

5.0 THE READMINISTRATION STUDY

I. Study Synopsis

This review concerns an open **label** protocol examining the effects of injection and **reinjection** of Abciximab after 14 weeks on healthy **volunteer** subjects and patients with stable coronary artery disease. Pharmacokinetics of Abciximab distribution **and clearance**, and **pharmacodynamic** effects on binding to platelets were examined, as well as immune responses to the antibody and adverse events were recorded. Effects on **all** these parameters were examined for the **first** injection as well as for the reinjection, and these results were compared.

A separate review of the PK and PD aspects of the study is provided by the Pharmacology Reviewer. No issues have been raised by that reviewer regarding the sponsor's following conclusions:

- . The pharmacokinetic assessments on the first and the second administration suggest comparable **rates** of clearance.
- . Both **platelet** aggregation **and** quantitative measurements of **GP IIb/IIIa** receptor blockade indicate similar anti-platelet effects following the first and the second **treatments**.
- . No differences were seen in the duration of or distribution of platelet bound Abciximab following the **first** and the second treatments. Platelet bound Abciximab was detected in the circulation for IS days in most patients.

The Pharmacology reviewer **notes** that there was a large individual variability in pharmacokinetics, but there were no differences notable between weight or dosage groups. That is, the weight adjusted and the non weight adjusted regimens had generally the same kinetics. That reviewer also noted that the percent inhibition of platelet aggregation- appeared quite constant at between 80 and 100 % over wide variances in Abciximab levels throughout the infusion times. Quite consistently, the inhibition of aggregation was maintained throughout the **infusion** and was restored gradually over the hours and days following **the injections**. **By 3 days, there was** a substantial return of function seen, though Abciximab remained in the circulation for up to **15** days.

This review will address the immune responses, bleeding, thrombocytopenia and the effect on clotting parameters reported in the study.

II Protocol and Amendments (originally submitted October 1994; trial dates October 24, 1994 to January 30, 1995)

A. Objectives

To determine the immune **response** and safety profile of patients receiving a repeat injection of Abciximab, and to **evaluate** the *in vivo* biologic activity and pharmacokinetics of **Abciximab**.

B. Study Design

Open label single center single dose injection (**bolus** 0.25 mg/kg and 12 hour **infusion**, either 10 ug/min or 0.125 ug/kg/min), followed by **reinjection** with the same dose at 14 **weeks** if **HACA** negative through 12 **weeks followup**. (Reviewer's Note: *The protocol specified that patients with a positive HACA at 12 weeks would not be reinjected. In actual practice, patients with a positive HACA or HAMA at any time during the 12 weeks were not reinjected.*)

C. Patients

Planned to enroll —, (actually 41) male and female, ages 21-80, with documented coronary artery disease (amended to allow volunteers without CAD to be enrolled in December 1994). Patients were paid for participating.

D. Inclusion/Exclusion Criteria

- **Included** subjects with stable coronary artery disease, defined by: prior acute MI, angiogram with $\geq 50\%$ narrowing of ≥ 1 coronary artery, or history of angina documented in medical records.
- Amended to include healthy volunteers when enrollment of stable CAD patients was slow.
- Excluded patients with potential increased risk for bleeding, on anticoagulants, elevated **baseline** PT, allergy to aspirin or **murine** proteins or have participated in a trial with **murine** or **chimeric mAb**, **vasculitis**, immune system disease, unstable cardiac patients, or arterial puncture in noncompressible site within 6 weeks prior to enrollment.

E. Treatment Groups

Subjects were randomized to receive either a weight adjusted (0.25 **ug/kg/min**) or a non weight adjusted (10 **ug/min**) 12 hour infusion, stratified by weight group and age ≤ 60 years, as follows:

Weight < 70 kg:	8 patients each weight adjusted and non weight adjusted infusion
Weight ≥ 70 kg, < 80 kg:	8 patients each weight adjusted and non weight adjusted infusion
Weight ≥ 80 kg:	8 patients non weight adjusted infusion

(note: all patients ≥ 80 kg received non-weight adjusted infusions in the EPILOG trial)

Reinjection was performed in the same manner. Each patient was **reinjected** with the same regimen as received the first time.

F. Concomitant Medications

Aspirin 325 mg po was given between 4 and 24 **hrs** prior to the abciximab. (**Heparin** was not used).

G. Precautions

Drugs for treatment of allergic reactions, including epinephrine, dopamine, **theophylline**, and **corticosteroids** were available for immediate use in the event of an allergic or **anaphylactic** reaction. The infusion was to be stopped if symptoms suggestive of an allergic reaction appeared.

H. Procedures

After screening and baseline laboratory assessments, patients received the first bolus and injection intravenously and were observed for 24 hours. Vital signs were recorded and blood was taken for CBC, serum chemistries, PT, **PTT**, platelet counts, platelet aggregation, flow cytometry, assay of **GPIIb/IIIa** receptor blockade, and plasma Abciximab concentration at appropriate intervals. Amendments were added to determine if Abciximab has anticoagulant properties in addition to its antiplatelet effects; AT III and fibrinopeptide A levels were measured to assess the state of thrombin generation, and comparison of platelet aggregation in PRP and whole blood, and ACT in 20 patients. **IgG recruitment to platelets was assessed by FACS analysis. Platelet counts were obtained at one hour**

after injection and daily through 7 days post injection. A 24 hour urine collection was obtained to assess creatinine clearance and urinary excretion of Abciximab. All **data** were recorded in the same manner and at the same timepoints following the second injection.

History and physical were **performed** at screening and prior to **reinjection**. Patients were also examined 30 days following each injection at a repeat visit. **History** of adverse events and medication use were recorded. Any bleeding was identified by type, location, **and** onset date.

HACA and **HAMA** measurements were collected at baseline, 24 hours, **1, 2, 4, 8,** and 12 weeks. Subjects who were HACA and **HAMA** negative were **reinjected** at 14 weeks. Subjects who were **HACA** or **HAMA** positive at any time were not i-e-injected.

*(Reviewer's Note: The protocol specified that patients with a positive **HACA** at 12 weeks would not be **reinjected**. Subject _____ who had a low titer (1/40) positive **HAMA** at 8 weeks after the first injection, had readministration and developed **thrombocytopenia**. It was thought by the investigator that the low level immune response to the **first** injection **may** have contributed to the **thrombocytopenia** after the second. After that point, patients with a **positive HACA** or **HAMA** at any time during the 12 week followup after the first injection were not reinjected.)*

Subjects **with** a positive HACA had **HACA** measurements made monthly for 4 months then every 3 months until negative. Enzyme **immunoassays** were used. The sample with peak reactivity **from** each patient was **titered** to quantify the response. Neutralization was required to confirm positive responses.

I. Statistics

No prospective hypothesis was stated. Descriptive statistics were used to analyze continuous variables, and categorical data **were** given by counts and percentages. Nonparametric rank based tests were used to examine changes in platelet counts and clearance of platelet-bound Abciximab. Correlation analysis was used to examine the relationship between variables. The **effects** of weight adjusted infusion dosing were **examined** using Fisher's exact test.

III. Study Results

A. Patient Disposition

Forty-one subjects were actually enrolled and received the initial injection. The distribution of subjects is shown in Table 1.

Table 1
DISTRIBUTION OF SUBJECTS

	Total	Body Weight				
		<70 kg		70 to 80 kg		> 80 k
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
No. of Subjects						
Initial injection	41	9	8	8	8	8
Reinjection	29	7	3	6	5	8
Wt-Adj	0.3mg/kg bolus plus weight-adjusted infusion (0.125 µg/kg/min)					
Non-Wt-adj	0.25mg/kg bolus plus non-weight-adjusted infusion (10 µg/min)					

Twenty-nine subjects received the second injection. Twelve subjects were not reinjected; the reasons are shown in Table 2.

Table 2
SUBJECTS NOT REINJECTED WITH ABCIXIMAB

<u>Subject</u>	<u>Reason</u>
}	HACA positive after first injection.
	Positive immune response based on HAMA assay.
	Positive immune response based on HAMA assay.
	Carotid artery surgery 14 weeks after first injection.
	Thrombocytopenia after first injection.
	HACA positive after first injection.
	HACA positive after first injection.
	HACA positive after first injection.
	HACA positive after first injection.
	Positive immune response based on HAMA assay.
	Positive immune response based on HAMA assay.
	Withdrew consent.

B. Discontinuation of Study Agent

All subjects received the **full first bolus and infusion**. Of the 29 subjects **reinjecte**d, one had the **infusion** discontinued after 9 hours due to the development of thrombocytopenia. All others received the **full bolus and infusion**.

C. Demographics

The demographic **characteristics** of all **subjects** enrolled are presented in Table 3, and subjects who were reinjected in Table 4 (following 2 pages). The mean age of all subjects was 62.9 years; the range **was** 43 to 79. Patients were stratified by weight **group**. Initially, patients with **CAD** were enrolled into the study; these were predominantly men, **who** predominantly **fell** into the 70 to 80 kg and over 80 kg groups. **After** the protocol was amended to allow healthy volunteers, mon women (who were mostly less than 70 kg) were **enrolled**. **There** are no important differences between the group initially injected and the group reinjected on demographic **characteristics**.

D. Medical History

Fifty-eight percent of the subjects enrolled had a **history** of CAD. Eighty percent of the subjects had a **family** history of cardiovascular disease, 17 % had a history of hypertension, 1 subject had a history of **IDDM**, 4 prior **CHF**, and **10** subjects (22 %) had a **history** of prior cardiovascular events. The incidence of these was well balanced across treatment groups. Eight subjects (20%) had a prior **PTCA** and 4 had a prior **CABG**. None of the subjects had received Abciximab **previously**.

E. Concomitant Medications

A variety of medications was being taken by patients enrolled in the study, largely cardiac medications (see Table 5 on 3rd page following). Aspirin was frequently used, **but** no anti-platelet medications were **allowed** within 7 days prior to either injection and oral anticoagulants were **allowed** but not within 3 days prior to either injection.

Table 3
PATIENT DEMOGRAPHICS- ALL SUBJECTS ENROLLED

	Total (n=41)	Body Weight				
		< 70 kg		70 to 80 kg		≥ 80 kg
		Wt-Adj (n=9)	Non-Wt-Adj (n=8)	Wt-Adj (n=8)	Non-Wt-Adj (n=8)	Non-Wt-Adj (n=8)
Age (yrs)						
Mean ± SD	62.9±10.0	60.2±11.8	64.1±10.6	62.9±9.5	63.9±9.9	63.8±10.0
Median	65	58	62	65	67	64
Range	43.79	45.74	51.78	49.74	46.73	43.79
Weight (kg)						
Mean ± SD	72.0±13.8	57.8±10.2	62.1±4.4	74.9±2.4	74.8±3.6	92.8±8.9
Median	72	63	62	75	76	89
Range	46,106	46.69	56.69	72.79	70.79	81,106
Height (cm)						
Mean ± SD	169.3±8.4	163.8±9.7	163.9±4.4	173.0±8.7	170.5±4.5	176.2±6.2
Median	170	165	165	172	170	176
Range	151,188	151,183	158,170	158,188	164,178	165,185
Race						
White	37 (90%)	9 (100%)	8 (100%;	7 (88%)	6 (75%)	7 (88%)
Black	3 (7%)	0	0	1 (12%)	2 (25%)	0
Other	1 (2%)	0	0	0	0	1 (12%)
Gender						
Female	17 (42%)	5 (56%)	7 (89%)	2 (25%)	3 (38%)	0
Male	24 (58%)	4 (44%)	1 (12%)	6 (75%)	5 (62%)	8 (100%)
History of CAD	24 (58%)	2 (22%)	2 (25%)	5 (62%)	7 (88%)	8 (100%)

Table 4
PATIENT DEMOGRAPHICS -SUBJECTS WHO WERE REINJECTED

	Total (n=29)	< 70 kg		Body Weight 70 to 80 kg		≥ 80 kg
		Wt-adj (n=7)	Non-Wt-Adj (n=3)	Wt-Adj (n=6)	Non-Wt-Adj (n=5)	Non-Wt-Adj (n=8)
Age (yrs)						
Mean ± SD	61.8±10.3	58.7±12.5	63.3±13.7	59.3±8.2	64.8±10.8	63.8±10.0
Median	65	54	61	62	67	64
Range	43.79	45.74	51.78	49.68	46.73	43.79
Weight (kg) at Initial Injection						
Mean ± SD	74.4±14.7	58.7±10.5	61.7±2.1	74.8±2.8	75.2±3.9	92.1±8.9
Median	74	64	61	74	77	89
Range	46.106	46.69	60.64	72.79	71.79	81.106
Weight (kg) at Re-injection						
Mean ± SD	76.8±15.1	61.1±11.9	63.0±4.6	79.0±5.5	76.0±3.9	94.6±7.9
Median	77	67	62	78	77	92
Range	47,106	47.72	59.68	72.87	71.80	85,106
Height (cm)						
Mean ± SD	171.9±7.8	166.8±8.6	165.1±5.1	176.1±6.8	170.9±5.9	176.2±6.2
Median	173	165	165	175	173	176
Range	158,188	158.183	160,170	170,188	164,178	165,185
Race						
White	27 (93%)	7 (100%)	3 (100%)	6 (100%)	4 (80%)	7 (88%)
Black	1 (3%)	0	0	0	1 (20%)	0
Other	1 (3%)	0	0	0	0	1 (12%)
Gender						
Female	8 (28%)	3 (43%)	2 (67%)	1 (17%)	2 (40%)	0
Male	21 (72%)	4 (57%)	1 (33%)	5 (83%)	3 (60%)	8 (100%)
History of CAD	20 (69%)	2 (29%)	1 (33%)	4 (67%)	5 0 0 0 %)	8 000%)

Table 5
MEDICATIONS ADMINISTERED WITHIN 7 DAYS PRIOR TO ABCIXIMAB INJECTION

	Total	Body Weight				
		< 70 kg		70 to 80 kg		> 80 kg
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
Initial Injection	(n=41)	(n=9)	(n=8)	(n=8)	(n=8)	(n=8)
Beta blocker	12 (29%)	0	3	3	1	5
Calcium channel blocker	10 (24%)	0	1	1	3	5
Nitrates	13 (32%)	2	1	0	3	7
Cardiac glycoside	1 (2%)	0	0	0	1	0
Oral anticoagulants	0	0	0	0	0	0
ACE inhibitor	1 (2%)	0	0	0	1	0
Diuretics	3 (7%)	1	0	0	1	1
Other antihypertensive	1 (2%)	1	0	0	0	0
Insulin	1 (2%)	0	0	0	1	0
Lipid lowering agent	4 (10%)	0	0	0	3	1
Aspirin ¹	21 (51%)	2	3	4	7	5
Reinjection	(n=29)	(n=7)	(n=3)	(n=6)	(n=5)	(n=8)
Beta blocker	7 (24%)	0	1	2	0	4
Calcium channel blocker	10 (34%)	0	1	1	2	6
Nitrates	8 (28%)	2	0	0	2	4
Cardiac glycoside	0	0	0	0	0	0
Oral anticoagulants	0	0	0	0	0	0
ACE inhibitor	0	0	0	0	0	0
Diuretics	2 (7%)	1	0	0	0	1
Other antihypertensive	1 (3%)	1	0	0	0	0
Insulin	0	0	0	0	0	0
Lipid lowering agent	4 (14%)	0	0	0	3	1
Aspirin ¹	17 (59%)	2	2	3	5	5

¹ Does not include protocol-mandated aspirin administered 4 to 24 hours prior to bolus administration

III. Immune Responses

HACA and HAMA antibody titers were measured at 1,2,4,8, and 12 weeks, and every 3 months thereafter to 15 months post injection or, if positive, monthly for four months then every 3 months until samples were negative.

A. Immune Responses - First Injection

After the first injection, 5 subjects (12 %) developed a positive HACA within 12 weeks. The onset in most was at 4 to 8 weeks; 1 subject became positive at 2 weeks. Two additional subjects became positive at 4 and 6 months after injection. Table 6 shows the subjects with positive titers, when they first developed, the peak titer observed, and the duration of positive responses.

Table 6 HACA Responses After First Injection

Subject #	Time First Positive	Peak Titer	Time to First Negative
—	4 weeks	1/400	7 months
—	4 weeks	1/50 ³	12 weeks
—	2 weeks	1/800	15 months
—	8 weeks ¹	1/400	-- ²
—	4 weeks	1/800	-- ²
—	6 months	1/200	9 months
—	4 months	1/100	9 months

¹ Reactive to 7E3 variable region at baseline

² Still positive at last follow-up at 9 months

³ Also had an early positive HAMA

All 5 of the subjects who were HACA positive within the first 12 weeks developed positive HAMA responses also. A total of 10 subjects (25 %) developed positive HAMA responses. Two subjects who had an early positive HAMA low titer later developed positive HACA (— and — in Table 6 above). There were more low titers among the HAMA responses, as the assay was more sensitive than the HACA assay. Five of the 10 who had a HAMA response were still HAMA positive at 8 to 9 months; one subject was still positive at 18 months.

Note that 8 subjects (20 %) had positive HACA results at baseline (prior to treatment). Five of these subjects showed a > 50 % decrease in signal at 24 hours after treatment with **Abciximab**, suggesting a possible immune complex consumption of the HACA antibodies. None of the subjects were noted to experience any clinically apparent **effects** of such a phenomenon, however. All patients showed a similar pharmacodynamic profile to patients who did not have HACA positive titers at baseline.

B. Immune Responses - Second Injection

Following reinjection, a greater proportion of subjects developed positive HACA responses; and the onset was typically **earlier** than occurred after the first injection. Seven subjects (24 %) became positive after reinjection; 2 had detectable HACA at 1 week and 4 were positive by 2 weeks after reinjection. Titers ranged from 1:50 to 1:6400. No correlation was seen with any particular weight or dose group. Table 7 shows the positive responses after reinjection and when they developed. All were still positive at 12 **weeks**, and 3 of the 7 were still positive at 12 to 15 months).

Subject — had a low titer positive **HAMA** after the first injection, and developed thrombocytopenia which was thought to be immune mediated after the second injection, and a positive **HACA** titer.

Table 7 **HACA Responses After Second Injection**

Subject #	Time First Positive	Peak Titer	Time to First Negative
—	4 weeks	1/200	8 months
—	2 weeks	1/400	--1
—	1 week	1/6400	--2
—	1 week	1/400	15 months ³
—	4 weeks	1/50	7 months
—	12 weeks	1/50	10 months ⁴
—	2 weeks	1/3200	--5

¹ Positive at last follow-up (12 weeks)

² Positive at last follow-up (15 months)

³ No data between 7 months (pos) and 15 months (neg)

⁴ No data between 4 months (pos) and 19 months (neg)

⁵ Positive at last follow-up (12 months)

Nine subjects developed **HAMA** responses after reinjection; all 7 of those who developed positive **HACA**, and 2 others. Titers ranged from 1:20 to 1:10,240. Seven of the nine were still positive at last followup at 12 to 15 months, and 2 were lost to followup.

There were two subjects who had a borderline positive **HAMA** response after the first injection who underwent **reinjection**, and had no clinical consequences (-- and —). Subject — developed a positive **HACA** after the second injection (Table 7 above).

IV. Clinical Consequences

A. Allergic and Anaphylactic Reactions

There were no reports of allergic or **anaphylactic** reactions after injection or reinjection in the study. One subject in the reinjection cohort! — had thrombocytopenia which was thought to be immune-mediated due to a coincident rise in **HACA** titer. There was no evidence in the **reinjected** patients of accelerated clearance of Abciximab or of diminished receptor blockade or reduced inhibition of platelet aggregation that would have indicated immune consumption.

One subject had a facial dermatitis at 6 weeks **after the** initial injection and also noted **after** reinjection. That subject developed positive **HAMA** and **HACA** titers at 4 weeks **after** reinjection; no antibodies were detected after the first injection.

B. Thrombocytopenia

One case was seen during the first infusion:

Patient — - Baseline 224,000. Platelets decreased to 78,000 @ 30 minutes post bolus, - was 2,000 at 12 hrs. Steady recovery was noted after 24 hrs by 20,000 per day to 139,000 on day 6, and back to baseline at 236,000 at 4 weeks. No bleeding.

Mechanism uncertain. Note that this patient was one who had a + HACA @ baseline, but all 4 other patients who were + at baseline had no adverse events recorded.

Reviewer Comment: It is possible that immune consumption played a role in the thrombocytopenia; the investigator and sponsor did not consider this evidence of an immune mechanism.

One case was seen during the second infusion:

Patient — - Baseline 170,000. Platelets 53,000 @ 9 hrs after 2nd injection; the infusion was stopped early. Platelets 67,000 @ 24 hrs, 90,000 @ 3 days, then 37,000 @ 8 days, 94,000 @ 11 days, stable at baseline by 2 and 4 weeks.

This patient was HACA + at 8 days after the reinjection. The investigator thought the platelet decrease was immune mediated, and definitely related to study agent. (The sponsor notes this patient had a + EIA @ baseline, and this obscured the probable immune response after the first injection. The neutralization profile showed an increasing proportion of serum antibodies reactive with the murine variable region to 21% at 4 weeks after the initial injection.)

This patient had moderate hematuria and hyperglycemia at 8 days, assessed as not related to study drug. It is not clear what was responsible, however.

One case of pseudothrombocytopenia occurred (assessed by a drop in EDTA counts but not in the citrated counts). It is noted by the sponsor that platelets swell in EDTA, causing the pseudothrombocytopenia. This is not seen when the sample is citrated.

C. Bleeding

There were 18 events in 8 patients after the first injection; there were 11 events in 9 patients after the second injection (see Table 8) Most (12 of 18 events after the first injection, 7 of 11 events after the second injection) were mucosal, lasting less than 5 minutes, mild, and no treatment was required. None were serious.

Bleeding sites involved nosebleeds, gingiva, and hematomata, ecchymoses and petechiae after both the first and the second injection. The onset of bleeding was during administration in most cases, ranging from within 11 minutes after injection to 9 and 11 hours after injection.

Bleeds were increased in patients < 70 kg who were treated with the non-weight adjusted infusion. Of the 17 subjects < 70 kg, 5 experienced bleeding after the initial injection; 3 in the non-weight adjusted and 2 in the weight adjusted group. (see Tables 9a and 9b)

D. Anticoagulation parameters

No notable changes were reported in PT or in aPTT after **Abciximab** injection. The median values were similar pre and post injection.

E. Thrombin Generation

No significant changes were observed in thrombin generation pre and post injection. The sponsor concludes that any changes were below the level of sensitivity of the assay, and that it is likely the subjects in this study would not have observable changes, as they were not in a state in which coagulation would be activated.

See Tables 8 and 9a and 9b on the following pages.

Table 8
SUBJECTS WITH ACUTE BLEEDING EVENTS

	<u>All Subjects (n=41)</u>	<u>Subjects Who Were Reinjecte</u>	
	<u>Initial Injection</u>	<u>Initial Injection</u>	<u>Reinjection</u>
Subjects with events	8 (20%)	4 (14%)	6 (21%)
Mucosal bleeding (gingival, nasal)			
Subjects with events	6 (15%)	3 (10%)	3 (10%)
Requiring pressure/packing	0	0	1 (3%)
Duration >5 min	0	0	1 (3%)
Onset after administration	3 (7%)	1 (3%)	2 (7%)
Superficial bleeding (hematoma ecchymosis, petechiae, catheter site)			
Subjects with events	4 (10%)	1 (3%)	4 (14%)
Requiring Pressure/packing Treatment	3 (7%)	1 (3%)	2 (7%)
Hematoma >5cm	3 (7%)	1 (3%)	0
Onset after administration	2 (5%)	0	3 (10%)

Table 9.a
NUMBER OF SUBJECTS WITH ACUTE BLEEDING EVENTS BY DOSE GROUP

	<u>Total</u>	<u>Body Weight</u>				
		<u>< 70 kg</u>		<u>70 to 80 kg</u>		<u>> 80 kg</u>
		<u>Wt-Adj</u>	<u>Non-Wt-Adj</u>	<u>Wt-Adj</u>	<u>Non-Wt-Adj</u>	<u>Non-Wt-Adj</u>
Initial Injection	<u>(n=41)</u>	<u>(n=9)</u>	<u>(n=8)</u>	<u>(n=8)</u>	<u>(n=8)</u>	<u>(n=8)</u>
Subjects with Acute Bleeding Events	8 (20%)	2 (22%)	3 (38%)	0	1 (12%)	2 (25%)
Reinjection	<u>(n=29)</u>	<u>(n=7)</u>	<u>(n=3)</u>	<u>(n=6)</u>	<u>(n=5)</u>	<u>(n=8)</u>
Subjects with Acute Bleeding Events	6 (21%)	0	1 (33%)	2 (33%)	1 (20%)	2 (25%)

Table 9.b
NUMBER OF SUBJECTS WITH ACUTE BLEEDING EVENTS BY WEIGHT GROUP

	<u>Total</u>	<u>Body Weight</u>		
		<u>< 70 kg</u>	<u>70 to 80 kg</u>	<u>> 80 kg</u>
Initial Injection	<u>(n=41)</u>	<u>(n=17)</u>	<u>(n=16)</u>	<u>(n=8)</u>
Subjects with Acute Bleeding Events	8 (20%)	5 (29%)	1 (6%)	2 (25%)
Reinjection	<u>(n=29)</u>	<u>(n=10)</u>	<u>(n=11)</u>	<u>(n=8)</u>
Subjects with Acute Bleeding Events	6 (21%)	2 (10%)	3 (27%)	2 (25%)

V. Sponsor's Conclusions

The sponsor concludes the following:

- The **HACA** assay yielded a higher than expected rate of positive responses in this trial: 5 of 41 subjects (12.2 %) after the first injection and 7 of 29 subjects (24 %) after the second injection. The larger clinical trials (EPIC, EPILOG and **CAPTURE**) have yielded only a rate of 5.1 to 6.5 % positive HACA responses. The same assay was used in this trial as in the **others**. The sponsor does not provide an explanation for this other than the small sample size in this trial compared to the others, or perhaps that the population in this trial is not representative of the patients who have received Abciximab in the large interventional trials.
- The safety of Abciximab is not altered upon retreatment (in **HACA-HAMA** non-responder patients), as 28 of 29 patients received **reinjection** without adverse events. There were no reports of **anaphylaxis** or allergic reactions in the study. Of the subjects with positive immune responses, only one exhibited an adverse event which was attributed to **an** immune response. This occurred after the second injection. That patient had thrombocytopenia occurring at 8 days after the second injection, concomitant with a rise in **HAMA** titer. Although the decrease in platelets was severe, the event resolved spontaneously.
- One other case of thrombocytopenia occurred in the study. This was a patient who had an immediate drop in platelets after the first dose **was** received. That patient was one of 8 who had a positive HACA response (low) prior to treatment. It was not felt that this was immune mediated, however, the investigators were uncertain of the mechanism that caused the thrombocytopenia in this case.

