World Neurosurgery: X 23 (2024) 100367

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Andexanet alfa therapy showed No increased rate of thromboembolic events in spontaneous intracranial hemorrhage patients: A multicenter electronic health record study

John Vellek [a], Omar H. Tarawneh [a], Syed Faraz Kazim [b], Oluwafemi P. Owodunni [b], Sophia Arbuiso [a], Smit Shah [c], Alis J. Dicpinigaitis [a], Meic H. Schmidt [b], Rohini G. McKee [d], Richard Miskimins [d], Fawaz Al-Mufti [e], Christian A. Bowers [f,*]

[a] School of Medicine, New York Medical College, Valhalla, NY, 10595, United States
[b] Department of Neurosurgery, University of New Mexico Hospital (UNMH), Albuquerque, NM, 87131, United States
[c] PRISMA Health Richland/University of South Carolina School of Medicine, 1 Medical Park, Suite 230, Columbia, SC, 29203, United States
[d] Department of Surgery, University of New Mexico, Albuquerque, NM, 87106, United States
[e] Department of Neurosurgery, Westchester Medical Center/New York Medical College, Valhalla, NY, 10595, United States
[f] Bowers Neurosurgical Frailty and Outcomes Data Science Lab, Sandy, UT, United States

ARTICLE INFO

Keywords:
Andexanet Alfa
Thromboembolism
Intracranial Hemorrhage
Anticoagulation

1. Introduction

Andexanet alfa (AA) is the first and only selective reversal drug licensed by the Food and Drug Administration to treat life-threatening hemorrhage caused by oral factor Xa inhibitors.[1–3] AA was approved in 2018, and it exerts its effects as an inactive protein that binds directly to factor Xa inhibitors, making them ineffective, consequently preventing thrombin activation.[1–4] AA is indicated for reversal of apixaban (Eliquis®) and rivaroxaban (Xarelto®),[1] with its use extended to the reversal of unfractionated heparin,[5] enoxaparin,[5] betrixaban,[6] and edoxaban.[6–8] There is a plethora of evidence supporting the efficacy of AA,[1,9–12] Nonetheless, more research into the therapeutic implications and its application is required, particularly in regard to patients with intracranial hemorrhage (ICH).[7,13]

Systemic anticoagulation (AC) is routinely prescribed for the purpose of preventing cerebrovascular accidents (CVA) in older patients due to the increased prevalence of coagulopathy,[14] as well as in patients who have an increased risk of CVA due to the presence of other medical conditions.[12,13,15] Hemorrhagic events are a risk for anticoagulant therapy, and it is estimated that 5% of individuals with AC will encounter a hemorrhagic event requiring reversal.[4] The prognosis for spontaneous ICH, which accounts for two out of every three major ICH and constitutes 64% of all major ICHs, is the worst of all CVA subtypes.[16] Trauma is responsible for the remaining one-third of ICHs.[16] As a result, when ICH patients are anticoagulated to avoid the spread of acute ICHs, all potential AC antidotes or reversal medications, such as AA, are critical.[13] Although AA can minimize hemorrhage expansion, its limited use in ICH patients and concerns about thromboembolic complications i.e., venous thromboembolism (VTE) which comprises of deep venous thrombosis (DVT) and pulmonary embolism (PE), MI, and/or CVA,[6,16–18] impedes its broad adoption in routine clinical practice.

This study examined a large group of patients from a multicenter data repository that were treated with AA and followed for a three-month period. The goal of this study was to examine the benefits of

* Corresponding author. Bowers Neurosurgical Frailty and Outcomes Data Science Lab, Sandy, UT, United States.
E-mail addresses: jvellek@student.nymc.edu (J. Vellek), otarawne@student.nymc.edu (O.H. Tarawneh), skazim@salud.unm.edu (S.F. Kazim), oowodun1@jhmi.edu (O.P. Owodunni), sarbuiso@student.nymc.edu (S. Arbuiso), spshah1991@gmail.com (S. Shah), adicpini@student.nymc.edu (A.J. Dicpinigaitis), MHSchmidt@salud.unm.edu (M.H. Schmidt), RmcKee@salud.unm.edu (R.G. McKee), RmisKimins@salud.unm.edu (R. Miskimins), fawaz.al-mufti@wmchealth.org (F. Al-Mufti), christianbowers4@gmail.com (C.A. Bowers).

