

Mortality Associated With Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery

Dennis T. Mangano, PhD, MD

Yinghui Miao, MD, MPH

Alain Vuylsteke, MD

Iulia C. Tudor, PhD

Rajiv Juneja, MD

Daniela Filipescu, MD

Andreas Hoefft, MD

Manuel L. Fontes, MD

Zak Hillel, PhD, MD

Elisabeth Ott, MD

Tatiana Titov, MD, PhD

Cynthia Dietzel, MD

Jack Levin, MD

for the Investigators of The Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation

APROTININ, A DRUG EFFECTIVE IN limiting blood loss in patients undergoing surgery, was first approved in the United States in 1993 for use in high-risk patients needing coronary artery surgery. In 1998, its use was broadened to include any patient undergoing coronary artery surgery using cardiopulmonary bypass.¹ More than 4 million patients worldwide have received aprotinin since 1985, principally during cardiac surgery, with annual use increasing to 600 000 patients (2005) throughout the world, including 246 000 uses in the United States in the past year.²

For editorial comment see p 527.

Context Acute safety concerns have been raised recently regarding certain hemorrhage-sparing medications commonly used in cardiac surgery. However, no comprehensive data exist regarding their associations with long-term mortality.

Objective To contrast long-term all-cause mortality in patients undergoing coronary artery bypass graft (CABG) surgery according to use of 2 lysine analog antifibrinolytics (aminocaproic acid and tranexamic acid), the serine protease inhibitor aprotinin, or no antibleeding agent.

Design, Setting, and Participants Observational study of mortality conducted between November 11, 1996, and December 7, 2006. Following index hospitalization (4374 patients; 69 medical centers), survival was prospectively assessed at 6 weeks, 6 months, and annually for 5 years after CABG surgery among 3876 patients enrolled in a 62-center international cohort study. The associations of survival with hemorrhage-sparing medications were compared using multivariable analyses including propensity adjustments.

Main Outcome Measure Death (all-cause) over 5 years.

Results Aprotinin treatment (223 deaths among 1072 patients [20.8% 5-year mortality]) was associated with significantly increased mortality compared with control (128 deaths among 1009 patients [12.7%]; covariate adjusted hazard ratio for death, 1.48; 95% confidence interval, 1.19-1.85), whereas neither aminocaproic acid (132 deaths among 834 patients [15.8%]; adjusted hazard ratio for death, 1.03; 95% confidence interval, 0.80-1.33) nor tranexamic acid (65 deaths among 442 patients [14.7%]; adjusted hazard ratio for death, 1.07; 95% confidence interval, 0.80-1.45) was associated with increased mortality. In multivariable logistic regression, either with propensity adjustment or without, aprotinin was independently predictive of 5-year mortality (adjusted odds ratio with propensity adjustment, 1.48; 95% confidence interval, 1.13-1.93; $P = .005$) among patients with diverse risk profiles, as well as among those surviving their index hospitalization. Neither aminocaproic nor tranexamic acid was associated with increased risk of death.

Conclusions These findings indicate that in addition to the previously reported acute renal and vascular safety concerns, aprotinin use is associated with an increased risk of long-term mortality following CABG surgery. Use of aprotinin among patients undergoing CABG surgery does not appear prudent because safer and less expensive alternatives (ie, aminocaproic acid and tranexamic acid) are available.

JAMA. 2007;297:471-479

www.jama.com

Author Affiliations: Ischemia Research and Education Foundation, San Bruno, Calif (Drs Mangano, Miao, Titov, and Dietzel); Department of Anesthesia, Papworth Hospital, Cambridge, England (Dr Vuylsteke); Department of Anesthesia, Escorts Heart Institute, New Delhi, India (Dr Juneja); Department of Cardiac Anesthesia and Intensive Care, Institute of Cardiology, Bucharest, Romania (Dr Filipescu); Klinik und Poliklinik für Anaesthesiologie und Spezielle Intensivmedizin, University of Bonn, Bonn, Germany (Dr Hoefft); Department of Anesthesiology, Yale University, New Haven, Conn (Dr Fontes); Department of

Cardiac Anesthesia, St Luke's Roosevelt Hospital, New York, NY (Dr Hillel); Institut für Anaesthesiologie, Ludwig-Maximilians Universität, Munich, Germany (Dr Ott); Department of Laboratory Medicine, University of California School of Medicine, San Francisco (Dr Levin). Dr Tudor is now with ALZA Corporation, Mountain View, Calif, and Dr Fontes is now with Weill Medical College of Cornell University, New York, NY. **Corresponding Author:** Dennis T. Mangano, PhD, MD, Editorial Office, Ischemia Research and Education Foundation, 1111 Bayhill Dr, Suite 480, San Bruno, CA 94066 (dtb@iref.org).

However, during 2006, the safety of aprotinin came under scrutiny. A sponsor-independent, propensity-adjusted, observational study reported that aprotinin use was associated with a doubling to tripling of the risk of perioperative renal dysfunction and failure requiring dialysis in patients undergoing primary, repeat, or complex coro-

nary artery surgery.¹ These findings were consistent with the original 1993 US Food and Drug Administration observation that in some patients involved in the initial 2 trials, aprotinin was associated with “kidney toxicity.”³ The 2006 study also raised other concerns regarding the association of aprotinin with cardiovascular events (myocardial infar-

tion, heart failure) and cerebrovascular events (encephalopathy) among patients undergoing primary surgery. Since then, several other reports have reached similar conclusions⁴⁻⁶ and a series of case studies indicated aprotinin’s disproportionate association with in-hospital death due to acute pulmonary vascular thromboses.⁷

