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Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study

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Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study

The CAPTURE investigators*

Summary

Background Platelet aggregation is a dominant feature in the pathophysiology of unstable angina. Percutaneous transluminal coronary angioplasty (PTCA) in patients with this disorder carries an increased risk of thrombotic complications. Abciximab (c7E3) blocks the platelet glycoprotein IIb/IIIa receptor, thus preventing platelet adhesion and aggregation. The CAPTURE study was a randomised placebo-controlled multicentre trial to assess whether abciximab can improve outcome in patients with refractory unstable angina who are undergoing PTCA.

Methods The study recruited patients with refractory unstable angina, defined as recurrent myocardial ischaemia under medical treatment including heparin and nitrates. Predefined stopping rules were met at a planned interim analysis of data for 1050 patients, and recruitment was stopped. Data for 1265 patients (of 1400 scheduled) are presented here. After angiography, patients received a randomly assigned infusion of abciximab or placebo for 18–24 h before PTCA, continuing until 1 h afterwards. The primary endpoint was the occurrence within 30 days after PTCA of death (any cause), myocardial infarction, or urgent intervention for recurrent ischaemia. Analyses were by intention to treat.

Findings By 30 days, the primary endpoint had occurred in 71 (11·3%) of 630 patients who received abciximab compared with 101 (15·9%) of 635 placebo recipients (p=0·012). The rate of myocardial infarction was lower in the abciximab than in the placebo group before PTCA (four [0·6%] vs 13 [2·1%], p=0·029) and during PTCA (16 [2·6%] vs 34 [5·5%], p=0·009). Major bleeding was infrequent, but occurred more often with abciximab than with placebo (24 [3·8%] vs 12 [1·9%], p=0·043). At 6-month follow-up, death, myocardial infarction, or repeat intervention had occurred in 193 patients in each group.

Interpretation In patients with refractory unstable angina, treatment with abciximab substantially reduces the rate of thrombotic complications, in particular myocardial infarction, before, during, and after PTCA. There was no evidence that this regimen influenced the rate of myocardial infarction after the first few days, or the need for subsequent reintervention.

See Commentary page 1409

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Introduction

In coronary artery disease, unstable angina may develop in association with plaque fissuring or rupture, with subsequent aggregation, platelet adhesion, and intracoronary thrombosis.[1,2] An episode of unstable angina may progress to myocardial infarction or death, or may stabilise after one or more ischaemic episodes. Different classes of unstable angina have been recognised, with different event rates.[3,4] In patients who have recurrent episodes of myocardial ischaemia despite intensive medical therapy (refractory unstable angina), percutaneous transluminal coronary angioplasty (PTCA) or coronary bypass surgery is commonly used to control symptoms and to avoid progression to myocardial infarction. However, the risk of infarction and other complications during the procedure is increased in patients with unstable angina, so the risk of an early procedure must be balanced against the risk of continuing instability.[5,6]

Platelet aggregation at the site of plaque rupture is a dominant feature in the pathophysiology of unstable angina. Accordingly, inhibitors of platelet aggregation may help to prevent recurrent ischaemic episodes and myocardial infarction and reduce the risk of complications during coronary intervention.[7,8] Abciximab (ReoPro, Centocor BV, Leiden, Netherlands), the Fab fragment of the chimeric antibody c7E3, is an inhibitor of platelet glycoprotein IIb/IIIa.[9] Activation of this receptor is the final common pathway of the platelet response to different stimuli, leading to platelet aggregation. A pilot study in patients with refractory unstable angina suggested that treatment with abciximab during the 24 h before PTCA might help to prevent thrombotic complications.[10] Furthermore, administration of abciximab during and after PTCA reduces the rate of complications associated with the procedure as well as during follow-up in patients with clinical or angiographic features indicating increased procedural risk.[11,12]

The CAPTURE (c7E3 Fab antiplatelet therapy in unstable refractory angina) study was designed to assess whether abciximab, given during the 18–24 h before PTCA and continued until 1 h after PTCA, could improve outcome (avoid death, myocardial infarction, or urgent intervention) in patients with refractory unstable angina. The trial was discontinued on the recommendation of the Safety and Efficacy Monitoring Committee after interim analysis of 1050 patients (planned 1400 patients). The main results at 30 days and 6-month follow-up are presented here.