https://doi.org/10.1016/j.wnsx.2024.100367
Received 8 December 2022; Received in revised form 6 March 2024; Accepted 20 March 2024
Available online 27 March 2024

AA in patients with ICH and its relationship with the rates thromboembolic complications (VTE, MI, and CVA), and all-cause mortality.

2. Methods

The data query for this for this retrospective study was from the TriNetX Analytics Research Network Platform (Cambridge, MA [TriNetX]). TriNetX represents a globally interconnected database, amassing more than 68 million distinct electronic health records sourced from upwards of 53 different healthcare organizations. (HCO).[19,20] The data provided by TriNetX is de-identified and aggregated, consisting of procedures, genomics, medications, vitals, and patient demographics. The identities of HCOs subscribed to the network are not provided; however, patient data is aggregated from academic medical centers and their affiliates. Given the de-identified nature of the records, the TrinetX platform is considered Health Insurance Portability and Accountability Act compliant.[20] Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempt from Institutional Review Board approval. Nonetheless, we adhered strictly to all ethical guidelines for conducting research and reporting.

2.1. Patient selection

Adult patients (≥18 years old) treated with AA for spontaneous ICH from January 1, 2018, through June 30, 2021, were included in the analysis. Patient data were queried using neurosurgery-specific International Classification of Disease 10th edition codes (ICD-10) associated with ICH i.e., nontraumatic subarachnoid hemorrhage (I60), nontraumatic intracerebral hemorrhage (I61), and other and unspecified nontraumatic ICH (I62).[21–24] In addition, patients were eligible for inclusion if they received AA (2045114) within 48 h of any spontaneous (nontraumatic) ICH. Data on patient demographics (age, sex, race, and ethnicity), thromboembolic complications occurring within a three-month period following AA administration (DVT [I82], PE [I25], MI [I21], and/or CVA [I63]), and last vital status (mortality) were included.[25–27]

2.2. Propensity score matching

The propensity-matched AA and control pairs were established using TrinetX data on age, sex, race, ethnicity, relevant preexisting comorbidities, and previous surgical procedures. These patients were also matched for presentation to the hospital for ICH while on anticoagulation, but with the stipulation that they did not receive AA. Briefly, propensity score matching is a statistical matching strategy that strives to evaluate the effect of a treatment by controlling for covariates that may introduce bias because of distinct group differences.[28] A total of 175,471 patients were identified as belonging to the control cohort. 376 propensity matched AA and control pairs were established.

2.3. Statistical analysis

Descriptive analyses were performed, and the findings are presented as frequencies and proportions for dichotomized and categorical variables; the means and standard deviation are reported for continuous variables. Patient characteristics are stratified by the AA or control cohorts. For continuous variables, the Student's *t*-test was employed, while for dichotomized or categorical variables, the Pearson's chi-square and Fisher exact tests were utilized. All tests are two-sided and have statistical significance at $p \leq 0.05$. Analyses were performed using Statistical Package for Social Sciences (SPSS), version 28.0 [International Business Machines (IBM Corp., Armonk, NY, USA)].

3. Results

Our inclusion criteria were met by a total of 175,849 patients, with 378 in the AA cohort and 175,471 in the control cohort (Table 1). Most patients (43%) were from Southern US, followed by Northeast (26%), and Midwest (25%) (data not reported). Unmatched patients were older in the AA cohort 74.9 years ± (SD 11.0) vs. 60.9 years ± (SD 21.4) in the control cohort, $p \leq 0.001$. However, propensity-matched patients were similar by age (Table 1). Unmatched patients were similar in terms of sex, race (Black or African American, Asian, Native Hawaiian or Pacific Islander), and few comorbidities (Table 2). On the other hand, they differed by white race, ethnicity, several comorbidities, and previous surgical procedure (Table 2). Except for a few comorbidities, all propensity-matched patients were similar.

