Costs and Healthcare Resource Utilization Associated with Idarucizumab or Andexanet Alfa Oral Anticoagulant Reversal in Patients Hospitalized with Life-Threatening Bleeds

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Abstract

Purpose: To assess costs and healthcare resource utilization (HCRU) associated with the use of idarucizumab for the reversal of dabigatran and andexanet alfa for the reversal of direct oral Factor Xa inhibitors. **Methods:** This retrospective study utilizing Premier Healthcare Database (PHD) included patients aged ≥18 years on direct oral anticoagulants (DOACs) who experienced life-threatening bleeds, discharged from the hospital during 5/1/2018–6/30/2019, and received idarucizumab or andexanet alfa. Inverse of treatment probability weighting (IPTW) method was used to balance patient and clinical characteristics between treatment cohorts. **Results:** Idarucizumab patients were older than andexanet alfa patients (median age 81 vs 77 years; p < 0.001), and less likely to experience intracranial hemorrhage (ICH) (37.1%vs 73.8%; p = 0.001). After IPTW adjustment, idarucizumab patients incurred lower mean total hospital costs ($30,413 ± $33,028 vs $44,477 ± $30,036; p < 0.001),and mean intensive care unit (ICU) cost ($25,114 ± $30,433 vs $43,484 ± $29,335; p < 0.001). **Conclusions:** Anticoagulant reversal therapy with idarucizumab was associated with significantly lower adjusted mean total hospital and ICU costs compared with andexanet alfa. However, a higher prevalence of ICH bleeds was noted in the andexanet alfa group. **Trial Registration:** Not applicable.

Keywords

anticoagulation, reversal, healthcare resource utilization, cost, idarucizumab, andexanet alfa

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Plain Language Summary

The costs and utilization of healthcare resources comparing two strategies used for reversing the anticoagulant effects of direct oral anticoagulants (DOACs) is unknown. Idarucizumab is a specific reversal agent for the DOAC dabigatran, and andexanet alpha is a specific reversal agent for the DOACs rivaroxaban and apixaban. We retrospectively measured the costs and healthcare resource utilization (HCRU) of a large healthcare database (Premier) in the US in patients aged ≥18 years on chronic DOACs discharged from the hospital during 5/1/2018–6/30/2019 who experienced a life-threatening bleed and who received the reversal agents idarucizumab or andexanet alfa. The results showed that length of stay (LOS) measures did not differ significantly between patient cohorts and that anticoagulant reversal therapy with idarucizumab was associated with significantly lower total hospital and ICU costs compared with andexanet alfa. However, a higher prevalence of ICH bleeds was noted in the andexanet alfa group.

Introduction

The past decade has witnessed the increased use of direct oral anticoagulation (DOAC) to prevent stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for venous thromboembolism (VTE).[1–3] The Food and Drug Administration (FDA) approved the oral direct thrombin inhibitor, dabigatran, for these indications in October 2010, and the oral direct Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban were similarly approved in 2011, 2014, and 2015, respectively.[3] Outpatient prescriptions for these oral anticoagulants have outpaced those for warfarin, reflecting their ease of use, predictable pharmacokinetics, and favorable benefit-risk profile to prevent embolic events.[1–4] Compared to warfarin, DOACs require no monitoring and less follow-up, have fewer drug and food interactions, and provide rapid onset and offset.[1] Notably, they are associated with lower risk for a major bleed.[4] While most bleeding can be managed by discontinuing the DOAC along with supportive measures, life-threatening bleeds such as gastrointestinal and ICH, require a more specific approach.[5] Prior to FDA-approved reversal agents, DOAC users relied on non-specific reversal strategies such as prothrombin complex concentrates, fresh frozen plasma, and cryoprecipitate.[5]

On October 16, 2015, Idarucizumab (Praxbind®, Boehringer Ingelheim Pharmaceutical Inc) received FDA approval as a specific reversal agent for dabigatran (Pradaxa®, Boehringer Ingelheim Pharmaceutical Inc). It is a humanized monoclonal antibody fragment that rapidly and effectively reverses anticoagulant activity by neutralizing free dabigatran and thrombin-bound dabigatran.[6] Its binding affinity is approximately 350 times greater than the binding affinity of dabigatran for thrombin.[7] No relevant safety issues have been identified.[6] On May 3, 2018, the FDA granted accelerated approval to coagulation factor Xa (recombinant), inactivated-zhzo [andexanet alfa (Andexxa®, Portola Pharmaceuticals, Inc)] for reversal of the Factor Xa inhibitors rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc) and apixaban

