Use of Factor Concentrates for the Management of Perioperative Bleeding: Guidance from the ISTH SSC Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis

Abstract

Perioperative bleeding remains a major cause of morbidity and resource utilization in patients undergoing major surgery, including cardiac, trauma, obstetric, and organ transplant. Acquired perioperative coagulopathy is multifactorial and may result from blood loss, hemodilution, hypothermia, acidosis, fibrinolysis, inflammation, and consumption of coagulation factors and platelets. Over the past decade, coagulation factor concentrates have been increasingly incorporated into perioperative bleeding management algorithms due to rapid availability, standardized dosing, lower infusion volumes, and pathogen inactivation, reducing dependence on plasma products. Since the 2018 publication of the International Society on Thrombosis and Haemostasis (ISTH) guidance on the use of factor concentrates for the management of perioperative bleeding, additional clinical studies, systematic reviews, and evolving bleeding management practices have expanded the evidence base regarding use of fibrinogen concentrate, prothrombin complex concentrate (PCC), recombinant activated factor VII (rFVIIa), and factor XIII (FXIII) concentrate for surgically acquired coagulopathy. This guidance document from the Perioperative and Critical Care Subcommittee of the ISTH reviews the contemporary literature and provides pragmatic guidance regarding the perioperative use of coagulation factor concentrates based on available evidence and expert consensus.

Key Words :

Factor VIIa, Factor XIII, Fibrinogen, Perioperative Hemorrhage, Prothrombin Complex Concentrates

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Introduction

Perioperative bleeding remains a common and clinically significant complication in patients undergoing major surgery. Despite advances in surgical technique and perioperative care, patients frequently develop acquired hemostatic abnormalities driven by multiple factors, including blood loss, dilution of coagulation factors and platelets during fluid resuscitation, hypothermia, metabolic acidosis, and tissue injury, with activation of fibrinolytic and inflammatory pathways [1, 2]. These processes interact to produce a complex and dynamic coagulopathy that contributes to perioperative bleeding. Thus, effective management requires a multimodal approach that extends beyond surgical hemostasis and includes targeted pharmacologic therapies, administration of allogeneic blood components and products, and replacement of key components necessary for thrombin generation and stable clot formation [3].

Over the past decade, advances in perioperative hemostatic resuscitation have been driven by randomized clinical trials of coagulation factor concentrates, the implementation of structured bleeding management algorithms, and the adoption of point-of-care viscoelastic testing [4-6]. In parallel with these developments, coagulation factor concentrates have been increasingly incorporated as adjuncts to conventional transfusion strategies, supported by regulatory approval and clinical availability. These agents offer several practical and biological advantages, including rapid availability for treatment, longer storage time facilitating better inventory management, viral inactivation, standardized dosing, lower infusion volumes than plasma-based therapies, and targeted replacement of critical hemostatic proteins without the need for pre-transfusion testing to match ABO compatible products [7]. Since the publication of prior guidance from the International Society on Thrombosis and Haemostasis (ISTH) [8], a number of clinical trials, observational studies, and systematic reviews have been published regarding the efficacy, safety, and optimal use of hemostatic agents in perioperative bleeding.

In addition, the COVID-19 pandemic exposed vulnerabilities in global blood supply systems, with many regions experiencing temporary shortages of transfusion products

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[9]. These developments have reinforced the potential role of coagulation factor concentrates as adjuncts or, in selected circumstances, alternatives to conventional blood component therapy, and have contributed to refinements in bleeding management algorithms across diverse surgical and critical care settings. The coagulation factor concentrates most commonly incorporated into perioperative bleeding management include fibrinogen concentrate, prothrombin complex concentrate (PCC), factor XIII (FXIII), and recombinant activated factor VII (rFVIIa), which differ substantially in their mechanisms, pharmacologic profiles, clinical indications, safety profiles, and supporting evidence. Given their expanding clinical use and the evolving evidence base, a systematic re-evaluation of available data is warranted.

