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## Final Report

# Risks of Renal Failure and Death following Use of Aprotinin or Aminocaproic Acid during CABG Surgery

## Part B

### Report on Medical Records Abstraction

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**EXECUTIVE SUMMARY**

We conducted a cohort study to quantify the association between agents used to reduce bleeding during cardiac surgery and serious cardiovascular and renal outcomes as well as in-hospital death. The study compared recipients of aprotinin with recipients of aminocaproic acid among patients undergoing Coronary Artery Bypass Graft (CABG) surgery. Using the Premier Perspective Comparative Database (PCD), a large and geographically representative hospital-based database, we identified 78,199 patients undergoing CABG surgery who received antifibrinolytic therapy during a three-year period starting in 2003.

We defined drug exposure groups, based on the use of intravenous (IV) aprotinin and IV aminocaproic acid on the day of the index CABG procedure. Covariates included 41 patient, doctor and hospital characteristics. Outcomes, assessed during the hospital stay following the day of the index CABG surgery, were renal failure requiring dialysis (indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration) and in-hospital all-cause death as indicated by mode of discharge. We calculated relative risks (RR) as the odds ratio (OR) derived from logistic regression.

Following CABG surgery 2,653 patients required renal dialysis and 2,613 patients died. The estimated risks of these outcomes were meaningfully higher for patients receiving aprotinin compared with aminocaproic acid with respect to renal failure (RR=1.65; 95% CI 1.48-1.84) and death (RR=1.64; 1.50-1.78). These results and those of numerous supplementary analyses support the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients relative to recipients of aminocaproic acid. The findings are not readily ascribable to chance or to distortions arising from any of the dozens of measured patient, hospital, and surgeon characteristics available in the data.

The data do indicate that patients who are more at-risk of study outcomes are somewhat more likely to receive aprotinin, and adjustment for the measured characteristics may not have adequately removed the confounding due to selective use of aprotinin among CABG patients at higher risk of study outcomes (post-CABG dialysis and death). A sensitivity analysis indicated that such an unmeasured confounding variable (or suite of them) defining higher risk of study outcomes would need to be fairly common and possess implausibly large associations with exposure and outcome in order to fully account for the associations we observed in the main study. Accordingly, we concluded that even though possible, it was not in our estimation probable that more detailed ascertainment of covariates could lead to adjustments that fully explain the apparent increases in risk we observed with aprotinin. In this report, we describe a review of individual patient records from which more detailed covariate data assessed residual imbalances in the original study analyses that might explain the differences observed in the primary study.

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We developed a medical record abstraction form to capture clinical data from the medical records of patients who underwent CABG surgery. This abstraction form included many data elements that represented plausible confounding variables (i.e., might be associated with aprotinin use and be risk factors for the study outcomes of post-CABG dialysis of death, and might be present with sufficient prevalence, and that might not be adequately represented in the Premier database).

We accessed patient medical records and completed our medical record abstraction form for a sample of patients undergoing CABG surgery constituting a selected subgroup of 78,199 patients of our cohort study based on administrative data. Nurse abstractors completed the abstract form at a single institution that was a CABG referral center performing all CABG surgeries within an affiliated system of hospitals.

We obtained data from the abstraction of 164 medical records (149 sampled patients without outcomes and 15 patients with outcomes). Of these, 98 (36 aprotinin patients and 62 aminocaproic acid patients) and 8 of the death outcomes (6 aprotinin patients and 2 aminocaproic acid patients) with data on exposure could be linked to CABG patients within the 78,199 patients in our main cohort study.

The data from these linked medical records show, as in the main cohort study, that there are differences between the aprotinin and aminocaproic acid patients with respect to characteristics that influence risk of study outcomes (such as redo CABG). Strong correlation is evident between the data from the medical records and the administrative data with respect to data elements that are common to them. Since there exist differences between the aprotinin and aminocaproic acid groups with respect to the medical record data and the medical record data is only partially represented in the administrative data, there will exist some residual imbalance between aprotinin and aminocaproic acid when adjustment is made using the administrative data only (as was done for the main cohort study). We accounted for the residual differences between the medical records data and the administrative data and developed projections of the effect that the misclassified administrative covariate measures could have on our results and conclude that the residual differences are insufficient to offer a complete explanation of the results from the main cohort study analysis. Indeed, accounting for the differences between the data from the two sources had only limited effect on the results. The present data underscore the robustness of the original analysis and offer a refutation of the hypothesis that the difference in dialysis and mortality outcomes observed among aprotinin users relative to aminocaproic acid users is due to incomplete capture of covariates in the administrative Premier data.

A limitation of this medical record abstraction effort and the analyses based on the resulting data is that these data come from a single institution out of the many that contributed data to the full cohort analysis. This fact limits the generalizability of this analysis accounting for differences between medical

records data and administrative data. Although accounting for the more detailed covariate data obtained from medical records from this one institution made minimal difference, it is possible to hypothesize that more of a difference might be observed if data from other institutions were included. However, this single institution was a large referral institution representing numerous surgeons and a variety of preferences with respect to aprotinin or aminocaproic acid use. Therefore, this sensitivity analysis provides a reasonable impression of the magnitude of the residual confounding that may be present in the main study based on administrative data only. The ability of this study to obtain medical record data on a subset of the patients in the main cohort study establishes the feasibility of this process, and means that medical record abstraction efforts could be employed to address any remaining uncertainty about the quality of the Premier administrative data and analyses based on them.

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## 1. BACKGROUND

i3 Drug Safety recently completed an analysis of the relation between use of aprotinin and aminocaproic acid and the risk of death, acute renal failure, stroke, acute heart failure and revascularization in patients undergoing CABG surgery. The study compared recipients of aprotinin with recipients of aminocaproic acid among patients undergoing Coronary Artery Bypass Graft (CABG) surgery. Using the Premier Perspective Comparative Database (PCD), a large and geographically representative hospital-based database, we identified 78,199 patients undergoing CABG surgery who received antifibrinolytic therapy during a three-year period starting in 2003. We defined drug exposure groups, based on the use of intravenous (IV) aprotinin and IV aminocaproic acid on the day of the index CABG procedure. Covariates included 41 patient, doctor and hospital characteristics. Outcomes, assessed during the hospital stay following the day of the index CABG surgery, were renal failure requiring dialysis (indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration) and in-hospital all-cause death as indicated by mode of discharge. We calculated relative risks (RR) as the odds ratio (OR) derived from logistic regression.

Following CABG surgery 2,653 patients required renal dialysis and 2,613 patients died. The estimated risks of these outcomes were meaningfully higher for patients receiving aprotinin compared with aminocaproic acid with respect to renal failure (RR=1.65; 95% CI 1.48-1.84) and death (RR=1.64; 1.50-1.78). These results and those of numerous supplementary analyses supported the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients relative to recipients of aminocaproic acid. The findings are not readily ascribable to chance or to distortions arising from any of the dozens of measured patient, hospital, and surgeon characteristics available in the data.

The data do indicate that patients who are more at-risk of study outcomes are somewhat more likely to receive aprotinin, and adjustment for the measured characteristics may not have adequately removed the confounding due to selective use of aprotinin among CABG patients at higher risk of study outcomes (post-CABG dialysis and death). A sensitivity analysis indicated that such an unmeasured confounding variable (or suite of them) defining higher risk of study outcomes would need to be fairly common and possess implausibly large associations with exposure and outcome in order to fully account for the associations we observed in the main study. Accordingly, we concluded that even though possible, it was not in our estimation probable that more detailed ascertainment of covariates could lead to adjustments that fully explain the apparent increases in risk we observed with aprotinin.

A remaining element of the study is a medical record abstraction process where medical records of patients in the main cohort study provided more detailed covariate and outcome data allowing for an assessment of the potential for residual confounding or misclassified outcomes to explain the findings in the main cohort study. In this report, we describe the review of individual patient records, the data obtained, and the effect that the more detailed data would have on the original study analyses.

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## 1.1 Patient and institutional characteristics in the main study cohort based on administrative data

The main cohort study included adjustment for 41 covariates that included doctor and hospital characteristics that could be derived from the Premier administrative database. These covariates were used to adjust for differences in patient characteristics among patients who received aprotinin or aminocaproic acid. All patient characteristics were assessed before the day of CABG surgery. Factors measured during surgery, including transfusions or DRG severity levels were not considered. Each of the surgery-related variables below is usually determined prior to surgery.

Socio-demographic factors: age, sex, race, low income status (Medicaid or indigent), marital status (living with partner), year of admission, and smoking status.

