

*Normalized to 24 h of recording **Median, 25, 75 percentiles, patients with ischaemia only.

Table 3

Clinical end-points at seven days from randomization.

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Composite end-point reached*	7 (70%)	13 (52%)	77 (63%)	17 (71%)	84 (66%)	87 (71%)	285 (66%)
Death	—	—	2 (1·6%)	—	—	—	2 (0·5%)
Myocardial infarction /reinfarction	—	—	3 (2·5%)	—	3 (2·3%)	3 (2·4%)	9 (2·1%)
Recurrent angina	6 (60%)	13 (52%)	76 (62%)	17 (71%)	84 (66%)	85 (69%)	282 (65%)
PTCA	—	—	11 (9%)	—	10 (8%)	5 (4%)	26 (6%)
CABG	1 (10%)	—	1 (0·8%)	—	3 (2·3%)	4 (3·3%)	9 (2·1%)

*Composite end-point defined as the occurrence of either death, myocardial infarction, recurrent angina or need for revascularisation

Table 4

Bleeding events

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Major bleeding (total)	—	—	1 (0·8%)	—	—	2 (1·6%)	3 (0·69%)
Haematoma at puncture site	—	—	1 (0·8%)	—	—	—	1 (0·2%)
Gastro-intestinal bleeding	—	—	—	—	—	1 (0·8%)	1 (0·2%)
M. psoas bleeding	—	—	—	—	—	1 (0·8%)	1 (0·2%)
Minor bleeding (total)	2 (20%)	8 (32%)	35 (29%)	4 (17%)	39 (31%)	13 (11%)	101 (23%)
Haematoma at puncture site	1 (10%)	5 (20%)	16 (13%)	2 (8%)	17 (13%)	4 (3%)	45 (10%)
Other	1 (10%)	3 (12%)	19 (16%)	2 (9%)	22 (18%)	9 (8%)	56 (13%)

Adverse events and bleedings

Patients receiving efegatran often developed a superficial thrombophlebitis that seemed to increase, although not significantly, in severity in the higher dose groups, the incidence ranging from 7·7% to 20%, which was significantly higher than with heparin (P=0·0001). For this reason the infusion rate in the highest dose group during the dose ranging phase was increased from 4 ml/h to 40 ml/h with a subsequent decrease in the concentration of efegatran administered. This regimen was also used for the subsequent phases of the study, and did reduce the severity of the events. However, it did not reduce the overall occurrence of phlebitis. In the second phase of the study, the number of patients with phlebitis in the 0·63 mg/kg.h^{-1} dose group was 13%, compared to 25% in the 1·2 mg/kg.h^{-1} dose group and 2% in the patients treated with heparin. In the great majority of patients, the severity of the phlebitis was only mild. The incidence of minor bleeding events was significantly higher in patients treated with efegatran (P=0·001) ranging from 17% to 32%, against 11% in patients under heparin (Table 4). There were three major bleedings, two of which occurred in patients treated with heparin. Spontaneous gross hematuria was equally distributed and observed in three patients (0·7%). Most minor bleedings were associated with a previous puncture site, and did not require specific measures. There were no strokes associated with administration of trial medication.

Discussion

In this multi-centre single-blind dose finding study, the antithrombotic effects of the direct acting thrombin inhibitor efegatran sulfate were compared with heparin in patients with unstable angina. At similar levels of ex-vivo anticoagulation, activated partial thromboplastin times were more stable for the direct thrombin inhibitor. However, no clinical advantages for efegatran were apparent, while mild or moderate bleeding and thrombophlebitis were more frequent.

Anticoagulant effects

Efegatran demonstrated a dose-dependent anticoagulant activity, with the highest dose level of 1·2 mg/kg.h^{-1} resulting in a steady state activated partial thromboplastin time value of about three times baseline. Furthermore, administration of efegatran was associated with a pronounced increase in thrombin time. Fibrinogen levels decreased in patients treated with efegatran. There were no demonstrable effects on the levels of coagulation activation markers. The extent of thrombin inhibition as measured by the activated partial thromboplastin time appeared to be more stable with efegatran than with heparin, especially during the first hours following initiation of therapy during which activated partial thromboplastin time

