Trauma and thrombosis in the DOAC era: promise and peril of direct oral anticoagulant use in injured patients

Nederpelt, C.J.

Chapter 7

Andexanet Alfa or Prothrombin Complex Concentrate for Factor Xa Inhibitor Reversal in Acute Major Bleeding: A Systematic Review and Meta-Analysis

Charlie J Nederpelt, Leon Naar, Pieta Krijnen, Saskia le Cessie, Haytham MA Kaafarani, Menno V Huisman, George C Velmahos, Inger B Schipper

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Abstract

Objective: To combine evidence on andexanet alfa and prothrombin complex concentrates (PCC) for FXa-associated bleeding to help guide clinicians on reversal strategies.

Data sources: Embase, Pubmed, Web of Science and the Cochrane Library

Study selection: Observational studies and randomized clinical trials studying hemostatic effectiveness of andexanet alfa or PCC for acute reversal of FXa-associated hemorrhage.

Data extraction: Two independent reviewers extracted the data from the studies. Visualization and comparison of hemostatic effectiveness using Sarode et al. or ISTH criteria at 12 and 24 hours, (venous) thrombotic event ([V]TE) rates, and in-hospital mortality was performed by constructing Forest plots. Exploratory analysis using logistic mixed model analysis was performed to identify factors associated with effectiveness and VTE.

Data synthesis: A total of 21 studies were included (andexanet: 438 patients; PCC: 1278 patients). The (weighted) mean effectiveness for andexanet alfa was 82% at 12 hours, and 71% at 24 hours. The (weighted) mean effectiveness for PCC was 88% at 12 hours and 76% at 24 hours. The mean 30-day symptomatic VTE rates were 5.0% for andexanet alfa and 1.9% for PCC. The mean 30-day total TE rates for andexanet alfa and PCC were 10.7% and 3.1% respectively. Mean in-hospital mortality was 23.3% for andexanet versus 15.8% for PCC. Exploratory analysis controlling for potential confounders did not demonstrate significant differences between both reversal agents.

Conclusions: Currently available evidence does not unequivocally support the clinical effectiveness of andexanet alfa or PCC to reverse FXaI-associated acute major bleeding, nor does it permit conventional meta-analysis of potential superiority. Neither reversal agent was significantly associated with increased effectiveness or higher rate of VTE. These results underscore the importance of randomized controlled trials comparing the two reversal agents, and may provide guidance in designing institutional guidelines.

Introduction

Improved effectiveness, safety, and cost-effectiveness make direct oral anticoagulants, and factor Xa (FXa) inhibitors in particular, popular alternatives to coumarin derivates for the treatment and prevention of venous thromboembolism and for the prevention of stroke in patients with non-valvular atrial fibrillation (1-8). Considering the widespread use of FXa inhibitors (FXaI) and the incidence of major bleeding events ([MBE], 3.1-4.1 per 100 patient years), there is an urgent demand for an effective reversal agent in the management of FXa-associated major bleeding events (3, 9, 10).

Reversal with plasma complex concentrates (PCC) induces a procoagulant state through replenishing coagulation factors II, VII, IX and X. One previous randomized controlled trial indicated superiority of 4 factor PCC over fresh frozen plasma in terms of hemostatic efficacy in patients on vitamin K antagonists (11). Using 4F-PCC for reversal of FXa-associated hemorrhage in healthy volunteers demonstrated its potential effectiveness (12). As a result, 4F-PCC has been recommended in numerous management guidelines for treatment of FXa-associated MBE (13-17).

Andexanet alfa is a recombinant FXa decoy molecule that binds to FXaIs with superior affinity compared to FXa. Following preliminary results from an open-label, non-randomized prospective cohort study, andexanet alfa received FDA approval in 2018, and EMA approval in 2019 (18). A randomized controlled trial comparing andexanet alfa to usual care in expected non-operatively managed (<12 hours post-randomization) intracranial hemorrhage (GCS >6, ICH volume <60 mL) patients is currently ongoing and results are expected in 2024 (ClinicalTrials.gov Identifier: NCT03661528).

Despite present clinical use of both andexanet alfa and PCC, head-to-head comparison has not been performed. In light of the urgent need for evidence-based reversal strategies, we performed a literature review and meta-analysis of available evidence describing the clinical effectiveness of PCC and andexanet alfa for FXa-associated bleeding.

