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ORIGINAL RESEARCH

The Practice of Emergency Medicine

Clinical and health care resource use burden of hospitalizations for oral factor Xa inhibitor-associated major bleeding: A real-world analysis of Medicare beneficiaries

James M. Williams DO[1] | Belinda Lovelace PharmD, MS[2] | Mary J. Christoph PhD, MPH[2] | Suying Li PhD[3] | Haifeng Guo MS[3] | Madison Hoover MS[3] | Craig I. Coleman PharmD[4,5]

[1]Medical Center Emergency Department, Meritus Health, Hagerstown, Maryland, USA

[2]Alexion, AstraZeneca Rare Disease, Boston, Massachusetts, USA

[3]Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, Minnesota, USA

[4]Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Connecticut, USA

[5]Evidence-based Practice Center, Hartford Hospital, Hartford, Connecticut, USA

Correspondence
James M. Williams, DO, MS, Department of Emergency Medicine, Meritus Medical Center, Hagerstown, MD 21742, USA.
Email: drjmwilliams@gmail.com

Belinda Lovelace Previous affiliation (while study and analyses were undertaken).

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Abstract

Objective: To characterize the burden of illness associated with oral factor Xa (FXa) inhibitor-related bleeding in the US Medicare population.

Methods: This retrospective cohort study used the full 20% Medicare random sample claims database to identify patients who experienced their first hospitalization for an FXa inhibitor-related major bleed between October 2013 and September 2017. Bleeding types were classified as intracranial hemorrhage (ICH), gastrointestinal (GI), and other. Associations between risk factors and outcomes (in-hospital and 30-day mortality, 30-day readmission, and discharge to a location other than home) adjusted for patient demographic characteristics, baseline clinical conditions, index event characteristics, treatment with hemostatic/factor replacement agents or transfusion (ie, usual care prereversal agent availability), multicompartment ICH and neurosurgical procedures (ICH cohort), and endoscopy (GI cohort) were assessed using multivariable regression and reported as crude incidences and adjusted odds ratios (ORs) stratified by bleed type.

Results: Of the 11,593 patients identified, 2737 (23.6%) had ICH, 8169 (70.5%) had GI bleeds, and 687 (5.9%) had other bleeds. The incidences of in-hospital mortality, 30-day mortality, need for postdischarge out-of-home care, and 30-day readmission were 15.7%, 29.1%, 78.3%, and 20.3% in the single-compartment ICH cohort, respectively; and 1.7%, 6.8%, 41.3%, and 18.8% in the GI bleeds cohort, respectively. Increased odds of both in-hospital mortality and 30-day mortality were significantly associated with: multicompartment ICH (reference, single compartment ICH; OR = 3.35 [95% confidence interval (CI): 2.41–4.66]; 2.18 [95% CI: 1.63–2.91]), loss of consciousness during index hospitalization (yes vs no; OR = 2.03 [95% CI: 1.38–2.97]; 1.49

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[95% CI: 1.11–2.02]), receiving usual care (yes vs no; OR = 1.55 [95% CI: 1.22–1.98]; 1.33 [95% CI: 1.09–1.63]) during index hospitalization, and increasing number of Elixhauser comorbidities at baseline (OR = 1.07 [95% CI: 1.03–1.10]; 1.09 [95% CI: 1.06–1.12]) in the ICH cohort; intensive care unit admission (yes vs no; OR = 1.88 [95% CI: 1.32–2.67]; 1.51 [95% CI: 1.26–1.81]), increasing number of Elixhauser comorbidities at baseline (OR = 1.12 [95% CI: 1.07–1.18]; 1.15 [1.12–1.18]), and increasing age on index date (OR = 1.04 [95% CI: 1.02–1.07]; 1.05 [95% CI: 1.04–1.07]) in the GI bleeds cohort.

Conclusions: In this large sample of Medicare patients, FXa inhibitor-related major bleeding was associated with substantial burden in terms of adverse clinical outcomes and health care resource use. Incidence of ICH was lower than GI bleeds; however, burden of illness was notably higher with ICH.

KEYWORDS
cost of illness, factor Xa inhibitors, gastrointestinal hemorrhages, intracranial hemorrhages

1 | INTRODUCTION

1.1 | Background

Within the past decade, factor Xa (FXa) inhibitors have become the preferred alternative to vitamin K antagonists, such as warfarin, for the prevention and treatment of venous thromboembolism and for the prevention of stroke in patients with non-valvular atrial fibrillation.[1–3] Current FXa inhibitors include apixaban, rivaroxaban, and edoxaban; the most prescribed FXa inhibitors in the United States are apixaban and rivaroxaban.[4] National clinical practice guidelines recommend FXa inhibitors as first-line anticoagulants over warfarin for most indications, especially among older adults with an elevated bleeding risk.[1] A study of patients in the United States enrolled in Medicare, a federal health insurance program, found that the proportion of Medicare beneficiaries using FXa inhibitors and the direct thrombin inhibitor dabigatran increased by approximately 60% from 2011 to 2019, with the number of users increasing from 0.2 million to 3.5 million.[4] Among Medicare beneficiaries, prescription volume of these direct oral anticoagulants has increased from 14.1% of all anticoagulant prescriptions in 2013 to 57.3% in 2018.[5]

1.2 | Importance

Although the risk of major bleeding is lower with FXa inhibitors compared with warfarin, as with any anticoagulant, FXa inhibitors still carry a risk of major bleeding, including intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeds.[6,7] Despite the rapid uptake of FXa inhibitors among clinician prescribers providing care to Medicare beneficiaries, there are limited nationally representative real-world data describing the burden of illness with oral FXa inhibitor-related major bleeding in this population.[8–12] In particular, there are limited data on health care resource use, both overall and by bleed subtype, as well as risk factors associated with poor outcomes, among patients hospitalized for FXa inhibitor-related bleeding.

