Technical Appendix

The 1997 Lindner Study of Abciximab use in Percutaneous Coronary Intervention: Tables, Figures and Discussion of Statistical Adjustment for Treatment Selection Bias and Incremental Cost-Effectiveness Ratios

Robert L. Obenchain, Ph.D., Senior Research Scientist
Lilly USA Health Outcomes Evaluation Group (HOEG)
Lilly Corporate Center, Indianapolis, IN 46285-1850
(317) 276-3150, ochain@lilly.com

The first part of this appendix consists primarily of Tables and Figures originally prepared for a May 1999 presentation at the American Heart Association by Dr. Dean Kereiakes entitled "Abciximab Provides Cost Effective Survival Advantage in High Volume Interventional Practice."

The remainder of this appendix describes (i) use of "propensity scoring" methodology to adjust for treatment selection bias and (ii) statistical inference (point estimation and confidence intervals) for Incremental Cost-Effectiveness Ratios (ICER) expressed as "Total Cardiac Related Cost per Discounted Life Year Gained."

The data we analyzed describe 1472 consecutive Percutaneous Coronary Interventions (PCIs) performed on 1011 different patients at the Ohio Heart Health Center (average 279 PCIs/operator/year) of Christ Hospital, Cincinnati, in 1997. Decisions of whether or not to administer abciximab (before, during and /or after) each of these PCIs were not made "at random." Rather, patients receiving abciximab tended (on average) to be more acutely diseased than those who did not receive abciximab. Observed differences in 6-month survival outcomes and in total cardiovascular costs thus need to be "adjusted" for corresponding differences in base-line measures of disease severity and presence or absence of a range of comorbid conditions and demographic characteristics.

PART ONE: TABLES and FIGURES

Table I. Patient and Procedural Demographics for 1472 Consecutive Percutaneous Coronary Interventions at Lindner in 1997

Treatment (sample size)	**Abcix (986)**	**No Abcix (486)**	**P - value**
Age Years ± SE	61.4 ± 0.38	61.3 ± 0.54	0.96
Weight Kg ± SE	84.9 ± 0.60	84.7 ± 0.86	0.84
% Female	34.1	36.4	0.38
% Diabetics	21.0	25.9	0.03
% Hypertension	70.2	76.3	0.01
% Smoke	58.0	58.2	0.88
% MI $\leq$ 30 Days	31.8	20.8	<0.0001
1 - 7 Days	17.3	5.8	<0.0001
$\leq$ 1 Day	13.1	12.7	0.82

Table I, Continued. Patient and Procedural Demographics for 1472 Consecutive Percutaneous Coronary Interventions at Lindner in 1997

Treatment (sample size)	**Abcix (986)**	**No Abcix (486)**	**P-value**
LVEF % ± SD %	50.7 ± 0.35	52.1 ± 0.50	0.03
# Stenoses Rx (%)			
1	62.3	80.4	
≥ 2	37.2	19.6	<0.0001
# Vessels Rx (%)			
1	64.4	82.6	<0.0001
2	27.9	15.8	
3	6.0	1.4	
4	1.7	0.2	
Stent (%)	69.5	60.0	<0.0001
First Procedure (%)	93.7	79.2	<0.0001

Data for Figure 1

Stent + Abciximab	0.57	0.89
Stent Alone	1.38	0.69
P-values	0.31	0.60

Figure 1.

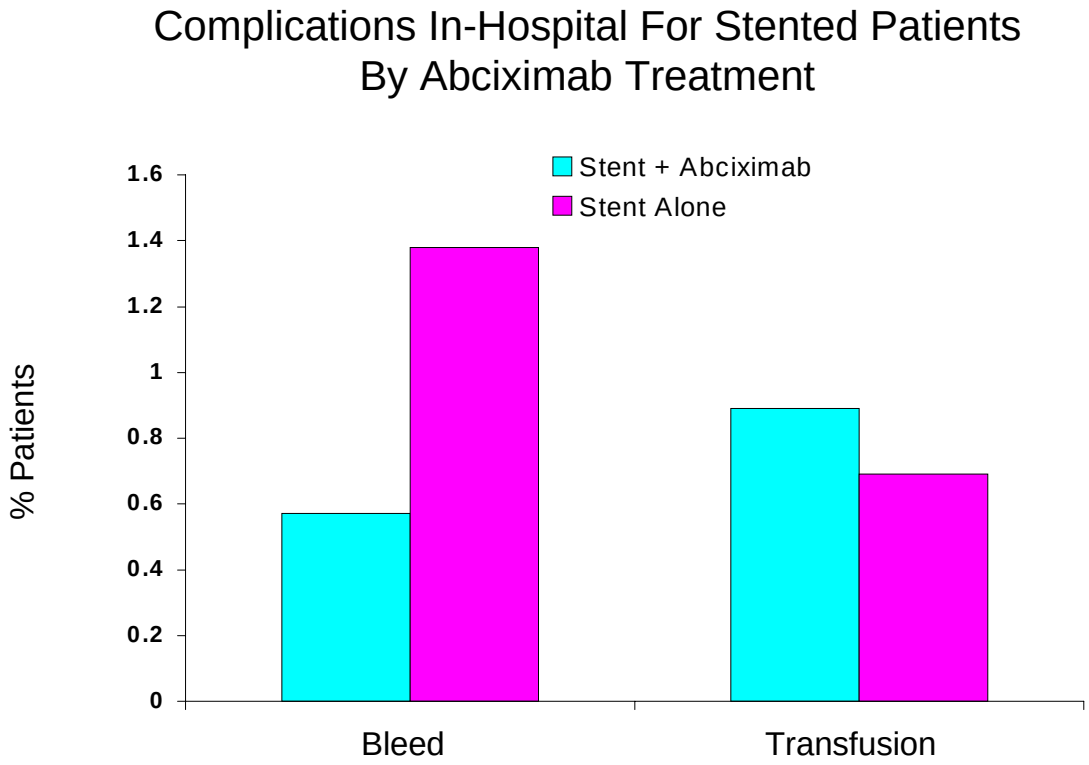


Table II. Payor Status by Abciximab Treatment for 1472 Procedures OHHC at The Christ Hospital 1997

ABCIXIMAB

Payor	*No (%)*	*Yes (%)*	*Totals (%)*
CHAMPUS	0	3	3
HMO/Med Car	5	10	15
Medicaid	7	21	28
Medicare	207 (14)	392 (27)	599 (41)
Other	1	0	1
Private	171 (12)	355 (24)	526 (36)
Private/Corporate	76 (5)	164 (11)	240 (16)
Uninsured	16 (1)	31 (2)	47 (3)
TOTAL	483 (33)	976 (67)	1459

The distributions by payor for the ABCIX=NO and ABCIX=YES cohorts are not significantly different (p=0.63.)

Table III. Use of Abciximab with Stents

	Stent+ Abciximab	Stent Alone		
Patients	499	176		
Primary Outcome Measures				
			Diff	P-value
DeathRate	1.60%	5.11%	-3.51%	0.02
Card_Bill	$16,576	$13,765	$2,811	<0.001
Key Covariates				
			Diff	P-value
Vess 1st Proc	1.44	1.20	0.24	<0.001
Total Vess	1.58	1.31	0.27	<0.001
Rept Vess	0.058	0.051	0.007	0.77

Table IV. Treatment Cohort Comparisons

Cardiac Re-hospitalizations within 6 Months

	No-Abcix	Abcix
Fraction ± SE	0.28 ± 0.03	0.25 ± 0.02

p-value = 0.104

Days of Cardiovascular Hospitalization within 6 Months

	No-Abcix	Abcix
Mean ±SE	4.7 ± 0.2	4.3 ± 0.1

p-value = 0.16

Total Cardiovascular Related Charges within 6 Months

	No Stent	Stent
No Abciximab (n=301)	$15,805	$13,765
Abciximab (n=710)	$15,054	$16,576*

*p<0.001

Total Cardiovascular Charges within 6 Months for all 1011 Patients

	No-Abcix	Abcix
Mean ± S.E.	$14,614 ± $647	$16,127 ± $423

p-value = 0.098

Total Cardiovascular Charges within 6 Months for 675 Stent Patients

	No-Abcix	Abcix
Mean ± S.E.	$13,765 ± $702	$16,576 ± $417

p-value < 0.001

Figure 2.