Markers of severity or worse prognosis:<sup>1,2,3</sup> admission type (emergency vs. elective), day of CABG surgery after admission, redo CABG surgery, any additional surgery on the day of the index surgery, complex CABG surgery (emergency admission or redo CABG or additional surgery on the day of CABG), number of vessels involved in CABG surgery (1 through 4), percutaneous coronary procedure or thrombolysis before CABG surgery.

Co-morbidities based on discharge diagnoses:<sup>4,5,6,7,8</sup> diabetes, hypertension, liver disease, COPD/asthma, cancer, old MI, old stroke, endocarditis, peripheral artery disease, chronic kidney disease, hemostatic disorder (idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia).

Co-morbidities or severity markers based on procedures and drug use before the index day:<sup>9,10,11</sup> angina as evidenced by nitrate use; renal failure as evidenced by dialysis; heart failure as evidenced by use of dopamine, dobutamine, digoxin, digitoxin, or furosemide; anti-arrhythmic drug use; diabetes as evidenced by antidiabetic drug use on more than 2 days; cardiac arrest as evidenced by a CPR procedure; warfarin use; use of fibrinolytic medications or direct thrombin inhibitors; use of clopidogrel or glycoprotein 2b/3a inhibitors; use of plasma expander; use of radiologic contrast medium.

Hospital and surgeon characteristics: teaching status (teaching vs. non-teaching), location (Midwest, Northeast, South, and West, and urban/rural), hospital size (number of beds), and hospital and surgeon CABG volume.

## 2. METHODS

### 2.1 Study design

We undertook a medical records abstraction study of patients who underwent CABG surgery identified in our main cohort study based on the Premier database. For practical reasons study subjects were selected from a single hospital that has an electronic medical records systems and that Premier has worked with in the past.

We identified patients to validate coding of renal failure, death outcomes, and covariate information not available in the Premier administrative database. It was aimed to identify the following numbers of patients in the validation study:

- (1) Patients with renal failure requiring dialysis following CABG (N=30)
- (2) patients who died during the hospital stay following CABG (N=30)
- (3) a random sample of CABG patients with neither outcome (N=140)

All patients in the main study cohort were grouped in into one of the 3 categories above. We used the identical outcome definitions as in the primary analysis to identify patients with renal failure requiring dialysis and those who died during the index hospitalization. Patients were selected across the entire study period of the main study cohort, i.e. April 1, 2003 to March 31, 2006. This complete and de-identified list was forwarded to Premier. Only Premier could link the data back to patient ID numbers and identify each patient in the hospital center that participated in the validation study (see Abstraction process).

## 2.3 Medical record abstraction

### Abstraction form

We developed a medical record abstraction form to record data about patient characteristics that may be associated with the choice of aprotinin or aminocaproic acid from patient medical records. (Appendix 1) Variables that might serve as proxies for some of these characteristics are available within the Premier administrative database used for the main study analyses, but this incomplete capture might therefore lead to confounding of the association between aprotinin and study outcomes if these factors are also independent predictors of the study outcomes.

Patient characteristics included in the medical record abstraction were identified by searching published literature for associations between patient characteristics and the choice of aprotinin or aminocaproic acid. (Table 1) The listed factors may not be causally related to treatment choice but these factors were mentioned in controlled and uncontrolled studies as well as case reports as factors that may influence the choice of aprotinin, especially relative to aminocaproic acid. We limited medical record abstraction to factors measurable before the start of CABG surgery.

**Table 1: Factors that may be associated with the choice of aprotinin**

	Characteristics	Ref.	Premier*	Comments
1	Previous cardiac surgery (redo surgery)	1	Incomplete	
2	History of liver cirrhosis	2	Yes	
3	History of hematologic (bleeding) disorder such as idiopathic thrombocytopenia (ITP), hemophilia, protein S	3,4, 5,6	No	There has been no clear evidence of the advantages. However, some surgeons and anesthesiologists choose to use antifibrinolytic agents in these cases

	deficiency, protein C deficiency and leukemia.			because of high risk of bleeding.
4	Use of clopidogrel within 96 hours prior to surgery	7,8,9	Incomplete	
5	Use of glycoprotein 2b/3a inhibitors within 24 hours prior to surgery	7,10	Incomplete	
6	Use of low-molecular-weight heparin within 24 hours	7	Incomplete	Unfractionated heparin is unlikely to influence the use of antifibrinolytics because it can be reversed with protamine.
7	Use of warfarin within 4 days prior to surgery	7	Incomplete	PT or INR are highly related to recent warfarin use.
8	Use of aspirin within 7 days prior to surgery	7,11	Incomplete	
9	Preoperative platelet count		No	There is no clear cut-off of those laboratory measures to determine the use of antifibrinolytic agent. However, lower platelet count, higher INR and lower hematocrit are likely associated with antifibrinolytic medication use
10	Preoperative PT, INR, or aPTT		No	
11	Preoperative hematocrit		No	
12	Non-elective surgery (emergency admission and same day surgery)		Yes	There is no clear evidence of the association. However, since nonelective patients could be on unrecognized antiplatelet or anticoagulation medications and require unexpected procedures, the urgency of surgery could be related to decision to use antifibrinolytic medications.

\* This field indicates whether the characteristic could be captured in the Premier database.

We also included in the form patient risk factors for worse health outcomes after CABG surgery. These were identified from established risk prediction models for patients undergoing CABG surgery to identify factors associated with increased risk of renal failure and death. We list all patient factors included in the final published multivariate analyses including model fit statistics. Our final model based on Premier data had c-statistics of 0.80 for renal failure and 0.79 for death, comparable or slightly superior to those models.

The Euroscore mortality risk prediction model has a c-statistic of 0.79 (<http://euroscore.org/index.htm>) for predicting death with the following characteristics.

Age, gender, chronic pulmonary disease, peripheral vascular disease, neurological dysfunction, previous cardiac surgery, creatinine>2.0, active endocarditis, critical preoperative state, unstable angina, left ventricular function, recent MI, pulmonary hypertension, emergency surgery, other than isolated CABG, thoracic aortic procedure, post-infarct septal rupture

The Society for Thoracic Surgery (STS) mortality risk prediction model (for isolated CABG) has a c-statistic of 0.78 (<http://66.89.112.110/STSWebRiskCalc/STS%20Web%20Risk%20Calculator%20Descriptor.pdf>) for predicting death using the following characteristics.

Age, gender, height, diabetes, diabetes control, dialysis-dependent renal failure, preoperative creatinine level, dyslipidemia, chronic lung disease, cerebrovascular disease, cerebrovascular accident, immunosuppressive treatment, previous cardiac intervention, previous PCI interval, MI, MI timing, cardiogenic shock, resuscitation, NYHA class, ejection fraction, number of diseased vessels, left main disease, mitral valve insufficiency, urgency of surgery, IABP timing.

There are a few patient factors listed in these established risk prediction models that may be related to aprotinin use and have not been measured in the database study, but can be identified in the medical records. We also included in the medical record abstraction form items to collect data to address some specific hypotheses that may lead to antifibrinolytic exposure misclassification in the Premier database such as incomplete vial use (resulting in incorrect dosage assignment). We also included items to address hypotheses about outcome misclassification in the Premier database such as hemofiltration used for volume reduction rather than renal failure or incomplete capture of dialysis or miscoding of death. Finally, we included items on the form that addressed issues of timing of aprotinin or aminocaproic acid administration or unplanned additional procedures or unexpected blood loss that may influence the choice to use aprotinin and may also be related to poor outcomes.

### Abstraction process

Medical records were identified and trained reviewers obtained the medical records (electronic or paper) and completed a Medical Records Abstraction (MRA) form. (Appendix 1) The clinical trials manager at the participating hospital system administratively managed the chart abstraction process. Clinicians with a background in cardiac care were responsible for completing the abstraction instrument for each medical record. Both the clinical trials manager and the research manager from Premier Inc. performed oversight and quality assurance review for each completed abstraction form. The research manager at Premier Inc. compiled the final data from the medical record abstraction effort.

### Privacy practices

i3 Drug Safety contracted with Premier to conduct this medical records validation study. For the original cohort study, Premier provided a de-identified data set, which was fully compliant with the 1996 Health Insurance Portability and Accountability Act. For this medical record abstraction study, Premier obtained necessary approvals from the institution where medical records were accessed and conducted all linkage from the original de-identified dataset to patient medical records to perform the abstraction. i3 Drug Safety did not receive individual patient medical records.

## **2.5 Statistical analysis**

### Covariate validation:

For comparison purposes, we tabulated the characteristics of all 78,199 patients in the main cohort study based on data derived from the Premier administrative database. We also tabulated the characteristics (as measured from the Premier administrative database) of the subset of patients for whom medical records were obtained, with stratification according to aprotinin or aminocaproic acid. We further tabulated the characteristics (as obtained from medical records) for the patients with medical record data stratified by aprotinin or aminocaproic acid use. We cross-tabulated patient characteristics obtained from the two sources (medical records and the Premier administrative database).