VI. Spontaneous Reporting (MedWatch) Data

Review has been completed of data on allergic phenomena reported through the spontaneous reporting (**MedWatch**) system in patients receiving commercial **ReoPro** since the marketing of the drug in December 1994. Four **reports** of allergic phenomena have been received, with ReoPro listed as one of the suspect medications. In all reports the patients were also receiving IV **heparin**, aspirin, and a contrast dye agent. Symptoms reported included shaking chills (3), fever (2), hypotension (2), **skin rash** (1), mucosal bleeding (1) and **thrombocytopenia** (1). One patient also developed pulmonary edema/ an **ARDS** syndrome. No data were available with these reports on HACA or **HAMA** antibody levels, or previous **exposure** to **ReoPro**. One patient was noted as having undergone PTCA x 2 previously, one within the previous 10 months.

VII. Reviewer Conclusions

1. It is unclear why the proportion of patients developing an immune response in this study is higher than that seen in the larger clinical trials. The same assay was used for all studies. It does not appear to be due to **the** more **frequent** sampling in this study; the patients in the larger **trials** were only drawn at 4 and 12 weeks, (30 days and 6 months in the EPILOG trial). If patients in this trial had been sampled at only 4 weeks and 12 weeks after each injection, there would have been 4 of 41 or 10 % with a positive **HACA** at 4 weeks and at 12 weeks after the first injection, and 6 of 29, or 22 %, at 4 weeks and 7 of 29, or 24 % at 12 weeks, **after** the second injection. These percentages are **still** higher than those seen in the larger clinical trials, which found a positive HACA rate of 5.1 to 6.5 %. However, there were more missing values in the patients studied in **each** of the larger trials than in this study. It is possible the missing values may have contributed. Based on the small sample

size in this study, the rate of 10% with a response **after** the first injection may not **be** substantially different than the rates seen in the **larger** studies. After the second injection, the rate of positive responses appears to be doubled, however.

2. There is a suggestion from this study that the antibody response after readministration of **Abciximab** occurs **earlier** and to a higher titer than **after** the first injection, and in a larger proportion of patients.

3. It is reassuring to see that there is no evidence of increased rates of clearance of Abciximab or of alterations in **pharmacodynamics** with **rejection** of patients without prior antibody responses. Thus the dose regimens proposed for initial administration may be used for readministration of Abciximab without diminution of effect in patients without a demonstrable HACA or **HAMA** response.

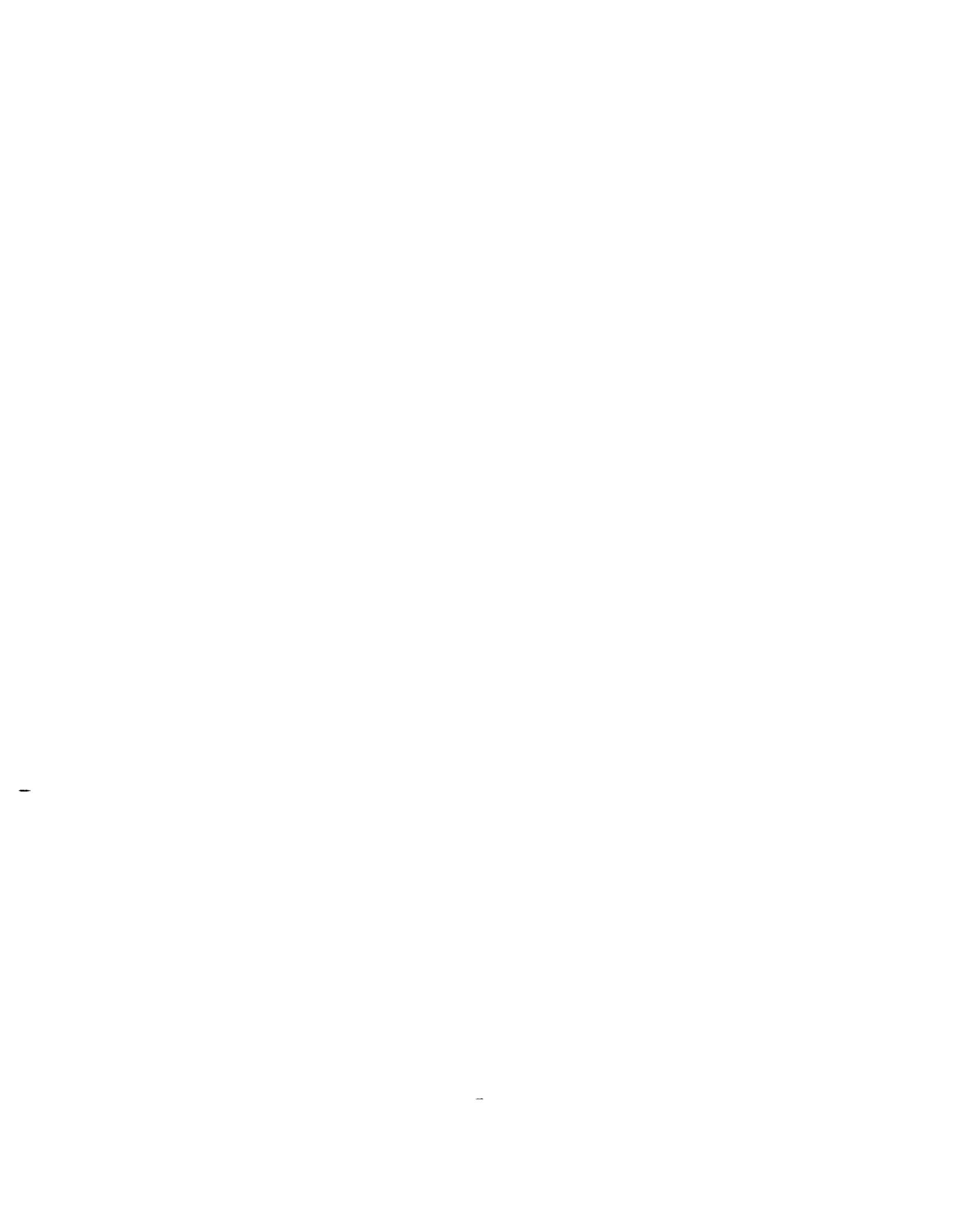
4. There is a concern that the development of antibodies relevant to the this type of **monoclonal** therapy may have significant adverse clinical consequences. There is no evidence of allergic or **anaphylactic** reaction to the agent in this study or in the larger clinical studies; a total of 3,900 patients have been treated with Abciximab. However, events that **may** occur with very low frequency may not yet be apparent. The data **from** the **MedWatch** reports raise some concern; however, the reactions reported may be **attributable** to other medications the patients had received, including contrast dye, in at least some of the **reports**, and suggest that close monitoring for such phenomena be a part of any further studies with Abciximab.

5. There are insufficient data at this point to adequately predict the immune response or the clinical consequences in patients who are reinjected and have had a positive antibody response. With the limited data gathered thus far, there have not been any cases of severe allergic or **anaphylactic** responses in patients reinjected (in the clinical studies). However, only antibody negative patients have been reinjected in the studies.

From data in this trial on repeat percutaneous interventions, it can be expected that 20 to 25 % of patients treated **initially** may have need for repeat administration of Abciximab within the following 6 months. This percentage is likely to increase over the **following** year(s), as the drug does not appear to retard the progression of atherosclerotic disease, and a given patient may have recurrent thrombotic episodes. From data in this study, 25 % of patients may have a positive antibody response after the second injection. It is thought that the **anamnesic** response following readministration of antigenic substances increases the likelihood of serious clinical consequences of readministration. The treatment effect of this drug has been shown to be 5 to 8 %. If the clinical effects of the development of antibodies to the drug **are** significant, the risk of treatment approaches the size of the benefit after repeat **administrations**. **The** development of antibodies to Abciximab and allergic phenomena after readministration should be assessed in patients who are antibody positive.

6. There is one case of thrombocytopenia in this study the sponsor attributes as immune-mediated. The clinical significance of this one case is unclear. **Thrombocytopenia** following Abciximab administration has occurred sporadically in the larger trials; the mechanism(s) responsible have not been elucidated.

7. This reviewer agrees with the sponsor's conclusions regarding thrombin generation in this study. This information would be interesting to see in patients receiving anticoagulation and being treated for active thrombus formation.



Abciximab/CAPTUF

Annotated Clinical Review of Product License Application Supplement

Product: Abciximab, ReoPro™, Chimeric Monoclonal Antibody (Fab)(c7E3) to Platelets (GPIIb/IIIa Receptor)

Sponsor: Centocor

Today's date: August 6, 1997

Reviewer: Dwaine Rieves, M.D. CBER/OTRR/DCTDA *Dwaine Rieves 8-6-97*

To: The File, BLA number 97-0202

Through: Marc Walton, M.D., Ph.D. *MKW 8/6/97*
 Chief, General Medicine Branch
 CBER/OTRR/DCTDA

Karen Weiss, M.D. *KW 8-6-97*
 Chief, Division of Clinical Trial Design and Analysis
 CBER/OTRR

Table of Contents

Section	Heading	Page
1.0.0	Introduction	3
	1.1.0 Materials reviewed	3
	1.2.0 Indication	3
	1.3.0 Clinical background	3
	1.4.0 Regulatory background	5
	1.4.1 Unstable angina regulatory considerations	6
2.0.0	CAPTURE overview	6
	2.1.0 Clinical protocol and amendments	6
	2.1.1 Prespecified trial plans	7
	2.1.1.1 CAPTURE objectives	7
	2.1.1.2 CAPTURE structure	7
	2.1.1.3 Enrollment criteria	8
	2.1.1.4 Randomization and blinding	a
	2.1.1.5 Dose	9
	2.1.1.6 Concomitant medications	9
	2.1.1.7 Evaluations	9
	2.1.1.6 Patient management guidelines	10
	2.1.1.9 Endpoint component definitions	10
	2.1.1.10 Prestated study endpoints and statistical analysis	11
	2.1.1.11 Additional prespecified statistical considerations/Interim	15
	2.1.1.12 Committees	15
	2.1.1.13 Contract research organizations	17
3.0.0	CAPTURE conduct	18
4.0.0	CAPTURE patient dispositions	18
	4.1.0 Blinding	20
	4.2.0 Patients with no index PTCA	20
	4.3.0 Patients lost to follow-up	21
	4.4.0 Protocol violations	21
	4.4.1 Selection criteria violations	21
	4.4.2 Randomization errors	21
	4.4.3 Timing of index PTCA	21
0.0	CAPTURE baseline characteristics	21
	5.1.0 Baseline EKG changes	22
	5.2.0 Baseline symptoms	22
	5.3.0 Screening arteriogram	22

5.4.0	Screening arteriographic findings	23
5.5.0	Evolving MI	23
5.6.0	Risk stratifying subgroups	23
6.0.0	CAPTURE efficacy	24
6.1.0	CAPTURE primary endpoint	24
6.1.1	Protocol specified analysis of primary endpoint	24
6.1.2	Exploratory analyses of primary endpoint	25
6.1.2.1	Primary endpoint in treated patients	25
6.1.2.2	Primary endpoint using the most serious event as endpoint event	26
6.1.2.3	First occurring events in primary endpoint	26
6.2.0	CAPTURE secondary endpoints	26
6.2.1	Analytical plan secondary endpoints	26
6.2.1.1	Components of primary endpoint	26
6.2.1.2	All cause mortality	28
6.2.1.3	Myocardial infarction	26
6.2.1.4	Urgent intervention	32
6.2.1.4.1	CABG	34
6.2.1.4.2	Stents	35
6.2.1.4.3	Intra-aortic balloon	35
6.2.1.6	Recurrent myocardial ischemia	35
6.2.1.6	Primary endpoint among subgroups	37
6.2.1.7	Ischemic/thrombotic complications	37
6.2.1.8	Long term outcome	39
6.3.0	CAPTURE safety	40
6.3.1	Mortality	41
6.3.2	stroke	41
6.3.3	Hemorrhage	41
6.3.3.1	Hemorrhage classification	41
6.3.3.2	Bleeding sites	43
6.3.3.3	Bleeding and heparin	44
6.3.3.4	Red blood cell transfusions	44
6.3.3.5	Hemorrhage among subgroups	45
6.3.4	Thrombocytopenia	45
6.3.5	Clinical chemistry	46
6.3.6	Vital signs	46
6.3.7	HACA responses	46
6.3.6	Adverse events	46
7.0.0	Appendix	48
7.1.0	Review of supplemental information	46
7.1.1	Overview of supplemental information	46
7.1.2	Questions and responses	48
7.2.0	Pertinent publications	51
8.0.0	Reviewer's conclusions	52

1.0.0 Introduction: Abciximab is a chimeric murine/human monoclonal antibody fragment (Fab) directed against the GPIIb/IIIa receptor of platelets. Binding of Abciximab to the GPIIb/IIIa receptor blocks platelet aggregation. In 1994, Abciximab was licensed for use as an adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PTCA) for the prevention of acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel. In the pivotal clinical trial (EPIC) supporting this indication, Abciximab dosing was begun one hour prior to performance of the PTCA procedure. A subsequent clinical trial (EPILOG) has been performed in patients at variable risk for abrupt vessel closure during PTCA and an indication for low risk patients is sought in BLA License Application Supplement number 97-0200. In the EPILOG clinical trial Abciximab dosing is also begun one hour prior to the planned PTCA procedure.

The license application supplement described in this review concerns a new dose strategy for Abciximab relative to the planned PTCA procedure. This dose regimen, initiation of Abciximab infusion approximately 8 hours prior to the planned PTCA procedure, was explored in a subgroup of unstable angina patients in a single phase 3 study, CAPTURE. This review explores CAPTURE, published medical literature and the proposed new indication for Abciximab. This reviewer's comments and interpretations are identified in ● m

1.1.0 Materials reviewed: Materials reviewed include all the material included in the product license application supplement (study summary reports, proposed labelling, statistical assessments, case report forms, SAS data sets and references), pertinent published literature and the relevant background IND documents (IND number 3449). Abciximab production and manufacturing has not been altered under this license application supplement. Consequently, manufacturing, production and preclinical testing will not be reviewed.

1.2.0 Indication: The sponsor seeks the following indication for Abciximab.

1. Percutaneous Coronary Intervention

As an adjunct to percutaneous coronary intervention (balloon angioplasty, atherectomy, stent placement) for the prevention of cardiac ischemic complications.

2. Unstable Angina

For the prevention of cardiac ischemic complications in unstable angina patients not responding to conventional medical therapy for whom percutaneous coronary intervention is planned."

Reviewer's comments: This PLA supplement concerns the unstable angina portion of the new proposed indication. The unstable angina indication noted above is a revision of the original indication included in the PLA supplement.

The revised indication was submitted on Apr 15, 1997 and it is this indication which will be the focus of this review. In this review "PTCA" denotes either balloon angioplasty or atherectomy.

1.3.0 Clinical Background: Unstable angina, like most forms of coronary artery disease, is a clinical condition related to an inadequacy of coronary arterial flow. The spectrum of coronary artery disease ranges between myocardial infarction at one end, through unstable angina and chronic stable angina, to asymptomatic myocardial ischemia at the other end.

Unstable angina is thought to be pathophysiologically related to the disruption of an atherosclerotic plaque, aggregation of platelets and partial thrombotic occlusion.¹ Other mechanisms, such as vasospasm and/or the formation of platelet aggregates have also been implicated in obstructing coronary flow. While some coronary arterial atherosclerotic narrowing is present in most patients with unstable angina, clinical trial data suggest that many patients do not have coronary artery stenoses greater than 59%. In the TIMI3B study of approximately 1,100 patients with unstable angina

¹Chesebro, JH. Thrombosis in unstable angina. N Engl J Med 1992;327:192-94

approximately 60% of the patients did not have an estimated stenotic segment that narrowed the lumen more than 50%.² However, the TIMI 3B study was not limited to the subset of unstable angina patients not responding to conventional medical therapy. These patients with refractory unstable angina symptoms are patients included studied in CAPTURE. The proportion of patients with refractory unstable angina who would not be eligible for inclusion in CAPTURE, either because of too extensive coronary disease or too mild coronary disease, is Unknown.

Clinical features of unstable angina relate to the pattern of symptoms and prognosis. The various symptom patterns subtended under the heading of unstable angina include crescendo angina, new onset angina and rest angina. In the TIMI 3B registry of 3,318 patients with unstable angina, 21% of the patients experienced a myocardial infarction (MI) during their hospitalization and the mortality at approximately one month was 24%. The public health impact of unstable angina is suggested by the 1991 US National Center for Health statistics reporting 570,000 hospitalizations within the year that carried a diagnosis of Unstable angina.

Reviewer3comment: CAPTURE assesses the safety and efficacy of Abciximab in a specific subset of unstable angina patients, specifically those:

- 1. not responding after two hours of conventional medical therapy and*
- 2. who, on screening arteriography have a stenosis of >50% in a single culprit native coronary artery.*

PTCA is a form of percutaneous coronary artery interventional treatment of arterial stenosis. In the procedure the stenotic segment is dilated with a balloon. (balloon dilation) or the occluding atheromata resected with a rotablate device. These procedures occasionally rupture an atherosclerotic plaque and may precipitate abrupt vessel closure and culminate in a myocardial infarction. Mechanisms for vessel occlusion in PTCA include coronary intimal dissection and/or thrombosis. Platelet activation and aggregation are thought to be pathophysiologically important in this thrombus formation. The use of heparin and aspirin have been shown to lessen the risk for abrupt vessel closure during PTCA procedures. The EPIC trial also demonstrated that Abciximab administration one hour prior to the PTCA procedure also decreased the acute ischemic complications associated with PTCA.³

²TIMI 3B Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. *Circulation* 1994;89:1545-1556.

³Epic investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.

1.4.0 Regulatory Background: The hallmarks pertinent to this submission **are summarized** below

- 1991-1993 EPIC Clinical Trial performed
- 1991-1992 Phase 2 Study in unstable angina (**Protocol CO1 16T07**)
- July, 1992 Original CAPTURE **clinical** protocol submitted to FDA

- November, 1992 Original Analytical plan submitted to FDA

- February, 1993 Prephase 3 meeting with FDA **re: CAPTURE**
- May, 1993 Revised protocol and Amendment number **1** to CAPTURE **clinical** protocol (**IND amendment no. 146**)
administrative clarifications
- May **15, 1993** Enrollment in CAPTURE began
- September 9, 1994 Revised **analytical** plan submitted and amendment number 2 to **protocol**

- September 13, **1994** First **interim analysis**
- May **19, 1995** Second interim analysis
- June **6, 1995** Recommendation for third interim **analysis reported** to FDA (**IND amendment no. 219**)
- December 15, 1995 **Third** interim analysis; **SEMC** recommends that CAPTURE cease enrollment based on the efficacy **results** of the **interim** analysis of 1050 patients
- December **21, 1995** Enrollment in CAPTURE ends
- May **24, 1996** Amendment number 1 to the **revised analytical** plan (IND amendment no. 262)
contains p value for third interim analysis
- February **18, 1997** Receipt of **PLA** supplement **application**

Reviewer's comment

2. Amendment number 2, February 16, 1994 (prior to completion of enrollment)

Reviewer's comments: Amendment **number 1** was **instituted** prior to **the** start of **enrollment** and amendment **number 2** was **instituted shortly after enrollment** was **begun**. **Consequently**, these amendments, **along with the** original **clinical protocol** will be referred to as **"the clinical protocol"**. **The third interim analysis was recommended by the SEMC committee. It was not part of the clinical protocol. At the SEMC's request, the statistical analysis was adjusted for the third interim analysis in a manner similar to that utilized in planning the first two interim analyses and expenditure of the overall alpha error was planned prior to performance of the third interim analysis. Before the performance of the third interim analysis these plans were described and the FDA was notified.**

2.1.1 **Prespecified trial** plans: The following areas were prospectively stated in the **clinical** protocol.

2.1.1.1 Objectives: In a population of patients with unstable angina:

1. **determine** whether new episodes of ischemia **leading** to urgent intervention or MI can be reduced in frequency or avoided with Abciximab administration during the 18-24 hour period between initiation of Abciximab and PTCA

Reviewer's comment **This** objective was not a **component of the primary endpoint analysis**. As **described below**, the **prespecified statistical** analysis plan **specifically** described the **"supportive" analytical approach to detection of outcomes prior to the planned PTCA**. **The statistical analytical plan stated that efficacy would only be equated with the outcome from the primary endpoint analysis, not from secondary endpoints. Consequently, the analytical plan stated there was no need for multiplicity allowances in analyses of the secondary endpoints.**

2. determine the efficacy of **Abciximab** in **reducing complications** of PTCA (death, MI, urgent intervention) within 30 days following the procedure

Reviewer's comment: **This** objective is **the primary** endpoint and **was the prestated criterion** for determination of efficacy.

3. assess the long term (6 month) effects of **Abciximab** in reducing the need for repeat PTCA or coronary bypass surgery (**CABG**), the incidence of new episodes of unstable angina, MI or death

4. evaluate the safety of Abciximab in unstable angina patients undergoing **urgent** PTCA

2.1.1.2 Trial structure:

Approximately 1,400 patients were to be enrolled at 75 sites. An initial screening **coronary arteriogram** was to be **performed** within 48 hours of an episode of myocardial ischemia in **hospitalized** patients with **refractory** unstable angina. If a single culprit **coronary** artery with a lesion was identified as being suitable for **PTCA**, and the **PTCA could** be performed within 24 hours after the **start** of **Abciximab/placebo**, the patient was to be randomized. **Abciximab/placebo** was to **begin** within 24 hours of the screening angiogram and was to continue for 18-26 hours; the PTCA was to be performed between 18 and 24 hours after the start of the study agents. The study agents were to be terminated one hour after the planned PTCA procedure. Patients were to be followed over **the** subsequent six months. The primary endpoint of the trial was to be assessed at day 30. The determination of **trial** endpoint events was made by a clinical endpoint committee (**CEC**), which was blinded to the randomization and study agent code. **Day 30** refers to 30 days after randomization.

21 .1.3 Enrollment criteria

1. inclusion criteria:

- during hospitalization exhibit angina at rest or with minimal exertion and dynamic **ST/T** wave changes on EKG
- have refractory angina (**at least one** episode of ischemia (chest pain **and/or ST/T** changes despite bed rest and two hours of oral or IV nitrates and IV heparin OR **persistent** new negative T waves **occurring** or continuing after two hours of treatment **with** oral or IV nitrates **and** IV heparin
- must have had an episode of chest pain **within 48** hours prior to start of the study agent; study agent has to **be initiated** within 24 hours following the screening **arteriogram**
- must exhibit a **culprit** lesion in a single **native coronary** artery suitable for **PTCA**, this includes those **with** total occlusions **and/or** restenosis
- females must not be **of child bearing potential**; males
- between the ages of **21** and **80**
- willing** to accept human **blood** products
- provide** consent

2 Exclusion criteria:

- recent MI, unless **creatinine kinase (CK)** has **returned** to less than twice normal
- exhibit features of ongoing ischemia requiring immediate intervention**
- inability to give informed consent
- PTCA** cannot be performed **within** 24 hours of study **agent initiation**
- greater than **50% occlusion** of the left main coronary artery unless **protected** by a **bypass graft**
- a **culprit** lesion in a **bypass graft**
- surgery **within** six week **prior** to enrollment
- Cerebrovascular** accident (**CVA**) within two **years** as **evidenced** by any significant **residual** neurological defect
- recent (within six **weeks**) **gastro-intestinal (GI)** or **genito-urinary (GU) bleeding**
- concurrent admllon of oral **anticoagulants** during the study period
- administration of IV dextran** prior to or **planned for use in PTCA**
- planned administration of thrombolytic** agent prior to or **during PTCA**
- persistent hypertension** at admission despite treatment (**SBP > 180 mm Hg**)
- retinal** hemorrhage
- history of hemorrhagic diathesis**
- platelet count **< 1 00,000 mm³**
- prior participation** in a murine or **chimeric 7E3 monoclonal antibody** trial or known allergy to **murine proteins**
- use of other investigational drug** in **preceding 30 days**
- any **underlying medical** condition which, **in** the opinion of the **investigator**, would place **the patient at** undue risk or make follow-up unlikely

*Reviewer's comments: Selection **criteria** for the **trial** were designed to eliminate those unstable angina patients who **were** at a known high **risk** for bleeding events and who **were** best managed by **measures** other than **PTCA**. **These selection criteria** would tend to eliminate those unstable angina **patients with** coronary **artery** lesions that **would** be best managed by CABG or another **therapy**. Consent for **enrollment** in the study was obtained once the **screening arteriogram demonstrated a coronary** lesion amenable to PTCA. Patients on oral **anticoagulants** were eligible for enrollment if the anticoagulants **could** be stopped at the time of **enrollment**.*

2.1.1.4 Randomization and blinding:

Patients were randomized in the order they were enrolled. Once a patient was identified as meeting the entrance criteria, the investigator phoned the central randomization office (---), The **investigator** was told which study agent product number to administer to the patient. Study agents were stored **at the investigative site** and **were** identified by code numbers. The code was known **only to** --- Study agents were manufactured and initially labeled by **Centocor**. An Independent contract research organization (---) utilized the numbers assigned to the study agents **by** --- to relabel the study agents. --- representatives did not have access to the study agent code. The placebo and Abciximab vials were identical in appearance. In emergencies, the **investigator** could unblind the study agent by wiping a blackened section of the label **with** an alcohol swab. The **reason for unblinding**, time of **unblinding** and the **unblinded** vial label were to be recorded on case report forms (**CRF**).

Randomization was to be blocked within sites, but was not to be stratified **otherwise**.

2.1.1.5 Dose:

Placebo: supplied as a sterile solution containing 0.15 **M** sodium chloride, 0.01 **M** sodium phosphate, and 0.001% polysorbate 80, **pH** 7.2

Abciximab: supplied as a sterile solution containing 2 mg of Abciximab per **mL** of 0.15 **M** sodium chloride, 0.01 **M** sodium phosphate and 0.001% polysorbate 80, **pH** 7.2.

Abciximab was administered as an intravenous **bolus** dose of 0.25 **mg/kg** was to be **administered followed** by a **10 mcg/min** continuous infusion for at least 18 hours but not longer than 26 hours.

An **identical** volume of placebo was administered to **patients** randomized to placebo.

Each study **kit** contained 3 vials, one 20 **mL vial** and two **5 mL** vials. For the continuous infusion, the study agent was **diluted (7.5 mL** in 250 **mL normal** saline) and infused at a rate of 10 **mL/hour**. All material was **pre-filtered** through a _____ filter prior to injection. All continuous infusions were filtered prior to dilution and **infused** through _____ filter. The placebo bolus and infusion were prepared and administered in an identical manner.