Table 1. Baseline Characteristics of 4374 Study Patients by Treatment

Characteristic	Control Group (n = 1374), No. (%)	Antifibrinolytic Group								
		Overall (n = 3000)		Aprotinin (n = 1295)		Aminocaproic Acid (n = 883)		Tranexamic Acid (n = 822)		
		No. (%)	P Value*	No. (%)	P Value*	No. (%)	P Value*	No. (%)	P Value*	
Age, mean (SD), y	63.2 (9.8)	64.6 (9.6)	<.001	64.9 (9.2)	<.001	65.1 (9.8)	<.001	63.4 (9.7)	.64	.72
Male sex	1110 (80.8)	2377 (79.2)	.24	1016 (78.5)	.14	690 (78.1)	.13	671 (81.6)	.63	.83
African American, American Indian, or Hispanic ethnicity†	53 (3.9)	300 (10.0)	<.001	56 (4.3)	.54	139 (15.7)	<.001	105 (12.8)	<.001	.24
Education: some college or above	496 (36.1)	918 (30.6)	<.001	280 (21.6)	<.001	398 (45.1)	<.001	240 (29.2)	<.001	.43
Surgery: urgent or emergency status	288 (21.0)	503 (16.8)	<.001	192 (14.8)	<.001	167 (18.9)	.24	144 (17.5)	.05	.63
Medical history										
Angina§	1273 (92.8)	2688 (89.8)	.002	1136 (87.8)	<.001	783 (89.3)	.004	769 (93.6)	.49	.53
Hypertension	831 (60.5)	2100 (70.0)	<.001	907 (70.0)	<.001	660 (74.7)	<.001	533 (64.8)	.04	.52
Myocardial infarction§	714 (52.3)	1548 (52.2)	.98	664 (52.1)	.94	433 (49.6)	.22	451 (55.1)	.19	.80
Congestive heart failure§	461 (33.6)	1078 (36.1)	.12	557 (43.1)	<.001	245 (27.9)	.004	276 (33.7)	.97	.46
Diabetes mellitus	385 (28.0)	898 (29.9)	.20	353 (27.3)	.66	325 (36.8)	<.001	220 (26.8)	.52	.37
Complex surgery	343 (25.0)	999 (33.3)	<.001	495 (38.2)	<.001	285 (32.3)	<.001	219 (26.6)	.38	.43
Ejection fraction ≤44%	247 (18.0)	508 (16.9)	.40	199 (15.4)	.07	169 (19.1)	.49	140 (17.0)	.57	.68
Pulmonary disease§	238 (17.4)	683 (22.8)	<.001	327 (25.3)	<.001	216 (24.6)	<.001	140 (17.1)	.84	.86
Creatinine >1.3 mg/dL on admission	189 (13.8)	449 (15.0)	.29	195 (15.1)	.34	132 (14.9)	.43	122 (14.8)	.48	.56
Renal disease§	183 (13.3)	525 (17.5)	<.001	241 (18.6)	<.001	132 (14.9)	.28	152 (18.5)	.001	.97
Valve disease§	169 (12.4)	622 (20.7)	<.001	329 (25.4)	<.001	168 (19.0)	<.001	125 (15.2)	.06	.62
Carotid disease	153 (11.1)	432 (14.4)	.003	223 (17.2)	<.001	108 (12.2)	.43	101 (12.3)	.41	.42
Percutaneous transluminal coronary angioplasty	138 (10.0)	542 (18.1)	<.001	223 (17.2)	<.001	173 (19.6)	<.001	146 (17.8)	<.001	.71
Liver disease§	106 (7.7)	283 (9.5)	.06	151 (11.7)	<.001	66 (7.5)	.86	66 (8.0)	.79	.90
Stroke§	89 (6.5)	191 (6.4)	.90	90 (7.0)	.62	64 (7.3)	.46	37 (4.5)	.05	.64
Type 1 diabetes mellitus	78 (5.7)	242 (8.1)	.005	116 (9.0)	.001	80 (9.1)	.002	46 (5.6)	.94	.50
Intracoronary stent	54 (3.9)	227 (7.6)	<.001	95 (7.3)	<.001	78 (8.8)	<.001	54 (6.6)	.006	.89
Heart block	10 (0.7)	37 (1.2)	.13	19 (1.5)	.07	5 (0.6)	.65	13 (1.6)	.06	.82
Coronary atherectomy	5 (0.4)	19 (0.6)	.26	11 (0.8)	.10	7 (0.8)	.24	1 (0.1)	.42	.99
Geographic region										
Europe	790 (57.5)	1304 (43.5)		899 (69.4)		0		405 (49.3)		
North America	328 (23.9)	1463 (48.8)		377 (29.1)		846 (95.8)		240 (29.2)		
Asia	227 (16.5)	21 (0.7)		0		0		21 (2.6)		
Middle East	19 (1.4)	66 (2.2)		2 (0.2)		0		64 (7.8)		
South America	10 (0.7)	146 (4.9)		17 (1.3)		37 (4.2)		92 (11.2)		

SI conversion: To convert the value for creatinine to mmol/L, multiply by 88.4.

*P values compare patients treated with an antifibrinolytic agent and control patients.

†P values calculated after adjustment to propensity score deciles in the 4374 study patients.

‡Race or ethnic group determined by clinical investigators.

§Missing data for patients with history of angina: 2 in control group, 1 who received aprotinin, and 6 who received aminocaproic acid; for patients with myocardial infarction missing data for 8 in control group, 21 who received aprotinin, 10 who received aminocaproic acid, and 4 who received tranexamic acid; for patients with congestive heart failure missing data for 4 in control group, 3 who received aprotinin, 5 who received aminocaproic acid, and 4 who received tranexamic acid; for patients with pulmonary disease missing data for 6 in control group, 5 who received aprotinin, 4 who received aminocaproic acid, and 1 who received tranexamic acid; for patients with renal disease missing data for 1 in control group; for patients with valve disease missing data for 9 in control group and 2 who received aprotinin; for patients with liver disease missing data for 1 in control group, 7 who received aprotinin, and 5 who received aminocaproic acid; for patients with stroke missing data for 2 in control group, 3 who received aprotinin, and 6 who received aminocaproic acid.

||Complex surgery was defined as surgery under any of the following conditions: current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively; a history of coronary artery bypass grafting, valve surgery, noncoronary angioplasty or stenting, or other cardiac or vascular noncardiac surgery; and combined current heart surgery.

Despite this evidence, however, recent commentary and regulatory reviews have claimed that perioperative adverse events associated with aprotinin use were transitory and concluded that there should be little concern for longer-term sequelae.^{8,9} However, no comprehensive data exist that describe the long-term effects on survival of either serine protease inhibitors or lysine analogs. Moreover, considerable evidence exists regarding the association of aprotinin with acute coronary graft occlusion in vitro,^{10,11} in animals,^{12,13} and in humans¹⁴⁻¹⁷—thrombotic events that can manifest clinically over months to years following arterial occlusion (long after hospital discharge).¹⁸⁻²⁶

Given the importance of documenting the long-term effects of blood-sparing therapies in general, and aprotinin and the lysine analogs in particular, we investigated this question hypothesizing that use of either serine protease inhibitors or lysine analogs in patients presenting for coronary artery surgery may be associated with higher long-term all-cause mortality.

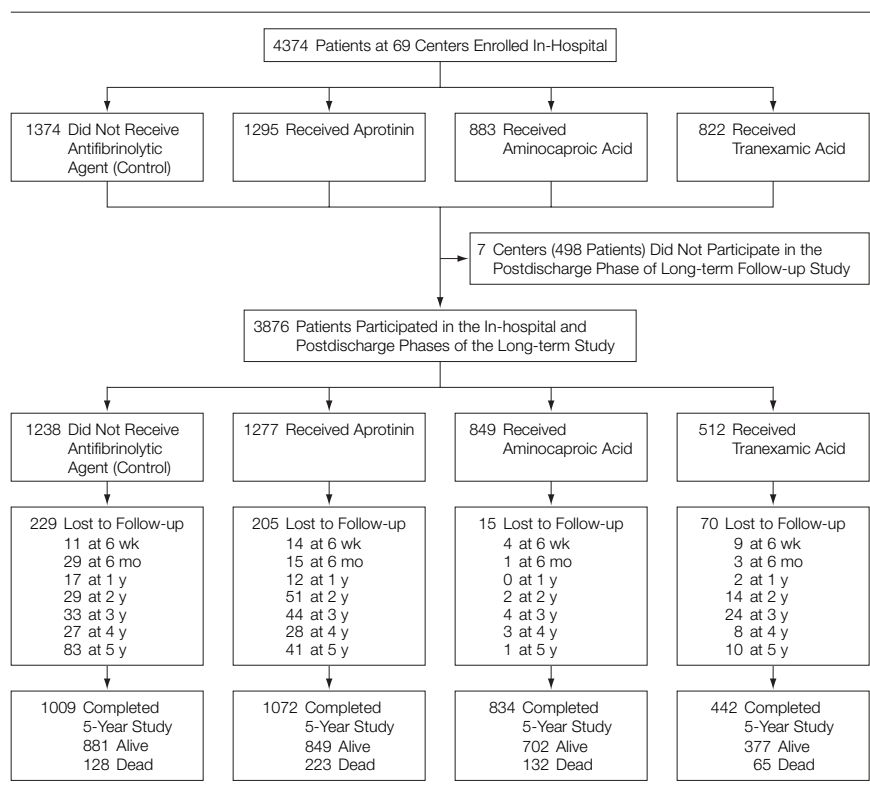
METHODS

Study Design

Following institutional review board approval and written informed consent, we prospectively enrolled at 69 international institutions every *n*th patient with medically refractory coronary artery disease who was scheduled for coronary artery bypass surgery using cardiopulmonary bypass. The sampling rate was $n = N \div 50$ (to the closest integer), where *N* was the number of patients expected to undergo myocardial revascularization surgery over a 1-year period at that institution.