In a last step, we assessed the potential residual confounding by these independent associations between patient factors not measured or incompletely measured in the main database study and treatment choice. To assess the residual confounding we also needed to estimate the independent effects of these patient factors on renal failure and death. As we could not estimate these associations robustly in the validation study data we used the published associations from the multivariate STS risk prediction models<sup>12,13</sup> and other large studies on patients undergoing CABG surgery<sup>14</sup> as much as possible to compute the potential residual confounding caused of each patient factor.

We tabulated the percent bias possibly caused by a selected number of patient factors identified in the medical records abstraction study for each factor individually. To illustrate the potential magnitude of confounding we included the following factors in the analysis: Redo CABG surgery, history of percutaneous coronary procedures, prior clopidogrel use, prior aspirin use, history of congestive heart failure, history of hypertension, history of diabetes. The combination of these individual bias estimates was calculated as the maximum range of aprotinin effect estimates if all confounders were to act additively (see technical appendix).<sup>15</sup> This sensitivity analysis was based on the in-hospital renal failure requiring dialysis (after excluding pre-existing RF) and death effect estimates combining all doses ( $RR_{\text{dialysis}} = 1.65$ ;  $RR_{\text{mortality}} = 1.64$ ) from the primary study cohort reported in the Addendum to Final Report A<sup>16</sup> and the corresponding outcomes within the first 7 days after CABG surgery ( $RR_{\text{dial-7d}} = 1.84$ ;  $RR_{\text{mort-7d}} = 1.78$ ).

### 3. RESULTS

#### 3.1 Abstraction results

The chart abstraction process was managed under the auspices of the clinical trials department located within the target healthcare system. This group was responsible for identifying and retrieving patient charts randomly identified from the observational study. The patient pool consisted of 269 discharges divided into three component subgroups groups. The distribution of the sample is defined below.

Patient group	N of discharges
Renal Failure	1
Mortality	14
Patients with neither outcome	254

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From this initial sample of 269 patients, a final sample consisting of 149 discharges from the patients with neither outcome, 14 discharges from the mortality group, and one discharge from the renal failure group was selected. Medical record data were obtained from all of the selected patients. The single discharge from the renal failure group was dropped from the study for incomplete data. Of these 163 patients, there were 106 (98 patients without outcome, and 8 deaths) who matched a subject in the original cohorts and analyses are based on these subjects.

### 3.2 Original study patients

The complete listing of patient characteristics based on the Premier administrative data for all 78,199 patients in the original cohort is tabulated. (**Table 3a**) The study outcomes among the aprotinin and aminocaproic acid patients are tabulated. (**Table 3b**)

### 3.3 Characteristics of patients abstracted

The patient characteristics based on the Premier administrative data for sampled patients in this validation study are presented. (**Table 4a**) The patient characteristics based on the Premier administrative data for patients who died are presented. (**Table 4b**)

The patient characteristics based on medical records abstraction data for sampled patients in this validation study are presented. (**Table 5a**) The patient characteristics based on medical records abstraction data for patients who died in this validation study are presented. (**Table 5b**)

### 3.4 Concordance between abstracted data and Premier data

The concordance between medical record abstracted data and Premier administrative data is tabulated. (**Table 6**) The correlations between medical record abstracted data and Premier administrative data is presented. (**Table 7**)

### 3.4 Projection of results to cohort analysis

Based on the effect estimates for in-hospital renal failure requiring dialysis (after excluding pre-existing RF) and death from the primary study cohort after combining all aprotinin and aminocaproic acid doses ( $RR_{\text{dialysis}} = 1.65$ ;  $RR_{\text{mortality}} = 1.64$ , see gray shaded area in **Table 3b**) we conducted a sensitivity analysis to assess the robustness of these estimates regarding residual confounding by factors unmeasured or incompletely measured in the database study. Several patient factors that are independent risk factors for the study outcomes were under-recorded in the database main study resulting in overestimation of the effect estimates. (**Table 2**) For example, incompletely recorded prior CABG surgery (“redo CABG”) resulted in an overestimation by 26%. The observed relative risk for in-hospital mortality of 1.64 (7-day  $RR = 1.78$ ) would change to a  $RR$  of 1.51 had this single factor be recorded accurately in the database study (7-day  $RR = 1.62$ ). Several other factors also reduced the observed  $RR$

had they be accurately recorded in the database. Pre-CABG clopidogrel use, however, was over-recorded in the database and bias correction would change the parameter estimates in the opposite direction, i.e. would result in larger relative risk estimates. This analysis is based on several assumptions as explained in the discussion section.

When all individual biases of the selection of patient factors were added, an overestimation of 35% persisted resulting in a corrected RR estimate for in-hospital mortality of 1.47 (7-day RR = 1.58). Bias assessment for the renal failure requiring dialysis showed similar results (**Table 2**).

**Table 2: Bias and corrected relative risk (RR) estimates of the database study informed by medical records review of selected risk factors.**

	Observed effect estimates according to database study <sup>16</sup>							
	RR <sub>dialysis</sub> = 1.65		RR <sub>mortality</sub> = 1.64		RR <sub>dial-7d</sub> = 1.84		RR <sub>mort-7d</sub> = 1.78	
	Bias estimate	Corrected RR	Bias estimate	Corrected RR	Bias estimate	Corrected RR	Bias estimate	Corrected RR
Redo CABG	8.95	1.60	25.80	1.51	8.95	1.77	25.80	1.62
PTCA	8.60	1.60	5.99	1.60	8.60	1.77	5.99	1.74
Clopidogrel	-4.95	1.68	-15.56	1.76	-4.95	1.88	-15.56	1.92
Aspirin	2.20	1.64	3.28	1.62	2.20	1.82	3.28	1.76
CHF	0.59	1.65	1.48	1.63	0.59	1.84	1.48	1.77
HTN	27.22	1.51	6.33	1.60	27.22	1.66	6.33	1.73
DM	1.75	1.64	0.75	1.64	1.75	1.83	0.75	1.77
Bypass time	4.07	1.62	7.01	1.60	4.07	1.81	7.01	1.73
<b>Additive bias effect</b>	<b>48.44</b>	<b>1.44</b>	<b>35.10</b>	<b>1.47</b>	<b>48.44</b>	<b>1.57</b>	<b>35.10</b>	<b>1.58</b>

#### 4. DISCUSSION

Confounding by indication may occur in non-randomized studies of drug effects if a drug is preferentially used in sicker patients.<sup>17</sup> With multivariate confounder adjustment in our primary cohort analysis we observed a weakening of the association between aprotinin and death (crude 1.83, adjusted 1.64), and renal failure (1.83 vs. 1.60).

The covariates used in the original cohort study were drawn from administrative data and sometimes involved inferences about patients' health state and risk factors from procedures and patterns of drug use. Despite the excellent predictive value of the covariates, as evidenced by the high c-statistics of outcome models comparable to those of accepted prediction scores, the covariates must still have some residual error. In the case of covariates measured with error, progression of risk estimates toward the null with increasing covariate control may suggest that the adjusted estimates are still somewhat biased away from the null although such a conclusion rests on untestable assumptions.

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Several studies had described preferential prescribing of aprotinin in patients undergoing redo CABG surgery while non-aprotinin antifibrinolytics are preferentially used in patients with renal insufficiency.<sup>18</sup> While incomplete measurement and adjustment for the first would lead to spuriously strong associations of aprotinin use with worse health outcomes (i.e. an overestimation of effect), the latter will result in an underestimation of an underlying aprotinin effect on acute renal failure in our study.

The strategies for addressing the potential for unmeasured or residual confounding in the original study: (1) a subset analysis (based on the data-dense population) restricted to patients with at least two hospital stays before the CABG surgery, allowing for more procedural and medication use information to be used in covariate assessment; 2) a subset analysis limited to high volume physicians, making patients more comparable with regard to study outcomes that may be associated with surgeons' CABG volume; 3) an assessment of predictive ability for study outcomes based on measured covariates independent of study drug use category; 4) a quantitative sensitivity analysis that indicated residual confounding would require implausibly strong associations; 5) an instrumental variable analysis based on surgeons' preference for aprotinin as an instrument or proxy for the actual exposure to control for unmeasured patient characteristics.

The results of this original cohort analysis of the experience of patients undergoing CABG, with more than 33,000 aprotinin recipients in comparison to some 45,000 aminocaproic acid recipients, support the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients. The findings are not readily ascribable to chance or to distortions arising from any of the dozens of measured patient, hospital, and surgeon characteristics available in the data. The data do indicate that patients who are more at-risk are somewhat more likely to receive aprotinin, and it is possible (though not in our estimation probable) that more detailed ascertainment of covariates could lead to adjustments that fully explain the apparent increases in risk.

