

4.0 THE ANGIOGRAPHIC SUBSTUDY OF THE EPILOG TRIAL

I. Overview

The Angiographic **Substudy** was a **substudy** within the context of the EPILOG trial. The objective was **to** compare the effects of the **three** regimens used on angiographic restenosis at 6 months post randomization. The **substudy** was planned to enroll 900 patients, but due to the main trial's early **termination**, enrolled less than one-third of this number, or 286 patients, at 17 sites.

The study report was not submitted with the licensing application supplement filed in February. The study report, containing data on angiographic and clinical outcome, was submitted just prior to the 6 month regulatory action date on BLA # 97-0200, and thus constituted a major amendment to that **file**. Hence, the **substudy** is reviewed here as a supplement to the main Medical Officer's Review of the EPILOG trial.

II. Substudy Protocol

A. Objectives

The objective of **the Angiographic Substudy** was to compare the effects of the three regimens used in the EPILOG trial in patients undergoing percutaneous coronary intervention with respect to angiographic restenosis at 6 months post randomization. Quantitative angiographic parameters were determined by computer-assisted analysis of coronary angiograms.

The incidence of HACA antibody responses was assessed in **substudy** patients, and have been reported with **the** main study report.

B. Investigators and Sites

Sites were selected which demonstrated expertise in performing high quality angiograms and in returning a high proportion of patients for follow-up angiography. All patients at the sites selected were enrolled in the substudy. Some of the **sites** selected were also participating in the STENT substudy, to ensure adequate representation of STENT patients in this **substudy**.

C. Study Design

The **substudy** protocol was submitted as an amendment to the EPILOG protocol dated June **15**, 1995, **well** after the trial was underway.

The patients in all arms of the **substudy** were to receive the same **treatment**, according to study arm, as the other patients in the EPILOG trial. At 6 **months** (at least 184 days, not \geq 275 days), **substudy** patients were to **return** to the study **site** for repeat angiography.

Quantitative computer assisted analysis of angiograms was **to** be performed by the Cleveland **Clinic** Angiography Core Laboratory.

D. Procedures

Angiograms were performed at baseline, at the end of the index **intervention**, and at 6 months in **substudy** patients. Every effort was made to perform follow-up angiograms at the same **cath lab** as **the** baseline films. Standard procedural guidelines **were** provided to all participating **sites by the Core** Lab. In some cases, a different lab performed the **follow-up** angiogram. In those cases, detailed instructions were provided to the lab to ensure the same procedural guidelines were followed.

All **angiograms** were analyzed by the Angiography Core Lab at Cleveland Clinic. **The** Core Lab

reviewers were blinded to study agent allocation. **Lesions** were assessed qualitatively by **Core** Lab reviewers and quantitatively using a previously validated computer-assisted technique. Logs were kept of films received, segments treated, angles of projection, and catheter sites.

Patients were not required to have a follow-up **6** month **angiogram** if:

- the patient had never received study agent (Abciximab or placebo)
- the index procedure was not attempted or was not successful in any of the attempted lesions (≥ 50 % residual stenosis)
- the patient had a CABG or repeat **PTCA** of all target vessels between randomization and the **6** month anniversary date
- repeat **angiogram** was done showing complete occlusion of **all** target lesions by the 3 month anniversary
- the patient had repeat coronary angiography for clinical indications between the 3 and 6 month anniversary dates

E. Endpoint Variables

1. Quantitative Angiographic Variables

The following parameters were studied:

- Minimum **luminal** diameter (**MLD**) at **6** months
- Late loss (**MLD** immediately post index procedure minus **MLD** at follow-up 6 months)
- Loss index (ratio of late loss to early gain; early gain = **MLD** post procedure minus **MLD** prior to procedure)
- Percent diameter stenosis

2. Qualitative Angiographic Variables

- Baseline **TIMI** grade
- Percent stenosis
- Morphological characteristics
- **Angiographic** success (residual stenosis ≤ 50 %)
- Complications of treatment (dissection, thrombus, abrupt occlusion, distal embolization, side branch occlusion)

3. Clinical Outcome

The 30 day and 6 month primary endpoints evaluated in the main study were computed for patients in the **substudy**.

F. Sample Size Predictions

The sample size required was calculated as 210 patients per arm to detect a 15% improvement in minimum **luminal** diameter in either Abciximab arm compared to placebo. Allowing for 2 % of patients not initially treated with study medication or coronary intervention, 8 % of patients without acute procedural success, and 20% of patients **without** follow-up or technically inadequate angiograms, the planned recruitment was to be 300 per arm.

G. Statistics

Survival **methods** were used; **pairwise** comparisons were made of each **of** the Abciximab groups vs the placebo arm, and of the combined Abciximab groups **vs** the placebo, using the **logrank** test. Event rates **were** computed using the Kaplan Meier **method**.

III. RESULTS

A. Study Sites

The majority of the patients enrolled were drawn from the Cleveland Clinic (83), The Christ Hospital in Cincinnati (64), and Duke University Medical Center (21). Ten of the 17 sites were Canadian, and accounted for 92 patients. The remainder came from four other US sites. Table 1 shows the distribution of patients among sites.

Table 1 Sites Enrolling Patients into Angiographic Substudy

<u>Site No.</u>	<u>Site</u>	<u>Principal Investigator</u>	<u>Patients Enrolled</u>
11	Cleveland Clinic Foundation, Cleveland, OH	A. Michael Lincoff , M.D.	83
14	The Christ Hospital, Cincinnati. OH	Dean J. Kereiakes , M.D.	64
24	Duke University Medical Center, Durham , NC	James E. Tcheng , M.D.	21
61	Ottawa Civic Hospital, Ottawa, Ontario	Jean-Francois Marquis, M.D.	21
72	University of Alberta Hospital, Edmonton. Alberta	Jeffrey Burton, M.D.	17
73	Mount Sinai Hospital, Toronto. Ontario	Alan G. Adelman , M.D.	13
75	Royal Columbian Hospital, New Westminster, BC	Robert I. G. Brown , M.D.	13
34	University of Florida Health Science Center, Jacksonville, FL	Theodore Bass, M.D.	10
08	Rochester General Hospital, Rochester, NY	Gerald Gacloch , M.D.	9
74	Health Sciences Centre , Winnipeg, MB	John Ducas , M.D.	7
02	St Louis University Hospital, St. Louis, MO	Frank V. Aguirre , M.D.	6
64	Victoria General Hospital, Halifax, NS	Blair J. O'Neill , M.D.	5
76	St. Boniface General Hospital, Winnipeg, MB	PO K. Cheung , M.D.	5
59	Vancouver General Hospital, Vancouver, BC	Donald R. Ricci , M.D.	4
66	Calgary Foothills Hospital, Calgary , AB	Merril L Knudson , M.D.	4
21	Graduate Hospital, Philadelphia, PA	Ronald Gottlieb , M.D.	2
77	Victoria Hospital Corporation , London, Ontario	David Almond, M.D.	2

B. Study Population

The distribution of patients across arms was similar, as shown in Table 2. STENT1 substudy patients accounted for 20 % of the patients in this substudy. Slightly more STENT1 substudy patients were randomized to PTCA, equally distributed across treatment arms (there were only 24 patients receiving primary STENTS in the angiographic substudy).

