BJA

British Journal of Anaesthesia, 119 (3): 354–68 (2017)

doi: 10.1093/bja/aex198
Advance Access Publication Date: 23 August 2017
Review Article

REVIEW ARTICLE

Perioperative management of rare coagulation factor deficiency states in cardiac surgery

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Abstract

Rare bleeding disorders (RBDs) include the hereditary deficiency of fibrinogen, factor (F)II, FV, FV + FVIII, FVII, FX, FXI or FXIII. RBDs do not confer a protective effect against atheromatous plaque formation, and thus the need for cardiovascular (CV) surgery in RBD patients is expected to increase with improved healthcare access (diagnosis and management) and longevity of the population. Clinical data regarding the management of RBDs in this setting are sparse, but the perioperative care team is obliged to gain a better understanding on available biological and pharmacological hemostatic agents. Perioperative management of RBDs in CV surgery is further complicated by heparin anticoagulation, haemodilution, and consumption of procoagulant and anticoagulant proteins associated with cardiopulmonary bypass (CPB). The aims of this review are to summarize pathophysiology of RBDs and laboratory monitoring pertinent to CV surgery, available factor replacement agents, and to provide the framework for perioperative coagulation management of RBD patients.

Key words: blood coagulation factors; blood transfusion; coagulants; thoracic surgery

Major bleeding requiring re-exploration occurs in about 3–14% patients undergoing various types of cardiovascular (CV) surgery.[1–3] Coexisting bleeding disorders can further complicate perioperative coagulation management. Multi-disciplinary approaches and careful surgical planning are thus crucial to prevent major bleeding, massive transfusion, and associated complications after CV surgery.[4] There have been numerous reports on the perioperative management of haemophilia, and von Willebrand disease (VWD).[5] The hereditary deficiency of fibrinogen, factor (F)II, FV, FV + FVIII, FVII, FX, FXI or FXIII is considered a rare bleeding disorder (RBD) (Table 1).[6–8] Diagnostic criteria, replacement therapy, and perioperative management of RBDs are not as standardized as haemophilia and VWD.[7–9] In recent years, our knowledge base and clinical management of RBDs have been significantly improved by early screening,[10] and shared medical information among the RBD networks.[6 7] Although RBDs are presumed to reduce the risk of thrombotic vascular occlusion, coronary atherosclerosis and plaque rupture seem to develop similarly between haemophilia and non-haemophilia subjects.[11–14] With the increasing globalization and longevity of the population, the need for CV surgery in patients with RBDs is expected to increase. CV procedures are often associated with major blood loss and haemodilution with the use of cardiopulmonary bypass (CPB). Multifactorial coagulopathy can develop, and thus it is important to better understand the bleeding risk and replacement strategies for RBDs in this setting.

The aims of this review are: i) to discuss the pathophysiology and laboratory monitoring of RBDs, ii) to review the published RBD cases pertinent to CV surgery, and iii) to summarize currently available replacement therapies, and perioperative coagulation management strategies.

Editorial decision: April 23, 2017; **Accepted:** May 27, 2017

Table 1 Bleeding symptoms of rare bleeding disorders. *Treatment effect could not be ruled out; †Percenages were calculated on the basis of the numbers of procedures; ‡Percentage was calculated based on one patient. Abbreviations: GI, gastrointestinal; CNS, central nervous system. Reprinted with a permission from: What are Rare Clotting Factor Deficiencies? 2009, World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1337.pdf (accessed August 3, 2017)

Symptom	Factor I	Factor II	Factor V	Factors V+VIII	Factor VII	Factor X	Factor XI	Factor XIII		
Nosebleed	common	common	common	occasional	common	common	common	common	rare	0–10% of patients
Easy bruising	common		common	common	common	common	common	common	occasional	10–30% of patients
Heave or prolonged menstrual bleeding	common	common	common	common	common	occasional	common	occasional	common	>30% of patients
Blood in urine	Absent	rare	Absent	Absent	rare	occasional	Absent	occasional	Absent	No bleeding symptom
GI bleeding	occasional	occasional	occasional	Absent	occasional	common	occasional	occasional		Insufficient data
Joint bleeding	common	common	rare	rare	occasional	common	common	common		
Muscle bleeds	common	common	occasional	occasional	occasional	common	Rare	occasional		
Umbilical cord bleeding	common	occasional	Absent	Absent	rare	common	Absent	common		
CNS bleeding	occasional	rare	rare	Absent	occasional	occasional	Absent	common		
Bleeding from mouth/gums	common	common	common	common	common	common	occasional	common		
Bleeding during pregnancy or childbirth*	Absent		Absent	Absent	occasional	Absent‡	Absent	Absent‡		
Major surgery†	occasional	occasional	occasional	common	occasional	common	common	Absent		
Minor surgery†	common	occasional	occasional	common	common	common	common	common		
Other	rare		Rare	occasional	Absent	occasional	Rare	Absent		

General considerations for RBDs

RBDs are generally inherited in an autosomal recessive fashion. The majority of RBDs is reported as a homozygous or double heterozygous mutation with estimated prevalence from 1:500,000 to 1:2 million. This is in contrast to symptomatic autosomal dominant VWD with a prevalence of 1:10,000 to 1:50,000.[15] FVII and FXI deficiencies are the most prevalent RBDs (37.5% and 26.5%, respectively), followed by deficiencies of fibrinogen, FV, and FX (8 to 9%) and FXIII (6%).[9]

It is common to make an assumption that residual coagulant factor activity inversely correlates with bleeding risk, but significant variability in symptoms exists among different RBDs (Table 2).[6 8] It is thus important to assess each patient with a RBD individually by comprehensive history taking, physical examination, and laboratory testing.

Cardiovascular disease and antithrombotic therapy in RBDs

Ischaemic heart disease (IHD) has been reported as an important cause of morbidity and mortality in the ageing haemophilia population.[11–14]

Early stages of atherosclerotic plaque formation may be delayed by coagulation factor deficiency,[16 17] but it generally does not prevent CV disease. The presence of typical risk factors, such as hypertension and diabetes, strongly influences the incidence of CV disease and subsequent mortality.[18]

Treatment algorithms for IHD in patients with RBDs should follow evidence-based guidelines for the general population, and for haemophilia patients.[5 19] In haemophilia patients undergoing percutaneous coronary interventions (PCI), a factor replacement target greater than 80% is used for 48 h to reduce bleeding risks associated with heparin and dual antiplatelet therapy.[20] Use of bare metal stents is preferred over drug-eluting stents for a shorter duration of dual antiplatelet therapy in high bleeding risk patients.[5] However, drug-eluting stents with enhanced endothelialisation are currently in development, and may prove to be safe in RBD patients with IHD.[21]

Maintenance of trough factor activity greater than 30% for the duration of dual antiplatelet therapy, and 5–10% thereafter are recommended for haemophilia patients.[5 19 22] Target factor activity in RBD should be individualized per case basis because significant variability in severity and symptoms exists among different RBDs (Tables 1 and 2).

Laboratory testing for RBDs

Standard diagnostic tests

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the most common screening tests for RBDs (Table 2). PT and aPTT are also the basis of 1-stage clotting assays to quantify residual factor activity (PT-based for FII, FV, FVII, FX, and aPTT-based for FVIII, FIX, FXI).[23] The results of 1-stage clotting assay is expressed as clotting activity (e.g. FVII:C) in %, or international units per dL (IU/dL). Plasma mixing test is useful when acquired factor inhibitors or non-specific antibodies (lupus anticoagulant) are suspected. In the case of an isolated factor deficiency, 1:1 mixing of the patient's and normal plasma corrects PT or aPTT, and non-correction calls for further testing for factor inhibitors or lupus anticoagulant.[24] Chromogenic and fluorogenic assays are also available for some factors (e.g. FII, FVIII).[25] The distinction of quantitative (type I) *vs*

Table 2 Haematological abnormalities and coagulant activities associated with bleeding for haemophilia and RBDs. RBD: rare bleeding disorder; ↔: no change; ↑: elevated; ↓: decreased; U.D., undetectable level. *FI: fibrinogen deficiency includes afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia; PT/aPTT may be normal in hypo- or dysfibrinogenemia. †Trough levels recommended to maintain asymptomatic state[7]

	Factor deficiency								
Test	**FVIII**	**FI***	**FII**	**FV**	**FV/VIII**	**FVII**	**FX**	**FXI**	**FXIII**
PT	↔	↑ or ↔	↑	↑	↑	↑	↑	↔	↔
aPTT	↑	↑ or ↔	↔	↑	↑	↔	↑	↑	↔
TT	↔	↑ or ↔	↔	↔	↔	↔	↔	↔	↔
Fibrinogen	↔	↓ or ↔	↔	↔	↔	↔	↔	↔	↔
Bleeding symptom	Coagulant factor activity in % (FI in g/L) associated with symptom								
Mild†	>5	>1	>10	≥10	>40	>20	>40	20–65	≥30
Moderate	1–5	0.1–1	≤10	<10	20–40	10–20	10–40	15–20	<30
Severe	<1	U.D.	U.D.	U.D.	<20	<10	<10	U.D.	U.D.

qualitative (type II) deficiency is important for some RBDs (e.g. dysfibrinogenemia), and enzyme-linked immunosorbent assay (ELISA) is utilized to quantify antigen concentrations.

