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Prothrombin complex concentrates and andexanet for management of direct factor Xa inhibitor related bleeding: a meta-analysis

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Abstract. – There are potential concerns related to bleeding caused by oral anticoagulants, especially in the elderly. Andexanet alfa has been authorized for use to reverse the effects of oral anticoagulants. Off-label use of four factor prothrombin complex concentrate (4F-PCC) for the reversal of oral factor Xa inhibitors is common. However, not much is known about their efficacy and safety profile. The intent of this meta-analysis was to evaluate the efficacy and safety of 4F-PCC and andexanet alfa for management of major bleeding due to oral factor Xa inhibitors. Comprehensive searches were done systematically through PubMed, Scopus and Google scholar databases. Studies that were retrospective record based or adopted prospective cohort approach and reported either of the three main outcomes, i.e., achieved hemostasis rate or rate of thrombotic events or mortality rate were included in the meta-analysis. Statistical analyses were done using STATA version 13.0. A total of 22 studies were included in the meta-analysis. All the studies had a single arm with no control/comparator group. The pooled rate of good to excellent hemostatic control upon use of andexanet was 80% (95% CI; 72% to 88%) and for 4F-PCC, it was 76% (95% CI; 70% to 83%). A comparatively higher pooled rate of thrombotic complications upon use of andexanet [13% (95% CI; 5% to 20%) was noted, compared to use of aPCC/4F-PCC [4% (95% CI; 3% to 5%). The pooled all-cause mortality rate within 30 days of administration was 24% (95% CI; 12% to 35%) with andexanet use and 19% (95% CI; 14% to 25%) for aPCC/4F-PCC. The findings suggest that use of both andexanet and aPCC/4F-PCC achieves a good hemostasis but there is an associated risk of thrombotic events and mortality. Future studies should have a control group to better establish evidence on efficacy and safety of these agents.

Key Words:
Anticoagulants, Prothrombin complex concentrate, Andexanet, Meta-analysis.

Introduction

There are significant advantages of direct oral anticoagulants, including factor Xa inhibitors such as rivaroxaban, apixaban, betrixaban, edoxaban, over warfarin. These include comparatively lesser food and drug interactions as well as the need for frequent laboratory monitoring[1,2]. However, there are potential concerns related to bleeding caused by oral anticoagulants[1-3]. The incidence of anticoagulant-related bleeding is projected to increase as the population continues to age. The reversal of the effects of oral anticoagulants is currently restricted to major bleeding episodes and before a surgical procedure[4,5].

Recently, in the United States, andexanet alfa for the reversal of apixaban and rivaroxaban has been authorized for use by the Food and Drug Administration (FDA)[6,7]. This agent has limited data, an unclear thromboembolic risk, and poses a considerable financial burden on the health system[6,7]. Besides this, four-factor prothrombin com-

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plex concentrates (4F-PCC) containing factors II, VII, IX, and X and proteins C and S, have also been shown to overcome inhibition of factor Xa and achieve hemostasis. This has led to the off-label use of 4F-PCC for the reversal of oral factor Xa inhibitors[7,8].

In 2019, Piran et al[9] have published a meta-analysis assessing the efficacy and safety of 4F-PCC for major-bleeding related to oral factor Xa inhibitors. Since then, several new studies have been published and there is updated evidence is needed. Also, clinicians have published their experience with the use of andexanet alfa in the past two years. Therefore, the aim of this study is to systematically search literature and perform a meta-analysis assessing the efficacy and safety of 4F-PCC and andexanet alfa for management of major bleeding due to oral factor Xa inhibitors. The specific objectives of the meta-analysis are (i) to separately evaluate the efficacy and safety of 4F-PCC and andexanet alfa for management of major bleeding due to oral factor Xa inhibitors (ii) to separately document the mortality rate upon use of 4F-PCC and andexanet alfa.

Materials and Methods

Search Strategy

A comprehensive search was done systematically through PubMed, Scopus and Google scholar databases for English, as well as non-English language papers published up to 15th October 2020. Free text words and medical subject heading (MeSH) terms were used. Details of the search strategy have been provided in supplementary document **(Supplementary Table I)**.

Selection Criteria and Methods

Two authors reviewed citations and selected studies. After removing the duplicates, screening of titles and abstracts was performed as a first step. Thereafter, review of the full text of potential studies was done. Any discrepancies related to the inclusion of studies were resolved through detailed discussion among the study authors. Only those studies were selected for the meta-analysis that adequately suited the inclusion criteria. The bibliographic list of the identified studies and relevant reviews on the subject were examined for additional possible studies.

Inclusion criteria: studies that were either retrospective record based study or prospective in design and reported either rates of hemostasis achieved or rates of thrombo-embolic events or mortality rates upon use of 4F-PCC or adexanet alfa were eligible to be included in the meta-analysis.

Exclusion criteria: review articles were excluded. Also, those studies that did not report on any outcomes of interest were excluded.

Data Extraction and Quality Assessment

Extraction of relevant data from included studies was done by two authors independently, using a data extraction sheet. Following data from eligible studies were extracted: surname of first author, year in which the study was published, geographical location where the study was done, sample size, characteristics of the study subjects, design of the study and key findings. Newcastle-Ottawa Quality Assessment Scale adapted for observational studies was used for quality assessment of included studies[10].

Statistical Analysis

Statistical analysis was done using STATA version 13.0. A meta-analysis of the reported prevalence in the included studies was done. The outcomes considered were rates of good to excellent hemostasis, rates of thrombotic complications and mortality rates. The final estimates of prevalence were reported as percentages with 95% CI. Heterogeneity of effects was assessed and quantified by the I^2. I^2 value >50% was considered to represent substantial heterogeneity[11]. In cases with substantial heterogeneity, random effects model was used. Also, subgroup analysis was conducted based on the location of bleeding and type of oral anticoagulant used. A p-value of <0.05 was considered statistically significant. Publication bias was assessed using Egger's test and visually inspected using funnel plots.

