Supplementary Appendix

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

Supplement to: Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. N Engl J Med 2008;358:771-83.

APPENDIX:

Technical notes on assessing residual confounding using covariate information from the validation study

Assuming a 2-by-2 table of a dichotomous exposure and a dichotomous confounder, the association between the confounder and exposure can then be measured by the confounder-exposure odds ratio or OR_{EC}, which is a function of the probability that a subject has the confounder and is exposed (P_{C1}) and the marginal probabilities of exposure P_E and confounder P_C :

$$OR_{EC} = \frac{P_{C1}[1 - P_C - P_E + P_{C1}]}{[P_C - P_{C1}][P_E - P_{C1}]} \qquad (1)$$

Assuming no underlying true exposure-disease association or $RR_{ED} = 1$, Walker[1] showed that the apparent relative risk (ARR) is a function of P_{C1}, the marginal probabilities P_E and P_C , and the confounder-disease association RR_{CD}:

$$ARR = \frac{P_{C1}[RR_{CD} - 1] + P_E}{[P_C - P_{C1}][RR_{CD} - 1] - P_E + 1} \frac{1 - P_E}{P_E} . \qquad (2)$$

If additional information is available, e.g., a medical records validation study in a sample of the main administrative database study, such univariate sensitivity analyses can be used to correct for confounders unmeasured in the main study. [2]

If the primary interest is to estimate ARR as a function of OR_{EC} , RR_{CD} , and the marginal probabilities P_E and P_C , we need to solve equation (3) for P_{C1}:

$$\underbrace{P_{C1}{}^2(OR_{EC} - 1)}_{a} + \underbrace{P_{C1}[-P_C OR_{EC} - P_E OR_{EC} + P_E + P_C - 1]}_{b} + \underbrace{P_C OR_{EC} P_E}_{c} = 0 \qquad (3)$$

and P_{C1} can be found as the solution of a quadratic equation of the form

$$P_{C1} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (4)$$

which will then be substituted for P_{C1} in equation (2).

In our internal validation study the following parameters were empirically derived:

$\mathbf{P_E}$, the prevalence of the exposure to aprotinin according to the main study (or validation study since perfectly agreeing)

$\mathbf{P_C}$, the residual prevalence of the confounder not measured or imperfectly measured in the main study. This was calculated after excluding those patients who were correctly captured in the main study as having the confounder present. Thus this is a measure of the prevalence of the confounding factor observed in the validation study in addition to the one already captures (and adjusted for) in the main analysis.

OR_{EC}, the association between study exposure and residual confounding not observed in the main study. This was calculated after excluding those patients who were correctly captured in the main study as having the confounder present. Thus this is a measure of the imbalance of the confounder between exposure groups as observed in the validation study in addition to the one already captures (and adjusted for) in the main analysis. Because of the small sample size of our validation study we encountered cell sizes with zero observations. Such zero cells were assigned 0.5.

RR_{CD}: Using these parameters we calculated the percent residual bias caused by each factor for a number of confounder-disease associations (RR_{CD}) ranging from 1.0 to 5.5. Finally, we picked the "literature-supported bias" estimate that corresponded to the RR_{CD} reported in earlier studies, particularly CABG risk prediction scores.[3,4] The following values of RR_{CD} were used:

	RR_{CD} for death
History of CABG surgery	2.60[1)]
History of percutaneous coronary interventions	1.32[2)]
Prior clopidogrel use	2.50[3)]
Prior aspirin use	1.50[3)]
History of congestive heart failure	1.50[1)]
Hypertension	1.10[2)]
Diabetes	1.15[2)]
Cardio pulmonary bypass time	2.0[3)]

1) According to EuroScore[3]
2) According to STS score[4]
3) Investigator assumption due to lack of confirmed data

All bias estimates are conservative estimates in the sense that they tend to overestimate the amount of bias present for two reasons:

1. This analysis examines each binary confounder variable separately and assumes that there is no association between any other observed and adjusted factors. However, it is likely that factors like age, sex, and diagnostic information that are well captured in the administrative data are associated with the partially unobserved confounder.
2. We further assumed that each of the assessed potential confounding factors act independently of each other and their effect would add up. This is a strong assumption considering that for example heart failure and hypertension are often observed together and will again lead to an overestimation of the combined bias effect by residual confounding.

Table A1: Multivariate adjusted relative risk of renal failure requiring dialysis and in-hospital death among 78,199 patients undergoing CABG surgery in the primary study cohort.

		In-hospital death	
Characteristic		**Odds ratio**	**95% confidence interval**
Aprotinin	Very low dose	1.32	1.08, 1.60
	Low dose	1.36	1.18, 1.56
	High dose	1.75	1.56, 1.97
Aminocaproic acid	Very low dose	0.83	0.72, 0.95
	Low dose	Reference	
	High dose	1.35	1.12, 1.64
Age		0.94	0.90, .98
Age^2		1.00	1.00, 1.00
Sex (male)		0.65	0.59, 0.71
Race/ethnicity	White	Reference	
	Black	1.14	0.96, 1.36
	Other	1.14	1.02, 1.27
Smoking (current, past)		0.74	0.65, 0.84
Admission Year	2003	Reference	
	2004	0.87	0.79, 0.97
	2005	0.78	0.70, 0.87
	2006 (Q1)	0.76	0.64, 0.91
Emergency Admission		1.30	1.13, 1.50
Day of CABG	Day 1	Reference	
	Day 2	1.60	1.41, 1.81
	Day 3 - 5	1.16	1.02, 1.31
	Day 6 +	1.58	1.39, 1.80
Low Income Status		1.26	1.01, 1.57
Marital Status (w/ partner)		0.93	0.86, 1.02
Redo Cardiac Surgery		1.80	1.48, 2.19
Additional cardiac surgery		1.69	1.52, 1.89

