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Postoperative Activity, but Not Preoperative Activity, of Antithrombin Is Associated with Major Adverse Cardiac Events After Coronary Artery Bypass Graft Surgery

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Abstract

BACKGROUND—Low levels of antithrombin (AT) have been independently associated with prolonged intensive care unit stay and an increased incidence of neurologic and thromboembolic events after cardiac surgery. We hypothesized that perioperative AT activity is independently associated with postoperative major adverse cardiac events (MACEs) in patients undergoing coronary artery bypass graft (CABG) surgery.

METHODS—We prospectively studied 1403 patients undergoing primary CABG surgery with cardio-pulmonary bypass (CPB) (<http://clinicaltrials.gov/show/NCT00281164>). The primary clinical end point was occurrence of MACE, defined as a composite outcome of any one or more of the following: postoperative death, reoperation for coronary graft occlusion, myocardial infarction, stroke, pulmonary embolism, or cardiac arrest until first hospital discharge. Plasma AT activity was measured before surgery, after post-CPB protamine, and on postoperative days (PODs) 1–5. Multivariate logistic regression modeling was performed to estimate the independent effect of perioperative AT activity upon MACE.

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The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

DISCLOSURE

There are four potential conflicts of interest. Dr. Garvin was the recipient of a Research Fellowship funded by Talecris Biotherapeutics, which allowed time for generation of this and other articles. Dr. Chen is an employee of Talecris Biotherapeutics and performed the majority of the analyses. To prevent the appearance or substance of conflict, Simon Body personally directed the conduct of all analyses and confirmed the conduct of the analyses by reviewing the code and output of all analyses. In addition, Simon Body personally reran the important components of the analyses to confirm the findings and can attest that there was no potential for conflict in the analysis phase. Dr. Body received a total of <\$5000 to allow his time for travel to Talecris in North Carolina to coordinate the analyses. Talecris also paid for the costs of antithrombin analyses performed by Charles River Laboratories in Ontario, Canada, but had no opportunity to intervene in these analyses. In brief, we believe there is no conflict of interest in the conduct of this study.

RESULTS—MACE occurred in 146 patients (10.4%), consisting of postoperative mortality ($n = 12$), myocardial infarction ($n = 108$), stroke ($n = 17$), pulmonary embolism ($n = 8$), cardiac arrest ($n = 16$), or a subsequent postoperative or catheter-based treatment for graft occlusion ($n = 6$). AT activity at baseline did not differ between patients with (0.91 ± 0.13 IU/mL; $n = 146$) and without (0.92 ± 0.13 IU/mL; $n = 1257$) ($P = 0.18$) MACE. AT activity in both groups was markedly reduced immediately after CPB and recovered to baseline values over the ensuing 5 PODs. Postoperative AT activity was significantly lower in patients with MACE than those without MACE. After adjustment for clinical predictors of MACE, AT activity on PODs 2 and 3 was associated with MACE.

CONCLUSIONS—Preoperative AT activity is not associated with MACE after CABG surgery. MACE is independently associated with postoperative AT activity but only at time points occurring predominantly after the MACE.

Antithrombin (AT) is a serine protease inhibitor (serpin) and the principal inhibitor of the final common pathway of the coagulation system by inactivation of circulating thrombin (factor IIa) and factor Xa, among other serine proteases. Heparin increases AT activity 2000- to 4000-fold due to a conformational change in the quaternary structure of AT by heparin binding and through formation of a ternary complex of thrombin, AT, and heparin. Heparin-augmented AT activity is still the principal mechanism of anticoagulation for cardiopulmonary bypass (CPB).

AT levels are decreased after administration of heparin due to degradation of the ternary complex. Additionally, acquired AT deficiency is common in patients with critical illness, severe hepatic dysfunction, and after major cardiovascular surgery.^{1,2} The magnitude of reduction in AT after cardiac surgery is similar to that in patients with heterozygous AT deficiency, which is associated with increased risk of thromboembolic events.^{3,4} After cardiac surgery, lower levels of AT have been independently associated with prolonged intensive care unit (ICU) stay and a higher incidence of neurologic and thromboembolic events.⁵ We therefore examined for independent association between perioperative AT activity and the frequency of postoperative major adverse cardiac events (MACEs) in patients undergoing coronary artery bypass graft (CABG) surgery.

