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Prothrombin Complex Concentrate, a General Antidote for Oral Anticoagulation

Herm Jan M. Brinkman

Additional information is available at the end of the chapter

Abstract

Prothrombin complex concentrate (PCC) is used for the rapid reversal of vitamin K antagonist (VKA) anticoagulation. PCC is also applicable in situations requiring rapid reversal of anticoagulation by non-vitamin K antagonist direct thrombin and factor Xa inhibitor oral anticoagulants (NOACs), thereby making PCC a general antidote for oral anticoagulation. In this chapter, the composition of different PCC brands is reviewed and a negative effect of heparin supplement in some products is recognized. Mode of action of anticoagulation reversal by PCC is explained. Dosage and clinical efficacy, two closely related issues, are discussed and based on reviewed data recommendations are given that may prohibit too low PCC dosing, especially in NOAC anticoagulation. Use of unsuitable laboratory assays has raised needless controversy as to the applicability of PCC to reverse anticoagulation by NOACs, in particular dabigatran. In this chapter, various laboratory assays are evaluated for their applicability in monitoring reversal of anticoagulation.

Keywords: vitamin K antagonists, rivaroxaban, dabigatran, direct oral anticoagulants, prothrombin complex concentrate

1. Introduction

Fluidity of circulating blood is maintained by a delicate balance between procoagulant and anticoagulant processes. A complex mechanism involving the vessel wall, platelets, and proteins in plasma (clotting factors) safeguards a normal blood flow by the formation of a blood clot at sites of vessel damage [1–3]. Upon vessel damage, platelets rapidly deposit at the site of vascular injury. Tissue factor that is normally sequestered from circulating blood, now triggers a cascade of biochemical reactions among coagulation proteins resulting in the

formation of thrombin, the enzyme that converts fibrinogen into fibrin (**Figure 1**). A blood clot consists of a mesh of fibrin threads, aggregated platelets, leukocytes, and erythrocytes. Thrombosis is the formation of blood clots or thrombi inside the blood vessel or on surgical implants. Clots can cause partial or complete blockade of the blood flow. A serious complication that can arise from thrombosis is embolism, which refers to a condition in which a portion of the blood clot breaks loose and travels in the bloodstream. Emboli can obstruct vessels in other parts of the body. Vessel occlusion can lead to severe tissue damage. Thrombosis is clearly one of the most common causes of death. A measure to prevent thrombosis is the use of anticoagulant drugs [4]. Classic oral anticoagulant drugs, the vitamin K antago-
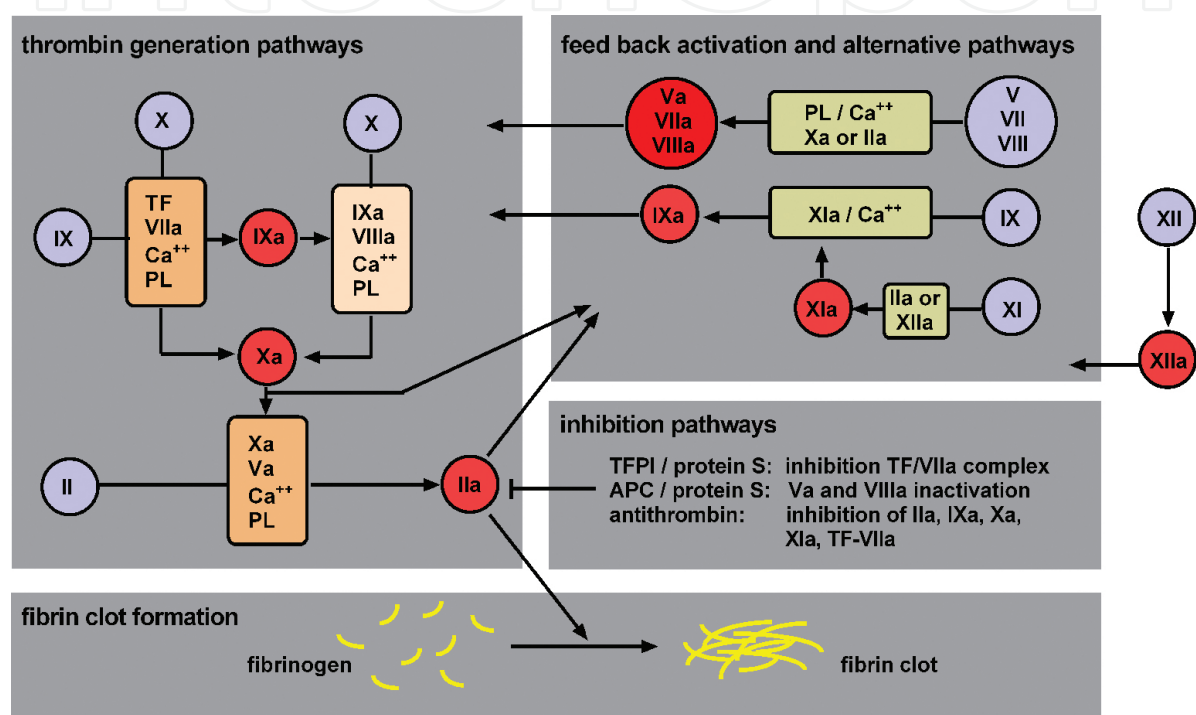

Figure 1. Pathways involved in thrombin generation and fibrin clot formation. Extrinsic coagulation starts with the binding of factor VII and activated factor VII (VIIa) to tissue factor (TF) on the outer layer of the lipid membrane of perivascular cells exposed to blood upon vessel wall damage. Factor VIIa bound to TF is able to proteolytically activate the coagulation factors IX and X. Additional factor X activation occurs by activated factor IX (IXa) when assembled with its active cofactor factor VIIIa on a negatively charged phospholipid surface (PL), e.g. the surface of an activated blood platelet. Subsequently, factor Xa assembles on a PL surface with its active cofactor, factor Va, as such able to proteolytically activate prothrombin (II). Without the respective active cofactors Va and VIIIa, factor IXa and factor Xa display very poor enzymatic activity. Formation of thrombin (IIa) is accelerated by feedback activation of factor V and VIII as well as factor VII by initially formed small amounts of factor Xa and thrombin. Another feedback loop involves the activation of factor XI by thrombin that facilitates additional factor IX activation. Note that reactions that require PL are calcium-ion (Ca++) dependent. Intrinsic coagulation (contact activation) is triggered by the conversion of factor XII into its enzymatic active form (XIIa) that occurs on negatively charged polyphosphates such as RNA, DNA, and inorganic polyphosphate that are released during cell damage and infection. Intrinsic coagulation is not regarded as the physiological pathway. Thrombin generation is under control of several inhibitory pathways. Tissue factor pathway inhibitor (TFPI) blocks the TF/VIIa complex when assembled with factor Xa. Protein C, once activated (APC) by thrombin when bound to thrombomodulin on the vessel wall, proteolytically inactivates the cofactors Va and VIIIa. Both processes are enhanced in the presence of protein S. Antithrombin inactivates thrombin, factor IXa, Xa, XIa, as well as factor VIIa bound to TF. The anticoagulant function of antithrombin is significantly enhanced by heparin-like structures on the vessel wall.

nists (VKAs), inhibit the essential modification of newly synthesized vitamin K-dependent coagulation factors in the liver. Other, more recently developed non-vitamin K antagonist oral anticoagulants (NOACs) only target specific clotting factors in their enzymatic active configuration. A significant side effect of (oral) anticoagulation therapy is the increased risk of bleeding [5–7]. Rapid reversal of anticoagulation might be required in anticoagulated patients presenting with major bleeding or requiring urgent surgery or invasive intervention.

