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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 7, 2007

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EXECUTIVE SUMMARY

We conducted a retrospective cohort study to quantify the association between agents used to reduce bleeding during cardiac surgery and renal failure as well as in-hospital death. The study compared recipients of aprotinin with recipients of aminocaproic acid among patients undergoing coronary artery bypass graft (CABG) surgery.

Using a large and geographically diverse hospital database in the United States, we identified 78,199 patients undergoing CABG surgery who received intraoperative intravenous (iv) aprotinin or aminocaproic acid on the day of surgery between January 1 2003 and March 30, 2006.

We defined two drug exposure groups and three levels of intensity of therapy, based on the use of iv aprotinin and iv aminocaproic acid on the day of the index CABG procedure. Covariates included 41 patient, doctor and hospital characteristics. Outcomes were renal failure requiring dialysis (indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration) on any day following CABG and in-hospital all-cause mortality. In analyses of renal failure, we excluded patients with pre-existing chronic kidney disease. We calculated relative risks and risk differences for the outcomes. Multivariable adjustment for the primary analysis was accomplished by logistic regression. The odds ratio (OR) derived from the logistic regression coefficient was the primary measure of association, and is an excellent approximation to the relative risk (RR).

About 43% of patients received aprotinin and 57% aminocaproic acid. Following the CABG surgery, 2,653 patients required renal dialysis and 2,613 patients died. After adjustment for 41 patient and hospital characteristics, the estimated risks were meaningfully higher for patients receiving low-dose aprotinin compared with low-dose aminocaproic acid with respect to renal failure (RR=1.36; 95% confidence interval [CI] 1.17-1.57) and death (RR=1.36; 95% CI: 1.18-1.56). The risk ratios, taken with respect to medium doses of aminocaproic acid, further increased with high aprotinin doses (RR= 1.59; 95% CI: 1.40-1.80 for renal failure and RR=1.74 for death; 1.55-1.96).

We examined the associations between aprotinin use and renal failure and death in subsets of the data chosen to isolate artifacts arising from possibly inadequate baseline patient information, doctors or hospitals with few recorded CABG procedures, or particularly at-risk patients. The increased relative risk for renal failure and death persisted after restriction of the study population to those with complex CABG surgeries, to patients treated by high-volume surgeons, and to patients having diabetes. The increased risks for renal failure and death were further confirmed (1) in a propensity score matched analysis that included 10 additional covariates only available for those who spent some time in the hospital prior to their CABG surgery; and (2) in an instrumental variable analysis that addressed possibly unmeasured patient characteristics by restricting attention to surgeons with strong preferences for either aprotinin or aminocaproic acid. Both

approaches gave results that were fully consistent with the primary analysis. In support of the instrumental variable analysis's implication that unmeasured confounders played little role in the findings, sensitivity analyses for potentially unmeasured confounding factors indicated that the requirements for association between postulated confounders and aprotinin use, renal failure and death, were extreme and ruled out any plausible unmeasured characteristic as an explanation for the findings.

The results of this analysis of the experience of patients undergoing CABG, with more than 33,000 aprotinin recipients in comparison to some 45,000 aminocaproic acid recipients, support the hypothesis that there is an elevated risk of death and acute renal failure in aprotinin recipients by comparison to similar recipients of aminocaproic acid. The findings are not readily ascribable to chance or to distortions arising from confounding factors.

1. BACKGROUND

Aprotinin (Trasylol®) is effective in reducing blood loss and preserving platelet function when administered during cardiac surgery.^{1,2} Most data on the cardiovascular and renal safety of aprotinin compared with alternative drugs for mitigating surgical bleeding such as aminocaproic acid (Amicar®) or tranexamic acid (Cyklokapron®) comes from observational studies. An international multi-center study of 4,374 patients undergoing CABG surgery found a higher occurrence of adverse cardiovascular and renal outcomes within 30 days among persons receiving aprotinin relative to aminocaproic acid or tranexamic acid.³ Longer-term follow-up of the same cohort found higher mortality among aprotinin users.⁴ A single-center study of 449 patients undergoing CABG surgery in Canada comparing aprotinin use with tranexamic acid found an increased risk of renal dysfunction.⁵ A single-center study published in 2007 found that aprotinin doubled the risk of renal dysfunction compared with no aprotinin.⁶ A recent meta-analysis of 138 randomized trials affirmed an elevated risk for renal dysfunction in aprotinin recipients, but not in aminocaproic acid recipients, compared to placebo, but identified only two trials with a total of 238 patients that provided head-to-head comparisons for the two agents with respect to renal dysfunction or death. The head-to-head comparisons did not find a difference between aprotinin and aminocaproic acid.⁷

i3 Drug Safety conducted an analysis of the relation between use of aprotinin versus aminocaproic acid or tranexamic acid and the risks of death, acute renal failure, stroke, acute heart failure and revascularization in patients undergoing CABG surgery. The preliminary report of that analysis was provided to Bayer (the manufacturer of aprotinin), Bayer's consultants and through Bayer to the FDA in September 2006. As a result of comments, queries and discussions related to the preliminary report, a revised analysis plan was developed and provided to Bayer and through Bayer to the FDA in December 2006. This report uses the revised and updated protocol. We have focused on death and renal failure, which are the most strongly supported outcomes in the data; we have eliminated the comparison with tranexamic acid, which had scant representation in the data available to us, and we have introduced new analyses to rule out unmeasured confounding as an explanation of the results.

2. METHODS

2.1 Study design

We conducted a retrospective, hospital-based cohort analysis of data drawn from the Premier Perspective Comparative Database (PCD). PCD includes approximately one-sixth of all hospitalizations in the United States, with broad geographic diversity. This analysis incorporates three years of PCD data starting April 1, 2003 for all hospitals. This starting date marked the beginning of system-wide reporting of hospital-day specific data. For some hospitals that began reporting hospital-day-specific information to the PCD earlier, cohort accrual extended back as far as January 1, 2003. Service-level information for each hospital day includes information on medications, procedures

and orders for laboratory tests.⁸ Further available are patient demographics, principal and secondary discharge diagnoses, mode of discharge including death (but not cause of death),⁹ as well as surgeon and hospital characteristics. Unique encrypted code numbers designate patients, surgeons and hospitals in the PCD by. Premier data routinely undergo quality and completeness checks including data verification, initial reconciliation, data validation, final reconciliation, clinical resource consumption quality assurance, manual data audit and warehouse audit.¹⁰ The Premier database is used for the Centers for Medicare and Medicaid Services Hospital Quality Incentive Demonstration Project that links hospital reimbursement to demonstrated quality of patient care and outcomes of care for selected clinical conditions, including CABG surgery, acute MI, and congestive heart failure.^{11,10} Premier data are currently used by the FDA and a variety of pharmaceutical manufacturers and research organizations.

