Efficacy and Safety of Andexanet Alfa for Bleeding Caused by Factor Xa Inhibitors: A Systematic Review and Meta-Analysis

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Abstract

Direct oral anticoagulants (DOAC) including factor Xa inhibitors are associated with bleeding events which can lead to severe morbidity and mortality. Reversal agents like andexanet alfa (AA) and 4F-PCC (four-factor prothrombin complex concentrate) are available for treating bleeding that occurs with DOAC therapy but a comparison on their efficacy is lacking. In this study, we analyzed the efficacy and safety of patients treated with andexanet alfa for bleeding events from DOAC. Databases were searched for relevant studies where AA was used to determine efficacy and safety in bleeding patients who were on factor Xa inhibitors. Published papers were screened independently by two authors. Bevan et al. (The Curacist Collaborative, 2019) was used for data synthesis. Odds ratio (OR) and mean difference (MD) was used to estimate the outcomes with a 95% confidence interval (CI). Among 1245 studies were identified after a thorough database search and three studies were included for analysis. AA resulted in lower odds of mortality compared to 4F-PCC (OR: 0.57; 95% CI: 0.20-0.71) among patients with intracranial hemorrhage. There was no difference in thrombotic events between patients receiving AA and 4F-PCC. However, there were no differences in thrombotic events, length of ICU, and hospital stay between patients treated with AA and 4F-PCC.

Keywords: control hemorrhage, meta-analysis, bleeding reversal, factor xa inhibitors, andexanet alfa

Introduction And Background

Direct oral anticoagulants (DOAC) have been increasingly used in patients for the prevention of systemic embolization in atrial fibrillation as well as treatment and prevention of deep vein thrombosis (DVT) and venous thromboembolism (VTE). As a result, the indications of DOAC have significantly expanded in the last decade [1-6]. Predictable pharmacokinetics and pharmacodynamics, rapid onset and offset of action, few drug interactions, and absence of need for regular laboratory monitoring provide an advantage to oral factor Xa inhibitors over traditional Vitamin K antagonists (VKA). Drug interactions and absence of need for regular laboratory monitoring provide an advantage to oral factor Xa inhibitors compared to 4F-PCC. However, there were no differences in thrombotic events, length of ICU, and hospital stay between patients treated with AA and 4F-PCC.

Before the introduction of andexanet alfa (AA), off-label use of 4-factor prothrombin complex concentrates (4F-PCC) was advised and used in the situation of life-threatening bleeding [7]. Prothrombin complex concentrates (PCCs) are isolated from fresh frozen plasma (FFP) and contain Vitamin K-dependent factors II, VII, IX, and X [8]. In May 2018, AA received FDA approval for use in patients treated with factor Xa inhibitors and application in the setting of life-threatening or uncontrolled bleeding following ANNEXA-A and ANNEXA-B trials in healthy participants [8,9]. AA is a modified recombinant, catalytically inactive form of human factor Xa, which binds and sequesters factor Xa inhibitor molecules that reduce anti-factor Xa activity rapidly in the body [9]. A multicenter, prospective, open-label, single-group study ANNEXA-4 was done in bleeding patients following FDA approval, which showed the drug’s good efficacy and safety profile [9]. Randomized controlled trials have not been done, given the risks of using a placebo in acutely bleeding patients. However, some retrospective observational studies and case series studying the efficacy and safety of AA in bleeding patients have been published. In addition, some studies have compared efficacy and safety with 4F-PCC. We have conducted this systematic review and meta-analysis to analyze the effectiveness and safety profile of AA in bleeding caused by factor Xa inhibitors.

Review

Methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the systematic review of available literature [10]. The study protocol was registered in the International prospective register of systematic reviews (PROSPERO): CRD42012124429.

Literature search

We searched PubMed, PubMed Central, Scopus, Embase, and Cochrane library for relevant studies published till February 2021. Searches were conducted using the keywords like “andexanet alfa,” “andexanet,” “andexanet alpha,” “bleeding,” “factor Xa inhibitor,” and “factor Xa inhibitors” and appropriate boolean operators. Details of the search strategy are available in Supplementary Material 1.