The Clauss fibrinogen assay is most commonly used to evaluate fibrinogen (FI) deficiency.[26] Functional FXIII activity can be assessed by chromogenic or fluorogenic assay, whereas clot solubility assay is poorly standardized and is only sensitive to severe FXIII deficiency.[7 27]

The above tests are central to the diagnosis and treatment of haemorrhage associated with RBDs. However, they are not well suited for rapid decision making (<15–20 min) required for perioperative replacement therapy. Further, high-dose heparin (>2 U/ml) during (CPB) renders PT and aPTT impractical.[28 29]

Adjunct coagulation assays

Viscoelastic coagulation tests (VCT), thrombelastography (TEG®, Haemonetics, Niles, IL), and rotational thromboelastometry (ROTEM®, TEM Innovations, Munich, Germany), have been extensively used in the haemostasis management during CV surgery.[2 30–32] Availability of heparin-neutralized tests makes VCTs useful in detecting gross coagulation abnormality during anticoagulation on CPB.[29] VCTs are most applicable in fibrin polymerization disorders. Thus qualitative and quantitative defects of fibrinogen can be monitored on these tests.[33] Severe FXIII deficiency also decreases stable fibrin polymerization on VCTs.[27 34] However, VCTs are global coagulation tests, and their utility is limited by non-specificity for most RBDs as a result of the presence of platelets, and potent coagulation activators used in different tests.[35–38]

Thrombin generation (TG) measurements by quantifying the cleavage of a fluorogenic thrombin substrate are available to assess residual coagulation factor activity, and bleeding phenotypes for various RBDs.[38–44] Assay variables (e.g. tissue factor concentration, platelet-poor or platelet-rich plasma) are not yet standardized for RBDs, and it is mainly performed at specialized haemophilia centres.[45]

Influences of CPB technique on coagulation factor levels

Initiation of extracorporeal circulation requires the priming (pre-filling) of the CPB circuit. The standard volume for adult circuit priming is about 1000–1800 ml.[46–50] Haemodilution of coagulation factors occurs because of the priming and other fluid administration (e.g. cardioplegia) during CPB, and coagulation factors are typically decreased by 30–50%.[46–49] There are several techniques to reduce haemodilution associated with CPB (Table 3). Intraoperative autologous blood collection before CPB spares the portion of coagulation factors and platelets from being consumed or damaged during CPB. Preservation of haemostasis by autologous blood collection is volume dependent (≥800 ml).[51] Retrograde autologous priming is a perfusion technique to lower the priming volume.[52 53] After placement of aortic cannula, the patient's own blood is drained into the CPB reservoir, and the original priming solution is discarded (i.e. net priming volume, 500–800 ml). Lastly, continuous ultra-filtration is effective in mitigating haemodilution by removing excess volume during CPB. Use of cell salvage unit is only effective for the recovery of erythrocytes from the shed blood, resulting in the loss of plasma coagulation factors and platelets.[54]

Preoperative therapeutic plasma exchange (TPE) can be used to replace deficient coagulation factor(s) if no factor concentrate is available, or there is a concern for volume overload from plasma transfusion.[55 56] TPE is also used to remove circulating inhibitors (antibodies) from the patient's blood.[55 57] One to 1.5 plasma volume runs of TPE generally remove 63–78% of alloantibodies, and three runs of TPEs can achieve 90% removal of antibodies.[58] Allogeneic plasma is used as an exchange fluid because TPE using 5% albumin results in the depletion of coagulation factors and inhibitors.[59 60]

Clinical features of RBDs

Reduced fibrin polymerization

Fibrinogen deficiency

Fibrinogen (Factor I) is the most abundant coagulation factor in human blood, and it plays crucial roles in haemostasis, fibrinolysis, and wound healing.[61 62] Three polypeptide (Aα, Bβ, and γ) chains comprising the fibrinogen molecule are encoded by separate genes (FGA, FGB, and FGG). Fibrinogen disorders include both quantitative (afibrinogenemia and hypofibrinogenemia), and qualitative defect (dysfibrinogenemia).[63] Afibrinogenemia is a RBD with an estimated incidence of one in one million, but the incidence may be higher in regions with high consanguinity.[63] Afibrinogenemia (FI < 0.1 g/L) is typically diagnosed by umbilical cord bleeding in the newborn.[63] Ecchymosis, epistaxis,

Table 3 Perioperative management of cardiac surgical patients with coagulation factor deficiency. Abbreviations: RBD, rare bleeding disorder; PK, pharmacokinetic; IAB, intraoperative autologous blood collection; RAP, retrograde autologous priming; SCD, sequential compression device; PLT, platelet concentrate; FC, fibrinogen concentrate; Cryo, cryoprecipitate (limited availability in UK and North America); POD, postoperative day; LMWH, low-molecular weight heparin; TPE, therapeutic plasma exchange; TEG, thrombelastography; ROTEM, rotational thromboelastometry; VKA, vitamin K antagonist

	Management	Intervention(s)
Preoperative period	Anaemia management	Iron therapy
	Assess bleeding risk	Coagulation panel
		Factor level, inhibitor titre
		PK study of factor concentrate or TPE
	Multidisciplinary care team	Detailed plans on surgery/CPB, hemostatic agents, laboratory monitoring
	Plasma exchange	If factor concentrate unavailable, or if inhibitor present
Intraoperative period	Factor replacement	Preop factor concentrate or plasma; top-up dose after CPB to compensate for haemodilution
	Blood conservation for Surgery/CPB	IAB, cell salvage
		RAP, miniaturized circuit, ultrafiltration
		Antifibrinolytic therapy
		Desmopressin
		Topical hemostatics
	Transfusion	TEG/ROTEM during rewarming to guide PLT and FC/Cryo after CPB
Postoperative period	Factor replacement	High factor level till POD three (removal of drain & pacer leads); lower dose of factor concentrate till POD7-10
	Thromboprophylaxis	Anticoagulation (LMWH) during high-level factor replacement
		VKA or alternative anticoagulant for three months after valve replacement
		Early ambulation, SCD
		Low-dose aspirin if indicated
	Follow-up	Factor level, inhibitor titre

oromucosal, muscle and joint bleeds are common (Table 1). Menorrhagia, spontaneous abortion, and postpartum haemorrhage have been reported.[63 64] Paradoxical arterial and venous thromboembolic events have been reported in afibrinogenemia with or without fibrinogen replacement or co-inherited thrombophilia.[65 66] There is some evidence that lack of fibrinogen or fibrin increases circulating thrombin, and distal embolization of platelet aggregates.[67 68]

Bleeding symptoms in hypofibrinogenemia (FI, 0.1–0.8 g/L) tend to be mild, and usually occur after surgery or major trauma.[6] There is an association between severity of bleeding, and residual fibrinogen concentration.[8] It is recommended to maintain at least 1 g/L to prevent spontaneous bleeding.[7 33] Clinical phenotype of dysfibrinogenemia is less predictable than hypofibrinogenemia. Half the patients remain asymptomatic, and the remaining patients present with either bleeding or thrombosis.[69]

Laboratory testing. Afibrinogenemia and severe hypofibrinogenemia cause prolongations of PT, aPTT, and TT (Table 2). Results of these tests should normalize *in vitro* with 1:1 mixing of normal plasma and patient plasma in the absence of an inhibitor. ACT can be infinitely prolonged in the presence of severe hypofibrinogenemia, but it does not guarantee therapeutic heparin concentrations for CPB. Standard heparin monitoring is feasible when fibrinogen concentrations are preoperatively corrected to 0.8–1 g/L. The anti-Xa heparin assay is unaffected by hypofibrinogenemia, but it is impractical for intraoperative heparin monitoring. Functional fibrinogen (TEG®) and FIBTEM (ROTEM®) are clinically useful in monitoring intraoperative fibrinogen changes.[29 70 71]

Perioperative Management. Perioperative bleeding is a major concern during and after CV surgery. Asymptomatic patients with hypofibrinogenemia or dysfibrinogenemia may develop bleeding after major surgery.[6] Fresh frozen plasma (FFP), and thawed plasma are ineffective as a source for fibrinogen,[72] and increase the risk of volume overload in CV patients.[73] There are several human plasma-derived fibrinogen concentrate (FC) products available (Table 4), and these pathogen-inactivated, lyophilized products are preferred to non-specific replacement therapy with allogeneic plasma or cryoprecipitate.[74] Development of an inhibitory antibody to fibrinogen is rare.