METHODS

The study cohort was obtained from a continuing prospective longitudinal parent study of 1447 patients undergoing primary CABG surgery with CPB between August 2001 and May 2006 at 2 United States academic medical centers (CABG Genomics Program; <http://clinicaltrials.gov/show/NCT00281164>). With IRB approval, written informed consent was obtained from each patient. Patients were excluded from the parent study if they were younger than 20 yr old, underwent repeat or off-pump CABG, had a preoperative hematocrit <25%, or if they had received leukocyte-rich blood products within 30 days before surgery. All patients enrolled in the parent study were included. Patients without postoperative cardiac troponin I (cTnI) levels ($n = 43$) were excluded from further analysis. Demographic data, medical and surgical history, medications, and outcomes were recorded by trained research staff using defined protocols in a purpose-built case report form. The examination of the relationship between AT levels and MACE was not prespecified in the original parent study.

Perioperative anticoagulation protocols differed between institutions. At Brigham and Women's Hospital, patients received 300 U per kg body weight of porcine heparin to achieve an activated clotting time (ACT) of >400 s, until February 2004. From February 2004, patients received a Hepcon HMS Plus (Medtronic, Minneapolis, MN) calculated dose of porcine heparin to achieve an ACT of either 300 or 350 s. At Texas Heart Institute, 300 U

per kg body weight of either bovine or porcine heparin was given to achieve an ACT of >400 s.

Clinical End Points for the Test Cohort

The primary clinical end point was prespecified as the occurrence of a MACE, defined as a composite outcome of any one or more of the following: postoperative mortality (defined as all deaths occurring within 30 days of the operation or occurring during the primary hospitalization), reoperation for coronary graft occlusion, myocardial infarction (MI) (predefined as peak postoperative cTnI concentration >12 ng/mL, being the upper 8th percentile), cardiac arrest (defined as a postoperative event requiring cardio-pulmonary resuscitation) until first hospital discharge, thromboembolic event consisting of stroke (defined as a clinical diagnosis of focal or global neurological deficit), or pulmonary embolism (diagnosed by ventilation perfusion scan of moderate to high probability or by a positive pulmonary angiogram).

Cardiac Biomarker Assay

Blood samples were obtained before surgery, 5 min after administration of post-CPB protamine, and on the mornings of postoperative days (PODs) 1–5. Citrated plasma was stored in vapor-phase liquid nitrogen until analysis for cTnI with a sandwich immunoassay on a Triage® platform using mono-clonal and polyclonal antibodies (Biosite, San Diego, CA) at a single core facility. Patient caregivers were not aware of the results of the assays as they were performed after patient discharge.

Antithrombin Assays

AT activity was measured with a colorimetric method using a Modular Analytics biochemistry analyzer (Siemens Health-care Diagnostics, Tarrytown, NY). The assay limit of quantitation was 21.6%. To report human plasma AT activity results in IU/mL, the National Institute for Biological Standards and Control Second International Reference Standard was used to determine a conversion factor of activity in IU/mL = activity in % $\times$ 0.0102. AT content was measured using an immuno-ephelometric method using a BN-100 ProSpec nephelometer (Dade Behring Diagnostics, Marburg, Germany). The assay limit of quantitation was 0.00672 mg/mL. To report human plasma AT content results in IU/mL, the National Institute for Biological Standards and Control Second International Reference Standard was used to determine a conversion factor of content in IU/mL = content in g/L $\times$ 3.64. Both assays measure free AT rather than AT complexed with heparin. Assays were performed by Charles River Laboratory in Montreal, Canada by personnel blinded to outcome status. Subsequent comparison of paired AT activity and content data revealed high correlation ($r^2 = 0.878$), so only the activity is reported.

