A comparison of red blood cell transfusion utilization between anti-activated factor X and activated partial thromboplastin monitoring in patients receiving unfractionated heparin

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To cite this article: Belk KW, Laposata M, Craver C. A comparison of red blood cell transfusion utilization between anti-activated factor X and activated partial thromboplastin monitoring in patients receiving unfractionated heparin. J Thromb Haemost 2016; 14: 2148–57.

Summary. Background: Anticoagulant activated factor X protein (Anti-Xa) has been shown to be a more precise monitoring tool than activated partial thromboplastin time (aPTT) for patients receiving unfractionated heparin (UFH) anticoagulation therapy. Objectives: To compare red blood cell (RBC) transfusions between patients receiving UFH who are monitored with Anti-Xa and those monitored with aPTT. Patients/Methods: A retrospective cohort study was conducted on patients diagnosed with acute coronary syndrome (ACS) (N = 14 822), diagnosed with ischemic stroke (STK) (N = 1568) or with a principal diagnosis of venous thromboembolism (VTE) (N = 4414) in the MedAssets data from January 2009 to December 2013. Anti-Xa and aPTT groups were identified from hospital billing details, with both brand and generic name as search criteria. Propensity score techniques were used to match Anti-Xa cases to aPTT controls. RBC transfusions were identified from hospital billing data. Multivariable logistic regression was used to identify significant drivers of transfusions. Results: Anti-Xa patients had fewer RBC transfusions than aPTT patients in the ACS population (difference 17.5%; 95% confidence interval [CI] 16.4–18.7%), the STK population (difference 8.2%; 95% CI 4.4–11.9%), and the VTE population (difference 4.7%; 95% CI 3.3–6.1%). After controlling for patient age and gender, diagnostic risks (e.g. anemia, renal insufficiency, and trauma), and invasive procedures (e.g. cardiac catheterization, hemodialysis, and coronary artery bypass graft), Anti-Xa patients were less likely to have a transfusion while hospitalized for ACS (odds ratio [OR] 0.16, 95% CI 0.14–0.18), STK (OR 0.41, 95% CI 0.29–0.57), and VTE (OR 0.35, 95% CI 0.26–0.48). Conclusion: Anti-Xa monitoring was associated with a significant reduction in RBC transfusions as compared with aPTT monitoring alone.

Keywords: activated partial thromboplastin time; anticoagulant factor Xa protein; cardiovascular diseases; red blood cell transfusions; unfractionated heparin.

Introduction

The accuracy of anticoagulation monitoring of patients receiving unfractionated heparin (UFH) is of critical importance to the treatment and safety of patients hospitalized for acute cardiovascular events [1]. Failure to consistently measure the anticoagulant effect of UFH has been linked to significantly higher rates of serious complications, including major bleeding, stroke, thrombocytopenia, and in-hospital mortality [1–3].

Recent studies have shown anticoagulant activated factor X protein (Anti-Xa) assays to constitute a more precise monitoring tool than activated partial thromboplastin time (aPTT) assays in hospitalized patients receiving UFH anticoagulation therapy [4]. Comparative analyses have shown that Anti-Xa monitoring of patients receiving UFH results in a higher percentage of within-range test results,
fewer monitoring tests for the patient to achieve results within the target range and fewer dose adjustments than a protocol based on UFH monitoring using aPTT [3]. With these advantages noted, the relationship between accurate UFH monitoring and improved clinical outcomes is less clear [4].

Previous analyses have shown that Anti-Xa monitored patients experience significantly fewer bleeding complications and lower rates of non-fatal myocardial infarction (MI) than patients monitored with aPTT [2,5]. The adoption of Anti-Xa monitoring in patients receiving UFH has also been shown to reduce both in-hospital stay and 30-day mortality rates in patients with a high risk of acute coronary syndrome (ACS) [5]. The impact of Anti-Xa monitoring on the need for blood and blood products is not yet clear [6].

The purpose of this study was to compare the need for red blood cell (RBC) transfusions among hospitalized UFH-treated cardiovascular patients receiving either anti-FXa or aPTT anticoagulation monitoring.

Materials and methods

Study population

A retrospective cohort study was conducted on patients receiving intravenous UFH, monitored with either anti-FXa or aPTT assays, and diagnosed with ACS (N = 14 822), diagnosed with ischemic stroke (STK) (N = 1568) or with a principal (condition primarily responsible for admission) diagnosis of venous thromboembolism (VTE) (N = 4,414) in the MedAssets Health System database (MAHSD) from January 2009 to December 2013. The MAHSD is a nationally representative administrative patient-level database with billing details from ~ 400 hospitals across 43 states in the USA.

