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Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

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ABSTRACT

BACKGROUND

Aprotinin (Trasylol) is used to mitigate bleeding during coronary-artery bypass grafting (CABG). Accumulating evidence suggests that this practice increases mortality.

METHODS

Using electronic administrative records of the Premier Perspective Comparative Database, we studied hospitalized patients with operating-room charges for the use of aprotinin (33,517 patients) or aminocaproic acid (44,682 patients) on the day CABG was performed. We tabulated the numbers of patients with a hospital-discharge status of death and performed three types of analyses: a multivariable logistic-regression analysis (primary analysis); propensity-score matching in the highly selected sub-cohort of patients who received full amounts of the study drug, who underwent CABG by surgeons who performed 50 or more CABG surgeries during the study period, and for whom information on 10 additional covariates was available because the surgery occurred on hospital day 3 or later; and an instrumental-variable analysis of data from patients whose surgeons showed a strong preference for one of the two study drugs.

RESULTS

In all, 1512 of the 33,517 aprotinin recipients (4.5%) and 1101 of the 44,682 aminocaproic acid recipients (2.5%) died. After adjustment for 41 characteristics of patients and hospitals, the estimated risk of death was 64% higher in the aprotinin group than in the aminocaproic acid group (relative risk, 1.64; 95% confidence interval [CI], 1.50 to 1.78). In the first 7 days after surgery, the adjusted relative risk of in-hospital death in the aprotinin group was 1.78 (95% CI, 1.56 to 2.02). The relative risk in a propensity-score-matched analysis was 1.32 (95% CI, 1.08 to 1.63). In the instrumental-variable analysis, the use of aprotinin was found to be associated with an excess risk of death of 1.59 per 100 patients (95% CI, 0.14 to 3.04). Postoperative revascularization and dialysis were more frequent among recipients of aprotinin than among recipients of aminocaproic acid.

CONCLUSIONS

Patients who received aprotinin alone on the day of CABG surgery had a higher mortality than patients who received aminocaproic acid alone. Characteristics of neither the patients nor the surgeons explain the difference, which persisted through several approaches to control confounding.

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THE ADMINISTRATION OF APROTININ (Trasylol, Bayer HealthCare) during cardiac surgery reduces blood loss and preserves platelet function.^{1,2} A recent international study of over 4000 patients undergoing coronary-artery bypass grafting (CABG) showed a 59% increase in the risk of in-hospital death (relative risk, 1.59; 95% confidence interval [CI], 0.76 to 3.34) in aprotinin recipients as compared with nonrecipients³ and a higher 5-year mortality among aprotinin recipients (relative risk, 1.48; 95% CI, 1.13 to 1.93).⁴ A meta-analysis of trials and a single-center observational study showed less worrisome results, though both lacked the statistical power of the earlier studies.^{5,6} Most recently, the data and safety monitoring board of a large randomized trial halted the recruitment of patients into the aprotinin group because of an elevated risk of death.⁷ The manufacturer has temporarily suspended the worldwide marketing of aprotinin, but it “believes that the totality of the available data continue to support a favorable risk-benefit profile for Trasylol when used according to labeling.”⁸

At the request of the manufacturer, we conducted a retrospective analysis of a large hospital inpatient database study in the United States to examine the association between aprotinin use and the risk of serious in-hospital events and to compare it with that for other antifibrinolytic agents. In this article, we focus on the outcome of death.

METHODS

The original study plan defined a single primary analysis. We developed several secondary analyses to assess the potential for bias.

DATA

The study cohort was drawn from the Premier Perspective Comparative Database, a repository of hospital administrative data that includes approximately one sixth of all hospitalizations in the United States. Premier provides data services to hospitals that include tabulation and benchmarking against the performance of other institutions. Service-level data that are recorded include charges for medications, procedures, and laboratory tests; characteristics of surgeons and hospitals are also available.⁹ The UB92 discharge form provides data on demographic characteristics, discharge diagnoses, and discharge status (including death, but not its cause).¹⁰ Premier data undergo

verification, reconciliation, validation, checks that the use of supplies and other hospital resources was within an acceptable range, and manual and data warehouse audits (Craver C: personal communication). Premier does not verify the submitted data against the original medical records. The Premier database is used in the Centers for Medicare and Medicaid Services Hospital Quality Incentive Demonstration, which links reimbursement of hospitals to the quality of patient care and outcomes of care for selected procedures or conditions, including CABG, acute myocardial infarction, and congestive heart failure.¹¹ The Food and Drug Administration (FDA) and a variety of pharmaceutical manufacturers and research organizations also use Premier data.

The full study period began on April 1, 2003, when all hospitals in the deidentified Premier data set were reporting services separately for each hospital day; some hospitals began reporting as early as January 1, 2003, and have been included from their start dates. The study period ended on March 31, 2006. The authors designed the study, including an a priori power calculation; obtained and analyzed the data; wrote all versions of the manuscript; and vouch for the accuracy of the analysis. The publication of findings was permitted, but not supported, under the original research agreement with the sponsor. This analysis was carried out using fully deidentified data, according to the 1996 Health Insurance Portability and Accountability Act.

PATIENTS

We selected inpatients 18 years of age or older whose hospital records contained a code for CABG (code 36.1, or any subcode thereof, in the *International Classification of Diseases, 9th Revision*) and a charge for the use of intravenous aprotinin or aminocaproic acid on the day of the surgery. We excluded patients who received multiple antifibrinolytic agents on the day of surgery. This was the primary study cohort (Fig. 1).