Selection of studies

A. Types of Studies

We included studies done to determine the efficacy and safety of andexanet alfa in patients who had bleeding in the setting of factor Xa inhibitor use. As randomized controlled trials were not available, we included prospective and retrospective studies and case series with more than two patients. AA was used to determine efficacy and safety in bleeding patients on factor Xa inhibitors in qualitative analysis. In addition, the studies with both treatment and control groups were included in the quantitative synthesis.

B. Types of Participants

The studies required patients to be more than 15 years of age and had bleeding in the setting of factor Xa inhibitor use. As randomized controlled trials were not available, we included prospective and retrospective studies and case series with more than two patients. AA was used to determine efficacy and safety in bleeding patients on factor Xa inhibitors in qualitative analysis.

C. Types of Interventions

Andexanet alfa was taken in the treatment arm, while 4F-PCC or other blood products were included in the control arm.

D. Types of Outcome Measures

Our outcome of interest was hemorrhagic efficacy, mortality within 30 days, the incidence of thrombotic events, and length of hospital and ICU stay following treatment with AA or other blood products.

We excluded types of studies with the following characteristics: meta-analysis, reviews, in-vitro studies, studies done on healthy subjects, case reports, editorials, opinions, letters, protocols,

How to cite this article

Shrestha D B, Budhathoki P, Adhikari A, et al. (December 23, 2021) Efficacy and Safety of Andexanet Alfa for Bleeding Caused by Factor Xa Inhibitors: A Systematic Review and Meta-Analysis. Cureus 13(12): e20632. DOI 10.7759/cureus.20632
abstracts, presentations, dissertation, and animal studies. Case series with fewer than ten patients, articles where full-text articles were not available, ongoing studies, and studies with incomplete data were also excluded.

Data extraction and management

Titles, abstracts, and full texts were screened for study and report characteristics that matched eligibility criteria. Studies were independently screened by two reviewers (AA and SS) using Covidence (Covidence systematic review software, Ventra Health Innovation, Melbourne, Australia) and data were extracted for both quantitative and qualitative synthesis. The conflicts were resolved by taking the opinion of the third reviewer (NK). The data extraction sheet was created using Microsoft Excel software. One reviewer collected the data from all articles; the second reviewer verified the data for accuracy and highlighted discrepancies; the third reviewer resolved any disagreements and carried out a thorough evaluation to ensure that only the outcomes of interest were taken into account. The following variables were included: first author, type of design, size of study, year of publication, sample size, mean age, percentage of male and female, indication for anticoagulation, hemostatic efficacy, mortality within 30 days, length of hospital stay, length of ICU stay and incidence of thrombotic events.

Table of Questionnaire Results

| Question | Ammar et al. [17] | Barnett et al. [18] | Coleman et al. [19] |
|----------|------------------|-------------------|-------------------|
| 1. Were there clear criteria for inclusion in the case series? | Yes | No | Yes |
| 2. Was the condition measured in a standard, reliable way for all participants included in the case series? | Yes | Yes | Yes |
| 3. Were valid methods used for identification of the condition for all participants included in the case series? | Yes | Yes | Yes |
| 4. Did the case series have consecutive inclusion of participants? | Yes | Yes | Yes |
| 5. Did the case series have the complete inclusion of participants? | Yes | No | Yes |
| 6. Was there clear reporting of the demographics of the participants in the study? | Yes | No | Yes |
| 7. Was there clear reporting of clinical information of the participants? | Yes | Yes | Yes |
| 8. Were the outcomes or follow-up results of cases reported? | Yes | Yes | Yes |
| 9. Was there clear reporting of the presenting symptoms/physical(s) demographic information? | Yes | Yes | Yes |
| 10. Was the follow-up complete, and if not, were the reasons for loss to follow-up described and explored? | Yes | Yes | Yes |
| 11. Were strategies to address incomplete follow-up utilized? | Yes | Yes | Yes |