An initial FC dose of 60–70 mg/kg achieves plasma concentrations of 1.3–1.5 g/L in afibrinogenemia and severe hypofibrinogenemia with a median half-life of three to five days.[33 75 76] Additional FC doses may be given according to plasma concentrations as follows;

$$\text{FC dose(mg/kg)} = [\text{target fibrinogen(g/L)} - \text{current level(g/L)}] \times 100 \div 1.7$$

Acquired fibrinogen deficiency is common in patients without RBDs after CV surgery, but optimal haemostatic fibrinogen concentrations after CPB remain controversial.[77–79] FIBTEM clot firmness (A_{10}, 8–10 mm) has been clinically used to guide fibrinogen supplementation with FC or cryoprecipitate.[2 32] FIBTEM-A_{10} of 8–10 mm corresponds to a plasma fibrinogen at 1.5–2 g/L, which appears to reduce the risk of major postoperative bleeding.

Perioperative thromboembolic risks should be carefully considered in fibrinogen-deficient patients. In one 22-yr-old male with afibrinogenemia who underwent CPB for suspected aortic valve vegetation, fibrinogen was preoperatively normalized with 10 g of FC to >2 g/L (Table 5).[80] Heparin anticoagulation was concurrently administered because of acute aphasia and right

Table 4 Commercially available factor concentrates for factor replacement. Abbreviations: N.A., not applicable; N.R., not reported; S/D, solvent-detergent treatment; nanofilt, nanofiltration; AT, antithrombin; PC, protein C; PS, protein S. *Only available in the form of prothrombin complex concentrate which contains therapeutic amounts of factors II, IX, and X, and various amounts of factor VII

		Unit dose per vial	Reconstituted concentration	Bolus dose for major bleed	Recovery % per unit/kg	Half-life (h)	Storage temp (°C)	Pathogen reduction	Anticoagulant content(s)
Fibrinogen concentrate									
RiaStap	CSL Behring	900–1300 mg	18–26 mg/ml	70 mg/kg	1.7 mg/dL	78.7	2–25	Pasteurized	No heparin
FibClot	LFB	1500 mg	15 mg/ml	50 mg/kg	2.3 mg/dL	69.3	2–25	S/D	No heparin
Fibryna	Octapharma	700–1300 mg	14–26 mg/ml	70 mg/kg	1.8 mg/dL	75.9	2–25	S/D, nanofilt	No heparin
Factor XIII concentrate									
Corifact	CSL Behring	250 or 1250 IU	62.5 IU/ml	40 IU/kg	2.0%	137–170	2–8	Pasteurized	No heparin
Tretten	NovoNordisk	2000–3125 IU	667–1042 IU/ml	35 IU/kg	1.7%	122–170	2–8	N.A.	No heparin
Factor VII concentrate									
NovoSeven	NovoNordisk	1,2,5 or 8 mg	1 mg/ml	15–20 μg/kg	3.8%	2.1	2–25	N.A.	No heparin
Factor FVII	Shire	600 IU	60 IU/ml	20–30 IU/kg	1.5%	3.2	2–8	Vapor heat	Trace heparin
Factor XI concentrate									
Hemoleven	LFB	1000 IU	100 IU/ml	15 IU/kg	2.0%	45.5	2–8	S/D, nanofilt	Heparin 4.5/AT 4 U/ml
Factor XI	BPL	1000 IU	100 IU/ml	15 IU/kg	2.2%	52	2–8	Dry heat	Heparin 10/AT 102 U/ml
Factor X concentrate									
Coagadex	BPL	250 or 500 IU	100 IU/ml	25–40 IU/kg	2.1%	29.4	2–30	S/D, nanofilt	No heparin
Factor X P	CSL Behring	600–1200 IU	30–60 IU/ml	20–40 IU/kg	3.3%	24.1	2–8	Pasteurized	Trace heparin/AT
Factor II concentrate *									
Kcentra	CSL Behring	250, 500 or 1000 IU	31 IU/ml	20–40 IU/kg	2.1%	59.7	2–25	Pasteurized, nanofilt	PC/PS, trace Heparin/AT
Octaplex	Octapharma	500 or 1000 IU	31.4 IU/ml	20–40 IU/kg	2.0%	N.R.	2–25	S/D, nanofilt	PC/PS; Heparin 6 U/ml
Cofact	Sanquin	250 or 500 IU	30.4 IU/ml	20–40 IU/kg	2.0%	N.R.	2–8	S/D, nanofilt	PC/PS/AT; no heparin
Bebulin	Shire	500 IU	N.R.	20–40 IU/kg	N.R.	N.R.	2–8	Vapor heat, nanofilt	Trace heparin
Profilnine	Grifols	500, 1000 or 1500 IU	N.R.	20–40 IU/kg	N.R.	N.R.	2–8	S/D	No heparin

haemiplegia. This patient suffered from intraoperative coronary thrombosis under full heparinization, and antifibrinolytic therapy (aprotinin), and later catheter-related thrombosis and amaurosis fugax. Co-administration of multiple haemostatic agents should be cautioned, and early thromboprophylaxis (e.g. aspirin, LMWH) should be considered during the high-intensity factor replacement therapy.[5]

FXIII deficiency

FXIII is a precursor of transglutaminase that is found in plasma and platelets. Plasma FXIII circulates as a tetramer (FXIII-A_2B_2) of two A subunits and two B subunits. Each A subunit contains a catalytic domain, and B subunits serve as a carrier. FXIII in platelets is a dimer of A subunits (FXIII-A_2), which amounts to 50% of total FXIII activity.[81] Once activated by thrombin, FXIIIa cross-links fibrin fibers via peptide bond formation on adjacent α and γ chains of fibrin. Clots formed in the absence of FXIII are permeable to FXa,[82] and prone to fibrinolysis.[83] In addition to clot stabilization, FXIIIa is known to reduce endothelial permeability.[84 85]

The majority of FXIII deficiency is related to A-subunit deficiency, and inherited as a rare autosomal recessive disorder (1 in 1 to 2 million).[86] Umbilical cord bleeding is the typical manifestation of severe FXIII deficiency (<1% activity) in the newborn.[87] Intracranial haemorrhage is the most serious, and relatively common complication (25–30%) of FXIII deficiency (Table 1). Ecchymosis, epistaxis, oromucosal and joint bleeds are also common. Spontaneous abortion, and postpartum haemorrhage are common unless FXIII replacement is implemented.[27] Delayed wound healing is reported in 30% of patients with FXIII deficiency.[88]

There is an association between severity of bleeding and residual FXIII activity, and it is recommended to maintain the activity above 30% to prevent spontaneous bleeding.[8] However, no additional haemostatic benefit was observed when plasma FXIII was increased to 140% using the FXIII concentrate when compared with the untreated post-CPB patients maintaining FXIII activity of 80%.[48]

Laboratory testing. Anaemia is reported in 24% of FXIII deficient patients.[6] FXIII deficiency does not affect PT, aPTT, TT or fibrinogen concentration (Table 2). Heparin anticoagulation can be managed by ACT per routine. Available FXIII assays (urea clot solubility, photometric assay, or ELISA) are time consuming,[89] and thus impractical for titration assessment of FXIII concentrate during surgery. Preoperative FXIII pharmacokinetic (PK)

Table 5 Use of factor concentrate for rare bleeding disorder in cardiac surgery. Abbreviations: RBD, rare bleeding disorder; U.D., undetectable; N.R., not reported; Factor:C, clotting activity of each factor; IU, international unit; POD, post-operative day; TXA, tranexamic acid; RBC, red blood cells, FFP, fresh frozen plasma, pd, plasma-derived; rFVIIa, recombinant activated factor VII; LMWH, low molecular weight heparin; SC, subcutaneous

Reference	Type of RBD (severity)	Age Gender	Procedure	Inhibitor (Y/N)	Replacement therapy	EACA/TXA	Additional products	Thromboprophylaxis	Adverse events
Chun and colleagues 2014[80]	FI deficiency (severe, U.D.)	22 Male	Aortic valve debridement	N	Preop pdFibrinogen 10 g for >200 mg/dL; repeated to maintain >80 mg/dL postop	Aprotinin	None	Heparin, transitioned to warfarin	Coronary thrombosis after CPB; amaurosis fugax and venous access thrombosis
Janbain and colleagues 2014[90]	FXIII deficiency (mild, 20%)	53 Male	Aortic valve replacement	N	Preop pdFXIII 40 IU/kg, repeated in 8 h; half-dose 20 IU/kg on POD8	N.R.	9U RBCs, 7U FFP, 3U PLTs, rFVIIa 90 μg/kg	N.R.	GI bleed requiring transfusion on POD14
Syburra and colleagues 2014[100]	FVII deficiency (severe, <2%)	67 Male	Mitral valve annuloplasty	N	No preop dose; post-CPB pdFVII 1800 IU for FVII:C 30%; repeated 600 IU twice at 12h interval	TXA	None	N.R.	No major complication
Frattini and colleagues 2013[102]	FVII deficiency (mild, 8%)	71 N.R.	CABG x3	N	Preop rFVIIa 15 μg/kg, repeated 7 μg/kg at 6, 24, 48, and 56 h	N.R.	None	LMWH till ambulation; then aspirin	No major complication
Howard & Lipe 2017[56]	FV/FVIII deficiency (mild, 11%/9%)	33 Male	Redo Mitral valve replacement	N	Preop pdFVIII 50 IU/kg, repeated every 8 h for >85% FVIII; tapered pdFVIII on POD4-7; preop TPE 15U FFP for FV:C >50%	N.R.	2U PLT; repeat TPE after surgery, POD 1,2,3 and 5	Heparin SC till POD7	No major complication
Petroulaki and colleagues 2017[122]	FXI deficiency (severe, 2.9%)	73 Female	Aortic valve replacement	N	Preop pdFXI 15 IU/kg for FXI:C 50%, repeated once on POD3	TXA	7U RBCs, 4U FFP, 5U PLTs	LMWH, transitioned to acenocoumarol	No major complication
Escobar and colleagues 2016[132]	FX deficiency (mild, 6%)	59 Male	CABG x3	N	Preop pdFX 40 IU/kg for FX:C >80%; 15 IU/kg twice daily for 50% FX:C for 3 PODs then once daily till discharge	TXA	None	Continued aspirin; LMWH from POD1	No major complication

analysis may be useful to assess individual therapeutic response to FXIII replacement.[90]