We also identified a highly selected subcohort, which was restricted to patients who underwent surgery on hospital day 3 or later (to provide more presurgery baseline information); patients treated by surgeons with records of at least 50 CABG procedures in the Perspective Comparative Database during the study period; patients for whom the charges were for at least 2 million kallikrein inhibitor units (KIU), or two vials, of aprotinin or at least 10 g, or two vials, of amino-

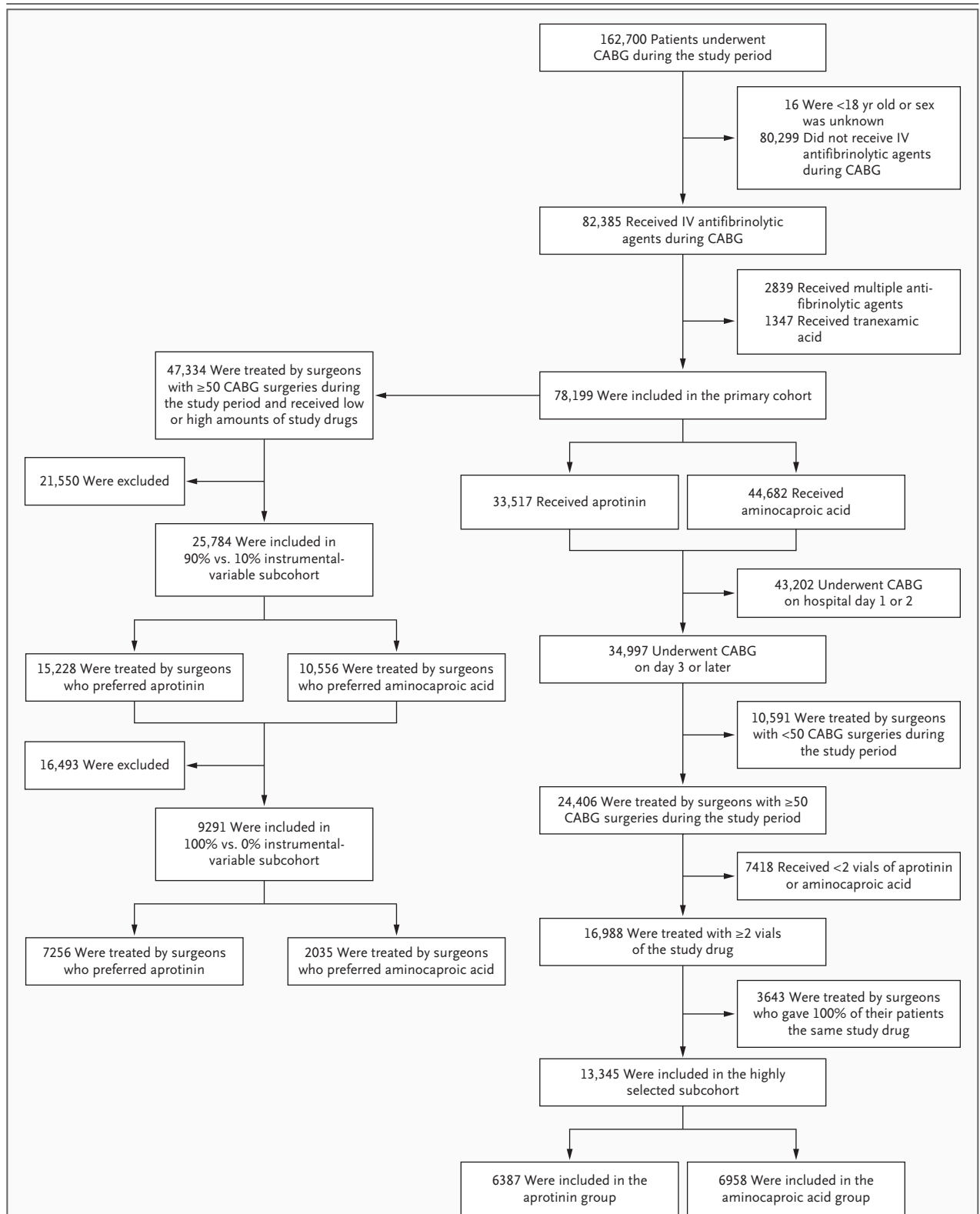


Figure 1. Enrollment of Study Patients and Distribution of Study Cohorts.

CABG denotes coronary-artery bypass surgery, and IV intravenous.

caproic acid; and patients treated by surgeons who did not always use the same antifibrinolytic agent (Fig. 1).

CLASSIFICATION OF DRUG EXPOSURE AND STUDY OUTCOME

The degree of drug exposure was classified as very low, low, or high, according to the amount of intravenous drug for which there was a charge on the day of surgery. Very low exposure was defined as the receipt of one vial, or less than 2 million KIU, of aprotinin or one vial, or less than 10 g, of aminocaproic acid. Low exposure was defined as the receipt of more than one vial, or 2 million to 4 million KIU, of aprotinin or more than one vial, or 10 g to 20 g, of aminocaproic acid. High exposure was defined as the receipt of more than 4 million KIU of aprotinin or more than 20 g of aminocaproic acid. Since the body weights of patients were not available, we could not conduct a dose–response analysis.