Selection of Articles, Study Characteristics and Quality of Included Studies

A total of 484 unique citations were obtained upon executing the search strategy in the PubMed, Scopus and Google scholar databases (Figure 1). Out of these, 398 were excluded based on title screening. Further, 56 citations were excluded after reading the abstract. Full text of the remaining 30 articles was reviewed. Out of these, 8 articles were excluded upon full text review. The final number of included articles in this meta-analysis was 22[12-33]. Table I presents the key characteristics of the included studies along with the key findings. Majority of the studies were done on United States (13/22) followed by Germany (3/22) and

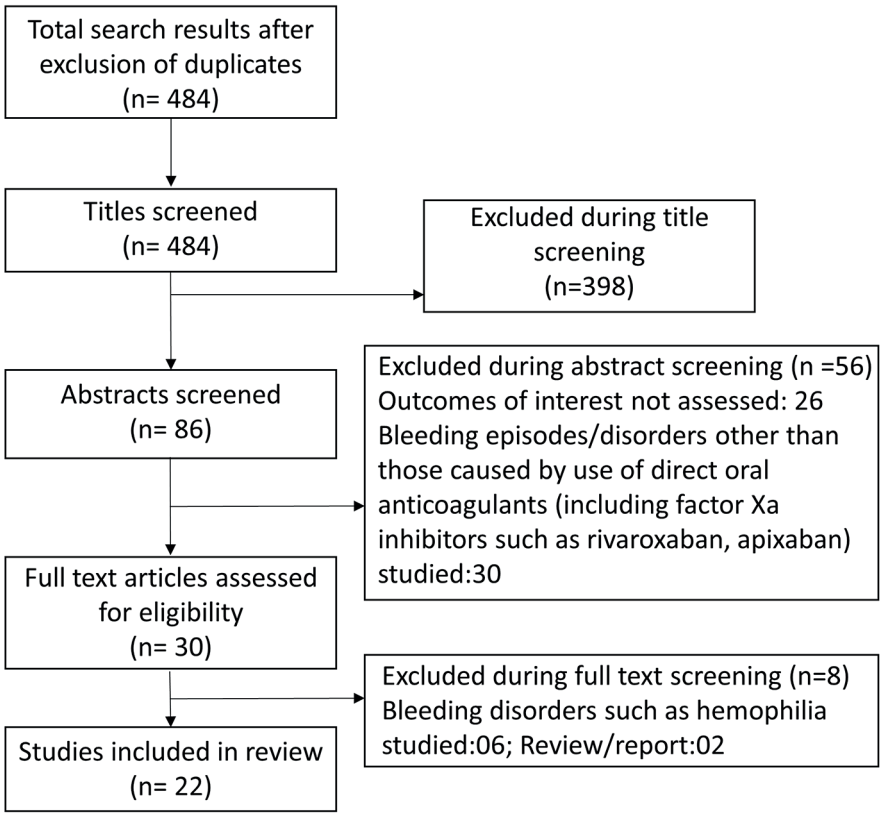

Figure 1. Selection process of the studies included in the review.

Canada (2/22). One study each was done in Japan, Sweden and Switzerland. One study was a multicentric study done in USA, United Kingdom and Canada (Table I)[13]. All the included studies were non-randomized and most were retrospective record based. Almost all the studies were done in elderly subjects aged above 70 years. **Supplementary Table II** presents the findings of the quality assessment of included studies. All the included studies had moderate to high quality **(Supplementary Table II)**.

Effect on Hemostatic Control

The pooled rate of good to excellent hemostatic control upon use of andexanet was 80% (95% CI; 72% to 88%, I^2=33.9%) (Figure 2). For four-factor or activated prothrombin complex concentrate (4F-PCC) use, the pooled rate of hemostatic control was 76% (95% CI; 70% to 83% I^2=80.2%) (Figure 2). There was no evidence of publication bias (Eggers *p*-value=0.33) **(Supplementary Figure 1)**.

Subgroup Analysis

Among subjects receiving andexanet, good to excellent hemostatic control in those with intracranial bleeding was 78% (95% CI; 66% to 89%) and in those with extracranial/gastrointestinal bleeding was 84% (95% CI; 75% to 92%) **(Supplementary Figure 2)**. This difference in pooled proportions was not statistically significant (p=0.26). Also, in those that had received the oral anticoagulant Apixaban, good to excellent hemostatic control was observed in 84% (95% CI; 78% to 89%) whereas in those receiving Rivaroxaban, this was 80% (95% CI; 71% to 87%) **(Supplementary Figure 3)**. However, this difference in pooled proportions was not statistically significant (p=0.40).

Among subjects receiving prothrombin complex concentrates (PCC), good to excellent hemostatic control in those with intracranial bleeding was 75% (95% CI; 68% to 83%) and in those with extracranial/gastrointestinal bleeding was 69% (95% CI; 56% to 82%) **(Supplementary Figure 4)**. In those that had received Apixaban, good to excellent hemostatic control was observed in 75% (95% CI; 67% to 83%) whereas in those receiving Rivaroxaban, this was 73% (95% CI; 62% to 85%) **(Supplementary Figure 5)**. These differences in proportions based on site of bleeding and type of oral anticoagulant used were not statistically

