Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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The Effect of Aprotinin on Outcome after CABG Surgery

Supplementary material

1. Propensity matched pairs analysis.

Our initial analysis, which uses the entire cohort of patients, employs statistical adjustment to account for patient characteristic differences between the aprotinin, EACA and no antifibrinolytic therapy groups. The interpretation of the variable of interest (i.e., aprotinin use) in the final model depends on our ability to successfully account for these group differences. Another approach to account for group differences, which does not rely on statistical adjustment, is to create a matched dataset. One-to-one matching is a way to balance the two groups with respect to factors that are known to be associated with aprotinin use; that is, matching constrains the non-aprotinin group to be similar to the aprotinin group.

Using the propensity score, we employed an iterative computer algorithm to match each patient who received aprotinin to the patient most similar in propensity score who did not receive aprotinin. Maximum difference allowed between pairs was 0.02, where the scale ranged from 0 to 1.00. As each match was identified, the pair was removed from the pool such that no aprotinin or control patient was included more than once. Survival and renal endpoints were examined in the resulting matched-pair dataset with statistical methods which take advantage of the pairing, including McNemar's test, generalized estimating equations for clustered logistic regression (for dialysis), and repeated-measures regression (for creatinine change). Models developed in the full cohort were applied to the matched pairs. In the Cox proportional hazards survival analysis, propensity score was accounted for as a covariable in the model, and

correlation of the paired data was accounted for using a robust sandwich covariance matrix estimate.

2. Survival analysis - matched pairs

The matching of aprotinin patients to non-aprotinin controls based on propensity score resulted in 996 pairs of aprotinin patients each matched with a separate control patient within the limit of 0.02; the last 230 were excluded from paired analyses due to no appropriate control patient. Patient characteristics in the matched groups are shown in the table below.

Patient characteristics

	Matched Pairs		
Variable	Control	Aprot	P Value
n	996	996	
Age at surgery	66.6	66.4	0.71
Angina	81.6	81.1	0.77
Aortic Regurgitation			0.68
None	96.18	95.68	
Mild	1.71	1.81	
Moderate	1.61	1.81	
Severe	0.5	0.7	
CPB* Used	97.9	97.9	1.00
Preoperative creatinine	1.3	1.4	0.06
Preoperative CVA*	11.5	11.7	0.89
Family History of CAD*	51.4	50.7	0.75
Hypertension	75.2	74.6	0.79
Hypercholesterolemia	65.2	64.9	0.89
IMA* Used	77.1	77.8	0.71
Left IMA*	75	72.79	
Right IMA*	0.5	3.21	
Both IMAs*	0.7	0.8	
No IMA*	23.8	23.19	
Preoperative NTG*	7.8	8.5	0.57
Preoperative ACEI*	39.2	40.7	0.49
Preoperative antiplatelet	9.8	9.3	0.70
Preoperative diuretic	25.6	24.2	0.48
Mitral valve procedure	15.2	15.7	0.84
None	88.15	87.95	
Annuloplasty	8.43	8.33	
Replacement	3.41	3.71	
CABG* + other procedure	15.4	15.6	0.90
Parsonnet score	13.1	13.1	0.95
Prior CV* intervention	40	38.8	0.57
CPR* at surgery	0.7	1	0.47

Time on CPB* (mins)	150	151.4	0.63
CKD*	6	7.3	0.25
Preoperative salicylates	22.3	23.3	0.57
Smoking history	50.7	51.8	0.63
Tricuspid valve procedure	0.6	1	0.32
Urgency of procedure			0.55
Elective	29.22	31.83	
Urgent	62.95	85.84	
Emergent	7.43	9.04	
Emergent-Salvage	0.4	0.3	
Valve surgery	22.7	22.6	0.96
Aortic stenosis	9.1	8.8	0.81
Aprotinin propensity score	0.31	0.31	0.42
Year of surgery (median)	2002	2003	<0.001
Euroscore	9.71	9.67	0.77
Any RBC's* given	51.6	68.4	<0.001
Diabetes (any type)	41	34.6	0.002
Female sex	35	29.8	0.014
Weight (kg)	84.8	83.7	0.14
Ejection fraction (%)	48.6	47.9	0.67
Ethnicity			0.22
White	84.44	84.34	
African American	14.66	14.76	
Hispanic	0.6	0.1	
Asian	0.3	0.8	

