ASA Transfusion Practice 2011R.1
Other Component Working Group (Tanaka, Pivalizza, Smith)

Cryoprecipitate
Cryoprecipitate is prepared by thawing a single unit of FFP at 1° to 6°C. This precipitated, cold-insoluble material is rich in Factor VIII (FVIII), von Willebrand factor (vWF), FXIII, fibrinogen and fibronectin. Cryoprecipitate was originally used for the replacement of congenital deficiency of FVIII (hemophilia A), vWF (von Willebrand disease), FXIII, or fibrinogen, but a plasma-derived or recombinant factor is available for these indications (1-3)(Table 1).
Cryoprecipitate is thus mainly used to manage bleeding due to acquired hypofibrinogenemia (<100–150 mg/dL) in patients undergoing an invasive procedure. Each unit of cryoprecipitate per 10-kg body weight increases plasma fibrinogen by approximately 50 mg/dL when there is no ongoing bleeding, whereas 30 ml/kg of FFP is required to raise plasma fibrinogen level by 1 g/L (4, 5). Although plasma fibrinogen level can be more rapidly restored by cryoprecipitate than FFP, it takes more time to thaw multiple units of cryoprecipitate (i.e., no readily available thawed units). Furhter, no virus-inactivated cryoprecipitate is available, and multiple donor exposures remain a serious concern (6). In this regard, the use of pasteurized plasma-derived fibrinogen concentrates is strongly recommended for patients with congenital afibrinogenemia or dysfibrinogenemia. In many European countries, cryoprecipitate is no longer available, and plasma-derived fibrinogen concentrates are used in many acquired indications (7).
The minimal level of plasma fibrinogen to minimize perioperative bleeding is not well defined. The international guidelines prior to 2009 recommended minimal fibrinogen levels between 80–100 mg/dL (8, 9), a level similar to the management of congenital afibrinogenemia. Higher fibrinogen cut-offs (150–200 mg/dL) are more recently recommended in the European guidelines for perioperative transfusion (10, 11). Recent clinical data demonstrate hemostatic levels of fibrinogen to be 200 mg/dL or above in postpartum hemorrhage (12), coronary bypass grafting surgery (13-15), aortic replacement (16), and cystectomy (17). The therapeutic response to cyoprecipitate or fibrinogen concentrate can be evaluated by measuring plasma fibrinogen (Clauss method) or thromboelastography/thromboelastometry (2).

Plasma-derived and recombinant factor concentrates
For the most congenital bleeding or thrombophilic disorder, plasma-derived or recombinant factor concentrate is preferred over FFP/cryoprecipitate to replace a specific protein. Recombinant proteins have major advantage of not carrying the risk of transmitting viral disease, while modern plasma-derived products are treated with multiple viricidal steps that prevent the transmission of lipid-enveloped viruses. These steps include solvent detergent exposure and nanofiltration as well as pasteurization in the aqueous phase, or exposure to vapor heat as a lyophilized product. Non-lipid enveloped, heat-resistant virus including parvovirus B19, or variant Creutzfeldt-Jakob disease (vCJD, or bovine spongiform encephalopathy; BSE) can be potentially transmitted via plasma-derived products, but the risks should be sufficiently low. The risk of transfusion-related acute lung injury associated with FFP could be minimized by lack of anti-HLA/anti-granulocyte antibodies in plasma-derived factor concentrates (18).

Therapies for Hemophilia and von Willebrand disease
For patients with hemophilia A (FVIII deficiency) and hemophilia B (FIX deficiency), both plasma-derived and recombinant FVIII and FIX concentrates are available for the prevention and treatment of recurrent bleeding. The development of alloantibodies to infused factors is observed in up to 36% of patients with severe hemophilia A, and 3-8% of patients with severe hemophilia B (19). These patients require alternative hemostatic therapies including factor eight bypassing activity (FEIBA) or recombinant activated factor VII (see below). Immune tolerance inductions have been attempted in some cases with inhibitors.

