

ORIGINAL ARTICLE

## The Risk Associated with Aprotinin in Cardiac Surgery

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### ABSTRACT

#### BACKGROUND

The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss. This approach appears counterintuitive to the accepted medical treatment of the same condition — namely, fibrinolysis to limit thrombosis. Despite this concern, no independent, large-scale safety assessment has been undertaken.

#### METHODS

In this observational study involving 4374 patients undergoing revascularization, we prospectively assessed three agents (aprotinin [1295 patients], aminocaproic acid [883], and tranexamic acid [822]) as compared with no agent (1374 patients) with regard to serious outcomes by propensity and multivariable methods. (Although aprotinin is a serine protease inhibitor, here we use the term antifibrinolytic therapy to include all three agents.)

#### RESULTS

In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31). Similarly, use of aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure ( $P<0.001$ ) and a 181 percent increase in the risk of stroke or encephalopathy ( $P=0.001$ ). Neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. Adjustment according to propensity score for the use of any one of the three agents as compared with no agent yielded nearly identical findings. All the agents reduced blood loss.

#### CONCLUSIONS

The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

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\*Investigators and centers participating in the study are listed in the Appendix.

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THE MAINSTAY OF MEDICAL THERAPY FOR patients with an acute coronary syndrome — when accompanied by myocardial infarction with ST-segment elevation — includes fibrinolytic and antiplatelet agents to mitigate thrombosis-related events.<sup>1</sup> However, if surgical therapy (coronary-artery surgery) is elected, fibrinolytic agents are not used before, during, or after surgery because of concerns regarding excessive bleeding. In fact, these bleeding-related concerns have given rise to the testing, regulatory approval, and widespread use of two classes of agents, both proven to mitigate bleeding: the lysine analogues (aminocaproic acid and tranexamic acid) and the serine protease inhibitors (aprotinin). Consequently, the majority of patients now routinely receive one or more of these agents during and after invasive cardiovascular procedures, including coronary-artery surgery.<sup>2-4</sup> Thus, at least for patients with ST-elevation myocardial infarction, the surgical approach (with the use of antifibrinolytic agents) is in stark contrast, and may seem counterintuitive, to the medical approach (with fibrinolytic therapy as a mainstay) for thrombosis-related events. (Although aprotinin is a serine protease inhibitor, here we use the term antifibrinolytic therapy to include all three agents.)

The question of the safety of serine protease inhibitors or lysine analogues for thrombosis-related events — though noted in a handful of early case reports and small, single-center experiences involving graft thrombosis<sup>5-7</sup> and creatinine elevation<sup>5,8,9</sup> — has largely been contested by a number of published secondary analyses that have nearly always concluded that antifibrinolytic therapy, as defined here, is safe.<sup>10</sup> Unfortunately, however, this “safety evidence” has three important limitations: no prior investigation was adequately powered to assess relatively infrequent, but clinically serious, safety events<sup>10</sup>; the comparative safety of the three agents has not been assessed within one study — an important consideration, given the large cost differential among agents (aprotinin being far more costly than either aminocaproic acid or tranexamic acid); and nearly all investigations were sponsor-supported<sup>10</sup> and therefore carried unavoidable bias.

Addressing these considerations, however, is not straightforward. After a decade of use, antifibrinolytic practice now is embedded and dictated by guidelines,<sup>2,4,11</sup> such that safety assess-

ment in independent, placebo-controlled clinical trials with unselected recruitment becomes difficult, if not impossible. In addition, regulatory approval for use of these agents differs among countries, making a large-scale, multicountry, comparative study challenging. Therefore, to address the safety of antifibrinolytic therapy for thrombosis-related cardiac, cerebral, and renal events, we conducted a non-sponsor-supported, prospective, international, multi-institutional study sufficiently powerful (with >800 patients per group) and comprehensive (with hundreds of covariate measurements per patient) to allow comparative safety assessment among the three agents by exacting propensity and multivariable analyses. We hypothesized that the use of either serine protease inhibitors or lysine analogues in patients with acute coronary syndromes presenting for coronary-artery surgery is unsafe.

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## METHODS

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After institutional approval and written informed consent had been obtained, patients scheduled for coronary-artery bypass surgery with cardiopulmonary bypass were prospectively enrolled according to a systematic sampling scheme at 69 institutions in North and South America, Europe, the Middle East, and Asia. To be eligible for entry into the study, patients had to be at least 18 years of age, could not be enrolled in another study or trial, and had to be able to engage in a preoperative interview. At each institution, every Rth patient meeting these entry criteria was enrolled, where  $R = N \div 50$  (to the closest integer) and where  $N$  is the number of patients expected to undergo myocardial revascularization surgery over a one-year period.<sup>12</sup> Data were collected throughout hospitalization, with approximately 7500 data fields per patient collected by independent investigators.

## MEASUREMENT OF OUTCOMES

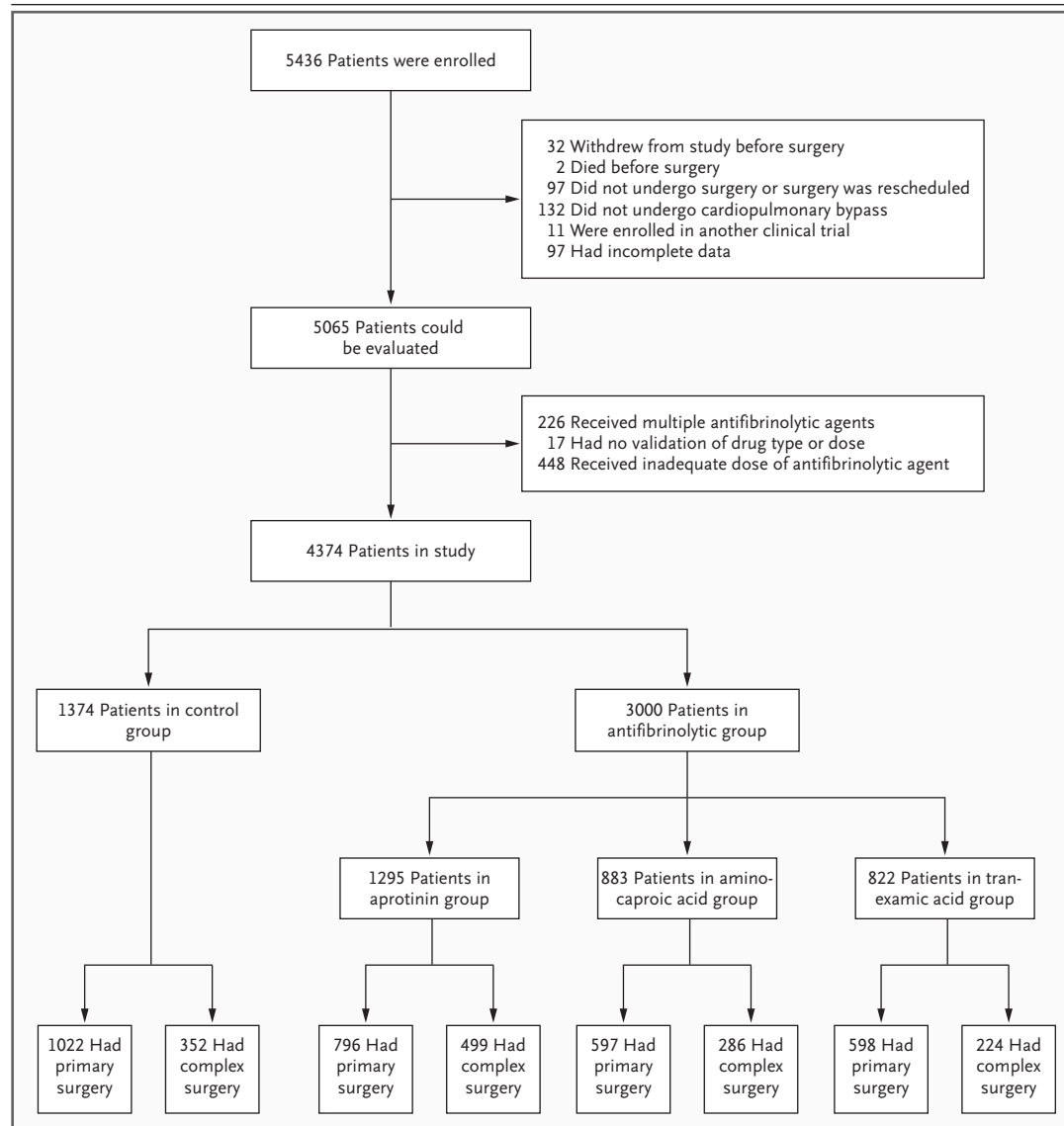
Each outcome event was prespecified, defined by the protocol, and classified as cardiovascular (myocardial infarction or heart failure), cerebrovascular (stroke, encephalopathy, or coma), or renal (dysfunction or failure). Myocardial infarction required either new Q waves (Minnesota code 1-1-1 or 1-2-7) or new, persistent ST-segment or T-wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2). Heart failure required a cardiac output of less than 2.0 liters per minute associated with a pulmo-