(Eliquis®, Bristol-Myers Squibb Company). It is a recombinant and inactive form of Factor Xa with a strong binding affinity to sequester rivaroxaban or apixaban and inhibit its binding to native Factor Xa.[8,9] The availability of native Factor Xa permits normal enzymatic activity of prothrombin activation.[4]

Most of the published information available on idarucizumab and andexanet alfa comes from clinical trials.[6,10] A recent publication by Spyropoulos *et al* compared the HCRU and costs between patients treated with idarucizumab for the reversal of dabigatran and those treated with prothrombin complex concentrate for the reversal of warfarin.[11] However, to date, there appears to be no published literature in real-world settings directly comparing the management of major bleeding with specific antidotes to reverse anticoagulation with dabigatran and apixaban/rivaroxaban, respectively. This study utilized a geographically diverse administrative hospital database to address this gap; examine patient, hospital, and clinical characteristics; and determine cost outcomes and hospital resource utilization (HRU) among NVAF and VTE patients admitted to the hospital for life-threatening bleeds.

Materials/Methods

Study Design and Data Source

This was a retrospective observational study utilizing the Premier Healthcare Database (PHD) to characterize hospitalized patients with life-threatening bleeds treated with idarucizumab or andexanet alfa to reverse anticoagulation with dabigatran or apixaban/rivaroxaban, respectively, and to compare cost, LOS, and intensive care unit (ICU) utilization between patients receiving the two reversal agents.

The PHD is a geographically diverse, all-payer, U. S. hospital administrative database.[12] The PHD accounts for approximately 25% of all inpatient admissions in the U.S., and contains patient and hospital information, visit characteristics, diagnosis and procedure codes, as well as costs and utilization of services at the hospitals. The PHD is exempt from Institutional Review Board oversight as dictated by *Title 45 Code of Federal Regulations, Part 46 of the United States, specifically 45 CFR 46.101(b)(4)*. In accordance with the HIPAA Privacy Rule, disclosed data from the PHD are considered de-identified per *45 CFR 164.506(d)(2)(ii)(B)* through the "Expert Determination" method.