For patients with Willebrand disease (vWD), plasma-derived FVIII products enriched in vWF is indicated for severe type 1 and type 3 variants (quantitative defects) and most type 2 variants (qualitative defects). Most patients with mild forms of type 1 variants respond well to desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP, 0.3 µg/kg iv), which releases both FVIII and vWF from endothelium.
For hemophilia

Prothrombin complex concentrates
Prothrombin complex concentrate (PCC) is a sterile, lyophilized concentrate of FII (prothrombin), FVII, FIX, and FX. Some PCC concentrates contain much lower FVII relative to FII, FIX and FX (referred as 3-factor PCCs). PCCs are derived from pooled human plasma, but multiple steps of viral inactivation are applied in addition to the donor screening. These products were historically used for FIX replacement, and thus the vial potency labeling is based on IU (international units) of FIX. The contents of FII, FIX, FX, protein C, protein S, heparin and antithrombin (AT, formerly ATIII) vary among different PCCs (20). Three-factor PCCs are indicated in the prevention or treatment of congenital FX or prothrombin deficiency. In Europe and Canada, PCCs containing clinically relevant FVII levels (4-factor PCC) are used for acute reversal of vitamin K antagonists (4-factor PCCs are not licensed for warfarin reversal in the US)(21). PCCs can be quickly reconstituted with sterile water (20 ml per 500 IU), and are intravenously administered at a rate of 6–10 ml/min. For example, 2000 IU of 3-factor PCC (i.e., 80 ml) can be administered within 15 min, and factors II, IX, and X are increased by 40–80% without lowering hematocrit and platelet count (22, 23).
The off-label use of 3-factor PCCs in acute warfarin reversal has been reported, but the recovery of PT/INR seems to be incomplete without additional FFP due to low FVII content (21). The recovery of PT/INR does not reflect the restoration of thrombin generation (24), and thus clinical hemostasis may not be achieved (25). The use of PCCs in dilutional coagulopathy due to massive transfusion (26), post-cardiopulmonary bypass (27), and coagulopathy associated liver failure (28) has been reported. PCCs are considered to be an acceptable alternative to FFP for some Jehovah's Witness patients (29). The optimal dosing and risk-benefit profiles are not yet known, and one should consult with experienced clinicians before using these agents alone or in combinations.

Recombinant activated factor VII (rFVIIa)
The use of rFVIIa has been approved by FDA for the following indications:

- Treatment of bleeding and prevention of bleeding in surgical or invasive procedures in patients with hemophilia A or B who have antibodies to factors VIII, IX or with acquired hemophilia

- Treatment of bleeding and prevention of bleeding in surgical or invasive procedures in patients with congenital FVII deficiency

Since the initial report of rFVIIa use in a trauma patient (30), there have been numerous case reports, reviews and meta-analyses of off-label rFVIIa use in multiple bleeding and surgical indications (31). Recombinant proteins such as rFVIIa and erythropoietin are generally acceptable to those who refuse transfusion of blood components.

Routine uses in either the prevention or treatment of bleeding in trauma and surgical patients is not recommended due to the lack of evidence to support the efficacy and safety of rFVIIa therapy. However, the limited numbers of RCTs do suggest some benefits in patients with refractory, life-threatening hemorrhage including those with traumatic injuries and after cardiac surgery. Use should be guided by individual patient risk-benefit analysis, specifically with the potential risk factors recently identified for arterial thromboembolic events. The use of rFVIIa may increase the risk of arterial thrombosis, primarily coronary events (odds ratio 1.68)(32). The risks of thrombosis also increase with the age (OR 2.4 if > 65 years, and 3.0 if > 75 years), and with higher rFVIIa dosage (> 80 µg/kg).

PT/INR is rapidly shortened after rFVIIa administration (25, 33). Normal PT/INR does not necessarily reflect the hemostatic efficacy in congenital or non-congenital hemorrhagic disorders. The use of thromboelastograph (TEG) and rotation thromboelastometry (ROTEM) has been anecdotally reported, but no standardization for monitoring rFVIIa exists. In hemophilia patients with inhibitors, kaolin activation seems to be more reproducible on TEG/ROTEM than diluted thromboplastin (tissue factor) as a trigger (34).

In the context of limited level 1A evidence with prospective randomized controlled trials (RCTs) in several of these clinical scenarios, there has recently been increasing appreciation for the potential risks of rFVIIa therapy, culminating in a black-box warning for serious thrombotic events). Perioperative and critically-ill patients are often depleted of endogenous coagulation inhibitors such as antithrombin (AT), protein C, protein S, and endothelial thrombomodulin (35). The clinical context of rFVIIa usage is thus vastly different between hemophiliac and (non-hemophiliac) surgical patients. Hemostatic activity of rFVIIa ultimately depends on the available prothrombin and fibrinogen. These factors should be sufficiently replaced by transfusion of plasma or cryoprecipitate before administering rFVIIa. Hypothermia and acidosis should be corrected as they also reduce the efficacy of rFVIIa. The following summary for "off-label" rFVIIa usage is based on the limited numbers of randomized clinical trials (RCTs):