nary-artery occlusion pressure above 18 mm Hg, a central venous pressure above 12 mm Hg, an S<sub>3</sub> gallop, or rales. Cerebrovascular events included clinically diagnosed stroke, encephalopathy, and coma. Renal dysfunction required a postoperative serum creatinine level of at least 177  $\mu\text{mol}$  per liter with an increase over preoperative baseline levels of at least 62  $\mu\text{mol}$  per liter; renal failure was defined as dysfunction requiring dialysis or

in-hospital death with evidence at autopsy of acute renal failure. Blood loss was assessed as chest-tube output during the first 24 hours after surgery.

#### CLINICAL CARE AND USE OF ANTIFIBRINOLYTIC AGENTS

Clinical decisions were not controlled by the study protocol, and all patients qualifying for enrollment within the prespecified enrollment period



**Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram of Patient Enrollment.**

The diagram shows the numbers of patients who met the criteria for inclusion in, or exclusion from, the study and their distribution among the four study groups and two surgery types. Inclusion in the aprotinin group required administration of a total of more than 2 million kallikrein-inhibitor units intravenously before the end of surgery; inclusion in the aminocaproic acid group, administration of more than 10 g; and inclusion in the tranexamic acid group, administration of more than 1 g.

**Table 1. Baseline Characteristics of the Patients, According to Study Group.\***

Characteristic	Control Group (N = 1374)		Overall (N = 3000)		Antifibrinolytic Group				Tranexamic Acid (N = 822)	
	no. (%)	P value†	no. (%)	P value‡	Aprotinin (N = 1295)	Aminocaproic Acid (N = 883)	no. (%)	P value†	no. (%)	P value†
Male sex	1110 (80.8)	0.24	2377 (79.2)	0.59	1016 (78.5)	690 (78.1)	671 (81.6)	0.13	105 (12.8)	<0.001
Black, American Indian, or Hispanic race or ethnic group¶	53 (3.9)	<0.001	300 (10.0)	0.88	56 (4.3)	139 (15.7)	105 (12.8)	<0.001	105 (12.8)	<0.001
Education: some college or above	496 (36.1)	<0.001	918 (30.6)	0.14	280 (21.6)	398 (45.1)	240 (29.2)	<0.001	240 (29.2)	<0.001
Surgery: urgent or emergency status	288 (21.0)	<0.001	503 (16.8)	0.38	192 (14.8)	167 (18.9)	144 (17.5)	0.24	144 (17.5)	0.05
History of diabetes mellitus	384 (28.0)	0.18	898 (30.0)	0.39	353 (27.3)	325 (36.8)	220 (26.8)	0.68	220 (26.8)	0.56
History of insulin-dependent diabetes	78 (5.7)	0.005	242 (8.1)	0.72	116 (9.0)	80 (9.1)	46 (5.6)	0.001	46 (5.6)	0.94
History of hypertension	824 (60.3)	<0.001	2091 (69.9)	0.76	905 (70.0)	657 (74.7)	529 (64.7)	<0.001	529 (64.7)	0.042
History of angina	1272 (92.8)	0.002	2688 (89.8)	0.83	1136 (87.8)	783 (89.3)	769 (93.6)	<0.001	769 (93.6)	0.49
History of congestive heart failure	457 (33.5)	0.13	1065 (35.8)	0.22	551 (42.8)	243 (27.7)	271 (33.3)	<0.001	271 (33.3)	0.95
History of myocardial infarction	714 (52.3)	0.97	1548 (52.2)	0.87	664 (52.1)	433 (49.6)	451 (55.1)	0.94	451 (55.1)	0.19
History of heart block	176 (12.8)	0.008	477 (15.9)	0.83	224 (17.3)	129 (14.6)	124 (15.1)	0.001	124 (15.1)	0.13
History of carotid disease	143 (11.0)	0.002	421 (14.4)	0.74	217 (17.2)	107 (12.4)	97 (12.2)	<0.001	97 (12.2)	0.38
History of stroke	89 (6.5)	0.75	186 (6.2)	0.83	88 (6.8)	61 (7.0)	37 (4.5)	0.73	37 (4.5)	0.05
History of liver disease	106 (7.7)	0.06	282 (9.4)	0.83	150 (11.7)	66 (7.5)	66 (8.0)	<0.001	66 (8.0)	0.79
History of renal disease	178 (13.0)	<0.001	523 (17.5)	0.92	240 (18.6)	131 (14.9)	152 (18.5)	<0.001	152 (18.5)	<0.001
History of pulmonary disease	238 (17.4)	<0.001	680 (22.8)	0.95	326 (25.3)	215 (24.5)	139 (17.0)	<0.001	139 (17.0)	0.79
Ejection fraction ≤4%	247 (18.0)	0.40	508 (16.9)	0.96	199 (15.4)	169 (19.1)	140 (17.0)	0.07	140 (17.0)	0.57
Creatinine >1.3 mg/dl on admission	189 (13.8)	0.29	449 (15.0)	0.92	195 (15.1)	132 (14.9)	122 (14.8)	0.34	122 (14.8)	0.48
History of CABG	31 (2.3)	<0.001	236 (7.9)	NA	148 (11.4)	51 (5.8)	37 (4.5)	<0.001	37 (4.5)	0.003
History of valve disease	167 (12.3)	<0.001	616 (20.7)	0.89	326 (25.4)	165 (18.8)	125 (15.2)	<0.001	125 (15.2)	0.05

History of valve surgery	1 (0.1)	26 (0.9)	0.002	NA	0.50	19 (1.5)	<0.001	3 (0.3)	0.14	4 (0.5)	0.05
History of percutaneous transluminal coronary angioplasty	138 (10.1)	542 (18.1)	<0.001	0.93	0.54	223 (17.3)	<0.001	173 (19.7)	<0.001	146 (17.8)	<0.001
History of aortic vascular surgery	15 (1.1)	32 (1.1)	0.94	NA	0.62	12 (0.9)	0.67	11 (1.3)	0.74	9 (1.1)	0.99
History of intracoronary stent	54 (3.9)	227 (7.6)	<0.001	0.87	0.17	95 (7.3)	<0.001	78 (8.8)	<0.001	54 (6.6)	0.006
History of coronary atherectomy	5 (0.4)	19 (0.6)	0.26	0.94	0.68	11 (0.9)	0.10	7 (0.8)	0.17	1 (0.1)	0.29
History of noncoronary angioplasty or stent	20 (1.5)	68 (2.3)	0.08	NA	0.60	40 (3.3)	0.002	11 (1.3)	0.68	14 (1.7)	0.65
Current CABG and valve surgery	96 (7.0)	378 (12.6)	<0.001	NA	0.18	201 (15.5)	<0.001	108 (12.2)	<0.001	69 (8.4)	0.23
Current CABG and other surgery	68 (5.0)	153 (5.1)	0.83	NA	0.99	72 (5.6)	0.48	41 (4.6)	0.74	40 (4.9)	0.93

\* NA denotes not applicable (because there were no patients with the characteristic in the subpopulation), and CABG coronary-artery bypass grafting.