Statistical Methods

Statistical analyses were performed using SAS, version 9.1.3, and JMP 7.0 (SAS Institute, Cary, NC). AT activity was normally distributed at all time points, so was not transformed. Data are presented as mean (SD) and median with 10%–90% interquartile range, unless otherwise stated. Continuous variables were compared using analysis of variance or Wilcoxon Mann-Whitney ranked sum test when appropriate. Categorical variables were compared with χ^2 or Fisher's exact test.

Multivariate logistic regression modeling was performed to identify and account for MACE risk factors that might confound any association between low AT activity and MACE. The multivariate analysis used a forward stepwise technique to identify independent risk factors for MACE, whereby clinically relevant demographic variables and variables with a two-

tailed univariate $P \leq 0.2$ were entered into the model and $P \leq 0.2$ was necessary to remain in the model. Age, gender, race, body mass index, and institution were forced into the model. Nagelkerke generalized r^2 and likelihood ratio test were used to determine the additional predictive value of AT upon MACE. F tests were used to compare generalized r^2 . Odds ratios and 95% confidence intervals for a 0.1 IU/mL decrease in AT activity were estimated. A two-sided $P < 0.05$ was considered significant.

RESULTS

The cohort comprised 1403 patients undergoing CABG surgery whose characteristics are described in Table 1. MACE occurred in 146 patients (10.4%), consisting of postoperative mortality ($n = 12$), MI ($n = 108$), stroke ($n = 17$), pulmonary embolism ($n = 8$), cardiac arrest ($n = 16$), or a subsequent postoperative or catheter-based treatment for graft occlusion ($n = 6$). Nineteen patients had 2 or 3 events, usually MI, with either subsequent death or stroke. Most adverse events occurred before or on POD 2. Of 12 patients with operative mortality, 2 patients died at POD 0 and 10 patients died on or after POD 5. Of 17 patients with stroke, 6 patients had a stroke on or before POD 2. Of 108 patients with MI, 89 patients had a diagnosis of MI first occurring on POD 1. MACE frequency did not differ between institutions (Table 1).

AT activity and content were measured at the 7 time points (Table 2). AT activity at baseline did not differ between patients with MACE (0.91 ± 0.13 IU/mL; $n = 146$) and those without MACE (0.92 ± 0.13 IU/mL; $n = 1257$) ($P = 0.18$). AT activity was significantly reduced at the post-CPB measurement compared with the preoperative time point ($P < 0.0001$) and returned to baseline levels over the ensuing 5-day period in patients with and without MACE. Postoperative AT activity was significantly lower in patients with MACE than those without MACE (Table 2).

Decreased preoperative AT activity was independently predicted by older age, male gender, and prior heparin use within the same hospitalization (Table 3). Other clinical variables that may possibly be indicative of recent heparin use at prior recent hospitalization, such as recent MI, were also independently predictive. Decreased preoperative AT activity was also independently associated with lower platelet count and increased partial thromboplastin time, independent of recent heparin use, perhaps indicating a dose effect of heparin administration upon decreased AT activity. In the 1205 patients who had complete data for all variables in the model, decreased post-CPB AT activity was independently predicted by lower preoperative AT activity and clinical variables that indicate greater hemodilution, such as lower body weight and height and increased transfusion incidence or a prolonged procedure (Table 4).

A clinical model predicting MACE was developed (Table 5; adjusted $r^2 = 0.156$) for 1403 patients who had complete data for all variables in the clinical model. Variables that have been associated with MACE in prior studies, notably recent MI, longer perfusion time, a requirement for intraaortic counterpulsation, and red blood cell transfusion were also associated with MACE in this study. AT activities at baseline, post-CPB, PODs 1–5, and the change from baseline at these time points for each patient were added to the clinical model, one time point at a time. Preoperative, post-CPB, and POD 1 AT activity were not independently predictive of MACE, whereas AT activity on PODs 2 and 3 was independently predictive of MACE. MACE was independently associated with change in AT activity from baseline on PODs 2–5 (Table 5). The receiver operating characteristic of the model was significantly improved by the addition of AT activity on PODs 2–4 to the model (Fig. 1).