Intravenous UFH treatment was identified from detailed billing description records, which identified dose, strength and day of service for each administration of UFH. The disease-based subpopulations were identified by use of the International Classification of Disease Category version 9 (ICD-9CM) codes for ACS, STK, and VTE (Table S1).

The anti-FXa and aPTT comparison cohorts were identified from a combination of detailed billing records and Current Procedural Terminology version 4 (CPT-4) codes (85520 and 85730). Each patient was assigned independently to the monitoring groups by use of a recursive text search algorithm of billing detail records or by the presence of the appropriate CPT-4 code. This process discretely assigned 99.99% of the 343 922 patients to either the anti-FXa group or the aPTT group. The 12 patients who were assigned to both groups were included in the anti-FXa group. Sensitivity analyses were conducted to examine the impact of dual assignment.

Study variables

The primary outcome of interest was in-hospital RBC transfusion risk. RBC transfusions were defined according to hospital billing records, and constructed as a binary variable. Salient patient-level covariate data were collected for the UFH treatment population, including patient demographics (age and gender) and encounter-specific variables (source of admission, discharge status, and length of stay). Age was reported as both a continuous variable and in 10-year cohorts. Patient comorbidities were identified by use of the Charlson–Deyo version of the Charlson Comorbidity Index [7,8]. Hospital-specific variables were also collected, including number of beds, teaching status, and geographic region. For analytic purposes, bed number was converted to standard categories similar to those reported by the American Hospital Association Annual Survey of Hospitals and Medicare.

Additional disease-specific comorbidities and complications were added to the ACS and VTE subpopulation cohorts. For the VTE population, these included: pneumonia, respiratory disease, urinary tract infections, and sepsis. In addition, the occurrence of pulmonary embolism (PE) and the coexistence of PE and deep vein thrombosis (DVT) were included as comorbidities in this population, given that PE is clinically more severe and often more resource-intensive than DVT. For the ACS population, disease-specific comorbidities and complications included: metabolic immunity disorders, cardiac dysrhythmias, obesity, ST-elevated MI (STEMI), hypertensive heart and chronic kidney disease (CKD), stroke, and major cardiac procedures, including coronary artery bypass graft (CABG). In addition, comorbidities affecting the risk of RBC transfusion were included in the analyses. These comorbidities included both invasive procedures such as heart valve procedures, pacemaker insertions, and chest drainage, and non-invasive procedures such as wound care. Clinical conditions affecting the likelihood of transfusion, such as anemia and coagulation defects, thrombocytopenia, diabetes, and trauma, were also included as comorbidities. All additional comorbidities were defined by the use of ICD-9CM codes, and are outlined in Tables S2 and S3.

Statistical analysis

Unadjusted bivariate descriptive analyses were performed, comparing the baseline population characteristics and the RBC transfusion outcome variable between the anti-FXa and aPTT groups in both the pre-match and post-match patient populations. Chi-squared tests (Fisher’s exact tests were used for low cell counts) were used to test for significant differences between the anti-FXa and aPTT groups and disease-specific cohorts for categorical variables. Analysis of variance was used for continuous variables (Mann–Whitney test for non-normal distributions).
Multivariate analysis for each disease-specific cohort was accomplished with a two-step process. First, within each cohort, anti-FXa patients were propensity-matched to aPTT controls at a 1:1 ratio by use of a Greedy matching algorithm [9–11]. The algorithm required probability scores to match to a minimum of four decimal places. This method was chosen to provide the optimal match for the greatest number of the exposed population, given the number of covariates included in the matching algorithm [9,12]. Cohort matching criteria included age, gender, discharge status (left against medical advice [AMA] and transfer to another facility), hospital demographics, and patient comorbidities for all disease groups, as well the VTE-specific and ACS-specific complications and comorbidities mentioned previously.

After matching, cohort-specific logistic regression models were created to compare the transfusion outcome between anti-FXa and aPTT control groups. All matching criteria variables were included in the final models to account for any uncontrolled variation between the matched cohorts, and to adjust for their impact on the outcome variable. Watkins–Durbin tests for collinearity were performed to identify any confounding relationships between the independent variables. Additional disease-specific surgical procedures (e.g. CABG and valve replacements) that could affect the likelihood of transfusion were added to the models to control for population heterogeneity unaccounted for in the matching process (Tables S2 and S3). For the adjusted analyses, patients with missing data elements were excluded pairwise from the regression models. Post-match analysis required the removal of one matched pair, because of missing gender information. Significance levels for the model parameter estimates were set at 0.05. All data analyses were performed and statistical models for this study were generated with SAS/STAT software, Version 9.3 of SAS for Windows (SAS Institute, Cary, NC, USA).