Methods

A systematic literature search was conducted to identify studies evaluating the use of coagulation factor concentrates in the management of perioperative bleeding. Searches were performed in Ovid MEDLINE from database inception through January 2026. The search strategy combined controlled vocabulary and free-text terms related to coagulation factor concentrates and perioperative bleeding, including prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), fibrinogen concentrate, recombinant activated factor VII (rFVIIa), and factor XIII (FXIII) concentrate, along with relevant product names and synonyms. These terms were combined with concepts related to surgical procedures, perioperative and intraoperative bleeding, postoperative hemorrhage, cardiopulmonary bypass, and surgical blood loss. Detailed search strategies are provided in the **Supplementary Appendix**.

Search results were limited to human studies, English-language publications, and studies published from 2018 onward, corresponding to the period following publication of the prior ISTH guidance document. Animal studies or those studies limited exclusively to pediatric populations were excluded. Following removal of duplicate records, titles and abstracts, and subsequently full-text articles, were independently

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reviewed in duplicate by authors with expertise in the relevant factor concentrate domain, including PCC, fibrinogen concentrate, rFVIIa, or FXIII. Conference abstracts and non–peer-reviewed reports were excluded when feasible to prioritize full-length peer-reviewed publications with sufficient methodological detail. Eligible study designs included randomized clinical trials, prospective and retrospective observational studies, systematic reviews, and meta-analyses. Studies were included if they evaluated the perioperative or procedural use of coagulation factor concentrates for the prevention or treatment of bleeding. Additional relevant publications were identified through manual review of reference lists and through expert input from panel members. Studies judged relevant to perioperative or procedural bleeding management were used to inform the evidence summaries and guidance statements.

The writing group comprised clinicians with expertise in perioperative hemostasis, anesthesiology, surgery, critical care, hematology, and transfusion medicine, convened under the auspices of the ISTH. Draft sections were prepared by designated authors and underwent iterative review and revision by the full panel. Guidance statements were developed through structured discussion and consensus, informed by the available evidence and clinical judgment. The overall approach was pragmatic and designed to inform guidance development rather than to perform a formal meta-analysis. The authors followed the ISTH Guidelines and Guidance Committee COI Policy and disclosed any relevant financial relationships with industry within the past 12 months. Authors who reported more than $5,000 relevant direct financial conflicts and/or had major conflicts recused themselves from voting on the guidance statements.

Consistent with ISTH guidance document policy, which consensus of the authors was achieved and the guidance statements were informed by higher quality clinical studies with greater certainty of evidence are available, the term to be used for those statements is **“we advise”** in which clinicians should consider adopting into practice in most cases. For guidance statements in which consensus of the authors was achieved but the guidance statements were informed by lower quality clinical studies with lower certainty of evidence, the term to be used for those statements is **“we suggest”** in which clinicians may or may not adopt.

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Evidence Review and Guidance

The following sections summarize the available evidence on the use of individual coagulation factor concentrates in perioperative bleeding management, followed by the panel's guidance statements.

Fibrinogen Concentrate

Fibrinogen is an essential part of the hemostatic response to bleeding. A low fibrinogen level is thought to be a core component of the pathophysiology of acute traumatic coagulopathy [10], acute obstetrical coagulopathy [11], and major bleeding after cardiac surgery [12]. Fibrinogen is the first coagulation factor to fall below a critical level after traumatic injury [13], and a level below 2.0 g/L is associated with worse outcomes in the setting of postpartum hemorrhage and cardiac surgery [12, 14].

There are three human-derived blood products available to replace fibrinogen deficits: pathogen-reduced fibrinogen concentrate, cryoprecipitate, and pathogen-reduced cryoprecipitate. The availability and cost of these products vary by country. The benefits of fibrinogen concentrate include a long shelf life (~4-5 years at room temperature, depending on the specific product), reduced waste, rapid reconstitution allowing for more timely treatment, and a more predictable dose response. Pathogen-reduced cryoprecipitate can be stored at room temperature for up to 5 days after thawing, reducing waste and facilitating more rapid treatment of coagulopathy in critically ill patients [15]. Cryoprecipitate is not available in all countries. Although cryoprecipitate acquisition costs are relatively low, processing costs and product wastage increase the total cost. Cryoprecipitate contains additional coagulation proteins, including von Willebrand Factor, Factor VIII, fibronectin, and alpha-2 antiplasmin. The clinical

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relevance of these differences, both in terms of efficacy and safety, remains unclear and may vary by patient population.