Congenital FXIII deficiency may be detected as delayed and reduced clot formation on TEG® or ROTEM®.[27 91 92] However, intraoperative coagulation changes are multi-factorial, and it is not feasible to specifically diagnose FXIII deficiency using VCTs.[34]

Perioperative Management. Perioperative bleeding is common in patients with FXIII deficiency (Table 1), and it is important to maintain FXIII activity of at least 50% in patients undergoing major surgery.[90] Commercially available FXIII concentrates include plasma-derived FXIII (pdFXIII; Corifact, CSL Behring) and recombinant FXIII A-subunit (rFXIIIA; Tretten, NovoNordisk) (Table 4). The latter is not for use in patients with FXIII B-subunit deficiency. Clinically tested doses are 40 IU/kg and 35 IU/kg for pdFXIII and rFXIIIA, and the recovery rates (per IU/kg dose) are 2% and 1.7%, respectively.[86 93] The half-lives of pdFXIII and rFXIIIA are 9.3 days and 11.8 days, respectively, and both are dosed every 28 days in non-surgical prophylaxis.

In a FXIII-deficient male (FXIII activity, 17%) undergoing aortic valve replacement, a dose of 40 IU/kg FXIII concentrate was administered to achieve an 80% increase in FXIII activity before surgery (Table 5).[90] Urgent institution of CPB because of haemodynamic instability resulted in extensive haemodilution, and measured FXIII activity was only 40% after the initial dose. Profuse intraoperative bleeding was reported in this case, requiring massive transfusion (9U RBCs, 3U platelets, and 7U FFP), and the use of rFVIIa (90 μg/kg). A repeat dose of FXIII (40 IU/kg) was given eight h after the initial FXIII dose. Before his discharge, a half-dose (20 IU/kg) was administered on postoperative day (POD) eight, but he was readmitted for ischaemic colitis and anaemia (haemoglobin, 7.5 g/dL) on POD14.[90] Additional RBCs and plasma were transfused, and 20 IU/kg of FXIII was administered. This case highlights the importance of re-dosing FXIII soon after CPB to compensate for 30–50% dilution of coagulation factors.[47 48 94] The half-dose regimen of FXIII (20 IU/kg) and rFXIIIA (17.5 IU/kg) should suffice to increase FXIII activity by 30–40%.

Cryoprecipitate is an additional source for FXIII, but it is not universally available. It may be useful in the correction of co-existing fibrinogen and FXIII deficiencies after CPB. A pooled unit (~90 ml) of cryoprecipitate contains approximately 100–250 IU of FXIII, and 1–1.5 g of fibrinogen.[95]

RBD in extrinsic pathway

FVII deficiency

Plasma FVII (FVII) is a vitamin K dependent zymogen with a short half-life (three to six h). One % of FVII circulates in plasma in activated serine protease (FVIIa), which plays a crucial role in triggering a procoagulant response via FX activation in the presence of tissue factor (TF).[96] Congenital FVII deficiency is a rare autosomal recessive disorder (1 in 500,000). In general, FVII activity below 8–10% is likely to exhibit bleeding symptoms, but clinical presentations of FVII deficiency vary among affected patients.[97] The majority of patients have quantitative defects (low activity and low antigen). However, it is not uncommon to observe qualitative defects (low activity and normal antigen) partly as a result of variable sensitivities of TF reagents to FVII variants.[98] Common bleeding sites include nose, oral cavity, surgical wound, and in female patients, menorrhagia and postpartum haemorrhage are reported (Table 1). Severe FVII deficiency below 1% activity may exhibit bleeding episodes similar to haemophilia, including haemarthrosis, and intracranial haemorrhage. Paradoxical thrombotic events have been reported in FVII-deficient patients, but these are mostly explained by coexisting thrombophilia trait(s) or replacement therapy.[99]

Laboratory testing. Anaemia is reported in about 20% of FVII deficient patients.[6] Isolated FVII deficiency only affects PT, and other tests including aPTT, TT and fibrinogen concentration remain normal (Table 2). Heparin anticoagulation can be managed by ACT per routine. A major discrepancy between low FVII activity and lack of bleeding is in part attributed to the source of TF. Some FVII variants give erroneous quantitation using TF derived from ox or rabbits, but demonstrate improved activity in the presence of human TF.[98]

Perioperative Management. Plasma FVII activity can be specifically restored by using rFVIIa or plasma-derived FVII (pdFVII) (Table 4).[100] Availability of pdFVII is limited to Canada and some European countries. The cross-over study data in congenital FVII deficiency (<2% baseline activity) demonstrated that 20 μg/kg of rFVIIa or 25–30 IU/kg of pdFVII is clinically useful in correcting delayed TF-triggered thrombin generation.[40] Peak level of rFVIIa (FVII:C, 59–138%) is achieved immediately (five min), lasting for four h, while peak level of pdFVII (FVII:C, 19–45%) appears in 60 min, lasting for six h.[40 101]

In one patient with severe FVII deficiency (<2%; INR 3.9) undergoing mitral valve surgery, no preoperative FVII replacement was given because the patient had no previous bleeding incident (Table 5).[100] Valve repair or bioprosthetic valve replacement is preferred in this setting because titration of vitamin K antagonist therapy is difficult with FVII deficiency. After the mitral repair on CPB, 1800 IU of pdFVII was administered before heparin neutralization. FVII:C was increased from 3% to 36%, and it remained between 15–20% in the following 12 h. An additional 600 IU of pdFVII was repeated twice at 12 h interval. No serious bleeding was reported after stopping FVII replacement despite plasma FVII activity of 2–5% (INR 4.6–5.0).

Preoperative FVII replacement with rFVIIa was described for elective CABG in a 71-yr-old patient with FVII deficiency (8%; INR 1.8) (Table 5).[102] The initial dose of rFVIIa, 15 μg/kg was given before surgery, and FVII activity was increased to 210%. High concentrations of heparin (>2 U/ml) used during CPB potentiates the inhibition of rFVIIa by AT,[103] and residual FVII activity was 36% at six h post-surgery. Additional doses of rFVIIa, 7 μg/kg were repeated at six, 24, 48, and 56 h after surgery, maintaining trough FVII:C of 9–12%.

The use of low molecular weight heparin has been reported for long-term thromboprophylaxis in FVII-deficient patients with baseline activity of at least 10–15%.[104]

RBDs in intrinsic pathway

FXI deficiency (haemophilia C)

FXI circulates in plasma in complex with high molecular weight kininogen (HMWK). FXI attaches to anionic surfaces (e.g. CPB circuit) via HMWK, and undergoes enzymatic cleavages by surface-activated FXIIa or FXIa (self-activation).[105] Another activation pathway of FXI involves FXI binding to activated platelets via prothrombin,[106] with subsequent activation by thrombin in the absence of FXIIa.[107 108] Platelets also contribute to FXI activation *in vivo* by expressing anionic polyphosphates, which trigger FXII activation, and serve as a cofactor in thrombin- and FXIa-mediated activations of FXI.[109 110] Multiple FXI activation pathways explain why FXII deficiency is not associated with clinical

bleeding. Amplified thrombin generation by FXIa confers antifibrinolytic activity via activation of thrombin activatable fibrinolysis inhibitor (TAFI).[111]

Severe FXI deficiency is a rare autosomal recessive disorder (1 in 1 million), but it is more prevalent among the Ashkenazi Jewish population (gene frequency, 4.3%).[112 113] There are two frequently reported mutations among Ashkenazi Jews; type II (nonsense mutation) with undetectable FXI activity, and type III (missense mutation) with about 10% FXI activity. Heterozygosity among Ashkenazi Jews is estimated to be 8%, resulting in a partial FXI deficiency (FXI:C, 15–65%).[114 115]