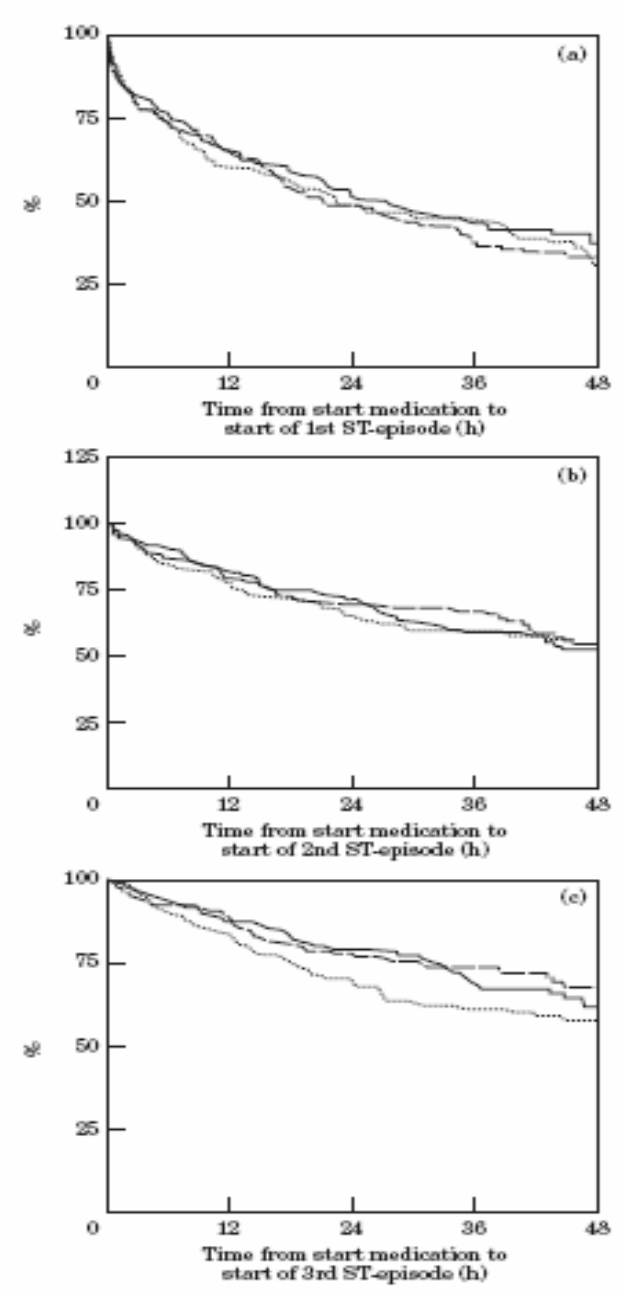

Figure 2

Kaplan–Meier estimate of the probability of remaining free of an ST-episode during the course of the monitoring period. (a) Probability of remaining free from a recurrent ST episode from the start of medication. The continuous curve represents the patients treated with efegatran 0·63 mg/kg.h^{-1} (115), the broken curve the patients treated with efegatran 1·2 mg/kg.h^{-1} (124) and the dotted curve the patients treated with heparin (120). (b) Probability of remaining free of a second ST episode from the start of medication. (c) Probability of remaining free of a third ST episode from the start of medication.

guided dose adjustments were made in the heparin treated patients. This may have been due to the effect of the relatively high initial dose of heparin, which has a pronounced effect on activated partial thromboplastin time. Similar observations have been reported for other direct thrombin inhibitors [10–14]. The incidence of minor bleeding was higher in patients treated with efegatran compared to patients treated with heparin. However, there was no excess in major bleeding for either dose of efegatran and there were no strokes associated with trial treatment. These results are similar to other studies in patients with acute coronary syndromes receiving anti-thrombin therapy, which reported no, or only a modest, increase in minor bleeding events compared to heparin [13,14,17]. A higher incidence of bleeding events was reported using thrombin inhibitors in combination with thrombolytic agents [11,12,15,16,18]. This led to interruption of three trials studying the effects of hirudin in patients with an acute myocardial infarction or acute coronary syndromes [15,16,18]. Two of these (TIMI 9b and GUSTO IIb) were restarted at lower doses of hirudin, with activated partial thromboplastin time guided dosing regimens [11,12]. In GUSTO IIb, 25% of patients received concomitant thrombolytic therapy. Compared to heparin, the administration of low dose hirudin appeared to be associated with an increased major bleeding rate (7·9% vs. 6·9%, P=0·03), with an excess of intracranial hemorrhages in patients without ST elevation, who had not received concomitant thrombolytic therapy (0·2% vs. 0·02%, P=0·06). In TIMI 9b, all patients received concomitant thrombolytic therapy, and similar bleeding rates were observed for hirudin and heparin treated patients.

Efficacy and clinical outcome

Neither dose of efegatran suppressed recurrent myocardial ischemia during 48h continuous ECG ischemia monitoring to a greater extent than that seen with heparin, and there were no differences in clinical outcome between the efegatran and heparin groups. Of note was the high incidence of patients with a myocardial infarction at the time of enrolment (58 patients, 13·4%) and the subsequent low incidence after enrolment into the study (14 patients, 3·2%). This was due to the selection process since the majority of patients was enrolled directly after admission to hospital, without knowledge of possibly elevated creatine kinase and creatine kinase-MB enzyme levels. Our data confirm the results of other studies on direct thrombin inhibitors, which reported only equivalent or slightly improved outcome compared to heparin, sometimes at the cost of a higher incidence of bleeding [11–19]. Of all studies with direct thrombin inhibitors, only the OASIS study reported superiority of hirudin over heparin in preventing both short- (7 days) and long-term (180 days) ischemic outcome in patients with acute myocardial ischemia without ST-segment elevation [17]. As in our study, there was no significant increase of major bleedings, while the incidence of minor bleeding events was higher for hirudin compared with heparin.

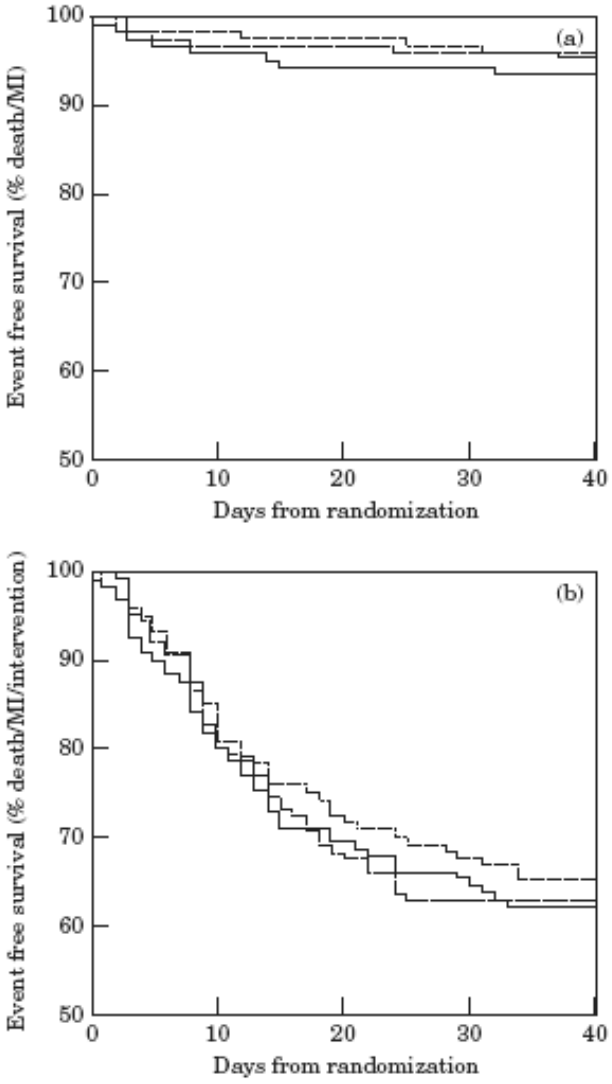

Figure 3

Kaplan–Meier event free survival from the moment of randomization un-til 30 days follow-up. (a) Event-free survival from death or myocardial infarction (MI). (b) Event-free survival from death, myocardial infarction (MI) or coronary intervention. Abbreviations as in Figure 2.