DISCUSSION

This prospective, observational, cohort study confirms earlier findings that preoperative AT activity is reduced in patients with recent exposure to heparin or recent MI.^{5,6} Furthermore, AT activity is reduced after CPB, likely due to consumption by heparin administration⁶ and dilution. AT activity remained significantly reduced from baseline levels over the postoperative period, recovering to baseline levels within 5 days, on average.

In this population of patients, MACE was associated with factors that have been previously associated with MI or mortality including recent MI, peripheral vascular disease, longer perfusion time, use of intraaortic counterpulsation, and red blood cell transfusion.^{7–10} The clinical model of MACE generated from this cohort had modest predictive value, similar to prior clinical models.⁹ The addition of AT activity on POD 2 and beyond to the model modestly improved model performance. However, the clinical value of AT activity as a predictor of MACE is limited by the majority of adverse events that comprised MACE occurring before POD 2. Specifically, the majority of MACE events were MI, which was typically manifested as the peak cTnI level occurring on POD 1. Rather, it may be that lower postoperative AT activity may be a consequence of more extensive surgery and other factors that are associated with increased incidence of MACE, although such assertion cannot be proven in this observational cohort. We cannot exclude the possibility that lower AT levels may have enhanced postoperative MACE.

Increased risk of adverse cardiovascular events has been associated with lower levels of AT in other critically ill populations, such as patients with severe sepsis.^{11–13} These observations have prompted clinical trials of supplemental AT administration.^{14–17} Although several trials have shown survival benefit, a meta-analysis of 20 trials encompassing 3458 patients failed to show a survival benefit of administration of AT to critically ill patients.¹⁸

There are limited data regarding AT activity and adverse outcomes after cardiac surgery. The majority of studies describe use of AT for “heparin resistance” during CPB and lack postoperative clinical outcome data.^{19–25} A single well-conducted observational study of 647 patients evaluated the association between preoperative and immediate postoperative AT levels and outcomes in cardiac surgery patients. Low levels of AT activity upon ICU arrival were associated with prolonged ICU stay, higher rate of reexploration for bleeding, thromboembolism, and adverse neurologic sequelae.⁵ Our study examined a longer time period that encompassed the period of MACE occurrence and the recovery of AT levels, thus providing additional insights. Importantly, we replicated the finding that AT level after CPB is associated with clinical factors indicative of longer, more extensive procedures, perhaps with more hemodilution.

Although our study contributes to our understanding of the role AT plays in the perioperative period, we are concerned by the absence of a temporal correlation between lower AT activity and MACE in our cohort, likely indicating that AT level is not an important determinant of thrombotic complications such as MI, stroke, and graft occlusion in the cardiac surgical setting. Thus, our observational cohort cannot directly address any putative biological mechanism for the role of AT in MACE generation.

CONCLUSION

In a large cohort of patients undergoing CABG surgery, postoperative AT activity was independently associated with MACE. Because this occurs at time points predominantly after the MACE event, the clinical utility of AT as a biomarker of risk remains unknown.

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Figure 1. Receiver operating characteristics of the addition of antithrombin (AT) activity on postoperative days (PODs) 2–4 to the clinical model.

