ANESTHESIOLOGY

Factor Eight Inhibitor Bypass Activity Use in Cardiac Surgery: A Propensity-matched Analysis of Safety Outcomes

Joshua A. Nicholas, M.D., Natasha Harrison, M.P.H., Dipro Chakraborty, M.S., Alan L. Chang, Ph.D., Nima Aghaeepour, Ph.D., Katherine Wirtz, R.N., M.S.N., Elaina Nielson, Pharm.D., Cody Parsons, Pharm.D., B.C.C.C.P., Ethan Jackson, M.D., Anil K. Panigrahi, M.D., Ph.D.

ANESTHESIOLOGY 2024; 141:1051–64

ABSTRACT

Background: Bleeding during cardiac surgery may be refractory to standard interventions. Off-label use of factor eight inhibitor bypass activity (FEIBA) has been described to treat such bleeding. However, reports of safety, particularly thromboembolic outcomes, show mixed results, and reported cohorts have been small.

Methods: Adult patients undergoing cardiac surgery on cardiopulmonary bypass between July 1, 2018, and June 30, 2023, at Stanford Hospital (Stanford, California) were reviewed (n = 3,335). Patients who received FEIBA to treat postcardiopulmonary bypass bleeding were matched with those who did not by propensity scores in a 1:1 ratio using nearest neighbor matching (n = 352 per group). The primary outcome was a composite outcome of thromboembolic complications including any one of deep vein thrombosis, pulmonary embolism, unplanned coronary artery intervention, ischemic stroke, and acute limb ischemia, in the postoperative period. Secondary outcomes included renal failure, reoperation, postoperative transfusion, intensive care unit length of stay, and 30-day mortality.

Results: A total of 704 encounters was included in this propensity-matched analysis. The mean dose of FEIBA administered was 7.3 ± 5.5 U/kg. In propensity-matched multivariate logistic regression models, there was no statistically significant difference in odds ratios for thromboembolic outcomes, intensive care unit length of stay, or mortality. Patients who received more than 750 U FEIBA had an increased odds ratio for acute renal failure (odds ratio, 4.14; 95% CI, 1.61 to 10.36; $P < 0.001$). In multivariate linear regression, patients receiving FEIBA were transfused more plasma and cryoprecipitate postoperatively. However, only the dose range of 501 to 750 U was associated with an increase in transfusion of erythrocytes (β, 2.73; 95% CI, 0.68 to 4.78; $P = 0.009$) and platelets (β, 1.74; 95% CI, 0.85 to 2.63; $P < 0.001$).

Conclusions: Low-dose FEIBA administration during cardiac surgery does not increase risk of thromboembolic events, intensive care unit length of stay, or mortality in a propensity-matched cohort. Higher doses were associated with increased acute renal failure and postoperative transfusion. Further studies are required to establish the efficacy of activated factor concentrates to treat refractory bleeding during cardiac surgery.

(ANESTHESIOLOGY 2024; 141:1051–64)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Prothrombin complex concentrates currently approved for vitamin K antagonist reversal are increasingly used and studied worldwide in clinical trials for perioperative bleeding management, including cardiac surgical patients
- An additional activated prothrombin complex concentrate, factor eight inhibitor bypass activity (FEIBA), has also been administered in small trials for patients at high risk for bleeding in this setting but with mixed safety and efficacy outcomes

What This Article Tells Us That Is New

- In a propensity-matched analysis of 704 cardiac surgical patients, administration of a low mean FEIBA dose of 7.3 ± 5.5 U/kg did not increase thromboembolic event risk, intensive care unit length of stay, or mortality
- In patients at a higher risk for bleeding and adverse events, higher FEIBA doses were associated with increased renal failure and postoperative transfusion, suggesting the need for additional prospective randomized clinical studies in this population

This article is featured in "This Month in ANESTHESIOLOGY," page A1. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has an audio podcast. This article has a visual abstract available in the online version.

Submitted for publication May 20, 2024. Accepted for publication August 14, 2024. Published online first on August 26, 2024.

Joshua A. Nicholas, M.D.: Department of Anesthesiology, Perioperative and Pain Medicine, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada.

Natasha Harrison, M.P.H.: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Dipro Chakraborty, M.S.: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Alan L. Chang, Ph.D.: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Nima Aghaeepour, Ph.D.: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Katherine Wirtz, R.N., M.S.N.: Cardiovascular Health, Stanford Health Care, Stanford, California.

 ANESTHESIOLOGY 2024; 141:1051–64. DOI: 10.1097/ALN.0000000000005208

<zdoi;10.1097/ALN.0000000000005208>

Massive hemorrhage during cardiac surgery is influenced by patient and procedural factors including, but not limited to, antiplatelet and anticoagulant medications, hyperfibrinolysis, prolonged cardiopulmonary bypass (CPB), and aortic cross clamp times. The estimated incidence is 2 to 10% and is associated with increased morbidity, mortality, and healthcare costs.[1–4] In cases where conventional medical hemostatic therapies have been applied, and a surgical source of bleeding cannot be identified, activated factors have been utilized as rescue therapies.[5] There are two available products: recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, USA) and factor eight inhibitor bypass activity (FEIBA; Baxter Healthcare, USA). Compared with rFVIIa, FEIBA contains zymogens of factors II, VII, IX, and X. The primary activated factor is VIIa, with trace content of IIa, IXa, and Xa. Additionally, it contains protein C, factor VIII, and citrate.[6]

The rationale for FEIBA to achieve hemostasis in refractory bleeding during cardiac surgery is similar to rFVIIa,[7] and there is also concern for thromboembolic events. A previous study comparing rFVIIa to FEIBA found similar rates of thromboembolic events between groups.[5] Average doses of rFVIIa and FEIBA were 90.5 μg/kg and 18.6 U/kg, respectively. However, these products are dosed in different units of measurement and may not have equivalent thromboembolic potential. As with rFVIIa, the risk of thromboembolic complications with FEIBA administration is likely dose-dependent, and lower-dose therapy is more representative of contemporary practice. A 2022 meta-analysis of FEIBA for refractory bleeding in cardiac surgery found insufficient evidence to make an aggregate conclusion about dosing, efficacy, or safety.[8]

Since then, retrospective studies of patients undergoing coronary artery bypass grafting, type A dissection repair, and left ventricular assist device placement have not shown increases in mortality or thromboembolic complications with FEIBA use.[9–12] These cohorts received small doses, 13 U/kg or less on average or a total of 500 to 1,000 U. The anticoagulant factor content in FEIBA has been proposed to reduce thromboembolic risk compared with rFVIIa.[4,7] However, given the limited cohort sizes to date, the safety profile of low-dose FEIBA administered during cardiac surgery cannot be certain. FEIBA use in the context of uncontrolled bleeding during cardiac surgery at Stanford Health Care dates back to the mid-2000s. Initial administration with doses ranging from 50 to 100 U/kg was associated with thromboembolic events. However, since then, a practice of titrated administration of 250 U at a time has been adopted.[5,9] Therefore, we sought to evaluate FEIBA administration during cardiac surgery on cardiopulmonary bypass at our institution during the past 5 yr to provide further safety data around contemporary practice.

Elaina Nielson, Pharm.D.: Cardiovascular Health, Stanford Health Care, Stanford, California.

Cody Parsons, Pharm.D., B.C.C.C.P.: Cardiovascular Health, Stanford Health Care, Stanford, California.

Ethan Jackson, M.D.: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Anil K. Panigrahi, M.D., Ph.D.: Department of Anesthesiology, Perioperative and Pain Medicine, and Department of Pathology, Division of Transfusion Medicine, Stanford University School of Medicine, Stanford, California.

Methods

Study Design and Database

This is a retrospective cohort study analyzing propensity-matched observational data merged from two databases: the Society of Thoracic Surgeons (Chicago, Illinois) Adult Cardiac Surgery Database, and STAnford medicine Research data Repository (STARR). Patient demographics, perioperative variables, and postoperative outcomes were obtained from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, versions 2.9 and 4.2 (https://www.sts.org/sts-national-database#adult-cardiac-surgery-database; accessed October 2, 2024). Definitions of patient characteristics, perioperative variables, and postoperative outcomes are according to the data dictionaries of these respective versions. History of thrombophilia, acquired factor inhibitors, and FEIBA administration data was obtained from International Classification of Diseases, Tenth Revision, codes and medical administration records in the STARR database. Only de-identified data were used, and the study was approved by the Stanford Health Care Institutional Review Board (No. 72852; November 6, 2023).

Our study adhered to the Reporting of studies conducted using Observational Routinely-collected Data (RECORD) statement extension of the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies as well as extension of STROBE for reporting of propensity-matched studies. A data analysis and statistical plan were written after the data were accessed. Data were extracted from the Society of Thoracic Surgeons Adult Cardiac Surgery Database and STARR. These were merged by patient medical record number and date of surgical procedure.