Methods

In reporting this systematic review and meta-analysis we adhere to the PRISMA statement (19). An experienced medical librarian wrote the literature search strategy built around the main terms ‘factor Xa inhibitors’, ‘hemorrhage’, ‘reversal’, ‘prothrombin complex concentrate’, ‘andexanet alfa’, and “treatment outcome” (**Appendix A**). The literature search was performed in Embase, Pubmed, Web of Science and the Cochrane Library. No time restriction was applied to the literature search. Inclusion criteria were: cohort studies (>10 patients) or randomized trials; including patients presenting with acute oral FXa-associated bleeding; treated with andexanet alfa or PCC; and assessing hemostatic effectiveness per the criteria of the International Society of Thrombosis and Hemostasis Scientific and Standardization Committee [ISTH], by the Sarode et al. criteria, or defined as intracranial hemorrhage expansion rate (11, 20). Studies were excluded if they did not report on bleeding etiology, if the use of direct thrombin inhibitors or factor Xa inhibitors was not described separately at baseline, and if patients receiving and not-receiving reversal agents for acute bleeding were not described separately at baseline. Both randomized and non-randomized comparative studies, as well as non-comparative cohort studies were included, given the relative novelty of the subject. Meeting abstracts were included for sensitivity analysis by both authors if the exact in- and exclusion criteria were described in the abstract, and disregarded otherwise. Sensitivity analyses are described and reported in the **Supplementary Material**.

Two authors, CN and LN, independently selected the studies, using Covidence (Covidence [Computer program], version accessed August 2020, Melbourne, Australia: Veritas Health Innovation). They then independently assessed the risk of bias using the MINORS checklist (21). Both authors extracted the data independently, after which agreement was confirmed. The following data were extracted: study setting and design; in- and exclusion criteria; indication for reversal; hemorrhage type and severity; age; sex; relevant comorbidity; indication for chronic anticoagulation; antiplatelet co-therapy; time since last dose; pre-injury

FXa inhibitor type and dose; reversal agent type, dose and timing; baseline platelet count (Plt) and hemoglobin (Hgb); surgical interventions; resuscitation adjuncts used; definition, measurement and rate of hemostatic effectiveness, venous thromboembolic events (VTE), total thrombotic event rate (including VTE, ischemic stroke, and myocardial infarction), and mortality.

Statistical analysis

Statistical analyses were performed in Stata 15.3 (Stata Corp., College Station, TX, USA) and Forest plots were constructed with R (version 4.0.2; R studio, Boston, Massachusetts). Studies reporting on 4F-PCC and aPCC were analyzed as one PCC treatment arm, as these studies reported no difference in effectiveness for both drugs in head-to-head comparison (22, 23). Hemostatic effectiveness measured at 12 and 24 hours was reported separately in the Forest plots. Effects on hemostatic effectiveness, (venous) thrombotic event rates and in-hospital mortality were visualized by constructing Forest plots with exact binomial 95% confidence intervals. The event rates were pooled using the Binomial–Normal model for meta-analysis of proportions as described by Stijnen et al. and Hamza et al, a more reliable method for lower event rates (24, 25). This is a logistic model with a random study intercept. Statistical heterogeneity was assessed, but between group differences were not statistically tested considering the inclusion of exclusively observational studies.

Subsequently, exploratory analysis using logistic mixed model analysis was performed to identify factors associated with hemostatic effectiveness and thromboembolism. In this analysis, hemostatic effectiveness was considered at a combined timepoint of 12 or 24 hours, to allow for inclusion of the largest sample of patients. The models for hemostatic effectiveness, (V)TE and in-hospital mortality included the following covariates: mean age, proportion of patients sustaining ICH versus extracranial hemorrhage, the proportion of patients receiving the high dose of reversal agent, reversal agent type, the proportion of patients requiring surgery, and study size. For hemostatic effectiveness in ICH patients, the median GCS score was included as a covariate. For 30-day mortality, no model could be

constructed due to collinearity issues arising from limited sample size; just 4 studies described this outcome.