1.3 | Goals of this investigation

The objectives of the current study were to characterize oral FXa inhibitor-associated major bleeding hospitalizations, to describe clinical outcomes and health care resource use by different bleed types, and to understand factors associated with each clinical outcome for ICH and GI bleeds in a US Medicare population.

2 | METHODS

2.1 | Study design

This retrospective cohort study used claims data from the Medicare 20% database, which the Centers for Medicare & Medicaid Services established to provide a representative random sample of 20% of all Medicare beneficiaries with simultaneous coverage of Parts A (inpatient/hospital coverage), B (outpatient/medical coverage), and D (prescription drug coverage). The entire Medicare 20% database was leveraged to identify fee-for-service beneficiaries who experienced their first hospitalization for oral FXa inhibitor-related bleeding (index event) from October 1, 2013 to September 30, 2017 (index window) (Figure S1). The index date was defined as the admission date for the major bleeding event, and the 6-month preindex date was defined as the baseline period. Patient data were collected until either death, end of Medicare Part A/B/D coverage, or December 31, 2017, whichever came first. The *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) diagnosis codes and procedure codes for index events (ICH, GI, and other bleeding) are listed in Table S1. ICD-9/10-CM codes were developed for this study based on prior bleeding algorithms and were further validated by a

clinical team.[13,14] To ensure that bleeding-related hospitalizations could be classified as major bleeding events, for GI or other bleeding events, the bleeding event was required to be the primary diagnosis. Due to the severity of ICH bleeds, ICH admission could be in any position (ie, primary or non-primary diagnosis) on a claim.

2.2 | Setting

This study included Medicare beneficiaries admitted to hospitals within the United States.

2.3 | Selection of participants

The following inclusion criteria were applied: ≥18 years of age at index event; continuous Medicare Parts A, B, and D coverage for ≥6 months before the index event; inpatient hospital admission for ICH, GI bleeding, or other bleeding; and at least 1 FXa inhibitor claim for apixaban, edoxaban, or rivaroxaban in the 6 months before the index event. Patients were excluded if: there were multiple bleeding types; pregnancy during the study period; treatment with any other oral anticoagulation, including warfarin and dabigatran in the 6 months before the index event; or the index hospitalization event was a same-day or >30-day stay. Patients taking antiplatelet drugs were not excluded.

2.4 | Exposures

Patients must have been taking apixaban, edoxaban, or rivaroxaban 6 months before index hospitalization for the major bleeding event. Oral FXa-inhibitor use was determined with National Drug Codes using the Medicare Part D prescription drug event files. Patient baseline characteristics included age on index date, sex, race, region, Medicare/Medicaid dual-eligibility status, index year, comorbidities (in 6 months before the index event; Elixhauser Comorbidity Index [total number of Elixhauser conditions], deep vein thrombosis [DVT]/pulmonary embolism [PE], and atrial fibrillation), and index hospitalization characteristics.

2.5 | Outcomes

Clinical and health care resource use outcomes included in-hospital mortality, 30-day postindex date mortality (including in-hospital mortality), length of stay, all-cause 30-day readmission among living discharged patients, and discharge status. Discharge status from the index hospitalization was determined from Patient Discharge Status Codes (Table S1).

2.6 | Data analysis

For patient baseline characteristics, numbers and percentages were reported for categorical variables and means and SDs or medians and interquartile range were reported for continuous variables. The mean, SD, median, and interquartile range for length of stay for index hospitalization and readmission were also reported. *P* values were reported for comparing differences between bleed types using the chi-square test for categorical variables and the *F*-test for continuous variables. For adjusted analyses, 12 multivariate logistic regression models were performed for the 4 different clinical and health care resource use outcomes and for ICH, GI bleeds, and other bleed types, respectively. Analyses were adjusted for patient demographic characteristics (age, sex, race, and index year), baseline clinical conditions (Elixhauser index, DVT/PE, and atrial fibrillation), index event characteristics (trauma status, ICU status, length of stay, loss of consciousness), if patients received treatment with hemostatic/factor replacement agents or transfusion (usual care prereversal agent availability, wherein usual care was defined as receiving any of the following: 4-factor prothrombin complex concentrate, factor VIII inhibitor bypassing activity, recombinant factor VIIa, transfusion, packed red blood cells, fresh frozen plasma, vitamin K, desmopressin acetate), multicompartment ICH and neurosurgical procedures for the ICH cohort, and whether patients underwent endoscopy for the GI cohort. Associations between bleed types and outcomes were reported as crude incidences and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using SAS version 9.4 (SAS, Cary, NC, USA).