Study Population

We included all patients 18 yr of age or older who underwent cardiac surgery on CPB from July 1, 2018, to June 30, 2023, at our institution and whose surgeries were recorded in the Society of Thoracic Surgeons database. Transplants and procedures for ventricular assist device implantation are not recorded in this database and therefore were not included. Patients who received FEIBA during or within 24 h of operation were identified. Patients with pre-existing indications or contraindications to receiving FEIBA were excluded. Specifically, patients

with congenital thrombophilia, hemophilia, and acquired factor inhibitors and those who received rFVIIa or were diagnosed postoperatively with heparin-induced thrombocytopenia were excluded. The final population eligible for propensity-matched analysis is illustrated in figure 1.

Exposure

The exposure of interest was administration and dose of FEIBA during and within 24 h of surgery. Administration of FEIBA was extracted from the Stanford Health Care electronic health record *via* the STARR database.

Use of FEIBA

At the authors' institution, FEIBA administration is not protocolized. Before separation from CPB, acidosis, temperature, and calcium concentrations are optimized, and blood products are transfused to correct coagulopathy as determined by coagulation testing. FEIBA is administered at the discretion of the surgeon, anesthesiologist, or intensivist if there is ongoing coagulopathy and continued bleeding after the transfusion of standard blood components (erythrocytes, platelets, plasma, and/or cryoprecipitate). FEIBA is administered a "half vial" at a time (approximately 250 U) with reassessment of coagulopathy by visual inspection, standard coagulation tests, and/or thromboelastography before re-dosing. As such, during analysis for dose effects, FEIBA administration was divided into groups: 1 to 250 U, 251 to 500 U, 501 to 750 U, and more than 750 U.

Outcomes

The primary outcomes of interest were postoperative thromboembolic complications. Deep vein thrombosis, pulmonary embolism, unplanned coronary artery intervention, ischemic stroke, and acute limb ischemia were discrete outcomes assessed. Events occurring from the time of intensive care unit (ICU) admission until hospital discharge are recorded. We defined a composite outcome of thromboembolic complications as any one of deep vein thrombosis, pulmonary embolism, unplanned coronary artery intervention, ischemic stroke, or acute limb ischemia. Secondary outcomes of reoperation for bleeding or tamponade, acute renal failure, ICU length of stay, transfusion of

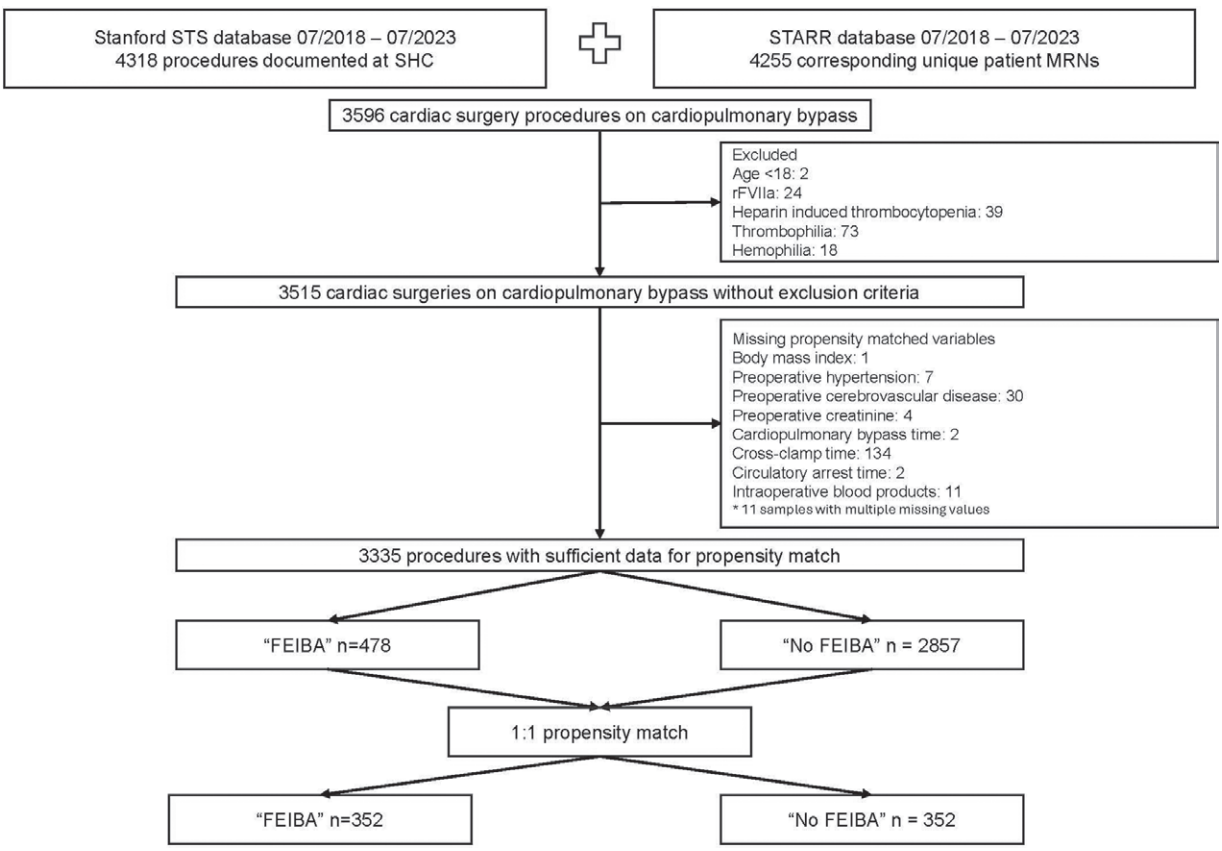

Fig. 1. Patient flow diagram. FEIBA, factor eight inhibitor bypass activity; MRN, medical record number; rFVIIa, recombinant activated factor VII; SHC, Stanford Health Care; STARR, STAnford medicine Research data Repository; STS, Society of Thoracic Surgeons.

blood components, and 30-day mortality, as recorded in the Society of Thoracic Surgeons database, were also assessed. The Society of Thoracic Surgeons outcome of acute renal failure is defined by an increase in creatinine by three times, 0.5 mg/dl increase from a baseline of 4 mg/dl, or new dialysis requirement.

Covariate Data

Patient and procedural characteristics were extracted from the Society of Thoracic Surgeons database, selected based on plausible association with likelihood of receiving FEIBA for bleeding after separation from CPB. Patient demographics and comorbidities included age, sex, height, weight, body mass index, pre-existing hypertension, diabetes, coronary artery disease, cerebrovascular disease, peripheral arterial disease, chronic lung disease, tobacco use, cirrhosis, renal function, dialysis dependence, cancer within 5 yr, and history of heparin-induced thrombocytopenia. Preoperative medication and laboratory variables included warfarin, aspirin, or adenosine diphosphate inhibitor within 5 days, direct oral anticoagulant within 3 days, heparin or low-molecular-weight heparin within 2 days, hemoglobin, platelet count, and international normalized ratio. Procedure variables included procedure type; reoperation; emergent status; prebypass transesophageal echocardiography left ventricular ejection fraction and right ventricular function; CPB time; cross-clamp time; circulatory arrest time; post-bypass transesophageal echocardiography left ventricular ejection fraction and right ventricular function; intraoperative transfusion of erythrocytes, platelets, plasma, and cryoprecipitate; nadir intraoperative hemoglobin; administration of antifibrinolytic; and use of viscoelastic monitoring. Postoperative variables included acute renal failure, ICU length of stay, 30-day mortality, platelet count and international normalized ratio at ICU admission, transfusion of erythrocytes, platelets, plasma and cryoprecipitate, reoperation for bleeding or tamponade, deep vein thrombosis, pulmonary embolism, unplanned coronary reintervention, ischemic stroke, and limb ischemia.

The following patient variables were extracted from the STARR database using International Classification of Diseases, Tenth Revision, codes: pre-existing thrombophilia, congenital coagulation factor deficiency, and acquired factor inhibitors. Medication administration details for FEIBA and rFVIIa including dose, date, and time were extracted from the medication administration record of the STARR database.

Statistical Analysis

Baseline patient and procedural characteristics were described with mean ± SD and number (percentage) for continuous and categorical data elements, respectively. Transfusion was described with median (interquartile range). Unadjusted outcomes were compared between groups with Mann–Whitney U tests for continuous and Pearson chi-square or Fisher exact test for categorical variables.

Propensity matching was utilized to control for potential confounders. These were identified as variables with large imbalances between groups and/or having clinical relevance to both treatment and outcomes. Baseline clinically relevant variables with a P value < 0.10 were given equal weighting and included in the final multivariate logistic regression model to calculate propensity scores. The variables included in the final propensity score model for direct matching were age, sex, body mass index, preoperative hypertension, cerebrovascular disease, and creatinine, procedure type, reoperation, emergent status, CPB, cross-clamp and circulatory arrest times, and intraoperative antifibrinolytic use and transfusion of erythrocytes, plasma, platelets, and cryoprecipitate. Missingness in these variables was measured and determined to be less than 5%. Missing values were assumed to be at random, and therefore, complete case analysis was performed.