Randomized controlled trials comparing fibrinogen concentrate to cryoprecipitate have been completed in cardiac surgery (adult and pediatric) [16], traumatic injury [17], major spine surgery, and gastrointestinal cancer surgery [18, 19]. Overall, these randomized trials show similar laboratory and clinical outcomes when the two products are compared, including no statistically significant differences in thromboembolic complication rates. Limitations of these trials include their open-label design, which may introduce bias. The largest trial comparing fibrinogen concentrate with cryoprecipitate enrolled 735 adult cardiac surgery patients; fibrinogen concentrate was found to be non-inferior to cryoprecipitate [4]. The economic analysis of this trial found that fibrinogen concentrate was cost-effective in the subgroup of non-critically ill patients, representing ~85% of patients [20]. A 208-patient randomized trial comparing cryoprecipitate with pathogen-reduced cryoprecipitate in cardiac surgery and liver transplant patients has been completed, with no difference in patient outcomes observed. [21, 22].

In addition to the trials detailed above comparing two different fibrinogen products, there have been trials comparing fibrinogen replacement to placebo across multiple patient populations. These have been conducted in both prophylactic and therapeutic settings. Prophylactic use of fibrinogen concentrate before confirmation of a low fibrinogen level and/or the onset of bleeding, compared with placebo, suggests no improvement in patient-important outcomes [23-25]. Similarly, prophylactic use of cryoprecipitate in traumatic injury was not found to be superior to cryoprecipitate transfusion based on laboratory testing [26]. Hence, in most patient scenarios, fibrinogen replacement should be considered only for low fibrinogen levels, although the optimal treatment threshold across populations remains uncertain. In a systematic review of all 13 randomized trials of fibrinogen concentrate versus placebo (n=900 patients, including prophylactic and therapeutic trials), fibrinogen concentrate reduced 12-hour blood loss but failed to show a benefit for other patient outcomes [27]. A difference in 24-hour blood loss was only seen among trials evaluating the therapeutic use of fibrinogen concentrate (-156 mL [95% CI -244 to -67]).

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The threshold for fibrinogen replacement has not been extensively studied in clinical trials. In trials where fibrinogen levels exceeded 1.5 g/L in the majority of patients, there appears to be no patient benefit to fibrinogen replacement over placebo [24, 25]. No studies have directly compared thresholds of 1.0 g/L, 1.5 g/L, or 2.0 g/L, which would provide clarity for an evidence-based fibrinogen threshold. It is reasonable to use a threshold of 1.5-2.0 g/L, or an equivalent threshold using viscoelastic testing, until clinical trials are conducted to evaluate transfusion thresholds [28, 29].

Regarding the dose of fibrinogen concentrate to administer, many studies have used 4 grams in adult patients as a single dose (~50 mg/kg) [4, 30]. There is evidence that the dose needs to be higher when the fibrinogen is <1.0 g/L, as compared to >1.0 g/L, to achieve a safe post-infusion fibrinogen level [31]. Each 10 mg/kg increase in fibrinogen concentrate increases the ROTEM FIBTEM A5 by ~1.4 mm in the setting of cardiac surgery-related bleeding, allowing clinicians to use laboratory test results to personalize dosing and minimize under- and over-transfusion. When fibrinogen concentrate is used, dosing may be guided by product-specific formulas that incorporate the patient's measured fibrinogen level, target fibrinogen level, body weight, and the concentrate-specific expected incremental recovery; clinicians should use the applicable product monograph, prescribing information, or institutional protocol rather than applying a single formula across all products.

Guidance for use of fibrinogen concentrate for bleeding management:

1. ***We advise*** *not administering fibrinogen concentrate for prophylaxis before confirming hypofibrinogenemia with laboratory or viscoelastic testing.*

2. ***We advise*** *measuring the fibrinogen level using laboratory testing or viscoelastic testing to minimize preventable blood loss and guide replacement.*

3. ***We advise*** *against the use of fibrinogen concentrate if the fibrinogen level exceeds 1.5-2.0 g/L (or a similar level based on viscoelastic testing).*

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4. ***We advise*** *that the dose administered be titrated to the degree of measured fibrinogen deficit to minimize under- and over-treatment.*