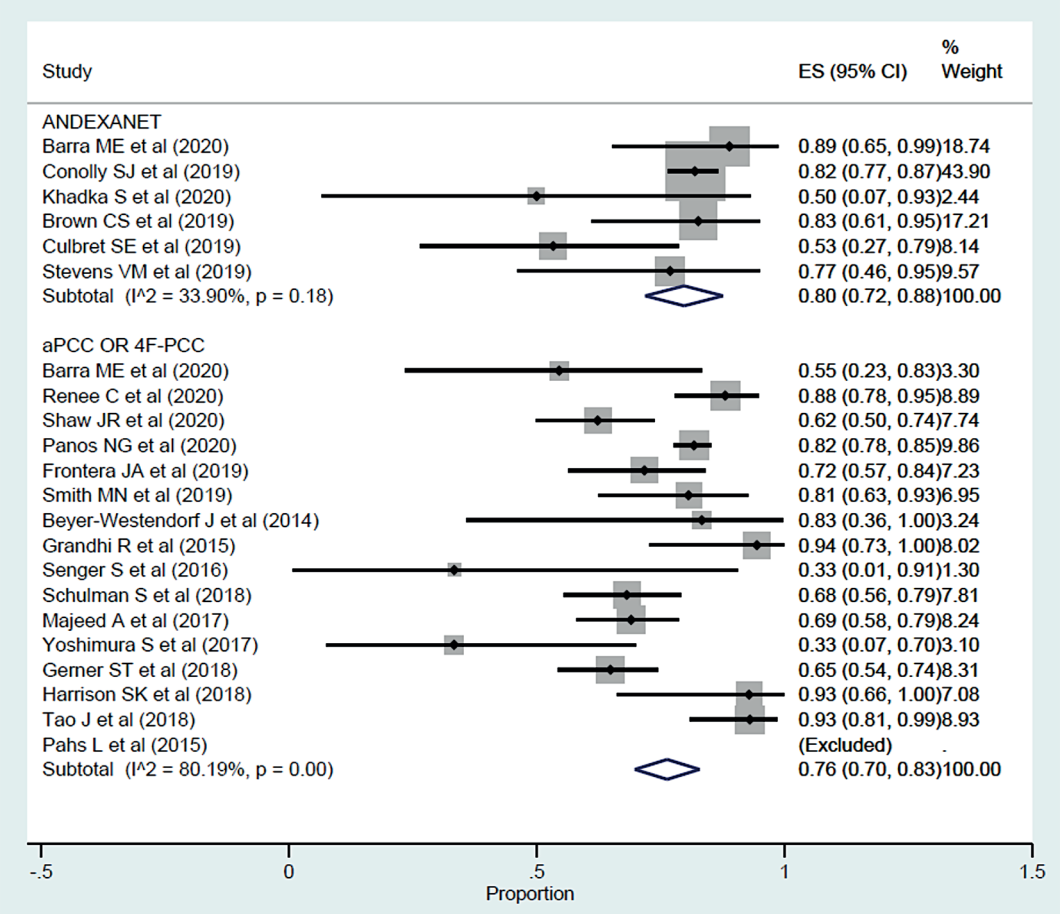

Figure 2. Effect of andexanet or prothrombin complex concentrates on haemostatic control during hospitalization.

different (p=0.43 for site of bleeding; p=0.51 for type of oral anticoagulant)

Effect on Rate of Thrombotic Events

A comparatively higher pooled rate of thrombotic complications upon use of andexanet [13% (95% CI; 5% to 20%, I^2=19.1%) was noted, compared to use of aPCC/4F-PCC [4% (95% CI; 3% to 5%, I^2=0.0%) (Figure 3). Three out of the 6 studies involving administration of andexanet documented no episode of thrombotic event whereas 5 out of 17 studies reporting on aPCC/4F-PCC documented no thrombotic event. There was no evidence of publication bias (Eggers p-value=0.12) **(Supplementary Figure 6)**.

Subgroup Analysis

In subjects receiving andexanet, among those with intracranial hemorrhage, the thrombosis rate within 90 days of administration was 18% (95% CI; 2.0% to 34%). This was similar to those that received Apixaban i.e., 19% (95% CI; 5.0% to 33%) **(Supplementary Figure 7)**.

Among subjects receiving prothrombin complex concentrates (PCC), among those with intracranial hemorrhage, the thrombosis rate within 90 days of administration was 4% (95% CI; 3% to 5%) **(Supplementary Figure 8)**. In those that had received Apixaban, the thrombosis rate was 4% (95% CI; 0.0% to 7.0%) whereas in those receiving Rivaroxaban, this was 3.0% (95% CI; 0.0% to 7.0%) **(Supplementary Figure 9)**. This difference in pooled proportions based on type of oral anticoagulant received was not statistically significant (p=0.31).

Effect on All-Cause Mortality Rate within 90 Days of Administration

With use of andexanet, the pooled all-cause mortality rate within 90 days of administration was 24% (95% CI; 12% to 35%, I^2=63.1%) (Figure 4). The pooled mortality rate was 19% (95%

CI; 14% to 25%; I^2=79.1%) when studies involving use of aPCC/4F-PCC were pooled (Figure 4). There was no evidence of publication bias (Eggers *p*-value=0.18) **(Supplementary Figure 10)**.

Subgroup Analysis

Among subjects receiving andexanet, mortality rate in those with intracranial bleeding was 34% (95% CI; 22% to 47%) and in those with extracranial/gastrointestinal bleeding was *22% (95% CI; 3.0% to 60%; n=1)* **(Supplementary Figure 11).** This difference in pooled proportions for mortality based on site of bleeding was not statistically significant (*p*=0.37). Also, in those that had received the oral anticoagulant Apixaban, mortality was observed in 20% (95% CI; 10% to 30%) **(Supplementary Figure 12)**.

Among subjects receiving prothrombin complex concentrates (PCC), pooled mortality rate in those with intracranial bleeding was 22% (95% CI; 15% to 29%) and in those with extracranial/gastrointestinal bleeding was 29% (95% CI; 13% to 45%) **(Supplementary Figure 13)**. In those that had received Apixaban, mortality was observed in 28% (95% CI; 15% to 45%; n=1) whereas in those receiving Rivaroxaban, this was 28% (95% CI; 16% to 41%) **(Supplementary Figure 14)**. These differences in proportions based on site of bleeding and type of oral anticoagulant used were not statistically different (*p*=0.21 for site of bleeding; *p*=0.74 for type of oral anticoagulant).

Discussion

The current meta-analysis was undertaken to provide synthesized evidence on the efficacy and safety of 4F-PCC and adexanet alfa for management of major bleeding due to oral factor Xa inhibitors. There was also an attempt to update the previous review by Piran et al[9] (2019) where they had assessed the efficacy and safety of 4F-PCC[9]. In view of the recently published studies on use of andexanet alpha, there was also a need to synthesize its efficacy in major bleeding events owing to use of oral factor Xa inhibitors. The meta-analysis