Patients who received FEIBA were matched with those who did not through a nearest-neighbor algorithm in a 1:1 ratio without replacement. We implemented a maximum caliper threshold at 0.10 times the SD of the logit-transformed propensity score. To assess the effectiveness of matching, the balance in baseline characteristics included in the propensity score between the FEIBA and no FEIBA groups was evaluated using the absolute standardized mean difference before and after matching. Differences exceeding 0.1 were considered indicative of imbalance (Supplemental Digital Content fig. 1, https://links.lww.com/ALN/D680). T-distributed stochastic neighbor embedding plots incorporating variables used to compute propensity scores of pre- and postmatched data corroborated an improved distribution of covariates between the FEIBA and no FEIBA groups after 1:1 matching. Supplemental Digital Content figure 2 (https://links.lww.com/ALN/D681) demonstrates the distinct cluster of FEIBA patients present in unmatched data resolving in the matched cohort, indicating successful alignment of characteristics between groups. Variables of clinical interest that were not exclusively matched for were adequately balanced between groups after 1:1 matching. The P values comparing covariates between unmatched and matched cohorts were calculated using the Mann–Whitney U test for continuous variables since none were normally distributed by the Kolmogorov–Smirnov test. Two-sample chi-square tests were applied for categorical variables when groups contained more than five samples. The Fisher exact test was applied for categorical variables with groups containing five or fewer samples. A P value > 0.05 implies similar covariate distribution between treatment groups. The final matched sample included a total of 704 patients, evenly distributed in a 1:1 ratio (352:352) between the FEIBA and no FEIBA groups. A *post hoc* analysis was conducted to characterize the population who received FEIBA but did

not obtain an acceptable match by the threshold described above (n = 126).

To evaluate whether exposure to FEIBA was related to postoperative thromboembolic outcomes, reoperation, acute renal failure, or 30-day mortality, we performed a multivariate logistic regression controlled for the same variables included in the propensity score to account for any residual confounding that may be present. Multivariate linear regressions were performed in the same manner to assess postoperative transfusion and ICU length of stay. Double adjustment has been demonstrated as a robust strategy for further mitigating confounding, particularly in scenarios where imbalance may persist after propensity score matching.[13] We assessed dose effect by binning FEIBA dose into the clinically relevant categories described under "Use of FEIBA" (1 to 250 U, 251 to 500 U, 501 to 750 U, and more than 750 U). There was an insufficient number of unplanned coronary reintervention, acute limb ischemia, or pulmonary embolism across groups to run a stable model; therefore, we did not assess for these outcomes in the model for dose effect. However, these remained captured by the composite thromboembolic outcome. All analyses were conducted in R statistical software (R version 4.2.1; https://www.r-project.org/, accessed January 22, 2024).

Results

Characteristics of Patients and Surgeries

Descriptive statistics of the study population before (n = 3,335) and after (n = 704) propensity score matching are summarized in table 1. Before matching, there was imbalance in almost every variable; patients who received FEIBA had higher severity of illness and procedural complexity. They were more likely to be male with pre-existing peripheral arterial and cerebrovascular disease. They underwent more aortic reconstruction procedures with circulatory arrest, had longer cross clamp and bypass times, required more intraoperative transfusion of all blood components, and had higher rates of perioperative mechanical circulatory support. After matching was completed, the FEIBA *versus* no FEIBA groups remained unbalanced in intraoperative transfusion of erythrocytes (median, 3 [1 to 4] *vs.* 2 [0 to 4] U) and plasma (median, 3 [2 to 5] *vs.* 2 [1 to 5] U). There was no statistically significant difference in the proportion of patients who underwent circulatory arrest, but the mean time was greater in the FEIBA group (36 ± 22 *vs.* 34 ± 25 min). Otherwise, there were no statistically significant differences in patient comorbidities or procedure characteristics in the matched cohort. The mean dose of FEIBA was 7.3 ± 5.5 U/kg.

Patients who received FEIBA but did not obtain an acceptable match in the propensity analysis (n = 126) are described in Supplemental Digital Content table 1 (https://links.lww.com/ALN/D683). Compared to the FEIBA group of the matched cohort, they were more likely to be male (79% *vs.* 69%) with peripheral arterial disease (28% *vs.* 16%), and underwent more emergent, aortic procedures, redo sternotomies, and longer duration of cardiopulmonary bypass (251 ± 72 *vs.* 215 ± 90 min) and aortic cross clamp (153 ± 60 *vs.* 142 ± 71 min). They also received higher volumes of intraoperative transfusion for all blood components and higher doses of FEIBA (10.2 ± 10.6 *vs.* 7.3 ± 5.5 U/kg).

Association of FEIBA with Thromboembolic Outcomes

There were no statistically significant differences in the primary outcomes—composite thromboembolic events, unplanned postoperative coronary intervention, stroke, deep vein thrombosis, pulmonary embolism, or limb ischemia—between the FEIBA and no FEIBA groups in the matched cohort. The rates of postoperative complications and unadjusted analysis of between-group differences are outlined in table 2. In a propensity-matched multivariate regression adjusted for potential confounders (fig. 2), we did not observe a statistically significant increase in the odds ratio for the primary outcomes. There was also no significant difference when adjusting for the same covariates *via* multivariate regression and accounting for dose in the pattern of 250-U increments typically administered at our institution (fig. 3).

Association of FEIBA with Reoperation, Acute Renal Failure, ICU Length of Stay, and Mortality

There was no difference in 30-day mortality between matched cohorts (table 2; figs. 2 and 3). However, patients who received FEIBA had higher rates of reoperation (8% *vs.* 3%; $P = 0.013$; odds ratio, 2.3; 95% CI, 1.07 to 5.19; $P = 0.039$; table 2; fig. 2). A small increase in ICU length of stay was observed in patients receiving FEIBA; however, this difference did not approach statistical significance (median, 4.2 *vs.* 3.9 days; $P = 0.051$) in unadjusted between-group comparisons and remained statistically insignificant in a multivariate linear regression grouped by dose and adjusted for potential confounders (table 2; Supplemental Digital Content fig. 3, https://links.lww.com/ALN/D682). In a multivariate regression accounting for dose (fig. 3), patients who received FEIBA at the highest dose range (greater than 750 U) had a higher odds ratio for acute renal failure (odds ratio, 4.14; $P = 0.003$; 95% CI, 1.61 to 10.36), but reoperation did not reach statistical significance. Doses 750 U or less did not have statistically significant associations with these outcomes.

Association of FEIBA with Postoperative Transfusion

Patients treated with FEIBA received more postoperative transfusion of all blood components. Median [interquartile range] transfusion of each component is shown in table 3. In the matched cohort, the FEIBA group was transfused a median of 2 [interquartile range, 1 to 5] erythrocyte units compared with 1 [interquartile range, 0 to 3] in the no