* CPB indicates cardiopulmonary bypass, CVA indicates cerebrovascular accident, CAD indicates coronary artery disease, IMA indicates internal mammary artery, NTG indicates nitroglycerin, ACEI indicates Angiotensin converting enzyme inhibitor, CABG indicates coronary artery bypass graft, CV indicates cardiovascular, CPR indicates cardiopulmonary resuscitation, CKD indicates chronic kidney disease defined as any of: preoperative serum creatinine > 3mg/dl, renal dialysis or renal transplant, RBC indicates red blood cell.

Numbers represent percentages for categorical variables and mean values for continuous variables except where otherwise specified.

Of 30 variables compared, the only significant preoperative differences between the matched pairs were gender, incidence of diabetes and date of surgery. Unadjusted mortality rates between the aprotinin and non-aprotinin groups were similar: simple 30-

day mortality was 4.74% in the aprotinin patients, compared to 4.24% in the non-aprotinin matched controls. One-year mortality was 13.1% in the aprotinin patients and 11.5% in the non-aprotinin matches. The paired McNemar's tests showed no significant difference in raw mortality (30-day P=0.58, 1-year P=0.36). However, when the survival model accounting for covariables was applied to this matched pair subset, the main effect of aprotinin was significant with no age interaction (P=0.002, hazard ratio=1.33, 95% CI 1.11 -1.58). The model adjusted for propensity score, Euroscore, age, date of surgery, and valve procedure. The EACA effect was not significant (P=0.47).

In the separate matching on date of surgery, 1,138 aprotinin patients were matched, with the greatest difference in paired dates being 93 days. With surgery date matched, however, there were significant differences in propensity score, age, and Euroscore (as in the full sample). Again in this subsample, the adjusted survival model showed a significant and consistent effect of aprotinin (P <0.001, hazard ratio 1.66, 95% CI 1.30 – 2.11).

3. Renal function analysis - matched pairs

In the matched-pairs subset, drug effects on creatinine percent-change were tested with a repeated-measures model adjusting for significant covariables from the whole-cohort analysis and accounting for the matching. There was a significant effect of antifibrinolytic treatment (P<0.001), and adjusted pairwise comparisons showed significantly higher increases in the aprotinin cases (mean, 95%CI 48.5, 44.1 - 52.9) when compared with either no-therapy controls (36.4, 27.8 - 45.0, Bonferroni adjusted P=0.04) or EACA controls (33.3,28.0 - 38.7, Bonferroni adjusted P<0.001). For post-operative dialysis, no effect of aprotinin was seen in the matched-pairs analyses either with the unadjusted McNemar's test (P=0.85) or in an adjusted logistic regression accounting for matching (P=0.84).

4. Survival model with creatinine change and blood transfusion included

Variable	DF[+]	Coefficient estimate	Chi-Square	P Value	Hazard ratio	95% CI[+] for HR
Antifibrinolytic treatment †	2		16.77	<0.001	---	---
Aprotinin vs None*	1	1.48	13.27	<0.001^	---	---
EACA vs aprotinin †	1		10.96	0.003^	---	---
EACA vs None	1	0.14	4.96	0.08^	1.15	1.02 - 1.30
Aprotinin propensity score	1	0.12	0.64	0.42	1.13	0.84 - 1.52
Age*	1	0.03	150.36	<0.001	---	---
Year of surgery	1	-0.04	11.02	<0.001	0.97	0.94 - 0.99
Euroscore (Additive)	1	0.12	242.66	<0.001	1.13	1.11 - 1.15
RBC's[+] given	1	0.01	0.01	0.93	1.01	0.89 - 1.14
Valve surgery	1	0.38	28.85	<0.001	1.46	1.27 - 1.67
50% increase in serum creatinine	1	0.16	281.15	<0.001	1.17	1.15 - 1.20
Age x aprotinin interaction*	1	-0.02	8.76	0.003	---	---

