

REVIEW

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# The impact of prothrombin complex concentrates when treating DOAC-associated bleeding: a review

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## Abstract

**Background:** Bleeding complications are a risk associated with all anticoagulants. Currently, the treatment options for the management of direct oral anticoagulant (DOAC)-associated bleeding are limited. Prothrombin complex concentrates (PCCs) have been proposed as a potential therapeutic option, and evidence regarding their use is increasing.

**Review:** Many studies supporting PCC have used preclinical models and healthy volunteers; however, more recently, observational studies have further improved insight into current DOAC reversal strategies. Multiple clinical practice guidelines now specifically suggest use of PCCs for this indication. Specific reversal agents for Factor Xa inhibitors may become available in the near future, but data on their efficacy are still emerging.

**Conclusions:** Ultimately, a multimodal approach may be the optimal strategy to restore haemostasis in patients presenting with DOAC-associated coagulopathy.

**Keywords:** Anticoagulants, Haemorrhage, Non-vitamin K antagonist oral anticoagulants, Dabigatran, Rivaroxaban, Edoxaban, Apixaban, Prothrombin complex concentrates, Anticoagulant reversal

## Background

Direct oral anticoagulants (DOACs; also known as non-vitamin K oral anticoagulants or target-specific oral anticoagulants) specifically inhibit either coagulation factor IIa (FIIa; dabigatran) or factor Xa (FXa; rivaroxaban, apixaban and edoxaban; Fig. 1) [1]. DOAC use has grown in recent years, especially for stroke prevention in patients with non-valvular atrial fibrillation [1].

Most evidence suggests rates of major bleeding and intracranial haemorrhage (ICH) with DOACs are similar to or lower than those with warfarin [2], although some studies have highlighted a higher rate of gastrointestinal bleeding with particular DOACs [2, 3]; high-dose dabigatran and high-dose edoxaban were associated with an increased risk of gastrointestinal bleeding versus warfarin ( $p < 0.001$  and  $p = 0.03$  respectively) [4, 5], and rivaroxaban was associated with an

increased incidence of major bleeding from a gastrointestinal site versus warfarin (3.2% vs 2.2%;  $p < 0.001$ ) [6]. Rates of major bleeding for dabigatran, rivaroxaban, apixaban and edoxaban (as compared with warfarin) are listed in Table 1 [7].

Guidance for the management of DOAC-associated bleeding is summarised in Fig. 2 and includes discontinuation of DOAC treatment (may be sufficient in cases of mild bleeding), local/surgical haemostatic control and blood volume replacement. However, these measures may not be sufficient to control bleeding and restore haemostasis in life-threatening situations.

Prothrombin complex concentrates (PCCs) routinely contain high concentrations of factors II, IX and X (three-factor [3F] PCCs) and potentially also high concentrations of factor VII (four-factor [4F] PCCs) [8]. These high clotting factor concentrations mean PCC administration may overcome the anticoagulant effects of DOAC administration by enhancing thrombin generation [9]. PCCs generally contain nonactivated clotting factors, but PCCs including activated

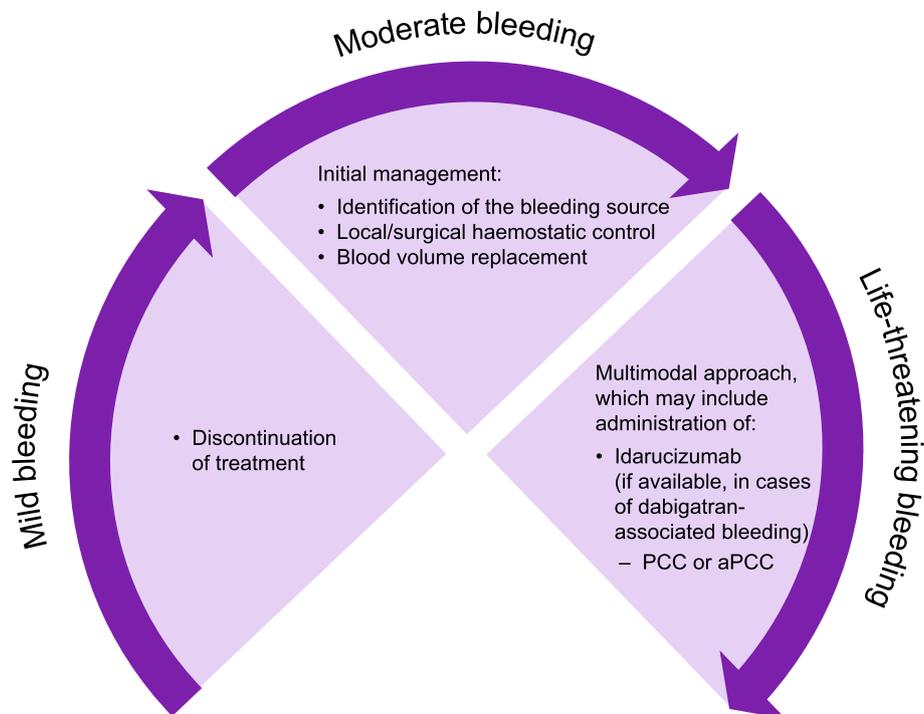
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**Fig. 2** Treatment of DOAC-associated bleeding. Figure legend: aPCC, activated prothrombin complex concentrate; DOAC, non-vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrate

The INR is used to monitor the degree of anticoagulation in VKA-treated patients and is not suitable for measuring the effect of DOACs [15]. The direct FXa inhibitors may prolong the PT, but the extent of prolongation is variable; impact varies by FXa inhibitor, thromboplastin reagent used and also the health status of the patient [16]. Other assays are generally not sensitive to these agents [15]. The direct thrombin inhibitor, dabigatran, prolongs aPTT (depending on the reagent/instrument system used) [17] and correlates with other assays when at therapeutic levels [18]. Specific assays, including calibrated anti-FXa assays for FXa inhibitors [15], and diluted TT (dTT) and ecarin clotting time (ECT; an assay that measures time to clot formation using ecarin as a reagent) for dabigatran [18], may be appropriate for monitoring the effects of DOACs, especially at lower plasma levels.