Study Population

This study included hospitalized patients with NVAF (ICD-10 Diagnosis I48) and/or VTE (ICD-10 Diagnosis I82.4, I82.5, I82.6, I82.7 [DVT] and I26 [PE]) who were ≥18 years of age, experienced a major life-threatening bleed between May 1, 2018 and June 30, 2019, and received specific reversal therapy with idarucizumab or andexanet alfa. Major bleeding events were based on the presence of ICD-10-CM diagnosis codes for gastrointestinal bleed (GIB), ICH, other bleed, or evidence of blood transfusion; an emergency or urgent hospital admission, or evidence of ICU use within 2 days following the admission. The lists of diagnosis codes to identify the bleeds are available from the authors upon request. The first hospitalization with use of idarucizumab or
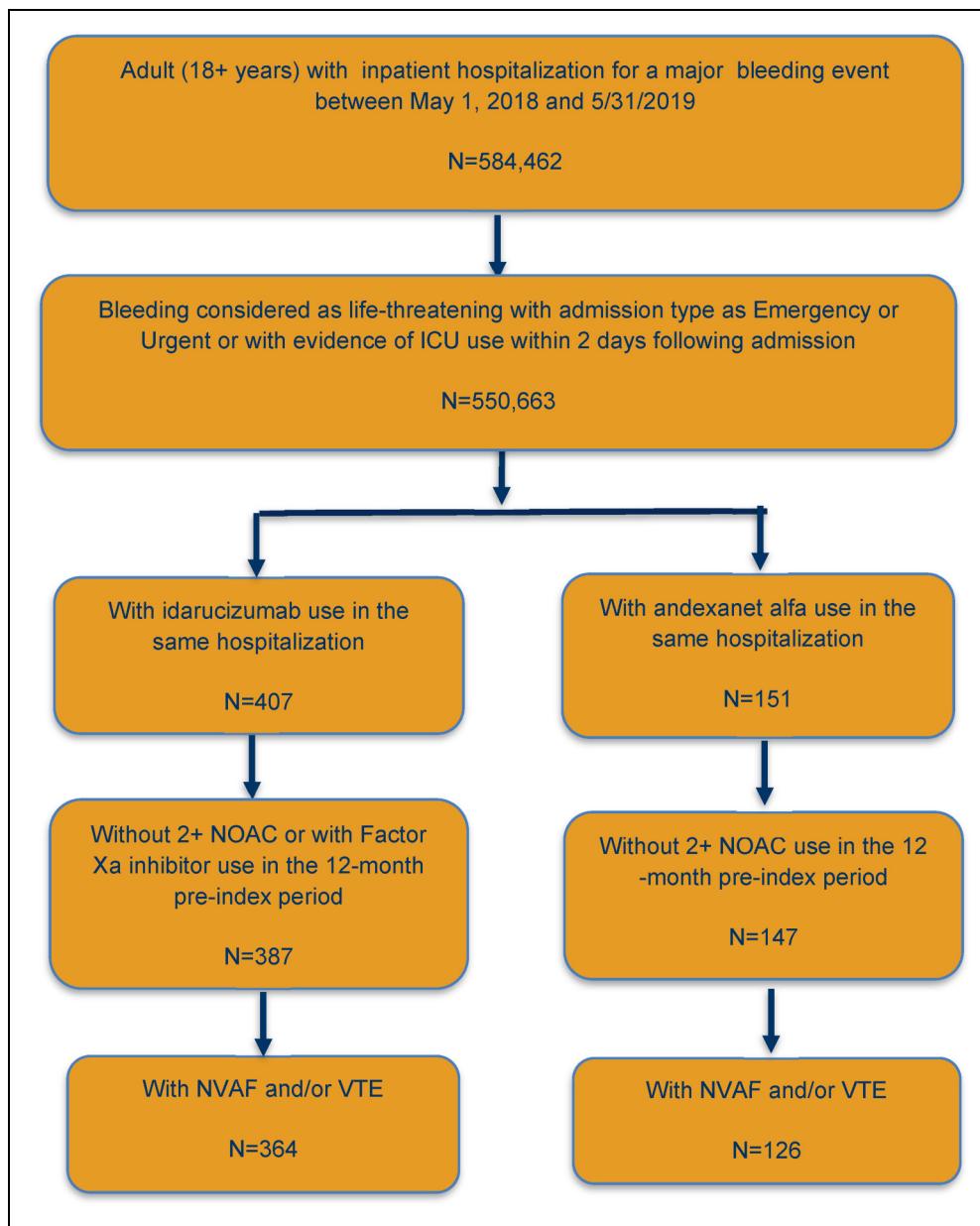
Figure 1. Patient Attrition

andexanet alfa was defined as the index hospitalization. A 12-month pre-index period was used to capture any evidence of prior DOAC use. Patients prescribed two or more DOACs during the pre-index period, and who might present with a higher disease burden that could influence study findings, were excluded from the study. Idarucizumab patients receiving a Factor Xa inhibitor during the pre-index period were also excluded. Figure 1 summarizes patient attrition and final study population.

Study Variables

The exposure variable was the anticoagulation reversal treatment with antidotes idarucizumab for dabigatran (idarucizumab

patients) versus andexanet alfa for rivaroxaban/apixaban (andexanet alpha patients) in the hospitalized NVAF and VTE study population.

Patient, Visit, and Hospital Characteristics

The demographic characteristics were examined for patients in the two treatment cohorts, including age, sex, race/ethnicity, and primary insurance payer. Visit characteristics captured admission type. Hospital characteristics reported urban and rural populations served, teaching status, US census division, and hospital bed size.

Clinical Characteristics

Patients' health status and risks were captured during the index hospitalization using 3M™ All Patient Refined Diagnosis Related Groups (APR-DRG) Severity of Illness and Risk of Mortality scales,[13] Deyo-Charlson Comorbidity Index (CCI) score,[14,15] HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) score,[16,17] CHA_2DS_2-VASc schema (Congestive heart failure, Hypertension, Age ≥75 Years, Diabetes mellitus, prior Stroke or transient ischemic attack (TIA), Vascular disease, Age 65–74 years, Sex category) score.[16,18] Same set of individual comorbidities as in Spyropoulos *et al* (2022)[11] were also examined in this study during the index hospitalization, which included bleeds (GIB, ICH), cardiovascular diseases (Coronary Artery Disease (CAD), congestive heart failure (CHF), myocardial infarction (MI), peripheral artery disease (PAD), ischemic stroke/transient ischemic attack (TIA)), renal diseases ;(Chronic Kidney Disease (CKD), Acute Kidney Failure), cardiac procedures (coronary artery bypass grafting (CABG), other open-heart surgery, percutaneous coronary intervention (PCI), other closed cardiac procedures), and other chronic conditions (hypertension, dyslipidemia, cirrhosis/hepatitis, diabetes mellitus, chronic obstructive pulmonary disease (COPD), history of cancer, history of falls, dementia, and depression/anxiety.