All patient data were deidentified and in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. Thus, our study was deemed exempt from institutional review board oversight. The preparation of the study report was done in accordance with the Reporting of studies Conducted using Observational Routinely collected health Data statement for Pharmacoepidemiology (RECORD-PE) statement.[15]

The Bottom Line

Although oral factor Xa (FXa) inhibitor is widely used, the burden of illness associated with FXa-inhibitor-related bleeding is unknown. This analysis using the 20% Medicare sample identified bleeding in 11,593 FXa users, including 23.6% intracranial hemorrhage, 70.5% gastrointestinal bleeds, and 5.9% other bleeds. FXa inhibitor-related major bleeding was associated with increased adverse clinical outcomes and health care resource use.

3 | RESULTS

3.1 | Demographics and clinical characteristics

The 2013–2017 20% Medicare random sample contained data on 301,134 patients with first bleeding occurring between October 1, 2013 and September 30, 2017. Of these, a total of 11,593 patients

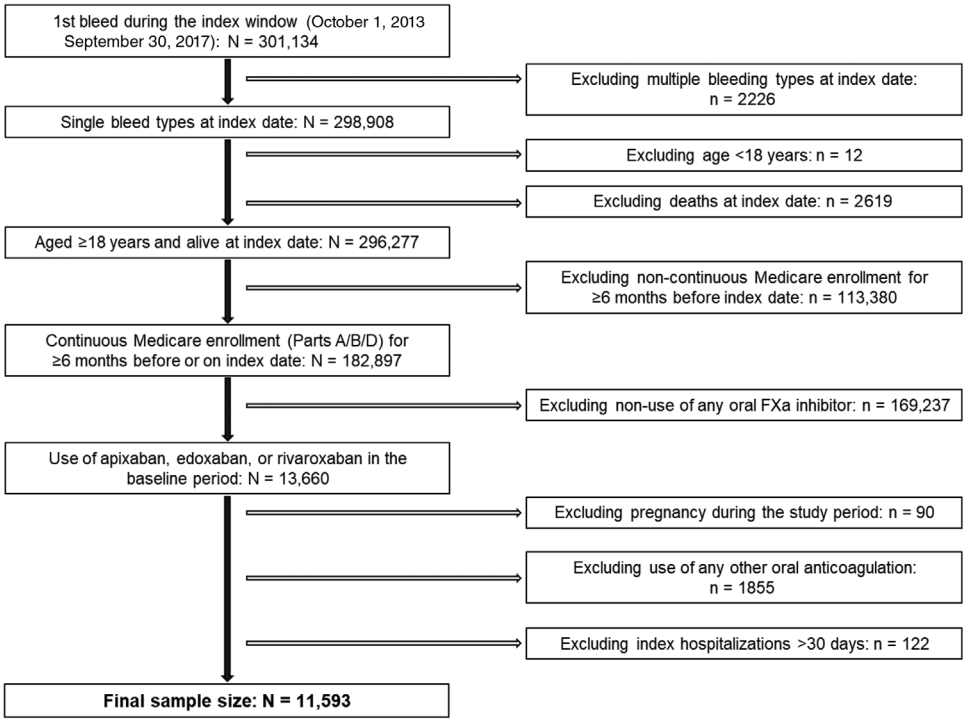

FIGURE 1 Patient selection. Abbreviation: FXa, factor Xa.

were eligible for inclusion in this analysis (Figure 1): 2464 (21.3%) patients had single-compartment ICH; 273 (2.4%) had multicompartment ICH; 8169 (70.5%) had GI bleeds; and 687 (5.9%) had other types of bleeds (Table 1). Mean (SD) age was 78.5 (9.5) years and 42.6% were male. Patients with ICH had fewer Elixhauser conditions compared with patients with GI or other types of bleeds (median 4 vs 5 and 5, respectively). Patients with ICH had a lower prevalence of history of DVT/PE (in 6 months before the index event) compared with patients with GI or other types of bleeds (single-compartment ICH, 20.1% and multicompartment ICH, 18.3% vs 24.0% and 25.6%, respectively). History of atrial fibrillation was prevalent across all bleed types and particularly high in those with ICH; however, differences were not statistically significant. Multicompartment ICH and other types of bleeds were more likely to be characterized as traumatic (70.3% and 71.6%, respectively; included procedure-related bleeds) than single-compartment ICH (43.0%) and GI bleeds (1.7%).

Among the 2464 patients with single-compartment ICH, 1,262 (51.2%) were other types of ICH (primarily intracerebral or other bleeds [unspecified intracranial, extradural, or epidural bleeds]), 409 (16.6%) were subarachnoid hemorrhage (SAH), and 793 (32.2%) were subdural hematoma (SDH; Table S2). Patients with SAH (72.1%) and SDH (75.3%) were more likely to be characterized as traumatic compared with patients with intracerebral or other types of ICH (13.2%).

3.2 | Patient discharge disposition from index hospitalization

Among the 11,593 index major bleeding events, 626 (5.4%) patients died during hospitalization. Rates of in-hospital mortality were 15.7%, 28.9%, 1.7%, and 3.2% for single-compartment ICH, multicompartment ICH, GI bleeds, and other types of bleeds, respectively (Table 2). Patients with ICH who survived initial hospitalization were more likely to be discharged to another hospital, skilled nursing facility, or rehabilitation facility and less likely to be discharged home or to a home health agency compared with patients with GI or other types of bleeds (Table 2).