Prothrombin Complex Concentrates

Non-activated prothrombin complex concentrates (PCCs) are lyophilized, human plasma-derived concentrates of vitamin K-dependent coagulation factors, prepared from pooled plasma using product-specific purification and fractionation processes, along with pathogen-reduction technologies. Based on the coagulation factors involved, they are categorized as three-factor PCCs (FII, FIX, and FX) or four-factor PCCs (including FVII). Although three-factor PCCs have been used for VKA reversal and in selected perioperative bleeding cohorts, direct comparative VKA-reversal data generally favor four-factor PCC for rapid INR correction [32]. Moreover, the contemporary evidence base for non-VKA perioperative bleeding indications, including cardiac surgery, non-cardiac surgery, and trauma, has largely evaluated four-factor PCC; therefore, this section focuses on four-factor PCC use.

Several commercial PCC products are available, which differ in the composition of procoagulant and natural anticoagulant factors (protein C/S and antithrombin), the amount of heparin, and purity. PCCs were originally developed as intermediate-purity factor IX–containing concentrates for patients with hemophilia B. With the availability of high-purity and recombinant factor IX products, this indication became obsolete, and PCC use shifted toward rapid replacement of vitamin K–dependent coagulation factors for urgent VKA reversal. More recently, PCCs have been evaluated for perioperative and traumatic bleeding, particularly as use of off-label rFVIIa has become more restricted because of thrombotic safety concerns [33-35].

In some locations, the clinical indications for PCCs are limited to the treatment of VKA-associated bleeding or for perioperative VKA reversal when urgent or emergent surgery is required. In many countries, 4-factor PCCs (4F-PCCs) are approved for the treatment of acquired coagulopathy and are increasingly used to manage perioperative bleeding in cardiac, non-cardiac, and trauma surgery. PCCs represent an important alternative to

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plasma because they do not require ABO compatibility or thawing, can be stored near the patient for rapid access, and contain no citrate. They can be administered as a low-volume intravenous infusion or a slow intravenous push injection over minutes and are therefore not associated with transfusion-associated circulatory overload (clinical dose of PCC is ~40 mL vs. plasma at ~1000 mL) or transfusion-related acute lung injury. PCC does not replace fibrinogen, FVIII, V, or vWF. In addition, PCC contains therapeutic levels of protein C and protein S, but only subtherapeutic levels of antithrombin [36]. As such, there are concerns that PCC may increase the risk of thromboembolic complications if used as a substitute for plasma for the management of perioperative bleeding in the setting of coagulation factor deficiency; however, these concerns have not been observed in clinical trials comparing PCC with plasma.

PCCs have been studied extensively for the management of perioperative bleeding in cardiac surgery [37-40]. In a multicenter, open-label RCT that included 430 patients who underwent cardiac surgery with cardiopulmonary bypass, those who received PCC at a mean dose of 24 IU/kg had less bleeding and fewer transfusions than those who received frozen plasma at a mean dose of 12 mL/kg [37]. Moreover, serious adverse events (including renal failure) were lower in the PCC patients. There was also no increased risk of thromboembolic events in any of the 4 randomized trials.

Data for use outside cardiac surgery are less clear, and therefore, no firm conclusions can be drawn about efficacy and safety [41-44]. In general non-cardiac surgery, no large randomized trial has compared PCC with plasma for non-VKA acquired coagulopathic bleeding, and available evidence is largely retrospective and observational. In a recent single-center cohort of 137 patients with massive intraoperative bleeding during non-cardiac surgery, 89 patients received 4F-PCC; an intermediate dose range of 6.7–11.5 IU/kg was associated with lower postoperative RBC transfusion, but this signal was not observed across all dose strata [45]. Major thromboembolic events were not statistically increased in the intermediate-dose group, although the study was not powered to establish safety. These findings are hypothesis-generating and are limited by confounding by indication, treatment, and selection bias; dosing heterogeneity; co-interventions, including plasma, platelets, fibrinogen concentrate, and antifibrinolytics;

and variation in bleeding phenotype. Therefore, routine empiric use of 4F-PCC as a substitute for plasma in non-cardiac surgery is not supported. 4F-PCC may be considered selectively as rescue therapy for ongoing bleeding with evidence of contributing coagulopathy, after surgical bleeding, fibrinogen deficiency, thrombocytopenia or platelet dysfunction, hypocalcemia, hypothermia, and fibrinolysis have been addressed, ideally using laboratory- or viscoelastic-guided algorithms.