Table 1. Patient Demographics and Procedure Characteristics

Variable	Unmatched			Matched		
	No FEIBA (n = 2,857)	FEIBA (n = 478)	*P* Value	No FEIBA (n = 352)	FEIBA (n = 352)	*P* Value
Demographics						
Age, yr	62 ± 14	61 ± 14	0.168	62 ± 14	61 ± 14	0.556
Female	984 (34%)	134 (28%)	0.007	111 (32%)	108 (31%)	0.871
Body mass index, kg/m^2	28.0 ± 6.0	27.2 ± 6.1	0.004	27.7 ± 6.2	27.2 ± 5.8	0.391
Comorbidities						
Diabetes	667 (23%)	85 (18%)	0.011	56 (16%)	63 (18%)	0.546
Hypertension	2,274 (80%)	419 (88%)	< 0.001	307 (87%)	304 (87%)	0.824
Dialysis-dependent renal failure	101 (4%)	29 (6%)	0.012	16 (5%)	25 (7%)	0.201
Cirrhosis	26 (1%)	8 (2%)	0.191	3 (1%)	7 (3%)	0.346
Current smoker	249 (9%)	63 (13%)	< 0.001	53 (15%)	44 (13%)	0.259
Former smoker	896 (31%)	130 (27%)		118 (34%)	103 (29%)	
Chronic lung disease	337 (12%)	68 (15%)	0.063	58 (17%)	52 (16%)	0.626
Malignancy within 5 yr	137 (5%)	16 (3%)	0.202	13 (4%)	11 (3%)	0.835
Peripheral arterial disease	207 (7%)	92 (19%)	< 0.001	58 (17%)	57 (16%)	1.000
Cerebrovascular disease	383 (13%)	107 (22%)	< 0.001	63 (18%)	73 (21%)	0.390
Preoperative laboratory results						
Preoperative hemoglobin, mg/dl	13.4 ± 2.1	12.6 ± 2.4	< 0.001	12.7 ± 2.4	12.7 ± 2.4	0.911
Preoperative platelet count, ×10^9/l	223 ± 69	208 ± 79	< 0.001	205 ± 70	211 ± 81	0.711
Preoperative INR	1.1 ± 0.3	1.2 ± 0.3	< 0.001	1.2 ± 0.3	1.2 ± 0.3	0.523
Preoperative creatinine, mg/dl	1.2 ± 1.2	1.3 ± 1.3	< 0.001	1.3 ± 1.1	1.3 ± 1.3	0.573
Preoperative medications						
Heparins < 48 h	526 (18%)	84 (18%)	0.708	65 (19%)	63 (18%)	0.922
Warfarin < 5 d	89 (3%)	25 (5%)	0.025	19 (5%)	14 (4%)	0.476
Direct oral anticoagulant ≤ 3 d	76 (3%)	16 (3%)	0.475	7 (2%)	9 (3%)	0.791
Aspirin < 5 d	1,190 (42%)	197 (41%)	0.920	141 (40%)	149 (43%)	0.535
P2Y12 inhibitor < 5 d	126 (4%)	19 (4%)	0.768	11 (3%)	15 (4%)	0.534
Procedure type			< 0.001			0.791
Isolated coronary artery bypass	523 (18%)	1 (<1%)		1 (<1%)	1 (<1%)	
Coronary artery bypass + valve	102 (4%)	5 (1%)		2 (1%)	5 (1%)	
Single valve	917 (32%)	38 (8%)		31 (9%)	35 (10%)	
Multivalve	50 (2%)	7 (2%)		4 (1%)	7 (2%)	
Aortic	808 (28%)	385 (81%)		279 (79.3%)	266 (76%)	
Ventricular assist device	12 (<1%)	1 (<1%)		2 (1%)	1 (<1%)	
Other	445 (16%)	41 (9%)		33 (9%)	37 (11%)	
Case status						
Emergency case	144 (5%)	153 (32%)	< 0.001	102 (29%)	99 (28%)	0.965
Redo sternotomy	406 (14%)	156 (33%)	< 0.001	107 (30%)	104 (30%)	0.869
Bypass details						
Circulatory arrest, n	368 (13%)	287 (60%)	< 0.001	193 (55%)	190 (54%)	0.880
Circulatory arrest time, min*	29 ± 21	36 ± 22	< 0.001	34 ± 25	36 ± 22	0.045
Cross clamp time, min	94 ± 56	145 ± 68	< 0.001	139 ± 72	142 ± 71	0.404
Bypass time, min	136 ± 74	224 ± 87	< 0.001	208 ± 90	215 ± 90	0.201
Transesophageal echocardiogram findings						
Preoperative left ventricular ejection fraction (%)	56 ± 11	56 ± 11	0.959	56 ± 10	55 ± 11	0.622
Preoperative right ventricular dysfunction			0.017			0.601
Moderate	130 (5%)	21 (5%)		16 (4.6%)	14 (4%)	
Severe	27 (1%)	13 (3%)		6 (1.7%)	10 (3%)	
Postoperative left ventricular ejection fraction (%)	56 ± 10	56 ± 11	0.763	55.9 ± 10.4	55 ± 11	0.233
Postoperative right ventricular dysfunction			< 0.001			0.652
Moderate	154 (6%)	41 (9%)		20 (6%)	27 (8%)	
Severe	49 (2%)	25 (5%)		13 (4%)	18 (5%)	
Perioperative mechanical circulatory support						
Intra-aortic balloon pump	183 (6%)	56 (12%)	< 0.001	39 (11%)	41 (12%)	0.807
ECMO			< 0.001			0.168
Veno-veno	6 (<1%)	5 (1%)		0 (0%)	3 (1%)	
Veno-arterial	39 (1%)	28 (6%)		16 (5%)	21 (6%)	
Intraoperative blood management						
Erythrocytes, units	0 [0–1]	3 [1–6]	< 0.001	2 [0–4]	3 [1–4]	0.001
Erythrocytes, transfused	746 (26.1%)	380 (79.5%)	< 0.001	224 (63.6%)	264 (75.0%)	0.001

(*Continued*)

Table 1. (Continued)

Variable	Unmatched			Matched		
	No FEIBA (n = 2,857)	FEIBA (n = 478)	*P* Value	No FEIBA (n = 352)	FEIBA (n = 352)	*P* Value
Plasma, units	0 [0–0]	4 [2–6]	< 0.001	2 [1–5]	3 [2–5]	0.014
Plasma, transfused	658 (23.0%)	410 (85.8%)	< 0.001	266 (75.6%)	287 (81.5%)	0.0663
Platelets, units	0 [0–1]	2 [2–3]	< 0.001	2 [1–3]	2 [1–3]	0.505
Platelets, transfused	818 (28.6%)	436 (91.2%)	< 0.001	292 (83.0%)	310 (88.1%)	0.0687
Cryoprecipitate, pools	0 [0–0]	2 [1–3]	< 0.001	2 [0–2]	2 [0–2]	0.202
Cryoprecipitate, transfused	434 (15.2%)	382 (79.9%)	< 0.001	236 (67.0%)	260 (73.9%)	0.0574
Nadir hemoglobin, mg/dl	8.6 ± 1.7	7.8 ± 1.4	< 0.001	8.0 ± 1.7	7.9 ± 1.4	0.757
Antifibrinolytic used	2,752 (96%)	470 (98%)	0.036	347 (99%)	348 (99%)	1.000
Viscoelastic test used	930 (33%)	333 (70%)	<0.001	223 (63%)	230 (65%)	0.637
FEIBA dose, U	N/A	620 ± 520		N/A	553 ± 380	
FEIBA dose, U/kg	N/A	8.0 ± 7.3		N/A	7.3 ± 5.5	

Values are n (%) for categorical and mean ± SD for continuous variables. Blood products and intensive care unit length of stay are reported as median [interquartile range]. *P* values are from Mann–Whitney U tests for continuous and Pearson chi-square or Fisher exact test for categorical variables.

*Mean circulatory arrest time is calculated from patients who underwent circulatory arrest.

ECMO, extracorporeal membrane oxygenation; FEIBA, factor eight inhibitory bypass activity; INR, international normalized ratio; N/A, not applicable.

Table 2. Rates of Postoperative Complications

Variable	Unmatched			Matched		
	No FEIBA (n = 2,857)	FEIBA (n = 478)	*P* Value	No FEIBA (n = 352)	FEIBA (n = 352)	*P* Value
Deep vein thrombosis	78 (3%)	49 (10%)	< 0.001	21 (6%)	30 (9%)	0.253
Pulmonary embolism	23 (1%)	9 (2%)	0.048	10 (3%)	8 (2%)	0.802
Unplanned coronary intervention	16 (1%)	6 (1%)	0.152	3 (1%)	4 (1%)	1.000
Ischemic stroke	64 (2%)	47 (10%)	< 0.001	26 (7%)	30 (9%)	0.692
Acute limb ischemia	11 (< 1%)	9 (2%)	< 0.001	4 (1%)	5 (1%)	1.000
Composite thromboembolism	173 (6%)	103 (22%)	< 0.001	56 (16%)	64 (18%)	0.483
Acute renal failure	57 (2%)	54 (11%)	< 0.001	20 (6%)	34 (10%)	0.066
Reoperation	53 (2%)	36 (8%)	< 0.001	11 (3%)	27 (8%)	0.013
ICU length of stay, d	2.8 [1.9–4.6]	4.7 [2.8–8.6]	< 0.001	3.9 [2.1–6.8]	4.2 [2.8–7.6]	0.051
30-day mortality	46 (2%)	30 (6%)	< 0.001	20 (6%)	21 (6%)	1.000

Values are n (%) or median [interquartile range]. *P* values are from Mann–Whitney U tests for continuous and Pearson chi-square or Fisher exact test for categorical variables.

FEIBA, factor eight inhibitory bypass activity; ICU, intensive care unit.

FEIBA group. Medians were 0 for all other components; however, interquartile ranges were higher for plasma and platelets in patients receiving FEIBA, and a higher proportion of patients in the FEIBA group were transfused for all components. The difference between groups was statistically significant for each component ($P < 0.001$). In a propensity-matched multivariate linear regression adjusting for potential confounders (fig. 4), increasing doses of FEIBA were associated with higher volumes of transfusion for plasma and cryoprecipitate. Compared with patients who did not receive FEIBA, those treated with more than 750 U were transfused an additional 1.6 plasma units (95% CI, 0.77 to 2.44; $P < 0.001$), and 0.57 cryoprecipitate pools of 4 to 5 units (95% CI, 0.23 to 0.92; $P = 0.001$). Patients treated with 501 to 750 U FEIBA were transfused 2.73 erythrocyte (95% CI, 0.68 to 4.78; $P = 0.009$) and 1.74 platelet units (95% CI, 0.85 to 2.63; $P < 0.001$) more than patients in the no FEIBA group. However, doses greater than 750 U and less than 501 U were not associated with statistically significant differences in erythrocyte or platelet transfusion.