#### Thrombin generation assays

While traditional assays reflect the formation of a fibrin clot, the thrombin generation assay (TGA) corresponds to the overall function of the coagulation system [13]. In this assay, the time course of thrombin generation is represented graphically, from which various parameters can be derived: lag time (the time until a measurable amount of thrombin is formed), peak height (the maximum level of thrombin attained), time to peak and

endogenous thrombin potential (ETP; total amount of thrombin formed, also described as the area under the curve). It has been suggested that TGAs show greater correlation with the degree of haemostatic impairment resulting from DOACs in vivo than other assays [8, 19, 20]. However, not all TGA results are comparable. The performance characteristics of TGAs depend on the agent used to initiate thrombin generation [19, 21] (for example, tissue factor or phospholipids), and results have historically been difficult to standardise between laboratories.

#### Viscoelastic tests

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) assays provide information on clot formation and dissolution, allowing measurement of the speed of clot formation, clot strength and clot lysis, among other characteristics [13]; both techniques have been shown to be of practical and diagnostic use in acute traumatic coagulopathy settings, but require further validation regarding therapeutic use [22]. Viscoelastic testing has not yet been proven to be useful for DOAC detection or reversal in general clinical practice, although preliminary testing of a commercial rapid TEG assay in healthy volunteers showed that detection and monitoring of rivaroxaban, apixaban and dabigatran is possible with this method

[23]. New reagents are also being developed to facilitate these analyses [24, 25].

#### Clinical relevance of laboratory assays: Summary

Effects on laboratory parameters do not necessarily correlate with bleeding measures [19, 20, 26–29], although some studies suggest that ETP may be an appropriate surrogate biomarker for assessing effects on bleeding [19, 30]. In addition, some of these tests are not available for use in emergency situations. Ultimately, studies evaluating the effect of various reversal agents on bleeding, rather than laboratory parameters, have more clinical relevance for evaluating treatment of DOAC-associated bleeding.

#### Overview of recent data (2013–2017)

A review and discussion of the most recent data are presented below. A limitation of many of the studies is that they were conducted in animal models or healthy volunteers.

#### Preclinical data

##### Animal studies

A number of studies have examined DOAC reversal in animals (Additional file 2) [19, 20, 28, 29, 31–38]. Most found improvements in bleeding parameters after PCC treatment. Moreover, studies conducted using a pig polytrauma model also demonstrated an improved survival rate in dabigatran-treated animals administered 4F-PCC or activated PCC (aPCC) compared with controlled-treated animals [34, 35, 38]. Effects on laboratory parameters, however, were inconsistent; of the assays employed, TGAs had the best correlation with bleeding parameters.

##### *In vitro* and *ex vivo* human studies

The potential role for PCCs in treating DOAC-associated bleeding has also been evaluated in studies using blood samples from patients and healthy volunteers (Additional file 3) [21, 39–56]. PCCs reversed some of the effects of DOACs on laboratory assays, including in two studies which utilised TEG and/or ROTEM to assess the impact of dabigatran/apixaban [41, 54]. However, these effects on laboratory assays do not necessarily correlate with bleeding.

##### Healthy volunteers

Several randomised trials have evaluated the effect of PCCs on DOAC-treated healthy volunteers (Table 2), but most assessed effects on laboratory parameters rather than bleeding.

#### Laboratory parameters

**Dabigatran and rivaroxaban** In a randomised, double-blind, placebo-controlled crossover study, administration of 4F-PCC was insufficient to correct the effects of dabigatran on various laboratory parameters, but did reverse the effects of rivaroxaban on ETP [9].

**Rivaroxaban** Three additional studies investigated the effect of PCCs on rivaroxaban-induced anticoagulation. In the first, a randomised, open-label, parallel-group study, 3F-PCC reversed the effects of rivaroxaban on TGA parameters (ETP and time to peak) to a greater extent than 4F-PCC [57]. The second, a randomised, double-blind, placebo-controlled, crossover trial, demonstrated a significant effect of a 4F-PCC (37.5 IU/kg) on rivaroxaban-induced ETP inhibition ( $p = 0.03$ ) [58]. The third, a randomised, double-blind, parallel-group study, showed that 4F-PCC (50 IU/kg) partially reversed the effects of rivaroxaban on PT and completely reversed the effects on ETP within 30 min following end of infusion, whereas tranexamic acid (1.0 g) showed no difference from saline on either PT or ETP [59].

**Edoxaban** A phase 1 study in healthy volunteers ( $n = 24$ ) showed 3F-PCC rapidly and completely reversed the effect of edoxaban on ETP versus placebo but had no effect on edoxaban-mediated PT prolongation [60].

**Apixaban** Three studies evaluated the effect of PCCs in apixaban-treated healthy volunteers. In a single-centre, randomised, double-blind, placebo-controlled, crossover study, apixaban produced significant modifications in ETP and PT ( $p < 0.01$  for both) [61]. Subsequent 4F-PCC administration increased ETP and normalised PT. Similarly, in an open-label, randomised, placebo-controlled 3-period crossover study, 4F-PCC rapidly reversed apixaban-mediated effects on PT, and ETP and peak height, but not other TGA parameters [62]. In another randomised, two-period crossover, assessor-blinded trial, 4F-PCC improved the effects of apixaban on some TGA parameters [63].

#### Bleeding

To date, two studies have investigated the effect of PCCs on bleeding parameters. The first was a phase 1 study conducted in two parts [30]. Part 1 determined the appropriate dose of edoxaban and assessed intra-individual variability of bleeding duration and volume following a skin punch biopsy in edoxaban-treated healthy volunteers. Part 2 was a double-blind, randomised, placebo-controlled, two-sequence, two-period crossover study with a relatively large sample size ( $n = 93$ ). Based on its lower intra-individual variability in part 1 of the study, bleeding duration rather

