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Differential Impact of Serial Measurement of Nonplatelet Thromboxane Generation on Long-Term Outcome After Cardiac Surgery

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Background—Systemic thromboxane generation, not suppressible by standard aspirin therapy and likely arising from nonplatelet sources, increases the risk of atherothrombosis and death in patients with cardiovascular disease. In the RIGOR (Reduction in Graft Occlusion Rates) study, greater nonplatelet thromboxane generation occurred early compared with late after coronary artery bypass graft surgery, although only the latter correlated with graft failure. We hypothesize that a similar differential association exists between nonplatelet thromboxane generation and long-term clinical outcome.

Methods and Results—Five-year outcome data were analyzed for 290 RIGOR subjects taking aspirin with suppressed platelet thromboxane generation. Multivariable modeling was performed to define the relative predictive value of the urine thromboxane metabolite, 11-dehydrothromboxane B2 (11-dhTXB2), measured 3 days versus 6 months after surgery on the composite end point of death, myocardial infarction, revascularization or stroke, and death alone. 11-dhTXB2 measured 3 days after surgery did not independently predict outcome, whereas 11-dhTXB2 >450 pg/mg creatinine measured 6 months after surgery predicted the composite end point (adjusted hazard ratio, 1.79; P=0.02) and death (adjusted hazard ratio, 2.90; P=0.01) at 5 years compared with lower values. Additional modeling revealed 11-dhTXB2 measured early after surgery associated with several markers of inflammation, in contrast to 11-dhTXB2 measured 6 months later, which highly associated with oxidative stress.

Conclusions—Long-term nonplatelet thromboxane generation after coronary artery bypass graft surgery is a novel risk factor for 5-year adverse outcome, including death. In contrast, nonplatelet thromboxane generation in the early postoperative period appears to be driven predominantly by inflammation and did not independently predict long-term clinical outcome. (J Am Heart Assoc. 2017;6:e007486. DOI: 10.1161/JAHA.117.007486.)

Key Words: aspirin • inflammation • oxidative stress • thrombosis • thromboxane

Thromboxane A2 (TXA2) is a signal-activated eicosanoid generated from the metabolism of arachidonic acid via the actions of cyclooxygenase (COX) and downstream thromboxane synthase enzymes.1 In healthy adults, TXA2 is produced predominantly by platelets in response to physiologic agonists, where it potentiates the activation of the platelet in which it is formed. TXA2 is also released, causing local amplification of thrombotic stimuli by directly activating adjacent platelets and vasoconstriction via binding to cellular thromboxane-prostanoid receptors.2 The cardioprotective effect of aspirin is principally mediated by the irreversible inhibition of the platelet COX-1 enzyme, which suppresses platelet TXA2 generation and platelet activation.3

A substantial percentage of patients with cardiovascular disease continue to generate significant amounts of TXA2 despite aspirin therapy, which places them at risk for adverse cardiovascular events.4–8 Although initially thought to represent a failure of aspirin to inhibit platelet TXA2 generation,
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Clinical Perspective

What Is New?

- Despite being greater in magnitude, nonplatelet thromboxane generation occurring immediately after cardiac surgery does not have the same long-term prognostic value as that occurring following recovery and return to a baseline state.
- Inflammation appears to be a major stimulus for nonplatelet thromboxane generation in the immediate postoperative state, whereas oxidative stress is the predominant stimulus in the long-term baseline state.
- These findings suggest that the source, and not necessarily only the overall magnitude, of nonplatelet thromboxane generation is an important determinant of its impact on cardiovascular risk.

What Are the Clinical Implications?

- Although nonplatelet thromboxane generation is emerging as a novel cardiovascular risk factor, the context in which it is assessed is important for its prognostic significance.
- Identifying the sources of nonplatelet thromboxane generation will facilitate a better understanding of the pathological characteristics of nonplatelet thromboxane generation and aid in the development of therapies to mollify its effects.

emerging evidence suggests that residual TXA2 generation derives principally from nonplatelet sources not suppressible by once-daily dosing regimens.6,9–13

In the RIGOR (Reduction in Graft Occlusion Rates) study, nonplatelet TXA2 generation was identified as a novel risk factor for saphenous vein graft thrombotic occlusion after first-time coronary artery bypass graft (CABG) surgery.6 Little is known about how extreme physiologic stress affects nonplatelet TXA2 generation, how it changes over time in a given patient, or how predictive it is of clinical outcome when measured in acute versus chronic conditions. To address these questions, we compared nonplatelet TXA2 generation in the RIGOR study population measured 3 days after surgery with that measured 6 months later and determined how predictive each was of 5-year outcome. To gain insight into possible sources of nonplatelet TXA2 generation, we also investigated if variables associated with nonplatelet TXA2 generation in the early postoperative period differed from those after a return to long-term baseline state.

Methods

Patient Population

The RIGOR study was a multicenter observational study of 368 subjects undergoing first-time CABG surgery between October, 2003 and October, 2006, designed to investigate the association between thrombotic risk factors and early saphenous vein graft occlusion. Detailed descriptions of the study design, patient characteristics, and principal findings have previously been published.6,14,15 Institutional review board approval was obtained at each participating site, and written consent was obtained from all subjects. Any patient ≥18 years old undergoing first-time CABG surgery with implantation of at least 1 saphenous vein graft was eligible for enrollment. Those with an anticipated requirement for postoperative oral anticoagulation or antiplatelet therapy other than aspirin were excluded, although subjects given these agents for unforeseen postoperative conditions (eg, atrial fibrillation) continued in the study. All patients were administered aspirin (300–325 mg) within 24 hours of surgery. At hospital discharge, patients were given a supply of 325-mg enteric-coated aspirin and instructed to take 1 tablet daily for 6 months, unless directed otherwise by their physician. Pill counts were performed at each postoperative encounter. Demographic, historical, procedural, clinical, and laboratory data were recorded for all patients. Subjects were contacted yearly around the surgical anniversary date for up to 5 years unless known to have expired. Intercurrent clinical end points were verified by review of medical records, and deaths were confirmed by medical and/or Social Security death records.

