



i3 Drug Safety
950 Winter Street, Suite 3800
Waltham, MA 02451-1424
Tel (781) 472 8449 | Fax (617) 552 5275

ADDENDUM

To the

Final Report

Risks of Renal Failure and Death following Use of
Aprotinin or Aminocaproic Acid during CABG Surgery

Part A

Report on Computerized Inpatient Data from
the Premier Perspective Comparative Database

August 31, 2007

Sebastian Schneeweiss, MD, ScD, John Seeger, PharmD, DrPH,
Alexander M. Walker, MD, DrPH

Analyst: Joan Landon, MPH

TABLE OF CONTENTS

1. BACKGROUND	3
2. ADDITIONAL ANALYSES.....	3
3. CORRECTION	4
FIGURES AND TABLES.....	5

1. BACKGROUND

The report entitled “Risks of Renal Failure and Death following Use of Aprotinin or Aminocaproic Acid during CABG Surgery Part A Report on Computerized Inpatient Data from the Premier Perspective Comparative Database” dated August 7, 2007 was discussed with Bayer and its consultants at a meeting on August 13, 2007. At the conclusion of that meeting, and in response to requests from Bayer, i3 Drug Safety agreed to conduct additional analyses, which are presented in this addendum.

Where one of the additional analyses agreed upon at that meeting has resulted in the modification of a table from the August 7 report, we have presented the full table here, which contains results from the additional analyses in **bold**.

2. ADDITIONAL ANALYSES

Analyses of the outcome “renal failure requiring dialysis” in the August 7 report were conducted after excluding all patients with discharge diagnoses of chronic kidney disease. In this further analysis we additionally excluded patients who had charge codes for hemo-dialysis, peritoneal-dialysis, or hemo-filtration before the day of CABG surgery. **Tables 1, 2a, 2b, 3, 5, 6, 7** of the August 7 report are affected by this restriction.

Table 2a was expanded by results from a multivariate adjusted analysis of all aprotinin doses combined and all aminocaproic acid doses combined and by a multivariate adjusted analysis after excluding very low doses of aprotinin and aminocaproic acid doses using the identical definition of very low doses as in the August 7 report.

In **Table 3** we added a line for diabetes. The original version of this table (presented in the August 7 report) contained results that were adjusted for diabetes in the analysis, but the line reporting the diabetes effect was omitted from the table. In-hospital death outcomes are adjusted for dialysis preceding CABG as well as for a diagnosis of chronic kidney disease.

Dialysis that occurred for the first time on the day of CABG surgery was not treated as indicative of preexisting renal failure nor was it counted as a study outcome (only dialyses following the day of CABG were defined as outcomes to ensure an unambiguous temporal sequence). In **Table 8** counts of patients with dialysis that occurred the first time on the day of CABG surgery are shown cross-classified by aprotinin use vs. aminocaproic acid use.

In **Figure 5** we have now provided a patient flow chart to clarify the patient selection for the instrumental variable (IV) analyses. For both IV analysis populations we have now provided information on the balance of measured covariates that were also adjusted in the IV analysis (**Table 9**).

In **Table 10** we have now provided Hosmer-Lemeshow Goodness-of-fit Statistics for both analyses shown in Table 3.

In **Table 11** we have now provided regression coefficients and odds ratio estimates of the logistic regression model estimating the propensity score. The greedy matching algorithm started with matching patients with propensity scores identical to the 8th decimal. The requirement was increasingly loosened up to the first decimal.

3. CORRECTION

The following sentence from the Final Report Part A pertains to analyses in the Preliminary Report, but not the Final Report, and should be struck:

Renal failure prior to CABG requiring dialysis was included as a covariate in multivariate analyses, and because of the very high associated coefficient for the renal outcome, modeling had the effect of removing patients with pre-CABG dialysis from the estimation of drug effects.

This is the last sentence on page 7.

Figure 5: Patient enrollment into instrumental variable analyses

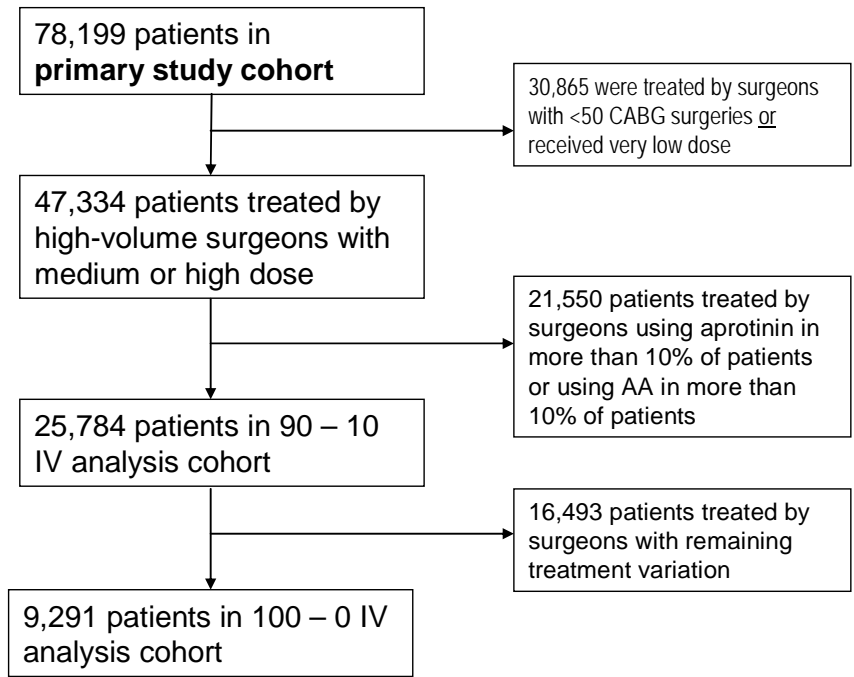


Table 1: Characteristics of patients undergoing CABG surgery in the primary and data-dense study cohorts.