To date, fresh frozen plasma (FFP) is still being used for the treatment of hemorrhages associated with the use of oral VKA anticoagulant drugs that interfere in the synthesis of vitamin K-dependent clotting factors in the liver. This is despite the availability of much more effective prothrombin complex concentrate or PCC [8–12]. Major disadvantages associated with FFP therapy include the risk of transfusion-related acute lung injury (TRALI), the need to consider blood group compatibility, and the large volume of intravenously administered plasma needed to stop bleeding episodes with concomitant risk of systemic volume overload [13]. In the late 1950s and much of the 1960s, FFP was the mainstay of treatment of bleeding associated with coagulation factor deficiencies like hemophilia A (congenital factor VIII deficiency) and hemophilia B (congenital factor IX deficiency). Hemophilia treatment improved in the late 1960s by the introduction of partly purified, human plasma-derived concentrates of either factor VIII or factor IX. Factor IX belongs to the group of vitamin K-dependent proteins, including, among others, the procoagulant factors II (prothrombin), VII, IX, and X. Due to the presence of the other vitamin K-dependent coagulation factors in partly purified factor IX concentrates, its use was also recognized for the treatment of congenital factor VII and factor X deficiencies, as well as for acquired deficiencies in vitamin K-dependent coagulation factors due to liver disease [14]. And last but not least, partly purified factor IX concentrates appeared extremely useful in rapid reversal of anticoagulation by vitamin K antagonists like warfarin [15, 16]. Nowadays, partly purified factor IX concentrate is referred to as prothrombin complex concentrate (PCC). An old abbreviation still being used is PPSB (prothrombin, proconvertin, Stuart-Prower-factor, Christmas factor/Factor B).

2. Prothrombin complex concentrate and indications of its clinical use

2.1. Reversal of vitamin K antagonists

Three different types of PCCs are commercially available for clinical use (**Table 1**): four-factor (4F) PCC, three-factor (3F) PCC, and activated PCC. The functional procoagulant components in 4F-PCC are the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X. Brand names, among others, are Beriplex® (Kcentra™ in the USA), Octaplex®, Prothromplex®, and Cofact®. 3F-PCC, in contrast to its 4F counterpart, does not contain significant levels of factor VII. Brand names include Profilnine® and Bebulin®. Activated PCC (Feiba®) contains the proenzymes prothrombin (factor II), factor IX, and factor X as in 3F-PCC and 4F-PCC, but in addition contains factor VII in its activated form (VIIa) (see **Figure 2**). Of these PCCs, 4F-PCC is approved as reversal agent for VKAs. In the US, approval is granted by the Food and Drug Administration (FDA) for urgent reversal of acquired coagulation factor
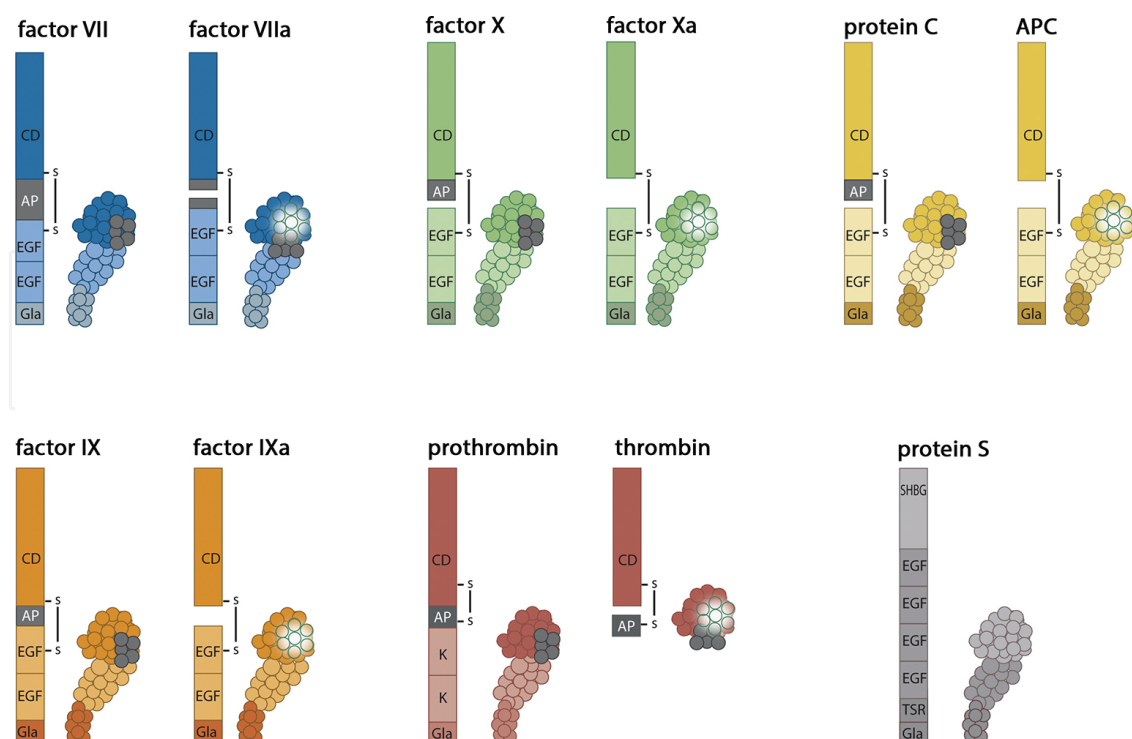
Figure 2. Vitamin K-dependent coagulation proteins. Vitamin K-dependent procoagulant factors (VII, IX, X, prothrombin) and vitamin K-dependent anticoagulant proteins (C and S) are depicted as bars illustrating their different domains as well as globular structures based on current knowledge of their three dimensional configuration [55–65]. Vitamin K-dependent clotting factors consist of a so-called Gla domain, one or more EGF or Kringle domains, and a catalytic domain (CD). Protein S does not contain a catalytic domain and instead contains a so-called SHBG domain. The Gla domain is essential for binding to negatively charged phospholipids, e.g. present in the outer layer of the membrane of activated platelets. The enzymatic activity of vitamin K-dependent clotting factors resides in the catalytic domain. In pro-enzymes, the site that is responsible for the proteolytic activity is masked. The active site becomes exposed upon proteolytic cleavage of the so-called activation peptide (AP). In factor VIIa and thrombin, the cleaved activation peptide remains attached. In factor IXa, factor Xa, and activated protein C, the activation peptide is cleaved out. Thrombin has lost its Kringle domains and its Gla domain and therefore is not able to bind to negatively charged phospholipids. Thrombin, in most cases, exerts its activity in solution and independent of a phospholipid membrane. Protein S does not contain an activation peptide and catalytic domain, and therefore cannot exhibit enzymatic activity.

deficiency induced by VKA therapy in patients with acute major bleeding only. In various countries outside the US, 4F-PCC is indicated for emergency as well as prophylactic reversal of VKA anticoagulation and for replacement therapy in patients with congenital or acquired factor deficiencies. Given their composition, 4F-PCCs may provide an off-label alternative for treatment of acute bleeds in patients with liver disease and in patients with trauma-induced coagulopathy [17]. 3F-PCC is approved in several countries including the US for hemophilia B treatment. Clinical studies indicate that 3F-PCC can also be used for the reversal of anticoagulation by vitamin K antagonists, albeit less effective than 4F-PCC [18–21]. Activated PCC is indicated in situations where a factor VIII or IX inhibitor bypassing procoagulant drug is required. Its off-label use as reversal agent for VKA-induced coagulopathy seems obvious because of its composition (presence of all procoagulant vitamin K-dependent factors, with factor VII in its activated form). The clinical usefulness of activated PCC in emergency reversal of vitamin K antagonists has been demonstrated in a limited number of clinical studies [10, 22].