Table 1

Demographic and Clinical Characteristics of the Cohort as a Whole and Stratified by the Occurrence of Major Adverse Cardiac Events (MACE)

	Entire cohort (n= 1403)	Patients with MACE (n = 146)	Patients without MACE (n = 1257)	P
Age				
<55 yr	240 (17.1)	22 (15.1)	218 (17.3)	
55 to <65 yr	494 (35.2)	51 (34.9)	443 (35.2)	
65 to <75 yr	422 (30.1)	42 (28.8)	380 (30.2)	
75 to <85 yr	231 (16.5)	29 (19.9)	202 (16.1)	
At least 85 yr	16 (1.1)	2 (1.4)	14 (1.1)	0.75
Male	1136 (81.0)	109 (74.7)	1027 (81.7)	0.045
Caucasian race	1189 (84.6)	116 (79.5)	1073 (85.4)	0.068
Body mass index (kg/m ²)	29.4 (5.5)	30.2 (5.5)	29.3 (5.4)	0.063
Institution				
BWH	1061 (75.6)	109 (10.3)	952 (89.7)	0.76
THI	342 (24.4)	37 (10.8)	305 (89.2)	
Medical history				
Diabetes (drug treated; %)	466 (33.2)	52 (35.6)	414 (32.9)	0.52
Pulmonary disease (%)	224 (16.0)	17 (11.6)	207 (16.5)	0.13
Creatinine (mg/dL)	1.10 (0.334)	1.13 (0.322)	1.10 (0.335)	0.27
Hematocrit (%)	40.11 (4.724)	39.48 (4.825)	40.2 (4.708)	0.099
Hypertension (%)	1051 (74.9)	117 (80.1)	934 (74.3)	0.12
Hypercholesterolemia (%)	1045 (74.5)	106 (72.6)	939 (74.7)	0.58
Previous MI	620 (44.2)	83 (56.9)	537 (42.7)	0.002
Time since last MI				
<2 wk	256 (18.3)	44 (30.1)	212 (16.9)	
2–13 wk	47 (3.4)	6 (4.1)	41 (3.3)	
>13 wk	266 (19.0)	31 (21.2)	235 (18.7)	
Never	834 (59.4)	65 (44.5)	769 (61.2)	0.0002
Previous thrombolysis	71 (5.1)	13 (8.9)	58 (4.6)	0.025
IABP placed preoperatively	38 (2.7)	11 (7.5)	27 (2.2)	0.001
Arrhythmia requiring therapy	148 (10.6)	19 (13.0)	129 (10.3)	0.31
Peripheral vascular disease	130 (9.3)	20 (13.7)	110 (8.8)	0.051
Prior PVD procedure	39 (2.8)	10 (6.9)	29 (2.3)	0.0049
Prior stroke	63 (4.5)	10 (6.9)	53 (4.2)	0.15
LVEF preoperative <40%	182 (13.0)	29 (19.9)	153 (12.2)	0.013
Medications—preoperative				
ACE inhibitor	648 (46.2)	66 (45.2)	582 (46.3)	0.86
Beta-blocker	1094 (78.0)	116 (79.5)	978 (77.8)	0.75
Ca ⁺⁺ antagonist	195 (13.9)	24 (16.4)	171 (13.6)	0.35
Aspirin	1072 (76.4)	113 (77.4)	959 (76.3)	0.84
HMG CoA reductase inhibitor	1082 (77.1)	107 (73.3)	975 (77.6)	0.24