In the HELVETICA study, treatment with hirudin peri- PTCA was associated with fewer early cardiac events during the first month, without an increased risk of bleeding, but no apparent benefit was present at 7 months follow-up [19,20]. A similar study of hirulog vs. heparin showed a reduction in immediate (in-hospital) ischemic complications in a pre-defined group of patients with post-infarction angina only [14]. Again, this difference was no longer apparent after 6 months follow-up. Dosing regimens and duration of

treatment of both heparin and anti-thrombins varied widely across these studies, making comparisons difficult. As only one study demonstrated a persisting beneficial effect from these agents, it is possible that the duration of treatment (24h to 5 days maximum) may have been too short to obtain long-term clinical benefit. Rebound effects may also have influenced long-term outcome, although these were not observed in the present study [17]. The lack of clinical benefit may be related to the mechanism of action of direct antithrombins, which have a greater ability to decrease thrombin activity (also clot-bound thrombin) than heparin, while the latter has a greater ability to decrease thrombin generation, as it inhibits earlier steps in the coagulation cascade, which are not affected by direct thrombin inhibitors [21]. Such combined inhibition of both thrombin generation and thrombin activity may in fact be advantageous. However, no such effect was observed in the present study.

Conclusions

We compared the effect of efegatran, a direct thrombin inhibitor with heparin. Administration of efegatran sulphate at levels of at least 0·63 $mg/kg.h^{-1}$ provided a pronounced increase in thrombin time, which is at least comparable to activated partial thromboplastin time adjusted heparin infusion. The level of thrombin inhibition by efegatran, as reflected by the activated partial thromboplastin time, appeared to be more stable than with heparin, especially during the first few hours following initiation of therapy, which may be due to the relatively high initial dose of heparin. This may reflect a more predictable dose response, suggesting that efegatran sulphate administration is probably easier to monitor than heparin. As thrombin plays a key role in the coagulation cascade it was expected that the direct effects of efegatran would result in a more potent antithrombotic effect compared to heparin, which acts indirectly, requiring antithrombin III as a cofactor. However, no clinical benefit of efegatran over heparin was apparent whereas minor bleeding was more frequent. Our findings are in concert with other studies investigating direct thrombin inhibitors.

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Summary, conclusions and perspective

When patients are suffering an acute coronary syndrome (ACS) it is important to know, for themselves, but also for their treating physicians and for allocation of available resources, what their risk will be for developing a new cardiovascular event not only at short-term but also during long-term follow-up. Risk assessment may help to select the optimal management to reduce the risk of untoward events. In this thesis we evaluated different aspects of this subject.

In chapter 1 long-term cardiovascular outcome of 1265 patients with refractory unstable angina treated with the glycoprotein IIb/IIIa receptor antagonist abciximab enrolled in the CAPTURE trial was investigated. Lower rates of the composite endpoint of death or myocardial infarction with abciximab vs. placebo were sustained from discharge until 4 year follow up: 15.7% vs. 17.2% (p=NS). The risk reduction was significant in patients with elevated troponin T: 16.9% for patients treated with abciximab vs. 28.4% receiving placebo (p=0.015) while no effect was observed in troponin negative patients. Both elevated troponin T and high sensitive C-reactive protein (hsCRP) were associated with impaired outcome, independently of other established risk factors, but with a different course in time. Elevated troponin as a marker of myocardial damage after a thrombotic occlusion was associated with increased procedure related risk, and elevated hsCRP as a marker of inflammation with increased risk for subsequent cardiovascular events. Elevated hsCRP was not associated with specific benefit of abciximab, suggesting that the chronic inflammatory process is not affected by abciximab. In contrast the benefit of treatment in patients with elevated troponin T implies that the acute thrombotic process in refractory unstable angina is treated effectively.

In chapter 2 the new biomarker placental growth factor (PlGF), a member of the vascular endothelial growth factor (VEGF) family and a more specific vascular inflammatory instigator of atherosclerotic plaque instability than a marker of general inflammation like hsCRP, is evaluated as predictor for long-term mortality and cardiovascular morbidity in the CAPTURE trial. Patients with PlGF levels in the fourth and fifth quintile (>27 ng/L) had higher mortality than those with lower levels (10.8% versus 3.2%; hazard ratio 3.3 and 95% CI 1.6 to 7.1), as well as higher incidence of the composite endpoint of death or myocardial infarction (27.6% vs. 11.3% events; hazard ratio 2.6 and 95%CI 1.7 to 3.9). The relation between PlGF and the composite endpoint remained significant after adjustment for different patient characteristics. The prognostic effect of hsCRP however became not significant in the multivariable analysis when adding PlGF suggesting that PlGF as a more specific marker of vascular inflammation should be considered for risk stratification in patients with ACS rather than a general marker of inflammation.