Unmatched patients in the AA were more likely documented to have been administered an anticoagulation medication i.e., anticoagulants: 326 (86.2%) AA, vs. 71,115 (40.5%) control; $p \leq 0.001$, apixaban: 216 (57.1%) AA, vs. 8289 (4.7%) control; $p \leq 0.001$, and rivaroxaban: 116 (30.7%) AA, vs. 4799 (2.7%) control; $p \leq 0.001$ (Table 3). However, propensity-matched patients did not differ by documented anticoagulation administration.

Thromboembolic complications did not differ significantly between the propensity-matched patients in the AA and the control cohorts (Table 4). Thromboembolic complication rates were similar across the board: 10.6% AA, vs. 13.8% control, for DVT, 6.1% AA, vs. 6.7% control, for PE, 7.2% AA, vs. 6.7% control, for MI, and 28.7% AA, vs. 25.3% control, for CVA; all $p > 0.05$ (Table 4). However, the all-cause mortality rate was significantly higher in the AA cohort 31.7% vs. 17.3% control; $p \leq 0.001$ (Table 4).

4. Discussion

In this study, we have shown that patients with ICH who received AA had lower thromboembolic complications rates (VTE, MI, and CVA) over a three-month follow-up period ($p > 0.05$). When we assessed all-cause mortality rates, we found that patients who received AA had a significantly increased rate of mortality during the three-month period, however this cannot be linked as a causal relationship because we were unable to control for bleed severity. To the best of our knowledge, this study represents the first large-scale, multi-center, population-based analysis delving into the role of AA in reversing Factor Xa inhibition in spontaneous ICH patients. This pioneering work not only pushes the boundaries of our understanding but also illuminates new possibilities for enhancing patient safety in this area of care, setting a solid foundation for future research.

There is a dearth of neurosurgical literature that reference the utilization of TriNetX because the database is relatively new; nonetheless, TriNetX is a robust database that has the potential to inform clinical practice. Some recent studies that used TriNetX have confirmed the

Table 1
Patient age distribution stratified by andexanet alfa and control cohorts for all intracranial hemorrhage patients.

Variable	Before Matching		
	$n = 378$	$n = 175,471$	
Age, years (SD)	Andexanet Alfa 74.9 ± (11.0)	Control 60.9 ± (21.4)	p-value ≤0.001
	After Propensity Score Matching [a]		
Age, years (SD)	Andexanet Alfa 74.8 ± (11.1)	Control 74.5 ± (11.5)	p-value 0.67

SD, Standard deviation.
Student's ttest, two-sided; statistical significance at $p \leq 0.05$.
[a] Propensity matched pairs for the Andexanet Alfa and control cohorts were established using TrinetX data on age, gender, ethnicity, relevant pre-existing comorbidities, and previous procedures.

Table 2
Patient demographics and clinical characteristics stratified by andexanet alfa and control cohorts for all intracranial hemorrhage patients before and after propensity score matching.