Concentrate	Major functional component(s)	Indications*	Off-label use/remark
4F-PCC	Coagulation factors II, VII, IX, X	Treatment and perioperative prophylaxis of bleeding – in acquired deficiency of PCC factors, such as deficiency caused by treatment with vitamin K antagonists – in congenital deficiency of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available	Treatment of trauma-induced coagulopathy Treatment of bleeds in patients with liver disease Reversal of anticoagulation by direct factor Xa and thrombin-inhibiting oral anticoagulants (evidence based on several bleeding models in animals and human volunteers; substantial clinical evidence is lacking)
3F-PCC	Coagulation factors II, IX, X	Prevention and control of bleeding in hemophilia B patients	Anticoagulant reversal agent – for vitamin K antagonists (4F-PCC is superior to 3F-PCC) – for direct oral thrombin and factor Xa inhibitors (evidence based on a few bleeding models in animals; substantial clinical evidence is lacking)
Activated-PCC	Coagulation factors II, IX, X, VII-activated form	Treatment and prophylaxis of bleeding in patients (hemophilia A and B as well as non-hemophiliacs) with inhibitors to factors VIII or IX	Anticoagulant reversal agent – for vitamin K antagonists (evidence based on a limited number of clinical studies) – for direct oral thrombin and factor Xa inhibitors (evidence based on bleeding models in animals; substantial clinical evidence is lacking)
Factor VIIa	Coagulation factor VII-activated form	Treatment and perioperative prophylaxis of bleeding – in hemophilia patients with acquired inhibitors to factors VIII or IX – in patients with congenital factor VII deficiency	Treatment of intracranial hemorrhage and control of bleeding in trauma and during surgery Anticoagulant reversal agent – for vitamin K antagonists (lacking substantial clinical evidence; may require co-administration of FFP or 3F-PCC) – for direct oral thrombin and factor Xa inhibitors (evidence based on bleeding models in animals; substantial clinical evidence is lacking)
Factor VIII	Coagulation factor VIII	Treatment and prophylaxis of bleeding in patients with hemophilia A	Not to be used as anticoagulant reversal agent
Factor IX	Coagulation factor IX	Treatment and prophylaxis of bleeding in patients with hemophilia B	Not to be used as anticoagulant reversal agent

*According to summary of product characteristics (SPC).

Table 1. Clotting factor concentrates; indications and off-label use.

In this context, we should also mention recombinant activated factor VII (VIIa) concentrate (NovoSeven®). This factor concentrate was originally developed for the treatment of bleeding in patients with hemophilia who developed antibodies to factor VIII. Off-label use of recombinant factor VIIa has been documented in a number of bleeding conditions including cardiovascular surgery, trauma, and intracranial hemorrhage [23]. Some case-control studies have suggested a beneficial effect of a factor VIIa concentrate in the treatment of VKA-associated bleeds [24–27]. Off-label use of recombinant factor VIIa as VKA antidote is usually in combination with FFP therapy. A recent report outlined the successful use of a combination of recombinant factor VIIa and 3F-PCC in the treatment of VKA-associated intracranial hemorrhage [28]. The idea behind the treatment of hemorrhages with recombinant factor VIIa is the delivery of a sufficient amount of already activated factor VII to exposed tissue factor at sites of vessel injury (**Figure 1**). In an alternative model, recombinant factor VIIa interacts with the GPIb-IX-V complex on platelets and this interaction enhances tissue factor-independent thrombin generation mediated by recombinant factor VIIa on the activated platelet surface [29]. When employing recombinant factor VIIa concentrate, one should keep in mind that sufficient plasma levels of other essential vitamin K-dependent coagulation factors are still needed (**Figure 1**). In VKA-anticoagulated subjects, levels of functional vitamin K-dependent clotting factors may be too low to support recombinant factor VIIa treatment in the absence of FFP or 3F-PCC. This notion is underscored by the absence of a significant correcting effect of recombinant factor VIIa concentrate in carefully controlled bleeding models in rats (tail injury), mice (tail injury), and human volunteers (punch biopsy) subjected to VKA anticoagulation [30–32]. Interestingly, correction of bleeding did occur in incomplete anticoagulated rats [30]. On the other hand, two studies reported recombinant factor VIIa to be effective in reducing VKA-associated experimental intracerebral hemorrhage in mice [33, 34]. Co-administration of FFP or 3F-PCC was omitted in all referred model studies. Thus, although data are inconclusive on this matter, effective emergency reversal of VKA anticoagulation by recombinant factor VIIa may require the co-administration of FFP or 3F-PCC.

2.2. Reversal of direct thrombin and factor Xa inhibitors

NOACs are the new generation oral anticoagulants that directly inhibit thrombin (factor IIa) or activated factor X (Xa). A treatment algorithm for NOAC-associated bleeds has been developed that includes the use of PCC [35]. Studies employing bleeding models in animals and healthy human volunteers have revealed that all PCCs as well as recombinant factor VIIa are potentially applicable in the treatment of NOAC-associated bleeds [36]. Most well studied is the reversal of NOAC anticoagulation by 4F-PCC, with seven out of eight studies showing partial to complete bleeding cessation in coagulopathy induced by direct factor Xa inhibitors (apixaban 2/2, edoxaban 2/2, rivaroxaban 3/4) and 5/6 in that induced by the direct thrombin inhibitor dabigatran [32, 37–49]. 3F-PCC was successfully explored in the reversal of dabigatran-induced hemorrhage in rat [48]. Activated PCC was shown to reduce dabigatran- as well as rivaroxaban-associated bleeds in various bleeding models [32, 45, 48, 50]. Results with factor VIIa concentrate were less conclusive, showing positive outcome in about half of the reported bleeding models [32, 43–49]. Several reasons may underlie the variability in study outcome, including the bleeding model used, plasma concentration of the NOAC

at the time of intervention, and the type and dosage of reversal agent administered. The composition of the PCC, that differs from brand to brand, may also be of influence. Case reports and clinical registries have described multiple interventions in the treatment of NOAC-associated emergency bleeds, including the use of 4F-PCC, activated PCC, and recombinant factor VIIa [51–54]. There is currently no strong clinical evidence (e.g. randomized controlled trials) to support the choice of one of the hemostatic agents.

3. What is in the vial?

3.1. Vitamin K-dependent coagulation proteins

PCC is a mixture of partly purified vitamin K-dependent coagulation proteins (**Figure 2**). PCCs are prepared from human plasma and are supplied as freeze-dried products. Dosage indicated on the label and package insert of 3F- and 4F-PCC is based on the factor IX content and is given in international activity units (IU) factor IX as assayed according the prescriptions in the European Pharmacopeia. In contrast, the potency of activated PCC (Feiba®) is expressed in arbitrary units defined as that amount able to shorten the clotting time of factor VIII inhibitor reference plasma to 50% of normal.

Some of the earlier PCCs available until the mid-1990s were associated with an increased risk of thrombosis [66]. Data published by Grundman et al. suggest that prothrombin overload caused by an imbalance of coagulation factors in PCC is the major thrombogenic trigger during PCC therapy [67]. An appropriate balance in the levels of coagulation factors may therefore have significant influence on the safety of PCC [68]. Most desirable are relative clotting factor quantities similar to that in plasma. In **Figure 3**, molar quantities of the different clotting factors
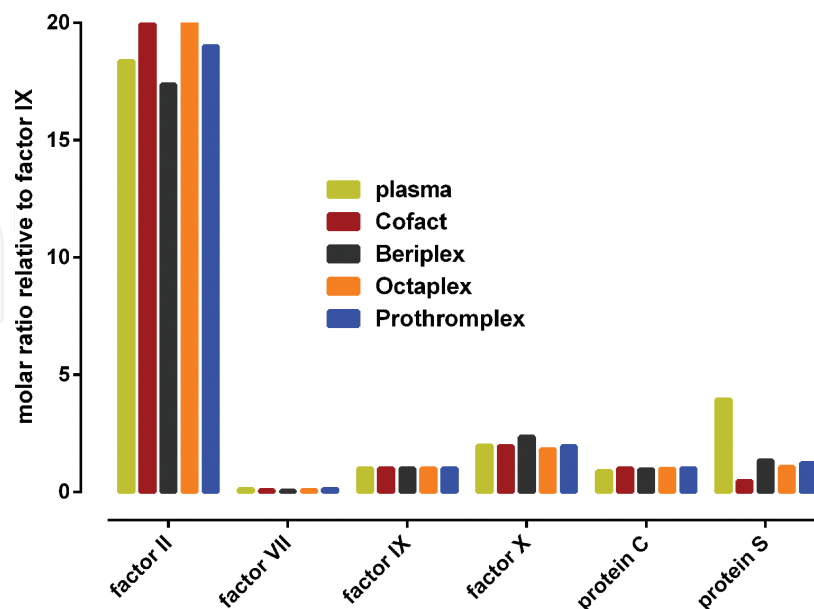

Figure 3. Vitamin K-dependent plasma proteins in plasma and in 4F-PCC. See legend **Table 2** for analytical details.

relative to factor IX are shown for some of the currently available PCCs. As can be appreciated, relative quantities of all procoagulant vitamin K-dependent clotting factors in PCC are almost identical to that in plasma. This is also true for the vitamin K-dependent coagulation inhibitor protein C. For protein S, however, levels are considerably lower than in plasma. Prothrombin is the most abundant vitamin K-dependent coagulation factor, while only trace amounts of factor VII are present in both plasma and PCC.