**Table 2** Randomised studies in healthy volunteers

Study	Design	N	DOAC	PCC	Results		
					Laboratory parameters tested	Reversal of DOAC effects with PCC	Bleeding
Barco et al. [58]	Randomised, double-blind, placebo-controlled, crossover	6	Rivaroxaban (15 mg BID)	4F-PCC (Cofact® 25 or 37.5 IU/kg)	PT	(+) with both doses of 4F-PCC	No deaths, SAEs or TEEs reported
Brown et al. [60]	Randomised, double-blind, placebo-controlled, three-way crossover	24	Edoxaban (60 or 120 mg)	3F-PCC (Bebulin® 25 or 50 IU/kg)	ETP	(+) with 4F-PCC 37.5 IU/kg	No deaths, SAEs or TEEs reported
					PT	(-)	
Cheung et al. [61]	Randomised, double-blind, placebo-controlled, crossover	6	Apixaban (10 mg BID)	4F-PCC (Cofact® 25 or 37.5 IU/kg)	ETP	(+)	No deaths, SAEs or TEEs reported
					PT	Partial	
Eerenberg et al. [9]	Randomised, double-blind, placebo-controlled, crossover	12	Dabigatran (150 mg BID)	4F-PCC (Cofact® 50 IU/kg)	TGA lag time, aPTT, ECT, TT	(-)	No deaths, SAEs or TEEs reported
					PT, ETP	(+)	
Levi et al. [57]	Randomised, open-label, parallel-group	35	Rivaroxaban (20 mg BID)	4F-PCC (Beriplex® 50 IU/kg) and 3F-PCC (Proflin® 50 IU/kg)	PT	(+) 4F-PCC > 3F-PCC	No deaths, SAEs or TEEs reported
					TGA	(+)	
Levy et al. [59]	Randomised, double-blind, parallel-group	147	Rivaroxaban (20 mg BID)	4F-PCC (Kcentra® 50 IU/kg)	ETP	(+) 3F-PCC > 4F-PCC	No deaths, SAEs or TEEs reported; no difference from saline control in reversal of effects on bleeding duration and volume after administration of 4F-PCC or TXA
					Peak TG	(+) with 3F-PCC only	
					Time to peak	(+)	
					Lag time	(-)	
					aPTT	(-)	
					PT	Partial	
Nagalla et al. [63]	Randomised, two-period crossover, assessor-blinded	12	Apixaban (5 mg BID)	4F-PCC (Kcentra®/Beriplex® 25 IU/kg)	TGA	(+)	No deaths, SAEs or TEEs reported
					ETP	(+)	
					PT	(+)	
					TGA parameters (peak, lag time, ETP)	(+) (significant dependent on reagents used)	
TGA parameters (time to peak, maximum velocity)	(-)						
aPTT	(-)						

**Table 2** Randomised studies in healthy volunteers (Continued)

Study	Design	N	DOAC	PCC	Results tested	Laboratory parameters	Reversal of DOAC effects with PCC	Bleeding
Song et al. [62]	Open-label, randomised, placebo-controlled, 3-period crossover	15	Apixaban (10 mg BID)	4F-PCC (Beriplex® or Cofact® 50 IU/kg)	TGA ETP Peak height Lag time Time to peak Velocity index	(+) (+) (-) (-) (-) (+)		No deaths, SAEs or TEEs reported
Zahir et al. [30]	Randomised, double-blind, placebo-controlled, two-sequence, two-period, crossover	93	Edoxaban (60 mg)	4F-PCC (Beriplex® 10, 25 or 50 IU/kg)	PT	Partial with 4F-PCC 50 IU/kg (+) with 50 IU/kg (partial with 25 IU/kg)		No deaths, SAEs or TEEs reported; reversal of effects on bleeding duration and volume (with 50 IU/kg; partial reversal with 25 IU/kg)

(-) negative result; (+) positive result. 3F-PCC three-factor prothrombin complex concentrate, 4F-PCC four-factor prothrombin complex concentrate, aPTT activated partial thromboplastin time, BID bis in die (twice daily), ECT ecarin clotting time, ETP endogenous thrombin potential, PT prothrombin time, TG4 thrombin generation assay, TT thrombin time, TXA tranexamic acid

than volume was the primary endpoint. 4F-PCC administration dose-dependently reversed the effects of edoxaban on bleeding duration. Complete reversal was achieved following administration of 4F-PCC 50 IU/kg, with partial reversal at a dose of 25 IU/kg and no reversal at 10 IU/kg. A similar trend was observed for bleeding volume and ETP. A dose-dependent reversal of PT was also observed, but this parameter was less well correlated with bleeding effects than ETP.

In the second study, bleeding duration and volume were assessed following administration of rivaroxaban 20 mg twice daily for 4 days and then following administration of 4F-PCC 50 IU/kg or tranexamic acid 1.0 g. For both 4F-PCC and tranexamic acid, no difference from a saline control was observed in either bleeding duration or volume, despite 4F-PCC demonstrating effects on PT and ETP [59].

#### **Clinical trials in healthy volunteers: summary**

Overall, as observed in the preclinical studies, PCC administration led to alterations in some, but not all, laboratory parameters affected by DOACs. Studies with the FXa inhibitors suggest that anticoagulation reversal can be demonstrated using ETP assays [9, 30, 59, 60]. A good correlation between effects on ETP and bleeding parameters was observed in the phase 1 study by Zahir and colleagues; this has also been demonstrated in preclinical studies in animal models [19, 31], suggesting that ETP could be an appropriate surrogate biomarker for assessing the effect of PCCs on bleeding, as mentioned previously.

Generally, PCCs were well-tolerated in healthy volunteers treated with DOACs; there were no reported thromboembolic events (TEEs), serious adverse events or deaths [9, 30, 57–61, 63]. However, it is important to consider that the risk of such events differs between healthy volunteers, patients with medical conditions requiring anticoagulation and patients suffering bleeding while receiving anticoagulants.

#### **Clinical data from DOAC-treated patients**

Few studies of anticoagulation reversal strategies have been conducted in patients presenting with major bleeding or requiring urgent surgery. However, data on patient outcomes are starting to emerge from registries and other observational studies, as well as in case reports from clinical practice.

#### **Registries and observational studies**

**Major bleeding** According to ISTH criteria, major bleeding in non-surgical patients is defined as:

- 1) Fatal bleeding
- 2) Symptomatic bleeding in a critical area or organ
- 3) Bleeding causing a fall in haemoglobin level of  $\geq 20$  g/L ( $\geq 1.24$  mmol/L), or leading to transfusion of  $\geq 2$  units of whole blood or red cells [64]

Data from the large, prospective Dresden DOAC registry was used to analyse rates, management and outcomes of rivaroxaban-related bleeding in 1776 patients [65]. Sixty-six major bleeding events (defined according to ISTH criteria) were reported in 59 patients. Most cases were treated conservatively, with haemostatic intervention only considered necessary in nine patients, highlighting that reversal of DOAC-mediated anticoagulation is rarely needed. PCC was administered in six patients; time between admission and PCC administration was 1–22 h, and the dose was 18–47 IU/kg. Of the four cases for which coagulation tests were repeated after PCC administration, one patient showed improvement (INR, PT and aPTT). Haemorrhage stabilisation was reported in 5/6 patients; the remaining patient who did not respond received the lowest dose of PCC (18 IU/kg), suggesting that the effective dose may be greater than this. Although the most appropriate dose of PCC for treatment of DOAC-associated bleeding has not been established, preclinical studies suggest it to be 25–50 IU/kg.