Overall Appraisal

Include Include Include

TABLE 1: JBI Critical Appraisal of Cohort Studies

| Question | Brown et al. 2019 [20] | Corridore et al. 2019 [21] | Culbreth et al. 2019 [22] | Culbreth et al. 2018 [23] | Giovine et al. 2020 [24] | Nederpelt et al. 2020 [25] | Stevens et al. 2019 [26] |
|----------|----------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| 1. Were there clear criteria for inclusion in the case series? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the condition measured in a standard, reliable way for all participants included in the case series? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Were valid methods used for identification of the condition for all participants included in the case series? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4. Did the case series have consecutive inclusion of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Did the case series have the complete inclusion of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 6. Was there clear reporting of the demographics of the participants in the study? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 7. Was there clear reporting of clinical information of the participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 8. Were the outcomes or follow-up results of cases reported? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 9. Was there clear reporting of the presenting symptoms/physical(s) demographic information? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was statistical analysis appropriate? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

TABLE 2: JBI critical appraisal of case series

| Question | Statistical Analysis | Risk of Bias |
|----------|---------------------|--------------|
| 1. Were there clear criteria for inclusion in the case series? | Yes | Yes |
| 2. Was the condition measured in a standard, reliable way for all participants included in the case series? | Yes | Yes |
| 3. Were valid methods used for identification of the condition for all participants included in the case series? | Yes | Yes |
| 4. Did the case series have consecutive inclusion of participants? | Yes | Yes |
| 5. Did the case series have the complete inclusion of participants? | Yes | Yes |
| 6. Was there clear reporting of the demographics of the participants in the study? | Yes | Yes |
| 7. Was there clear reporting of clinical information of the participants? | Yes | Yes |
| 8. Were the outcomes or follow-up results of cases reported? | Yes | Yes |
| 9. Was there clear reporting of the presenting symptoms/physical(s) demographic information? | Yes | Yes |
| 10. Was statistical analysis appropriate? | Yes | Yes |

Overall Appraisal

Include Include Include

Statistical Analysis

RevMan 5.4 (The Cochrane Collaboration, 2020) was used for statistical analysis. Odds ratio (OR) and mean difference (MD) were used to estimate the outcome with a 95% confidence interval (CI).

Assessment of Heterogeneity

The statistical heterogeneity among the studies was calculated and assessed with the I² test based on previously recommended stratifications. In the case of heterogeneity, we used the inverse and random-
Results

A total of 1245 studies were identified after thorough database searching, and 351 duplicates were removed. Title and abstracts of 894 studies were screened, and 860 irrelevant studies were excluded. The full-text eligibility of 34 studies was assessed, and 24 studies were excluded for definite reasons (Figure 1). A total of 10 studies were included in the qualitative summary (Table 3), and three studies were included in the quantitative analysis.