[+] DF indicates degrees of freedom, CI indicates confidence intervals, RBC's indicates red blood cells.* Significant interaction makes direct interpretation of parameters for these terms invalid. ^ P value adjusted by Bonferroni for pairwise comparisons † Term not in model: Effect tested by model estimation

5. Causes of death

Cause of Death	AntiFibrinolytic Treatment						All	
	APROT		EACA		NONE			
	N	Tmt %	N	Tmt %	N	Tmt %	N	%
Congestive Heart Failure	13	3.4	36	1.9	7	1.8	56	2.1
Definite Myocardial Infarction	15	4	31	1.6	8	2	54	2
During Cardiac Catheterization	1	0.3	0	0	1	0.3	2	0.1
During or Post Cardiac Surgery	79	20.8	136	7	44	11.2	259	9.5
Noncardiac Medical	80	21.1	652	33.6	115	29.3	847	31.2
Noncardiac Related to Procedure	1	0.3	4	0.2	5	1.3	10	0.4
Other Cardiac Cause	58	15.3	444	22.9	73	18.6	575	21.2
Post-Resuscitation	2	0.5	12	0.6	7	1.8	21	0.8
Probable Myocardial Infarction	0	0	5	0.3	1	0.3	6	0.2
Sudden	9	2.4	54	2.8	10	2.6	73	2.7
To be determined	92	24.3	347	17.9	83	21.2	522	19.2
Trauma	4	1.1	38	2	7	1.8	49	1.8
Unknown	2	0.5	5	0.3	1	0.3	8	0.3
Unobserved	5	1.3	52	2.7	9	2.3	66	2.4
Vascular Cause	18	4.7	126	6.5	21	5.4	165	6.1

6. Propensity score variable selection

104 variables were identified from the database as potentially useful preoperative or procedure-descriptive variables. 20 of these were dropped because of duplicates/illogicals/bad data. 10 were dropped after data inspection (incomplete or unuseful information). 84 (Col A) were tested separately for association with aprotinin use, of which 73 had P<0.1 with aprotinin (2 deemed too clinically important to discard) (Col. B). After further data inspection, 24 either contributed to jointly missing >5% or were used in constructing composite variables or had good duplicate/surrogate alternatives. 51 (Col. C) were tested jointly in a logistic stepwise variable selection process, and 30 (Col. D) were jointly significant and thus selected for the final logistic model.

Column	A	B	C	D
# Variables	84	75	51	30
Variable Label	P<.1	Chk N	Joint Test	FINAL
Age at Surgery	Y	Y	Y	Y
Angina present	Y	Y	Y	Y
Aortic Regurg Grade	Y	Y	Y	Y
Cardiopulmonary Bypass Used	Y	Y	Y	Y
Last Creatinine Before Surgery	Y	Y	Y	Y
Preop CVA	Y	Y	Y	Y
Family History of CAD	Y	Y	Y	Y
Hypertension	Y	Y	Y	Y
Hycholesterolemia	Y	Y	Y	Y
Which Internal Mammary Artery Used	Y	Y	Y	Y
PreOp Inotropic Drugs	Y	Y	Y	Y
PreOp: IV Nitroglycerin	Y	Y	Y	Y
ACE Inhibitors within 24H PREOP	Y	Y	Y	Y
Anti Platelet within 24H PREOP	Y	Y	Y	Y
Diurectics within 24H PREOP	Y	Y	Y	Y
Mitral Valve Procedure	Y	Y	Y	Y
# IMA Distal Anastamoses	Y	Y	Y	Y
Other Cardiac Surgery	Y	Y	Y	Y
Parsonnet Additive Risk Score	Y	Y	Y	Y
Prior Cardiovascular Intervention	Y	Y	Y	Y
PreOp: Cardiac Arrest w/ CPR at Op	Y	Y	Y	Y
Minutes on CPBypass	Y	Y	Y	Y
Preop Renal Dz	Y	Y	Y	Y
PreOp: Salicylates	Y	Y	Y	Y