Results

The initial study population included 343,922 patient discharges in the ACS cohort (72.5%), accounting for the largest portion of the group (Table 1). Anti-FXa-monitored patients accounted for just over 3% of the total population (Table 1). Among the individual cohorts, anti-FXa monitoring accounted for 5.2% of VTE discharges, 1.8% of STK discharges, and 3.2% of ACS discharges (Table 1).

Population characteristics

The average age of the anti-FXa group was slightly higher in the ACS (66.7 years versus 66.2 years), STK (68.1 years versus 67.7 years) and VTE (63.3 years versus 62.5 years) populations than that of the aPTT group (Table 2). Within the anti-FXa group, both the ACS (61.0%) and the STK (49.3%) populations contained more males than females, whereas the VTE population was 50.3% female (Table 2). By comparison, the aPTT group contained 61.7%, 49.3% and 47.3% males, respectively, in the ACS, STK and VTE subpopulations (Table 2). The proportion of patients transferred to another facility was < 2% for all cohorts, and < 1% of patients left AMA (Table 2). For both the anti-FXa and aPTT groups, the majority of discharges were treated in larger facilities (≥ 300 beds) that were non-teaching and located in urban settings (Table 2).

Although the Charlson Comorbidity Index profile varied across and within the anti-FXa and aPTT groups, congestive heart failure, chronic pulmonary disease, diabetes and renal disease were common among all three disease populations (Table 3). Additionally, among ACS patients, MI (anti-FXa, 79.4%; aPTT, 65.4%) was prevalent as compared with cerebrovascular disease (anti-FXa, 99.3%; aPTT, 89.8%), hemiplegia or paraplegia (anti-FXa, 28.9%; aPTT, 28.2%) in the STK population, and malignancy and tumors (anti-FXa, 29.3%; aPTT, 25.9%) in the VTE population. Overall, among the anti-FXa group patients, those in the STK population had the highest average Charlson Comorbidity Index score (4.70), followed by those in the ACS population (3.83) and those in the VTE population (2.86) (Table 2). In the aPTT group, similar rankings were found among the subpopulations; however, the Charlson Comorbidity Index scores were significantly lower than in the anti-FXa group (Table 3).

In the anti-FXa group, metabolic immunity disorders (82.4%), cardiac dysrhythmias (38.2%), obesity (21.4%), STEMI (16.2%), CABG (20.3%), hypertensive heart disease and CKD (26.2%) were the most prevalent ACS-

| Table 1 Cohort patient populations |
|-----------------------------------|
| Cohort                         | aPTT | Anti-FXa | Total | % Total | % Anti-FXa | Anti-FXa match population | aPTT match population | Total match population | Match rate (%) |
|---------------------------------|------|----------|-------|---------|-----------|---------------------------|-----------------------|-----------------------|-----------------|
| Venous thromboembolism         | 46336| 2565     | 48901 | 14.2    | 5.2       | 2207                      | 2207                  | 4414                  | 86.0            |
| Stroke                         | 44887| 817      | 45704 | 13.3    | 1.8       | 784                       | 784                   | 1568                  | 96.0            |
| Acute coronary syndrome        | 241420| 7897    | 249317| 72.5    | 3.2       | 7411                      | 7411                  | 14822                 | 93.8            |
| Total                          | 332643| 11279   | 343922| 100.0   | 3.3       | 10402                     | 10402                 | 20804                 | 93.8            |

aPTT, activated partial thromboplastin time; Anti-FXa, anticoagulant activated factor X protein.

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## Table 2: Base population demographic characteristics