† P values are for the comparison between patients treated with an antifibrinolytic agent and control patients.

‡ P values are those calculated after adjustment according to the propensity score (for the use of an antifibrinolytic agent) in 3013 patients undergoing primary surgery.

§ P values are those calculated after adjustment according to the propensity score (for the use of an antifibrinolytic agent) in 1361 patients undergoing complex surgery. Complex surgery was defined as surgery under any of the following conditions: a history of coronary-artery bypass grafting, valve surgery, noncoronary angioplasty or stenting, or other cardiac or vascular noncardiac surgery; combined current heart surgery; and current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively.

¶ Race or ethnic group was determined by the clinical investigator.

|| To convert the value for creatinine to micromoles per liter, multiply by 88.4.

were entered into the study (Fig. 1). Patients were classified as undergoing primary surgery if the index surgery was elective and involved only coronary-artery revascularization (with no history of cardiac or vascular surgery) or angioplasty. Otherwise, patients were classified as undergoing complex surgery.

#### STATISTICAL ANALYSIS

Baseline medical characteristics were compared statistically (Table 1). The effect of the drugs on outcome was assessed with the use of multivariable logistic regression and propensity-score adjustment. Initially, 97 perioperative risk factors were evaluated for univariate association with outcome (two-tailed  $P \leq 0.20$ ) and then entered stepwise (backward and forward) into multivariable logistic models, with assessment of the association between treatment (aprotinin, aminocaproic acid, or tranexamic acid vs. no treatment) and outcome in the presence of the significant covariates. Comparison between drugs was assessed with the use of contrast functions.

Selection bias not controlled by multivariable methods was assessed with a propensity-adjustment method. Using nonparsimonious logistic-regression modeling, we developed propensity scores for the use of any antifibrinolytic treatment (vs. no treatment), including 45 treatment-selection covariates, and propensity scores for specific treatments. Covariate interactions proved unnecessary for the balance of baseline characteristics. The discriminate power of the propensity scores was quantified by measurement of the receiver-operating-characteristic area (the C-index). Covariate adjustment was performed with the derived propensity scores and drug-indicator variables. The interaction of the differential drug effect and surgery status (with the propensity score as the adjustment variable<sup>13,14</sup>) was not significant. Propensity-score analyses according to specific treatment confirmed our findings according to drug class. Finally, the dose response (weight-adjusted) was assessed among 596 patients in the aprotinin group who were receiving either a low-dose regimen (loading dose, 1 million kallikrein-inhibitor units [KIU]; total dose, >2 million KIU) or a high-dose regimen (loading dose, 2 million KIU; total dose, >4 million KIU).

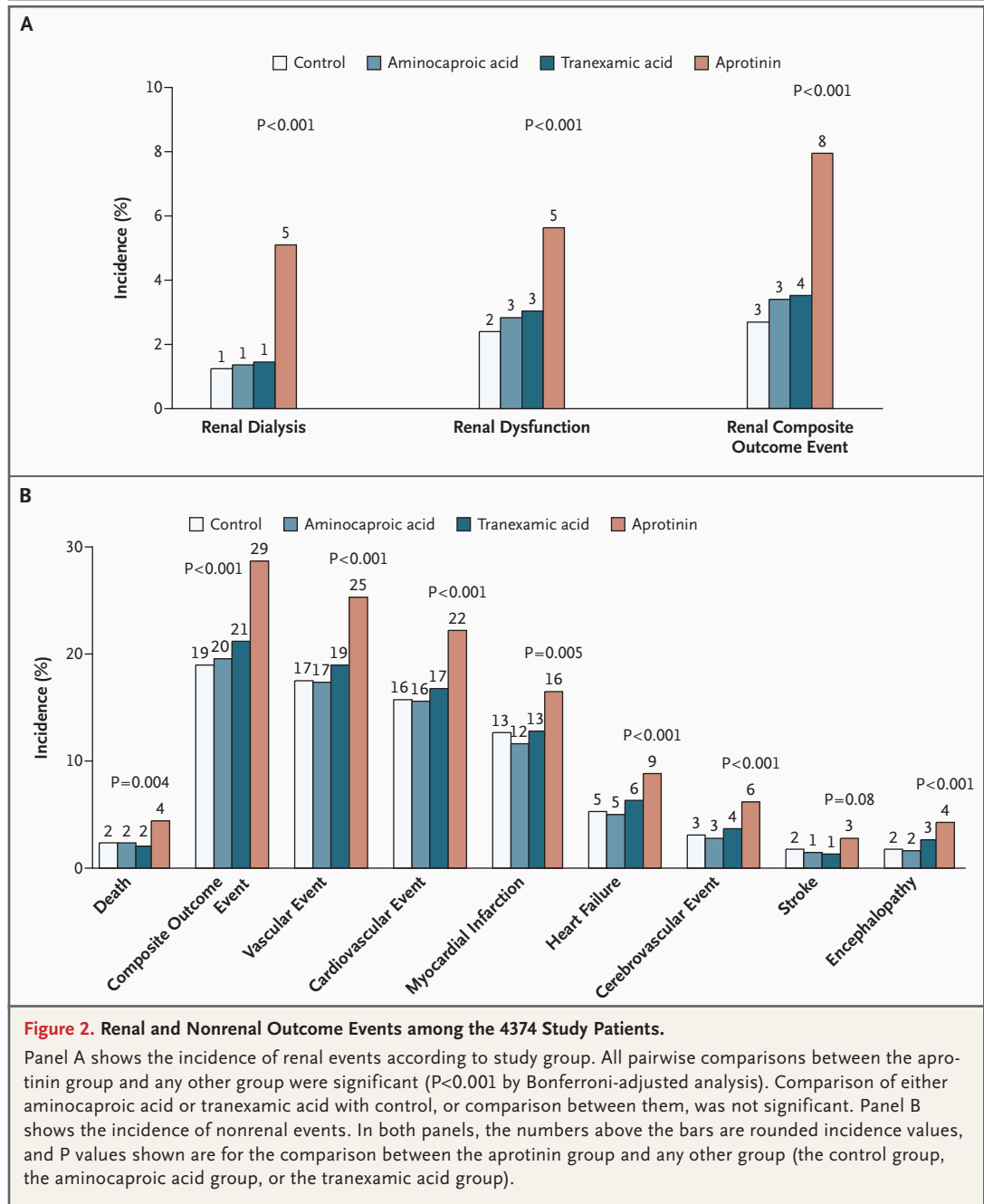
SAS statistical software (version 8.2) was used; a P value of less than 0.05 (two-tailed) was considered to indicate statistical significance. Multiple comparison adjustments were assessed.

RESULTS

As expected, patients had evidence of acute and chronic vascular disease. Several imbalances were noted between the treatment groups and the control group before propensity adjustment, but not thereafter (Table 1).