The review of individual patient medical records to assess the quality of covariate data allowed us to re-examine the sensitivity analysis and permitted further adjustment. We conducted a sensitivity analysis informed by results from the medical records validation study to assess whether it is likely that residual confounding could explain the observed associations. Sensitivity analyses of both study outcomes based on the distribution of a selected number of patient factors observed in both the medical records validation study and the database study showed that it is unlikely that the primary study findings can be explained by residual confounding. The relative risk estimates in the pre-specified primary study cohort changed from 1.65 to 1.44 for renal failure requiring dialysis based on this sensitivity analysis. For in-hospital mortality estimates changed from 1.64 to 1.47. Relative risk estimates were higher for the same outcomes when limited to the first 7-days after CABG surgery.

This sensitivity analysis is only a partial demonstration of the potential effects of bias and has several limitations. Most importantly, this analysis is limited to few patient characteristics. These characteristics were selected because they demonstrated larger differences between database recording and results from the medical records review.

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Other factors may have increased the confounding effect, however, the factors included in our sensitivity analyses were considered potentially strong confounders. Nevertheless, they were not able to explain the primary study findings.

The data from these linked medical records show, as in the main cohort study, that there are differences between the aprotinin and aminocaproic acid patients with respect to characteristics that influence risk of study outcomes (such as redo CABG). Strong correlation is evident between the data from the medical records and the administrative data with respect to data elements that are common to them. Since there exist differences between the aprotinin and aminocaproic acid groups with respect to the medical record data and the medical record data is only partially represented in the administrative data, there will exist some residual imbalance between aprotinin and aminocaproic acid when adjustment is made using the administrative data only (as was done for the main cohort study). We accounted for the residual differences between the medical records data and the administrative data and developed projections of the effect that the misclassified administrative covariate measures could have on our results and conclude that the residual differences are insufficient to offer a complete explanation of the results from the main cohort study analysis. Indeed, accounting for the differences between the data from the two sources had only limited effect on the results. The present data underscore the robustness of the original analysis and offer a refutation of the hypothesis that the difference in dialysis and mortality outcomes observed among aprotinin users relative to aminocaproic acid users is due to incomplete capture of covariates in the administrative Premier data.

A limitation of this medical record abstraction effort and the analyses based on the resulting data is that these data come from a single institution out of the many that contributed data to the full cohort analysis. This fact limits the generalizability of this analysis accounting for differences between medical records data and administrative data. Although accounting for the more detailed covariate data obtained from medical records from this one institution made minimal difference, it is possible to hypothesize that more of a difference might be observed if data from other institutions were included. However, this single institution was a large referral institution representing numerous surgeons and a variety of preferences with respect to aprotinin or aminocaproic acid use. Therefore, this sensitivity analysis provides a reasonable impression of the magnitude of the residual confounding that may be present in the main study based on administrative data only. The ability of this study to obtain medical record data on a subset of the patients in the main cohort study establishes the feasibility of this process, and means that medical record abstraction efforts could be employed to address any remaining uncertainty about the quality of the Premier administrative data and analyses based on them.

The sensitivity analysis could not explain the primary study findings despite the fact that it tended to overestimate any bias, because it assumed that all bias estimates were independent of patient factors already adjusted for in the main analysis and because it was assumed that each bias estimate is independent from each other and would add up for the net confounding. Since the regression model in the primary database analysis already adjusted for 41 covariates with good model prediction ( $c=0.8$ ) it is likely that the

potential confounders addressed in the sensitivity analyses were already partially adjusted for in the main analysis although this is not testable.

Thus, the conclusion of this sensitivity analysis informed by detailed covariate data obtained from medical records review in a small study sample confirms our earlier conclusion that it is not probable that confounding due to some mismeasured or unmeasured covariate can explain our primary study findings. The feasibility of abstracting medical records within the Premier database has been confirmed by this effort, and a larger medical records abstraction study could address issues of exposure and outcome misclassification that could not be addressed in the current effort.

## 5. DATA TABLES

**Table 3a: Characteristics of patients undergoing CABG surgery in the primary study cohorts as measured in the Premier database**

Characteristic		Primary study cohort		
		N = 78,199		p-value from Chi <sup>2</sup> test
		Aprotinin N (%)	Aminocaproic acid N (%)	
Number of patients		33,517(42.9)	44,682(57.1)	
Very low dose		3,741(11.2)	19,191(43.0)	
Low dose		10,144(30.3)	19,813(44.3)	
High dose		19,632(58.6)	5,678(12.7)	
Age	18 – 24	2(0.0)	3(0.0)	<0.0001
	25 – 34	64(0.2)	82(0.2)	
	35 – 44	803(2.4)	1,317(3.0)	
	45 – 54	4,141(12.4)	6,198(13.9)	
	55 – 64	8,683(25.9)	12,475(27.9)	
	65 – 74	10,861(32.4)	14,329(32.1)	
	75 +	8,963(26.7)	10,278(23.0)	
Sex (male)		23,637(70.5)	31,906(71.4)	0.01
Race/ethnicity White		26,468(79.0)	33,062(74.0)	<0.0001
	Black	2,119(6.3)	2,254(5.0)	
	Other	4,930(14.7)	9,366(21.0)	
Smoking (current, past)		7,851(17.6)	6,265(18.7)	<0.0001
Admission Year	2003	7,134(21.3)	15,393(34.5)	<0.0001
	2004	10,862(32.4)	14,460(32.4)	
	2005	13,211(39.4)	11,558(25.9)	
	2006 (Q1)	2,310(6.9)	3,271(7.3)	
Emergency Admission		16,540(49.4)	23,721(53.1)	<0.0001
Day of CABG	Day 1	11,432(34.1)	15,621(35.0)	<0.0001
	Day 2	6,762(20.2)	9,387(21.0)	
	Day 3-5	9,552(28.5)	13,011(29.1)	
	Day 6+	5,771(17.2)	6,663(14.9)	
Low Income Status		1,211(3.6)	1,979(4.4)	<0.0001
Marital Status (w/ partner)		21,008(62.7)	28,384(63.5)	0.02
Redo Cardiac Surgery		1,347(4.0)	744(1.7)	<0.0001
Additional cardiac surgery		8,516(25.4)	8,197(18.4)	<0.0001
Complex CABG surgery		21,562(64.3)	28,084(62.9)	<0.0001
Number of vessels	1	6,894(20.6)	8,142(18.2)	<0.0001
	2	10,741(32.1)	15,080(33.8)	
	3	10,270(30.6)	13,861(31.0)	
	4+	5,612(16.7)	7,599(17.0)	
Preexisting Percutaneous coronary procedures		4,448(13.3)	5,677(12.7)	0.02

* Angina (nitrate use)	12,466(37.2)	16,733(37.5)	0.46
* Renal failure requiring dialysis	570(1.7)	469(1.1)	<0.0001
* Heart failure (use of furosemide, digoxin, digitoxin, or dobutamine)	7,048(21.0)	7,346(16.4)	<0.0001
* Anti-arrhythmic drug use	2,867(8.6)	4,161(9.3)	0.0002
* Cardiac arrest	234(0.7)	214(0.5)	<0.0001
* Warfarin use	287(0.9)	257(0.6)	<0.0001
* Fibrinolytic medications or direct thrombin inhibitors	478(1.4)	668(1.5)	0.43
* Use of clopidogrel or glycoprotein 2b/3a inhibitors	6,275(18.7)	6,884(15.4)	<0.0001
* Use of plasma expander	2,447(7.3)	2,817(6.3)	<0.0001
* Use of radiologic contrast medium	6,536(19.5)	10,785(24.1)	<0.0001
Diabetes (Dx, or antidiabetic therapy on more than 2 days)	14,565(43.5)	19,275(43.1)	0.38
Hypertension (Dx)	21,835(65.2)	29,369(65.7)	0.09
Liver disease (Dx)	474(1.4)	422(0.9)	<0.0001
COPD/asthma (Dx)	7,976(23.8)	10,992(24.6)	0.01
Cancer (Dx)	3,064(9.1)	3,785(8.5)	0.0001
Old MI (Dx)	5,051(15.1)	6,278(14.1)	<0.0001
Old Stroke (Dx)	1,758(5.3)	1,945(4.4)	<0.0001
Endocarditis (Dx)	171(0.5)	83(0.2)	<0.0001
Peripheral artery disease (Dx)	3,257(9.7)	3,840(8.6)	<0.0001
Chronic kidney disease (Dx)	714(2.1)	622(1.4)	<0.0001
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	124(0.4)	111(0.3)	0.002
Hosp. CABG volume 0-99	952(2.8)	973(2.2)	<0.0001
100-500	13,070(39.0)	14,439(32.3)	
>500	19,495(58.2)	29,270(65.5)	
Hospital size (beds) < 400	12,609(37.6)	16,733(37.5)	<0.0001
400 – 649	10,208(30.5)	14,396(32.2)	
650 +	10,700(31.9)	13,553(30.3)	
Region Midwest	5,913(17.6)	8,523(19.1)	<0.0001
Northeast	2,992(8.9)	6,743(15.1)	
South	19,865(59.3)	23,686(53.0)	
West	4,747(14.2)	5,730(12.8)	
Teaching hospital	17,014(50.8)	24,828(55.6)	<0.0001
Rural hospital	2,323(6.9)	3,190(7.1)	0.26

\* These conditions were assessed during the day(s) before CABG surgery in a subpopulation of 34,997 patients who had CABG surgery on day 3 or later.