Bleeding as a result of FXI deficiency is generally mild, and there is a poor correlation between bleeding and the residual activity, even in FXI deficiency below 15–20% activity).[8 116] Spontaneous bleeding is infrequent, and usually preceded by major injury or surgery, particularly involving sites with high fibrinolytic activity (e.g. oropharynx; Table 1).[116] Women with FXI deficiency are at increased risk for post-partum haemorrhage and menorrhagia.[114]

Laboratory testing. Normal FXI activity ranges from 70 to 150%.[115] Severely decreased FXI activity below 15% affects contact-activated aPTT and ACT, but PT and TT remain normal (Table 2). Heterozygous patients with partial deficiency are often undiagnosed because of normal aPTT.[115] Baseline ACT prolongation in severe FXI deficiency complicates heparin management unless FXI is preoperatively corrected. A practical alternative is to run ACTs after 1:1 *in vitro* mixing of normal plasma and patient's whole blood.[117 118] *In vitro* plasma supplementation provides sufficient intrinsic pathway factors, and normalizes ACT responses to heparin. This technique can be used for CPB cases with non-haemorrhagic contact pathway factor deficiencies (FXII, high molecular weight kininogen, etc.).[117 119] The anti-Xa activity assay is unaffected by FXI deficiency, but it is not suitable for intraoperative heparin titration. Thromboelastometry with no or minimal TF may be used to assess FXI levels, or haemostatic interventions.[37 38] The TG assay has been shown to be useful in the bleeding risk assessment of FXI-deficient patients, but the technique is not standardized.[38 41]

Perioperative management. The indication and need for FXI replacement should be carefully assessed before CV surgery. Perioperative bleeding because of FXI deficiency seems to increase with fibrinolytic activity of surgical sites,[120] and thus the use of antifibrinolytic agent is important in CV surgery prone to profibrinolytic state during CPB. Preoperative FXI replacement is indicated in patients with significant bleeding history, but exposure to FXI may pose a risk of inhibitor development in severe FXI deficiency.[121]

Two commercial plasma-derived FXI (pdFXI) concentrates are currently available in the UK, France and Canada; Hemoleven (LFB, France), and Factor XI concentrate (Bio Products Laboratory, UK). Both products are relatively similar except for the higher heparin/AT contents in the BPL product (Table 4).

The recommended initial dose of FXI concentrate is 15 IU/kg, achieving 30–45% activity in severe deficiency. A repeat dose (10–15 IU/kg) can be given every 72 h to maintain 30–40% FXI activity.[122] Normalization of FXI above 70% is not recommended because of the risk of thrombosis.[123]

In one patient with severe FXI deficiency (2.9%) and aPTT 59.4 s undergoing aortic valve surgery, 15 IU/kg of FXI concentrate (Hemoleven) was given before surgery, normalizing aPTT and FXI level (36 s, and 54.2%, respectively; Table 5). A bioprosthetic aortic valve replacement was performed during CPB (total 143 min) under full heparinization (300 units/kg, ACT 460 s). This patient also received tranexamic acid, 4U of plasma, 2 g of fibrinogen, and a platelet concentrate for haemostasis after CPB. FXI activity was maintained above 60% until POD three, when 15 IU/kg of FXI concentrate was repeated. Postoperative thromboprophylaxis was started after POD three using acenocoumarol (vitamin K antagonist) without bleeding complications.

Preoperative therapeutic plasma exchange (TPE) may be considered in a patient with a FXI inhibitor (observed in about 6% of severe FXI deficiency).[55] Three runs of TPEs generally remove 90% of antibodies,[58] but the peak FXI levels after TPEs remain in the 20% range, and additional plasma administration and/or TPE are often required to sustain FXI activity.[55]

The use of rFVIIa has been reported in the perioperative management of severe FXI deficiency,[124] or FXI inhibitor.[125] Enhanced activations of FX and FIX theoretically reduces FXI requirement in thrombin generation. The doses of 15–30 μg/kg seem to be effective when given at 2–4 h intervals with antifibrinolytic therapy.[37 124] Anti-inhibitor coagulant complex (AICC) also contains FVIIa, and it has been used in severe FXI deficiency, but there is concern for increased thrombosis in CV patients outside the labeled indications.[126 127]

RBDs in common pathway

FX deficiency

Plasma FX (FX) is a vitamin K-dependent zymogen with a long half-life (40–60 h). Upon vascular injury, a small fraction of FX is converted to FXa by the extrinsic tenase complex comprised of FVIIa and tissue factor (TF). This initial FXa formation supports thrombin generation, and ensuing platelet activation near the vessel wall. Subsequently, FXa activation is mainly sustained by intrinsic tenase, a complex of FIXa and FVIIIa on activated platelets. Propagation of thrombin generation takes place when FXa is in complex with FVa and substrate prothrombin on activated platelets.[128]

Congenital FX deficiency is an autosomal recessive RBD with an estimated incidence of 1 in 500,000–one million. FX deficiency was traditionally classified based on FX activity less than 1% as severe, and 1–5% as moderate deficiency,[129] but the recent European registry indicates that FX activity below 10% is associated with Grade III bleeding including intracranial haemorrhage, GI bleeding and haemarthrosis, while above 40% activity is typically symptom-free (Table 1).[7] Acquired FX deficiency as a result of amyloid protein adsorption of FX may be severe enough to cause haemarthrosis.[130]

Laboratory testing. Anaemia is frequently reported (34%) in homozygous FX deficiency.[6] Moderate to severe FX deficiency prolongs both PT and aPTT, but TT and fibrinogen remain normal (Table 2). Plasma FX levels can be measured by PT-based one-stage clotting assay (FX:C) or chromogenic FX assay.[130–132] Standard heparin management with ACT monitoring can be used when FX activity is normalized using FX concentrate before surgery.[132] Heparin activity measured by anti-Xa assay is unaffected by FX deficiency as exogenous FXa is used to quantify heparin concentrations. The dose of protamine should be optimized to minimize residual anti-Xa activity of heparin, and to avoid the potential anticoagulant activity of protamine, as discussed below.[50 133] TF-activated thromboelastometry (EXTEM) is sensitive to moderate FX deficiency (≤5% activity), which demonstrates a prolonged clotting time (CT).[35 134]

Perioperative management. There are 2 commercially available plasma-derived (pd) FX concentrates; one is a high-purity FX concentrate (pd-FX; Coagadex, BPL, UK), and the other is a mixture of FX and FIX (pd-FX/FIX; Factor X P; CSL Behring, Germany) (Table 4). Effective haemostasis was reported after a median pd-FX dose of 48.9 IU/kg in five FX deficient subjects (FX:C ≤8%) undergoing surgery (Table 5).[132] In CABG surgery, pd-FX was repeated (median, 16.1 IU/kg) twice daily for three days, and then once daily until discharge. In this CABG patient, the peak FX:C and post-operative trough levels were reported to be 91%, and 42–58%, respectively. The dose of pd-FX can be calculated as follows:

$$\text{FX dose (IU)} = [\text{target FX : C (\%)} - \text{current FX : C (\%)}] \times \text{weight(kg)} \div 2$$

Plasma transfusion has been commonly used for FX replacement when pd-FX is unavailable. A loading dose of 15–20 ml/kg of body weight is followed by 5–10 ml/kg every 24 h. TPE is preferable than transfusion if volume overload is a concern.[135] Plasma FX activity of 10–20% appears to be sufficient for the treatment of minor bleeding.[136] Most prothrombin complex concentrate (PCC) products are considered to be an alternative source (Table 4), because they contain therapeutic amounts of FX in addition to FII and FIX.[137] Target FX levels with PCCs are in the range of 35–50% for major surgery, and 10–20% after surgery to avoid accumulation of prothrombin, which is associated with venous thrombosis.[138 139]

FV deficiency

FV is a labile glycoprotein (half-life, 13–15 h) which plays multiple regulatory functions in coagulation as a cofactor for FXa and activated protein C (aPC).[140 141] Plasma FV is endocytosed by megakaryocytes, and stored as a proteolyzed (partially activated) form in platelet α granules (20–25% of total FV).[142 143] Upon vascular injury and platelet activation, thrombin-activated FV (FVa) primarily serves as a cofactor for FXa in thrombin generation.

Congenital FV deficiency is inherited as an autosomal recessive RBD (1 in 1 million), and severe FV deficiency (undetectable activity) is usually caused by homozygous or double heterozygous mutations. A relatively poor association between residual FV activity, and bleeding severity has been attributed to platelet-derived FV,[43 143] and coexisting lower tissue factor pathway inhibitor (TFPI) levels.[42] Spontaneous bleeds are infrequent when FV is above 10%.[7, 8]

Common bleeding symptoms include ecchymosis, epistaxis, oropharyngeal bleed, and in female patients, menorrhagia (Table 1). GI and postsurgical bleeds may also occur.

