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Clinical pathways and outcomes of andexanet alfa administration for reversal of critical bleeding in patients on oral direct factor Xa inhibitors

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Abstract:
Background: Andexanet is FDA-approved for reversal of critical bleeding from factor Xa inhibitors and off-label for surgical reversal. Data are lacking on andexanet administration processes.
Methods: We retrospectively studied patients at a 23-hospital system who received andexanet from November 2019 to March 2023. Abstractors coded demographics, comorbidities, anticoagulant use, andexanet indication, and process times. The primary outcome was presentation-to-andexanet time; diagnosis, ordering, and administration times were calculated. Secondary outcomes included in-hospital post-andexanet major thromboembolism/bleeding and mortality.
Results: 141 patients were analyzed. Andexanet indications were predominantly neurologic bleeding (85.8%). 24 patients (17.0%) transferred from non-tertiary/academic centers to tertiary/academic centers. Median presentation-to-administration time was 192.5 minutes (interquartile range [IQR] 108.0 - 337.0 minutes). Components were: 72.5 minutes (IQR 39.0 - 137.5 minutes) for bleeding diagnosis; 35.5 minutes (IQR 0 - 96.5 minutes) for andexanet ordering; and 53.0 minutes (IQR 38.5 - 78.5 minutes) for administration, which was longer at tertiary/academic hospitals (Ratio 1.5, 95% Confidence Interval [CI] 1.2 – 2.0, $p = 0.002$). Gastrointestinal or other critical bleeding (Ratio 2.59, 95% CI 1.67 – 4.02, $p < 0.001$), and tertiary/academic center treatment (Ratio 1.58, 95% CI 1.15 – 2.18, $p = 0.005$), were associated with increased time. Major thromboembolism, bleeding, and mortality occurred in 10.6%, 12.0%, and 22.9% of patients, respectively.

Conclusions: In our cohort, median presentation-to-administration time was over 3 hours. Cumulative times were longer at tertiary/academic hospitals and for gastrointestinal/other bleeding. Post-andexanet major thromboembolism/bleeding occurred more at tertiary/academic hospitals, possibly related to transfers. Prospective studies may elucidate clinical decision-making bottlenecks.

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Clinical pathways and outcomes of andexanet alfa administration for reversal of critical bleeding in patients on oral direct factor Xa inhibitors

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ABSTRACT

Background: Andexanet is FDA-approved for reversal of critical bleeding from factor Xa inhibitors and off-label for surgical reversal. Data are lacking on andexanet administration processes.

Methods: We retrospectively studied patients at a 23-hospital system who received andexanet from November 2019 to March 2023. Abstractors coded demographics, comorbidities, anticoagulant use, andexanet indication, and process times. The primary outcome was presentation-to-andexanet time; diagnosis, ordering, and administration times were calculated. Secondary outcomes included in-hospital post-andexanet major thromboembolism/bleeding and mortality.

Results: 141 patients were analyzed. Andexanet indications were predominantly neurologic bleeding (85.8%). 24 patients (17.0%) transferred from non-tertiary/academic centers to tertiary/academic centers. Median presentation-to-administration time was 192.5 minutes (interquartile range [IQR] 108.0 - 337.0 minutes). Components were: 72.5 minutes (IQR 39.0 - 137.5 minutes) for bleeding diagnosis; 35.5 minutes (IQR 0 - 96.5 minutes) for andexanet ordering; and 53.0 minutes (IQR 38.5 - 78.5 minutes) for administration, which was longer at tertiary/academic hospitals (Ratio 1.5, 95% Confidence Interval [CI] 1.2 – 2.0, p = 0.002).

Gastrointestinal or other critical bleeding (Ratio 2.59, 95% CI 1.67 – 4.02, p < 0.001), and tertiary/academic center treatment (Ratio 1.58, 95% CI 1.15 – 2.18, p = 0.005), were associated with increased time. Major thromboembolism, bleeding, and mortality occurred in 10.6%, 12.0%, and 22.9% of patients, respectively.