Characteristic	Primary study cohort N = 78,199			Data-dense study cohort after 1:1 matching by propensity score N = 9,598			Data-dense study cohort with predetermined exposure using assigned instrumental variable status N = 3,643		
	Aprotinin N (%)	Amino- caproic acid N (%)	p-value from Chi ² test	Aprotinin N (%)	Amino- caproic acid N (%)	p-value from Chi ² test	Treated by a surgeon who always uses aprotinin N (%)	Treated by a surgeon who always uses amino- caproic acid N (%)	p-value from Chi ² test
Number of patients	33,517(42.9)	44,682(57.1)		4,799(50.0)	4,799(50.0)		2,839(77.9)	804(22.1)	
Very low dose	3,741(11.2)	19,191(43.0)							
Low dose	10,144(30.3)	19,813(44.3)		1,535(32.0)	3,983(83.0)		1,115(39.3)	446(55.5)	
High dose	19,632(58.6)	5,678(12.7)		3,264(68.0)	816(17.0)		1,724(60.7)	358(44.5)	
Age									
18 - 24	2(0.0)	3(0.0)	<.0001	0 (0.0)	0 (0.0)	0.98	0 (0.0)	0 (0.0)	0.001
25 - 34	64(0.2)	82(0.2)		11(0.2)	9(0.2)		5(0.2)	1(0.1)	
35 - 44	803(2.4)	1,317(3.0)		127(2.7)	121(2.5)		66(2.3)	33(4.1)	
45 - 54	4,141(12.4)	6,198(13.9)		620(12.9)	629(13.1)		353(12.4)	133(16.5)	
55 - 64	8,683(25.9)	12,475(27.9)		1,263(26.3)	1,237(25.8)		737(26.0)	210(26.1)	

i3 Drug Safety

August 31, 2007

	65 - 74	10,861(32.4)	14,329(32.1)		1,502(31.3)	1,518(31.6)		891(31.4)	246(30.6)	
	75 +	8,963(26.7)	10,278(23.0)		1,276(26.6)	1,285(26.8)		787(27.7)	181(22.5)	
Sex (male)		23,637(70.5)	31,906(71.4)	0.01	3,270(68.1)	3,250(67.7)	0.66	1,933(68.1)	566(70.4)	0.21
Race/ethnicity	White	26,468(79.0)	33,062(74.0)	<.0001	3,708(77.3)	3,738(77.9)	0.61	2,345(82.6)	574(71.4)	<.0001
	Black	2,119(6.3)	2,254(5.0)		334(7.0)	311(6.5)		261(9.2)	28(3.5)	
	Other	4,930(14.7)	9,366(21.0)		757(15.8)	750(15.6)		233(8.2)	202(25.1)	
Smoking (current, past)		7,851(17.6)	6,265(18.7)	<.0001	834(17.4)	861(17.9)	0.47	549(19.3)	106(13.2)	<.0001
Admission Year	2003	7,134(21.3)	15,393(34.5)	<.0001	1,143(23.8)	1,150(24.0)	0.88	590(20.8)	241(30.0)	<.0001
	2004	10,862(32.4)	14,460(32.4)		1,678(35.0)	1,675(34.9)		1,006(35.4)	304(37.8)	
	2005	13,211(39.4)	11,558(25.9)		1,665(34.7)	1,680(35.0)		1,056(37.2)	221(27.5)	
	2006 (Q1)	2,310(6.9)	3,271(7.3)		313(6.5)	294(6.1)		187(6.6)	38(4.7)	
Emergency Admission		16,540(49.4)	23,721(53.1)	<.0001	3,480(72.5)	3,481(72.5)	0.98	2,051(72.2)	652(81.1)	<.0001
Day of CABG	Day 1	11,432(34.1)	15,621(35.0)	<.0001	0 (0.0)	0 (0.0)	0.86	0 (0.0)	0 (0.0)	0.14
	Day 2	6,762(20.2)	9,387(21.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
	Day 3-5	9,552(28.5)	13,011(29.1)		3,102(64.6)	3,094(64.5)		1,798(63.3)	486(60.5)	
	Day 6+	5,771(17.2)	6,663(14.9)		1,697(35.4)	1,705(35.5)		1,041(36.7)	318(39.6)	
Low Income Status		1,211(3.6)	1,979(4.4)	<.0001	222(4.6)	214(4.5)	0.70	94(3.3)	35(4.4)	0.16
Marital Status (w/ partner)		21,008(62.7)	28,384(63.5)	0.02	3,079(64.2)	3,071(64.0)	0.86	1,628(57.3)	445(55.4)	0.31

Redo Cardiac Surgery	1,347(4.0)	744(1.7)	<.0001	90(1.9)	91(1.9)	0.94	106(3.7)	10(1.2)	0.000
Additional cardiac surgery	8,516(25.4)	8,197(18.4)	<.0001	891(18.6)	918(19.1)	0.48	650(22.9)	201(25.0)	0.21
Complex CABG surgery	21,562(64.3)	28,084(62.9)	<.0001	3,742(78.0)	3,740(77.9)	0.96	2,205(77.7)	688(85.6)	<.0001
Number of vessels									
1	6,894(20.6)	8,142(18.2)	<.0001	684(14.3)	679(14.2)	0.82	557(19.6)	192(23.9)	<.0001
2	10,741(32.1)	15,080(33.8)		1,526(31.8)	1,564(32.6)		910(32.1)	363(45.2)	
3	10,270(30.6)	13,861(31.0)		1,618(33.7)	1,581(32.9)		855(30.1)	194(24.1)	
4+	5,612(16.7)	7,599(17.0)		971(20.2)	975(20.3)		517(18.2)	55(6.8)	
Pre-existing Percutaneous coronary procedures	4,448(13.3)	5,677(12.7)	0.02	690(14.4)	678(14.1)	0.73	430(15.2)	119(14.8)	0.81
* Angina (nitrate use)	12,466(37.2)	16,733(37.5)	0.46	3,294(68.6)	3278(68.3)	0.73	1,539(54.2)	506(62.9)	<.0001
* Renal failure requiring dialysis	570(1.7)	469(1.1)	<.0001	104(2.2)	93(1.9)	0.43	57(2.0)	14(1.7)	0.63
* Heart failure (use of furosemide, digoxin, digitoxin, or dobutamine)	7,048(21.0)	7,346(16.4)	<.0001	1,738(36.2)	1,720(35.8)	0.70	1,056(37.2)	258(32.1)	0.01
* Anti-arrhythmic drug use	2,867(8.6)	4,161(9.3)	0.0002	773(16.1)	768(16.0)	0.89	344(12.1)	84(10.5)	0.19
* Cardiac arrest	234(0.7)	214(0.5)	<.0001	41(0.9)	43(0.9)	0.83	50(1.8)	8(1.0)	0.13
* Warfarin use	287(0.9)	257(0.6)	<.0001	63(1.3)	66(1.4)	0.79	69(2.4)	7(0.9)	0.01
* Fibrinolytic medications or direct thrombin inhibitors	478(1.4)	668(1.5)	0.43	116(2.4)	122(2.5)	0.69	84(3.0)	16(2.0)	0.14
* Use of clopidogrel or glycoprotein 2b/3a inhibitors	6,275(18.7)	6,884(15.4)	<.0001	1,487(31.0)	1,483(30.9)	0.93	1,105(38.9)	288(35.8)	0.11