Table 2 Accounting of Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts enrolled in Primary Stent Substudy	57 (19.9%)	17 (17.9%)	22 (21.6%)	18 (20.2%)	40 (20.9%)
Randomized to stent	24 (8.4%)	7 (7.4%)	9 (8.8%)	8 (9.0%)	17 (8.9%)
Randomized to PTCA	33 (11.5%)	10 (10.5%)	13 (12.7%)	10 (11.2%)	23 (12.0%)

C. Patients Lost to Follow-up

A total of 284 patients (99 %) had baseline films reviewed. Baseline films were lost for 2 patients; one did not receive study agent, the other had a failed intervention in all lesions attempted: No followup films were received by the core lab for these 2 patients.

A total of 230 patients (80%) had followup films reviewed. Table 3 shows the percentage was consistent across treatment arms, and lists the reasons the other 56 patients did not have followup films reviewed (20 patients refused, 8 were not treated with study agent, 8 had failed PTCA in all lesions). Of the 230 patients with followup films, only 157 (55%) had films done > 183 days post randomization. Fifty-five patients (19%) were done between 3 and 6 months, and 18 patients (6 %) were done at less than 3 months.

Table 3 Angiographic Follow up

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts with films reviewed by Core Lab	284 (99.3%)	95 (100.0%)	100 (98.0%)	89 (100.0%)	189 (99.0%)
Index procedure	284 (99.3%)	95 (100.0%)	100 (98.0%)	89 (100.0%)	189 (99.0%)
Index procedure and follow-up	230 (80.4%)	74 (77.9%)	84 (82.4%)	72 (80.9%)	156 (81.7%)
≤3 mos post randomization	18 (6.3%)	5 (5.3%)	11 (10.8%)	2 (2.2%)	13 (6.8%)
>3- 6 mos post randomization	55 (19.2%)	19 (20.0%)	18 (17.6%)	18 (20.2%)	36 (18.8%)
>6 mos post randomization ^a	157 (54.9%)	50 (52.6%)	55 (53.9%)	52 (58.4%)	107 (56.0%)
Follow-up only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with no follow-up films	56 (19.6%)	21 (22.1%)	18 (17.6%)	17 (19.1%)	35 (18.3%)
Pt not treated with study agent	8 (2.8%)	3 (3.2%)	4 (3.9%)	1 (1.1%)	5 (2.6%)
PCI not attempted	3 (1.0%)	1 (1.1%)	2 (2.0%)	0 (0.0%)	2 (1.0%)
PCI failed in all lesions	8 (2.8%)	4 (4.2%)	4 (3.9%)	0 (0.0%)	4 (2.1%)
Not required per protocol	8 (2.8%)	4 (4.2%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Pt died	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.5%)
Pt refused	20 (7.0%)	6 (6.3%)	4 (3.9%)	10 (11.2%)	14 (7.3%)
Unable to schedule/administrative	6 (2.1%)	2 (2.1%)	3 (2.9%)	1 (1.1%)	4 (2.1%)
Pt lost to follow up	1 (0.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Angiography contraindicated	1 (0.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Films lost	2 (0.7%)	0 (0.0%)	1 (1.0%)	1 (1.1%)	2 (1.0%)

^a >183 days post randomization.

D. Study Agent Administration

Nearly all of the **substudy** patients (278, or 97 %) **were** treated as randomized. Eighty-one percent received the **full** dose overall; more had the dose discontinued early in the placebo arm than in the Abciximab arms, consistent with what occurred in the overall **study** (see **Table 4**).

Table 4 Number of Angiographic Substudy Patients Receiving Study Agent

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts treated with study agent	278 (97.2%)	92 (96.8%)	98 (96.1%)	88 (98.9%)	186 (97.4%)
Full dose administered					
Yes	234 (81.8%)	70 (73.7%)	86 (84.3%)	78 (87.6%)	164 (85.9%)
No	40 (14.0%)	21 (22.1%)	11 (10.8%)	8 (9.0%)	19 (9.9%)
Unknown	4 (1.4%)	1 (1.1%)	1 (1.0%)	2 (2.2%)	3 (1.6%)
Pts not treated with study agent	8 (2.8%)	3 (3.2%)	4 (3.9%)	1 (1.1%)	5 (2.6%)

E. Demographics

Demographic characteristics were generally **similar** to those of the **overall EPILOG** study population, as shown in Table 5.

Table 5 Demographics of Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Gender					
Male	210 (73.4%)	69 (72.6%)	76 (74.5%)	65 (73.0%)	141 (73.8%)
Female	76 (26.6%)	26 (27.4%)	26 (25.5%)	24 (27.0%)	50 (26.2%)
Age (years)					
n	286	95	102	89	191
Mean ± SD	59.6 +/- 10.6	59.5 +/- 11.3	59.2 +/- 10.8	60.0 +/- 9.8	59.6 +/- 10.3
Median	60.0	60.0	59.0	61.0	60.0
Range	(32.0, 83.0)	(36.0, 81.0)	(32.0, 83.0)	(39.0, 80.0)	(32.0, 83.0)
Weight (kg)					
n	286	95	102	89	191
Mean ± SD	84.2 +/- 16.8	81.9 +/- 14.9	83.6 +/- 17.1	87.2 +/- 18.2	85.3 +/- 17.6
Median	82.6	80.0	83.4	84.3	84.0
Range	(50.0, 164.0)	(55.0, 132.0)	(50.0, 163.0)	(50.0, 164.0)	(50.0, 164.0)
Height (cm)					
n	284	95	101	88	189
Mean ± SD	171.8 +/- 10.0	171.4 +/- 11.8	171.6 +/- 8.8	172.5 +/- 9.4	172.0 +/- 9.1
Median	173.0	175.0	173.0	172.6	172.7
Range	(126.0, 196.0)	(126.0, 191.0)	(152.0, 196.0)	(152.0, 193.0)	(152.0, 196.0)
Race					
Caucasian	267 (93.4%)	91 (95.8%)	94 (92.2%)	82 (92.1%)	176 (92.1%)
Black	13 (4.5%)	3 (3.2%)	5 (4.9%)	5 (5.6%)	10 (5.2%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian	3 (1.0%)	0 (0.0%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Other	3 (1.0%)	1 (1.1%)	1 (1.0%)	1 (1.1%)	2 (1.0%)

F. Risk Status

Approximately 60% of patients in **the substudy** were classified as high risk at randomization. Note that this percentage is slightly higher in the **placebo arm** than in the Abciximab arms. Note also that the **Core Lab** classified patients differently **than** the randomization classification. The same lesion morphology characteristics were used to identify high-risk patients as those used in the **overall** trial. The classification **scheme** used by the core lab **for** lesion morphology Mixed slightly **from** the **ACC/AHA** classification, in the criteria for **classification** of **angulation**. The **core** lab was not able to **classify** certain attributes (bifurcation, degenerated vein grafts, age of a total occlusion); **CRF** data were used for these attributes. Clinical history was taken from the **CRFs** for risk status assessment.