Outcomes

The primary outcome of this study was total hospital cost during the index hospitalization. The secondary HRU outcomes during the index hospitalization included total hospital LOS as well as LOS and costs associated with any ICU admission.

Statistical Analysis

Descriptive analysis was used to characterize the patient population and describe cost and HRU outcomes. Bivariate analysis provided pairwise comparisons between idarucizumab and andexanet alfa cohorts. Wilcoxon tests were used to assess differences in continuous variables, and Chi-square tests were used to examine any differences for categorical variables.

The descriptive analysis was followed by adjustment using the inverse probability of treatment weighting (IPTW) method to balance the distribution of demographic, visit, hospital, and clinical characteristics between the two treatment cohorts.[19–21] A logistic regression of treatment (idarucizumab vs andexanet alfa) on patient and hospital characteristics was performed. The covariates included in the regression were preselected based on an inspection of the unadjusted descriptive results and clinical rationale, and backward selection was used to determine the final model specification at a cutoff p value of 0.05 with a Bonferroni correction factor. The matching covariates that were retained in the model after backward selection included age, sex, race; urban versus rural and census

region (South, Midwest vs other); and HAS-BLED and CHA_2DS_2-VASc scores. Propensity scores were calculated as the conditional probability of receiving idarucizumab. The common support regions were examined between idarucizumab and andexanet alfa cohorts, and patients whose propensity score was outside of the region were excluded from the adjusted analysis. In the second step, the inverse of the probability of receiving the actual treatment was used as the probability weight in the estimation of the descriptive statistics. Standardized differences were used to examine the balance of covariates.[22,23] Standardized differences lower than 0.1 were considered negligible difference and indicated good balance between the groups.[23] Weighted means and standard deviations were reported for the outcomes. P values were reported for the weighted means of the outcomes. SAS 9.4 was used for the statistical analysis. An alpha value of <0.05 was considered statistically significant.

Results

Study Population

Among the 550,663 adult patients with an inpatient hospitalization with major life-threatening bleeds, 364 patients received idarucizumab (NVAF, 360; VTE, 18), and 126 received andexanet alfa (NVAF, 116; VTE, 16) (Figure 1).

Unadjusted Descriptive Analysis

Unadjusted patient, visit, and hospital characteristics. Unadjusted demographic, visit, and hospital characteristics are reported in Table 1. The idarucizumab patients were older (median 81 years, 25–75th percentile: 73.5–86 years) compared with the andexanet alfa patients (median 77 years, 25–75th percentile: 68–83 years; p < 0.001). The proportion of females was similar between the idarucizumab (42.9%) and andexanet alfa patients (46.8%; p = 0.439). Among the idarucizumab patients, 84.9% were white compared with 72.2% of the andexanet alfa patients (p = 0.002). Hispanic/Latino ethnicity accounted for 3.8% of the idarucizumab patients and 4.0% of the andexanet alfa patients (p = 0.154). Given the age distribution, patients from both idarucizumab and andexanet alfa cohorts subscribed to Medicare as their primary insurance payer (84.3.1% vs 78.6% in; p = 0.196). Most patients had an emergency or urgent admission or were admitted through a trauma center. A few patients had an elective or unknown type of admission, although these were identified with ICU use during the first two days of admission. Both idarucizumab (86.0%) and andexanet alfa (99.2%) patients were more often treated in urban hospitals (p < 0.001). Among idarucizumab patients, 51.9% were treated in teaching hospitals, while 75.4% of the andexanet alfa patients were also treated in teaching hospitals (p < 0.001). Idarucizumab patients were most likely treated in hospitals in the South Atlantic region (28.3%), whereas andexanet alfa patients were more likely treated in hospitals in the East North Central region (51.6%; p

Table 1. Patient and Hospital Characteristics.