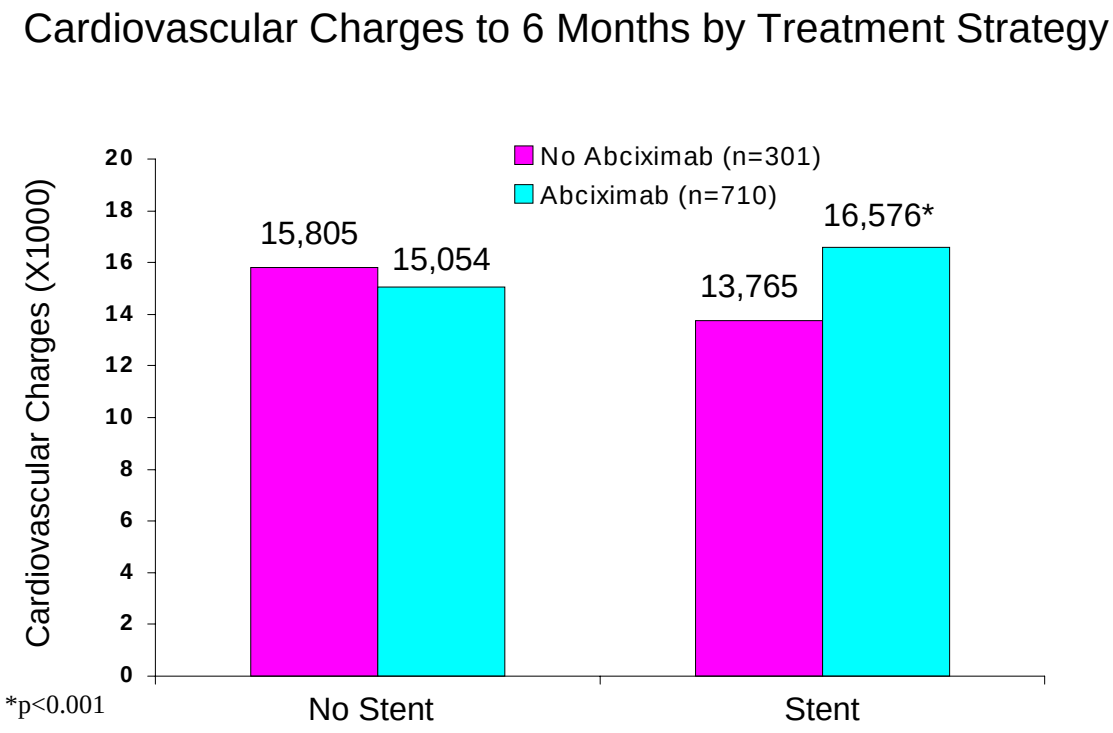
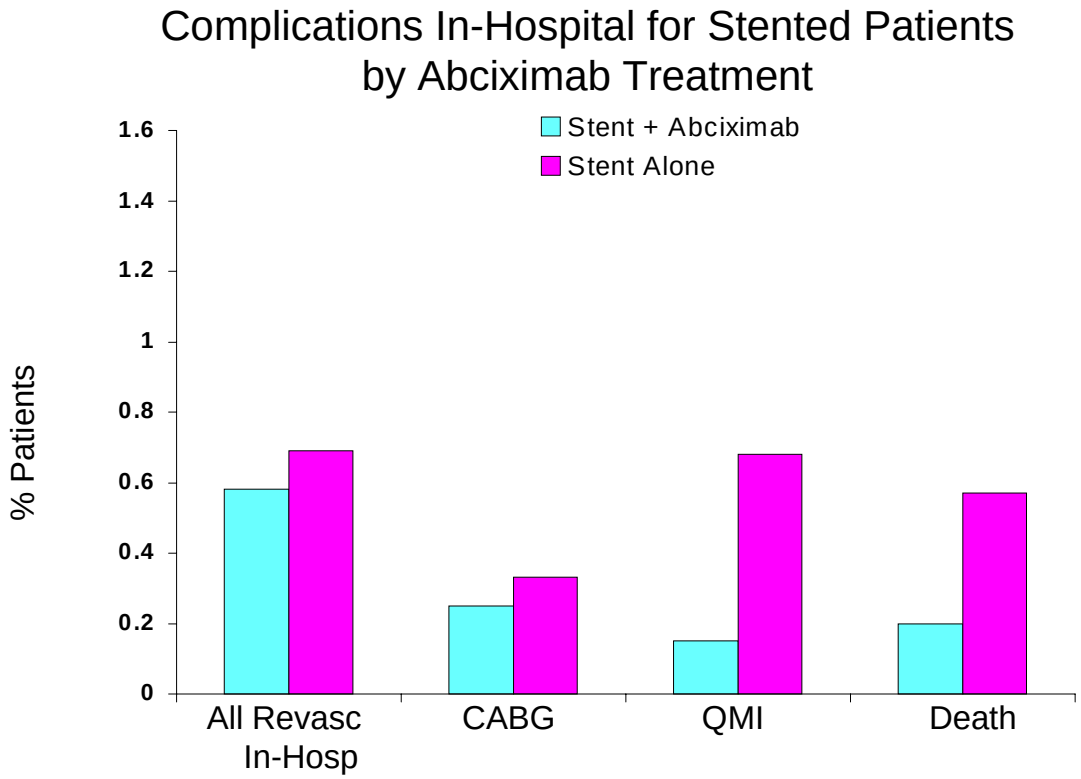
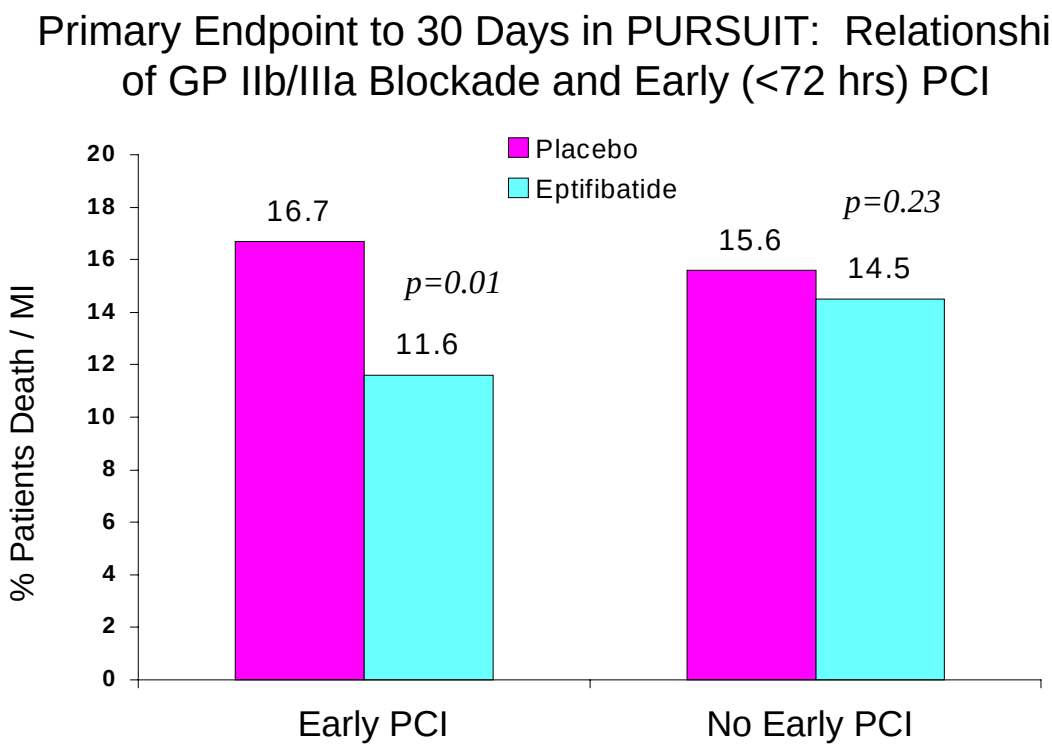

Cardiovascular Charges to 6 Months by Treatment Strategy
No Abciximab (n=301)
Abciximab (n=710)
Cardiovascular Charges (X1000)
20
18
16
14
12
10
8
6
4
2
0
15,805
15,054
13,765
16,576*
No Stent
Stent
*p<0.001

Figure 3.



P-value	0.77	0.77	0.44	0.44

Figure 4.



NEJM 1998;339:439

Table V.

EPISTENT Cost-Effectiveness Analysis*

	6 Month Analysis	*1 Year Analysis*
*Mortality (Reduction): Stent vs. AB+Stent	1.2 vs. 0.5 (0.7%)	2.4 vs. 1.0 (1.4%)
*Incremental Drug Cost (Abciximab)	$1,472	$1,472
*Gain in Life Years with AB+Stent	0.085	0.158
*Cost Per Life Year Gained	$17,318	$9,316

*Bala, Anderson, Barber. JACC 1999;33:15A

Figure 5.

Cumulative Cardiovascular Charges to 6 Months by Device and Abciximab Therapy

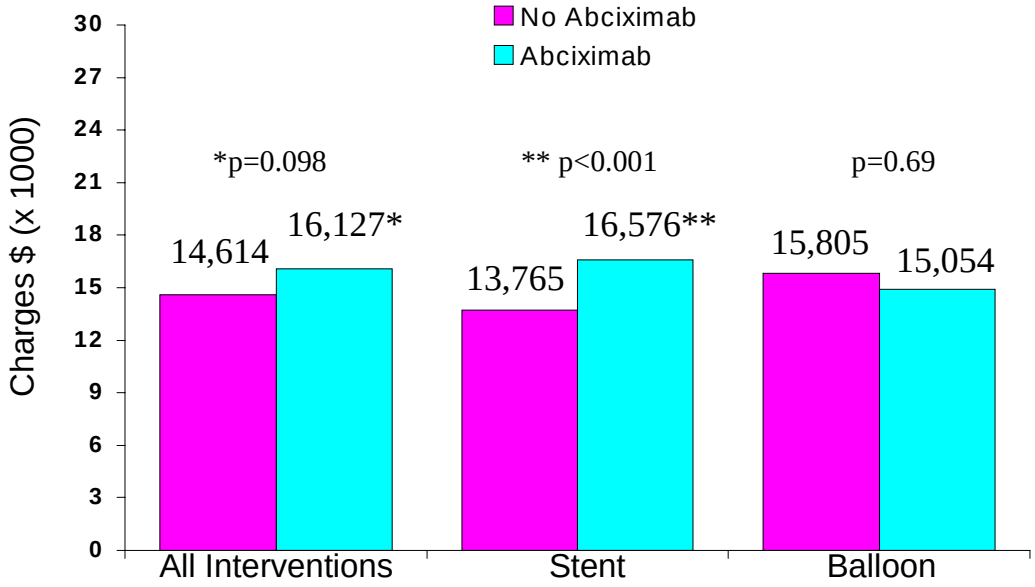


Figure 6.