2.1.1.6 Concomitant medications:

-Heparin--All patients were to be treated with **heparin**. Each Investigator was told to administer heparin to maintain an **APTT** between 2.0 and 2.5 times normal. **Heparin** was to be continued until at least one hour after completion of the **PTCA**, but was to be discontinued for 4-6 **hours prior** to sheath removal. Additional **heparin** was allowed during the **PTCA** procedure. The recommended **APTT** during the PTCA procedure was 70 seconds and the recommended **activated** clotting time was **300** seconds. The initial **in-cath heparin bolus** dose was not to exceed **100 U/kg** or **10,000 U**, whichever was less. The subsequent, **in-cath** lab heparin dose was to be adjusted by the operator.

Reviewer's comment: When the sponsor refers to a use of weight-adjusted heparin, this refers only to the initial bolus of heparin given during catheterization. The heparin dosing used in CAPTURE is similar to the "standard-dose weight adjusted regimen" used in EPILOG. However, the total heparin dose in CAPTURE is likely to be greater than A EPILOG since the patients were already being treated with heparin as part of the therapy for unstable angina.

-Nitrates-Patients were to be treated **with IV nitrates** in a dose required by the **clinical** status.

-Aspirin-All patients were to be treated with aspirin (unless contraindicated) at a dose of **50-500** mg per day through day 30.

-Beta adrenergic blockers-The use of beta **blockers** was recommended.

-Calcium channel antagonists-These antagonists were allowed.

-Oral anticoagulants-Patients who were **receiving** oral **anticoagulants** prior to the study entry were to have these medications stopped at study enrollment. For planned stent **implantations**, **oral warfarin** was allowed.

-Dextran--Dextran was not allowed except in the setting of stent placement, and then only at the investigator's **discretion**. If **dextran** were used, the study agent was to be terminated.

-Thrombolytics--No IV thrombolytics were allowed in the **trial**. Guidelines were **available** for **intracoronary administration of thrombolytics (maximum** dose 20 **mg tPA** or 500,000 U urokinase or 150,000 U **streptokinase)**.

There were no other **restrictions** on concomitant medications.

2.1.1.7 Evaluations:

- Vital signs were to be monitored closely during the study agent infusion period and for 24 hours after PTCA.
- EKG's were to be obtained prior to initiation of the Study agent infusion, once every six hours until PTCA, just prior to PTCA, immediately after PTCA, six and 24 hours after PTCA and immediately prior to discharge. EKG's were also obtained with ischemic symptoms-
 - Platelet counts were to be determined at 30 minutes, two hours and 12 hours following initiation of the study agent, just prior to PTCA, at six hours post-PTCA and then daily until three days following PTCA. All platelet counts $< 100,000/\text{mm}^3$ were to be repeated and confirmed by peripheral blood smears. All thrombocytopenic patients were to have daily platelet counts until the counts returned to normal. Platelet transfusions were recommended if the platelet count dropped to below 50,000 mm^3 . Heparin and aspirin were to be discontinued if the platelet count decreased to 66,600 mm^3 .
 - CK and CK-MB were to be obtained at 6, 12, and 24 hours following the initiation of the study agent infusion, at 2, 6, 12 and 18 to 24 hours following PTCA and then every 6 hours until 46 hours after PTCA (total of at least 10 CK determinations).
 - APTT or ACT were to be measured at 6 and 12 hours following the onset of infusion, pre-PTCA, at the end of PTCA, 6 and 24 hours after PTCA.
 - Hematology tests were to be obtained at enrollment, at PTCA, 24 hours following PTCA and prior to discharge. Standard chemistry tests were to be obtained at enrollment, 24 hours after PTCA and discharge.
 - HACA sera were to be collected at baseline, discharge and at four and 12 weeks after the study agent infusion. To maintain blinding each serum sample was labeled with 8 discrete random numbers provided by the label manufacturer (Becket Corp). At the site each patient will have a HACA log that is a record of the discrete serum sample number. The cover page of the HACA carbon copy log identified the patient by initials and ID number. The back page of the HACA log did not have the patient ID number or initials accessible. Only the back page of the HACA log was shipped to Centocor, along with the HACA serum samples for assay. Once all four serum samples for 8 patients (baseline, discharge, 4 weeks and 12 weeks) have been collected the samples were to be sent, along with the back page of the HACA log to Centocor for analysis. The front page of the HACA log was to be transferred to an independent research organization, Besselaar, Inc. Besselaar was to enter the random serum sample label number and the patient's ID number into the data base. This data base was to remain with Besselaar until the end of the trial. It was then to be transferred to Centocor for matching the serum sample numbers to the patients.
 - Arteriography was to be performed at screening and prior to PTCA. Standard arteriographic procedures were outlined in the protocol. Both the baseline and PTCA arteriograms were to be submitted to Cardialysis for review. Stenoses had to be $> 60\%$ to be considered for PTCA. A standard TIMI grading scale was to be used by the investigator to grade coronary flow. The arterial sheath from the screening arteriogram was to be left in place or removed, at the investigator's discretion but the choice was to be noted on the case report form (CRF). Sheaths that were left in place or that were inserted during the study period were not to be removed until six hours after discontinuation of the study agent. Heparin was to be discontinued four to six hours before sheath removal. Stent placement during the planned PTCA (when placed to maintain the immediate patency of the dilated vessel) was considered a primary endpoint. Leaving the cath lab with a balloon perfusion in place also constituted a study primary endpoint. The investigator was to grade the type of culprit stenosis using the standard ACC scale (A, B, C, D lesions) on the CRF. The investigator was to grade coronary flow using the standard TIMI classification on the CRF. Dissections were to be noted by the investigator on the CRF. Qualitative arteriographic differences between the first and second coronary arteriograms was prespecified as a secondary endpoint in the clinical protocol. A core arteriographic review committee was set up that included five of the study investigators who were assigned the responsibility to "qualitatively assess all coronary arteriograms for secondary analyses."

Reviewer's comment: The SOP for the arteriographic committee is not included in the PLA supplement. This was submitted in an amendment to the license application.

- Late follow-up included an investigator's visit with the patient at day 30 at which time and EKG was obtained, HACA blood samples and the patient queried for endpoint assessments. Blood for HACA at 12 weeks was to be drawn either by the site investigator or a referring physician. Patients were to return to the site or surveyed by telephone for major clinical outcomes at six months. A six month EKG was to be obtained either at the investigative site or by the referring physician.

2.1.1.B Patient management guidelines:

- Serious Weeding or the need for surgery was to prompt the investigator to measure a bleeding time. It was permissible for the investigator to unblind the study agent if necessary. If the bleeding time was greater than nine minutes, 10 units of platelet were to be given, at the investigator's direction. An algorithm for the use of cryoprecipitate and fresh frozen plasma was also recommended to the investigator (reprinted from Ann Int Med 1989;12:1011).

Transfusion guidelines were provided in the protocol and followed the recommendations included in the American College of Physicians Clinical Guideline: Practice Strategies for Elective Red Blood Cell Transfusion. These guidelines stated that normovolemic patients with hemoglobin values of 7 to 10 g/dL may be managed without transfusion if they were asymptomatic. If the following signs or

symptoms occurred in these patients then transfusion was recommended: **syncope, dyspnea, postural hypotension, tachycardia, angina, transient ischemic attacks.**

2.1.1.9 Endpoint component definitions:

-MI was defined based upon whether the patient was in the **hospital** or not.

An MI during hospitalization required one of the **following**:

- CK-MB** or CK levels exceed 3X the upper limit of **normal** and represent an increase of 50% over the previous value in two samples collected at different sampling times. CK-MB was to take precedence over CK.
- new **Q** wave on the EKG of ≥ 0.94 seconds duration or a depth \geq one-fourth of the corresponding **R** wave amplitude, or both in two or more contiguous leads.

An MI following **hospital** discharge required satisfying one of the following:

- CK-MB** or CK levels exceeded by two times the upper limit of normal; **CK-MB** was to take precedence over CK
- new **Q** wave on the EKG of ≥ 0.04 seconds duration or a depth \geq one-fourth of the corresponding **R** wave amplitude, or both in two or more contiguous leads.

-Urgent intervention (a component of the primary endpoint) was defined prospectively as the following:

- a second PTCA (**repeat** angioplasty) **occurring** after **removal** of the **guidewire while** the patient is still in the **catheterization** laboratory. A return to the catheterization **laboratory** for urgent angioplasty to treat recurrent ischemia **was** also a primary endpoint. Scheduled PTCA (staged procedures) were not to be considered endpoint events.
- CABG** **was** considered an endpoint when **it** was performed to treat recurrent ischemia caused by a failed PTCA. Electively scheduled surgery to treat **pre-existing multivessel** disease was not to be considered an endpoint event.
- stent** placement, when done to **maintain** the immediate patency of the dilated vessel was to be considered an endpoint event.
- intra-aortic** balloon pump placement (**IABP**), when **placed** after the **initial** PTCA for recurrent ischemia in patients not considered candidates for repeat **angioplasty** or surgical Intervention **was** to be considered a study endpoint.

-**"patency"** was defined as **TIMI** grade 2 or 3 **flow** as determined by the operator and no EKG evidence of ischemia.

- **"angioplasty success"** was defined as reduction of the luminal **narrowing** to less than or equal to 59% without major complications.

bleeding events were **classified** as major, **minor** or insignificant using the **TIMI** Study Group criteria. To account for transfusions, hematocrit and hemoglobin measurements were to be adjusted for **any** packed red blood cells or whole blood transfused within **48** hours prior to measurement. The number of units of **red** blood cells combined were to be added to the **change** in hemoglobin. **Three** times the number of **units** of **red** blood cells were to be added to the **change** in hematocrit.

- "major"** bleeding included intracranial hemorrhage OR bleeding **associated** with a decrease in hemoglobin by greater than **5 g/dL** or a decrease in **hematocrit** by greater than 15%
- "minor"** bleeding Included spontaneous events observed as **gross hematuria** or hematemesis OR when bleeding is observed (either due to **spontaneous** events or iatrogenic) and a decrease in hemoglobin occurs to greater than **3 g/dL** or a decrease in hematocrit by 10% OR a decrease in hemoglobin greater than **4 g/dL** or a decrease in hematocrit greater than 12% when no bleeding site is identifiable
- "insignificant"** refers to minor bleeding that does not meet the above criteria.

2.1.1.10 Prestated study endpoints and their statistical analysis:

-The primary endpoint was the occurrence of the first of any one of the following events **within** 30 days following randomization:

1. Death from **any** cause
2. MI

3. **Urgent** intervention defined as:

- Signs** of recurrent ischemia during the infusion period requiring urgent CABG
- Abrupt** closure during the planned PTCA requiring urgent CABG or stent placement
- Recurrent ischemia following the planned PTCA requiring an urgent intervention with one of the following: PTCA, stent placement, CABG or **IABP**

The primary endpoint was to be analyzed using the log-rank test (). Patients lost to follow-up with no primary endpoint prior to the time they were lost were to be censored at that time in the analysis.

The protocol stated "Analysis of the primary endpoint will be the only analysis used to directly establish efficacy." Consequently, the sponsor prespecified that no adjustment for testing of multiple endpoints would be necessary.

Time **zero** in the Log-rank analyses referred to the time of **randomization**. The 30 day assessment was not to occur before day 27.

The **primary** endpoint analysis was to **utilize** an intent-to-treat approach, such that all **patients randomized** would be included in the endpoint analyses. If a patient **were** treated with a study agent but not randomized into the study, that patient was not to be included in efficacy analyses, but was to be analyzed for safety according to the actual treatment received.

A patient was to be counted **in** the primary endpoint analysis **only** once (the **first occurring** endpoint component).

*Please note that **there** are two major components of the **clinical protocol**—the original **clinical** protocol which was dated **prior** to the beginning of enrollment and the **analytical plan**, which was dated **after enrollment** had **begun**. The **analytical** plan contained **certain** secondary **endpoints** that **were different** from **those** in the original **clinical** protocol. However, all revisions and amendments to the **original clinical** protocol and the **analytical** plan **were performed** prior to **unblinding** of the study data base. **The sponsor chose to use a log-rank test to analyze the primary endpoint.***

Nevertheless, the **protocol specified the use of the log-rank test** and, as **will** be shown in the results **section (6.0.0)** the **statistical significance** was **maintained using** either the **log-rank test** or a **Chi-square test**.

-The secondary endpoints were stated in two separate **portions** of the **clinical** protocol. **In** the original clinical protocol the following secondary endpoints were **identified**.

1. Incidence of new **ischemia** during the hospitalization manifest **by**:
 - chest** pain of the same pattern **as** at study entry **without** EKG changes
 - chest pain with EKG changes**
 - EKG changes **without** chest pain

*The **incidence** of new **ischemia** was to be assessed during two observation periods (**from onset** of infusion to **PTCA** and from **PTCA** through **24 hours** after **PTCA**).*

2 **PTCA complications not specified as primary endpoints**. These **include** the **following**:

- presence of thrombi on the guidewire**
- presence of thrombi in PTCA segment**
- transient occlusion** of PTCA segment
- occlusion** of side branch within the balloon dilated area
- occlusion** of another vessel
- coronary spasm**
- coronary embolism**
- coronary perforation**
- dissection types **D, E, F** (dissections types **A, B, C** are not considered a complication)
- any additional **procedures** during the **PTCA**
- femoral** artery **complications** (**hematoma, pseudoaneurysm formation**)
- blood loss requiring **transfusion**
- complications requiring surgery

Reviewer's comments: While the protocol did not explicitly state whether the arteriographic committee would adjudicate or review these complications, these complications were captured by the investigators' notations on the CRF.

3. Qualitative arteriographic differences between **first** and second arteriographic **procedures**.
4. Use of thrombolytic agents in the catheterization laboratory.
5. Use of a balloon perfusion catheter during the procedure when not originally planned.
- 6. Cause specific mortality.**
7. Incidence of late **major clinical** events (MI, **PTCA, CABG**, death) occurring between 30 **days** and six months.

-Safety endpoints were to include the following:

1. Assessment of bleeding complications
2. **Hematocrit/hemoglobin changes**
3. Platelet count changes
4. HACA development

The above secondary endpoints were **included** in the original **clinical** protocol submitted in May, 1992. The analytical plan for CAPTURE was submitted in November, 1992 and contains certain additional secondary endpoints. These **secondary** endpoints were further modified and described in a September, 1994 submission to the FDA. These plans were made during the conduct of the study, but prior to the **unblinding** of the trial. The secondary endpoints described in the analytical plan are described below. The sponsor listed these secondary endpoints in terms of **"importance."**

*Reviewer's comment: The **analytical plan** for the **clinical protocol** was **drafted several months** after the **original clinical protocol**. The **analytical plan differs** from the **original clinical protocol** most **remarkably in the** statement regarding secondary endpoints. **Details for analysis of six of the original seven secondary endpoints were included in the analytical plan.** However, the analytical plan contained **five** new **secondary endpoints**. The **secondary endpoints were prioritized by "importance" in the analytical plan.** **Notably the most "important" secondary endpoint in the analytical plan was the intention to examine the individual components of the primary endpoint (death, MI, urgent intervention) in the treatment period (prior to the planned PTCA) and after the planned PTCA.***

1. Components of the primary endpoint

All components of the **primary** endpoint will be analyzed **in** the patient population that **achieve primary endpoint components (the analysis of the primary endpoint analyzed only the first occurring component of the primary endpoint)**. The analytical plan predated that the objective of these **analyses was:**

- to **distinguish** between component events **prior** to and after the planned PTCA
- to examine which components **of the primary endpoint** are consistent **with** and may explain the primary efficacy analysis
- to count the total number of primary endpoint components per **patient**.

The components of the primary endpoint to be individually analyzed include the following:

- all **cause** mortality
- MI**
- urgent **intervention (CABG, repeat PTCA, stent placement qualifying as a primary endpoint, IABP qualifying as a primary endpoint)**
- cause-specific mortality** that **is** a) related to **thrombotic** complication b) related to bleeding complication or c) other.

For time until death, MI and urgent **intervention**, **log-rank tests were** to be **used** to compare the treatment **arms**. Counts of **total** number of events per patient were to be compared in the two treatment **arms using** the **Cochran-Mantel-Haenszel** test for **trend**. Treatment **arms** were to be **compared by counting** initial primary endpoint events occurring prior to the planned **PTCA** and **Fisher's exact test was** to be used to establish a **significance** level. Among those not having an event prior to treatment **PTCA, Fisher's exact test was** to be **used** to **compare** event fates of the primary endpoint during and after treatment **PTCA**.

2 Recurrent myocardial ischemia:

A composite endpoint will be **formed** to include the **primary** endpoint plus these two **"softer"** events-
 -urgent PTCA before planned PTCA

-pain with EKG changes.

This composite (the "recurrent myocardial **ischemia endpoint**") will be examined among those not achieving a **primary** endpoint and compared with the overall primary endpoint result. These comparisons were to utilize risk ratios formed from proportional hazards regression analyses.

3. Analysis of the primary endpoint among the following subgroups:

1. Time between **start of study treatment** and the most recent prior angina attack-divided into intervals of **0-12** hours, 12-24 hours and greater than 24 hours
2. Single vs. multiple vessel disease at study entry.
3. American College of Cardiology (ACC) classification of the culprit **lesion with** the subgroups being the high risk subgroup vs. others. The high **risk** subgroup was defined as: a) at least one type C lesion, b) two or more type **B** lesions, c) one type **B** lesion and **either** diabetic or a female at least **65** years of age
4. Urgent PTCA performed before the planned PTCA. Comparisons were to be made **using the logrank statistic in** each subgroup. When **3 subgroups and/or event rates** were small, additional comparisons were to be **made** using the recurrent **myocardial** ischemia endpoints.

4. Ischemic/Thrombotic complications:

1. **Thrombotic** complications **during** the planned PTCA were to be examined **using** a composite endpoint that consisted of:
 - new thrombus **appearing** during the planned PTCA as documented by **arteriography**
 - need for thrombolytics during the planned PTCA
 - placement of a perfusion catheter during the planned PTCA to treat abrupt closure
 Counts in each treatment arm among those receiving PTCA were to be compared using **Fisher's** exact test.
2. Incidence of recurrent **ischemia** before or after the planned **PTCA**:

These **analyses will** be done for two **time** periods-the **time** periods before and after (not during) the planned **PTCA** **Analyses were to be conducted based on whether patients had chest pain with EKG changes, chest pain without an EKG available, chest pain alone, or EKG changes alone.** In a subset of the study **sites**, continuous vector **electrocardiography** (CVECG) was to be performed beginning soon after the patient was **randomized and** ending approximately six **hours post- PTCA.** **Patients were to be analyzed according to** whether or not they **received** CVECG **Of** these **analyses**, the most important one **will** be the comparison of recurrent **ischemia, as** defined by chest **pain with** associated ST-T **changes, in** the two **treatment** arms. This comparison was to be made **using** the Mantel-Haenszel statistic, **stratifying** by CVECG. Among patients **with** CVECG, the number of **occurrences** of **ischemic** events as judged by the CVECG (silent of symptomatic) was to be **compared** by treatment arm using the **Cochran-Mantel-Haenszel** method.
3. Differences in the **culprit lesion between the first and second arteriograms**:

The analytical section of the clinical protocol stated: **"Qualitative** assessment of **differences in** lesion characteristics between diagnostic and treatment angiography **will** be performed to **evaluate** medical therapy alone." These analyses were to compare:

 - presence of thrombus
 - TIMI flow grade

In each case the change from the first to the second arteriogram was to be the **measurement studied** **Patients were to be divided into three groups based on whether there was** improvement or worsening in the culprit lesion. Those patients requiring urgent intervention, **having** an MI or dying **with** an apparent thrombotic complication prior to treatment PTCA were to be included in the **"worsened"** category. Comparisons were to be made between the treatment arms using the **Cochran-Mantel-Haenszel** method.

5. Analysis of the primary endpoint by age and sex

The rates of occurrence of the **primary** endpoint were to be presented by age (**<65** or **≥ 65** years) and sex. The recurrent myocardial **ischemia** composite endpoint was also to be analyzed by age and sex.

6. Reanalysis of the primary endpoint using the assumption of primary endpoint occurrence in patients lost to 30

day follow-up.

7. Economic consequences of treatment:

It was anticipated that these **analyses** would be country-specific, **with** cost for **items** being assigned from **external** databases.

8. Long term outcome:

The incidence of a composite endpoint that **consists** of MI, death, PTCA or **CABG** between **randomization** and the **six** month **follow-up time** point **was** to be performed. This **analysis** was **NOT** to **distinguish** between urgent and non-urgent **procedures**. The log-rank test was to be **used** to **compare** treatment arm. **Additionally, stress test results were to** be compared between the treatment **arms** among those **patients having stress tests** between the **30-day** and **six** month follow-up point.

2.1.1.11 . Additional prespecified statistical considerations and interim analyses:

-Sample size was chosen to maintain a power greater than 0.8 for detecting a **decrease** in event rate from 15% in the placebo group to 10% in **the Abciximab** group. The overall Type 1 error rate was to be maintained at 0.05. **With** these assumptions a sample size **of 1,400** was planned.

-interim **analyses** were planned for evaluation of both safety and efficacy. Stopping guidelines were prestated for efficacy (on the primary endpoint). Efficacy assessments were **prespecified** using **Lan-DeMets** spending function methodology such that the final type 1 **error** would **be** maintained at 0.05. interim analyses were planned after the enrollment of approximately 350 and 700 patients.

The corresponding nominal **2-sided** p-values for these analyses were the following:

- for first interim analysis (after 350 patients) $P < 0.0001$
- for **second** interim **analysis** (after 700 patients) $P < 0.001$
- for third interim **analysis** (after 1050 patients) $P < 0.0072$

The nominal, two sided p-value for the final **analysis** given three **interim analyses** was 0.0417.

*Reviewer's comment **These p-values were to be determined using the logrank test (both interim and final analyses). The interim analyses were statistically designed to detect efficacy as defined by attainment of the study's primary endpoint - a 30 day outcome. The interim analyses were not statistically planned to terminate enrollment based upon an analysis of secondary endpoints. All p-values (both logrank and ttest values are two sided-values).***

2.1.1.12 Committees involved in conduct of the trial:

1. Executive committee:

Richard McCloskey, M.D.	Centocor
Harlan Weisman, M.D.	Centocor
Maarten Simoons, M.D., Ph.D.	Investigator
Wolfgang Rutsch, M.D., Ph.D.	Investigator

This committee was to be responsible for making decisions on operational issues of the study requiring immediate attention; receiving recommendations from the Safety and Efficacy Monitoring Committee (SEMC) regarding the termination or modification of the study; consulting with the FDA on decisions related to the SEMC recommendation.

2 Steering committee:

Maarten Simoons, M.D., Ph.D. (Chairman)	Investigator
Wolfgang Rutsch, MD., Ph.D. (Co-Chairman)	Investigator
Alec Vahaian, M.D.	Investigator
Jennifer Adgey, M.D.	Investigator
Attilio Maseri, M.D.	Investigator
Corrado Vassanelli, M.D.	Investigator
Jacques Col, M.D., Ph.D.	Investigator
Allan Adelman, M.D.	Investigator

Carolos Macaya, M.D.	Investigator
Hylton Miller, M.D.	Investigator
Menko-Jan de Boer, M.D.	Investigator
Richard McCloskey , M.D.	Centocor
Harlan Weisman, M.D.	Centocor

This committee was to be responsible for approval of the protocol, amendments, and analytic plan; **reviewing** the progress of the study; and participating in the decisions for terminating or modifying the **trial** based on the results of **interim analyses**.

3. Safety and Efficacy Monitoring Committee (SEMC):

Marc Verstraete, M.D. **Ph.D. (Chairman, hematologist)**
David de Bono, M.D., Ph.D. (cardiologist)
Karl Svedberg, M.D. (cardiologist)
E. Lesaffre, Ph.D. (statistician)
Paul Schotsmans (ethicist)

This committee consisted of **noninvestigators** and was to be responsible for making recommendations for the **termination** or modification of the study based on **the review** of safety and **efficacy results** of the interim analyses. The chairman was also responsible for reviewing IND safety reports and recommending whether or not to stop or modify enrollment in the study based on the review of the safety data. Averse events (**AE**) that were serious, reasonably related to the study agent and unexpected were **to** be monitored on a **case-by-case** basis by Dr. **Verstraete** and Dr. **Tijssen**. Efficacy data were to be made **available** to the **SEMC** only at the time of the scheduled **interim** analyses. All recommendations for termination of the study were to be made to the **Executive** Committee. The **Executive Committee** was to then discuss the study termination with the **FDA**. The **SEMC** was to make recommendations regarding continuation of the **trial** to the **Executive** Committee without supplying the rationale. All initial reports from the **SEMC** were to be relayed first to Dr. Richard **McCloskey** (Centocor).

Data reviewed:

-Safety **data: AE** that are serious and **reasonably** related to the study agent. These safety reports are **initially** completed by the study **investigator**. They were to be submitted to the medical **monitor** at **Bio-Pharm**, Inc (an independent **research** organization). The **Bio-Pharm** medical monitor was to **submit** each safety report to Dr. **Tijssen** on a blinded, continuous basis during the **course of the trial**. These were to be **summarized in** a database by Dr. **Tijssen** and presented to Dr. **Verstraete** on a biweekly basis. **The** safety reports were to be unblinded at the request of **the** **SEMC**. The only efficacy endpoint to be **regularly** reported to the **SEMC** was to be death. If safety reviews prompted **the** **SEMC** to request other efficacy **data, such an analysis was to count** as an interim efficacy analysis.

-Efficacy **data:** The preferred source of data was from the Clinical **Endpoint** Committee. When this was not available, the second choice was to be monitored case report form data. **If** neither of these sources was **available**, data **from** unmonitored safety summary **forms** was to be used. The review of interim analysis results were to **occur within** seven weeks of enrollment of the **last** patient to be included in that **analysis**. Data **summaries were** to be presented by the treatment group by Dr. **Tijssen**. **The** treatment **group designations were** to be coded to maintain blinding. **The Committee** was to **unblind itself** only if it was thought necessary to come to a **decision** on altering or stopping **the** study. The safety and **efficacy analyses** were to have different codes for **the** treatment **arms** so that one of them might be **unblinded** without **unblinding** the other. At the interim analyses, the demographics of the enrolled patients were to be described. Safety data presented include the **incidence** of **hemorrhagic** and non-hemorrhagic stroke, major **bleeding** events, and **thrombocytopenia** and the number of patients who were transfused. The **logrank** test comparing the rate of **primary** endpoints in **the** two treatment **arms** was to be presented in all randomized patients. Survival curves by coded treatment **arm** were to be presented. The event rates of the components of the primary endpoint were to be presented by coded treatment **arm**. Conditional power was to be examined to **project** the outcome of future **analyses** based upon plausible event **rates given the** outcome of patients included in the interim analyses. If the Interim **analysis** reached **statistical significance, decisions** to stop or **modify the trial were** to be based on the quality of the data as judged by the **SEMC** and the balance between the efficacy endpoint results and safety considerations.