The French Working Group on Perioperative Haemostasis (GIHP) has also conducted a large, prospective, multicentre registry to evaluate the management of major bleeding in 732 patients treated with dabigatran, rivaroxaban or apixaban [66]. Overall, 208/732 (28%) and 73/732 (10%) patients received 4F-PCC (either Confidex®/Beriplex®, Octaplex® or Kanokad®) and aPCC, respectively. Although the study was not designed to evaluate the efficacy of PCC, investigator-assessed haemostasis was totally or partially achieved in 44% and 37% of those who received these agents, respectively.

In another multicentre, prospective study (the Unactivated Prothrombin complex concentrates for the Reversal of Anti-factor Ten inhibitors [UPRATE] study) evaluating the use of 4F-PCC (Beriplex® or Octaplex®) for the management of rivaroxaban- or apixaban-associated major bleeding, haemostasis was judged effective in 58/84 (69%) patients [67].

A prospective, non-interventional, multicentre cohort study conducted in nine Canadian hospitals has evaluated the use of 4F-PCC (Beriplex® or Octaplex®) at a fixed dose of 2000 U for the management of major bleeding in 66 patients treated with rivaroxaban or apixaban [68]. Haemostatic effectiveness was assessed as good by the treating physician in 43

(65%) patients, moderate in 13 (20%) and poor/none in 10 (15%). It should be noted that there was a dose deviation in 12 (18%) patients.

Use of aPCC has been evaluated in a prospective study of 14 patients with dabigatran-associated bleeding [69]. The effectiveness of aPCC was considered by the treating physician to be good in nine (64%) patients and moderate in five (36%).

A further prospective, non-interventional study (the Reversal Agent use in patients treated with Direct Oral Anticoagulants or vitamin K antagonists [RADOA] registry) is currently being conducted in Germany to evaluate the reversal strategies used in patients treated with oral anticoagulants [70].

A small single-centre prospective trial monitoring laboratory parameters in 13 patients who received 4F-PCC (Beriplex®) following major bleeding (majority intra-cranial or subdural haemorrhage) found that the ETP and peak thrombin generation improved from baseline by 68% ( $p = 0.001$ ) and 54% ( $p = 0.001$ ), respectively, 10 min after completion of PCC treatment [71]. Improvements in several other laboratory parameters were observed and bleeding ceased in 77% of patients receiving 4F-PCC. No thromboses associated with treatment were identified at 7 days post administration [71].

Retrospective studies have also provided insight into DOAC-associated bleeding management in real-world settings. In a large chart review, PCCs (median dose 1500 IU) and aPCCs (median dose 3534 IU) were used in 57 (12.4%) and 24 (5.2%) out of 460 cases of DOAC-associated bleeding, respectively; however, clinical outcomes by treatment type were not reported [72]. In a retrospective review of 25 patients presenting with dabigatran- or rivaroxaban-associated haemorrhage, PCC (median dose 40 IU/kg) was administered in three cases (all rivaroxaban) [73]. Haemorrhages resolved in these cases. Based on data from this study, the institutions involved developed protocols for DOAC-associated haemorrhage, including use of PCCs for severe bleeding events. In another chart review, 28 patients received 4F-PCC (Kcentra®/Beriplex®) according to an institutional protocol designed for the treatment of FXa inhibitor-associated major bleeding or for those requiring emergency surgery [74]. One patient experienced a TEE; although the relationship between this event and 4F-PCC treatment was not established, the patient had a history of TEEs and was not re-anticoagulated after treatment. No data on bleeding outcomes were reported.

**ICH** In cases of coagulopathic ICH, the hematoma may continue to expand for up to 24 h; it is therefore essential to apply coagulopathy reversal treatment

promptly and at an effective dose in order to obtain the best outcome for the patient [75].

An analysis of data from the multicentre, prospective, observational Registry of Acute Stroke Under New Oral Anticoagulants (RASUNOA) was performed to evaluate the management of a subgroup of patients with DOAC-associated intracerebral haemorrhage ( $n = 61$ ) [76]. Consistent with prescribing data [77], rivaroxaban was the most commonly used DOAC (80%), with 12% and 8% of patients receiving dabigatran and apixaban, respectively. 4F-PCC was administered to 35/61 (57%) patients (mean [SD] dose, 2390 [980] IU). When comparing patients who did/did not receive 4F-PCC, there was no significant difference with regard to early haematoma expansion (4F-PCC, 43%; no 4F-PCC, 29%;  $p = 0.53$ ) or 3-month functional outcome. This may be attributed to delayed administration of 4F-PCC (which was often not administered for  $\geq 5$  h), or differences in patient baseline characteristics in each group; patients who received 4F-PCC generally had a worse clinical status, and more frequently had a deep haemorrhage location, than those who did not receive 4F-PCC. Timely intervention is thought to be critical in ICH cases [78] to limit haematoma expansion and improve patient outcomes.

The second part of the Germany-wide RETRACE study, a retrospective cohort analysis of 190 patients with DOAC-associated ICH, investigated the effect of PCC administration on haematoma enlargement [79]. Overall, PCC at any dose prior to follow-up imaging was not statistically significantly associated with a reduced risk of haematoma enlargement in the DOAC-ICH cohort (risk ratio (RR) = 1.150; 95% confidence interval (CI) 0.632–2.090). Importantly, the chance that the nonsignificant nature of these findings is a result of a power issue and small patient numbers cannot be excluded [79].

A single-centre retrospective analysis evaluated outcomes among 55 DOAC-anticoagulated patients presenting with ICH [80]. 4F-PCC (Beriplex® or Octaplex®) was administered in 31/55 (56%) cases (median dose 2000 IU). The 30-day mortality rate was 20%, which is slightly lower than the rate observed at discharge in the literature for patients with anticoagulation-related ICH [81].

In another retrospective study, 90-day outcomes were favourable in 6/18 (33%) patients treated with 4F-PCC (Kcentra®/Beriplex®) for FXa inhibitor-associated ICH, with the authors concluding that 4F-PCC appeared effective in reducing haematoma expansion in this small patient population [82].

Two small retrospective analyses investigated the effect of aPCC in patients presenting with DOAC-associated ICH [83, 84]. In one of the studies, 6/11 (55%) patients

demonstrated stable ICH after aPCC administration [83], and in the other study, no cases of haematoma expansion occurred in the six patients who were previously receiving DOACs [84].