Liver surgery, liver transplantation, and cirrhosis should be considered separately from general non-cardiac surgery. In cirrhosis, INR prolongation does not necessarily reflect correctable bleeding risk. A recent systematic review of PCC in liver transplantation identified no randomized trials; all included studies were retrospective. PCC-treated patients were generally sicker and more coagulopathic, with likely residual confounding [46]. Viscoelastic testing-based algorithms incorporating PCC were associated with reduced odds of RBC and plasma exposure, but studies isolating PCC exposure did not show consistent reductions in mean RBC, plasma, or platelet transfusion, and safety estimates were heterogeneous. Individual propensity-matched or cohort studies are also inconsistent. Srivastava et al. reported reduced RBC and plasma transfusion without thromboembolic events, Kirchner et al. reported no significant increase in thrombotic or ischemic events with ROTEM-guided factor concentrate therapy, whereas Colavecchia et al. found no reduction in RBC or plasma transfusion and noted substantial concomitant use of fibrinogen concentrate [47-49]. PCC should therefore not be used solely to normalize INR in cirrhosis or liver transplantation. When considered, use should be individualized, rescue-oriented, and guided by bleeding phenotype or viscoelastic testing, ability to tolerate the volume required with plasma (15 mL/kg), fibrinogen replacement, platelet management, and thrombotic risk.

Trauma should be considered separately from non-trauma perioperative bleeding. PROCOAG randomized 324 trauma patients at risk of massive transfusion to early 4F-PCC or placebo in addition to ratio-based plasma transfusion; 226 patients (approximately 69%) required surgical or interventional radiology hemorrhage control, but the trial was not a surgery-only study [42]. PCC did not reduce 24-hour total blood product consumption, RBC, plasma, or platelet use, time to prothrombin time ratio (PTr)

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correction, mortality, or time to anatomic hemostasis; thromboembolic events were more frequent with PCC. FiiRST-2 similarly found that a fixed early fibrinogen concentrate plus PCC strategy was not superior to plasma for 24-hour allogeneic blood product use in patients with massive hemorrhage protocol activation; thromboembolic events were not statistically different when corrected for more survivors in the PCC group. Overall, the trauma evidence does not support routine empiric PCC administration in patients at risk of massive transfusion. PCC use in trauma should be limited to established indications such as VKA reversal or selected patients with demonstrable coagulopathy within protocolized laboratory- or viscoelastic-guided resuscitation pathways, or in remote settings where a plasma-based resuscitation protocol is not possible.

There is an urgent need for randomized controlled trials in settings such as severe traumatic injury and liver transplantation, where the risk-benefit profile of PCC compared with plasma may be different from that in cardiac surgery. Given the pro-hemostatic balance of PCC, caution is advised when using PCC in patients with acquired procoagulant status, such as ongoing disseminated intravascular coagulation, especially with high and/or repeated dosing.

Guidance for the use of PCC for perioperative bleeding management

1. ***We advise*** *that PCC be used over plasma for the treatment of perioperative coagulopathic bleeding in the setting of cardiac surgery.*

2. *In non-cardiac surgery, evidence is insufficient to recommend PCC over plasma or plasma over PCC for routine perioperative bleeding management.* ***We suggest*** *that PCC not be used routinely or empirically as a substitute for plasma in this setting, except in remote settings where plasma is unavailable. Selective rescue use may be considered for ongoing bleeding with evidence of coagulopathy within a protocolized laboratory- or viscoelastic-guided algorithm.*

3. *In liver surgery, liver transplantation, and cirrhosis, evidence is insufficient to recommend PCC over plasma or plasma over PCC for routine perioperative*

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bleeding management. ***We suggest*** *that PCC not be used routinely or empirically to reduce transfusion requirements or to manage perioperative bleeding in this population. PCC could be considered within a protocolized laboratory- or viscoelastic-guided strategy, a clinical trial, or an individualized rescue context when plasma would otherwise be considered but is unavailable or the required plasma volume is clinically unacceptable.*

4. We suggest against *routine empiric early PCC administration in trauma patients at risk of massive transfusion when timely plasma-based resuscitation is feasible. PCC could be considered for urgent VKA reversal in selected patients with demonstrable coagulopathy within a protocolized laboratory- or viscoelastic-guided pathway, or in remote/small-centre settings where plasma-based resuscitation is unavailable or delayed.*

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Recombinant Activated Factor VII (rFVIIa)

Activated Factor VII (FVIIa) was first considered for clinical use as a universal hemostatic agent in the late 1970s [50]. Although it was initially developed and approved for the treatment of bleeding in hemophilia patients with inhibitors, the use of recombinant FVIIa (rVIIa) expanded to off-label treatment for bleeding in surgery, trauma, cardiac surgery, and obstetrics [51-53].