* Use of plasma expander	2,447(7.3)	2,817(6.3)	<.0001	525(10.9)	505(10.5)	0.51	432(15.2)	163(20.3)	0.001
* Use of radiologic contrast medium	6,536(19.5)	10,785(24.1)	<.0001	1,703(35.5)	1,733(36.1)	0.52	907(32.0)	361(44.9)	<.0001
Diabetes (Dx, or antidiabetic therapy on more than 2 days)	14,565(43.5)	19,275(43.1)	0.38	2,163(45.1)	2,252(46.9)	0.07	1,236(43.5)	359(44.7)	0.57
Hypertension (Dx)	21,835(65.2)	29,369(65.7)	0.09	3,058(63.7)	3,041(63.4)	0.72	1,859(65.5)	497(61.8)	0.06
Liver disease (Dx)	474(1.4)	422(0.9)	<.0001	70(1.5)	74(1.5)	0.74	51(1.8)	13(1.6)	0.73
COPD/asthma (Dx)	7,976(23.8)	10,992(24.6)	0.01	1,358(28.3)	1,381(28.8)	0.60	768(27.1)	192(23.9)	0.07
Cancer (Dx)	3,064(9.1)	3,785(8.5)	0.0001	421(8.8)	425(8.9)	0.89	291(10.3)	51(6.3)	0.001
Old MI (Dx)	5,051(15.1)	6,278(14.1)	<.0001	693(14.4)	707(14.7)	0.69	406(14.3)	103(12.8)	0.28
Old Stroke (Dx)	1,758(5.3)	1,945(4.4)	<.0001	250(5.2)	257(5.4)	0.75	173(6.1)	24(3.0)	0.001
Endocarditis (Dx)	171(0.5)	83(0.2)	<.0001	22(0.5)	21(0.4)	0.88	17(0.6)	3(0.4)	0.44
Peripheral artery disease (Dx)	3,257(9.7)	3,840(8.6)	<.0001	492(10.3)	486(10.1)	0.84	313(11.0)	68(8.5)	0.04
Chronic kidney disease (Dx)	714(2.1)	622(1.4)	<.0001	97(2.0)	92(1.9)	0.71	61(2.2)	15(1.9)	0.62
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	124(0.4)	111(0.3)	0.002	17(0.4)	19(0.4)	0.74	11(0.4)	0(0.0)	0.08
Hosp. CABG volume 0-99	952(2.8)	973(2.2)	<.0001	0 (0.0)	0 (0.0)	0.53	0 (0.0)	0 (0.0)	0.01
100-500	13,070(39.0)	14,439(32.3)		1,283(26.7)	1,256(26.2)		1,024(36.1)	247(30.7)	
>500	19,495(58.2)	29,270(65.5)		3,516(73.3)	3,543(73.8)		1,815(63.9)	557(69.3)	

Hospital size (beds)	< 400	12,609(37.6)	16,733(37.5)	<.0001	1,548(32.3)	1,565(32.6)	0.90	797(28.1)	621(77.2)	<.0001
	400 – 649	10,208(30.5)	14,396(32.2)		1,590(33.1)	1,571(32.7)		922(32.5)	57(7.1)	
	650 +	10,700(31.9)	13,553(30.3)		1,661(34.6)	1,663(34.7)		1,120(39.5)	126(15.7)	
Region	Midwest	5,913(17.6)	8,523(19.1)	<.0001	804(16.8)	845(17.6)	0.66	487(16.8)	297(36.9)	<.0001
	Northeast	2,992(8.9)	6,743(15.1)		690(14.4)	703(14.7)		163(5.7)	0(0.0)	
	South	19,865(59.3)	23,686(53.0)		3,024(63.0)	2,973(62.0)		1,714(60.4)	456(56.7)	
	West	4,747(14.2)	5,730(12.8)		281(5.9)	278(5.8)		484(17.1)	51(6.3)	
Teaching hospital		17,014(50.8)	24,828(55.6)	<.0001	2,717(56.6)	2,711(56.5)	0.90	1,685(59.4)	415(51.6)	<.0001
Rural hospital		2,323(6.9)	3,190(7.1)	0.26	453(9.4)	459(9.6)	0.83	102(3.6)	230(28.6)	<.0001
Outcomes during entire follow-up:										
Dialysis noted only after surgery †		875(2.8)	665(1.5)	<.0001	116(2.4)	112(2.3)	0.78	70(2.6)	8(1.0)	0.01
In-hospital deaths		1,512(4.5)	1,101(2.5)	<.0001	210(4.4)	158(3.3)	0.01	128(4.5)	20(2.6)	0.01
Outcomes during the first 7 days of follow-up:										
Dialysis noted only after surgery †		627(2.0)	422(1.0)	<.0001	76(1.6)	59(1.2)	0.14	50(1.8)	5(1.0)	0.02
In-hospital deaths		631(1.9)	435(1.0)	<.0001	71(1.5)	51(1.1)	0.07	38(1.3)	7(0.9)	0.29

* These conditions were assessed during the day(s) before CABG surgery in a subpopulation of 34,997 patients who had CABG surgery on day 3 or later.

** Dx = based on recorded discharge diagnosis

† For the analysis of the renal failure outcome we excluded patients with pre-existing renal failure and chronic kidney disease (number of patients excluded from primary study cohort: **2,165**; propensity score matched cohort: **355** patients; no treatment variation cohort: **136**).