\*\* Dx = based on recorded discharge diagnosis

**Table 3b: Relative risk of renal failure requiring dialysis and in-hospital death among 78,199 patients undergoing CABG surgery in the primary study cohort.\***

**From final report Part A, Addendum. The gray shaded area indicates the RR estimates used for the sensitivity analysis described in this report.**

Outcome	Aprotinin use – any dose	Aminocaproic acid use – any dose	Any dose RR, 95% CI	Any dose, multivariate adjusted RR, 95% CI	Excluding very low dose, multivariate adjusted RR, 95% CI
	N; # events (%)	N; # events (%)			
Renal failure requiring dialysis <sup>‡</sup>	31,644; 875 (2.8)	43,054; 665 (1.5)	1.79 (1.62 – 1.98)	1.65 (1.48, 1.84)	1.57 (1.38, 1.79)
In-hospital all-cause death	33,517; 1,512 (4.5)	44,682; 1,101 (2.5)	1.83 (1.70 – 1.98)	1.64 (1.50, 1.78)	1.50 (1.36, 1.66)
Renal failure requiring dialysis within 7 days of CABG <sup>‡</sup>	31,644; 627 (2.0)	43,054; 422 (1.0)	2.02 (1.79 – 2.29)	1.84 (1.61, 2.10)	1.76 (1.50, 2.06)
In-hospital all-cause death within 7 days of CABG	33,517; 631 (1.9)	44,682; 435 (1.0)	1.93 (1.71 – 2.18)	1.78 (1.56, 2.02)	1.64 (1.41, 1.91)

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

<sup>‡</sup> For the analysis of renal failure, we excluded patients with dialysis before surgery and those with a discharge diagnosis of chronic kidney disease (number of patients excluded from primary study cohort: **2,165**).

**Table 4a: Characteristics of sampled patients in the validation study as measured in the Premier administrative database**

<b>Characteristics as measured in the Premier database: Sampled patients N = 98</b>					
Characteristic		Aprotinin N (%)	Aminocaproic acid N (%)	OR	p-value from Chi <sup>2</sup> test
Number of patients		29 (100.0)	69 (100.0)		
Very low dose		13 (44.8)	3 (4.4)		<0.0001
Low dose		3 (10.3)	63 (91.3)		
High dose		13 (44.8)	3 (4.4)		
Age	18 – 24	0 (0.0)	0 (0.0)		0.55
	25 – 34	0 (0.0)	0 (0.0)		
	35 – 44	0 (0.0)	4 (5.8)		
	45 – 54	4 (13.8)	9 (13.0)		
	55 – 64	10 (34.5)	29 (42.0)		
	65 – 74	9 (31.0)	14 (20.3)		
	75 +	6 (20.7)	13 (18.8)		
Sex (male)		24 (82.8)	49 (71.0)	1.96	0.22
Race/ethnicity	White	20 (69.0)	54 (78.3)		0.61
	Black	7 (24.1)	12 (17.4)		
	Other	2 (6.9)	3 (4.4)		
Smoking		6 (20.7)	8 (11.6)	1.99	0.24
Admission Year	2003	0 (0.0)	3 (4.4)		<0.0001
	2004	1 (3.5)	4 (5.8)		
	2005	18 (62.1)	62 (89.9)		
	2006 (Q1)	10 (34.5)	0 (0.0)		
Emergency Admission		20 (69.0)	34 (49.3)	2.29	0.07
Day of CABG	Day 1	5 (17.2)	20 (29.0)		0.43
	Day 2	5 (17.2)	10 (14.5)		
	Day 3-5	12 (41.4)	30 (43.5)		
	Day 6+	7 (24.1)	9 (13.0)		
Low Income Status		2 (6.9)	2 (2.9)	2.48	0.36
Marital Status (w/ partner)		17 (58.6)	45 (65.2)	0.76	0.54
Redo Cardiac Surgery		1 (3.5)	0 (0.0)		0.12
Additional cardiac surgery		23 (79.3)	56 (81.2)	0.89	0.83
Complex CABG surgery		27 (93.1)	62 (89.9)	1.52	0.61
Number of vessels	1	4 (13.8)	5 (7.3)		0.78
	2	10 (34.5)	24 (34.8)		
	3	13 (44.8)	35 (50.7)		
	4+	2 (6.9)	5 (7.3)		
Pre-existing Percutaneous coronary procedures		3 (10.3)	13 (18.8)	0.50	0.30
* Angina (nitrate use)		16 (55.2)	17 (24.6)	3.76	0.004
* Renal failure requiring dialysis		0 (0.0)	0 (0.0)		
* Heart failure (use of		3 (10.3)	6 (8.7)	1.21	0.80

furosemide, digoxin, digitoxin, or dobutamine)				
* Anti-arrhythmic drug use	3 (10.3)	0 (0.0)		0.007
* Cardiac arrest	1 (3.5)	0 (0.0)		0.12
* Warfarin use	0 (0.0)	0 (0.0)		
* Fibrinolytic medications or direct thrombin inhibitors	0 (0.0)	0 (0.0)		
* Use of clopidogrel or glycoprotein 2b/3a inhibitors	8 (27.6)	8 (11.6)	2.90	0.05
* Use of plasma expander	1 (3.5)	4 (5.8)	0.58	0.63
* Use of radiologic contrast medium	4 (13.8)	3 (4.4)	3.52	0.10
Diabetes (Dx, or antidiabetic therapy on more than 2 days)	14 (48.3)	29 (42.0)	1.29	0.57
Hypertension (Dx)	22 (75.9)	56 (81.2)	0.73	0.55
Liver disease (Dx)	0 (0.0)	0 (0.0)		
COPD/asthma (Dx)	2 (6.9)	8 (11.6)	0.56	0.48
Cancer (Dx)	5 (17.2)	5 (7.3)	2.67	0.14
Old MI (Dx)	3 (10.3)	8 (11.6)	0.88	0.86
Old Stroke (Dx)	2 (6.9)	2 (2.9)	2.48	0.36
Endocarditis (Dx)	0 (0.0)	0 (0.0)		
Peripheral artery disease (Dx)	0 (0)	1 (1.5)		0.51
Chronic kidney disease (Dx)	1 (3.5)	0 (0.0)		0.12
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)	0 (0.0)	0 (0.0)		
Hosp. CABG volume 0-99	0 (0.0)	0 (0.0)		
100 – 499	0 (0.0)	0 (0.0)		
>500	29 (100.0)	69 (100.0)		
Hospital size (beds) 0-400	0 (0.0)	0 (0.0)		
400 – 649	29 (100.0)	69 (100.0)		
650 +	0 (0.0)	0 (0.0)		
Region Midwest	0 (0.0)	0 (0.0)		
Northeast	0 (0.0)	0 (0.0)		
South	29 (100.0)	69 (100.0)		
West	0 (0.0)	0 (0.0)		
Teaching hospital	29 (100.0)	69 (100.0)		
Rural hospital	29 (100.0)	69 (100.0)		

**Table 4b: Characteristics of patients with death outcome in the Validation Study: characteristics measured in the Premier database**