Patients and methods

Patients were recruited from 69 centres in 12 countries, between May, 1993, and December, 1995. Patients were eligible for CAPTURE if they had refractory unstable angina defined as: chest pain at rest with concomitant electrocardiographic (ECG)
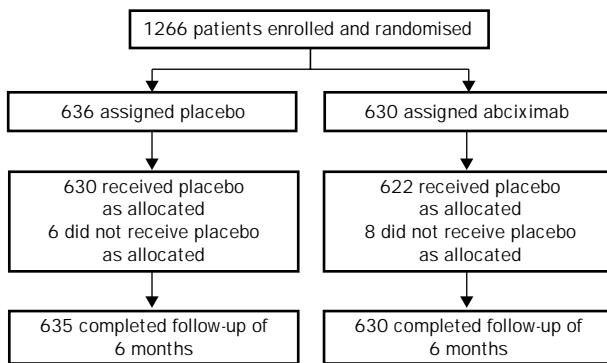
Figure 1: **Trial profile**

	Placebo (n=635)	Abciximab (n=630)
M/F	459/176	461/169
Mean (SD) age in years	61 (10)	61 (10)
Anthropometry: mean (SD)		
Weight (kg)	76 (12)	76 (12)
Height (cm)	170 (9)	170 (9)
Number of patients with		
Angina >7 days previously*	322 (51·4%)	300 (48·6%)
Infarction within previous 7 days	78 (12·3%)	88 (14·0%)
Infarction 8–30 days	43 (6·8%)	53 (8·4%)
Infarction >30 days previously	116 (18·3%)	116 (18·4%)
Infarction, date not reported	6 (0·9%)	7 (1·1%)
PTCA	86 (13·5%)	84 (13·3%)
CABG	21 (3·3%)	11 (1·7%)
Risk factors		
Diabetes*	82 (13·0%)	95 (15·1%)
Hypertension*	261 (41·4%)	271 (43·4%)
Current smokers*	255 (40·8%)	235 (37·5%)
Medication within 7 days before enrolment		
Aspirin	582 (91·7%)	586 (93·0%)
Intravenous heparin	634 (99·8%)	627 (99·5%)
Nitrates	633 (99·7%)	627 (99·5%)
β-blockers	392 (61·7%)	400 (63·5%)
Calcium antagonists	297 (46·8%)	286 (45·4%)
Medication after enrolment		
Aspirin	608 (95·7)%	604 (95·9%)
Ticlopidin	25 (3·9%)	25 (4·0%)
Intravenous heparin	616 (97·0%)	613 (97·3%)
β-blockers	395 (62·2%)	412 (65·4%)
Nitrates	616 (97·0%)	613 (97·3%)
Calcium antagonists	314 (49·4%)	289 (45·9%)

*In a few patients no data were available for these items; percentages calculated for patients in whom these data were reported.

Table 1: **Baseline data and concomitant medication**

abnormalities compatible with myocardial ischaemia (ST-segment depression, ST-segment elevation, or abnormal T waves), and one or more episodes of typical chest pain, ECG abnormalities, or both, compatible with myocardial ischaemia during therapy with intravenous heparin and glyceryl trinitrate, started at least 2 h previously. The latest episode of ischaemia should have occurred within the 48 h before enrolment, corresponding to Braunwald class III "acute" unstable angina.[3,4] All patients had undergone angiography and had significant coronary artery disease with a culprit lesion suitable for angioplasty. Patients were enrolled within 24 h of angiography, and angioplasty was scheduled 18–24 h after the start of study medication. If necessary because of recurrent ischaemia, angioplasty could be done earlier, at the discretion of the investigator.

Reasons for exclusion from the study were: recent myocardial infarction, unless creatine kinase values had returned to below two times the upper limit of normal; features of persisting ischaemia that would require immediate intervention; a greater than 50% occlusion of the left main coronary artery or a culprit lesion located in a bypass graft; bleeding risk factors such as surgery, gastrointestinal or genitourinary bleeding during the 6 weeks before enrolment, or a cerebrovascular accident within the previous 2 years; planned administration of oral anticoagulants, intravenous dextran, or a thrombolytic agent before or during PTCA; underlying medical conditions such as persistent hypertension despite treatment; history of haemorrhagic diathesis; history of autoimmune disease, or a platelet count below 100×10^9/L.