Premier provided a de-identified data set for the present analysis, which was fully compliant with the 1996 Health Insurance Portability and Accountability Act.

2.3 Study populations

The patient flowchart in **Figure 1** provides an overview of the patient selection.

2.3.1 Primary study population

We identified all patients 18 years and older who underwent CABG surgery (ICD-9 36.1x) and received intravenous administration of aprotinin or aminocaproic acid on the same day during the study period. Patients receiving multiple different antifibrinolytic agents during surgery were excluded. For the analysis of renal failure, we further excluded patients with a discharge diagnosis of chronic kidney disease.

2.3.2 “Data-dense” study population

A second study population was derived by applying multiple restrictions selected to isolate patients with clearer exposure histories and fuller characterization of baseline health, patients who moreover had the surgery performed by surgeons known to have performed numerous CABG surgeries and surgeons who demonstrated a willingness to use either study drug.

This “data-dense” study cohort was derived by eliminating from the primary study cohort: (1) patients who had surgery before the third hospital day; (2) patients who received less than 2 million units aprotinin or fewer than 2 vials; (3) patients who received less than 10g of aminocaproic (as in the majority of randomized trials); (4) patients treated by surgeons who performed fewer than 50 CABG procedures during the study period; and (5) patients treated by surgeons who always used the same antifibrinolytic agent (see **Figure 1**).

The data-dense study population was further reduced to form covariate-balanced treatment groups of equal size, as described later.

2.3.3 Data-dense population with predetermined exposures

Patients who were not included in the data-dense study population solely because their surgeons either always used aprotinin or always used aminocaproic acid were used to create a data-dense population with predetermined exposures. In secondary analyses, we relaxed the requirement from absolute preference to strong preference, as evidenced by use of aprotinin or aminocaproic acid in at least 90 percent of cases.

2.3.4 Follow-up

Follow-up for renal failure started on the day following the index CABG surgery. Follow-up for in-hospital mortality started on the date of the index CABG surgery. Follow-up continued to hospital discharge. In an alternate analysis, follow-up was limited to the first seven days after the index CABG surgery.

2.4 Drug exposure

The use of iv aprotinin or iv aminocaproic acid on the day of the index CABG procedure formed the basis for three cumulative dose categories (very low, low and high), as follows:

	Very low	Low	High
Aprotinin in total Kallikrein Inhibitor Units (KIU)	1 vial <u>or</u> < 2 Mm KIU	>1 vial <u>and</u> ≥ 2 to ≤ 4 Mm KIU	> 4 Mm KIU
Aminocaproic acid in total grams (g)	1 vial <u>or</u> <10 g	>1 vial <u>and</u> ≥ 10 g to ≤ 20 g	> 4 vials <u>or</u> > 20 g

For the few uses of aprotinin or aminocaproic acid that were coded without exact dose information (“miscellaneous”) we counted the vials but not their doses.

The data-dense study cohort omitted patients with very low doses of either drug.

2.5 Outcomes

2.5.1 Renal Failure

Renal failure requiring dialysis was defined to have occurred if there were codes for hemo- or peritoneal dialysis or hemofiltration on any hospital day following CABG. In analyses for which renal failure was an outcome, we excluded patients identified as having chronic kidney disease. 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.

2.5.2 Death

In-hospital mortality was ascertained from hospital discharge mode, and included deaths on and after the day of CABG surgery.

2.6 Patient and institutional characteristics

All patient characteristics were assessed using data pertaining to time before CABG surgery. Factors recorded during surgery, including transfusions, and factors influenced by events after surgery, such as DRG severity levels, were not considered. Each of the surgery-related variables below is a factor that is usually determined prior to surgery.

Socio-demographic factors included age, sex, race, low-income status (Medicaid or indigent), marital status (living with partner), year of admission, and smoking status.

Markers of severity or worse prognosis were admission type (emergency vs. elective), day of CABG surgery after admission, redo CABG surgery, any additional surgery on the day of the index surgery, complex CABG surgery (emergency admission or redo CABG or additional surgery on the day of CABG), number of vessels involved in CABG surgery (1 through 4), percutaneous coronary procedure or thrombolysis before CABG surgery.^{12,13, 14} In an alternative analysis, we omitted emergency admission as a possible way of meeting the definition of complex CABG surgery, giving a somewhat more stringent definition.

Co-morbidities based on discharge diagnoses were included for conditions that almost certainly preceded surgery: diabetes, hypertension, liver disease, COPD/asthma, cancer, old MI, old stroke, endocarditis, peripheral artery disease, chronic kidney disease, hemostatic disorder (idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia).^{15,16,17,18,19}

Hospital and surgeon characteristics included in the analysis were teaching status (teaching vs. non-teaching), location (Midwest, Northeast, South, and West, and urban/rural), hospital size (number of beds), and hospital and surgeon CABG volume.

For patients in the data-dense population (whose CABG procedures occurred on the third day of hospitalization or later), further co-morbidity and severity markers were based on procedures and drug use before the day of surgery:^{20,21,22} angina as evidenced by nitrate use; renal failure as evidenced by dialysis; heart failure as evidenced by use of dopamine, dobutamine, digoxin, digitoxin, or furosemide; anti-arrhythmic drug use; diabetes as evidenced by antidiabetic drug use on more than 2 days; cardiac arrest as evidenced by a CPR procedure; warfarin use; use of fibrinolytic medications or direct thrombin inhibitors; use of clopidogrel or glycoprotein 2b/3a inhibitors; use of plasma expander; use of radiologic contrast medium.

2.7 Statistical analysis

Preliminary, unadjusted risk ratios for developing study outcomes during hospital stay were calculated for each study outcome, including 95% confidence intervals. Using logistic regression for the primary analysis, we estimated odds ratios adjusted for 41 patient and hospital covariates. Because the odds ratio is an excellent approximation to the risk ratio in the case of rare outcomes, the results of the logistic regression will be referred to as “relative risks” (RR) in what follows.²³ We estimated robust standard errors using generalized estimating equations (GEE) with an independence working correlation structure to explore to what extent adjusting for clustering of patients within hospitals would increase standard errors of the main effects in the regression analyses.²⁴ To explore the quality and completeness of the covariate assessment, we calculated model prediction statistics, including the c-statistic, which can range from 0.5 (chance prediction of outcome) to 1.0 (perfect prediction), separately for both drug exposure categories. We also performed a conditional logistic regression analysis conditioning on the treating surgeon and adjusting for all the above covariates.²⁵

We repeated the analyses in a number of ways: limiting to outcomes that occurred within seven days post-CABG, restricting the study population to complex CABG surgeries, limiting to patients treated by high-volume surgeons and restricting the analysis to patients having diabetes.