Conclusions: In our cohort, median presentation-to-administration time was over 3 hours. Cumulative times were longer at tertiary/academic hospitals and for gastrointestinal/other bleeding. Post-andexanet major thromboembolism/bleeding occurred more at tertiary/academic hospitals, possibly related to transfers. Prospective studies may elucidate clinical decision-making bottlenecks.

Key Words: direct acting oral anticoagulant (DOAC), bleeding reversal, andexanet alfa, clinical pathway, thromboembolism

Summary Table:

What is known on this topic?

- Andexanet alfa is approved by the US Food and Drug Administration (FDA) for reversal of critical bleeding associated with apixaban and rivaroxaban.
- Prompt administration of andexanet alfa is essential for reducing morbidity and mortality.

- Few previous studies have reported times from patient presentation to andexanet alfa administration, and thus, relatively little is known about optimal processes at a health system level.

What does this paper add?

- This study showed that in a cohort of 141 patients from a 23-hospital integrated health system, median cumulative process time from patient presentation to andexanet alfa administration was more than 3 hours; time from presentation to diagnosis of critical bleeding, as well as time from andexanet alfa order to administration, represented longer component times and potential process bottlenecks.
- Care at a tertiary/academic center, or presentation with gastrointestinal bleeding were associated with longer cumulative process times, likely related to variable facility adherence to health system andexanet alfa protocols.
- Post-andexanet major thromboembolism or bleeding occurred more often at tertiary/academic centers, but there was no difference in mortality.

INTRODUCTION

Andexanet alfa is a recombinant protein similar in structure to endogenous Factor Xa (FXa), that acts as a decoy in binding FXa receptors to counteract direct oral anticoagulants (DOACs). It was the first agent approved by the US Food and Drug Administration (FDA) for reversal of critical bleeding associated with apixaban and rivaroxaban (1). Efficacy and safety of andexanet alfa was demonstrated in the ANNEXA-4 trial (2), which enrolled 479 patients with major

bleeding (including 69.1% intracranial hemorrhage [ICH] and 22.8% gastrointestinal bleeding) who had taken a FXa inhibitor within the preceding 18 hours. The final study population showed excellent or good hemostasis in 80% of evaluated patients, compared with 72% in a previous study of prothrombin complex concentrate (PCC) in patients with bleeding while taking vitamin K antagonist therapy (3). Moreover, rates of post-andexanet thrombosis and death were comparable to those in previous studies of patients who stopped FXa inhibitors due to acute bleeding (4,5). These findings, along with data showing less mortality benefit when using prothrombin complex concentrates (PCCs) (2,5), led professional society expert panels to recommend andexanet alfa for reversal of critical bleeding in patients on oral direct FXa inhibitors (6–8).

A recently published study of time to anticoagulation reversal and outcomes in ICH suggested a 1-hour door-to-treatment time or less as being optimal for improved survival (9). In addition, a "call-to-action" for mandating a multidisciplinary and process-centered "Code ICH" also suggested a 1 – hour window for reversal of anticoagulation in the setting of ICH (10). As such, it has been suggested that pre-hospital protocols and early administration of andexanet in cases of life-threatening bleeding should be prioritized to reduce morbidity and mortality (11). To date, data are lacking on the optimal processes at a health care system level to assess administration times of andexanet alfa. Our study aimed to evaluate institutional processes, hospital types, and clinical outcomes regarding reversal with andexanet alfa for patients on oral direct FXa inhibitors with critical bleeding.

METHODS

Study Oversight

This was an investigator-initiated, retrospective, observational study conducted at a large, 23-hospital, integrated healthcare delivery network in the New York metropolitan area, supported by AstraZeneca Pharmaceuticals, PC. The funders had no role in study design or conduct, data collection or analysis, or writing of the manuscript. The study was approved by the health system Institutional Review Board overseeing all study hospitals with waiver of informed consent for this retrospective, non-interventional study. Authors assume responsibility for the accuracy and completeness of the data and analyses.