Actions:

If an interim efficacy **analysis** showed a suggestive but not a statistically significant **result**, and there was no major safety concern the **SEMC** was to recommend continuation of the **trial**. If there was a statistically significant efficacy finding at the interim analysis, the **SEMC** was to report this to the

Executive Committee. **This** report could be delayed by the **SEMC** if it **was** felt that the **positive** finding could easily be reversed when the **finalized** data on the **patients** were available. In **this case**, the SEMC was to recommend continuing the **trial**, but was to do a reanalysis of the reviewed data when it became available.

4. Clinical Endpoint Committee (CEC):

- J. Bar, M.D. (Chairman)
- J. W. **Deckers**, M.D.
- J. **Piek**, M.D.
- P. J. **Klootwijk**, M.D.
- P. Block, M.D.
- V. Manger Cats, M.D.
- w. **Bruggeling**, M.D.
- F. **Jonkman**, M.D.
- P. van der **Meer**, M.D.
- V. **Uman**, M.D. (investigator)
- D. P. Foley, M.D.
- D. **Keane**, M.D.
- T. **Ansink**, M.D.
- Peter **Koudstaal**, M.D. (neurology consultant)
- David Sane, M.D. (hematology consultant)

The CEC consisted of 12 physicians who were not **investigators** in the study and one **physician-investigator**. The CEC was to be responsible for the review of **all CRF's** EKG. and **supporting documents** for the occurrence of endpoints (**MI**, death, urgent intervention), the **incidence** of recurrent ischemia for **the** secondary analysis, major safety events (**bleeding** stroke and **thrombocytopenia**) and **confirmation that** patients **fulfilled** the **study** entry **criteria** for unstable angina. The CEC was blinded to **study** treatment throughout the study. The CEC **reviewed** data for the **period from randomization** throughout **30** days and for **the period from 30 days through six months**. **CEC members did not review cases from their own centers.**

The CEC coordinator received day 30 CRF and CEC CRFs from Besselaar and Associates (Independent research organization).

5. Arteriographic Committee (**all, except De Scheeder, were investigators** in the study):

- Marcel van den Brand**, M.D., Ph.D. (Chairman)
- Geert Laaman**, M.D.
- Guy **Hendrickx**, M.D.
- Ivan De Scheeder, M.D.
- Philippe Gabriel Steg**, M.D.
- Keavan Beat4** M.D.

The members were responsible for assessing all available arteriograms from the first 30 days. Members did not review the arteriograms from their investigative sites.

21.1.13 Independent research **organizations** involved in conduct of the trial: Four **research** organizations **were** to be involved in conduct of this study and are **summarized** below.

1. _____ **was the statistical coordinating center** during the conduct of the study. _____ **was headed by** _____ **a member of the SEMC.** _____ **was responsible for creating and maintaining security of the randomization codes;** developing the **patient allocation** program and its maintenance at the **randomization center;** assignment of treatment **kits** to study **sites;** providing **statistical analyses** for the **SEMC;** preparing safety event **listings** for the **SEMC chairman.** _____ **and** _____ **were the only individuals** who had access to the **randomization** code **prior to** the **finalization** of the **30** day data-base.
2. _____ **was responsible** for **coordinating** the CEC review and **the** management of the core laboratory **services** and database of coronary arteriograms.
3. _____ **was to be regarded** as the primary contract research **organization** for the study. _____ **was responsible for** monitoring all **CRF's** completed at **non-Canadian sites;** storage of **all CRF's** until the end of the **study;** medical monitoring of all

CRFs; data entry on the CRF and the CEC CRF, data verification, editing and forwarding of cases to Cardialysis for CEC review; transferring data files from CEC CRFs and site CRFs for interim analyses to Canadian sites were monitored by _____

4. _____ was responsible for the physical numbering and assembly of treatment kits, storage and accountability of used and unused kits.

3.0.0 CAPTURE clinical trial conduct:

The plan was to enroll 1,490 patients into CAPTURE, with interim analyses performed after the enrollment of 350 and 700 patients. However, the trial was stopped after an interim analysis of 1,050 patients. By the conclusion of enrollment there were 1,267 patients enrolled (between May 15, 1993 and December 21, 1995). Two of these patients were not randomized-one due to withdrawal of consent and one due to an apparent error. Sixty nine investigative sites enrolled patients. Ethical committees at all sites reviewed and approved the clinical protocol. All patients provided informed consent The randomization plan developed (prior to study initiation) by _____ was for 75 potential sites in blocks of six with a maximum of three identical consecutive medication allocations in each block The block size was known not only by _____ but also by Dr. K. Anderson of Centocor. All CRF monitoring was performed by _____ However, Centocor representatives did make covisits with all _____ clinical research associates. Copies of CT and MRI scans were reviewed by the neurological consultant to the CEC. All contract research organizations were audited at least once during the trial by Centocor. _____ audited five sites independently, Centocor audited three sites independently and both _____ and Centocor jointly audited one site - - performed a 100% audit on all primary endpoint and the major bleeding events and a 100% audit of all CRF. _____ performed an audit of the CEC CRF for 10% of the patients. SAE reports were submitted to _____ for reporting to regulatory authorities and the SEMC.

4.0.0 Patient disposition:

Overall, 1,257 patients were enrolled in the study between May 15, 1993 and December 21, 1995.

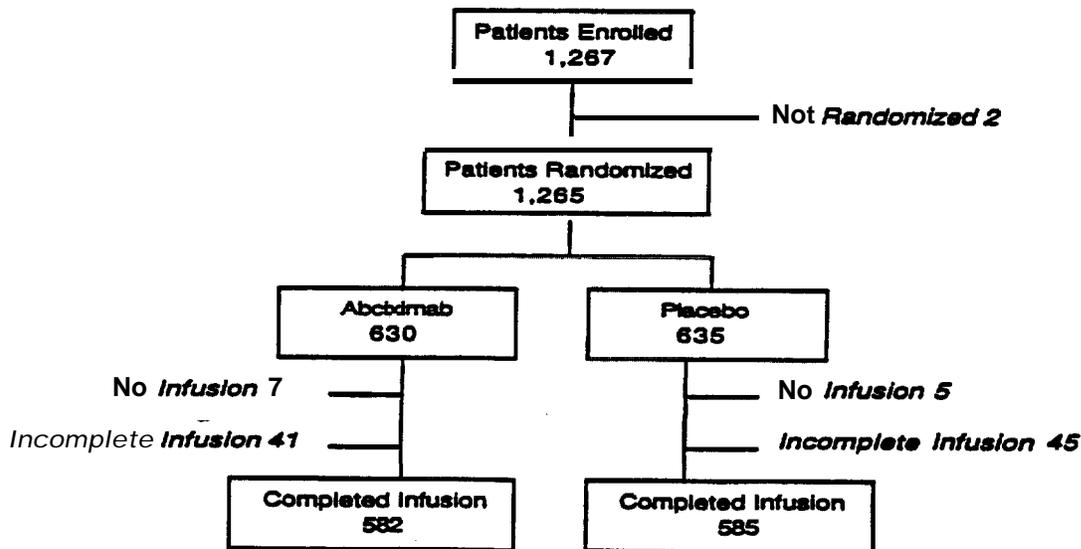


Figure 1 Patient Disposition

CAPTURE was conducted primarily in Europe, as shown in Table 1.

Table 1. Number of Randomized Patients by Country

Country	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630
Netherlands	364 (28.8%)	183 (28.8%)	181 (28.7%)
France	175 (13.8%)	87 (13.7%)	88 (14.0%)
Belgium	146 (11.5%)	74 (11.7%)	72 (11.4%)
Germany	134 (10.6%)	67 (10.6%)	67 (10.6%)
Spain	131 (10.4%)	68 (10.7%)	63 (10.0%)
UK	101 (8.0%)	53 (8.3%)	48 (7.6%)
Italy	96 (7.6%)	47 (7.4%)	49 (7.8%)
Israel	49 (3.9%)	25 (3.9%)	24 (3.8%)
Switzerland	39 (3.1%)	17 (2.7%)	22 (3.5%)
Canada	17 (1.3%)	9 (1.4%)	8 (1.3%)
Portugal	12 (0.9%)	5 (0.8%)	7 (1.1%)
Austria	1 (0.1%)	0 (0%)	1 (0.2%)

Two patients were not randomized --one subsequently refused to provide consent and the reason for not randomizing the other patient is to be described. The reasons for not treating 12 of the randomized patients are shown in Table 2

Table 2. Reasons Randomized Patients Were Not Treated

Reason	Total, n = 12	Placebo, n = 5	Abciximab, n = 7
Consent withdrawn	9	2	7
Randomized in error (child bearing potential)	1	1	0
Investigator withdrew	1	1	0
Randomized in error (not refractory unstable angina)	1	1	0

Reviewer's comment: The number of patients not treated and the attributable reasons are unremarkable.

For this review, as in the sponsor's review, discontinuation of study agent refers to termination of the study agent earlier than 30 minutes after the PTCA. Of the 1,253 patients who received some study medication, 86 (6.9%) had the study agent discontinued. Of the 66 patients, 14 had the study agent stopped early because PTCA was not performed; 42 patients had study agent stopped before PTCA; 11 patients had study agent stopped during PTCA; 19 patients had the study agent stopped within 30 minutes after PTCA. The reasons for discontinuation are shown in Table 3.

Table 3. Reasons for Study Agent Discontinuation

Reason	Total, n=86	Placebo, n= 45	Abciximab, n=41
Non-medical*	26	13	13
Other**	21	12	9
Stent placement	11	8	3
Adverse event	11	5	6
Bleeding	10	1	9
CABG	6	5	1
Consent withdrawn	2	1	1
Insufficient study agent	1	1	0

*administration mistakes, organizational reasons

**nonmedical reason (5), myocardial infarction (4), concomitant thrombolytics (2), concomitant dextran (2), low platelet counts (3), urgent PTCA (2), menstruation (1), no PTCA (1), death (1)

The nine patients who had premature discontinuation of Abciximab because of bleeding are identified below. Five of the nine required transfusion and one patient died.

number	narrative
1	hematuria and hematemesis: not transfused
1	73 year old female, 85 kg, received approximately 23 hours of study agent and

- _____ began the PTCA procedure; one hour into the procedure (following 10,000 U heparin) she developed massive hemoptysis, shock and died; The APTT prior to the PTCA was 55, the APTT at the time of hemoptysis was >240
- _____ hematoma at the sheath site: no transfusion
- _____ hematoma at the sheath site: required transfusion
- _____ melena, sheath site hematoma, and epistaxis after 20 hr of infusion: required transfusion
- _____ hematoma at the sheath site; required transfusion
- _____ hematochezia (angiodysptasia); no transfusion
- _____ hematoma at the sheath site; required transfusion
- _____ hematoma at the sheath site: required transfusion

Reviewer's comment: The patient who died because of massive hemoptysis began hemorrhaging approximately one hour after receiving 10,000 U heparin in the cath laboratory. It is likely that the heparin contributed to the bleed

4.1 .O Blinding

Eleven patients (0.9%) were unblinded during the study; six placebo patients and five Abciximab patients. The investigator ordered unblinding for 10 of these patients; in one case the cover layer on the label did not completely obscure the study code. The reasons for unblinding, as described by the investigator are shown in Table 4.

Table 4. Reason8 for Unblinding

Reason	Total	Placebo	Abciximab
CABG	5	4	1
Other	3	2 (bad label, accident)	1 (thrombocytopenia-ps)
Bleeding	2	0	2
Adverse event	1	0	1 (bleeding)

thrombocytopenia-ps refers to thrombocytopenia that was subsequently determined to be pseudothrombocytopenia

42.0 Patients with No index PTCA

'Index PTCA' refers to the PTCA that was planned toward the end of the study agent infusion. Twentyfour patients did not undergo the index PTCA, 11 in the placebo group and 13 in the Abciximab group. Table 4 list8 the reasons, as classified by the investigator.

Table 5. Reasons for Not Performing PTCA

Reason	Placebo	Abciximab
Other*	4	5
CABG	3	1
Bleeding	1	3
Thrombocytopenia	0	2
Adverse events	2 (death 1, stroke 1)	0
Consent withdrawn	1	1
No narrowing detected	0	1
Unknown	1 (also classified as Other)	0
Total	11 patients	13 patients

*one patient in the placebo group had more than one reason; includes an episode of sepsis occurring 3 hours following initiation of Abciximab, an administrative error in an Abciximab patient, a MI in an Abciximab patient, a technically impossible procedure in an Abciximab patient, a lesion in an Abciximab patient determined to be severe for PTCA and subsequently managed by CABG 16 days later, a MI in a placebo patient, a placebo patient who was not treated or studied because of lack of 'refractory' symptoms, a placebo patient who developed a pericardial effusion, a placebo patient classified as 'other' but had CABG instead of PTCA

Reviewer's comment: No disparity is evident among the patients who did not have PTCA performed.

4.3.0 Patients Lost to Follow-up

Thirty day follow-up was complete in all patients. Nine patients (6 placebo and 3 Abciximab) did not have six month follow-up mortality data. Eight patients (4 placebo and 4 Abciximab) did not have six month follow-up MI/revascularization data.

4.4.0 Protocol Violations

4.4.1 Selection Criteria Violations

The 38 patients who were enrolled with selection criteria violations subsequently identified were approximately even & divided between the two study arms and are shown in Table 6.

Table 6. Patients Who Did Not Meet Entry Criteria

	Placebo	Abciximab
Total	19	19
Reason		
Treatment >24 hrs after screening angiography	8	8
Vasculitis/autoimmune disease	4	3
Recent MI; CK exceeding twice normal value	2	3
Childbearing potential	4	3
Treatment >48 hrs after most recent chest pain	3	0
Surgery within prior 6 weeks	0	2
Investigational drug within prior 30 days	1	0
Inability to perform PTCA within 24 hrs of study agent initiation	0	1
Recent GI or GU bleeding	0	1
History of retinal hemorrhage	1	0
Platelet count < 100,000 mm ³	0	1

4.4.2 Randomization Errors

There were three patients with randomization errors. One patient received a study agent prior to notifying the randomization center. Two patients were assigned kit numbers previously assigned other patients, and did not receive study agents. These three patients are not included in the study.

Five patients were administered Study agents by the Site investigators without notifying the randomization center. Incomplete outcome data is available from these patients and these patients are not included in the Study.

4.4.3 Timing of index PTCA: Table 7 illustrates the timing of PTCA.

Table 7. Performance of Index PTCA

Event	Total, n = 1265	Placebo, n = 635	Abciximab, n = 630	P*
No PTCA	24 (1.9%)	11 (1.7%)	13 (2.1%)	0.69
Prior to scheduled time	23 (1.8%)	14 (2.2%)	9 (1.4%)	0.40
At scheduled time	1125 (88.9%)	560 (88.2%)	565 (89.7%)	0.42
> 24 to 26 hr post treatment	70 (5.5%)	42 (6.6%)	26 (4.4%)	0.11
>26 to 48 hr post treatment	20 (1.6%)	8 (1.3%)	12 (1.9%)	0.38
> 48 hr post treatment	3 (0.2%)	0	3 (0.5%)	0.12

*Fisher's exact test

Reviewer's comment: Approximately 96% of the index PTCA events were performed within a couple of hours of the planned performance time-in both study arms.

5.0.0 Baseline Characteristics:

At study entry, the two treatment groups were similar for major demographic attributes, cardiovascular risk factors, history of cardiovascular events, signs and symptoms and screening arteriographic findings. Notable findings at baseline are shown in Table 8. Most of the patients were Caucasian (98%).

Table 8. Baseline Characteristics, Symptoms, EKG Findings, Screening Arteriogram

Characteristic	Placebo, n = 635	Abciximab, n = 630
Male	459 (72.3%)	461 (73.2%)
Median Age (range, yrs)	62 (32, 80)	62 (32, 80)
Median Weight (range, kg)	75 (42, 116)	75 (42, 125)
History		
Diabetes	82 (12.9%)	95 (15.1%)
<i>Diabetes Missing Data</i>	2 (0.3%)	1 (0.2%)
Prior Myocardial Infarction	231 (36.3%)	250 (39.7%)
<i>Prior Myocardial Infarction Missing Data</i>	6 (0.9%)	7 (1.1%)
Smoking (current or within 1 year)	255 (40.1%)	235 (37.3%)
<i>Smoking Missing Data</i>	10 (1.6%)	4 (0.6%)
Prior PTCA	86 (13.5%)	84 (13.3%)
Prior Coronary Surgery	102 (16.1%)	97 (15.4%)
Hypertension	261 (41.1%)	271 (43.0%)
<i>Hypertension Missing Data</i>	4 (0.6%)	6 (1.0%)
Baseline EKG Findings*		
Ischemic Changes on Baseline EKG	605 (95.3%)	591 (93.8%)
No Ischemic Changes on Baseline EKG	21 (3.3%)	36 (5.7%)
Unknown	9 (1.4%)	3 (0.5%)
Baseline Symptoms*		
Angina Symptoms on Treatment ≥ 2 hrs	598 (94.2%)	604 (95.9%)
Angina Symptoms on Treatment <2 hrs	22 (3.5%)	15 (2.4%)
Unknown duration of Angina Symptoms on Treatment	15 (2.4%)	11 (1.7%)
Median Onset of Last Ischemia Episode (range, hr)	9.4 (0.1, 47.9)	8.7 (0.0, 48.0)
Screening Arteriogram*		
Screening arteriogram ≤ 24 hrs before Treatment	597 (94.0%)	595 (94.4%)
Screening arteriogram >24 hrs before Treatment	27 (4.3%)	19 (3.0%)
Time of Screening arteriogram Unknown	11 (1.7%)	16 (2.5%)

*CEC assessments;

5.1.0 Baseline EKG Changes:

At study entry patients were supposed to have symptoms of unstable angina with EKG changes indicative of ischemia. Most of the patients had EKG changes indicative of ischemia at study entry.

5.2.0 Baseline Symptoms:

At study entry patients were supposed to have symptoms of unstable angina with Ischemic EKG changes that persisted despite two hours of therapy with nitrates and heparin. The two hour period defined the existence of refractory symptoms. The two hour criterion was met in most of the patients (placebo 94.2% and Abciximab 95.9%). The number of patients with symptoms that had persisted for less than two hours or who had missing data are shown in Table 8.

5.3.0 Screening Arteriogram:

Patients were to be screened with a coronary arteriogram that was performed within 24 hours prior to treatment. Most of the patients met this time line (placebo 94.0% and Abciximab 94.4%). The number of patients who had the screening arteriogram > 24 hours before treatment or who have this data missing are shown in Table 8.

5.4.0 Screening Arteriographic Findings:

The culprit lesion location, the proportions of patients with various TIMI classifications of coronary arterial flow, and the proportions of patients with various degrees of stenosis were similar between the two trial arms (determinations assessed for each patient by the site investigator). While all but one of the patients had screening arteriographic assessments performed and recorded by the site investigator, 89% Of the patients (1,126) had screening arteriograms reviewed by the core arteriographic committee (placebo 570 and Abciximab 556). While all the patients who underwent PTCA had PTCA arteriographic assessments performed by the site investigator, 90% (1,137) of the patients had the index PTCA arteriograms reviewed by the core arteriographic committee (placebo 574 and Abciximab 563). The screening arteriographic findings (based on investigator assessments) are shown in Table 9.

Table 9. Screening Arteriographic Findings*

Finding	placebo, n = 635	Abciximab, n = 630
Culprit Lesion Location		
LAD	383 (60.3%)	385 (61.1%)
LCX	104 (16.4%)	105 (16.7%)
RCA	144 (22.7%)	138 (21.9%)
Graft	2 (0.3)	1 (0.2%)
Left main	1 (0.2%)	1 (0.2%)
Unknown	1 (0.2%)	1 (0.2%)
TIMI Flow		
0	23 (3.6%)	28 (4.4%)
1	17 (2.7%)	28 (4.4%)
2	161 (25.4%)	137 (21.7%)
3	434 (68.3%)	436 (69.2%)
Percent Stenosis		
≤50%	54 (8.5%)	66 (10.5%)
51-90%	259 (40.8%)	240 (38.1%)
91-99%	286 (45.0%)	284 (45.1%)
100%	27 (4.3%)	32 (5.1%)
Unknown	9 (1.4%)	8 (1.3%)

● investigator assessment

- Reviewer's comment: The two trial arms appeared balanced with respect to baseline patient arteriographic characteristics.
- The protocol specified that the site investigator would provide the assessment of the baseline arteriographic findings, not the arteriographic committee. The arteriographic committee reviewed arteriograms to determine PTCA and thrombotic complications (section 6.2.1.7). Consequently, there was not a rereview of the site investigator's assessments by the arteriographic committee. This conduct is appropriate, since the perceptions of the treating physician are especially pertinent and randomization should prevent a single investigator from biasing the assessments.

5.5.0 Evolving MI

The sponsor reports that the CEC determined that 20/635 placebo patients (3.1%) had an evolving MI at enrollment, while 17/630 (27%) of the Abciximab patients had an evolving MI ($p = 0.739$, Fisher's exact t test).

Reviewer's comment: The clinical protocol did not specify how 'evolving MI' was to be assessed. The SOP for the CEC committee is not submitted with this submission.

5.6.0 Risk Stratifying Subgroups

The analytical plan stated that the primary endpoint would be explored in certain risk subgroups. These risk subgroups included the following (see Table 10):

1. Time between start of study treatment and the most recent prior angina attack; divided into intervals of 0-12 hrs, 12-24

hrs and greater than 24 hrs.

Reviewer's comment: The CRF tracked the time from the onset of the most recent angina attack. Consequently, this is a stratification from the onset of the most recent attack to the onset of treatment.

2 Single vs. Multiple vessel disease

Reviewer's comment: Again, the analytical plan did not state whether this would be based on a determination by the investigator or the arteriographic committee. The data are analyzed based upon the investigator's determination.

3. AHA/ACC lesions classification

Reviewer's comment: The directions to the arteriographic committee in the analytical plan implied that their assessment of the lesion classification would be the assessment utilized in this analysis. The data are analyzed based upon the arteriographic committee's assessment

4. Urgent PTCA performed before the planned PTCA

Table 10 describes the baseline characteristics for the patients utilizing this risk stratification plan.

Table 10. Risk Classification at Baseline

Category	placebo	Abciximab
Symptoms, interval between last ischemic episode and treatment	n = 636	n = 630
≤ 12 hrs	382 (60.2%)	384 (61.0%)
>12 to ≤ 24 hrs	111 (17.5%)	107 (17.0%)
> 24 hrs	141 (22.2%)	139 (22.1%)
Vessel Disease	n = 635	n = 630
Single	333 (52.4%)	336 (53.3%)
Multiple	297 (46.8%)	292 (46.3%)
Lesion Characteristics	n = 570	n = 556
At Least 1 Type C Characteristic	11 (1.9%)	9 (1.6%)
At Least 2 Type B Characteristics	343 (60.1%)	317 (57.0%)
At Least 1 Type B Characteristic and Diabetic	21 (3.7%)	25 (4.5%)
Female, > 66 yrs Old with at Least 1 Type B Characteristic	26 (4.6%)	19 (3.4%)
1 Type B Characteristic	124 (21.8%)	135 (21.4%)
Type A characteristics Only	45 (7.9%)	51 (9.2%)

Reviewer's comment: The type A characteristics are associated with the most readily accessible coronary stenoses, while the type C characteristics are associated with the most difficult lesions to treat with PTCA. Type B characteristics are intermediate between A and C. These characteristics were assessed by the arteriographic committee.

6.0.0 Efficacy

6.1 .0 Primary Endpoint

6.1.1 Protocol Specified Analysis of the Primary Endpoint

The following notations from the protocol are relevant to the analysis. • A single, composite primary endpoint has been chosen to demonstrate efficacy of the experimental treatment regimen. A patient can have only one occurrence of the composite primary endpoint. In a patient experiencing the occurrence of more than one component of the primary endpoint, the first occurring component will be considered as the occurrence of the composite primary endpoint. A logrank test will be performed at interim and final analyses to test for differences in the rates of occurrence of the primary endpoint in the c7E3 Fab vs. placebo arms of the trial. This test will not be stratified by site or any other variable. Analysis of the primary endpoint will be the only analysis used to directly establish efficacy of the c7E3 Fab treatment arm. Other endpoint analyses are considered secondary."

The primary endpoint outcome is shown in Table 11.

Table 11. Primary Endpoint Event Rates*

All Randomized Patients	Total, n = 1265	Placebo, n = 636	Abciximab, n = 630	P
		172 (13.6%)	101 (15.9%)	71 (11.3%)
All Treated Patients	Total, n = 1253	Placebo, n = 630	Abciximab, n = 623	
		169 (13.5%)	100 (15.9%)	69 (11.1%)

*patients with more than one event are counted only once; the p-value is a log-rank test of time-to-event of "TTPRIMARY" from the SAS data sets. The Fisher's Exact test result for all randomized patients is 0.017 and the Fisher's Exact test result for all treated patients is 0.013.

Reviewer's comment: The data base contains an error that was identified by the sponsor. Patient number - (placebo) is listed as having sustained an endpoint event—the patient did not. This error does not notably change the results. Correcting for this data base error changes the number of patients with the primary endpoint from 101 in the placebo group to 100. The log-rank test p-value for the corrected comparison is 0.016

The Kaplan-Meier time-to-event rate curves are shown in Figure 2.

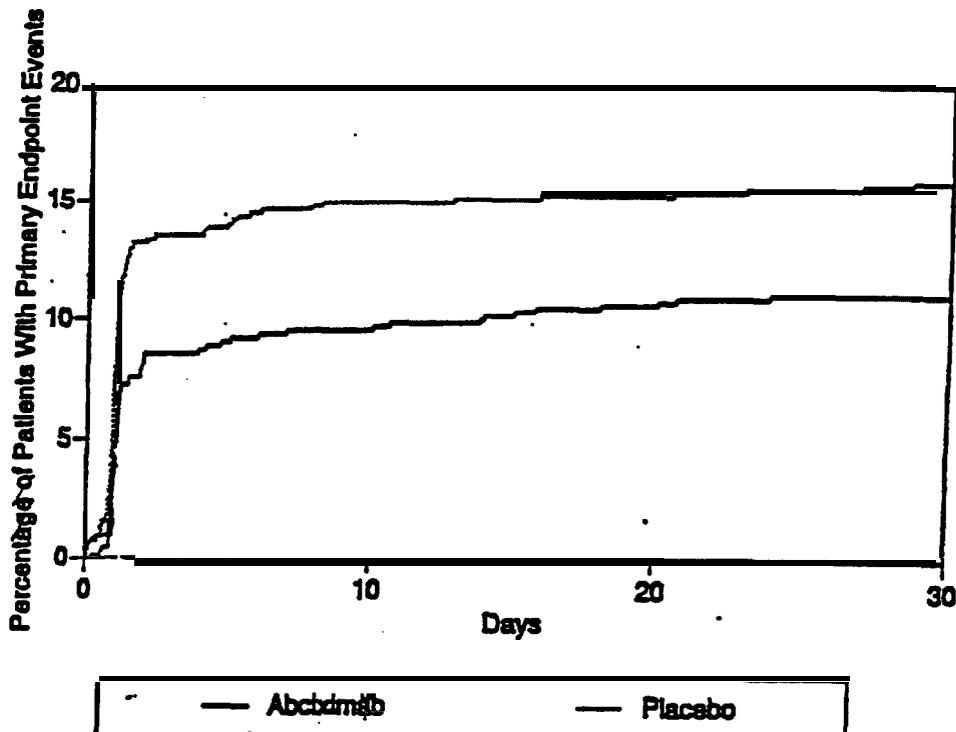


Figure 2. Kaplan-Meier Time-to-Event Curves for the Primary Endpoint

Reviewer's comment: The time-to-event curves illustrate that most of the endpoints occur by day 4 and appear temporally related to performance of the PTCA. Note that at the third interim analysis the data were analyzed using preliminary assessments. The SEMC committee noted, using the preliminary findings, that the event rate in the 1,060 patients was 16.4% for placebo and 10.6% for Abciximab (p=0.006, less than the p<0.007 required to stop the trial). The final data for the 1,060 patients showed an event rate of 15.6% for placebo and 10.6% for Abciximab (p=0.011).