Follow-up began on the day of surgery. The study outcome was a discharge status of death, according to the routinely submitted UB92 hospital claims form.

CHARACTERISTICS OF THE STUDY PATIENTS AND HOSPITALS

Four types of characteristics were extracted from the Perspective Comparative Database records. The sociodemographic factors studied were age, sex, race, income status (with low-income status defined as receipt of Medicaid or classification as indigent), whether or not patients were living with a domestic partner, smoking status, and year of admission. The markers of prognosis were the type of admission (emergency vs. elective); the day of hospitalization on which CABG was performed; the number of vessels involved in CABG; the presence or absence of repeat CABG, any additional surgery on the day of the index surgery, and percutaneous coronary procedure or thrombolysis before CABG surgery; and complex or non-complex CABG.^{12–14} Complex CABG surgery was defined as emergency admission, repeat CABG, or additional cardiac surgery on the day of CABG.

Information on two types of coexisting conditions was considered. Chronic conditions noted in discharge diagnoses included diabetes, hypertension, liver disease, chronic obstructive pulmonary disease or asthma, cancer, previous myocardial infarction, previous stroke, endocarditis,

peripheral-artery disease, chronic kidney disease, and hemostatic disorders (idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia).^{15–19} Coexisting conditions or markers of disease severity inferred from procedures and drug use before surgery were also considered. These included angina, renal failure, heart failure, arrhythmia, diabetes, cardiac arrest, and use of warfarin, fibrinolytic medications or direct thrombin inhibitors, clopidogrel or glycoprotein IIb/IIIa inhibitors, plasma expanders, or radiologic contrast medium.^{20–22} In the absence of a recorded diagnosis, the value of this covariate was set at 0.

Finally, we studied characteristics of hospitals and surgeons. These consisted of hospital teaching status (teaching or nonteaching hospital), hospital region (Midwest, Northeast, South, or West), hospital location (urban or rural), hospital size (number of beds), and the number of CABG procedures performed during the study period at each hospital and by each surgeon.

STATISTICAL ANALYSIS

We examined the risk of death during the entire hospitalization period and also within the first 7 days after CABG.

Primary Study Cohort

We calculated crude risks and risk ratios and the associated 95% confidence intervals, without correcting for multiple analyses. Using a logistic-regression analysis, we estimated the odds ratios adjusted for all 41 covariates for patients and hospitals, without further selection of variables. We used generalized estimating equations to account for clustering within a hospital.²³ Because the odds ratio is an excellent approximation of the risk ratio in the case of rare outcomes, the results of the logistic-regression analysis are referred to as relative risks.²⁴ To explore the utility of the covariates for the prediction of mortality, we calculated model-prediction c statistics separately for each drug group.²⁵ We performed a conditional logistic-regression analysis with matching on the basis of the hospital.²⁶ We repeated the analyses for mortality within 7 days after CABG, and examined the experiences of specific subcohorts: patients who underwent complex surgeries, patients who were treated by surgeons who had conducted 50 or more CABG surgeries during the study period, and patients with diabetes.

We performed sensitivity analyses to quantify the size of the association between an unmeasured confounding variable and aprotinin use or death that would be required to fully explain our study findings. We gathered data on additional risk factors not observed in the main study from the medical records of 98 study patients who underwent CABG in a single, urban teaching hospital of medium size (400 to 649 beds) at which a moderate number of CABG surgeries (100 to 500) were performed during the study period. This information was used to correct the relative-risk estimates for selected unobserved confounders (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).²⁷

Highly Selected Subcohort

We calculated the propensity for treatment with aprotinin on the basis of the 41 covariates used in the logistic-regression analysis, as well as 10 markers of coexisting conditions and disease severity measured before CABG surgery.²⁸ We matched each patient in the aprotinin group to the patient in the aminocaproic acid group with the closest propensity score, using a standard greedy-matching algorithm after excluding patients who received very low amounts of either antifibrinolytic agent.²⁹

Instrumental-Variable Subcohorts

When surgeons always or nearly always use one of the two antifibrinolytic agents, the choice is evidently independent of characteristics of the patient, and it is possible to use the surgeon's preferred agent as a substitute for the actual exposure (i.e., as an "instrumental variable") in analyses.^{30,31} We examined 47,334 patients who received low or high amounts of aprotinin or aminocaproic acid and who were treated by surgeons who performed 50 or more CABG surgeries during the study period (Fig. 1). We classified surgeons who administered aprotinin to 90% or more of their patients as surgeons who preferred aprotinin and those who administered aprotinin to 10% or fewer of their patients as those who did not prefer the drug. Using this preference or lack thereof as an instrumental variable, we computed differences in the risk of the primary outcome between the aprotinin group and the aminocaproic acid group, using a two-stage linear regression analysis that also adjusted for all 41 measured covariates.³² We also ran the analysis using

a stricter definition of surgeons' preference (administration of aprotinin to 100% vs. 0% of patients).

RESULTS

PRIMARY STUDY COHORT

A total of 78,199 patients were in the primary study cohort (Fig. 1); 33,517 (42.9%) were given aprotinin. Characteristics of patients and markers of the severity of their disease were balanced in the aprotinin group and in the aminocaproic acid group, with instructive exceptions (Table 1). In particular, repeat CABG surgeries were recorded more often for aprotinin recipients than for aminocaproic acid recipients (4.0% vs. 1.7%), as were additional cardiac procedures (25.4% vs. 18.4%), mostly valve surgeries.