| Characteristic | VTE | Stroke | ACS |
|----------------|-----|--------|-----|
|                | Anti-FXa | aPTT | P-value | Anti-FXa | aPTT | P-value | Anti-FXa | aPTT | P-value |
| Age group (years) | Patients | % | Patients | % | Patients | % | Patients | % | Patients | % |
| < 18            | 13 | 0.5 | 203 | 0.4 | 8 | 1.0 | 412 | 0.9 | 1 | 0.0 | 71 | 0.0 |
| 18–29           | 97 | 3.8 | 1973 | 4.3 | 7 | 0.9 | 549 | 1.2 | 19 | 0.2 | 714 | 0.3 |
| 30–39           | 142 | 5.5 | 3192 | 6.9 | 18 | 2.2 | 1124 | 2.5 | 129 | 1.6 | 4379 | 1.8 |
| 40–49           | 297 | 11.6 | 5590 | 12.1 | 65 | 8.0 | 3298 | 7.3 | 619 | 7.8 | 21310 | 8.8 |
| 50–59           | 407 | 15.9 | 7948 | 17.2 | 114 | 14.0 | 7224 | 16.1 | 1453 | 18.4 | 50324 | 20.8 |
| 60–69           | 535 | 20.9 | 9420 | 20.3 | 178 | 21.8 | 10129 | 22.6 | 2192 | 27.8 | 65654 | 27.2 |
| 70–79           | 533 | 20.8 | 8999 | 19.4 | 200 | 24.5 | 10532 | 23.5 | 1885 | 23.9 | 55422 | 23.0 |
| 80–89           | 380 | 14.8 | 7214 | 15.6 | 178 | 21.8 | 9232 | 20.6 | 1150 | 14.6 | 35888 | 14.9 |
| ≥ 90            | 93 | 3.6 | 1698 | 3.7 | 32 | 3.9 | 2335 | 5.2 | 211 | 2.7 | 7219 | 3.0 |
| Unknown         | 68 | 2.7 | 99 | 0.2 | 17 | 2.1 | 52 | 0.1 | 238 | 3.0 | 439 | 0.2 |
| Total           | 2565 | 100.0 | 46336 | 100.0 | 817 | 100.0 | 44887 | 100.0 | 7897 | 100.0 | 241420 | 100.0 |
| Mean (SD)       | 63.27 | 17.39 | 62.51 | 17.74 | 68.06 | 15.89 | 67.68 | 16.09 | 66.06 | 15.89 | 66.15 | 13.35 |
| Gender          | Female | 1290 | 50.3 | 24256 | 52.3 | 397 | 48.6 | 22690 | 50.5 | 2838 | 35.9 | 91702 | 38.0 |
|                | Male   | 1207 | 47.1 | 21897 | 47.3 | 403 | 49.3 | 22122 | 49.3 | 4820 | 61.0 | 148989 | 61.7 |
|                | Unknown | 68 | 2.7 | 183 | 0.4 | 17 | 2.1 | 75 | 0.2 | 239 | 3.0 | 729 | 0.3 |
| Total           | 2565 | 100.0 | 46336 | 100.0 | 817 | 100.0 | 44887 | 100.0 | 7897 | 100.0 | 241420 | 100.0 |
| Urban and rural | Rural | 0 | 0.0 | 230 | 0.5 | 0 | 0.0 | 117 | 0.3 | 0 | 0.0 | 857 | 0.4 |
|                | Urban | 2565 | 100.0 | 46106 | 99.5 | 817 | 100.0 | 44770 | 99.7 | 7897 | 100.0 | 240563 | 99.6 |
|                | Unknown | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Total           | 2565 | 100.0 | 46336 | 100.0 | 817 | 100.0 | 44887 | 100.0 | 7897 | 100.0 | 241420 | 100.0 |
| Hospital bed number | < 100 | 4 | 0.2 | 1605 | 3.5 | 2 | 0.2 | 1378 | 3.1 | 5 | 0.1 | 8888 | 3.7 |
|                | 100–199 | 21 | 0.8 | 6525 | 14.1 | 6 | 0.7 | 4850 | 10.8 | 28 | 0.4 | 27390 | 11.3 |
|                | 200–299 | 68 | 2.7 | 6323 | 13.6 | 26 | 3.2 | 5465 | 12.2 | 106 | 1.3 | 27801 | 11.5 |
|                | 300–499 | 1420 | 55.4 | 14973 | 32.3 | 330 | 40.4 | 12421 | 27.7 | 2824 | 35.8 | 80256 | 33.2 |
|                | ≥ 500 | 1052 | 41.0 | 15355 | 33.1 | 453 | 55.4 | 19754 | 44.0 | 4934 | 62.5 | 90698 | 37.6 |
| Unknown         | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1019 | 2.3 | 0 | 0.0 | 6387 | 2.6 |
| Total           | 2565 | 100.0 | 46336 | 100.0 | 817 | 100.0 | 44887 | 100.0 | 7897 | 100.0 | 241420 | 100.0 |
| Teaching status | Major teaching | 228 | 8.9 | 12148 | 26.2 | 189 | 23.1 | 16884 | 37.6 | 1207 | 15.3 | 78064 | 32.3 |
|                | Minor teaching | 734 | 28.6 | 14483 | 31.3 | 96 | 11.8 | 12356 | 27.5 | 534 | 6.8 | 61351 | 25.5 |
|                | Non-teaching | 1603 | 62.5 | 19705 | 42.5 | 532 | 65.1 | 15647 | 34.9 | 6156 | 78.0 | 101805 | 42.2 |
| Unknown         | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Total           | 2565 | 100.0 | 46336 | 100.0 | 817 | 100.0 | 44887 | 100.0 | 7897 | 100.0 | 241420 | 100.0 |
| Discharge status | Transfer to another healthcare facility | 12 | 0.5 | 757 | 1.6 | 13 | 1.6 | 977 | 2.2 | 0.2290 | 51 | 0.6 | 11797 | 4.9 |
|                | Left against medical advice | 12 | 0.5 | 235 | 0.5 | 6550 | 1 | 0.1 | 162 | 0.4 | 0.2488 | 42 | 0.5 | 1486 | 0.6 |