Sensitivity analysis to assess the influence of within study bias and publication bias were performed on studies with low risk of bias, and on combined published and unpublished literature (including meeting and conference abstracts). Methodology and results of sensitivity analysis are presented in detail in the **Supplementary Material.**

Results

Study selection & risk of bias

The final search strategy was performed on August 11, 2020, resulting in 554 unique titles of scientific publications on the topic, as well as 351 abstracts presented at scientific conferences. A total of twenty-one studies were included (22, 23, 26-44). The study selection process is depicted in **Figure 1**. An overview of all extracted data, including study characteristics and meeting abstracts, as well risk of bias assessment, is provided in the **Supplementary Material**. Five studies reported on andexanet alfa use alone (29, 30, 32, 38, 44). Eleven studies described 4F-PCC use alone (26, 27, 31, 33-36, 39-41, 43). One study reported the use of both andexanet alfa and 4F-PCC (28). Two studies studied patients receiving activated PCC (aPCC) and 4F-PCC as one cohort (22, 23). Two studies reported solely on aPCC (37, 42). In total, 438 patients were reversed with andexanet alfa, and 1392 with PCC. Five studies were prospective, 17 were retrospective cohort studies, none were randomized control trials. All studies were performed at designated teaching hospitals, described as either a level I/II trauma center or a comprehensive stroke center, or were performed in multicenter collaborations.

All studies reported patients with exclusively major bleeding events. Ten studies included exclusively intracranial hemorrhage, one study included exclusively extracranial hemorrhage, and the remaining studies included mixed hemorrhage locations. One study was

limited to spontaneous bleeding, whilst all other studies included hemorrhage of mixed etiologies. Four studies excluded patients expected to undergo surgery within 12 hours (23, 29, 30, 35). Three studies excluded patients presenting with a GCS below 7 (29, 30, 43). Three studies excluded patients presenting with an ICH of over 60 mL (23, 29, 30).

Twenty studies reported mortality outcomes (in-hospital: 22, 30-day: 4). Hemostatic effectiveness was defined by Sarode/ISTH criteria in 14 studies and as ICH progression in 6, and was measured on first follow-up imaging (n=4), or at 12 hours (n=5), 24 hours (n=10), or 48 hours after initial evaluation (n=1). VTE rates were reported in 19 studies (In-hospital: 13, 30-day: 12). One study commented on the symptomatic or asymptomatic nature of thrombotic events; other studies did not mention or rule out routine screening protocols (22).

The median MINORS score for all studies was 10 out of 16 points [IQR 9-10]. Bias was potentially introduced through retrospective study designs (17 studies), unblinded outcome assessments (20 studies), and lack of study size calculations (20 studies).

Study populations

Baseline characteristics and treatment information of included patient cohorts are presented in **Table 1**. Upon comparing the included study populations, all studies included geriatric patients (median age 77, andexanet: 80, PCC: 76). In studies that reported the dose of anticoagulation (n=8), the minority of patients used high low doses of anti-FXa (defined as >10mg/day for apixaban, >20 mg/day for rivaroxaban; andexanet: 33.0%, PCC: 45.5%). Time since last dose was reported in 9 studies (<8 hours – andexanet: 13-33%, PCC: 18-50%; and <18 – andexanet: 46-85%, PCC: 27-100%). In studies including all hemorrhage locations, the majority of patients suffered from ICH (andexanet: 68.9%, PCC 87.7%) and gastrointestinal hemorrhage (andexanet 19.6%, PCC 7.0%). Median GCS on admission (reported in 10 studies) was higher in andexanet patients (andexanet: 14 [IQR 14-15], PCC: 14 [12-15]). The proportion of patients suffering traumatic hemorrhage, reported in 15 studies, was similar for both reversal agents (andexanet: 45.2%, PCC: 48.4%). The primary indication for

anticoagulation was atrial fibrillation in all studies, followed by treatment of/prevention of recurrent venous thromboembolism. Concomitant antiplatelet use was reported in 15 studies and was similar for both reversal agents (andexanet: 35.9%, PCC 32.8%). PCC patients more frequently received high dose reversal (andexanet: 16.0%, PCC: 53.4%). Andexanet patients more often underwent additional surgical intervention (andexanet: 0-62%, PCC: 0-40%)

Hemostatic effectiveness

Hemostatic effectiveness ranged between 58-89% in six andexanet cohorts analyzing 335 patients and between 60-94% in sixteen 4F-PCC cohorts analyzing 1041 patients. Fourteen studies reported 12-hour (n=5) or 24-hour (n=9) hemostatic effectiveness by the ISTH or Sarode et al. criteria (**Figure 2**). Mean effectiveness for andexanet alfa was 82% at 12 hours and 71% at 24 hours. Mean effectiveness for PCC was 88% at 12 hours and 76% at 24 hours. On exploratory logistic mixed model analysis, a higher proportion of surgical requirement and a lower proportion of ICH was statistically significantly associated with lower hemostatic effectiveness (**Supplementary Material)**.