Characteristics		Before Matching			*After Propensity Score Matching*[b]		
		AA	Control	P value	AA	Control	P value
T	Total Patients	378	175,471		376	376	
M[a]	Male	216 (57.1)	95,168 (54.2)	0.26	214 (56.9)	208 (55.3)	0.66
F[a]	Female	162 (42.9)	80,202 (45.7)	0.27	162 (43.1)	168 (44.7)	0.66
UN	Unknown Gender	0 (0)	101 (0.1)	0.64	0 (0)	0 (0)	–
2106-3[a]	White	292 (77.3)	118,114 (67.3)	≤0.001	290 (77.1)	301 (80.1)	0.33
2054-5[a]	Black or African American	54 (14.3)	27,124 (15.5)	0.53	54 (14.4)	45 (12.0)	0.33
2028-9[a]	Asian	≤10 (2.7)	4103 (2.3)	0.69	≤10 (2.7)	≤10 (2.7)	1.00
1002-5[a]	American Indian or Alaska Native	≤10 (2.7)	711 (0.4)	≤0.001	≤10 (2.7)	≤10 (2.7)	1.00
2076-8[a]	Native Hawaiian or Pacific Islander	0 (0)	178 (0.1)	0.54	0 (0)	0 (0)	–
2131–1	Unknown Race	20 (5.3)	25,241 (14.4)	≤0.001	20 (5.3)	23 (6.1)	0.64
2135-2[a]	Hispanic or Latino	≤10 (2.7)	12,431 (7.1)	0.001	≤10 (2.7)	≤10 (2.7)	1.00
2186-5[a]	Not Hispanic	283 (74.9)	119,572 (68.1)	0.01	282 (75.0)	300 (79.8)	0.12
UN	Unknown Ethnicity	86 (22.8)	43,468 (24.8)	0.36	85 (22.6)	69 (18.4)	0.15
100-199[a]	Diseases of the Circulatory System	378 (100)	175,471 (100)	1.00	376 (100)	376 (100)	1.00
ROO-R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	335 (88.6)	149,179 (85.0)	0.05	334 (88.8)	340 (90.4)	0.47
Z00-Z99	Factors influencing health status and contact with health services	328 (86.8)	141,594 (80.7)	0.003	326 (86.7)	337 (89.6)	0.21
EOO-E89[a]	Endocrine, nutritional, and metabolic disorders	291 (77.0)	119,817 (68.3)	0.0003	290 (77.1)	303 (80.6)	0.25
G00-G99[a]	Diseases of the nervous system	298 (78.8)	122,975 (70.1)	0.0002	296 (78.7)	294 (78.2)	0.86
MOO-M99[a]	Diseases of the musculoskeletal system and connective tissue	231 (61.1)	93,335 (53.2)	0.002	231 (61.4)	243 (64.6)	0.36
NOO–N99	Diseases of the genitourinary system	219 (57.9)	81,407 (46.4)	≤0.001	219 (58.3)	232 (61.7)	0.33
JOO-J99[a]	Diseases of the respiratory system	240 (63.5)	92,159 (52.5)	≤0.001	239 (63.6)	238 (63.3)	0.94
S00-T88	Injury, poisoning and certain other consequences of external causes	254 (67.2)	107,852 (61.5)	0.02	254 (67.6)	256 (68.1)	0.88
KOO–K95	Diseases of the digestive system	190 (50.3)	82,473 (47.0)	0.20	190 (50.5)	231 (61.4)	0.003
D50-D89[a]	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	201 (53.2)	72,714 (41.4)	≤0.001	200 (53.2)	211 (56.1)	0.42
F01–F99	Mental, Behavioral, and Neurodevelopmental disorders	155 (41.0)	81,351 (46.4)	0.04	155 (41.2)	199 (52.9)	0.001
LOO-L99	Diseases of the skin and subcutaneous tissue	134 (35.5)	45,561 (26.0)	≤0.001	134 (35.6)	145 (38.6)	0.40
VOO-Y99[a]	External causes of morbidity	168 (44.4)	69,272 (39.5)	0.05	168 (44.7)	166 (44.2)	0.88
COO-D49[a]	Neoplasms	123 (32.5)	48,535 (27.7)	0.03	123 (32.7)	140 (37.2)	0.19
AOO-B99	Certain infections and parasitic diseases	125 (33.1)	50,616 (28.9)	0.07	125 (33.3)	142 (37.8)	0.20
HOO–H59	Diseases of the eye and adnexa	105 (27.8)	48,255 (27.5)	0.90	105 (27.9)	137 (36.4)	0.01
H60–H95	Diseases of the ear and mastoid process	54 (14.3)	27,134 (15.5)	0.53	54 (14.4)	84 (22.3)	0.005
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	40 (10.6)	19,831 (11.3)	0.66	39 (10.4)	52 (13.8)	0.15
POO-P96	Certain conditions originating from the perinatal period	≤10 (2.7)	4159 (2.4)	0.73	≤10 (2.7)	≤10 (2.7)	1.00
000-09A	Pregnancy, childbirth and the puerperium	≤10 (2.7)	2653 (1.5)	0.07	≤10 (2.7)	≤10 (2.7)	1.00
UOO-U85	Codes for special purposes	≤10 (2.7)	2059 (1.2)	0.01	≤10 (2.7)	≤10 (2.7)	1.00
1003143[a]	Previous Surgery	254 (67.2)	95,984 (54.7)	≤0.001	253 (67.3)	250 (66.5)	0.82