ACS, acute coronary syndrome; Anti-FXa, anticoagulant activated factor X protein; aPTT, activated partial thromboplastin time; VTE, venous thromboembolism.

*Fisher's exact was used for low volume in some cells.
Table 3 Base population comorbidities

| Charlson comorbidities | VTE | Stroke | ACS |
|------------------------|-----|--------|-----|
|                        | Anti-FXa | aPTT | P-value | Anti-FXa | aPTT | P-value | Anti-FXa | aPTT | P-value |
| Myocardial infarction  | 105  | 4.1   | 1520 | 3.3 | 0.0253 | 180  | 22.0 | 4932 | 11.0 | < 0.0001 |
| Old myocardial infarction | 208  | 8.1   | 3281 | 7.1 | 0.0489 | 108  | 13.2 | 4501 | 10.0 | 0.0027 |
| Congestive heart failure | 446  | 17.4  | 7532 | 16.3 | 0.1307 | 323  | 39.5 | 1110 | 24.8 | < 0.0001 |
| Peripheral vascular disease | 216  | 8.4   | 3551 | 7.7 | 0.1614 | 137  | 16.8 | 5190 | 11.6 | < 0.0001 |
| Cerebrovascular disease | 287  | 11.2  | 4196 | 9.1 | 0.0003 | 811  | 99.3 | 40304 | 89.8 | < 0.0001 |
| Dementia | 40  | 1.6   | 552  | 1.2 | 0.0970 | 21  | 2.6  | 1016 | 2.3 | 0.5593 |
| Chronic pulmonary disease | 680  | 26.5  | 10780 | 23.3 | 0.0002 | 214  | 26.2 | 8464 | 18.9 | < 0.0001 |
| Rheumatic disease | 128  | 5.0   | 1856 | 4.0 | 0.0139 | 38  | 4.7  | 1313 | 2.9 | 0.0039 |
| Peptic ulcer disease | 74  | 2.9   | 1216 | 2.6 | 0.4226 | 37  | 4.5  | 1076 | 2.4 | < 0.0001 |
| Diabetes without chronic complications | 667  | 26.0  | 11214 | 24.2 | 0.0383 | 295  | 36.1 | 14706 | 32.8 | 0.0436 |
| Diabetes with chronic complications | 62  | 2.4   | 1258 | 2.7 | 0.3650 | 43  | 5.3  | 2423 | 5.4 | 0.8657 |
| Hemiplegia or paraplegia | 42  | 1.6   | 817  | 1.8 | 0.6369 | 236 | 28.9 | 12647 | 28.2 | 0.6544 |
| Renal disease | 512  | 20.0  | 8195 | 17.7 | 0.0034 | 242 | 29.6 | 10611 | 23.6 | < 0.0001 |
| Any malignancy | 489  | 19.1  | 7982 | 17.2 | 0.0167 | 96  | 11.8 | 3516 | 7.8 | < 0.0001 |
| Moderate/severe liver disease | 17  | 0.7   | 367  | 0.8 | 0.4703 | 8  | 1.0  | 341  | 0.8 | 0.4751 |
| Metastatic solid tumor | 262  | 10.2  | 4027 | 8.7 | 0.0079 | 27  | 3.3  | 1186 | 2.6 | 0.2429 |
| AIDS/HIV | 0  | 0.0   | 0    | 0.0 | NA | 0  | 0.0  | 0    | 0.0 | NA |
| Mean Charlson score (SD) | 2.86 | 3.24  | 2.56 | 3.08 | < 0.0001 | 4.70 | 2.96 | 3.86 | 2.89 | < 0.0001 |
| Other comorbidities |  |  |  |  |  |  |  |  |  |  |
| Concurrent antiplatelet use | 1965 | 76.6  | 31162 | 67.3 | < 0.0001 | 549 | 67.2 | 32176 | 71.7 | 0.0048 |
| Antiphospholipid syndrome | 0  | 0.0   | 0    | 0.0 | NA | 0  | 0.0  | 0    | 0.0 | NA |
| Vitamin K deficiency | 2  | 0.1   | 19   | 0.0 | 0.3025 | 0  | 0.0  | 1    | 0.0 | 0.6545 |
| VTE in prior 12 months | 327  | 12.7  | 7895 | 17.0 | < 0.0001 | 20  | 2.4  | 884  | 2.0 | 0.3302 |
| ICU at first heparin administration | 786  | 30.6  | 12993 | 28.0 | 0.0043 | 427 | 52.3 | 19916 | 44.4 | < 0.0001 |
| Atrial fibrillation | 329  | 12.8  | 4874 | 10.5 | 0.0002 | 372 | 45.5 | 12373 | 27.6 | < 0.0001 |
| Cardiomyopathy | 85  | 3.3   | 1569 | 3.4 | 0.8437 | 81 | 9.9  | 3016 | 6.7 | 0.0003 |
| Coronary artery disease | 477  | 18.6  | 8151 | 17.6 | 0.1935 | 318 | 38.9 | 13907 | 31.0 | < 0.0001 |
| Hyperlipidemia | 879  | 34.3  | 14440 | 31.2 | 0.0010 | 432 | 52.9 | 21600 | 48.1 | 0.007 |
| Hypertension | 1113 | 43.4  | 20205 | 43.6 | 0.8318 | 411 | 50.3 | 24128 | 53.8 | 0.0502 |