Patients and Data Collection

Clinical pharmacy colleagues compiled and maintained a database using REDCap (Research Electronic Data Capture)(12,13) of all patients admitted to health system hospitals who received andexanet alfa for reversal of oral direct FXa inhibitor critical bleeding starting from November 3, 2019, when andexanet alfa was first added to our formulary, through March 4, 2023. Our system developed a centralized protocol that came into place at the time of formulary approval for use of andexanet in critical site bleeding related to ICH, whereas use for other critical site bleeding and limited neurosurgical procedures required a Medical Director or designee approval. The protocol is included in the **Appendix.** A dedicated team of abstractors manually collected demographics and other characteristics including age, sex, race, weight, estimated glomerular filtration rate (eGFR), baseline cardiovascular conditions (including history of myocardial infarction, ischemic stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], atrial fibrillation, congestive heart failure, diabetes mellitus, and hypertension), type of DOAC (i.e., apixaban or rivaroxaban), indication for anticoagulation, total daily anticoagulant dose, and time of last dose prior to presentation to the Emergency Department (ED). We also collected data on concomitant use of

antiplatelet agents (e.g., aspirin and P2Y12 inhibitors). We recorded bleeding indications for reversal with andexanet alfa, which included intracranial hemorrhage, other central nervous system (CNS) bleeding, gastrointestinal bleeding, and other critical site bleeding (which included intraocular hemorrhage with vision compromise, airway bleeding/pulmonary hemorrhage, hemopericardium, aortic rupture/dissection/hemorrhage, closed space hemorrhage/compartment syndrome risk, hepatic artery bleeding, and bleeding due to perforated viscus) and need for urgent surgery. We also coded cases in which the indication for andexanet was urgent surgical reversal. Finally, each patient was categorized as receiving treatment at a tertiary/academic center versus a non-tertiary/academic center; the number of patients transferred from non-tertiary/academic centers to tertiary/academic centers was tallied.

Outcomes

The primary outcome was cumulative process time from patient presentation to the ED to administration of andexanet alfa. This cumulative time was divided into three segments. The first segment was time from patient presentation to the ED until diagnosis of critical bleeding. Diagnosis time was generally coded as the time a final radiologic report was submitted in the electronic health record (EHR), in cases that depended on imaging for confirmation of bleeding, for example, ICH, other central nervous system bleeding, and hemopericardium. In cases of gastrointestinal bleeding, diagnosis time was coded as the time of EHR documentation by a specialist recommending a confirmatory study (e.g., endoscopy). The second segment was time from diagnosis of critical bleeding to ordering of andexanet alfa within the EHR, and the final segment was time from ordering of andexanet alfa to administration of andexanet alfa (as documented by Nursing within the medication administration record of the EHR). Manual chart

review revealed frequent instances in which patients were presumptively diagnosed with critical bleeding and andexanet alfa was ordered before radiologic studies were obtained. In these cases, time from diagnosis of critical bleeding to andexanet alfa ordering was coded as zero.

Secondary outcomes were clinical and included a composite of in-hospital post-andexanet venous thromboembolism (VTE) (including DVT, PE, or splanchnic vein thrombosis); arterial thromboembolism (ATE) (including myocardial infarction, acute ischemic stroke, systemic embolism, or major adverse limb event); and major bleeding, defined according to International Society on Thrombosis and Haemostasis criteria (14), and in-hospital mortality.