In-hospital data (more than 7500 fields per patient) were collected through discharge among 4374 patients, with race/ethnicity determined by the clinical investigator at each institution (TABLE 1).¹ Thereafter, 62 sites in North and South America, Europe, and Asia agreed to and completed the 5-year long-term study. Investigators prospectively assessed patients using a formal interview and validated instruments at each of 7 long-term time points: at 6 weeks, 6 months,

Figure 1. Flow of Patients Through the Study



and annually at 1, 2, 3, 4, and 5 years after hospital discharge, with all data fields adjudicated centrally (Ischemia Research and Education Foundation) by blinded investigators. National death registries, such as the Social Security Death Registry, were used to supplement death information. Enrollment commenced on November 11, 1996, the in-hospital phase was completed on June 30, 2000, and the long-term program 5-year data collection was completed on January 5, 2006, with the long-term database locked (for all-cause survival) on December 7, 2006.

Outcomes were prespecified and defined by protocol. Clinical decisions were not controlled by study protocol, and all patients participating in the long-term program, as well as those who had died in-hospital, were included (FIGURE 1).

Statistical Analysis

The long-term mortality study was designed prospectively prior to completion of 5-year data collection, database

locking, and study group unblinding. Baseline medical characteristics were compared between the control group and each drug group using the 2-tailed χ^2 test or Fisher exact test, the risk of 5-year mortality was compared with control using the 2-tailed χ^2 test or Fisher exact test, and 5-year mortality of the treated groups was compared with control using the 2-tailed χ^2 test or Fisher exact test. Odds ratios (ORs) with 95% confidence intervals (CIs) with *P* values are presented. Continuous variables were described as mean plus or minus 1 SD, for comparison of 2 groups we used Wilcoxon rank-sum, and for more than 2 groups we used Kruskal-Wallis. Three methods were used to assess drug associations with outcome: survival analysis, multivariable logistic regression, and propensity score adjustment.

Survival analysis was performed on all 4374 patients enrolled in the in-hospital study¹ using Cox regression, illustrated using covariate-adjusted survival with origin time set at the time and

date of surgery, and including right censoring (date of last contact) applied to those patients completing the in-hospital phase but choosing not to participate thereafter, and to those lost to follow-up. The proportional hazards assumption was evaluated by including time-dependent covariates in the model, and found to be appropriate. Imputation for continuous variables, such as body surface area (4 missing values), was performed using mean values by sex; otherwise, a combined variable approach was used. Analyses using nonimputed data produced similar findings as that presented here for imputed data (data available from authors upon request, or from the Ischemia Research and Education Foundation Web site).²⁷ For covariate adjustment of survival curves, the corrected-group-prognosis method was used^{28,29}; the average-of-covariates method produced similar results. Cumulative mortality was calculated as 1 minus adjusted survival.²⁷

We performed multivariable logistic regression using the 97 perioperative risk factors²⁷ to further evaluate the association of drug group with 5-year mortality among patients participating in and completing the 5-year follow-up program

(Figure 1). Univariate associations significant at a nominal 2-tailed $P \leq .20$ were entered stepwise into multivariable logistic models. The final model assessed the association of each treatment (aprotinin, aminocaproic acid, or tranexamic acid vs no treatment) with 5-year mortality in the presence of the significant covariates, also including in-hospital outcome events. Additionally, post hoc, we expanded the list of predefined covariates²⁷ to challenge these findings, but found no material differences.

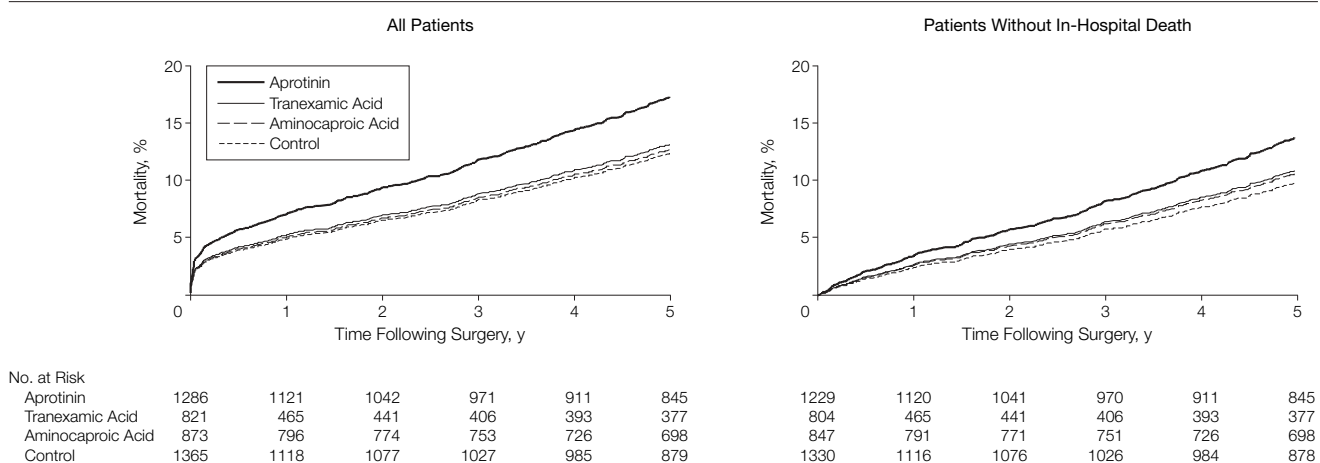
To assess selection bias not adequately controlled by standard multivariable approaches, we used propensity score adjustment methods.^{1,30-32} Using nonparsimonious logistic regression models, we developed propensity scores for any antifibrinolytic treatment (vs no treatment), including 45 treatment selection covariates.²⁷ Covariate interactions were assessed but were found unnecessary for balance of any baseline characteristic. The area under the receiver operating characteristic, referred to as the C-index, was used to assess the discriminate power of the propensity score. The derived propensity scores were then used for multivariable covariate adjustment together with the

antifibrinolytic drug indicator variables. Additionally, we assessed the Cox model findings with and without propensity score adjustment. We also expanded (post hoc) the list of propensity covariates²⁷ to challenge these findings, but found no material differences.

In secondary analyses, we assessed the dose relationship¹ among aprotinin patients who received either a low-dose regimen (loading=1 million KIU; total >2 million KIU), or a high-dose regimen (loading=2 million KIU; total >4 million KIU), compared with control patients. We also repeated the analyses post hoc, forcing each of 3 sets of covariates into the multivariable and propensity models: (1) covariates for all variables in Table 1; (2) covariates for in-hospital and long-term mortality using 5 independent risk indices³³⁻⁴¹; and (3) covariates for combined and individual in-hospital outcomes (cardiovascular, cerebrovascular, renal). These additional covariates are available from the authors upon request or from the Ischemia Research and Education Foundation Web site.²⁷

All statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC). Statistical significance was set at $P < .05$

Figure 2. Cumulative Mortality Curves Compared Among Study Groups



Left, mortality was calculated from the adjusted survival distributions as 1 minus adjusted survival among 4345 patients by study group: control (1365 patients), aminocaproic acid (873 patients), tranexamic acid (821 patients), aprotinin (1286 patients). Patients with missing covariates were excluded (n=29). Survival was significantly different between aprotinin and control ($P < .001$), but not between aminocaproic acid and control ($P = .81$), or between tranexamic acid and control ($P = .64$). Survival was adjusted using the correct-group-prognosis method (see Methods). Patients participating in the in-hospital, but not long-term phase were censored at 6 weeks. Right, mortality calculated as 1 minus adjusted survival among patients without in-hospital death (n=125): control (1330 patients), aminocaproic acid (847 patients), tranexamic acid (804 patients), aprotinin (1229 patients). Patients with missing covariates were excluded (n=39).