6.1.2 Exploratory analyses of the primary endpoint (these exploratory analyses were not prespecified in the protocol)

6.1.2.1 Primary endpoint in only treated patients

Twelve randomized patients were not treated with the study agents. One of the five untreated placebo group patients had an endpoint event and two of the seven untreated Abciximab patients had an endpoint event. The primary endpoint results in all treated patients is shown in Table 10.

6.1.2.2 Primary endpoint events when analyzed using the most serious event as the endpoint event

Table 12 describes the outcome of the primary endpoint among the 172 patients with primary endpoint events, when the events are counted by the most severe component. In this analysis patients are counted only once for the most severe component of the primary endpoint according to the following hierarchy: death>MI>urgent intervention.

Table 12. Number- of Patients Who Had Endpoint Events According to the Most Severe Event

Patients	Total, n = 1265	Placebo, n = 635	Abciximab, n = 630	P
with any primary endpoint	172 (13.6%)	101 (15.9%)	71 (11.3%)	0.017
with death	14 (1.1%)	8 (1.3%)	6 (1.0%)	0.789
with MI	73 (5.8%)	49 (7.7%)	24 (3.8%)	0.004
with urgent intervention	85 (6.7%)	44 (6.9%)	41 (6.6%)	0.823

P-values are from Fisher's Exact test

6.1.2.3 First Occurring Events in the Primary Endpoint

Of the 172 patients with a primary endpoint event, 96 of these events were urgent interventions, 67 were MI and seven were deaths. Several of the 172 patients with at least one endpoint event had other endpoint events. Overall, there were 234 endpoint events occurring in the 172 patients. Sixty-two patients had more than one endpoint event. Table 13 shows the-number of events that were the first primary endpoint event relative to the total number of patients with events by component.

Table 13. Number of Events That Were the First Primary Endpoint Event Relative to the Total Number of Patients with Events by Component

Event	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630
Death	7/14 (50.0%)	3/8 (37.5%)	4/6 (37.5%)
MI	67/78 (85.9%)	44/52 (84.6%)	23/26 (88.5%)
Urgent Intervention	98/142 (69.0%)	54/81 (66.7%)	44/61 (72.1%)

62.0 Secondary Endpoints

The secondary endpoints were prospectively identified in two pans of the protocol. The original clinical protocol included certain secondary endpoints and the separate analytical plan listed certain secondary endpoints. While the analytical plan stated that the secondary endpoints were ranked in order of importance, the endpoints listed in the protoooi were not ranked by importance. The following review of the secondary endpoints will be divided into two parts. The first part describes the secondary endpoints as specified in the analytical plan and the second part describes the secondary endpoints included in the original protocol but not described in the analytical plan.

6.2.1 Analytical Plan Secondary Endpoints

6.2.1.1 Components of the Primary Endpoint

Each component of the primary endpoint (MI, death, urgent intervention) was to be analyzed in the patient population that achieved the specific endpoint component. There were 210 of these endpoint component events among the 172 patients who achieved the primary endpoint. Thirty-eight patients had attained more than one of these endpoint components. These 210 components are described in Table 14. The table divides the study into three time intervals. The analytical plan stated that these components were to be analyzed in two intervals--prior to PTCA and after PTCA

Reviewer's comments: Since the analytical plan stated that the two intervals to be analyzed were the intervals preceding PTCA and the interval after PTCA, the analysis of these components in three intervals is not a prespecified analytical plan. However, this type of analysis highlights the tight correlation of endpoint events with the performance of PTCA--70% of the composite endpoint events occurred either during PTCA or 24 hours after PTCA. The interval prior to PTCA contained 11% of the composite endpoint events and the interval 24 hours post PTCA through 30 days contained 79% of the composite endpoint events. Note that there was a total of 234 endpoint event among the 172 patients. In this analysis, on/y the first occurring event (ie., a "component") is analyzed. The difference between 234 endpoint events and 210 endpoint components relates to the 24 patients who had more than one urgent intervention.

Table 14. Patients with One of the Three Major Components of the Primary Endpoint

Patients with Component	Component	Total n = 1,265	Placebo n = 635	Abciximab n = 630	P
Randomization to Start of PTCA Period 1	<i>Composite Endpoint</i>	19 (1.5%)	13 (2.0%)	6 (1.0%)	0.108
	Death	2 (0.2%)	1 (0.2%)	1 (0.2%)	0.997
	M	17 (1.3%)	13 (2.0%)	4 (0.6%)	0.029
	Urgent Intervention	2 (0.2%)	1 (0.2%)	1 (0.2%)	0.996
During PTCA and 24 hrs after Period 2	<i>Composite Endpoint</i>	121 (9.6%)	72 (11.2%)	49 (7.9%)	0.044
	Death	4 (0.3%)	3 (0.5%)	1 (0.2%)	0.321
	M	50 (4.0%)	34 (5.3%)	16 (2.6%)	0.014
	Urgent Intervention	90 (7.2%)	54 (8.5%)	36 (5.8%)	0.064
24 hrs post PTCA through 30 Days Period 3	<i>Composite Endpoint</i>	32 (2.6%)	16 (2.6%)	16 (2.6%)	0.983
	Death	8 (0.6%)	4 (0.7%)	4 (0.7%)	0.987
	M	11 (0.9%)	5 (0.8%)	6 (1.0%)	0.753
	Urgent Intervention	26 (2.1%)	14 (2.3%)	12 (2.0%)	0.702

p-values are Fisher's Exact test results

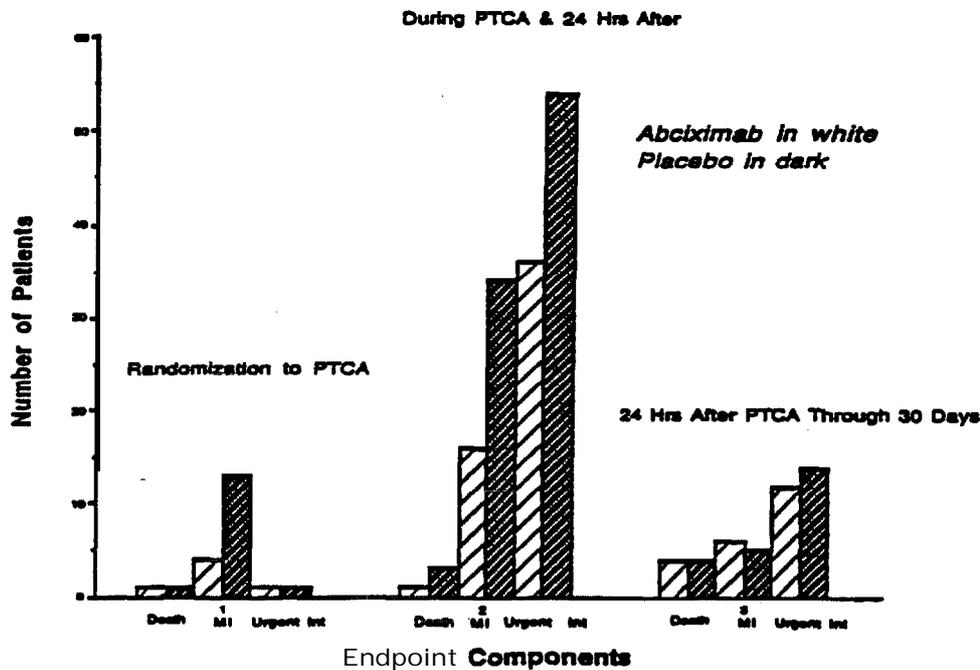


Figure 3.
Number of Patients with Endpoint Components in Each of Three Periods

Reviewer's comment: Figure 3 reiterates the connection of the endpoint events with performance of PTCA. Approximately 67% (144/210) of the endpoint component events occurred during PTCA and the 24 hours after PTCA. Similarly, 70% of all patients experiencing a primary endpoint (121/172) experienced the event during PTCA or the 24 hours after PTCA.

621.2 All Cause Mortality

The plan ranked all cause mortality as the most important component of this secondary endpoint. There were 14 deaths by 30 days during the clinical trial, eight deaths in the placebo group and 6 in the Abciximab group (P = 0.789). Seven of the 14 deaths were included in the primary endpoint calculation. The other seven deaths occurred in patients who had preceding endpoint events. The CEC classification of the cause of death is shown in Table 15. The Kaplan-Meier fatality curves are shown in Figure 4.

Table 15. Number of Patients who died by Cause of Death

Patients	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630
Cardiac	10	7	3
Sudden	1	1	0
MI	5	4	1
Cath	3	2	1
Other Cardiac	1	0	1
Vascular	2	0	2
Stroke (patient	1	0	1*
Pulmonary Hemorrhage	1	0	1
General Medical	2	1	1

*no CT scan obtained, unknown type of stroke (the stroke occurred 15 days after completion of the study agent). General Medical includes one patient with hepatitis who developed renal failure and died and another patient with diabetes mellitus who developed septic shock and died.

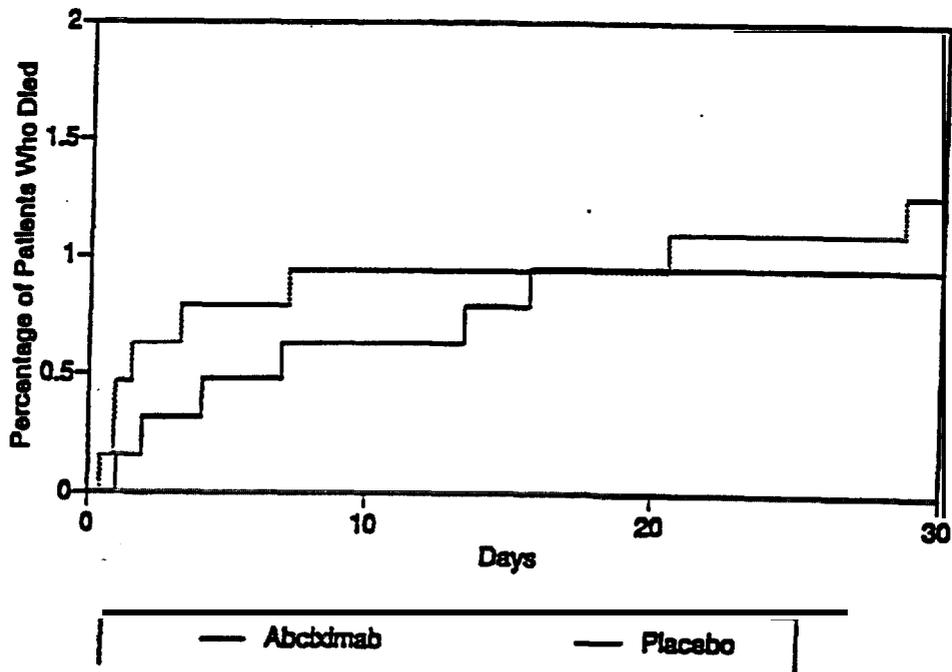


Figure 4. Kaplan-Meier Event Rates for Death

6.2.1.3 Myocardial Infarction

There were a total of 78 patients with at least one MI. The MI was the first occurring endpoint event for 67 of these patients. The number of patients with MI by the type of MI are shown in Table 16.

Table 16. Number of Patients with MI by Type of MI

Type	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630	P
All MI	78 (6.2%)	52 (8.2%)	26 (4.1%)	0.003
Q wave	23 (1.8%)	16 (2.5%)	7 (1.1%)	0.090
Large non-Q-wave during index hospitalizations ^a	32 (2.5%)	22 (3.5%)	10 (1.6%)	0.047
Small non-Q-wave during index hospitalization ^b	20 (1.6%)	13 (2.0%)	7 (1.1%)	0.259
Non-Q-wave after index hospitalization ^c	3 (0.2%)	1 (0.2%)	2 (0.3%)	0.623

^a CK ≥ 5 times the upper limit of normal

^b CK < 5 times the upper limit of normal

^c No CK measurements after Index hospitalization were collected on CRF

p-values are Fisher's exact test results

There were 12 placebo patients with Q wave or large non-Q wave infarctions prior to PTCA and 2 Abciximab patients with Q wave or large non-Q wave infarctions prior to PTCA.

The Kaplan-Meier MI event rates are shown in Figure 5.

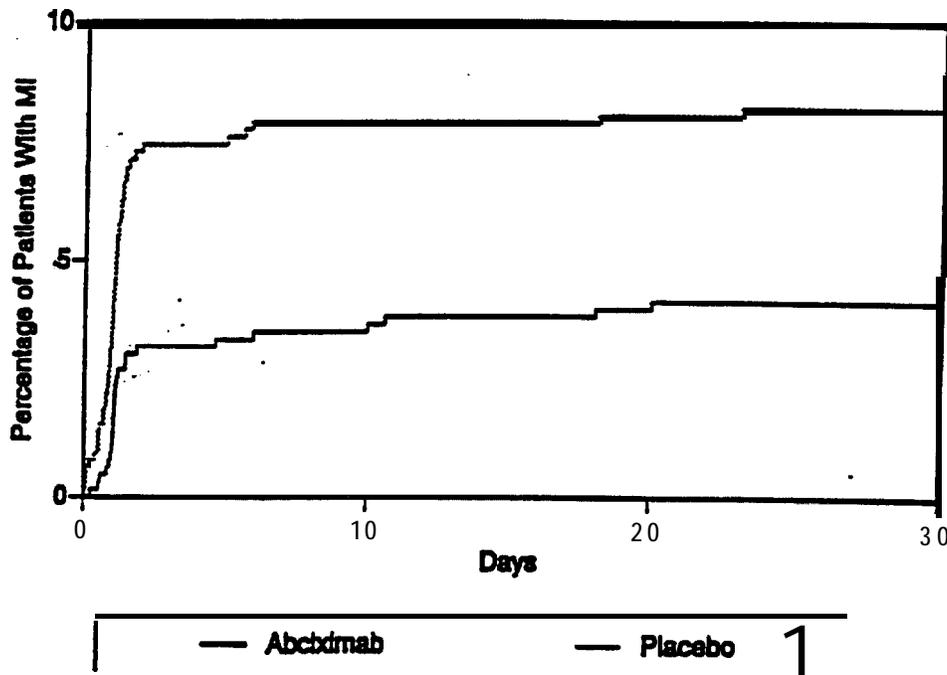


Figure 6. Kaplan-Meier Event Rates for MI

Reviewer's comment: Overall, it appears Abciximab's benefit is especially notable for reducing the number of large MI.

The MI event rate prior to PTCA and during the 24 hours after PTCA are shown in Figure 6.

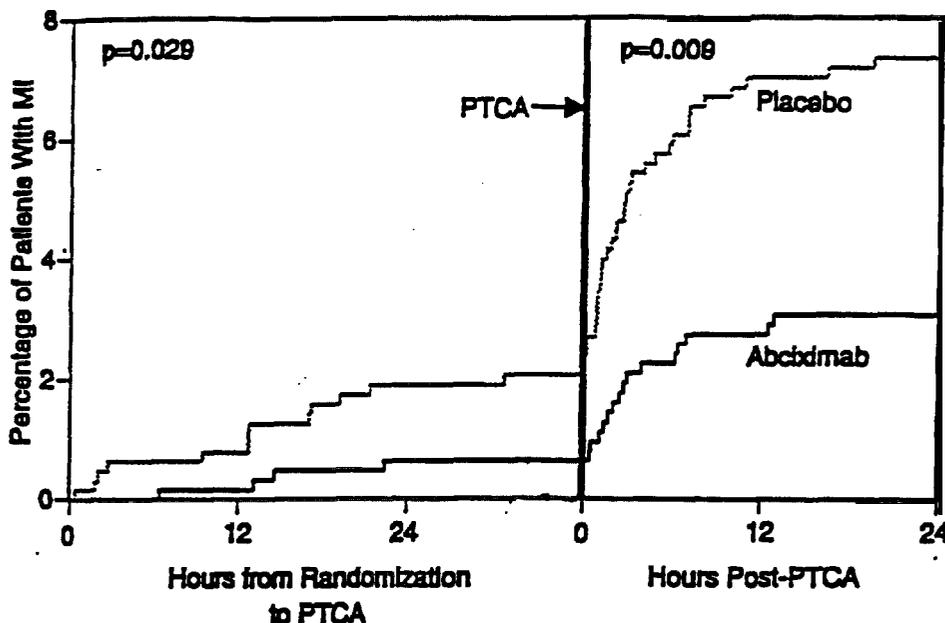


Figure 6. Kaplan-Meier Event Rates Prior to PTCA and 24 Hours After PTCA

The time occurrence of each MI is shown in Table 17.

Table 17. Occurrence of MI According to Study Interval

Patients with MI	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630	P
Randomization to PTCA	17 (1.3%)	13 (2.0%)	4 (0.6%)	0.029
During PTCA & 24 hrs after	50 (4.0%)	34 (5.3%)	16 (2.6%)	0.014
> 24 hrs post PTCA	11 (0.9%)	5 (0.8%)	6 (1.0%)	0.753

P-values are from Fisher's Exact test

Reviewer's comment: These data suggest that the **benefit** of Abckimab in **reducing** the incidence of MI is tied to the **performance of PTCA.** The data are not adequate to **reliably** assess the **effect** of Abckimab in the study interval prior to PTCA. For example, if there **were** one less MI in the **placebo group**, the **difference in rates** would no longer be statistically significant (if the placebo MI number **were** 12 and the **Abciximab** MI number **were** 4, the p-value would be 0.075". This reviewer reviewed all **enzyme** values for patients with MI and noted that **two** patients **were** especially unusual in the designated timing of the onset of the **MI—two** patients in the **placebo group** who **were** assessed as having an MI **prior** to the PTCA. These two patients are **described below:**

Patient — his 63 year old female was admitted to the hospital on November 22, 1994. The patient underwent screening arteriography on November 22, 1994 and began the study agent (placebo) shortly **thereafter**. Following 22 hours of study agent administration the patient underwent the planned PTCA. The PTCA began at **15:40** on November 23, 1994 and was **successful**. The study agent was continued one hour following the PTCA. The **PTCA procedure** lasted 2.5 hours, and was assessed as **uncomplicated**. A few hours after completion of the PTCA the patient **suffered** chest pain and a third **arteriographic procedure** was begun at **20:05** on November 23, 1994 (1.5 hours after completion of the index PTCA). CK enzymes **were** elevated during this period and the CEC assessed the MI as **occurring** on November 23, 1994 at **09:00** (six hours prior to the index PTCA). The CEC **felt** that a second MI had **occurred** on November 24 at **06:00** (15 hours after the index **PTCA**).

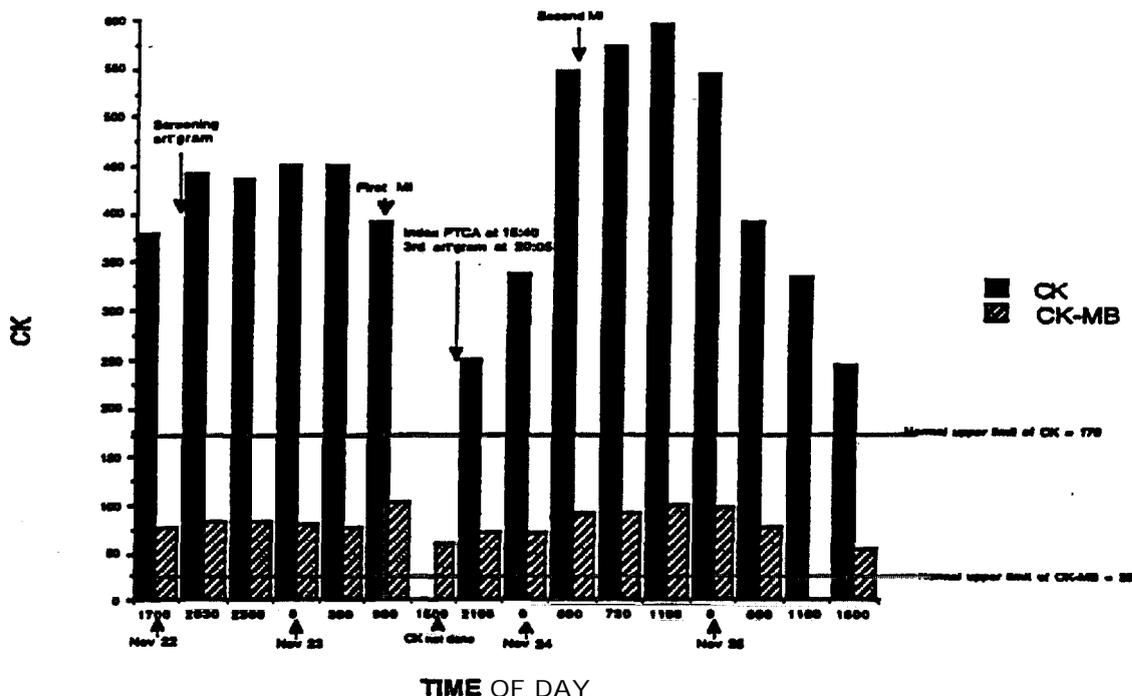


Figure 7 . Patient — CK and CK-MB Enzymes

Patient number ---- experienced chest pain following the index PTCA and the CEC felt this chest pain, coupled with elevated cardiac enzymes indicated an MI. The CEC also felt that the patient experienced an MI prior to the PTCA—but using the protocol enzyme criteria for the diagnosis of MI, this is incorrect. The patient did not develop a C-wave on the EKG during the hospitalization. Overall, the assessment of the endpoint MI being prior to PTCA appears questionable.

Patient: — This 66 year old male was hospitalized on August 23, 1994. The patient had a screening arteriogram performed at 14:48 on August 23, 1994 and the study agent was begun at 11:20 on August 24, 1994. The patient had a PTCA performed at 10:50 on August 25, 1997. The study agent was stopped one hour following the PTCA. The patient received 25 hours of the study agent. The initial EKGs following hospitalization showed an acute Q-wave MI. The CEC felt that since the EKG was obtained 30 minutes after randomization but before administration of the study agent, the MI should not be classified as 'evolving upon admission..' Hence, the assessment of the time of this MI is very questionable.

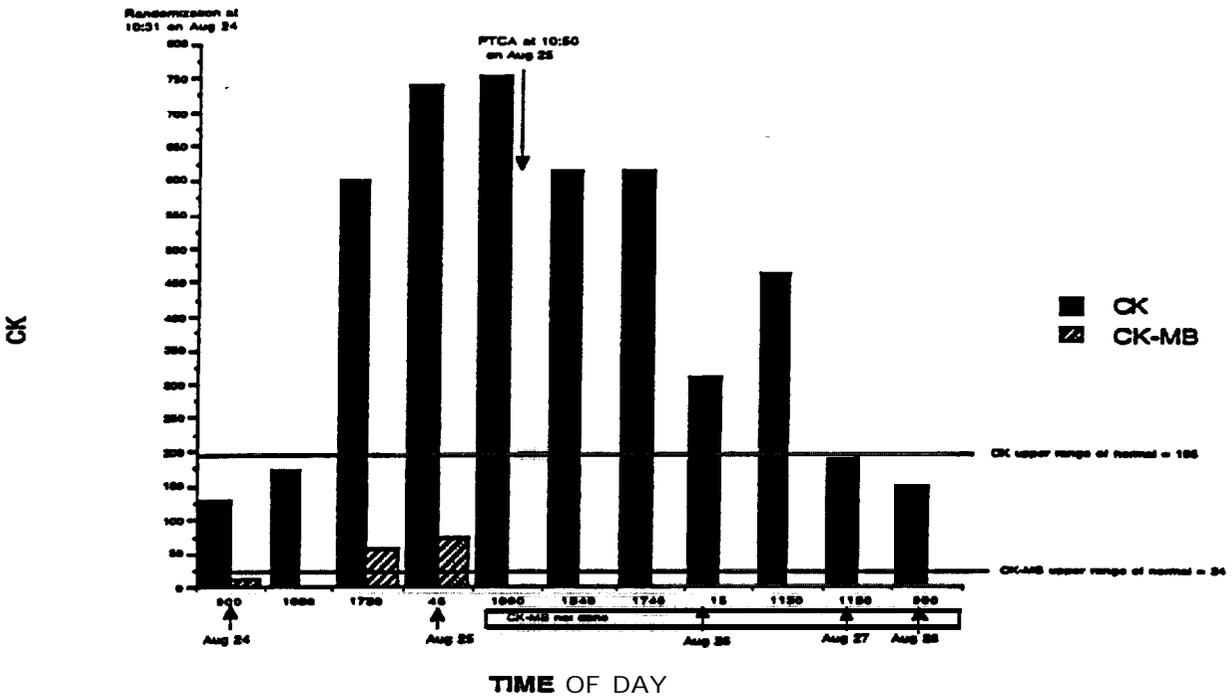


Figure 8. Patient CK and CK-MB Enzymes

These findings suggest that any implications as to the performance of Abciximab using an assessment of the the of MI prior to PEA are subject to significant limitations of the endpoint time determination.

6.2.1.4 Urgent Intervention

The endpoint of urgent intervention included the performance of any unplanned PTCA after the index PTCA (not before), unplanned CABG at any time point, stent placement for immediate patency (not elective stent placement) after the index PTCA and the unplanned use of intra-aortic balloon pump (IABP) at any time. There were 141 endpoint urgent interventions that occurred in 117 patients. In 98 of these 117 patients the urgent intervention was the first occurring event. Twenty-four patients had more than one urgent intervention. The incidence of urgent interventions is shown in Table 18.

Table 18. Number of Patients Who Had Any Urgent Intervention by Component

Component	Total, n = 1265	Placebo, n = 636	Abciximab, n = 630	P
Any Urgent Intervention ^a	117 (9.2%)	88 (10.7%)	49 (7.8%)	0.067
Repeat PTCA	47 (3.8%)	28 (4.4%)	19 (3.1%)	0.186
CABG	17 (1.3%)	11 (1.7%)	6 (1.0%)	0.226
Stent	76 (6.0%)	41 (6.5%)	35 (5.8%)	0.408
IABP	1 (0.1%)	0	1 (0.2%)	0.316

^a the data base includes patient number - who was incorrectly listed as having an endpoint stent, this patient is not counted as having an urgent intervention in this table. P-values are from Fisher's Exact test.