Statistical Analysis

Descriptive statistics (median, interquartile range, minimum, maximum for continuous variables, and frequency distribution for categorical variables) were calculated. Univariable linear regression was used to screen variables which were associated with the log transformed cumulative time from patient presentation to andexanet administration with a p-value criterion of $p < 0.05$ for entry into the model selection procedure. Backward selection was used with variable entry and retention criteria of $p < 0.05$ to select the final multivariable model. This procedure was also used to screen variables associated with the three time segments of interest (diagnosis, ordering, and administration times). Log transformation was performed to meet the assumption of the regression model. We included sensitivity analyses where these time segments were analyzed separately for tertiary versus non-tertiary hospitals. Univariable logistic regression was also used to screen variables which were associated with the composite secondary outcomes of post-andexanet alfa ATE/VTE/major bleeding or in-hospital mortality with a p-value criterion of

$p < 0.05$ for entry into the model selection procedure. Backward selection was used with variable entry and retention criteria of $p < 0.05$ to select the final multivariable model.

RESULTS

Characteristics of the Population

The initial study population consisted of 165 patients. In 13 cases, technical limitations precluded extraction of electronic health record (EHR) data from outside our system's main facilities. An additional 6 patient records were excluded for lack of a documented ED arrival time. Finally, 5 patient records were excluded for unreliable component times. After manual review of the remaining 141 records, there were rare instances of missing data: baseline anticoagulant dose was not captured in approximately 10 cases, time of diagnosis in approximately 4 cases, and vital status was unknown in 1 case. Thus, the final study population consisted of 141 patients: mean age was 77.3 years; 56.7% of patients were men; self-identified race breakdown was 73.8% White, 8.5% Black or African American, 2.1% Asian, and 14.2% Other/Multiracial; mean weight was 79.6 kilograms (kg); and mean eGFR was 65.7 ml/min/1.73m^2 (**Table 1**). At baseline, 73.8% of patients were prescribed apixaban and 25.5% rivaroxaban; 31.2% of patients were categorized as taking a low dose, and 68.1% a high (treatment) dose. Most patients (66.7%) had taken their most recent dose of anticoagulant within 24 hours preceding ED presentation. Concomitant single antiplatelet therapy had been prescribed in 34.8% of patients (27.7% aspirin, 6.4% clopidogrel); only 4.3% of patients had been prescribed dual antiplatelet therapy at baseline.

Indications for andexanet alfa were predominantly neurological, with 83.0% for ICH and 2.8% for other CNS bleeding. Gastrointestinal bleeding comprised 2.1% of indications. Additional reversal agents were given in 17.9% of patients and included fresh frozen plasma, desmopressin, tranexamic acid and KCentra (a PCC, which was given to 10 patients). Most patients (86.6%) had at least two cardiovascular comorbidities at baseline, and 13.5% had at least four (**Table 1**).

Approximately three-quarters of patients (72.3%) were treated at tertiary/academic centers; 24 patients (17.0%) were transferred from non-tertiary academic centers to receive definitive treatment at tertiary/academic centers (**Table 1**).

Primary Outcome

For the full study population, median cumulative time from patient presentation in the ED to andexanet alfa administration was 192.5 minutes (interquartile range [IQR] 108.0 - 337.0 minutes). Median time from ED presentation to diagnosis of critical bleeding was 72.5 minutes (IQR 39.0 - 137.5 minutes). Median time from diagnosis of critical site bleeding to andexanet alfa ordering was 35.5 minutes (IQR 0 - 96.5 minutes). Median time from andexanet alfa ordering to andexanet alfa administration was 53.0 minutes (IQR 38.5 - 78.5 minutes) (**Table 2**).