Overall, 62 % of **substudy** patients were randomized as high risk and 37 % as low risk.’ This was **consistent with the overall** study (64 and 36% high and low risk, respectively). The Core Lab identified 79 % as high risk and 21 % as **low** risk, again **similar** to the reclassification seen in the overall trial when the more structured approach to lesion classification was used to complete the **CRFs**. (see Table 6)

Table 6 Number of Angiographic Substudy Patients by Risk Classification at Time of Randomization vs Risk Classification Based on Angiographic Core Lab Data

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts randomized as high risk	179 (62.6%)	64 (67.4%)	61 (59.8%)	54 (60.7%)	115 (60.2%)
High risk based on Core Lab data	149 (52.1%)	57 (60.0%)	47 (46.1%)	45 (50.6%)	92 (48.2%)
Lower risk based on Core Lab data	28 (9.8%)	7 (7.4%)	12 (11.8%)	9 (10.1%)	21 (11.0%)
Unknown	2 (0.7%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (1.0%)
Pts randomized as lower risk	107 (37.4%)	31 (32.6%)	41 (40.2%)	35 (39.3%)	76 (39.8%)
High risk based on Core Lab data	78 (27.3%)	21 (22.1%)	28 (27.5%)	29 (32.6%)	57 (29.8%)
Lower risk based on Core Lab data	29 (10.1%)	10 (10.5%)	13 (12.7%)	6 (6.7%)	19 (9.9%)

G. Indication for the Procedure

The majority of patients **were being** treated for **unstable** angina (**42%, similar** to the overall study), followed by a positive functional test (**25 %**, more than there were in the overall study) and recent **MI** (**22 %**, similar to the overall). The arms do not appear as **well** balanced with regard to these factors. More of the Abciximab-low dose **heparin** patients had unstable angina (**50 %**), and more of the **Abciximab** standard dose heparin patients had a positive functional study (**30 %**). (see Table 7)

Table 7 Primary Indication for Index Intervention Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Primary indication for intervention					
Unstable angina	120 (42.0%)	37 (38.9%)	51 (50.0%)	32 (36.0%)	83 (43.5%)
Chronic stable angina	25 (8.7%)	9 (9.5%)	8 (7.8%)	8 (9.0%)	16 (8.4%)
Recent myocardial infarction	62 (21.7%)	24 (25.3%)	20 (19.6%)	18 (20.2%)	38 (19.9%)
Positive functional study	70 (24.5%)	23 (24.2%)	20 (19.6%)	27 (30.3%)	47 (24.6%)
Other	9 (3.1%)	2 (2.1%)	3 (2.9%)	4 (4.5%)	7 (3.7%)

H. Cardiovascular Risk Factors

Overall, 17% of patients in the **substudy** had diabetes, less than in the overall study population (**22 %**). (see Table 8) Somewhat fewer patients in the **substudy** had hypertension compared to the overall (**55 vs 59 %**), and more **substudy** patients had a **family** history of premature CAD (**56 vs 47 %**).

Table 8 Cardiovascular Risk Factors Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Diabetes	49 (17.2%)	14 (14.7%)	15 (14.9%)	20 (22.5%)	35 (18.4%)
Smoking					
Within past year	86 (30.1%)	32 (33.7%)	28 (27.5%)	26 (29.2%)	54 (28.3%)
Quit more than 1 year ago	106 (37.1%)	32 (33.7%)	38 (37.3%)	36 (40.4%)	74 (38.7%)
Never smoked	89 (31.1%)	30 (31.6%)	33 (32.4%)	26 (29.2%)	59 (30.9%)
Unknown	5 (1.7%)	1 (1.1%)	3 (2.9%)	1 (1.1%)	4 (2.1%)
Hypercholesterolemia	161 (61.0%)	50 (56.2%)	59 (62.8%)	52 (64.2%)	111 (63.4%)
Hypertension	158 (55.4%)	54 (56.8%)	55 (53.9%)	49 (55.7%)	104 (54.7%)
Family history of premature coronary artery disease	151 (55.5%)	52 (56.8%)	51 (50.0%)	41 (47.2%)	103 (55.0%)

I. Concomitant Medications--Heparin

The amount of heparin given during the procedure and the ACT values achieved were similar in the **substudy** to those in the **overall** study (see Table 9). A smaller proportion of patients in the **substudy** received post-procedure heparin in all treatment groups (20 to 27 %) than in the overall study. **Substudy** patients received **less heparin post** sheath removal also.

J. Other Medications

The use of cardiac medications was similar among **substudy** patients to the **overall** study. More **substudy** patients received ticlopidine (21 vs 14%); **reflecting the** larger proportion of **substudy** patients who were also in the **STENT** substudy.

Open label Abciximab was used during the 6 month study period in 1.4 % of patients in the overall study. **In the substudy**, 11 patients (3.8 %) received open label or commercial Abciximab during this period (see Table IO), 7 placebo, 1 Abciximab-low dose, and 3 Abciximab-standard dose **heparin**. For all 7 placebo patients, study agent was discontinued and Abciximab started within one hour. **Two** Abciximab plus standard dose heparin patients received commercial **ReoPro** between **30 days and 6** months post randomization.

Table 9 appears on the following two pages.

Table 10 Open-Label and Commercial Abciximab Use Between Study Entry and 6 Months Post Randomization Among Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts receiving open-label or commercial abciximab	11 (3.8%)	7 (7.4%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Start of abciximab administration					
<1 hr after end of study agent	8	7	0	1	1
≥1 hr after end of study agent to discharge	0	0	0	0	0
Discharge^a to 30 days	0	0	0	0	0
30 days to 6 months	2	0	0	2	2
Not treated with study agent	1	0	1	0	1

^a Or Day 7, whichever came first.