Complex CABG surgery		1.10	0.93, 1.30
Number of vessels	1	Reference	
	2	0.94	0.84, 1.05
	3	0.94	0.84, 1.06
	4+	0.93	0.81, 1.07
Pre-existing Percutaneous coronary procedures		0.87*	0.75, 1.00
Diabetes (Dx or medication)		1.45	1.34, 1.58
Hypertension (Dx)		0.46*	0.43, 0.50
Liver disease (Dx)		8.86	7.50, 10.48
COPD/asthma (Dx)		1.37	1.26, 1.50
Cancer (Dx)		0.78	0.67, 0.90
Old MI (Dx)		0.86*	0.75, 0.98
Old Stroke (Dx)		0.87*	0.72, 1.06
Endocarditis (Dx)		2.69	1.88, 3.87
Peripheral artery disease (Dx)		1.28	1.12, 1.45
Chronic kidney disease (Dx) or dialysis before surgery		1.67	1.35, 2.04
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)		2.32	1.45, 3.72
Hosp. CABG volume	0-99	1.47	1.17, 1.85
	100-500	1.17	1.06, 1.29
	>500	Reference	
Hospital size (beds)	< 400	0.98	0.87, 1.12
	400 - 649	1.00	0.89, 1.12
	650 +	Reference	
Region	Midwest	0.82	0.73, 0.92
	Northeast	0.65	0.56, 0.75
	South	Reference	
	West	0.79	0.69, 0.90
Teaching hospital		1.10	1.00, 1.22
Rural hospital		0.80	0.67, 0.96

* Apparent protective effects of factors that are well known risk factors for death are widely observed phenomenon in pharmacoepidemiologic studies using administrative databases and is of little relevance to the interpretation of the main exposure effect:

The sicker patients are the more likely the most acute conditions will be recorded and less acute issues will often remain unrecorded. It was shown that coding of conditions less relevant to the acute care of the index condition represent markers for good health.[5,6] The fact that hypertension was coded in a patient who underwent CABG surgery indicates that this patient was healthy enough that somebody recorded such an obvious and highly prevalent condition, while a severely sick CABG patient would receive codes for several life-preserving procedures. Although such covariates should not be interpreted directly, they nevertheless numerically contribute to the adjustment of the exposure effect of interest.

Table A2: Results from multivariate logistic regression analyses for selected patient subgroups of the 78,199 patients of the primary study cohort stratified by the amount of aprotinin used during the index CABG surgery.*

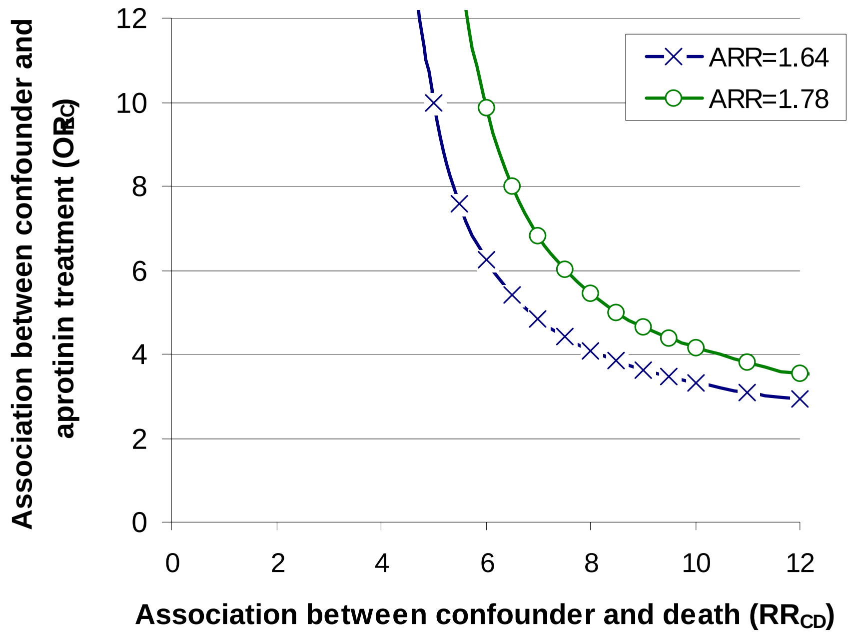
Amount of aprotinin	**Patient with Diabetes** N = 33,840 RR, 95% CI**	**Patients with complex CABG surgery** N = 49,646 RR, 95% CI	**Patients with complex CABG surgery***** N = 18,183 RR, 95% CI	**Patient treated by high-volume surgeons** N = 67,088 RR, 95% CI
Very low	1.36 (1.05 – 1.76)	1.47 (1.18 – 1.82)	1.60 (1.18 – 2.17)	1.44 (1.15 – 1.80)
Low	1.25 (1.03 – 1.52)	1.49 (1.27 – 1.75)	1.64 (1.30 – 2.07)	1.38 (1.18 – 1.61)
High	1.63 (1.39 – 1.91)	1.78 (1.56 – 2.04)	1.81 (1.49 – 2.20)	1.78 (1.56 – 2.02)

* Common reference group was low amount of aminocaproic acid

** RR = relative risk; CI = confidence interval.

*** Complex CABG surgery (stringent definition): redo CABG or other cardiac surgery on the day of CABG.

Figure A1: Sensitivity analysis of the observed associations between aprotinin use and in-hospital death.*



* Assuming the prevalence of an unmeasured confounder of 10% [P(c)=0.1], and treatment prevalence of 43% [p(e) = 0.43].

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