Outcomes for FEIBA Recipients Who Were Not Matched

In unadjusted comparisons between FEIBA recipients (Supplemental Digital Content table 2, https://links.lww.com/ALN/D684), patients who received FEIBA but did not meet thresholds for nearest neighbor matching did not have statistically significant differences in individual thromboembolic outcomes, acute renal failure, reoperation, or mortality compared with FEIBA recipients in the matched

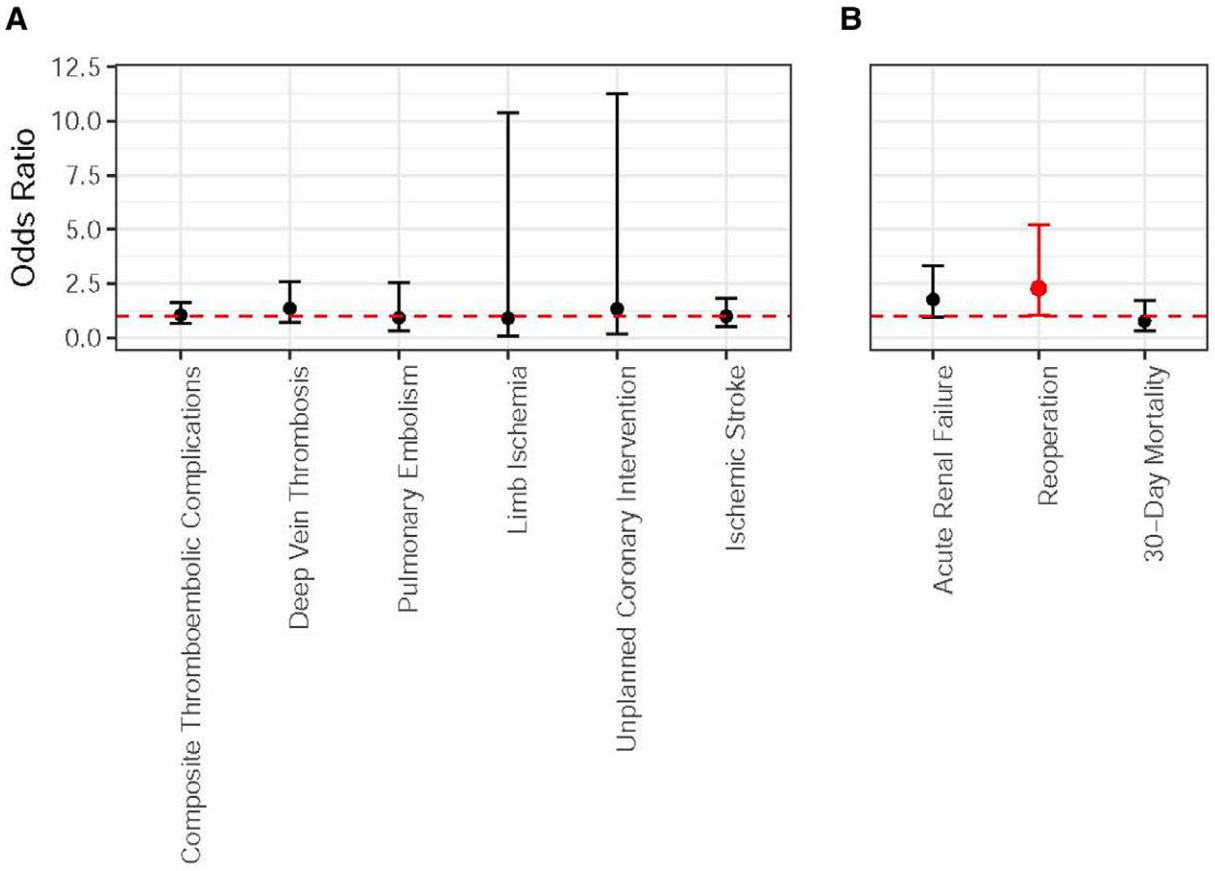

Fig. 2. Adjusted postoperative outcomes for patients receiving FEIBA *versus* no FEIBA. Multivariate logistic regressions with 1:1 nearest neighbor propensity score matched cohort (n = 704). (*A*) Primary outcomes. (*B*) Secondary outcomes. Both models were adjusted for age, sex, body mass index, preoperative hypertension, cerebrovascular disease, creatinine, procedure type, reoperation, emergent status, cardiopulmonary bypass, cross clamp and circulatory arrest times, antifibrinolytics, and intraoperative transfusion of erythrocytes, plasma, platelets, and cryoprecipitate. Adjusted odds ratios represent the estimated multiplicative increase in odds of developing each of the listed postoperative complications for patients who received FEIBA compared with those who did not. Outcomes with *P* values < 0.05 indicated with *red bars*. FEIBA, factor eight inhibitor bypass activity.

cohort. However, they had higher rates of composite thromboembolism (31% *vs.* 18%; $P = 0.004$) and ICU length of stay (median, 5.5 *vs.* 4.2 days; $P = 0.003$).

Discussion

In our analysis of FEIBA use during cardiac surgery at a single institution, we did not find increased risk of postoperative thromboembolic events or 30-day mortality. This held true for unadjusted between-group comparisons, and propensity-matched multivariate logistic regression models adjusting for dose and potential confounding variables. We sought to explore these outcomes because, similar to off-label rFVIIa, FEIBA is increasingly described as both a salvage therapy[8–11] and a first-line agent to prevent ongoing coagulopathy.[12] However, the primary outcomes of these studies have been related to hemostatic efficacy rather than thromboembolic events.

Off-label rFVIIa use has previously been discouraged due to increased thromboembolic events without improved mortality. Specifically, prophylactic rFVIIa after weaning from CPB is associated with increased risk of thromboembolic complications.[14,15] However, early studies of rFVIIa in cardiac surgery administered high doses between 40 and 90 μg/kg.[16–18] The risk of thromboembolic complications may be dose-dependent, and this is reflected in the decreasing doses published by contemporary studies.[19] Cardiothoracic surgery and cardiac anesthesia society guidelines now include low-dose rFVIIa for bleeding refractory to standard hemostatic interventions.[20–23] Observational studies of rFVIIa using "very low dose" strategies, described as less than 20 μg/kg, in goal-directed hemostatic protocols have found efficacy without an increase in thromboembolic complications.[19,24–26] Similarly, recent studies of FEIBA in cardiac surgery[8–11] have administered doses much lower than the package insert recommendation of 50 to 100 U/