Thirteen studies reported hemostatic effectiveness for ICH-patients at 12 or 24-hours using the ISTH or Sarode et al. criteria (**Supplementary Material**). Mean effectiveness in ICH patients was 57% at 12 hours and 89% at 24 hours for andexanet alfa. Mean effectiveness for PCC was 88% at 12 hours and 73% at 24 hours. Exploratory logistic mixed model analysis did not indicate a significant associations between studied covariates and hemostatic effectiveness in ICH patients (**Supplementary Material**).

Safety outcomes

Twelve studies reported 30-day symptomatic VTE rates, which ranged between 2.9-16.7% for andexanet patients (4 studies, 402 patients) and between 0-9.1% for PCC patients (9 studies, 1044 patients). Mean 30-day symptomatic VTE rate was 5.0% for andexanet alfa and 1.9% for PCC (**Figure 3**). Exploratory logistic mixed model analysis did not indicate a statistically significant difference in 30-day VTE rates (**Supplementary Material**).

The 30-day rate of total symptomatic thrombotic events (VTE, MI and ischemic stroke) was reported in 12 studies, and ranged between 5.5-30.8% for andexanet patients (4 studies, 402 patients) and 0-15.4% (9 studies 1044 patients). The pooled event rates for andexanet alfa and PCC were 10.7% and 3.1%, respectively (**Supplementary Material).** Exploratory logistic mixed model analysis identified a statistically significant association between a higher proportion of patients receiving high dose reversal and lower odds of TE (OR 0.97 per %: 0.97, 95% CI 0.95-1.00, p=0.038).

Mortality

Twenty-two studies reported in-hospital mortality. In-hospital mortality ranged between 10.3-40.0% for andexanet alfa patients (4 studies, 93 patients) and between 0-63.6% in PCC patients (19 studies, 1174 patients) (**Supplementary Material**). Mean in-hospital mortality was 23.3% for andexanet versus 15.8% for PCC. Exploratory logistic mixed model analysis did not show a statistically significant lower risk for andexanet alfa compared to PCC (**Supplementary Material)**. Four studies reported 30-day mortality, which ranged between 14.0-15.4% for andexanet alfa (2 studies, 345 patients) and between 32.0-33.0% for PCC patients (2 studies, 164 patients) (**Supplementary Material**).

Discussion

Meta-analysis of the available literature on the use of reversal agents for factor Xa-inhibitor associated acute major bleeding demonstrated slightly higher rates of hemostatic effectiveness for PCC on meta-analysis. Thromboembolic complications were more common in patients treated with andexanet alfa. Exploratory logistic mixed model analysis adjusted for confounding factors resulted in non-significant associations between reversal agent type and effectiveness, incidence of thromboembolic complications, and mortality. The presented clinical evidence may guide decision-making regarding reversal of FXaI-associated MBE, a challenging scenario that will become increasingly prevalent.

Hemostatic effectiveness in real-world data is confounded by surgical treatment. Adequate bleeding source control remains of paramount importance in attaining bleeding control for certain hemorrhage types. Four of the included studies excluded patients expected to undergo surgery <12 hours post-reversal in an attempt to describe a more direct relation between reversal agent and effectiveness (23, 29, 30, 35). Of these studies, one nonetheless reported a surgery rate of 40% in FXaI-associated ICH, whereas the other studies did not report on actual surgical requirement (30). In the design for a phase 2 trial, the exclusion of patients undergoing surgery in studying in-vivo effectiveness and safety of andexanet alfa is sensible. In guiding clinical management, however, the ANNEXA-4 offers limited information as did not include a comparator arm and found no association between the proposed mechanism, lowering anti-factor Xa plasma-activity and hemostatic effectiveness (29). Comparable evidence for PCC is not available, and therefore future studies should randomize or prospectively compare either drug versus usual care and include patients undergoing surgery to accurately reflect clinical reality.

