Prothrombin Complex Concentrates for Bleeding in the Perioperative Setting
Kamrouz Ghadimi, MD, Jerrold H. Levy, MD, FAHA, FCCM, and Ian J. Welsby, BSc, MBBS, FRCA

Prothrombin complex concentrates (PCCs) contain vitamin K-dependent clotting factors (II, VII, IX, and X) and are marketed as 3 or 4 factor-PCC formulations depending on the concentrations of factor VII. PCCs rapidly restore deficient coagulation factor concentrations to achieve hemostasis, but like with all procoagulants, the effect is balanced against thromboembolic risk. The latter is dependent on both the dose of PCCs and the individual patient prothrombotic predisposition. PCCs are approved by the US Food and Drug Administration for the reversal of vitamin K antagonists in the setting of coagulopathy or bleeding and, therefore, can be administered when urgent surgery is required in patients taking warfarin. However, there is growing experience with the off-label use of PCCs to treat patients with surgical coagulopathic bleeding. Despite their increasing use, there are limited prospective data related to the safety, efficacy, and dosing of PCCs for this indication. PCC administration in the perioperative setting may be tailored to the individual patient based on the laboratory and clinical variables, including point-of-care coagulation testing, to balance hemostatic benefits while minimizing the prothrombotic risk. Importantly, in patients with perioperative bleeding, other considerations should include treating additional sources of coagulopathy such as hypofibrinogenemia, thrombocytopenia, and platelet disorders or surgical sources of bleeding. Thromboembolic risk from excessive PCC dosing may be present well into the postoperative period after hemostasis is achieved owing to the relatively long half-life of prothrombin (factor II, 60–72 hours). The integration of PCCs into comprehensive perioperative coagulation treatment algorithms for refractory bleeding is increasingly reported, but further studies are needed to better evaluate the safe and effective administration of these factor concentrates.

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Table 1. Common Commercially Available Formulations of Prothrombin Complex Concentrates

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Factor II*</th>
<th>Factor VII*</th>
<th>Factor IX</th>
<th>Factor X*</th>
<th>IV composition*</th>
<th>Added anticoagulants*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-factor PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profilnine SD</td>
<td>Grifols Biologicals, Los Angeles, CA</td>
<td>148</td>
<td>Negligible</td>
<td>100</td>
<td>65</td>
<td>1000 IU/10 mL</td>
<td>None</td>
</tr>
<tr>
<td>Bebulin</td>
<td>Baxter Healthcare, Bloomington, IN</td>
<td>120</td>
<td>Negligible</td>
<td>100</td>
<td>100</td>
<td>500–700 IU/20 mL</td>
<td>15 U heparin*</td>
</tr>
<tr>
<td>4-factor PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex P/N</td>
<td>CSL Behring, Europe/United States</td>
<td>130</td>
<td>70</td>
<td>100</td>
<td>50–150</td>
<td>500 IU/20 mL</td>
<td>Minimal amount of protein C and S, AT, and heparin</td>
</tr>
<tr>
<td></td>
<td>(also manufactured as KCentra or Conifex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cofact/PPSB SD</td>
<td>Sanquin, The Netherlands</td>
<td>60–140</td>
<td>30–80</td>
<td>100</td>
<td>160</td>
<td>250 IU/10 mL</td>
<td>Minimal amount of AT Heparin &lt;15 IU/mL</td>
</tr>
<tr>
<td>Prothrombex Total</td>
<td>Baxter Bioscience, Austria</td>
<td>100</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>600 IU/20 mL</td>
<td>Protein C: 52–124 IU*</td>
</tr>
<tr>
<td>Octaplex</td>
<td>Octapharma, Austria</td>
<td>56–152</td>
<td>36–96</td>
<td>100</td>
<td>72–120</td>
<td>500 IU/20 mL</td>
<td>Protein S: 48–128 IU*</td>
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<tr>
<td></td>
<td></td>
<td>66.7</td>
<td>66.7</td>
<td>100</td>
<td>66.7</td>
<td>500 IU/20 mL</td>
<td>Protein C: 66.7*</td>
</tr>
<tr>
<td>aPCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEIBA NF</td>
<td>Baxter Healthcare, Bloomington, IN</td>
<td>86.7</td>
<td>66.7</td>
<td>100</td>
<td>66.7</td>
<td>500 IU/20 mL</td>
<td>Protein C: 66.7*</td>
</tr>
</tbody>
</table>

aPCC = activated prothrombin complex concentrates; AT = antithrombin; FEIBA = factor eight inhibiting activity; IU = international units; NF = nanofiltration (refers to process of viral inactivation); PCCs = prothrombin complex concentrates; P/N = pasteurization and nanofiltration (refers to process of viral inactivation); SD = solvents and detergents (refers to process of viral inactivation).

*aIU per 100 IU of factor IX.

*bIU of factor IX included per volume of sterilized water.

Most PCC formulations contain anticoagulants to prevent activation of coagulation factors when the solute is diluted in sterile water.

Figure 1. A depiction of the coagulation cascade with focus on factor–enzyme complexes (tenase, prothrombinase) and target locations for direct factor repletion by prothrombin complex concentrates, activated prothrombin complex concentrates, activated recombinant factor VII, and cryoprecipitate. Extrinsic tenase contains TF, factor X, and factor VIIa, whereas intrinsic tenase contains factor X, factor IXa, and factor VIIIa. Both types of tenase influence the production of factor Xa, which then joins with factor Va to form prothrombinase. Prothrombinase converts the substrate prothrombin (factor II) into thrombin (factor IIa). Thrombin facilitates (1) the conversion of FGN into fibrin monomers and (2) converts fibrin-stabilizing factor (XIII) into its activated form (XIIIa) to facilitate fibrin polymerization and cross-linkage (scanning electron micrographic image insert of normal, dense fibrin deposition). These 2 reactions occur independent of one another in the presence of thrombin. The color-coded legend below the coagulation model delineates which factor concentrate repletes individual factor constituents. FGN concentrate repletes FGN alone, but for purposes of clarity, it is not illustrated. In addition, aPCCs contain clinically negligible concentrations of factors IIa, IXa, and Xa (not illustrated). aPCCs = activated prothrombin complex concentrates; FGN = fibrinogen; PCCs = prothrombin complex concentrates; rFVIIa = activated recombinant factor VII; TF = tissue factor; Xase = tenase.
further discuss the formulations of PCCs commercially available and their approved and off-label indications. Of note, localized thrombus formation is important for clinical hemostasis, and clinicians are reminded that PCCs are only one component of multimodal therapy for coagulopathic bleeding.