AA, Andexanet Alfa.
Pearson and Fishers exact tests, two-sided; statistical significance at $p \leq 0.05$.

[a] Indicates criteria for matching.
[b] Propensity matched pairs for the Andexanet Alfa and control cohorts were established using TrinetX data on age, gender, ethnicity, relevant pre-existing comorbidities*, and previous procedures*.

Table 3
Anticoagulation medication stratified by andexanet alfa and control cohorts for all intracranial hemorrhage patients before and after propensity score matching.

Characteristics		Before Matching			*After Propensity Score Matching*[b]		
		AA	Control	P value	AA	Control	P value
T	Total Patients	378	175,471		376	376	
BL110[a]	Anticoagulants	326 (86.2)	71,115 (40.5)	≤0.001	324 (86.2)	334 (88.8)	0.27
1364430[a]	Apixaban	216 (57.1)	8289 (4.7)	≤0.001	214 (56.9)	238 (63.3)	0.07
1114195[a]	Rivaroxaban	116 (30.7)	4799 (2.7)	≤0.001	114 (30.3)	91 (24.2)	0.06

AA, Andexanet Alfa.
Pearson and Fishers exact tests, two-sided; statistical significance at $p \leq 0.05$.
[a] Indicates criteria for matching.
[b] Propensity matched pairs for the Andexanet Alfa and control cohorts were established using TrinetX data on age, gender, ethnicity, relevant pre-existing comorbidities, and previous procedures.

Table 4
Adverse Events occurring within Three Months Stratified by Andexanet Alfa and Control Cohorts for All Intracranial Hemorrhage Patients After Propensity Score Matching.

ICD-10 Codes	Characteristics	*After Propensity Score Matching*[a]		
		AA	Control	P value
–	Mortality	119 (31.7%)	65 (17.3%)	≤0.001
I82	Venous Thromboembolism	40 (10.6%)	52 (13.8%)	0.18
I25	Deep Venous Thrombosis Pulmonary Embolism	23 (6.1%)	25 (6.7%)	0.77
I21	Myocardial Infarction	27 (7.2%)	25 (6.7%)	0.77
I63	Cerebrovascular Accident	108 (28.7%)	95 (25.3%)	0.29

AA, Andexanet Alfa.
Pearson and Fishers exact tests, two-sided; statistical significance at $p \leq 0.05$.
[a] Propensity matched pairs for the Andexanet Alfa and control cohorts were established using TrinetX data on age, gender, ethnicity, relevant pre-existing comorbidities, and previous procedures.

usefulness of the ICD-10 and CPT codes aggregated into TriNetX, particularly those used to identify individuals with ICH in this study.[23,24] Furthermore, these studies support our finding about the utility of AA in reference to thromboembolic events.[23,24] Wang et al described the use of heparin in patients who had an ischemic stroke, and they found no change in mortality rates when compared to the untreated group.[29] In addition, they reported postoperative DVT rates as high as 31% in patients with intracranial hemorrhage.[29] Other direct-acting oral anticoagulants, according to Rivera-Caravaca et al, were not related with improved clinical outcomes or a decreased hospitalization rate.[24]