An insignificant increase in VTE risk associated with andexanet alfa was reported. Concerns about potentially increased thrombotic risk associated with andexanet alfa use have previously been voiced, both by the FDA and by physicians (45, 46). Our study neither confirms nor disproves this concern, as our analysis may not have been powered to detect a significant difference (type 2 error). At the same time, it is not appropriate to attribute this increased risk directly to the reversal agent in the absence of information on restarting anticoagulant medication and baseline coagulation assays. Upon assessing known risk factors for VTE, we did not detect skewed distributions of age, sex, antiplatelet co-therapy, reversal agent dose, FXaI type and indication, and surgical requirement. It remains crucial to continually weigh hemorrhagic and thrombotic risks and restart anticoagulant medication as soon as deemed safe and appropriate. Of note is that 0% of thrombotic events occurred after OAC was restarted in the ANNEXA-4 trial, and just 4% of VTE in the largest study into PCC (22, 29).

Authoritative clinical guidelines on FXaI reversal now recommend the use of andexanet alfa over 4F-PCC, as both the pre-clinical and clinical evidence supporting its effectiveness is more robust than the evidence supporting PCC (47). The risk of bias assessment performed in our study confirms this assertion. A lack of standardized repeat imaging and a difference in the time of hemostatic effectiveness evaluation were noted. Interestingly, effectiveness was higher and 30-day mortality was lower in studies evaluating at 12 hours than those evaluating at 24 hours, potentially owing in part to the exclusion of the most severely affected patients (e.g. expected prognosis <30 days, ICH volume >60 mLs, expected surgical requirement <12 hours) in ANNEXA-4, the largest study using these timepoints. Therefore, interpretation of mortality rates in the included studies does not favor either reversal agent, and hemostatic effectiveness should be interpreted with caution.

Strengths and limitations

This study is the largest meta-analysis into the effectiveness of FXaI-associated acute bleeding reversal. By including all available literature, we were able to describe real-world effectiveness of both andexanet alfa and PCC. Moreover, the logistic mixed model analysis method by Stijnen et al. offers several advantages: it does not assume a normal within-study likelihood; it accounts for uncertainty in estimating standard errors, which results in more realistic standard errors of the effect parameters; and it allows inclusion of covariates in the logistic mixed model analysis (24).

Our study is limited by several factors. First of all, meta-analysis of non-randomized, single arm studies remains an imperfect methodological exercise. Observational cohort studies of reversal agents may lack important information such as medication dosing, time since last dose, and routine screening of outcomes at standardized timepoints (48). The statistical approach decided on is an appropriate method for studying event rates across different studies at standardized timepoints, but without (placebo) controlled randomized trials, or a known rate of “hemostatic effectiveness” in the untreated population, treatment

effects of both drugs remain unconfirmed. The between-study variance and statistical heterogeneity are to be considered a second limitation of our study. The included studies did not delineate institutional protocols for reversal agent use, nor did they detail definitions and use of screening protocols for (venous) thromboembolic complications or provide institutional thromboprophylaxis guidelines. Differences between centers may have existed in the threshold to administer PCC or andexanet alfa, due to cost, availability, logistics and ethical concerns associated with both drugs. Patients in the andexanet cohorts more frequently presented with GI hemorrhage, PCC patients more often received a high dose reversal. Exploratory analysis demonstrated favorable hemostatic effectiveness in studies with larger proportions of ICH as well as larger proportions of high dose reversal, potentially biasing our study towards increased effectiveness for PCC. These and further effects of residual confounding by indication cannot be ruled out, and thus our conclusion is limited to reporting an association between reversal agent types and outcomes.

Conclusion

Currently available evidence does not unequivocally support the clinical effectiveness of andexanet alfa or PCC to reverse FXaIs in the setting of acute major bleeding, nor does it permit conventional meta-analysis to study potential superiority. In exploratory analysis of observational studies, neither reversal agent was significantly associated with increased effectiveness or higher rate of (venous) thromboembolism. These results underscore the importance of randomized controlled trials comparing the two reversal agents, and may provide guidance in designing institutional guidelines.

