Use of factor concentrates for the management of perioperative bleeding: guidance from the SSC of the ISTH

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Perioperative bleeding is a common complication following major surgery. Despite surgical measures to minimize bleeding, patients develop acquired hemostatic defects as a result of multiple factors that include hemorrhagic loss, consumption, dilution of coagulation factors and platelets, hypothermia, acidosis, and activation of fibrinolytic and inflammatory pathways. Therapeutic approaches for restoring hemostasis include allogeneic blood product administration. However, there is increasing use of clotting factor concentrates that not only include fibrinogen and prothrombin complex concentrate (PCC), but also factor XIII (FXIII) and recombinant activated factor VII (rFVIIa).

In this guidance document, we review available evidence for clotting factor concentrate administration in the management of perioperative bleeding to provide practical guidance for clinicians. The wording used herein to reflect the strength of recommendations is based on a standardized format used in guidance documents by the International Society on Thrombosis and Haemostasis [1]. Thus, the wording «we recommend» indicates a strong consensus among the panel members and/or the availability of high-quality evidence, which the clinician should consider adopting into practice in most cases. The wording «we suggest» reflects a weak guidance statement with moderate consensus among the panel members and/or the availability of lower-quality evidence, which the clinician may or may not adopt.

Fibrinogen concentrates

Fibrinogen is a critical factor for hemostasis in the context of perioperative bleeding [2]. Depending on the country and availability of cryoprecipitate, fibrinogen concentrates (FCs) are often the standard of care in patients with fibrinogen deficiency [2]. The normal plasma fibrinogen concentration ranges from 2 to 4 g L⁻¹, and without supplementation, fibrinogen is the first coagulation factor to fall to critically low levels (<1.0 g L⁻¹) during major hemorrhage [2]. Moreover, a decrease in fibrinogen concentration is a predictor of the severity of the hemorrhage in trauma patients and with postpartum hemorrhage [2]. Multiple in vitro and clinical studies reported that low fibrinogen levels impair fibrin clot strength and that clot strength is restored with fibrinogen repletion [2].

The efficacy of FCs in stopping bleeding remains unproven. Small uncontrolled studies evaluating FCs for perioperative use have yielded conflicting results, but most have been negative [2]. When compared with placebo in seven randomized double-blind studies, FCs failed to reduce bleeding or the need for allogeneic transfusion in cardiac surgery [3–5], urologic surgery [6], obstetric procedures [7], orthotopic liver transplantation [8] and trauma [9]. Conversely, two single-center, randomized trials showed results that were at least partly positive. After complex cardiac surgery, FC administration guided by viscoelastic tests induced a decrease in postoperative bleeding, albeit weakly clinically relevant (300 mL vs. 355 mL), leading to a reduction in allogeneic blood product transfusions [10]. In coagulopathic trauma patients, administration of clotting factor concentrates (primarily FC) guided by viscoelastic tests failed to reduce the
primary endpoint, namely multiple organ failure, but decreased the need for massive transfusion [11]. Of note, positive studies are mainly based on an initial dose of 25–50 mg kg⁻¹, often individualized using viscoelastic tests [2].

However, despite considerable work in this area, there may be several reasons why FC alone is unlikely to be of benefit. They include the use of a single coagulation factor to treat a coagulopathy characterized by a decrease in all factors, prophylactic administration before any hemorrhage, and the mixed inclusion of high and low-bleeding-risk surgeries that may dilute the potential FC efficacy. Further, instead of single preemptive administration, FC should rather be used in patients with major bleeding and as part of multimodal therapy, including other treatments for coagulopathy and bleeding. The use of point-of-care testing should be considered to guide therapy, but this has to be further studied, and the target for repletion remains unknown, even if lower quality studies suggest a target fibrinogen level of 1.5–2.0 g L⁻¹.

Regarding safety, epidemiologic studies suggest a strong association between long-term hyperfibrinogenemia and both arterial and venous thrombosis, but it remains unknown whether hyperfibrinogenemia is only a biomarker of the cardiovascular risk or is a causative mechanism of thrombosis [2]. Nevertheless, in a mouse model, fibrinogen infusion, increasing fibrinogen concentration up to 4 g L⁻¹, directly promoted thrombosis after vascular injury, with a dose-ranging effect, which supports a causative role for short-term hyperfibrinogenemia in thrombosis [12] and suggests the monitoring of fibrinogen concentration and limitation of the amount of fibrinogen concentrates administered. Of note, the FC doses used in clinical studies did not produce significant increases in postoperative plasma fibrinogen concentrations. However, no study has been adequately designed to assess the thrombotic risk of FC supplementation and to account for multiple potential causes of thrombosis in the complex setting of perioperative bleeding.