In the chapter 3 we studied the relation between a series of biomarkers each reflecting distinct pathophysiological aspects of vascular inflammation and the occurrence of cardiovascular events in the CAPTURE trial. After adjustment, either in patients receiving placebo or in the entire study population, troponin T, interleukin-10 (IL-10), myeloperoxidase (MPO), and

placental growth factor (PlGF) remained significant predictors of all-cause death or non-fatal myocardial infarction independent of clinical variables. In a simple model counting the presence or absence of these biomarkers, 4 year risk was 3.3% in placebo patients with all markers within the normal range, as compared to 38.6% in patients with 3 or more markers in the abnormal range. For the entire study population, event rates were 6.0% and 35.8%, respectively. These results confirm that in patients with ACS, long-term adverse cardiac outcome can be predicted using biochemical markers characterizing distinct aspects of the underlying inflammatory atherosclerotic process and the myocardial damage of the accompanying cardiac event.

By treating "more aggressively" with anti-thrombotic medication like the glycoprotein IIb/IIIa receptor antagonist abciximab in combination with aspirin, clopidogrel and heparin patients have higher risk for bleeding events. In chapter 4 bleeding events in the GUSTO IV-ACS study, where placebo was compared with a 24 or 48 hour infusion of abciximab in patients with ACS, were analysed. Bleeding in hospital or within 7 days was observed in 19.3% of the 7800 patients enrolled. Major bleeding occurred in 1.2% in total and in 1.8% with 48 hours of abciximab, 1.0% with 24 hours of abciximab and 0.9% with placebo ($p<0.0001$, for 48 hour infusion against placebo). In 2.8% a minor and in 15.3% an insignificant bleeding event was reported. Most bleeding was spontaneous; however major and minor bleeding were more frequently associated with procedures, particularly with PCI or CABG. Predictors for major bleeding after adjustment were performance of CABG or PCI, the 48 hour infusion of abciximab and advanced age. Treatment with abciximab in NSTE ACS patients is not associated with a large excess of major bleeding events and the majority of bleeds is clinically manageable or has little clinical consequences. Guidelines for use of abciximab, especially in combination with other anti-thrombotic medication, should be respected and specific dosing guidelines for combination with e.g. low molecular weight heparins should be developed for patients who subsequently will undergo a PCI.

As patients are getting older the need for risk models developed in appropriate patient populations increases. In chapter 5 we describe risk predictors for all cause mortality in 433 consecutive patients older than 75 years of age having their first ST-elevation myocardial infarction. We also evaluate to what extent existing models can be used for risk stratification in the elderly. After adjustment, a higher Killip class was the most important predictor of 30-day mortality (OR 16.1; 95% CI:5.7, 45.6). Elevated heart rate, longer time delay between first pain and admission and hyperglycaemia at admission were other independent predictors. Age also remained an independent predictor. Patients with hypercholesterolemia had a significant lower risk (OR 0.46; 95% CI:0.24, 0.86). Discrimination (c-statistic:0.79, 95% CI:0.75-0.84) and calibration (Hosmer-Lemeshow: 6 and $p=0.5$) of our model were good. The often used GUSTO and TIMI risk scores produced adequate discrimination within our dataset (c-statistic:0.76, 95% CI:0.71-0.81; and 0.77, 95% CI:0.72-0.82, respectively). Calibration however was

not good (HL 21.8, p=0.005 for GUSTO, and HL 20.6, p=0.008 for TIMI). It appears therefore that existing risk models created in a study population with younger patients can produce a rough estimate of the mortality risk but are not adequate for providing an exact estimate of the risk of death in this elderly population.

When patients are hospitalised their risk is modified by treatment given in hospital. Risk calculation for future events using variables obtained at discharge therefore seems more appropriate than risk assessment based on admission data only. In chapter 6 we describe the result of 5-year survival data as collected in 1043 patients discharged alive after a myocardial infarction, who were enrolled in the two European Cooperative Study Group trials and were treated with placebo, recombinant tissue plasminogen activator (rTPA), or rTPA with additional immediate PTCA. Mortality was 10.7% in the placebo group versus 11.0% in the comparative rTPA group. The patients treated with rTPA and immediate PTCA had a mortality rate of 10.5% versus 8.9% in the rTPA group without PTCA (all P=NS). Multivariate proportional hazards analysis, including discharge angiographic data, demonstrated that long-term survival depended on infarct size, residual left ventricular function, number of diseased vessels and TIMI perfusion grade at discharge. Patients with TIMI grade 2 flow at discharge had mortality rates similar to those with TIMI flow grades 0 and 1, while prognosis was better in patients with TIMI flow grade 3. TIMI perfusion grade 2 at discharge should therefore be considered as an inadequate result of therapy. This finding has been confirmed afterwards in a study using TIMI flow grade [1] and also in several studies using the derived TIMI frame count [2,3].

In chapter 7 we demonstrate in a large cohort of 10484 consecutive patients with an ACS that 1426 survivors of the first 24 hours receiving statins for the first time as compared to 6771 first day survivors not receiving statin therapy had a significantly reduced all cause 7 day mortality (0.4% vs. 2.6%; unadjusted HR 0.16; 95% CI: 0.08-0.37, adjusted HR 0.34; 95% CI 0.15-0.79). Statistical significance was observed in patients presenting with STE-ACS (adjusted HR 0.17; 95%CI 0.04-0.70) and not in NSTE-ACS patients (adjusted HR 1.0; 95%CI 0.34-2.9). However no statistical evidence of heterogeneity in treatment effect was observed between these groups. These data suggest that very early statin therapy is associated with reduced mortality in patients presenting with STE-ACS and should be initiated immediately after hospitalisation without delay. These observations should be confirmed by a randomized trial.