After enrolment, patients received aspirin at a minimum daily dose of 50 mg. In patients not previously on aspirin, the first dose was at least 250 mg. Heparin was administered from before randomisation until at least 1 h after the PTCA procedure, and adjusted to achieve an activated partial thromboplastin time between 2·0 and 2·5 times normal. The protocol recommended that the initial bolus dose before PTCA should not exceed 100 units/kg or 10000 units, whichever was lower. Subsequent heparin boluses were given during PTCA after clotting time had been checked. The recommended anticoagulation target was an activated clotting time of 300 s or an activated partial thromboplastin time of 70 s. Heparin was administered until at least 1 h after PTCA. All patients received intravenous glyceryl trinitrate. β-blockers, calcium-channel blockers, and other cardiovascular drugs were allowed.

In addition, patients were randomly assigned abciximab (0·25 mg/kg bolus followed by a continuous infusion of 10 μg/min) or matching placebo. Randomisation was obtained by telephone call to an independent service organised by the Department of Clinical Epidemiology of the University of Amsterdam. The randomised treatment was started within 2 h of allocation and given during the 18–24 h before angioplasty and for 1 h after completion of the procedure.

Arterial sheaths were kept in place after the diagnostic angiogram, during administration of study drug, and were exchanged before angioplasty. Balloon angioplasty was done by standard techniques. The use of stents was not encouraged,

unless required to maintain immediate patency of the dilated segment. Sheaths remained in place from the time of the qualifying angiogram until 4–6 h after discontinuation of heparin and study drug. Special care was given to obtain complete haemostasis at the site of arterial access. During the hospital stay and 30-day follow-up all events and medication were recorded, with special attention to bleeding complications and recurrent ischaemic symptoms.

The primary endpoint in the trial was the occurrence, within 30 days after randomisation, of death (from any cause), myocardial infarction, or an urgent intervention for treatment of recurrent ischaemia (angioplasty, coronary artery bypass surgery, intracoronary stent placement, intra-aortic balloon pump). A Clinical Endpoint Committee reviewed all case-report forms, ECGs, and supporting documents for confirmation that patients met the study entry criteria for refractory unstable angina; the occurrence of endpoints; the frequency of recurrent ischaemia; and important adverse events (bleeding, thrombocytopenia, and stroke).

Myocardial infarction during the index hospital stay was defined as values of creatine kinase or its MB isoenzyme more than three times the upper limit of normal in at least 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 as concentrations of creatinine kinase or its MB isoenzyme above two times the upper limit of normal, or new significant Q waves in two or more contiguous ECG leads.

Bleeding was classified as major, minor, or insignificant, by previously published criteria.[13] Major bleeds were defined as intracranial bleeding or episodes associated with a decrease in haemoglobin of more than 3·5 mmol/L (5 g/L). Bleeding was defined as minor if it was spontaneous and observed as gross haematuria or haematemesis, of if blood loss (spontaneous or not) was observed with a decrease in haemoglobin of more than 2·1 mmol/L, or if there was a decrease in haemoglobin of more than 2·8 mmol/L with no significant bleeding site identified. Blood loss insufficient to meet criteria for minor bleeding was

	Placebo (n=635)	Abciximab (n=630)
Artery with culprit lesion		
Left anterior descending	383 (60·3%)	385 (61·1%)
Left circumflex	104 (16·4%)	105 (16·7%)
Right coronary	144 (22·7%)	138 (21·9%)
PTCA timing		
Urgent (before planned)	14 (2·2%)	9 (1·4%)
18–26 h*	613 (96·5%)	597 (94·8%)
Delayed (>26 h)	8 (1·3%)	15 (2·4%)
No PTCA	11 (1·7%)	13 (2·1%)
PTCA result		
Attempted	624	617
Succeeded†	554 (88·8%)	580 (94·0%)
Failed†	70 (11·2%)	37 (6·0%)

*Prespecified time window was 18–24 h after enrolment; in 70 patients procedure was done between 24 h and 26 h for logistic reasons.
†Percentages of those attempted.

Table 2: **Angiography and PTCA results**

classified as insignificant. To account for transfusion, packed-cell volume and haemoglobin measurements were adjusted for any transfusion of packed red blood cells or whole blood within the 48 h before measurement by the method of Landefeld and colleagues.[14] Thrombocytopenia was defined as an acute fall in placelet count during or after administration of the study agent to below 100×10^9/L or a decrease of 25% or more from baseline. The protocol recommended that blood transfusion should be given according to the guidelines of the American College of Physicians.[15] These guidelines state that normovolaemic anaemia is acceptable for patients without symptoms and that those with symptoms should receive transfusions on a unit-by-unit basis to relieve symptoms.