**MECHANISMS OF ACTION**

Knowledge of the mechanism of the procoagulant effects of rFVIIa, aPCCs, and PCCs is important to understand the indications and limitations of their use in various clinical scenarios. The calcium-dependent reactions of vitamin K-dependent proteases (factors IIa, VIIa, IXa, and Xa) and their nonenzymatic cofactor proteins (TF, factor VIIIa, and factor Va) are illustrated in a simplified model of hemostasis (Fig. 1). The noted cofactors are localized to the site of coagulation by receptors on the surface of activated platelets forming anticoagulant-resistant, enzymatic complexes. Briefly, TF-dependent generation of small quantities of factor Xa by the extrinsic Xase complex (TF and factor VIIa) initiates prothrombinase (factors Va and Xa)-dependent thrombin (factor IIa) generation. Thrombin activates platelets and factors V, VIII, and XI and catalyzes intrinsic Xase assembly that efficiently accelerates the generation of factor Xa. Intrinsic Xase generates factor Xa by 100 times more than extrinsic Xase. Factor Xa supplies the prothrombinase complex, which is now 10,000 times more effective in the presence of factor Va. Thrombin generation rapidly converts fibrinogen to fibrin and crosslinked fibrin monomers (through factor XIIIa) into a dense, lysis-resistant thrombus (Fig. 1). The loss of intrinsic Xase activity in hemophiliacs because of the presence of inhibitor alloantibodies minimizes factor Xa production, depriving the prothrombinase complex of its thrombin generation capacity. Partial restoration of factor Xa activity can occur with the administration of rFVIIa and possibly more so with aPCCs (containing variable amounts of both factors VIIa and Xa). Furthermore, the additional prothrombin (factor II) provided by aPCCs may better restore thrombin generation, albeit at the expense of thromboembolic risk when repeat dosing excessively increases prothrombin concentrations.1

Non-aPCCs, as previously mentioned, are categorized as 3- or 4-factor (3F or 4F) on the basis of the presence or absence of appreciable concentrations of factor VII. Table 1 outlines the factor VII concentrations in each PCC formulation. The values for formulations containing appreciable concentrations of factor VII range from 30 to 100 IU per 100 IU of factor IX. Of note, the concentrations of procoagulants (factors II, IX, X, and VII when present) and anticoagulants (antithrombin III or heparin and proteins C, S, and Z) present are variable and depend on the formulation (Table 1). These anticoagulants are present presumably to prevent activation of coagulation factors when the solute is diluted in sterile water. 3F-PCCs have also been used to acutely reverse the procoagulant effects of warfarin but may be less effective in normalizing the prothrombin time (PT) or international normalized ratio (INR) because of the lack of factor VII. Factor VII has a profound in vitro effect on the INR test.13 This notion is supported by the observation that clinically important hemostasis may be achieved when only 30% of normal factor VII activity is present in the setting of increased INR values.4 Furthermore, the rapid correction of INR shortly after the administration of rFVIIa may mask other coagulation deficiencies that may contribute to a prolonged INR value.

Nonactivated, 4F-PCCs are FDA-approved for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists in adult patients with acute major bleeding (Fig. 2).13 Restoring depleted levels of factors II, VII, IX, and X restores factor Xa generation in warfarin-treated patients, resulting in the replenishment of the prothrombinase complex and subsequent thrombin generation. Prothrombotic tendency and thromboembolic risk increase if excessive factor II is formed. In contrast, rFVIIa may restore factor Xa generation,12,13 but rFVIIa has a short half-life, it does not directly replenish factor II or restore thrombin generation. Because factor II levels are proportional to thrombin (factor IIa) generation, factor II is essential in preserving and promoting hemostatic efficacy.13 Inappropriate repeat dosing of rFVIIa may be used in an attempt to achieve hemostasis.
in the perioperative setting. However, once factor II concentrations are subsequently restored (i.e., with plasma or PCCs), excessive, residual rFVIIa-related factor Xa production may lead to pathologic thrombus formation. Although factor II levels are considered most important, even mild factor X deficiency (25%–50% activity) can be associated with periprocedural bleeding complications in patients with acquired deficiencies. Therefore, initially replacing all depleted factors with PCCs is preferred to repeated dosing of rFVIIa from a mechanistic point of view.

Coagulopathy resulting from cardiopulmonary bypass (CPB) and trauma occurs in part because of the hemodilution of additional components necessary for the coagulation cascade. This occurs in trauma as a result of administering nonplasma intravascular volume expanders (e.g., crystalloid solutions, packed red blood cells) in the setting of hypotension during hemorrhage. During cardiac surgery, hemodilution is encountered on initiation of CPB when patients’ whole blood volume is combined with nonplasma volume expanders primed in the CPB circuit. These scenarios may lead to a decrease in both procoagulant and anticoagulant factors. In addition, existing consumptive coagulopathy may lead to decreased procoagulant constituents. Factor concentrations initially maintain clinically important hemostasis, to generate thrombin, until critically low levels of procoagulant components are reached. Fibrinogen is the first constituent to reach these critical levels during acquired surgical bleeding, and replenishing this alone has been sufficient for the correction of coagulopathy related to complex cardiac surgery. Cryoprecipitate will restore fibrinogen, factors VIII and XIII, and von Willebrand Factor (Fig. 1). When considering rFVIIa, aPCCs, or PCCs to restore thrombin generation, clinicians should keep in mind that only aPCCs and PCCs provide factor II (prothrombin). However, these compounds will be ineffective in correcting clinically important coagulopathy without adequate repletion of critical hemostatic components such as fibrinogen and platelets.

Although the potential for unopposed thrombin generation remains a concern with the administration of 4F- or 3F-PCCs, FFP contains both coagulation factors and naturally occurring anticoagulants. Furthermore, FFP administration should always be considered with ongoing intravascular volume resuscitation in the setting of active bleeding. With that said, large volumes of plasma only slowly normalize depleted factor levels when compared with the rapid correction that occurs with PCCs. Therefore, it is reasonable to consider the administration of FFP with PCCs to mitigate the prothrombotic risk.