Newer medication is not always better as contemporary treatment. In chapter 8 a phase II trial of efegatran, a direct thrombin inhibitor, is described in which five dose levels, ranging from 0.105 to 1.2 mg/kg per hour during a 48 hour infusion were studied and compared to unfractionated heparin in patients with unstable angina pectoris. Administration of efegatran sulphate at levels of at least 0.63 provided an antithrombotic effect which was comparable to an activated partial thromboplastin time adjusted heparin infusion. The level of thrombin inhibition by efegatran, as measured by activated partial thromboplastin time, appeared to be more stable

than with heparin. However, neither of the efegatran doses studied were able to suppress myocardial ischemia during continuous ECG ischemia monitoring to a greater extent than that seen with heparin. There were no statistically significant differences in clinical outcome or major bleeding between the efegatran and heparin groups. Occurrence of minor bleeding and thrombophlebitis was significantly higher in efegatran compared to heparin treated patients (32% vs. 11%). Thus, efegatran is easier to administer than heparin, however, no clinical benefits over heparin were apparent and minor bleeding complications more frequent. Therefore further development for use of this drug was discontinued by the manufacturer.

Perspective

Cardiovascular diseases are a major cause of the loss of healthy life-years in Western countries. Annually, in The Netherlands approximately 45.000 patients die due to cardiovascular diseases, which is one third of all-cause mortality, whereas the number of hospital admissions for these diseases amounts 300.000 each year. Ischemic heart diseases are responsible for approximately 30% of cardiovascular deaths and hospital admissions [4]. Ischemic heart diseases will remain a major health issue during the decades ahead, for several reasons. First, ischemic heart diseases will continue to occur at early ages in individuals with an adverse life style, in subjects with unrecognised and untreated mediating conditions (e.g. the metabolic syndrome), and in those with a genetic predisposition. Furthermore, patients with established cardiac disease are at increased risk of future events and finally, the Western world is ageing, and heart diseases come with age. Therefore, the development and implementation of risk stratification and -modification strategies are crucially important for patients and society.

During the last decades our understanding of the pathophysiology of ischemic heart diseases has considerably improved. Based on these insights, a broad range of treatment strategies have been developed to optimise patient management and outcome. For example, fibrinolytic therapy and direct PCI was introduced to reduce infarct size in patients presenting with ST-elevation, statin therapy for secondary prevention of acute coronary syndromes, ACE-inhibition to slow progression and improve survival in heart failure and implantable cardioverter defibrillators for the prevention of sudden arrhythmic death. One of the challenges for contemporary cardiology is to rationally implement the available therapies in clinical practice, in the appropriate patients at the appropriate time. Before a certain therapy will be initiated, a physician must consider the probability that the patient will improve with or may deteriorate without therapy, the risks of adverse events, and, last but not least, the therapy-related costs. For this reason, the improvement of our ability to make accurate predictions should be one of the key aspects of future research. The risk-stratification and -modification models as presented in this thesis form a (small) link in this research chain. To move the field forward, efforts should

be made on three main (and coherent) aspects: the readability and applicability of treatment guidelines, the accessibility of the non-trial-related part of our acquired knowledge, and the development of automated decision-information systems.

Clinical trials and guidelines

Newly developed therapies are usually introduced in clinical practice after proof of their efficacy and safety by (randomised) clinical trials. The results of these trials apply basically to a patient population that is defined by the trial in- and exclusion criteria. In clinical practice, however, cardiologists do not treat study population, but individual patients, in whom the benefits, risks, effectiveness, and cost/effectiveness of therapy depend on a large number of related characteristics. Furthermore, clinical trials that study one and the same subject do not always demonstrate unequivocal results, whereas observational studies and clinical trials not infrequently show even opposite results. Consequently, estimates of treatment effects in clinically relevant groups of patients may be uncertain. Therefore, in clinical practice, cardiologists who intend to implement evidence-based medicine face considerable difficulties.

Part of these problems might be solved by implementation of the treatment guidelines of the European Society of Cardiology (ESC) or other societies, which summarise the evidence of several treatment options that have emerged from clinical research. At the same time, one should realise that adherence to guidelines can be a challenge by itself, as these usually contain a large number of recommendations. For example, it has been estimated that guidelines for ischemic heart disease present almost 500 recommendations [5], and it is unrealistic to assume that physicians will be able to adhere to all of these without further assistance. Indeed, the Euro Heart Survey programme demonstrated that adherence to clinical practice guidelines is suboptimal, regardless the target population [6]. Significant deviations from guideline recommendations were observed in patient populations ranging from ACS [7] to heart failure [8] and endocarditis [9]. International surveys show that this problem is not restricted to Europe [10]. It is true that other factors than the complexity of the guidelines have played a role in this respect, including disbeliefe, non-rational behaviour, and the availability of resources. Still, professional societies should be encouraged to remove obstacles that they have introduced. One might think of the development of summary guidelines that are available for hand-held Personal Digital Assistants [11], or, even better, the introduction of hyperlinks in the electronic versions of the full guideline reports, which can then be approached by hospital information systems.

Surveys, registries and hospital information systems

Guidelines do not unlock the knowledge that exists in national and international surveys and registries of routine clinical practice. These datasets, which are currently being generated for a broad range of cardiac

disease profiles (including ischemic heart diseases), provide unique opportunities to evaluate relations between patient characteristics, treatment and outcome. It will be of great value if these databases are opened up to the broader cardiology community. Particularly if on-line access to these data can be realised, then the practicing cardiologist will be able to evaluate the consequences of the treatment choices that he has in mind within an acceptable time-frame. It is important to note that large databases could (and are) also filled during routine practice. Most hospital information systems contain information on in-patients, out-patients, as well as on diagnostic evaluations, which often remain unused for optimising local care.

It is clear that database-standardisation is crucial to enable communication via computer networks. By launching the Cardiology Audit & Registration Data Standards (CARDS) project, the ESC has taken the initiative to develop data standards for acute coronary syndromes, percutaneous coronary intervention and electrophysiology.[12] The CARDS methodology can easily be applied to develop standards for other fields as well.