Total Cardiovascular Days in Hospital to 6 Months By Treatment

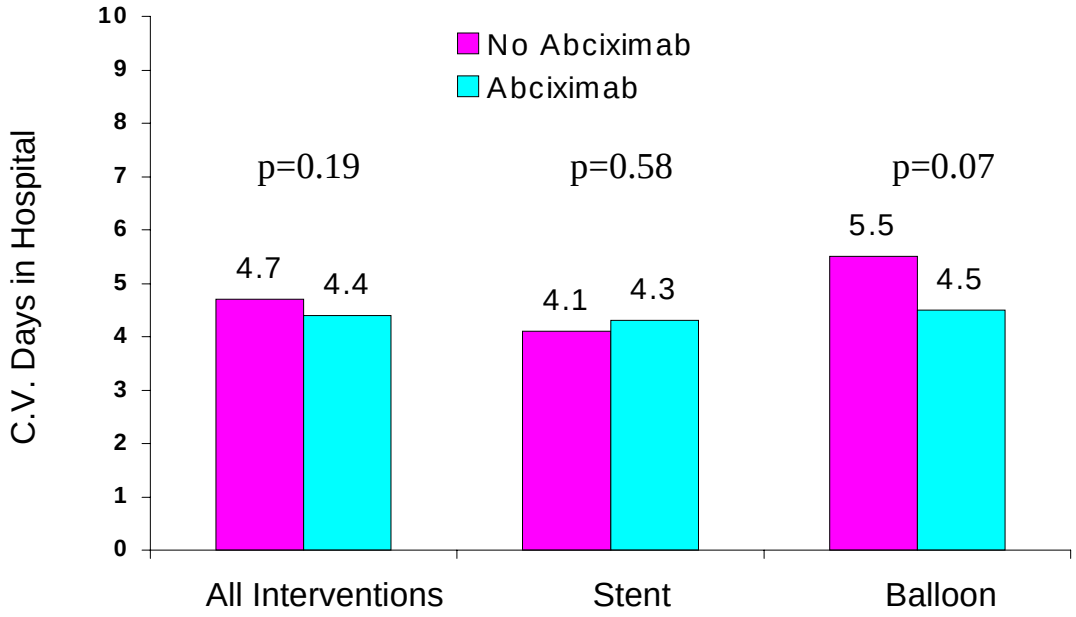


Figure 7.

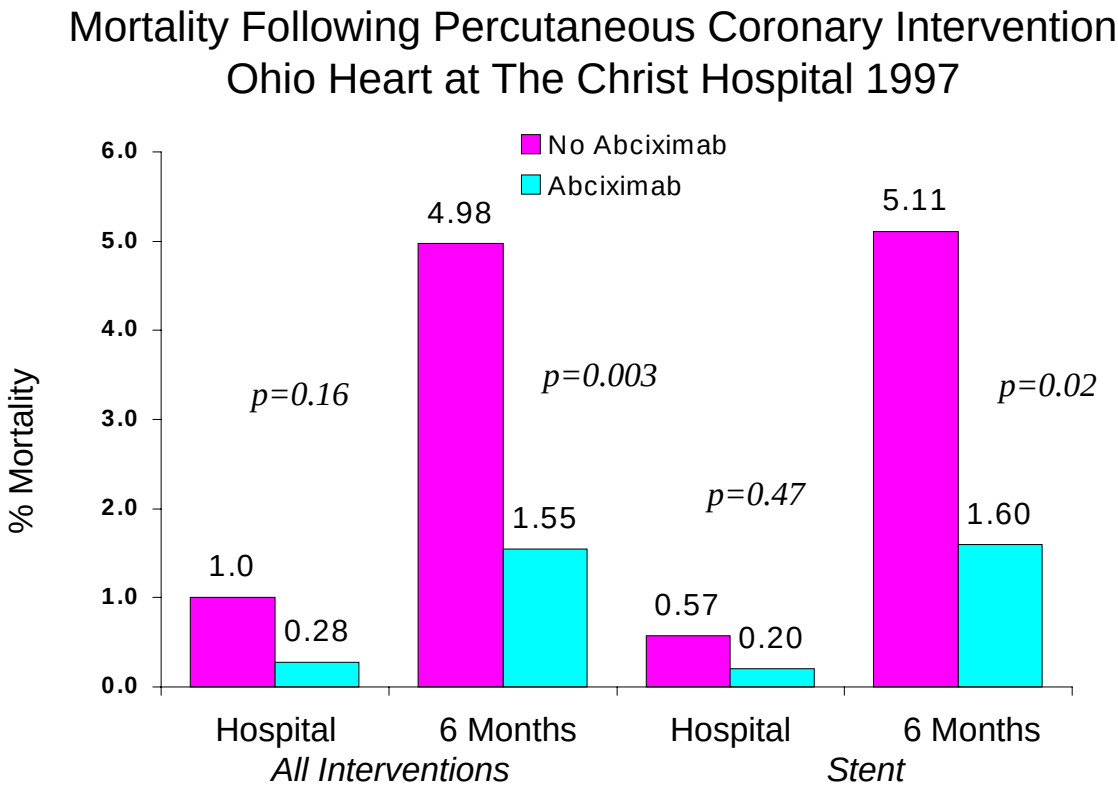

Mortality Following Percutaneous Coronary Intervention
Ohio Heart at The Christ Hospital 1997
No Abciximab
Abciximab
% Mortality
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.0
0.28
4.98
1.55
0.57
0.20
5.11
1.60
p=0.16
p=0.003
p=0.47
p=0.02
Hospital
6 Months
Hospital
6 Months
All Interventions
Stent

Table VI. Comparison of Patient Populations

	EPISTENT	LINDNER(1997)	P-value
Patients	**2,374**	**1,011**	
Mean Age	**59.5**	**62.5**	**< 0.001**
Median Age	**59**	**64**	
Age Range	**(27, 90)**	**(30, 89)**	
Diabetic	**20.5%**	**22.5%**	**0.196**
Male Gender	**75%**	**65%**	**< 0.0001**
Smokers	**36.6%**	**57.4%**	**< 0.0001**
Hypertension	**52.5%**	**72.0%**	**< 0.0001**
Myocardial Infarction			
≤ 12 hours	**1%**	**14.5%**	**< 0.0001**
≤ 7 days	**16.4%**	**26.9%**	
Number of Native Vessels Attempted			
0	**67 (2.8%)**	**4 (0.4%)**	
1	**2103 (88.6%)**	**688 (68.1%)**	**< 0.0001**
2	**197 (8.3%)**	**257 (25.4%)**	
≥ 3	**7 (0.3%)**	**62 (6.1%)**	

Table VII.

Target Vessel Revascularization*

	N	Mean	Std Error	P
Abciximab				
No	301	.0797	0.01893	0.918
Yes	710	.0775	0.01233	
Stent				
No	336	.1220	0.01784	0.009
Yes	675	.0563	0.01258	

*Repeat PCI only

PART TWO: PROPENSITY SCORING

We decided to make our adjustments of non-randomization using Propensity Scoring (PS) methodology which, essentially, looks at only cost and effectivenss differences (Abcix minus non-Abcix) within groups of patients who are relatively "well matched" on disease severity, comorbidity, etc. Ultimately, one ends up calculating an "overall difference" (Abcix minus non-Abcix) as a weighted average (across groups) of observed within-group differences.

> In summary, adjustment for treatment selection bias resulting from lack-of-randomization in an observational study involves making comparisons only between patients who received different treatments but were otherwise relatively "well matched."

Early contributions to the PS approach employed here include those of Cochran(1968) and Rosenbaum & Rubin(1984). More recent descriptions can be found in Rubin(1997), Obenchain & Melfi(1997) and especially D'Agostino(1998). The PS calculations and graphics presented here were generated using S-plus functions described in Obenchain(1999).

Our propensity scoring approach consisted of the following four steps:

1. Construct a (logit) model that predicts the probability of receiving abciximab at Christ hospital in 1997. Because our ultimate goal was to make cost-effectiveness inferences, we first restricted attention to the 1011 distinct patients receiving the 1472 PCIs performed at Ohio Heart Health Center in 1997. This is commonly called an "intent to treat" analysis because emphasis is placed on the abciximab treatment decision made for the first PCI performed at Ohio Heart Health Center in 1997. The estimated probability of abciximab use in the first PCI for each patient is called that patient's "propensity score."

   > Logistic Regression is a highly specialized form of "multiple regression" used to predict a binary valued variable. Here that binary response variable is "abciximab use" (0 => No, 1 => Yes) at Lindner in 1997.
   >
   > In our logistic regression models, prediction of ABCIX treatment selection was modeled as a function of 14 patient characteristics: HEIGHT, AGE, STENT, FEMALE, BLACK, DIABETIC, HYPERT, SMOKE, MI, ACUTE, EVOLV, RECENT, EJECTFMI and VES1PROC. Note that only 4 of the above variables are continuous measures (HEIGHT, AGE, EJECTFMI and VES1PROC); the other 11 are all "indicator" variables, with 0 => No and 1 => Yes.

We decided to not use indicator variables for complications, major bleeding and transfusions in our model for predicting treatment selection because these indicators may represent "outcomes" that occurred only after the initial decision to use or not to use abciximab was made. There is no apparent consensus among practitioners of propensity scoring about excluding "outcomes" that can be viewed as surrogate measures of disease severity, but most econometric methods (such as Heckman's inverse Mills ratio adjustment and instrumental variables models) routinely exclude such terms.

We definitely wanted to include a count of the total number of lesions treated in the initial PCI as a predictor of abciximab use. Unfortunately, that field was left blank in the Ohio Heart Health Center SUMMIT database for more than half of the 1011 patients.