Laboratory Studies

Details of the laboratory methods used have been described previously.16 Platelet function studies could only be performed 3 days after CABG surgery in subjects enrolled at the Johns Hopkins Hospital (Baltimore, MD) but were performed in all subjects 6 months after surgery, at the time of graft patency assessment. Platelet-rich plasma was prepared from citrated blood, and the platelet count was adjusted to 180 000/mm3 by the addition of platelet-poor plasma. Undiluted samples with a platelet count of <100 000/mm3 were excluded from analysis. Impedance platelet aggregometry was performed on platelet-rich plasma by stimulation with a panel of agonists, including 0.5 mmol/L arachidonic acid, using an aggregometer, and the maximum aggregation response within 5 minutes was recorded (in ohms). Platelet COX-1 activity and TXA2 generation were considered to be fully suppressed by aspirin if arachidonic acid–induced platelet aggregation was ≤1 Ω (normal range in our laboratory for aspirin-naive subjects, 5–17 Ω) on the basis of data demonstrating that suppression of platelet TXA2 generation >99% is required to suppress arachidonic acid–induced platelet aggregation by 95%.17 Systemic TXA2 generation was quantified by measuring the concentration of its stable metabolite, 11-dehydrothromboxane B2 (11-dhTXB2), in urine.

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by ELISA and expressed as pg/mg of urine creatinine (coefficients of variance, ≤10%; lower limit of detection, 25 pg/mL).

Assessment of Graft Patency and Left Ventricular Ejection Fraction

The patency of venous and arterial grafts was assessed 6 months after CABG surgery by computed tomographic angiography, as previously described.\textsuperscript{14,15} Data from clinically driven invasive coronary angiograms could be used for the primary end point analysis if performed within 6 weeks of the anticipated 6-month follow-up visit or if it was the only assessment of graft patency before a clinical end point. Multisegmented grafts were statistically considered as separate grafts, according to the Society of Thoracic Surgeons criteria. Two blinded reviewers analyzed reconstructed 3-dimensional images to classify grafts as patent (containing stenoses of 0%–75%), significantly diseased (containing stenoses of 76%–99%), or occluded (containing a 100% stenosis). In cases of discordance, a third reviewer adjudicated all grafts in that patient. Left ventricular ejection fractions were calculated from reconstructed computed tomographic angiography images using computer software.

Statistical Analysis

Data from patients who survived the index hospitalization and underwent graft patency assessment were included in the present analysis. Baseline characteristics are presented as mean±SD or median (interquartile range) for continuous variables and as proportions for categorical variables. Proportions were compared using a Fisher exact test, and continuous variables were compared by Student \( t \) test or Wilcoxon rank-sum test, as appropriate. For graft patency analysis, the small proportion of grafts classified as severely diseased was considered as occluded. Nonnormally distributed variables were transformed using natural log or negative inverse square, as indicated. Median, upper quartile, or upper tertile splits were used to categorize continuous variables that could not be normalized, as indicated. Differences were considered significant when \( P<0.05 \). A proportional hazard Cox survival model was used to evaluate the independent determinants of the predefined composite outcome of death, myocardial infarction, revascularization (both surgical and percutaneous), and stroke, as well as death alone (because it was a major determinant of the composite outcome). The time origins for the survival analyses were set at the time of surgery and the time of graft patency assessment when urine 11-dhTXB\(_2\) was measured 6 months after surgery. For analyses involving the latter, events occurring before the 6-month landmark were excluded. Cox modeling was performed using clustering by patient; for the composite end point, stratification by individual end point was used. Kaplan-Meier survival plots comparing various predictors were constructed. Predictors with unadjusted \( P \leq 0.15 \) were included in the initial multivariable Cox model. The explained relative risk by the models was assessed using the Royston modified version of the Nagelkerke \( R^2 \), including a bootstrap confidence interval.\textsuperscript{18} Backward stepwise modeling with bootstrapping was performed, and predictors appearing in >50% of resulting models were considered in the final model, with selection guided by the Bayesian information criterion and \( R^2 \). Multivariable fractional polynomial interaction analysis was used to assess for interactions between covariates. The assumption of proportionality was evaluated by introducing natural log-time–dependent covariates for predictors in the Cox model and testing for significance. The final optimized multivariable Cox proportional hazard models were used to derive adjusted hazard ratios. Robust univariate regression was performed for predictors of 11-dhTXB\(_2\) using variables deemed biologically plausible or supported by the literature. Highly collinear covariates were identified using the Fisher exact test and Pearson correlation for categorical and continuous variables, respectively, and were eliminated on the basis of clinical significance. Variables with \( P \leq 0.15 \) on the initial univariate analysis were included in the initial multivariate model. The Furnival-Wilson leaps-and-bounds algorithm was used for variable subset selection, and the model was optimized on the basis of the Akaike information criteria. The coefficient estimates are reported standardized to a variance of 1 (\( \beta \) coefficients), to facilitate comparison of the predicted magnitude of change in the dependent variable per unit change in the predictor. The relative importance of each variable in the multivariable model was assessed by dominance analysis.\textsuperscript{13,19} Analyses were performed using Stata 13.0 for Windows.

Results

Study Population Characteristics

Of the 368 subjects enrolled in the RIGOR study at the 4 participating sites, 293 survived the index hospitalization, were receiving long-term aspirin therapy, and had measurement of both urine 11-dhTXB\(_2\) and arachidonic acid–induced platelet aggregation at the time of graft patency assessment at 6 months (median, 189 days; interquartile range, 182–202 days) after CABG surgery. Because 3 subjects were excluded from analysis because of persistent arachidonic acid–induced platelet aggregation, despite aspirin therapy at this time point, 290 subjects formed the study cohort. Of these subjects, 271 also had measurement of urine 11-
dhTXB₂ a median of 3 days (interquartile range, 3–4 days) after CAGB surgery. Only 198 subjects also had verified suppression of arachidonic acid–induced platelet aggregation at this time point, given that platelet function testing was only available at only 1 enrolling site. The median duration of clinical follow-up in the study cohort was 1828 days (interquartile range, 1482–1846 days) after surgery. The characteristics of the study cohort as a whole and in subjects