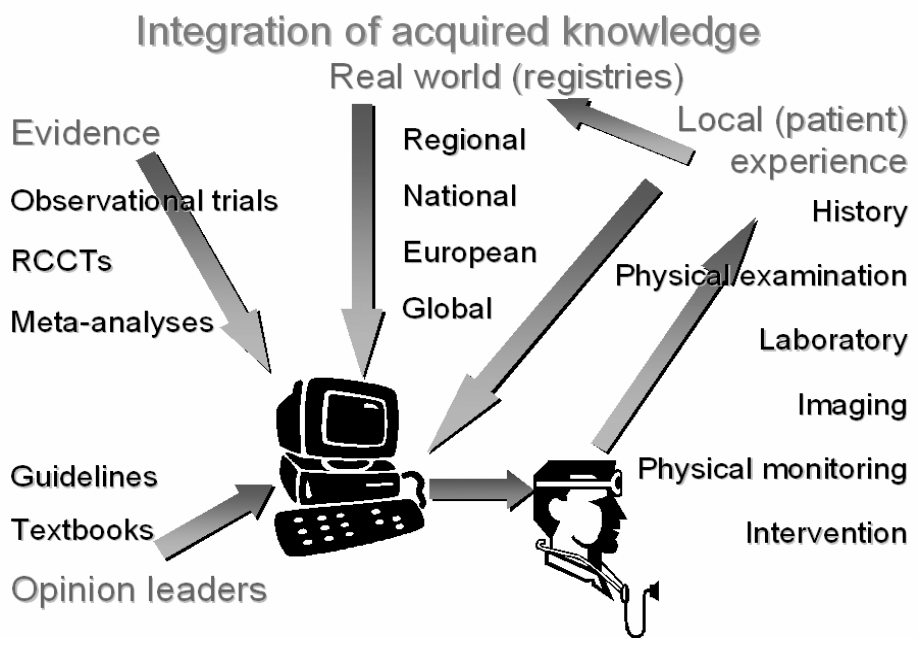

Figure 1

Automated decision support systems

The ultimate solution to make evidence-based medicine more accessible might be delivered by automated decision support systems (Figure 1). Such

systems will allow on-line access to all the collected knowledge, and simultaneously provide quantitative insight into the short- and long-term consequences of available treatment options. Such 'intelligent' tools may utilise a range of risk-evaluation and -modification models (for example the risk-models for the relation between patient characteristics and mortality after myocardial infarction, as described in this thesis). However, one might also think of more sophisticated simulation models.

Conclusion

With the use of data obtained from studies and registries the short- and long-term risk of cardiovascular events can adequately be determined in patients with acute coronary syndromes. We believe that the real-time implementation of these models in hospital information systems will help to bring evidence-based medicine nearer, as these will act as a bridge between clinical practice - and its wide variety of patients and situations - and the integrated knowledge database. Future research should focus on the development of such systems.

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Samenvatting en conclusies

Wanneer patiënten lijden aan een acuut coronair syndroom (ACS), is het belangrijk te weten, niet alleen voor henzelf, maar ook voor de behandelende artsen, wat de kans zal zijn op het krijgen van een nieuwe cardiovasculaire gebeurtenis. Hierbij is niet alleen het korte termijn risico maar ook het lange termijn risico van belang. Daarnaast is het met deze kennis ook mogelijk een eventuele betere verdeling van alle beschikbare middelen te maken. Risicoschatting kan helpen om de meest optimale behandeling te selecteren en om de lans op ongewilde uitkomsten te verminderen. In dit proefschrift worden de verschillende aspecten van dit onderwerp behandeld.

In *hoofdstuk 1* wordt een studie beschreven, die de lange termijn cardiovasculaire uitkomst onderzocht in 1265 patiënten met refractaire onstabiele angina pectoris, ingesloten in de CAPTURE studie. In deze studie werden zij behandeld met de glycoproteine IIb/IIIa receptor antagonist abciximab. Met abciximab kregen patiënten, vanaf ontslag tot en met vier jaar follow up, minder vaak een hartinfarct of overleden in vergelijking met placebo: 15.7% vs. 17.2% (p=NS). Bij patiënten met een verhoogd troponine T, die tevens abciximab ontvingen was de risicoreductie significant in vergelijking met patiënten met een verhoogd troponine T, die placebo kregen: 16.9 % versus 28.4% (p=0.015). Er was geen effect te zien bij patiënten met normaal troponine.
Zowel verhoogd troponine T als hoog sensitief C-reactive proteïne (hsCRP) waren gekoppeld aan slechtere uitkomsten onafhankelijk van andere bekende risicofactoren, ze hadden ieder echter wel een verschillend verloop in de tijd. Verhoogd troponine als een teken van myocardschade na een trombotische afsluiting was geassocieerd met een verhoogd risico tijdens de interventie procedure en verhoogd hsCRP als een teken van ontsteking was geassocieerd met een verhoogd risico op later optredende cardiovasculaire gebeurtenissen. Verhoogd hsCRP was niet gekoppeld aan een specifiek voordeel van abciximab, wat suggereert dat het chronische ontstekingsproces niet te beïnvloeden is door abciximab. Dit in tegenstelling tot het effect van behandeling met abciximab bij patiënten met verhoogd troponine T, wat suggereert dat het acute trombotische proces bij refractaire onstabiele angina pectoris effectief behandeld wordt.