Median cumulative time from presentation to andexanet administration was significantly longer at tertiary/academic hospitals (223.0 minutes, IQR 142.0 – 358.0 minutes) than at non-tertiary/academic hospitals (130.0 minutes, IQR 87.0 – 253.0 minutes) (Ratio 1.6, 95% CI 1.2 – 2.3, p = 0.005). There was no difference in median time from ED presentation to diagnosis of critical bleeding (90.0 minutes [IQR 39.0 – 162.0 minutes] versus 65.0 minutes [IQR 39.0 –

98.0]) (Ratio 1.41, 95% CI 0.91 – 2.17, p = 0.122) and no difference in median time from diagnosis of critical site bleeding to andexanet alfa ordering (45.0 minutes [IQR 0 – 98.0 minutes] versus 16.0 minutes [IQR 0 – 82.0 minutes]) (Ratio 1.40, 95% CI 0.62 – 3.16, p = 0.418) when comparing tertiary/academic hospitals versus non-tertiary/academic hospitals. Longer times from andexanet alfa ordering to administration were observed at tertiary/academic hospitals (median 59.0 minutes, IQR 46.0 – 82.0 minutes) compared to non-tertiary/academic hospitals (median 39.0 minutes, IQR 32.0 – 62.0 minutes) (Ratio 1.5, 95% CI 1.2 – 2.0, p = 0.002) (**Supplemental Table 1**).

Secondary Outcomes

Post-andexanet major thromboembolism, bleeding, and mortality occurred in 10.6%, 12.0%, and 22.9% of the overall population, respectively **(Table 2)**. The composite of post-andexanet major thromboembolism or bleeding occurred more often in patients at tertiary/academic centers (29.4% versus 5.1%, Odds Ratio [OR] 7.71, 95% CI 1.75 - 34.04, p = 0.007). This was driven by numerical but non-significant differences in thromboembolism (14.7% versus 0%, p = 0.07). There was no difference in post-andexanet alfa major bleeding or in-hospital mortality (**Supplemental Table 1**).

Regression Analyses

Age, sex, race, time from last anticoagulant dose, baseline antiplatelet use, other reversal agent use, category of andexanet alfa indication (ICH or other neurologic bleeding, gastrointestinal or other critical site bleeding, or urgent surgery), and treatment at a tertiary/academic versus non-tertiary academic hospital were screened for association with cumulative process time and the

three time segments of interest. Our final linear regression model showed that diagnoses of gastrointestinal bleeding or other critical site bleeding (Ratio 2.59, 95% CI 1.67 – 4.02, p< 0.001), as well as treatment at a tertiary/academic center (Ratio 1.58, 95% CI 1.15 – 2.18, p = 0.005), were risk factors for increased cumulative time from ED presentation to andexanet alfa administration. None of the tested factors were associated with increased individual time segments.

Age, sex, race, weight, eGFR, type of baseline anticoagulant, total daily anticoagulant dose, time from last anticoagulant dose, baseline antiplatelet use, other reversal agent use, number of baseline cardiovascular risk factors, category of andexanet alfa indication (ICH or other neurologic bleeding, gastrointestinal or other critical site bleeding, or urgent surgery), and time segments of interest (time from ED presentation to critical bleeding diagnosis, time from diagnosis to andexanet alfa order, and time from andexanet alfa order to andexanet alfa administration) were screened for association with post-andexanet thromboembolism or major bleeding. None of these factors showed a significant association with the composite clinical outcome.

DISCUSSION

This retrospective study of andexanet alfa use for reversal of critical bleeding associated with oral direct FXa inhibitors evaluated process times as well as clinical outcomes for 141 patients at both tertiary/academic and non-tertiary/academic facilities within a 23-hospital system. Median cumulative time from patient presentation to the ED until dosing of andexanet alfa was approximately three hours. Final linear regression showed that care at a tertiary/academic facility

conferred 58% increased cumulative time, while gastrointestinal or other critical site bleeding conferred 2.5 times increased cumulative time. Median time from andexanet alfa order to administration was 20 minutes longer at tertiary/academic facilities, a significant difference. The secondary, composite clinical outcome of post-andexanet thromboembolism or major bleeding occurred more often at tertiary/academic centers, but there was no difference in mortality.