### Table 1. Baseline, Operative, and Postoperative Characteristics of Subjects Stratified by 11-dhTXB₂ Measured at 3 Days and 6 Months After CAGB Surgery

| Characteristic | Cohort (n=288) | 3 Days | 6 Months | P Value | 3 Days | 6 Months | P Value |
|----------------|---------------|--------|----------|---------|--------|----------|---------|
| Age, mean±SD, y |               |        |          |         |        |          |         |
| Serum creatinine <891 pg/mg | 214 (74) | 68.4±9.9 | 62.4±9.7 | 0.12    | 65.9±10.7 | 62.4±9.7 | 0.01    |
| Serum creatinine ≥891 pg/mg | 74 (26) | 64.8±10.1 | 66.9±10.7 | 0.03    | 62.4±9.7 | 65.9±10.7 | 0.01    |
| Male sex | 229 (80) | 173 (81) | 178 (84) | 0.13 | 187 (87) | 178 (84) | 0.003    |
| White race | 250 (87) | 187 (87) | 192 (91) | 0.01 | 187 (87) | 192 (91) | 0.003 |
| Body mass index, median (interquartile range), kg/m² | 30 (26–33) | 29 (26–33) | 30 (26–33) | 0.55 | 29 (26–33) | 29 (26–33) | 0.21 |
| Medical history | | | | | | | |
| Hypertension | 236 (82) | 173 (81) | 174 (83) | 0.49 | 161 (72) | 177 (84) | 1.0 |
| Dyslipidemia | 241 (84) | 178 (84) | 177 (84) | 0.86 | 178 (84) | 177 (84) | 0.86 |
| Diabetes mellitus | 99 (35) | 68 (32) | 63 (30) | 0.12 | 63 (30) | 63 (30) | 0.007 |
| Heart failure | 35 (12) | 18 (8) | 20 (9) | 0.024 | 18 (8) | 20 (9) | 0.024 |
| Peripheral/cerebral-vascular disease | 50 (17) | 31 (14) | 33 (16) | 0.216 | 31 (14) | 33 (16) | 0.216 |
| Atrial fibrillation | 10 (3) | 5 (2) | 6 (3) | 0.30 | 5 (2) | 6 (3) | 0.30 |
| Tobacco use at surgery | 68 (24) | 42 (20) | 45 (21) | 0.12 | 42 (20) | 45 (21) | 0.12 |
| Myocardial infarction | 118 (41) | 78 (36) | 81 (38) | 0.009 | 78 (36) | 81 (38) | 0.009 |
| Prior PCI | 59 (20) | 40 (19) | 45 (21) | 0.74 | 40 (19) | 45 (21) | 0.74 |
| Preoperative LVEF, % | | | | | | | |
| ≤30 | 24 (8) | 11 (5) | 16 (8) | 0.61 | 11 (5) | 16 (8) | 0.61 |
| 30–50 | 97 (34) | 75 (35) | 70 (33) | 0.74 | 75 (35) | 70 (33) | 0.74 |
| >50 | 167 (58) | 128 (60) | 126 (59) | 0.74 | 128 (60) | 126 (59) | 0.74 |
| Urgent/emergent surgery | 178 (62) | 120 (56) | 128 (60) | 0.41 | 120 (56) | 128 (60) | 0.41 |
| EuroScore, median (interquartile range) | 4 (2–5) | 3 (2–5) | 3 (2–5) | 0.005 | 3 (2–5) | 3 (2–5) | 0.005 |
| Arterial graft implanted | 280 (97) | 208 (97) | 206 (97) | 0.93 | 208 (97) | 206 (97) | 0.93 |
| No. of SVGs per subject | | | | | | | |
| 1 | 78 (27) | 55 (26) | 57 (27) | 0.25 | 55 (26) | 57 (27) | 0.25 |
| ≥2 | 121 (42) | 90 (42) | 85 (40) | 0.47 | 90 (42) | 85 (40) | 0.47 |
| ≥3 | 89 (31) | 69 (32) | 70 (33) | 0.25 | 69 (32) | 70 (33) | 0.25 |
| Medications at urine 11-dhTXB₂ measurement | | | | | | | |
| Aspirin | 288 (100) | 214 (100) | 212 (100) | 1.0 | 214 (100) | 212 (100) | 1.0 |
| Dose, <325 mg/d | 30 (10) | 0 (0) | 1.0 | 0.046 | 0 (0) | 1.0 | 0.046 |
| Nonaspirin antiplatelet agent | 32 (11) | 27 (13) | 20 (9) | 0.14 | 27 (13) | 20 (9) | 0.14 |
| Oral anticoagulation | 14 (5) | 17 (8) | 20 (9) | 0.06 | 17 (8) | 20 (9) | 0.06 |
| β Blocker | 240 (83) | 210 (85) | 181 (85) | 0.15 | 210 (85) | 181 (85) | 0.15 |
| ACE inhibitor/ARB | 178 (62) | 107 (50) | 133 (63) | 0.59 | 107 (50) | 133 (63) | 0.59 |
| Lipid-lowering agent | 255 (89) | 207 (97) | 192 (91) | 0.09 | 207 (97) | 192 (91) | 0.09 |

Data are given as number (percentage) unless otherwise indicated. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAGB, coronary artery bypass graft; 11-dhTXB₂, 11-dehydrothromboxane B₂; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and SVG, saphenous vein graft. All statistically significant P values were in bold.
stratified by urine 11-dhTXB\textsubscript{2} values of 891 pg/mg creatinine, measured 3 days after surgery (upper-tertile threshold), and 450 pg/mg creatinine, measured 6 months after surgery (upper-quartile threshold previously shown to independently correlate with vein graft thrombotic occlusion\textsuperscript{6}), are shown in Table 1. Similar to other studies, older age, female sex, and nonwhite race were demographic characteristics associated with higher 11-dhTXB\textsubscript{2} levels when measured 6 months after surgery.\textsuperscript{5,20} In contrast, no demographic characteristics were associated with higher 11-dhTXB\textsubscript{2} levels when measured 3 days after surgery.

Median 11-dhTXB\textsubscript{2} in the study cohort was significantly higher 3 days (648 pg/mg creatinine; interquartile range, 398–1171 pg/mg creatinine) compared with 6 months after surgery (331 pg/mg creatinine; interquartile range, 232–462 pg/mg creatinine; \(P<0.0001\)) (Figure 1A). In the 198 subjects with paired samples and verified suppression of platelet thromboxane generation, the change in urine 11-dhTXB\textsubscript{2} over time was linearly related with 151 subjects (76%) manifesting a net decrease in 11-dhTXB\textsubscript{2} after 6 months (median change, 323 pg/mg creatinine; interquartile range, 173–668 pg/mg creatinine) and only 48 subjects (24%) manifesting a net increase (median change, 119 pg/mg creatinine; interquartile range, 48–201 pg/mg creatinine) (Figure 1B).