Some studies that evaluated the utility of AA did not compare their rates to a control group, therefore the clinical implications of utilizing AA were not highlighted. Nonetheless, these authors reported a wide range of 30-day mortality rates for distinct categories of hemorrhages.[1,9,16] The risk of VTE in this wide variety of patients is multifactorial, with the type of acquired brain injury influencing the patient's risk. As a result, the variations in reports on the prevalence of VTE, and its occurrences cannot be attributed to AA alone. Geraldini et al found that individuals who had suffered from subarachnoid hemorrhage had an incidence of DVT that was 17% within 10 days of surgery.[30] Notably, Divito et al examining 112 patients with ICH found that VTE occurred in 54 (48.2 %) patients, prior to the administration of AC.[31] Yablon et al reported DVT in 16% of ICH patients, and 11.1% of all brain injury patients.[32] Other studies of AA in patients with active hemorrhage have also reported thromboembolic events at rates of 9.7%,[16] and 11.0%.[33]

The rates of thromboembolic complications in our AA cohort are consistent with other studies of ICH patients and did not indicate a significantly higher risk when compared to the control group, showing that AA did not raise the risk of DVT or PE in our ICH patients.[30-33] The increasing use of Factor Xa inhibitors for CVA prevention in our patient population highlights the importance of assessing the full spectrum of AA therapy in ICH patients.[34] The current study notes an increased rate of all-cause mortality within three months of admission, however the authors of this work emphasize that this finding cannot be solely attributed to AA therapy. Efforts were made to control for risk strata, but unfortunately this was not possible within the confines of the current database. We report the finding here to underscore the importance of further study of AA therapy in real-time, but also highlight the presence of other studies which have showed excellent efficacy and safe use. Lu et al demonstrates a phase II randomized control trial of 76 patients receiving AA therapy for reversal of either rivaroxaban or edoxaban with no deaths reported.[7] Milling Jr et al reports a recent randomized control trial documenting 479 patients who received AA therapy with a mortality rate of 15.7% within 30 days.[35] Given that these findings in randomized control trials are not in congruence with our findings and the cited difficulty in controlling for bleed severity, it is more likely that our mortality rate is artificially increased by a confounding factor. We report this finding with the caveat that further, prospective study of real-time AA therapy in ICH patients is warranted before any definitive conclusion can be made.

4.1. Limitations

It is important to keep in mind the following limitations while interpreting the findings of this study. First, because of the data abstraction approach, the de-identified nature of the data, and the retrospective study design, this study used a database that is relatively new and lacks enough granularity to allow for the evaluation of individualized data. The lack of granularity made it difficult to investigate confounders or independent effect modifiers for the mortality variable. Nonetheless, the database provides users access to a variety of data points that have the potential to inform clinical practice. Furthermore, data were analyzed with a strong statistical protocol, and findings were accurately represented. Second, because neither the ICH score nor the Glasgow Coma Scale score was available, it was impossible to characterize patients by risk strata and therefore the utility of certain findings, such as our increased mortality rate, should be examined with caution. Additionally, while attempts were made to further subclassify ICH by size and location, this information was not readily available and may be attributed to the data collection strategy. Future prospective studies should aim to include a baseline risk stratification and control for it in the analysis. Thirdly, initial assessments revealed discrepancies in the anticoagulant usage within the AA cohort, most likely due to differing coding and billing delays across multiple emergency rooms. These disparities may have led to variations in the reporting times. However, it's

important to note that these limitations did not meaningfully alter the evaluation of thromboembolic events. Moreover, we utilized propensity score matching to create comparable matched pairs, effectively mitigating the majority of uncontrolled confounding variables, thus enhancing the reliability and robustness of our findings.

5. Conclusions

In this large-scale, multi-center, population-based evaluation study of AA in reversing Factor Xa inhibition in patients who have spontaneous ICH, we found that patients had a lower rate of developing thromboembolic events (such as DVT, PE, MI, and/or CVA). Despite the lack of granularity preventing the examination of confounders or independent effect modifiers for mortality, our findings create an opportunity for future studies to expand on these findings and highlight the benefits of AA and its relationship to mortality.