Table 2a: Relative risk of renal failure requiring dialysis and in-hospital death among 78,199 patients undergoing CABG surgery in the primary study cohort.*

Outcome	Aprotinin use – any dose N; # events (%)	Aminocaproic acid use – any dose N; # events (%)	Any dose RR, 95% CI	Any dose, multivariate adjusted RR, 95% CI	Excluding very low dose, multivariate adjusted RR, 95% CI
Renal failure requiring dialysis †	31,644; 875 (2.8)	43,054; 665 (1.5)	1.79 (1.62 – 1.98)	1.65 (1.48, 1.84)	1.57 (1.38, 1.79)
In-hospital all-cause death	33,517; 1,512 (4.5)	44,682; 1,101 (2.5)	1.83 (1.70 – 1.98)	1.64 (1.50, 1.78)	1.50 (1.36, 1.66)
Renal failure requiring dialysis within 7 days of CABG †	31,644; 627 (2.0)	43,054; 422 (1.0)	2.02 (1.79 – 2.29)	1.84 (1.61, 2.10)	1.76 (1.50, 2.06)
In-hospital all-cause death within 7 days of CABG	33,517; 631 (1.9)	44,682; 435 (1.0)	1.93 (1.71 – 2.18)	1.78 (1.56, 2.02)	1.64 (1.41, 1.91)

* RR = relative risk; CI = confidence interval.

† For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (number of patients excluded from primary study cohort: **2,165**).

Table 2b: Relative risk of renal failure requiring dialysis and in-hospital death in the data-dense cohort with predetermined exposure (N = 3,643) using assigned instrumental variable status.*

Outcome	Treated by a high-volume surgeon who always used aprotinin N; # events (%)	Treated by a high-volume surgeon who always used aminocaproic acid N; # events (%)	RR, 95% CI
Renal failure requiring dialysis †	2,729; 70 (2.6)	778; 8 (1.0)	2.58 (1.25 – 5.33)
In-hospital all-cause death	2,839; 128 (4.5)	804; 20 (2.6)	1.81 (1.14 – 2.88)
Renal failure requiring dialysis within 7 days of CABG †	2,729; 50 (1.8)	778; 5 (0.6)	2.85 (1.14 – 7.12)
In-hospital all-cause death within 7 days of CABG	2,839; 38 (1.3)	804; 7 (0.9)	1.54 (0.69 – 3.43)

* RR = relative risk; CI = confidence interval.

† For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (number of patients excluded from cohort: **136**).

Table 3: Multivariate adjusted relative risk of renal failure requiring dialysis and in-hospital death among 78,199 patients undergoing CABG surgery in the primary study cohort.

Characteristic		Renal failure requiring dialysis [‡]		In-hospital death	
		Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
Aprotinin	Very low dose	1.22	0.95, 1.58	1.32	1.08, 1.60
	Low dose	1.35	1.13, 1.61	1.36	1.18, 1.56
	High dose	1.58	1.36, 1.83	1.75	1.56, 1.97
Aminocaproic acid	Very low dose	0.79	0.67, 0.94	0.83	0.72, 0.95
	Low dose	Reference		Reference	
	High dose	0.78	0.59, 1.03	1.35	1.12, 1.64
Age		0.96	0.91, 1.01	0.94	0.90, .98
Age ²		1.00	1.00, 1.00	1.00	1.00, 1.00
Sex (male)		0.82	0.73, 0.92	0.65	0.59, 0.71
Race/ethnicity	White	Reference		Reference	
	Black	1.56	1.27, 1.92	1.14	0.96, 1.36
	Other	1.12	0.98, 1.29	1.14	1.02, 1.27
Smoking (current, past)		0.62	0.52, 0.74	0.74	0.65, 0.84
Admission Year	2003	Reference		Reference	

	2004	0.86	0.72, 0.98	0.87	0.79, 0.97
	2005	0.80	0.70, 0.91	0.78	0.70, 0.87
	2006 (Q1)	0.55	0.42, 0.72	0.76	0.64, 0.91
Emergency Admission		1.21	1.01, 1.45	1.30	1.13, 1.50
Day of CABG	Day 1	Reference		Reference	
	Day 2	0.90	0.77, 1.06	1.60	1.41, 1.81
	Day 3 - 5	0.77	0.66, 0.90	1.16	1.02, 1.31
	Day 6 +	1.06	0.90, 1.24	1.58	1.39, 1.80
Low Income Status		1.08	0.82, 1.43	1.26	1.01, 1.57
Marital Status (w/ partner)		0.92	0.82, 1.03	0.93	0.86, 1.02
Redo Cardiac Surgery		0.98	0.71, 1.34	1.80	1.48, 2.19
Additional cardiac surgery		1.72	1.49, 1.99	1.69	1.52, 1.89
Complex CABG surgery		0.99	0.80, 1.24	1.10	0.93, 1.30
Number of vessels	1	Reference		Reference	
	2	1.11	0.95, 1.29	0.94	0.84, 1.05
	3	1.15	0.99, 1.35	0.94	0.84, 1.06
	4+	1.04	0.86, 1.25	0.93	0.81, 1.07
Pre-existing Percutaneous coronary		0.87	0.72, 1.05	0.87	0.75, 1.00

procedures				
Diabetes (Dx or medication)	3.15	2.81, 3.54	1.45	1.34, 1.58
Hypertension (Dx)	0.23	0.21, 0.26	0.46	0.43, 0.50
Liver disease (Dx)	12.48	10.38, 15.00	8.86	7.50, 10.48
COPD/asthma (Dx)	1.39	1.24, 1.55	1.37	1.26, 1.50
Cancer (Dx)	0.66	0.53, 0.82	0.78	0.67, 0.90
Old MI (Dx)	0.64	0.53, 0.77	0.86	0.75, 0.98
Old Stroke (Dx)	0.76	0.57, 1.00	0.87	0.72, 1.06
Endocarditis (Dx)	1.83	1.07, 3.11	2.69	1.88, 3.87
Peripheral artery disease (Dx)	1.14	0.95, 1.35	1.28	1.12, 1.45
Chronic kidney disease (Dx) or dialysis before surgery	(excluded from analysis)		1.67	1.35, 2.04
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	1.86	1.00, 3.46	2.32	1.45, 3.72
Hosp. CABG volume 0-99	0.94	0.67, 1.32	1.47	1.17, 1.85
100-500	1.04	0.92, 1.18	1.17	1.06, 1.29
>500	Reference		Reference	
Hospital size (beds) < 400	0.84	0.71, 0.99	0.98	0.87, 1.12
400 - 649	0.86	0.74, 0.99	1.00	0.89, 1.12
650 +	Reference		Reference	

Region	Midwest	0.97	0.83, 1.13	0.82	0.73, 0.92
	Northeast	0.92	0.72, 1.09	0.65	0.56, 0.75
	South	Reference		Reference	
	West	0.92	0.77, 1.10	0.79	0.69, 0.90
Teaching hospital		1.03	0.90, 1.18	1.10	1.00, 1.22
Rural hospital		0.68	0.52, 0.82	0.80	0.67, 0.96

⊕ For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (N = **2,165**).