As discussed earlier, rFVIIa triggers extrinsic Xase complex-related generation of factor Xa without directly providing factor II substrate for thrombin generation, which is otherwise directly provided with PCCs. Therefore, initial administration of rFVIIa may appear clinically inadequate for hemostasis and lead to repeated administration and eventual overcorrection of thrombin generation by indirectly increasing the prothrombinase levels (Fig. 1). Notably, the longer half-lives of factor II (60–72 hours) and factor X (40–45 hours) provided by PCCs either confer a longer duration of hemostasis than rFVIIa or a predisposition to thrombosis depending on the clinical circumstances.

**SIGNIFICANCE OF THROMBIN GENERATION**

The capacity to restore thrombin generation is critical to the mechanism of action of PCCs (Fig. 1). The ability of PCCs to support the enzyme complexes that convert factor II to prothrombin illustrates their efficacy as hemostatic agents and potentially contributing to the prothrombotic risk. In vitro assays such as the calibrated automated thrombogram (CAT®; Thrombinoscope, Inc., Parsippany, NJ) provide a sensitive blood assay for thrombin generation. Determining thrombin generation capacity after the administration of hemostatic agents may be a worthwhile model of determining clinical response to treatment during vitamin K antagonist reversal. Of note, in vivo thrombin generation may be inferred by increased serum levels of prothrombin F1.2 levels and thrombin–antithrombin complexes. Prothrombin F1.2 is a peptide with a 90-minute half-life, which is cleaved into circulation when prothrombin is transformed into thrombin. The assay for quantification of this fragment is currently unavailable in the clinical setting for acute decision-making.

Thrombin generation is impaired during CPB in a manner similar to that of consumptive coagulopathy. Interestingly, however, there is a >50% reduction in antithrombin III levels secondary to hemodilution. Coagulation factor consumption after CPB may be associated with the coagulopathy set in motion during CPB and inadequate clot stabilization. Reduced preoperative thrombin-generating capacity has strongly correlated with increased postoperative bleeding (r = 0.7, P < 0.001), illustrating the predictive value of this assay. Low values of peak thrombin generation were predictive of blood loss after CPB in a study of 30 patients undergoing coronary artery bypass graft surgery, when thrombin generation was measured both before heparinization and after an appropriate dose of protamine had been administered. Similarly, during pediatric cardiac surgery, thrombin generation variables were uniformly improved after platelet and cryoprecipitate transfusions. After administration of cryoprecipitate and platelets, the rate and peak of thrombin generation were modeled to increase with the in vitro addition of 3F-PCCs, but not with the addition of rFVIIa. This difference in thrombin generation curves between administration of PCCs and rFVIIa is consistent with the mechanism of generalized factor deficiency where PCCs provide factor II but rFVIIa does not (Fig. 1). In a cell-based model of coagulation, most factors display a threshold relationship with thrombin generation such that marked coagulation factor deficiency is required before thrombin generation is adversely affected. In contrast, factor II levels are understandably in direct proportion to thrombin generation. This effect is relevant both for physiologic hemostasis and pathologic thrombosis. Even patients with congenital coagulation factor deficiency (e.g., hemophiliacs) have merely a mild bleeding phenotype.
if thrombin generation is maintained by compensatory increases in other factors.\textsuperscript{26,27} Conversely, thromboembolic disease is associated with excessive prothrombin/FII levels\textsuperscript{14,40} and high levels of thrombin generation.\textsuperscript{31–33} Once again, the long half-lives of administered factor II and factor X may persist after a period of coagulopathy, which may turn result in a bleeding tendency to a thrombotic risk. In this setting, careful consideration should be paid to postoperative venous thromboembolism prophylaxis and that adequate levels of anticoagulants such as antithrombin III are present.

The promise of the ability to clinically determine thrombin generation during the perioperative period may provide a potential guide for targeted PCC administration while avoiding thromboembolic events. Efforts to develop readily available viscoelastic tests to also provide an estimate of thrombin generation are, currently, being evaluated in pediatric cardiac surgery.\textsuperscript{41}

**APPROVED AND OFF-LABEL USES FOR PCCS**

As discussed earlier, the FDA-approved indication for 4F-PCCs is for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure (Table 2; Fig. 2).\textsuperscript{36,42–52} KCentra\textsuperscript{®} (CSL Behring, King of Prussia, PA) is the only 4-factor formulation approved for this indication in the United States. Vitamin K antagonists such as warfarin effectively prevent essential posttranslational γ-carboxylation of the hepatically synthesized coagulation factors (II, VII, IX, and X; Fig. 2) and anticoagulants (proteins C, S, and Z).\textsuperscript{54} In the past, the administration of FFP was the only option for the urgent reversal of the effects of vitamin K antagonists, which included patients requiring urgent or emergent surgery. \textsuperscript{55}