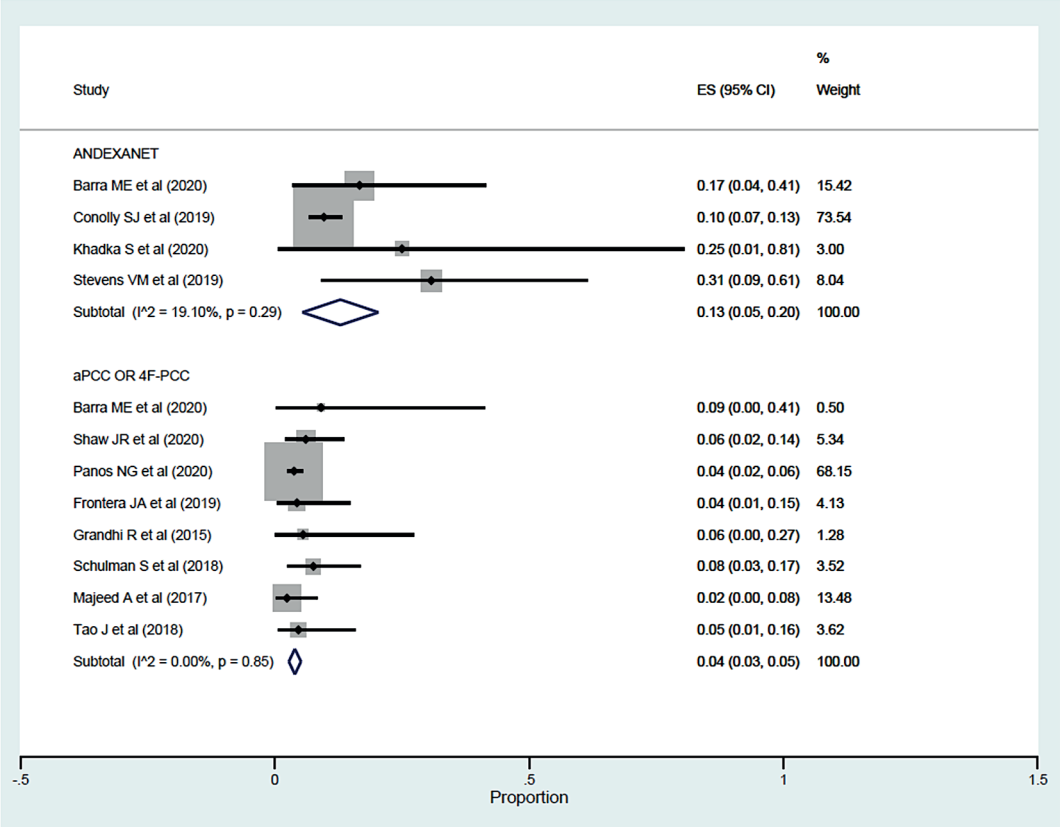

Figure 3. Effect of andexanet or prothrombin complex concentrates on thrombotic rates within 90 days of administration.

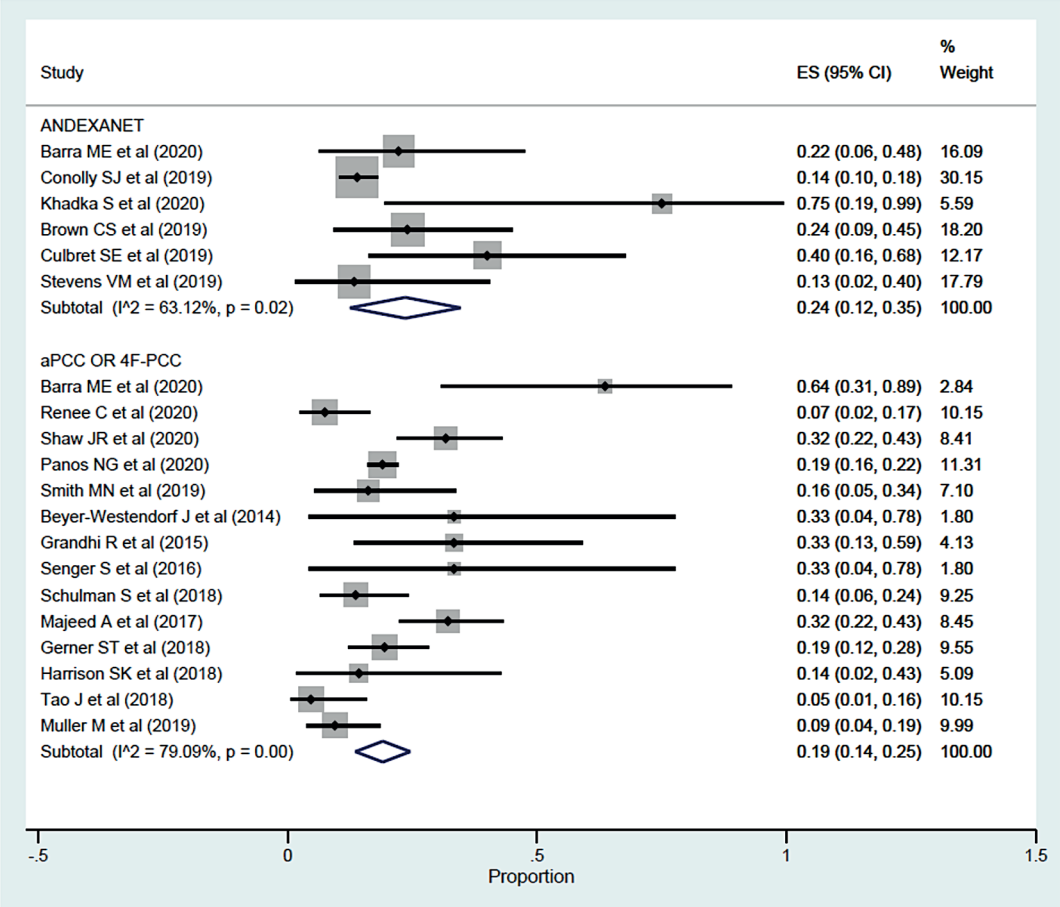

Figure 4. Effect of andexanet or prothrombin complex concentrates on mortality rate within 90 days of administration.

found that the pooled rate of adequate hemostatic control, rates of thrombotic events and mortality upon use of 4F-PCC were 76%, 4% and 19% respectively which are similar to that reported by Piran et al[9] i.e., 77% for adequate hemostasis, 16% for all cause mortality and 4% for thrombotic events. The present meta-analysis also documented these outcomes in relation to the use of andexanet and found the pooled rates for the outcomes to be higher than those of aPCC/4F-PCC, especially in terms of rates of thrombotic events (24% *vs.* 19%) and mortality within 30 days of administration (13% *vs.* 4%). Because only single arm studies were pooled, the quality of evidence may not be robust enough to conclusively guide management strategies. Nonetheless, the findings indicate that the use of prothrombin complex concentrates over andexanet might be preferred particularly because the rate of good hemostasis is similar in the two groups and the complication rates are comparatively higher in the latter.