### Urine 11-dhTXB\textsubscript{2} as a Predictor of Outcome

Univariate analyses were used to explore the association of urine 11-dhTXB\textsubscript{2}, along with a wide array of demographic, clinical, and laboratory variables, to the primary composite outcome of death, myocardial infarction, revascularization, or stroke at 6 months (Table S1) and both the composite outcome and death alone at 5 years (Table S2). Urine 11-dhTXB\textsubscript{2}, measured 3 days after surgery and expressed as a dichotomous (using the upper-tertile threshold of 891 pg/mg creatinine) but not as a continuous variable, was significantly associated with the composite outcome end point at 6 months. Urine 11-dhTXB\textsubscript{2} measurements at both 3 days and 6 months were significantly associated with the 5-year composite outcome end point and death, a major determinant of the composite end point (Figure 2). Interestingly, there was no association with revascularization, the other major driver of the composite end point (Table S3). To determine the relative predictive value of 11-dhTXB\textsubscript{2} measured at both time points, multivariable models were constructed to identify independent predictors of outcome. Urine 11-dhTXB\textsubscript{2} measured 3 days after CABG surgery was not an independent predictor of the composite outcome at 6 months (Table S4) or at 5 years (Table 2). In contrast, urine 11-dhTXB\textsubscript{2} measured 6 months after surgery was an independent predictor of both the composite outcome and death at 5 years (Table 2).

### Occlusion of left internal mammary grafts, but not vein grafts, 6 months after CABG surgery predicted the composite end point, which was predominantly driven by revascularization. Not unexpectedly, concurrent peripheral or cerebrovascular disease, postoperative renal insufficiency, and reduced ejection fraction independently predicted higher long-term mortality; statin therapy predicted lower long-term mortality.

### Variables Associated With Nonplatelet TXA\textsubscript{2} Generation Early After Surgery

In a prior analysis of this study cohort,\textsuperscript{13} oxidative stress, as measured by urine 8-iso-prostaglandin F\textsubscript{2\alpha}, was identified as the strongest variable associated with urine 11-dhTXB\textsubscript{2}, measured 6 months after surgery, accounting for approximately half of the modeled effect and consistent with data from other study populations.\textsuperscript{20,21} Age, race, statin use, and aspirin dose were also associated, but to lesser degrees. Given the observed differences in subject characteristics associated with high 11-dhTXB\textsubscript{2} levels when measured at
different time points (Table 1), we sought to understand if stimuli for nonplatelet TXA2 generation during the early perioperative period, when subjects were under acute physiologic stress, differed from those 6 months later, when subjects would more likely to be at their physiologic baseline. Modeling of variables associated with 11-dhTXB2 measured 3 days after surgery revealed that red cell distribution width, a novel marker of inflammation and cardiovascular risk, was the strongest associated variable, accounting for nearly a third of the modeled effect (Table 3). Other markers and modulators of inflammation, such as C-reactive protein and statin use, were also associated to lesser degrees, as was oxidative stress, as measured by urine 8-iso-prostaglandin_2.

Discussion
The major findings of this study were as follows: (1) in patients undergoing CABG surgery, nonplatelet TXA2 generation is markedly higher in the early postoperative period than 6 months later; (2) nonplatelet TXA2 generation measured 6 months after CABG surgery, but not that measured in the early postoperative period, independently predicted long-term outcome, particularly mortality; and (3) although oxidative stress is a major stimulus for nonplatelet TXA2 generation 6 months after CABG surgery, inflammation is a stronger stimulus for nonplatelet TXA2 generation in the early postoperative period.

Studies have emerged in recent years demonstrating that persistent TXA2 generation in patients with cardiovascular disease undergoing aspirin therapy predicts an increased risk of atherothrombosis and death. Although initially assumed to be attributable to the failure of aspirin to inhibit platelet COX-1 and consequent platelet activation, it is now recognized that aspirin is efficient at inhibiting platelet COX-1 and that much of the residual TXA2 generation in patients taking aspirin originates from nonplatelet sources. A unique feature of our analysis was that it only included subjects in whom inhibition of platelet thromboxane generation was verified, conclusively demonstrating that TXA2 originating from nonplatelet tissue adversely affects clinical outcome and survival.
Sources of nonplatelet TXA2 generation have not been conclusively identified and may conceivably vary depending on the patient population and conditions under study. Many tissues and cell types produce TXA2, which is quickly degraded to TXB2, a relatively stable metabolite that circulates widely. TXB2 itself is extensively metabolized via enzyme-mediated β oxidation and dehydrogenation to dozens of different stable end-order metabolites, including 11-dhTXB2, that are concentrated in the urine.29 Because TXB2 produced from TXA2 generated in the kidney does not circulate and is, therefore, not subjected to extensive further metabolism, urine levels of TXB2 are considered to predominantly represent renal TXA2 generation; those of 11-dhTXB2 are considered to predominantly represent extrarenal systemic TXA2 generation.30 Measurement of urine 11-dhTXB2 in our study was performed using an ELISA with high specificity for this metabolite and strong correlation with values measured by mass spectrometry.31 Two candidate sources for significant nonrenal, nonplatelet TXA2 generation in our study population include vascular endothelial and inflammatory cells based on convincing in vitro data showing that each is capable of producing TXA2.13,32–34

A second unique feature of our study that helps gain insight into potential sources of nonplatelet TXA2 generation was the serial measurement of urine 11-dhTXB2 in individual subjects during 2 markedly different physiologic states: a period of intense physiologic stress and inflammation induced by cardiac surgery and then 6 months later when subjects would have likely returned to their physiologic baseline. We previously found that urine 11-dhTXB2 levels measured in subjects 6 months after CABG surgery were strongly correlated with evidence of increased oxidative stress and were influenced by age, sex, and race, similar to other studies of patients with stable cardiovascular disease or diabetes.

Table 2. Multivariable Cox Proportional Hazard Models for 5-Year Outcomes

| Variable                                      | Death, Myocardial Infarction, Revascularization, and Stroke | Death |
|-----------------------------------------------|---------------------------------------------------------------|--------|
|                                               | Adjusted HR 95% CI P Value                                   | Adjusted HR 95% CI P Value |
| Model 1*                                       |                                                                |        |
| Peripheral/cerebrovascular disease            | 2.47 1.42–4.32 0.001                                         | 3.34 1.52–7.32 0.003         |
| Insulin therapy                               | 2.31 1.31–4.08 0.004                                         |        |
| Lipid-lowering agent                          | 0.34 0.15–0.77 0.01                                          |        |
| eGFR, mL/min per 1.73 m²                       | 0.98 0.95–1.0 0.04                                          |        |
| Urine 11-dhTXB2 at 6 mo (ln pg/mg creatinine) | 1.59 1.0–2.54 0.05                                          | 2.36 1.24–4.50 0.009         |
| LIMA occlusion                                | 2.95 1.50–5.81 0.002                                        |        |
| Postoperative LVEF, %                         |                                                                |        |
| ≤30                                           | 2.58 1.10–6.03 0.03                                          | 5.45 0.94–14.85 0.06          |
| 30–50                                         | 2.67 1.54–5.63 <0.001                                        | 3.67 1.50–8.14 0.004          |
| >50                                           | Reference                                                   | Reference |
| Model 2†                                       |                                                                |        |
| Peripheral/cerebrovascular disease            | 2.50 1.41–4.42 0.002                                         | 3.58 1.63–7.89 0.002          |
| Insulin therapy                               | 2.21 1.22–3.98 0.009                                         |        |
| Lipid-lowering agent                          | 0.34 0.16–0.75 0.007                                         |        |
| eGFR, mL/min per 1.73 m²                       | 0.97 0.95–1.0 0.03                                          |        |
| Urine 11-dhTXB2 at 6 mo (>450 pg/mg creatinine)| 1.79 1.08–2.96 0.02                                          | 2.90 1.29–6.50 0.01          |
| LIMA graft occlusion                          | 3.20 1.62–6.34 0.001                                        |        |
| Postoperative LVEF, %                         |                                                                |        |
| ≤30                                           | 2.80 1.14–6.90 0.025                                         | 3.51 0.71–17.33 0.12          |
| 30–50                                         | 2.66 1.53–4.62 0.001                                         | 3.43 1.53–7.67 0.003          |
| >50                                           | Reference                                                   | Reference |