(2-tailed). Bonferroni adjustment was used, as appropriate, to adjust the significance limit for multiple comparisons.

RESULTS

Baseline characteristics according to treatment are summarized in Table 1. Acute and chronic vascular disease was prevalent among all patients, with several imbalances noted before propensity adjustment.

Long-term Mortality and Survival

During 5 years, 223 deaths occurred among 1072 aprotinin-treated patients (20.8%), a death rate nearly two-thirds greater than control patients (128 deaths among 1009 patients, 12.7%; covariate adjusted hazard ratio [without propensity adjustment], 1.48; 95% CI, 1.19-1.85; *P*<.001). Rates were similar for aminocaproic acid patients (132 deaths among 834 patients, 15.8%; adjusted hazard ratio, 1.03; 95% CI, 0.80-1.33; *P* = .81) and for tranexamic acid patients (65 deaths among 442 patients, 14.7%; adjusted hazard ratio, 1.07; 95% CI, 0.80-1.45; *P* = .64). Covariate-adjusted survival analyses demonstrated significant association with death for aprotinin, but not for either aminocaproic or tranexamic acid (FIGURE 2)—the latter 2 biochemically similar lysine analogs having nearly indistinguishable mortality (survival) patterns despite disparate use and approval among countries and centers. Aprotinin’s association with mortality persisted among patients who survived their index hospitalization (Figure 2). Proportional hazards analysis using multiple covariates confirmed the survival associations (TABLE 2, TABLE 3).

Multivariable logistic regression confirmed these findings, which indicates that aprotinin was an independent predictor of 5-year mortality (covariate adjusted OR, 1.51; 95% CI, 1.17-1.96) without propensity adjustment, or with adjustment (*C*-index=0.70; OR, 1.48; 95% CI, 1.13-1.93), as well as among those surviving their index hospitalization.²⁷ In contrast, neither aminocaproic nor tranexamic acid was associated with increased 5-year mortality.²⁷

We investigated whether the occurrence of in-hospital ischemic events (cardiovascular, cerebrovascular, renal) affected our findings on mortality over the 5 years following discharge by including in-hospital nonfatal events as covariates. Findings were similar to those in Table 2, Table 3; the OR for aprotinin vs control was 1.52 (95% CI, 1.14-2.02), aminocaproic acid vs control, 1.06 (95% CI, 0.77-1.45), and tranexamic acid vs control, 1.10 (95% CI, 0.74-1.62), and with in-hospital complications significantly associated with postdischarge death, 1.41 (95% CI, 1.10-1.82).

In secondary descriptive analyses, the association of aprotinin with death was found among diverse patient risk profiles³³⁻⁴¹ and surgical factors (FIGURE 3), and among high-risk patients identi-

fied using in-hospital and long-term risk indices (Figure 3).

Finally, the association between aprotinin dose and mortality was assessed using prospective dose definitions as previously reported.¹ We found differences in the point estimates for 5-year mortality (control, low-dose aprotinin vs high-dose aprotinin): 12.7%, 22.8%, 37.9% (*P*<.001); in the ORs (low-dose vs control, 1.58; 95% CI, 1.14-2.20 and high-dose vs control, 2.07; 95% CI, 1.08-3.95); and in the Kaplan-Meier survival differences (control, low-dose aprotinin vs high-dose aprotinin, *P*<.001 [log-rank]).²⁷

COMMENT

Our study, assessing the long-term safety of antifibrinolytic agents, demonstrated that aprotinin—but not aminocaproic acid

Table 2. Cox Proportional Hazards Model for 5-Year Mortality Among 4374 Patients by Study Group*

Risk Factor	Analysis Without Propensity Adjustment†		Analysis With Propensity Adjustment‡	
	Hazard Ratio (95% Confidence Interval)	<i>P</i> Value	Hazard Ratio (95% Confidence Interval)	<i>P</i> Value
Aprotinin vs control	1.48 (1.19-1.85)	<.001	1.37 (1.09-1.73)	.008
Aminocaproic acid vs control	1.03 (0.80-1.33)	.81	0.89 (0.68-1.17)	.40
Tranexamic acid vs control	1.07 (0.80-1.45)	.64	1.04 (0.77-1.41)	.79
Propensity score, deciles			1.06 (1.02-1.10)	.001
Complex vs primary surgery§	1.59 (1.32-1.90)	<.001	1.52 (1.25-1.83)	<.001
Age per 10 y or part thereof older than age 60 y	1.52 (1.37-1.69)	<.001	1.49 (1.34-1.66)	<.001
Medical history				
Congestive heart failure with hospitalization	1.61 (1.29-2.01)	<.001	1.64 (1.31-2.06)	<.001
Diabetes mellitus	1.40 (1.17-1.67)	<.001	1.36 (1.13-1.64)	.001
Multiple occurrences of myocardial infarction	1.27 (1.01-1.61)	.05	1.25 (0.98-1.59)	.07
Peripheral vascular disease	1.46 (1.20-1.76)	<.001	1.46 (1.20-1.77)	<.001
Pulmonary disease	1.31 (1.09-1.58)	.004	1.26 (1.04-1.52)	.02
Syncope	1.41 (1.08-1.84)	.01	1.41 (1.08-1.85)	.01
Valve disease without prior or current valve surgery	1.39 (1.07-1.80)	.01	1.32 (1.01-1.72)	.04
Warfarin in the past week of admission	1.68 (1.29-2.17)	<.001	1.60 (1.23-2.10)	<.001
Creatinine >1.3 mg/dL on admission	1.77 (1.46-2.15)	<.001	1.75 (1.44-2.13)	<.001
Preoperative congestive heart failure	1.27 (1.05-1.53)	.01	1.29 (1.06-1.56)	.01
Preoperative myocardial infarction	2.02 (1.33-3.06)	.001	1.82 (1.16-2.85)	.009
Stroke on admission	1.26 (1.06-1.50)	.01	1.26 (1.05-1.50)	.01

SI conversion: To convert the value for creatinine to mmol/L, multiply by 88.4.
 *Cohort includes patients who died in-hospital and patients who survived their index hospitalization.
 †Excluded were 29 patients with missing values for at least 1 of the risk factors in the model, including the covariates.
 ‡Excluded were 129 patients with missing values for at least 1 of the risk factors in the model, including the covariates.
 §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, or current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively.

or tranexamic acid—is associated with an increased risk of death during the first 5 years following surgery. Importantly, aprotinin’s association with death sustained comprehensive covariate challenges, remaining significant when assessed among multiple subgroups with differing risk profiles and among patients surviving their index hospitalization. The minimal associations of the lysine analogs aminocaproic acid and tranexamic acid with long-term death, along with their previously reported efficacy and safety profiles,^{1,4,6} indicate that safe and inexpensive alternatives exist. Based on our data, we therefore believe that additional concern is now warranted regarding the long-term safety of aprotinin among patients undergoing coronary artery bypass surgery.