Most of the studies looking at the efficacy and safety of 4F-PCC and andexanet alfa for management of major bleeding due to oral factor Xa inhibitors have not employed a comparator group/supportive care group. Therefore, it would not be possible to conclusively ascertain if these agents are better or worse or similar to the supportive care. It is imperative that future studies are done with a control group in order to be able to ascertain whether reversal with andexanet/4F-PCC is more effective than supportive care alone. The rate of thrombotic events must be taken into account as well. We noted a high pooled prevalence rate of thrombotic events with use of adexanet alfa and this finding suggests that closed supervision and follow-up should be done in patients receiving andexanet. Further, it is advisable that the clinicians should refrain from the routine use of these agents and reserve their usage for life-threatening bleeding only. This is also important because of the high cost of these agents and the high rate of

Table I. Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Studies on Andexanet						
Barra et al (2020)[12]	USA	Rivaroxaban or apixaban; Majorly Apixaban (83.3% of subjects) Intracranial hemorrhage (ICH) Primary indication for oral anticoagulation: Atrial fibrillation (86.2%) Median age of subjects:73.2 years	Low dose: 400 mg intravenous (iv) bolus over 15 min followed by 480 mg over 2 hours High dose: 800 mg iv bolus over 30 min followed by 960 mg over 2 hours	Review of CT/MRI: ≤20% increase in intracerebral hematoma volume/ subarachnoid hemorrhage thickness/ subdural hematoma thickness, compared to baseline on a repeat CT scan performed within 24 h of reversal agent administration	Retrospective, single-center case series analysis	Good to excellent hemostasis on imaging (within 24 hours of andexanet alfa): 16/18 (88.9%) Good functional outcome (Glasgow scale >3 at hospital discharge): 10/18 (55.6%) Thrombotic complications (new thrombosis within 30 days of anti-thrombotic reversal): 3/18 (16.7%) Mortality (in-hospital): 4/18 (22.2%)
Conolly et al (2019)[13]	Multicentric (USA, UK and Canada)	Rivaroxaban (in 36% subjects) or apixaban (in 55% subjects) Gastro-intestinal (GI)-in 26% subjects Intracranial hemorrhage (ICH)-in 64% subjects Primary indication for oral anticoagulation: Atrial Fibrillation (80%) Mean age:77.0 years	Low dose regimen: 400 mg bolus, delivered at 30 mg/min, followed by a 4 mg/min infusion for 120 minutes. High dose regimen: 800 mg bolus, delivered at 30 mg/min, followed by an 8 mg/min infusion for 120 minutes.	ICH: a ≤20% increase in volume compared to baseline at both 1 and 12 hours after post infusion Gastrointestinal (GI) bleeding: evaluated based on corrected hemoglobin and hematocrit at 12 hours compared to baseline, with "excellent" hemostasis having a < 10% decrease	Prospective open label single group study	Good to excellent hemostasis at 12 hrs after administration: 204/249 (82.0%) Thrombotic complications (within 30 days of anti-thrombotic reversal): 34/352 (10.0%) Mortality (with 30 days): 49/352 (14.0%) Functional outcome (in a subsample of 67 subjects): Mean scores on modified Rankin scale for global disability and handicap were similar at baseline (Mean; 2.2±1.9) and at 30 days (Mean; 2.0±2.0) of anti-thrombotic reversal for patients with ICH ***Subgroup analysis*** In patients with ICH: good to excellent hemostasis: 135/168 (80.0%) In patients with GI bleeding: good to excellent hemostasis: 51/60 (85.0%) In those receiving apixaban: good to excellent hemostasis:109/131 (83%) In those receiving Rivaroxaban: good to excellent hemostasis:79/99 (80%)

Table I. (Continued). Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Studies On Andexanet						
Khadka et al (2020)[14]	USA	Rivaroxaban (in 50% subjects; n=2) or apixaban (in 50% subjects; n=2) Intracranial hemorrhage (ICH) Primary indication for oral anticoagulation: Atrial Fibrillation (100%) Mean age: 72 years	Low-dose regimen (N=3): 400 mg IV bolus followed by IV infusion at 4 mg/min for two hours. High-dose regimen (N=1): 800 mg IV bolus followed by IV infusion at 8 mg/min for two hours	Less than 20% increase in the volume of intracranial hemorrhage in one hour and 12 hours after the infusion of andexanet	Single institute retrospective review	Good to excellent hemostasis on imaging: 2/4 (50.0%) Thrombotic complications: 1/4 (25.0%) Mortality (within 30 days): 3/4 (75.0%)
Brown et al (2019)[15]	USA	Rivaroxaban (in 20% subjects; n=5) or apixaban (in 80% subjects; n=20) Presenting with ICH (n=13) or GI/ bleeding at other sites (n=9) Primary indication for oral anticoagulation: Atrial Fibrillation (60%) Mean age: 75years	Low-dose regimen: 400 mg IV at rate of 30 mg/min followed by IV infusion at 4 mg/min for two hours. High-dose regimen: 800 mg IV at rate of 30 mg/min followed by IV infusion at 8 mg/min for two hours	For ICH: defined as ≤ 20% increase from pre-treatment hematoma volume, and subdural hematoma (SDH) expansion was defined as ≤ 20% increase in maximal hematoma diameter For GI bleeding/ bleeding at other sites: No evidence of uncontrolled bleed in the operating room as per review of the medical records, and no need for blood products	Retrospective case series review	Good to excellent hemostasis on imaging: 19/23 (82.6%) No thrombotic events Mortality (within 30 days): 6/25 (24.0%) **Subgroup analysis** In patients with ICH: good to excellent hemostasis: 10/11 (90.9%) In patients with GI bleeding: good to excellent hemostasis: 6/9 (66.7%) In patients with ICH: mortality- 4/11 (36.4%) In patients with GI bleeding: mortality- 2/9 (22.2%)
Culbret et al (2019)[16]	USA	Rivaroxaban (in 53.3% subjects; n=8) or apixaban (in 46.7% subjects; n=7) Presenting with ICH Primary indication for oral anticoagulation: Atrial Fibrillation (83%) Mean age: 82 years	Low-dose regimen (N=11): 400 mg IV bolus followed by IV infusion at 4 mg/min for two hours. High-dose regimen (N=4): 800 mg IV bolus followed by IV infusion at 8 mg/min for two hours	For ICH: defined as ≤ 20% increase from pre-treatment hematoma volume, and subdural hematoma (SDH) expansion was defined as ≤ 20% increase in maximal hematoma diameter	Prospective single group study	Good to excellent hemostasis on imaging: 8/15 (53.3%) No thrombotic events Mortality: 6/15 (40.0%)