Table 9a. Heparin Administration and ACT Measurements Prior to and During the Index Intervention Among Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts with PCI attempted	283	94	100	89	189
Pts receiving pre-cath lab heparin	110 (38.9%)	37 (39.4%)	40 (40.0%)	33 (37.1%)	73 (38.6%)
Total dose during procedure (U)					
n	280	94	97	89	186
Median	8600.0	11105.4	6000.0	8613.3	7000.0
Interquartile range	(6300.0, 11100.0)	(9500.0, 13637.5)	(4900.0, 7000.0)	(7800.0, 10169.2)	(5500.0, 9557.5)
Range	(210.0, 39700.0)	(4700.0, 39700.0)	(210.0, 14126.6)	(1600.0, 38600.0)	(210.0, 38600.0)
Total dose during procedure (U/kg)					
n	280	94	97	89	186
Median	100.0	147.2	71.0	101.4	85.0
Interquartile range	(73.1, 142.9)	(104.5, 169.5)	(67.8, 86.3)	(86.4, 122.2)	(70.1, 103.6)
Range	(2.3, 470.7)	(73.7, 300.8)	(2.3, 186.4)	(25.4, 470.7)	(2.3, 470.7)
Median ACT (sec)					
Pre-initial heparin ^a	131.0	135.0	128.0	134.0	130.0
Pre-device ^b	326.0	325.5	286.0	374.5	329.0
Minimum at or after device activation	304.0	313.0	265.0	333.0	301.5
Maximum during procedure ^c	341.0	342.5	300.5	387.5	341.0

^a Last ACT prior to initial heparin bolus in cath lab

^b Last ACT prior to first device activation

^c Includes ACT pre-device activation.

Table 9b Heparin Administration After Index Intervention Among Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts with PCI attempted	283	94	100	89	189
Pts receiving post-procedural heparin prior to sheath removal	67 (23.7%)	26 (27.7%)	23 (23.0%)	18 (20.2%)	41 (21.7%)
Duration					
<2 hours	5 (1.8%)	0 (0.0%)	3 (3.0%)	2 (2.2%)	5 (2.6%)
2-6 hours	15 (5.3%)	4 (4.3%)	7 (7.0%)	4 (4.5%)	11 (5.8%)
6-12 hours	8 (2.8%)	4 (4.3%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
> 12 hours	32 (11.3%)	14 (14.9%)	7 (7.0%)	11 (12.4%)	18 (9.5%)
Unknown duration	7 (2.5%)	4 (4.3%)	3 (3.0%)	0 (0.0%)	3 (1.6%)
Dose (U)					
n	61	22	21	18	39
Median	8967.5	10876.7	3080.0	10742.5	7220.8
Interquartile range	(3000.0, 14277.6)	(6262.5, 15615.0)	(2056.3, 9882.3)	(4025.0, 15208.3)	(2251.1, 13600.0)
Range	(95.0, 31516.7)	(1750.0, 21608.4)	(642.8, 31516.7)	(95.0, 27380.8)	(95.0, 31516.7)
Pts receiving heparin after sheath removal	90 (31.8%)	34 (36.2%)	33 (33.0%)	23 (25.8%)	56 (29.6%)
Duration					
<12 hours	14 (4.9%)	5 (5.3%)	5 (5.0%)	4 (4.5%)	9 (4.8%)
12-24 hours	45 (15.9%)	14 (14.9%)	16 (16.0%)	15 (16.9%)	31 (16.4%)
>24 hours	29 (10.2%)	14 (14.9%)	11 (11.0%)	4 (4.5%)	15 (7.9%)
Unknown duration	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)

K. Index Intervention Characteristics

All but 3 **substudy** patient had intervention attempted. Seventy percent had balloon angioplasty only (compared to 78 % in the overall study). **More substudy** patients had either primary (8 vs 2 %) or bail out **STENTS** (15 vs 11 %) than the overall **trial** (see Table 11). Bail-out STENT use was lowest in the Abciximab-low dose **heparin** arm, as was the case in the overall trial. **The** median duration of the procedure **was** similar to that in the overall trial; however in the overall trial the procedure times were shorter in the Abciximab arms.

Most Abciximab Standard Dose Heparin patients had lesions in the **LAD** treated (**54%**), and more patients in the other two arms had RCA lesions (**Table 12**). The minimum pre-intervention **TIMI** grade was 3 in 70% of **patients** (a bit less in placebo patients). The maximum pre-intervention stenosis in any target lesion was 71 %, similar among **groups, but** the range was lower in the Abciximab-standard dose heparin **arm** (see Table 12).

Lesion characteristics as assessed by the Core Lab appear in Table 13. Imbalance in several characteristics is noted among the treatment arms; notably, more patients in the Abciximab Standard Dose treatment arm had a smooth contour, no side branches and **absent** thrombus compared with the other two arms.

Complications occurring during the index procedure appear in Table 14. Complications **occurred** in 52 % of **substudy** patients overall, including Type B dissection (a tear) in 36 %. The proportions were similar across treatment arms. The outcome was successful in all treated lesions in 76 % placebo patients, and in 80 % of the Abciximab - treated **patients (both arms)**.

*Reviewer Comment: Dissection during the procedure is a common factor which may change a patient thought to be low risk for **ischemic** complications at enrollment into a high risk patient. If dissection occurs in one-third of patients undergoing percutaneous intervention, that is a **significant** factor suggesting that predicting risk status-prior to intervention may not be **meaningful**.*

Table 11 Number of Angiographic **Substudy** Patients with Index Intervention Attempted and Intervention Characteristics

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	9s	102	89	191
Pts with intervention attempted	283	94	100	89	189
Intervention type - all treated lesions^a					
Balloon angioplasty	273 (96.5%)	90 (95.7%)	94 (94.0%)	89 (100.0%)	183 (96.8%)
Balloon only	200 (70.7%)	61 (64.9%)	7s (75.0%)	64 (71.9%)	139 (73.5%)
Directional atherectomy	7 (2.5%)	1 (1.1%)	4 (4.0%)	2 (2.2%)	6 (3.2%)
Rotational atherectomy	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
TEC atherectomy	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Laser	2 (0.7%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomized primary stent	23 (8.1%)	7 (7.4%)	8 (8.0%)	8 (9.0%)	16 (8.5%)
Bail-out stent	43 (15.2%)	19 (20.2%)	10 (10.0%)	14 (15.7%)	24 (12.7%)
Number of native vessels with lesions attempted					
0	7 (2.5%)	3 (3.2%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
1	256 (90.5%)	87 (92.6%)	89 (89.0%)	80 (89.9%)	169 (89.4%)
2	20 (7.1%)	4 (4.3%)	8 (8.0%)	8 (9.0%)	16 (8.5%)
≥ 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with grafts attempted	7 (2.5%)	3 (3.2%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
Number of segments attempted^b					
1	214 (75.6%)	71 (75.5%)	76 (76.0%)	67 (75.3%)	143 (75.7%)
2	59 (20.8%)	21 (22.3%)	22 (22.0%)	16 (18.0%)	38 (20.1%)
≥ 3	10 (3.5%)	2 (2.1%)	2 (2.0%)	6 (6.7%)	8 (4.2%)
Duration of procedure (min)					
n	267	88	9:	86	179
Median	31.0	28.5	38.0	31.0	33.0
Interquartile range	(17.0, 53.0)	(18.0, 58.5)	(17.0, 52.0)	(17.0, 53.0)	(17.0, 53.0)
Range	(2.0, 226.0)	(3.0, 169.0)	(2.0, 226.0)	(2.0, 187.0)	(2.0, 226.0)

^a Some patients had more than one type of intervention.