**FIGURE 1: PRISMA Flow Diagram**

| Study ID | Population | Intervention | Comparator | Outcome |
|----------|------------|--------------|------------|---------|
| Ammar et al., 2021. A retrospective single-center cohort study, US [17] | Patients with life-threatening traumatic or spontaneous intracranial bleeds in the setting of FXa (apixaban or rivaroxaban) use: N=44 (T=28, C=16); male: T=61%, C=69%; female: T=39%, C=31%; age (median, IQR) T: 78 (70–87), C: 80 (74–84); GCS on admission (median, IQR), T: 14 (11–15), C: 14 (7–15) | Andexanet alfa low dose or high dose based on product labeling, low dose 480 mg bolus followed by 480 mg infusion, high dose 960 mg bolus followed by 960 mg infusion; low dose 22/28 (79%), high dose 6/28 (21%) | T: Andexanet alfa | Stable CT scan head at six hours T: 21/28 (79%), C: 25/35 (71%); pre-reversal ICH volume T: 20.6 (2.0–41.3), C: 37.4 (22.8–88.2); post-reversal ICH volume T: 22.6 (2.0–51.7) C: 60.4 (33.2–106.7); hemostatic efficacy T: excellent T=14/16, good T=1/16, poor T=1/16; ICU admission T: 12/18 (67%), C: 6/11 (55%); in-hospital mortality T: 4/18 (22.2%), C: 1/11 (9.1%); NIHSS at discharge (median, IQR) T: 4 (3–10), C: 3 (2–8) | |
| Barra et al., 2020. A retrospective single-center cohort study, US [18] | Patients who received andexanet alfa or 4F-PCC for rivaroxaban- and apixaban-associated traumatic or spontaneous ICH N=29 (T=18, C=11); male: T=55.6%, C=81.8%; female: T=44.4%, C=18.2%; age (Median, IQR), T: 83.4 (70.3-88.8), C: 71.0 (68.6-73.2); GCS on admission (median, IQR), T: 15 (14-15), C: 10 (9-13); FXa inhibitor T: apixaban 15, rivaroxaban 3, C: apixaban 3, rivaroxaban 8 | Andexanet alfa low-dose 400 mg IV bolus over 15 minutes followed by 480 mg infusion over two hours for last known apixaban or rivaroxaban dose 8 hours before administration, apixaban 5 mg or rivaroxaban 10 mg with last dose 8 hours prior or unknown, rivaroxaban ≤ 5 mg with last dose 8 hours prior or unknown; high-dose 850 mg IV bolus over 30 minutes followed by 960 mg infusion over two hours apixaban ≥ 5 mg or rivaroxaban ≥ 10 mg with last dose 8 hours prior or unknown; high-dose 4F-PCC 25–50 units/kg, dosing per treating physician discretion, with a maximum dose of 5000 units | C: 4F-PCC | Stable CT scan head at six hours T: 21/28 C: 10/16; stable CT scan head at 24 hours T: 15/28 C: 6/16; NIHSS baseline T: 8.5 (5.8–12), C: 8.3 (4.6–16); spontaneous ICH volume at six hours post-reversal T: 8.2 (6.1–18), C: 9.9 (6.4–21.1); good outcome (NIHSS<3) on discharge T: 10/28 (36%), C: 6/16 (38%); length of hospital stay (median, IQR) T: 7 (4-11), C: 6 (4-11); length of ICU stay (median, IQR) T: 2 (1-4), C: 1 (1-4); thrombotic events T: 2/28, DVT 2, superficial thrombosis 1; C: 0/16 | |
Patients who received andexanet alfa for the reversal of factor Xa inhibitor-associated bleeding or reversal after surgical procedures

| Authors | Year | Study Design | Results |
|---------|------|--------------|---------|
| Brown et al., 2019 | Retrospective multicenter, open-label, single-group study, North America and Europe | 2019 | None |
| Connolly et al., 2019 | Prospective multicenter, open-label, single-group study, North America and Europe | 2019 | None |
| Culbert et al., 2018 | Observational case series | 2018 | Repeat CT scan: stable 8/13, worsening 5/13 (one patient died during surgery and didn’t have repeat CT); excellent mortality 6/15 (40%); thrombotic events 0/19 |
| Culbert et al., 2019 | Observational case series | 2019 | None |
| Gianfriddo et al., 2020 | Retrospective case series | 2020 | None |
| Radel et al., 2020 | Retrospective case series | 2020 | None |
| Stevens et al., 2019 | Retrospective case series | 2019 | None |

Note: The table provides a summary of the studies included in the review, their design, and the results related to the use of andexanet alfa.
TABLE 3: Narrative summary of the included studies

| FXai: factor Xa inhibitor; GCS: Glasgow Coma Scale; DVT: deep vein thrombosis; ICH: intracerebral hemorrhage; IPI: intraparenchymal hemorrhage; MI: myocardial infarction; TIA: transient ischaemic attack; PE: pulmonary embolism; VTE: venous thromboembolism; 4F-PCC: four-factor prothrombin complex concentrate; N: total number, C: control group, T: treatment group |

**Quantitative Analysis**

Only three studies reported the use of AA contrasting with 4F-PCC among ICH patient groups used in this analysis.