Cigarette Smoking History	Y	Y	Y	Y
Tricuspid Valve Procedure	Y	Y	Y	Y
Urgency of Procedure	Y	Y	Y	Y
Valve Surgery	Y	Y	Y	Y
Aortic Valve Stenosis	Y	Y	Y	Y
Caucasian Race	Y	Y	Y	Y
Aortic Valve Procedure	Y	Y	Y	
Preop Arrhythmia	Y	Y	Y	
Cannulation	Y	Y	Y	
Congestive Heart Failure	Y	Y	Y	
Chronic Lung Disease	Y	Y	Y	
Cerebrovascular Disease	Y	Y	Y	
Diabetes, with Sequelae	Y	Y	Y	
Ejection Fraction (%)	Y	Y	Y	
Endocarditis in last 6 months	Y	Y	Y	
Immunosuppressive Therapy	Y	Y	Y	
Digitalis within 24H PREOP	Y	Y	Y	
Mitral Regurg Grade	Y	Y	Y	
# Diseased Vessels >50%	Y	Y	Y	
NYHA Class for CHF	Y	Y	Y	
Prior MI	Y	Y	Y	
Peripheral Vascular Disease	Y	Y	Y	
Steroids within 24H PREOP	Y	Y	Y	
Date of Surgery	Y	Y	Y	
Preop TIA	Y	Y	Y	
Mitral Valve Stenosis	Y	Y	Y	
Diabetes (any type)	~~	Y	Y	
Aortic Occlusion Type	Y	Y		
ASA Class 'E'	Y	Y		
ASA Class Number	Y	Y		
Can Cardiovasc System Angina Class	Y	Y		
Creatinine Day1 Preop	Y	Y		
Creatinine Day2 Preop	Y	Y		
Creatinine Day3 Preop	Y	Y		
Hannan Risk	Y	Y		
Most Recent Preop MI Date	Y	Y		
Left Main Dz Max % Stenosis	Y	Y		
LVA Repair	Y	Y		
Atrial Septal Defect Repair	Y	Y		
Ventral Septal Defect Repair	Y	Y		
Prior Cardiac Operations on Bypass	Y	Y		
Prior Cardiac Operations Not on Bypass	Y	Y		
Aprotinin Given at Prev Surg	~~	Y		
Prior CABG	Y	Y		
Prior non-CABG Cardiac Surgery	Y	Y		
Prior PTCA	Y	Y		
Prior Non Surgical Stent Placement	Y	Y		
Prior Valve procedure	Y	Y		
ANGINA 0:Stable 1:UNStable	Y	Y		
Transmural Myocardial	Y	Y		

Revascularization		
Cross-clamp time	Y	Y
Beta Blocker Preop	~~	
HeartPort	~~	
Height (cm)	~~	
Anti Coagulant within 24H PREOP	~~	
Aspirin within 24H PREOP	~~	
Pulmonary Valve Procedure	~~	
Rheumatologic Disease	~~	
FEMALE sex	~~	
Weight (kg)	~~	

7. Patients censored and died by treatment type

	APROT				EACA				NONE			
YEAR	# at Risk	# Deaths	# Censored	K-M Survival Est.	# at Risk	# Deaths	# Censored	K-M Survival Est.	# at Risk	# Deaths	# Censored	K-M Survival Est.
0	1340	6	3	0.9955	6766	9	2	0.9987	2026	1	2	0.9995
1	1331	199	40	0.8459	6755	422	16	0.9363	2023	130	12	0.9352
2	1092	54	276	0.7927	6317	179	163	0.9091	1881	54	109	0.907
3	762	47	189	0.7311	5975	194	247	0.8786	1718	62	153	0.8717
4	526	29	126	0.6816	5534	232	348	0.8397	1503	45	224	0.8421
5	371	16	109	0.6428	4954	211	430	0.8012	1234	37	305	0.8098
6	246	14	100	0.5885	4313	185	400	0.7639	892	28	333	0.7713
7	132	6	46	0.5502	3728	205	562	0.7161	531	15	241	0.7375
8	80	1	36	0.5387	2961	139	657	0.6747	275	12	109	0.6915
9	43	5	19	0.4469	2165	107	771	0.6273	154	4	51	0.6676
10	19	2	12	0.3575	1287	48	641	0.5875	99	3	40	0.6342
11					598	10	549	0.5215	56	1	49	0.5765
All		379	956			1941	4786			392	1628	