Table 5: Results from different multivariate analyses of 78,199 patients of the primary study cohort comparing three aprotinin dose categories with low-dose aminocaproic acid.*

Outcome	Standard logistic regression RR, 95% CI	Standard logistic regression limited to 7 days of follow up RR, 95% CI	Logistic regression with GEE-adjusted errors RR, 95% CI	Conditional logistic regression RR, 95% CI
Renal failure requiring dialysis: †				
Very low dose	1.22 (0.95 – 1.58)	1.60 (1.20 – 2.12)	1.22 (0.89 – 1.69)	1.50 (1.10 – 2.05)
Low dose	1.35 (1.13 – 1.61)	1.65 (1.34 – 2.03)	1.35 (0.99 – 1.83)	1.94 (1.53 – 2.46)
High dose	1.58 (1.36 – 1.83)	1.71 (1.42 – 2.04)	1.58 (1.15 – 2.15)	2.01 (1.64 – 2.47)
In-hospital all-cause death				
Very low dose	1.32 (1.09 – 1.61)	1.31 (0.97 – 1.78)	1.32 (1.07 – 1.62)	1.82 (1.42 – 2.34)
Low dose	1.36 (1.18 – 1.56)	1.39 (1.12 – 1.73)	1.36 (1.16 – 1.60)	1.78 (1.47 – 2.16)
High dose	1.74 (1.55 – 1.96)	1.91 (1.60 – 2.28)	1.74 (1.51 – 2.01)	2.47 (2.10 - 2.90)

* RR = relative risk; CI = confidence interval.

† For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (N = **2,165**).

Table 6: Results from multivariate logistic regression analyses for selected patient subgroups of the 78,199 patients of the primary study cohort comparing three aprotinin dose categories with low-dose aminocaproic acid.*

	Patient with Diabetes N = 33,840	Patients with complex CABG surgery N = 49,646	Patients with complex CABG surgery** N = 18,183	Patient treated by high volume surgeons N = 67,088
Outcome	RR, 95% CI	RR, 95% CI	RR, 95% CI	RR, 95% CI
Renal failure requiring dialysis: †				
Very low dose	1.24 (0.91 – 1.67)	1.30 (0.98 – 1.74)	1.35 (0.91 – 2.02)	1.17 (0.87 – 1.58)
Low dose	1.23 (0.99 – 1.53)	1.34 (1.09 – 1.64)	1.43 (1.07 – 1.92)	1.34 (1.10 – 1.62)
High dose	1.55 (1.30 – 1.86)	1.59 (1.34 – 1.89)	1.51 (1.18 – 1.92)	1.56 (1.33 – 1.83)
In-hospital all-cause death				
Very low dose	1.36 (1.05 – 1.76)	1.47 (1.18 – 1.82)	1.60 (1.18 – 2.17)	1.44 (1.15 – 1.80)
Low dose	1.25 (1.03 – 1.52)	1.49 (1.27 – 1.75)	1.64 (1.30 – 2.07)	1.38 (1.18 – 1.61)
High dose	1.63 (1.39 – 1.91)	1.78 (1.56 – 2.04)	1.81 (1.49 – 2.20)	1.78 (1.56 – 2.02)

* RR = relative risk; CI = confidence interval.

** A more stringent definition of complex: redo CABG or other cardiac surgery on the day of CABG.

† For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (number of patients excluded from diabetes cohort: **492**; complex CABG: **1,571**; complex CABG**: **631**; high-volume surgeons: **1,772**).

Table 7: Results from the propensity score matched analyses and instrumental variable analyses in the data-dense cohort.*

Outcome	Propensity score matched analysis (c=0.70) (n = 9,598) RR, 95% CI	Instrumental variable analysis (100 – 0)** (n = 9,291) RD, 95% CI	Instrumental variable analysis (90 – 10)*** (n = 25,784) RD, 95% CI
Renal failure requiring dialysis \dagger	1.04 (0.80 – 1.34)	+1.27 % (+0.01% – +2.56%)	+0.74 % (+0.12% – +1.36%)
In-hospital all-cause death	1.32 (1.08 – 1.63)	+1.59 % (+0.14% – +3.04%)	+0.60 % (+0.00% – +1.21%)
Renal failure requiring dialysis within 7 days \dagger	1.28 (0.92 – 1.81)	+1.29 % (0.00% – +2.62%)	+0.74 % (+0.33% – +1.16%)
In-hospital all-cause death within 7 days	1.39 (0.97 – 1.99)	+0.38 % (-0.27 – +1.04%)	+0.06 % (-0.29% – +0.42%)

* RR = relative risk; RD = risk difference in percent; CI = confidence interval.

** Instrument variable (100 – 0): Physicians who prescribed aprotinin to 100% or more of their patients who required antifibrinolytic therapy: IV = 1; Physicians who prescribe aminocaproic acid to 100% or more: IV = 0.

*** Instrument variable (90 – 10): Physicians who prescribed aprotinin to 90% or more of their patients who required antifibrinolytic therapy: IV = 1; Physicians who prescribe aminocaproic acid to 90% or more: IV = 0.

\dagger For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (number of patients excluded from propensity score matched cohort: **355**; IV analysis 100-0: **226**; IV analysis 90-10*: **636**).

Table 8: Newly emergent dialyses that appeared the first time on the day of CABG surgery (N = 78,199)

	Aprotinin N = 33,517	Amioproic acid N = 44,682
Dialysis on the day of CABG	454 (1.35%)	792 (1.77%)
Dialysis on the day of CABG after excluding patients with dialysis before surgery* or a discharge diagnosis of chronic kidney failure	305 (0.94%)	668 (1.53%)

* Pre-existing dialysis can only be identified in a subgroup of patients who have CABG surgery on day 2 or later.

Table 9: Characteristics of patients undergoing CABG surgery in the instrumental variable analysis.