The average follow-up period was 7.6 days in the aprotinin group and 8.2 days in the aminocaproic acid group. For the 7-day analysis, the average follow-up period was nearly identical in the two groups (4.8 days and 5.0 days, respectively). The hospital-discharge status was death in 2613 patients, within the first 7 days after CABG for 1066 of them (Table 2).

In unadjusted analyses, in-hospital death occurred in 4.5% of patients who received aprotinin, as compared with 2.5% of patients who received aminocaproic acid; thus, the risk was 83% higher with aprotinin than aminocaproic acid (relative risk, 1.83; 95% CI, 1.70 to 1.98) (Table 2). The relative risks based on the 7-day results were similar. In multivariate analyses, the overall risk of death was increased by 64% in the aprotinin group (relative risk as compared with the aminocaproic acid group, 1.64; 95% CI, 1.50 to 1.78), and the 7-day mortality was increased by 78% (relative risk, 1.78; 95% CI, 1.56 to 2.02). Increased risk in the patients who received aprotinin, as compared with those who received aminocaproic acid, persisted in analyses stratified according to the amount of aprotinin administered (Table 3).

The relative risks of in-hospital death were similar among patients seen by surgeons who performed 50 or more CABG surgeries during the study period and among patients with diabetes (Table A2 in the Supplementary Appendix). Adjustment with the use of generalized estimating equations for clustering according to the hospital yielded nearly identical results; a conditional logistic-regression analysis with matching on

Table 1. Baseline Characteristics of Study Patients Undergoing Coronary-Artery Bypass Grafting (CABG), According to Cohort.

Characteristic	Primary Cohort		Highly Selected Subcohort		Instrumental-Variable Subcohort (90% vs. 10%)*	
	Aprotinin (N=33,517)	Aminocaproic Acid (N=44,682)	Aprotinin (N=4799)	Aminocaproic Acid (N=4799)	Aprotinin (N=15,228)	Aminocaproic Acid (N=10,556)
	<i>percent of patients</i>					
Age						
18–24 yr	0	0	0	0	0	0
25–34 yr	0.2	0.2	0.2	0.2	0.2	0.2
35–44 yr	2.4	3.0	2.7	2.5	2.4	3.1
45–54 yr	12.4	13.9	12.9	13.1	12.4	13.6
55–64 yr	25.9	27.9	26.3	25.8	26.1	28.2
65–74 yr	32.4	32.1	31.3	31.6	32.7	32.2
≥75 yr	26.7	23.0	26.6	26.8	26.2	22.7
Male sex						
	70.5	71.4	68.1	67.7	71.5	70.5
Race or ethnic group†						
White	79.0	74.0	77.3	77.9	79.8	77.3
Black	6.3	5.0	7.0	6.5	7.0	6.0
Other	14.7	21.0	15.8	15.6	13.2	16.7
Past or current smoker						
	17.6	18.7	17.4	17.9	19.5	16.5
Low-income status‡						
	3.6	4.4	4.6	4.5	2.9	4.1
Living with domestic partner						
	62.7	63.5	64.2	64.0	64.0	65.9
Previous percutaneous coronary procedure						
	13.3	12.7	14.4	14.1	13.7	13.0
Index CABG						
Year of admission						
2003	21.3	34.5	23.8	24.0	21.1	30.6
2004	32.4	32.4	35.0	34.9	34.6	36.1
2005	39.4	25.9	34.7	35.0	38.2	28.2
2006 (first quarter only)	6.9	7.3	6.5	6.1	6.1	4.8
Emergency admission						
	49.4	53.1	72.5	72.5	46.2	52.9
Hospital day of CABG						
1	34.1	35.0	0	0	36.5	40.0
2	20.2	21.0	0	0	19.8	15.8
3, 4, or 5	28.5	29.1	64.6	64.5	27.9	28.3
≥6	17.2	14.9	35.4	35.5	15.8	15.9
Repeat CABG						
	4.0	1.7	1.9	1.9	3.3	1.4
Additional cardiac surgery						
	25.4	18.4	18.6	19.1	21.15	18.0
Complex CABG surgery						
	64.3	62.9	78.0	77.9	59.7	62.4
Number of vessels						
1	20.6	18.2	14.3	14.2	19.5	17.9
2	32.1	33.8	31.8	32.6	31.2	35.7
3	30.6	31.0	33.7	32.9	30.6	29.7
≥4	16.7	17.0	20.2	20.3	18.7	16.8