^b Includes **grafts**

Table 12 Number of **Angiographic Substudy Patients by Number**, Location, Minimum **Pre-Intervention TIMI** Grade and Maximum **Pre-Intervention** Stenosis of Lesions Evaluated During Index Intervention: Aangiographic Core Laboratory Assessment

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with index angiograms evaluated by Core Lab	284	95	100	89	189
Vessels with lesions evaluated ^a					
LAD	117 (41.2%)	32 (33.7%)	54 (54.0%)	31 (34.8%)	85 (45.0%)
LCX	69 (24.3%)	25 (26.3%)	20 (20.0%)	24 (27.0%)	44 (23.3%)
RCA	107 (37.7%)	38 (40.0%)	31 (31.0%)	38 (42.7%)	69 (36.5%)
RCX	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Ramus	4 (1.4%)	1 (1.1%)	0 (0.0%)	3 (3.4%)	3 (1.6%)
SVG	5 (1.8%)	2 (2.1%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
LIMA	3 (1.1%)	1 (1.1%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
Minimum pre-intervention TIMI grade in any target lesion					
3	202 (71.1%)	64 (67.4%)	72 (72.0%)	66 (74.2%)	138 (73.0%)
2A	31 (10.9%)	13 (13.7%)	12 (12.0%)	6 (6.7%)	18 (9.5%)
2B	18 (6.3%)	3 (3.2%)	6 (6.0%)	9 (10.1%)	15 (7.9%)
2c	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
1	19 (6.7%)	8 (8.4%)	5 (5.0%)	6 (6.7%)	11 (5.8%)
0	13 (4.6%)	7 (7.4%)	4 (4.0%)	2 (2.2%)	6 (3.2%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Maximum pre-intervention stenosis in any target lesion (%)					
n	279	93	98	88	186
Median	70.5	69.6	71.8	68.7	70.7
Interquartile range	(64.2, 76.9)	(63.5, 76.2)	(65.2, 78.9)	(62.9, 75.8)	(64.7-76.9)
Range	(22.8, 100.0)	(42.2, 100.0)	(40.8, 100.0)	(22.8, 100.0)	(22.8, 100.0)

^a Some patients are included in more than one category.

^b See Attachment 4 for Angiographic **Core** Laboratory definitions.

Table 13 Number of Angiographic **Substudy** Patients **by** Baseline Angiographic Characteristics of Lesions Attempted During the Index Intervention: Angiographic Core Laboratory Assessment

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with index angiograms evaluated by Core Lab	284	95	100	89	189
Angiographic characteristics ^a					
Length					
<10 mm	87 (30.6%)	29 (30.5%)	34 (34.0%)	24 (27.0%)	58 (30.7%)
10-20 mm	135 (47.5%)	39 (41.1%)	47 (47.0%)	49 (55.1%)	96 (50.8%)
>20 mm	49 (17.3%)	20 (21.1%)	15 (15.0%)	14 (15.7%)	29 (15.3%)
Eccentricity					
Concentric	159 (56.9%)	55 (57.9%)	53 (53.0%)	51 (57.3%)	104 (55.0%)
Eccentric	111 (39.1%)	33 (34.7%)	42 (42.0%)	36 (40.4%)	78 (41.3%)
Proximal tonusity					
None	154 (54.3%)	49 (51.6%)	59 (59.0%)	46 (51.7%)	105 (55.6%)
1-60°	81 (28.5%)	32 (33.7%)	22 (22.0%)	27 (30.3%)	49 (25.9%)
2-60° or 1-90°	45 (15.8%)	14 (14.7%)	18 (18.0%)	13 (14.6%)	31 (16.4%)
2 or more 90°	4 (1.4%)	0 (0.0%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Angulation					
45°	237 (83.5%)	78 (82.1%)	84 (84.0%)	75 (84.3%)	159 (84.1%)
45° -60°	35 (12.3%)	11 (11.6%)	11 (11.0%)	13 (14.6%)	24 (12.7%)
>60°	5 (1.8%)	2 (2.1%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Contour					
Smooth	161 (56.7%)	44 (46.3%)	62 (62.0%)	55 (61.8%)	117 (61.9%)
Irregular	88 (31.0%)	32 (33.7%)	28 (28.0%)	28 (31.5%)	56 (29.6%)
Ulcerated	21 (7.4%)	11 (11.6%)	5 (5.0%)	5 (5.6%)	10 (5.3%)
Side branch					
None	108 (38.0%)	30 (31.6%)	39 (39.0%)	39 (43.8%)	78 (41.3%)
Qmm	136 (47.9%)	51 (53.7%)	46 (46.0%)	39 (43.8%)	85 (45.0%)
>2 mm	21 (7.4%)	6 (6.3%)	7 (7.0%)	8 (9.0%)	15 (7.9%)
Analysis^b	11 (3.9%)	3 (3.2%)	5 (5.0%)	3 (3.4%)	8 (4.2%)
Location					
Not ostial	243 (85.6%)	81 (85.3%)	90 (90.0%)	72 (80.9%)	162 (85.7%)
Ostial	41 (14.4%)	14 (14.7%)	10 (10.0%)	17 (19.1%)	27 (14.3%)
Local calcification					
None or mild	264 (93.0%)	86 (90.5%)	94 (94.0%)	84 (94.4%)	178 (94.2%)
Moderate to severe	17 (6.0%)	8 (8.4%)	5 (5.0%)	4 (4.5%)	9 (4.8%)
Thrombus					
Absent	67 (23.6%)	14 (14.7%)	27 (27.0%)	26 (29.2%)	53 (28.0%)
Low probability	110 (38.7%)	36 (37.9%)	42 (42.0%)	32 (36.0%)	74 (39.2%)
Possible	41 (14.4%)	15 (15.8%)	14 (14.0%)	12 (13.5%)	26 (13.8%)
Probable	23 (8.1%)	7 (7.4%)	9 (9.0%)	7 (7.9%)	16 (8.5%)
Definite	29 (10.2%)	15 (15.8%)	4 (4.0%)	10 (11.2%)	14 (7.4%)
Vessel occluded	13 (4.6%)	7 (7.4%)	4 (4.0%)	2 (2.2%)	6 (3.2%)

^a For each characteristic, the most **severe classification** across all lesions attempted is counted. **See** Attachment 4 for Angiographic Core Laboratory morphology definitions.

^b A side branch within an intervened lesion which is also intervened.