**Periprocedural bleeding** In a retrospective, multicentre study, 4F-PCC (Kcentra®/Beriplex®) was part of the institutional protocol to mitigate the effects of FXa inhibitors [85]. Here, 4F-PCC was effective for the management of acute pericardial effusion in patients undergoing atrial fibrillation ablation while anticoagulated with rivaroxaban or apixaban.

#### **Case studies/series**

A number of case reports have discussed individualised treatment of DOAC-associated bleeding (Table 3) [27, 86–107]. The number and diversity of these reports suggest that many hospitals are adopting PCCs as part of treatment strategies for DOAC-associated bleeding.

#### **Clinical practice guidelines**

Based on the data currently available, many clinical practice guidelines suggest that PCC administration should be considered in cases of serious or life-threatening bleeding (Table 4) [78, 108–118]. This is also reflected in other expert proposals and recommendations [119–122], in DOAC prescribing information [123, 124] and in a recent clinical practice survey in the Netherlands, in which most of the 61 neurologist respondents used PCC for the treatment of intracerebral haemorrhage associated with factor IIa inhibitors (74%) or factor Xa inhibitors (72%) [125].

Perioperative management of patients receiving DOACs remains a challenge, particularly in cases of emergency surgery. A treatment algorithm proposed by the GIHP and other experts in the field suggests a multimodal approach to managing perioperative bleeding, which includes haemodynamic monitoring, standard resuscitation measures, and then ultimately PCC or aPCC administration [109].

Despite proposals recommending use of PCCs for treatment of DOAC-associated bleeding in certain clinical situations, one recent review suggested PCCs may not be useful for this purpose [126]. The author emphasises that addition of PCC usually does not correct the PT and may not completely normalise TGA parameters in the presence of FXa inhibitors. In addition, PCCs do not reduce the level of anti-Xa activity present in the plasma. The latter finding is expected, because PCCs do not directly inactivate FXa inhibitors as a true “reversal agent” would. It is important to note that laboratory parameters do not necessarily correlate well with clinical bleeding [19,

20, 26, 27, 32, 33]. Therefore, in cases where laboratory parameters are not fully normalised, a lack of clinically relevant benefit should not be assumed.

#### **Specific reversal agents**

Specific reversal agents for DOACs are in development or have recently been licenced for DOAC-associated bleeding. The currently available agent, idarucizumab, is a monoclonal antibody fragment (Fab) that binds with high affinity to dabigatran. It was approved in the USA in October 2015 for dabigatran reversal in cases of major/uncontrolled bleeding or prior to emergency surgery/procedures [127]. This approval was based on data from studies in both healthy volunteers and patients requiring dabigatran reversal from the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) cohort study [127, 128], which included a total of 503 patients presenting with serious bleeding (group A;  $n = 301$ ) or requiring an urgent surgical or invasive procedure (group B;  $n = 202$ ). dTT and ECT were normalised in 100% of patients in both groups A and group B, and the 30-day mortality rate was 13.5% in group A and 12.6% in group B, respectively.

Although idarucizumab is now licenced for dabigatran reversal, FXa inhibitors are more widely used than dabigatran [77]. The specific FXa inhibitor reversal agent Andexanet alfa (andexanet), a modified FXa mimetic that acts as a decoy and binds FXa inhibitors, has now received accelerated approval from the US Food and Drug Administration (FDA) for treatment of patients treated with rivaroxaban or apixaban who require reversal of the anticoagulant effects in life-threatening or uncontrolled bleeding. Although this agent reversed the anticoagulant effects of apixaban and rivaroxaban in a randomised controlled trial in healthy volunteers aged 50–75 years, data indicated that continuous infusions of andexanet are required to maintain this effect; anticoagulation reversal was maintained for the 2-h infusion period, with anti-Xa activity rebounding to placebo levels 1–3 h after the end of infusion [129]. The ETP increased above the normal range during the 2-h period, then declined after infusion was stopped. Of potential concern is that transient increases in D-dimer and prothrombin fragments 1 and 2 were observed in some patients, which may be related to the binding of andexanet to tissue factor pathway inhibitor [129]. In healthy volunteers, these elevations were not associated with thromboses; however, thrombotic events occurred in 12/67 (18%) patients included in a multicentre study evaluating andexanet in patients with acute major bleeding associated with the use of FXa inhibitors

**Table 3** Case studies on the use of PCC for DOAC reversal, January 2013–February 2017

Study citation	Study setting	Cases (N)	DOAC	PCC used	Outcomes following PCC administration
Patients presenting with major bleeding					
Denerclaw et al. [96]	Gluteal arterial extravasation	1	Apixaban	3F-PCC (Proflinine®)	<ul style="list-style-type: none"> <li>Clinical examination suggested the haematoma had not expanded since PCC administration</li> <li>The patient was discharged in a stable condition on Day 7</li> <li>No TEEs or VTEs reported</li> </ul>
Diaz et al. [97]	GI bleeding	5	Dabigatran	4F-PCC (Octaplex®)	<ul style="list-style-type: none"> <li>Cessation of bleeding in 4/5 patients</li> <li>No TEEs or VTEs reported during 6 months of follow-up</li> </ul>
Dibu et al. [86]	ICH	5	Rivaroxaban, apixaban, dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>None of the patients had ICH expansion</li> <li>No TEEs, VTEs or haemorrhagic complications reported</li> </ul>
Durie et al. [101]	Life-threatening bleed due to trauma	1	Apixaban	4F-PCC (Kcentra®/Beriplex®)	<ul style="list-style-type: none"> <li>Despite aggressive treatment, and PCC administered at the maximum dose, haemostasis was not achieved and the patient died</li> </ul>
Faust et al. [102]	Subdural haematoma	3	Rivaroxaban	3F-PCC (Proflinine®)	<ul style="list-style-type: none"> <li>Haematoma volume remained stable in all patients</li> <li>No TEEs or VTEs reported</li> </ul>
Faust et al. [107]	Subdural haematoma	2	Apixaban	3F-PCC (Proflinine®)	<ul style="list-style-type: none"> <li>Minimal or no progression in haematoma volume</li> <li>No TEEs or VTEs reported</li> </ul>
Faust and Peterson [87]	Intracerebral haemorrhage	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>Coagulation parameters were not normalised</li> <li>Despite initial increase in haematoma, the patient avoided surgical intervention and remained stable</li> <li>After approximately 2 weeks, the patient developed a new ischemic stroke and was discharged to a hospice</li> </ul>
Jones et al. [104]	GI bleeding and haemorrhagic shock	1	Dabigatran	4F-PCC (Kcentra®/Beriplex®)	<ul style="list-style-type: none"> <li>Rapid correction of coagulation parameters and achievement of haemostasis</li> <li>No TEEs or VTEs reported</li> </ul>
Kauffmann et al. [98]	Subdural haematoma	1	Rivaroxaban	4F-PCC (Kanokad®)	<ul style="list-style-type: none"> <li>Improvement in TGA parameters lasting at least 18 h (normalisation of lag time, elevated peak height and ETP)</li> <li>Favourable clinical outcome</li> <li>No TEEs or VTEs reported</li> </ul>
Masotti et al. [27]	GI bleeding	8	Dabigatran	4F-PCC (Confidex®/Beriplex®)	<ul style="list-style-type: none"> <li>Cessation of bleeding, despite uncorrected coagulation parameters (aPTT, PT/INR)</li> <li>No TEEs or VTEs reported</li> </ul>
McGovern et al. [99]	GI bleeding	1	Dabigatran	4F-PCC (unspecified)	<ul style="list-style-type: none"> <li>Normalisation of coagulation profile (PT, INR, aPTT)</li> <li>No active sites of bleeding identified, and no further blood transfusions required</li> <li>Patient discharged 4 days later, without experiencing any further morbidity related to his condition</li> <li>No TEEs or VTEs reported</li> </ul>
Means et al. [103]	Rectal bleeding	1	Rivaroxaban	3F-PCC (Proflinine®)	<ul style="list-style-type: none"> <li>PCC administration helped control bleeding</li> <li>No TEEs or VTEs reported</li> </ul>
Rinehart et al. [88]	Subdural haematoma	1	Apixaban	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>PT and INR normalised within 24 h</li> <li>Slight improvement in subdural haematoma on Day 2</li> <li>Patient remained stable, with further improvement in the subdural haematoma before discharge on Day 7</li> </ul>