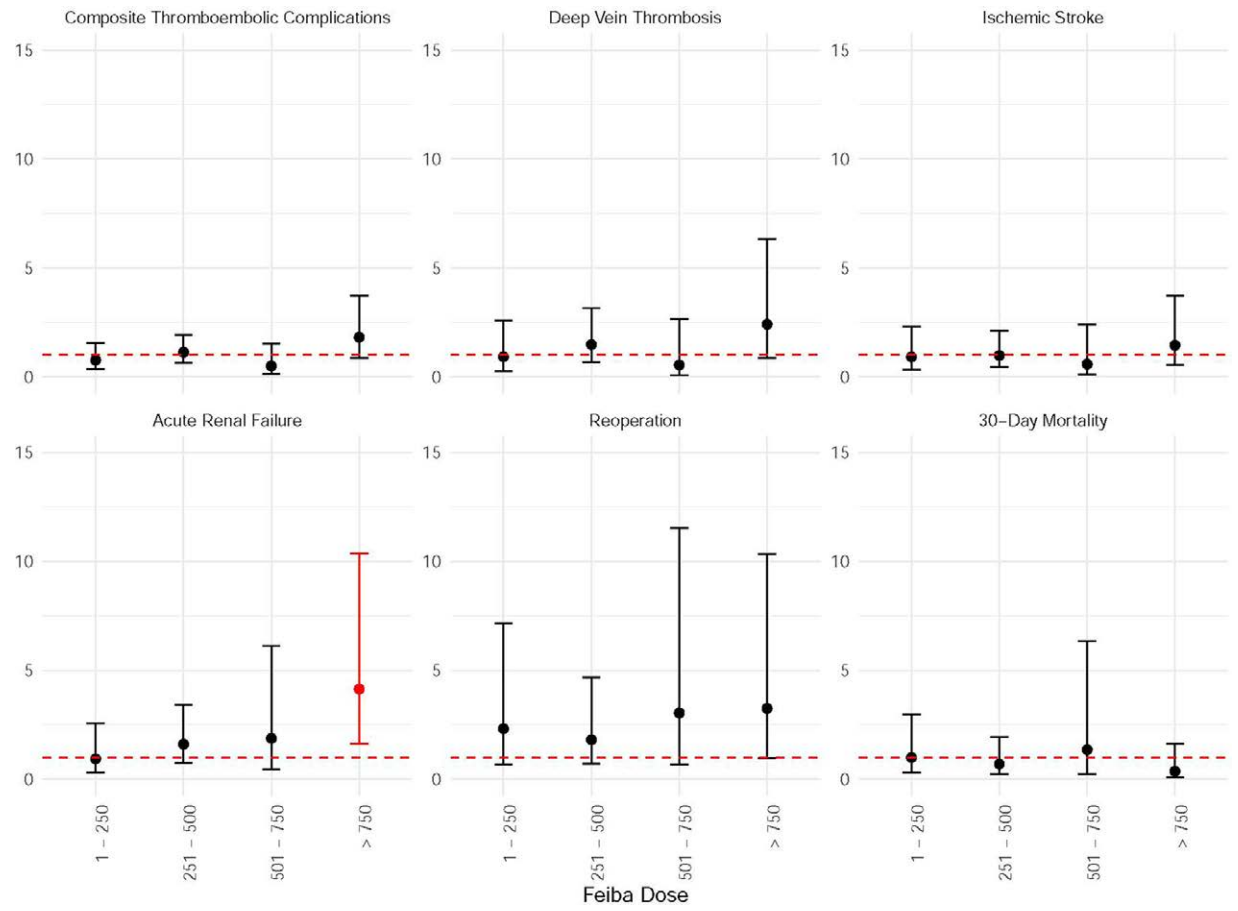

Fig. 3. Adjusted postoperative outcomes by dose of FEIBA. Models were adjusted for age, sex, body mass index, preoperative hypertension, cerebrovascular disease, creatinine, procedure type, reoperation, emergent status, cardiopulmonary bypass, cross clamp and circulatory arrest times, antifibrinolytics, and intraoperative transfusion of erythrocytes, plasma, platelets, and cryoprecipitate. Adjusted odds ratios represent the estimated multiplicative increase in odds of developing each of the listed postoperative complications associated with increasing doses of FEIBA. Outcomes with *P* values < 0.05 indicated with *red bars*. FEIBA, factor eight inhibitor bypass activity.

kg intended for treating bleeding patients with acquired coagulation factor inhibitors.[6]

In the current study, the highest dose range of FEIBA was more than 750 U (mean ± SD, 15 ± 10 U/kg), and this was associated with increased risk of postoperative acute renal failure. Patients undergoing cardiac surgery are exposed to multiple risk factors for renal injury, and the incidence of acute kidney injury is 20 to 30%, with 2 to 3% of those patients requiring renal replacement therapy. Compared with coronary artery bypass graft, valve and aortic procedures are associated with higher risk.[27] We included preoperative creatinine in our propensity match and multivariate regression analysis along with risk factors for acute renal failure, including cardiopulmonary bypass, aortic cross clamp, and circulatory arrest times, and transfusion. Most previous studies of perioperative FEIBA use have not assessed postoperative acute renal failure[4,5,7,9] or used dialysis-dependent acute renal failure as the outcome measure.[11] Murphy *et al.*[28] reported acute renal failure in 25.8% and 14.3% of patients receiving intraoperative and postoperative FEIBA, respectively, but there was no formal comparison with patients who did not receive FEIBA. The relative imbalance of pro- to anticoagulant components in FEIBA may increase risk of acute renal failure in escalating doses. However, patients receiving FEIBA have failed to achieve hemostasis with standard transfusion therapy. Ongoing hemorrhage, hypoperfusion, and blood component therapy, particularly plasma, are all associated with renal injury.[27] Additionally, there may be unmeasured characteristics contributing to acute renal failure for which we were unable to control.

In the only available meta-analysis of FEIBA use in cardiac surgery, Khoury *et al.*[8] report an aggregate 12.5% incidence for acute renal failure (compared with 11% for all patients receiving FEIBA in our study). They note this is a relatively high rate compared with studies of prothrombin complex concentrates (PCC). These, especially four-factor PCC, have increasingly been used as an alternative to

Table 3. Postoperative Transfusion

Blood Component	Unmatched			Matched		
	No FEIBA (n = 2,857)	FEIBA (n = 478)	*P* Value	No FEIBA (n = 352)	FEIBA (n = 352)	*P* Value
Erythrocytes, units	0 [0–1]	2 [1–5]	< 0.001	1 [0–3]	2 [1–5]	< 0.001
Erythrocytes, transfused	1,032 (36.1%)	377 (78.9%)	< 0.001	214 (61.1%)	272 (77.3%)	< 0.001
Plasma, units	0 [0–0]	0 [0–2]	< 0.001	0 [0–0]	0 [0–1]	< 0.001
Plasma, transfused	294 (10.3%)	177 (37.0%)	< 0.001	68 (19.4%)	116 (33.0%)	< 0.001
Platelets, units	0 [0–0]	0 [0–2]	< 0.001	0 [0–0]	0 [0–1]	< 0.001
Platelets, transfused	257 (9.0%)	177 (37.0%)	< 0.001	61 (17.4%)	116 (33.0%)	< 0.001
Cryoprecipitate, pools	0 [0–0]	0 [0–0]	< 0.001	0 [0–0]	0 [0–0]	< 0.001
Cryoprecipitate, transfused	146 (5.1%)	115 (24.1%)	< 0.001	26 (7.4%)	85 (24.1%)	< 0.001

Values are median [interquartile range]. *P* values are from the Mann–Whitney U test. The number of patients receiving each blood component is listed below along with percentage values in parentheses. *P* values are from the Pearson chi-square test.

FEIBA, factor eight inhibitory bypass activity.

plasma to treat coagulopathy during cardiac surgery.[20,22] Similar to FEIBA, they have advantages over plasma including pathogen inactivation and decreased volume. Unlike FEIBA, four-factor PCCs contain additional anticoagulant components—protein S, antithrombin, and heparin—and do not contain activated clotting factors.[29] In theory, this may reduce the risk of thromboembolic complications; however, the antithrombin and heparin content in various PCC formulations is low.[30] There are concerns that treatment with PCC alone after long CPB runs or ongoing massive hemorrhage may contribute to relative antithrombin deficiency and subsequent thromboembolic risk.[29] Notably, recent randomized trials have studied PCCs as an alternative to plasma, not as a rescue therapy for refractory bleeding.[31,32] These studies report procedures with bypass times of 172 ± 71 min and 161 min (interquartile range, 116 to 215), respectively, whereas the mean bypass time was 224 ± 87 min for patients in our study who received FEIBA. Cross clamp and circulatory arrest times were also longer compared to those of Smith *et al*.[32] Our institution does not routinely use PCCs in the context of cardiac surgery. FEIBA administration typically takes place after blood component therapy including plasma and cryoprecipitate have been administered. Thus, the context of FEIBA administration in our study is different, and direct comparisons of postoperative complication rates with use of PCC as an alternative to blood products cannot be made. Further investigation is required because there are no current comparisons between PCC and FEIBA to treat refractory bleeding during cardiac surgery.

There also may be a relationship between FEIBA dose and postoperative transfusion that differs by component. For cryoprecipitate, all doses of FEIBA were associated with increased transfusion, and doses greater than 500 U were associated with increased plasma transfusion. Given the usual practice at our institution—administering FEIBA 250 U at a time with reassessment of bleeding and effect of other hemostatic therapies—this may reflect the anticipated treatment course of refractory bleeding since patients who stop bleeding stop receiving hemostatic therapies. Erythrocyte and platelet transfusion did not fit this pattern. The only dose range found to be statistically significant for increased transfusion of these components corresponds with approximately three "doses" of FEIBA. It is likely that lower doses reflect milder cases and higher doses reflect more aggressive treatment. Both situations may result in early achievement of hemostasis. However, given the retrospective nature of our dataset, we can only state that this finding is an association, particularly because hemostatic efficacy was not an outcome measured in this study. Other retrospective studies of FEIBA administration in cardiac surgery have found mixed results of reduced or increased transfusion within the first 48 h postoperatively.[9,11] Randomized studies of active and placebo comparators have shown decreased postoperative transfusion, but results are also variable.[8]

Similarly, the effect on reoperation has been mixed,[5,11,28] and this outcome is influenced by successful hemostasis. Differences may be related to the specific surgical populations and context of FEIBA administration in these studies. The current study was not designed to assess the hemostatic efficacy of FEIBA, and we cannot say whether this cohort would have higher rates of reoperation and transfusion if they had not received FEIBA as a hemostatic agent after CPB.