The Kaplan-Meier urgent intervention rates are shown in Figure 9.

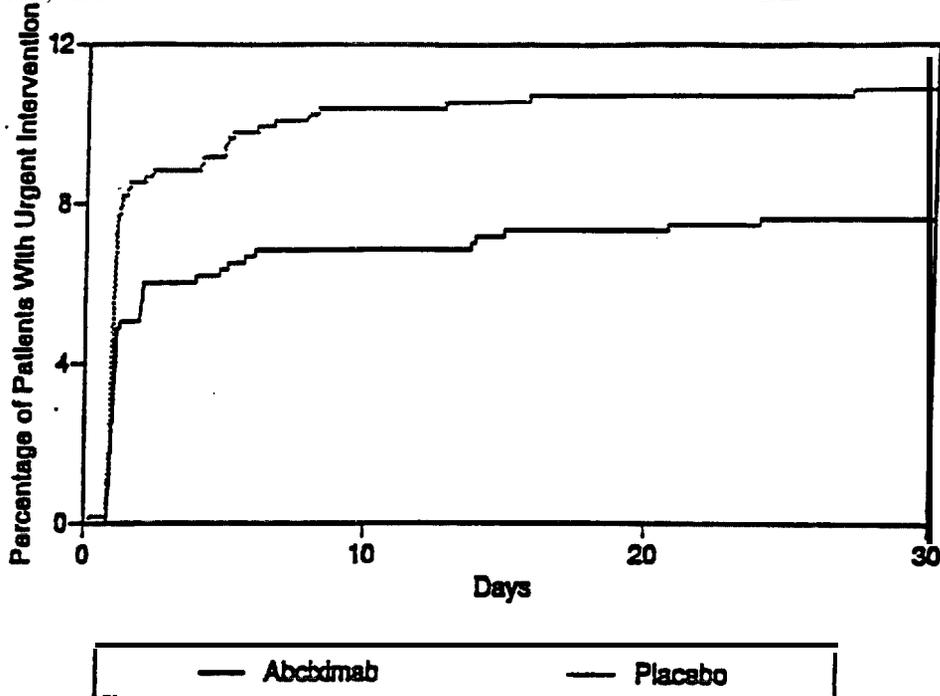


Figure 9. Kaplan-Meier Event Rates for Urgent Intervention

The occurrence of urgent interventions according to the study interval is shown in Table 19.

Table 19. Occurrence of Urgent Intervention Components According to Study Interval

Component	Total, n = 1,265	Placebo, n = 635	Abciximab, n = 630	P
Randomization to PTCA Start (CABG)	2	1	1	N/A
During PTCA & 24 hrs after				
CABG	8 (0.6%)	6 (1.0%)	2 (0.3%)	0.159
PTCA	27 (2.2%)	16 (2.6%)	11 (1.8%)	0.339
Stent	70 (5.5%)	38 (6.0%)	32 (5.2%)	0.054
24 hrs post PTCA				
CABG	7 (0.6%)	4 (0.6%)	3 (0.5%)	0.712
PTCA	20 (1.6%)	12 (1.9%)	8 (1.3%)	0.374
Stent	6 (0.5%)	3 (0.5%)	3 (0.5%)	0.995
IABP	1	0	1	N/A

P-values are from Fisher's Exact test

All 17 patients with CABG had the CABG performed during the index hospitalization.

Reviewer's comment: Only six patients treated with Abciximab underwent urgent CABG while 11 placebo treated patients underwent urgent CABG. Consequently, the information about the use of Abciximab in patients with refractory unstable angina who require urgent CABG is relatively limited. Three of the Abciximab patients (numbers _____ and ---) had CABG either prior to PTCA or within 24 hours after the PTCA. Seven placebo treated patients (numbers _____) had CABG either prior to PTCA or within 24 hours after the PTCA.

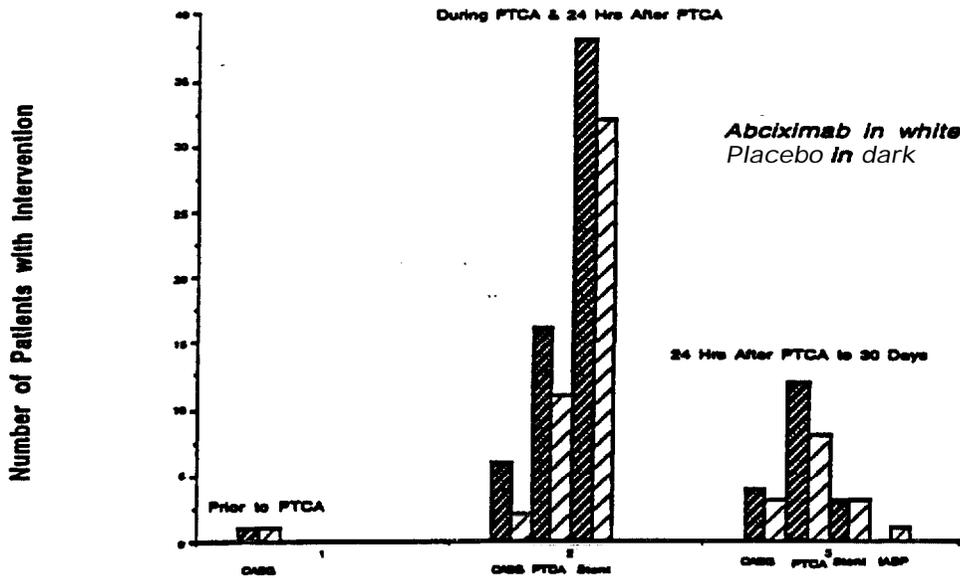


Figure 10. Occurrence of Urgent Interventions According to Study Intervals

Reviewer's comment *Approximately 75% of the urgent interventions occurred either during PTCA or during the 24 hours after PTCA. These findings emphasize the close association of Abciximab benefit with performance of PTCA.*

6.2.1.4.1 Total CABG

There were a total of 30 patients who underwent CABG during the initial 30 days of the trial. Of these 30 patients, 17 patients had the CABG performed as an urgent intervention and 13 had the CABG performed as a planned intervention. Table 20 presents the CABG data.

Table 20. Patients with Urgent and Non-urgent CABG

Event	Placebo, n = 635	Abciximab, n = 630	P
Patients with any CABG	20 (3.2%)	10 (1.6%)	0.068
with urgent CABG	11 (1.7%)	6 (1.0%)	0.226
with non urgent CABG	9 (1.4%)	4 (0.6%)	0.169

P-values are from Fisher's Exact test

Patients who underwent CABG are summarized in Table 21 according to the use of red blood cell transfusions.

Table 21. Patients with CABG and Red Blood Cell Transfusions

event	Placebo, n = 20	Abciximab, n = 10
Units of Transfused Blood	43 +	35
Units/patient	2.2+	3.5
Death	0	1

One placebo patient was transfused with blood, but did not have the number of units recorded. Consequently, it is not possible to directly compare the two treatment arms.

6.2.1.4.2 Stents

Stents placed only for immediate patency were assessed as endpoint events. The endpoint stent could have been placed during either emergency PTCA or a planned PTCA. Table 22 shows compares the incidence of endpoint stents in the trial groups. There was a total of 77 endpoint stents and 96 non-endpoint stents for a total of 173 stents placed overall.

Table 22. Stents

Number of Patients	Placebo, n = 635	Abciximab, n = 630	P
With any Stent	88 (13.9%)	84 (13.3%)	0.806
With an Endpoint Stent	41 (6.5%)	35 (5.6%)	0.555
With a Non-Endpoint Stent	47 (7.4%)	49 (7.8%)	0.832

P-values are from Fisher's Exact test

6.2.1.4.3 Intra-aortic Balloon Placement

Intra-aortic balloon placement was considered an endpoint event when it was placed in a patient who was not regarded as a candidate for PTCA or CABG. Only one patient met this endpoint However, eleven other patients had IABPs placed as part of their management. Table 23 describes the use of IABP.

Table 23. IABP

Patients	Placebo, n = 635	Abciximab, n = 630	P
With any IABP	10 (1.6%)	2 (0.3%)	0.021

P-value is from Fisher's exact t-test

6.2.1.5 Recurrent Myocardial Ischemia

The second most important set of secondary endpoints **prespecified** in the analytical plan was an analysis of the incidence of recurrent **myocardial** ischemia The analytical plan stated that a composite endpoint would be **formed** to include the following two events:

- urgent **PTCA** before planned PTCA
- pain with EKG changes.

This composite was to be combined with the primary composite endpoint to form a "recurrent **myocardial** ischemia **endpoint**" and was to be compared with the overall primary endpoint result.

Reviewer's comment The sponsor did not **include** this **analysis** in the **BLA** submission. **The** wording of **this analysis** in the analytical plan is unclear and open to **multiple** interpretations. **The** sponsor did attempt to analyze the **importance** of **recurrent myocardial ischemia** using **certain analyses**. **The analytical plan was also unclear as to whether** these analyses were to be subdivided (before **PTCA**, after **PTCA**). ,

Additional, some of these analyses **were clearly not prospectively** stated (these **will** be **identified**).

Table 20 states the results of the "**recurrent myocardial** ischemia **endpoint**."

Table 24. Recurrent Myocardial Ischemia Endpoint
Patients Counted Once with the Priority of Primary Endpoint>Pain & EKG Changes>Urgent PTCA Before Planned PTCA

Event	Placebo, n = 635	Abciximab, n = 630	P
Primary Endpoint	100 (15.7%)	71 (11.3%)	0.021
Pain & EKG Changes	69 (10.9%)	86 (13.7%)	0.145
Urgent PTCA Before Planned PTCA	1 (0.2%)	3 (0.5%)	0.313
Composite of Above	170 (26.8%)	160 (25.4%)	0.609

P-values are from Fisher's Exact test

Reviewer's comment **This type of analysis** assesses **equal** weight to the **"hard" outcomes** identified in the primary endpoint to the **"soft" outcomes** of pain and EKG changes and **urgent** PTCA. This analysis **is** therefore of limited **benefit**, but it does suggest that the **Abciximab benefit** is confined to lowering the incidence of ● h& clinical endpoints (death, MI, urgent intervention) with less effect upon **symptomatology**.

Since the incidence of death was **very** low in **this trial** (limited censoring) another way of examining the effect of Abciximab upon symptoms is to examine the incidence of pain and EKG changes among all 1,265 patients. Table 25 examines the incidence of pain and EKG changes by periods.

Table 25. Patients with Pain and EKG Changes

Pain and EKG Changes	Placebo, n = 635	Abciximab, n = 630	P
Before Planned PTCA	62 (9.8%)	59 (9.4%)	0.849
First 24 Hrs Following Planned PTCA	41 (6.5%)	28 (4.4%)	0.137
>24 Hrs Following Planned PTCA	34 (5.4%)	15 (2.4%)	0.008

P-values are from Fisher's Exact test; patients are counted once within a row, but may be counted more than once among the three rows

Reviewer's comment **This analysis is consistent** with the finding of **Abciximab's benefit** being temporally related to the **performance** of PTCA.

The sponsor utilized the results of a CAPTURE **substudy** to examine the effect of Abciximab upon **myocardial ischemia**. This **substudy** was **summarized** in the **clinical** protocol as a study to be performed at 15 sites in approximately 250 patients. This **substudy** utilized continuous vector EKG monitoring and was coordinated by **Cardialysis**. In this study an ischemic episode was defined as ST deviation of at least 1 mm appearing in at least 2 **consecutive** EKG readings spaced 1 minute apart. The end of EKG monitoring was to be six hours following the planned PTCA

Reviewer's comment **The analytical plan** stated that **this analysis would involve** a **comparison** of **recurrent ischemia**, as defined by chest pain with ST changes in the two treatment arms. **These analyses were to be made for the time periods** before and **after** treatment PTCA. **The duration of ischemia** was not **explicitly** identified as an outcome **variable** in the **analytical plan**. As with all the **secondary endpoints**, these **data** were to be **viewed** as **exploratory** and **potentially confirmatory** of the **primary endpoint**.

The results of the continuous EKG monitoring are shown in Table 26.

Table 26. Continuous EKG Monitoring of Ischemic Episodes (Start of Study Agent Through End of EKG Monitoring)

	Placebo	Abciximab	P
Patients in Substudy	165	182	0.951
Evaluable Patients	163	169	0.655
Duration of Monitoring, median (range, hrs)	26 (10.1, 62.0)	26 (12.1, 67.8)	0.811
Patients with Ischemic Episodes	37	30	0.277
Median Duration of Ischemia (range, hrs)	38 (2.0, 365.9)	8 (1.0, 325.1)	0.041

P-values are from Fisher's Exact test

Analysis of these data according to study intervals (**prior** to PTCA and after PTCA) showed no **statistically** significant difference in either the number of ischemic episodes in the two groups or in the **duration** of the **ischemic** episodes (there are slightly different number of **evaluable** patients when the data are analyzed in this manner).

Reviewer's **comment:** These data **are consistent** with the observation that the Abciximab group of patients had fewer **myocardial infarctions**.

Another way of examining the **Abciximab** effect upon ischemia is a review of the **performance** of PTCA Table **27** examines the **performance** of the index PTCA.

Table 27 Index PTCA

Patients	Placebo, n = 635	Abciximab, n = 630	P
With Urgent PTCA before Planned PTCA	14	9	0.401
With PTCA Performed as Planned	610	608	0.767
With no PTCA Attempted but CABG Performed	3	3	1.000
With No PTCA Attempted and No CABG Performed	8	10	0.644

P-values are from Fisher's Exact test

Of the 24 patients who did not have the index PTCA performed, five patients had primary endpoint events (three placebo patients and two Abciximab patients).

Reviewer's comment: These data also provide no meaningful evidence of a difference in a treatment effect based upon the performance of emergency PTCA or emergency CABG prior to the planned PTCA.

6.2.1.6 Analysis of the primary endpoint among subgroups

The analytical plan specified that the primary endpoint would be analyzed in the following subgroups:

- by time periods between the start of study treatment and the most recent angina episode (0-12 hrs, 12-24 hrs and > 24 hrs)
- single vs. multiple vessel disease
- ACC classification of the culprit lesion with the subgroups being the high risk subgroup (one type C or two or more type B or one type B and either diabetic or a female at least 65 yrs of age)
- urgent PTCA performed before the planned PTCA. These analyses are shown below, in Table 26.

Table 28. Preplanned Subgroup Analyses of the Primary Endpoint

Event	Placebo, patients with event / patients at risk (%)	Abciximab, patients with event / patients at risk (%)	P
Angina			
Angina < 12 Hrs before Study Agent	71 / 382 (18.6%)	45 / 384 (11.7%)	0.009
Angina 12 - 24 Hrs before Study Agent	11 / 111 (9.9%)	10 / 107 (9.3%)	1.000
Angina > 24 Hrs before Study Agent	19 / 141 (13.5%)	16 / 139 (11.5%)	0.719
Vessel Disease			
Single Vessel Disease	53/333 (15.9%)	35/336 (10.4%)	0.040
Multiple Vessel Disease	48/297 (16.2%)	36/292 (12.3%)	0.196
1 Type C Lesion	3 / 11 (27.3%)	0 / 9	0.218
2 Type B Lesions	67 / 343 (16.6)	41 / 317 (12.9%)	0.191
Urgent PTCA before Planned PTCA	8/14 (67.1%)	1/9 (11.1%)	0.040
Baseline Characteristics			
Men	73/459 (15.9%)	55/461 (11.9%)	0.087
Men < 65 Years of Age	43/298 (14.6%)	36/301 (12%)	0.399
Men ≥ 65 Years of Age	30/161 (18.6%)	19/160 (11.9%)	0.120
Women	28/176 (15.9%)	16/169 (9.5%)	0.080
Women < 65 Years of Age	24/114 (21%)	12/94 (12.8%)	0.142
Women ≥ 65 Years of Age	4/62 (6.5%)	4/75 (5.3%)	1.000

P-values are from Fisher's Exact test; Vessel Disease refers to investigator assessment of vessels with >50% stenosis; seven patients with no vessel containing >50% stenosis are excluded from this analysis, none of these seven patients experienced the primary endpoint

Reviewer's comments: These subgroup analyses suggest that Abciximab maybe most efficacious in patients with the recent (<12 hours) onset of angina, patients with single vessel disease, and patients requiring an urgent PTCA. In general, patients with single vessel disease are among the best candidates for PTCA and the use of Abciximab may enhance the benefit of PTCA. The clinical implications of Abciximab efficacy in the setting of recent onset of angina is less clear, but provides additional evidence of efficacy in patients with unstable angina.

6.21.7 Ischemic/thrombotic complications

The analytical plan stated that the following analyses will be performed:

1. Complications during the planned PTCA were to be examined using a composite endpoint **consisting of**:
 - new thrombus (thrombus on second **arteriogram** but not on first)
 - need for thrombolytics during planned PTCA
 - placement of a perfusion catheter during planned PTCA to treat abrupt closure.

Table 29 shows the results of this composite. There was no **difference** in the proportion of **patients with this thrombotic composite**.

Table 29. New Thrombus, Need for Thrombolytics or Perfusion Catheter during the Planned PTCA

Patients with PTCA Attempted	Placebo, n = 624	Abciximab, n = 617	P
Patients with New Thrombus, Thrombolytics or Perfusion Catheter	34 (5.4%)	33 (5.3%)	1.000

P-value is from Fisher's Exact test

2 **Differences in the culprit lesion** between the first and second **arteriograms**

The **analytical** plan stated that these **analyses were to compare** the change from **first arteriogram** to second **arteriogram** for the following outcomes:

- presence of thrombus
- TIMI flow grade

The **patients** were to be divided into three groups (improved, no change, worsened) and the two **treatment** arms compared.

Table 30 presents the incidence of thrombus at the two **arteriograms**. The **arteriographic committee** assessment is **utilized** if available, if not, then the **investigator** assessment is **utilized**.

Table 30. **Presence of Thrombus**

Patients	Placebo, n = 635	Abciximab, n = 630	P
<i>With evaluable arteriograms</i>	631 (99.4%)	625 (99.2%)	1.000
<i>With Thrombus on First Arteriogram</i>	39 (6.2%)	45 (7.2%)	0.499
<i>Without Thrombus on First Arteriogram</i>	592 (93.8%)	580 (92.1%)	0.499
<i>Who Had a Thrombus on First Arteriogram, but No Thrombus on Second Arteriogram</i>	8 (20.5%)	19 (42.2%)	0.038
<i>Who Did Not Have a Thrombus on First Arteriogram, but Did Have Thrombus on Second Arteriogram</i>	1 (0.2%)	4 (0.7%)	0.213

P-values are from Fisher's Exact test

Table 31 presents the **TIMI** flow grade **comparison** between the two **arteriograms**.

Table 31. TIMI Flow Comparisons

Patients	Placebo, n = 635	Abciximab, n = 630	P
<i>With evaluable arteriograms</i>	631 (99.4%)	625 (99.2%)	1.000
<i>With No Perfusion or Partial Perfusion (TIMI 0/1/2) on First Arteriogram</i>	200 (31.5%)	188 (30.1%)	0.542
<i>With No Perfusion or Partial Perfusion on First Arteriogram and Flow Improvement on Second Arteriogram</i>	40 (20.0%)	56 (29.8%)	0.034
<i>With Normal Perfusion or Partial Perfusion (TIMI 2/3) on First Arteriogram</i>	590 (93.5%)	566 (90.1%)	0.061
<i>With Normal Perfusion or Partial Perfusion on First Arteriogram and Flow Worsening on Second Arteriogram</i>	46 (7.8%)	31 (5.5%)	0.126

P-values are from Fisher's Exact test

The changes from the first arteriogram to the second arteriogram are summarized in Table 32.

Table 32. Trend in Thrombus and Coronary Arterial Flow

Patients	Placebo, n = 635	Abciximab, n = 630	P
With evaluable arteriograms	631 (99.4%)	625 (99.2%)	
With Thrombus Improved	8	19	
With Thrombus Unchanged	622	602	
With Thrombus Worsening	1	4	
Trend To Improved Thrombus with Abciximab			0.150
With TIMI Flow Improvement	40	56	
With TIMI Flow Unchanged	544	533	
With TIMI Flow Worsening	46	31	
Trend To Improved Flow with Abciximab			0.018

P-values for trend are from Jonckheere-Terpstra tests

Reviewer's comment *These data do not provide evidence of a harmful effect of Abciximab upon coronary arterial flow. Indeed, the data suggest that Abciximab improves arterial flow. However, findings from these secondary analyses are exploratory and no adjustment for multiplicity was utilized in their assessment*

6.2.1.8 Long Term Outcome

The analytical plan stated that the six month outcome data would be analyzed by using a composite endpoint that consisted of MI, death, PTCA or CABG. This analysis was not to distinguish between urgent and non-urgent procedures.

Six month revascularization follow-up data were missing were four patients in each treatment group (data complete for 99.4% of randomized patients). Six month mortality data were missing for nine patients, six placebo patients and 3 abciximab patients). Table 33 presents the results of the six month composite outcome. The clinical endpoint committee did not review the six month revascularization data. The Kaplan-Meier time-to-composite event curves are shown in Figures 11.

Table 33. Number of Patients Who Had Death, MI or Repeat PTCA or CABG During Six Month Follow-up

Patients	Placebo, n = 635	Abciximab, n = 630	Log-rank P
Composite Event	193 (30.4%)	193 (30.6%)	0.770

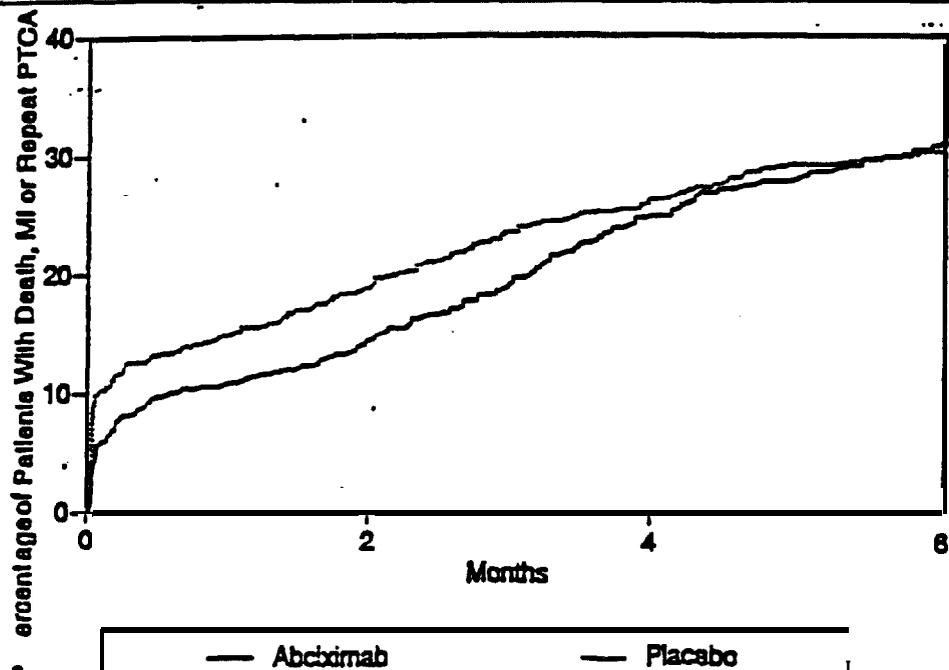


Figure 11. Kaplan-Meier Event Rates for Six Month Composite Endpoint

Reviewer's comment **The composite event analysis at six month shows that the benefit of Abciximab is no longer apparent at six month. However, there are limitations in this analysis because the clinical monitoring for myocardial infarction was much less intense after the initial 30 days of follow-up. A sizable proportion of the 30 day efficacy of Abciximab was attributable to intensive monitoring of CK enzymes. After discharge from the hospital, only ischemic events requiring intervention or hospitalization were recorded. Epidemiological data suggest that "Went infarctions" contribute to long term morbidity and mortality.**

The components of the six month composite endpoint are shown in Table 34.

Table 34. Number of Patients Who Had Death, MI or Repeat Revascularization During Six Month Follow-up by Component

Patients	Placebo, n = 635	Abciximab, n = 630	P
With Death	14 (2.2%)	17 (2.7%)	0.591
With MI	59 (9.3%)	41 (6.6%)	0.076
With Repeat Intervention	154 (24.3%)	156 (24.8%)	0.845

P-values are from Fisher's Exact test. Patients were counted only once within a component, but could be counted in more than one component. Mortality data were missing for six placebo patients and three Abciximab patients.

Revascularization/MI data were missing for four patients in each trial arm. The corresponding logrank P values for death, MI, repeat vascularization are 0.581, 0.055 and 0.972

Table 35 presents the six month outcome data in a sensitivity analysis with the worst-case assumption for the missing data-*ie.*, there were three additional Abciximab deaths and four additional Abciximab patients with MI.

Table 35. Sensitivity Analysis of Six Month Follow-up by Component

Patients	Placebo, n = 635	Abciximab, n = 630	P
With Death	14 (2.2%)	20 (3.2%)	0.302
With MI	59 (9.3%)	45 (7.1%)	0.184

P-values are from Fisher's Exact test

Table 36 presents the number of events occurring after 30 days of follow-up.

Table 36. Endpoint Events Occurring after 30 Days

Event	Placebo, n = 635	Abciximab, n = 630	P
Death	6	11	0.234
MI	7 (all Q wave)	15 (13 Q wave)	0.089
Revascularization (PTCA/CABG)	87	98	0.381

P-values are from Fisher's Exact test and are calculated among the patients with complete six month follow-up data

Reviewer's comment **These was no remarkable imbalance of endpoint events occurring after 30 days of follow-up.**

Of the 185 patients with revascularization events occurring after 30 days, 164 patients had the events classified as "urgent" by the investigator (64 patients in the Placebo arm and 80 patients in the Abciximab arm, P = 0.802 using Fisher's Exact test).