Characteristic	Patients with predetermined exposure N = 9,291			Patients of physicians with strong treatment preferences N = 25,784		
	Treated by a 100% aprotinin preferring physician N (%)	Treated by a 100% Amino- caproic acid preferring physician N (%)	p-value from Chi ² test	Treated by a 90% aprotinin preferring physician N (%)	Treated by a 90% Amino- caproic acid preferring physician N (%)	p-value from Chi ² test
Number of patients	7,256 (78.1)	2,035 (21.9)		15,228 (59.1)	10,556 (40.9)	
Very low dose	-	-	-	-	-	-
Low dose	2,594 (27.9)	957 (10.3)	-	5,561 (21.6)	8,503 (33.0)	-
High dose	4,662 (50.2)	1,078 (11.6)	-	9,667 (37.5)	2,053 (8.0)	-
Age			0.0014			<.0001
	18 - 24	0(0.00)		0(0.00)	2(0.02)	
	25 - 34	18 (0.25)		34(0.22)	25(0.24)	
	35 - 44	172(2.37)		362(2.38)	324(3.07)	
	45 - 54	929(12.80)		1,890(12.41)	1,440(13.64)	
	55 - 64	1,936(26.68)		3,977(26.12)	2,976(28.19)	
	65 - 74	2,365(32.59)		4,977(32.68)	3,395(32.16)	
	75 +	1,836(25.30)		3,988(26.19)	2,394(22.68)	
Sex (male)	5,225(72.01)	1,398(68.70)	0.0035	10,893(71.53)	7,438(70.46)	0.0623
Race/ethnicity			<.0001			<.0001
	White	5,713(78.73)		12,149(79.78)	8,162(77.32)	
	Black	526(7.25)		1,065(6.99)	631(5.98)	
	Other	1,017(14.02)		2,014(13.23)	1,763(16.70)	

Smoking (current, past)		1461(20.14)	300(14.74)	<.0001	2,971(19.51)	1,740(16.48)	<.0001
Admission Year	2003	1,557	739	<.0001	3,209	3,226	<.0001
	2004	2,670	777		5,267	3,810	
	2005	2,556	436		5,815	2,975	
	2006 (Q1)	453	83		937	505	
Emergency Admission		3,445(47.48)	898(44.13)	0.0074	7,034(46.19)	5,585(52.91)	<.0001
Day of CABG	Day 1	2,829(38.99)	922(45.31)	<.0001	5,563(36.53)	4,220(39.98)	<.0001
	Day 2	1,383(19.06)	265(13.02)		3,009(19.76)	1,669(15.81)	
	Day 3-5	1,930(26.60)	511(25.11)		4,253(27.93)	2,990(28.33)	
	Day 6+	1,114(15.35)	337(16.56)		2,403(15.78)	1,677(15.89)	
Low Income Status		195(2.69)	91(4.47)	<.0001	443(2.91)	434(4.11)	<.0001
Marital Status (w/ partner)		4,356(60.03)	1,063(52.24)	<.0001	9,751(64.03)	6,951(65.85)	0.0027
Redo Cardiac Surgery		279(3.85)	29(1.43)	<.0001	497(3.26)	142(1.35)	<.0001
Additional cardiac surgery		1,745(24.05)	327(16.07)	<.0001	3,220(21.15)	1,896(17.96)	<.0001
Complex CABG surgery		4,459(61.45)	1,095(53.81)	<.0001	9,090(59.69)	6,582(62.35)	<.0001
Number of vessels	1	1,561(21.51)	531(26.09)	<.0001	2,973(19.52)	1,886(17.87)	<.0001
	2	2,299(31.68)	937(46.04)		4,749(31.19)	3,766(35.68)	
	3	2,145(29.56)	447(21.97)		4,657(30.58)	3,132(29.67)	
	4+	1,251(17.24)	120(5.90)		2,849(18.71)	1,772(16.79)	
DRG severity coding	Level 1	731(10.07)	353(17.35)	<.0001	1,449(9.52)	1,221(11.57)	<.0001
	Level 2	3,304(45.53)	1,099(54.00)		7,046(46.27)	5,119(48.49)	
	Level 3	2,157(29.73)	459(23.05)		4,635(30.44)	2,975(28.18)	
	Level 4	1,064(14.66)	114(14.66)		2,098(13.78)	1,241(11.76)	
Preexisting Percutaneous		1,019(14.04)	279(13.71)	0.7014	2089(13.72)	1,374(13.02)	0.1041

coronary procedures						
* Angina (nitrate use)	2,055(28.32)	651(31.99)	0.0013	5,295(34.77)	3,692(34.98)	0.7355
* Renal failure requiring dialysis	89(1.23)	22(1.08)	0.5935	199(1.31)	117(1.11)	0.1544
* Heart failure (use of furosemide, digoxin, digitoxin, or dobutamine)	1,295(17.85)	292(14.35)	0.0002	2,938(19.29)	1,651(15.64)	<.0001
* Anti-arrhythmic drug use	544(7.50)	125(6.14)	0.0367	1,348(8.85)	825(7.82)	0.0032
* Cardiac arrest	65(.90)	15(.74)	0.4935	112(.74)	54(.51)	0.0271
* Warfarin use	80(1.10)	6(.29)	0.0008	135(.89)	61(.58)	0.0050
* Fibrinolytic medications or direct thrombin inhibitors	112(1.54)	21(1.03)	0.0860	208(1.37)	144(1.36)	0.9905
* Use of clopidogrel or glycoprotein 2b/3a inhibitors	1,461(20.14)	319(15.68)	<.0001	2983(19.59)	1646(15.59)	<.0001
* Use of plasma expander	557(7.68)	175(8.60)	0.1719	1,216(7.99)	705(6.68)	<.0001
* Use of radiologic contrast medium	1,298(17.89)	485(23.83)	<.0001	2,781(18.26)	2,723(25.80)	<.0001
Diabetes (Dx, or antidiabetic therapy on more than 2 days)	3,000(41.35)	849(41.72)	0.7616	6,307(41.42)	4,408(41.76)	0.5847
Hypertension (Dx)	4,817(66.39)	1,258(61.82)	0.0001	10,227(67.16)	6,766(64.10)	<.0001
Liver disease (Dx)	89(1.23)	20(0.98)	0.3668	172(1.13)	112(1.06)	0.6044
COPD/asthma (Dx)	1,674(23.07)	476(23.39)	0.7622	3,529(23.17)	2,700(25.58)	<.0001
Cancer (Dx)	687(9.47)	123(6.04)	<.0001	1,397(9.17)	823(7.80)	0.0001
Old MI (Dx)	1,069(14.73)	247(12.14)	0.0030	2,238(14.70)	1,469(13.92)	0.0791
Old Stroke (Dx)	400(5.51)	78(3.83)	0.0024	839(5.51)	438(4.15)	<.0001
Endocarditis (Dx)	34(.47)	2(0.10)	0.0175	63(0.41)	31(.29)	0.1158