Acquired FV deficiency has been reported after exposure to bovine thrombin which contains bovine FV, inducing autoantibodies against human FV.[144] Bovine thrombin is no longer in use, but an anti-FV antibody should be in the differential diagnosis of FV deficiency after surgery.[145]

Laboratory testing. Anaemia is frequently reported (36%) in homozygous FV deficiency.[6] Severe FV deficiency prolongs the PT and aPTT, but the TT remains normal.[36] TF-activated and contact-activated clotting time (EXTEM and INTEM) on thromboelastometry were two to three-fold prolonged over the normal values in nine patients with reduced plasma FV activity [mean, 1.7(2.2%)].[36] However, the bleeding phenotype exhibits rather poor correlations with PT, aPTT or thromboelastometry profiles.[42 43]

ACT prolongation in FV deficiency complicates heparin management after haemodilution on CPB, and thus preoperative TPE should be considered.[56] Protamine overdose should be avoided because it inhibits FVa, thereby reducing thrombin generation.[50 133]

Perioperative management. No commercial FV concentrate is available, and plasma transfusion or TPE is the main therapy. A loading dose of 15–20 ml/kg of plasma is followed by 3-6 ml/kg every 24 h to achieve 25% of normal activity. TPE is preferred to achieve higher FV levels (40–60%), especially when there are concerns for volume overload or FV inhibitor.[56 146 147] FFP and solvent-detergent (SD) plasma are similar as a source of FV, but thawed FFP or thawed SD-plasma may yield lower FV recovery when stored at 4–6 °C for 5 days.[148 149] Transfused FV is endocytosed by megakaryocytes, and proteolyzed FV appears in platelet α-granules within 6 h, and peaks at 24 h. TPE or plasma transfusion 24 h before surgery may be thus effective in restoring platelet-derived FV. Allogeneic platelet transfusion is also effective in the case of FV inhibitors,[150] but repeated transfusions of platelets carry the risk of alloantibody formation.

FV + FVIII deficiency

Combined FV and FVIII deficiency (FV + FVIII deficiency) is a rare autosomal recessive RBD (1 in 1 million), characterized by concomitantly low FV and FVIII (activities between 5% and 20%). The estimated prevalence is higher (~1:100,000) among the Middle Eastern Jewish, and non-Jewish Iranian populations.[151] Congenital FV + FVIII deficiency is caused by a defect in intracellular transport of FV and FVIII proteins from endoplasmic reticulum to Golgi apparatus. The mutations in the genes encoding LMAN1 (Lectin Mannose Binding Protein), and MCFD2 (Multiple Coagulation Factor Deficiency 2) which is a cofactor for LMAN1, have been associated with this transport defect.[152 153] There is insufficient data on the FV content of platelet α granules in combined FV + FVIII deficiency.

Bleeding tendency is not worsened by combined FV + FVIII deficiency relative to the separate defects. Common bleeding symptoms include ecchymosis, epistaxis, oropharyngeal and post-trauma/surgery bleeds (Table 1).

Laboratory testing. Combined FV + FVIII deficiency prolongs both PT and aPTT, but the TT remains normal (Table 2). Specific clotting activity and antigen measurements should be performed for FV and FVIII along with a genetic testing for LMAN1 and MCFD2 mutations.

Preoperative PK evaluation can be useful to assess therapeutic responses to TPE (FV), DDAVP (FVIII) or various FVIII concentrates.[56 154] Intraoperative heparin management should follow the standard protocol when FV and FVIII levels are corrected before CV surgery.

Perioperative management. Although bleeding symptoms from combined FV + FVIII deficiency are generally mild, the bleeding risk is higher after CV surgery as a result of the loss and dilution of multiple procoagulant factors and platelets. Perioperative replacement regimens thus follow the protocol for isolated FV deficiency as above, and haemophilia A.[155]

One case of CV surgery in a combined FV + FVIII deficiency has been reported in the literature (Table 5).[56] A 33-yr-old male previously diagnosed with combined FV + FVIII deficiency (FV 11%, FVIII 9%; no inhibitors) presented for redo mitral valve (MV) replacement because of bioprosthetic MV stenosis. Perioperative TPE was performed to achieve 50% FV activity using 15U of FFP

immediately before surgery, along with FVIII concentrate (50 IU/kg; Hemofil M, Baxter). Platelets were empirically administered after CPB. TPE was repeated on the evening of surgery, on PODs one, two, three and five. FVIII infusion (50 IU/kg) was repeated every eight h (target FVIII>85%) till POD three, and tapered off over the subsequent four days. Thromboprophylaxis should be considered during the period of FVIII replacement.[5]

Prothrombin deficiency

Prothrombin (FII) is a vitamin K-dependent factor with a long half-life (three to four days). As a precursor of thrombin, it plays pivotal roles in fetal survival, haemostasis, wound healing, and pathological thrombosis.[156–158] Congenital FII deficiency is an autosomal recessive RBD (1 in 2 million), and most cases are "dysprothrombinemias" caused by a missense mutation. Homozygous and double heterozygous patients show lower FII activity, and severe symptoms while heterozygous patients remain asymptomatic or have minor bleeding tendency.[159 160]

Common bleeding patterns include ecchymosis, epistaxis, muscle and joint bleeds, and in female patients, menorrhagia (Table 1). Umbilical cord and GI bleeds may occur in severe FII deficiency.

Laboratory testing. Homozygous FII deficiency affects both PT and aPTT, but the TT remains normal (Table 2). PT-based coagulant activity of FII is decreased in dysprothrombinemia, but antigenic FII level may be normal or mildly decreased. TF-triggered thrombin generation assay is highly sensitive to prothrombin concentrations,[161] and it has been used to monitor prophylactic FII replacement with PCC.[44]

Perioperative management. There is a paucity of clinical data on FII replacement as a result of the rarity of the disease. FFP, SD-plasma, and thawed plasma can be used for FII replacement because prothrombin remains stable at 4–6°C for five days.[162] Pathogen-reduced SD-plasma is preferred for repeated administration.[9] A loading dose of 15–20 ml/kg of plasma is followed by 3–6 ml/kg every 12–24 h, in order to achieve 25% of normal activity. Currently there is no available purified prothrombin concentrate, but there are several PCCs that contain therapeutic amounts of prothrombin and other vitamin K dependent factors (Table 4). PCCs are packaged according to the content of FIX, and one should be aware of FII content relative to FIX in each product. Plasma half-life of prothrombin is about three days, and prophylactic dosing of 40 IU/kg every fifth day has been reported to prevent spontaneous bleeding episodes in severe type I deficiency with baseline FII:C of 8%.[44] Another regimen is to use an initial PCC dose of 20 IU/kg, followed by 5 IU/kg every 24 h.[160]

To date, no reported case of FII deficiency undergoing CPB is available. In theory, a preoperative dose of 40 IU/kg should increase FII level from<10% to nearly 100% before CPB. Intraoperative loss of FII as a result of haemorrhage and haemodilution can lower FII levels to 20–40%,[49 163 164] and thus an additional dose of PCC at 10–20 IU/kg may be required to correct FII:C above 50%.

Conclusion

Improved healthcare access and medical informatics have expanded the knowledge on diagnosis and treatment of RBDs around the globe. Neither haemophilia nor RBDs impart any inherent decreased risk of CV disease. The need for CV procedures for patients with RBDs is likely to increase, as witnessed by the ageing haemophilia population who have received factor replacement over several decades. Available replacement therapies for RBDs are not only plasma transfusion, but also factor concentrates that are manufactured with several pathogen reduction steps. For each RBD patient undergoing CV procedure, the perioperative care team needs to develop an individualized plan for surgery and concurrent factor replacement strategy (Table 3). Comprehensive patient blood management strategies for the general population are also applicable to patients with RBDs, which include preoperative anaemia correction, intraoperative blood conservation, optimized postoperative care and thromboprophylaxis.

Authors' contributions

Review design/planning: K.A.T., N.S.K.
Writing paper: E.R.S., M.A.M., B.W., K.A.T.
Revising paper: all authors

Declaration of interest

Dr Tanaka served on an endpoint adjudication committee for Octapharma. The other authors state that they have no conflict of interest.