**Table 2. Guideline Recommendations for the Administration of Prothrombin Complex Concentrates**

<table>
<thead>
<tr>
<th>Country/Professional Organization</th>
<th>Year</th>
<th>Recommendation for PCCs</th>
<th>Dose of PCCs and other agents$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Anesthesiologists\textsuperscript{52}</td>
<td>2015</td>
<td>Urgent VKA reversal or excessive bleeding and increased INR</td>
<td>No specific dosing regimen; consider FFP or PCCs for urgent warfarin reversal</td>
</tr>
<tr>
<td>European Task Force for Advanced Bleeding in Trauma\textsuperscript{17}</td>
<td>2013</td>
<td>Reversal of VKA and factor Xa inhibitors (but not recommended for reversal of DTIs)</td>
<td>Dosing based on point-of-care testing algorithm (e.g., TEG®, ROTEM®) Vitamin K 5–10 mg IV + 4F-PCCs (no specific dosing regimen)</td>
</tr>
<tr>
<td>American College of Chest Physicians\textsuperscript{56}</td>
<td>2012</td>
<td>First-line agent for urgent VKA reversal</td>
<td>No specific dose provided</td>
</tr>
<tr>
<td>STS/Society of Cardiovascular Anesthesiologists Blood Conservation\textsuperscript{44}</td>
<td>2011</td>
<td>First-line for urgent VKA reversal (4F-PCCs) (may substitute FFP for 3F-PCCs if continued bleeding)</td>
<td>INR unknown: 80 mL (4F-PCCS, 2000 IU) INR &lt;3.0: 40 mL (4F-PCCS, 1000 IU) INR 3.0–5.0: 80 mL (4F-PCCS, 2000 IU) INR &gt;5.0: 120 mL (4F-PCCS, 3000 IU) 3F-PCCs or FFP (no specific dosing regimen) Vitamin K 5–10 mg orally + INR unknown: 4F-PCCs, 25 IU/kg INR known: use SPC Vitamin K 5–10 mg IV + 4F-PCCs 10–50 IU/kg or 10–40 mL/kg FFP (initial INR-dependent dose) Vitamin K 5–10 mg orally + “factor concentrate” (3F- or 4F-PCCs not specified, no specific dosing regimen) Vitamin K 1 mg IV + 3F-PCCs 25–50 IU/kg + 150–300 mL FFP</td>
</tr>
<tr>
<td>Canadian National Advisory Committee on Blood and Blood Products\textsuperscript{50}</td>
<td>2011</td>
<td>VKA reversal for bleeding manifestations or surgical intervention required &lt;6 h of presentation</td>
<td></td>
</tr>
<tr>
<td>AHA/American Stroke Association\textsuperscript{45}</td>
<td>2010</td>
<td>VKA-associated ICH, elevated INR</td>
<td>3F-PCCs or FFP (no specific dosing regimen)</td>
</tr>
<tr>
<td>French Clinical Practice Guidelines\textsuperscript{59}</td>
<td>2010</td>
<td>First-line agent for urgent VKA reversal</td>
<td>Vitamin K 5–10 mg orally + INR unknown: 4F-PCCs, 25 IU/kg INR known: use SPC</td>
</tr>
<tr>
<td>European Stroke Initiative\textsuperscript{54}</td>
<td>2006</td>
<td>VKA-associated ICH, increased INR</td>
<td>Vitamin K 5–10 mg IV + 4F-PCCs 10–50 IU/kg or 10–40 mL/kg FFP (initial INR-dependent dose)</td>
</tr>
<tr>
<td>British Committee for Standards in Haematology\textsuperscript{12}</td>
<td>2005</td>
<td>First-line agent for VKA reversal</td>
<td>Vitamin K 5–10 mg orally + “factor concentrate” (3F- or 4F-PCCs not specified, no specific dosing regimen)</td>
</tr>
<tr>
<td>Australasian Society of Thrombosis and Haemostasis\textsuperscript{53}</td>
<td>2004</td>
<td>VKA reversal if any significant bleeding or INR &gt; 9</td>
<td>Vitamin K 1 mg IV + 3F-PCCs 25–50 IU/kg + 150–300 mL FFP</td>
</tr>
</tbody>
</table>

DTIs = direct thrombin inhibitors; FFP = fresh-frozen plasma; ICH = intracranial hemorrhage; INR = international normalized ratio; PCCs = prothrombin complex concentrates; ROTEM = rotational thromboelastometry; SPC = summary of product characteristics (document required by European Commission and available online); STS = Society of Thoracic Surgeons; TEG = thromboelastography; VKA = vitamin-K antagonist; 3F-PCC = 3-factor PCCs; 4F-PCC = 4-factor PCCs.

$^a$Vitamin K alone continues to be recommended by guideline committees in the setting of nonurgent VKA reversal.
faster in the PCCs group ($P < 0.0001$), but both groups displayed statistically similar corrected INR values at 24 hours (INR ≤ 1.3, $P = 0.08$). Importantly, the safety profiles (adverse events, serious adverse events, thromboembolic episodes, and death) were similar between the groups.11

A consistent feature among studies evaluating the reversal of vitamin K antagonist-induced coagulopathy has been the reduction of an increased pretreatment INR of >2 to 6 to an INR of <1.5 at approximately 15 to 60 minutes after administration of 4F-PCCs.11,55–58 Concomitant administration of IV vitamin K is essential to promote the hepatic synthesis of procoagulant and anticoagulant factors for sustained normalization of coagulation and modulation of thrombosis. However, IV vitamin K often requires at least 12 hours before clinical efficacy is observed.20 Oral vitamin K is less reliably absorbed, and timing is less clear.29 Although PCCs more rapidly correct coagulopathy related to vitamin K antagonists compared with FFP, current guidelines continue to recommend vitamin K administration along with PCCs. Restoration of endogenous thrombin generation after administration of 4F-PCCs (Beriplex P/N) or rFVIIa (NovoSeven) for vitamin K antagonist reversal has been evaluated in animal and human subjects.12 Thrombin generation is only restored with 4F-PCCs but not rFVIIa (150 vs 50 nM; $P < 0.05$), although both drugs correct INR values. This observation reiterates the importance of prothrombin for thrombin generation and the significance of factor VII simply for INR value normalization.12 Of note, aPCCs (FEIBA) and rFVIIa have been described for the reversal of vitamin K antagonists, but their use is not approved for this indication.10,61

**Lessons from Activated Recombinant Factor VII**

Before embarking on extensive perioperative use of PCCs, there is an opportunity to learn from our overenthusiastic initial adoption of rFVIIa, which was subsequently tempered by potential thromboembolic risk.4,5,62 The half-life of factor VII is approximately 6 hours, whereas that of factor II is 60 to 72 hours.24 Moreover, the half-life of rFVIIa may be even shorter than 6 hours owing to the increased volume of distribution when compared with the longer plasma-derived factor VII.63 This is an important fact, which merits caution against zealous PCC administration because of a far greater thromboembolic risk when compared with rFVIIa. The use of rFVIIa in high-risk cardiac surgical cases with refractory hemorrhage has been described in retrospective studies.23,64,65 Identified predictors of treatment failure included baseline INR >2.0, platelet count <80 × 10⁹/L, fibrinogen levels <100 mg/dL, and >15 units of packed red blood cells transfused before administration of rFVIIa.21 High thromboembolism rate (≥20%),21 a complication rate of 44%,21 and a mortality of 32%21 were also described.