3.2. Other plasma protein constituents

PCCs not only contain vitamin K-dependent coagulation proteins. Mass spectrometric analysis revealed the presence of a variety of common plasma proteins such as fibrinogen, vitronectin, inter-alpha-trypsin inhibitor, complement, albumin, ceruloplasmin, C4b-binding protein, and apolipoprotein [69, 70]. The amount of co-purified plasma constituents may vary between the different PCC brands. Copper-containing ceruloplasmin is responsible for the bluish colour of some PCCs.

Biochemical characteristics		PCC product			
		Cofact	Beriplex	Octaplex	Prothromplex
Specific activity	IU factor IX/mg total protein	1.7 (1.1)	4.8 (3.3)	0.9 (1.0)	1.7 (1.5)
Vitamin K-dependent coagulation proteins	mg, % of total protein	22 (23)	59 (42)	12 (14)	24 (-)
Antithrombin	IU/IU factor IX	0.01 (0.01)	0.02 (0.02)	0.004 (0.003–0.004)	0.03 (0.03–0.06)
Heparin supplement	IU/IU factor IX	<0.01 (<0.01)	0.03 (0.02–0.03)	0.25 (0.15–0.88)	0.38 (0.15–0.72)
Thrombin generation	ETP, % of control plasma	217	162	71	18

From each product, a single lot was analyzed at Sanquin laboratories. Factor IX activity (clotting assay) was determined against the European Pharmacopoeia reference standard for factor IX concentrates. Prothrombin, factor VII, factor X, protein C, antithrombin (all chromogenic assays), and protein S (total antigen) were calculated against WHO calibrated normal plasma. IU was recalculated to mg based on reference plasma quantities as listed in the corresponding ISTH-SSC subcommittee communication [72]. Total protein was determined according to Bradford [71]. Heparin was determined against the 6th international standard for unfractionated heparin [73]. Thrombin generation (CAT method) in normal plasma supplemented with 1 IU/ml PCC was performed as described using a tissue factor concentration of 5 pM [73]. ETP values (extrinsic thrombin generation, area under the thrombin generation cure) are expressed as % of those obtained in normal plasma supplemented with saline instead of PCC. Content may vary from lot to lot. Data obtained are in good agreement with values from the literature, as can be appreciated from the data between parentheses that were taken directly from reports by Kalina et al., Sadeghi et al. and Grottke et al. or that were calculated from the reported values [74–76]. -, no literature data available.

Table 2. Biochemical characterization of 4F-PCC.

Specific activity is a measure of purity. Specific activity of 3F- and 4F-PCC is the amount of factor IX activity (in IU) over the total amount of all proteins (in mg) present in the product. Total protein is determined spectrophotometrically employing a protein dye and the levels are calculated using a calibration curve of an albumin solution with known protein content [71]. Specific activities of some currently available PCCs are listed in **Table 2**. Dissimilar specific

activities of the different PCCs are indicative for differences in composition and purity. Specific activity based on factor IX coagulant activity, however, does not take into account therapeutic vitamin K-dependent coagulation factors other than factor IX. In **Table 2**, the sum of mg quantities of the factors II, VII, IX, X, protein C, and protein S in 4F-PCC is expressed as percentage of total protein. This calculation reveals a purity that varies between 12 and 59%.

3.3. Heparin and antithrombin supplement: its influence on PCCs procoagulant potential

In the early days of PCC utilization, clinicians were facing an increased incidence of thrombosis in PCC-treated patients [66]. To minimize thrombogenicity, heparin and antithrombin were advised as supplements in PCC [68]. With the inclusion of coagulation inhibitors and other manufacturing improvements and the implementation of thrombogenicity release tests, today's PCCs can be considered safer than earlier products [77]. The rationale behind heparin and antithrombin supplementation is to inactivate any activated coagulation factor in the final PCC product. Levels of heparin and antithrombin supplement, however, vary considerably between different PCC brands (**Table 2**). The ability of heparin and antithrombin supplement to inhibit any active coagulation factor in PCC can be demonstrated, e.g. by mixing PCC with active thrombin. The level of antithrombin appeared to have greater impact on thrombin inhibition than either heparin content or the ratio of antithrombin to heparin [74].

The presence of antithrombin and heparin supplement may have influence on the procoagulant potential of the PCC, i.e. the ability to reverse oral anticoagulation. A negative effect of anticoagulant supplement can be easily demonstrated in the so-called thrombin generation test. In this test, thrombin generation in a plasma sample is initiated by the addition of calcium-ions and a trigger of coagulation, usually tissue factor. A fluorogenic, thrombin-sensitive substrate is present in the incubation mixture, allowing to monitor in time the generation and subsequent inhibition of thrombin [78]. The area under the thrombin generation curve (endogenous thrombin potential, ETP), one of the parameters that can be derived from the curve, is frequently used as a measure for the amount of thrombin generated. When PCC is added to normal plasma, an increase in ETP is to be expected because of an increase in level of all essential coagulation factors. An increase in ETP can indeed be observed with Cofact® and to a lesser extent with Beriplex®, PCCs that contain no or little heparin (**Table 2**). Octaplex® and Prothromplex®, PCCs with a considerable amount of heparin supplement, show inhibition of coagulation with this test (**Table 2**). A correlation between ETP and the quantity of antithrombin supplement seems absent.

Several reports have pointed to a potential negative effect of heparin supplement on the procoagulant efficacy of PCC [73, 76, 79–81]; though all of these are in vitro studies, a clinical effect should not be ruled out. Let us envision a patient on rivaroxaban anticoagulation treated for an emergency bleed with the advised dose of PCC of 50 IU factor IX/kg body weight (bw), infused at a generally practiced flow rate of 2.5 IU factor IX/kg bw per min [82]. This means that, depending on the PCC administered (see **Table 2**), in total up to 36 IU heparin/kg bw at a rate of 1.8 IU heparin/kg bw per min (108 IU heparin/kg bw per h) is infused. Clinicians thus should be aware of the possibility that during PCC infusions and depending on the PCC brand administered, levels of co-administered heparin may be within the heparin therapeutic

window [83]. PCC infusion, however, is temporary (±25 min for 50 IU/kg) and the half-life of heparin (30–60 min) is relatively short as compared to that of factor II (45–66 h), factor VII (4–7 h), factor IX (14–68 h) and factor X (24–41 h) [83, 84]. It is therefore to be expected that co-infused heparin may only transiently counteract the prohemostatic efficacy of administered clotting factor concentrate. Additional complicating aspect when treating emergency bleeds in patient on rivaroxaban or any other NOAC, is the fact that co-infused heparin supplement will enhance the anticoagulant effect of the NOAC (see **Figure 4** and reference [73]). Thus, an inhibitory effect of heparin during and shortly after infusion of heparin-containing PCC should be taken into account, especially when treating emergency bleeds associated with NOAC anticoagulation. PCC brands containing no or low heparin do not have this side effect.
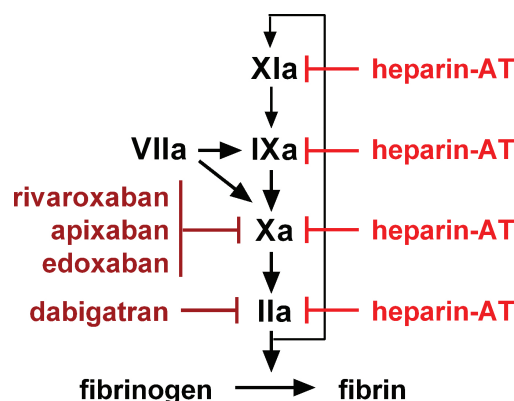