For patients who underwent CABG on the third hospital day or later, who had low or high doses of aprotinin or aminocaproic acid, and who were treated by surgeons with at least 50 CABG procedures in the database and no absolute preference for either study drug (i.e. for the data-dense population), we estimated the probability of receiving aprotinin as a function of patient and hospital characteristics, incorporating all measured covariates described above using logistic regression, including the 10 markers of comorbidity and severity recorded in-hospital before CABG surgery. We designated the fitted probability for each patient as his/her propensity score for aprotinin treatment.²⁶ Each aprotinin-treated patient (low and high dose combined) was then matched to the patient treated by aminocaproic acid (low and high dose combined) with the closest propensity score using a greedy matching algorithm.²⁷

Potential confounders, including history of cardiac surgery and coronary revascularizations, pre-existing heart failure, pre-existing renal insufficiency and renal failure may not be recorded in the PCD database.^{28, 37} Propensity matching captures unmeasured predictors of outcome that are correlated with the measured covariates, so the effects of these will have been at least partially controlled in the propensity analysis. Nonetheless, we took two further approaches to explore the possibility that unmeasured covariates might have distorted the primary analysis, sensitivity and instrumental variable analyses. The sensitivity analyses quantified how strongly underreported factors would have to be associated with aprotinin use and study outcomes to explain our study findings.²⁹

For the instrumental variable analysis, we compared patient outcomes between surgeons who had strong preferences for or against aprotinin, with adjustment for all measured covariates, limiting analysis to patients who, apart from surgeon preference,

would qualify for the data-dense study cohort. Within the population of patients treated by surgeons with absolute preferences, “surgeon preference” is a perfect correlate of exposure and can be translated into unbiased estimates of risk differences between aprotinin and aminocaproic acid.^{30, 31, 32, 33} In a second analysis, we classified physicians who prescribed aprotinin to 90% or more of their patients as aprotinin-preferring and we assigned the instrument the value 1. Physicians who prescribed aprotinin to 10% or fewer we assigned the instrument the value 0. We used 2-stage linear regression to calculate risk difference estimates with full covariate adjustment³⁴ and computed robust 95% confidence limits.²⁴

3. RESULTS

78,199 patients fulfilled all inclusion and exclusion criteria for the primary study cohort (**Figure 1**), and of these, 33,517 used aprotinin (43%). Patient characteristics and severity markers were balanced between the aprotinin and aminocaproic acid groups with few exceptions (**Table 1**). Aprotinin recipients had redo CABG surgeries recorded more often (4.0% vs. 1.7%) and had a higher proportion of patients simultaneously undergoing other cardiac surgeries (25.4% vs. 18.4%, mostly valve surgeries) compared to aminocaproic acid recipients. 13,345 patients qualified for the data-dense study population and of these, 9,598 were successfully matched by propensity score, producing covariate-balanced and equally sized comparison populations of recipients of aprotinin or aminocaproic acid (**Table 1**, second set of columns).

The average length of stay after the index CABG surgery was 7.6 days (standard deviation [SD] = 7.8; median = 5.0). The stay was slightly longer among aprotinin users (8.2 days; SD. = 8.6). We observed 2,653 renal failures and 2,613 deaths (**Table 1**, bottom). Unadjusted analyses showed increased relative risks associated with aprotinin use compared with aminocaproic acid for renal failure requiring dialysis (RR=1.83; 95% CI: 1.69-1.98), and all-cause in-hospital death (RR=1.83; 95% CI: 1.70-1.98, see **Table 2a**). Seven-day results were similar (**Table 2b**). In primary multivariable analyses, the risk for renal failure requiring dialysis was higher by 36% for recipients of low-dose aprotinin (RR=1.36; 95% CI: 1.17 - 1.57) and by 59% for high-dose aprotinin (RR=1.59; 95% CI: 1.40 - 1.80) compared with low-dose aminocaproic acid (**Table 3**). In-hospital all-cause mortality was increased with a similar dose-dependence (low-dose RR=1.36; 95% CI: 1.18 - 1.56; high-dose RR=1.74; 95% CI: 1.55 - 1.96).

Logistic regression model prediction of renal failure and death was high ($c=0.83$ and $c=0.79$) and similar between drug exposure groups indicating the completeness of covariates is balanced between drug exposure groups (**Table 4**). Model prediction of health outcomes did not improve further after inclusion of 10 additional covariates in the data-dense study cohort. For comparison two widely accepted CABG risk scores as well as other model fit statistics are presented.^{35,36,37}

Multivariable adjusted results for outcomes occurring within seven days post-CABG were more pronounced than in the overall analysis (**Table 5**). GEE adjustment for clustering of patients in hospitals did not change 95% confidence intervals meaningfully

and a logistic regression analysis additionally conditioning on the performing surgeon substantially increased relative risk estimates for renal failure and in-hospital death (**Table 5**). When the analysis was restricted to patients with diabetes or patients with complex CABG surgery or patients treated by high-volume surgeons the relative risk estimates did not change meaningfully (**Table 6**).

Figure 2 shows the distribution of propensity scores for the 13,345 aprotinin and aminocaproic acid users in the data-dense study cohort before matching.

The analysis of the covariate-balanced data-dense cohort that combined low and high doses of the agents confirmed the increased risk for renal failure (RR=1.39; 95% CI: 1.04 - 1.87) and in-hospital death (RR=1.32; 95% CI: 1.08-1.63, see **Table 7**).

Sensitivity analyses to explore how strong an unmeasured confounder would have to be to explain the present findings regarding death indicate that an unmeasured confounder that is found in 10 percent of patients would need to elevate the risk for death five-fold, and would also need to have a five-fold greater prevalence in aprotinin users to produce sufficient confounding to explain the low-dose RR of 1.32. Even stronger and more prevalent unmeasured confounders would be required to explain the high-dose findings (**Figure 3**).

Among the high-volume surgeons, there was substantial variation in the proportion of patients receiving aprotinin (**Figure 4**). The two definitions of the instrumental variable showed very good correlation with the actual treatment in the first stage regression. For the 100% aprotinin vs. 0% aprotinin ("100-0") instrument, $r = 1.0$. For the 90-10 instrument, $r = 0.94$. The multivariable-adjusted instrumental variable analysis indicated significantly increased risk differences (RD) for death (RD= +1.59 per 100; 95% CI: +0.14 - +3.04) and renal failure (RD=+1.19 per 100; 95% CI: 0.00 - +2.41) in the aprotinin group using the instrument based on absolute preference. Comparison of these risk differences to the crude risk differences that can be calculated from the right-hand-most columns in Table 1 shows effect estimates that are reduced through the instrumental variable analysis and the multivariable control, but in the same direction and of a similar order of magnitude as the crude results. Findings based on the weaker (90-10) instrument indicated reduced but still significant differences (**Table 7**).