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Figures and Tables

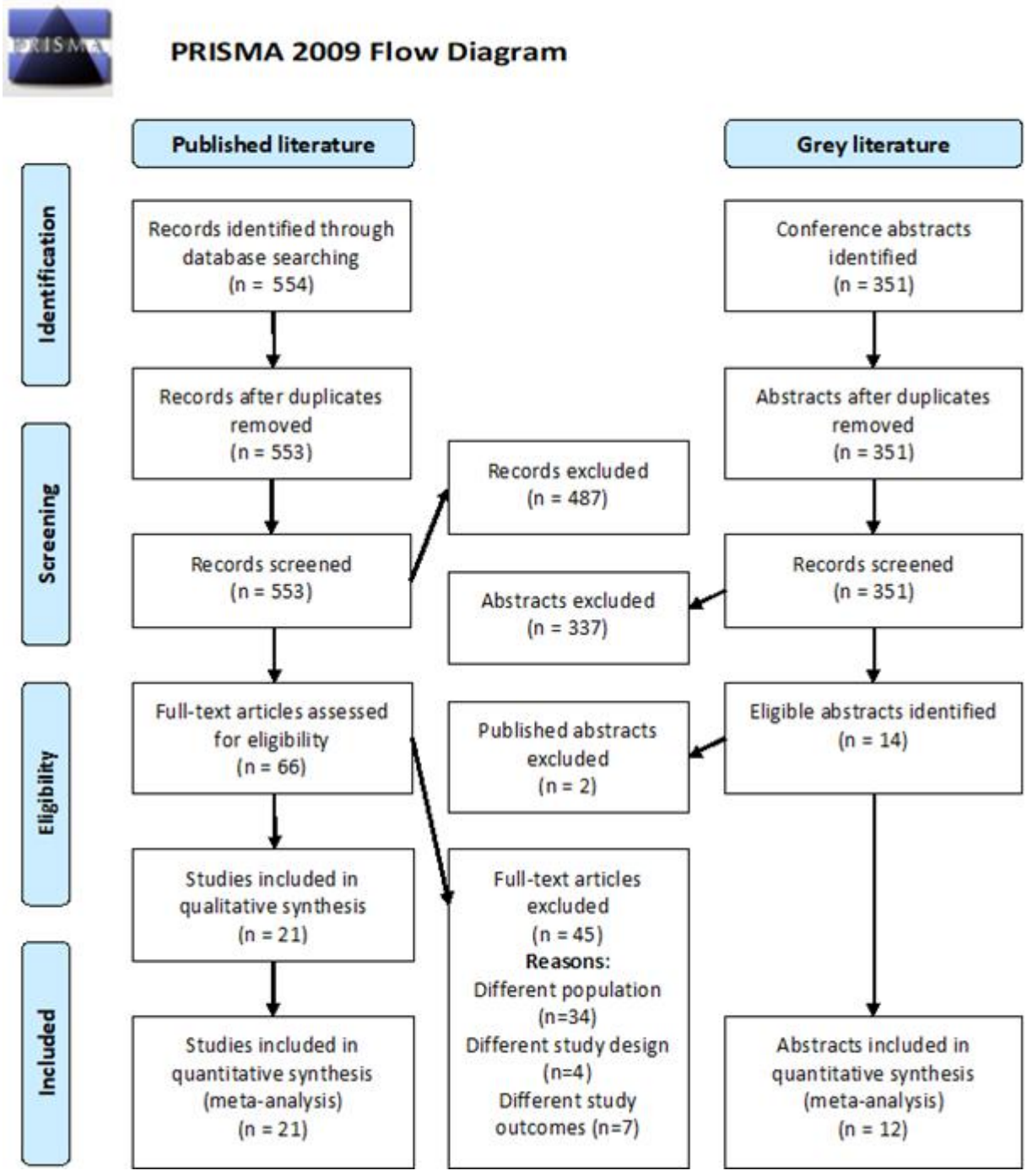

Figure 1. PRISMA flowchart of the study selection process

Table 1. Characteristics of patients requiring acute reversal of Factor Xa Inhibitor-associated major bleeding with andexanet alfa or prothrombin complex concentrate.