CI indicates confidence interval; 11-dhTXB2, 11-dehydrothromboxane B2; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LIMA, left internal mammary artery; and LVEF, left ventricular ejection fraction.

*For death, myocardial infarction, revascularization, and stroke: pseudo R² 0.47 (95% CI: 0.31–0.69). For death: pseudo R² 0.71 (95% CI: 0.49–0.93).
† For death, myocardial infarction, revascularization, and stroke: pseudo R² 0.47 (95% CI: 0.31–0.70). For death: pseudo R² 0.70 (95% CI: 0.49–0.92).
mellitus receiving aspirin therapy. Our findings that cultured endothelial cells under oxidative stress generate TXA2 and have the enzymatic capacity to metabolize it to 11-dhTXB2 provide evidence that dysfunctional vascular endothelium may be a significant source of in vivo nonplatelet TXA2 generation. In contrast, urine 11-dhTXB2 measured in the early postoperative period was associated with multiple markers of inflammation, but not with age, race, or sex. This suggested that inflammatory cells, such as monocytes, that produce TXA2 when activated may be a significant source of in vivo nonplatelet TXA2 generation during conditions of intense inflammation. The marked nonplatelet TXA2 generation that occurred during the immediate postoperative period did not independently predict long-term outcome, whereas the nonplatelet TXA2 generation that was produced over a long time did independently predict long-term outcome. This raises the possibility, analogous to that observed with C-reactive protein, that the source of nonplatelet TXA2 generation, rather than its overall magnitude, might be the more important determinant of its impact on clinical outcome.

How nonplatelet TXA2 generation modifies cardiovascular risk and mortality is also unknown. The lack of relationship between urine 11-dhTXB2 and platelet function in the RIGOR study and the inability of dual antiplatelet therapy to alter the associated hazard of 11-dhTXB2 to outcome in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study suggest that increased platelet reactivity is not the predomi-

Table 3. Risk Factors for Urine 11-dhTXB2 (ln pg/mg Creatinine) Measured Early After CABG Surgery After Adjustment of Other Variables by Multivariable Regression Analysis

| Variable                | Standardized Coefficient | P Value | Dominance Weight | Dominance Ranking |
|-------------------------|--------------------------|---------|------------------|------------------|
| RDW (–% 3)              | −0.34                    | <0.001  | 0.33             | 1                |
| Heparin use before surgery | 0.26                    | <0.001  | 0.18             | 2                |
| FFP transfusion (≤2 vs ≥2 U) | 0.21                    | <0.001  | 0.17             | 3                |
| Urine 8-iso-PGF2α (ln pg/mg creatinine) | 0.19 | 0.002 | 0.17             | 4                |
| C-reactive protein (mg/L –1/2) | 0.15 | 0.017 | 0.08             | 5                |
| Lipid-lowering therapy | −0.12                    | 0.002   | 0.07             | 6                |

Pseudo R² (95% confidence interval), 0.45 (0.34–0.56). CABG indicates coronary artery bypass graft; 11-dhTXB2, 11-dehydrothromboxane B2; FFP, fresh-frozen plasma; 8-iso-PGF2α, 8-iso-prostaglandin 2α; and RDW, red cell distribution width.

atherothrombosis and death. We previously found that nonplatelet TXA2 generation is a novel risk factor for early vein graft failure, which is predominantly attributable to thrombotic occlusion. TXA2 has been shown to be capable of stimulating expression of tissue factor and adhesion molecules in endothelial cells, suggesting that alteration in endothelial thromboresistance may be one mechanism by which it mediates thrombosis. Whether nonplatelet TXA2 generation may also promote the progression of atherosclerosis. This is supported by studies in apolipoprotein E-deficient mice that revealed that atherogenesis was suppressed by deletion or pharmacologic inhibition of the thromboxane-prostanoid receptor but not by the administration of aspirin. Whether nonplatelet TXA2 generation is a marker or mediator of atherothrombosis in humans will need to be determined by clinical trials aimed at reducing its production or blocking its effects on the thromboxane-prostanoid receptor.

There are several limitations to the present study. Although the RIGOR study cohort was extremely well phenotyped, thus permitting exclusion of subjects with persistent platelet TXA2 generation, it was of moderate size and composed only of subjects with established cardiovascular disease who, by definition, had undergone surgical revascularization. The impact of nonplatelet TXA2 generation on outcome in other larger and nonselected study populations will need to be determined. Because the cause of death could not be ascertained for all expired subjects, the end point analysis was performed for all-cause mortality, although most deaths were known to be cardiovascular in origin. Although compliance with aspirin therapy was verified during the 6-month active phase of the study by pill counts, it could not be verified during the 5-year follow-up phase of the study and was dependent on subject self-reporting. Given that standard aspirin therapy does not suppress nonplatelet TXA2 generation but is only critical for its identification, the effects on outcome of noncompliance during the follow-up period would be expected to be distributed between groups and not likely affect the results of the study. Finally, because platelet function testing was only available at 1 of the enrolling sites, not all subjects in whom urine 11-dhTXB2 was measured early after surgery were included in the analysis. Thus, this could have conceivably biased the results. However, additional analyses (data not shown) with inclusion of these subjects, 95% of whom would be expected to have aspirin-induced suppression of platelet thromboxane generation at this time point, did not alter findings that nonplatelet thromboxane generation measured in the early perioperative period does not independently predict outcome.