Table 1. (Continued.)						
Characteristic	Primary Cohort		Highly Selected Subcohort		Instrumental-Variable Subcohort (90% vs. 10%)*	
	Aprotinin (N=33,517)	Aminocaproic Acid (N=44,682)	Aprotinin (N=4799)	Aminocaproic Acid (N=4799)	Aprotinin (N=15,228)	Aminocaproic Acid (N=10,556)
<i>percent of patients</i>						
Inpatient use of drugs or services before CABG‡						
Nitrates	37.2	37.5	68.6	68.3	34.8	35.0
Dialysis	1.7	1.1	2.2	1.9	1.3	1.1
Furosemide, digoxin, digitoxin, or dobutamine	21.0	16.4	36.2	35.8	19.3	15.6
Antiarrhythmic agent	8.6	9.3	16.1	16.0	8.85	7.8
Cardiac resuscitation	0.7	0.5	0.9	0.9	0.7	0.5
Warfarin	0.9	0.6	1.3	1.4	0.9	0.6
Fibrinolytic agent or direct thrombin inhibitor	1.4	1.5	2.4	2.5	1.4	1.4
Clopidogrel or glycoprotein IIb/IIIa inhibitor	18.7	15.4	31.0	30.9	19.6	15.6
Plasma expander	7.3	6.3	10.9	10.5	8.0	6.7
Antidiabetic therapy for >2 days	19.5	24.1	35.5	36.1	18.3	25.8
Discharge diagnoses						
Diabetes recorded on discharge or antidiabetic therapy for >2 days	43.5	43.1	45.1	46.9	41.4	41.8
Hypertension	65.2	65.7	63.7	63.4	67.2	64.1
Liver disease	1.4	0.9	1.5	1.5	1.1	1.1
Chronic obstructive pulmonary disease or asthma	23.8	24.6	28.3	28.8	23.2	25.6
Cancer	9.1	8.5	8.8	8.9	9.2	7.8
Previous myocardial infarction	15.1	14.1	14.4	14.7	14.7	13.9
Previous stroke	5.3	4.4	5.2	5.4	5.5	4.2
Endocarditis	0.5	0.2	0.5	0.4	0.4	0.3
Peripheral-artery disease	9.7	8.6	10.3	10.1	9.7	8.1
Chronic kidney disease	2.1	1.4	2.0	1.9	1.7	1.2
Hemostatic disorder	0.4	0.3	0.4	0.4	0.3	0.2
Amount of study drug administered						
Very low	11.2	43.0	—	—	—	—
Low	30.3	44.3	32.0	83.0	36.5	80.6
High	58.6	12.7	68.0	17.0	63.5	19.4
Hospital						
No. of CABG surgeries						
0–99	2.8	2.2	0	0	0.3	0.5
100–500	39.0	32.3	26.7	26.2	39.1	33.6
>500	58.2	65.5	73.3	73.8	60.6	65.9
No. of beds						
<400	37.6	37.5	32.3	32.6	38.6	33.1
400–649	30.5	32.2	33.1	32.7	33.7	26.9
≥650	31.9	30.3	34.6	34.7	27.7	40.0

Table 1. (Continued.)

Characteristic	Primary Cohort		Highly Selected Subcohort		Instrumental-Variable Subcohort (90% vs. 10%)*	
	Aprotinin (N=33,517)	Aminocaproic Acid (N=44,682)	Aprotinin (N=4799)	Aminocaproic Acid (N=4799)	Aprotinin (N=15,228)	Aminocaproic Acid (N=10,556)
	<i>percent of patients</i>					
Region						
Midwest	17.6	19.1	16.8	17.6	16.6	20.2
Northeast	8.9	15.1	14.4	14.7	6.7	18.2
South	59.3	53.0	63.0	62.0	60.9	48.9
West	14.2	12.8	5.9	5.8	15.8	12.7
Teaching hospital	50.8	55.6	56.6	56.5	48.7	62.1
Rural hospital	6.9	7.1	9.4	9.6	5.5	10.3
Study outcome						
In-hospital death	4.5	2.5	4.4	3.3	3.6	2.7
In-hospital death during the first 7 days after CABG	1.9	1.0	1.5	1.1	1.4	1.1
Possible adverse events¶						
Need for acute coronary revascularization	0.3	0.3	0.3	0.2	0.3	0.2
Stroke	0.04	0.05	0.02	0.08	0.03	0.04
Acute heart failure	14.4	11.5	11.4	12.9	12.3	12.3
Need for dialysis	2.7	1.5	2.5	2.4	2.3	1.8
Possible adverse events during the first 7 days after CABG¶						
Need for acute coronary revascularization	0.26	0.21	0.23	0.06	0.26	0.15
Stroke	0.02	0.04	0.02	0.06	0.01	0.03
Acute heart failure	14.03	11.21	11.00	12.65	11.98	12.10
Need for dialysis	1.94	0.97	1.65	1.28	1.66	0.99

* In this subcohort, CABG was performed by surgeons who used aprotinin in 90% or more of their patients or by those who used aprotinin in 10% or fewer of their patients.

† Race or ethnic group was self-reported.

‡ Low-income status was defined as receipt of Medicaid or classification as indigent.

§ These uses were assessed during the day or days before CABG in patients who underwent the surgery on day 3 or later.

¶ Acute coronary revascularization was indicated by the presence of charge codes for thrombolysis, percutaneous transluminal coronary angioplasty, or repeat CABG; stroke was indicated by procedural and discharge diagnoses related to stroke, except hemorrhagic stroke; acute heart failure was indicated by the presence of charge codes for the use of dobutamine or a left ventricular assist device; and dialysis was indicated by the presence of charge codes for hemodialysis, peritoneal dialysis, or hemofiltration. For the analysis of the dialysis outcome, we excluded the 3156 patients with preexisting renal failure and chronic kidney disease (2165 patients in the primary cohort; 355 in the highly selected subcohort, and 636 in the instrumental-variable subcohort).

the basis of the hospital yielded higher relative risks. The model prediction of death was high in both drug groups ($c=0.79$).