		Idarucizumab		Andexanet Alfa		Idarucizumab versus Andexanet Alfa
		N	%	N	%	p-value
# of Patients		364		126		
Age Group	18–44	2	0.5	1	0.8	0.008
	45–54	5	1.4	6	4.8	
	55–64	21	5.8	13	10.3	
	65–74	74	20.3	37	29.4	
	75–84	147	40.4	42	33.3	
	85 +	115	31.6	27	21.4	
Sex	Female	156	42.9	59	46.8	0.439
	Male	208	57.1	67	53.2	
Race	Black	23	6.3	10	7.9	0.002
	Other	32	8.8	25	19.8	
	White	309	84.9	91	72.2	
Ethnicity	Hispanic or Latino	14	3.8	5	4.0	0.154
	Not Hispanic or Latino	286	78.6	108	85.7	
	Unknown	64	17.6	13	10.3	
Health Care Coverage	Commercial	42	11.5	18	14.3	0.196
	Medicaid	3	0.8	4	3.2	
	Medicare	307	84.3	99	78.6	
	Other	12	3.3	5	4.0	
Hospital Urbanicity	Rural	51	14.0	1	0.8	<0.001
	Urban	313	86.0	125	99.2	
Hospital Teaching Status	Non-Teaching	175	48.1	31	24.6	<0.001
	Teaching	189	51.9	95	75.4	
Hospital Census Division	East North Central	47	12.9	65	51.6	<0.001
	East South Central	15	4.1	6	4.8	
	Middle Atlantic	81	22.3	12	9.5	
	Mountain	9	2.5	0	0	
	New England	7	1.9	5	4.0	
	Pacific	44	12.1	0	0	
	South Atlantic	103	28.3	37	29.4	
	West North Central	30	8.2	1	0.8	
	West South Central	28	7.7	0	0	
Hospital Bed Size	<099	13	3.6	0	0	<0.001
	100–199	53	14.6	0	0	
	200–299	53	14.6	11	8.7	
	300–499	106	29.1	29	23.0	
	500 +	139	38.2	86	68.3	

<0.001). Andexanet alfa patients were more likely treated in larger hospitals with 500 or more beds compared with idarucizumab patients (68.3% vs 38.2%; p < 0.001).

Unadjusted clinical characteristics. Table 2 presents the unadjusted descriptive analysis of the clinical characteristics and comorbid conditions. The proportion of patients with extreme APR-DRG severity of illness was lower in idarucizumab patients compared to the andexanet alfa patients (35.2% vs 51.6%; p < 0.001). Lower proportions of idarucizumab patients with extreme risk of mortality score compared with the andexanet alfa patients (37.6% vs 50.8%; p = 0.049) were similarly noted. During the index hospitalization, idarucizumab patients displayed lower HAS-BLED scores than andexanet alfa patients (Median 3.4, 25–75th percentiles: 2–

4 vs Median 3.8, 25–75th percentiles: 3–5; p = 0.014). CHA_2DS_2-VASc scores and Deyo-Charlson Comorbidity Index scores were not statistically different between idarucizumab and andexanet alfa patients.

During index hospitalization, idarucizumab patients had a significantly higher prevalence of GIB (56.3% vs 24.6%; p < 0.001) and lower prevalence of prevalence of ICH (37.1% vs 73.8%; p = 0.001) compared with andexanet alfa patients. A significantly higher prevalence of acute kidney failure was seen in the idarucizumab patients compared with the andexanet alfa patients (36.8% vs 25.4%; p = 0.020). We also examined the drug costs of idarucizumab and andexanet alfa, respectively. The median pharmacy cost was approximately 6-fold lower for idarucizumab ($3604) than andexanet alfa ($22,074).

Table 2. Clinical Characteristics and Comorbid Conditions During Index Hospitalization.