The diagnosis phase comprised the component time with the longest median duration, at 72.5 minutes; this is despite the fact that in some instances, patients were presumptively diagnosed with critical bleeding based on initial clinical data, before radiographic studies results were officially reported. We suspect this was due to Radiology staff contacting the ordering providers to verbally convey critical imaging results in advance of submitting formal EHR reports, which historically has been common within our institution. Overall, this suggests our data overestimate diagnosis times. Conversely, time from diagnosis of critical bleeding to andexanet alfa order was the shortest time component, at 35.5 minutes. The above assumption thus would imply our data underestimate ordering time. Per our institutional policy (**Appendix**), andexanet alfa is a restricted medication and formal approval from site designees (typically the hospital Medical Director) must be obtained in advance of ordering. We suspect this approval is the limiting step within the diagnosis-to-order time segment. Finally, the median order-to-administration time was nearly one hour. There are many steps within this time segment that are not typically documented within our EHR, including Pharmacy verification of order, compounding, and delivery to the point of care. Moreover, it has been observed historically that the time of documentation of medication administration varies widely among Nursing staff, and in some cases occurs well after drug has been administered. This implies our data overestimate this time segment.

Differences in these Pharmacy or Nursing processes may also account for longer order-to-administration times at tertiary/academic hospitals in our study. Finally, the fact that gastrointestinal or other critical site bleeding conferred 2.5 times increased cumulative time likely relates to our institutional policy that prioritizes ICH as the preferred indication for andexanet alfa and does not include gastrointestinal bleeding, which in our system can typically be treated with other reversal agents, such as PCCs. Considering that gastrointestinal or other critical site bleeding comprised less than 15% of the cohort, process differences at tertiary/academic versus non-tertiary/academic facilities are likely of greater clinical significance.

The increased frequency in clinical outcomes at tertiary/academic hospitals was driven by rates of thromboembolism, which may reflect greater severity of illness or baseline risk related to cardiovascular co-morbidities in these facilities. This may also relate to frequent transfers of high acuity patients from non-tertiary community hospitals to the tertiary/academic hub of our system. However, considering the predominance of ICH, the rate of thromboembolism in the full population (10.6%) was comparable to that of an ICH sub-study population of the ANNEXA-4 trial (9.3%), albeit with greater ICH-related mortality in our study (22.4% vs. 15.0%) (15).

Few studies have reported process times for andexanet alfa administration. In a single center cohort of 44 patients receiving andexanet alfa within 24 hours of surgery, the median time from andexanet alfa order to administration was 30 minutes [IQR 19.8-43.0], while cumulative time from hospital presentation to andexanet administration was 2.6 hours [IQR 1.2-5.5] (16), similar to the process time in our study. One additional study comparing andexanet and 4-factor PCC for

ICH found longer median times from order entry to administration with andexanet (1.1 hours [IQR 0.8-1.3] versus 0.5 hours [0.1-0.8]), which was attributed to drug compounding complexity (17). In a descriptive, preliminary analysis of the ANNEXA-4 study that analyzed 67 patients, mean time from ED presentation to andexanet administration was 4.8 ± 1.8 hours (18), a relatively longer process time in the context of randomized controlled trial protocol compared to our study results.

Study of health facility protocols and restrictions on andexanet alfa administration may help elucidate differences in process times. A broad effort (19) describing 89 sites within the United Kingdom National Health System found that 58% had formal andexanet protocols in place, all of which specified gastrointestinal bleeding as the only approved indication. Of these protocols, 70% contained guidance on timing of last DOAC dose. Authors highlighted the practice of gatekeeping, in which andexanet ordering required approval of a specialist; this was a hematologist in 43%, a gastroenterologist in 14%, and both specialists in 4% of centers. While reasonable for judicious administration of a costly drug, gatekeeping also self-evidently increases clinical decision-making times. In our institution, typically a physician administrator served as the gatekeeper. Medical directors at study hospitals were most commonly intensivists, hospitalists, or Emergency Medicine specialists; to our knowledge none were primarily neurologists, hematologists, or gastroenterologists. It is possible that gatekeeper specialty training, as well as proximity to front-line medical care, would influence process efficiency.