**Guidance for use of FC for perioperative bleeding management**

*We suggest against FC preemptive administration. We suggest that FC should only be used as part of multimodal therapy.*

*We suggest laboratory assessment of fibrinogen concentration or viscoelastic monitoring of functional fibrinogen before FC administration.*

*We recommend against FC administration if the plasma fibrinogen concentration is over 1.5 g L⁻¹ or if there is no evidence of functional fibrinogen deficiency on viscoelastic point-of-care analysis.*

*If FC is given, we suggest using an initial dose of 25–50 mg kg⁻¹.*

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**Prothrombin complex concentrates (PCCs)**

Non-activated PCCs are lyophilized human plasma-derived vitamin K-dependent coagulation factor concentrates. According to the content of coagulation factors, they are categorized as three-factor PCCs (FII, FIX and FX) and four-factor PCCs (also including FVIII). Several commercial PCC products are available, which differ in their composition of coagulation factors and inhibitors, the presence of heparin and antithrombin, and their purity.

In most jurisdictions, the clinical indications for PCCs are limited to the perioperative prophylaxis and treatment of bleeding in the setting of acquired deficiency of prothrombin complex coagulation factors, such as that caused by vitamin K antagonist therapy. However, the off-label use of PCCs is increasing for the management of trauma and perioperative bleeding based on multiple published but non-validated algorithms [13]. PCC represents an important option compared with fresh frozen plasma (FFP): PCC is immediately available because it does not require ABO compatibility or thawing; it can be rapidly administered; and it is not associated with transfusion-associated circulatory overload or transfusion-related acute lung injury [13]. However, PCC only supplies factors II, VII, IX and X and does not replace fibrinogen or factor V. In addition, PCC is typically administered together with crystalloid or colloid for intravascular volume resuscitation, which may induce hemostatic abnormalities related to dilutional effects on coagulation factors, but also related to interference with platelet activity, decreased activity of von Willebrand factor or impairment of fibrin polymerization.

Administration of PCC for the management of perioperative bleeding is based on low-quality evidence. Whereas preclinical studies in animal models demonstrated that PCC reduced blood loss or improved survival [13], trials in patients with bleeding are lacking. Retrospective studies reported that PCC alone might attenuate bleeding [13]. Five studies assessed the use of PCC as part of a concentrate-based approach guided by a viscoelastic point-of-care device for management of bleeding after trauma or surgery [13]. Although favorable results were reported, the studies were observational and mainly retrospective in design. In the only randomized trial that compared a concentrate-based approach with FFP in trauma patients, only 16% of patients received PCC. Therefore, no conclusion could be drawn about efficacy and safety. There is an urgent need, therefore, for randomized controlled trials to assess PCC for the management of perioperative bleeding.

PCC may be associated with thromboembolic complications, but the risk of PCC-associated thromboembolic events in non-anticoagulated patients is uncertain. Nevertheless, two randomized studies performed in a porcine model of hemodilution and hepatic injury highlighted the thromboembolic risk [14,15]. In the first one, PCC
(35 IU kg\(^{-1}\)) with FC (200 mg kg\(^{-1}\)) reduced blood loss compared with saline, but a fatal thromboembolic complication was reported in 1 of the 10 treated animals [14]. In the second study, animals randomly received PCC (35 or 50 IU kg\(^{-1}\)) or saline. PCC reduced blood loss but thromboembolism was found in all animals treated with 50 IU kg\(^{-1}\) PCC; moreover, 44% of animals also showed signs of disseminated intravascular coagulation (DIC) [15]. These side-effects may be attributable to an imbalance of prohemostatic factors and inhibitors, specifically an insufficient level of antithrombin compared with the potential for thrombin generation [13,15]. Historically, DIC and other thrombotic complications were reported with older PCCs, which contained traces of activated factors in the concentrate. These PCCs were withdrawn but today’s PCCs are still not balanced regarding their pro- and anticoagulants [16]. These data suggest a potential increased risk of thromboembolic complications with PCC, especially with high, repeated or rapidly infused doses, and special caution is advocated with the use of PCC in patients with acquired procoagulant status, including ongoing DIC.