		Idarucizumab		Andexanet Alfa		Idarucizumab versus Andexanet Alfa
		N	%	N	%	p-value
# of Patients/Discharges		364		126		
Oral Anticoagulation Indication	NVAF	360	98.9%	116	92.1%	
	VTE	18	4.9%	16	12.7%	
APR-DRG Severity of Illness	Minor	10	2.7%	3	2.4%	<.001
	Moderate	59	16.2%	12	9.5%	
	Major	167	45.9%	46	36.5%	
	Extreme	128	35.2%	65	51.6%	
APR-DRG Risk of Mortality	Minor	17	4.7%	4	3.2%	0.049
	Moderate	78	21.4%	17	13.5%	
	Major	132	36.3%	41	32.5%	
	Extreme	137	37.6%	64	50.8%	
HAS-BLED* Score Index	Mean	3.4	—	3.8	—	
	SD	1.5	—	1.3	—	
	Median	3	—	4	—	0.014
	25th percentile	2	—	3	—	
	75th percentile	4	—	5	—	
CHA$_2$DS$_2$-VASc** Score Index	Mean	3.9	—	3.7	—	
	SD	1.7	—	1.6	—	
	Median	4	—	4	—	0.209
	25th percentile	3	—	2	—	
	75th percentile	5	—	5	—	
Deyo-Charlson Comorbidity Index	Mean	3.6	—	4.0	—	
	SD	2.8	—	3.2	—	
	Median	3	—	3	—	0.597
	25th percentile	2	—	1	—	
	75th percentile	5	—	6	—	
Individual Comorbidities	Gastrointestinal Bleed	205	56.3%	31	24.6%	<.001
	Intracranial Bleed	135	37.1%	93	73.8%	<.001
	Coronary Artery Disease (CAD)	161	44.2%	54	42.9%	0.789
	Peripheral Artery Disease (PAD)	39	10.7%	11	8.7%	0.526
	Myocardial Infarction (MI)	56	15.4%	23	18.3%	0.450
	Congestive Heart Failure (CHF)	169	46.4%	50	39.7%	0.189
	Chronic Kidney Disease (CKD)	119	32.7%	33	26.2%	0.174
	Acute Kidney Failure	134	36.8%	32	25.4%	0.020
	Cirrhosis/hepatitis	20	5.5%	6	4.8%	0.752
	Hypertension	184	50.5%	65	51.6%	0.841
	Dyslipidemia	223	61.3%	73	57.9%	0.510
	Diabetes Mellitus	133	36.5%	43	34.1%	0.627
	Chronic Obstructive Pulmonary Disease (COPD)	80	22.0%	34	27.0%	0.252
	History of Cancer	95	26.1%	34	27.0%	0.846
	Ischemic Stroke/Transient Ischemic Attack (TIA)	17	4.7%	8	6.3%	0.460
	CABG	0	0.0%	1	0.8%	0.089
	Other Open-Heart Surgery	1	0.3%	6	4.8%	<.001
	Percutaneous Coronary Intervention (PCI)	0	0.0%	0	0.0%	—
	Other Closed Cardiac Procedures	64	17.6%	26	20.6%	0.446
	History of Falls	19	5.2%	12	9.5%	0.087
	Dementia	52	14.3%	20	15.9%	0.664
	Depression/Anxiety	72	19.8%	21	16.7%	0.442

* NVAF: non-valvular atrial fibrillation; VTE: venous thromboembolism; A patient may have both NVAF and VTE diagnoses during the index hospitalization.

** HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol.

*** CHA$_2$DS$_2$-VASc: Congestive heart failure, Hypertension, Age ≥75 Years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category.

Table 3. Inverse Probability of Treatment Weighted Covariates.

		Idarucizumab		Andexanet Alfa		Standardized Differences	Idarucizumab versus Andexanet Alfa p value
		N	%	N	%		
# of Patients		266		101			
Age	Mean	77.1	—	76.4	—	0.065	0.598
	Std Dev	10.7	—	13.1	—		
Sex	Female	114	43.2%	53	45.5%	0.039	0.673
	Male	150	56.9%	63	54.5%	0.039	
Race	Black	17	6.5%	10	8.7%	0.068	0.704
	Other	30	11.3%	11	9.7%	0.041	
	White	217	82.2%	95	81.6%	0.013	
Urbanicity	Rural	6	2.3%	3	2.3%	0.004	0.965
	Urban	258	97.7%	113	97.8%	0.004	
Provider area	Midwest	77	29.3%	25	21.7%	0.141	0.300
	Other	73	27.7%	35	29.8%	0.039	
	South	114	43.1%	56	48.5%	0.090	
HAS-BLED* Score Index	Mean	3.5	—	3.4	—	0.067	0.781
	Std Dev	1.5	—	1.5	—		
CHA_2DS_2-VASc** Score Index	Mean	3.8	—	3.7	—	0.061	0.459
	Std Dev	1.7	—	1.6	—		

* HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol.
** CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 Years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category.