Figure 4. Heparin intensifies NOAC anticoagulation. Coagulation enzymes are inhibited by antithrombin (AT), a process significantly enhanced by heparin. Rivaroxaban, apixaban, and edoxaban are direct Xa inhibitors. Dabigatran is a direct thrombin inhibitor. Heparin supplement present in some PCCs and direct Xa and thrombin inhibitors (NOACs) act synergistically to depress coagulation [73]. It would therefore be more beneficial to treat emergency bleeds in NOAC-anticoagulated individuals with PCCs containing no or low dose heparin than with PCCs containing high dose heparin. (Coagulation cofactors are not depicted in this schematic representation.)

3.4. Activated coagulation factors and release tests

Release tests for manufactured PCC should comply with European Pharmacopoeia monographs [85]. Release tests, among others, include solubility, sterility, bacterial endotoxins, coagulation factor II, VII, IX, X, and activated coagulation factors. Heparin, if present in the PCC, must be neutralized when performing coagulation factor and activated coagulation factor release tests. Thrombin is measured by mixing prescribed volumes of PCC and fibrinogen solution. If thrombin is present, fibrin will be formed. PCC batches only pass this test if fibrin formation is absent in one test tube kept at 37°C for 6 h and in another tube kept at room temperature for 24 h. For comparison, coagulation occurs within 30 s in a reference tube containing a prescribed mixture of fibrinogen and thrombin instead of PCC. The absence of thrombin in currently available PCCs was recently confirmed by immunological techniques [75]. A second test for activated clotting factors that must be performed according to the European Pharmacopoeia is the so-called non-activated partial thromboplastin time (NAPTT). Prescribed dilutions of PCC, phospholipids (blood platelet substitute), and calcium chloride

are added to plasma anticoagulated with citrate and the time to clot formation is recorded. The test is valid when clotting time in the reference sample (with buffer instead of PCC) ranges between 200 and 350 s. PCC batches pass this test when clotting times are not less than 150 s. The NAPTT is extremely sensitive to activated factor IX (IXa). Release tests do not focus on activated factor VII (VIIa) and activated factor X (Xa). While 3F- and 4F-PCCs are virtually devoid of factor Xa, they do contain some factor VIIa [86]. Thrombotic complications, however, are a rare side effect of activated PCC (Feiba®) that contain substantial amounts of factor VIIa [87].

4. Mode of action

4.1. Vitamin K antagonists and reversal of anticoagulation by 4F-PCC

VKA anticoagulant coumarins like warfarin and phenprocoumon act by inhibiting the enzyme vitamin K reductase [88]. This enzymes shuffles vitamin K back into its active form. This "reactivated" vitamin K is needed to support the enzyme glutamylcarboxylase that converts glutamic acid residues into gamma glutamic acid (Gla) residues. During this process, vitamin K loses its activity again. Gla residues bind calcium-ions and this is essential for vitamin K-dependent coagulation factors to bind to negatively charged phospholipids and to partake in coagulation [89]. As a result of VKA therapy, fewer Gla residues are incorporated. The consequence of this is that circulating vitamin K-dependent coagulation factors are less functional. Upon triggering of the coagulation system, less prothrombin will be converted to
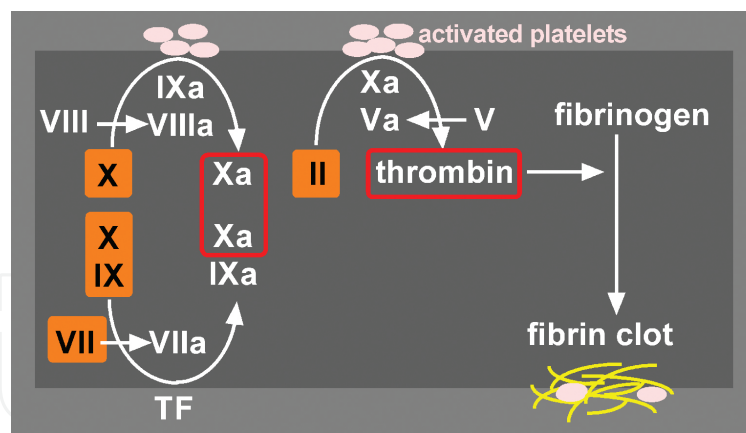

Figure 5. Anticoagulation targets and reversal of anticoagulation by 4F-PCC. Filled orange boxes indicate the vitamin K-dependent coagulation factors, targets for VKA therapy (vitamin K-dependent anticoagulant protein S and C are not depicted). Due to VKA therapy, vitamin K-dependent coagulation factors are synthesized with reduced procoagulant activity. Reversal of VKA anticoagulation by 4F-PCC infusion is accomplished by prompt replenishment of functional vitamin K-dependent coagulation factors. Red boxes indicate the NOAC targets. In NOAC-treated individuals, normal levels of fully functional clotting factors are to be expected. PCC infusion will increase the concentration of vitamin K-dependent coagulation factors above normal and more factor Xa and thrombin will be generated that escapes from NOAC inhibition, resulting in increased feedback amplification of the coagulation processes (see **Figure 1**). Similar mechanisms for VKA and NOAC reversal also apply to 3F-PCC (contains no factor VII) and activated PCC (contains factor VIIa instead of factor VII).

thrombin and time to clot formation will be markedly increased. Due to lower obtained levels of thrombin, also less thrombin-activatable fibrinolysis inhibitor (TAFI) will be activated. This inhibitor, once activated by thrombin, retards the clot lysis process. Thus, VKA therapy not only downscales clot formation but also enhances clot degradation [90].

Reversal of VKA anticoagulation can be done by cessation of VKA therapy together with the administration of vitamin K that boosts the synthesis of functional, Gla-domain-containing vitamin K-dependent coagulation factors [91, 92]. This "de novo" synthesis of coagulation factors, that takes place in the liver, may take too long. For immediate emergency reversal, replenishment of functional vitamin K-dependent clotting factors seems more appropriate. This can be achieved by intravenous administration of 4F-PCC (**Figure 5**).

4.2. Direct thrombin and factor Xa inhibitors and reversal of their anticoagulant action by 4F-PCC

Vitamin K-dependent coagulation factors circulate in plasma in their pro-enzymatic, inactive form. Enzymatic activity resides in their active center that is located in the catalytic domain (see **Figure 2**). In their pro-enzymatic form, the active center is shielded from interaction with target proteins. Direct thrombin and factor Xa inhibitor non-vitamin K oral anticoagulants (NOACs) are designed to target the respective active sites. Vitamin K administration is standard treatment to support VKA reversal by PCC. Obviously, in NOAC-treated individuals clotting factors are processed properly (normal posttranslational Gla residue incorporation) and hence vitamin K administration is usually not required. Cessation of NOAC therapy is one approach to reverse anticoagulation in NOAC-treated individuals. Due to the half-life of NOACs (5–17 h) [93], additional reversal measures may be needed in emergency situations.