ACS, acute coronary syndrome; Anti-FXa, anticoagulant activated factor X protein; aPTT, activated partial thromboplastin time; ICU, intensive care unit; NA, Not applicable; VTE, venous thromboembolism.
specific comorbidities and procedures (Table 4). In the VTE population, 37% of anti-FXa patients experienced a PE only, and 30.8% experienced a DVT only. Nearly one-third (32.2%) of the VTE population had both a PE and a DVT. In VTE patients monitored with anti-FXa, bacterial infections, including pneumonia (9.6%), other respiratory disease (19.7%), urinary tract infection (8.9%), and sepsis (2.8%), were common (Table 4).

**Post-match analysis**

The matching algorithm collectively assigned nearly 94% of the anti-FXa group to aPTT control discharges. Individually, the match rate for VTE was 86.0%, and STK and ACS were matched at 96.0% and 93.8%, respectively (Table 1).

The post-match comparison showed no significant difference between the anti-FXa study group and the aPTT comparison group across patient demographic characteristics among the disease-specific patient populations (Table S4). With the exception of concurrent antiplatelet use, other comorbidities and CABG procedures in the ACS population, and atrial fibrillation and hyperlipidemia in both the ACS and STK populations, no significant differences were found among patient comorbidities and procedures (Tables S5 and S6).

The results of post-match unadjusted outcome comparisons showed that anti-FXa patients had fewer RBC transfusions than aPTT patients in the ACS (7.0% versus 24.6%, \( P < 0.0001 \)), STK (13.8% versus 21.9%, \( P = 0.0001 \)), and procedures (Tables S5 and S6).

**Table 4 Pre-match population-specific comorbidities and procedures**

| Comorbidity                         | Anti-FXa Patients | aPTT Patients | \( P \)-value |
|-------------------------------------|-------------------|---------------|--------------|
| **ACS-specific comorbidities**      |                   |               |              |
| Metabolic immunity disorders        | 6508              | 180 515       | 74.8         | \(< 0.0001\) |
| Cardiac dysrhythm                   | 3019              | 78 351        | 32.5         | \(< 0.0001\) |
| Obesity                             | 1692              | 37 785        | 15.7         | \(< 0.0001\) |
| Hypertensive heart and chronic kidney disease | 2069              | 53 520        | 22.2         | \(< 0.0001\) |
| Stroke                              | 196               | 5299          | 2.2          | 0.0873       |
| ST-elevated myocardial infarction   | 1278              | 51 040        | 21.1         | \(< 0.0001\) |
| Coronary artery bypass graft        | 1601              | 38 376        | 15.9         | \(< 0.0001\) |
| **VTE-specific comorbidities**      |                   |               |              |
| Pneumonia                           | 245               | 3123          | 6.7          | \(< 0.0001\) |
| Other respiratory disease           | 506               | 8482          | 18.3         | 0.0704       |
| Urinary tract infection             | 227               | 3858          | 8.3          | 0.3507       |
| Sepsis                              | 72                | 800           | 1.7          | \(< 0.0001\) |

ACS, acute coronary syndrome; Anti-FXa, anticoagulant activated factor X protein; aPTT, activated partial thromboplastin time; VTE, venous thromboembolism.