2. Sort all 1011 patients by their estimated score, then group patients into 5 adjacent "bins," containing 202, 202, 203, 202 and 202 patients, respectively. Bin 1 contains the 202 patients with lowest estimated propensity score; bin 5 contains the 202 patients with highest estimated propensity scores.

3. Calculate the difference (abiximab minus non-abciximab) in average cost or effectiveness within each bin. Obviously, this sort of difference cannot be calculated if all the patients in any one bin received the same treatment.

4. Calculate an overall weighted-average difference in cost or effectiveness over the 5 bins.

Initially, we considered weighting each within-bin difference inversely proportional to its own estimated variance. After all, this is the weighting scheme that will always minimize the estimated variability of the overall difference. Unfortunately, we found that this tactic tended to severely down-weight results from cells that contained "high cost" outliers …almost all of which occurred for patients who had not received abciximab.

In other words, because administration of abciximab increases average cardiac costs by about $1,500, the total cardiac costs of abciximab treated patients are unlikely to be very low. On the other hand, the 1997 Lindner data also clearly show that total cardiac costs of abciximab treated patients are also highly unlikely to be very high. Specifically, these data provide more support for the hypothesis (a) that abciximab treatment decreases the variability of the distribution of total cardiac costs than for the hypothesis (b) that abciximab treatment increases the mean of the distribution of total cardiac costs.

> Ultimately, we decided to weight each within-bin difference directly proportional to the total number of patients (abciximab plus non-abciximab) within that bin. A survey of published case-studies using propensity scoring revealed that this is the weighting scheme most commonly used in actual practice. While this weighting scheme does yield larger estimated variability in the resulting overall difference estimate, it appears to be more consistent with the primary imperative of propensity scoring to reduce bias!

An important phase of our analyses (and one that is separate from the four steps listed above) involves verifying that the "fundamental theorem" of propensity scoring has been at least approximately satisfied. This theorem states that, if an appropriate logistic regression model has been found, then there will be no difference in the distributions of covariate measurements **between treatments within bins**. In other words, although this distribution may be different in different bins, patients who have been treated or untreated with abciximab have been relatively "well matched" within bins. Thus abciximab treated and untreated patients are expected to display identical covariate distributions within each bin.

The **PSdifcov()** function of Obenchain(1999) is ideal for detecting violations of the fundamental theorem of propensity scoring, thereby implying that the current logistic regression model is inadequate to explain treatment selection. Every variable used in the logistic regression model as a "covariate" is a candidate for formal significance testing and graphical display of potential within-bin differences. Examples of this are given in Figures 15 and 16 where graphical outputs from PSdifcov() function are displayed for the VES1PROC covariate. These figures use "box plots" to show that, although abciximab treated patients tend to have much larger values of VES1PROC than patients who were not administered abciximab, the corresponding WITHIN BIN distributions of VES1PROC tend to be identical (and, thus, independent of treatment.)

Table VIII. Outcome Differences by Subgroup, Before and After Adjustment for Treatment Selection Bias.

All 1011 Patients: Abcix minus non-Abcix

	Unadjusted		Adjusted	
	Difference	Std.Dev.	Difference	Std.Dev.
DIE6MO	-0.034	0.013	-0.049	0.043
CARDBILL	$1,512	$908	$942	$2,118
MAJOR BLEED	-0.008	0.007	-0.005	0.013
COMPLICATIONS	+0.017	0.013	+0.014	0.033

675 Stent Patients: (Abcix+Stent) minus (Stent-alone)

	Unadjusted		Adjusted	
	Difference	Std.Dev.	Difference	Std.Dev.
DIE6MO	-0.035	0.018	-0.076	0.075
CARDBILL	$2,811	$768	$2,272	$2,309

Table VIII, Continued. Outcome Differences by Subgroup.

227 Diabetic Patients: Abcix minus non-Abcix

	Unadjusted		Adjusted	
	Difference	Std.Dev.	Difference	Std.Dev.
DIE6MO	-0.059	0.034	-0.083	0.103
CARDBILL	$3,274	$1,369	$792	$4,224

884 Non-diabetic Patients: Abcix minus non-Abcix

	Unadjusted		Adjusted	
	Difference	Std.Dev.	Difference	Std.Dev.
DIE6MO	-0.024	0.013	-0.033	0.044
CARDBILL	$958	$1,137	$544	$2,732

Table IX. Logistic Regression Model to Predict Treatment Selection.

```
S-PLUS version 4.5 function call:

glm(formula = ABCIX ~ HEIGHT + AGE + STENT + FEMALE + BLACK + DIABETIC +
                      HYPERT + SMOKE + MI + ACUTE + EVOLV + RECENT +
                      EJECTFMI + VES1PROC,
    family = binomial, data = df, na.action = na.omit, link = logit)


Deviance Residuals:
       Min        1Q    Median        3Q      Max
 -2.561467 -1.202266 0.6349861 0.8839838 1.488743

Coefficients:
                    Value  Std. Error      t value

(Intercept)  3.07109698717 1.860877820  1.650348537

     HEIGHT -0.01407267429 0.009577904 -1.469285409
        AGE  0.00002248341 0.006680846  0.003365353

      STENT  0.54982362153 0.150252031  3.659342355
     FEMALE -0.33439767276 0.207416177 -1.612206325
      BLACK -0.79175189036 0.627007052 -1.262747983

   DIABETIC -0.37699012308 0.172701070 -2.182905542
     HYPERT -0.08788478911 0.167804633 -0.523732794
      SMOKE -0.09158191244 0.150716760 -0.607642525

         MI -0.62198568738 1.013958579 -0.613423171
      ACUTE  1.82988352612 1.041087620  1.757665244
      EVOLV  0.47346922364 1.026185585  0.461387521
     RECENT  0.59582227839 1.309801266  0.454895177

   EJECTFMI -0.01805610162 0.007850693 -2.299937408
   VES1PROC  0.75497089905 0.137535946  5.489262411

    Null Deviance: 1231.245 on 1010 degrees of freedom
Residual Deviance: 1134.941 on 996 degrees of freedom

Correlation of Coefficients:
        (Intercept)     HEIGHT        AGE      STENT     FEMALE      BLACK   DIABETIC
  HEIGHT -0.9321867
     AGE -0.3477676   0.1142105
   STENT -0.0538259  -0.0069139  0.0489273
  FEMALE -0.6071540   0.6693690 -0.0314883  0.0090823
   BLACK -0.0280974  -0.0010800  0.0621722  0.0103876 -0.0251970
DIABETIC -0.0286155  -0.0097939  0.0301414  0.0080526 -0.0517981 -0.0694022
  HYPERT -0.0518633  -0.0037756 -0.0640292  0.0271834 -0.0727047 -0.0019781 -0.1436881
   SMOKE -0.0832800  -0.0201484  0.2131155 -0.0149517  0.0149290  0.0387995  0.0383814
      MI -0.0481653   0.0322460  0.0220674  0.0037187 -0.0155879  0.0165117 -0.0558335
   ACUTE  0.0438774  -0.0440771 -0.0132592  0.0093320 -0.0019261 -0.0285492  0.0515248
   EVOLV  0.0181186  -0.0255660 -0.0042314  0.0008659  0.0152341 -0.0233164  0.0665057
  RECENT -0.0019640   0.0070548 -0.0245720 -0.0288813  0.0464421 -0.0092163  0.0537049
EJECTFMI -0.2402095  -0.0007748  0.0664903 -0.0325081 -0.0667640  0.0507702  0.0991003
VES1PROC -0.0739182  -0.0165501 -0.0156137  0.0280981  0.0315419  0.0084001 -0.0491396

            HYPERT      SMOKE         MI      ACUTE      EVOLV     RECENT   EJECTFMI
   SMOKE  0.0212682
      MI -0.0239606 -0.0322961
   ACUTE  0.0442104  0.0244537 -0.9647552
   EVOLV  0.0293563  0.0251348 -0.9760938  0.9505452
  RECENT  0.0361922  0.0082385 -0.7662737  0.7449164  0.7557999
EJECTFMI  0.0309034  0.0249233  0.0910792 -0.0554621 -0.0240207 -0.0294718
VES1PROC -0.0124144 -0.0034897 -0.0497259  0.0528005  0.0596333  0.0377268 -0.0119780
```

Table X. Logistic Regression Model Forces Average Patient Characteristics to Vary by Assigned Propensity Score Bin.

	BIN_1	BIN_2	BIN_3	BIN_4	BIN_5
Patients	202	202	203	202	202
STENT	0.21	0.74	0.82	0.76	0.80
FEMALE	0.50	0.41	0.27	0.28	0.29
HEIGHT	170.48	172.39	171.81	171.93	170.54
AGE	63.03	60.93	63.03	63.03	62.23
DIABETIC	0.42	0.24	0.09	0.24	0.14
HYPERT	0.85	0.73	0.69	0.69	0.63
SMOKE	0.57	0.64	0.51	0.60	0.54
MI	0.17	0.18	0.18	0.25	0.62
ACUTE	0.00	0.00	0.02	0.14	0.56
EVOLV	0.16	0.16	0.14	0.10	0.05
RECENT	0.00	0.00	0.01	0.01	0.01
EJECTFMI	54.31	53.57	51.59	48.80	46.41
VES1PROC	1.00	1.07	1.17	1.64	2.06
Propensity Score	0.51	0.63	0.70	0.78	0.89

Figure 8. The higher his/her assigned Bin Number, the more likely a patient was to receive Abciximab at Lindner in 1997.