**In-Hospital Mortality**

Pooling data on hospital mortality in ICH group using fixed-effect model showed significant lower odds of mortality among AA group (OR, 0.37; 95% CI, 0.20-0.71; n= 310; I² = 49%) (Figure 2). However, re-running the analysis using a random-effect model considering moderate heterogeneities across studies did not reach the statistical significance (OR, 0.39; 95% CI, 0.14-1.06) (Figure 3). Further analysis including two studies and excluding outlier study (Ammar et al.) showed significant lower odds of in-hospital mortality (OR, 0.25; 95% CI, 0.11-0.56; n = 266; I² = 0%) (Figure 4).

**Length of Hospital Stay**

Length of stay in days did not differ significantly between treatment and control groups (MD, 0.41; 95% CI, -0.25 to 1.06; n = 310; I² = 0%) (Figure 5).

**ICU Length of Stay**

Length of ICU stay in days did not differ significantly between treatment and control groups (MD, -0.07; 95% CI, -0.68 to 0.54; n = 310; I² = 0%) (Figure 6).

**Thrombosis**

Thrombotic events were reported in two studies. Pooling of the data using fixed-effect model did not show significant difference between two groups (OR, 2.40; 95% CI, 0.36 to 15.84; n= 73; I² = 0%) (Figure 7).
Discussion

Our meta-analysis is the most comprehensive meta-analysis to evaluate the effect of andexanet alfa in bleeding caused by factor Xa inhibitors evaluating the mortality, length of hospital stay, length of ICU stay, and thrombosis in comparison to 4-F PCC. The main finding of our study was that andexanet alfa reduced mortality in patients who had intracerebral bleeding due to factor Xa inhibitors compared to 4-F PCC. There were 356 mortalities in fact Xa inhibitor group (21.1%) versus 234 patients across two studies. In contrast, overall mortality rate in a recent 4-F PCC meta-analysis in ICH inhibitor bleeding was 18% compared to 12.1% in our analysis and 14% in the ANNEXA-4 trial [27]. The studies done by Ammar et al. and Barra et al. showed a higher mortality risk of 39% and 22% respectively which is higher than that of other studies as these studies included also ICH patients [11, 13]. Mortality was also significant in a study done by Culbreth et al. where 14 out of 15 patients had ICH. The Ammar et al. study showed a similar mortality rate in the andexanet alfa group and 4-F PCC group (54% and 35% respectively) while the Barra et al. study showed higher mortality in the 4-F PCC group (16.7%) than andexanet receiving patients [11, 15]. In the 4-F PCC group in the Barra et al. study had lower baseline GCS and higher baseline hematoma volume which might have contributed to the higher mortality [14].

We found no difference in the incidence of thrombotic events caused by AA in comparison to 4-F PCC for the reversal of bleeding caused by factor Xa inhibitor. A recent meta-analysis of seven studies including 240 patients showed thrombotic events of 4% with the use of 4-F PCC [25]. In contrast, we found incidences of thrombosis among 121 patients in the nine studies included in our analysis. A prior meta-analysis done by Rodrigues et al. also estimated the risk of thrombosis with andexanet alfa and fvacatuzumab at 5.5%. However, the analysis just included three studies for evaluation of thrombosis risk associated with AA and evaluated the cumulative risk of thrombosis associated with both andexanet alfa and fabatuzumab [26]. The incidence of thrombotic events ranged from none to 30.7%, with a relatively higher incidence in studies by Stevens et al. (36.7%) and Nederpelt et al. (19%) [25, 26]. Culberth et al. did also study also done by Brown et al. and two studies in 2016, and 2019 had zero incidence of thrombotic events [29, 30, 31]. A retrospective study done by Coleman et al. did not include the incidence of thrombotic events [19]. The most common thrombotic event reported was DVT; 19 out of all patients with thrombotic events had DVT only. The Connolly et al. study had more incidence of stroke (15%) than DVT (13%) [29]. Ammar et al. reported thrombotic event in the 4-F PCC group, while one event was reported in the Barra et al. study, which is fewer than that reported in the AA group [11, 17]. Restoring anticoagulation showed a significant decrease in thrombotic events in studies by Connelly et al. and Stevens et al. [21, 26]. Only one patient (8%) in the Steven et al. study and eight patients (2%) in the Connolly et al. study developed thrombotic events after restarting anticoagulation [21, 26]. Concomitant use of additional blood products – platelets, PRBCs, and FFP was common in multiple studies. However, the association between the use of additional products and thrombotic events could not be made. Time-frame for reporting thrombotic events also differed between studies. Studies done by Smith et al. and Tao et al. on 4-F PCC use in factor Xa inhibitor bleeding showed 0% (0/4) and 4 (2.5%) thrombotic events [30, 31].