Major trauma
Despite advances in the diagnosis and management of traumatic coagulopathy, one-third of trauma deaths result from hemorrhage and rFVIIa therapy may effect and improve

hemostasis in this population. In an early study, rFVIIa use (200, 100, 100 µg/kg – max 3 doses) reduced 48h RBC requirement by 2.6 units compared with placebo (p=0.02) in the blunt injury, but only showed a trend for reduced 48h RBC transfusion (1.0 units, p=0.10) in the penetrating injury. Similarly, the incidence of massive transfusion (> 20 units RBC) was reduced from 20 of 61 (33%) patients in the placebo group to 8 of 56 (14%) in the rFVIIa group. This represents a relative risk reduction of 56% (95% CI, 9–79%; p<0.03). Reduced multi-organ failure was significant in the blunt trauma (ARDS) but not in the penetrating trauma group (p=0.09)(36). Thromboembolic adverse events were similar between rFVIIa and placebo groups.

A recent larger, multi-center study (the CONTROL trial, same doses as initial study) was terminated early because of unexpected low mortality, high likelihood of futility in demonstrating the primary endpoint (30 day mortality) and difficulty consenting and enrolling severely injured patients (37, 38). Total allogeneic blood product use, but not mortality, was decreased with rFVIIa. There was no difference in arterial and venous thrombotic events in the rFVIIa vs. placebo. In patients undergoing reconstruction surgery for traumatic pelvic fractures, there was no change in blood loss, transfusion or outcome with no adverse events related to rFVIIa (90 µg/kg, max 2 doses)(39). The post-hoc analysis of a subset of polytrauma patients with traumatic brain injury (TBI) was not associated with changes in intensive care unit stay or mortality (40).

Cardiac surgery
Use of recombinant factor VIIa concentrate may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB (Level of evidence B)(29).
In a pediatric congenital heart surgery population, small dose (40 µg/kg, max 3 doses), rFVIIa administration after protamine did not affect blood loss, transfusion or outcome (41). In a small adult cardiac surgery study (20 patients, 90 µg/kg after protamine), there were no differences in outcome in the rFVIIa arm (42). Given the paucity of data, a Canadian consensus group recommended against prophylactic or routine use in cardiac surgery but suggested a smaller initial dose (35-70 µg/kg) when indicated (43). A recent study of bleeding patients after cardiac surgery identified fewer reoperations for bleeding and decreased allogeneic blood transfusions (in both 40 and 80 µg/kg groups) with a non-statistically significant increase in adverse events (44).

Intracranial hemorrhage (ICH)
An initial study of rVIIa (40, 80 or 160 µg/kg) within 1 hour of baseline CT scan showed smaller change (volume and %) in volume of ICH with improved functional outcome and mortality (45). A subsequent large follow-up study by the same investigators (FAST trial) confirmed the reduced hematoma expansion in the 80 µg/kg group (not the 20 µg/kg) but did not demonstrate improved outcome (46).

Cirrhosis, Liver Transplantation
Cirrhotic patients often demonstrate complex coagulopathy which affects both procoagulant and anticoagulant elements. Prolonged PT or INR does not necessarily indicate the hypocoagulable state (47). The initial and repeat investigations of rFVIIa in cirrhotic patients with upper gastrointestinal (48), and variceal bleeding (49)

demonstrated no benefit in the composite end-points of bleeding and transfusion. Use of a single dose (20, 40 or 80 mcg/kg) prior to liver transplantation (LT) similarly did not affect transfusion requirements (50), although a study with more frequent dosing (60 and 120 µg/kg repeated every 2 hours) did show a small decrease in the number of transfused patients (51).

Anticoagulant protein concentrates
Antithrombin (AT) is a serine protease inhibitor which mainly regulates plasma thrombin and FXa activity. Hereditary deficiency of AT is inherited as an autosomal dominant trait. Affected individuals have plasma AT activity of 40–60% of normal; thus plasma half-lifes of thrombin and FXa are prolonged (52). The increased risk of venous thrombosis has been reported in patients with low AT levels in pregnancy, major surgery, and trauma. Acquired AT deficiency may be observed in cardiovascular patients who had been preoperatively treated with intravenous heparin (53), or in leukemia patients who received asparaginase (54). Heparin insensitivity is often associated with low plasma AT activity. There is sufficient evidence (Level of evidence A)(29) that the use of AT concentrates improves heparin anticoagulation more efficiently than 2 units of FFP (55, 56). Currently both plasma-derived (Thrombate) and recombinant (ATryn) concentrates of AT are available. Recombinant AT is produced as a recombinant human protein in the milk of transgenic goats; the half-life of recombinant AT is significantly shorter than plasma-derived AT (11-hr vs. 60-hr)(57). A prophylactic treatment with AT concentrate is indicated for patients with hereditary AT deficiency who have a history of thromobembolism or are undergoing surgical or obstetrical procedures associated with a high incidence of thromboembolism.