**Table 3** Case studies on the use of PCC for DOAC reversal, January 2013–February 2017 (Continued)

Study citation	Study setting	Cases (N)	DOAC	PCC used	Outcomes following PCC administration
Schulman et al. [100]	Subdural haematoma	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>No TEEs or VTEs reported</li> <li>Normalisation of thrombin time at Day 3</li> <li>Patient underwent an uneventful haematoma drainage procedure and was discharged a day later</li> <li>No TEEs or VTEs reported</li> </ul>
	Intra-axial haemorrhage	1			<ul style="list-style-type: none"> <li>Mild increase in haematoma size after 3 days; no further progression of symptoms</li> <li>No TEEs or VTEs reported</li> </ul>
	Pericardial bleeding	1			<ul style="list-style-type: none"> <li>Cessation of bleeding</li> <li>No TEEs or VTEs reported</li> </ul>
	Upper GI bleeding	1			<ul style="list-style-type: none"> <li>Stabilisation of clinical condition</li> <li>No TEEs or VTEs reported</li> </ul>
Smith et al. [106]	Left frontal lobe parenchymal haemorrhage	1	Rivaroxaban	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>After aPCC administration, the patient was admitted to the trauma in-patient unit; neurological exam remained normal for 24 h and the patient was discharged</li> <li>No TEEs or VTEs reported</li> </ul>
Patients requiring urgent/emergent surgery					
Beynon et al. [89]	Emergency neurosurgery	2	Apixaban	4F-PCC (Beriplex®)	<ul style="list-style-type: none"> <li>No bleeding complications occurred during surgery</li> <li>No symptoms suggestive of thromboembolic events</li> </ul>
Chic Acevedo et al. [90]	Urgent surgery due to an abdominal haematoma	1	Rivaroxaban	4F-PCC (Octaplex®)	<ul style="list-style-type: none"> <li>PT normalisation</li> <li>No complications reported during or after surgery</li> </ul>
Dager et al. [95]	Ablation procedure	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>Normalisation of INR and aPTT, but not thrombin time</li> <li>Bleeding slowed 5 min into the infusion and had stopped by the end of the 15-min infusion</li> <li>No evidence of thrombosis observed</li> </ul>
Liu et al. [105]	Coronary artery bypass graft	1	Rivaroxaban	4F-PCC (Kcentra®/Beriplex®)	<ul style="list-style-type: none"> <li>Patient lost 650 mL blood during the procedure, necessitating the transfusion of 2 units each of PRBCs and platelets</li> <li>Patient was discharged with no sequelae on postoperative day 9</li> <li>Follow-up visit at 1 month did not reveal any new significant events</li> <li>No TEEs or VTEs reported</li> </ul>
Maurice-Szamburski et al. [91]	Subdural haematoma requiring neurosurgical intervention	1	Rivaroxaban	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>No abnormal bleeding during surgery</li> <li>Good surgical result with no rebleeding</li> <li>No TEEs or VTEs reported</li> </ul>
Neyens et al. [92]	Subdural haematoma requiring neurosurgical intervention	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>Therapeutic impact uncertain</li> <li>Coagulation parameters (aPTT and TT) remained prolonged, delaying surgical intervention; thromboelastography may be more appropriate for monitoring dabigatran anticoagulation</li> <li>No TEEs or VTEs reported</li> </ul>

**Table 3** Case studies on the use of PCC for DOAC reversal, January 2013–February 2017 (Continued)

Study citation	Study setting	Cases (N)	DOAC	PCC used	Outcomes following PCC administration
Puttick et al. [93]	Emergency surgery for an incarcerated femoral hernia	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>• Surgery was successful, with no complications</li> <li>• The patient made an uneventful recovery and was discharged the next day</li> <li>• No TEEs or VTEs reported</li> </ul>
Wong and Keeling [94]	Urgent percutaneous transhepatic drainage of a gall bladder empyema	1	Dabigatran	aPCC (FEIBA®)	<ul style="list-style-type: none"> <li>• No bleeding complications occurred during surgery and the clinical state of the patient improved</li> <li>• No TEEs or VTEs reported</li> </ul>

3F-PCC three-factor prothrombin complex concentrate, 4F-PCC four-factor prothrombin complex concentrate, aPCC activated prothrombin complex concentrate, aPTT activated partial thromboplastin time, ETP endogenous thrombin potential, INR international normalised ratio, PRBC packed red blood cells, PT prothrombin time, TGA thrombin generation assay, TEE thromboembolic event, TT thrombin time, VTE venous thromboembolism