Sensitivity analyses showed that an unmeasured confounder present in 10% of patients would be required to elevate the risk of in-hospital death by a factor of 6 and would also have to have a prevalence among aprotinin recipients

that would be six times that among aminocaproic acid recipients to explain a relative risk of 1.64 (Fig. A1 in the Supplementary Appendix). A history of CABG was strongly associated with aprotinin use, as compared with aminocaproic acid use, in the validation study (relative risk, 24.6), and this risk factor was frequently incompletely recorded in the Premier Perspective Comparative

Table 2. Relative Risk of In-Hospital Death among the 78,199 Patients Undergoing Coronary-Artery Bypass Grafting (CABG) in the Primary Study Cohort.

Outcome	Any Amount of Aprotinin (N=33,517) no. of patients (%)	Any Amount of Aminocaproic Acid (N=44,682) no. of patients (%)	Any Amount of Study Drug		
			Unadjusted	Adjusted	Low or High Amount of Study Drug Adjusted
			relative risk (95% CI)		
In-hospital death from any cause	1512 (4.5)	1101 (2.5)	1.83 (1.70–1.98)	1.64 (1.50–1.78)	1.50 (1.36–1.66)
In-hospital death from any cause within 7 days after CABG	631 (1.9)	435 (1.0)	1.93 (1.71–2.18)	1.78 (1.56–2.02)	1.64 (1.41–1.91)

Table 3. Relative Risk of In-Hospital Death in the Aprotinin Group as Compared with the Aminocaproic Acid Group, Based on Multivariate Analyses of the 78,199 Patients in the Primary Study Cohort, According to the Amount of Aprotinin.*

Amount of Aprotinin	Standard Logistic-Regression Analysis	Standard Logistic-Regression Analysis Limited to 7 Days of Follow-up	Logistic-Regression Analysis with GEE-Adjusted Errors	Conditional Logistic-Regression Analysis
		relative risk (95% CI)		
Very low	1.32 (1.08–1.60)	1.31 (0.97–1.78)	1.32 (1.07–1.62)	1.82 (1.42–2.34)
Low	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	1.75 (1.56–1.97)	1.91 (1.60–2.28)	1.74 (1.51–2.01)	2.47 (2.10–2.90)

* The reference group was the group of patients who received a low amount of aminocaproic acid. For more details about the standard logistic-regression analysis, see Table A1 in the Supplementary Appendix. GEE denotes generalized estimating equation.

Database file. An increase in the risk of death by a factor of 2.6 in association with repeat CABG¹⁴ would produce a 25.8% overestimate in the adjusted relative risk of in-hospital death in the aprotinin group, reducing the relative risk from 1.64 to 1.51. The addition of data on history of percutaneous coronary intervention, history of congestive heart failure, hypertension, diabetes, previous use of clopidogrel or aspirin, and a long duration of cardiopulmonary bypass surgery (>120 minutes) from the validation study would reduce the relative risk to 1.47, assuming additivity and independence of these confounders (Table 4).

HIGHLY SELECTED SUBCOHORT

In all, 13,345 patients qualified for the highly selected subcohort, and of these, 9598 were successfully matched on the basis of the propensity score. There were no differences of any consequence between recipients of aprotinin and recipients of aminocaproic acid (Table 1). The risk of death was 32% higher in the aprotinin group

than in the aminocaproic acid group (relative risk, 1.32; 95% CI, 1.08 to 1.63). Model prediction of mortality improved, but only slightly, after inclusion of the 10 additional covariates.

INSTRUMENTAL-VARIABLE SUBCOHORTS

The multivariable analysis of surgeons' preference for aprotinin (the instrumental-variable analysis, in which preference was defined as administration of the drug to at least 90% of patients) or lack of preference (defined as administration to no more than 10% of patients) yielded an increased risk of 0.60 death per 100 patients receiving aprotinin rather than aminocaproic acid (95% CI, 0.00 to 1.21). The estimated increase in risk of in-hospital death was slightly higher with the stricter definition of surgeons' preference (100% vs. 0% of patients given aprotinin): 1.59 deaths per 100 patients (95% CI, 0.14 to 3.04). The corresponding estimates for the unadjusted instrumental-variable analyses and those adjusted for age and sex were 1.59 and 1.47, respectively.

Table 4. Percent Overestimation of Relative Risks of Death in the Aprotinin Group as Compared with the Aminocaproic Acid Group and Corrected Estimates Based on Data from Medical Records from 98 Study Patients, According to Selected Risk Factors.*

Risk Factor	Percent Overestimation of Relative Risk	In-Hospital Death (Adjusted Relative Risk=1.64)	In-Hospital Death within 7 days after CABG (Adjusted Relative Risk=1.78)
History of CABG	25.8	1.51	1.62
History of percutaneous coronary intervention	6.0	1.60	1.74
Previous clopidogrel use	-15.6	1.76	1.92
Previous aspirin use	3.3	1.62	1.76
History of congestive heart failure	1.5	1.63	1.77
Hypertension	6.3	1.60	1.73
Diabetes	0.8	1.64	1.77
Long duration of cardiopulmonary bypass surgery (>120 min)	7.0	1.60	1.73
All selected factors	35.1	1.47	1.58

* Several characteristics of patients that were under-recorded in the database during the main study are independent risk factors for the study outcomes, resulting in overestimation of the effect estimates. For example, the adjusted relative risk of in-hospital death of 1.64 would have been calculated as a relative risk of 1.51 had repeat coronary-artery bypass grafting (CABG) been recorded accurately. In contrast, the example of previous clopidogrel use illustrates a strength of administrative data; computerized drug-dispensing information is generally seen as more reliable than physicians' records of their prescribing patterns.³³ When the effects of all selected risk factors were summed, overestimation persisted, resulting in a corrected relative-risk estimate for in-hospital death in the aprotinin group of 1.47.