FEIBA dosing likely influences the aforementioned thromboembolic and transfusion outcomes. Studies included by Khoury *et al.* report mean doses from 11 to 20 U/kg.[8] This is slightly higher than the average doses reported in two subsequent studies, which ranged from 9.7 to 13 U/kg.[9,10] The mean dose of FEIBA in our propensity-matched cohort was lower (7.5 ± 5.5 U/kg). A study of FEIBA in type A dissection by Pupovac *et al*.[11] included a population similar to our cohort, but dosing was not

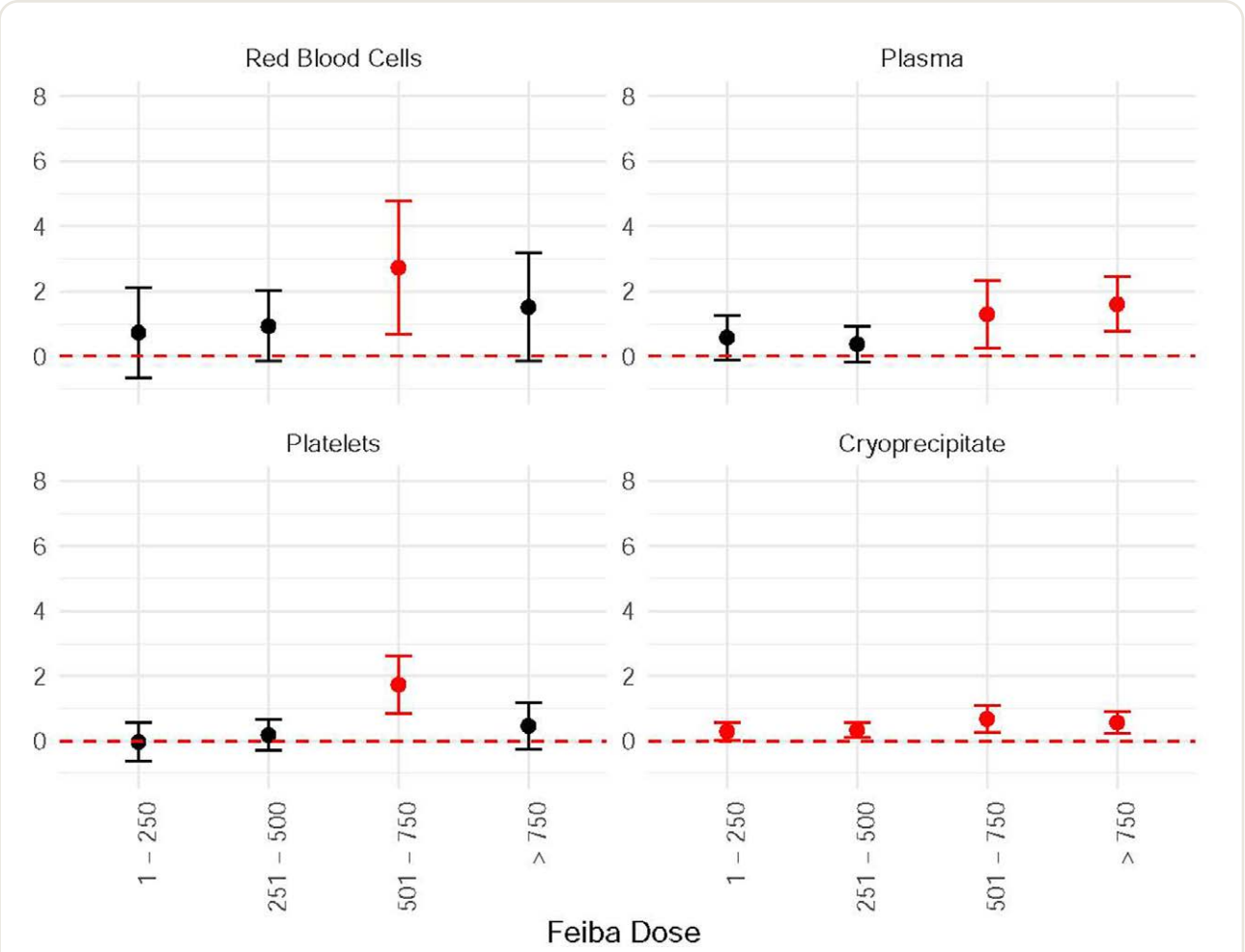

Fig. 4. Adjusted postoperative transfusion outcomes by dose of FEIBA. Models were adjusted for age, sex, body mass index, preoperative hypertension, cerebrovascular disease, creatinine, procedure type, reoperation, emergent status, cardiopulmonary bypass, cross clamp and circulatory arrest times, antifibrinolytics, and intraoperative transfusion of erythrocytes, plasma, platelets, and cryoprecipitate. Adjusted coefficients (β) represent the estimated increase in number of units administered for each dose of FEIBA compared with patients who did not receive FEIBA. Outcomes with *P* values < 0.05 indicated with *red bars*. FEIBA, factor eight inhibitor bypass activity.

reported. It should be noted that this "low dose" happens to be within the numeric range of contemporary low-dose strategies described for rFVIIa (less than 20 μg/kg) that have reported no increased risk of thromboembolic events.[19,25,26,33] Factor VII is the primary activated product in FEIBA, but the units of measurement are different. rFVIIa is dosed in micrograms per kilogram, and observed *in vivo* recovery varies between hemophiliacs, VII deficiency, and healthy controls.[34] FEIBA is dosed in units per kilogram; 1 U is defined by the manufacturer as the amount of FEIBA that shortens the activated partial thromboplastin time of high-titer factor VIII inhibitor reference plasma to 50% of the blank value.[6] Therefore, dosing of these products and what constitutes a "low-dose" strategy are not interchangeable. Future prospective studies with protocolized dosing are required to determine the appropriate use of FEIBA in refractory bleeding after cardiac surgery.

Limitations

This is a single-center, retrospective study with several limitations. First, the true incidence of thromboembolic outcomes may be higher than those reported here due to lack of prospective surveillance. While propensity matching can limit differences in covariates between cohorts, circulatory arrest time and intraoperative erythrocyte and plasma transfusion remained unbalanced between our matched cohorts. We controlled for these variables in the final regression model to account for this residual confounding, but the inherent differences in patients who receive FEIBA as rescue therapy for refractory bleeding may not be fully accounted for. These unmeasured differences are an inherent limitation to observational data and may have contributed to the differences in acute renal failure, reoperation, and postoperative transfusion between groups. Furthermore, 126 patients who received FEIBA did not obtain a sufficient match

among patients who did not receive FEIBA. These patients had more pre-existing comorbidity and underwent higher acuity procedures with risk for thromboembolism. This is not unexpected since patients with refractory coagulopathy are inherently different than those successfully treated with standard transfusion, but our analysis does not assess additional risk that FEIBA may incur for them. Additionally, there is no standardized protocol for FEIBA use, and we are unable to control for interprovider variation in decision-making around indication, dose, timing, and comanagement of transfusion and hemostatic agents. Our data are insufficient to distinguish between cases where FEIBA was administered early to treat measured coagulopathy or as a last resort for clinical bleeding despite normalized coagulation markers. We excluded all patients with on-label indications or contraindications to FEIBA to reduce confounding; therefore, we are unable to comment on these populations. This also limits the generalizability of findings for other institutions that may administer FEIBA in the context of cardiac surgery. Finally, heart transplants and ventricular assist device procedures are not captured by the Society of Thoracic Surgeons database, and our results are not necessarily applicable to these populations. Although this is the largest cohort of cardiac surgery patients treated with FEIBA reported to date, the overall population is small and cannot independently define the safety profile.

Conclusions

The results of this study suggest that low-dose FEIBA to treat bleeding during cardiac surgery on CPB does not increase risk of thromboembolic complications or mortality. This is the largest cohort of cardiac surgery patients treated with FEIBA analyzed to date and concurs with the thromboembolic safety profile suggested by previous studies. Importantly, these findings were consistent despite a population with high baseline risk factors for adverse outcomes including longer cardiopulmonary bypass, aortic cross clamp, and circulatory arrest times. However, we did find an association with postoperative acute renal failure and transfusion among patients receiving relatively higher doses of FEIBA, despite controlling for risk factors. Patients at increased risk of these outcomes may have unmeasured characteristics that increase the likelihood of requiring rescue hemostatic agents. Ongoing massive hemorrhage itself is a risk factor for acute renal failure and reoperation, and rates could be higher if activated factor concentrate were not administered for rescue therapy. Due to the available data and retrospective nature of this study, we cannot rule out the potential that FEIBA contributes to these complications at higher doses. Nevertheless, these data suggest a favorable risk profile for FEIBA when administered in low doses to treat refractory bleeding during cardiac surgery. However, individual patient risk should be strongly considered, particularly when administering doses greater than 15 U/kg. Prospective, randomized studies directly comparing the safety and efficacy of FEIBA with contemporary practices of rFVIIa and PCC are required.