Protein C concentrate
Protein C is a vitamin K-dependent zymogen similar to prothrombin, FVII, FIX, and FX. Commercial PCC products contain smaller amounts of protein C and protein S relative to FIX (**Table 2**), but these products are not appropriate for thrombophilia associated with hereditary protein C deficiency. Homozygous protein C deficiency in newborns manifests with purpura fulminans which causes thromboses in small vessels and skin necrosis (58). The incidence of venous thromboembolism is 8 to 10-fold higher in individuals with heterozygous protein C deficiency compared to the general population (59).
For the prevention and treatment of purpura fulminans and venous thrombosis, the lyophilized, non-activated protein C concentrate (Ceprotin) is available for intravenous iThe infectious risks of plasma-derived protein C is very low due to viral inactivation steps including polysorbate-80, vapor-heat and ion exchange chromatography. The precautions for the use include bleeding, sodium overload, rare allergic reactions and heparin-induced thrombocytopenia (the concentrate contains trace amounts of heparin).
Plasma protein C is activated by thrombin bound to endothelium-bound thrombomodulin. Elevated thrombin activity in systemic circulation thus increases protein C activation as observed in thrombophilia (60), sepsis (61), and traumatic injury (62). Activated protein C with protein S down-regulates activated FV and FVIII, and exerts anti-inflammatory and cytoprotective functions by modulating endothelial protein C receptor and protease-activated receptor-1 (PAR-1, thrombin receptor)(63). Anti-inflammatory effects of

activated protein C (recombinant) may be beneficial in patients with severe sepsis (APACHE score > 25), but serious bleeding is the major side effect (64).

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Table 1: **Plasma levels and Half-lifes of Plasma Coagulation Factors**

	Level (µM)	Half-life (h)	Available concentrate(s)
Fibrinogen	7.6	72 – 120	pd-fibrinogen, cryoprecipitate
Prothrombin	1.4	72	PCC, FEIBA
Factor V	0.03	36	None
Factor VII	0.01	3 – 6	pd-FVII, r-FVIIa, PCC*, FEIBA
Factor VIII	0.00003	12	pd-FVIII, r-FVIII
Factor IX	0.09	24	pd-FIX, r-FIX, FEIBA
FX	0.17	40	pd-FX, PCC, FEIBA
Factor XI	0.03	80	pd-FXI
Factor XIII	0.03	120 – 200	pd-FXIII, r-FXIII, cryoprecipitate
vWF	0.03	10 – 24	pd-vWF, r-vWF, cryoprecipitate
Protein C	0.08	10	pd-Protein C, PCC*
Protein S	0.14	42.5	PCC*
Antithrombin	2.6	48 – 72	pd-antithrombin, r-antithrombin

Adapted from Bolliger, et al.(35) with permission.
Abbreviations: FEIBA = Factor eight inhibitor bypassing activity; PCC = prothrombin complex concentrate (*some PCC products contain minimal levels of FVII, protein C and S; see Table 2); pd = plasma-derived; r = recombinant; vWF = von Willebrand factor

Table 2: **Contents of Commercial Prothrombin Complex Concentrates in the North America**

Product	Manufacturer	Factor II %	Factor VII %	Factor IX %	Factor X %	Protein C U/ml	Protein S U/ml	Antithrombin U/ml	Heparin U/ml
Bebulin*	Baxter	120	13	100	139	Present	Present	Not in label	<0.15 U per IU of FIX
Beriplex	CSL Behring	111	57	100	150	15-45	13-26	0.2-1.5	0.4-2.0
Octaplex	Octapharma	98	66	100	96	7-32	7-32	Not in label	Not in label
Profilnine*	Grifols	148	11	100	64	Not in label	Not in label	Not in label	Not present

Each PCC vial is labeled according to the FIX content in International Units (IU). The contents of other procoagulant factors are shown relative to FIX (e.g., one 500 IU vial of Bebulin contains 65 IU of FVII and 600 IU of FII).

Bebulin and Profilnine contain therapeutic levels of prothrombin (FII), FIX, and FX, but non-therapeutic levels of FVII; thus they are called 3-factor PCCs. Beriplex and Octaplex are 4-factor PCCs containing sufficient FII, FVII, FIX, and FX.

*FDA-approved PCCs are indicated for congenital FIX deficiency (hemophilia B), FX deficiency or prothrombin (FII) deficiency.