These observations suggest that the deleterious perioperative safety find-

ings previously reported for the serine protease antagonist aprotinin are not self-limited, as has been suggested,^{8,9} but that their consequences likely continue over months to years following administration of aprotinin. To provide insight into this observation, we cite 3 related areas of research: (1) clinical experiences suggesting an association of aprotinin with thrombosis (arterial, venous, coronary graft); (2) the natural history of acute thrombosis as it relates to long-term outcome; and (3) prior experiences addressing long-term effects of acute, time-limited therapy.

Concerns of a possible relationship between aprotinin and thrombosis arose soon after approval,^{14,15} suggesting that an antagonist of serine protease activity (aprotinin) might be expected to promote thrombosis, given that tissue plasminogen activator, an agonist of ser-

ine protease activity, prevents coronary occlusion effects in similar patients.⁴² Several other studies, however, did not find an association of aprotinin with thrombosis.⁴³⁻⁴⁵

The US Food and Drug Administration then conducted a retrospective review of 1307 placebo-treated and 2004 aprotinin-treated patients, finding a statistically significant association between aprotinin use and coronary graft closure (occluded grafts).⁴⁶ Based on those data, a prospective randomized trial (International Multicenter Aprotinin Graft Patency Experience [IMAGE]) was conducted, which found a statistically significant 41% increase in coronary graft occlusion occurring within 2 weeks of aprotinin use vs placebo (the primary end point).¹⁶ Given the US Food and Drug Administration’s analysis and the prospective results of the IMAGE study, there exists reasonable evidence to suggest that graft occlusion may occur within days of aprotinin use in at least some at-risk patients.

The natural history of acute coronary thrombosis and occlusion, as well as the experiences in the settings of medical and surgical revascularization, also suggests that clinical sequelae may manifest after months to years following arterial occlusion,¹⁸⁻²⁶ as also noted in the accompanying commentary to the IMAGE study.⁴⁷ Our observation of significant effects long after aprotinin administration is not surprising given the experiences with the serine protease agonist therapy, tissue plasminogen activator, the acute administration of which produces effects lasting for 5 years or longer.⁴⁸ Similar examples are provided by the long-term effects of fibrinolytics (streptokinase),^{49,50} as well as β -blockers (atenolol) in surgical patients.⁵¹ Other perioperative studies indicate that seemingly reversible perioperative adverse events, such as postoperative myocardial ischemia, can have fatal consequences that only are realized months to years after hospital discharge.^{52,53} Accordingly, the long-term adverse effects of aprotinin detected in our study

Table 3. Cox Proportional Hazards Model for 5-Year Mortality Among 4249 Patients Who Survived Index Hospitalization

Risk Factor	Analysis Without Propensity Adjustment*		Analysis With Propensity Adjustment†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Aprotinin vs control	1.47 (1.14-1.90)	.004	1.43 (1.10-1.88)	.009
Aminocaproic acid vs control	1.09 (0.82-1.46)	.56	1.05 (0.77-1.41)	.78
Tranexamic acid vs control	1.12 (0.79-1.60)	.51	1.12 (0.79-1.60)	.52
Propensity score, deciles			1.03 (0.99-1.07)	.22
Complex vs primary surgery‡	1.61 (1.31-1.97)	<.001	1.61 (1.30-1.99)	<.001
Age per 10 y or part thereof over 60 y	1.58 (1.40-1.79)	<.001	1.57 (1.39-1.77)	<.001
Medical history				
Smoking	1.35 (1.07-1.70)	.01	1.33 (1.05-1.69)	.02
Congestive heart failure with hospitalization	1.60 (1.24-2.08)	<.001	1.60 (1.23-2.08)	<.001
No angina§	1.44 (1.09-1.90)	.01	1.47 (1.11-1.95)	.007
Diabetes mellitus	1.47 (1.19-1.80)	<.001	1.48 (1.20-1.82)	<.001
Pulmonary disease	1.37 (1.11-1.69)	.004	1.37 (1.10-1.70)	.005
Peripheral vascular disease	1.51 (1.22-1.89)	<.001	1.54 (1.23-1.92)	<.001
Warfarin in the past week of admission	1.53 (1.12-2.08)	.007	1.50 (1.09-2.06)	.01
Creatinine >1.3 mg/dL on admission	1.60 (1.27-2.00)	<.001	1.55 (1.23-1.95)	<.001
Stroke on admission	1.40 (1.15-1.71)	.001	1.40 (1.15-1.72)	.001
Preoperative myocardial infarction	2.37 (1.48-3.81)	<.001	2.22 (1.35-3.64)	.002
In-hospital composite outcome events	1.46 (1.17-1.81)	<.001	1.47 (1.18-1.83)	<.001

SI conversion: To convert the value for creatinine to mmol/L, multiply by 88.4.
 *Excluded were 39 patients with missing values for at least 1 of the risk factors in the model, including the covariates.
 †Excluded were 128 patients with missing values for at least 1 of the risk factors in the model, including the covariates.
 ‡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, or current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively.
 §No angina indicates admission to cardiac surgery without angina, and generally for other reasons, such as: heart failure, myocardial infarction, sudden death, or failed percutaneous intervention.
 ||In-hospital outcome events included: cardiovascular events (myocardial infarction, congestive heart failure), cerebrovascular events (stroke, encephalopathy), and renal events (renal dysfunction, renal failure).

appear consistent with reported clinical observations in similar patients, in whom the effects of an acutely administered therapy can manifest over multiple years.