	Entire cohort (n= 1403)	Patients with MACE (n = 146)	Patients without MACE (n = 1257)	P
Heparin (intravenous)	351 (25.0)	47 (32.2)	304 (24.2)	0.035
Platelet inhibitor (not aspirin)	304 (21.7)	32 (21.9)	272 (21.6)	0.94
Preoperative laboratory data				
Hemoglobin (g/dL)	13.7 (1.7)	13.5 (1.7)	13.7 (1.6)	0.12
Creatinine (mg/dL)	1.10 (0.33)	1.13 (0.32)	1.10 (0.34)	0.27
Platelet count (10 ⁹ /mL)	240 (72)	234 (70)	241 (72)	0.32
cTnI (ng/mL)	0.4 (2.5)	1.9 (7.4)	0.2 (0.7)	0.006
Intraoperative management				
Number of grafts				
1	28 (2.0)	2 (1.4)	26 (2.1)	
2	188 (13.4)	27 (18.5)	161 (12.8)	
3	627 (44.8)	63 (43.2)	564 (44.9)	
≥4	558 (39.8)	54 (37.0)	504 (40.2)	0.28
CPB duration (min)	99.2 (42.21)	119.63 (57.821)	96.78 (39.353)	<0.0001
Aortic cross-clamp duration (min)	71.5 (35.03)	81.92 (45.125)	70.27 (33.471)	0.003
IABP placed intraoperatively	63 (4.5)	23 (15.8)	40 (3.2)	<0.0001
Heparin administration (mg)				
BWH before February 2004	206 (83.7)	208 (76.0)	206 (85.0)	0.8319
BWH after February 2004	194 (61.0)	187 (54.7)	195 (61.5)	0.4608
THI	306 (92.0)	300 (80.6)	306 (93.4)	0.6998
Other surgical procedure				
Concurrent mitral valve	35 (2.5)	10 (6.9)	25 (2.0)	0.0020
Concurrent aortic valve	22 (1.6)	3 (2.1)	19 (1.5)	0.49
Concurrent other valve	2 (0.1)	2 (1.4)	0	0.01
Other cardiac surgery	108 (7.7)	24 (16.4)	84 (6.7)	<0.0001
Other noncardiac surgery	17 (1.2)	1 (0.7)	16 (1.3)	1.0
Intraoperative inotropes				
Epinephrine	345 (24.6)	59 (40.4)	286 (22.8)	<0.0001
Norepinephrine	169 (12.1)	20 (13.7)	149 (11.9)	0.52
Phenylephrine	668 (47.6)	63 (43.2)	605 (48.1)	0.25
Dopamine >5μg · kg ⁻¹ · min ⁻¹	38 (2.7)	3 (2.1)	35 (2.8)	0.79
Dobutamine	18 (1.3)	1 (0.7)	17 (1.4)	1.0
Milrinone	29 (2.1)	6 (4.1)	23 (1.8)	0.11
Vasopressin	17 (1.2)	3 (2.1)	14 (1.1)	0.41
Postoperative inotropes				
Epinephrine	230 (16.4)	51 (34.9)	179 (14.2)	<0.0001
Norepinephrine	143 (10.2)	31 (21.2)	112 (8.9)	<0.0001
Phenylephrine	113 (8.1)	11 (7.5)	102 (8.1)	0.81
Dopamine 5μg · kg ⁻¹ · min ⁻¹	30 (2.1)	8 (5.5)	22 (1.8)	0.009
Dobutamine	12 (0.9)	3 (2.1)	9 (0.7)	0.12
Milrinone	32 (2.3)	9 (6.2)	23 (1.8)	0.004

	Entire cohort (n= 1403)	Patients with MACE (n = 146)	Patients without MACE (n = 1257)	P
Vasopressin	91 (6.5)	26 (17.8)	65 (5.2)	<0.0001
Intraoperative and postoperative transfusion ^a (median, 10–90 percentile)				
Red blood cell transfusion (units)	1 (0–5)	2 (0–8)	1 (0–5)	<0.0001
Coagulation factor transfusion (units)	0 (0–2)	0 (0–4)	0 (0–2)	0.0055
Postoperative events				
vHLOS (d) >12 d	130 (9.3)	43 (29.5)	87 (6.9)	<0.0001
ICU LOS (d) >4 d	136 (9.7)	44 (30.1)	92 (7.3)	<0.0001
Peak postoperative cTnI >12 ng/mL	108 (8.0)	108 (76.6)	0	<0.0001
Peak postoperative cTnI	4.06 (8.6)	21.9 (17.8)	2.0 (2.1)	<0.0001

^a All blood products administered during the hospital stay. Red blood cell transfusion includes both packed red blood cells and whole blood. Coagulation factor transfusion includes fresh frozen plasma, cryoprecipitate, and platelet transfusion.

BWH = Brigham and Women's Hospital; THI = Texas Heart Institute; MI = myocardial infarction; cTnI = cardiac troponin I; IABP = intraaortic balloon pump; LVEF = left ventricular ejection fraction; ACE = angiotensin converting enzyme; CPB = cardiopulmonary bypass; HLOS = hospital length of stay; ICU LOS = intensive care unit length of stay; PVD = peripheral vascular disease.