The definition of hematostatic efficacy and time for AA administration for determining efficacy was different in between studies. Hemostatic efficacy was measured and reported as good/excellent or poor/failing according results by Speer et al. in five studies in which the ANNEXA-4 study. The Ammar et al. study used different values for hematoma expansion, the Culberth et al. 2018 study reported COP CT as stable or worsening while the Culberth et al. 2019 study which included patients requiring emergent surgery reported hematostatic effectiveness as per surgeon [21, 22]. Coleman et al. did not study hematostatic efficacy while Brown et al. evaluated hemostatic efficacy in ICH and surgery requiring patients as hemostasis or expansion of the hematoma diameter [22]. The studies done by Ammar et al. and Stevens et al. showed similar results in meeting end of 12 hours while Brown et al. evaluated hemostatic efficacy in ICH and surgery requiring patients as hemostasis or expansion of the hematoma diameter [21, 22]. The Nederpelt et al. study showed lower efficacy of 47.2% while the Barra et al. study showed higher efficacy of 86.8% [12, 27]. Different inclusion and exclusion criteria of patients, a wide range of definitions of hemostatic efficacy, and the time frame for judging led to the difference in hemostatic efficacy. Recent studies on the hemostatic efficacy of 4-F PCC have shown efficacy rates between 80% and 90% [25, 26]. We found no difference in the length of hospital and ICU stay in patients receiving andexanet alfa in comparison to 4-F PCC for reversal of bleeding caused by Factor Xa inhibitors. The median and IQR of the length of hospital stay varied from 45-66 in the Brown et al. study to 147-221 in the Stevens et al. study [21, 26]. Patients comparatively stayed in the hospital for longer in studies: Stevens et al., 147-221 days and Nederpelt et al., 45-66 days. Length of hospital stay was relatively longer in the AA group than 4-F PCC group in studies by Ammar et al. and Barra et al., while it was similar in the Coleman et al. study. The median and interquartile range of the length of ICU stay ranged from 21-6 in the Ammar et al. study and 27.5-5.5 in the Barra et al. study. Length of ICU stay was longer in the AA group than 4-F PCC group in the Barra et al. study, while it was shorter in the AA group in the Coleman et al. study [21].

Clinical benefit of AA use was observed in bleeding due to factor Xa inhibitors in our analysis; however, the cost of stocking AA in most hospitals might be prohibitive for the immediate use for reversible DOAC related life-threatening bleeding. The median projected cost of andexanet alfa was $21,213 (patient compared to $26,500/patient for 4-F PCC). 4-F PCC currently is more widely available and less expensive, but that may change if the cost for AA comes down in the future [17]. 4-F PCC and andexanet alfa have not been compared in a prospective randomized clinical trial, and results of such studies are needed to inform clinical practice differences in DOAC related bleeding events. There is an ongoing randomized, multicenter clinical trial evaluating the efficacy and safety of andexanet alfa versus the usual standard of care in patients with ICH anticoagulated with a DOAC, which might be completed in 2023 [17].