ADVERSE SAFETY OUTCOMES

Overall, the use of aprotinin was associated with an increased risk of renal and nonrenal events when compared with aminocaproic acid, tranexamic acid, or no antifibrinolytic therapy (Fig. 2) — a finding confirmed by multivariable logistic regression (Table 2). Interaction by drug



**Table 2. Results of Multivariable Logistic Regression for the Renal Composite Outcome in 4374 Patients.\***

Risk Factor	Analysis in Presence of Covariates without Propensity Adjustment†		Analysis in Presence of Covariates with Propensity Adjustment‡	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Aprotinin vs. control	2.52 (1.66–3.82)	<0.01	2.41 (1.49–3.90)	<0.001
Aminocaproic acid vs. control	1.03 (0.61–1.76)	0.91	0.84 (0.44–1.58)	0.58
Tranexamic acid vs. control	1.25 (0.74–2.13)	0.40	1.23 (0.68–2.21)	0.49
Propensity score	—	—	1.03 (0.97–1.11)	0.33
Complex vs. primary surgery	1.55 (1.12–2.16)	0.009	1.47 (1.02–2.13)	0.04
History of renal disease	2.50 (1.76–3.57)	<0.001	2.53 (1.70–3.75)	<0.001
Creatinine >1.3 mg/dl on admission§	2.71 (1.91–3.87)	<0.001	3.12 (2.11–4.60)	<0.001
Heart failure on admission	2.33 (1.68–3.24)	<0.001	2.64 (1.84–3.80)	<0.001
History of angina	0.57 (0.36–0.89)	0.01	0.58 (0.35–0.96)	0.03
History of liver disease	0.35 (0.18–0.68)	0.002	0.28 (0.13–0.61)	0.001
History of intravenous drug use	3.29 (1.08–10.04)	0.04	2.98 (0.82–10.84)	0.10
Preoperative nitrate administration	1.95 (1.29–2.93)	0.001	2.15 (1.36–3.40)	0.001
Preoperative inotrope administration	2.31 (1.45–3.67)	<0.001	2.36 (1.42–3.92)	<0.001
Preoperative administration of ACE inhibitor	1.38 (1.00–1.91)	0.05	1.57 (1.10–2.24)	0.01
Intraoperative transfusion of fresh frozen plasma	2.51 (1.72–3.65)	<0.001	2.40 (1.58–3.66)	<0.001
Intraoperative transfusion of red cells	1.64 (1.15–2.34)	0.007	1.71 (1.16–2.52)	0.007

\* CI denotes confidence interval, and ACE angiotensin-converting enzyme.

† Excluded were 43 patients with missing values for at least one of the risk factors in the model, including the covariates. The Hosmer–Lemeshow goodness-of-fit chi-square test statistic was 10.3 ( $P=0.24$ ). The C-index for the model was 0.84. Direct comparisons of treatment groups by contrast functions on model parameters demonstrated increased risk with aprotinin as compared with aminocaproic acid (odds ratio, 2.44; 95 percent confidence interval, 1.54 to 3.86;  $P<0.001$ ) and as compared with tranexamic acid (odds ratio, 2.01; 95 percent confidence interval, 1.27 to 3.18;  $P=0.003$ ). There was no difference in risk associated with the use of aminocaproic acid as compared with tranexamic acid.

‡ Excluded were 410 patients with missing values for at least one of the covariates or the propensity score. The Hosmer–Lemeshow goodness-of-fit chi-square test statistic was 7.17 ( $P=0.52$ ). The C-index for the model was 0.86. Direct comparisons of treatment groups by contrast functions on model parameters demonstrated increased risk with aprotinin as compared with aminocaproic acid (odds ratio, 2.88; 95 percent confidence interval, 1.69 to 4.90;  $P<0.001$ ) and as compared with tranexamic acid (odds ratio, 1.96; 95 percent confidence interval, 1.19 to 3.23;  $P=0.009$ ). There was no difference in risk associated with the use of aminocaproic acid as compared with tranexamic acid.

§ To convert the value for creatinine to micromoles per liter, multiply by 88.4.

group and complexity of surgery was not significant.

Among the 3013 patients undergoing primary surgery, aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death (2.8 percent vs. 1.3 percent,  $P=0.02$ ), cardiovascular events (20.4 percent vs. 13.2 percent,  $P<0.001$ ), cerebrovascular events (4.5 percent vs. 1.6 percent,  $P<0.001$ ), and renal events (5.5 percent vs. 1.8 percent,  $P<0.001$ ). Specifically, with regard to cardiovascular events, aprotinin was associated with a 48 percent increase in the risk of myocardial infarction ( $P<0.001$ ) and a

109 percent increase in the risk of heart failure ( $P<0.001$ ). After propensity adjustment (C-index, 0.71), multivariable analysis continued to demonstrate a significant association between the use of aprotinin and an increased risk of adverse events (Table 3) as well as an absence of association between either aminocaproic acid or tranexamic acid and such events. Propensity adjustment by drug (C-index for aprotinin, 0.72; for aminocaproic acid, 0.80; and for tranexamic acid, 0.68) yielded similar findings. For example, as compared with control, aprotinin nearly doubled the odds of a renal event (odds ratio, 1.89; 95 per-

**Table 3. Propensity-Adjusted Effect of Treatment on Ischemic Outcome Events.\***

Outcome Event	Predictors in Multivariable Logistic-Regression Model	Patients Undergoing Primary Surgery (N=3013) <sup>†</sup>		Patients Undergoing Complex Surgery (N=1361) <sup>‡</sup>	
		P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)
Death	Aprotinin vs. control	0.22	1.59 (0.76–3.34)	0.66	0.86 (0.44–1.70)
	Aminocaproic acid vs. control	0.65	0.81 (0.33–2.02)	0.01	0.25 (0.09–0.72)
	Tranexamic acid vs. control	0.94	1.03 (0.44–2.45)	0.13	0.49 (0.19–1.23)
	Propensity score	<0.001	1.22 (1.09–1.36)	0.004	1.18 (1.06–1.32)
Renal event <sup>§</sup>	Aprotinin vs. control	0.006	2.34 (1.27–4.31)	0.004	2.59 (1.36–4.95)
	Aminocaproic acid vs. control	0.86	0.93 (0.43–2.02)	0.23	0.56 (0.22–1.44)
	Tranexamic acid vs. control	0.75	0.88 (0.40–1.94)	0.33	1.47 (0.68–3.19)
	Propensity score	<0.001	1.19 (1.08–1.30)	0.58	1.02 (0.94–1.11)
Cardiovascular event <sup>¶</sup>	Aprotinin vs. control	0.01	1.42 (1.09–1.86)	0.67	1.08 (0.75–1.57)
	Aminocaproic acid vs. control	0.13	0.78 (0.56–1.08)	0.18	0.74 (0.48–1.15)
	Tranexamic acid vs. control	0.73	0.95 (0.70–1.29)	0.93	1.02 (0.66–1.57)
	Propensity score	<0.001	1.08 (1.03–1.12)	0.16	1.04 (0.99–1.09)
Cerebrovascular event <sup>  </sup>	Aprotinin vs. control	0.02	2.15 (1.14–4.06)	0.41	1.29 (0.71–2.35)
	Aminocaproic acid vs. control	0.84	0.92 (0.42–2.05)	0.07	0.45 (0.19–1.06)
	Tranexamic acid vs. control	0.21	1.57 (0.77–3.19)	0.38	0.70 (0.32–1.55)
	Propensity score	<0.001	1.19 (1.08–1.30)	0.87	0.99 (0.91–1.08)
Composite outcome event <sup>**</sup>	Aprotinin vs. control	0.002	1.49 (1.15–1.91)	0.13	1.30 (0.93–1.83)
	Aminocaproic acid vs. control	0.28	0.85 (0.63–1.15)	0.09	0.71 (0.47–1.06)
	Tranexamic acid vs. control	0.69	0.94 (0.71–1.26)	0.44	1.17 (0.79–1.73)
	Propensity score	<0.001	1.09 (1.05–1.14)	0.65	1.01 (0.97–1.06)

\* CI denotes confidence interval.