Funding

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References

1. Alstrom U, Levin LA, Stahle E, Svedjeholm R, Friberg O. Cost analysis of re-exploration for bleeding after coronary artery bypass graft surgery. *Br J Anaesth* 2012; **108**: 216–22
2. Weber CF, Gorlinger K, Meininger D, *et al*. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology* 2012; **117**: 531–47
3. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. *J Thoracic Cardiovasc Surg* 2013; **145**: S178–85
4. Karkouti K, Wijeysundera DN, Yau TM, *et al*. The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion* 2004; **44**: 1453–62
5. Ferraris VA, Boral LI, Cohen AJ, Smyth SS, White GC 2nd. Consensus review of the treatment of cardiovascular disease in people with hemophilia A and B. *Cardiol Rev* 2015; **23**: 53–68
6. Acharya SS, Coughlin A, Dimichele DM. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost* 2004; **2**: 248–56
7. Peyvandi F, Di Michele D, Bolton-Maggs PH, Lee CA, Tripodi A, Srivastava A. Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity. *J Thromb Haemost* 2012; **10**: 1938–43
8. Peyvandi F, Palla R, Menegatti M, *et al*. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. *J Thromb Haemost* 2012; **10**: 615–21
9. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood* 2015; **125**: 2052–61

10. Shetty S, Shelar T, Mirgal D, *et al*. Rare coagulation factor deficiencies: a countrywide screening data from India. *Haemophilia* 2014; **20**: 575–81
11. Sramek A, Reiber JH, Gerrits WB, Rosendaal FR. Decreased coagulability has no clinically relevant effect on atherogenesis: observations in individuals with a hereditary bleeding tendency. *Circulation* 2001; **104**: 762–7
12. Foley CJ, Nichols L, Jeong K, Moore CG, Ragni MV. Coronary atherosclerosis and cardiovascular mortality in hemophilia. *J Thromb Haemost* 2010; **8**: 208–11
13. Sharathkumar AA, Soucie JM, Trawinski B, Greist A, Shapiro AD. Prevalence and risk factors of cardiovascular disease (CVD) events among patients with haemophilia: experience of a single haemophilia treatment centre in the United States (US). *Haemophilia* 2011; **17**: 597–604
14. Tuinenburg A, Rutten A, Kavousi M, *et al*. Coronary artery calcification in hemophilia A: no evidence for a protective effect of factor VIII deficiency on atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012; **32**: 799–804
15. Nichols WL, Rick ME, Ortel TL, *et al*. Clinical and laboratory diagnosis of von Willebrand disease: a synopsis of the 2008 NHLBI/NIH guidelines. *Am J Hematol* 2009; **84**: 366–70
16. Khallou-Laschet J, Caligiuri G, Tupin E, *et al*. Role of the intrinsic coagulation pathway in atherogenesis assessed in hemophilic apolipoprotein E knockout mice. *Arterioscler Thromb Vasc Biol* 2005; **25**: e123–6
17. Shnerb Ganor R, Harats D, Schiby G, *et al*. Factor XI deficiency protects against atherogenesis in apolipoprotein E/factor XI double knockout mice. *Arterioscler Thromb Vasc Biol* 2016; **36**: 475–81
18. Sait AS, Kuo A, Bettencourt R, Bergstrom J, Allison M, von Drygalski A. Risk assessment for coronary heart disease in patients with haemophilia: a single centre study in the United States. *Haemophilia* 2014; **20**: 763–70
19. Mannucci PM. Management of antithrombotic therapy for acute coronary syndromes and atrial fibrillation in patients with hemophilia. *Expert Opin Pharmacother* 2012; **13**: 505–10
20. Zawilska K, Podolak-Dawidziak M. Therapeutic problems in elderly patients with hemophilia. *Pol Arch Med Wewn* 2012; **122**: 567–76
21. Petrillo G, Cirillo P, Leosco D, Maresca F, Piscione F, Chiariello M. Percutaneous coronary intervention in a patient with acute non-ST-elevation myocardial infarction and haemophilia A: a 'genous' experience. *Haemophilia* 2011; **17**: e245–6
22. Lim MY, Pruthi RK. Outcomes of management of acute coronary syndrome in patients with congenital bleeding disorders: a single center experience and review of the literature. *Thromb Res* 2012; **130**: 316–22
23. Acharya SS. Rare bleeding disorders in children: identification and primary care management. *Pediatrics* 2013; **132**: 882–92
24. Kershaw G, Orellana D. Mixing tests: diagnostic aides in the investigation of prolonged prothrombin times and activated partial thromboplastin times. *Semin Thromb Hemost* 2013; **39**: 283–90
25. Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost* 2016; **14**: 248–61
26. Miesbach W, Scharrer I, Henschen A, Neerman-Arbez M, Spitzer S, Galanakis D. Inherited dysfibrinogenemia: clinical phenotypes associated with five different fibrinogen structure defects. *Blood Coagul Fibrinolysis* 2010; **21**: 35–40
27. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia* 2008; **14**: 1190–200
28. Tanaka KA, Bader SO, Sturgil EL. Diagnosis of perioperative coagulopathy—plasma versus whole blood testing. *J Cardiothorac Vasc Anesth* 2013; **27**:
29. Williams B, McNeil J, Crabbe A, Tanaka KA. Practical use of thromboelastometry in the management of perioperative coagulopathy and bleeding. *Transfus Med Rev* 2017; **31**: 11–25
30. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999; **88**: 312–9
31. Nuttall GA, Oliver WC, Santrach PJ, *et al*. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. *Anesthesiology* 2001; **94**: 773–81
32. Karkouti K, Callum J, Wijeysundera DN, *et al*. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. *Circulation* 2016; **134**: 1152–62
33. Manco-Johnson MJ, Dimichele D, Castaman G, *et al*. Pharmacokinetics and safety of fibrinogen concentrate. *J Thromb Haemost* 2009; **7**: 2064–9
34. Korte WC, Szadkowski C, Gahler A, *et al*. Factor XIII substitution in surgical cancer patients at high risk for intraoperative bleeding. *Anesthesiology* 2009; **110**: 239–45
35. Sorensen B, Ingerslev J. Whole blood clot formation phenotypes in hemophilia A and rare coagulation disorders. Patterns of response to recombinant factor VIIa. *J Thromb Haemost* 2004; **2**: 102–10
36. Spiezia L, Radu C, Campello E, *et al*. Whole blood rotation thromboelastometry (ROTEM®) in nine severe factor V deficient patients and evaluation of the role of intraplatelets factor V. *Haemophilia* 2012; **18**: 463–8
37. Riddell A, Abdul-Kadir R, Pollard D, Tuddenham E, Gomez K. Monitoring low dose recombinant factor VIIa therapy in patients with severe factor XI deficiency undergoing surgery. *Thromb Haemost* 2011; **106**: 521–7
38. Livnat T, Shenkman B, Martinowitz U, *et al*. The impact of thrombin generation and rotation thromboelastometry on assessment of severity of factor XI deficiency. *Thromb Res* 2015; **136**: 465–73
39. Al Dieri R, Peyvandi F, Santagostino E, *et al*. The thrombogram in rare inherited coagulation disorders: its relation to clinical bleeding. *Thromb Haemost* 2002; **88**: 576–82
40. van Geffen M, Mathijssen NC, Holme PA, *et al*. Pharmacodynamics of recombinant activated factor VII and plasma-derived factor VII in a cohort of severe FVII deficient patients. *Thromb Res* 2013; **132**: 116–22
41. Rugeri L, Quelin F, Chatard B, De Mazancourt P, Negrier C, Dargaud Y. Thrombin generation in patients with factor XI deficiency and clinical bleeding risk. *Haemophilia* 2010; **16**: 771–7
42. Duckers C, Simioni P, Spiezia L, *et al*. Low plasma levels of tissue factor pathway inhibitor in patients with congenital factor V deficiency. *Blood* 2008; **112**: 3615–23
43. Duckers C, Simioni P, Spiezia L, *et al*. Residual platelet factor V ensures thrombin generation in patients with severe congenital factor V deficiency and mild bleeding symptoms. *Blood* 2010; **115**: 879–86
44. Mathias M, Pollard D, Riddell A. Prophylaxis in severe prothrombin deficiency. *Br J Haematol* 2011; **152**: 243–4
45. Dargaud Y, Bordet JC, Lienhart A, Negrier C. Use of the thrombin generation test to evaluate response to treatment