Peripheral artery disease (Dx)	683(9.41)	186(9.14)	0.7087	1,483(9.74)	851(8.06)	<.0001
Chronic kidney disease (Dx)	119(1.64)	15(0.74)	0.0025	258(1.69)	121(1.15)	0.0003
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	23(.32)	3(0.15)	0.2007	50(0.33)	23(.22)	0.1007
Hosp. CABG volume 0-99	51(.70)	11(0.54)	0.6466	51(0.33)	55(0.52)	<.0001
100-500	2,952(40.68)	817(40.15)		5,957(39.12)	3,547(33.60)	
>500	4,253(58.61)	1,207(59.31)		9,220(60.55)	6,954(65.88)	
Hospital size (beds) < 400	2,090(28.80)	1,814(89.14)	<.0001	5,873(38.57)	3,493(33.09)	<.0001
400 - 649	2,566(35.36)	119(5.85)		5,131(33.69)	2,843(26.93)	
650 +	2,600(35.83)	102(5.01)		4,224(27.74)	4,220(39.98)	
Region Midwest	1,462(20.15)	705(34.64)	<.0001	2,526(16.59)	2,137(20.24)	<.0001
Northeast	232(3.20)	0(0.00)		1,017(6.68)	1,916(18.15)	
South	3,915(53.96)	1,263(62.06)		9,280(60.94)	5,162(48.90)	
West	1,647(22.70)	67(3.29)		2,405(15.79)	1,341(12.70)	
Teaching hospital	4,069(56.08)	904(44.42)	<.0001	7,413(48.68)	6,552(62.07)	<.0001
Rural hospital	145(2.00)	483(23.73)	<.0001	831(5.46)	1,082(10.25)	<.0001

* These conditions were assessed during the day(s) before CABG surgery in a subpopulation of 34,997 patients who had CABG surgery on day 3 or later.

** Dx = based on recorded discharge diagnosis

Table 10: Hosmer-Lemeshow goodness-of-fit statistics for the logistic regression analysis of the primary study cohort (N = 78,199)

Renal failure outcome (referring to Table 3 left column):

Association of Predicted Probabilities and Observed Responses

Percent Concordant	82.2	Somers' D	0.660
Percent Discordant	16.2	Gamma	0.671
Percent Tied	1.7	Tau-a	0.038
Pairs	170193842	c	0.830

Partition for the Hosmer and Lemeshow Test

Group	Total	renal f = 1		renal f = 0	
		Observed	Expected	Observed	Expected
1	7474	14	19.75	7460	7454.25
2	7824	23	32.67	7801	7791.33
3	7799	49	42.85	7750	7756.15
4	7659	59	54.11	7600	7604.89
5	7752	73	72.28	7679	7679.72
6	7660	103	103.18	7557	7556.82
7	7681	151	168.28	7530	7512.72
8	7671	243	268.60	7428	7402.40
9	7686	439	425.68	7247	7260.32
10	7657	1128	1090.89	6529	6566.11

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-Square	DF	Pr > Chi Sq
12.1487	8	0.1447

Death outcome (referring to Table 3 right column):

Association of Predicted Probabilities and Observed Responses

Percent Concordant	77.8	Somers' D	0.573
Percent Discordant	20.5	Gamma	0.582
Percent Tied	1.7	Tau-a	0.037
Pairs	197506218	c	0.786

Partition for the Hosmer and Lemeshow Test

Group	Total	death = 1		death = 0	
		Observed	Expected	Observed	Expected
1	7922	26	34.18	7896	7887.82
2	7889	47	57.16	7842	7831.84
3	7911	75	79.02	7836	7831.98
4	7914	97	102.96	7817	7811.04
5	7819	132	130.54	7687	7688.46
6	7788	158	166.89	7630	7621.11
7	7854	226	219.65	7628	7634.35
8	7839	319	299.74	7520	7539.26
9	7822	477	450.77	7345	7371.23
10	7441	1056	1068.29	6385	6372.71

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-Square	DF	Pr > Chi Sq
8.1038	8	0.4234

Table 11: Parameter estimates of the propensity score model of the data-dense study cohort (N = 13,345)

The LOGISTIC Procedure

Model Information		
Data Set	A. DATAD_COHORT2	
Response Variable	aprot	Aprotinin IV
Number of Response Levels	2	
Number of Observations	13345	
Model	binary logistic	
Optimization Technique	Fisher's scoring	

Response Profile

Ordered Value	aprot	Total Frequency
1	1	6387
2	0	6958

Type III Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > Chi Sq
age	1	5.0906	0.0241
age2	1	9.4650	0.0021
male	1	1.6205	0.2030
racecat2	1	0.8898	0.3455
racecat3	1	0.2173	0.6411
smoking	1	2.4125	0.1204
adm2004	1	74.9940	<.0001
adm2005	1	284.6821	<.0001
adm2006	1	1.8092	0.1786
adm_cat	1	13.1786	0.0003
cabg_day2	0	.	.
cabg_day3	1	0.0303	0.8619
cabg_day4	0	.	.
income_cat	1	0.7284	0.3934
marital	1	5.4300	0.0198
recardf	1	51.9271	<.0001
adcard	1	72.1587	<.0001
complex	1	0.7929	0.3732
vessel	3	16.3420	0.0010
precor	1	0.0099	0.9208
hyper	1	0.8501	0.3565
liver	1	1.5933	0.2069
asthma	1	9.6390	0.0019
cancer	1	0.0443	0.8333
oldmi	1	13.3839	0.0003
oldstr	1	1.1570	0.2821
endo	1	5.2025	0.0226
artery	1	2.8645	0.0906
kidney	1	1.6733	0.1958
hemodis	1	0.5799	0.4464
hospvol1	0	.	.
hospvol2	0	.	.
bedcat1	1	3.9751	0.0462
bedcat2	1	155.3055	<.0001
midwest	1	77.2957	<.0001
northeast	1	36.0303	<.0001
west	1	199.1473	<.0001
teach	1	109.1270	<.0001
rural	1	10.9055	0.0010
angina	1	13.5372	0.0002
prerenal	1	13.3298	0.0003
heartdr	1	105.4943	<.0001
warfarin	1	1.7499	0.1859
cprf	1	1.6554	0.1982
icdmedf	1	0.5558	0.4560
clonid	1	44.5671	<.0001
plasma	1	1.2813	0.2577
radio	1	113.9475	<.0001
arr	1	14.6241	0.0001