For the RBC transfusion outcome, the logistic regression model reinforced the post-match unadjusted results. Anti-FXa patients were less likely to receive a transfusion than aPTT patients in the ACS (odds ratio [OR] 0.16, 95% confidence interval [CI] 0.14–0.18), STK (OR 0.41, 95% CI 0.29–0.57) and VTE (OR 0.35, 95% CI 0.26–0.48) populations (Table 6).

Within the ACS population, patients diagnosed with anemia were nearly three times more likely to receive an RBC transfusion (OR 2.80, 95% CI 2.49–3.14). Likewise, patients undergoing cardiovascular procedures, including CABG (OR 9.12, 95% CI 7.45–11.16), heart valve procedures (OR 2.04, 95% CI 1.47–2.84), other vascular catheterization procedures (OR 2.07, 95% CI 1.79–2.38), and endarterectomy (OR 1.69, 95% CI 1.02–2.81), were significantly more likely to receive a transfusion. ACS patients undergoing other (non-cardiac) surgical procedures (OR 2.78, 95% CI 2.14–3.61) and wound care (OR 1.69, 95% CI 1.12–2.56) were also more likely to require RBC transfusions, whereas diagnostic procedures such as diagnostic cardiac catheterizations (OR 0.87, 95% CI 0.76–1.00) and spinal tap (OR 0.32, 95% CI 0.13–0.83), as well as extracorporeal membrane oxygenation (ECMO) (OR 0.79, 95% CI 0.65–0.95), were associated with a significantly lower probability of requiring a transfusion (Table 6).

Among patients in the STK study population, those with anemia (OR 3.09, 95% CI 2.15–4.43), trauma (OR 1.66, 95% CI 1.14–2.41), cancer (OR 2.78, 95% CI 1.68–4.62), infectious disease (OR 1.92, 95% CI 1.27–2.92), CABG (OR 3.51, 95% CI 1.74–7.08), other heart procedures (OR 3.34, 95% CI 1.75–6.40), other surgical procedures (OR 2.32, 95% CI 1.32–4.07), and other (non-cardiac) vascular catheterization (OR 1.98, 95% CI 1.36–2.88) had significantly higher probabilities of receiving a transfusion (Table 6). Only age in years (OR 0.99, 95% CI 0.98–0.99) was significantly associated with a lower probability of transfusion (Table 6).

In the VTE population, males were more likely than females to require a RBC transfusion (OR 1.39,
95% CI 1.04–1.86), as were patients with anemia (OR 5.01, 95% CI 3.70–6.79), renal insufficiency (OR 1.65, 95% CI 1.17–2.33), prior VTE/PE (OR 1.48, 95% CI 1.04–2.10), cancer (OR 2.51, 95% CI 1.85–3.40), and trauma (OR 1.82, 95% CI 1.25–2.65). Patients who received diagnostic and therapeutic procedures, including biopsy (OR 1.81, 95% CI 1.17–2.79), chest drainage (OR 2.57, 95% CI 1.32–4.99), other (non-head or neck) vessel procedures (OR 2.40, 95% CI 1.73–3.34), and other (non-cardiac) vascular catheterization (OR 2.18, 95% CI 1.52–3.12), as well as patients receiving ECMO (OR 6.27, 95% CI 1.43–27.44), were also significantly more likely to receive a transfusion than patients who did not (Table 6).

### Post hoc analysis

Additional potential confounding factors considered after the completion of the initial protocol included the...
The modified models showed no significant changes in the associations found in the original analysis. Anti-FXa patients were still less likely to receive an RBC transfusion in the ACS (OR 0.16, 95% CI 0.14–0.18), STK (OR 0.39, 95% CI 0.27–0.55), and VTE (OR 0.34, 95% CI 0.25–0.46) populations. Mirroring results from recent studies, the modified models also indicated that patients in the ACS population were less likely to receive a transfusion in 2013 than in 2009 (OR 0.87, 95% CI 0.68–0.97).

Furthermore, sensitivity analyses were performed on dual-monitored patients by removing these patients pairwise from the study population, with no significant difference in the transfusion outcomes. In the sensitivity analysis, anti-FXa patients were less likely to receive a transfusion than aPTT patients in the ACS (OR 0.16, 95% CI 0.14–0.18), STK (OR 0.41, 95% CI 0.29–0.57) and VTE (OR 0.35, 95% CI 0.26–0.48) populations.