In summary, nonplatelet TXA2 generation is a predictor of early graft failure after CABG surgery and of long-term outcome, including mortality. The source of nonplatelet TXA2 generation, which can vary in individual patients under
different physiologic conditions, may be a more important determinant of outcome than its overall magnitude.

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Disclosures
None.

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Table S1. Univariate analyses of variables associated with 6-month composite endpoint (death, myocardial infarction, revascularization and stroke).

| Variable                                      | Composite endpoint |
|-----------------------------------------------|--------------------|
| **Demographic/pre-operative variables**       | HR | P-value |
| Age (years)                                   | 1.0 | 0.98    |
| Male sex                                      | 2.01 | 0.18   |
| White race (vs. non-white race)               | 0.58 | 0.39    |
| Body mass index (kg/m2)                       | 0.96 | 0.46    |
| Medical History of:                           |     |        |
| Hypertension                                  | 1.75 | 0.47    |
| Dyslipidemia                                  | 1.54 | 0.51    |
| Diabetes                                      | 1.32 | 0.58    |
| Heart failure                                 | 1.71 | 0.32    |
| Peripheral/cerebrovascular disease            | 0.95 | 0.92    |
| Atrial fibrillation                           | 6.47 | **0.001** |
| Preoperative tobacco use                      | 1.73 | 0.28    |
| Myocardial infarction                         | 1.02 | 0.97    |
| Prior PCI                                     | 1.65 | 0.35    |
| Pre-operative LVEF                           |     |        |
| ≤30%                                          | 1.35 | 0.66    |
| 30-50%                                        | 0.88 | 0.81    |
| >50%                                          | Reference        |
| **Surgical variables**                        |     |        |
| Urgent/Emergent surgery                       | 1.64 | 0.31    |
| Euroscore                                     | 1.05 | 0.48    |
| Arterial graft implanted                      | 0.86 | 0.88    |
| Number of SVG per subject                    |     |        |
| 1                                             | Reference        |
| 2                                             | 0.22 | **0.01** |
| ≥3                                            | 0.54 | 0.35    |
| CABG only (vs concurrent valve surgery)       | 0.38 | **0.04** |
| Cardiopulmonary bypass time (ln min)          | 2.15 | 0.21    |
| Cross clamp                                  | 1.0  | 1.0     |
| Cross clamp time (ln min)                    | 1.2  | 0.75    |
| Heparin units (ln units)                      | 0.61 | 0.49    |
| Protamine dose (mg^2)                         | 1.0  | 0.86    |
| Crystalloid dose (mL^{1/2})                   | 1.03 | **0.05** |
| Colloid dose (mL)                             | 1.0  | 0.55    |
| Packed RBC transfusion                        | 1.70 | 0.25    |
| Packed RBC units – None                       | Reference        |
| 1-2                                           | 1.66 | 0.34    |
| ≥3                                            | 1.73 | 0.27    |
| Cell saver volume (mL^{1/2})                  | 1.0  | 0.90    |
| FFP transfusion                               | 1.15 | 0.74    |
| FFP units: None                               | Reference        |
| 1-2                                           | 4.96 | 0.12    |
| >2                                            | 17.4 | **0.008** |
| Variables                                  | Mean | SD  |
|-------------------------------------------|------|-----|
| **Platelet transfusion**                  | 1.80 | 0.12|
| Platelet units -None                      | Reference |     |
| 1-2                                       | 1.55 | 0.34|
| >3                                        | 2.21 | 0.10|

**Post-operative variables**

**Medications:**

- Non-aspirin antiplatelet: 2.89 ± 0.08
- Oral anticoagulation: 2.51 ± 0.38
- Beta-blocker: 0.29 ± 0.05
- ACE Inhibitor/ARB: 1.35 ± 0.54
- Insulin: 0.64 ± 0.63
- Insulin sensitizer: 1.30 ± 0.68
- Insulin secretagogue: 1.68 ± 0.37

- eGFR (mL/min/1.73m²): 1.0 ± 0.27
- Leukocyte count (10³/mm³): 0.96 ± 0.64
- Hematocrit (%): 0.96 ± 0.40
- Red cell distribution width (<14.5 vs >14.5%): 1.46 ± 0.43
- Platelet count (<150 vs. ≥150 x 10³/mm³): 1.16 ± 0.75
- Reticulocyte (ln %): 0.67 ± 0.55
- Blood Group: O vs. other: 0.58 ± 0.28
- C-reactive protein (mg/L⁰.⁵): 0.96 ± 0.67
- Fibrinogen (<390 vs. ≥390 mg/dL): 1.08 ± 0.91
- vonWillebrand factor ( >150 vs. ≤150%): 4.22 ± 0.16
- Urine 8-isoPGF2α (ln pg/mg creatinine): 1.72 ± 0.15
- Urine 8-isoPGF2α (<1870 vs. ≥1870 pg/mg creatinine): 1.32 ± 0.61
- Urine 11-dhTXB² (ln pg/mg creatinine): 1.72 ± 0.08

- Urine 11-dhTXB² tertiles
  - ≤ 487 pg/mg creatinine: Reference
  - >487 to ≤891pg/mg creatinine: 1.98 ± 0.25
  - > 891 pg/mg creatinine: 3.56 ± 0.03
- Impedance platelet aggregometry (ohms)
  - ADP (20μM): 0.90 ± 0.11
  - ADP (10μM): 0.87 ± 0.03
  - ADP (5μM): 0.90 ± 0.06
  - Collagen (1 μg/mL): 0.99 ± 0.74
  - Epinephrine (50 μM): 0.98 ± 0.67
- PFA-100 Collagen-ADP (Closure Time in sec⁻¹)
  - 1.01 ± 0.01
- PFA-100 Collagen-ADP (Closure Time ≤88 sec vs. >88 sec)
  - 0.27 ± 0.03
- PFA-100 Collagen-Epinephrine (Closure Time in sec⁻¹)
  - 0.90 ± 0.11

Abbreviations: PCI= percutaneous coronary intervention; LVEF= left ventricular ejection fraction; SVG= saphenous vein graft; RBS= red blood cell; FFP= fresh-frozen plasma; ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; 11-dhTXB2= 11-dehydro thromboxane B₂; eGFR= estimated glomerular filtration rate; ADP= adenosine diphosphate; PFA-100= Platelet Function Analyzer-100
Table S2. Univariate analyses of variables associated with 5-year composite endpoint (death, myocardial infarction, revascularization and stroke) and mortality.