3.3 | Crude incidences

The rate of 30-day mortality, including those who died during the index hospitalization, was 12.3% in the overall study population and 29.1%, 39.2%, 6.8%, and 6.6% for patients with single-compartment ICH, multicompartment ICH, GI bleeds, and other types of bleeds, respectively (Table 3). Among living discharged patients, the mean (SD) length of stay of index hospitalization was 7.4 (5.2), 8.2 (6.4), 5.4 (3.1), and 6.0 (3.7) days for single-compartment ICH, multicompartment ICH, GI bleeds, and other types of bleeds, respectively; all-cause 30-day readmission rates were 20.3%, 18.0%, 18.8%, and 19.7%, respectively.

3.4 | Adjusted odds ratios

3.4.1 | ICH cohort

Upon multivariable regression analysis, the adjusted odds for in-hospital mortality (OR = 3.35 [95% CI: 2.41–4.66]) and 30-day mortality (OR = 2.18 [95% CI: 1.63–2.91]) were statistically significantly higher among patients with multicompartment ICH compared with

TABLE 1 Patient demographics and baseline characteristics.

	Total	Single-compartment ICH	Multicompartment ICH[a]	GI bleeds	Other bleeds	*P* value[‡]
Overall *N* (%)	11,593	2464 (21.3)	273 (2.4)	8169 (70.5)	687 (5.9)	
Age, mean (SD), years	78.5 (9.5)	79.3 (9.1)	79.8 (9.0)	78.4 (9.5)	75.7 (11.3)	<0.0001
Sex, *n* (%)	<0.0001					
Male	4933	1110 (45.0)	117 (42.9)	3366 (41.2)	340 (49.5)	
Female	6660	1354 (55.0)	156 (57.1)	4803 (58.8)	347 (50.5)	
Race, *n* (%)	<0.0001					
White	9940	2098 (85.1)	244 (89.4)	6994 (85.6)	604 (87.9)	
Black	1098	188 (7.6)	11 (4.0)	849 (10.4)	50 (7.3)	
Other	555	178 (7.2)	18 (6.6)	326 (4.0)	33 (4.8)	
Region, *n* (%)[b]	<0.0001					
Northeast	2358	480 (19.5)	58 (21.2)	1628 (19.9)	192 (27.9)	
Midwest	2550	480 (19.5)	66 (24.2)	1859 (22.8)	145 (21.1)	
South	5098	1093 (44.4)	109 (39.9)	3655 (44.7)	241 (35.1)	
West	1582	411 (16.7)	40 (14.7)	1022 (12.5)	109 (15.9)	
Insurance type, *n* (%)	0.0003					
Medicare only	8694	1909 (77.5)	216 (79.1)	6034 (73.9)	535 (77.9)	
Dual Medicare/Medicaid	2899	555 (22.5)	57 (20.9)	2135 (26.1)	152 (22.1)	
Index year, *n* (%)	<0.0001					
October 1, 2013 to December 31, 2015	4866	983 (39.9)	76 (27.8)	3587 (43.9)	220 (32.0)	
January 1, 2016 to September 30, 2017	6727	1481 (60.1)	197 (72.2)	4582 (56.1)	467 (68.0)	
Baseline conditions						
Elixhauser Comorbidity Index	<0.0001					
Mean (SD)	5.6 (3.5)	4.9 (3.3)	4.6 (3.2)	5.8 (3.5)	5.8 (3.5)	
Median (IQR)	5.0 (3.0, 8.0)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	5.0 (3.0, 8.0)	5.0 (3.0, 8.0)	
DVT/PE, *n* (%)	2681	496 (20.1)	50 (18.3)	1959 (24.0)	176 (25.6)	<0.0001
Atrial fibrillation, *n* (%)	8818	1896 (76.9)	215 (78.8)	6196 (75.8)	511 (74.4)	0.3311
Index hospitalization characteristics, *n* (%)						
Trauma-related bleed	1884	1059 (43.0)	192 (70.3)	141 (1.7)	492 (71.6)	<0.0001
ICU admission	5433	1760 (71.4)	211 (77.3)	3241 (39.7)	221 (32.2)	<0.0001
Loss of consciousness—for ICH	389	321 (13.0)	68 (24.9)	–	–	<0.0001
Neurosurgical procedures—for ICH	946	767 (31.1)	179 (65.6)	–	–	<0.0001
Endoscopy—for GI	3537	–	–	3537 (43.3)	–	–
Intubation	399	257 (10.4)	52 (19.0)	79 (1.0)	11 (1.6)	<0.0001
Usual care for index bleed event, *n* (%)[c]	4598	607 (24.6)	81 (29.7)	3737 (45.7)	173 (25.2)	<0.0001

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; DVT, deep vein thrombosis; FEIBA, factor VIII inhibitor bypassing activity; GI, gastrointestinal; ICH, intracranial hemorrhage; IQR, interquartile range; PE, pulmonary embolism; rVIIa, recombinant factor VIIa.

[a]Multicompartment ICH included ICH bleeds in different sites in the same event.

[b]Missing region excluded.

[c]Usual care included use of 4F-PCC, FEIBA, rFVIIa, transfusion, packed red blood cells, fresh frozen plasma, vitamin K, and desmopression acetate.