<sup>†</sup> The control group included 1022 patients, and the antifibrinolytic group 1991 patients. Values for the propensity score were missing for 87 patients in the control group and 157 in the antifibrinolytic group.

<sup>‡</sup> The control group included 352 patients, and the antifibrinolytic group 1009 patients. Values for the propensity score were missing for 49 patients in the control group and 114 in the antifibrinolytic group.

<sup>§</sup> A renal event was defined as either renal dysfunction or renal failure requiring dialysis.

<sup>¶</sup> A cardiovascular event was defined as either myocardial infarction or heart failure.

<sup>||</sup> A cerebrovascular event was defined as stroke, encephalopathy, or coma.

<sup>\*\*</sup> The composite outcome event category included all the other outcome event categories (death, renal event, cardiovascular event, and cerebrovascular event).

cent confidence interval, 1.01 to 3.55;  $P=0.04$ ), whereas neither aminocaproic acid (odds ratio, 0.85; 95 percent confidence interval, 0.37 to 1.95;  $P=0.69$ ) nor tranexamic acid (odds ratio, 1.43; 95 percent confidence interval, 0.62 to 3.27;  $P=0.40$ ) was associated with increased renal risk.

Among the 1361 patients undergoing complex surgery, aprotinin was associated with increased renal dysfunction and renal failure re-

quiring dialysis, whereas aminocaproic acid and tranexamic acid were not. Propensity adjustment (C-index, 0.73) confirmed these findings (Table 3), and adjustment by specific drug (C-index for aprotinin, 0.78; for aminocaproic acid, 0.78; and for tranexamic acid, 0.76) yielded similar results, as illustrated for renal events: odds ratio with aprotinin, 2.79 (95 percent confidence interval, 1.44 to 5.44;  $P=0.002$ ); with aminocaproic acid,

0.48 (95 percent confidence interval, 0.17 to 1.34;  $P=0.16$ ); and with tranexamic acid, 1.01 (95 percent confidence interval, 0.44 to 2.33;  $P=0.98$ ). A dose–response relationship was found for aprotinin with respect to renal, cardiovascular, and composite outcomes (Fig. 3).

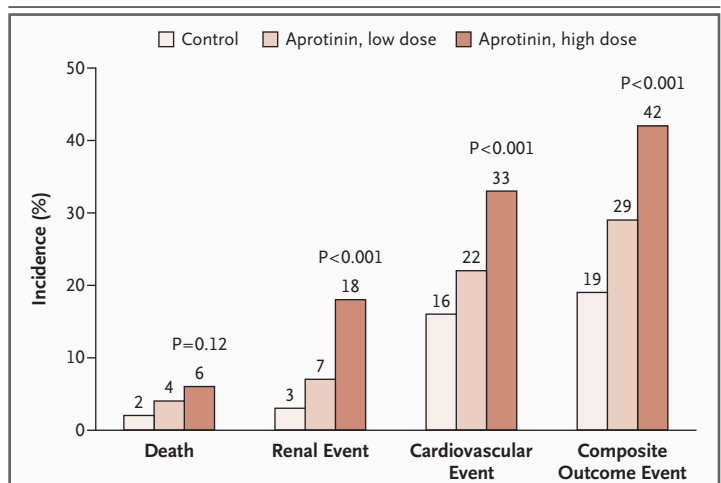
#### EFFICACY

The three medications reduced blood loss to similar extents. As compared with the control group, in which mean ( $\pm$ SD) estimated blood loss was  $827\pm 573$  ml, blood loss was  $753\pm 660$  ml in the aprotinin group ( $P<0.001$ ),  $719\pm 578$  ml in the aminocaproic acid group ( $P<0.001$ ), and  $676\pm 741$  ml in the tranexamic acid group ( $P<0.001$ ).

#### DISCUSSION

Our findings raise serious concerns regarding the safety of an approved drug intended to limit blood loss in at-risk patients undergoing surgery. Specifically, the use of aprotinin was associated with a dose-dependent doubling to tripling in the risk of renal failure requiring dialysis among patients undergoing primary or complex coronary-artery surgery. Furthermore, for the majority of patients undergoing primary surgery, we found evidence of multiorgan damage involving the heart (myocardial infarction or heart failure) and the brain (encephalopathy) in addition to the kidneys, suggesting a generalized pattern of ischemic injury. Unlike the serine protease inhibitors, analysis of the less costly lysine analogues aminocaproic acid and tranexamic acid demonstrated no such safety concerns, although these two agents were equally effective in reducing blood loss. Thus, our findings indicate that reconsideration of the safety of aprotinin among patients undergoing cardiac surgery is warranted and indicate replacement of aprotinin with either aminocaproic acid or tranexamic acid.

Blood loss and its replacement merit careful redress — particularly in cardiac surgery, for which large amounts of blood loss occur not only because of direct vascular interruption, but also because of exposure and autotransplantation of blood elements after contact with the foreign surfaces of the bypass circuitry.<sup>2,12</sup> Consequently, prostacyclins, desmopressin, lysine analogues, and serine protease inhibitors were developed. The latter two classes are now used in the majority of the 1 million cardiac surgical operations



**Figure 3. Aprotinin Dose Response.**

$P$  values shown are for the comparison between a high dose of aprotinin and either a low dose of aprotinin or no antifibrinolytic therapy (control). Pairwise comparison between a high dose of aprotinin and control was significant with respect to renal events, cardiovascular events, and composite outcome events ( $P<0.001$  for all three comparisons by Bonferroni-adjusted analyses) but not for death ( $P=0.12$ ). Pairwise comparison between a low dose of aprotinin and no antifibrinolytic therapy was significant (in Bonferroni-adjusted analyses) with respect to renal events ( $P<0.001$ ) and composite outcome events ( $P=0.003$ ) but not cardiovascular events ( $P=0.08$ ) or death ( $P=0.14$ ). Pairwise comparison between a high dose of aprotinin and a low dose of aprotinin was significant (in Bonferroni-adjusted analyses) with respect to renal events ( $P<0.001$ ) but not cardiovascular events ( $P=0.04$ ), composite outcome events ( $P=0.03$ ), or death ( $P=0.38$ ).

performed annually worldwide<sup>2-4,10,12,15</sup> — a practice consistent with consensus guidelines.<sup>2,4,11</sup>

Unlike lysine analogues, aprotinin has high affinity for the kidneys<sup>16-19</sup> — a property that may explain our renal findings. After free glomerular passage, aprotinin binds selectively to the brush border of the proximal tubule membrane, and then, by pinocytosis, it enters into and accumulates within the cytoplasm, inhibiting tubule protease secretion (kallikrein and, secondarily, kinin), prostaglandin and renin synthesis, prostaticin secretion, and bradykinin release.<sup>18-22</sup> Under normothermic ischemia, hypothermia, and other states of high kallikrein activity, these untoward tubular effects are magnified and are complicated by dose-dependent renal afferent vasoconstriction; deep cortical and medullary perfusion and its autoregulation are thereby impaired, and focal tubular necrosis ensues.<sup>20-26</sup> Furthermore, because of its interference with the synthesis and release of endothelial nitric acid, aprotinin also may instigate macrovascular or microvascular thrombosis.<sup>27,28</sup>