4. DISCUSSION

This large, retrospective, hospital-based cohort study using administrative data found clinically meaningful increases in the risk of renal failure requiring dialysis and all-cause in-hospital death for recipients of aprotinin in comparison to recipients of aminocaproic acid during CABG surgery. The increases were largely independent of the complexity of the CABG surgery, the CABG volume of the surgeon and a diagnosis of diabetes. The strength of the association of aprotinin with renal failure compared with aminocaproic acid is somewhat lower than that reported by Mangano et al. (RR=2.44 compared with aminocaproic acid) and Karkouti et al. (RR=1.80 vs. tranexamic acid).

We also observed a significant association of aprotinin use with all-cause in-hospital death compared with aminocaproic acid, consistent with trends observed by Mangano et al. The observed dose-dependency of the present findings is consistent with earlier studies. The presence of diabetes did not increase the relative risk for renal failure, in contrast to Mangano et al.'s findings of a more adverse aprotinin effect in patients with a history of diabetes.³⁸

Studies have described preferential prescribing of aprotinin in patients undergoing redo CABG surgery and preferential prescribing of non-aprotinin antifibrinolytics in patients with renal insufficiency.^{3,39} Incomplete measurement and adjustment for the first could lead to spuriously strong associations of aprotinin use with worse health outcomes (i.e. an overestimation of effect). By contrast, incomplete measurement and adjustment could result in an underestimation of a deleterious aprotinin effect on acute renal failure.

The examples above are instances of “confounding by indication,” which occurs when a drug is preferentially used in patients who are more likely to experience an adverse outcome.⁴⁰ The various covariate analyses that we undertook were intended to address this possibility thoroughly. With multivariable confounder adjustment, we observed a diminution of the association between aprotinin and death (crude 1.83, adjusted 1.36) and renal failure (crude 1.83, adjusted 1.36), suggesting that some channeling had occurred. Progression of risk estimates toward the null with control for confounding by indication leaves open the possibility that even the adjusted estimates are somewhat biased, to the extent that relevant patient characteristics have been mismeasured or omitted. However, matching on a propensity score that included an additional 10 covariates resulted in associations that were close to the multivariable-adjusted estimates, suggesting that additional adjustment would not change the effect estimate much further.

We assessed the quality of our covariate assessment by computing the covariates' predictive ability for both study outcomes independent of antifibrinolytic drug use category. The prediction of all-cause in-hospital death and renal failure in our multivariable models is as good as or better than that of widely accepted risk prediction models for patients with CABG surgery^{35, 36} and substantially better than model prediction in other large CABG studies. Prediction was similar in both drug exposure groups, indicating that any under-ascertainment or misclassification of patient risk factors was non-differential.

A quantitative sensitivity analysis of residual confounding showed that any unmeasured confounder would have to have high prevalence and strong associations with drug choice, death and renal failure. There is no plausible candidate for such a confounder.

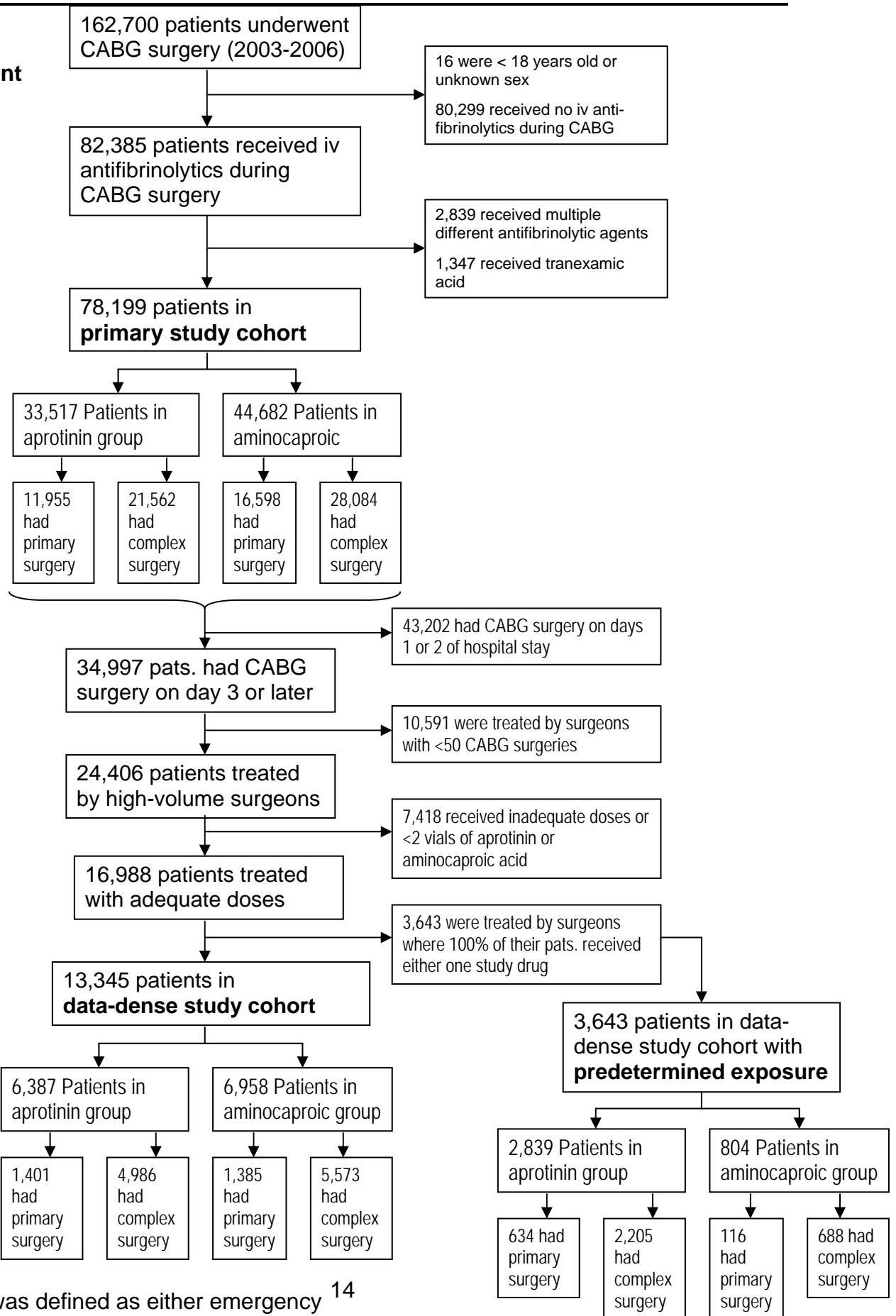
Finally, we used instrumental variable methods that incorporated surgeons' preference for aprotinin (at two different levels) as an instrument for the actual exposure. This technique has the effect of being free from the influence of unmeasured patient characteristics that in other settings might affect drug choice. The results were entirely consistent with those of the logistic regression models. The stronger instrument gave results that are more pronounced. Instrumental variable methods can produce results

similar to those of randomized trials in database studies on the safety of prescription drugs.⁴¹