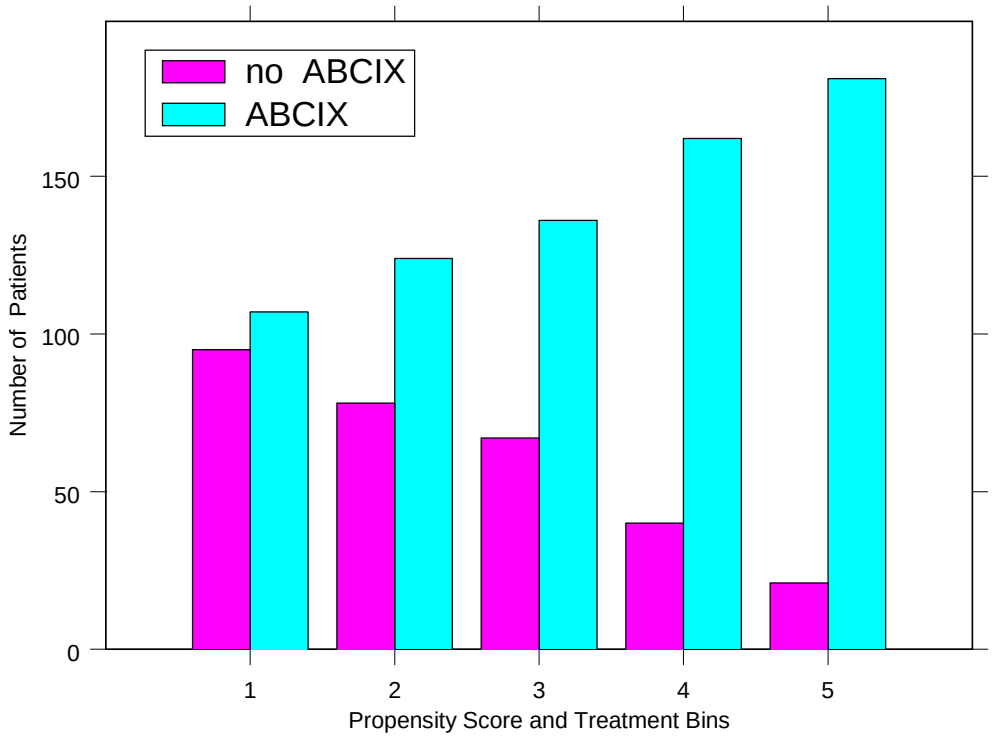
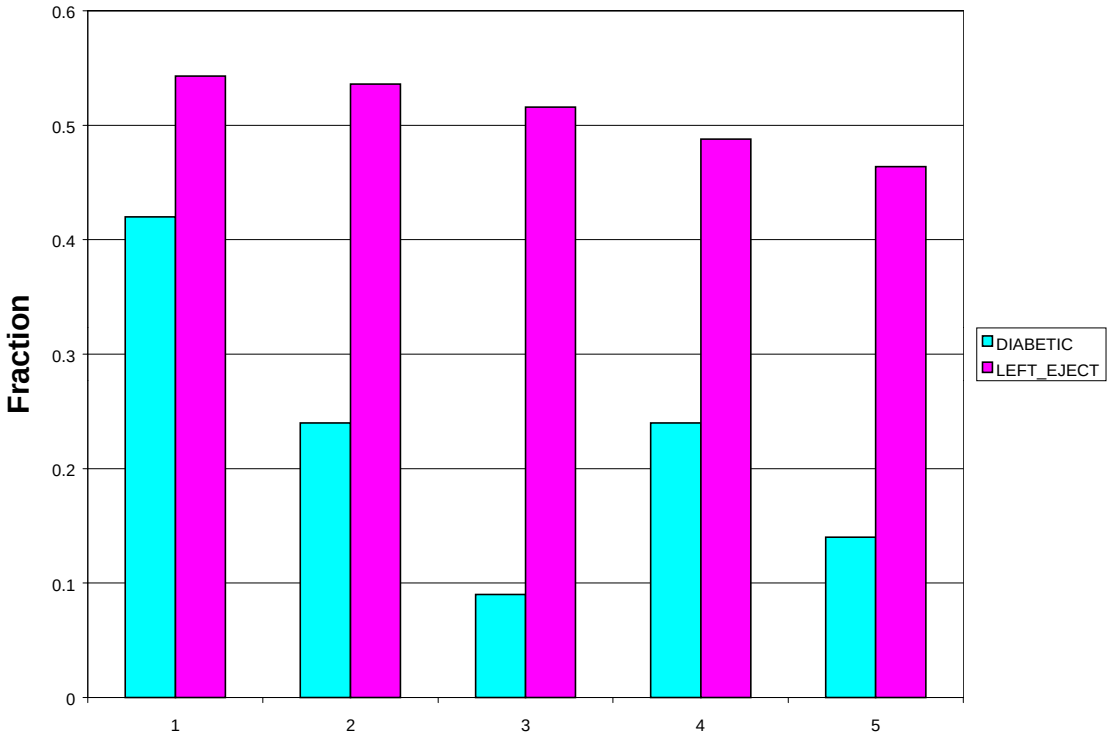
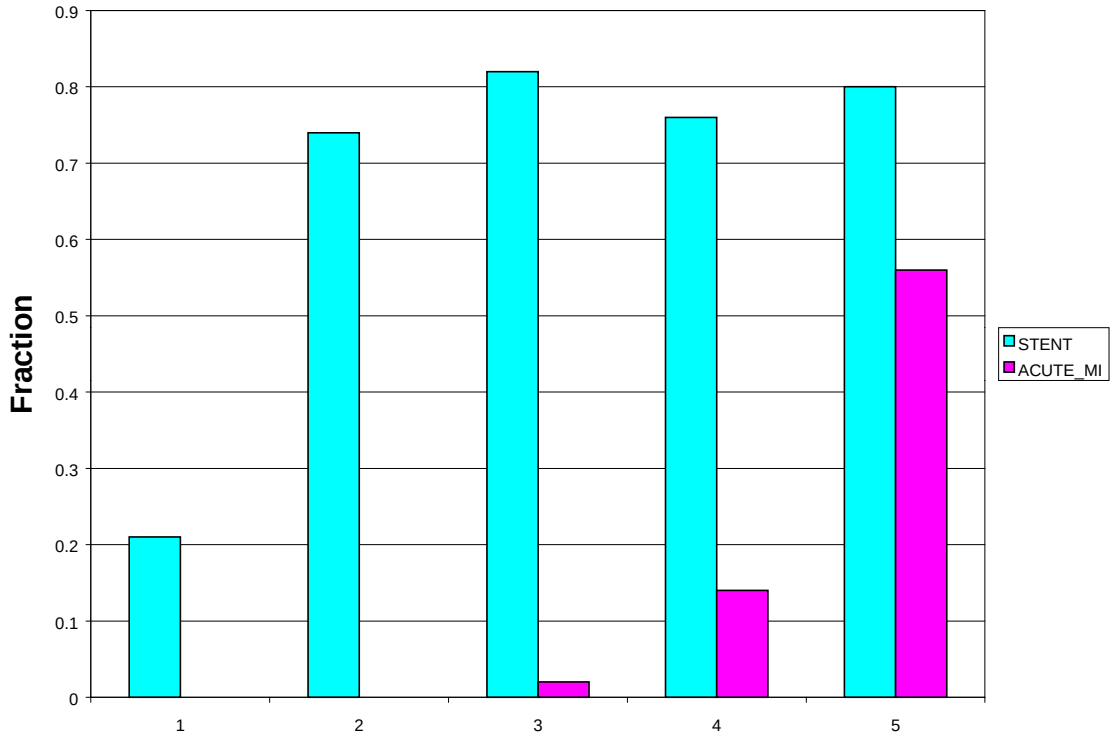


Figure 9. Diabetics tended to not receive Abciximab; Patients with Low Left Ejection Fraction tended to receive Abciximab.



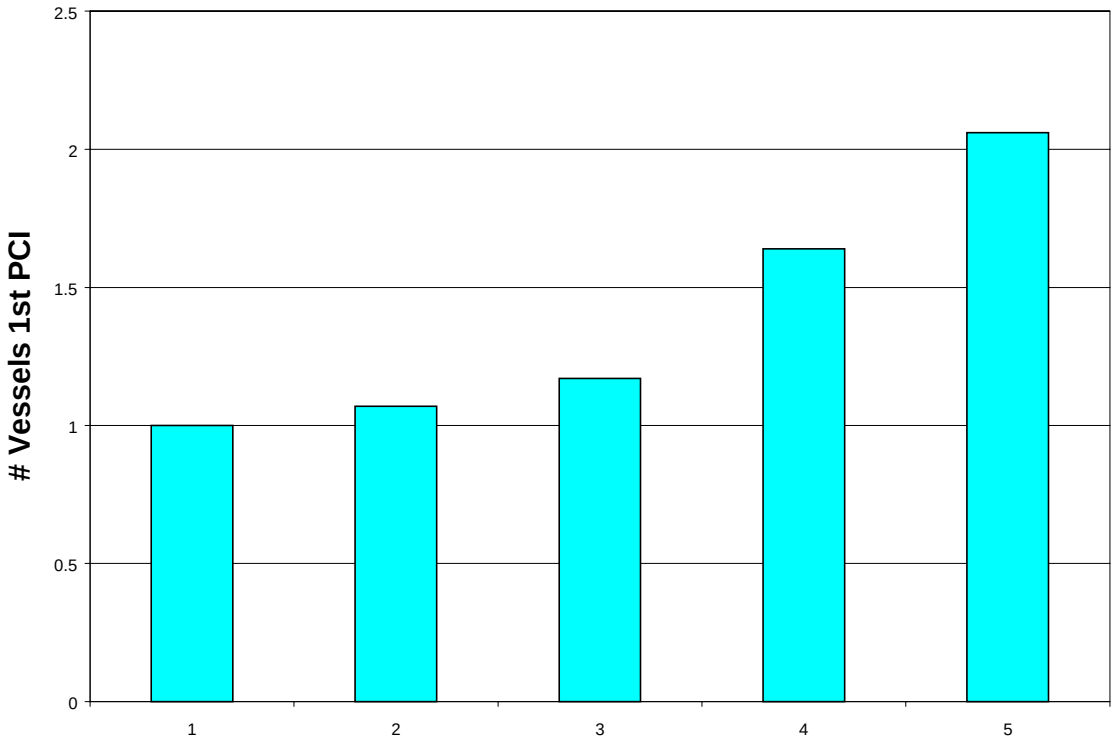
(The higher his/her assigned Bin Number, the more likely a patient was to receive Abciximab at Lindner in 1997.)