DISCUSSION

This large, hospital-based cohort study using administrative data showed meaningful increases in inpatient mortality among recipients of aprotinin during CABG surgery, as compared with recipients of aminocaproic acid, both within the overall cohort and in all predefined subcohorts. The increased mortality in a multicenter registry study,^{3,4} the recently suspended head-to-head randomized trial,⁷ and our finding need to be set against the solid evidence that the use of aprotinin reduces the number of blood transfusions during cardiac surgery. However, aprotinin shows little or no benefit above that from aminocaproic acid. A meta-analysis of head-to-head trials showed that the use of aprotinin resulted in 0.20 fewer unit of blood transfused per patient (95% CI, -0.49 to 0.10), with no reduction in mortality (relative risk of death, 1.27; 95% CI, 0.30 to 5.42).³⁴

Concerns about the potential intravascular thrombosis due to aprotinin are not new,³⁵ and a prolonged celite-based activated clotting time among patients receiving aprotinin has been documented.³⁶ The greater frequency of revasculariza-

tion and dialysis among aprotinin recipients than among aminocaproic acid recipients in our highly selected subcohort (Table 1) may point to more frequent hypercoagulable states, but the overall evidence of consequential hypercoagulability associated with aprotinin is weak.

Aprotinin rather than aminocaproic acid was used in sicker patients, and the modest reduction in the relative mortality estimates after the control of confounding by covariates is consistent with the hypothesis of confounding on the basis of indication.³⁷ Multivariate analyses resulted in weaker associations between aprotinin and death than those reported in unadjusted analyses (unadjusted relative risk, 1.83; adjusted relative risk, 1.64). Matching according to propensity score permitted us to control for an additional 10 covariates in a highly selected cohort, which further reduced the relative-risk estimate.

Our analyses were adjusted for some, but not all, covariates typically included in risk-prediction scores for patients undergoing CABG.^{13,14,38} However, we adjusted for many covariates not typically included, and controlling for proxies of confounders results in control of the confound-

ers themselves if the proxies capture the relations with the true confounding variable, exposure, and outcomes. Our joint adjustment for 41 characteristics before CABG was performed resulted in the prediction of in-hospital death that is as good as that from widely accepted clinical risk-prediction models for patients undergoing CABG.^{13,14} Prediction was almost identical for patients receiving aprotinin and for those receiving aminocaproic acid.

Drawing covariates from administrative data involves making inferences from procedures and patterns of drug use. Despite their excellent predictive value, the covariates may have residual error. For example, several studies have described preferential prescribing of aprotinin in patients undergoing repeat CABG surgery, a potent risk factor for in-hospital death^{3,5,39}; failure to fully adjust for this confounder, as we saw in the sensitivity analysis, somewhat inflates the association between aprotinin use and mortality. A quantitative sensitivity analysis of residual confounding showed that implausible levels of unmeasured confounding would be required to explain the present observations. A small number of abstracted medical records of study patients, which we cannot claim to be representative or to contain all possible risk factors, nevertheless provides some insight into how little the difference in the primary effect estimates between the two drug groups would be diminished if residual confounding were captured. The estimated reduction of relative risk of in-hospital death in the aprotinin group from 1.64 to 1.47 probably overstates the role of residual confounding, because the component biases were summed as if they were entirely independent of each other and independent of the 41 adjusted covariates.²⁷

We used some surgeons' preference for (or avoidance of) aprotinin to bypass the analytic problems posed when patients' risk profiles drive treatment selection, as they may do for surgeons who regularly use either of the study drugs.³⁰ Instrumental-variable analysis has produced results similar to those from randomized trials but is less efficient and thus produces wider confidence intervals.⁴⁰ The results of our instrumental-variable analysis were similar to those obtained from traditional regression models. The estimated excess risk of death of 1.6 percentage points in aprotinin recipients as compared with amino-

caproic acid recipients, added to the overall risk of death among recipients of aminocaproic acid of 2.5 percentage points, would translate into a relative risk on the order of 1.6. An instrumental variable such as a strong treatment preference of surgeons should not be correlated with patients' risk factors after adjustment for the measured covariates. The possibility that clustering of sicker patients treated by surgeons who performed 50 or more CABG surgeries and who had a strong preference for aprotinin was greater than clustering captured by the use of the 41 measured covariates requires the unlikely scenario that patients choose their surgeon on the basis of the surgeon's preference for a specific antifibrinolytic agent.

On September 13, 2006, we transmitted a preliminary version of this report to the manufacturer of aprotinin, which passed it on to the FDA 2 weeks later. The revised and final analysis was presented on September 12, 2007, at an FDA Advisory Committee meeting. We have provided the study data to the manufacturer and to the FDA, which has independently evaluated the data using different methods and has reported substantially similar results.⁴¹ Representatives of and consultants for the manufacturer have disagreed with our methods and conclusions.⁴²⁻⁴⁵

Our analysis of hospital administrative data for patients undergoing CABG, involving more than 33,000 aprotinin recipients in comparison with some 45,000 aminocaproic acid recipients, supports the hypothesis that there is an increased risk of in-hospital death among aprotinin recipients. The findings are not readily attributable to chance or to distortions arising from any of the dozens of measured characteristics of patients, hospitals, and surgeons. Clinicians need to weigh this increased risk of death among aprotinin recipients, as compared with aminocaproic acid recipients, against the reduction in the need for transfusions during CABG.