IPTW-Adjusted Results

IPTW-adjusted demographic, visit, hospital, and clinical characteristics. Table 3 provides the IPT-weighted descriptive statistics for the covariates included in the IPTW regression. After excluding patients whose probability of treatment were outside the common support region, 266 idarucizumab and 101 andexanet alfa patients remained in the weighted analysis. Standardized differences for the covariates that were included in the IPTW regression were below 0.1, except the proportion of idarucizumab patients treated in hospitals located in the Midwest division, which was slightly higher than what was observed in the andexanet alfa patients (standardized difference = 0.141).

IPT-weighted costs and hospital resource utilization. The IPT-weighted outcomes are presented in Table 4. The weighted mean total hospital cost among idarucizumab patients was significantly lower than among andexanet alfa patients ($30,413 ± $33,028 vs $44,477 ± $30,036; p < 0.001). The weighted mean total LOS was similar between idarucizumab and andexanet alfa (9.0 ± 8.6 days vs 7.8 ± 7.1 days; p = 0.166). The differences in the percentage of ICU admissions were not statistically significant between the idarucizumab and andexanet alfa cohorts (70.9% vs 67.9%; p = 0.559) nor was the respective ICU LOS (5.2 ± 8.3 days vs 3.6 ± 4.5 days; p = 0.108). However, the weighted mean for ICU LOS costs was found to be significantly lower in idarucizumab patients compared with andexanet alfa patients ($25,114 ± $30,433 vs $43,484 ± $29,335, p < 0.001).

Discussion

This retrospective observational study compared treatment of two FDA-approved antidotes for oral anticoagulation reversal in patients on chronic DOACs hospitalized for life-threatening bleeds. The key findings indicated that patients treated with idarucizumab incurred an adjusted mean lower total hospital and ICU cost that was approximately $13,000 less compared with those patients treated with andexanet alfa, after adjusting for demographic, hospital, and clinical characteristics. Despite these differences in costs, no significant between-group differences were observed for percentage of ICU admission and total hospital and ICU LOS.

In the recently published study by Spyropoulos et al,[11] patients treated with idarucizumab for the reversal of dabigatran had lower ICU admission rate, hospital cost, and shorter LOS, when compared to those treated with a non-specific, PCC-based strategy for the reversal of warfarin. As an extension of that research, the current study revealed that, the patients receiving idarucizumab also had a lower cost than those receiving using andexanet alfa for the specific reversal of DOACs rivaroxaban and apixaban, although the LOS and ICU admission rate were not statistically different among those receiving specific reversal therapies.

The higher total costs in andexanet alfa patients are likely attributable to several factors. First, the treatment cost of andexanet alfa is much higher than that of idarucizumab, which may be a key driver of higher total hospital costs in patients receiving andexanet alfa. Andexanet alfa costs range from $24,750 (low-dose regimen) to $49,500 (high-dose regimen).[9,24] Its dosing regimen is dependent on the strength

Table 4. Inverse Probability of Treatment Weighted Outcomes

		Idarucizumab	Andexanet Alfa	Normalized Difference for Idarucizumab versus Andexanet Alfa	Idarucizumab versus Andexanet Alfa p value
Total Cost ($)	N	266	101		
	Mean	$30,413	$44,477	0.446	<0.001
	Std Dev	$33,028	$30,036		
Total Hospital Length of Stay (Days)	N	266	101		
	Mean	9.0	7.8	0.161	0.166
	Std Dev	8.6	7.1		
ICU Admission (Percentage)*	N	179	82		
	%	70.9	67.9	0.066	0.559
ICU Length of Stay (Days)	N	179	73		
	Mean	5.2	3.6	0.238	0.108
	Std Dev	8.3	4.5		
ICU Cost ($)	N	179	73		
	Mean	$25,114	$43,484	0.615	<0.001
	Std Dev	$30,433	$29,335		

*ICU: Intensive Care Unit
Legends:
DOAC: direct oral anticoagulation
NVAF: non-valvular atrial fibrillation
VTE: venous thromboembolism