Broadly, the data and our experience suggest several possible explanations for differences in overall process times when comparing academic and non-academic centers. First, as noted, the

transfer rate of 17% suggests that a substantial proportion of academic center patients required additional time for evaluation and vetting of information from the transferring (non-academic) hospital. In our experience, it is typical that additional handoffs between providers as well as our system's transfer center may reduce efficiency. Second, variable adherence to our system andexanet policy may have contributed; non-academic centers may be less aware of the policy and thus less likely to wait for site approvals.

Our study has several strengths and limitations. While our data are retrospective and from a single health system, the sample population is relatively large for a study of clinical process. Data were also acquired from nearly two dozen facilities, both tertiary/academic and non-tertiary/academic, over a period of four years. Moreover, our study period began approximately one year following FDA approval of andexanet alfa, when experience with the drug was limited worldwide, and difficulty with generalizability could reasonably apply to data from any center. There were substantial challenges in calculating component times due to the organization of our EHR, as well as historical lack of granularity in staff documentation and reliance on verbal communication of imaging results. However, as nearly 5 in 6 cases analyzed were ICH or other central nervous system bleeding, the majority of cases were coded strictly according to radiologic report times, which presumably were entered into the EHR shortly after verbal communication of critical results.

While our findings suggest that individual centers may present different bottlenecks after patients have arrived, the presence of both pre-hospital procedures and use of multidisciplinary teams that already exist for critical medical emergencies such as Code Stroke may improve overall process

times and clinical outcomes. A “call-to-action” using an existing hospital-based multidisciplinary team to initiate a “Code ICH” has recently been proposed using bundled care and defined metrics to initiate timely treatment of ICH, including anticoagulant-related reversal using specific and non-specific reversal agents (10). This type of intervention is supported by recently published data from the American Heart Association Get With The Guidelines-Stroke registry, which revealed that patients with anticoagulation-associated ICH who received reversal agents within 60 minutes of hospital arrival had decreased mortality or discharge to hospice, although no difference in functional outcome (9).

In conclusion, our cohort median time from ED presentation to andexanet alfa administration was approximately three hours. Cumulative times were longer at tertiary/academic hospitals, which may relate to delays between drug ordering and administration. Gastrointestinal bleeding was associated with longer process time, likely due to more nuanced decision-making in light of system policy favoring andexanet for ICH. Post-andexanet thromboembolism or major bleeding occurred more often at tertiary/academic hospitals, likely due to transfers of high acuity patients. Prospective studies may elucidate Pharmacy, Nursing, or clinical decision-making bottlenecks. Pre-hospital procedures involving activation teams for ICH or other critical bleeding in the community and in-hospital multidisciplinary “Code ICH” teams may be practical strategies for improving efficiency.

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contributed statistical analysis. A.C.S, M.G., K.S., I.K., T.L., K.O., N.T., and J.J. contributed to data interpretation. A.C.S, M.G., and N.T. drafted the first manuscript version. All authors have read, critically revised, and approved the final version. All authors had access to study data and take responsibility for data/analysis accuracy. The study was presented at the American Heart Association Scientific Sessions (11/1/2023).

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Table 1. Demographics and other characteristics of cohort

Age in years, mean (SD)	77.3 (10.5)
Sex (%)	
Male	56.7
Female	43.3
Race, %	
Asian	2.1
Black/African American	8.5
White	73.8
Other/Multiracial	14.2
Weight in kg, mean (SD)	79.6 (22.5)
Estimated GFR in ml/min/1.73m^2, mean (SD)	65.7 (26.0)
Baseline anticoagulant use, %	
Apixaban	73.8
Rivaroxaban	25.5
Anticoagulant total daily dose, %	