Despite this *in vitro* and *in vivo* evidence, only a minority of the reports of 45 trials of aprotinin in surgical patients even comment on renal function, and of those trials, none were powered to discern renal failure, leaving earlier concerns unchecked.<sup>10</sup> However, review of this evidence suggests the presence of several renal “safety signals,” including aprotinin-associated  $\alpha_1$ -microglobulin production,<sup>8</sup> tubule-cell deposition of protein bands and proteinuria,<sup>8</sup> dose-dependent increases in creatinine,<sup>5,9</sup> renal dysfunction,<sup>9</sup> and platelet-fibrin thrombotic occlusions of the renal arterioles after death.<sup>7</sup> Of note, even in a small study (involving 57 patients) that concluded that aprotinin was safe (albeit with concern regarding a possible type 1 statistical error), 90 percent suppression of urinary kallikrein excretion occurred, with arithmetic increases in sodium excretion and osmolar clearance.<sup>29</sup>

Our data from approximately 1300 aprotinin-treated patients as compared with about 1300 control patients, then, clearly give credence to early concerns stemming from findings in animal models<sup>20-24,26</sup> and preliminary findings in patients<sup>5,7-9</sup> — namely, that aprotinin is associated with severe renal adverse events and that this association is dose-dependent. The lysine analogues, in contrast, are excreted nearly intact within 24 hours after intravenous administration, with their renal clearance approximating creatinine clearance. Moreover, few reports document an association between these agents and renal dysfunction<sup>3</sup> — a renal-safety profile validated by our results.

Our findings raise concerns regarding the proclivity of aprotinin, but not the lysine analogues, to instigate cardiovascular and cerebrovascular thrombosis. Although questions regarding each of the agents have been raised, as indicated by early case reports showing a propensity for thrombosis, most compelling is the evidence relating to aprotinin, which distinguishes itself by at least five properties: inhibition of soluble proteases (e.g., kallikreins, plasmin, and trypsin); inhibition of activated protein C; preservation of platelet adhesive and aggregatory properties; impairment of vascular endothelial-cell function (in the coronary and cerebral arteries and aorta)<sup>20,21,23,27,28,30,31</sup>; and selective impairment of endothelium-derived relaxation by dose-dependent inhibition of nitric oxide synthesis and release.<sup>27,32</sup>

A possible link between aprotinin and intravascular thrombosis has been observed in several *in vivo* animal models<sup>27,28</sup> as well as in humans — in association with biogenic materials (catheters, cannulas, and oxygenators); within coronary grafts; within the native coronary microcirculation; in the aorta; and disseminated throughout the microvasculature of the heart, lung, brain, and kidneys.<sup>5-7,33-36</sup> Randomized clinical trials yielded mixed findings.<sup>5,7,37-39</sup> Noteworthy, however, are the findings of a larger, more recent, sponsor-supported trial,<sup>33</sup> which demonstrated that aprotinin-treated patients (vs. those given placebo) had a significantly greater risk of saphenous-vein occlusion, but even then the results were interpreted as inconclusive. For both aminocaproic acid and tranexamic acid — although reports of related intravascular thrombosis exist — no study has reported a significant association.<sup>3</sup>

Our findings in patients undergoing primary surgery — namely, that aprotinin-treated patients are at greater risk for ischemic damage to the heart than are either control patients or those receiving aminocaproic acid or tranexamic acid — are thus in agreement with data from the prior *in vivo* and *in vitro* studies<sup>27,28,30,34</sup> and the majority of the coronary-graft investigations.<sup>5,7,33,37</sup> Similarly, with regard to encephalopathy, our findings are consistent with those of earlier studies of microvascular thrombosis<sup>28,34</sup> and specifically with those described by Sundt et al.,<sup>7</sup> who reported platelet-fibrin thrombi among multiple vessels, including the cerebral arteries, on postmortem examination of patients who had received aprotinin. In contrast, among patients undergoing complex procedures, aside from renal outcomes, we found no other drug associations, probably because the proven blood-sparing salutary effects of antifibrinolytic therapy in patients undergoing complex surgery<sup>10</sup> may offset any thrombotic effects. This hypothesis is supported by our secondary finding that among patients with hemorrhage, aprotinin was associated with an increase in the risk of cardiovascular events (34 percent, vs. 19 percent in the control group;  $P=0.04$ ), whereas no such difference existed among patients without hemorrhage (23 percent and 24 percent, respectively;  $P=0.79$ ).

Given our findings, especially with regard to serious renal events among patients undergoing either primary or complex surgery, and given the

cost of aprotinin therapy, which is at least 10 times that of aminocaproic or tranexamic acid, we estimate that considerable global health care savings would accrue if aprotinin were replaced by either aminocaproic acid or tranexamic acid. Specifically, extrapolating international-use patterns, we estimate that for renal complications alone, the replacement of aprotinin with aminocaproic acid would prevent renal failure requiring dialysis in 11,050 patients per year, yielding an indirect savings (from the saved cost of dialysis) of more than \$1 billion per year, in addition to direct savings (from reduced drug costs) of nearly \$250 million per year. Replacement of aprotinin with tranexamic acid would prevent 9790 complications necessitating dialysis each year, yielding similar direct and indirect savings.

Regarding potential study limitations, we should note that large-scale, randomized, controlled trials — though ideal for assessing post-marketing drug safety — are difficult (if not impossible) to conduct in the setting of embedded practice, for several reasons: there is inherent bias in the selection of patients to be subjected to “nonroutine” treatments; it is necessary to withhold salutary blood-sparing therapies from those assigned to placebo; there may be reluctance to include the sickest patients, who are those most likely to have adverse events; the required sample size and cost (to detect less frequent safety events) are substantial; and there may be reluctance (a disincentive) on the part of sponsors to discern carefully the risk of a marketed drug. Given that, assessment of safety in observational studies, when sufficiently comprehensive and large, may offer critical insights, even in light of recognized limitations.

Therefore, we assessed safety in a comprehensive, large-scale, observational study based on randomized patient selection, inclusion of more than 800 high-risk patients per group, and measurement of more than 200 covariates (by drug and by outcome) per patient — an approach that permitted nonparsimonious propensity analyses as well as multivariable corrections for the multiple covariates of organ-specific outcomes.<sup>40</sup> As such, we believe that our findings, particularly with respect to renal failure, are substantive with respect to effect size, consistency between the primary-surgery and complex-surgery groups, and dose response and that they are notable for their consistency with early *in vivo* and *in vitro* animal studies and several suggestive case reports. In addition, our specific analyses of aprotinin as compared with aminocaproic acid and tranexamic acid allowed us to compare patients to whom an antifibrinolytic agent had been administered, thereby mitigating selection bias.

In conclusion, the observed association between aprotinin and serious end-organ damage indicates that continued use is not prudent, whereas the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

The Ischemia Research and Education Foundation (IREF) is an independent, nonprofit foundation, formed in 1987, that mentors clinical investigators through observational studies and clinical trials addressing ischemic injury of the heart, brain, kidney, and gastrointestinal tract. The Multicenter Study of Perioperative Ischemia (McSPI) Research Group, formed in 1988, is an association of 160 international medical centers located in 23 countries, organized through, and supported by grants from, IREF.

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No potential conflict of interest relevant to this article was reported.

#### APPENDIX

The following institutions and persons coordinated the Multicenter Study of Perioperative Ischemia Epidemiology II (McSPI EPI-II) study: *Study Chairman* — D. Mangano; *Senior Editors* — J. Levin and L. Saidman; *Study Design and Analysis Center, IREF* — P. Barash, M. Brual, C. Dietzel, A. Herskowitz, Y. Miao, T. Titov, and I.C. Tudor; *Editorial/Administrative Group* — D. Beatty, I. Lei, and B. Xavier.