Effective hemostasis with low-dose rFVIIa (defined as ≤40 μg/kg) in cardiac surgery has been reported in prospective66 and retrospective64 studies. Reduced bleeding is observed in propensity-matched studies when patients undergoing cardiac surgery receive low-dose rFVIIa compared with placebo.64,65 Intuitively, fewer adverse thromboembolic effects would be expected with lower doses of rFVIIa, and the higher doses (70–90 μg/kg) used for bypassing activity in hemophiliacs are unnecessary in the nonhemophilic surgical patient because the intrinsic Xase enzyme complex is intact. Failure to address platelet; fibrinogen; and factors II, VIII, IX, or X deficiencies in patients with severe hemorrhage will limit the effectiveness of rFVIIa to restore thrombin generation and fibrin clot formation (Fig. 1, normal coagulation model). This assertion is supported by Karkouti et al.21 who observed that hypofibrinogenemia (<100 mg/dL) and thrombocytopenia (<80 × 10⁹/L) before and after rFVIIa administration are associated with hemostasis failure, as previously discussed.

Administration of rFVIIa has profound effects on the INR, which is a test that is very sensitive to factor VII levels.10 Therefore, failure to decrease INR below a value of 1.0 with low-dose rFVIIa administration indicates profound predose factor VII deficiency.66 Similarly, a prolonged activated partial thromboplastin time (aPTT, a measure of the intrinsic and common coagulation pathways) is independently associated with failure of hemostasis after rFVIIa for refractory hemorrhage.67 Addressing concomitant deficiencies of other coagulation components before administering rFVIIa is, therefore, prudent. Conversely, the use of high-dose rFVIIa followed by correction of these deficiencies may lead to thromboembolic complications. With that said, rFVIIa as a general hemostatic agent remains unproven in addition to concerns about thromboembolism.4,5,62 A 2011 Cochrane database review of 3500 patients across 25 randomized controlled trials (nonsurgical as well as noncardiac and cardiac surgery patients) found modest blood loss after rFVIIa administration either for prophylactic or therapeutic means.4 Eleven of the 25 trials ($n = 2366$) involving therapeutic use of rFVIIa found an increase in the thromboembolic events (relative ratio [RR], 1.21; 95% confidence interval, 0.93–1.58). Thirteen trials ($n = 1137$) assessing the prophylactic use also found a trend toward thromboembolisms (RR, 1.32; 95% confidence interval, 0.84–2.06).4 Interestingly, no differences were found in thromboembolic events when comparing all comers receiving low-dose rFVIIa (defined as <80 μg/kg) and standard/higher doses (280 μg/kg), but the authors of the Cochrane review indicated inadequate statistical power and variable definitions of high- and low-dosage levels as contributors to these statistically nonsignificant findings regarding thromboembolism.4

Preliminary observational reports support the use of PCCs for refractory high-risk cardiovascular surgical bleeding. This approach may be more mechanistically logical compared with rFVIIa administration as previously discussed and depicted (Fig. 1).70,71 Investigators in one propensity-matched study administered 10 to 15 IU/kg of 4F-PCCs before low-dose rFVIIa (median, 18 μg/kg; interquartile range, 9–16 μg/kg) and found reduced bleeding after cardiac surgery.52 This combination of low-dose rFVIIa and PCCs may confer advantages over the use of rFVIIa alone. There is insufficient evidence, however, to support this approach without using point-of-care and laboratory-guided testing within an algorithm for refractory bleeding to help prevent thromboembolic disease.52,72,73

**Cardiac Surgery and Cardiopulmonary Bypass**

Determining the serum levels of factors II, VII, IX, and X in individual patients before PCC administration in each
clinical scenario may be helpful to guide appropriate PCC dosing assuming that laboratory values may be reported in a timeframe to be clinically useful. This strategy may be especially helpful to account for the different concentrations of factor levels among various PCC formulations (Table 1). In a porcine model of dilutional coagulopathy, anesthetized pigs underwent CPB with hypothermia for 2 hours at 25°C followed by 1 hour of normothermia. After CPB, the levels of factor II, VII, IX, and X were decreased from baseline by 32% to 48%. Approximately 1 hour after CPB, the pigs randomly received either isotonic saline (1 mL/kg) or 30 IU/kg of 4F-PCCs (Beriplex P/N). In that study, the administration of PCCs led to overcorrection of these coagulation factor concentrations and reduced bleeding but did not display evidence of thromboembolism. Factor II levels have been shown to decrease to ~50% of normal after CPB in patients undergoing complex cardiac surgery. This is accompanied, however, by a similar decrease in anticoagulant factors (e.g., antithrombin III). Therefore, administering a dose of 4F-PCCs to achieve a 50% increase in factor II level may not be needed to ensure coagulation and could promote prothrombotic complications. Similar to the use of initial INR values dictating PCC dosage administration for vitamin K antagonist reversal, laboratory data-driven algorithms for bleeding will, therefore, guide therapy in the perioperative realm.

In addition to other etiologies of bleeding experienced during cardiac surgery, extracorporeal flow of blood within a CPB circuit induces coagulopathy by dilution of procoagulants with circuit prime volume and activation of inflammatory cascades triggered by exposure of blood components to the surface of these artificial conduits and other such diverse mechanisms. Thus, the resulting coagulopathy after CPB may be an amalgam of pre-existing procoagulant deficiencies compounded by this extracorporeal membrane exposure, intravascular volume expansion, consequences of inflammation, and organ ischemia–reperfusion injury. This is a unique feature of cardiac surgery, which increases predilection toward bleeding when compared with other types of operations. Small, retrospective studies have described using PCCs to correct warfarin-related hemorrhage after CPB by using the same INR, weight-based dosing algorithm previously described by Sarode et al. in nonsurgical patients. In a randomized, prospective, single-center study of 40 patients undergoing cardiac surgery, the use of 4-F PCCs (Cofact®; Sanquin, Amsterdam, The Netherlands) was shown to be more effective than the use of FFP in the timely correction of INR and led to less frequent bleeding after surgery with less increase in cardiac filling pressures. In addition, in a retrospective, propensity-matched study of patients undergoing pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension, increased blood loss was seen 12 hours after intensive care unit admission in the group of patients receiving FFP compared with PCCs (median [interquartile range], 650 [325–1075] mL vs 277 [175–608] mL, P = 0.008). No differences in clinical outcomes were noted.