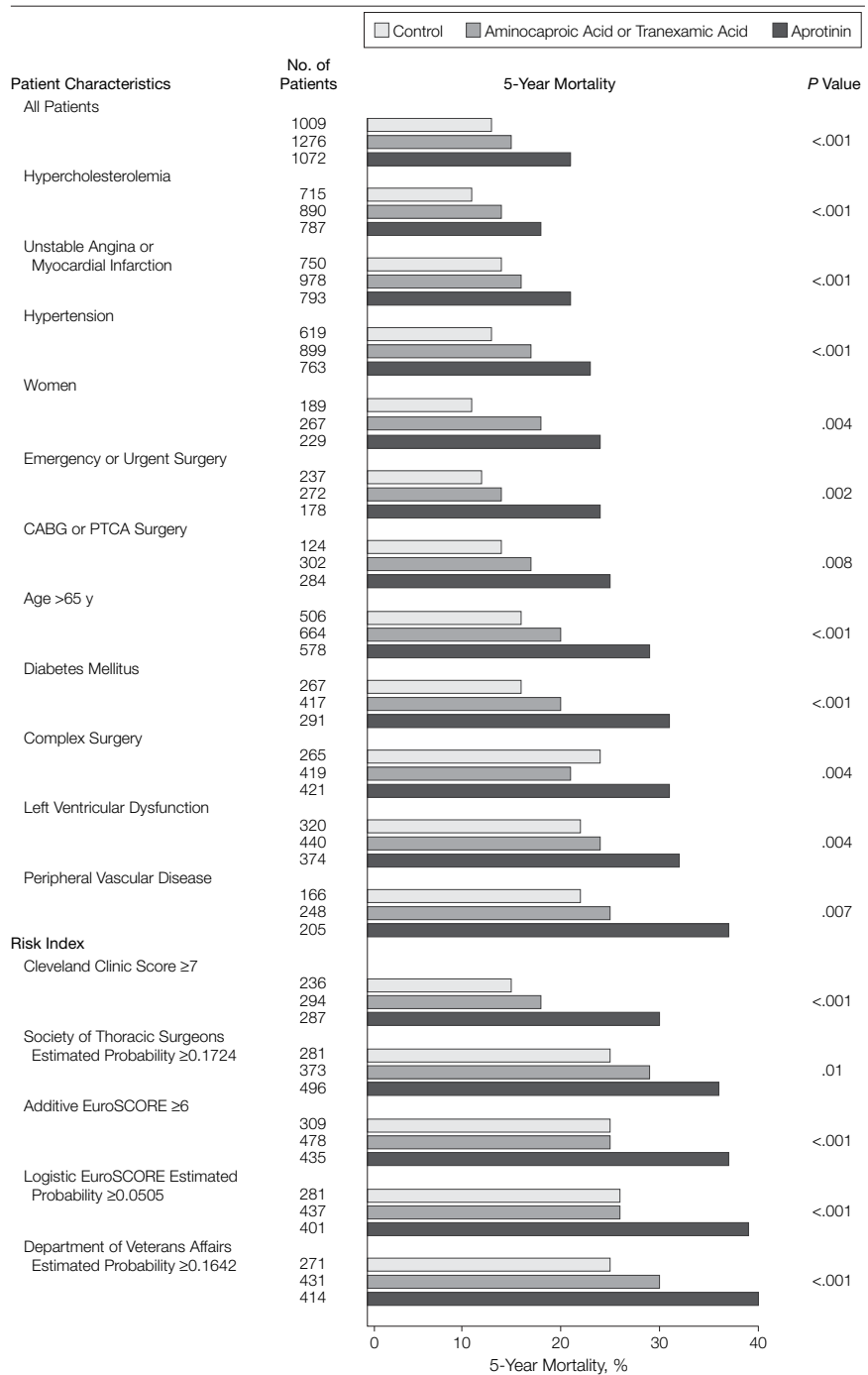
Clinical Implications

We estimate that over the past year, aprotinin was prescribed worldwide to at least 200 000 cardiac surgery patients having a profile similar to patients in our study.² For such patients, our study found a 5% absolute increase in 5-year mortality (1% per year for 5 years) associated with aprotinin use, compared with either aminocaproic or tranexamic acid use. Thus, in 2006 alone, had aprotinin been replaced with either of these generic agents, we estimate that approximately 2000 deaths per year for the next 5 years (or 10 000 total deaths) might have been avoided.

Limitations

Large-scale randomized controlled trials are accepted as the criterion standard for efficacy,⁵⁴ but for assessment of post-marketing safety, these are uncommonly performed even when mandated by regulatory agencies.⁵⁵ Further, even clinical trials are subject to the serious limitation of patient selection bias, given post-marketing imbedded practice—a consideration that has been recognized¹ and thoroughly addressed and is based on a clinician’s hesitancy to either withhold a perceived effective therapy (placebo group assignment) or administer a perceived unsafe drug (drug group assignment).³² Despite the well-known limitations of observational studies, we note that our conclusions survived multiple primary and secondary covariate challenges and were consistent across multiple risk groups (Figure 3). Despite differences in use patterns by center and by country for the biochemically similar lysine analogs, aminocaproic acid and tranexamic acid, their long-term survival patterns were virtually identical (Figure 2). This likely reflected that drug effect predominated over any selection pattern biases that may have existed, findings confirmed by the

Figure 3. Long-term Mortality by Patient Characteristics and Risk Indices



CABG denotes coronary artery bypass graft surgery; PCTA, percutaneous transluminal coronary angioplasty 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; or current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively. Adapted scores for risk indices are based on in-hospital indices: Cleveland Clinic (24% of patients met score criterion)^{33,34}; Society of Thoracic Surgeons (score denotes estimated probability for mortality, 34% met score criterion)^{35,36}; additive European system for cardiac operative risk evaluation (EuroSCORE) (36% met score criterion)³⁷; logistic EuroSCORE (score denotes estimated probability for mortality, 33% met score criterion)³⁸; and Department of Veterans Affairs (score denotes estimated probability for mortality, 33% met score criterion).^{39,40} P values were calculated using 2-tailed χ^2 comparisons among the 3 groups.

negligible effects of propensity adjustment on their relative survival patterns, even when a nonparsimonious approach was taken.

Regarding the concern that patients receiving aprotinin may have had more complex or advanced preoperative disease (Table 1), we believe that such differences had little effect on our 5-year mortality findings for a number of reasons: (1) all variables included in Table 1 were assessed in proportional hazard and logistic regression analyses and found to have little effect on the association between aprotinin and mortality with or without propensity correction; (2) none of the imbalances (bleeding agent vs no bleeding agent groups) shown in Table 1 remained significant following propensity adjustment; (3) among the patients with risk factors for in-hospital renal, cardiovascular, and cerebrovascular events (Figure 3), the associations for aprotinin—and lack of association for aminocaproic and tranexamic acid—persisted; (4) these associations prevailed for at-risk patients as characterized by risk indices for in-hospital and long-term events³³⁻⁴¹ (Cleveland Clinic, Society of Thoracic Surgeons, additive EuroSCORE, logistic EuroSCORE, Veterans Affairs indices) (Figure 3) and although these indices were developed primarily for in-hospital events, we believe they are useful in this study for descriptive purposes; and (5) regarding survival, our findings using proportional hazard techniques (Table 2, Table 3) and adjusted mortality (survival) curves (Figure 2) indicate that the association between aprotinin and mortality remained significant when adjusted for pre-existing disease. Thus, we believe that our findings are substantive for effect size and consistency among risk groups, as well as for their conformity with the earlier IMAGE trial and US Food and Drug Administration review findings regarding aprotinin's association with acute occlusion of newly placed coronary vein grafts.

We acknowledge that 7 of the original 69 centers did not participate in our long-term program, reducing our cohort by 11%; however, we believe this reduction had little effect because the

in-hospital mortality by study group was similarly distributed among the 62 centers participating in this study vs the 7 centers that did not (data available from authors upon request). Additionally, although 87% of participating centers had complete 5-year survival data, 13% of patients were lost to follow-up between 6 weeks and 5 years and were censored in survival analyses. The distribution of these patients among the study groups, however, was similar.

Regarding secondary dose-relationship analyses, we suggest cautious interpretation. The relationships, which contrasted 3 groups (control-no drug, low-dose, high-dose) were based on dose criteria that—although defined prospectively—were made intentionally rigid, thereby minimizing clinician subjectivity in dose choice, use of comingled (low-high) doses, or inadequate- or excessive-dose regimens. While we believe our findings are reliable for the predefined subgroup, we recognize that a sizeable number of patients not meeting the criteria were not included in the analysis. Thus, the dose/relationship findings only are suggestive and should be interpreted as such.

CONCLUSIONS

The association between aprotinin and long-term mortality indicates that serious safety concerns extend beyond the perioperative period. Therefore, continued use of aprotinin in this population does not appear prudent, given that safer alternatives—aminocaproic acid and tranexamic acid—are available.

Author Contributions: Dr Mangano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mangano.

Acquisition of data: Vuylsteke, Juneja, Filipescu, Hoeft, Fontes, Hillel, Ott, Titov, Dietzel.

Analysis and interpretation of data: Mangano, Miao, Tudor.

Drafting of the manuscript: Mangano.

Critical revision of the manuscript for important intellectual content: Mangano, Miao, Vuylsteke, Tudor, Juneja, Filipescu, Hoeft, Fontes, Hillel, Ott, Titov, Dietzel, Levin.

Statistical analysis: Mangano, Miao, Tudor.

Obtained funding: Mangano.

Administrative, technical, or material support: Mangano, Vuylsteke, Juneja, Filipescu, Hoeft, Fontes, Hillel, Ott, Titov, Dietzel.