[‡]*P* value to compare between single-compartment ICH, multicompartment ICH, GI, and other.

single-compartment ICH (Table 4). Adjusted ORs for both in-hospital mortality and 30-day mortality were significantly higher with increasing number of Elixhauser comorbidities at baseline (OR = 1.07 [95% CI: 1.03–1.10] and 1.09 [95% CI: 1.06–1.12]), loss of consciousness during the index hospitalization (OR = 2.03 [95% CI: 1.38–2.97] and 1.49 [95% CI: 1.11–2.02]), and in patients who received usual care agents or transfusion (OR = 1.55 [95% CI: 1.22–1.98] and 1.33 [95% CI: 1.09–1.63]). Adjusted ORs for both in-hospital mortality and 30-day mortality were significantly lower with traumatic (vs non-traumatic) bleeding events (OR = 0.20 [95% CI: 0.14–0.28] and 0.27 [95% CI: 0.21–0.35]) and longer hospital index length of stay (3–5 days [vs 1–2 days], OR = 0.21 [95% CI: 0.16–0.29] and 0.23 [95% CI: 0.18–0.31]; ≥6 days

TABLE 2 Patient discharge disposition from index hospitalization.

	Total	Single-compartment ICH	Multicompartment ICH	GI bleeds	Other bleeds	*P value*
Patients, *N*	11,593	2464	273	8169	687	
In-hospital death, *n* (%)	626 (5.4)	388 (15.7)	79 (28.9)	137 (1.7)	22 (3.2)	<0.0001
Other hospital, *n* (%)	297 (2.6)	100 (4.1)	18 (6.6)	164 (2.0)	15 (2.2)	<0.0001
Skilled nursing facility, *n* (%)[a]	2359 (20.3)	657 (26.7)	53 (19.4)	1490 (18.2)	159 (23.1)	<0.0001
Rehabilitation facility, *n* (%)	576 (5.0)	380 (15.4)	40 (14.7)	125 (1.5)	31 (4.5)	<0.0001
Home/home health agency, *n* (%)	7,291 (62.9)	718 (29.1)	62 (22.7)	6062 (74.2)	449 (65.4)	<0.0001
Others, *n* (%)[b]	444 (3.8)	221 (9.0)	21 (7.7)	191 (2.3)	11 (1.6)	<0.0001

Abbreviations: GI, gastrointestinal; ICH, intracranial hemorrhage.
[a]Including long-term care facility.
[b]Such as hospice, another institution for outpatient services as specified by the discharge plan of care, or another type of health care institution not defined elsewhere in the code list.

TABLE 3 Unadjusted clinical and health care resource use outcomes by bleed type.

	Overall	Single-compartment ICH	Multicompartment ICH	GI bleeds	Other bleeds	*P*
Total, *N*	11,593	2464	273	8169	687	
Index hospitalization						
ICU, *n* (%)	5433 (46.9)	1760 (71.4)	211 (77.3)	3241 (39.7)	221 (32.2)	<0.0001
LOS, mean (SD), days	5.9 (3.9)	7.1 (5.2)	7.7 (6.1)	5.4 (3.1)	6.0 (3.7)	<0.0001
LOS, median (IQR), days	5.0 (4.0, 7.0)	5.0 (4.0, 9.0)	5.0 (4.0, 10.0)	5.0 (4.0, 6.0)	5.0 (3.0, 7.0)	
Mortality						
In-hospital death, *n* (%)	626 (5.4)	388 (15.7)	79 (28.9)	137 (1.7)	22 (3.2)	<0.0001
30-day mortality, *n* (%)[a]	1,427 (12.3)	716 (29.1)	107 (39.2)	559 (6.8)	45 (6.6)	<0.0001
Living discharged patients, *n*	10,967	2076	194	8032	665	
Index hospitalization						
ICU, *n* (%)	4992 (45.5)	1472 (70.9)	150 (77.3)	3165 (39.4)	205 (30.8)	<0.0001
LOS, mean (SD), days	5.9 (3.8)	7.4 (5.2)	8.2 (6.4)	5.4 (3.1)	6.0 (3.7)	<0.0001
LOS, median (IQR), days	5.0 (4.0, 7.0)	6.0 (4.0, 9.0)	6.0 (4.0, 11.0)	5.0 (4.0, 6.0)	5.0 (3.0, 7.0)	
Discharge status						
Discharge to other facility, *n* (%)[b]	5464 (49.8)	1626 (78.3)	150 (77.3)	3319 (41.3)	369 (55.5)	<0.0001
Discharge to home, *n* (%)	5503 (50.2)	450 (21.7)	44 (22.7)	4713 (58.7)	296 (44.5)	<0.0001
Readmission in 30 days, *n* (%)	2098 (19.1)	422 (20.3)	35 (18.0)	1510 (18.8)	131 (19.7)	0.4271
Readmission LOS, mean (SD), days	7.8 (5.8)	8.8 (6.7)	8.4 (6.8)	7.5 (5.5)	8.2 (6.0)	0.0003
Readmission LOS, median (IQR), days	6.0 (4.0, 10.0)	7.0 (4.0, 11.0)	6.0 (4.0, 10.0)	6.0 (4.0, 10.0)	6.0 (4.0, 11.0)	

Abbreviations: GI, gastrointestinal; ICH, intracranial hemorrhage; IQR, interquartile range; LOS, length of stay;.
[a]Including hospital death.
[b]Includes other hospital, nursing facility, rehabilitation, hospice, home health, and others.