Table continued

Table I. (Continued). Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Studies On Andexanet						
Stevens et al (2019)[17]	USA	Patients presenting with Rivaroxaban (31%; n=4) or apixaban (69%; n=9) Presenting with ICH (46%; n=6) or bleeding at other sites (54%; n=7) Primary indication for oral anticoagulation: Atrial Fibrillation (62%; n=8) Mean age: 69±10 years	Low-dose regimen: 400 mg IV at rate of 30 mg/min followed by IV infusion at 4 mg/min for two hours. High-dose regimen: 800 mg IV at rate of 30 mg/min followed by IV infusion at 8 mg/min for two hours	ICH: hematoma volume did not increase by more than 35% on repeat imaging. Nonintracranial bleeding: hemoglobin/ hematocrit did not decrease by more than 20% within 12 hours	Retrospective cohort	Good to excellent hemostasis (within 12 hours of andexanet alfa): 10/13 (77.0%) Thrombotic events (within 30 days of andexanet alfa): 4/13 (31.0%) Mortality (within 30 days of andexanet alfa): 2/15 (15.0%) Subgroup analysis In patients with ICH: good to excellent hemostasis: 3/6 (50.0%) In patients with non-intracranial bleeding: good to excellent hemostasis: 7/7 (100.0%) In patients with ICH: mortality- 2/6 (33.3%) In patients with non-intracranial bleeding: mortality- 0/7 (0.0%)
Studies on APCC Or 4f-PCC						
Barra et al (2020)[12]	USA	Patients with Rivaroxaban (72.7%; n=8) or apixaban (27.3%; n=3) Intracranial hemorrhage (ICH) Indication for oral anticoagulant: Atrial fibrillation (72.7%; n=8) and deep vein thrombosis (27.3%; n=3) Median age:73.2 years	The median [IQR] dose of 4F-PCC administered was 26.9 units/kg [21.8-43.7]	Review of CT/MRI: ≤20% increase in intracerebral hematoma volume/subarachnoid hemorrhage thickness/ subdural hematoma thickness, compared to baseline on a repeat CT scan performed within 24 h of reversal agent administration	Retrospective, single-center case series analysis	Good to excellent hemostasis on imaging: 6/11 (60.0%) Good functional outcome (GOS>3 at hospital discharge): 1/11 (9.1%) Thrombotic complications (within 30 days of reversal): 1/11 (9.1%) Mortality (in-hospital): 7/11 (63.6%)
Renee et al (2020)[18]	USA	Patients with Rivaroxaban (56.7%; n=38) or apixaban (43.3%; n=29) Intracranial hemorrhage (ICH) Primary indication: Atrial fibrillation (77.6%; n=52) Mean age: 77 years	aPCC: dose of 8–50 units per kg 4F-PCC: dose at a range of 25 or 50 units per kg	≤20% increase in intracerebral hematoma volume/subarachnoid hemorrhage thickness/ subdural hematoma thickness compared to baseline on a repeat CT scan performed within 12 h of reversal agent administration	Multicenter retrospective study	Good to excellent hemostasis (within 12 hours of administration of reversal agent): 59/67 (88.1%) No thrombotic complications (within 30 days of admission) In-patient mortality: 5/67 (7.5%)

Table continued

Table I. (Continued). Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Shaw et al (2020)[19]	Canada	Dabigatran (17%; n=14); Rivaroxaban (47.6%; n=39); apixaban (35.4%; n=29) Bleeding sites: ICH (53.7%), upper gastrointestinal (GI) bleeding (14.8%) and lower GI bleeding (14.8%) Primary indication: Atrial fibrillation (81.7%; n=67) Mean age: 77 years	Recommended aPCC dosing was 25-50 IU/kg. Mean aPCC dosing was 2974 IU (SD ± 857 IU)	ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point Non-intracranial bleeding: ≤10% decrease in both Hb/ hematocrit at 24 hours compared to baseline	Retrospective study	Good to excellent hemostasis (within 24 hours): 43/69 (62.3%) Thrombotic complications (within 30 days): 5/82 (6.1%) Mortality (within 30 days): 26/82 (31.7%)
Panos et al (2020)[20]	USA	Patients with Rivaroxaban (n=297; 44.8%) or Apixaban (n=366; 55.2%) associated intracranial hemorrhage (ICH) Majority of patients aged over 75 years Primary indication: Atrial fibrillation (78%; n=521)	4PCC at a median initial dose of 43.8 [25.6 – 49.8] units per kilogram (kg) aPCC at a median initial dose of 26.7 [23.8 – 48.3] units per kg	Patients were classified as having excellent hemostasis if a 0-20.0% increase in hematoma size was seen when each follow-up (within 24 hours of administration of reversal agent) CT or MRI was compared to baseline imaging	Multicenter retrospective observational cohort study	Good to excellent hemostasis (within 24 hrs of reversal agent): 354/433 (81.7%) Thrombotic complications (within 30 days): 25/663 (3.8%) In-hospital Mortality: 126/663 (19.0%) Subgroup analysis In patients with Apixaban: Good to excellent hemostasis: 186/234 (79.5%) In patients with Rivaroxaban: Good to excellent hemostasis: 168/199 (84.4%)
Frontera et al (2019)[21]	USA	Patients with Rivaroxaban (n=15; 33%) or apixaban (n=31; 67%) associated hemorrhage ICH (n=32; 70%); GI bleeding (n=11; 24%); other non-intracranial sties (n=3; 6%) Primary indication: Atrial fibrillation (94%; n=43) Mean age: 79±9 years	The dose of 4F-PCC was weight based, and hospital institutional guidelines suggested Kcentra 50 u/kg for the reversal of oral dFXaI based on national guidelines	ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point Non-intracranial bleeding: ≤10% decrease in both Hb/ hematocrit at 24 hours compared to baseline	Retrospective review	Good to excellent 24 hr-hemostasis: 33/46 (72.0%) Thrombotic complications (within 30 days): 2/46 (4.0%) Subgroup analysis For ICH, good to excellent hemostasis: 22/32 (69.0%) For GI bleeding, good to excellent hemostasis: 9/11 (81.8%) ICH: thrombotic complications (within 30 days):2/32 (6.25%) GI bleeding: Thrombotic complications (within 30 days): 0/11 (0.0%)