The primary mechanism of FVIIa is to activate Factor X via the FVIIa-tissue factor complex, thereby increasing downstream thrombin generation [54, 55]. FVIIa can also activate Factor X independent of tissue factor on activated platelet and monocyte surfaces [56]. In most (non-hemophilic) patients, FVIIa activates FIX [57]. FIXa, along with FVIIIa, forms the intrinsic tenase complex, which activates Factor X and subsequently increases thrombin generation [58]. Other possible procoagulant mechanisms of action for FVIIa include activation of thrombin-activatable fibrinolysis inhibitor (TAFI) and direct platelet activation [56, 59].

Multiple randomized trials have demonstrated the efficacy of rFVIIa in surgical patients with major bleeding. Initial randomized studies evaluated doses of up to 100-120 ug/kg [60], which were approximately half of the dose used in hemophilia patients with inhibitors who often received doses of ≥200 ug/kg [61]. In various patient populations (liver resection, cardiac surgery, and prostatectomy), rFVIIa reduced red blood cell (RBC) transfusion [60, 62]. In one meta-analysis of seven randomized controlled trials in surgical patients, the use of rFVIIa was associated with reduced odds of RBC transfusion (odds ratio = 0.29; 95% CI = 0.10-0.80).

A landmark RCT comparing placebo, 40 ug/kg, or 80 ug/kg of rFVIIa in cardiac surgical patients with major postoperative bleeding in the intensive care unit showed that rFVIIa was associated with more serious adverse events within 30 days [63]. A key secondary analysis showed that treatment with rFVIIa reduced reoperations for bleeding by almost 50% compared with placebo, although there was no significant difference in effect between 40 ug/kg and 80 ug/kg doses [63]. There was also less use of blood products after treatment in those who received rFVIIa, suggesting an overall reduction in bleeding [63].

Although rVIIa was effective in multiple randomized trials in surgical patients with major bleeding, treatment also increased the risk for thromboembolism. In a systematic review and meta-analysis of 35 randomized trials, most of which enrolled non-surgical patients, rFVIIa treatment was associated with increased risk of arterial thrombosis compared with placebo (odds ratio = 1.68; 95% CI = 1.20 to 2.36) [64]. Recombinant FVIIa was also associated with increased coronary thrombosis (odds ratio = 2.39; 95% CI = 1.39 to 4.09). The risk for thrombosis appeared to be elevated in elderly (age >65) patients [64]. There also appeared to be a dose-dependent risk for thrombosis, with the rate of arterial thrombosis being 6.0% in patients who received less than 80 ug/kg of rFVIIa, 10.3% in those who received between 80 and 120 ug/kg, and 11.9% in those who received more than 120 ug/kg [64].

Given the significant thrombotic risk associated with high-dose rFVIIa treatment, there has been a movement towards using lower-dose rFVIIa treatment and restricting its use in surgical patients with major bleeding. Observational studies of low-dose (≤20 ug/kg)

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rFVIIa in cardiac surgical patients suggest that these doses may be efficacious without increasing thrombotic risk. For these reasons, lower doses are more commonly used in contemporary cardiac surgical practice [65-67]. In a single-center retrospective study of cardiac surgery patients, “early” administration of ultra-low-dose (approximately 10 ug/kg) rFVIIa after heparin reversal during cardiopulmonary bypass was associated with lower allogeneic transfusion and thrombosis rates [68]; however, these single-center data require further validation in an RCT.