Reviewer's comment **A portion of the six month follow-up data were obtained after the trial had been unblinded. Consequently, the determination of events may have been performed with knowledge of which study agent the patient received. The six month data may be subject to some bias. Note that the number of patient with MI during follow-up was small (only 22) and that the vast majority of these were Q wave MI (20). A significant proportion of the 30 day benefit of Abciximab was related to the lower incidence of non-Q wave MI. Since cardiac enzyme monitoring was less intense during the six month follow-up period, non-Q wave MIs may not have been detected. Also note that the prespecified revascularization outcome was not "urgent" revascularization, but was any (PTCA/CABG) revascularization.**

6.3.0 CAPTURE Safety Review

This safety analysis prespecified in the analytical plan included the following area:

-bleeding

analyzed by three periods (onset of treatment to PTCA, from PTCA to 24 hours after PTCA, and **from** 24 hours after PTCA until hospital discharge)

analyzed by grades using the **TIMI** classification

analyzed by incidence of transfusion

analyzed through the index hospitalization period or 30 days, whichever is first

important subgroups to be analyzed are patients with a history of peripheral vascular disease, **diabetes** and women over the age of **65** years

-**thrombocytopenia** through 30 days of follow-up

-stroke

-**HACA**

6.3.1 Mortality

There were a total of 31 deaths during the clinical **trial**. Fourteen of these deaths occurred during the initial 30 days of follow-up (eight placebo patients and six Abciximab patients). Seventeen of these deaths occurred after 30 days (six placebo patients and 11 Abciximab patients). The clinical endpoint committee classified the cause of death as card&c for 22 of the **31** deaths. Seven of the 31 deaths were **unobserved** and sudden (**all** in the long term follow-up group). The clinical endpoint committee assessed three patients as dying from vascular causes—a patient **with** pulmonary hemorrhage, a patient with a **stroke** 15 days following study agent administration and a patient with a **stroke (infarction)** three months following study agent administration.

Reviewer's comment: Of the 31 deaths at least one death may be directly related to the **study** agent **This** patient has been described previously and was noted to develop pulmonary **hemorrhage following the administration of heparin and Abciximab**. **This patient did not have an autopsy performed.**

6.3.2 Stroke

There was a total of eight patients who experienced a stroke during six months of **followup** with four patients in each **trial** arm. Half of these strokes **occurred** during the initial 30 day follow-up period and **half** occurred after 30 days. Of the four patients experiencing **strokes** during the initial 30 day follow-up period, three were in the placebo group and one was in the Abciximab group. The Abciximab patient had a **stroke** 15 days following the study agent administration and did not have a CT scan. Of the **three** placebo patients with a stroke during the 30 days, **one was of the** hemorrhagic type and the other two were nonhemorrhagic. After 30 days, three **Abciximab** patients experienced strokes (one hemorrhagic and two nonhemorrhagic) and one placebo patient experienced a stroke (nonhemorrhagic). Overall, there were two known hemorrhagic strokes, one in each trial **arm**, plus an Abciximab patient who had a stroke of unknown type.

Reviewer's comment: The only **lethal stroke** was in an **Abciximab** treated patient who **suffered a nonhemorrhagic stroke** and died **approximately** six weeks **after receiving the** study agent. Overall, the **stroke data from** CAPTURE reveal no safety signals. Of the 3711 patients **receiving** Abciximab in **CAPTURE, EPIC and EPILOG, there were** seven patients who experienced **intracranial hemorrhages** (0.22%). **The corresponding intracranial hemorrhage rate for placebo** patients was 0.14% (**3/2226**), not a **statistically** significant difference. The **current** labeling for Abciximab does not mention the incidence of **intracranial** hemorrhage (beyond the heading of major bleeding events) and the **CAPTURE data are** consistent with the **current** wording.

6.3.3 Hemorrhage

6.3.3.1 Hemorrhage Classification

The Clinical Endpoint Committee classified bleeding events using the **TIMI** Study Group **classification** of bleeding. **To** account for transfusions, hematocrit and hemoglobin measurements were to be adjusted for any packed **red** blood cells or whole blood transfused within 46 hours **prior** to measurement. The number of units of red blood cells combined were to be added to the change in hemoglobin. Three times the number of units of red blood cells were to be added to the change in **hematocrit**. The **TIMI** Study **Group** recognized three classifications of hemorrhage.

- “major”** bleeding included intracranial hemorrhage OR bleeding associated with a decrease in hemoglobin by greater than 5 g/dL or a decrease in **hematocrit** by greater than 15%
- “minor”** bleeding included spontaneous events observed as gross **hematuria** or hematemesis OR when bleeding is observed (either due to spontaneous events or iatrogenic) and a decrease in hemoglobin occurs to greater than 3 g/dL or a decrease in **hematocrit** by 19% OR a decrease in hemoglobin greater than 4 g/dL or a decrease in hematocrit greater than 12% when no bleeding site is identifiable
- “insignificant” refers to minor bleeding that does not meet the above criteria.

Within each of three time periods the Clinical Endpoint Committee identified the most severe bleeding event and determined whether the bleeding event was related to CABG. **All** hemorrhage within **48** hours after CABG was considered CABG-related hemorrhage and was not classified into a major or minor bleeding category by the Committee. **For** bleeding not related to CABG, the Committee **determined** the bleeding location. Table 37 summarizes the hemorrhage data.

Table 37. Numbers of Patients with Hemorrhage

Patients	Placebo, n = 635	Abciximab, n = 630	P
With Major Non-CABG Hemorrhage	12 (1.9%)	24 (3.8%)	0.043
With CABG Hemorrhage	10 (1.6%)	6 (1.0%)	0.452
With Minor Non-CABG Hemorrhage	13 (2.0%)	30 (4.8%)	0.008
With Insignificant or No Non-CABG Hemorrhage	599 (94.3%)	569 (90.3%)	0.008
Not Evaluated	1 (0.2%)	1 (0.2%)	n/a

Patients who had blood loss in more than one **classification** are counted **only** once according to the most severe classification. Patients with blood loss of the same **classification** on more than one occasion are counted once within that classification. P-values are from **Fisher’s** Exact test.

Overall, 79 patients had major or minor **non-CABG** hemorrhages (28 in the placebo group and 84 in the **Abciximab** group).

Reviewer’s comments: The incidence of bleeding in **CAPTURE** was less than that detected in **EPILOG**, but higher than that detected in **EPILOG**. The sponsor attributes the lower incidence of hemorrhage to better **arterial puncture** site care and the use of weight adjusted **heparin** at the time of **coronary catheterization**. The finding of more hemorrhage among **Abciximab** patients is supported by the sponsor’s analysis of hemoglobin values (Table 129, volume 3). These analyses show that the decrease in hemoglobin values is greater for **Abciximab** patients than for placebo patients.

The incidence of major **non-CABG** hemorrhage in **EPILOG** is shown below=

placebo	10/939 (1.1%)
Abciximab (Std dose heparin)	17/918 (1.9%)
Abciximab (Low dose heparin)	10/935 (1.1%)

The higher major **non-CABG** hemorrhage rate among patients in **CAPTURE** may be related to their **total heparin** dose and duration of anticoagulation.

Table 38 summarizes the time occurrence of the hemorrhagic events.

Table 38. Timing of Major and Minor Hemorrhagic Events Not Associated with CABG Among Patients with PTCA

Patients	Placebo	Abciximab
With Major Hemorrhage	11	23
Study Agent until PTCA	1 (9.1%)	4 (17.4%)
PTCA to 24 Hours After	7 (63.6%)	17 (73.9%)
24 Hours After PTCA until Discharge	3 (27.3%)	2 (6.7%)
With Minor Hemorrhage	13	29
Study Agent until PTCA	3 (23.1%)	10 (34.5%)
PTCA to 24 Hours After	5 (38.5%)	16 (55.2%)
24 Hours After PTCA until Discharge	5 (38.5%)	3 (10.3%)

This table excludes two patients with major hemorrhages (one in each trial arm) who did not undergo PTCA. The table also excludes one patient (Abciximab) with minor hemorrhage who did not undergo PTCA.

The Clinical Endpoint Committee also determined whether patient who experienced major **non-CABG hemorrhages** experienced spontaneous or nonspontaneous hemorrhages. Of the 34 patients with *major non-CABG* hemorrhages, only eight had spontaneous hemorrhages (six **Abciximab** patients and two placebo patients, $p = 1.000$).

6.3.3.2 Bleeding Sites .

The location of the bleeding site for the 36 patients with major **non-CABG** hemorrhage is shown in Table 39.

Table 39. Bleeding Site for Patients with Major Non-CABG Hemorrhage

Patients with Major Non-CABG Hemorrhage	Placebo, n = 12	Abciximab, n = 24
Sheath Site	6 (50%)	17 (70%)
Other Puncture Site	2 (17%)	2 (8%)
Retroperitoneal	0	2 (8%)
Decrease in hgb/hct without Known Site	2 (17%)	1 (4%)
G	0	3 (13%)
Pulmonary	0	1 (4%)
Intracranial	1 (8%)	0
GU	1 (8%)	0

The location of the bleeding site for the 43 patients with minor **hemorrhages** is shown in Table 40.

Table 40. Bleeding Site for Patients with Minor Hemorrhages

Patients with Minor Hemorrhages	Placebo, n = 13	Abciximab, n = 30
Sheath Site	6 (46%)	21 (70%)
G	1 (8%)	3 (10%)
GU	0	4 (13%)
Decrease in hgb/hct without Known Site	2 (15%)	1 (3%)
Other Puncture Site	1 (2%)	0

Reviewer's comment In general, the most common site of significant hemorrhage was the sheath site. This is not an unexpected finding and signals no new safety concerns.

In general, most patients had the sheath that was **utilized** for the first **arteriogram** also **utilized** for the PTCA. Of the 1,241 patients who had PTCA attempted, the length of **time** the original sheath was left in place was recorded for **1,213** patients (607 in the placebo group and 606 in the **Abciximab** group). The median **duration of sheath placement** was **41.8 hours** for the placebo group and 39.1 hours for the **Abciximab** group.

Table 41 summarizes the incidence of sheath **site** bleeding by the timing of the sheath removal.

Table 41. Patients with Sheath Site Bleeding Events by Timing of Sheath Removal

Patients With PTCA Attempted	Placebo, n = 624	Abciximab, n = 617
Who had one of the following: prolonged bleeding, hematoma >5 cm, or retroperitoneal hemorrhage	92 (14.7%)	170 (27.6%)
Who had sheath removed ≤ 5 hrs after the end of PTCA	n = 57	n = 43
Who had sheath removed ≤ 5 hrs after the end of PTCA, with at least one of the bleeding events	6 (10.5%)	14 (32.6%)
Who had sheath removed > 5 hrs after end of PTCA	n = 547	n = 559
Who had sheath removed > 5 hrs after end of PTCA, with at least one of the bleeding events	81 (14.8%)	152 (27.2%)
Who have no recorded time of sheath removal	n = 20	n = 15
Who have no recorded time of sheath removal, with at least one of the bleeding events	5 (25.0%)	4 (26.7%)

Reviewer's comment: **The** sheath was intended to be removed no sooner than **six** hours after discontinuation of the study agent. **The** above data suggest that removal of the sheath less than six hours prior to the **discontinuation** of **Abciximab** was associated with a higher incidence of minor puncture site bleeding. **The numbers** of patients in these subsets are small, and it is difficult to reach **substantial conclusions** from these findings.

6.3.3.3 Bleeding and Heparin

The impact of **heparin** use may be assessed by comparing the major **non-CABG** bleeding rate among the patients when the patients are divided into subsets based upon **APTT** measurements. Table 42 summarizes the number of **patients with** major **non-CABG** hemorrhage events by **APTT**.

Table 42. Number of Patients with Major Bleeding Events by APTT

Sampling Time	Placebo	Abciximab	P
Pre-PTCA			
Patients with APTT < 40 sec	91	89	
with major bleeding	4 (4.4%)	2 (2.2%)	0.682
Patients with APTT 40 - 70 sec	228	211	
with major bleeding	1 (0.4%)	6 (2.8%)	0.059
Patients with APTT > 70 sec	229	248	
with major bleeding	6 (2.6%)	14 (5.6%)	0.113
Patients with APTT not measured	87	82	
with major bleeding	1 (1.1%)	2 (2.4%)	0.612
Six hrs Post-PTCA			
Patients with APTT < 40 sec	111	134	
with major bleeding	0	4 (3.0%)	0.129
Patients with APTT 40 - 70 sec	127	126	
with major bleeding	1 (0.8%)	2 (1.6%)	0.622
Patients with APTT > 70 sec	310	305	
with major bleeding	6 (1.9%)	14 (4.6%)	0.072
Patients with APTT not measured	87	65	
with major bleeding	5 (5.7%)	4 (6.2%)	1.000

-values are from Fisher's Exact test

Reviewer's comment: In **general, these** data suggest that patients with prolonged **APTT** may experience a higher rate of major bleeding events.

6.3.3.4 Red Blood Cell Transfusions

The red blood cell transfusion data are shown in Table 43. Major **non-CABG** hemorrhage occurred in 36 patients. 24 of these patients received red blood cell **transfusions**. Three of the 36 patients with major **non-CABG hemorrhages** died. The two Abciximab patients who died **included** a death due to a stroke and a death due to pulmonary hemorrhage. The one placebo patient who died experienced **hypoxic** encephalopathy following a cardiac **arrest**.

Table 43. Red Blood Cell Transfusions

Patients	Placebo, n = 635	Abciximab, n = 630	P
Receiving red blood cell transfusion for either major CABG or non-CABG hemorrhage	30 (4.7%)	45 (7.1%)	0.080
Receiving red blood cell transfusion for major non-CABG hemorrhage	9 (1.4%)	15 (2.4%)	0.709

P-values are from Fisher's Exact test

6.3.3.5 Analysis of Hemorrhage Among Subsets

The analytical plan identified the following subsets for hemorrhage analysis:

- patients with a history of peripheral vascular disease
- patients with a **history** of diabetes
- women over the age of 65

Reviewer's comment *The current labeling notes that the risk for major bleeding is increased in the following subsets:*

- patients **who** weigh less than 75 kg
- patients **> 55 years old**
- patients **with** a history of prior **GI disease**
- patients receiving **thrombolytics**

Table 44 summarizes the subset **hemorrhage** analysis.

Table 44. Subset Analysis for Major Non-CABG Bleeding Events

Subset	Placebo, number of patients with event/ n	Abciximab, number of patients with event/n	P
Age ≥ 65 years	5/360 (1.4%)	10/376 (2.7%)	0.298
Age ≥ 65 years & 75 kg	8/392 (2.4%)	18/330 (5.5%)	0.047
Body Weight > 75 kg	4/302 (1.3%)	6/299 (2.0%)	0.544
Body Weight Not Stated	1	11	-
Female	6/176 (3.4%)	12/169 (7.1%)	0.149
Male	6/298 (2.0%)	12/301 (4.0%)	0.231
History of Prior GI Disease	2/12	6/24	0.691
Receipt of Thrombolytics	0/9	1/9	-
History of Peripheral Vascular Disease	0/12	2/24	0.543
History of Diabetes	0/12	6/24	0.079

P-values are nominal univariate values from Fisher's Exact test. The sponsor notes that weight is associated with a P-value of 0.398 when the weight categories are compared and adjusted for gender, age and height.

Reviewer's comment *The subset of Abciximab-treated patients with a body weight ≤ 75 kg had a rate of major non-CABG bleeding significantly exceeding that for the comparable group of patients receiving placebo. This finding will impact subset statements in the proposed label. The same subset analyses for all major bleeding events shows that no Abciximab-treated patient subset has a significant & higher rate than the comparable placebo group (data not shown). However, the analysis of major non-CABG bleeding is the most clinically pertinent analysis.*

6.3.4 Thrombocytopenia

Platelet counts were collected at the following time points: baseline: at 30 minutes, two and 12 hours following initiation of the study agent, just prior to PTCA and daily until discharge of day seven, whichever came first. Following discharge, platelet counts were performed at four and 12 weeks. Thrombocytopenia (a platelet count < 100,000/mcL with a 225% decrease from baseline) developed in 43 patients. The findings are summarized in Table 45.

Table 45. Number of Patients with Thrombocytopenia

Number of Patients	Placebo, n = 635	Abciximab, n = 630	P
With Thrombocytopenia	8 (1.3%)	35 (5.6%)	< 0.001

P-value is from Fisher's Exact test

Thirteen of the 43 patients with thrombocytopenia had platelet counts below 50,000 mc/L.

Reviewer's comment *The incidence of thrombocytopenia in EPIC was 5.2% for patients receiving Abciximab by infusion. The results of CAPTURE confirm the occurrence of Abciximab-related thrombocytopenia, and at an incidence similar to that*

previously seen.

6.3.5 Clinical Chemistry

The data showed no statistically significant **difference** in values for serum electrolytes, **creatinine**, BUN or glucose between the two study groups. These data are presented in Table 156, volume 3 of the submission.

6.3.6 Vital Signs

An increase in the systolic blood pressure by ≥ 20 mm Hg or diastolic blood **pressure** by ≥ 15 mm Hg Identified patients who were **classified** as having an increase in blood pressure. A decrease in the systolic blood pressure ≥ 20 mm Hg or diastolic blood pressure by ≥ 15 mm Hg Identified patients who were **classified** as **having** a decrease in **blood** pressure. A change in the heart rate by ≥ 15 bpm was **utilized to classify** patients as having either an **increase** or a decrease in heart rate. More patients treated **with** placebo experienced an increase in blood pressure than **patients treated with Abciximab. However, the** proportion of patients **experiencing** a decrease in blood **pressure** was not **statistically different**.

These data are shown in Table 159, volume 3 of the submission. The increase in blood pressure was noted in **26** placebo patients and 11 Abciximab patients.

6.3.7 HACA Responses

Of the 585 **Abciximab** treated patients who had a baseline serum sample for HACA **determination**, 467 had a follow-up serum sample available for analysis. The follow-up time point was 12 weeks for 63% (397) of these patients and four weeks for 14% (66) of these patients. Two patients had **follow-up serum** obtained at hospital discharge. Of the 467 patients, 25 (5.1%) had a positive HACA response,

Reviewer's comment: The HACA response in the infusion group of EPIC was 6.5%. The CAPTURE HACA result is similar to the EPIC experience.

6.3.6 Adverse Events

6.3.6 Adverse Events through 30 Day Follow-up

Of the 1,253 patients **receiving** the study agents, 676 patients (54%) experienced at least one adverse event, as described in Table 46.

Table 46. Patients with Adverse Events through 30 Days by WHOART Preferred Term

Patients treated	Total, n = 1,253	Placebo, n = 630	Abciximab, n = 623
With one or more event	676 (54.0%)	345 (54.8%)	331 (53.1%)
Hypotension	88 (7.0%)	39 (6.2%)	49 (7.9%)
Headache	70 (5.6%)	40 (6.3%)	30 (4.8%)
Fever	67 (5.3%)	34 (5.4%)	33 (5.3%)
Chest pain	59 (4.7%)	27 (4.3%)	32 (5.1%)
Pain	58 (4.6%)	36 (5.7%)	22 (3.5%)
Back pain	54 (4.3%)	28 (4.4%)	26 (4.2%)
Nausea	37 (3.0%)	19 (3.0%)	18 (2.9%)
Thrombocytopenia	35 (2.8%)	7 (1.1%)	28 (4.5%)
Abdominal pain	32 (2.6%)	19 (3.0%)	13 (2.1%)
Vomiting	30 (2.4%)	17 (2.7%)	13 (2.1%)
Fatigue	27 (2.2%)	14 (2.2%)	13 (2.1%)
Constipation	25 (2.0%)	11 (1.7%)	14 (2.2%)
Renal failure	23 (1.8%)	12 (1.9%)	11 (1.8%)
Bradycardia	20 (1.6%)	13 (2.1%)	7 (1.1%)
Dyspnea	19 (1.5%)	10 (1.6%)	9 (1.4%)
Dyspepsia	18 (1.4%)	8 (1.3%)	10 (1.6%)
Anemia	18 (1.4%)	5 (0.8%)	13 (2.1%)
Vascular injury	18 (1.4%)	10 (1.6%)	8 (1.3%)
Dizziness	16 (1.3%)	12 (1.9%)	4 (0.6%)
Cardiac failure	15 (1.2%)	8 (1.3%)	7 (1.1%)
Circulatory failure	14 (1.1%)	6 (1.0%)	8 (1.3%)
Hypertension	13 (1.0%)	6 (1.0%)	7 (1.1%)
Pulmonary edema	12 (1.0%)	9 (1.4%)	3 (0.5%)

AE with incidences under 1% are not listed.

Reviewer's comment: *The most remarkable finding from the AE description is the difference in the incidence of thrombocytopenia.*

Table 47 presents a listing of the patients who experienced adverse events that were attributed by the site investigator as reasonably related to the study agent.

Table 47. Patients who Experienced Adverse Events Reasonably Related to Study Agent by WHOART Preferred Term

Patients treated	Total, n = 1,253	Placebo, n = 630	Abciximab, n = 623
With one or more events	114 (9.1%)	61 (9.7%)	83 (13.3%)
Thrombocytopenia	23 (1.8%)	1 (0.2%)	25 (4.0%)
Fever		14 (2.2%)	9 (1.4%)
Hypotension	10 (0.8%)	3 (0.5%)	7 (1.1%)
Anemia	10 (0.8%)	3 (0.5%)	7 (1.1%)
Nausea	7 (0.6%)	4 (0.6%)	3 (0.5%)
Vascular injury	7 (0.6%)	4 (0.6%)	3 (0.5%)
Injection site inflammation	5 (0.4%)	2 (0.3%)	3 (0.5%)
Puncture site hemorrhage	4 (0.3%)	2 (0.3%)	2 (0.3%)
Puncture site hematoma	4 (0.3%)	3 (0.5%)	1 (0.2%)
Renal failure	4 (0.3%)	1 (0.2%)	3 (0.5%)
Pseudoaneurysm	4 (0.3%)	3 (0.5%)	1 (0.2%)
Dermatitis	3 (0.2%)	1 (0.2%)	2 (0.3%)
Rash	2 (0.2%)	1 (0.2%)	1 (0.2%)
Paresthesia	2 (0.2%)	0	2 (0.3%)
Dyspepsia	2 (0.2%)	0	2 (0.3%)
SGPT increased	2 (0.2%)	2 (0.3%)	0
Pulmonary hemorrhage	2 (0.2%)	0	2 (0.3%)
Allergic reaction	2 (0.2%)	2 (0.3%)	0
Fatigue	2 (0.2%)	1 (0.2%)	1 (0.2%)
Pain	2 (0.2%)	0	2 (0.3%)
Hematoma	2 (0.2%)	1 (0.2%)	1 (0.2%)
Subfebrile fever	2 (0.2%)	1 (0.2%)	1 (0.2%)
Chills	2 (0.2%)	1 (0.2%)	1 (0.2%)
Creatinine increased	2 (0.2%)	2 (0.3%)	0
Erythema	2 (0.2%)	1 (0.2%)	1 (0.2%)

AE with incidences under 0.2% are not listed.

Reviewer's comment: Again, the incidence of thrombocytopenia is most notable.

7.0.0 Appendix

7.1.0 Review of Supplemental Information Submitted on May 16, 1997

7.1.1 Overview: On May 12, 1997 the sponsor was notified in a letter of certain questions relevant to review of the CAPTURE clinical trial. These questions are described in the following sections along with the sponsor's response.

7.1.2 Questions and Responses. The original question is shown in bold.

7.1.2.1 Many clinical laboratories utilize immunoassay techniques for the mass measurement of CPK-MB. Please provide data assessing any interaction between various potential blood concentrations of Abciximab and the results of representative serum immunoassays for CPK-MB.

Response: The sponsor presents the results of "spiking" experiments (of sera) in which clinically attainable blood concentrations of Abciximab (0 to 2 mcg/mL) were tested as well as concentrations 10 fold higher than clinically attainable levels. The assay kits of _____ (used in CAPTURE) and _____ were utilized. These assays showed no alteration (either reduction or elevation) of CPK-MB mass. Additional tests of CPK activity showed no alterations.

Reviewer's comment: The sponsor has studied the potential interactions of clinically appropriate concentrations of Abciximab versus various concentrations of CPK and CPK-MB and has found no interaction. These studies support the

reliability of the assays utilized in the **CAPTURE trial** and support the **reliability** of the diagnoses of myocardial infarction.

7.1.2.2 To help assess whether subjects in the CAPTURE study are representative of other patients with refractory unstable angina, please submit any available data regarding demographics, baseline characteristics and reasons for ineligibility for the patients with unstable angina who were screened but not enrolled in the CAPTURE trial. Please also submit any information relating to clinical outcomes of these patients.

Response: These data are not available.

Reviewer's comment: *The lack of information regarding the number of patients screened for enrollment in CAPTURE allows no conclusions to be drawn regarding the applicability of the study findings to the broad population of unstable angina patients. This finding allows no expansion of the implications of the CAPTURE study to a broader population of unstable angina patients.*

7.1.2.3 in the study report it is noted that five patients received study agent but were not assigned kit numbers and were not included in the study. Were these patients assigned randomization numbers? Were these patients monitored for any outcomes? Please clarify the circumstances of these patients' involvement with the study, including the reasons for their exclusion from the study.

Response: These five patients did not receive patient numbers or randomization kit numbers. Efficacy outcomes were not databased for these five patients. In all five instances the patients received study agent without the site calling for kit randomization. The exclusion of these patients is consistent with the clinical protocol.

Reviewer's comment. *The exclusion of these patients from the database appears appropriate. The dose administration was based upon site envts. Efficacy outcome data are not available.*

7.1.2.4 in the study report it is noted that approximately 1% of the enrolled patients were lost to follow-up for the efficacy endpoint components of survival and MI/revascularization procedures. The SAS data sets indicate that six month follow-up data for these components are not missing. Please explain.

Response: Data for survival and MI/revascularization are not missing but are listed as "incomplete" for six month follow-up if the patient was not followed for at least five months.

Reviewer's comment: *The sponsor indirectly notes that the study report statement is correct. The format of the SAS data sets suggests that six month data are complete for all patients, but closer examination of the timing of the events reveals some patients with missing data—however, the number is unremarkable.*

7.1.2.5 On page 219 of volume 4, it is stated that Centocor may alter the risk criteria for classification of culprit coronary lesions. Were the risk criteria altered during the trial?

Response: The criteria were not altered.

7.12.6 Please submit copies of pages 1 through 67 of the case report forms for the following patients. It is preferable to submit the forms on paper. Patient identification numbers are:

Response: These are submitted.

Reviewer's comments: *These forms provide details of the time of myocardial infarction and demonstrate how relatively arbitrary the exact timing of the onset of the infarction may be. Many decisions as to the timing of infarction in these patients were value judgements by the Clinical Endpoint Committee. These evaluations were performed in a blinded manner, so they are valid. However, the number of patients who experienced an infarction prior to the PTCA is so very small, a difference of even one patient in the time classification significantly alters the "stabilization" claims.*

7.1.2.7 We note that although two interim analyses were planned, the trial was terminated after a third interim analysis was performed. Please submit copies of all minutes of the Safety and Efficacy Monitoring Committee meetings, all communications from the SEMC to the executive committee and/or Centocor and copies of all SEMC communications that were held in escrow by the law firm of _____ These documents should include copies of all communications from the SEMC regarding the results of interim analyses.

Response: These are submitted.

Reviewer's comments: These documents reveal no evidence of release of unblinded efficacy data to the sponsor prior to conclusion of the trial. All communications from the SEMC are appropriately worded such that conduct and conclusions from the trial's interim analyses are reliable. The sponsor states that the minutes of the interim analyses deliberations were not received by them until May, 1997 (in response to our request).