Variable	Andexanet Alfa (n=438)	PCC (n=1,278)	Total (n=1,716)
n Patients	438	1278	1716
Mean age (IQR)	80 (71-82)	76 (74-78)	77 (74-79)
Male (%)	221 (52.2%)	695 (54.8%)	916 (54.2%)
High dose FXaI (%)	22 (33.0%)	63 (45.5%)	85 (48.8%)
Traumatic bleeding (%)	42 (45.2%)	527 (48.4%)	569 (48.2%)
Hemorrhage location (%)			
Intracranial hemorrhage	302 (68.9%)	1120 (87.7%)	1422 (82.9%)
Gastro-intestinal bleeding	86 (19.6%)	87 (7.0%)	173 (10.1%)
Other hemorrhage	50 (11.4%)	71 (5.5%)	121 (7.1%)
Median GCS [IQR] in ICH patients	14 [14-15]	14 [12-15]	14 [14-15]
Primary FXaI indication (%)			
Atrial Fibrillation	271 (78.6%)	959 (79.5%)	1230 (79.2%)
Venous Thrombo-embolism	78 (19.3%)	199 (16.5%)	277 (17.1%)
Both or other indication	10 (2.6%)	61 (5.1%)	71 (4.5%)
Antiplatelet co-therapy (%)	28 (35.9%)	391 (32.8%)	419 (33.0%)
High dose reversal agent (%)	69 (16.0%)	682 (53.4%)	751 (43.8%)
Required surgical intervention (%)	40 (9.1%)	252 (21.0%)	292 (17.9%)

Not all variables were reported in all studies. The proportions listed are the average of the studies that reported each variable. Therefore, not all percentages add up to 100% in their respective category. Full extracted data available in the Suplementary Material.

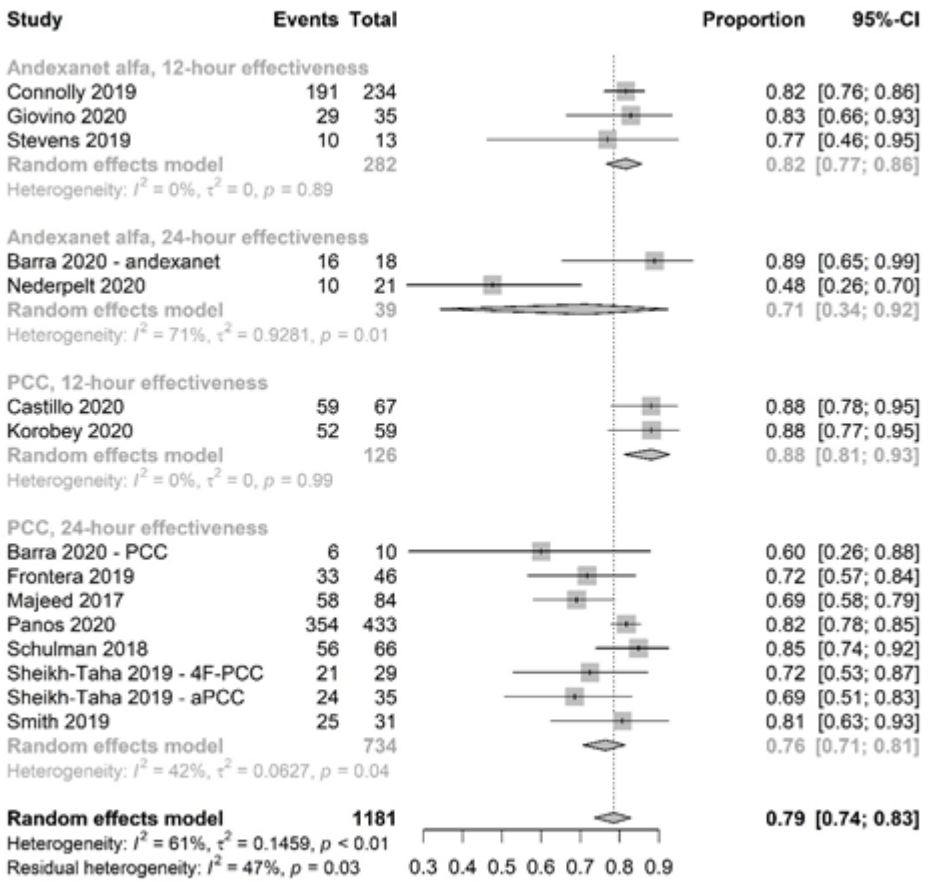

Figure 2. Hemostatic effectiveness rate as assessed by Sarode or ISTH criteria, or ICH progression at 12 or 24 hours post-reversal.