| Variable                                      | Composite endpoint |        | Death            |        |
|-----------------------------------------------|--------------------|-------|------------------|-------|
|                                               | HR                | P-value | HR              | P-value |
| **Demographic/pre-operative variables**        |                    |       |                  |        |
| Age (years)                                   | 0.99              | 0.63  | 1.04             | 0.07  |
| Male sex                                      | 2.07              | **0.015** | 1.60         | 0.29  |
| White race (vs. non-white race)               | 0.48              | **0.034** | 0.39         | **0.046** |
| Body mass index (kg/m2)                       | 0.99              | 0.75  | 0.98             | 0.63  |
| **Medical History of:**                       |                    |       |                  |        |
| Hypertension                                  | 1.43              | 0.38  | 1.50             | 0.51  |
| Dyslipidemia                                  | 1.29              | 0.49  | 1.01             | 0.98  |
| Diabetes                                      | 2.34              | **0.002** | 2.30         | **0.04** |
| Heart failure                                 | 2.38              | **0.013** | 2.84         | **0.02** |
| Peripheral/cerebrovascular disease            | 3.94              | **<0.001** | 4.11         | **0.001** |
| Atrial fibrillation                           | 1.77              | 0.32  | 2.33             | 0.25  |
| Preoperative tobacco use                      | 1.70              | 0.08  | 2.42             | **0.03** |
| Myocardial infarction                         | 1.26              | 0.40  | 0.99             | 0.98  |
| Prior PCI                                     | 0.83              | 0.59  | 0.17             | 0.08  |
| **Pre-operative LVEF**                        |                    |       |                  |        |
| >50%                                          | Reference         |       | Reference        |       |
| 30-50%                                        | 1.40              | 0.25  | 1.31             | 0.55  |
| ≤30%                                          | 1.63              | 0.39  | 2.38             | 0.13  |
| **Surgical variables**                        |                    |       |                  |        |
| Urgent/Emergent surgery                       | 1.1               | 0.84  | 0.87             | 0.73  |
| Euroscore                                     | 1.12              | **0.02** | 1.18         | **0.005** |
| Arterial graft implanted                      | 1.93              | 0.51  | 0.81             | 0.84  |
| Number of SVG per subject                     |                    |       |                  |        |
| 1                                             | Reference         |       | Reference        |       |
| 2                                             | 1.31              | 0.42  | 0.98             | 0.95  |
| 3                                             | 0.63              | 0.29  | 0.40             | 0.17  |
| ≥4                                            | 0.52              | 0.28  | 1.0              | 1.0   |
| CABG only (vs concurrent valve surgery)       | 0.52              | 0.11  | 0.27             | **0.01** |
| Cardiopulmonary bypass time (ln min)          | 2.97              | **0.003** | 4.78         | **0.005** |
| Cross clamp                                   | 0.48              | 0.16  | 0.84             | 0.87  |
| Cross clamp time (ln min)                     | 2.0               | 0.08  | 2.44             | 0.16  |
| Heparin units (ln units)                      | 0.37              | **0.01** | 0.14         | **0.003** |
| Protamine dose (mg\(^{1/2}\))                 | 1.0               | 0.14  | 1.0              | 0.62  |
| Crystalloid dose (mL\(^{1/2}\))              | 1.0               | 0.38  | 1.0              | 0.56  |
| Colloid dose (mL)                             | 1.0               | 0.73  | 1.0              | 0.85  |
| Packed RBC transfusion                        | 3.5               | **<0.001** | 4.78         | **0.01** |
| Packed RBC units : None                       | Reference         |       | Reference        |       |
| 1-2                                           | 2.70              | 0.012 | 3.38             | 0.08  |
| >3                                            | 4.16              | **<0.001** | 5.94         | **0.005** |
| Cell saver volume (mL\(^{1/2}\))             | 1.04              | **0.003** | 1.06         | **0.02** |
| FFP transfusion                               | 2.18              | **0.003** | 3.18         | **0.005** |
| FFP units: None                               | Reference         |       | Reference        |       |
| 1-2                                           | 0.63              | 0.15  | 0.54             | 0.24  |
|                             | >2 |        |        |        |
|-----------------------------|----|--------|--------|--------|
| Platelet transfusion        | 1.67 | 0.045 | 2.71 | 0.01  |
| Platelet units – None       | 1.63 | 0.10   | 2.49  | 0.046  |
|                             | 1.75 | 0.13   | 3.15  | **0.03** |

**Post-operative laboratory variables**

| Urine 11-dhTXB2 (ln pg/mg creatinine) | 1.59 | **0.03** | 2.43 | **0.001** |
| Urine 11-dhTXB2 tertiles            |     |         |      |          |
| < 487 pg/mg creatinine              |     |         |      |          |
| ≥487 to <891 pg/mg creatinine       | 1.25 | 0.54   | 2.55 | 0.13    |
| ≥ 891 pg/mg creatinine              | 2.11 | 0.06   | 4.46 | **0.01** |

**6-month follow-up variables**

**Medications:**

| Non-aspirin antiplatelet         | 1.85 | 0.10 | 1.60 | 0.39  |
| Aspirin <325 mg daily            | 0.94 | 0.88 | 0.89 | 0.85  |
| Oral anticoagulation             | 2.16 | 0.11 | 4.02 | **0.01** |
| Beta-blocker                     | 0.82 | 0.60 | 0.42 | 0.06  |
| ACE Inhibitor/ARB                | 1.04 | 0.88 | 1.25 | 0.60  |
| Lipid-lowering agent             | 0.59 | 0.16 | 0.33 | **0.01** |
| Diuretic                        | 1.21 | 0.54 | 1.58 | 0.26  |
| Insulin                         | 2.67 | **0.002** | 1.73 | 0.32  |
| Insulin sensitizer               | 1.29 | 0.43 | 1.23 | 0.66  |
| Insulin secretagogue             | 1.50 | 0.19 | 1.86 | 0.16  |
| eGFR (mL/min/1.73m²)             | 1.0 | 0.59 | 0.98 | **0.016** |

**LVEF at 6 Months**

| >50%                          |     | Reference | Reference |
| 30-50%                        | 2.88 | <0.001 | 4.55 | <0.001 |
| ≤30%                          | 5.66 | **0.001** | 9.58 | <0.001 |

**Graft occlusion**

| None                         |     | Reference | Reference |
| 1                            | 0.81 | 0.54 | 0.50 | 0.17  |
| 2+                           | 1.88 | 0.06 | 0.48 | 0.34  |
| Percent of grafts occluded   | 1.0 | **0.03** | 1.0 | 0.69  |
| LIMA graft occlusion         | 3.26 | **0.001** | 0.90 | 0.89  |