	Placebo (n=635)	Abciximab (n=630)	p*
Death, infarction, or urgent intervention	101 (15·9%)	71 (11·3%)	0·012
Death	8 (1·3%)	6 (1·0%)	>0·1
Myocardial infarction			
Before PTCA	13 (2·1%)	4 (0·6%)	0·029
During PTCA (<24 h)	34 (5·5%)	16 (2·6%)	0·009
After PTCA (2–30 days)	5 (0·9%)	6 (1·0%)	>0·1
Non-Q-wave	36 (5·5%)†	19 (3·0%)	0·036
Q-wave	17 (2·7%)†	7 (1·1%)	0·067
Peak CK >5×normal	21 (3·3%)	10 (1·6%)	0·067
Peak CK >10×normal	15 (2·6%)	5 (0·8%)	0·040
All myocardial infarction	52 (8·2%)	26 (4·1%)	0·002
Myocardial infarction/death	57 (9·0%)	30 (4·8%)	0·003
Urgent intervention			
Urgent PTCA			
Before planned time	14 (2·2%)	9 (1·4%)	>0·1
Repeat PTCA	28 (4·4%)	19 (3·1%)	>0·1
Urgent CABG	11 (1·7%)	6 (1·0%)	>0·1
Urgent stent	42 (6·6%)	35 (5·6%)	>0·1
All urgent interventions	69 (10·9%)	49 (7·8%)	0·054
Non-urgent interventions			
Repeat PTCA	16 (2·6%)	21 (3·4%)	>0·1
CABG	9 (1·4%)	4 (0·6%)	>0·1
Stent	47 (7·4%)	49 (7·8%)	>0·1
Stroke	3 (0·5%)	1 (0·2%)	>0·1
Major bleeding‡			
Puncture site	9	19	>0·1
Retroperitoneal	0	2	>0·1
Pulmonary	0	1	>0·1
Gastrointestinal	0	3	>0·1
Urogenital	1	0	>0·1
All major bleeding	12 (19%)	24 (3·8%)	0·043
Minor bleeding‡	13 (2·0%)	30 (4·8%)	0·008
Transfusion‡	21 (3·4%)	44 (7·1%)	0·005

CK=creatine kinase; CABG=coronary artery bypass graft.
*p values (two-sided) <0·1 are reported. †One patient had both.
‡Excluding those in patients who underwent CABG.

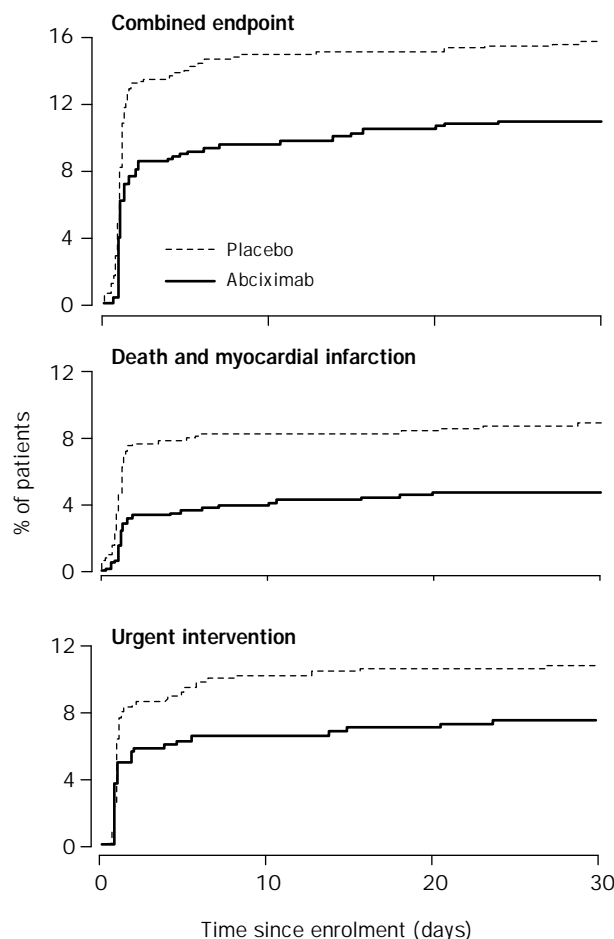Table 3: **Clinical events, 30 days' follow-up**