Bearing in mind that nonspecific measures of study outcomes may lead to biased effect estimates, we focused on highly specific outcome markers, which produce unbiased relative effect measures (i.e. relative risk) even if sensitivity is less than 100%.⁴² We assessed renal failure requiring dialysis after the index CABG surgery using highly specific procedure codes that resulted in hospital charges. It is likely that if such charges were generated that the patient actually underwent the procedure. Coding of in-hospital death as mode of discharge is a highly specific and sensitive marker for death.

The results of this analysis of the experience of patients undergoing CABG, with more than 33,000 aprotinin recipients in comparison to some 45,000 aminocaproic acid recipients, support the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients. The findings are not readily ascribable to chance or to distortions arising from baseline differences in any of the dozens of measured patient, hospital and surgeon characteristics available in the data. The data do indicate that patients who are more at-risk for death or renal failure are somewhat more likely to receive aprotinin, and it is possible (though not in our estimation probable) that a more detailed ascertainment of covariates could lead to adjustments that explain the apparent increases in risk.

Figure 1:
Patient enrollment



* Complex surgery was defined as either emergency admission, or redo CABG, or CABG in combination with other cardiac surgery

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)	

	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:										
Renal failures requiring dialysis		1,499(4.5)	1,154(2.6)	<.0001	222(4.6)	194(4.0)	0.16	130(4.6)	23(2.9)	0.03
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:										
Renal failures requiring dialysis		1,215(3.6)	888(2.0)	<.0001	178(3.7)	137(2.9)	0.02	110(3.9)	20(2.5)	0.06
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

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	Aminocaproic acid use – any dose	RR, 95% CI
	N, # events (%)	# events (%)	
Renal failure requiring dialysis [‡]	32,803; 1,433 (4.4)	44,060; 1,052 (2.4)	1.83 (1.69 – 1.98)
In-hospital all-cause death	33,517; 1,512 (4.5)	44,682; 1,101 (2.5)	1.83 (1.70 – 1.98)
Renal failure requiring dialysis within 7 days [‡]	32,803; 1,027 (3.1)	44,060; 750 (1.7)	1.84 (1.68 – 2.02)
In-hospital all-cause death within 7 days	33,517; 631 (1.9)	44,682; 435 (1.0)	1.93 (1.71 – 2.18)

* RR = relative risk; CI = confidence interval.

[‡] For the analysis of renal failure, we excluded patients with pre-existing chronic kidney disease.

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	2,839; 130 (4.6)	804; 23 (2.9)	1.60 (1.03 – 2.48)
In-hospital all-cause death	2,839; 128 (4.5)	804; 20 (2.6)	1.81 (1.14 – 2.88)

* RR = relative risk; CI = confidence interval.

‡ For the analysis of renal failure, we excluded patients with pre-existing chronic kidney disease.

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	1.37	1.11, 1.68	1.32	1.09, 1.61
	Low dose	1.36	1.17, 1.57	1.36	1.18, 1.56
	High dose	1.59	1.40, 1.80	1.74	1.55, 1.96
Aminocaproic acid	Very low dose	0.87	0.75, 1.00	0.83	0.72, 0.95
	Low dose	Reference		Reference	
	High dose	0.85	0.68, 1.07	1.37	1.13, 1.65
Age		1.03	0.99, 1.07	0.95	0.91, 0.99
Age ²		1.00	1.00, 1.00	1.00	1.00, 1.00
Sex (male)		0.73	0.66, 0.80	0.63	0.58, 0.69
Race/ethnicity	White	Reference		Reference	
	Black	2.95	2.56, 3.39	1.18	1.00, 1.40
	Other	1.36	1.21, 1.53	1.17	1.05, 1.30
Smoking (current, past)		0.69	0.60, 0.79	0.73	0.65, 0.83
Admission Year	2003	Reference		Reference	

	2004	0.99	0.89, 1.10	0.88	0.79, 0.98
	2005	0.87	0.78, 0.98	0.8	0.72, 0.89
	2006 (Q1)	0.5	0.39, 0.65	0.79	0.66, 0.94
Emergency Admission		1.08	0.92, 1.26	1.31	1.14, 1.50
Day of CABG	Day 1	Reference		Reference	
	Day 2	1.01	0.88, 1.16	1.59	1.40, 1.80
	Day 3 - 5	1.08	0.95, 1.23	1.16	1.03, 1.32
	Day 6 +	1.93	1.69, 2.21	1.64	1.44, 1.87
Low Income Status		1.08	0.88, 1.34	1.29	1.04, 1.61
Marital Status (w/ partner)		0.90	0.82, 0.99	0.93	0.85, 1.02
Redo Cardiac Surgery		0.89	0.68, 1.18	1.82	1.50, 2.22
Additional cardiac surgery		1.43	1.26, 1.61	1.71	1.53, 1.90
Complex CABG surgery		1.06	0.88, 1.28	1.09	0.92, 1.29
Number of vessels	1	Reference		Reference	
	2	1.13	0.99, 1.28	0.95	0.85, 1.07
	3	1.20	1.05, 1.36	0.97	0.86, 1.08
	4+	1.12	0.96, 1.31	0.96	0.84, 1.10
Pre-existing Percutaneous coronary procedures		0.83	0.71, 0.97	0.87	0.76, 1.01