and timing of the last dose of apixaban.[25] The dose cost of idarucizumab is much lower at $3500.[26] In the present study, the unadjusted mean cost for andexanet alfa was $28,940 (SD: $21,756) compared with $4393 (SD: $3258) for idarucizumab, consistent with reported wholesale acquisition costs during the study period (May 1, 2018–June 30, 2019). It is worth noting that, Portola Pharmaceuticals, the manufacturer of andexanet alfa was acquired by Alexion Pharmaceuticals in July 2020, and the price of andexanet alpha decreased afterwards. Although the price change did not affect the present study, it could impact the patient treatment costs in studies covering year 2020 or later. Second, although the adjusted percentage of ICU admission or LOS did not differ significantly between idarucizumab and andexanet alfa patients, andexanet alfa patients incurred higher ICU costs when they were admitted to the ICU, indicating greater HCRU. Finally, increased costs also may be related to the overall health of the andexanet alfa cohort. The unadjusted descriptive analysis indicated that the severity level of illness of the two cohorts was different. Andexanet alfa patients were considered more severe with higher proportions of patients with "extreme" APR-DRG severity of illness and risk of mortality. The andexanet alfa patients had a greater propensity for bleeding as evidenced by significantly higher HAS-BLED scores. Notably, the study found that the andexanet alfa patients were more likely to present with an ICH than idarucizumab patients, while the idarucizumab patients were more likely to experience GI bleeding, suggesting some disparity in the reason for treatment with reverse anticoagulant agents in these populations. To this end, the costs associated with ICH bleeding may reflect another underlying reason as to the cost differences observed between

both andexanet alfa and idarucizumab patients, respectively. This study documented that 73.8% of patients in the andexanet alfa group had experienced an ICH, while only 37.1% of idarucizumab patients had suffered an ICH. These observations are in line with findings from previous clinical trials and retrospective studies. Indeed, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study showed that patients receiving low-dose (110 mg) and high-dose (150mg) dabigatran had yearly respective ICH rates of 0.23% and 0.30%, respectively.[27] The Apixaban for Reduction in Stroke and Other Embolic Events in Atrial Fibrillation (ARISTOTLE) study demonstrated an ICH rate of 0.33% per year,[28] and the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study demonstrated a 0.4% ICH rate per year in patients treated with apixaban.[29] Another study also found that the rivaroxaban-associated ICH rate was 0.57% per year.[30] In a more recent comparative propensity-matched study of US Medicare patients diagnosed with NVAF, who newly received dabigatran versus apixaban between October 2010 and September 2015, adjusted hazard ratios (HR; 95% Confidence Interval) showed a reduced risk for ICH (0.7; 0.53–0.94) compared with an increased risk for major GIB (2.23; 1.93–2.58).[31]

Several limitations of this study warrant discussion. First, the history of prior DOAC use may not have been fully captured in the PHD database, since it could not account for those patients taking DOAC therapy at home. Second, IPTW adjustment was used to control for the difference in patient, hospital, and clinical characteristics between both cohorts. Given the limited sample size, only the most parsimonious patient and clinical

characteristics were included in the propensity score model after backward selection. Although most covariates appeared to be well balanced when weighted, we cannot discount the possibility that other unmeasured factors that were not accounted for after applying the weights could have led to potential bias. Finally, due to the relatively small sample size, subgroup analysis within patients who experienced an ICH and/or GIB was not feasible.

Conclusions

In the present study, following adjustment for key demographic and clinical characteristics, patients treated with idarucizumab appeared to incur an adjusted mean lower total cost that was approximately $13,000 less compared with those patients treated with andexanet alfa. One potential cost driver for andexanet alfa was the cost for the agent itself. In addition, there was a higher severity of illness and higher proportion of ICH bleeds displayed in those who received andexanet alfa to suggest that this patient group was more likely to have undergone more intensive treatment approaches than those administered idarucizumab. Despite these limitations, this study is the first to compare the real-world healthcare cost and resource utilization between patients receiving the first two FDA-approved reversal therapies for direct thrombin and Factor Xa inhibitors.

Authors' Note

AS,BH, ZC, HC, and CW were responsible for the design of the study. ZC and CL took the responsibility for the integration of the data and the accuracy of the data analysis AS,BH, ZC, HC, and CL interpreted the study findings. All authors were responsible for drafting and critical revision of the manuscript and for important intellectual content, and provided approval of the final draft.

Availability of data and materials

The data that support the findings of this study are available from Premier Inc., but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Premier Inc.

Declaration of Conflicting Interests

A. Spyropoulos is a consultant for Boehringer Ingelheim Pharmaceuticals; B. ÓHartaigh, H. Caberwal, M. Petrini, C. Wang are employees of Boehringer Ingelheim Pharmaceuticals; Z. Cao and C. Lipkin are employees of Premier Inc, which received payment from Boehringer Ingelheim Pharmaceuticals to conduct the study.

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Supplemental material

Supplemental material for this article is available online.

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