Low (Apixaban ≤ 5 mg **OR** Rivaroxaban ≤ 10 mg)	31.2
High (Apixaban > 5 mg **OR** Rivaroxaban > 10 mg)	68.1
Time of last anticoagulant dose before andexanet, %	
≤ 24 hours	66.7
> 24 hours	33.3
Baseline antiplatelet use, %	
Aspirin	27.7
Clopidogrel	6.4
Aspirin and clopidogrel	4.3
No antiplatelets	61.7
Other reversal agent administered, %*	17.9
Number of baseline cardiovascular risk factors, %	
0-1	13.5
2-3	73.1
≥ 4	13.5
Indication for reversal, %	
Intracranial hemorrhage	83.0
Other central nervous system bleeding	2.8
Gastrointestinal bleeding	2.1
Other critical site bleeding	9.9
Pre-surgery	5.0
Type of facility, %	
Tertiary/academic	72.3
Non-tertiary/academic	27.7
Transfers from non-tertiary/academic to tertiary/academic facilities, no. (%)	24 (17.0)

SD = standard deviation, eGFR = estimate glomerular filtration rate

* Includes KCentra, fresh frozen plasma, desmopressin, tranexamic acid

† Sum > 100% as some patients received andexanet and underwent surgery to treat bleeding.

Table 2. Major process and clinical outcomes

Primary Outcome	
Median cumulative time from ED presentation to andexanet administration, min (IQR)	192.5 (108.0 – 337.0)
Median time from ED presentation to diagnosis, min (IQR)	72.5 (39.0 – 137.5)
Median time from diagnosis to andexanet alfa order, min (IQR)	35.5 (0 – 96.5)
Median time from andexanet alfa order to administration, min (IQR)	53.0 (38.5 – 78.5)
Secondary Outcomes	
Composite of post-andexanet VTE*, ATE†, or major bleeding‡, %	22.7
VTE or ATE	10.6
Major bleeding	12.0
In-hospital mortality (full population), %	22.9
Intracranial hemorrhage	22.4
Other central nervous system bleeding	25.0
Gastrointestinal bleeding	33.3
Other critical site bleeding	25.0
Pre-surgery	0

Min = minutes, SD = standard deviation, IQR = interquartile range, VTE = venous thromboembolism, ATE = arterial thromboembolism, P = p-value

* VTE includes deep vein thrombosis and pulmonary embolism

† ATE includes myocardial infarction, ischemic stroke, systemic embolism, and major adverse limb event

‡ Major bleeding per International Society on Thrombosis and Haemostasis definition

Supplemental Table 1. Major process and clinical outcomes by type of facility

Primary Outcome	Tertiary	Non-Tertiary	P
Median cumulative time from ED presentation to andexanet administration, min (IQR)	223.0 (142.0 – 358.0)	130.0 (87.0 – 253.0)	0.005
Median time from ED presentation to diagnosis, min (IQR)	90.0 (39.0 – 162.0)	65.0 (39.0 – 98.0)	0.122
Median time from diagnosis to andexanet alfa order, min (IQR)	45.0 (0 – 98.0)	16.0 (0 – 82.0)	0.418
Median time from andexanet alfa order to administration, min (IQR)	59.0 (46.0 – 82.0)	39.0 (32.0 – 62.0)	0.002
Secondary Outcomes			
Composite of post-andexanet VTE*, ATE†, or major bleeding‡, %	29.4	5.1	0.007
VTE or ATE	14.7	0	0.072
Major bleeding	14.7	5.1	0.173
In-hospital mortality, %	20.1	28.2	0.351

Min = minutes, SD = standard deviation, IQR = interquartile range, VTE = venous thromboembolism, ATE = arterial thromboembolism, P = p-value

* VTE includes deep vein thrombosis and pulmonary embolism

† ATE includes myocardial infarction, ischemic stroke, systemic embolism, and major adverse limb event

‡ Major bleeding per International Society on Thrombosis and Haemostasis definition