Comparative Analysis of Real-World Outcomes with Reversal Agent Use in Direct Oral Anticoagulant-Associated Severe Bleeding

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Background

- Direct oral anticoagulants (DOACs) are known to increase the risk of serious, sometimes fatal, bleeding events[1]
- Four-factor prothrombin complex concentrate (4F-PCC), andexanet alfa and idarucizumab can be used in DOAC-associated bleeding to reverse DOAC effects
- Targeted reversal agents, andexanet alfa and idarucizumab, remain a financial burden for many hospitals
- Larger studies are warranted to characterize readmission rates and confirm findings of similar length of stay between agents and increased risk of thromboembolism with andexanet alfa[1,2]

Objective

- Assess safety and effectiveness of reversal agents for severe bleeding in patients receiving DOACs using real-world data

Methods

- Clinical encounters between January 1, 2019, and September 9, 2021, captured using Agilum's Comparative Rapid Cycle Analytics™ P&T platform
- Patients ≥18 years old admitted with ICD-10 code for bleeding
- Dispensation of 4F-PCC with documented DOAC use, or received andexanet alfa or idarucizumab
- Continuous data: median and interquartile range; Kruskal-Wallis test for comparison. Categorical data: frequency; Chi-squared or Fisher's exact tests for comparison
- Alpha <0.05

Outcomes

Primary outcome
- In-hospital length of stay (LOS)

Secondary outcomes
- In-hospital LOS by intracranial vs extracranial bleeding
- 30-day all-cause readmission rate, overall and by intracranial and extracranial bleeding

Safety outcomes
- Disability
- Thromboembolic event (by overall, venous, and arterial)

Results

Table 1. Baseline Characteristics	4F-PCC N=6,735	Andexanet alfa N=242	Idarucizumab N=129	P value
Median age (yrs)	74	76	78	***<0.01***
Male, n (%)	3,913 (58.1)	132 (54.5)	63 (48.8)	0.06
Comorbidities, n (%)				
Atrial fibrillation	4,299 (63.8)	162 (66.9)	111 (86)	***<0.01***
Venous thromboembolism	392 (5.8)	22 (9.1)	3 (2.3)	***0.03***
Deep vein thrombosis	319 (4.7)	19 (7.9)	3 (2.3)	***0.04***
Pulmonary embolism	116 (1.7)	8 (3.3)	0	0.07
Hypertension	2,146 (31.9)	95 (39.3)	44 (34.1)	***0.05***
Congestive heart failure	2,598 (38.6)	71 (29.3)	51 (39.5)	***0.01***
Diabetes mellitus	2,182 (32.4)	69 (28.5)	39 (30.2)	0.40
Excessive alcohol use/drinking disorder	345 (5.1)	10 (4.1)	12 (9.3)	0.08
Cirrhosis	215 (3.2)	2 (0.8)	3 (2.3)	0.09
Chronic kidney disease	1,912 (28.4)	57 (23.6)	32 (24.8)	0.18
Bleeding Type, n (%)				
Intracranial hemorrhage (ICH)	2,567 (38.1)	150 (62)	39 (30.2)	***<0.01***
Nontraumatic	1,420 (21.1)	89 (36.8)	18 (14)	***<0.01***
Traumatic	1,228 (18.2)	69 (28.5)	23 (17.8)	***<0.01***
Extracranial hemorrhage	4,168 (61.9)	92 (38)	90 (69.8)	***<0.01***
Gastrointestinal	1,788 (26.5)	34 (14)	46 (35.7)	***<0.01***
Critical compartment	391 (5.8)	9 (3.7)	2 (1.6)	***0.04***
Traumatic, not including ICH	605 (9)	32 (13.2)	14 (10.9)	0.06
Other	2,689 (39.9)	62 (25.6)	49 (38)	***<0.01***

Table 2. In-hospital length of stay (days)	4F-PCC N=6,735	Andexanet alfa N=242	Idarucizumab N=129	P value
Overall	6 (3 – 11)	6 (3 – 10)	5 (3 – 9)	0.94
Intracranial Bleeding	5 (2 – 10)	6 (3 – 10)	4 (3 – 8)	0.10
Extracranial Bleeding	6 (3 – 12)	6 (3 – 9.25)	5.5 (3 – 10.75)	0.28

Figure 1. All-Cause 30-day Readmission Rates

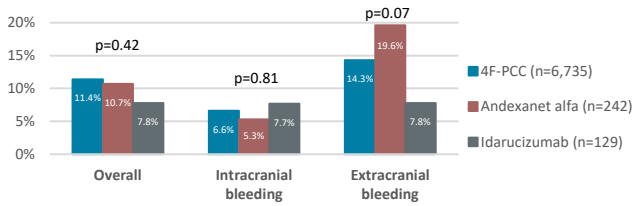
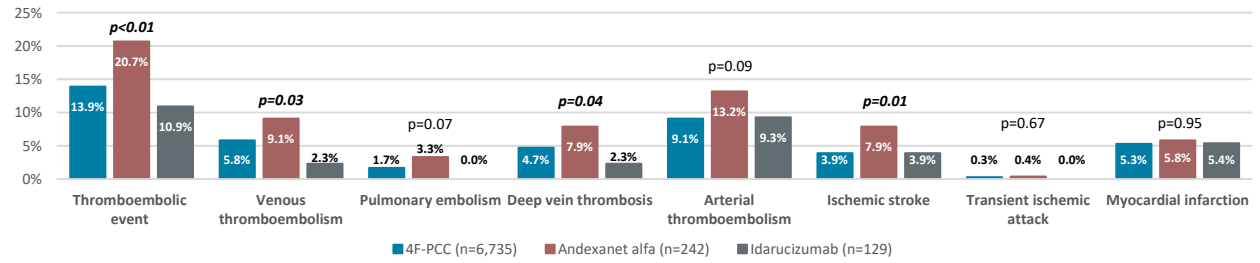


Figure 2. Safety Outcomes by Reversal Agent



Discussion

- Significantly different baseline characteristics between groups may affect interpretation of outcomes
- Lower utilization of targeted reversal agents vs. 4F-PCC
- 4F-PCC and idarucizumab used >60% for extracranial encounters vs. andexanet alfa used >60% for intracranial encounters
- Bleeding types were not mutually exclusive between categories
- LOS and thromboembolism findings parallel previous findings[1,2]
- Higher rate of thromboembolic events, including deep vein thrombosis and ischemic stroke, with andexanet alfa
- Large, current, and generalizable data set for insight into outcomes
- Readmission data not collected 30 days past September 9, 2021 end date
- Unable to assess dose of agents, number of doses, blood products received, or timing of reversal agent compared to last DOAC dose
- Unable to evaluate achievement of hemostasis

Conclusion

- Similar LOS and all-cause 30-day readmission rates between agents
- Real-world evidence suggests 4F-PCC as a more affordable alternative with similar effectiveness and improved safety compared to higher cost reversal agents

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