In a contemporary meta-analysis of RCTs that included additional surgical populations (urologic, obstetric, orthopedic), rFVIIa use was associated with lower blood loss and fewer allogeneic RBC transfusions in patients undergoing pancreatic, spinal, and prostatectomy surgery, with no increased risk of thrombosis observed [69]. The doses of rFVIIa used in the various studies differed widely, ranging from 20 to 120 ug/kg [69].

Taken together, the current body of evidence suggests that rFVIIa helps reduce bleeding and the need for allogeneic transfusions in surgical patients with major hemorrhage. However, there appears to be a dose-dependent risk of thrombosis with doses greater than 80 ug/kg, particularly in patients over 65 years of age. Lower doses of rFVIIa (approximately 20 ug/kg) are more commonly used in contemporary surgical practice, and most data support a lower thrombotic risk with this dose. It should be noted that most clinical trials using rFVIIa in the setting or surgical bleeding were performed before prothrombin complex concentrate (PCC) was widely available. As PCC appears to have a lower thrombotic risk than rVIIa, the role of rFVIIa in contemporary surgical practice has become limited [70, 71].

Guidance for the use of rFVIIa for perioperative bleeding management

1. ***We suggest*** *that rFVIIa may be considered as a hemostatic therapy in surgical patients when other procoagulant factor deficiencies have been corrected, and refractory microvascular bleeding persists.*

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2. ***We suggest*** *initially using a low dose (20-40 ug/kg) of rFVIIa based on the increased thrombotic risk associated with higher doses.* ***We suggest*** *considering an additional dose of rFVIIa if bleeding persists despite correction of other procoagulant factor deficiencies.*

3. ***We suggest*** *caution if combining rFVIIa with other potent coagulation factor concentrates, such as factor eight inhibitor bypass activity (FEIBA) or PCC, given an increased potential risk for thrombosis. In cases of severe life-threatening bleeding, combination therapy can be considered, but vigilance for thrombosis is warranted, and multidisciplinary risk-benefit analysis should be performed.*

Factor XIII

Two forms of factor XIII (FXIII) concentrate are available: plasma-derived (Corifact®, Fibrogammin® P) and recombinant (rFXIII; catridecacog/Tretten®). Plasma-derived concentrates are highly purified and pathogen-reduced by heat treatment or pasteurization, and contain both FXIII-A and FXIII-B subunits. In contrast, rFXIII consists solely of recombinant FXIII-A_2 homodimers, which bind to circulating endogenous FXIII-B_2 subunits to form functional FXIII-A_2B_2 heterotetramers.

Both agents are FDA-approved for congenital FXIII deficiency, a rare autosomal recessive bleeding disorder characterized by impaired wound healing, spontaneous intracranial hemorrhage, delayed umbilical cord bleeding, and recurrent pregnancy loss [72]. Plasma-derived concentrates remain the standard of care due to greater availability, lower cost, and efficacy in treating both FXIII-A and FXIII-B deficiencies. Conversely, rFXIII is limited by high cost, restricted access, and applicability to FXIII-A deficiency only. Despite theoretical advantages, including lower risk of blood-borne pathogen transmission, the absence of plasma-derived allergens, and reduced potential for neutralizing antibody development, rFXIII is not widely used.

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Although high-quality evidence remains limited, FXIII supplementation has been proposed for the management of perioperative bleeding. FXIII is a critical transglutaminase that, when activated by thrombin in the presence of calcium, covalently cross-links fibrin α- and γ-chains, thereby stabilizing fibrin clots, increasing clot mechanical strength, and conferring resistance to plasmin-mediated fibrinolysis [73]. Acquired FXIII deficiency (levels below 60-70%) has been associated with increased rebleeding risk and transfusion requirements in surgical patients [74-80]. However, whether FXIII supplementation improves clinical outcomes remains uncertain.