Hypertension (Dx)	0.15	0.13, 0.16	0.47	0.43, 0.51
Liver disease (Dx)	9.21	7.72, 10.99	9.24	7.82, 10.91
COPD/asthma (Dx)	1.16	1.06, 1.28	1.37	1.25, 1.50
Cancer (Dx)	0.71	0.60, 0.85	0.77	0.67, 0.89
Old MI (Dx)	0.74	0.64, 0.86	0.86	0.75, 0.98
Old Stroke (Dx)	1.00	0.81, 1.24	0.88	0.72, 1.07
Endocarditis (Dx)	2.91	2.01, 4.21	2.72	1.89, 3.90
Peripheral artery disease (Dx)	1.58	1.39, 1.81	1.30	1.15, 1.48
Chronic kidney disease (Dx)	(excluded from analysis)		1.79	1.46, 2.20
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	1.44	0.81, 2.56	2.36	1.47, 3.78
Hosp. CABG volume 0-99	1.24	0.96,1.61	1.49	1.19, 1.88
100-500	1.07	0.97,1.19	1.18	1.07, 1.30
>500	Reference		Reference	
Hospital size (beds) < 400	0.77	0.67, 0.88	0.97	0.86, 1.10
400 - 649	0.81	0.72, 0.92	1.00	0.89, 1.12
650 +	Reference		Reference	
Region Midwest	1.03	0.90, 1.16	0.83	0.74, 0.93

Northeast	1.08	0.94, 1.24	0.67	0.58, 0.77
South	Reference		Reference	
West	1.07	0.92, 1.24	0.79	0.69, 0.91
Teaching hospital	1.05	0.94, 1.17	1.10	0.99, 1.22
Rural hospital	0.74	0.60, 0.92	0.79	0.66, 0.95

⊕ For the analysis of renal failure, we excluded patients with pre-existing chronic kidney disease.

Table 4: Model fit measured in c-statistics of the multivariate logistic regression analyses of 78,199 patients of the primary study cohort compared with widely accepted risk prediction scores in CABG patients.*

Study and Outcome	Entire study population	Aprotinin users	Aminocaproic acid users
Primary study cohort			
Death	0.79	0.78	0.78
Renal failure	0.83	0.82	0.83
Euroscore			
Death	0.79	N/A	N/A
Renal failure	N/A		
Society of Thoracic Surgeons			
Death	0.78	N/A	N/A
Renal failure	0.76		

* The c-statistic ranges from 0.5 (= chance prediction) to 1.0 (= perfect prediction)

N/A = not applicable

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	1.37 (1.11 – 1.68)	1.65 (1.33 – 2.06)	1.37 (1.08 – 1.73)	1.78 (1.38 – 2.30)
Low dose	1.36 (1.17 – 1.57)	1.56 (1.32 – 1.84)	1.36 (1.12 – 1.63)	2.06 (1.69 – 2.51)
High dose	1.59 (1.40 – 1.80)	1.65 (1.43 – 1.90)	1.59 (1.34 – 1.87)	2.09 (1.76 – 2.48)
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 pre-existing chronic kidney disease.

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.*

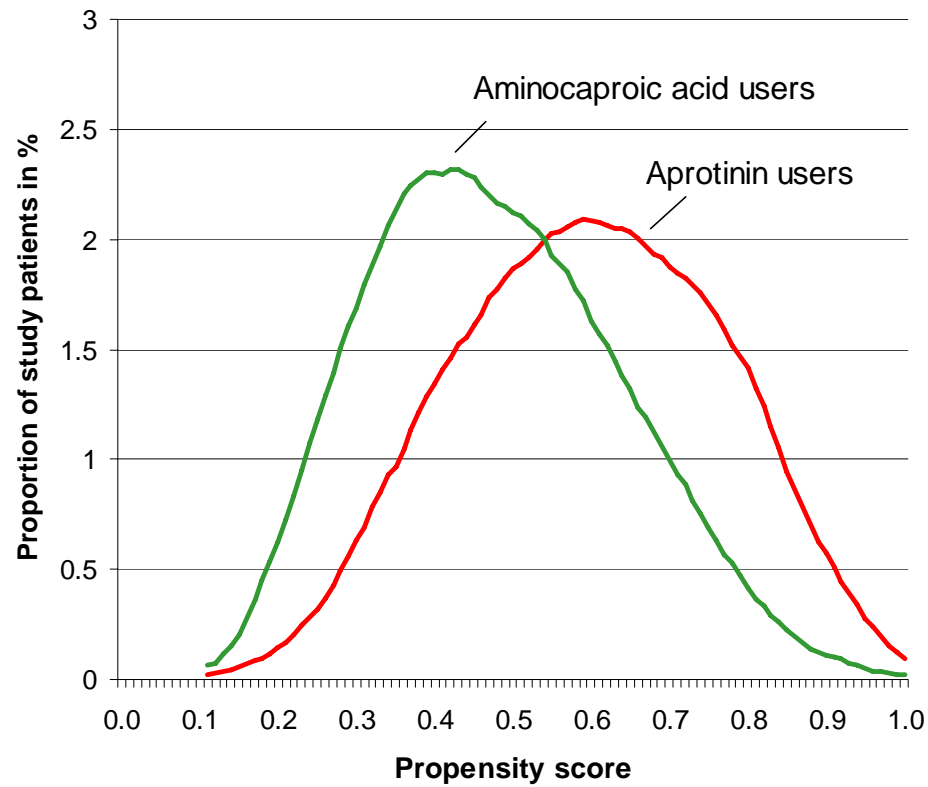
	Patient with Diabetes N = 33,840	Patients with complex CABG surgery N = 49,646	Patients with complex CABG surgery** N = 18,183	Patient treated by high volume surgeons N = 67,088
Outcome	RR, 95% CI	RR, 95% CI	RR, 95% CI	RR, 95% CI
Renal failure requiring dialysis: †				
Very low dose	1.30 (1.02 – 1.67)	1.38 (1.09 – 1.45)	1.33 (0.94 – 1.87)	1.32 (1.04 – 1.67)
Low dose	1.27 (1.06 – 1.52)	1.30 (1.09 – 1.54)	1.39 (1.07 – 1.80)	1.38 (1.17 – 1.62)
High dose	1.55 (1.33 – 1.81)	1.58 (1.37 – 1.83)	1.43 (1.16 – 1.77)	1.59 (1.39 – 1.82)
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 pre-existing chronic kidney disease.

Figure 2: Propensity score distribution for aprotinin and aminocaproic acid users in the data-dense study cohort (N = 13,345).*



* The propensity score was estimated using all patient characteristics listed in **Table 1**, including age and age².

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 = 9,538) 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	1.39 (1.04 – 1.87)	+1.19% (0.00% – +2.41%)	+0.80 % (+0.21% – +1.39%)
In-hospital all-cause death	1.32 (1.08 – 1.63)	+1.59% (+0.14% – +3.04%)	+0.60 % (+0.00% – +1.21%)

* 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 pre-existing chronic kidney disease.

Figure 3: Sensitivity analysis of the observed associations between aprotinin and renal failure and death.