**Guidance for use of PCC for perioperative bleeding management**

*We suggest against the use of PCC as a monotherapy for perioperative bleeding management.*

*We suggest against the use of PCC in bleeding patients with DIC.*

**FXIII concentrates**

Plasma-derived FXIII concentrate and recombinant FXIII (rFXIII) are two forms of FXIII concentrate available for FXIII supplementation [17,18]. The first one is a highly purified, pasteurized, plasma-derived concentrate, whereas the second is a recently marketed recombinant FXIII-A subunit that binds to the endogenous FXIII-B subunit in plasma and forms a stable FXIII heterotramer. Both agents are indicated for patients with congenital FXIII deficiency, which is a rare, autosomal-recessive bleeding diathesis that is associated with impaired wound healing, intracranial hemorrhage and recurrent miscarriages [17]. FXIII supplementation has also been suggested for perioperative bleeding management, although there are few data to support this indication [17]. FXIII is a pivotal enzyme in the coagulation process because once activated it stabilizes clots by cross-linking them and rendering them more resistant to degradation. Acquired FXIII deficiency (defined as a FXIII plasma concentration < 60% of normal) has been reported with perioperative bleeding and postpartum hemorrhage, and several clinical studies have observed an increased bleeding tendency in surgical patients with FXIII deficiency [17,19]. In cardiac surgery, a reduction in FXIII concentration occurs after cardiopulmonary bypass (CPB) and an inverse relationship between FXIII levels and postoperative blood loss has been reported [20]. The association between FXIII deficiency and postoperative hemorrhage has also been assessed in a series of 1264 patients who underwent neurosurgery [21]. Measurement of FXIII activity was performed postoperatively in 34 patients in whom coagulopathy was suspected despite normal platelet counts, fibrinogen levels, prothrombin times and partial thromboplastin times, and eight of them had FXIII deficiency.

As acquired FXIII deficiency and perioperative bleeding are related, a few studies assessed whether FXIII supplementation decreased perioperative bleeding. None demonstrated improved hemostasis or reduced need for other prohemostatic therapies. In a preliminary study of patients undergoing myocardial revascularization, Levy et al. showed that rFXIII at doses of 25–50 IU kg\(^{-1}\) effectively restored FXIII plasma levels to normal after CPB without apparent safety issues [22]. Their data suggested that 35 IU kg\(^{-1}\) may be the appropriate dose for replacement therapy. The efficacy of rFXIII was assessed in a double-blinded, placebo-controlled, multicenter trial: 409 cardiac surgical patients at moderate risk of transfusion received either rFXIII (17.5 IU kg\(^{-1}\) or 35 IU kg\(^{-1}\)) or placebo after CPB [23]. [7] Although rFXIII significantly increased post-CPB FXIII levels, it had no effect on transfusion requirements nor did it influence the rate of surgical re-explosion for bleeding. FXIII supplementation was also assessed in 22 patients undergoing elective surgery for gastrointestinal cancer who were at risk of intraoperative bleeding. Patients were randomized to receive either FXIII (30 U kg\(^{-1}\)) or placebo early during surgery [24]. The study confirmed that although compared with saline, intraoperative FXIII administration maintained clot firmness measured using viscoelastic assays, it had little effect on blood loss and no effect on red blood cell transfusion requirements. No studies have assessed the efficacy of FXIII supplementation in postpartum hemorrhage. Lastly, FXIII supplementation may increase the risk of thrombotic events, but this potential has not been adequately assessed [25]. To summarize, the benefit of FXIII supplementation on bleeding and transfusion requirement remains unproven in the context of acquired FXIII deficiency.

**Guidance for use of FXIII concentrate for perioperative bleeding management**

*We suggest against the use of FXIII concentrate.*

**rFVIIa**

rFVIIa is approved for the prevention and treatment of bleeding events in patients with hemophilia A and B with inhibitors. For this indication, the approved dose is 90 μg kg\(^{-1}\) every 2–3 h until cessation of bleeding. In
patients with congenital FVII deficiency, a rFVIIa dose of 15–30 µg kg⁻¹ every 6 h is recommended until cessation of bleeding, and then every 12 h, and in patients with Glanzmann’s thrombasthenia with antibodies to HLA and/or GPIIb/IIIa, 3 x bolus 80–120 µg kg⁻¹ before and during interventions with 2 h between dosing [26]. rFVIIa is also effective in other inherited platelet disorders (e.g. Bernard-Soulier syndrome and severe storage pool disease). The above-mentioned dosing of rFVIIa should also be used for perioperative management in these patients with rare bleeding disorders.