Figure 2: **Time course of combined primary endpoint and its major components**

ECGs were obtained before enrolment and both during and after episodes of chest pain. Additional ECGs were recorded at enrolment; 6 h, 12 h, and 18 h after enrolment; just before PTCA; 1 h, 6 h, and 24 h after PTCA; at discharge; and whenever patients experienced recurrent chest pain. In a subgroup of 365 patients, the ECG was recorded continuously from enrolment until 6 h after angioplasty. These recordings were processed as described elsewhere.[16,17] Computed 12-lead printouts were made immediately before, during, and after each episode of chest pain as well as for each episode with changes of the ST segment or T wave.[17] All ECGs were reviewed by the Clinical Endpoint Committee for signs of recurrent ischaemia or myocardial infarction. The coronary angiograms at baseline, as well as those done immediately before, during, and after angioplasty were reviewed by the Angiographic Committee.

A Safety and Efficacy Monitoring Committee was established to monitor safety data continuously, and to carry out interim analysis after enrolment of 350 and 700 patients. After the second interim analysis, the Committee recommended a third interim analysis after 1050 patients. The protocol specified that the trial would be stopped if the difference in the rate of the primary endpoint between the abciximab and placebo groups was significant with a probability value of 0·0001, 0·001, or 0·0072 at the first (350 patients), second (700 patients), or third interim analysis, respectively.

The study design was group sequential, with plans for accrual of up to 1400 patients. This sample would allow detection of a reduction in the primary endpoint from 15% to 10% with $\alpha=0·05$ and power=0·80. The Lan-DeMets method was used to assign p values for interim analyses.[18] A log-rank test was done at interim and final analyses to test for differences in the rates of occurrence of the primary endpoint in the abciximab and placebo
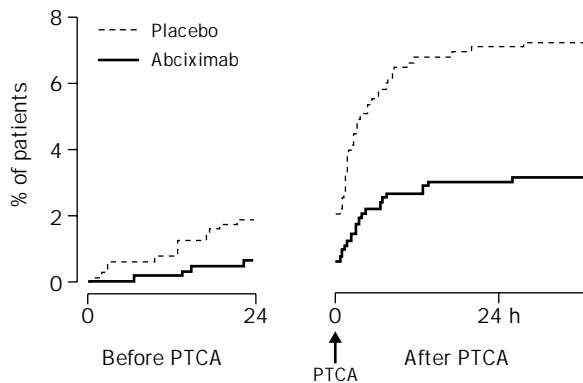
Figure 3: **Development of myocardial infarction during treatment with abciximab or placebo, before and in association with PTCA**

groups. Event rates were calculated for patients in each treatment group by the Kaplan-Meier method. Fisher's exact test was used to make pairwise comparisons between the groups for binary measurements. Logistic regression analysis was used to verify the association between bleeding complications, bodyweight, and heparin dose. Analyses were by intention to treat.

Results

The CAPTURE trial was discontinued after the third interim analysis of 1050 patients. Complete data, fully reviewed by the Clinical Endpoint Committee, were available for 976 patients, and 74 patients had been reviewed partially. By that point, 87 (16·4%) of 532 patients in the placebo group and 56 (10·8%) of 518 in the abciximab group had had a primary endpoint (death, myocardial infarction, or urgent intervention within 30 days). Since the p value for the difference (p=0·0064) was below the prespecified stopping criterion (p=0·0072), and since the data were consistent among all subgroups analysed, the Safety and Efficacy Monitoring Committee recommended that recruitment should cease. This recommendation was followed by the Steering Committee, after consultation with regulatory authorities.

Figure 1 shows the flow of patients through the trial. 1266 patients were enrolled, of 1400 scheduled. Follow-up data were complete for all but one patient (placebo) who withdrew consent after randomisation. Five other patients in the placebo group did not receive placebo (two refused but allowed follow-up and three for logistic reasons). Eight patients did not receive abciximab (one received other therapy, five withdrew consent but allowed follow-up, two for logistic reasons).