A large, multicenter, double-blind, randomized controlled trial (RCT) enrolled 409 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Patients received placebo, 17.5 IU/kg, or 35 IU/kg of rFXIII after CPB. All three groups experienced an approximate 40% decrease in FXIII levels after CPB. Although FXIII concentrations increased in a dose-dependent manner, with 85-95% of rFXIII-treated patients achieving levels above the 2.5th percentile of the normal range versus 49% in the placebo group, no differences were observed in transfusion avoidance rates, total transfusion requirements, blood loss, or clinical outcomes, suggesting that FXIII restoration alone is insufficient to reduce perioperative transfusion in this population [81]. In contrast, a small proof-of-concept RCT in high-risk gastrointestinal cancer surgery demonstrated that intraoperative plasma-derived FXIII (30 IU/kg) preserved ROTEM® clot firmness (MCF declined by 8% versus 38% in placebo; $p = 0.004$) and reduced intraoperative blood loss by 29% ($p = 0.041$). However, the study was terminated early following an interim analysis with the primary endpoint of maximal clot firmness (MCF) reached and only assessed surrogate endpoints (clot stability and blood loss) rather than clinical transfusion rates or patient-centered outcomes [82]. An RCT of 50 patients undergoing pancreatic surgery found that early postoperative FXIII supplementation did not reduce the duration of drain placement in patients with postoperative pancreatic fistula, suggesting no benefit for fistula-related complications [83]. Conversely, a small retrospective study of 40 burn surgery patients showed that correcting preoperative FXIII deficiency (all intervention patients had FXIII activity <60%) significantly reduced red blood cell transfusion requirements (1.95 versus 4.05

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units, p = 0.001). However, the retrospective, unblinded design and small sample size limit generalizability [84].

Safety concerns associated with FXIII use persist. Theoretically, FXIII supplementation may increase the risk of thrombosis. While the safety profile appears favorable in congenital deficiency, the potential for thrombotic complications in acquired deficiency remains inadequately evaluated.

In summary, the benefits of FXIII supplementation for reducing bleeding, transfusion requirements, and improving wound healing remain unproven in acquired FXIII deficiency. Further high-quality, adequately powered trials are needed to establish its role in perioperative management.

Guidance for the use of FXIII for perioperative bleeding management:

1. *We advise against the use of FXIII concentrate for the management of acquired bleeding in perioperative or critical care settings outside of clinical trials.*

Summary and Conclusions

Perioperative bleeding remains a complex and clinically important challenge across cardiac surgery, trauma, organ transplantation, obstetrics, and major non-cardiac surgical procedures. Advances in perioperative hemostatic resuscitation over the past decade have been driven by increasing use of structured bleeding management algorithms, viscoelastic testing, and targeted coagulation factor replacement strategies. As a result, coagulation factor concentrates have been integrated into contemporary perioperative bleeding management.

Current evidence supports the selective use of fibrinogen concentrate, prothrombin complex concentrate (PCC), recombinant activated factor VII (rFVIIa), and, in selected settings, factor XIII (FXIII) concentrate as adjuncts to conventional blood component therapy. These agents offer several practical advantages, including rapid availability,

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standardized dosing, reduced infusion volumes, pathogen inactivation, no need for ABO compatibility, and greater logistical flexibility compared with traditional plasma products, such as plasma and cryoprecipitate. However, important differences exist among these products with respect to mechanisms of action, evidence base, efficacy, safety, thrombotic risk, and optimal clinical application.

Among currently available factor concentrates, the strongest evidence supports targeted fibrinogen replacement in acquired hypofibrinogenemia and selective use of PCC for acquired coagulation factor deficiencies in perioperative bleeding, particularly in cardiac surgery. In contrast, rFVIIa should generally be reserved for rescue therapy due to its dose- and age-dependent thrombotic risk. The role of FXIII supplementation in acquired perioperative deficiency remains incompletely defined. Importantly, available evidence does not support empiric or prophylactic administration of coagulation factor concentrates in the absence of demonstrated coagulation abnormalities or ongoing clinically significant bleeding.

The optimal use of coagulation factor concentrates requires integration into multimodal bleeding management strategies incorporating surgical hemostasis, correction of hypothermia and acidosis, platelet management, antifibrinolytic therapy, and targeted laboratory- or viscoelastic-guided resuscitation. Although increasing evidence supports factor-concentrate-based approaches, important uncertainties remain regarding patient selection, dosing thresholds, comparative effectiveness relative to plasma-based therapy, and thromboembolic safety in selected populations.

Further adequately powered randomized clinical trials are needed across diverse perioperative and critical care settings, including trauma, liver transplantation, obstetric hemorrhage, and non-cardiac surgery. Future investigations should focus on individualized hemostatic resuscitation strategies, optimization of viscoelastic-guided algorithms, comparative effectiveness among products, and patient-centered outcomes.

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