The off-label use of rFVIIa has been studied in the treatment of severe bleeding after surgery, obstetric procedures or trauma [27]. The rationale for using rFVIIa for such indications is based on its local action at the site of vascular injury. Under physiologic conditions, ~1% of circulating FVII is in the activated form. This concentration is markedly increased after intravenous administration of rFVIIa. This allows interaction of rFVIIa with tissue factor (TF) exposed at sites of vascular injury, and binding of rFVIIa to activated platelets, where it induces TF-independent activation of FX and enhanced thrombin generation. To be effective, rFVIIa requires fibrinogen concentrations ≥1 g L⁻¹, platelet counts ≥ 50 × 10⁹ L⁻¹, pH ≥ 7.2 and body temperature > 34 °C [28].

The efficacy of rFVIIa for these off-label indications remains unclear and randomized controlled trials are scarce. In trauma patients with severe bleeding, rFVIIa reduced transfusion requirements and acute respiratory distress syndrome compared with placebo, but it did not reduce mortality [27]. For adult cardiac surgery, there was a trend toward reduced transfusion requirement with rFVIIa, but there was no mortality difference [27]; however, there was reduced surgical re-exploration in patients who bled postoperatively. In severe postpartum hemorrhage, rFVIIa (60 µg kg⁻¹) reduced the need for specific second-line therapies, including artery embolization, artery ligation and hysterectomy, compared with control [29]. A meta-analysis of randomized trials confirmed that there was no mortality reduction with rFVIIa [27]. Thus, current data suggest that rFVIIa has a potential role in minimizing bleeding or blood product use during major hemorrhage management but overall survival may not improve.

Although several observational studies and case reports suggested that in patients with massive bleeding rFVIIa (one or more boluses of 90–140 µg kg⁻¹) helps to control bleeding, off-label use of rFVIIa has been associated with venous and especially arterial thromboembolic complications [27,29,30], although these complications are very rare in the approved indications (< 1:25 000).

**Guidance for use of rFVIIa for management of perioperative bleeding**

We suggest using rFVIIa in patients with hereditary platelet disorders and HLA or anti-HPA antibodies to control bleeding over transfusion of platelets, as platelet transfusions may induce further alloantibodies.

We recommend against the off-label use of rFVIIa as first-line therapy.

We suggest the use of rFVIIa only if all other options to control hemostasis have failed, with special caution in patients with risk factors for arterial thrombosis (e.g. atherosclerosis, trauma/surgery-induced vessel lesions).

If rFVIIa is used, we suggest that measures should first be taken to increase the fibrinogen > 1.5 g L⁻¹, platelet count ≥ 50 × 10⁹ L⁻¹, pH ≥ 7.2 and body temperature > 34 °C.

**Addendum**

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**Disclosure of Conflict of Interests**

C. M. Samama reports personal fees from LFB and Octapharma, during the conduct of the study. A. Godier reports personal fees from CSL Behring, LFB, Octapharma, Boehringer Ingelheim, Bayer, and Sanofi; and personal fees and non-financial support from BMS Pfizer, outside the submitted work. A. Greinacher reports grants and non-financial support from Aspen, Boehringer Ingelheim, MSD, BMS, Paringenix, Bayer Healthcare, Gore Inc., Rovi, Sagent, and Biomarin/Proensa; personal fees from Aspen, Boehringer Ingelheim, MSD, Macopharma, BMS, Chromatec, and Instrumentation Laboratory; and non-financial support from Boehringer Ingelheim and Portula, outside the submitted work. J. H. Levy has sat on advisory boards or steering committees for Boehringer Ingelheim, CSL Behring, Grifols, and Octapharma, during the conduct of the study; and has also sat on advisory boards or steering committees for Janssen, Pfizer, and Portola, outside the submitted work.

**References**


10 Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A; Surgical Clinical Outcome REsearch (SCORE) Group. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. *J Am Heart Assoc* 2015; **4**: e002066.