**SVG occlusion**

| None                        |     | Reference | Reference |
| 1                           | 0.89 | 0.73 | 0.61 | 0.33  |
| 2+                          | 1.44 | 0.35 | 0.38 | 0.34  |

**Laboratory variables:**

**Leukocyte count**

| 4.5-11x10⁹/mm³               |     | Reference | Reference |
| ≤4.5x10⁹/mm³                 | 1.02 | 0.96 | 1.67 | 0.36  |
| ≥11x10⁹/mm³                  | 4.16 | **0.02** | 4.73 | **0.04** |
| Hematocrit (%)               | 0.89 | **0.005** | 0.85 | **0.003** |
| Red cell distribution width (≤14.5 vs >14.5%) | 1.44 | 0.18 | 1.46 | 0.35  |
| Platelet count (<150 vs. ≥150 x10⁹/mm³) | 1.44 | 0.32 | 6.47 | 0.07  |
| Reticulocyte (ln %)           | 1.89 | 0.27 | 0.34 | 0.09  |
| Blood Group: O vs. other      | 1.23 | 0.46 | 1.36 | 0.44  |
| Rh factor (positive vs. negative) | 1.64 | 0.35 | 1.64 | 0.50  |
|                                | Value1 | Value2 | Value3 | Value4 |
|--------------------------------|--------|--------|--------|--------|
| C-Reactive Protein (<5 vs. ≥5 mg/l) | 1.87   | 0.03   | 2.33   | 0.04   |
| Fibrinogen (<390 vs. ≥390 mg/dL)   | 1.86   | 0.03   | 1.86   | 0.15   |
| vonWillebrand factor (>150 vs. ≤150%) | 1.50   | 0.17   | 1.52   | 0.34   |
| eGFR (ml/min/1.73m²)              | 1.0    | 0.59   | 0.98   | 0.016  |
| Urine 8-iso Prostaglandin F₂α (ln pg/mg creatinine) | 1.53   | 0.02   | 1.52   | 0.13   |
| Urine 8-iso Prostaglandin F₂α (≥1620 vs. <1620 pg/mg creatinine) | 1.96   | 0.03   | 1.68   | 0.24   |
| Urine TXB₂ (ln pg/mg creatinine)  | 1.97   | 0.004  | 2.94   | <0.001 |
| Oxidized LDL (<2.8 vs. ≥2.8 U/mL) | 0.90   | 0.74   | 0.69   | 0.44   |
| Oxidized LDL                      |        |        |        |        |
| <1.32 U/mL                       |        |        |        |        |
| 1.32 to 5.04 U/mL                |        |        |        |        |
| >5.04 U/mL                       |        |        |        |        |
| Cotinine (≤10 vs. >10 ng/mL)      | 2.89   | 0.004  | 2.0    | 0.22   |
| Impedance platelet aggregometry (ohms) |        |        |        |        |
| ADP (20µM)                       | 0.99   | 0.80   | 0.99   | 0.83   |
| ADP (10µM)                       | 0.98   | 0.53   | 0.95   | 0.19   |
| ADP (5µM)                        | 1.0    | 0.95   | 0.98   | 0.51   |
| Collagen (1 µg.ml⁻¹)             | 1.0    | 0.94   | 0.96   | 0.24   |
| Epinephrine (50 µM)              | 1.0    | 0.51   | 0.99   | 0.77   |
| PFA-100 Collagen-ADP (Closure Time in sec⁻¹) | 1.0    | 0.63   | 1.0    | 0.18   |
| PFA-100 Collagen-ADP (Closure Time ≤88 sec vs. >88 sec) | 0.87   | 0.59   | 1.41   | 0.40   |
| PFA-100 Collagen-Epinephrine (Closure Time in sec⁻¹) | 1.0    | 0.41   | 1.0    | 0.62   |

Abbreviations: PCI= percutaneous coronary intervention; LVEF= left ventricular ejection fraction; SVG= saphenous vein graft; CABG= coronary artery bypass graft; RBS= red blood cell; FFP= fresh-frozen plasma; ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; LIMA= left internal mammary; 11-dhTXB₂= 11-dehydro thromboxane B₂; LDL= low density lipoprotein; eGFR= estimated glomerular filtration rate; ADP= adenosine diphosphate; PFA-100= Platelet Function Analyzer-100
Table S3. Univariate analyses of the association of urine 11-dhTXB₂ with the individual components of the 5-year composite endpoint.

| Time of measure | 3 Days (n=198) | 6 Months (n=288) |
|-----------------|----------------|-----------------|
|                 | 11-dhTXB₂ (ln pg/mg creatinine) | 11-dhTXB₂ (≤ 891 vs. > 891 pg/mg creatinine) | 11-dhTXB₂ (ln pg/mg creatinine) | 11-dhTXB₂ (≤ 450 vs. > 850 pg/mg creatinine) |
| Outcome         | HR  | P-value | HR  | P-value | Event Rate | HR  | P-value | HR  | P-value | Event Rate |
| Death           | 2.43 | 0.001   | 2.66 | 0.017   | 12/146 vs. 11/52 | 2.94 | 0.001   | 3.3  | 0.003   | 12/213 vs. 13/75 |
| MI              | 2.68 | 0.11    | 5.82 | 0.044   | 2/146 vs. 4/52  | 2.30 | 0.23    | 2.28 | 0.28    | 4/213 vs. 3/75  |
| Revascularization | 0.65 | 0.16    | 0.58 | 0.39    | 14/146 vs. 3/52 | 0.395| 0.83    | 1.06 | 0.90    | 17/213 vs. 6/75 |
| Stroke          | 2.99 | 0.035   | 3.01 | 0.26    | 2/146 vs. 2/52  | 2.77 | 0.027   | 3.26 | 0.092   | 4/213 vs. 4/75  |
Table S4. Multivariable Cox proportional hazard models for 6-month composite outcome.

| Variable          | Adj HR | CI     | P-value |
|-------------------|--------|--------|---------|
| Atrial fibrillation | 5.73   | 1.62-20.24 | 0.007   |
| Number of SVG: 1  | Reference |        |         |
| 2                 | 0.22   | 0.07-0.68 | 0.008   |
| ≥3                | 0.76   | 0.19-2.98 | 0.69    |
| FFP units: None   | Reference |        |         |
| 1-2               | 5.40   | 0.68-42.9 | 0.11    |
| >2                | 14.62  | 1.62-132.2 | 0.017   |
Differential Impact of Serial Measurement of Nonplatelet Thromboxane Generation on Long−
Term Outcome After Cardiac Surgery

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