4F-PCC can be used in situations requiring immediate reversal of anticoagulation by NOACs. Mechanism of action of PCC in NOAC reversal differs from that in VKA reversal (**Figure 5**). With respect to VKA reversal, PCC replenishes the level of functional vitamin K-dependent clotting factors. With regard to NOAC reversal, normal levels of fully functional clotting factors already are present in the circulation. The idea behind 4F-PCC as reversal agent for NOACs is that by increasing the concentration of vitamin K-dependent procoagulant factors, slightly more factor Xa and thrombin will be generated that escapes from inhibition by either a direct Xa or direct thrombin inhibitor resulting in increased feedback amplification of the coagulation processes [94]. This latter mechanism also underscores the general applicability of PCCs as an antidote for current and future direct oral anticoagulants.

5. Dosage, efficacy, and safety

5.1. PCC dosing for reversal of vitamin K antagonists

Despite decades of clinical experience with PCC, dosing is still a matter of debate [95]. The international normalized ratio or INR is a frequently used laboratory parameter to guide PCC dosing. This parameter is derived from the prothrombin time (PT) test. In this test, a plasma

sample (citrate anticoagulated) is mixed with calcium-ions, tissue factor, and phospholipids and the time to clot formation is measured. The INR aims to harmonize PT results obtained with VKA-anticoagulated plasma regardless of the reagents and instrument used [4]. It should be noted, however, that PT to INR correction factors used for VKA-anticoagulated plasma do not apply for NOAC-anticoagulated plasma [96, 97]. INR values in normal individuals range between 0.8 and 1.2. The target level INR for people on VKA anticoagulation is usually between 2 and 3 [4]. In the "real world", INR values of 7 or higher can be observed as well. Target INR values for emergency reversal of anticoagulation vary between institutional protocols. A target INR of 1.3 or 1.5 is most often used [95].

PCC dosing strategies usually take into account the INR at presentation and the body weight of the patient. For example, 25 IU per kg body weight for a baseline INR < 4, 35 IU per kg for an INR between 4 and 6 and 50 IU per kg for an INR > 6. Other strategies also take into account the reason for which reversal by PCC is required [98, 99]. For example, a target INR of 2.1 for small urgent interventions and minor bleedings and a target INR of 1.5 for major bleeding [98]. More simplified regimens are also practiced, namely a fixed dose per individual (usually 1000 IU), a fixed dose per kg body weight (depending on the protocol ranging from 8 to 50 IU/kg), and a dose based on the clinical experience of the doctor. Relatively good INR outcomes were reported with the use of any treatment protocol while INR outcome in general was less satisfactory when a predefined protocol was missing (doctor strategy). Lowest PCC dosages will be infused in the fixed dose strategy [95].

Major advantage of a fixed dose per individual is a shorter time to infusion (median 130 min) as compared to strategies that require dosing calculation based on body weight and INR at presentation (median 160 min, p=0.015) [100]. One should also take into account that time is wasted between the first and, if clinically required, subsequent PCC infusions that may range between 1.5 and 8 hours [101]. In vitro spiking of plasma samples taken from VKA-treated individuals with increasing PCC dose has revealed INR normalization by 0.5 IU PCC per ml plasma, irrespective of the initial INR [101]. This value recalculates to a fixed dose of 20 IU/kg body weight or 1500 IU for a man with an average weight of 75 kg.

5.2. 4F-PCC versus plasma for rapid INR correction in VKA-anticoagulated individuals

Prospective studies in VKA-anticoagulated individuals have shown almost immediate INR correction after PCC infusion (6–83 IU/kg) and reached INR levels remained stable for at least 6 hours irrespective of the dosing regimen used [9, 11, 12, 98, 99, 102–105]. Infusion time of PCC is relatively low (7–75 min). This is in contrast to FFP, for which infusion times up to 900 min have been reported (**Table 3**) [11, 104, 105]. Importantly, infusion volume of PCC (25–320 ml) is considerably lower than that of FFP (350–1525 ml) [11, 12, 99, 102, 104]. Comparative prospective studies have revealed rapid INR reduction (INR ≤ 1.3 at 1 hour after start of the infusion) in 54–69% of individuals treated with PCC versus no patients in the plasma group [11, 12]. At the end of infusion, 55–100% of the patients treated with PCC had an INR of 1.3 or lower compared with no more than 10% of the patients treated with plasma instead (**Table 3**). Rapid INR reduction associated with the use of PCC, alone or as an adjunct to FFP, translates

to a significant shorter time to invasive intervention in VKA patients requiring urgent surgery as compared to patients receiving FFP only [12, 106–109].

	PCC		FFP	
Reversal agent infusion				
- volume administered, ml	25-320	[11, 12, 99, 102, 104, 105]	353-1525	[11, 12]
- time to end of infusion, min	7-75	[11, 104, 105]	26-928	[11]
Clinical efficacy, % of study population				
- INR at target 1 hour after start infusion	54-69	[11, 12]	0	[11, 12]
- INR at target at end of infusion	55-100	[9, 11, 12, 99, 102–105]	0-10	[9, 11, 12]
- hemostatic efficacy, good or excellent	72-100	[11, 12, 99, 103, 105]	65-75	[11, 12]
Adverse events, % of study population(treatment related)				
- volume overload	0-5	[11, 12, 13]	7-13	[11-13]
- thromboembolic complications	2-8 (2-3)	[102, 104, 105, 110]	8 (3)	[110]
- mortality	1-19 (0-2)	[99, 102–105, 110]	13 (2)	[110]

Table 3. Comparison of FFP with 4F-PCC for the reversal of warfarin anticoagulation.

5.3. INR versus clinical efficacy

The INR is the outcome of standardized laboratory testing and is a tool to monitor VKA treatment and to guide reversal by PCC. Effective hemostasis or clinical efficacy is usually defined as a rating of excellent or good as judged by the attending physician and is confirmed when no additional measures are needed to maintain normal hemostasis in patients needing urgent surgical or invasive interventions, or when visual bleeding has stopped, no further decrease in hemoglobin is observed, blood pressure is normalized, and no further PCC or blood transfusion (plasma or red blood cells) is required in patients presenting with major bleeding. INR at end point and clinical efficacy, thus, are different albeit related parameters. It should be noted that the choice of a target INR is arbitrary, with no clear clinical proof for the advantage of a low target INR. Obviously, choosing a high INR target will result in a higher relative number of individuals reaching this target. For example, a study among 103 PCC-treated VKA patients revealed that 86 patients (83.5%) had an excellent clinical response (control of bleeding, no additional hemostatic measures required) while only 50 patients (48.5%) had a final INR response of ≤ 1.5. On the other hand, 95 patients (92.2%) were on target when an INR of 2.0 was considered [111]. Thus, clinical efficacy may serve as a more reliable measure for the usefulness of PCC in VKA reversal than the percentage of individuals reaching a certain INR target. It is worth mentioning that the INR is neither a reliable predictor of hemorrhage nor an appropriate guide for PCC dosing strategies [101, 112–114]. Nevertheless, the INR remains a useful tool to monitor VKA treatment and reversal of anticoagulation [114].

5.4. Clinical efficacy of 4F-PCC for rapid VKA reversal: influence of dosing regimen

The question seems relevant whether different dosing regimens result in different clinical outcomes. Using initial INR and body weight-guided dosing regimen (25, 35, and 50 IU/kg for

baseline INR of 2–3, 4–6, or > 6 respectively), good to excellent hemostasis was observed in 72–100% of the included individuals [11, 12, 102, 104, 105]. Studies with dosing regimens also including the target INR show similar clinical outcome [98, 100]. An observational, prospective, two-cohort Dutch comparison of a fixed 1000 IU versus variable dosing strategy (dosing based on patient body weight, baseline INR and target INR) revealed a successful clinical outcome in 96 and 88% of the included patients, respectively. This study thus shows a slight albeit significant (p=0.015) beneficial effect of a fixed dose of 1000 IU over variable dosing [100]. In a recent retrospective Canadian study, a total of 103 patients requiring urgent warfarin reversal were treated with PCC at a single fixed dose of 1000 IU. Excellent clinical response was observed in 83% of treated patients [111]. Based on higher expected patient weight, a US trauma center used a fixed dose of 1500 IU with a successful clinical outcome of 80% [115]. A systematic review including 27 studies revealed no clear evidence that one dosing strategy is superior [95]. Studies so far performed on clinical outcome have disregarded compositional differences between PCC products (see **Table 2**). Whether heparin-free PCC is of clinical benefit thus remains to be established. Differences between clinical outcome and cause of required VKA reversal, either a major bleeding or the need for urgent surgical intervention, are not reported. Given the shorter time to PCC infusion when using a fixed dose regimen compared to variable dosing, fixed dosing of 1000–1500 IU 4F-PCC may be preferred. Concurrent laboratory testing on patient's baseline plasma sample could then be used to guide additional PCC treatment.