Table 14 Number of Angiographic **Substudy Patients** with Complications During **Index Intervention** and Type of Complications: Angiographic Core Laboratory **Assessment**

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Patients with index angiograms evaluated by Core Lab	284	95	100	89	189
Angiographic outcome					
Successful in all treated lesions ^a	223 (78.5%)	72 (75.8%)	80 (80.0%)	71 (79.8%)	151 (79.9%)
Failed in at least one treated lesion	40 (14.1%)	14 (14.7%)	13 (13.0%)	13 (14.6%)	26 (13.8%)
Unknown outcome	18 (6.3%)	8 (8.4%)	5 (5.0%)	5 (5.6%)	10 (5.3%)
PCS not attempted	3 (1.1%)	1(1.1%)	2 (2.0%)	0 (0.0%)	2 (1.1%)
Patients with complications	147 (51.8%)	50 (52.6%)	50 (50.0%)	47 (52.8%)	97 (51.3%)
% difference from placebo			-5.0%	0.3%	-2.5%
p-value vs placebo			1.000	1.000	1.000
Type of complication^{b,c}					
Dissection morphology					
Type B	102 (35.9%)	31 (32.6%)	35 (35.0%)	36 (40.4%)	71 (37.6%)
Type C	16 (5.6%)	7 (7.4%)	6 (6.0%)	3 (3.4%)	9 (4.8%)
Type D	9 (3.2%)	2 (2.1%)	4 (4.0%)	3 (3.4%)	7 (3.7%)
Type E	4 (1.4%)	2 (2.1%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
Type F	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Dissection length					
≤2 mm	38 (13.4%)	11 (11.6%)	14 (14.0%)	13 (14.6%)	27 (14.3%)
2-10 mm	83 (29.2%)	29 (30.5%)	27 (27.0%)	27 (30.3%)	54 (28.6%)
>10 mm	11 (3.9%)	3 (3.2%)	4 (4.0%)	4 (4.5%)	8 (4.2%)
Abrupt occlusion	10 (3.5%)	3 (3.2%)	3 (3.0%)	4 (4.5%)	7 (3.7%)
Thrombus					
Possible	2 (0.7%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (0.5%)
Probable	6 (2.1%)	2 (2.1%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
Definite	7 (2.5%)	4 (4.2%)	1 (1.0%)	2 (2.2%)	3 (1.6%)
Vessel occluded	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Distal embolization	6 (2.1%)	3 (3.2%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Side branch occlusion	15 (5.3%)	8 (8.4%)	4 (4.0%)	3 (3.4%)	7 (3.7%)

^a A successful intervention is defined as a residual stenosis \leq 50%.

^b Some patients had more than one complication.

^c See Attachment 4 for Angiographic Core Laboratory morphology definitions.

Table 15 Minimum Luminal Diameter at Baseline, Post Procedure, and Follow Up: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Minimum luminal diameter (mm)^a				
Baseline (preprocedure)				
n^b	101 (73)	106 (82)	98 (73)	204 (155)
Mean ± SD	.88 ± .34	.80 ± .32	.85 ± .36	.82 ± .34
Median	.85	.78	.78	.78
Interquartile range	(.67, 1.07)	(.62, .96)	(.57, 1.05)	(.61, 1.02)
Range	(0, 2)	(0, 2.27)	(0, 2.31)	(0, 2.31)
Post procedure				
n^b	101 (74)	110 (84)	100 (72)	210 (156)
Mean ± SD	1.75 ± .48	1.66 ± .49	1.70 ± .49	1.68 ± .48
Median	1.70	1.59	1.64	1.61
Interquartile range	(1.42, 1.94)	(1.33, 1.99)	(1.31, 2.07)	(1.32, 2.01)
Range	(.95, 3.23)	(.70, 3.15)	(.81, 3.05)	(.70, 3.15)
Follow up				
n^b	99 (71)	106 (81)	98 (72)	204 (153)
Mean ± SD	1.35 ± .51	1.29 ± .58	1.34 ± .50	1.32 ± .54
Median	1.36	1.24	1.32	1.27
Interquartile range	(1.05, 1.61)	(.87, 1.62)	(.99, 1.63)	(.94, 1.62)
Range	(0, 2.7)	(0, 3.36)	(0, 3.11)	(0, 3.36)
ANOVA model				
Estimated mean ± SE	1.35 ± .06	1.30 ± .06	1.34 ± .06	1.32 ± .04
Treatment effect ± SE	-	-.04 ± .08	-.01 ± .08	-.03 ± .07
p-value	-	.581	.925	.713

^a Distribution is based on average minimum luminal diameter across 2 views. If only one view has data, the value for the non-missing view is used in place of the average.

^b Number of lesions (patients).

Table 16 Early Gain and Late Loss: **Angiographic Core Laboratory Assessment**

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Early gain^a				
n ^b	99 (73)	103 (80)	95 (72)	198 (152)
Mean ± SD	.89 ± .52	.87 ± .49	.87 ± .52	.87 ± .50
Median	.82	.80	.82	.81
Interquartile range	(.54, 1.23)	(.58, 1.21)	(.51, 1.24)	(.54, 1.21)
Range	(-.34, 2.38)	(-.19, 2.37)	(-.21, 2.00)	(-.21, 2.37)
ANOVA model				
Estimated mean ± SE	.91 ± .06	.92 ± .05	.90 ± .06	.91 ± .04
Treatment effect ± SE	-	.01 ± .08	-.01 ± .08	-.00 ± .07
p-value	-	.883	.881	.997
Late loss^a				
n ^b	95 (70)	102 (78)	93 (70)	195 (148)
Mean ± SD	.40 ± .58	.35 ± .55	.37 ± .54	.36 ± .54
Median	.34	.37	.33	.37
Interquartile range	(-.01, .76)	(.01, .61)	(-.05, .66)	(-.03, .65)
Range	(-.80, 2.06)	(-.92, 2.29)	(-.41, 2.06)	(-.92, 2.29)
ANOVA model				
Estimated mean ± SE	.42 ± .06	.38 ± .06	.40 ± .06	.39 ± .04
Treatment effect ± SE	-	-.03 ± .09	-.02 ± .09	-.03 ± .07
p-value	-	.689	.813	.715

^a Distribution is based on average across 2 views. If only one view has data, the value for the non-missing view is used in place of the average.

^b Number of lesions (patients).

2. Early Gain and Late Loss — Early gain reflects the immediate increase in luminal diameter as a result of the procedure. Late loss reflects the loss in luminal diameter during the period **from** post-procedure **through 6** months. No meaningful differences were **observed among** treatment groups on either of these parameters (see Table 16). The mean and median values were **similar** among treatment groups, although the range for both early gain and late loss was slightly smaller for the Abciximab Standard Dose **Heparin arm** compared to the other **2** arms. There was no discernable treatment effect by the sponsor's analysis using the **ANOVA** model.
3. Net Gain and Loss Index -- Net gain reflects the net gain in MLD over follow-up relative to the pre-treatment value, and is calculated by subtraction of the MLD prior to the procedure from the MLD at 6 months follow-up. The loss **index** reflects the loss in **MLD** over time relative to the initial gain, and is calculated as a ratio of **(MLD post procedure - MLD at follow-up)/ (MLD post procedure - MLD pre-procedure)**. (A good result on the loss index will yield a number less than 1. A negative number will be obtained if the procedure was successful and the MLD at follow-up is even larger than the post-procedure value, or if the procedure was not **successful**). No significant differences were **observed** among treatment groups on this calculated value (see Table 17).