NOTE: The following parameters have been set to 0, since the variables are a linear combination of other variables as shown.

```
cabg_day2 = 0
cabg_day4 = 1 * Intercept - cabg_day3
hospvol1 = Intercept
hospvol2 = 0
```

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > Chi Sq
Intercept	1	0.4445	0.5383	0.6818	0.4090
age	1	-0.0376	0.0167	5.0906	0.0241
age2	1	0.000396	0.000129	9.4650	0.0021
male	1	0.0535	0.0420	1.6205	0.2030
racecat2	1	-0.0727	0.0770	0.8898	0.3455
racecat3	1	-0.0247	0.0530	0.2173	0.6411
smoking	1	0.0773	0.0497	2.4125	0.1204
adm2004	1	0.4263	0.0492	74.9940	<.0001
adm2005	1	0.8344	0.0495	284.6821	<.0001
adm2006	1	0.1117	0.0830	1.8092	0.1786
adm_cat	1	-0.3353	0.0924	13.1786	0.0003
cabg_day2	0	0	.	.	.
cabg_day3	1	-0.00718	0.0413	0.0303	0.8619
cabg_day4	0	0	.	.	.
income_cat	1	-0.0788	0.0923	0.7284	0.3934
marital	1	-0.0944	0.0405	5.4300	0.0198
recardf	1	0.9535	0.1323	51.9271	<.0001
adcard	1	0.4894	0.0576	72.1587	<.0001
complex	1	0.0915	0.1027	0.7929	0.3732
vessel	2	-0.1826	0.0594	9.4619	0.0021
vessel	3	-0.0846	0.0595	2.0254	0.1547
vessel	4	0.00378	0.0661	0.0033	0.9543
precor	1	-0.00559	0.0563	0.0099	0.9208
hyper	1	-0.0367	0.0398	0.8501	0.3565
liver	1	0.1965	0.1556	1.5933	0.2069
asthma	1	-0.1299	0.0418	9.6390	0.0019
cancer	1	-0.0140	0.0665	0.0443	0.8333
oldmi	1	0.1990	0.0544	13.3839	0.0003
oldstr	1	0.0920	0.0855	1.1570	0.2821
endo	1	0.6244	0.2738	5.2025	0.0226
artery	1	0.1054	0.0623	2.8645	0.0906
kidney	1	0.1711	0.1323	1.6733	0.1958
hemodis	1	0.2348	0.3083	0.5799	0.4464
hospvol1	0	0	.	.	.
hospvol2	0	0	.	.	.
bedcat1	1	0.1034	0.0519	3.9751	0.0462
bedcat2	1	0.6025	0.0483	155.3055	<.0001
midwest	1	-0.4753	0.0541	77.2957	<.0001
northeast	1	-0.3508	0.0584	36.0303	<.0001
west	1	-1.1430	0.0810	199.1473	<.0001
teach	1	-0.4844	0.0464	109.1270	<.0001
rural	1	-0.2338	0.0708	10.9055	0.0010
angina	1	0.1530	0.0416	13.5372	0.0002
prerenal	1	0.4965	0.1360	13.3298	0.0003
heartdr	1	0.4315	0.0420	105.4943	<.0001
warfarin	1	0.2064	0.1560	1.7499	0.1859
cprf	1	0.2629	0.2043	1.6554	0.1982
icdmedf	1	-0.0903	0.1212	0.5558	0.4560
clopi d	1	0.2822	0.0423	44.5671	<.0001
plasma	1	0.0718	0.0635	1.2813	0.2577
radio	1	-0.4268	0.0400	113.9475	<.0001
arr	1	-0.1988	0.0520	14.6241	0.0001

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits
age	0.963	0.932 0.995
age2	1.000	1.000 1.001
male	1.055	0.972 1.146

racecat2		0.930	0.800	1.081
racecat3		0.976	0.879	1.082
smoking		1.080	0.980	1.191
adm2004		1.532	1.391	1.687
adm2005		2.303	2.091	2.538
adm2006		1.118	0.950	1.316
adm_cat		0.715	0.597	0.857
cabg_day3		0.993	0.916	1.077
income_cat		0.924	0.771	1.108
marital		0.910	0.841	0.985
recardf		2.595	2.002	3.363
adcard		1.631	1.457	1.826
complex		1.096	0.896	1.340
vessel	2 vs 1	0.833	0.742	0.936
vessel	3 vs 1	0.919	0.818	1.032
vessel	4 vs 1	1.004	0.882	1.143
precor		0.994	0.891	1.110
hyper		0.964	0.892	1.042
liver		1.217	0.897	1.651
asthma		0.878	0.809	0.953
cancer		0.986	0.866	1.123
oldmi		1.220	1.097	1.358
oldstr		1.096	0.927	1.297
endo		1.867	1.092	3.193
artery		1.111	0.983	1.255
kidney		1.187	0.916	1.538
hemodis		1.265	0.691	2.314
bedcat1		1.109	1.002	1.228
bedcat2		1.827	1.662	2.008
midwest		0.622	0.559	0.691
northeast		0.704	0.628	0.790
west		0.319	0.272	0.374
teach		0.616	0.563	0.675
rural		0.792	0.689	0.909
angina		1.165	1.074	1.264
prerenal		1.643	1.259	2.145
heartdr		1.540	1.418	1.672
warfarin		1.229	0.905	1.669
cprf		1.301	0.871	1.941
icmedf		0.914	0.721	1.159
clonid		1.326	1.221	1.441
plasma		1.074	0.949	1.217
radio		0.653	0.603	0.706
arr		0.820	0.740	0.908

Association of Predicted Probabilities and Observed Responses

Percent Concordant	69.5	Somers' D	0.392
Percent Discordant	30.2	Gamma	0.393
Percent Tied	0.3	Tau-a	0.196
Pairs	44440746	c	0.696