5.5. 4F-PCC dosing for effective reversal of direct thrombin and factor Xa inhibitors

Clinical experience regarding the effectiveness and implementation of 4F-PCC in the treatment of NOAC-associated bleeds is limited. Though there have been several studies of NOAC reversal in healthy volunteers that focus on normalization of certain in vitro laboratory parameters [38, 116–119], well-designed randomized controlled clinical trials aiming at bleeding cessation measurements are difficult to perform in this setting. Most studies on the hemostatic effectiveness of PCC in NOAC reversal therefore have been performed in animal bleeding models (**Table 4**). One elegant double-blind, randomized, placebo-controlled study has explored the reversal of edoxaban by 4F-PCC in human volunteers using the punch biopsy bleeding model [38]. A total of 110 subjects were treated. Intravenous administration of 4F-PCC at a dose of 50, 25, or 10 IU/kg following administration of edoxaban (60 mg) dose-dependently reversed edoxaban's effects on bleeding duration, with complete reversal at 50 IU/kg. A similar dose-dependent reversal of edoxaban-associated bleeding by 4F-PCC was observed in rabbits following kidney incision [39]. The same bleeding model was used to demonstrate successful reversal of apixaban- as well as rivaroxaban-associated bleeds [37, 40]. In the aforementioned study, reversal by PCC was examined at different rivaroxaban concentrations. Low dose rivaroxaban (0.15 mg/kg) was almost completely reversed by low dose 4F-PCC (25 IU/kg). Intermediate rivaroxaban dose (0.30 mg/kg) required four times as much PCC (100 IU/kg) to obtain a similar reversal effect, while high dose rivaroxaban (0.45 mg/kg) could not be reversed [40]. This observation clearly illustrates a NOAC concentration dependent reversal by PCC. Two studies showed unsuccessful reversal of apixaban and rivaroxaban anticoagulation, that may relate to the bleeding model used (poly trauma) as well

as to the NOAC and PCC dose administered [43, 44]. Dabigatran has been examined in six different animal bleeding models (**Table 4**). One study using PCC at a dose of 14 IU/kg did not reveal any improvement in dabigatran-associated hemorrhage [32]. The 5 other studies however showed partial to complete correction of dabigatran-associated bleeds [41, 42, 46, 48, 49]. The general consensus emerging from these studies is that a PCC dose ≤ 25 IU/kg is too low to be successful. Almost complete to complete correction of NOAC-associated bleeds requires a PCC dose of at least 50 IU/kg.

Study	Bleeding model	NOAC		PCC, IU/kg		Correction of blood loss (BL)/ bleeding time (BT)
[43]	Rabbit, poly trauma	Apixaban 0.4 mg/kg single bolus iv + 0.6 mg/kg.h continuous infusion iv		Kanokad	100	no / partial
[37]	Rabbit, kidney incision	Apixaban 1.2 mg/kg single dose iv		Beriplex	100 25 6	almost complete almost complete partial
[38]	Human, skin biopsy	Edoxaban 60 mg single dose orally		Beriplex	50 25 10	complete partial no
[39]	Rabbit, kidney incision	Edoxaban 1.2 mg/kg single dose iv		Beriplex	75 50 25	almost complete partial no
[44]	Rabbit, poly trauma	Rivaroxaban 5 mg/kg single dose iv		Kaskadil	40	no
[45]	Rat, small artery incision	Rivaroxaban 2 mg/kg single dose iv		Beriplex	50 25	almost complete (no BL data) no (no BL data)
[40]	Rabbit, kidney incision	Rivaroxaban single dose iv	0.45 mg/kg 0.30 mg/kg 0.30 mg/kg 0.30 mg/kg 0.15 mg/kg	Beriplex	100 100 50 25 25	no almost complete partial no almost complete
[47]	Mouse, intracerebral hemorrhage	Rivaroxaban 30 mg/kg single dose orally		Beriplex	100	almost complete (no BT data)
[46]	Mouse, tail bleeding and intracerebral hemorrhage	Dabigatran etexilate 9 mg/kg single dose ip		Beriplex	100 50 25	almost complete partial partial
[32]	Mouse, tail bleeding	Dabigatran etexilate 60 mg/kg single dose orally		Octaplex	14	no
[41]	Rabbit, kidney incision	Dabigatran 0.4 mg/kg single dose iv		Beriplex	50 20	complete/almost complete partial
[48]	Rat, tail bleeding	Dabigatran etexilate 30 mg/kg single dose orally		Beriplex	50 20	almost complete (no BL data) partial (no BL data)
[42]	Pig, poly trauma	Dabigatran etexilate 30 mg/kg bid (3d) orally + dabigatran 0.5 mg/kg iv prior trauma		Beriplex	100 50 25	yes* (no BT data) yes* (no BT data) no (no BT data)
[49]	Mouse, saphenous vein incision	Dabigatran 0.015 mg/kg single iv dose		Beriplex	50 25	complete (no BL data) no (no BL data)

*Data on bleeding tendency in normal, not NOAC treated animals was not provided in the study report. iv, intravenous. ip, intraperitoneal.

Table 4. NOAC reversal by 4F-PCC *in vivo*: effect on bleeding diathesis.

5.6. Safety profile of PCC

PCCs may have a better safety profile than FFP. Freeze-dried 4F-PCC products can be reconstituted in a small volume of diluent. Due to the small volume of the reconstituted product, PCCs can be administered in shorter infusion times with lower risk of volume overload than FFP [13]. Importantly, there is minimal risk of transfusion-related acute lung injury as PCCs lack anti-human leukocyte antigen/anti-granulocyte antibodies [120]. PCCs carry a negligible risk for viral transmission due to the incorporation of viral reduction steps in the manufacturing process. PCCs in contrast to FFP do not need AB0 typing. Adverse events associated with the use of PCC may include heparin-induced thrombocytopenia type II for those brands that contain heparin [121]. One retrospective study reported a slight increased risk of acute kidney injury associated with PCC as compared to FFP [122]. Mortality and thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation, and deep vein thrombosis in cohorts treated with either FFP or PCC are similar (**Table 3**).
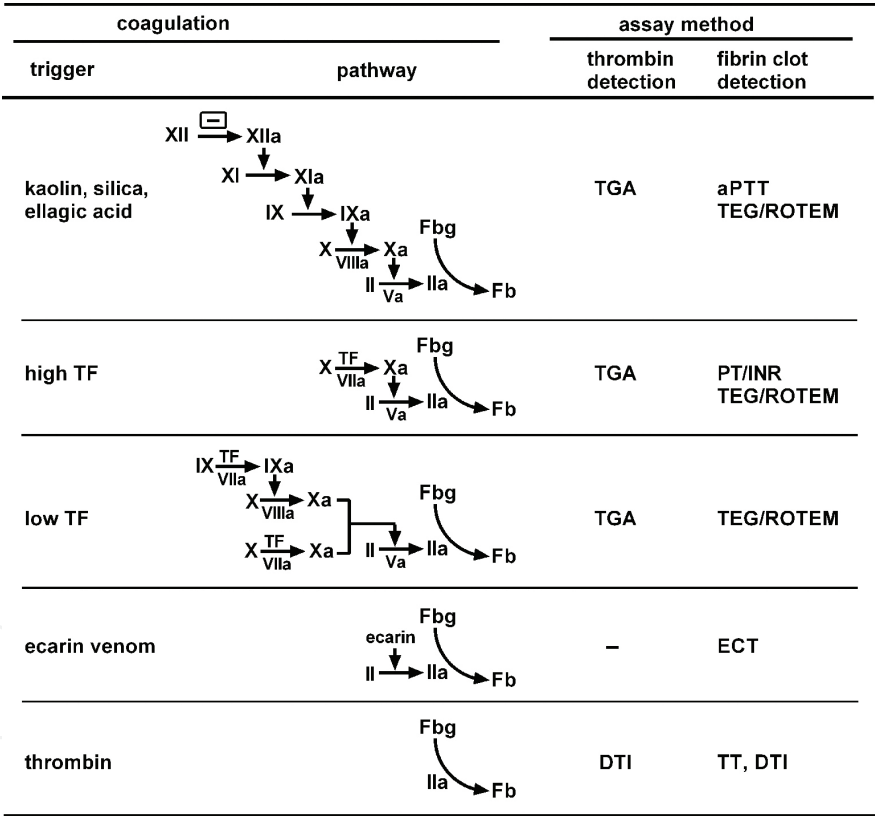