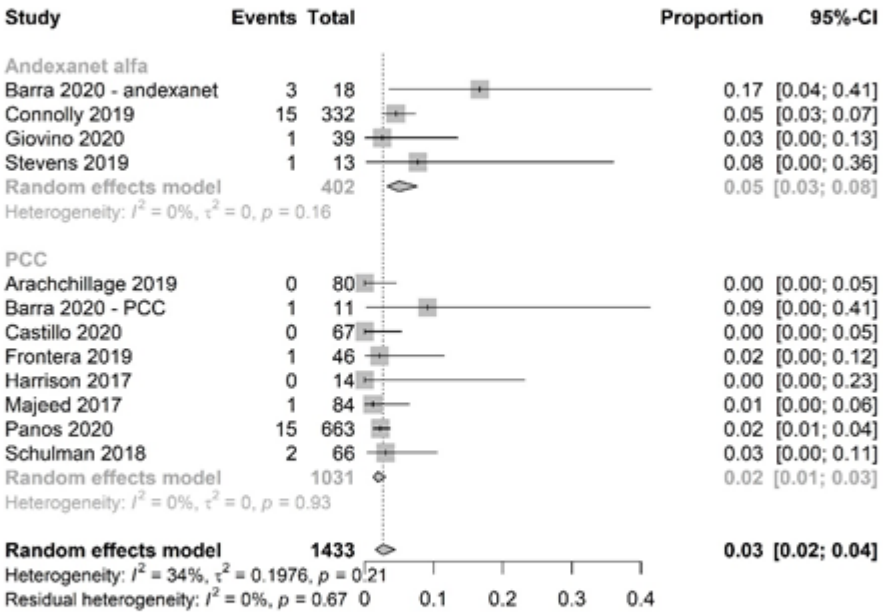

Figure 3. Incidence of venous thromboembolic complications at 30 days post-reversal.

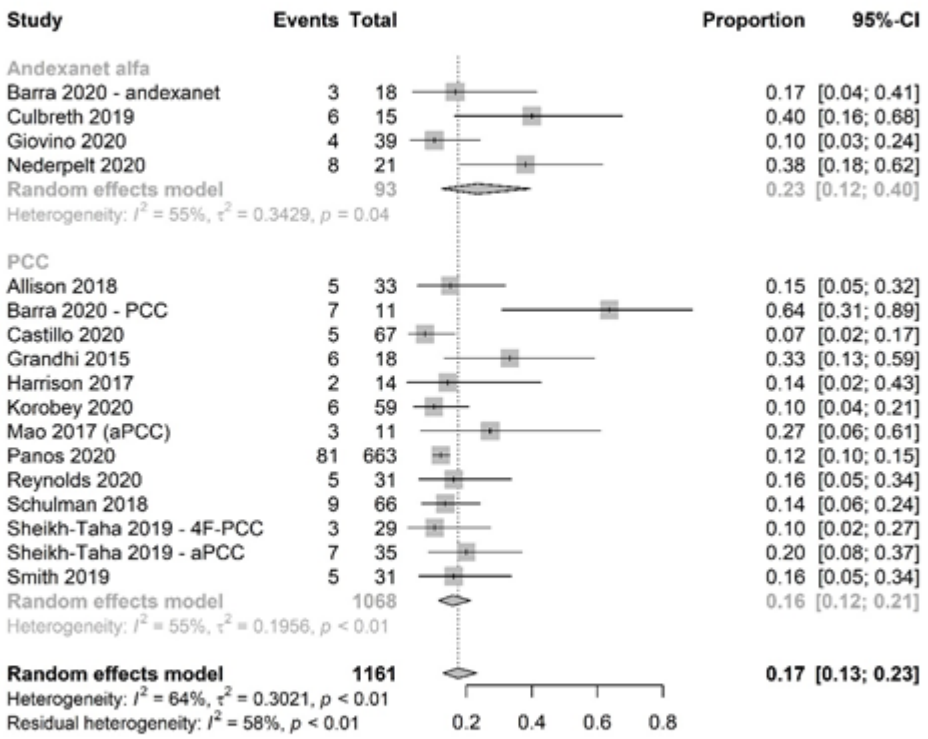

Figure 4. In-hospital mortality rates.