The following institutions and persons participated in the McSPI EPI-II Study: *United States*: University of Chicago, Weiss Memorial Hospital — S. Aronson; Beth Israel Deaconess Medical Center, Boston — M. Comunale; Massachusetts General Hospital — M. D’Ambra; University of Rochester — M. Eaton; Baystate Medical Center — R. Engelman; Baylor College of Medicine — J. Fitch; Duke Medical Center — K. Grichnik; University of Texas Health Science Center at San Antonio (UTHSCSA) Hospital and Audie L. Murphy Memorial Veterans Hospital — C.B. Hanter; St. Luke’s-Roosevelt Hospital — Z. Hillel; New York University Medical Center — M. Kanchuger and J. Ostrowski; Stanford University Medical Center — C.M. Mangano; Yale University School of Medicine — J. Mathew, M. Fontes, and P. Barash; University of Wisconsin — M. McSweeney and R. Wolman; University of Arkansas for Medical Sciences — C.A. Napolitano; Discovery Alliance — L.A. Nesbitt; Veterans Affairs (VA) Medical Center, Milwaukee — N. Nijhawan; Texas Heart Institute, Mercy Medical Center — N. Nussmeier; University of Texas Medical School, Houston — E.G. Pivalizza; University of Arizona — S. Polson; Emory University Hospital — J. Ramsay; Kaiser Foundation Hospital — G. Roach; Thomas Jefferson University Hospital, MCP Hahnemann University Hospital — N. Schwann; VA Medical Center, Houston — S. Shenaq; Maimonides Medical Center — K. Shevde; Mt. Sinai Medical Center — L. Shore-Lesserson and D. Bronheim; University of Michigan — J. Wahr; University of Washington — B. Spiess; and VA Medical Center, San Francisco — A. Wallace. *Austria*: University of Graz — H. Metzler. *Canada*: University of British Columbia — D. Ansley and J.P. O’Connor; the Toronto Hospital — D. Cheng; Laval Hospital, Quebec — D. Côte; Health Sciences Centre—Uni-

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cine with the goal of simply becoming competent. I want to be the kind of doctor whom a patient can trust, the kind who listens and touches and takes the

time to look at a patient to see how he or she is truly faring. For now, I can count my improved sense of smell as a small victory in that quest.

(Identifying details about the patient have been changed to protect his privacy.)

Dr Bombback is a resident in internal medicine University of North Carolina Hospitals Chapel Hill

#### FOCUS ON RESEARCH

## First, Gather the Data

David Hunter, M B , B S.

It is a cornerstone of medical practice to "first, do no harm." Yet the body of evidence that is sufficient to demonstrate efficacy for a new drug is rarely large enough to provide absolute assurance that harmful side effects do not exist. Thus, ongoing surveillance is necessary to detect adverse events.

There are many reasons why the randomized trials that are adequate for demonstrating drug efficacy may not be adequate for the recognition of important side effects (see table). Randomized trials may be too small to permit the detection of adverse events. For instance, for a continuous outcome such as blood pressure or the change in a pain scale, in a trial with a before-and-after or crossover design, even a few dozen patients may be an adequate number to demonstrate an effect. Trials are often conducted over weeks or a few months, obviating any possibility of detecting longer-latency effects that require exposure for many months or years. Finally, trials may be conducted in a population from which patients with coexisting illnesses have been excluded and thus do not address the question of whether the drug may do harm once approved and prescribed to these patients.

The detection of adverse events also depends on the background incidence of these conditions. The occurrence of two cases of progressive multifocal leukoencephalopathy among 3000 patients treated with natalizumab (Tysabri) in clinical trials was enough to cause the drug to be withheld from the market. Less remarkable conditions, such as heart attacks associated with the use of cyclooxygenase-2 (COX-2) inhibitors, are less likely to raise flags. To detect an increase in the incidence of these conditions requires careful statistical analyses of unblinded data and adequate study power. In this paradoxical manner, we may be better protected from exposure

to drugs that cause very rare medical conditions than from exposure to those that cause common, unremarkable conditions.

Once concern has been expressed about a drug and specific adverse events, it is often proposed that the Food and Drug Administration mandate that companies conduct clinical trials to prove whether the drug does or does not cause the events. This approach is always preferred, but such studies may have to be almost unfeasibly large, and for drugs shown to be efficacious in the treatment of serious conditions, it may be argued that it is unethical to conduct a placebo-controlled trial to search for adverse events (see table). In

Related article, page 353

#### Some of the Reasons That Results of Randomized, Controlled Trials May Not Be Available for Assessment of Adverse Events Associated with Prescription Drugs.

- Trials powered for efficacy may be too small to detect adverse events
- Monitoring of adverse events may not be sensitive or specific for the actual events caused
- Duration of trials may be too short for detection of events requiring longer exposure
- Stopping rules in clinical trials may further shorten the duration of exposure after randomization
- Enrollment criteria may exclude susceptible subgroups
- For industry-sponsored trials, head-to-head comparison of adverse events due to drugs from different manufacturers may not be available
- Follow-up studies to detect adverse events that involve the denial of an efficacious medication to patients may be deemed unethical. Patients may not wish to enroll in such a study
- Funding to conduct trials solely to quantify adverse events may be difficult to obtain

some cases, adverse events have come to light in trials that studied a drug's usefulness in preventing a condition other than the original indication. In the wake of the withdrawal of most of the COX-2 inhibitors, however, it may be difficult to persuade companies to sponsor or cooperate in this type of trial, which was helpful in clinching the case that these drugs caused harm. In any case, it is only a minority of drugs for which evidence may suggest that such large-scale trials for a different indication would be worthwhile.

The main alternative to evidence from randomized trials is evidence from observational studies, in which the occurrence of adverse events in patients who receive a specific drug is compared with this occurrence in patients who do not. The obvious concern in these nonrandomized studies is that the patients who receive a specific drug may have a different level of risk of the adverse events under study from that in the patients who receive no therapy or other drugs — that is, the drug–outcome association is confounded by demographic and lifestyle characteristics or by the presence of coexisting conditions. As in any observational study, there are a variety of design strategies (e.g., matching patients according to potential confounding factors) and methods of analysis (e.g., multivariate regression) that can be used to control for confounding. Yet it is not possible to control for confounding factors that have not been measured. Many drug-surveillance studies rely on large administrative databases, such as those of Medicare and

health maintenance organizations, in which information about individual lifestyle factors (such as cigarette smoking) may not be available, and information on coexisting illnesses or the adverse events themselves may have to be inferred from billing records or hospital admission or discharge codes. To the extent that the information is either nonexistent or only a weak surrogate for the actual events, even the most rigorous statistical methods cannot correct for confounding. Concern about the potential for residual confounding has led to reluctance to consider the results of these studies as anything more than hypothesis-generating or preliminary, and action that could modify the use of harmful drugs has been delayed as a result.

How, then, to reconcile the reasonable skepticism about the results of observational studies with the fact that they may be the only source of evidence on the side effects of drugs? In this issue of the *Journal*, Mangano and colleagues (pages 353–365) provide an example of the type of study that may be a model for the future. Faced with a question regarding the safety of specific antifibrinolytic agents given to minimize blood loss after certain cardiac surgical procedures, which they determined could not be answered with a randomized trial because of ingrained practice, the authors conducted a large multi-institutional study with the aim of optimizing the availability of data on potential confounding factors. The authors collected a large amount of data (about 7500 data fields per patient) on the characteristics of the patients, patients' co-

existing illnesses and selected adverse outcomes. This approach permitted the use of propensity-score and conventional multivariate techniques to control confounding and ensured that the clinical outcomes of interest were not obscured by misclassification due to a lack of clinical detail or an inaccurate administrative assignment of diagnostic codes. These prodigious data pointed to an increase in the risk of renal failure and cardiac events with the use of one of three drugs. Because extensive data were collected, the estimates of risk could be analyzed in conjunction with an extensive array of potentially confounding variables.