Figure 10. Patients receiving stents tended to also receive Abciximab; patients suffering Acute Myocardial Infarctions tended to receive Abciximab.



(The higher his/her assigned Bin Number, the more likely a patient was to receive Abciximab at Lindner in 1997.)

Figure 11. Patients with higher numbers of diseased vessels tended to receive Abciximab.



(The higher his/her assigned Bin Number, the more likely a patient was to receive Abciximab at Lindner in 1997.)

Figure 12. Patients receiving Abciximab suffered dramatically lower Death Rates within 6 months of their initial PCI.

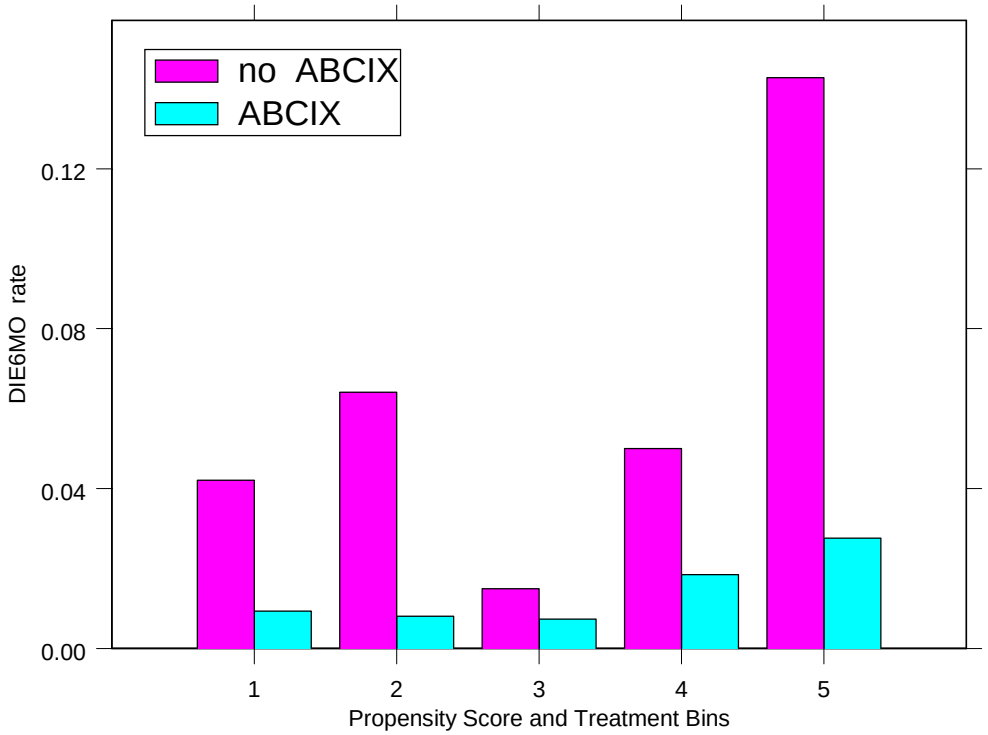


Figure 13. Total Cardiac Related Charges within 6 months of the initial PCI were lower for Abciximab treated patients in Bins 5 and 1. Bin 5 contains the patients most highly targeted to receive Abciximab at Lindner in 1997; Bin 1 tends to contain diabetic patients.

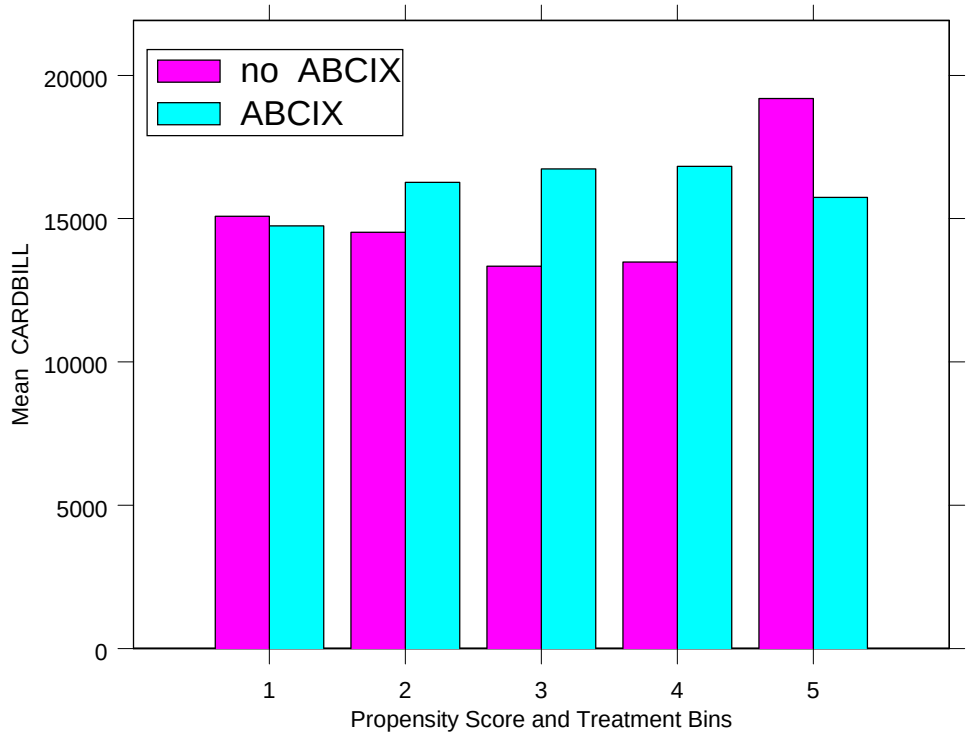
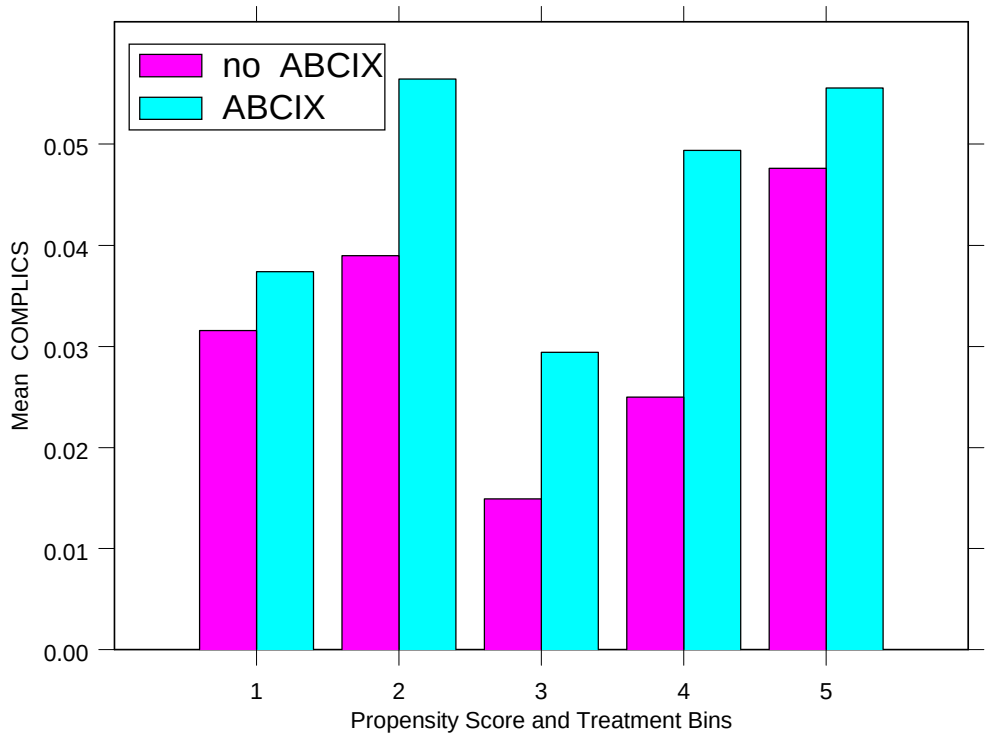
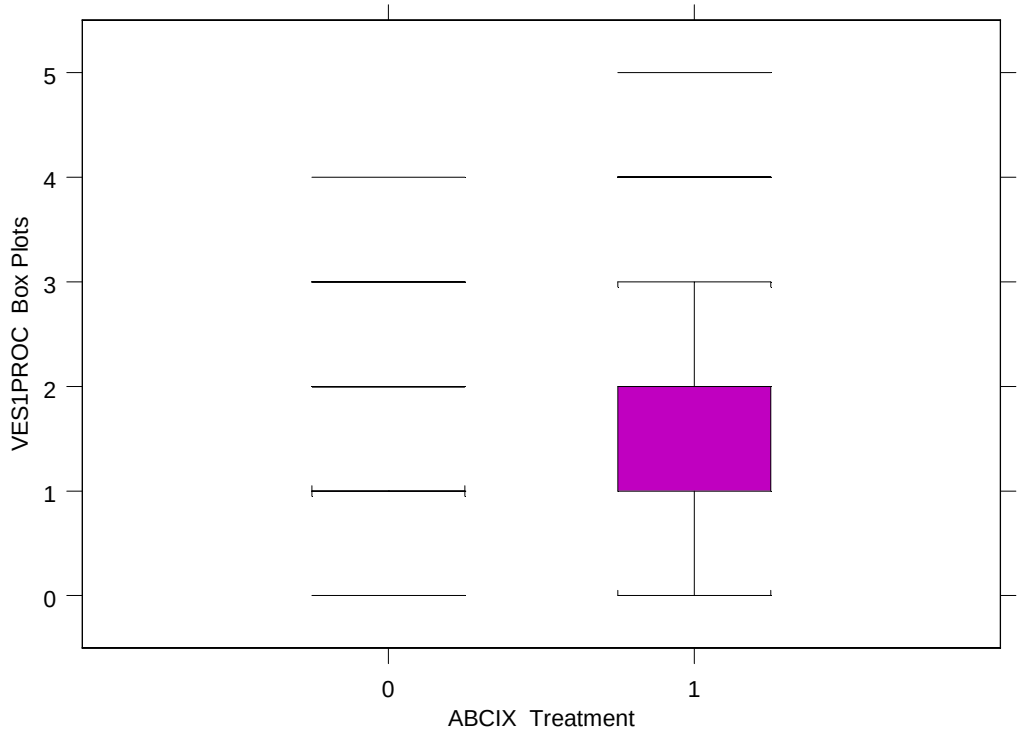