**Table 4** Use of PCCs to reverse the anticoagulant effect of DOACs: summary of guidelines and proposals

Society/group (citation)	Need for DOAC reversal	Guidelines or proposals regarding the use of PCCs
Thrombosis and Hemostasis Summit of North America [113]	Critical bleeding or emergent surgery	<ul style="list-style-type: none"> <li>• Use of PCCs seems to be a reasonable approach in dire clinical situations</li> <li>• Consensus was not reached because two authors believed that PCC could not be recommended due to absence of data at the time</li> </ul>
Task Force for Advanced Bleeding Care in Trauma [117]	Life-threatening bleeding	<ul style="list-style-type: none"> <li>• PCC (25–50 IU/kg) suggested for reversal of FXa inhibitors</li> <li>• Not suggested for patients treated with dabigatran</li> </ul>
European Society of Cardiology; European Heart Rhythm Association [111, 112]	Life-threatening bleeding	<ul style="list-style-type: none"> <li>• Administration of PCC (25 IU/kg, repeated if clinically indicated) or aPCC (50 IU/kg) can be considered</li> </ul>
European Society of Anaesthesiology [114]	Life-threatening bleeding or ICH	<ul style="list-style-type: none"> <li>• PCC or aPCC suggested</li> </ul>
Australasian Society of Thrombosis and Haemostasis [118]	Life- or limb-threatening bleeding	<ul style="list-style-type: none"> <li>• Reasonable to consider the use of PCCs; risk and benefit of these agents should be assessed in each individual patient</li> </ul>
<i>Groupe d'Intérêt en Hémostase Périopératoire</i> (GIHP; working group on perioperative haemostasis) [115]	ICH, or haemorrhage in a critical organ Emergent surgery	<ul style="list-style-type: none"> <li>• Use of aPCC (30–50 IU/kg) or PCC (50 IU/kg) warranted, possibly re-administered once after an 8-h interval</li> <li>• PCCs should not be used for prophylactic reversal of anticoagulation, but PCC (25–50 IU/kg) or aPCC (30–50 IU/kg) should be considered to control perioperative bleeding events</li> </ul>
<i>Groupe d'Intérêt en Hémostase Périopératoire</i> (GIHP; working group on perioperative haemostasis) [109]	Major intraoperative bleeding	<ul style="list-style-type: none"> <li>• Multimodal approach, including 4F-PCC (25–50 IU/kg) or aPCC (30–50 IU/kg) administration</li> </ul>
American Heart Association; American Stroke Association [78]	ICH	<ul style="list-style-type: none"> <li>• aPCC or PCC may be considered on an individual basis</li> </ul>
Neurocritical Care Society; Society of Critical Care Medicine [110]	ICH	<ul style="list-style-type: none"> <li>• 4F-PCC (50 IU/kg) or aPCC (50 IU/kg) is suggested for FXa inhibitor-associated ICH</li> <li>• aPCC (50 IU/kg) or 4F-PCC (50 IU/kg) is suggested for dabigatran-associated ICH (if idarucizumab is not available)</li> </ul>
Anticoagulation Forum [108]	Severe haemorrhage	<ul style="list-style-type: none"> <li>• 4F-PCC (50 IU/kg) or aPCC (80 IU/kg) may be considered for reversal of direct FXa inhibitors and direct thrombin inhibitors, respectively</li> </ul>
American Heart Association [116]	Serious bleeding or ICH	<ul style="list-style-type: none"> <li>• 4F-PCC (50 IU/kg) is suggested for the treatment of patients receiving FXa inhibitors until more specific antidotes become available</li> </ul>

4F-PCC four-factor prothrombin complex concentrate, aPCC activated prothrombin complex concentrate, F factor, h hour, ICH intracranial haemorrhage, IU international unit, PCC prothrombin complex concentrate

[130]. Patients (mean age, 77 years) presented predominantly with gastrointestinal or intracranial bleeding and were treated with an andexanet bolus (time from admission to therapy  $4.8 \pm 1.8$  h), followed by a 2-h infusion. After bolus administration, median anti-factor Xa activity decreased by 89% and 93% in rivaroxaban- and apixaban-treated patients, respectively; these levels remained stable during the 2-h infusion, but partially returned to pre-treatment values shortly after. Clinical haemostasis 12 h after infusion was adjudicated as excellent or good in 37/47 (79%) patients included in the efficacy analysis, although it should be noted that TEEs occurred in 12 patients (18%).

Ciraparantag/aripazine (PER977), a small molecule that binds several anticoagulants, including DOACs and low molecular weight heparin, is in early phase 2 development [131]. A zymogen-like FXa variant is also in preclinical development [132].

Overall, more real-life data are needed for specific DOAC reversal agents, as there is some uncertainty about how they might perform in clinical practice. Agents have only been investigated in single-arm studies with no comparison group, making any effect on clinical haemostasis uncertain. Currently, there are no data in patients requiring FXa inhibitor reversal prior to emergency surgery.

### PCCs versus specific reversal agents

As PCCs are the most commonly used DOAC reversal agents, it is important to compare their mechanism of action with those of the specific reversal agents. Specific reversal agents are enzymatically inactive and abrogate the effect of DOACs by direct binding, reducing the concentration of the anticoagulant in the blood. This effect can be measured

by anti-Xa assays, in the case of FXa inhibitors, or the dTT, in the case of dabigatran. However, stoichiometric amounts of specific reversal agents (i.e. 1 molecule of antidote per molecule of anticoagulant) are needed to reverse the anticoagulant effect of DOACs (5 g of idarucizumab [127], 0.88–1.76 g of andexanet [129]). In contrast, PCCs are thought to mitigate the anticoagulant effect of DOACs by increasing the levels of non-activated clotting factors (Fig. 3), which can be activated in case of an active bleed. Therefore, small amounts of PCC can increase the potential to produce thrombin (which ultimately leads to the conversion of fibrinogen to fibrin and a stable clot). This suggests that administration of PCCs may be able to increase thrombin generation and reduce bleeding, without any effect on dTT or anti-Xa levels.

Although patient data on specific reversal agents are promising, the availability, cost and lack of data on these agents for surgical patients may impact widespread use [133]. The widespread use of PCCs for VKA reversal means that these agents are readily available in clinical practice.