Table continued

Table I. (Continued). Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Smith et al (2019)[22]	USA	Patients with Rivaroxaban (45%; n=14) or apixaban (55%; n=17) associated hemorrhage Mainly ICH (58%) and pericardial effusion (16%) Primary indication: Atrial fibrillation (90.3%; n=28) Median age: 74 years	Patients received 4F-PCC 25–50 units/kg of actual body weight with a maximum dose of 5000 units	ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point Non-intracranial bleeding: ≤10% decrease in both Hb/ hematocrit at 24 hours compared to baseline	Observational retrospective study	Good to excellent hemostasis (within 24 hrs of reversal agent): 25/31 (80.6%) No thrombotic complications during the hospital stay Mortality (in-hospital): 5/31 (16.0%)
Beyer-Westendorf et al (2014)[23]	Germany	Patients with Rivaroxaban associated hemorrhage Intracranial bleeding (n=2; 33.3%) Non-intracranial bleeding/GI bleed (n=4; 66.6%) Primary indication: cardiovascular condition (%83.3; n=5) Age of participants >65 years	Patients received 4F-PCC 18–47 units/kg of actual body weight with a maximum dose of 5000 units	Defined as documented need for transfusion of <2 Units of RBCs or a drop in hemoglobin of <2 g/L or a lack of increase in size of hematoma within 24 hours	Secondary data analysis using data from a prospective, noninterventional oral anticoagulation registry	Good to excellent hemostasis (within 24 hours of administration of reversal agent): 5/6 (83.3%) No thrombotic complications (within 90 days) Mortality (within 90 days of administration of reversal agent): 2/6 (33.3%)
Grandhi et al (2015)[24]	USA	Patients with Rivaroxaban (88.8%; n=16) or apixaban (11.2%; n=2) associated hemorrhage Primary indication: cardiovascular condition (89.0%) Intracranial hemorrhage (ICH)	Patients received 4F-PCC 25–50 units/kg of actual body weight with a maximum dose of 5000 units	Progression of intracranial hemorrhage was identified through review of subsequent head CTs and confirmed by radiology reports noting increased size of intracranial hemorrhage on follow-up scans.	Retrospective review	Good to excellent hemostasis (in-hospital): 17/18 (94.0%) Thrombotic complications (within 90 days of administration of reversal agent): 1/18 (6.0%) Mortality (in-hospital): 6/18 (33.3%)

Table continued

Table I. ***(Continued).*** Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Pahs et al (2015)[25]	USA	Patients with Rivaroxaban or dabigatran associated hemorrhage Majority with gastro-intestinal bleeding	PCC- median dose of 40U/kg	Defined as documented need for transfusion of <2 Units of RBCs or a drop in hemoglobin of <2 g/L or a lack of increase in size of hematoma within 24 hours	Retrospective review	Good to excellent hemostasis (within 24 hours of reversal agent): 3/3 (100.0%)
Senger et al (2016)[26]	Germany	Patients with Rivaroxaban or dabigatran associated hemorrhage Median age: 80.4 years All subjects with ICH Primary reason for giving oral anticoagulants: Atrial fibrillation	Not specified	Operational definition not specified	Retrospective review	Good to excellent hemostasis (in hospital; within 24 hrs of reversal agent): 1/3 (33.3%) Mortality: 2/6 (33.3%)
Schulman et al (2018)[27]	Canada	Patients with Rivaroxaban (56%; n=37) or apixaban (44%; n=29) associated hemorrhage ICH (55%; n=36); GI bleeding (24%; n=16) Primary indication for oral anticoagulant: Atrial fibrillation (82%; n=54)	A fixed dose of PCC 2,000 units	ICH: ≤20% increase in haematoma volume compared with baseline on repeat CT scan performed and/or any neurological improvement noted over the following 12 h Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 h after the end of infusion; and the condition has not deteriorated during and after 24 h	Prospective cohort	Good to excellent hemostasis (within 24 hours of reversal agent): 45/66 (68.2%) Thrombotic complications (within 30 days of administration of reversal agent): 5/66 (8.0%) Mortality (within 30 days of administration of reversal agent): 9/66 (14.0%) Subgroup analysis ICH: Good to excellent hemostasis (within 24 hours of reversal agent): 24/36 (67.0%) GI bleeding: Good to excellent hemostasis (within 24 hours of reversal agent): 11/16 (68.7%) ICH: Mortality (within 30 days of administration of reversal agent): 8/36 (22.2%) GI bleeding: Mortality (within 30 days of administration of reversal agent): 0/16 (0.0%)

Table continued

Table I. *(Continued)*. Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Majeed et al (2017)[28]	Sweden	Patients with Rivaroxaban (53.4%; n=45) or apixaban (46.4%; n=39) associated hemorrhage ICH (70.2%; n=59); GI bleeding (15.5%; n=13) Primary indication for oral anticoagulant: Atrial fibrillation (75%; n=63) Median age: 75 years	PCC was given at a median (interquartile range) dose of 2000 IU (1500-2000).	ICH: ≤20% increase in haematoma volume compared with baseline on repeat CT scan performed and/or any neurological improvement noted over the following 24 h Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 h after the end of infusion; and the condition has not deteriorated during and after 24 h	Prospective cohort	Good to excellent hemostasis (within 24 hours of administration of reversal agent): 58/84 (69.1%) Thrombotic complications (at 30 days post reversal): 2/84 (2.4%) Mortality (at 30 days post reversal): 27/84 (32.0%) Subgroup analysis ICH: Good to excellent hemostasis (within 24 hours): 43/59 (72.9%) Extracranial bleeding location: Good to excellent hemostasis (within 24 hours): 15/25 (60.0%) Apixaban: Good to excellent hemostasis (within 24 hours):26/39 (66.7%) Rivaroxaban: Good to excellent hemostasis (within 24 hours):32/45 (71.1%) ICH: Thrombotic complications (within 30 days post reversal): 2/59 (3.4%) Apixaban: Thrombotic complications (within 30 days post reversal): 1/39 (2.6%) Rivaroxaban: Thrombotic complications (within 30 days post reversal): 1/45 (2.2%) ICH: Mortality (within 30 days post reversal): 20/59 (33.9%) Extracranial bleeding location: Mortality (within 30 days post reversal): 7/25 (28.0%) Apixaban: Mortality (within 30 days post reversal): 11/39 (28.2%) Rivaroxaban: Mortality (within 30 days post reversal): 16/45 (35.5%)
Yoshimura et al (2017)[29]	Japan	Patients with non-vitamin K antagonist oral anticoagulant (NOAC) associated hemorrhage : Apixaban (20.0%; n=2); Rivaroxaban (70.0%; n=7); Dabigatran (10%; n=1) Primary indication: Atrial fibrillation (n=7;70.0%) All subjects with ICH Median age: 74 years	1000 international units (IU) of PCC intravenously as a bolus.	Defined as <33% or 6 mL growth of hematoma from baseline to 36 hours CT scan	Prospective cohort	Good to excellent hemostasis (in hospital): 3/9 (33.3%) No thrombotic complications (in-hospital) Mortality (in-hospital): 0/9 (0.0%)

Table continued

Table I. ***(Continued)***. Key details of the studies included in the meta-analysis.