Figure 14. Since abciximab treated patients tended to be more seriously diseased (more vessels involved, more acute MI, lower ejection fraction, etc.), it is perhaps not surprising that these patients also tended to suffer more in-hospital complications.



Complications are frequently "outcomes" observed only after the abciximab treatment decision has been made. Therefore, counts of complications were not used in our logistic regression models to help predict treatment selection.

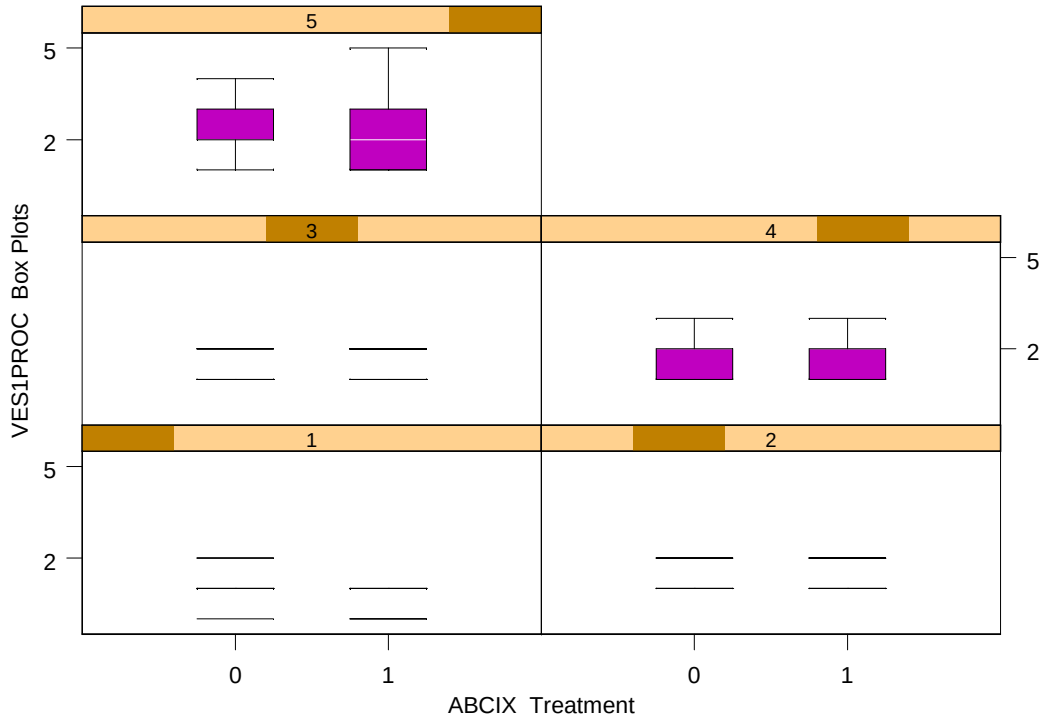
Figure 15. The "box plots" below compare the distributions of "Number of Vessels in First PCI" for 0 => non-abciximab and 1 => abciximab treated patients.



More than 80% of non-abciximab patients had VES1PROC = 1, while 37% of abciximab treated patients had VES1PROC at least 2.

	Non-Abciximab		Abciximab	
Number of Vessels	Number of Patients	Percentage	Number of Patients	Percentage
0	1	0.3%	3	0.4%
1	245	81.4%	443	62.4%
2	48	16.0%	209	29.5%
3	6	2.0%	41	5.8%
4	1	0.3%	13	1.8%
5	0	0.0%	1	0.1%

Figure 16. These "box plots" show that, within the 5 propensity scoring bins, the distributions of "Number of Vessels in First PCI" are <u>much more nearly identical</u> for 0 => non-abciximab and 1 => abciximab treated patients.



PART THREE: Cost-Effectiveness

ICER = Incremental Cost Effectiveness Ratio

$$= \frac{\text{Difference in Cost}}{\text{Difference in Effectiveness}}$$

Difference = (Average for abciximab treated patients) minus
(Average for non-abciximab treated patients)

Cost Measure = Cardiac Charges (including abciximab) x 0.75

While the appropriate multiplicative factor for converting typical hospital billing charges into actual costs may be as low as 0.50 for many types of hospital services, 0.75 is the most appropriate factor for abciximab treatment at Lindner in 1997. Ohio Heart Health Center typically billed $600 per abciximab unit when their average cost was $450 per unit. Assuming (on long range average) that charges and costs for all "other" hospital services would be the same for abciximab treated patients as for non-abciximab patients, almost all of any observed difference in the form of a moderate increase in total costs can reasonably be attributed directly to the cost of abciximab itself.

Effectiveness Measure = 1 or 0 for six-month survival x 11.6

The expected total survival time, given 6-month post-index procedure survival, from Mark et al.(1995) is 14 years. These 14 years are then discounted [at 3% per year, as recommended by Lipscomb et al., (1996)] to yield 11.6 years of discounted, total expected survival given 6-month survival.

Table XI gives ICER point estimates …both raw (unadjusted) and also adjusted for treatment selection bias. The unadjusted estimates are all quite favorable to use of abciximab (at least when compared to typical findings for cardiac surgery or cancer treatment), and the adjusted estimates are even lower!

Table XII gives 95% confidence ICER limits for unadjusted estimates. Unfortunately, the bootstrap methodology used in Table XII and Figures 17, 18 and 19 cannot be applied to the adjusted estimates of Table XI. Bootstrap calculations can only be performed using patients with known (non-missing) values for both their cost and their effectiveness measure. While six-month-survival status was know for all 1011 patients, total cost was unknown for 15 of these patients. Thus, unlike the unadjusted ICER estimates reported in Table XI above, the estimates and limits reported here in Table XII use data from only 996, 666 and 223 patients, respectively.

Table XI. Incremental Cost per Life Year Gained by Subgroup, Before and After Adjustment.

1011 Patients: Abcix minus non-Abcix

	Formula =	Result	Rounded
Unadjusted	$1,512 x 0.75 / (0.034 x 11.6)=	$2,875	$2,900
Adjusted	$942 x 0.75 / (0.049 x 11.6)=	$1,243	$1,250

675 Stent Patients: (Abcix+Stent) minus (Stent-alone)

	Formula =	Result	Rounded
Unadjusted	$2,811 x 0.75 / (0.035 x 11.6)=	$5,193	$5,200
Adjusted	$2,272 x 0.75 / (0.076 x 11.6)=	$1,933	$1,900

227 Diabetic Patients: Abcix minus non-Abcix

	Formula =	Result	Rounded
Unadjusted	$3,274 x 0.75 / (0.059 x 11.6)=	$3,588	$3,600
Adjusted	$792 x 0.75 / (0.083 x 11.6)=	$617	$600

884 Non-diabetic Patients: Abcix minus non-Abcix

	Formula =	Result	Rounded
Unadjusted	$958 x 0.75 / (0.024 x 11.6)=	$2,626	$2,650
Adjusted	$544 x 0.75 / (0.033 x 11.6)=	$1,066	$1,050

Table XII. ICER Bootstrap Confidence Limits for Incremental Cost per Life Year Gained: ABCIX minus non-ABCIX (Unadjusted)

	95% Confidence Lower Limit	Bootstrap ICER (Unadjusted)	95% Confidence Upper Limit
996 Patients (668 ABCIX, 328 non-ABCIX)	–$1,153 / YR	$2,121 / YR	$8,191 / YR
666 Stent Patients (492 ABCIX, 174 non-ABCIX)	+$1,158 / YR	$5,125 / YR	$33,116 / YR
223 Diabetic Patients (143 ABCIX, 80 non-ABCIX)	+$203 / YR[1]	$3,556 / YR	+∞ / YR[1]

[1] Note: The 95% bootstrap ICER confidence region for diabetic patients contains almost all of the (+, +) => (more costly, more effective) quadrant of the cost-effectiveness plane. In terms of polar coordinates, the (+, +) quadrant is 45^o < ICER angle < 135^o, while the above 95% interval corresponds to 49.28^o < ICER angle < 135.23^o. See Figure 19.

Figure 17. The bootstrap distribution of ICER uncertainty for all 996 patients and the corresponding 95% confidence interval of (–1153, +8191) dollars per life year gained.