Point-of-Care Testing
Quantifying thrombin generation would likely provide the most accurate approach to determining the mechanism of post-CPB coagulopathy even before the onset of CPB, but there are currently no clinically available thrombin generation assays. However, several available point-of-care tests provide an estimation of thrombin generation that may be used for goal-directed hemostatic treatment of perioperative bleeding. Although point-of-care testing is not yet available in many hospitals, the importance of this technology should be discussed as it pertains to perioperative coagulopathic management. Briefly, both rotational thromboelastometry or ROTEM® (TEM International, Munich, Germany) and thromboelastography (TEG®; Haemonetics, Braintree, MA) are point-of-care devices that allow for the visual assessment of blood coagulation. The process of coagulation includes clot formation, propagation, stabilization, and clot dissolution. In the case of TEG, PCCs are indicated if R time (clot formation time) is prolonged, K time (occurrence of clot firmness) is prolonged, or α angle (kinetics of clot formation) is reduced. The newer version of TEG includes different assays, which allow for determination of PCC indication by using the RapidTEG™ (intrinsic and extrinsic activated assay), the kaolin TEG (intrinsic pathway-activated assay), and kaolin with heparinase (used with kaolin TEG and eliminates heparin effect). In the case of ROTEM, there are multiple assays that provide information regarding factor deficiencies in the clinical setting and included INTEM® (information similar to PT/INR), EXTEM® (information similar to PT/INR), and HEPTEM® (contains heparinase to neutralize unfractionated heparin and used in conjunction with the INTEM reagent). When using these ROTEM assays, PCCs are indicated if the clotting time (CT) or clot firmness time is prolonged or if the α angle is reduced. The reader is directed to literature that comprehensively outlines the interpretation and technology regarding ROTEM and TEG forms of coagulation testing. The use of point-of-care-based transfusion algorithms, which include PCCs, has been suggested to reduce allogeneic blood transfusions. Allergic blood transfusions have demonstrated increased morbidity and mortality in several trials involving surgical and nonsurgical patients. Such an approach has been successfully implemented in the coagulation management related to cardiovascular surgery, and reduced allogeneic blood transfusions, FFP, and cryoprecipitate have been observed along with an increase in the administration of fibrinogen concentrate and PCCs.

More recently, an observational study of 25 patients found that the administration of aPCCs (FEIBA) for refractory bleeding after complex cardiac surgery reduced the frequency of FFP and platelet transfusions. Point-of-care laboratory testing was performed after FFP administration and again after aPCCs. FEIBA was more effective at normalizing INR compared with FFP without evidence for thromboembolism.

In a single-center, retrospective analysis of patients undergoing cardiac surgery, implementation of a coagulation management algorithm based on point-of-care testing (ROTEM) using first-line therapy with coagulation factor concentrates (including 4F-PCCs) was associated with reduced allogeneic blood transfusions and decreased thromboembolic events compared with historical controls. In this study, 20 to 25 IU/kg 4F-PCCs were administered in case of severe, diffuse bleeding after heparin reversal if EXTEM CT was >90 seconds, and 35 to 40 IU/kg 4F-PCCs
were administered if CT was >100 seconds.\textsuperscript{53} Improved outcomes were not demonstrated after the institutional implementation of this algorithm, but this study may have been limited by using historical controls that included fewer emergency cases and less complex procedures when compared with the contemporary cohort.\textsuperscript{53} Thoracic aortic operations requiring hypothermic circulatory arrest are a category of cardiothoracic surgery, which often require multiple transfusions of blood products, procoagulants, and factor concentrates after separation from CPB.\textsuperscript{87} The use of ROTEM in a single-center, prospective, randomized trial (n = 56) was noted to reduce the transfusion of allogeneic blood (9 vs 16 units; P = 0.02) when compared with standard management of coagulopathy in patients undergoing thoracic aortic surgery with hypothermic circulatory arrest.\textsuperscript{88} Improved outcomes and reduced transfusion of allogeneic blood products were found in another study using 20 to 30 IU/kg 4F-PCCs (Beriplex®) was observed among 2 groups of patients: (1) those requiring reversal of warfarin for increased INR or in preparation for urgent/emergent surgery; and 2) those needing treatment of severe diffuse perioperative bleeding but not on preoperative warfarin.\textsuperscript{89} The administration of 4F-PCCs resulted in correction of abnormal INR in the 12 nonsurgical patients (P < 0.001), and correction of diffuse bleeding was observed in 26 of 27 surgical patients (96%).\textsuperscript{89} No thromboembolic events were observed in either group.

There is a paucity of research regarding the impact of PCCs on perioperative and nonsurgical bleeding in patients with hepatic failure.\textsuperscript{90} Animal studies with bleeding after induced liver injury, however, have shown promise regarding the beneficial impact of PCCs. In a laboratory study using a porcine model of blunt liver injury, induced coagulopathy, and hemodynamic instability related to bleeding, 27 anesthetized pigs displayed improved hemodynamics, increased thrombin generation, and correction of abnormal INR and EXTEM values (namely CT and clot firmness time) after 4F-PCCs (low-dose group: 35 IU/kg) when compared with saline. Two animals in the saline group had a singular lung arteriole thromboembolus of 1 to 2 mm in diameter, whereas 3 animals from the lower PCC dosing group had several thromboemboli each measuring 1 to 2 mm in diameter.\textsuperscript{91} Interestingly in those receiving higher doses of PCCs (50 IU/kg), disseminated intravascular coagulation was observed based on the International Society of Thrombosis and Hemostasis criteria,\textsuperscript{92} and all of these animals contained >4 mm of multiple lung arteriole thromboembolisms on autopsy. In addition, a net-like fibrinogen deposition was noted in the lung capillaries of the higher dosage group, which was present but not as well developed in the control and low-dosage animals.\textsuperscript{93} In an ongoing multicenter, randomized, controlled trial from The Netherlands, the utility of 4F-PCCs (Cofact) is being studied with respect to reducing allogeneic red blood cell transfusions during orthotopic liver transplantation in cirrhotic patients with INR ≥1.5 (PROTON Trial; Netherlands Trial Register: 3174).\textsuperscript{93}