CRediT authorship contribution statement

John Vellek: Writing – original draft, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Omar H. Tarawneh:** Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Syed Faraz Kazim:** Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Oluwafemi P. Owodunni:** Writing – review & editing, Writing – original draft, Visualization, Project administration. **Sophia Arbuiso:** Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Smit Shah:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Alis J. Dicpinigaitis:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Meic H. Schmidt:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Rohini G. McKee:** Writing – review & editing, Writing – original draft, Supervision. **Richard Miskimins:** Writing – review & editing, Writing – original draft, Supervision. **Fawaz Al-Mufti:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Christian A. Bowers:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Brown CS, Scott RA, Sridharan M, et al. Real-world utilization of Andexanet alfa. *Am J Emerg Med*. 2020;38(4):810–814.
2. Portola Pharmaceuticals Inc. *ANDEXXA [Complete Prescribing Information]* [Internet]; 2018 [cited 2022 May]. Available at: https://www.andexxa.com/prescribing-information.html.
3. Ammar AA, Ammar MA, Owusu KA, et al. Andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of factor Xa inhibitors in intracranial hemorrhage. *Neurocrit Care*. 2021;35:255–261.
4. Milling TJ, Pollack CV. A review of guidelines on anticoagulation reversal across different clinical scenarios - is There a general consensus? *Am J Emerg Med*. 2020;38(9):1890–1903.
5. Siddiqui F, Tafur A, Bontekoe E, et al. Assay-based differentiation in the neutralization profile of unfractionated heparin, enoxaparin, and fondaparinux by Andexanet alfa. *Clin Appl Thromb Hemost*. 2020;26, 1076029619895120.
6. Siddiqui F, Tafur A, Ramacciotti LS, et al. Reversal of factor Xa inhibitors by Andexanet alfa may increase thrombogenesis compared to pretreatment values. *Clin Appl Thromb Hemost*. 2019;25, 1076029619863493.
7. Lu G, Conley PB, Leeds JM, et al. A phase 2 PK/PD study of Andexanet alfa for reversal of rivaroxaban and edoxaban anticoagulation in healthy volunteers. *Blood Adv*. 2020;4(4):728–739.
8. Lu G, Pine P, Leeds JM, et al. Andexanet alfa effectively reverses edoxaban anticoagulation effects and associated bleeding in a rabbit acute hemorrhage model. *PLoS One*. 2018;13(3), e0195122.
9. Dobesh PP, Bhatt SH, Trujillo TC, et al. Antidotes for reversal of direct oral anticoagulants. *Pharmacol Ther*. 2019;204, 107405.
10. Tornkvist M, Smith JG, Labaf A. Current evidence of oral anticoagulant reversal: a systematic review. *Thromb Res*. 2018;162:22–31.
11. Heo Y-A. Andexanet alfa in the treatment of acute major bleeding related to apixaban and rivaroxaban: a profile of its use in the USA. *Drugs Ther Perspect*. 2018;34(11):507–512.
12. Sartori M, Cosmi B. Andexanet alfa to reverse the anticoagulant activity of factor Xa inhibitors: a review of design, development, and potential place in therapy. *J Thromb Thrombolysis*. 2018;45(3):345–352.
13. Flaherty D, Connors JM, Singh S, et al. Andexanet alfa for urgent reversal of apixaban before aortic surgery requiring cardiopulmonary bypass: a case report. *In Pract*. 2019;13(7):271–273.
14. Capodanno D, Angiolillo D, et al. Antithrombotic therapy in the elderly. *J Am Coll Cardiol*. 2010 Nov;56(21):1683–1692.
15. Henke PK, Kahn SR, Pannucci CJ, American Heart Association Advocacy Coordinating Committee. Call to action to prevent venous thromboembolism in hospitalized patients: a policy statement from the American heart association. *Circulation*. 2020 Jun 16;141(24):e914–e931.
16. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of Andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326–1335.
17. Majeed A, Eelde A, Agren A, et al. Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy. *Thromb Res*. 2012;129(2):146–151.
18. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128(12):1300–1305. e2.
19. Nia AM, Srinivasan VM, Lall RR, et al. Middle meningeal artery embolization for chronic subdural hematoma: a national database study of 191 patients in the United States. *World Neurosurg*. 2021;153:e300–e307.
20. [Internet]. *TriNetX Analytics Research Network Platform. See the World in Remarkable Clinical Detail*; 2022 [cited 2022 May]. Available at: https://trinetx.com/real-world-data/.
21. Hussain MA, Alali AS, Mamdani M, et al. Risk of intracranial hemorrhage after carotid artery stenting versus endarterectomy: a population-based study. *J Neurosurg*. 2018;129(6):1522–1529.
22. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776–1781.
23. Taquet M, Geddes JR, Husain M, et al. PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatr*. 2021;8(5):416–427.
24. Rivera-Caravaca JM, Buckley BJR, Harrison SL, et al. Direct-acting oral anticoagulants use prior to COVID-19 diagnosis and associations with 30-day clinical outcomes. *Thromb Res*. 2021;205:1–7.
25. Lawrence K, Joos C, Jones AE, et al. Assessing the accuracy of ICD-10 codes for identifying acute thromboembolic events among patients receiving anticoagulation therapy. *J Thromb Thrombolysis*. 2019;48(2):181–186.
26. Harrison SL, Fazio-Eynullayeva E, Lane DA, et al. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. *PLoS Med*. 2020;17(9), e1003321.
27. Harrison SL, Buckley BJR, Fazio-Eynullayeva E, Underhill P, Lane DA, Lip GYH. End-stage renal Disease and 30-day mortality for adults with and without COVID-19. *Eur J Intern Med*. 2021;83:93–95.
28. Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. *J Econ Surv*. 2008 Feb;22(1):31–72.
29. Wang X, Zhou Y-C, Zhu W-D, et al. The risk of postoperative hemorrhage and efficacy of heparin for preventing deep vein thrombosis and pulmonary embolism in adult patients undergoing neurosurgery: a systematic review and meta-analysis. *J Invest Med*. 2017;65(8):1136–1146.
30. Geraldini F, De Cassai A, Correale C, et al. Predictors of deep-vein thrombosis in subarachnoid hemorrhage: a retrospective analysis. *Acta Neurochir*. 2020;162(9):2295–2301.
31. Divito A, Kerr K, Wilkerson C, , et alKitagawa RS. Use of anticoagulation agents after traumatic intracranial hemorrhage. *World Neurosurg*. 2019;123:e25–e30.
32. Yablon SA, Rock Jr WA, Nick TG, et al. Deep vein thrombosis: prevalence and risk factors in rehabilitation admissions with brain injury. *Neurology*. 2004;63(3):485–491.
33. Milling TJ Jr, Clark CL, Feronti C, et al. Management of factor Xa inhibitor-associated life-threatening major hemorrhage: a retrospective multi-center analysis. *Am J Emerg Med*. 2018;36(3):396–402.
34. Merkler AE, Pearce LA, Kasner SE, et al. Left ventricular dysfunction among patients with embolic stroke of undetermined source and the effect of rivaroxaban vs aspirin: a subgroup analysis of the navigate esus randomized clinical trial. *JAMA Neurol*. 2021;78(12):1454–1460.
35. Milling TJ Jr, Middeldorp S, Xu L, et al. Final study report of Andexanet alfa for major bleeding with factor Xa inhibitors. *Circulation*. 2023;147(13):1026–1038.

Abbreviations

(AA): Andexanet alfa
(ICH): Intracranial hemorrhage
(VTE): Venous thromboembolism
(DVT): Deep vein thrombosis
(PE): Pulmonary embolism
(MI): Myocardial infarction
(CVA): Cerebrovascular accidents