Reviewer's Note: The range of values is markedly different in the placebo arm compared to the Abciximab arms, and contains some negative values. The mean and median values are not different enough to yield significantly different results, however. The values for the Abciximab arms are quite similar on this parameter.

Table 17 Net Gain and Loss Index: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose <u>Heparin</u>	Abciximab + Low-Dose <u>Heparin</u>	Abciximab + Std-Dose <u>Heparin</u>	Combined Abciximab <u>Groups</u>
Pts in Angiographic Substudy	95	102	19	191
Pts index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Net gain¹				
n ^b	95 (68)	101 (78)	93 (72)	194 (150)
Mean ± SD	.49 ± .54	.51 ± .54	.49 ± .55	.50 ± .54
Median	.48	.45	.41	.44
Interquartile range	(.17, .79)	(.16, .83)	(.15, .81)	(.15, .82)
Range	(-.38, 2.15)	(-.73, 2.28)	(-1.0, 1.91)	(-1.0, 2.28)
ANOVA model				
Estimated mean ± SE	.50 ± .06	.51 ± .06	.49 ± .06	.50 ± .04
Treatment effect ± SE		.01 ± .08	-.01 ± .08	.01 ± .07
p-value		.846	.952	.940
Loss index¹				
n ^b	90 (66)	93 (75)	89 (70)	182 (145)
Mean ± SD	-.14 ± 1.43	.54 ± 1.00	.22 ± 1.47	.28 ± 1.25
Median	.39	.49	.47	.48
Interquartile range	(-.02, .75)	(.10, .76)	(-.07, .78)	(-.04, .76)
Range	(-.38, 1.6)	(.1, 1.0)	(-.8, 2.7)	(-.8, 2.7)
ANOVA model				
Estimated mean ± SE	.07 ± .26	.57 ± .26	.23 ± .26	.30 ± .19
Treatment effect ± SE		.44 ± .37	-.29 ± .37	.36 ± .32
p-value		.235	.435	.257

¹ Distribution is based on average across 2 views. If only one view has data, the value for the non-imaging

4. Percent Diameter Stenosis -- **The** means for this parameter were similar in all treatment groups at baseline, **post** procedure, and at followup. Standard deviations and ranges were mildly different, but **there** was no **discernable** treatment **effect** using the **ANOVA model** (see Table 18).

Table 18 Percent Diameter Stenosis: Angiographic Core **Laboratory** Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Percent diameter stenosis ^a				
Baseline (preprocedure)				
n^b	100 (72)	106 (83)	97 (72)	203 (155)
Mean \pm SD	65.2 \pm 12.9	69.1 \pm 13.5	64.3 \pm 14.9	66.8 \pm 14.4
Median	65.8	69.3	66.1	68.3
Interquartile range	(57.8, 72.6)	(59.7, 76.8)	(56.4, 74.8)	(58.6, 75.8)
Range	(28.1, 100.0)	(30.6, 100.0)	(22.8, 100.0)	(22.8, 100.0)
Post procedure				
n^b	99 (72)	109 (83)	101 (71)	210 (154)
Mean \pm SD	31.1 \pm 15.1	35.0 \pm 12.7	32.1 \pm 13.4	33.6 \pm 13.1
Median	33.7	35.8	32.6	33.8
Interquartile range	(22.9, 38.8)	(26.4, 43.2)	(23.8, 40.9)	(24.4, 42.9)
Range	(-30.8, 70.4)	(21, 79.3)	(-3.2, 64.9)	(-3.2, 79.3)
Follow up				
n^b	97 (71)	105 (81)	95 (71)	200 (152)
Mean \pm SD	47.9 \pm 18.4	49.8 \pm 20.1	47.8 \pm 16.7	48.9 \pm 18.6
Median	49.4	51.3	47.0	48.5
Interquartile range	(35.6, 57.5)	(34.0, 64.3)	(34.6, 59.6)	(34.3, 61.8)
Range	(8.8, 100.0)	(11.2, 100.0)	(13.0, 100.0)	(11.2, 100.0)
ANOVA model				
Estimated mean \pm SE	48.3 \pm 2.0	49.8 \pm 1.9	47.9 \pm 2.0	48.9 \pm 1.4
Treatment effect \pm SE	-	1.6 \pm 2.8	-0.4 \pm 2.8	0.6 \pm 2.4
p-value	-	.572	.899	.805
Lesions with restenosis (>50%)	46 (47%)	54 (51%)	43 (45%)	97 (49%)

- ^a Distribution is based on average stenosis across 2 views. **If** only one view has data, the value for the **non-**missing view is used in place of the average.
- ^b Number of lesions (patients).

IV. Results

A. Quantitative Angiographic Variables

1. Minimum **Luminal Diameter (MLD)** **Abciximab** had no significant effect on MLD during the study follow-up period (median values, **standard** deviation and range of values similar among treatment groups both post-procedure and at follow-up; see Table 15). There was no difference when **STENT** patients were excluded from the analysis.

The results are displayed graphically in Figure 1.

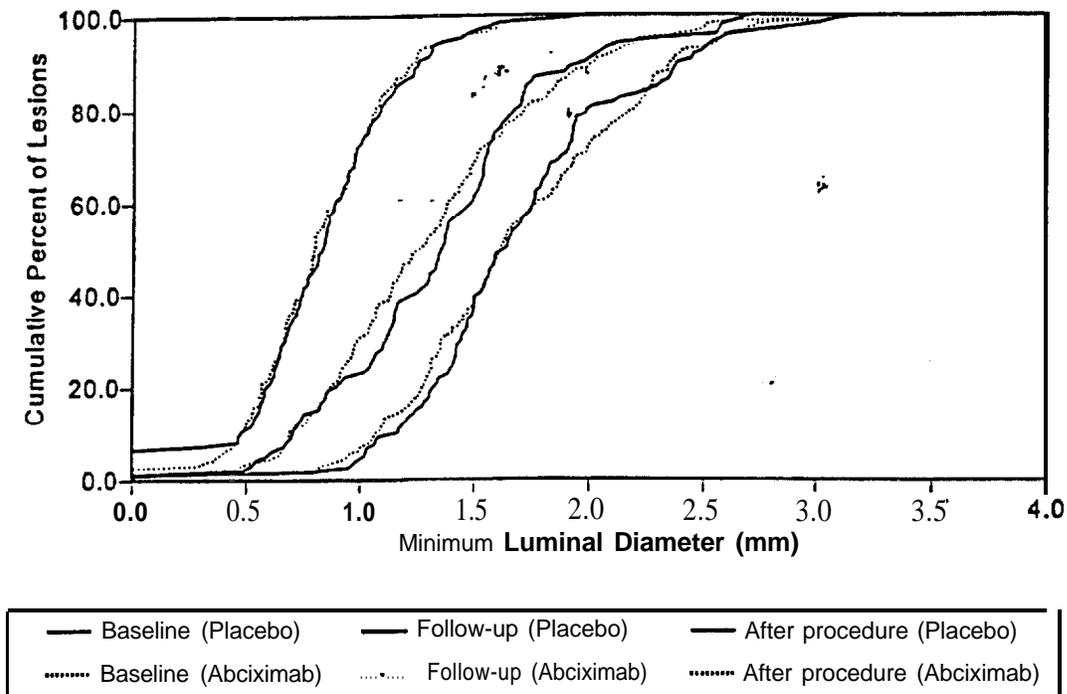


Figure 1 Minimum **Luminal Diameter** (mm) at Baseline, Immediately Post **Intervention, and** at Follow Up. The pair of lines to the left represent baseline values, those in the middle represent follow-up values, and those to the right represent **values immediately** post intervention.