In *hoofdstuk 2* wordt de nieuwe biomarker placental growth factor (PlGF), een lid van de vasculaire endotheliale groeifactoren familie (VEGF) onderzocht. PlGF is een meer specifieke instigator van het vasculaire ontstekingsproces met als gevolg atherosclerose en plaque instabiliteit. Er vond een vergelijking plaats met de meer algemene marker voor ontsteking hs-CRP, ter bepaling van het lange termijn risico op mortaliteit en cardiovasculaire morbiditeit in de CAPTURE studie.
Patiënten met PlGF waarden in het vierde en vijfde quintiel (> 27 ng/L) hadden een hogere mortaliteit dan patiënten met een lagere waarde (10.8 % vs. 3.2 % ; hazard ratio 3.3 en 95% BI 1.6 – 7.1), ook overleden meer patienten of kwamen er meer hart infarcten voor (27.6 % vs. 11.3 % ; hazard ratio 2.6 en 95% BI 1.7 – 3.9). De relatie tussen PlGF en het gecombineerde eindpunt van overlijden of hart infarct bleef significant na correctie voor

verschillende patiënten eigenschappen. De significantie van hsCRP verdween echter in de multivariaat analyse wanneer PlGF werd toegevoegd, wat suggereert dat PlGF een meer specifiek kenmerk is voor vasculaire ontsteking bij patiënten met een ACS dan een biomarker voor meer algemene ontstekingsprocessen.

In *hoofdstuk 3* onderzochten we in the CAPTURE studie de relatie tussen het krijgen van een cardiovasculaire aandoening en een aantal biomarkers, die ieder voor zich een verschillend onderdeel van het vasculaire onstekings proces kenmerken. Na correctie voor enkele klinische variabelen bleven, zowel bij patiënten die abciximab als die placebo kregen, troponine T, interleukine-10 (IL-10), myeloperoxidase (MPO) en PlGF significant belangrijke voorspellers van zowel mortaliteit als niet-fataal hart infarct.
In een eenvoudig model dat alleen de aan-, of afwezigheid telt van een biomarker was het 4 jaars risico op het ontwikkelen van het gecombineerde eindpunt in de groep die placebo kreeg en waarbij alle biomarkers normaal waren 3.3%. Bij patiënten waarbij 3 of meer biomarkers afwijkend waren was dit 38.6%. In de volledige studie populatie was dit risico respectievelijk 6.0% en 35.8%. Deze resultaten bevestigen dat het risico op lange termijn cardiovasculaire gebeurtenissen in patiënten met ACS goed voorspelbaar lijken met behulp van biomarkers die omschreven aspecten van het onderliggende inflammatoire proces bij atherosclerose aangeven. Dit naast de myocardschade die ontstaat door het begeleidende cardiale event zelf.

Door “meer agressief” te behandelen met behulp van anti-thrombotische medicatie, zoals abciximab, in combinatie met aspirine, clopidogrel en heparine zal er ook een hoger risico op (ernstige) bloedingen ontstaan. In *hoofdstuk 4* werden het aantal en soort bloedingen onderzocht die zich voordeden in de GUSTO IV-ACS studie, waarin placebo werd vergeleken met een 24 of 48 uur s regime van abciximab bij ACS patiënten.
Bloedingen die zich in het ziekenhuis of binnen 7 dagen ontwikkelden werden gezien bij 19.3% van de 7800 ingesloten patiënten. Ernstige bloedingen kwamen voor bij 1.2% van de totale populatie en bij 1.8% van de patiënten die 48 uur abciximab ontvingen. Voor het 24 uurs infuus was dit 1.0% en 0.9% voor de patiënten die placebo ontvingen ($p<0.0001$, voor 48 uurs infuus vs. placebo). Bij 2.8% van de gehele studie populatie trad een minder belangrijke bloeding op en bij 15.3% slechts een geringe bloeding. De meeste bloedingen waren spontaan; echter de ernstige en minder belangrijke bloedingen waren meer geassocieerd met procedures, in het bijzonder PCI en CABG. Na correctie waren voorspellende factoren voor het ontwikkelen van een ernstige bloeding: het doen van een CABG of PCI, het 48 uurs infuus met abciximab en hogere leeftijd. Behandeling met abciximab in patiënten met NSTE-ACS is niet geassocieerd met een forse toename van ernstige bloedingen. De meeste bloedingen zijn gemakkelijk te behandelen en hebben klinisch geringe consequenties. Richtlijnen voor het gebruik van abciximab, vooral in combinatie met andere anti-thrombotische medicatie, zullen nauwkeurig gevolgd moeten worden. Specifieke dosering richtlijnen voor patiënten die tevens een PCI zullen ondergaan en bij ge-

bruik in combinatie met bv. laag moleculair gewicht heparine's zullen ontwikkeld moeten worden.

Naarmate de patiënten ouder worden neemt de behoefte aan risico modellen in de juiste patiënten populatie toe. In *hoofdstuk 5* beschrijven we de risico factoren die mortaliteit voorspellen bij 433 patiënten ouder dan 75 jaar die opeenvolgend opgenomen zijn in verband met hun eerste hart infarct. We onderzoeken ook in hoeverre bekende risicomodellen gebruikt kunnen worden voor stratificatie bij oudere patiënten.
Een hogere Killip klasse was na correctie de belangrijkste voorspeller van 30 dagen mortaliteit (OR 16.1; 95% CI:5.7, 45.6). Een snellere hartslag, langere duur tussen opname en eerste pijnklachten en hyperglycaemie bij opname waren andere onafhankelijke voorspellers. Ook leeftijd bleef een onafhankelijke risico factor. Patiënten met hypercholesterolemie hadden een significant lager risico (OR 0.46; 95% CI:0.24, 0.86). Discriminatie (c-statistic:0.79, 95% CI:0.75-0.84) en calibratie (Hosmer-Lemeshow: 6 and p=0.5) van ons model waren goed. De vaak gebruikte GUSTO en TIMI risico scores leverden adequate discriminatie met onze dataset (c-statistic:0.76, 95% CI:0.71-0.81; and 0.77, 95% CI:0.72-0.82, respectievelijk). Calibratie was echter minder goed (HL 21.8, p=0.005 voor GUSTO, en HL 20.6, p=0.008 voor TIMI). Het lijkt dus waarschijnlijk dat bestaande risico scores ontwikkeld in jongere patiënten populaties onvoldoende exact het risico op overlijden in deze oudere populatie kunnen aangeven.