Table 2

Postoperative Changes in Antithrombin Activity in Patients with Major Adverse Cardiac Events (MACE) ($n = 146$) and Without MACE ($n = 1257$): Results of Univariate Analysis at Each Time Point

	Baseline	Post-CPB	Postoperative day				
			1	2	3	4	5
Antithrombin activity (IU/mL)							
Patients with MACE	0.91 ± 0.13	0.59* ± 0.12	0.66* ± 0.12	0.72* ± 0.12	0.78* ± 0.13	0.85* ± 0.15	0.90 [†] ± 0.16
Patients without MACE	0.92 ± 0.13	0.62 ± 0.11	0.71 ± 0.13	0.77 ± 0.12	0.83 ± 0.12	0.90 ± 0.13	0.95 ± 0.14
Change in antithrombin activity from baseline (IU/mL)							
Patients with MACE	—	−0.32 ± 0.13	−0.24 [†] ± 0.13	−0.19 [†] ± 0.13	−0.13 [†] ± 0.14	−0.06* ± 0.15	−0.00 [†] ± 0.16
Patients without MACE	—	−0.30 ± 0.12	−0.22 ± 0.13	−0.16 ± 0.13	−0.09 ± 0.13	−0.02 ± 0.13	0.03 ± 0.13
Percentage change in antithrombin activity from baseline (%)							
Patients with MACE	—	−34.7 [†] ± 12.8	−26.2 [†] ± 12.3	−20.4* ± 12.7	−13.5 [†] ± 15.0	−5.9 [†] ± 16.4	0.7 [†] ± 17.9
Patients without MACE	—	−32.0 ± 11.2	−22.7 ± 13.5	−16.1 ± 13.3	−9.2 ± 14.7	−1.1 ± 14.5	4.6 ± 15.5

Data are reported as mean $\pm$ standard deviation.

CPB = cardiopulmonary bypass.

Significance is reported between MACE groups at each time point:

* $P \leq 0.001$ and

$^\dagger P < 0.05$ by Student's t -test.

Table 3**Multivariable Predictors of Preoperative Antithrombin Activity**

Predictor	Predictors of preoperative AT activity (U/mL) (<i>n</i> = 1194^a; <i>r</i>² = 0.168)			
	Univariate estimate	Multivariate estimate	Standard error of multivariate estimate	<i>P</i>
Age (1 yr increment)	−0.0020	−0.0022	0.0004	<0.0001
Gender (female)	0.0288	0.0177	0.0059	0.0028
Race (Caucasian)	−0.0078	−0.0026	0.0054	0.624
Weight (1 kg increment)	−0.0003	−0.0003	0.0002	0.233
Height (1 cm increment)	−0.0007	−0.0031	0.0005	0.568
Institution	0.0183	0.0081	0.0053	0.129
Previous MI (Y)	−0.0273	−0.0104	0.0036	0.004
Preoperative platelet count (10 × 10 ⁹ /mL increment)	0.0023	0.0013	0.0005	0.006
Preoperative PTT (1 s increment)	−0.0014	−0.0008	0.0002	<0.0001
Preoperative heparin use	−0.0863	−0.0352	0.0042	<0.0001
Preoperative diuretic use	0.0275	0.0147	0.0042	0.0005

^a209 subjects were missing one or more of the model's predictor variables and are not included in this analysis.

AT = antithrombin; MI = myocardial infarction; PTT = partial thromboplastin time.