Study supervision: Mangano, Dietzel, Titov.

Financial Disclosures: Drs Filipescu and Fontes re-

port receiving grants and meeting expense reimbursement from Bayer Incorporated. No other authors reported financial disclosures.

Funding/Support: The Ischemia Research and Education Foundation (IREF) funded the EPI-II in-hospital and long-term follow-up study.

Role of the Sponsor: The IREF supported data collection, including site grants, central analysis and data disposition, manuscript grants, and publication of the findings.

McSPI EPI-II In-Hospital/Long-term Study: The following institutions and individuals took part in the McSPI EPI-II study: D. Mangano, study chairman; J. Levin and L. Saidman, senior editors; P. Barash, M. Brual, C. Dietzel, A. Herskowitz, Y. Miao, T. Titov, I. C. Tudor, study design and analysis center: Ischemia Research and Education Foundation; D. Beatty, I. Lei, and B. Xavier, editorial/administrative group. **United States:** S. Aronson, M. Chaney, University of Chicago, Weiss Memorial Hospital; M. Comunale, Beth Israel Hospital; M. D'Ambra, Massachusetts General Hospital; R. Engelman, Baystate Medical Center; J. Fitch, F. Masud, Baylor College of Medicine; K. Grichnik, Duke Medical Center; C. B. Hantler, UTHSCSA-Audie Murphy VA, UTHSCSA-University Hospital; Z. Hillel, St. Luke's Roosevelt Hospital; M. Kanchuger and J. Ostrowski, New York University Medical Center; C. M. Mangano, Stanford University Medical Center; J. Mathew, M. Fontes, P. Barash, Yale University School of Medicine; M. McSweeney and R. Wolman, University of Wisconsin; C. A. Napolitano, University of Arkansas for Medical Sciences; L. A. Nesbitt, Discovery Alliance, Inc; N. Nijhawan, D. Warltier, VA Medical Center, Milwaukee; N. Nussmeier, Texas Heart Institute, Mercy Medical Center; E. G. Pivalizza, University of Texas Medical School, Houston; S. Polson, University of Arizona; J. Ramsay, Emory University Hospital; G. Roach, Kaiser Foundation Hospital; N. Schwann, Thomas Jefferson University Hospital; S. McNulty, N. Schwann, MCP Hahnemann University Hospital; S. Shenau, VA Medical Center Houston; K. Shevde, Maimonides Medical Center; L. Shore-Lesserson and D. Bronheim, Mt Sinai Medical Center; J. Wahr, M. Greenfield, University of Michigan; B. Spiess, University of Washington; A. Wallace, VA Medical Center, San Francisco; **Austria:** H. Metzler, University of Graz; **Canada:** D. Ansley and J.P. O'Connor, University of British Columbia; D. Cheng, J. Karski, The Toronto Hospital; D. Côte, Laval Hospital, Quebec; P. Duke, Health Sciences Centre-University of Manitoba; J. Y. Dupuis and M. Hynes, University of Ottawa Heart Institute; B. Finegan, University of Alberta Hospital; R. Martineau and P. Couture, Montreal Heart Institute; D. Mazer, St Michael's Hospital, University of Toronto; **France:** C. Girard, CHRU Le Bocage; C. Isetta, Hospital Pasteur; **Germany:** C. A. Greim and N. Roewer, F. Kehl, Universität Würzburg; A. Hoeft, Universität Bonn; R. Loeb and J. Radke, University of Halle; T. Mollhoff, H. van Aken, Westfälische Wilhelms-Universität Münster; J. Motsch and E. Martin, Universität Heidelberg; E. Ott and P. Ueberfuhr, Ludwig-Maximilians Universität; J. Scholz and P. Tonner, Universität Krankenhaus Ependorf; H. Sonntag, Georg-August Universität Göttingen; **Great Britain:** D. J. R. Duthie, Glenfield Hospital; R. O. Feneck, St. Thomas' Hospital; M. A. Fox, The Cardiothoracic Centre, Liverpool; J. D. Park, South Cleveland Hospital; D. Smith, Southampton General Hospital; A. Vohra, Manchester Royal Infirmary; A. Vuylsteke and R. D. Latimer, Papworth Hospital; **Hungary:** A. Szekely, Orszagos Kardiologiai Intezet; **India:** R. Juneja, Escorts Heart Institute; **Poland:** R. Pfitzner, Institute of Cardiology; **Romania:** D. Filipescu, Institute of Cardiology.

The following individuals and institutions did not participate in the in-hospital phase and the postdischarge phase of the EPI-II study: **United States:** M. Eaton, University of Rochester. The following individuals and institutions participated in the in-hospital

phase but not the postdischarge phase of the EPI-II study: *Colombia*: J. C. Villalba and M. E. Colmenares, Fundacion Clinico Shao; *India*: G. Mani, Apollo Hospital; *Israel*: B. Drenger, Y. Gozal, and E. Elami, Hadassah University Hospital; *Italy*: C. Tommasino, San Faffaello Hospital, Universita de Milano; *Mexico*: P. Luna, Instituto Nacional de Cardiologia; *the Netherlands*: P. Roekaerts and S. DeLange; and *Thailand*: U. Prakanrattana, Siriraj Hospital.

Acknowledgment: We would like to express appreciation to Warren Browner, MD, MPH, California Pacific Medical Center, San Francisco, for his invaluable advice on study design and analysis. There was no financial compensation for the work of Dr Browner.

REFERENCES

1. Mangano DT, Tudor IC, Dietzel C; for the Multicenter Study of Perioperative Ischemia (McSPI) Research Group and the Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med.* 2006;354:353-365.
2. US Food and Drug Administration. Meeting of the cardiovascular and renal advisory committee, September 21, 2006. <http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal>. Accessed January 16, 2007.
3. US Food and Drug Administration. Approval of aprotinin, press release 93-48, December 30, 1993. <http://www.fda.gov/bbs/topics/NEWS/NEW00453.html>. Accessed January 16, 2007.
4. Ad N, Barnett S, Hunt SL, Fitzgerald D, Speir AM; for INOVA Heart and Vascular Institute Falls Church, VA. The use of aprotinin in cardiac surgery is associated with increased risk of renal failure and neurological events [abstract]. *Circulation.* 2006;114(suppl II):1476.
5. Brown JR, Birkmeyer NJ, O'Connor GT. Aprotinin in cardiac surgery. *N Engl J Med.* 2006;354:1953-1957.
6. Karkouti K, Beattie WS, Dattilo KM, et al. Blood conservation and transfusion alternatives. *Transfusion.* 2006;46:327-338.
7. Cooper JR Jr, Abrams J, Frazier OH, et al. Fatal pulmonary microthrombi during surgical therapy for end-stage heart failure. *J Thorac Cardiovasc Surg.* 2006;131:963-968.
8. US Food and Drug Administration. FDA public health advisory aprotinin injection (marketed as Trasylyl), FDA alert P06-19, February 8, 2006. <http://www.fda.gov/cder/drug/advisory/aprotinin.htm>. Accessed January 16, 2007.
9. US Food and Drug Administration. Questions and answers on aprotinin (marketed as Trasylyl). <http://www.fda.gov/cder/drug/infopage/aprotinin/aprotininQA.htm>. Accessed January 16, 2007.
10. Havel MP, Griesmacher A, Weigel G, et al. Aprotinin decreases release of 6-keto-prostaglandin F1 alpha and increases release of thromboxane B2 in cultured human umbilical vein endothelial cells. *J Thorac Cardiovasc Surg.* 1992;104:654-658.
11. Hill GE, Taylor JA, Robbins RA. Differing effects of aprotinin and episolon-aminocaproic acid on cytokine-induced inducible nitric oxide synthase expression. *Ann Thorac Surg.* 1997;63:74-77.
12. Samama CM, Mazoyer E, Bruneval P, et al. Aprotinin could promote arterial thrombosis in pigs. *Thromb Haemost.* 1994;71:663-669.
13. Ülker S, Pascal P, McKeown P, Bayraktutan U. Aprotinin impairs coronary endothelial function and down-regulates endothelial NOS in rat coronary microvascular endothelial cells. *Cardiovasc Res.* 2002;55:830-837.
14. Cosgrove DM III, Heric B, Lytle BW, et al. Aprotinin therapy for reoperative myocardial revascularization. *Ann Thorac Surg.* 1992;54:1031-1038.
15. Saffitz JE, Stahl DJ, Sundt TM, Wareing TH,