		Characteristics measured in the Premier database: Patients with Death Outcome N = 8			
Characteristic		Aprotinin N (%)	Aminocaproic acid N	OR	p-value from Chi <sup>2</sup> test
Number of patients		5 (100.0)	3 (100.0)		
Very low dose		0 (0.0)	2 (66.7)		0.08
Low dose		2 (40.0)	1 (33.0)		
High dose		3 (50.0)	0 (0.0)		
Age	18 – 24	0 (0.0)	0 (0.0)		0.64
	25 – 34	0 (0.0)	0 (0.0)		
	35 – 44	0 (0.0)	0 (0.0)		
	45 – 54	1 (20.0)	0 (0.0)		
	55 – 64	0 (0.0)	0 (0.0)		
	65 – 74	2 (40.0)	1 (33.3)		
	75 +	2 (40.0)	2 (66.7)		
Sex (male)		1 (20.0)	2 (66.7)	0.13	0.19
Race/ethnicity	White	3 (60.0)	2 (66.7)	1.33	0.85
	Black	2 (40.0)	1 (33.3)		
	Other	0 (0.0)	0 (0.0)		
Smoking (current, past)		1 (20.0)	0 (0.0)		0.37
Admission Year	2003	1 (20.0)	2 (66.7)		
	2004	1 (20.0)	0 (0.0)		
	2005	3 (60.0)	1 (33.3)		
	2006 (Q1)	0 (0.0)	0 (0.0)		
Emergency Admission		3 (60.0)	3 (100.0)	1.67	0.21
Day of CABG	Day 1	1 (20.0)	0 (0.0)		0.69
	Day 2	3 (60.0)	2 (66.7)		
	Day 3-5	0 (0.0)	0 (0.0)		
	Day 6+	1 (20.0)	1 (33.3)		
Low Income Status		0 (0.0)	0 (0.0)		
Marital Status (w/ partner)		4 (80.0)	1 (33.3)	8.00	0.19
Redo Cardiac Surgery		0 (0.0)	0 (0.0)		
Additional cardiac surgery		3 (60.0)	3 (100.0)	1.67	0.21
Complex CABG surgery		4 (80.0)	3 (100.0)		0.41
Number of vessels	1	1 (20.0)	1 (33.3)		0.67
	2	4 (80.0)	2 (66.7)		
	3	0 (0.0)	0 (0.0)		
	4+	0 (0.0)	0 (0.0)		
Pre-existing Percutaneous coronary procedures		0 (0.0)	0 (0.0)		
* Angina (nitrate use)		1 (20.0)	2 (66.7)	0.13	0.19
* Renal failure requiring dialysis		0 (0.0)	0 (0.0)		
* Heart failure (use of furosemide, digoxin, digitoxin,		1 (20.0)	2 (66.7)	0.13	0.19

or dobutamine)				
* Anti-arrhythmic drug use		1 (20.0)	0 (0.0)	0.41
* Cardiac arrest		0 (0.0)	0 (0.0)	
* Warfarin use		1 (20.0)	0 (0.0)	0.41
* Fibrinolytic medications or direct thrombin inhibitors		0 (0.0)	0 (0.0)	
* Use of clopidogrel or glycoprotein 2b/3a inhibitors		0 (0.0)	2 (66.7)	0.04
* Use of plasma expander		0 (0.0)	0 (0.0)	
* Use of radiologic contrast medium		0 (0.0)	1 (33.3)	0.17
Diabetes (Dx, or antidiabetic therapy on more than 2 days)		3 (60.0)	2 (66.7)	0.75 0.85
Hypertension (Dx)		2 (40.0)	2 (66.7)	0.33 0.47
Liver disease (Dx)		0 (0.0)	1 (33.3)	0.17
COPD/asthma (Dx)		2 (40.0)	1 (33.3)	1.33 0.85
Cancer (Dx)		2 (40.0)	0 (0.0)	0.21
Old MI (Dx)		0 (0.0)	0 (0.0)	
Old Stroke (Dx)		0 (0.0)	0 (0.0)	
Endocarditis (Dx)		0 (0.0)	0 (0.0)	
Peripheral artery disease (Dx)		0 (0.0)	0 (0.0)	
Chronic kidney disease (Dx)		0 (0.0)	0 (0.0)	
Hemostatic disorder (Dx of idiopathic thrombocytopenia, hemophilia, protein S deficiency, protein C deficiency, or leukemia)		0 (0.0)	0 (0.0)	
Hosp. CABG volume	0-99	0 (0.0)	(0.0)	
	100-500	0 (0.0)	(0.0)	
	>500	5 (100.0)	3 (100.0)	
Hospital size (beds)	< 400	0 (0.0)	0 (0.0)	
	400 – 649	5 (100.0)	3 (100.0)	
	650 +	0 (0.0)	0 (0.0)	
Region	Midwest	0 (0.0)	0 (0.0)	
	Northeast	0 (0.0)	0 (0.0)	
	South	5 (100.0)	3 (100.0)	
	West	0 (0.0)	0 (0.0)	
Teaching hospital		5 (100.0)	3 (100.0)	
Rural hospital		5 (100.0)	3 (100.0)	

**Table 5a: Characteristics of patients in the validation study: characteristics measured in the Validation Study (sampled patients)**

		Analysis of characteristics measured in the Validation Study: Sampled patients N = 98			
Characteristic according to validation study		Aprotinin N (%)	Aminocaproic acid N (%)	OR	p-value from Chi <sup>2</sup> test
Number of patients		36 (100.0)	62 (100.0)		
Dose	Very Low	0 (0)	2 (3.2)		<0.0001
	Low	21 (58.3)	59 (95.2)		
	High	15 (41.7)	1 (1.6)		
Age	18 – 24	0 (0.0)	0 (0.0)		0.39
	25 – 34	0 (0.0)	0 (0.0)		
	35 – 44	0 (0.0)	4 (6.5)		
	45 – 54	4 (11.1)	9 (14.5)		
	55 – 64	13 (36.1)	26 (41.9)		
	65 – 74	11 (30.6)	12 (19.4)		
	75 +	8 (22.2)	11 (17.7)		
Sex (male)		27 (75.0)	45 (72.6)	1.13	0.38
Race/ethnicity	White	25 (69.4)	49 (79.0)		0.43
	Black	8 (22.2)	11 (17.7)		
	Other	3 (8.3)	2 (3.2)		
Admission Year	2003	1 (2.8)	2 (3.2)		0.0002
	2004	1 (2.8)	4 (6.5)		
	2005	24 (66.7)	56 (90.3)		
	2006 (Q1)	10 (27.8)	0 (0.0)		
Smoking		19 (52.8)	38 (61.3)	0.71	0.41
Weight (kg)		88.2	89.2		
Height (cm)		172.5	171.2		
BMI		29.5	31.8		
BSA		2.0	2.0		
Emergency Admission		6 (16.7)	4 (6.5)	2.90	0.11
Fractional vials used		2 (5.6)	1 (1.6)	3.59	0.19
Admin before incision		33 (91.7)	42 (67.7)	5.24	0.007
Admin before bypass		3 (8.3)	15 (24.2)	0.28	0.05
Renal Hemodialysis		0 (0.0)	0 (0.0)		
Peritoneal dialysis		0 (0.0)	0 (0.0)		
Hemofiltration		0 (0.0)	0 (0.0)		
Hemofiltration / Vol Reduction		0 (0.0)	0 (0.0)		
Platelet count		227.7	244.4		
INR		1.2	1.1		
Hematocrit		37.9	40.8		
Creatinine		1.0	1.1		
GFR		58.8	56.73		
Prior CABG		6 (16.7)	0 (0.0)		0.003
Prior Cardiac Surgery		2 (5.6)	2 (3.2)	1.76	0.57
Prior PTCA		8 (22.2)	13 (21.0)	1.08	0.88
Prior clopidogrel		5 (13.9)	5 (8.1)	1.84	0.36

Prior glycoprotein 2b/3a	3 (8.3)	3 (4.8)	1.79	0.49
Prior LMW heparin	5 (13.9)	5 (8.1)	1.84	0.36
Prior Warfarin	1 (2.8)	5 (8.1)	0.33	0.30
Prior Aspirin	29 (80.6)	43 (69.4)	1.83	0.23
Non-Elective Surgery	25 (69.4)	38 (61.3)	0.70	0.4167
Concomitant aortic surgery	0 (0.0)	1 (1.6)		0.44
Conc. single valve surgery	3 (8.3)	0 (0.0)		0.02
Conc. Multiple valve surgery	0 (0.0)	0 (0.0)		
Conc. Vent. Assist device	0 (0.0)	1 (1.6)		0.32
Deep Hypothermic Arrest	32 (88.9)	56 (90.3)	0.86	0.82
Bypass use	34 (94.4)	61 (98.4)	3.59	0.27
Bypass time	129.7	109.2		
Transfusion refusal	1 (2.8)	0 (0.0)		0.19
Prior ACE inhibitor	13 (36.1)	26 (41.9)	0.78	0.57
Prior IV contrast	18 (50.0)	33 (53.2)	0.88	0.76
History of renal insufficiency	2 (5.6)	2 (3.2)	1.76	0.57
Pre-CABG chronic dialysis	0 (0.0)	0 (0.0)		
History of liver cirrhosis	0 (0.0)	0 (0.0)		
History of heart failure	4 (11.1)	5 (8.1)	1.43	0.61
History of hypertension	28 (77.8)	55 (88.7)	0.44	0.15
History of diabetes	15 (41.7)	21 (33.9)	1.39	0.44
History of arrhythmia	7 (19.4)	7 (11.3)	1.90	0.27