Research Support

Support for this study was provided solely from institutional and departmental sources. Dr. Aghaeepour is supported by the National Institutes of Health (Bethesda, Maryland; R35GM138353).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Panigrahi: Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Room H3580, MC 5640, Stanford, California 94305. anilpani@stanford.edu

Supplemental Digital Content

Supplemental Digital Content Figure 1. Covariate balance before and after nearest neighbor matching, https://links.lww.com/ALN/D680

Supplemental Digital Content Figure 2. T-distributed stochastic neighbor embedding plots of prematched (*A*) and postmatched (*B*) data, https://links.lww.com/ALN/D681

Supplemental Digital Content Figure 3. Adjusted ICU length of stay by dose of FEIBA, https://links.lww.com/ALN/D682

Supplemental Digital Content Table 1. Patient demographics and procedure characteristics of unmatched FEIBA recipients, https://links.lww.com/ALN/D683

Supplemental Digital Content Table 2. Unadjusted rates of postoperative complications among FEIBA recipients, https://links.lww.com/ALN/D684

References

1. Christensen MC, Krapf S, Kempel A, von Heymann C: Costs of excessive postoperative hemorrhage in cardiac surgery. J Thorac Cardiovasc Surg 2009; 138:687–93
2. Dyke C, Aronson S, Dietrich W, et al.: Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg 2014; 147:1458–63.e1
3. Ranucci M: Hemostatic and thrombotic issues in cardiac surgery. Semin Thromb Hemost 2015; 41:84–90
4. Song HK, Tibayan FA, Kahl EA, et al.: Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery. J Thorac Cardiovasc Surg 2014; 147:1036–40
5. Rao VK, Lobato RL, Bartlett B, et al.: Factor VIII inhibitor bypass activity and recombinant activated factor

VII in cardiac surgery. J Cardiothorac Vasc Anesth 2014; 28:1221–6
6. Takeda P. FEIBA (anti-inhibitor coagulant complex) [package insert]. U.S. Food and Drug Administration. 2013. Available at: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/feiba. Accessed April 30, 2024.
7. Sera VA, Stevens AE, Song HK, Rodriguez VM, Tibayan FA, Treggiari MM: Factor VIII inhibitor bypass activity (FEIBA) for the reduction of transfusion in cardiac surgery: A randomized, double-blind, placebo-controlled, pilot trial. Pilot Feasibility Stud 2021; 7:1–9
8. Khoury W, Servito M, Wang L, et al.: The use of FEIBA for refractory bleeding in cardiac surgery – A systematic review. Expert Rev Cardiovasc Ther 2022; 20:403–8
9. O'Donnell C, Rodriguez AJ, Madhok J, et al.: The use of factor eight inhibitor bypass activity (FEIBA) for the treatment of perioperative hemorrhage in left ventricular assist device implantation. J Cardiothorac Vasc Anesth 2021; 35:2651–8
10. Pupovac SS, Catalano MA, Hartman AR, Yu PJ: Factor eight inhibitor bypassing activity for refractory bleeding in coronary artery bypass grafting: A propensity-matched analysis. Res Pract Thromb Haemost 2022; 6:e12838
11. Pupovac SS, Levine R, Giammarino AT, et al.: Factor eight inhibiting bypass activity for refractory bleeding in acute type A aortic dissection repair: A propensity-matched analysis. Transfusion 2022; 62:2235–44
12. Kim H, Manetta F, Hartman A, Huang X, Yu P-J: Factor eight inhibitor bypassing activity as first-line therapy for coagulopathy in cardiac surgery. J Cardiothorac Vasc Anesth 2024; 38:1875–81
13. Nguyen T-L, Collins GS, Spence J, et al.: Double-adjustment in propensity score matching analysis: Choosing a threshold for considering residual imbalance. BMC Med Res Methodol 2017; 17:78–78
14. Lin Y, Moltzan CJ, Anderson DR; National Advisory Committee on Blood and Blood Products: The evidence for the use of recombinant factor VIIa in massive bleeding: Revision of the transfusion policy framework. Transfus Med 2012; 22:383–94
15. Yank V, Tuohy CV, Logan AC, et al.: Systematic review: Benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Ann Intern Med 2011; 154:529–40
16. Diprose P, Herbertson MJ, O'Shaughnessy D, Gill RS: Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: Randomized double-blind placebo-controlled pilot study. Br J Anaesth 2005; 95:596–602
17. Gill R, Herbertson M, Vuylsteke A, et al.: Safety and efficacy of recombinant activated factor VII: A randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation 2009; 120:21–7
18. Levi M, Levy JH, Andersen HF, Truloff D: Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 2010; 363:1791–800
19. Flynn BC, Steiner ME, Mazzeffi M: Off-label use of recombinant activated factor VII for cardiac surgical bleeding. Anesthesiology 2023; 139:197–210
20. Tibi P, McClure RS, Huang J, et al.: STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. J Extra Corpor Technol 2021; 53:97–124
21. Boer C, Meesters MI, Milojevic M, et al.; Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA): 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018; 32:88–120
22. Raphael J, Mazer CD, Subramani S, et al.: Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. Anesth Analg 2019; 129:1209–21
23. Kietaibl S, Ahmed A, Afshari A, et al. Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022. Eur J Anaesthesiol 2023; 40:226–304
24. Brase J, Finger B, He J, et al.: Analysis of outcomes using low-dose and early administration of recombinant activated factor VII in cardiac surgery. Ann Thorac Surg 2016; 102:35–40
25. Cotter E, Sharma A, Campton A, et al.: Very low-dose recombinant factor VIIa administration for cardiac surgical bleeding reduces red blood cell transfusions and renal risk: A matched cohort study. Blood Coagul Fibrinolysis 2021; 32:473–9
26. Hoffmann T, Assmann A, Dierksen A, et al.: A role for very low-dose recombinant activated factor VII in refractory bleeding after cardiac surgery: Lessons from an observational study. J Thorac Cardiovasc Surg 2018; 156:1564–73.e8
27. Cheruku SR, Raphael J, Neyra JA, Fox AA: Acute kidney injury after cardiac surgery: Prediction, prevention, and management. Anesthesiology 2023; 139:880–98
28. Murphy T, Forgie R, MacLeod J, Brown C, Hassan A, Pelletier M: Severe coagulopathy after cardiac surgery: Is FEIBA a viable therapy? Can J Cardiol 2016; 32(suppl 1):S113
29. Tanaka KA, Shettar S, Vandyck K, Shea SM, Abuelkasem E: Roles of four-factor prothrombin complex concentrate in the management of critical bleeding. Transfus Med Rev 2021; 35:96–103
30. Tanaka KA, Esper S, Bolliger D: Perioperative factor concentrate therapy. Br J Anaesth 2013; 111:i35–49

31. Karkouti K, Bartoszko J, Grewal D, et al.: Comparison of 4-factor prothrombin complex concentrate with frozen plasma for management of hemorrhage during and after cardiac surgery: A randomized pilot trial. JAMA Netw Open 2021; 4:e213936
32. Smith MM, Schroeder DR, Nelson JA, et al.: Prothrombin complex concentrate vs plasma for post–cardiopulmonary bypass coagulopathy and bleeding: A randomized clinical trial. JAMA Surg 2022; 157:757–64
33. Sutherland L, Houchin A, Wang T, et al.: Impact of early, low-dose factor VIIa on subsequent transfusions and length of stay in cardiac surgery. J Cardiothorac Vasc Anesth 2022; 36:147–54
34. Novo Nordisk, Inc.: NovoSeven Coagulation Factor VII (Recombinant) [package insert]. U.S. Food and Drug Administration. 2014. Available at: https://www.fda.gov/vaccines-blood-biologics/blood-blood-products/novoseven. Accessed April 30, 2024.

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Anesthesia per Rectum: Gwathmey's Oil-Ether Approach

Mere months after the historic display of inhalational ether anesthesia in Boston in 1846, Russian surgeon Nikolai Pirogoff and French scientist Marc Dupuy simultaneously proposed rectal ether to induce surgical unconsciousness. Although initially unpopular, rectal anesthesia enjoyed a resurgence in 1884, with several case reports appearing in the literature. In 1910, American surgeon Walter Sutton published 140 successful cases of rectal ether-oxygen and celebrated its advantages: (1) continuous delivery of anesthesia during head and neck surgery, (2) reduced postoperative nausea and vomiting, and (3) greater hemodynamic stability. Inspired by Sutton's findings, pioneering anesthesiologist James Tayloe Gwathmey presented his classic oil-ether technique in 1913. Mixing ether with olive oil (*lower right*) mitigated the diarrhea and melena described in prior reports. Gwathmey used a 28-inch-long catheter for afferent rectal delivery, along with a 30-inch "Gwathmey tube" for efferent fluid removal. On the morning of surgery, the patient received hourly warm-water enemas and premedication with subcutaneous morphine and scopolamine. Anesthetic induction began with the patient positioned left lateral recumbent (*image above*). Gwathmey trickled 6 ounces of oil-ether into a funnel connected to the rectal catheter, and then clamped the catheter. Within minutes, unconsciousness ensued. At surgery's end, he poured a gallon of soapy water into the catheter, only to siphon it off with the tube. A final colonic rinse with olive oil, then either pure water or black coffee, prepared the patient for emergence. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

Jane S. Moon, M.D., Assistant Clinical Professor, Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, California.