Wanneer patiënten opgenomen zijn veranderd het vervolg risico door de behandeling die hen gegeven wordt. Risico inschatting aan de hand van gegevens verkregen bij ontslag lijkt voor dat moment dan ook meer geschikt dan op basis van opname gegevens alleen. In *hoofdstuk* 6 beschrijven we de resultaten van de 5-jaars overleving verzameld bij 1043 patiënten, die ontslagen waren na een hart infarct en waren opgenomen in twee studies van de European Cooperative Study Group. Zij waren behandeld met placebo, recombinant tissue plasminogen activator (rTPA), of rTPA met aanvullend een onmiddellijke PTCA. Mortaliteit was 10.7% in de placebo groep vs. 11.0% in de vergelijkende rTPA groep. De patiënten die behandeld werden met rTPA en onmiddellijke PTCA hadden een mortaliteit van 10.5% vs. 8.9% bij patiënten in de rTPA groep zonder PTCA (allen P=NS). Multivariaat analyse met onder andere catheterisatie gegevens bij ontslag toonde aan dat lange termijn overleving afhankelijk is van infarctgrootte, resterende linker ventrikel functie, het aantal aangedane coronairen en de TIMI doorbloedings graad bij ontslag. Patiënten met een TIMI graad 2 doorbloeding bij ontslag hadden een vergelijkbare mortaliteit als de groep met TIMI 0 of 1, terwijl de prognose beter was bij patiënten met TIMI graad 3. TIMI doorbloedings graad 2 bij ontslag dient daarom als onvoldoende adequaat behandelings resultaat te worden beschouwd. De resultaten uit deze studie zijn ondertussen bevestigd in zowel een studie die dezelfde doorbloedings classificatie gebruikt [1] als in studies met een gemodificeerde TIMI classificatie [2,3].

In *hoofdstuk 7* wordt een analyse beschreven, die gedaan is bij patiënten met een ACS, genomen uit een groot cohort van 10484 opeenvolgende

patiënten. Hierin worden gegevens van 1426 overlevenden van de eerste 24 uur na opname en die voor het eerst een statine krijgen vergeleken met 6771 patiënten die geen statine hadden gekregen. Er was een significant verminderde 7 dagen mortaliteit bij patiënten die een statine kregen (0.4% vs. 2.6%; ongecorrigeerde HR 0.16; 95% BI: 0.08-0.37, gecorrigeerde HR 0.34; 95% BI 0.15-0.79). Statistische significantie werd wel gezien bij patienten met een STE-ACS (gecorrigeerde HR 0.17; 95% BI 0.04-0.70) maar niet bij patiënten met een NSTE-ACS (gecorrigeerde HR 1.0; 95% BI 0.34-2.9), statistisch bewijs voor heterogeniteit in behandel effect werd echter niet waargenomen. Deze resultaten suggereren dat het zeer vroeg beginnen met statine's is geassocieerd met een verminderde mortaliteit tijdens opname bij patienten die een STE-ACS hebben en daarom direct na opname gestart moeten worden. Deze observatie dient nog wel bevestigd te worden in een gerandomiseerd onderzoek.

Nieuwere medicatie is niet altijd beter in vergelijking met bestaande medicatie. In *hoofdstuk 8* wordt een phase II studie beschreven met vijf doseringen efegatran, een directe thrombine inhibitor, oplopend van 0.105 tot 1.2 mg/kg per uur, die vergeleken worden met ongefractioneerde heparine in patienten met onstabiele angina pectoris. De doseringen efegatran van tenminste 0.63 mg/kg per uur gaven een vergelijkbaar antithrombotisch effect als een aPTT gestuurde behandeling met heparine. Het niveau van thrombine inhibitie gemeten aan de hand van de aPTT leek echter wel stabieler dan met heparine. Desondanks kon geen van de doseringen efegatran ischemie van het myocard, gemeten aan de hand van continue ECG meting, beter onderdrukken dan heparine. Er waren geen statistisch significante verschillen in klinische eindpunten of ernstige bloedingen tussen de efegatran doseringen en heparine. Het voorkomen van minder belangrijke bloedingen en thrombophlebitis was significant hoger bij patiënten die behandeld werden met efegatran in vergelijking met heparine behandelde patiënten (32% vs. 11%). Hieruit volgde dat efegatran makkelijker te doseren was dan heparine, maar omdat er geen klinisch voordeel was en omdat minder belangrijke bloedingen vaker voorkwamen, besloot de fabrikant niet verder te gaan met de ontwikkeling van dit medicijn.

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Dankwoord

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Curriculum vitae

Timo Lenderink werd geboren op 26 mei 1964 te Apeldoorn. Hij voltooide zijn middelbare school opleiding aan het Stedelijk Gymnasium te Haarlem. De studie geneeskunde werd doorlopen aan de Rijksuniversiteit Leiden, alwaar ook het artsexamen werd behaald. Na een verplicht verblijf in Hare Majesteits rok werkte hij 7 jaar bij Cardialysis, een "Contract Research Organisatie" met voornamelijk onderzoek op cardiovasculair gebied. Hij coördineerde en begeleidde naast kleinere fase II en III studies met medicatie en stents ook grote internationale studies zoals onder andere de eerste GUSTO studie, de CAPTURE studie en de PURSUIT studie. In 1997 startte hij zijn opleiding tot cardioloog met twee jaar vooropleiding in het Elisabeth ziekenhuis te Leiderdorp (opleider: dr. F. H. Cluitmans) en vervolgde de opleiding vanaf november 1999 aan het Erasmus medisch centrum te Rotterdam (opleiders: prof. dr. J.R.T.C Roelandt en prof. dr M.L. Simoons.). Sinds 1 december 2003 is hij als cardioloog werkzaam in het Atrium Medisch Centrum te Heerlen.

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