Pharmacoepidemiologists are exploring new ways to minimize the potential for confounding in observational studies of the effects of prescription drugs. For instance, the propensity-score approach estimates the probability that a person will be given a prescription for a particular drug on the basis of his or her demographic, lifestyle, and clinical characteristics; this score can then be used to control for potential confounding from these characteristics. Another potential application of the score is to match patients who received the study drug with control patients who did not but who have the same propensity score; in essence, this is an attempt to replicate the process of randomization, in which other unmeasured and potentially confounding characteristics are randomly distributed among those who receive a drug and those who do not. Obviously, a propensity score is only as good as the information used to

calculate it, and it does not account for unmeasured potential confounding factors — this accounting is the main virtue of randomization. Furthermore, in some analyses and simulation studies, the use of the propensity-score approach has not resulted in a measurable improvement in the control of confounding as compared with conventional multivariate methods involving the use of the same information.

In the final analysis, confounding cannot be controlled in an observational study unless information on the confounding factors, or on good surrogates for them, is collected for analysis. Studies such as the one by Mangano and colleagues point the way to the prospective design of studies to assess drug safety and to the collection of as much information as necessary to provide answers of the highest quality. Sub-

stantial questions remain about how to fund and administer these studies, but we need to ensure that skepticism about the value of observational studies does not engender nihilism. In the absence of evidence from randomized trials, the best-quality data must be made available to ensure the safety of medications.

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kidneys from expanded-criteria donors who have acceptable characteristics (age, serologic results, creatinine levels, biopsy results, and pulsatile flow).<sup>13</sup> Such a system can reduce the cold-ischemia time (the time between procurement and transplantation of the organ) and can thereby facilitate the identification of a suitable recipient for a kidney from an expanded-criteria donor.

We are confident that the transplantation community can change the current situation — in which 40 percent of kidneys from expanded-criteria donors are discarded. Innovative strategies can be developed to account for the quality of the potential donor's kidney and the potential benefit to the recipient, and an efficient system of allocation can be put into place that will enhance the opportunities for successful transplantation.

Dr. Delmonico is the president of the OPTN and UNOS. Dr. Burdick is the director of the Division of Transplantation of the Health Resources and Services Administration. No other potential conflict of interest relevant to this article was reported.

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## The Value of Phase 4 Clinical Testing

Gus J. Vlahakes, M.D.

Since its inception in 1988, the Multicenter Study of Perioperative Ischemia Research Group has examined a number of critical issues concerning the outcomes of cardiac surgery and anesthesia. The group's database is a powerful research tool. Its power derives from the high quality of the participating institutions, the capability of these institutions to recruit a large number of patients, and an absence of potential conflict of interest, in part due to the large number of participating institutions and investigators.

In this issue of the *Journal*, Mangano et al.<sup>1</sup> report the findings from a large clinical database built on the data-collection efforts of this group in the United States, Canada, and else-

where. On the surface, this study might appear to be of interest only to those in the specialty fields of cardiac surgery and cardiac anesthesia. However, the importance of this study goes beyond the specific findings of the use of aprotinin to limit blood loss in patients undergoing cardiac surgery. Surgeons and anesthesiologists have long questioned whether the use of aprotinin increases the risk of renal dysfunction and thrombosis.<sup>2</sup> As a consequence, their use of this drug has ranged from use in all patients to minimize postoperative bleeding to use only in patients who have a high risk of substantial postoperative bleeding.

There are two primary reasons why aprotinin

is not used in all patients undergoing cardiac surgery: cost and potential risks. Some surgeons and anesthesiologists who use the drug have been concerned about its potential risks since it was first approved for clinical use; yet until the report by Mangano et al., sufficient data have not been available for an analysis of the risks and benefits of aprotinin. Furthermore, data-driven marketing efforts are under way to expand the indications for this drug. There is evidence that aprotinin modulates the systemic inflammatory response associated with cardiac surgery.<sup>3</sup> This new application of aprotinin may require doses higher than those used for its primary indication — the reduction of bleeding and, hence, of required blood transfusion.<sup>4,5</sup> The possibility of the use of higher doses has raised concern about increased toxicity. Accordingly, until the safety of higher doses is fully explored in a prospective study, the expansion of indications for aprotinin may be premature.

These concerns about the use of aprotinin can be addressed only by the analysis of data obtained from clinical practice and from well-designed clinical trials. Mangano et al. show the value of entities, such as the Multicenter Study of Perioperative Ischemia Research Group, that explore adverse outcomes in post-approval, or phase 4, studies. As pointed out by the authors, although this observational study was not a randomized trial, the incorporation of a large number of patients gives it credibility. In addition, the authors' conduct of an observational study implies an interesting point. When a clinical study is conducted long after a new drug has been approved and introduced into practice, established clinical practice (whether data-driven or not) makes stepping back to perform even an important clinical trial difficult — and makes observational studies a necessary alternative. It would be ideal, therefore, for phase 4 studies to be conducted as soon as possible after a drug has been introduced into clinical practice.

Clinical trials conducted by drug companies are designed to meet Food and Drug Administration (FDA) requirements for safety and efficacy. Under the current regulations, it is understandable that the indications tested in clinical trials are selected to achieve approval expeditiously and to balance patient care, the regulatory process, and business considerations. Although some exclusion criteria in clinical trials are used to ensure patient safety, such criteria decrease

the number of adverse events that might interfere with regulatory approval. Regulatory requirements and the desire to ensure approval often dominate the design of clinical trials. As a result, current phase 3 trials sometimes do not reliably gather information that is clinically useful for the safe expansion of indications, particularly for high-risk patients.

The study of aprotinin by Mangano et al. stands as an example of the importance of phase 4 clinical trials. Although the FDA can mandate the post-approval gathering of data, vendors are given the task of designing the subsequent clinical trials. Thus, the design of clinical trials may still be subject to business considerations. This conflict of interest creates a disincentive to fully explore the safety of a drug in various patient populations. Clinical-investigation groups such as the Multicenter Study of Perioperative Ischemia Research Group, which is able to recruit a large number of patients from excellent clinical centers, may offer the pharmaceutical industry a faster and more economical means of gathering phase 4 data. From the standpoint of patient safety, such research entities can explore new indications and dosing regimens in various patient populations and in a setting relatively free of conflicts of interest. In addition, input from academic medical centers may increase the likelihood of broader applications not originally considered by drug companies in the design of clinical trials.

Phase 4 clinical trials should be required before the indications for pharmaceutical agents are expanded, particularly when increased doses are required or administration in high-risk patients is proposed. Phase 3 studies may suggest that in certain settings, adverse events may occur in some patients, although the incidence in these trials may have been too low to allow full characterization of the events or exclusion criteria may have masked other important issues. Independent clinical research may be ideal for informing decisions to expand indications for pharmaceutical agents, for appropriate patient populations, or for dosing regimens to include previously unapproved doses.

The role of independent clinical research in phase 4 testing should be encouraged and supported by the FDA. The application of FDA data-quality practices in such studies would preclude criticisms of the data analysis, such as the lack of source documentation and the lack of on-site

review of the accuracy of data entry in the study by Mangano et al. Too many pharmacologic agents have entered into clinical practice for which considerable and potentially life-threatening outcomes were recognized only after a large number of patients had been treated. The recent example of cyclooxygenase-2 inhibitors is a high-profile case in point. Recognition of drug-induced toxic effects in certain patient populations or with increased dosing regimens must be reflected in clinical practice as early as possible in order to optimize patient safety.

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