The two treatment groups were similar in terms of baseline characteristics (table 1): 73% were male, 50% had a history of angina, and 41% had had a previous myocardial infarction. 72% of patients were enrolled within 6 h of the first (diagnostic) angiogram, 60% had experienced myocardial ischaemia within the 12 h before treatment, and 95% had an ischaemic episode after a minimum of 2 h treatment with nitrates and intravenous heparin. Study drug was started in 1253 patients. It was discontinued early (before 30 min after PTCA) in 86 patients (45 placebo, 41 abciximab) for various reasons, including bleeding (one *vs* nine), bypass surgery (five *vs* one), and stent placement (eight *vs* three). Angioplasty was attempted in 1241 patients (98%). The procedure was done earlier than planned in 23 patients (1·8%), 14 of whom were in the placebo group (table 2). According to the investigators, the procedure was not successful,

	Placebo	Abciximab
Death, infarction, or intervention	193 (30·8%)	193 (31·0%)
Death	14 (2·2%)	17 (2·8%)
Myocardial infarction	59 (9·3%)	41 (6·6%)
Repeat intervention	154 (24·9%)	156 (25·4%)
Repeat PTCA	127 (20·7%)	131 (21·4%)
CABG	44 (7·1%)	33 (5·4%)

None of the differences was significant at p<0·01 (two sided).

Table 4: **Clinical events during 6 months of follow-up**

with a residual stenosis greater than 50%, in 70 patients receiving placebo and in 37 receiving abciximab (11·2 *vs* 6·0%, p=0·001). Treatment with abciximab also resulted in lower rates of urgent repeat PTCA, urgent stent placement, and bypass surgery (table 3); however, these differences were not statistically significant.

The primary endpoint (death, myocardial infarction, or urgent intervention within 30 days of enrolment) occurred in 101 (15·9%) patients in the placebo group and 71 (11·3%) in the abciximab group (p=0·012; table 3, figure 2). This difference was due mainly to a difference in the proportion with myocardial infarction (52 [8·2%] *vs* 26 [4·1%], p=0·002; table 3). The findings were consistent in all subgroups studied and were independent of age, sex, ECG findings at enrolment, and the presence of diabetes, peripheral vascular disease, or renal dysfunction.

Progression to myocardial infarction during the first 18–24 h after enrolment was rare, despite the inclusion of patients with acute, refractory, unstable angina. Even so, the frequency of myocardial infarction before PTCA was significantly lower in patients receiving abciximab than in those receiving placebo (table 3, p=0·029). Most infarcts occurred during or within 24 h of PTCA (p=0·021, figure 3), whereas infarction rates were low in both groups 2–30 days after PTCA (table 3). The lower rate of myocardial infarction in patients receiving abciximab than in those receiving placebo was found for both Q-wave and non-Q-wave infarcts, and independently of the creatine kinase threshold used to define an infarct (table 3).

Major bleeding complications occurred in only 3·8% of patients, although both major and minor bleeding events were more common during treatment with abciximab than during placebo treatment (table 3). No excess strokes were observed with abciximab. In the placebo group, two patients had non-haemorrhagic stroke and one had an intracranial haemorrhage (1, 5, and 7 days after enrolment, respectively). Stroke occurred in a single patient treated with abciximab (15 days after enrolment), but the type of stroke could not be determined. Most bleeding complications occurred at arterial puncture sites. In both treatment groups, bleeding was more common in

	Discharge		6 months	
	Placebo	Abciximab	Placebo	Abciximab
Aspirin	93·5	94·3	88·0	88·4
Other antiplatelet*	11·8	10·9	7·0	6·3
Coumadin	7·7	6·8	4·1	5·2
LMW heparin	3·3	3·3	..	..
β-blockers	59·8	60·2	54·5	53·8
Calcium antagonists	54·0	47·0	43·7	48·8
ACE inhibitors	16·4	17·9	20·0	19·3

LMW=low molecular weight; ACE=angiotensin-converting enzyme.
Data not available for 18 patients (placebo, abciximab) at discharge and 12 patients at 6 months. None of the differences was significant.
*Mostly ticlopidin.

Table 5: **Medication at discharge and at 6-month follow-up (% of patients)**
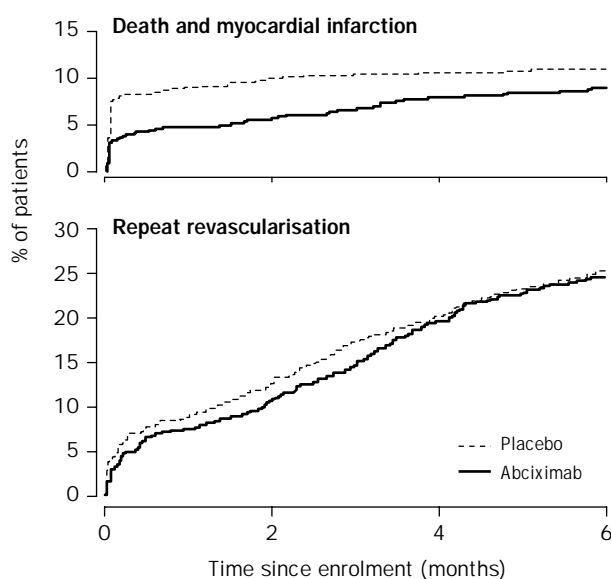
Figure 4: **Time course of death and myocardial infarction and repeat revascularisation during 6-month follow-up**