Limitations of the study

Most of the studies included were case series and retrospective observational studies. Only one prospective study, the ANNEXA-4 trial, was included. There were control groups in only three of our studies which were all prospective. The sample size was less in our studies. Therefore, there was a moderate to high risk of bias in our studies. ANNEXA-4 trial had wide exclusion criteria: planned surgery within 12 hours after andexanet administration, ICH with GCS less than 7, hematoma volume more than 30 cc, expected survival less than one month, use of VKA, dabigatran, PCC, WB, or plasma in last seven days, Glatira’s study also included patients with GCS less than 7 and hematoma volume >40 mL. However, patients requiring surgical intervention, patients who received other blood products before AA administration, unknown time of the last factor Xa inhibitor dose, patients with low GCS and higher hematoma volume were included in other studies. In real clinical practice, patients with low GCS and expected mortality of less than one month required AA administration and were included in other studies. Knowledge about the administration of other blood products and time since the last factor Xa inhibitor was not feasible due to the retrospective nature of some studies and were thus included. Culberth et al. 2019 included patients with bleeding due to factor Xa inhibitor who required emergent surgery.

Conclusions

Andexanet alfa reduced in hospital mortality in patients who had bleeding due to factor Xa inhibitors compared to 4-F PCC. There was no difference in thrombotic events, length of ICU, and hospital stay between andexanet alfa and 4-F PCC. Thus, AA is a promising therapeutic agent for the reversal of factor Xa-anticoagulated bleeding. However, the cost of stocking AA in most hospitals might be prohibitive for the
immediate use for reversal of DOAC-related life-threatening bleeding. 4F-PCC currently is more widely available and less expensive, but that may change when the cost for AA decreases. More studies are required in the future to determine the effect of AA as compared to 4F-PCC in patients with DOAC-related bleeding other than intracranial bleeding.

Appendices
Supplementary Material. 1. Details of the search strategy
Published
"(andexanet alfa" OR "andexanet" OR "andexanet alpha") AND "bleeding" AND ("Factor Xa inhibitor" OR "Factor Xa inhibitors")
Hits: 117
https://pubmed.ncbi.nlm.nih.gov/?term=%22andexanet%20alfa%22%20OR%22andexanet%22%20OR%22andexanet%20alpha%22%20AND%22bleeding%22%20AND%22Factor%20Xa%20inhibitor%22%20OR%22Factor%20Xa%20inhibitors%22
PubMed Central
"(andexanet alfa" OR "andexanet" OR "andexanet alpha") AND "bleeding" AND ("Factor Xa inhibitor" OR "Factor Xa inhibitors")
Hits: 452
https://www.ncbi.nlm.nih.gov/pmc/?term=%22Factor+%20Xa%20inhibitor%22+OR+%22Factor+%20Xa%20inhibitors%22)
Supervision
"(andexanet alfa" OR "andexanet" OR "andexanet alpha") AND "bleeding" AND ("Factor Xa inhibitor" OR "Factor Xa inhibitors")
Hits: 164
https://www.scopus.com/results/results.url?srcid=6234-2-s2.0-85032928048-srceid=104&searchtype=author&k=1-150k&title=AND-%20KEY%20(%22Factor%20Xa%20inhibitor%22%20OR%22Factor%20Xa%20inhibitors%22)
Embase
Search: (andexanet alfa:exp OR andexanet:exp OR andexanet alpha:exp AND bleeding:exp AND "Factor Xa inhibitor":exp OR "Factor Xa inhibitors":exp OR Factor Xa inhibitor:exp OR Factor Xa inhibitors:exp)
Hits: 594
Link: https://www.embase.com/embase/search/resultspage/history?c=1&d=1&i=items&industry=data&source=
Cochrane Library
"andexanet alfa OR 'andexanet alfa' OR 'andexanet alpha' in All Text AND 'bleeding' in All Text AND 'Factor Xa inhibitor' OR 'Factor Xa inhibitors' in Title/Abstract/Keywords"
Hits: 9
Additional Information
Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.
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