- Kouchoukos NT. Disseminated intravascular coagulation after administration of aprotinin in combination with deep hypothermic circulatory arrest. *Am J Cardiol.* 1993;72:1080-1082.
16. Alderman EL, Levy JH, Rich JB. Analyses of coronary graft patency after aprotinin use. *J Thorac Cardiovasc Surg.* 1998;116:716-730.
17. Alvarez JM, Chandraratna H, Newman MA, Levy JH. Case 3-1999: intraoperative coronary thrombosis in association with low-dose aprotinin therapy. *J Cardiothorac Vasc Anesth.* 1999;13:623-628.
18. Rodriguez A, Bouillon F, Perez-Balino N, et al. Argentine randomized trial of percutaneous transluminal coronary angioplasty vs coronary artery bypass surgery in multivessel disease (ERACI). *J Am Coll Cardiol.* 1993;22:1060-1067.
19. King SB III, Lembo NJ, Weintraub WS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. *N Engl J Med.* 1994;331:1044-1050.
20. CABRI Trial Participants. First-year results of CABRI (Coronary Angioplasty vs Bypass Revascularisation Investigation). *Lancet.* 1995;346:1179-1184.
21. Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome. *J Am Coll Cardiol.* 1996;28:616-626.
22. The Writing Group for the Bypass Angioplasty Revascularization Investigators (BARI). Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. *JAMA.* 1997;277:715-721.
23. Henderson RA, Pocock SJ, Sharp SJ, et al. Long-term results of RITA-1. *Lancet.* 1998;352:1419-1425.
24. Feit F, Brooks MM, Sopko G, et al. Long-term clinical outcome in the Bypass Angioplasty Revascularization Investigation Registry. *Circulation.* 2000;101:2795-2802.
25. Keeley EC, Velez CA, O'Neill WW, Safian RD. Long-term clinical outcome and predictors of major adverse cardiac events after percutaneous interventions on saphenous vein grafts. *J Am Coll Cardiol.* 2001;38:659-665.
26. Kaehler J, Koester R, Billmann W, et al. 13-Year follow-up of the German angioplasty bypass surgery investigation. *Eur Heart J.* 2005;26:2148-2153.
27. Ischemia Research and Education Foundation. http://www.iref.org/LTFU_Death_Appendices1_to_8.html. Accessed January 16, 2007.
28. Lee J, Yoshizawa C, Wilkens L, Lee HP. Covariance adjustment of survival curves based on Cox's proportional hazards regression model. *Comput Appl Biosci.* 1992;8:23-27.
29. Nieto FJ, Coresh J. Adjusting survival curves for confounders. *Am J Epidemiol.* 1996;143:1059-1068.
30. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41-55.
31. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998;17:2265-2281.
32. Hunter D. First, gather the data. *N Engl J Med.* 2006;354:329-331.
33. Higgins TL, Estafanos FG, Loop FD, Beck GJ, Blum JM, Parandil L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. *JAMA.* 1992;267:2344-2348.
34. Brenner SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation.* 2004;109:2290-2295.
35. Hattler BG, Madia C, Johnson C, et al. Risk stratification using the Society of Thoracic Surgeons Program. *Ann Thorac Surg.* 1994;58:1348-1352.
36. Papadimos TJ, Habib RH, Zacharias A, et al. Early

- efficacy of CABG care delivery in a low procedure-volume community hospital. *BMC Surg.* 2005;5:10.
37. Nashef SA, Roques F, Michel P, et al. European System for Cardiac Operative Risk Evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16:9-13.
38. Michel P, Roques F, Samer AM, Nashef SAM. Logistic or additive EuroSCORE for high-risk patients? *Eur J Cardiothorac Surg.* 2003;23:684-687.
39. Grover FL, Shroyer AL, Hammermeister KE. Calculating risk and outcome. *Ann Thorac Surg.* 1996;62(suppl):S6-S11.
40. Gao D, Grunwald GK, Rumsfeld JS, Schooley L, MacKenzie T, Shroyer LW. Time-varying risk factors for long-term mortality after coronary artery bypass graft surgery. *Ann Thorac Surg.* 2006;81:793-799.
41. Nilsson J, Algotsson L, Höglund P, et al. Comparison of 19 pre-operative risk stratification models in open-heart surgery. *Eur Heart J.* 2006;27:867-874.
42. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med.* 1993;329:1615-1622.
43. Bidstrup BP, Underwood SR, Sapsford RN, et al. Effect of aprotinin (Trasylyl) on aorta-coronary bypass graft patency. *J Thorac Cardiovasc Surg.* 1993;105:147-153.
44. Lemmer JH Jr, Stanford W, Bonney SL, et al. Aprotinin for coronary bypass operations. *J Thorac Cardiovasc Surg.* 1994;107:543-553.
45. Havel M, Grabenwoger F, Schneider J, et al. Aprotinin does not decrease early graft patency after coronary artery bypass graft despite reducing postoperative bleeding and use of donated blood. *J Thorac Cardiovasc Surg.* 1994;107:807-810.
46. US Food and Drug Administration, Center for Drug Evaluation and Research. Trasylyl application 020304/S004: administrative documents/correspondence, medical officer review (part 2, pages 4, 5, 6), January 3, 1997. <http://www.fda.gov/cder/foi/nda/98/020304s004.htm>. Accessed January 16, 2007.
47. Westaby S, Katsumata T. Aprotinin and vein graft occlusion—the controversy continues. *J Thorac Cardiovasc Surg.* 1998;116:731-733.
48. Kaul P, Armstrong PW, Chang WC, et al. Long-term mortality of patients with acute myocardial infarction in the United States and Canada. *Circulation.* 2004;110:1754-1760.
49. Franzosi MG, Santoro E, De Vita C, et al. Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction. *Circulation.* 1998;98:2659-2665.
50. Baigent C, Collins R, Appleby P, et al. 10-Year survival among patients with suspected acute myocardial infarction in randomized comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ.* 1998;316:1337-1343.
51. Mangano DT, Layug EL, Wallace AW, Tateo IM; for the Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med.* 1996;335:1713-1720.
52. Mangano DT, Browner WS, Hollenberg M, Li JM, Tateo IM; Study of Perioperative Ischemia (SPI) Research Group. Long-term cardiac prognosis following noncardiac surgery. *JAMA.* 1992;268:233-239.
53. Browner WS, Li JM, Mangano DT; SPI Research Group. In-hospital and long-term mortality in male veterans following noncardiac surgery. *JAMA.* 1992;268:228-232.
54. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342:1887-1892.
55. US Food and Drug Administration. Report on the performance of drug and biologics firms in conducting postmarketing commitment studies; availability. *Fed Regist.* 2006;71:10978-10979.