Figure 6. Coagulation assay methods. Global coagulation assays are either based on the measurement of thrombin or on the measurement of fibrin. aPTT is triggered by a negatively charged surface like kaolin, as such facilitating the contact activation pathway (intrinsic coagulation). Kaolin, silica, or ellagic acid triggering can also be used in TGA and TEG/ROTEM. Tissue factor (TF) triggering facilitates the extrinsic coagulation pathway. PT/INR is triggered by high TF concentrations, a condition that also can be used in TGA and TEG/ROTEM. Low TF concentration improves sensitivity, a condition frequently applied in TGA and TEG/ROTEM. The ecarin clotting time (ECT) is triggered by the venom from viper *Echis carinatus*. The thrombin time (TT) and direct thrombin inhibitor test (DTI) are both triggered by thrombin.

6. Reversal assessment by laboratory coagulation assays

6.1. Global coagulation tests

Global coagulation assays are most suited for the assessment of reversal of anticoagulation [114]. Global coagulation tests do not pinpoint any specific coagulation factor but instead generate data on the coagulation potential of a plasma sample as a whole. Global coagulation tests focus either on the generation of thrombin (thrombin generation assay, TGA) or on the generation of fibrin clots (PT, aPTT, ROTEM, TEG). PT and aPTT are clotting time based assays, while ROTEM (rotational thromboelastometry) and TEG (thromboelastograpy) also generate data on kinetics of clot formation, clot strength, and clot stability. Sensitivity of global assays for certain coagulation factors is determined by the choice and concentration of the coagulation trigger used (see **Figure 6** and reference [114]).

6.2. Monitoring PCC treatment in VKA-anticoagulated individuals

The contact activation-triggered aPTT in general is less sensitive to VKA treatment than the TF-triggered PT test [114]. This is probably due to the fact that the aPTT does not detect variations in factor VII, the most significant vitamin K-dependent clotting factor in determining the PT outcome in VKA-anticoagulated plasma [123]. The PT with its derived international normalized ratio (INR) is worldwide the most commonly used assay to monitor VKA treatment and reversal of anticoagulation by PCC. TF-triggered TEG/ROTEM and TGA also show good sensitivity to assess VKA anticoagulation and reversal thereof [101, 114].

6.3. Monitoring PCC treatment in NOAC-anticoagulated individuals

NOACs may affect any assay that depends on factor Xa or IIa (thrombin) activity, including the PT, aPTT, TGA, and TEG/TEM (see **Figure 6** and reference [114]). Two other clotting time based tests, the thrombin time (TT) and ecarin clotting time (ECT) are affected in particular by direct thrombin inhibitors. Sensitivity of a certain test to NOACs, however, does not directly mean that the test is suitable to assess reversal of anticoagulation by PCC. For example, clotting in the TT test is triggered by adding excess thrombin to a plasma sample, as such overruling the complete coagulation cascade (see **Figure 6**). As a consequence, dabigatran in the plasma sample will inhibit the added thrombin without being affected by increased clotting factor levels due to PCC administration. Likewise, PCC administration will be unnoticed in the ECT test in which coagulation in a sample is triggered by snake venom that completely converts prothrombin into thrombin [114]. Similarly, assays that are triggered by the addition of excess factor Xa (e.g. anti-Xa assays designed for rivaroxaban determinations) will not reveal reversal of anticoagulation by clotting factor concentrates.

The most promising assay parameter to reveal reversal of NOAC anticoagulation by PCC infusion is the area under the thrombin generation curve (TGA-AUC or ETP). The PT is less sensitive while the aPTT is insensitive in this respect [94, 114, 124]. Zahir et al. have explored the reversal of edoxaban by 4F-PCC in human volunteers using the punch biopsy bleeding model [38]. The effect of 4F-PCC on TGA-ETP was similar to the effects on bleeding duration

and bleeding volume, suggesting that TGA-ETP is an appropriate surrogate biomarker for assessing the effect on bleeding. Several studies on NOAC reversal by PCC in healthy human volunteers have used the TGA-AUC as outcome measure, showing partial to complete normalization 30 min post dose (**Table 5**). Of note is the observed overcorrection of TGA-AUC 24 hours post dose that can be explained by a relative short half-life of NOACs as compared to PCC.

Study	NOAC	PCC, IU/kg		Correction of TGA-AUC	
				30 min Post dose	24 hour Post dose
[118]	Apixaban	Cofact	37	Partial	Overcorrection
	10 mg bid, 2.5 days		25	Partial	Overcorrection
[38]	Edoxaban	Beriplex	50	Complete	Overcorrection
	60 mg single dose		25	Partial	Overcorrection
			10	No	No
[116]	Rivaroxaban	Cofact	50	Complete	Overcorrection
	20 mg bid, 2.5 days				
[119]	Rivaroxaban	Cofact	37	Partial	Overcorrection
	15 mg bid, 2.5 days		25	Partial	Complete
[117]	Rivaroxaban	Beriplex	50	Partial	Overcorrection
	20 mg bid, 5.5 days	Profilnine	50	Partial	Overcorrection

Effect on ex vivo thrombin generation in healthy human volunteers.

Table 5. NOAC reversal by PCC *in vivo*.

7. Concluding remarks

Clinical emergency situations may require rapid reversal of anticoagulation. 4F-PCC seems very suitable to reverse VKA as well as NOAC anticoagulation. Activated PCC can also be used. 3F-PCC seems less effective in the reversal of VKA anticoagulation. Several laboratory assays are suited for monitoring VKA reversal, including the INR as well as other global assays such as thrombin generation and thromboelastography. As to NOAC reversal monitoring, one should be aware of the fact that several laboratory assays including direct thrombin and direct factor Xa inhibitor assay do not reveal an increase in procoagulant potential upon PCC infusion. The ETP seems an appropriate biomarker for assessing the effect of PCC adminis-tration on NOAC anticoagulation. In contrast, PT is less sensitive and the aPTT is insensitive in this respect.

Clinically effective reversal of VKA anticoagulation can be obtained with the use of any treatment protocol. Time till PCC infusion and consequently time till follow up treatment can be shorted by prompt infusion of a fixed dose of 1000–1500 IU 4F-PCC per individual,

irrespective of INR at presentation, target INR, and body weight. For NOAC reversal, at least 50 IU/kg or 4000 IU for a body weight of 80 kg seems required. Its non-specific nature is a major advantage of PCC over specific agents that block NOACs. PCCs can readily be infused, while specific NOAC antidotes require the need for laborious anticoagulant identification prior to antidote selection and administration. PCCs also are probably cheaper and more widely available in general hospitals than specific NOAC antidotes. Some PCCs are supplemented with heparin that may counteract the prohemostatic effect of the PCC. Safety profile of PCC is similar to that of FFP.

8. Conflict of interest statement

The author is employee of Sanquin Research, a division of Sanquin. Sanquin is manufacturer of 4-factor PCC (Cofact®).

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