7.1.2.8 Please describe the source case report form information flow through all contract research organizations and committees participating in conduct of the trial. Please submit the standard operating procedure used by the Clinical Endpoint Committee. Did _____ complete CEC source forms and forward these to Cardlalysis with Cardlalysis subsequently handling the CEC evaluations? Did Centocor have access to the data during these interactions? If so, please describe.

Response: The case report form (CRF) was completed by the site, monitored and retrieved by _____ and sent to the European Data Management Center (EDMC). The EDMC completed the CEC forms and submitted these to _____. At _____ pages of the CRF with relevant information were copied for the Angiographic Core Lab within _____. The chairman of the Angiographic Committee, Dr. Marcel van den Brand and a second assessor then reviewed the angiograms on an ongoing basis. - - - - then forwarded the CEC-CRF, EKGs and relevant CRF to two CEC members or organized a CEC meeting for review. The results of the CEC review and the CEC-CRF were collected by the CEC coordinator and returned to _____ then forwarded the CEC-CRF to _____ for data entry by the EDMC. The SOP for these committees are submitted. Centocor did not have access to the datasets during these interactions. After enrollment in the trial ended in December 1995, Centocor did receive blinded CRF and CEC-CRF data on February 13, 1996 for the purposes of testing the computerized data system. The 30 day database lock occurred on May 30, 1996. Centocor did not receive unblinded data prior to the database lock. Centocor received the randomization code and final 30 day database on May 30, 1996. With respect to the six month CRF and CEC-CRF data, Centocor received blinded CRF and CEC-CRF data just prior to the six month database lock on August 12, 1996 to confirm that the six month data sets were free of internal discrepancies and capable of computer acceptance. These data were not unblinded to Centocor prior to the receipt of the unblinded analysis datasets on August 12, 1996. The treatment code from the 30 day data was available to a limited number of programmers and biostatisticians at Centocor prior to the lock of the six month database.

- No one at Centocor with responsibility for the conduct of the clinical trial had access to the treatment code prior to the six month database lock.

Reviewer's comments: These data clarify the flow of information and are in accord with the clinical protocol. The conduct of the trial appears reliable.

7.1.2.9 Please submit the SOP for the core arteriographic committee that describes when the committee was to meet and how the arteriograms were to be reviewed.

Response: Two cardiologists, blinded to the patient identification, reviewed the angiograms in a consensus format. The readings were performed at _____ in accordance with SOP specified definitions. There were a total of six angiogram assessors. Consensus was required on: TIMI flow, dissection greater than type C, ischemia related artery and thrombus in the vessel. Three films were reviewed on each patient: baseline, pre-PTCA and post-PTCA. The post-PTCA was reviewed at the same time as the other films, so the timing of the film was recognizable. The core arteriographic source data are stored at _____.

Reviewer's comment: These procedures appear appropriate. This response clarifies the conduct of the arteriographic review.

7.1.2.10 Did Centocor have access to the randomization code after all 30 day evaluations had been

completed but prior to completion of six month follow-up data collection? When was the randomization code provided to Centocor and when was the trial unblinded?

Response: The randomization code was transferred to Centocor on May 30, 1996 at the time of the 30 day database lock. No one at Centocor with responsibility for the conduct of the clinical trial had access to the treatment code prior to the six month database lock. The randomization code for the HACA log was not supplied to Centocor until the locked six month follow up database had been submitted.

Reviewer's comment: There is no evidence of any compromise of six month data integrity.

7.1.2.11 Dr. Anderson of Centocor is described as being aware that randomization within a center was in blocks of six, with no more than three consecutive medication allocations. Please explain why Dr. Anderson needed to know this information.

Response: Dr. Anderson was the chief statistician for the CAPTURE trial. As such, he was responsible for the study design and was integral to the discussions of the randomization scheme to assure that the procedures would have reasonable properties. The randomization criteria were devised in a conversation between Dr. Anderson and _____ in the summer of 1992. Dr. Anderson was not involved in generation of the randomization code and did not have any access to computerized data records until February 13, 1996 and no access to the randomization code until May 30, 1996.

Reviewer's comment These comments clarify Dr. Anderson's involvement in randomization. The actions appear appropriate.

7.1.2.12 Please submit an exemplary copy of the enrollment data form.

Response: A copy is submitted.

Reviewer's comment This is a copy of the form utilized to track enrollment. Minimal information is contained on this form. No outcome data is available from this form. Hence, no real time monitoring of endpoint events was possible by _____

7.1.2.13 On what date was the HACA log code data base transferred from _____ to Centocor?

Response: August 12, 1996

Reviewer's comment: This is after database locks.

7.1.2.14 Please clarify the procedures and scheduling of clinical trial monitoring. Was Centocor involved in monitoring of case report form data entry? If so, please describe.

Response: The pre-study and site initiation visits were performed by Centocor monitors. When possible, the _____ monitor joined the initiation visit. A site was visited again as soon as possible after the first patient was enrolled. This visit was typically performed by a Centocor clinical research associate (CRA) and a _____ monitor. There were no formal rules on the interval between site visits and monitoring visits were scheduled on the basis of number of patients enrolled. In general, sites were visited every six to eight weeks by the _____ monitor. A Centocor CRA regularly accompanied the _____ monitor on his/her monitoring visit to identify issues which sites may have had with the protocol. Centocor was not involved in monitoring data entry. Data entry was performed by the _____ EDMC; editing programs were run by the EDMC and resulted in edit queries which were sent to the _____ monitor for resolution with the sites. After trial enrollment was complete, Centocor CRAs assisted _____ monitors with edit query resolution to speed database closure.

Reviewer's comment These statements confirm that the sponsor did not influence data entry on CRF.

7.2.0 Pertinent Publications: The CAPTURE study results were published in **Lancet** volume 349, pages 1429-1435, 1997. This publication presents no unreviewed findings from the clinical trial.

Reviewer's comment *The publication clearly places the use of Abciximab within an adjunctive role with PTCA.*

3.0.0 Review & Conclusions: *The CAPTURE clinical trial confirms a reduction in the incidence of certain acute cardiac ischemic events among patients with refractory unstable angina who are undergoing PTCA. The trial only evaluated the subset of unstable angina patients who were screened and found to be appropriate candidates for PTCA. Consequently, generalizability of these findings to the broader patient population of unstable angina patients is not appropriate. The safety profile detected in CAPTURE is consistent with the known actions of Abciximab and no new safety concerns are evident. The CAPTURE clinical trial allows an indication and dose regimen to be proposed for a very narrow indication—a decrease in the incidence of acute cardiac ischemic complications among patients with unstable angina who are refractory to standard medical therapy and who have been screened with coronary arteriography. In this scenario, Abciximab would be infused in anticipation of performance of PTCA.*

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.

Lancet 1997; 349: 1429–35
See Commentary page 1409

*Writing committee, study organisation, and investigators given at end of paper

Correspondence to: Prof Maarten L Simoons, Thoraxcenter, BD 434, University Hospital Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands

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. 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.⁹ 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.^{10,11}

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)

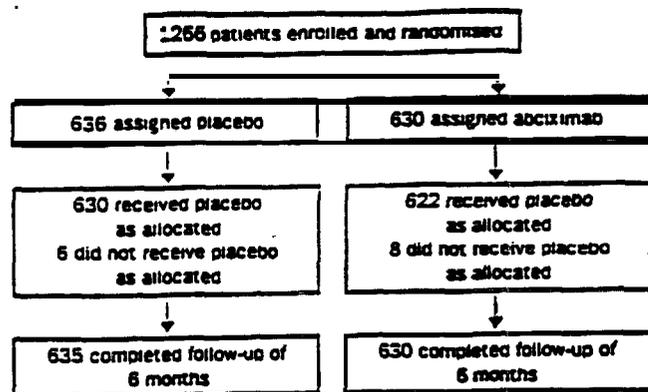


Figure 1: Trial profile

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.¹⁴ 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 $100 \times 10^9/L$.

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 $\mu g/min$) 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

	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%)	118 (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 (12.9%)	95 (15.1%)
Hypertension*	281 (44.4%)	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%)
Ticlopidine	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

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 medications 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.¹⁵ Major bleeds were defined as haemorrhagic 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, or 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.

	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%)
15-26 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 15-24 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.⁴⁴ Thrombocytopenia was defined as an acute fall in platelet count during or after administration of the study agent to below $100 \times 10^9/L$ 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.⁴⁵ 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 (5.3%)	28 (4.4%)	0.009
After PTCA (2-30 days)	5 (0.8%)	6 (1.0%)	>0.1
Non-Q-wave	36 (5.7%)†	29 (4.6%)	0.036
Q-wave	17 (2.7%)†	7 (1.1%)	0.087
Peak CK >5x normal	21 (3.3%)	10 (1.6%)	0.067
Peak CK >10x normal	15 (2.4%)	5 (0.8%)	0.040
All myocardial infarction	52 (8.2%)	28 (4.4%)	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 (3.0%)	>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
Nonmyocardial infarction			
Repeat PTCA	18 (2.8%)	21 (3.4%)	>0.1
CABG	9 (1.4%)	4 (0.6%)	>0.1
Stent	47 (7.4%)	40 (6.4%)	>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 (1.9%)	24 (3.8%)	0.043
Minor bleeding‡	13 (2.0%)	30 (4.8%)	0.008
Transfusions‡	21 (3.4%)	44 (7.1%)	0.005

CK=creatinine kinase; CABG=coronary artery bypass graft.

*p values (two-sided) <0.1 are reported. †One patient had both.

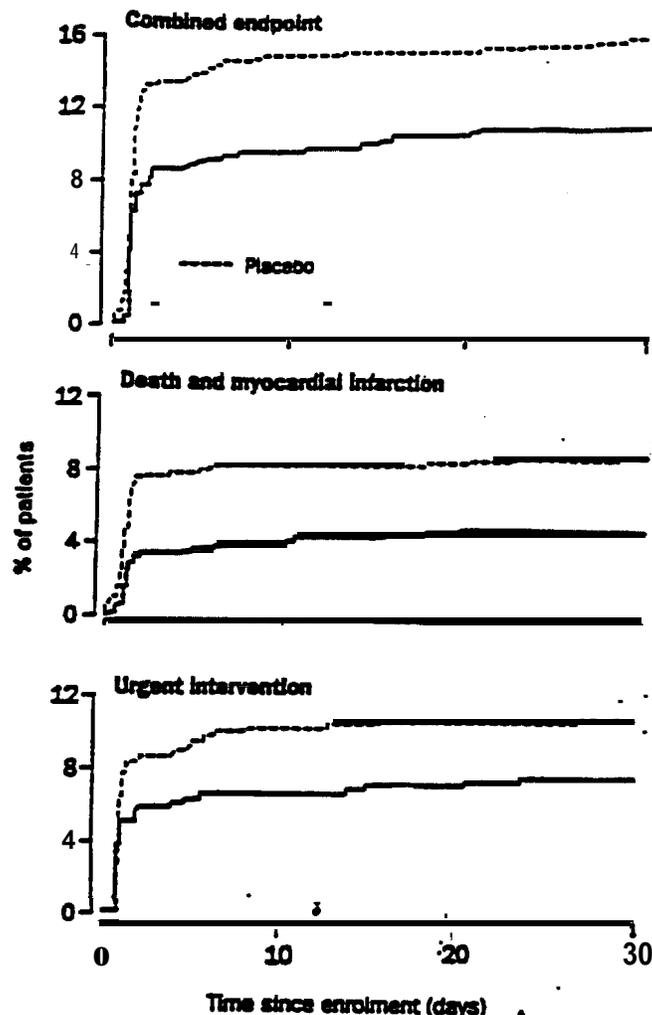


Figure 2: Time course of combined primary endpoint and its major components

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.^{36,37} 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.³⁸ 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.³⁹ A log-rank test was done at

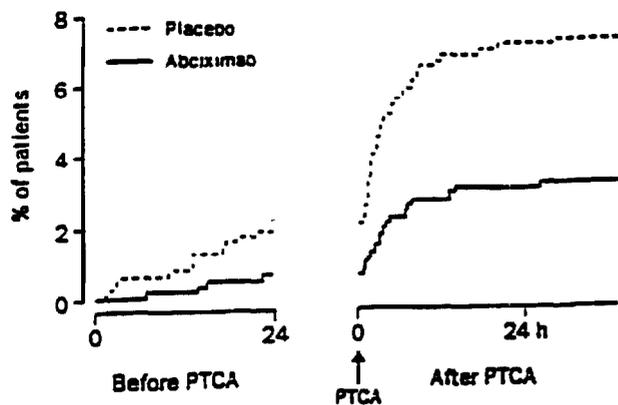


Figure 3: Development of myocardial infarction during treatment with abciximab or placebo, before and in association with PTCA

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 or nine), bypass surgery (five or one), and stent placement (eight or 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

	Placebo	Abciximab
Descri. 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*	12.8	10.9	7.0	6.3
Coumadin	7.7	6.8	4.1	5.2
LMW heparin	3.3	3.3
β -blockers	59.6	60.2	54.5	53.8
Calcium antagonists	54.0	47.0	43.7	48.8
ACE inhibitors	18.4	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

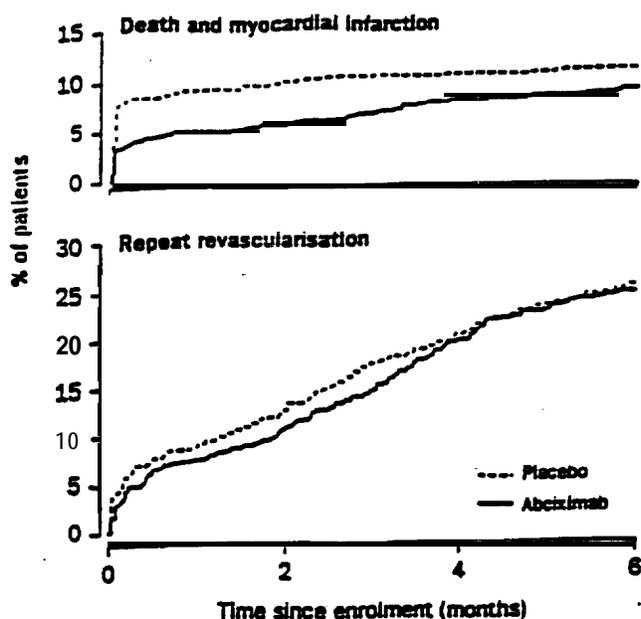


Figure 4: Time course of death and myocardial infarction and repeat revascularisation during 6-month follow-up

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 ($<100 \times 10^9/L$) occurred in 5.6% of the abciximab group and 1.3% of the placebo group. Ten patients receiving abciximab had platelet counts below $50 \times 10^9/L$ within 24 h; no placebo recipient had this complication. None of these patients had bleeding complications. Two patients had platelet counts below $20 \times 10^9/L$. Treatment with study drug (abciximab) was discontinued in five patients, who all received platelet transfusions. Full recovery of platelet counts (to more than $100 \times 10^9/L$) 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

corresponding reduction in the rate of myocardial infarction was 50%. These findings accord with those of other clinical studies of abciximab^{18,19} 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,¹⁸ 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.¹⁸ 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 eptifibatid ($p=0.06$)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^{18,19} 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 study¹⁹ 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

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.^{11,12,26} 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 $\alpha_2\beta_1$ (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 EPILOG²⁸ 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

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.

CAPTURE study organisation

Writing Committee and Steering Committee M L Simoons (chairman, Netherlands); W Rutsch (co-chairman, Germany); A Vahanian (France); J Adgey (UK); A Maseri, C Vassanelli (Italy); J Col (Belgium); A Adelman (Canada); C Macaya (Spain); H Miller (Israel); M J de Boer (Netherlands); R McCloskey, H Weisman (Centocor, USA).

Safety and Efficacy Monitoring Committee M Verstraen (chairman, Leuven); D de Bono (Leicester); K Swedberg (Göteborg); E Lessafer (Leuven); P Schoonmans (Leuven); J Tijssen (Amsterdam; non-voting member).

Clinical Endpoint Committee F Bär (chairman, Maastricht); J W Deckers (Rotterdam); J J Plek (Amsterdam); A P J Kloorwijk (Rotterdam); P Block (Brussels); V Manger-Cas (Leiden); W Bruggeling (Oosterhout); F Joolman, P van der Meer (Rotterdam); V Umans (Alkmaar); D Foley (Rotterdam); T Assink (Rotterdam); D Keane (Rotterdam); D Sane (Winston-Salem, NC; thrombocytopenia review); P Koudestaal (Rotterdam; stroke review).

Angiography Committee M J B M van den Brand (chairman), G J Laarman, G Hendrickx, I de Scheerder, P G Song, K Beert.

Coordinating centre M Hoyack van Papendrecht (Centocor); T Immink (Cardialysis); S Malbrain (Corning Bazelas); J Paul (Corning Bazelas); T de Craen (Academic Medical Center, Amsterdam); S Cabacovic (Euro-BioPharm); T Scheible, K Anderson, A Wang, S Fitzpatrick, M Daniels, T Foutounen, J de Graff, M Dijkhuizen, K Verhamme, I Nelissen, M Gibbs, S Maron, S Lochu, C Guiof, P Ferrati, A Vizzotto, A Alfémany, E Mahillo, S Hoffmann, L Stahl, D Kafka.

Study centres, principal investigators, and study coordinators

Netherlands (366 patients) Ziekenhuis De Weezenlanden, Zwolle (M J de Boer, H Suryapranata, A L Liem, G Vetsink); Onze Lieve Vrouwe Gasthuis, Amsterdam (G J Laarman, R van der Wieken, J P Emswille, S Zomerfeld); Thoraxcentrum Dijkzigt Ziekenhuis Rotterdam (M L Simoons, M van den Brand, C van der Zwaan, P P Kint); Catharina Ziekenhuis, Eindhoven (R M Michels, J Boumier, I v d Kerckhof, C Hasekamp); Antonius Ziekenhuis Groningen (J Peels, L Drot, P den Heijer); St Antonius Ziekenhuis, Nieuwegein (T Plokker, E G Mast, K Marquet); St Ignatiusziekenhuis, Breda (A A Van den Bos, U Chin); Medisch Centrum Alkmaar (V Umans, J H Cornel, A Arnold).

France (175 patients) Hôpital Tenon, Paris (A Vahanian, E Garbarz, O Nallet, B Farrah); Hôpital De Purpan, Toulouse (D Casiri, J Puel, M Jean); Hôpital Trouessart, Tours (B Chaboussier, G Pacourret, R Raymond); CHU de Grenoble (B Bertrand, G Vanzetto); CHU Coe de Nièvre, Caen (G Grullier, B Valente); Hôpital Cardiologique, Lille (C Thery, J M Lablanche); Hôpital Hante-Leveque, Pessac (F Duclos, P Coste); Hôpital Laiboisiere, Paris (P Benfella, E Eifenmann); CHR Hôtel Dieu, Rennes (C Daubert, C Lacieron); Hôpital Bichat, Paris (J M Juliard, P G Song); CHR St Jacques, Besançon (J P Beaumont, N Meneveau); Hôpital Broussais, Paris (J L Guerciopret).

Belgium (146 patients) St Jansziekenhuis, Gent (M Vrolix, J Van Lierde, S Jacobs); Hôpital de la Citadelle, Liège (J Boland, G Sant, P Baumann); Onze Lieve Vrouwe Ziekenhuis, Aalst (G Heyndrickx, F Scaelens, B De Bruyne); Universitair Ziekenhuis Gent (Y Tacymans, P Ghacraert); Hôpital St Luc, Brussels (J Col, K al-Schwaf); A Z Middelheim, Antwerp (P van den Heuvel, R Rogiers); Clinique Générale St Jean, Brussels (M Casadot, E de Wit).

Germany (134 patients) Universitätsklinikum Rudolf Virchow, Berlin-Buch (D Gulbs, R Dechend, S Christow); Klinikum der Christian Albrechts Universität, Kiel (R Simon, N Al Molkhari); Klinikum der Rheinisch-Westfälischen Technischen Hochschule, Aachen (J von Dahl, U Janssens); Universitätsklinikum, Essen (M Hande, D Baumgart); Medizinisch Universitätsklinik, Tübingen (K R Karach, R Maser); Universitätsklinikum Charité, Berlin (W Rutsch, C Brunschweert); Rotes Kreuz Krankenhaus/Ambulantes Herzzentrum, Frankfurt (N Reifart, M Kraicar); Universitätsklinikum, Mainz (H J Rupprecht, M Cobough).

Spain (131 patients) Hospital Universitario San Carlos, Madrid

Valle de Hebron, Barcelona (J Angel, R Balaster); Hospital Central de Asturias, Oviedo (C Morra de la Tassa, F Barrales); Hospital Sanz Creu i San Pau, Barcelona (J Augé, J Garcia); Hospital Virgen de la Nieves, Granada (R Melgares).

UK (101 patients) Royal Victoria Hospital, Belfast (J Adgey, M Khan, P Johnston, Y McKay); Walsgrave Hospital, Coventry (M Been, A Kahn); Harefield Hospital, Harefield (C Isley, A Ewan); Freeman Hospital, Newcastle (D Reid, A McDermott); St Georges Hospital, London (D Ward); Royal Brompton Hospital (N Buller); London Chest Hospital, London (R Balcon).

Italy (96 patients) Ospedale Civile Maggiore, Verona (C Vassanelli, P Zardini, I Loschiavo); Ospedali Riuniti di Bergamo, Bergamo (A Casari, A Pici, A Costalunga); Ospedale Circolo di Varese, Varese (S Repetto, S Carella); Istituto di Fisiologia Clinica, Pisa (M Marzilli, S Fedele); Policlinico Padova, Padova (R Chioini, B Reimers); Policlinico A Gemelli (A Mazzari); Policlinico San Matteo Pavia (G Specchia); Università degli Studi Federico II, Naples (M Chierello).

Israel (49 patients) Tel Aviv Medical Center, Tel Aviv (H Miller, D Sheppe); Beilinson Medical Center, Tel Aviv (S Sclarovski, B Gal); Kaplan Hospital, Rehovot (A Caspi, O Ayzenberg); Sheba Medical Center, Tel Aviv (T Sharir, H Hod).

Switzerland (39 patients) Kantonsspital Basel, Basel (P Buser, M Pfisterer, R Ritz); Städtspital Triemli, Zürich (O Berci, F Rohrer).

Canada (18 patients) Winnipeg Health Sciences Center, Winnipeg (J Duca, U Shick); Saint Boniface General Hospital, Winnipeg (P Cheung); St Michaels Hospital, Toronto (R Chisholm); Mount Sinai Hospital, Toronto (A Adelman); Sunnybrook Health Science Center, Toronto (E Cohen).

Portugal (12 patients) Hospital de Santa Cruz, Lisbon (R Seabra Gomez, J Ferreira).

Austria (1 patient) Medizinische Universitätsklinik Innsbruck, Innsbruck (V Mühlberger).

References

- Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* 1985; 53: 363–73.
- Falk E. Unstable angina pectoris with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985; 71: 699–705.
- Branzwald E. Unstable angina: a classification. *Circulation* 1989; 80: 410–14.
- Miltenburg AIM van, Simoons ML, Verhoeck RJ, Bossuyt PBM. Incidence and follow-up of Branzwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995; 25: 1286–92.
- Feyrer PJ de, Brand M van den, Larman GJ, Domburg R van, Serruys PW, Suryapranata H. Acute coronary artery occlusion during and after percutaneous transluminal coronary angioplasty: frequency, prediction, clinical course, management, and follow-up. *Circulation* 1991; 33: 927–36.
- Feyrer PJ de, Ruygrok PN. Coronary intervention: risk stratification and management of abrupt coronary occlusion. *Eur Heart J* 1995; 16: 97–103.
- Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988; 319: 1105–11.
- The RISC group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990; 3376: 827–30.
- Coller BS, Pocznebski EL, Scudder LE, Sullivan CA. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces a thromboasthenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. *J Clin Invest* 1983; 72: 325–38.
- Simoons ML, Boer MJ de, Brand MJB van den, et al. Randomised trial of a GP IIb/IIIa platelet receptor blocker in refractory unstable angina. *Circulation* 1994; 89: 596–603.
- EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. *N Engl J Med* 1994; 330: 956–61.
- Topol EJ, Calif RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for minimisation of clinical restenosis: results at six months. *Lancet* 1994; 343: 881–86.
- Rao AK, Pratt C, Berke A, et al. Thrombolysis in myocardial infarction trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988; 11: 1–11.
- Landefeld LS, Cook EF, Hasley M. Identification and preliminary validation of predictors of major bleeding in hospitalised patients starting anticoagulant therapy. *Am J Med* 1987; 82: 703–13.
- American College of Physicians Clinical Guideline: Practice strategies for elective red blood cell transfusion. *Ann Intern Med* 1992; 116: 403–06.
- Kloorwijk P, Langer A, Meij S, et al. Noninvasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. *Eur Heart J* 1996; 17: 689–98.
- Kloorwijk P, Meij S, van Es GA, et al. Comparison of usefulness of computer assisted continuous 48 hours 3-lead with 12-lead ECG-interpretation for detection and quantification of ischaemia in patients with unstable angina. *Eur Heart J* 1996; 17: 689–98.
- Lee KK, deMets DL. Discrete sequential boundaries for clinical trials. *Biometrics* 1983; 70: 659–63.
- Topol EJ. Angiographic and clinical results of trials with glycoprotein IIb/IIIa blockers (IMPACT, EPILOG), presented at Congress European Society of Cardiology, Birmingham, 1996.
- Tcheng JA, Lincoff AM. IMPACT-II. Innegrelin (platelet IIb/IIIa receptor blocker) in coronary angioplasty: clinical and angiographic endpoints. Presented at the Congress European Society of Cardiology, Amsterdam, 1995.
- King SB. 6 months angiographic and clinical follow-up of patients undergoing PTCA, treated with a platelet IIb/IIIa receptor blocker or placebo. Presented at European Congress of Cardiology, Birmingham, 1996.
- Agnire FV, Topol EJ, Ferguson JJ, et al. Bleeding complication with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. *Circulation* 1995; 91: 2882–90.
- Serruys PW, Jaegere P de, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331: 489–95.
- Fischman DL, Leon MB, Bain DS, et al. A randomised comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994; 331: 496–501.
- Serruys PW, Emmelhoven H, Giessen W van der, et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries: early outcome of the BENESTENT-II Pilot study. *Circulation* 1996; 93: 412–22.
- Schömig A, Neumann FJ, Kastrati A, et al. A randomised comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; 334: 1084–89.
- Choi ET, Engel L, Callow AD, et al. Inhibition of neointimal hyperplasia by blocking $\alpha_2\beta_1$ integrin with a small peptide antagonist GpeGRGDSFCA. *J Vasc Med* 1994; 19: 125–34.
- Ward SR, Lincoff M, Miller DP, et al. Clinical outcome is improved at 30 days, regardless of pre-treatment clinical and angiographic risk in patients receiving abciximab for angioplasty: results from the EPILOG study. *Circulation* (in press).
- Mark DB, Talley JD, Topol EJ, et al. Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. *Circulation* 1996; 94: 629–35.