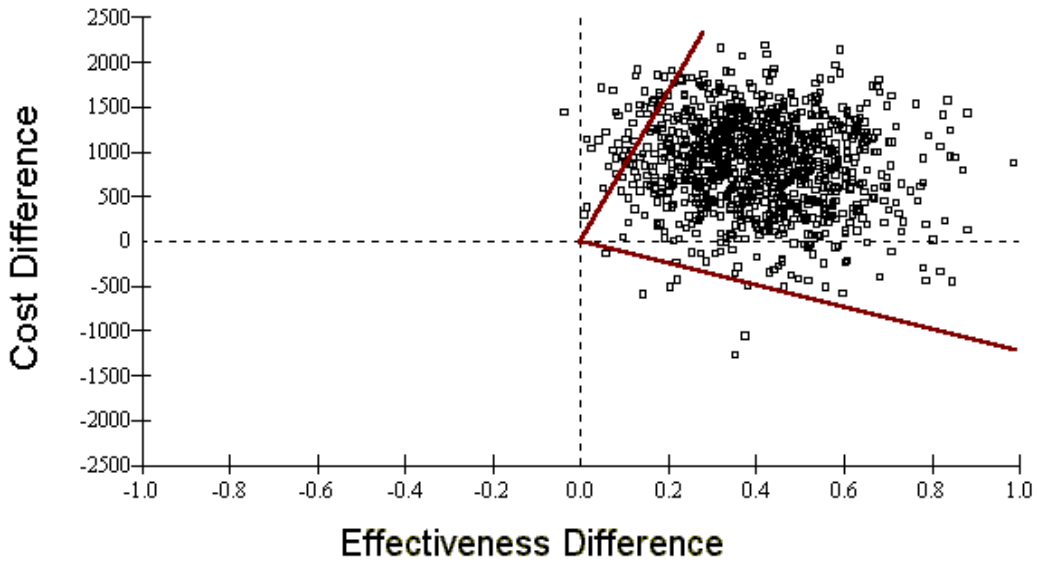


Figure 18. The bootstrap distribution of ICER uncertainty for all 666 stent patients and the corresponding 95% confidence interval of (+1158, +33116) dollars per life year gained.

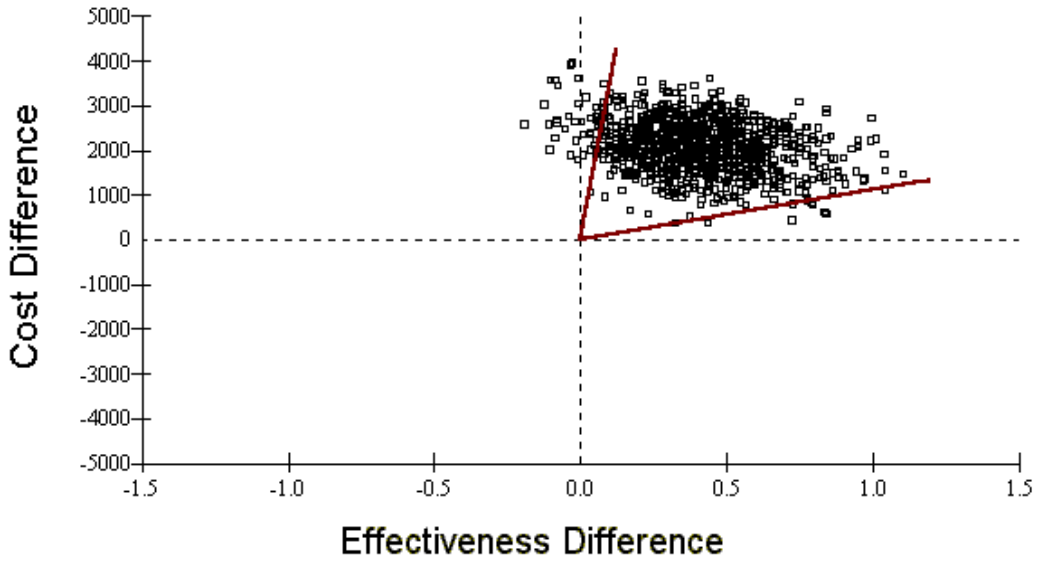
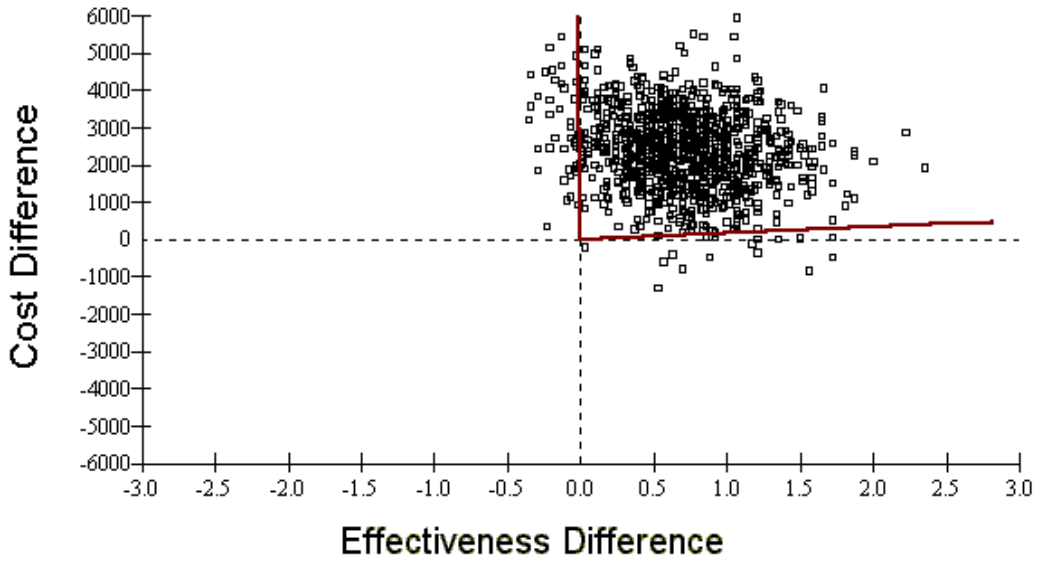


Figure 19. The bootstrap distribution of ICER uncertainty for 223 diabetic patients and the corresponding 95% confidence interval of (+203, +infinity) dollars per life year gained.



Abciximab Survival Advantage: Conclusions

1. Abciximab provides a dramatic survival advantage when administered prophylactically during PCI in high volume clinical practice.

2. Procedures in follow-up (TVR by PCI) not influenced by abciximab (similar to EPISTENT).

3. Unadjusted treatment comparisons suggest an average reduction in mortality at 6 months of 3.4% at an average charge increment of $1,512. This corresponds to an ICER of $2,900 per life year gained.

4. Adjustment for non-randomization (based upon differences between relatively well-matched patients) reveals an average reduction in mortality at 6 months of 4.9% at an average charge increment of only $950. This corresponds to an ICER of only $1,250 per life year gained.

5. Comparisons of (abcix+stent) with (stent alone) were slightly less favorable; that ICER was $5,200 per life year gained [unadjusted] and $1,900 after adjustment.

6. Use of abciximab on diabetic patients at Ohio Heart Health Center tended to be restricted in 1997 to truly severe cases; that ICER was $3,600 per life year gained [unadjusted] but dropped to $600 after adjustment for non-randomization. (For non-diabetics, the unadjusted ICER was $2,650; adjustment for non-randomization reduced this estimate to $1,050.)

7. Cost-efficacy of abciximab in high volume interventional practice compares very favorably with other widely accepted therapeutic standards.

REFERENCES

1. Cochran WG. The effectiveness of adjustment by subclassification in removing bias in observational studies. **Biometrics** 1968, 24: 205-213.

2. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. **J Am Stat Ass** 1984, 79: 516-524.

3. Rubin DB. Estimating causal effects from large data sets using propensity scores. **An Internal Med** 1997, 127: 757-763.

4. Obenchain RL, Melfi CA. Propensity score and Heckman adjustments for treatment selection bias in database studies." **Proc Biopharm Sec** 1997**,** 297-306. Washington, DC: American Statistical Association.

5. D'Agostino RB Jr. Tutorial in Biostatistics: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. **Stat in Med** 1998, 17: 2265-2281.

6. Obenchain RL. PSdefine(), PSdifcov() and PSdifout(): S-PLUS functions for propensity score adjustment using bins. Download from the internet at URL http://www.math.iupui.edu/~indyasa/download.htm 1999.

7. Data Analysis Products Division of MathSoft, Inc. S-PLUS, Version 4.5 for Windows. Seattle: MathSoft, Inc. 1998.

8. Becker RA, Chambers JM, Wilks AR. The New S Language. Pacific Grove, CA: Wadsworth and Brooks/Cole, 1988.

9. Lipscomb J, Weinstein MC, Torrence GW. Time preference. In: Gold MR, Siegel JE, Russell LB, et al, eds. **Cost-Effectiveness in Health and Medicine.** New York, NY: Oxford University Press, 1996, 214-246.

10. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasmingen activator as compared with streptokinase for acute myocardial infarction. **New Eng J Med** 1995**,** 332;1418-1424.

11. Obenchain RL Resampling and multiplicity in cost-effectiveness inference. **J Biopharm Stat** 1999, 9: 563-582.

12. Obenchain RL CEplane: calculation and graphical display of bootstrap ICER confidence and tolerance regions and quadrant acceptability fractions. Copyright © **Pharmaceutical Research and Manufacturers of America, PhRMA,** Washington, D.C. 1999, http://www.math.iupui.edu/~indyasa/download.htm.