### Trauma-Related Bleeding and Intracranial Hemorrhage

There have been several reports on the use of PCCs in trauma patients.\textsuperscript{94,95} In a retrospective, observational single-center study of 45 trauma patients, 3F-PCCs (Profilnine®; Grifols Biologicals, Los Angeles, CA) reversed clinical bleeding and INR to ≤1.5 at a mean dose of 25 IU/kg in both warfarin (n = 25, P ≤ 0.001) and nonwarfarin (n = 20, P ≤ 0.001) groups.\textsuperscript{96} Both groups experienced refractory bleeding after receiving plasma.\textsuperscript{96} The primary anatomic site of injury was intracranial (68% of patients in the preoperative warfarin group and 40% in the nonwarfarin group). Mortality was 28% among the preoperative warfarin group and 40% among those patients who did not receive warfarin before injury.\textsuperscript{96}

Point-of-care coagulation testing has also been used in human studies related to bleeding in adult trauma patients requiring reversal of vitamin K antagonist-induced coagulopathy; improvement in hemostatic efficacy after PCC administration has been illustrated.\textsuperscript{97–99} PCCs were administered in 1 retrospective analysis of 131 trauma patients who received ≥5 units of packed red blood cells within 24 hours as a part of a factor concentrate-driven, multimodal, coagulation management algorithm using ROTEM guidance. The survival benefit of this approach was determined by predicted mortality modeling in the population compared with actual observed mortality.\textsuperscript{99} In this study, fibrinogen concentrate was given if maximum clot firmness was low on FIBTEM®, which is the ROTEM assay measure of fibrinogen activity. PCCs were then administered in case of recent warfarin intake or CT > 1.5 times normal on EXTEM. Lack of improvement of maximum clot firmness on EXTEM after fibrinogen concentrate and PCCs was an indication for platelet concentrate. The authors reported a 14% observed mortality compared with 28% predicted mortality (P = 0.0018).\textsuperscript{99} PCCs may be administered in trauma patients at varying doses based on CT prolongation.\textsuperscript{99,100} A prevailing theme has evolved whereby using initial INR and/or EXTEM CT may provide a basis for initial dosing.\textsuperscript{11,53,72,73,100}

Administration of PCCs has been used in the reversal of coagulopathy and control of intracranial hemorrhage. In a prospective, observational single-center study involving 33 patients, emergent reversal of coagulopathy was observed after administration of 4F-PCCs (KCentra). In that study, a mean dose of 2200 IU (range, 1500–2500 IU) of PCCs led to a faster correction of an abnormal INR (<1.4) compared with FFP (65 vs 256 minutes, P < 0.05).\textsuperscript{101} Kerebel et al. performed a phase III, prospective, randomized, open-label study of 59 patients with warfarin-associated intracranial hemorrhage involving 22 centers. The patients received either 25 IU/kg (n = 29) or 40 IU/kg (n = 30) of 4F-PCCs (Octaplex®; Octapharma, Vienna, Austria).\textsuperscript{102} Despite more rapid reversal of INR and normalization of INR II and X and proteins C and S concentrations, there was no difference in hematoma volume (P = 0.71), clinical (P = 0.73) or neurologic outcomes (P = 0.83) as well as thromboembolic
events \((P = 1.0)\) between the 2 groups. In contrast, use of rFVIIa in this patient population was associated with an increased incidence of thromboembolic events in the 80-\(\mu g/kg\) treatment group without benefit in clinical outcomes. There are no data to describe or support the use of PCCs in patients with normal coagulation profiles, but similar thromboembolic complications may be anticipated.

### 3F-PCCs Versus 4F-PCCs

There are increasing reports comparing the safety and efficacy of both 3F- and 4F-PCCs that deserve particular attention. Special consideration to the importance of one composition containing appreciable amounts of anticoagulants may further contribute to the overall safety and efficacy of 4F-PCC solutions. In a case report, massive intracardiac and aortic thrombus formation was noted by emergency transesophageal echocardiography after administration of 50 IU/kg of 3F-PCCs (Profilnine) for warfarin reversal (initial INR, 5.5) before urgent spine surgery with an indwelling mechanical mitral valve. Thromboembolism was likely because of the higher dosage of PCCs, the higher concentration of factor II present in Profilnine compared with KCentra (Table 1; 150 vs 130 IU, respectively, per 100 IU of PCCs) and the absence of anticoagulants in Profilnine, which may otherwise be present in FFP and to a certain degree in 4F-PCCs (KCentra). In a meta-analysis of 18 studies (12 prospective and 6 retrospective) involving 654 elderly patients presenting for emergent warfarin reversal, INR was corrected in 75% of patients after 3F-PCC administration and in 92% of patients after 4F-PCCs. Eighty-one patients receiving either low-dose 3F-PCCs (profilnine, 25 IU/kg) or high-dose 3F-PCCs (50 IU/kg) were compared against patients who had received FFP for supratherapeutic INR and warfarin reversal. Administering FFP alone (3.6 units [range, 2–8 units]) corrected the initial INR from 9.4 (range, 5.1–9.4) to 2.3 (range, 1.2–5.0). 3F-PCCs were able to reduce initial INR in both the low-dose group (initial INR, 9.0 [range, 5.2–15.0] to INR, 4.6 [range, 1.4–15.0]) and high-dose group (initial INR, 8.6 [range, 5.3–15.0] to INR, 4.7 [range, 1.4–15.0]), but complete correction to an INR <1.5 was not achieved without additional FFP. Although these study results support the sensitivity of INR to factor VII levels, INR values in this increased range may also reflect clinically relevant bleeding or potential for bleeding, which were not evaluated in this study.

### PCCs for Reversal of Direct Oral Anticoagulants

There are increasing data regarding the use of PCCs for the management of bleeding related to direct oral anticoagulants, including the direct thrombin inhibitor dabigatran (Pradaxa®; Boehringer Ingelheim, Ridgefield, CT) and factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban). A recent volunteer study compared the effects of 3F-PCCs (Profilnine) with 4F-PCCs (Beriplex P/N) on PT, thrombin generation, aPTT, and antifactor Xa activity of rivaroxaban. Volunteers received 50 IU/kg of 3F-PCCs \((n = 12)\), 4F-PCCs \((n = 10)\), or saline \((n = 12)\). The better response of thrombin generation to 3F-PCCs was likely reflective of the higher factor II concentration in Profilnine compared with Beriplex (Table 1). In another study, 50 IU/kg 4F-PCCs (Cofact) was given to healthy male volunteers treated with rivaroxaban \((n = 6)\) or dabigatran \((n = 6)\). Normalization of thrombin generation was seen in rivaroxaban-treated subjects but not those treated with dabigatran. This is consistent with in vitro, TEG evidence that PCCs are not able to reverse the coagulopathic effects of dabigatran in healthy volunteers.