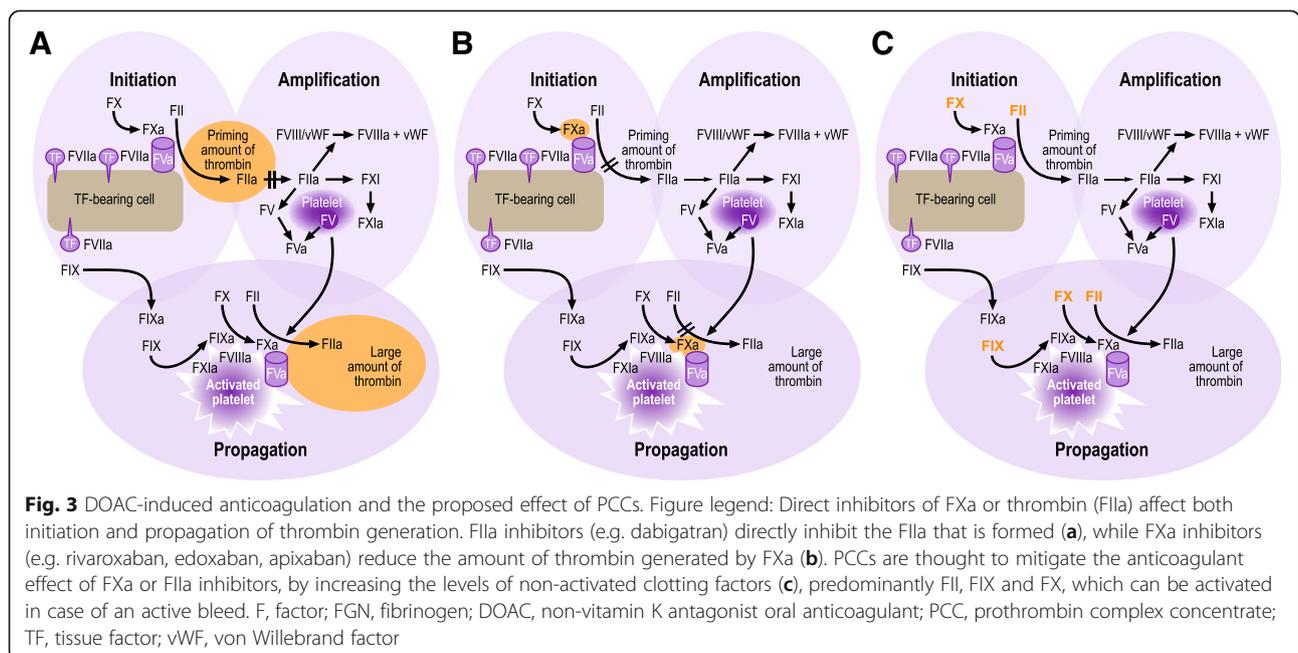
In terms of safety, limited data are available regarding the incidence of thrombosis in patients receiving DOACs who are treated with PCCs; however, no such events occurred in the Dresden registry [65] or in a prospective observational study conducted in Japan [134]. A deep vein thrombosis was reported in a small chart review [74], and suspected or confirmed TEEs occurred in 3/84 patients treated with 4F-PCC (median dose 26.7 IU/kg) in the UPRATE study [67].

The authors note that this low rate (2.4%) is in line with that observed in VKA-treated patients or in cases where anticoagulation was discontinued without a reversal agent. TEEs were reported in 12/67 patients treated with andexanet for major bleeding associated with FXa inhibitors [130], and 5/90 patients treated with idarucizumab for dabigatran reversal due to serious bleeding or prior to urgent surgery [135]. Anticoagulant therapy had not been re-initiated in any of the cases in the idarucizumab study, which may suggest the occurrence of these events is due to underlying predisposing risk factors or a delay in re-initiating treatment, rather than the reversal agent used.

There have been no clinical studies directly comparing PCCs with specific antidotes; however, a preclinical study in a dabigatran-treated porcine polytrauma model showed that, as part of a multimodal therapy, high-dose 4F-PCC (50 IU/kg) was similarly effective to idarucizumab in reducing blood loss [38]. Furthermore, TEEs were not observed in either treatment group.

**Conclusion: PCCs as part of a clinical strategy for DOAC-associated bleeding**

Despite a paucity of clinical data from patients with bleeding complications, an expanding body of evidence from preclinical models, healthy volunteers and clinical reports suggests PCCs have a potential role in the management of DOAC-associated bleeding. This is also reflected in a number of patient management guidance and guideline documents. Data are beginning to emerge



from observational studies and large patient registries, which may assist the development of specific guidelines and strategies for DOAC reversal.

Although specific reversal agents for DOACs are available or in development, there may still be a role for PCCs, for example, in centres without access to these specific agents and in situations where the anticoagulant agent is unknown. Furthermore, once the anticoagulant effects of DOACs have been reversed using a specific reversal agent, patients may continue to bleed [133]. Concentrations of endogenous coagulation factors may be reduced due to loss during bleeding, consumption and dilution if patients are treated with fluids. Therefore, in cases where the bleeding event is particularly severe or prolonged, removing the anticoagulant effect may be insufficient to correct the coagulopathy. General consensus is that a multimodal approach should be used to restore haemostasis in patients presenting with DOAC-associated bleeding, and this may include the use of PCCs and other haemostatic agents.

## Additional files

**Additional file 1:** Search strategy and selection criteria. (DOCX 12 kb)

**Additional file 2:** Preclinical studies showing the effect of PCCs on bleeding in NOAC-treated animals (January 2013–February 2017). (DOCX 15 kb)

**Additional file 3:** Summary of ex vivo and in vitro studies showing the effect of PCCs on NOAC-induced coagulation (January 2013–February 2017). (DOCX 20 kb)

## Abbreviations

3F-PCC: Three-factor prothrombin complex concentrate; 4F-PCC: Four-factor prothrombin complex concentrate; aPCC: Activated prothrombin complex concentrate; aPTT: Activated partial thromboplastin time; DOAC: Direct-acting oral anticoagulant; dTT: Diluted thrombin time; ECT: Ecarin clotting time; ETP: Endogenous thrombin potential; F: Factor; GIHP: *Groupe d'Intérêt en Hémostase Périopératoire* (French Working Group on Perioperative Haemostasis); ICH: Intracranial haemorrhage; INR: International normalised ratio; ISTH: International Society on Thrombosis and Haemostasis; PCC: Prothrombin complex concentrate; PT: Prothrombin time; RASUNOA: Registry of Acute Stroke Under New Oral Anticoagulants; RE-VERSE AD: Reversal Effects of Idarucizumab on Active Dabigatran; ROTEM: Rotational thromboelastometry; TEE: Thromboembolic event; TEG: Thromboelastography; TGA: Thrombin generation assay; TT: Thrombin time; VKA: Vitamin K antagonist

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## Authors' contributions

All authors contributed to the development of the literature search strategy, interpretation of the literature and critical revision of the manuscript. All authors approved the final version for submission.

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