patients who received a high dose of heparin during PTCA, and in patients with low bodyweight. For patients receiving less than 100 IU/kg heparin, the bleeding rates were 1·2% and 4·4% in the placebo and abciximab groups, respectively. The corresponding rates were 2·7% and 6·6% in those receiving 100–149 IU/kg and 7·9% and 14·8% in patients receiving 150 IU/kg heparin or more. In logistic regression analysis both heparin dose per kg (p=0·0001) and use of abciximab (p=0·0008) were significantly related to bleeding risk. By contrast, the reduction in primary endpoint was related only to use of abciximab (p=0·016) and not to heparin dose (p=0·70).

Thrombocytopenia ($<100\times10^9$/L) occurred in 5·6% of the abciximab group and 1·3% of the placebo group. Ten patients receiving abciximab had platelet counts below 50×10^9/L within 24 h; no placebo recipient had this complication. None of these patients had bleeding complications. Two patients had platelet counts below 20×10^9/L. Treatment with study drug (abciximab) was discontinued in five patients, who all received platelet transfusions. Full recovery of platelet counts (to more than 100×10^9/L) occurred within 24 h in three patients, within 48 h in three, and within 5 days in three. Follow-up measurements were not available in one patient.

At follow-up 6 months later, death or myocardial infarction had occurred in 56 (9·0%) abciximab-treated patients and 69 (10·9%) placebo recipients (p=0·19, figure 4). Bypass surgery had been required by 33 (5·4%) and 44 (7·1%), respectively (p=0·20). PTCA was needed for similar proportions of patients in both groups, mainly because of restenosis (table 4). Also, medication up to 6 months of follow-up was similar in the two groups (table 5). At 6 months, 242 events had occurred in 193 abciximab-treated patients compared with 274 events in 193 placebo recipients. Thus, the number of events per patient was lower after abciximab (p=0·067).

Discussion

In this trial, patients treated with abciximab had a 29% lower rate of the primary endpoint of death, myocardial infarction, or urgent repeat intervention up to 30 days after PTCA than patients who received placebo. The

corresponding reduction in the rate of myocardial infarction was 50%. These findings accord with those of other clinical studies of abciximab[10–12,19] and studies with other inhibitors of the platelet glycoprotein IIb/IIIa receptor.[20,21] In the EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications) trial,[11] administration of a bolus of abciximab followed by 12 h infusion at the same dose as in our study reduced the rate of death or myocardial infarction from 9·6% (placebo) to 6·1% (p=0·015) and reduced the need for urgent reintervention. A bolus-only regimen was less effective.[11] In our study, pretreatment with abciximab reduced the rates of these events both before and during and immediately after the intervention. In the EPILOG (Evaluation of PTCA to Improve Long-term Outcome by ReoPro GPIIb/IIIa receptor blockade) study,[19] which was also stopped early by the Safety and Efficacy Monitoring Committee, similar results were obtained in patients undergoing elective PTCA. In all three studies with abciximab, the initial treatment effects were maintained for at least 30 days. Modest reductions in the same events, although not statistically significant, were observed in patients undergoing PTCA and treated with eptifibatide (p=0·06)[20] or tirofiban (p=0·16).[21] These two agents differ from abciximab in that they are small molecules with short half-lives and with more reversible binding to the IIb/IIIa receptor. Nevertheless, these studies consistently support the efficacy of platelet glycoprotein IIb/IIIa receptor blockers in preventing thrombotic complications before and during coronary intervention.

In contrast with other studies, patients in CAPTURE with more severe, refractory, unstable angina were treated during the 18–24 h before planned PTCA. Abciximab resulted in a reduction of events during this period as well as of procedure-related events (figure 2). Apparently, some stabilisation of the unstable plaque was achieved during this treatment period. Since most infarctions occurred during or after the intervention, further event reduction might have been achieved by a longer treatment period before PTCA. PTCA might even have been avoided in some of these patients after stabilisation of the plaque had been achieved. Thus, further studies can be justified to investigate the efficacy of abciximab and related drugs in patients with unstable angina but no planned coronary revascularisation procedure.