**Table 5b: Characteristics of patients in the validation study with death outcome: characteristics measured in the Validation Study (patients with death outcome)**

<b>Characteristics measured in the Validation Study: Patients with death outcome N = 8</b>					
Characteristic according to Excel Spreadsheet		Aprotinin N (%)	Aminocaproic acid N (%)	OR	p-value from Chi <sup>2</sup> test
Number of patients		6	2		
Dose	Very Low	0 (0.0)	0 (0.0)		0.04
	Low	1 (16.7)	2 (100.0)		
	High	5 (83.3)	0 (0.0)		
Age	18 – 24	0 (0.0)	0 (0.0)		0.64
	25 – 34	0 (0.0)	0 (0.0)		
	35 – 44	0 (0.0)	0 (0.0)		
	45 – 54	1 (16.7)	0 (0.0)		
	55 – 64	1 (16.7)	0 (0.0)		
	65 – 74	0 (0.0)	0 (0.0)		
	75 +	4 (66.7)	2 (100.0)		
Sex (male)		1 (16.7)	1 (50.0)	0.20	0.35
Race/ethnicity	White	4 (66.7)	1 (50.0)		0.67
	Black	2 (33.3)	1 (50.0)		
	Other	0 (0.0)	0 (0.0)		
Admission Year	2003	2 (33.3)	1 (50.0)		0.80
	2004	1 (16.7)	0 (0.0)		
	2005	3 (50.0)	1 (50.0)		
	2006 (Q1)	0 (0.0)	0 (0.0)		
Smoking		4 (66.7)	2 (100.0)		0.35
Weight (kg)		71.9	88.0		
Height (cm)		158.6	171.0		
BMI		25.2	30.2		
BSA		1.7	2.0		
Emergency Admission		2 (33.3)	1 (50.0)	0.50	0.67
Fractional vials used		0 (0.0)	0 (0.0)		
Admin before incision		4 (66.7)	1 (50.0)	2.00	0.67
Admin before bypass		1 (16.7)	0 (0.0)		0.54
Renal Hemodialysis		0 (0.0)	0 (0.0)		
Peritoneal dialysis		0 (0.0)	0 (0.0)		
Hemofiltration		0 (0.0)	0 (0.0)		
Hemofiltration / Vol Reduction		0 (0.0)	0 (0.0)		
Other indication hemofiltration		0 (0.0)	0 (0.0)		
Platelet count		258.8	280.0		
INR		1.2	1.1		
Hematocrit		35.6	36.1		
Creatinine		1.0	1.3		
GFR		60.00	48.0		
Prior CABG		5 (83.3)	2 (100.0)		0.54
Prior Cardiac Surgery		0 (0.0)	0 (0.0)		

Prior PTCA	0 (0.0)	0 (0.0)		
Prior clopidogrel	0 (0.0)	0 (0.0)		
Prior glycoprotein 2b/3a	0 (0.0)	0 (0.0)		
Prior LMW heparin	0 (0.0)	0 (0.0)		
Prior Warfarin	0 (0.0)	0 (0.0)		
Prior Aspirin	4 (66.7)	2 (100.0)		0.35
Non-Elective Surgery	5 (83.3)	2 (100.0)		0.54
Concomitant aortic surgery	3 (50.0)	0 (0.0)		0.21
Conc. Single valve surgery	1 (16.7)	0 (0.0)		0.54
Conc. Multiple valve surgery	4 (66.7)	0 (0.0)		0.10
Conc. Vent. Assist device	0 (0.0)	0 (0.0)		
Deep Hypothermic Arrest	5 (83.3)	1 (50.0)	5.00	0.35
Bypass use	6 (100.0)	2 (100.0)		
Bypass time	390.2	108.5		
Transfusion refusal	0 (0.0)	0 (0.0)		
Prior ACE inhibitor	1 (12.5)	0 (0.0)		0.54
Prior IV contrast	3 (50.0)	1 (50.0)	1.00	1.00
History of renal insufficiency	1 (16.7)	1 (50.0)	0.20	0.35
Pre-CABG chronic dialysis	0 (0.0)	0 (0.0)		
History of liver cirrhosis	0 (0.0)	0 (0.0)		
History of heart failure	2 (33.3)	1 (50.0)	0.50	0.67
History of hypertension	6 (100.0)	2 (100.0)		
History of diabetes	2 (33.3)	0 (0.0)		0.35
History of arrhythmia	3 (50.0)	0 (0.0)		0.21

**Table 6: Cross-tabulation of characteristics measured in the Validation Study with characteristics measured in Premier administrative database (sampled patients)**

<b>Cross tabulations of Validation study and Premier Analytic file: N = 98</b>						
Characteristic according to Medical Records		N (%)	Characteristic according to Analytic File		N (%)	p-value from Chi <sup>2</sup> test
Aprotinin		36 (36.7)	Aprotinin		29 (29.6)	<0.0001
Dose	Very Low	2 (2.0)	Dose	Very Low	16 (16.3)	0.02
	Low	80 (81.6)		Low	66 (67.4)	
	High	16 (16.3)		High	16 (16.3)	
Age	18 – 24	0 (0.0)	Age	18 – 24	0 (0.0)	<0.0001
	25 – 34	0 (0.0)		25 – 34	0 (0.0)	
	35 – 44	4 (4.1)		35 – 44	4 (4.1)	
	45 – 54	13 (13.3)		45 - 54	13 (13.3)	
	55 – 64	39 (39.8)		55 - 64	39 (39.8)	
	65 – 74	23 (23.5)		65 – 74	23 (23.5)	
	75 +	19 (19.4)		75 +	19 (19.4)	
Sex (male)		72 (73.5)	Sex (male)		73 (74.5)	<0.0001
Race/ethnicity	White	74 (75.5)	Race/ethnicity	White	74 (75.5)	<0.0001
	Black	19 (19.4)		Black	19 (19.4)	
	Other	5 (5.1)		Other	5 (5.1)	
Admission Year 2003		3 (3.1)	Admission Year 2003		3 (3.1)	<0.0001
2004		5 (5.1)	2004		5 (5.1)	
2005		80 (81.6)	2005		80 (81.6)	
2006 (Q1)		10 (10.2)	2006 (Q1)		10 (10.2)	
Smoking		57 (58.2)	Smoking		14 (14.3)	
Emergency Admission		10 (10.2)	Emergency Admission		54 (55.1)	<0.0001
Prior CABG		6 (6.1)	Redo CABG		1 (1.0)	0.0004
Prior Cardiac Surgery		4 (4.1)	Prior Cardiac Surgery		1 (1.0)	0.96
Prior clopidogrel		10 (10.2)	Prior clopidogrel		16 (16.3)	0.009
Prior Warfarin		6 (6.1)	Prior Warfarin		0 (0.0)	
Prior Aspirin		72 (73.5)	Prior Aspirin		48 (49.0)	0.003
Non-Elective Surgery		63 (64.3)	Emergency Admission		54 (55.1)	<0.0001
Prior IV contrast		51 (52.0)	Prior IV contrast		7 (7.1)	0.79
History of renal insufficiency		4 (4.1)	History of renal insufficiency		1 (1.0)	<0.0001
History of liver cirrhosis		0 (0.0)	History of liver cirrhosis		0 (0.0)	
History of heart failure		9 (9.2)	History of heart failure		9 (9.2)	0.005
History of hypertension		83 (84.7)	History of hypertension		78 (79.6)	<0.0001
History of diabetes		36 (36.7)	History of diabetes		43 (43.9)	<0.0001
History of arrhythmia		14 (14.3)	History of arrhythmia		3 (3.1)	0.09

**Table 7: Correlations of characteristics measured in the Validation Study and characteristics measured in Premier Data. (sampled patients and patients with death outcome)**

<b>Correlations of characteristics measured in the Validation study and Premier Analytic file:</b>					
<b>N = 98</b>					
<b>Characteristic</b>	<b>N</b>	<b>Mean from Medical Records</b>	<b>Mean from Analytic file</b>	<b>Pearson's r</b>	<b>p-value</b>
Age	98	63.2	63.2	0.99	<0.0001
Age	8	71.8	74.1	0.87	0.005
Admission Year	98	2005	2005	1.00	<0.0001
Admission Year	8	2004	2004	1.00	<0.0001