[vs 1–2 days], OR = 0.13 [95% CI: 0.09–0.17] and 0.21 [95% CI: 0.16–0.28]). An ICU admission was associated with higher risk of in-hospital mortality (OR = 1.45 [95% CI: 1.12–1.87]). Female sex was associated with lower risk of 30-day mortality (OR = 0.82 [95% CI: 0.69–0.98]).

The adjusted OR for 30-day readmission was significantly higher with increasing number of Elixhauser comorbidities at baseline. The adjusted ORs for discharge to a location other than home were significantly higher with increasing age, female sex, increasing number of Elixhauser comorbidities at baseline, longer hospital index length of stay, and in patients who received usual care; adjusted OR for discharge to a location other than home was significantly lower with traumatic bleeding events.

TABLE 4 Adjusted clinical and health care resource use outcomes: ICH cohort.

	In-hospital mortality OR (95% CI)	30-day mortality OR (95% CI)	30-day readmission OR (95% CI)	Discharge to a location other than home OR (95% CI)
Index hospitalization bleeding type				
Single-compartment ICH (reference)	1.00	1.00	1.00	1.00
Multicompartment ICH	**3.35 (2.41, 4.66)**	**2.18 (1.63, 2.91)**	0.85 (0.57, 1.27)	1.09 (0.73, 1.64)
Demographics				
Age on index date, years	1.00 (0.99, 1.02)	**1.03 (1.02, 1.04)**	1.00 (0.99, 1.01)	**1.05 (1.04, 1.07)**
Female (male as reference)	0.82 (0.66, 1.03)	**0.82 (0.69, 0.98)**	0.92 (0.74, 1.13)	**1.43 (1.14, 1.79)**
White (non-white as reference)	**0.68 (0.51, 0.91)**	1.00 (0.78, 1.28)	0.77 (0.57, 1.02)	0.89 (0.63, 1.26)
Index year as a continuous variable	0.97 (0.87, 1.07)	1.02 (0.94, 1.11)	0.99 (0.90, 1.09)	0.99 (0.89, 1.09)
Baseline conditions				
Elixhauser index	**1.07 (1.03, 1.10)**	**1.09 (1.06, 1.12)**	**1.08 (1.05, 1.12)**	**1.12 (1.07, 1.16)**
DVT/PE (yes vs no)	0.82 (0.59, 1.14)	0.96 (0.74, 1.23)	0.76 (0.56, 1.02)	0.85 (0.61, 1.18)
Atrial fibrillation (yes vs no)	**1.45 (1.00, 2.11)**	0.96 (0.72, 1.28)	0.84 (0.61, 1.18)	**0.69 (0.49, 0.98)**
Index hospitalization characteristics				
Trauma (non-trauma as reference)	**0.20 (0.14, 0.28)**	**0.27 (0.21, 0.35)**	1.10 (0.84, 1.44)	**0.51 (0.38, 0.68)**
ICU (yes vs no)	**1.45 (1.12, 1.87)**	1.20 (0.98, 1.47)	1.01 (0.80, 1.29)	1.13 (0.89, 1.44)
Loss of consciousness (yes vs no)	**2.03 (1.38, 2.97)**	**1.49 (1.11, 2.02)**	1.05 (0.76, 1.46)	1.07 (0.78, 1.46)
LOS, days				
1–2 (as reference)	1.00	1.00	1.00	1.00
3–5	**0.21 (0.16, 0.29)**	**0.23 (0.18, 0.31)**	1.11 (0.71, 1.73)	**1.86 (1.32, 2.63)**
≥6	**0.13 (0.09, 0.17)**	**0.21 (0.16, 0.28)**	1.55 (1.00, 2.41)	**9.71 (6.58, 14.33)**
Usual care (yes vs no)[a]	**1.55 (1.22, 1.98)**	**1.33 (1.09, 1.63)**	0.98 (0.77, 1.26)	**1.36 (1.02, 1.80)**
Procedure (yes vs no)	1.06 (0.79, 1.44)	1.04 (0.82, 1.32)	1.11 (0.86, 1.43)	1.10 (0.84, 1.45)

Note: **Bold text** indicates significant values.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; CI, confidence interval; DVT, deep vein thrombosis; FEIBA, factor VIII inhibitor bypassing activity; ICH, intracranial hemorrhage; LOS, length of stay; OR, odds ratio; PE, pulmonary embolism; rVIIa, recombinant factor VIIa.

[a]Patients who received therapy with 4F-PCC, FEIBA, rFVIIa, transfusion, packed red blood cells, fresh frozen plasma, vitamin K, and desmopression acetate.

3.4.2 | GI bleed cohort

Among patients with GI bleeds, adjusted ORs for both in-hospital mortality and 30-day mortality were significantly higher with increasing age (OR = 1.04 [95% CI: 1.02–1.07] and 1.05 [95% CI: 1.04–1.07]), increasing number of Elixhauser comorbidities at baseline (OR = 1.12 [95% CI: 1.07–1.18] and 1.15 [95% CI: 1.12–1.18]), and ICU admission (OR = 1.88 [95% CI: 1.32–2.67] and 1.51 [95% CI: 1.26–1.81]; Table 5). Adjusted ORs for both in-hospital mortality and 30-day mortality were significantly lower with longer hospital index length of stay (3–5 days

TABLE 5 Adjusted clinical and health care resource use outcomes: GI bleed cohort.