Renal Failure: Assuming $P(c)=0.1$, $p(e) = 0.43$

Death: Assuming $P(c)=0.1$, $p(e) = 0.43$

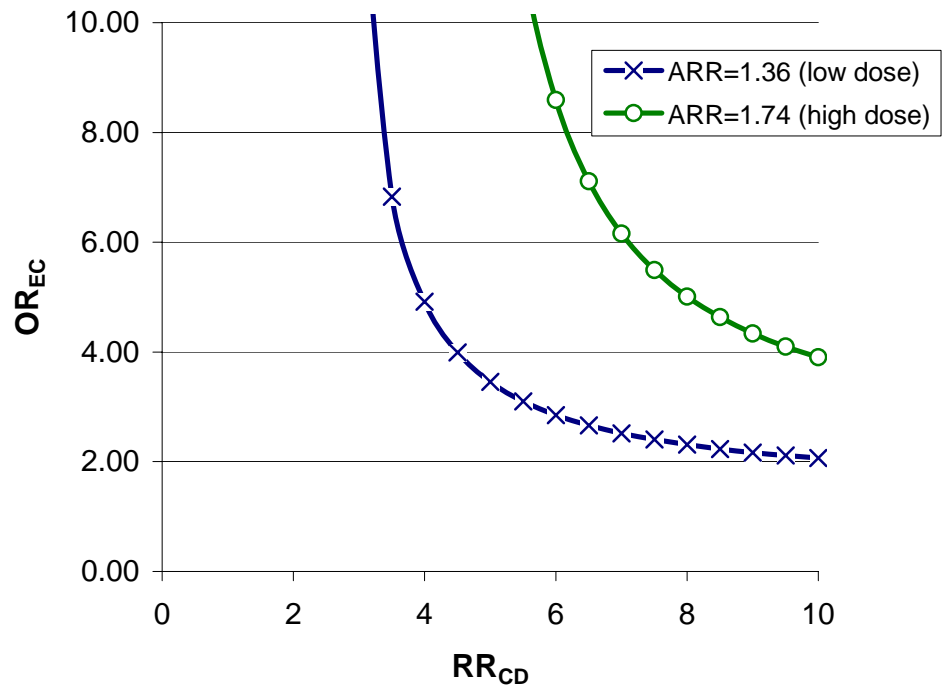
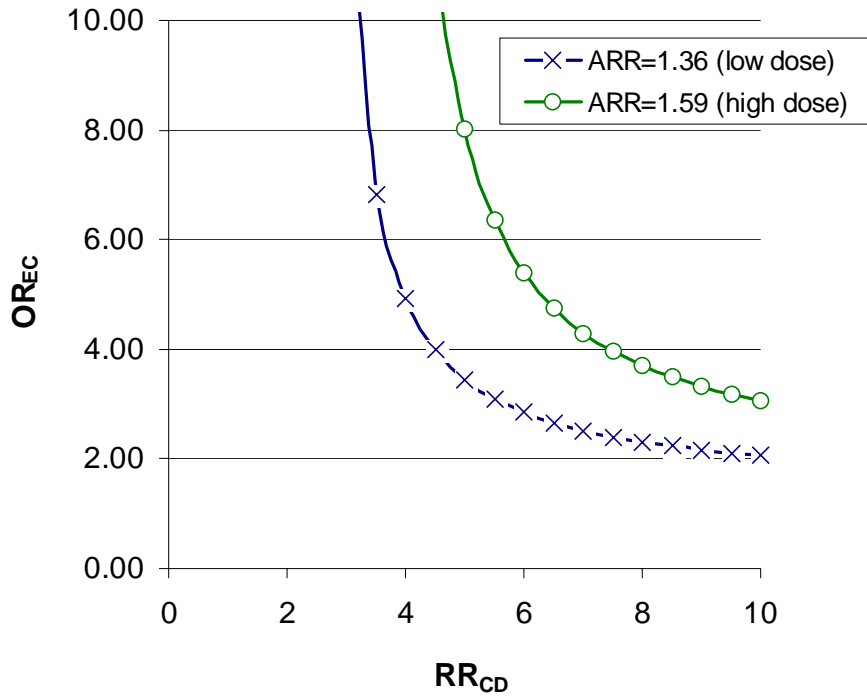
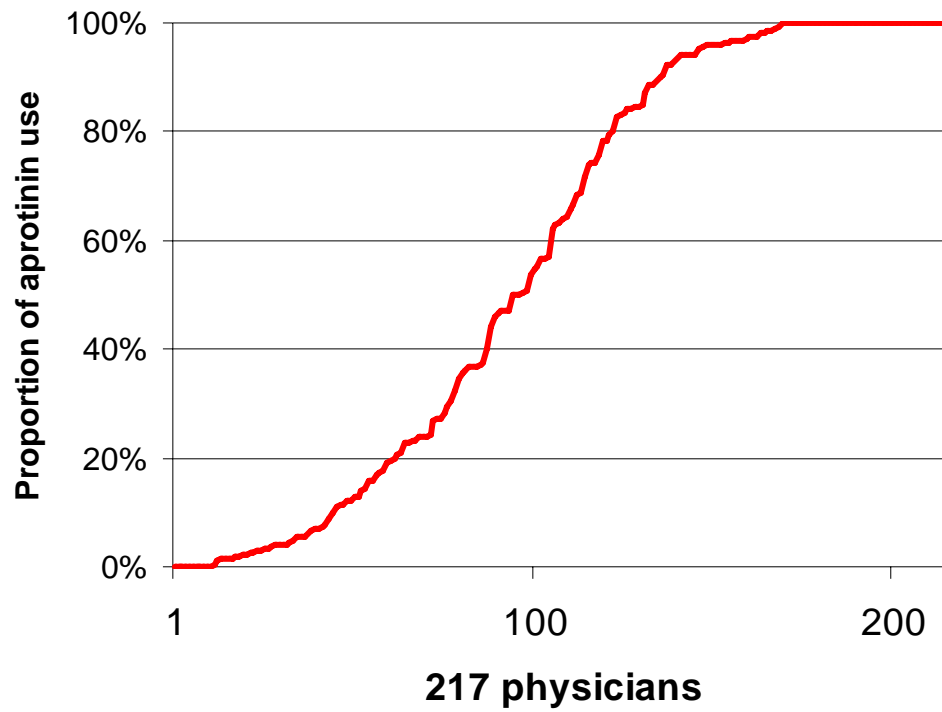


Figure 4: Distribution of aprotinin use* of 217 medium-and-high volume physicians (≥ 50 CABG).