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**APPENDIX 1. MEDICAL RECORD ABSTRACTION FORM**

Abstract ID: \_\_\_\_\_

**APROTININ Chart Abstraction Data Sheet**

Medical Record Number: \_\_\_\_\_

Admission Date (MM/DD/YYYY): \_\_\_\_\_

Hospital Discharge Date (4/1/03 – 3/31/06): \_\_\_\_\_

Hospitalization Status (inpatient) \_\_\_\_\_

**INCLUSION CRITERIA**

- (1) Patients suffering from renal failure after CABG surgery identified by requiring dialysis (N=30)
- (2) Patients who have died during the hospital stay (N=30)
- (3) A random sample of patients with neither outcome (N=140)

**PATIENT CHARACTERISTICS**

Age (years): \_\_\_\_\_ [ -OR- Subtract Birth Date: \_\_\_\_\_ from Hospital Admit Date: \_\_\_\_\_ ]

Gender: Female  Male  Unknown

Race: White 1 Black 2 Hispanic 3 American Indian 4  
 Asian/Pacific Islander 5 Other 9 Not Provided U

Body weight: \_\_\_\_\_ pounds or \_\_\_\_\_ kg

Height: \_\_\_\_\_ feet \_\_\_\_\_ inches or \_\_\_\_\_ cm

Admission Type: Emergency 1 Urgent 2 Elective 3 Trauma 5 Other

Discharge Status: Home 1,6,8 Short-Term Hosp 2 Intermed Care 4 Other Institution 5  
 Left AMA 7 Swing Bed 61 LTC Hosp 7 Psych Hosp 65  
 Expired 20,40-42 SNF 3 Hospice 50,51 Other

Safety of Aprotinin use in Patients undergoing CABG Surgery

Abstract ID:

*Intravenous antifibrinolytic drug use during CABG surgery*

<b>i.v. Aprotinin during CABG surgery</b>		
	Response	
What was the total i.v. Aprotinin dose used?		
What was size of the Aprotinin vial used?		
	Yes	No
Was a vial opened, but never used?		
Was a vial opened, but only a fraction was used?		
Was Aprotinin started before the skin incision?		
Was Aprotinin started after skin incision but before cardiopulmonary bypass?		
Was Aprotinin used in the past?		
History of allergic reaction to Aprotinin?		

<b>i.v. Aminocaproic acid during CABG surgery</b>		
	Response	
What was the total i.v. Aminocaproic acid dose used?		
What was size of the Aminocaproic acid vial used?		
	Yes	No
Was a vial opened, but never used?		
Was a vial opened, but only a fraction was used?		
Was Aminocaproic acid started before the skin incision?		
Was Aminocaproic acid started after skin incision but before cardiopulmonary bypass?		
Was Aminocaproic acid used in the past?		
History of allergic reaction to Aminocaproic acid?		

Abstract ID:

<b>Tranexamic acid during CABG surgery</b>		
	Response	
What was the total i.v. Tranexamic acid dose used?		
What was size of the Tranexamic acid vial used?		
	Yes	No
Was a vial opened, but never used?		
Was a vial opened, but only a fraction was used?		
Was Tranexamic acid started before the skin incision?		
Was Tranexamic acid started after skin incision but before cardiopulmonary bypass?		
Was Tranexamic acid used in the past?		
History of allergic reaction to Tranexamic acid?		

Safety of Aprotinin use in Patients undergoing CABG Surgery

Abstract ID:

**Recording of Renal Failure outcomes**

	Yes	No
Was post-CABG surgery renal failure recorded?		
Was hemodialysis used for treatment of renal failure?		
Was peritoneal dialysis used for treatment of renal failure?		
Was hemofiltration used for treatment of renal failure?		
Was hemofiltration used for post surgical volume reduction?		
Other indicatins for hemofiltration: _____		

**Patient Characteristics**

	Results	
Preoperative platelet count (pick value closest to surgery)		
Preoperative INR (pick value closest to surgery)		
Preoperative hematocrit (pick value closest to surgery)		
Preoperative serum creatinine level (pick value closest to surgery)		
Preoperative glomerular filtration rate (GFR)		
	Yes	No
Previous CABG surgery (re-do surgery, redo, reop, reoperative)		
Date of previous CABG surgery: _____		
Previous non-CABG cardiac surgery		
Date of previous non-CABG cardiac surgery: _____		
Previous percutaneous coronary intervention (PTCA, PCI, stent implantation)		
Date of previous percutaneous coronary intervention: _____		
Use of clopidogrel (Plavix) prior to surgery		
When was the last dose of clopidogrel (Plavix)? _____ hours before surgery		
Use of glycoprotein 2b/3a inhibitors (Abciximab, ReoPro, Eptifibatide, Integrilin, Tirofiban, Aggrastat) within 24 hours prior to surgery		

Safety of Aprotinin use in Patients undergoing CABG Surgery

Abstract ID:

	Yes	No
<p>Use of low-molecular-weight heparin within 24 hours?</p> <p>ardeparin (Normiflo®), certoparin (Sandoparin®), enoxaparin (Lovenox® and Clexane®), parnaparin (Fluxum®), tinzaparin (Innohep® and Logiparin®), dalteparin (Fragmin®), reviparin (Clivarin®), and nadroparin (Fraxiparin®)</p>		
Use of warfarin within 4 days prior to surgery		
Use of aspirin within 7 days prior to surgery		
<p>Non-elective surgery?</p> <p>This includes:</p> <ul style="list-style-type: none"> <li>- cases with preoperative intra-aortic balloon pump (IABP) placement,</li> <li>- preoperative use of inotrope agents (dopamine, dobutamine, epinephrine, norepinephrine, milrinone),</li> <li>- IV heparin or IV nitroglycerin,</li> <li>- surgery performed in the same hospitalization during which coronary catheterization was done or a patient was transferred from another hospital</li> </ul>		
<p>Concomitant aortic surgery?</p> <p>This includes: ascending aortic replacement/resection, aortic arch replacement/resection, hemiarch replacement/resection, total arch replacement/resection, aortic root replacement, Bentall procedure, Yacoub procedure, David procedure</p>		
<p>Concomitant single valve surgery?</p> <p>This includes: aortic valve replacement/repair, AVR, AVP, mitral valve replacement/repair, MVR, MVP, tricuspid valve replacement/repair, TVR, TVP, or pulmonary valve replacement</p>		
Concomitant multiple valve surgery (more than one valve procedure)?		
<p>Concomitant ventricular assist device implant?</p> <p>Abbreviations: VAD, LVAD, LVAS, RVAD, BiVAD, Commercial names: Thoratec, Heartmate, Abiomed</p>		
Deep hypothermic circulatory arrest (hypothermic circ arrest, circ arrest, DHCA, etc)		
<p>Cardiopulmonary bypass use?</p> <p>Record of CPB time or description of CPB: YES, Description of "off-pump" or "without CPB": NO</p>		
Cardiopulmonary bypass time: _____ minutes		

Safety of Aprotinin use in Patients undergoing CABG Surgery

Abstract ID:

	Yes	No
Patients who refuse blood transfusion (e.g. Jehovah's witness) Clear statement for refusal: YES, Signed consent for blood product use: NO, otherwise missing)		
Preoperative use of ACE-inhibitors?		
Previous use of intra venous (i.v.) contrast medium?  Percutaneous coronary interventions, angiogram, intravenously contrasted CT within 72 hours prior to surgery. Do NOT include contrast MRI or CT with oral contrast alone.		
History of renal insufficiency (renal failure, renal dysfunction, kidney failure)		
Preoperative chronic dialysis (end-stage renal disease, ESRD, end stage renal failure)		
History of liver cirrhosis (liver failure)		
History of heart failure		
History of hypertension		
History of diabetes mellitus		
History of smoking		
History of arrhythmia		
History of liver cirrhosis (liver failure)		

## **APPENDIX 2. 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 prevalence of the confounder among exposed ( $P_{C1}$ ) and the marginal probabilities of exposure  $P_E$  and confounder  $P_C$  :

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

Assuming no underlying true exposure-disease association or  $RR_{ED} = 1$ , Walker<sup>19</sup> 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  $RR_{CD}$ :

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

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.<sup>20</sup>

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  $P_{C1}$ :

$$\underbrace{P_{C1}^2 (OR_{EC} - 1)}_a + \underbrace{P_{C1}[-P_C OR_{EC} - P_E OR_{EC} + P_E + P_C - 1]}_b + \underbrace{P_C OR_{EC} P_E}_c = 0 \quad (3)$$

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

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

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

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

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

$P_C$ , 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.

Using these parameters we calculated the percent residual bias caused by each factor for a number of exposure-disease associations ( $RR_{ED}$ ) ranging from 1.0 to 5.5. Finally, we picked the “literature-supported bias” estimate that corresponded to the  $RR_{ED}$  reported in earlier studies, particularly CABG risk prediction scores.<sup>2,3</sup>

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 one 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.

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