	In-hospital mortality OR (95% CI)	30-day mortality OR (95% CI)	30-day readmission OR (95% CI)	Discharge to a location other than home OR (95% CI)
Demographics				
Age on index date, years	**1.04 (1.02, 1.07)**	**1.05 (1.04, 1.07)**	**0.99 (0.99, 1.00)**	**1.05 (1.04, 1.06)**
Female (male as reference)	0.79 (0.56, 1.13)	0.90 (0.75, 1.08)	1.11 (0.99, 1.26)	1.47(1.32, 1.62)
White (non-white as reference)	0.78 (0.50, 1.23)	1.19 (0.92, 1.55)	0.96 (0.82, 1.12)	1.01 (0.88, 1.17)
Index year as a continuous variable	1.05 (0.90, 1.23)	1.00 (0.92, 1.08)	0.99 (0.94, 1.04)	1.00 (0.96, 1.05)
Baseline conditions				
Elixhauser index	**1.12 (1.07, 1.18)**	**1.15 (1.12, 1.18)**	**1.10 (1.09, 1.12)**	**1.16 (1.14, 1.18)**
DVT/PE (yes vs no)	1.50 (0.98, 2.30)	1.31 (1.05, 1.65)	1.09 (0.93, 1.27)	1.24 (1.08, 1.42)
Atrial fibrillation (yes vs no)	0.85 (0.51, 1.42)	0.73 (0.56, 0.96)	1.02 (0.85, 1.23)	0.72 (0.62, 0.85)
Index hospitalization characteristics				
Trauma (non-trauma as reference)	0.90 (0.21, 3.75)	0.34 (0.11, 1.10)	0.48 (0.28, 0.85)	0.69 (0.45, 1.05)
ICU (yes vs no)	**1.88 (1.32, 2.67)**	**1.51 (1.26, 1.81)**	1.01 (0.90, 1.14)	**1.28 (1.16, 1.42)**
LOS, days				
1–2 (as reference)				
3–5	**0.18 (0.11, 0.30)**	**0.40 (0.29, 0.56)**	1.27 (0.97, 1.67)	**1.37 (1.09, 1.72)**
≥6	**0.28 (0.17, 0.46)**	0.88 (0.63, 1.23)	**1.70 (1.28, 2.25)**	**4.49 (3.55, 5.68)**
Usual care (yes vs no)[a]	**1.85 (1.29, 2.66)**	1.13 (0.94, 1.36)	1.02 (0.91, 1.15)	**1.11 (1.01, 1.23)**
Endoscopy (yes vs no)	**0.44 (0.29, 0.66)**	**0.56 (0.46, 0.68)**	0.97 (0.86, 1.08)	**0.75 (0.68, 0.83)**

Notes: **Bold text** indicates significant values.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; CI, confidence interval; DVT, deep vein thrombosis; FEIBA, factor VIII inhibitor bypassing activity; GI, gastrointestinal; LOS, length of stay; OR, odds ratio; PE, pulmonary embolism; rVIIa, recombinant factor VIIa.

[a]Patients who received therapy with 4F-PCC, FEIBA, rFVIIa, transfusion, packed red blood cells, fresh frozen plasma, vitamin K, and desmopression acetate.

[vs 1–2 days], OR = 0.18 [95% CI: 0.11–0.30] and 0.40 [95% CI: 0.29–0.56]) and in patients who underwent an endoscopy (OR = 0.44 [95% CI: 0.29–0.66] and 0.56 [95% CI: 0.46–0.68]). Usual care was associated with higher risk of in-hospital mortality (OR = 1.85 [95% CI: 1.29–2.66]), whereas DVT/PE at baseline was associated with higher risk of 30-day mortality (OR = 1.31 [95% CI: 1.05–1.65]).

The adjusted OR for 30-day readmission was significantly higher with increasing number of Elixhauser comorbidities at baseline and longer hospital index length of stay (≥6 days) and significantly lower with traumatic events. The adjusted ORs for discharge to a location other than home were significantly higher with increasing age, female sex, increasing number of Elixhauser comorbidities at baseline, DVT/PE at baseline, ICU admission, longer hospital index length of stay, and in patients who received usual care; adjusted OR for discharge to a location other than home was significantly lower in patients who underwent an endoscopy.

3.4.3 | Other types of bleed cohort

One in 5 bleeds in the other bleeds category was described as a "non-traumatic hematoma of soft tissue," and most of the remaining

bleeding codes were reflective of critical compartment bleeds or procedural complications (Table S3). Among patients with other types of bleeds, adjusted ORs for both in-hospital mortality and 30-day mortality were significantly higher with ICU admission (OR = 7.76 [95% CI: 2.75–21.87] and 4.07 [95% CI: 2.05–8.08]; Table S4). Increasing number of Elixhauser comorbidities at baseline was associated with higher risk of 30-day mortality (adjusted OR = 1.17 [95% CI: 1.06–1.29]). The adjusted OR for 30-day readmission was significantly higher with increasing number of Elixhauser comorbidities at baseline. The adjusted ORs for discharge to a location other than home were significantly higher with increasing age, female sex, increasing number of Elixhauser comorbidities at baseline, and longer hospital index length of stay (3–5 days).