Observational studies evaluating the use of PCCs in the treatment of coagulopathy related to the direct factor Xa inhibitors suggest that these compounds are able to reverse the anticoagulant effects by increasing the production of prothrombinase, thereby leading to thrombin generation (Fig. 3). Conversely, direct thrombin inhibitors impact fibrin production downstream from where PCCs may have the most impact. This proposed mechanism is supported by available data, which suggest that PCCs may not be effective in treating direct thrombin inhibitor-related coagulopathy. PCCs (FEIBA), on the other hand, have shown efficacy in dabigatran-associated intracranial bleeding in a single-case study. Safety concerns related to thrombotic risk in experimental models, however, persist regarding the fact that procoagulant effects of PCCs (because of variable
amounts of activated factors; Table 1) may outlast the duration of action of dabigatran. Although PCCs are, currently, an important therapeutic consideration to reverse direct oral anticoagulant-related bleeding, discussion of additional therapeutic strategies for specific reversal is prudent. Reversal agents are relevant because of the longer half-life of PCCs compared with direct oral anticoagulants and the potential for thromboembolism should PCCs be administered for coagulopathy reversal. These reversal agents include idarucizumab (Praxbind®; Boehringer Ingelheim) for dabigatran, Andexanet alfa (Portola Pharmaceuticals, San Francisco, CA) for factor Xa inhibitors, and Ciraparantag (PER977®; Perisphere Inc., Danbury, CT) for dabigatran and the factor Xa inhibitors. Idarucizumab, a humanized monoclonal antibody fragment, binds dabigatran with an affinity 350 times that of thrombin and, therefore, binds to both free dabigatran and dabigatran bound to thrombin, rendering the drug inactive. Idarucizumab has recently received FDA approval for use in patients who are receiving dabigatran during emergency situations when there is a need to reverse coagulopathy related to the direct thrombin inhibitor (www.fda.gov, accessed October 16, 2015). Andexanet alfa is a recombinant protein analog of factor Xa that binds to factor Xa inhibitors and antithrombin but does not trigger prothrombotic activity. This drug is in phase 3b–4a trials at the time of this writing (NCT02329327). Ciraparantag is a small synthetic molecule that competitively binds the direct oral anticoagulants, restoring the activity of blocked coagulation factors. Currently, this agent is in phase 2 studies evaluating its efficacy in healthy volunteers receiving edoxaban (NCT02207257). Despite the potential for future specific reversal agents, a multimodal approach to hemostatic resuscitation is still required during direct oral anticoagulant-related hemorrhage, which may include PCCs to restore deficient factor levels.

Thromboembolism and Off-Label Use of PCCs

Using PCCs beyond the approved use of vitamin K antagonist reversal warrants emphasis regarding the potential for thromboembolism. Prothrombotic risk is increased with repeat or excessive dosing because of promotion of thrombin generation and therefore fibrin crosslinkage (Fig. 1). Prothrombin/factor II levels are directly related to thrombin generation, and therefore, increasing serum factor II concentrations will lead to increased thrombin generation. The use of PCCs may be warranted in clinical scenarios in which factor II concentrations are reduced such as from hemodilution or direct consumption from continuous bleeding. In other scenarios, activated factor concentrations (aPCCs or rFVIIa) may be required to bypass inhibitor activity despite normal factor II levels, as seen in hemophiliacs. Higher dose administration of PCCs (>25 IU/kg) in the reversal of factor Xa inhibitors may lead to thrombosis, for example, because the effects of both apixaban and rivaroxaban dissipate in <24 hours (assuming normal renal function), whereas factor II levels will remain increased for 248 hours. Close attention to mechanical and/or pharmacologic thromboprophylaxis is warranted when these longer acting factor concentrates are used to treat a brief period of intraoperative or drug-related coagulopathy.

CONCLUSIONS

PCCs have recently entered the perioperative setting for the off-label indication of diffuse coagulopathy without a vascular source for bleeding. Evidence thus far for the safe and effective use of PCCs is limited to retrospective, observational studies and historical controls. Clinicians managing patients with perioperative bleeding should have an understanding of the mechanisms by which PCCs impact the coagulation cascade and the importance of a multimodal approach to the management of diffuse bleeding related to surgery. Correction of hypofibrinogenemia and thrombocytopenia before the administration of PCCs may be prudent to maximize the efficacy of lower PCC dosing and to minimize the risk for adverse thromboembolic events. Lessons from the higher dosing of rFVIIa in nonhemophilic surgical patients should be incorporated into the advent of perioperative PCC use to help avoid such events. Administration should be based on clinically observed bleeding as well as laboratory and point-of-care data incorporated into an institutionally derived approach to coagulopathic management. In addition, prospective, randomized controlled trials are needed to evaluate the off-label use of PCCs in this setting.

DISCLOSURES

Name: Kamrouz Ghadimi, MD.
Contribution: This author helped perform the literature search and prepare the manuscript.
Attestation: Kamrouz Ghadimi approved the final manuscript.
Conflicts of Interest: Kamrouz Ghadimi is a coinvestigator in a prospective, open-label study of Andexanet-Alfa in patients receiving factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals.
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Attestation: Jerrold H. Levy approved the final manuscript.
Conflicts of Interest: Jerrold H. Levy serves on steering committees for Boehringer-Ingelheim, CSL Behring, Grifols, and Janssen; he is a consultant to Instrumentation Laboratories.
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Attestation: Ian J. Welsby approved the final manuscript.
Conflicts of Interest: Ian J. Welsby is the principal investigator in a prospective, open-label study of Andexanet Alfa in patients receiving factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals, and has recently received grant support from CSL Behring and Terumo BCT.
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