* As proportion of antifibrinolytic use

REFERENCES

- ¹ Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004;128:442-8.
- ² Munoz JJ, Birkmeyer NJO, Birkmeyer JD, O'Conner GT, Dacey LJ. Is e-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery? A meta-analysis. *Circulation* 1999;99:81-9.
- ³ Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354:353-65.
- ⁴ Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, Hoeft A, Fontes ML, Hillel Z, Ott E, Titov T, Dietzel C, Levin J; Investigators of The Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007;297:471-9.
- ⁵ Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, Wijeyesundera DN, Fedorko L, Yau TM. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006;46:327-38.
- ⁶ Coleman CI, Rigali VT, Hammond J, Kluger J, Jeleniowski KW, White CM. Evaluating the safety implications of aprotinin use: the Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS). *J Thorac Cardiovasc Surg* 2007;133:1547-52.
- ⁷ Brown JR, Birkmeyer JO, O'Conner GT. Meta-Analysis Comparing the Effectiveness and Adverse Outcomes of Antifibrinolytic Agents in Cardiac Surgery. *Circulation* 2007;115;2801-13, Table 2.
- ⁸ Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;353:349-61.
- ⁹ Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004;291:2092-9.
- ¹⁰ Conlyn T. Premier Perspective Comparative Database. Personal Communication. 2005
- ¹¹ Lindenauer PK, Remus D, Roman S, Rothberg MB, Benjamin EM, Ma A, Bratzler DW. Public reporting and pay for performance in hospital quality improvement. *N Engl J Med* 2007;356:486-96.

-
- ¹² Jamieson WR, et al. Beneficial effect of both tranexamic acid and aprotinin on blood loss reduction in reoperative valve replacement surgery. *Circulation* 1997;96(p Suppl):II-96-100.
 - ¹³ Shroyer ALW, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, Ferguson TB, Grover FL, Edwards FH. The Society of Thoracic Surgeons: 30-Day Operative Mortality and Morbidity Risk Models. *Ann Thorac Surg* 2003;75:1856-65.
 - ¹⁴ Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999;15:816-22.
 - ¹⁵ Gunawan B, Runyon B. The efficacy and safety of epsilon-aminocaproic acid treatment in patients with cirrhosis and hyperfibrinolysis. *Aliment Pharmacol Ther* 2006;23:115-20.
 - ¹⁶ Kakaiya R. Cardiopulmonary bypass surgery in ITP patients: Outcomes. The institute for transfusion medicine. <http://www.itxm.org/TMU2004/Issue2004-2.htm>.
 - ¹⁷ Villar A, Jimenez-Yuste V, Quintana M, Hernandez-Navarro F. The use of haemostatic drugs in haemophilia: desmopressin and antifibrinolytic agents. *Haemophilia* 2002;8:189-93.
 - ¹⁸ Spanier TB, Chen JM, Mancini DM, Smith CR, Edwards NM. Cardiac transplantation in a patient with protein S deficiency. (Case Report) *Ann Thorac Surg* 1999;68:1078-80.
 - ¹⁹ Sievert A, McCall M, Blackwell M, Bradley S. Use of aprotinin during cardiopulmonary bypass in a patient with protein C deficiency (Case Report). *J Extra Corpor Technol* 2003;35:39-43.
 - ²⁰ Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet* 2004;43:963-81.
 - ²¹ Van der Linden J, Lindvall G, Sartipy U. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: a double-blind, placebo-controlled, randomized clinical trial. *Circulation* 2005;112(9 Suppl):I276-80.
 - ²² Schmer RG, Stammers AH, Ahlgren RL, Ellis TA, Gao C, Nutter BT, Holcomb HB, Hock LM. The effects of aprotinin on platelet function in blood exposed to eptifibatid: an in vitro analysis. *J Extra Corpor Technol* 2003; 35:304-11.
 - ²³ Rothman K, Greenland S. *Modern Epidemiology*, 2nd ed. Lippincott Williams & Wilkins, Philadelphia, PA, 1998.

- ²⁴ Liang K-Y, Zeger SL: Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
- ²⁵ DeLong ER, Coombs LR, Ferguson TB, Peterson ED. The evaluation of treatment when center-specific selection criteria vary with respect to patient risk. *Biometrics* 2005;61:942-9.
- ²⁶ Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
- ²⁷ Seeger JD, Williams P, Walker AM. An application of propensity score matching using claims data. *Pharmacoepidemiol Drug Saf.* 2005;14:465-76.
- ²⁸ Wijeyesundra DN, Karkouti K, Beattie WS, Rao V, Ivanov J. Improving identification of patients at risk of postoperative renal failure after cardiac surgery. *Anesthesiology* 2006;104:65-72.
- ²⁹ Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Safety* 2006;15:291-303.
- ³⁰ Angrist JD, Imbens GW, Rubin DB: Identification of causal effects using instrumental variables. *J Am Stat Soc* 1996;91:444-55.
- ³¹ Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects in claims databases using physician-specific prescribing preferences as an instrumental variable. *Epidemiology*, 2006;17:268-75.
- ³² Hernan MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology* 2006;17:360-72.
- ³³ Cole JA, Norman H, Weatherby LB, Walker AM. Drug copayment and adherence in chronic heart failure: effect on cost and outcomes. *Pharmacotherapy* 2006;26:1157-64.
- ³⁴ Greene WH. *Econometric analysis*. 5th ed. Upper Saddle River, N.J.: Prentice Hall; 2003.
- ³⁵ Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999;15:816-22.
- ³⁶ Shroyer ALW, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, Ferguson TB, Grover FL, Edwards FH. The Society of Thoracic Surgeons: 30-Day Operative Mortality and Morbidity Risk Models. *Ann Thorac Surg* 2003; 75: 1856-65.
- ³⁷ Peterson ED, DeLong ER, Muhlbaier LH, Rosen AB, Buell HE, Kiefe CI, Kresowik TF. Challenges in comparing risk-adjusted bypass surgery mortality results. *J Am Coll Cardiol* 2000;36:2174-84.

- ³⁸ Mangano DT. Author's reply: Aprotinin in cardiac surgery. *N Engl J Med* 2006;354:1957.
- ³⁹ Winterstein A, Gerhard T, Beaver TM. Safety of aprotinin in cardiac surgery. Poster presented at the annual meeting of the International Society of Pharmacoepidemiology, Lisbon, 2006.
- ⁴⁰ Walker AM. Confounding by indication. *Epidemiology* 1996;7:335-336.
- ⁴¹ Schneeweiss S, Solomon DH, Wang PS, Brookhart MA. Simultaneous assessment of short-term gastrointestinal benefits and cardiovascular risks of selective COX-2 inhibitors and non-selective NSAIDs: an instrumental variable analysis. *Arthritis Rheum*, 2006 in press.
- ⁴² Kelsey JL, Whittemore AS, Evans AS, Thompson WD: *Methods in observational epidemiology*, 2nd ed. Oxford University Press, New York, NY, 1996:341-390.