Table 4

Multivariable Predictors of Post-CPB Antithrombin (AT) Activity

Predictor	Predictors of post-CPB AT activity (U/mL) ($n = 1205^a$; $r^2 = 0.504$)			
	Univariate estimate	Multivariate estimate	multivariate estimate estimate Standard error of	P
Age (1 yr increment)	−0.0030	−0.0006	0.0002	0.0110
Gender (female)	0.0356	0.0023	0.0039	0.5581
Race (Caucasian)	−0.0068	−0.0022	0.0033	0.4979
Height (1 cm increment)	0.0023	0.0010	0.0003	0.0045
Weight (1 kg increment)	0.0015	0.0006	0.0001	<0.0001
Institution	−0.0492	−0.0236	0.0038	<0.0001
Preoperative AT activity (U/mL)	0.4870	0.4698	0.0174	<0.0001
CPB duration (10 min increment)	−0.006	−0.004	0.001	<0.0001
Lowest venous temperature during CPB (1°C increment)	0.0030	0.0044	0.0011	<0.0001
Intraoperative packed red blood cell transfusion (1 unit increment)	−0.0095	−0.0085	0.0021	<0.0001
Intraoperative cryoprecipitate transfusion (1 pooled unit increment)	0.0497	0.0491	0.0150	0.0011
Post-CPB hemoglobin (1 g/dL increment)	0.0177	0.0184	0.0018	<0.0001

^a 198 subjects were missing one or more of the model's predictor variables and are not included in this analysis.

CPB = cardiopulmonary bypass.

Table 5**Multivariable Predictors of Major Adverse Cardiac Events (MACE)**

Without AT activity information in model ($n = 1403$; $r^2 = 0.156$)			
Predictor	Odds ratio	95% confidence interval	P
Age			
<55 yr	1.00	—	
55–64 yr	1.26	0.72–2.21	
65–74 yr	1.26	0.70–2.28	
75–84 years	1.66	0.86–3.20	
≥85 yr	0.70	0.11–4.36	0.58
Gender (female)	1.13	0.72–1.78	0.60
Race (Caucasian)	0.59	0.36–0.95	0.03
Body mass index			
<20	0.67	0.15–3.04	
20–24.9	0.52	0.28–0.96	
25–34.9	0.48	0.30–0.77	
≥35	1.00	—	0.03
Institution	0.73	0.44–1.21	0.22
Myocardial infarction <2 wk prior	1.70	1.11–2.59	0.014
Prior peripheral vascular procedure	3.38	1.53–7.46	0.003
Perfusion time (10 min increment)	1.09	1.05–1.14	<0.0001
Concurrent other cardiac procedure	1.47	0.82–2.67	0.20
Preoperative or intraoperative IABP	4.02	2.18–7.42	<0.0001
RBC transfusion during hospital stay (per unit)	1.10	1.04–1.16	0.0004

Additional Predictive Value of AT Activity at Each Time Point Added to the Clinical Model				
AT activity (0.1 IU/mL decrease)	Odds Ratio	95% Confidence interval	P value of AT variable	P value of improvement in overall model
Preoperative AT activity	0.98	0.85–1.13	0.7820	0.7822
Postoperative AT activity	1.10	0.91–1.31	0.3193	0.3179
POD 1 AT activity	1.13	0.96–1.33	0.1565	0.1543
POD 2 AT activity	1.26	1.07–1.48	0.0056	0.0053
POD 3 AT activity	1.19	1.01–1.41	0.0412	0.0399
POD 4 AT activity	1.17	1.00–1.37	0.0506	0.0493
POD 5 AT activity	1.17	1.00–1.37	0.0553	0.0546
Change in AT activity Post-CPB ^a	1.15	0.93–1.41	0.1888	0.4058
Change in AT activity Day 1 ^a	1.20	1.00–1.45	0.0558	0.1394
Change in AT activity Day 2 ^a	1.36	1.13–1.62	0.0009	0.0035
Change in AT activity Day 3 ^a	1.26	1.04–1.52	0.0163	0.0525
Change in AT activity Day 4 ^a	1.26	1.06–1.51	0.0104	0.0294
Change in AT activity Day 5 ^a	1.20	1.01–1.44	0.0407	0.1201

^aRefers to change in AT activity from the baseline level.

AT = antithrombin; RBC = red blood cell; POD = postoperative day.