B. Primary Clinical Endpoints

Angiographic **Substudy** patients had **modestly higher event rates than were seen in the overall trial; however** the magnitude of reductions in **Abciximab** treated patients compared to placebo are **consistent with the results of the overall trial**. Trends toward substantial reduction of the composites including **death** and MI and death, MI and urgent revascularization are seen in the Abciximab arms compared with placebo (see Table 19). Of interest, a significant reduction in the composite including death, MI or repeat revascularization at 6 months is seen in the patients in the Abciximab Standard Dose **heparin arm** compared to placebo. Patients in the Abciximab Low Dose Heparin group showed no real difference on this endpoint compared to placebo, as was the case for the overall trial.

Table 19 Primary Efficacy Endpoint Events among Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts with death or MI at 30 days	24 (8.4%)	12 (12.7%)	7 (6.9%)	5 (5.6%)	12 (6.3%)
% change vs placebo			-46.0%	-55.8%	-50.6%
p-value			0.0871	0.0555	0.0360
Pts with death, MI, or urgent revascularization at 30 days	27 (9.5%)	14 (14.8%)	8 (7.8%)	5 (5.6%)	13 (6.8%)
% change vs placebo			-47.1%	-62.1%	-54.1%
p-value			0.0646	0.0244	0.0167
Pts with death, MI, or repeat revascularization at 6 months	64 (22.5%)	25 (26.3%)	26 (25.6%)	13 (14.7%)	39 (20.5%)
% change vs placebo			-2.9%	-44.1%	-22.0%
p-value			0.3825	0.0239	0.1047

C. Secondary Clinical Endpoints

Secondary endpoint events included clinical events in the angiographic **substudy** patients. Trends **appear** consistent with the overall trial results in **the** placebo **and** Abciximab Low Dose Heparin arms (see Table 20). Here also, the Abciximab Standard Dose Heparin patients appeared to have fared better at 6 months compared to placebo than did the **Abciximab** Standard Dose patients. The Abciximab Standard Dose patients experienced significantly lower event rates than **patients in the** placebo arm on the composite including death, MI, **and** target vessel **revascularization** at 6 months. Trends showed substantially lower rates of death and MI and death, MI and urgent **revascularization** at 6 months, as well as target vessel **revascularization**, in patients in the Abciximab standard Dose arm compared to placebo.

Table 20 Secondary Efficacy Endpoint Events among Angiographic Substudy Patients

	<u>Total</u>	<u>Placebo + Std-Dose Heparin</u>	<u>Abciximab + Low-Dose Heparin</u>	<u>Abciximab + Std-Dose Heparin</u>	<u>Combined Abciximab Groups</u>
Pts in Angiographic Substudy	286	95	102	89	191
Pts with death or MI at 6 months	26 (9.1%)	12 (12.6%)	9 (8.9%)	5 (5.6%)	14 (7.4%)
% change vs placebo			-29.5%	-55.5%	-41.5%
p-value			0.187	0.055	0.071
Pts with death, MI, urgent revascularization at 6 months	35 (12.3%)	15 (15.8%)	13 (12.8%)	7 (7.9%)	20 (10.5%)
% change vs placebo			-18.8%	-50.0%	-33.2%
p-value			0.252	0.052	0.093
Pts with death, MI, TVR at 6 months	61 (21.4%)	25 (26.3%)	25 (24.6%)	11 (12.4%)	36 (19.0%)
% change vs placebo			-6.6%	-52.7%	-28.0%
p-value			0.324	0.009	0.058
Pts with TVR at 6 months	46 (16.2%)	17 (17.9%)	20 (19.7%)	9 (10.3%)	29 (15.4%)
% change vs placebo			9.9%	-42.6%	-14.2%
p-value			0.398	0.072	0.280

*Reviewer's Comment: It is not clear what the factors are contributing to the results **demonstrating** a more substantial benefit in the Abciximab Standard Dose Heparin patients at 6 months,*

W4

V. Sponsor's Conclusions

Despite reductions in clinical endpoints among **substudy** patients in the Abciximab arms at both 30 **days** and 6 months, no differences were observed in quantitative angiographic variables. The sponsor notes that given the small number of patients enrolled in the **substudy** prior to the early termination of **the** main trial, there was low statistical power to detect the **anticipated** 15 % reduction in minimum **luminal** diameter. They comment **that the** ongoing **EPILOG STENT** Study may provide a more meaningful assessment of the effect of Abciximab on angiographic **restenosis**.

VI. Reviewer's Conclusions

This reviewer agrees that the small sample **size** in this study led to a **reduced** power to detect a **meaningful difference** in angiographic parameters **among** treatment arms. It is interesting that clinical benefit is seen in the Abciximab treated patients in this study, but the angiographic results are truly equivocal.

One of the reviewer's questions in reviewing these data was whether **the** "catch up" in total revascularization procedures seen among Abciximab treated patients compared to the placebo **arm** over the 6 month follow-up had any physiologic correlates discernable by the angiographic parameters measured in this study. The fact that there were no meaningful 6 month **angiographically** demonstrable benefits in Abciximab-treated patients at 6 months is consistent with the hypothesis that Abciximab does not retard the process of atherosclerosis. This may be the reason for the equivalent number of total revascularization procedures seen among treatment arms at 6 months, despite a persistent reduction in urgent procedures. The data do not definitively establish this as the reason, however. Nor do the results of this **substudy** do not show any evidence of a negative **effect** of Abciximab that might be responsible.

A surprising finding from this **substudy** is the **reduced** incidence of clinical endpoints in **the Abciximab** Standard Dose **Heparin** arm compared to the **other** 2 treatment arms, both at 30 days **and** at 6 months. Many mild imbalances are evident in the characteristics of patients in this group compared to the other 2 groups. Perhaps those factors are responsible for the selection of an atypical sample in this **substudy**. Or perhaps the group selected represents a subgroup of patients **who actually** benefitted more from the combination of Abciximab with standard dose **heparin**.

Overall, the Angiographic **Substudy** results do not **demonstrate** any meaningful **differences** in 6 month angiographic outcomes between patients **treated** with placebo and those treated with Abciximab.