Author, year of publication	Country	Oral anticoagulant used and site of bleeding	Dose of reversal agent used	Definition of excellent hemostasis	Study design	Key outcome
Gerner et al (2018)[30]	Germany	Patients with non-vitamin K antagonist oral anticoagulant (NOAC) associated hemorrhage: Apixaban (14.0%); Rivaroxaban (75.0%); Dabigatran (11%) All patients with ICH	Weight adjusted dosages: ≥25 international-units (IU)/kg bodyweight	Defined as a relative parenchymal volume increase of >33% from initial to follow-up imaging	Retrospective cohort	Good to excellent hemostasis (during the period of hospitalization): 61/94 (64.9%) Mortality (within 30 days): 20/103 (19.4%)
Harrison et al (2018)[31]	USA	Patients with oral anticoagulant (Apixaban or Rivaroxaban) associated hemorrhage (Specific nos. receiving Apixaban or Rivaroxaban not provided) All patients with ICH Primary indication: Atrial fibrillation (85.7%; n=12)	4F-PCC: 25-50 units/ kg to a maximum of 5000 units	Initial hematoma location, size (estimated as part of standard radiologist assessment using simple ellipsoid measurements), and volume were documented. Defined as a hematoma volume increase of >33% from initial to follow-up imaging	Multicentric registry of patients with oral anticoagulant associated ICH	Good to excellent hemostasis (during the period of hospitalization): 13/14 (92.8%) No thrombotic complications (within 30 days post reversal) Mortality (in-hospital): 2/14 (14.3%)
Tao et al (2018)[32]	USA	Patients with rivaroxaban (48.8%; n=21) or apixaban (51.2%; n=22) associated hemorrhage Primary indication: Atrial fibrillation (70%; n=30) and deep vein thrombosis (21%; n=9) Majorly ICH (37.2%; n=16) and GI bleeding (40.0%; n=17)	4F-PCC: 25-50 units/kg to a maximum of 5000 units	The hemostatic efficacy was determined by the treating physician based on clinical measures These included patient hemodynamics, trend of hemoglobin and hematocrit, and active bleeding as seen on imaging or invasive procedures	Single centre retrospective review of medical records	Good to excellent hemostasis (during the period of hospitalization): 40/43 (93.0%) Thrombotic complications (within 90 days of administration of reversal agent): 2/43 (4.6%) Mortality (within 90 days of administration of reversal agent): 2/43 (4.6%) Subgroup analysis Apixaban: Thrombotic complications (within 90 days post reversal): 1/22 (4.54%) Rivaroxaban: Thrombotic complications (within 90 days post reversal): 1/21 (4.76%)
Muller et al (2019)[33]	Switzerland	Patients with non-vitamin K antagonist oral anticoagulant (NOAC) associated hemorrhage : rivaroxaban (90.5%; n=67) or apixaban (6.7%; n=5); one patient each dabigatran or edoxaban Indication: Atrial fibrillation (64.9%; n=48) and thromboembolism (17.6%; n=13) ICH (45; 60.8%) and GI bleeding (19%; n=24)	Median (IQR) dose: 2000 (1700 to 3000) Units	------	Retrospective cohort	Mortality (in-hospital): 7/74 (9.5%)

in-hospital mortality or mortality in the first 90 days of administration.

One limitation of this meta-analysis is the high degree of heterogeneity. This could be related to differences in operational definitions adopted by the studies particularly in relation to how "good or excellent hemostasis" was defined and the time points of assessment. While some studies defined it based on the International Society on Thrombosis and Haemostasis (ISTH) criteria, others did not use these criteria. There were also differences in the timing of assessment with some studies using imaging techniques within 12 hours of intervention and some at 24 hours after intervention. More harmonized protocols are required for conducting studies so that the evidence generated is reliable and useful. One of the reasons for the observed heterogeneity could also be related to the type of bleeding that resulted in hospital admission and/or the type of oral anticoagulant used. To understand whether these factors could account for the observed heterogeneity, we conducted subgroup analysis based on these two factors. We noted that the rate of good to excellent hemostatic control was similar in both andexanet and PCC group for intracranial hemorrhage, but it was better in andexanet group for extra-cranial bleeding, although statistical significance for difference in rates of hemostatic control was not achieved. Further, the hemostatic control seemed slightly better with andexanet in subjects that had received Apixaban or Rivaroxaban. The rate of thrombotic events was much higher with andexanet in all the subgroups, compared to PCC. In subjects with intracranial hemorrhage, the mortality rates seemed lower with use of PCC and in subjects that had received either Apixaban or Rivaroxaban, the mortality rates seemed lower with use of andexanet. Further, there were differences in the dose of andexanet or PCC used in different studies and that may also explain a part of the heterogeneity. One of the limitations of this meta-analysis is that most of the included studies had limited sample size. Studies with small sample size are often met with the limitation of lack of generalizability of the findings. Consequently, there is a need for large studies with longer follow up on a wide range of outcomes.

The findings add to the previous meta-analysis that looked at the efficacy and safety of prothrombin complex concentrates in management of major bleeding due to oral factor Xa inhibitors. The findings suggest that use of both andexanet and aPCC/4F-PCC achieves a good hemostasis. However, the rate of effective hemostasis achieved was slightly better for andexanet, compared to aPCC/4F-PCC. The findings of the meta-analysis indicate that andexanet could be preferred for reversing the effects of life-threatening or uncontrolled bleeding caused by apixaban or rivaroxaban anticoagulation agents. Nonetheless, there is an associated risk of thrombotic events and mortality with use of both andexanet and 4F-PCC. They, should therefore, be used for major life-threatening bleeding episodes. It is still unclear whether these pooled estimates reflect a true picture as in all the included studies, a comparative group was missing. Future studies should have a control group to better establish evidence on efficacy and safety of these agents.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
CL conceived and designed the study. FC, YC, CZ, CF, HL, DZ and QL collected the data and performed the literature search. CL was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical approval
Not applicable.

Patients consent
Not applicable.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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