4 | LIMITATIONS

This study had some limitations. This study used a retrospective cohort design and was based on routinely collected claims data, which are subject to misclassification bias. FXa inhibitor-related major bleeding events were defined using inpatient claims and ICD-9/10-CM diagnosis codes based on a combination of 2 previously validated schema for identifying major bleeding in anticoagulated patients, with high sensitivity and specificity above 90% for ICD-10 codes.[13,14] Our use of these validated coding schema thereby minimized the risk of misclassification. To address the risk of confounding bias, our analysis performed multivariable logistic regression modeling using several important baseline covariates. The severity variables included in the analysis (eg, ICU admission, intubation, receiving usual care treatments or transfusion) could only serve as surrogates of severity since specific measures, such as bleed size, could not be analyzed due to limitations of the claims data. Upper and lower GI bleeds are associated with varying risk of mortality,[16,17] a small percentage of GI bleeds were related to trauma, and the non-ICH, non-GI other bleeds cohort was composed of many different bleed subtypes with varying severities; the low numbers of each subtype precluded statistical analysis for this subgroup and robust conclusions. Additionally, preadmission residential situation was unknown, and it is possible that patients who were discharged to nursing homes were also residing in nursing homes before the major bleeding event. Lastly, the study findings represent outcomes in Medicare fee-for-service beneficiaries and might not be generalizable to other populations.

5 | DISCUSSION

This real-world analysis characterized the clinical outcomes and health care resource use associated with oral FXa inhibitor-related major bleeds within a nationally representative US Medicare population. GI bleeds were most common, accounting for nearly three quarters of all bleeding-related hospitalizations, ICH accounted for about one quarter of all bleeding-related hospitalizations, and other bleeds made up the remaining 6%. ICH was associated with higher mortality and morbidity compared with GI bleeds and other bleed types.

In both ICH and GI bleeds, variables measuring or indicating the severity of the index hospitalizations were significant predictors of in-hospital and 30-day mortality. Patients with multicompartment ICH had higher odds of mortality compared to patients with single-compartment ICH. Variables associated with higher odds of in-hospital or 30-day mortality for ICH included comorbidities, receiving usual care interventions, and loss of consciousness. For GI and other bleeds, increased age, ICU admission, comorbidities, and DVT/PE were related to higher odds of in-hospital or 30-day mortality.

Readmission rates were similar across all bleed types, with almost 1 in 5 patients being readmitted within 30 days regardless of bleed type, and a higher number of comorbidities associated with an increased risk of readmission. These results should be interpreted in the context of potential survival bias, with patients with GI and other bleeds being more likely to survive to 30 days compared to ICH.

For all types of bleeds, we found that older age, female sex, a higher number of comorbidities, and longer duration of index hospitalization were associated with a higher probability of discharge to a location other than home. This may imply that these risk factors relate to the need for more institutionalized services after discharge from the index hospitalization and potentially extending the health care resource use burden. The results of this study are consistent with another real-world study of bleeding-related hospitalizations in patients with atrial fibrillation, in which ICH was associated with higher odds of in-hospital mortality, longer hospitalization length of stay, and need for postdischarge out-of-home care versus GI bleeding.[18] Previous studies have shown that discharge destination can provide highly predictive values and likelihood ratios for death and disability in patients with ICH.[19,20] Prior research has also found poor functional trajectories for patients entering nursing facilities after an acute hospitalization.[17] Poor functional outcomes contribute to high health care resource use even compared to other bleeding events, with 1 study finding that all-cause health care costs were $34,522 higher per ICH patient compared to GI bleed patients in the year after the bleeding event.[21]

In conclusion, in a large sample of 11,593 Medicare patients experiencing major bleeding events in the presence of FXa inhibitors, rates of 30-day mortality were 29.1% (single-compartment ICH), 39.2% (multicompartment ICH), 6.8% (GI), and 6.6% (other types of bleeds). Health care resource use was substantial, with 22% (GI bleeds) to 46% (single-compartment ICH) of patients being discharged to skilled nursing, rehabilitation, or acute care facilities. Across all bleed types, approximately 1 in 5 patients were readmitted within 30 days. Major bleeding associated with FXa inhibitors corresponds to substantial morbidity and mortality and clinical costs to the US health care system.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Suying Li, Haifeng Guo, Madison Hoover. Obtained funding: not applicable. Study supervision: James M. Williams, Belinda Lovelace, Mary J. Christoph, Suying Li, Craig I. Coleman.

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CONFLICT OF INTEREST STATEMENT

J.M.W. has received consulting honoraria from Janssen and AstraZeneca. B.L. is a former employee of Alexion, AstraZeneca Rare Disease. M.J.C. is an employee of Alexion, AstraZeneca Rare Disease. C.I.C. has received research funding and/or consulting honoraria from Janssen Scientific Affairs, LLC, Bayer AG, and Alexion, AstraZeneca Rare Disease. S.L., H.G., and M.H. have no conflicts of interest.

ORCID

James M. Williams DO https://orcid.org/0000-0001-8417-040X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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AUTHOR BIOGRAPHY

James M. Williams, DO, MS, is a clinical professor and physician in the Department of Emergency Medicine at Meritus Medical Center in Hagerstown, Maryland.