As in the EPIC trial[11,12] patients treated with abciximab in CAPTURE had higher bleeding rates than those in the placebo group. However, the rate of major bleeding complications was much lower in CAPTURE than in the previous study (3·8 vs 10·6%), by the same definitions. Minor bleeding rates were also lower in our study (4·8 vs 18·8% in EPIC). This reduction was achieved by reduction of the heparin dose, and greater attention to the site for vascular access. However, we also observed a significant relation between heparin use and bleeding risk. A further reduction of heparin doses and early sheath removal in the EPILOG study[19] avoided excess bleeding episodes in patients receiving abciximab. Heparin dose should be monitored closely in patients treated with abciximab. During PTCA, heparin dose should be restricted to 70 IU/kg.

Complications during coronary angioplasty are of either mechanical or thrombotic origin. Balloon angioplasty results in a disruption or dissection of the arterial wall, which leads to exposure of plaque contents, collagen, and other components of the vascular wall to the blood,

resulting in platelet activation and thrombosis. Mechanical complications from large dissection flaps can now be treated by stents.[23-25] Stents may also reduce the area of exposure of thrombogenic components of the vascular wall. Many of the thrombotic complications and associated myocardial infarctions can be avoided when abciximab is given, whether for 18–24 h before the procedure as in CAPTURE, or for 10–30 min before and 12 h after intervention as in the other studies.[11,12,19] In CAPTURE, treatment with abciximab was effective both in patients with thrombus visible on the angiogram and in those without visible thrombus. Angiography is not, however, an adequate method to detect thrombus, particularly when it is adherent to the vessel wall. Pretreatment with abciximab reduced the need for stent implantation as a bail-out procedure (table 3), although the reduction was not statistically significant. In many patients, combined treatment with abciximab and stent may be especially effective. Comparative studies of abciximab and ticlopidin in patients with stents are warranted.[26]

The short course of abciximab treatment did not affect the rate of recurrent myocardial infarction after the first few days; such infarctions are probably due to new plaque rupture at the same or at another coronary segment. Furthermore, there was no indication that abciximab influenced the restenosis process, since rates of repeat PTCA were the same in abciximab and placebo groups. These results contrast with those of the EPIC study, in which a consistently lower rate of target lesion revascularisation was observed with abciximab up to 6 months and 3 years after enrolment.[12] This difference between CAPTURE and EPIC follow-up results may be a chance finding, or it may be due to the difference in treatment regimen. In CAPTURE, abciximab infusion was discontinued 1 h after PTCA, whereas the infusion continued for 12 h in EPIC. Higher plasma concentrations of abciximab after PTCA might result in binding of abciximab to the $\alpha_v\beta_3$ (vitronectin) receptor, which is exposed on vascular smooth-muscle cells after vessel injury. This receptor, to which abciximab binds with the same affinity as to the glycoprotein platelet IIb/IIIa receptor, is thought to be involved in migration and proliferation of smooth-muscle cells.[27] This hypothesis should be studied in more detail. Follow-up data from EPILOG[28] show results intermediate between those of CAPTURE and EPIC; there was sustained benefit of treatment with abciximab, with similar low event rates between 1 month and 6 months in the two treatment groups.[28]

The collective experience in large trials with more than 6000 patients has shown unequivocally that treatment with abciximab greatly reduces the rate of thrombotic complications in association with PTCA. Treatment with abciximab during and after the intervention can be recommended in all patients undergoing PTCA, if the drug costs are not prohibitive.[29] Patients with unstable angina are at particular risk of myocardial infarction and will benefit most from pretreatment with abciximab. A longer pretreatment period, for example 2 or 3 days, may be even more beneficial, though there is not yet sufficient evidence. Continuation of treatment for at least 12 h after PTCA seems prudent in view of the long-term efficacy observed with that regimen.[12] Additional long-term benefit might be obtained by long-term treatment with related agents that can be taken orally.

In view of the costs of abciximab, some physicians may decide to use this drug only or mainly to treat thrombotic complications when these occur during an intervention. Such use may be effective, but it has not been tested rigorously in randomised trials. Currently available data indicate that pretreatment with abciximab is warranted in all patients undergoing PTCA, and particularly in patients with refractory unstable angina.

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