Discussion

The results of the study indicate a significant relationship between the use of anti-FXa levels to monitor UFH in hospitalized cardiovascular patients and a reduction in RBC transfusions as compared with similar patients monitored with aPTT. This association was most prevalent within the ACS population, specifically among patients undergoing major heart procedures. In the STK and VTE populations, anti-FXa monitoring also had a significant impact on the number of patients receiving transfusions.

The impact of a reduced need for blood transfusions could greatly lessen the risk of complications among hospitalized UFH-treated patients, as well the intensity and duration of UFH treatment [15,16]. Previous studies have found that transfusions significantly increase the risks for all types of complications and for adverse outcomes, including mortality, cardiac events (atrial fibrillation), infections (pneumonia and sepsis), renal failure, and pulmonary hypertension [15–17].

From a resource utilization perspective, transfusions have been associated with increased total hospitalization costs, driven by increased length of stay, prolonged dependence on mechanical ventilation, and treatment costs associated with the complications described previously [17–19]. The economic impact of unnecessary RBC transfusion imposes a significant burden on this patient population. Estimated incremental hospitalization costs associated with RBC transfusions range from $4408 for intraoperative transfusions to over $10 000 for postoperative transfusions [17,20]. Among stroke patients, transfusions have been shown to be significantly associated with an increased use of thrombolytic drugs and with an associated increase in resource utilization [21].

It should be noted that these results suggest only a strong association between anti-FXa use and a reduction in RBC transfusions in this population, and do not imply causation. It is likely that other factors combined with the use of the anti-FXa assay for UFH treatment play a role in the reduction in bleeding complications [22,23]. Chief among these may be that the higher level of accuracy of the anti-FXa test provides a more concrete foundation for treatment modifications, which may lead to more timely and appropriate action [2,5].

Limitations

Given the robust sample size, the demographic and geographic diversity of the patient population, and the clinical capabilities of the sample hospitals, these results can be considered to be representative of treatment patterns within the USA. However, there are some limitations of this study that warrant mention. The data source is subject to those limitations known to be associated with the use of large-scale administrative data, including inconsistent coding and billing practices, and incomplete records [24,25]. The study was also limited to the analysis of the acute inpatient hospitalizations, and did not account for all levels and settings of care required for patient management. Finally, this study does not account for the presence of any differences in hematologic expertise in the use and monitoring of anticoagulants, potentially increased vigilance for bleeding by physicians comfortable with the anti-FXa assay, hospital protocols designed to optimize anticoagulation treatment or minimize transfusions, or programs designed to minimize the loss of blood during and after major surgical procedures [22,23].

Conclusions

The use of the anti-FXa assay was associated with a significant reduction in RBC transfusions as compared with the use of aPTT. Implementation of an anticoagulation protocol based on anti-FXa monitoring could serve to reduce the need for transfusions among hospitalized cardiovascular patients, as well as associated complications.
However, to better understand the critical factors associated with UFH treatment monitoring and the role that anti-FXa plays, future studies should employ more rigorous observational or prospective methods that could address factors not included in this study, such as differences in hospital expertise.

Addendum
In addition to meeting all ICMJE requirements for authorship, specific author contributions were as follows: K.W. Belk conceptualized the study design, was responsible for implementation, and contributed to manuscript writing and editing. M. Laposata provided clinical guidance during and after study design, and editorial support during manuscript preparation. C. Craver provided statistical methods support during study design, assisted with statistical analysis, and served as the technical writer during preparation of the manuscript.

Acknowledgements
The authors would like to thank T. E. Warkentin of McMaster University and A. M. Winkler of Emory University for their clinical guidance during the editorial and review process for this study. Funding for this analysis was provided by Instrumentation Laboratory, Bedford, MA, USA.

Disclosure of Conflict of Interests
K. W. Belk and C. Craver report receiving grants from Instrumentation Laboratory, during the conduct of the study. M. Laposata sat on an advisory board and acted as a consultant for Instrumentation Laboratory, during the conduct of the study.

Supporting Information
Additional Supporting Information may be found in the online version of this article:

Table S1. Population cohort code listing.
Table S2. Comorbidities and procedure definitions.
Table S3. Disease-specific comorbidities and procedure definition.
Table S4. Post-match patient characteristics.
Table S5. Post-match patient comorbidities.
Table S6. Post-match population-specific comorbidities and procedures.

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