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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'Connor GT, Dacey LJ. Is epsilon-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, Vuytsteke A, et al. 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, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006;46:327-38.
6. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007;115:2801-13.
7. Early communication about an ongoing safety review aprotinin injection (marketed as Trasylol). October 19, 2007. (Accessed January 29, 2008, at http://www.fda.gov/cder/drug/early_comm/aprotinin.htm.)
8. Bayer HealthCare. Bayer temporarily suspends global Trasylol marketing. November 5, 2007. (Accessed January 29, 2008, at <http://www.bayer.com/en/News-Detail.aspx?id=10280>.)
9. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;353:349-61.
10. 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.
11. Lindenauer PK, Remus D, Roman S, et al. Public reporting and pay for performance in hospital quality improvement. *N Engl J Med* 2007;356:486-96.
12. Jamieson WR, Dryden PJ, O'Connor JP, Sadeghi H, Ansley DM, Merrick PM. Beneficial effect of both tranexamic acid and aprotinin on blood loss reduction in reoperative valve replacement surgery. *Circulation* 1997;96:Suppl II:II-96-II-100.
13. Shroyer ALW, Coombs LP, Peterson ED, et al. 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, et al. 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. Pittsburgh: Institute for Transfusion Medicine, 2004. (Accessed January 29, 2008, at <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. *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. *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:Suppl I:I-276-I-280.
22. Schmer RG, Stammers AH, Ahlgren RL, et al. The effects of aprotinin on platelet function in blood exposed to epifibatide: an in vitro analysis. *J Extra Corpor Technol* 2003;35:304-11.
23. Liang KY, Zeger SL. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
24. Rothman KJ, Greenland S. *Modern epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998.
25. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
26. DeLong ER, Coombs LR, Ferguson TB Jr, Peterson ED. The evaluation of treatment when center-specific selection criteria vary with respect to patient risk. *Biometrics* 2005;61:942-9.
27. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303.
28. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
29. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. *Pharmacoepidemiol Drug Saf* 2005;14:465-76.
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 using physician-specific prescribing preferences as an instrumental variable. *Epidemiology* 2006;17:268-75.
32. Greene WH. *Econometric analysis*. 5th ed. Upper Saddle River, NJ: Prentice-Hall, 2003.
33. West SL, Strom BL, Freundlich B, Normand E, Koch G, Savitz DA. Completeness of prescription recording in outpatient medical records from a health maintenance organization. *J Clin Epidemiol* 1994;47:165-71.
34. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007;4:CD001886.
35. Sundt TM III, Kouchoukos NT, Saffitz JE, Murphy SF, Wareing TH, Stahl DJ. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. *Ann Thorac Surg* 1993;55:1418-24.
36. Despotis GJ, Joist JH. Anticoagulation and anticoagulation reversal with cardiac surgery involving cardiopulmonary bypass: an update. *J Cardiothorac Vasc Anesth* 1999;13:Suppl 1:18-29.
37. Walker AM. Confounding by indication. *Epidemiology* 1996;7:335-6.
38. Peterson ED, DeLong ER, Muhlbaier LH, et al. Challenges in comparing risk-adjusted bypass surgery mortality results: results from the Cooperative Cardiovascular Project. *J Am Coll Cardiol* 2000;36:2174-84.
39. Winterstein A, Gerhard T, Beaver TM. Safety of aprotinin in cardiac surgery. Presented at the Annual Meeting of the International Society of Pharmacoepidemiology, Lisbon, Portugal, August 24-27, 2006. *Pharmacoepidemiol Drug Saf* 2006;15:Suppl:S120.
40. Schneeweiss S, Solomon DH, Wang PS, Rassen J, Brookhart MA. Simultaneous assessment of short-term gastrointestinal benefits and cardiovascular risks of selective cyclooxygenase-2 inhibitors and non-selective nonsteroidal antiinflammatory drugs: an instrumental variable analysis. *Arthritis Rheum* 2006;54:3390-8.
41. Advisory FDA. Committee briefing document, joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. September 12, 2007. (Accessed January 29, 2008, at <http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4316b1-01-FDA.pdf>.)
42. Malik K. Before the FDA Cardiovascular and Renal Drugs Advisory Committee. September 12, 2007:94. (Accessed January 29, 2008, at <http://www.fda.gov/ohrms/>)

- dockets/ac/07/transcripts/2007-4316t1-part1.pdf.)
43. Makuch R. Before the FDA Cardiovascular and Renal Drugs Advisory Committee. September 12, 2007:130-42. (Accessed January 29, 2008, at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4316t1-part2.pdf>.)
44. Rubin D. Before the FDA Cardiovascular and Renal Drugs Advisory Committee. September 12, 2007:227-9. (Accessed January 29, 2008, at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4316t1-part3.pdf>.)
45. *Idem*. Before the FDA Cardiovascular and Renal Drugs Advisory Committee. September 12, 2007:301-26. (Accessed January 29, 2008, at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4316t1-part4.pdf>.)

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