with recombinant activated factor VII. *Semin Hematol* 2008; **45**: S72–3
46. Chandler WL. Effects of hemodilution, blood loss, and consumption on hemostatic factor levels during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2005; **19**: 459–67
47. Karkouti K, McCluskey SA, Syed S, Pazaratz C, Poonawala H, Crowther MA. The influence of perioperative coagulation status on postoperative blood loss in complex cardiac surgery: a prospective observational study. *Anesth Analg* 2010; **110**: 1533–40
48. Karkouti K, von Heymann C, Jespersen CM, *et al*. Efficacy and safety of recombinant factor XIII on reducing blood transfusions in cardiac surgery: a randomized, placebo-controlled, multicenter clinical trial. *J Thorac Cardiovasc Surg* 2013; **146**: 927–39
49. Tanaka KA, Egan K, Szlam F, *et al*. Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. *Transfusion* 2014; **54**: 109–18
50. Meesters MI, Veerhoek D, de Lange F, *et al*. Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery. A randomised clinical trial. *Thromb Haemost* 2016; **116**: 251–61
51. Goldberg J, Paugh TA, Dickinson TA, *et al*. Greater volume of acute normovolemic hemodilution may aid in reducing blood transfusions after cardiac surgery. *Ann Thorac Surg* 2015; **100**: 1581–7; discussion 7
52. Balachandran S, Cross MH, Karthikeyan S, Mulpur A, Hansbro SD, Hobson P. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion after coronary artery surgery. *Ann Thorac Surg* 2002; **73**: 1912–8
53. Severdija EE, Heijmans JH, Theunissen M, Maessen JG, Roekaerts PH, Weerwind PW. Retrograde autologous priming reduces transfusion requirements in coronary artery bypass surgery. *Perfusion* 2011; **26**: 315–21
54. Djaiani G, Fedorko L, Borger MA, *et al*. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation* 2007; **116**: 1888–95
55. Teruya J, Styler M. Management of factor XI inhibitor for cardiac intervention: successful treatment with immunosuppressive therapy and plasma exchange. *Haemophilia* 2000; **6**: 158–61
56. Howard C, Lipe B. Combined deficiency of factor V and factor VIII: management during cardiothoracic surgery. *Blood Coagul Fibrinolysis* 2017; **28**: 267–8
57. Roman PE, DeVore AD, Welsby IJ. Techniques and applications of perioperative therapeutic plasma exchange. *Current Opin Anaesthesiol* 2014; **27**: 57–64
58. Rummler S, Barz D. Plasma exchange and immunoadsorption of patients with thoracic organ transplantation. *Transfus Med Hemother* 2012; **39**: 234–40
59. Crabbe A, McNeil JS, Deshpande SP, Kon Z, Pham SM, Tanaka KA. Therapeutic plasma exchange in heart transplantation: role of coagulation assessment with thromboelastometry. *JA Clinical Reports* 2016; **2**: 31
60. Williams B, Mazzeffi MA, Sanchez PG, Pham SM, Kon Z, Tanaka KA. Case report of severe antithrombin deficiency during extracorporeal membrane oxygenation and therapeutic plasma exchange for double lung transplantation. *AA Case Rep* 2017; **8**: 11–3
61. Mosesson MW. Fibrinogen and fibrin structure and functions. *J Thromb Haemost* 2005; **3**: 1894–904
62. Laurens N, Koolwijk P, de Maat MP. Fibrin structure and wound healing. *J Thromb Haemost* 2006; **4**: 932–9
63. Acharya SS, Dimichele DM. Rare inherited disorders of fibrinogen. *Haemophilia* 2008; **14**: 1151–8
64. Lak M, Keihani M, Elahi F, Peyvandi F, Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenaemia. *Br J Haematol* 1999; **107**: 204–6
65. Girolami A, Ruzzon E, Tezza F, Scandellari R, Vettore S, Girolami B. Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. *Haemophilia* 2006; **12**: 345–51
66. Dupuy E, Soria C, Molho P, *et al*. Embolized ischemic lesions of toes in an afibrinogenemic patient: possible relevance to in vivo circulating thrombin. *Thromb Res* 2001; **102**: 211–9
67. Mosesson MW. Fibrinogen gamma chain functions. *J Thromb Haemost* 2003; **1**: 231–8
68. Mosesson MW, Antithrombin I. Inhibition of thrombin generation in plasma by fibrin formation. *Thromb Haemost* 2003; **89**: 9–12
69. Haverkate F, Samama M. Familial dysfibrinogenemia and thrombophilia. Report on a study of the SSC Subcommittee on Fibrinogen. *Thromb Haemost* 1995; **73**: 151–61
70. Girdauskas E, Kempfert J, Kuntze T, *et al*. Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg* 2010; **140**: 1117–24.e2
71. Fabbro M 2nd, Gutsche JT, Miano TA, Augoustides JG, Patel PA. Comparison of thrombelastography-derived fibrinogen values at rewarming and following cardiopulmonary bypass in cardiac surgery patients. *Anesth Analg* 2016; **123**: 570–7
72. Hunault-Berger M, Chevallier P, Delain M, *et al*. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica* 2008; **93**: 1488–94
73. Refaai MA, Goldstein JN, Lee ML, Durn BL, Milling TJ Jr, Sarode R. Increased risk of volume overload with plasma compared with four-factor prothrombin complex concentrate for urgent vitamin K antagonist reversal. *Transfusion* 2015; **55**: 2722–9
74. Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. *J Thromb Haemost* 2011; **9**: 1687–704
75. Kreuz W, Meili E, Peter-Salonen K, *et al*. Pharmacokinetic properties of a pasteurised fibrinogen concentrate. *Transfus Apher Sci* 2005; **32**: 239–46
76. Negrier C, Rothschild C, Goudemand J, *et al*. Pharmacokinetics and pharmacodynamics of a new highly secured fibrinogen concentrate. *J Thromb Haemost* 2008; **6**: 1494–9
77. Bolliger D, Tanaka KA. Haemostatic efficacy of fibrinogen concentrate: is it the threshold or the timing of therapy? *Br J Anaesth* 2015; **115**: 158–61
78. Bolliger D, Tanaka KA. Fibrinogen-is it a universal haemostatic agent? *Br J Anaesth* 2016; **117**: 548–50
79. Rahe-Meyer N, Levy JH, Mazer CD, *et al*. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. *Br J Anaesth* 2016; **117**: 41–51
80. Chun R, Poon MC, Haigh J, Seal D, Donahue B, Royston D. Case 1-2005: cardiac surgery in congenital afibrinogenemia with thrombo-occlusive disease. *J Cardiothorac Vasc Anesth* 2005; **19**: 109–17

81. Muszbek L, Bereczky Z, Bagoly Z, Komaromi I, Katona E. Factor XIII: a coagulation factor with multiple plasmatic and cellular functions. *Physiol Rev* 2011; **91**: 931–72
82. Hathcock JJ, Nemerson Y. Platelet deposition inhibits tissue factor activity: in vitro clots are impermeable to factor Xa. *Blood* 2004; **104**: 123–7
83. Dirkmann D, Gorlinger K, Gisbertz C, Dusse F, Peters J. Factor XIII and tranexamic acid but not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. *Anesth Analg* 2012; **114**: 1182–8
84. Noll T, Wozniak G, McCarson K, *et al*. Effect of factor XIII on endothelial barrier function. *J Exp Med* 1999; **189**: 1373–82
85. Nahrendorf M, Hu K, Frantz S, *et al*. Factor XIII deficiency causes cardiac rupture, impairs wound healing, and aggravates cardiac remodeling in mice with myocardial infarction. *Circulation* 2006; **113**: 1196–202
86. Inbal A, Oldenburg J, Carcao M, Rosholm A, Tehranchi R, Nugent D. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012; **119**: 5111–7
87. Karimi M, Bereczky Z, Cohan N, Muszbek L. Factor XIII Deficiency. *Semin Thromb Hemost* 2009; **35**: 426–38
88. Ivaskevicius V, Seitz R, Kohler HP, *et al*. International registry on factor XIII deficiency: a basis formed mostly on European data. *Thromb Haemost* 2007; **97**: 914–21
89. Kohler HP, Ichinose A, Seitz R, Ariens RA, Muszbek L. Diagnosis and classification of factor XIII deficiencies. *J Thromb Haemost* 2011; **9**: 1404–6
90. Janbain M, Nugent DJ, Powell JS, St-Louis J, Frame VB, Leissinger CA. Use of Factor XIII (FXIII) concentrate in patients with congenital FXIII deficiency undergoing surgical procedures. *Transfusion* 2015; **55**: 45–50
91. Chakroun T, Gerotziafas GT, Seghatchian J, Samama MM, Hatmi M, Elalamy I. The influence of fibrin polymerization and platelet-mediated contractile forces on citrated whole blood thromboelastography profile. *Thromb Haemost* 2006; **95**: 822–8
92. Jambor C, Reul V, Schnider TW, Degiacomi P, Metzner H, Korte WC. In vitro inhibition of factor XIII retards clot formation, reduces clot firmness, and increases fibrinolytic effects in whole blood. *Anesth Analg* 2009; **109**: 1023–8
93. Nugent DJ, Ashley C, Garcia-Talavera J, Lo LC, Mehdi AS, Mangione A. Pharmacokinetics and safety of plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. *Haemophilia* 2015; **21**: 95–101
94. Ternstrom L, Radulovic V, Karlsson M, *et al*. Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: a prospective observational study. *Thromb Res* 2010; **126**: e128–33
95. Caudill JS, Nichols WL, Plumhoff EA, *et al*. Comparison of coagulation factor XIII content and concentration in cryoprecipitate and fresh-frozen plasma. *Transfusion* 2009; **49**: 765–70
96. Lu G, Broze GJ, Jr, Krishnaswamy S. Formation of factors IXa and Xa by the extrinsic pathway: differential regulation by tissue factor pathway inhibitor and antithrombin III. *J Biol Chem* 2004; **279**: 17241–9
97. Barnett JM, Demel KC, Mega AE, Butera JN, Sweeney JD. Lack of bleeding in patients with severe factor VII deficiency. *Am J Hematoly* 2005; **78**: 134–7
98. Girolami A, Berti de Marinis G, Bonamigo E, Sartori R, Vettore S. Ox brain versus rabbit brain thromboplastin assays are the best tool for a preliminary diagnosis of the Arg304Gln factor VII defect (FVII Padua). *Acta Haematol* 2010; **124**: 229–34
99. Girolami A, Tezza F, Scandellari R, Vettore S, Girolami B. Associated prothrombotic conditions are probably responsible for the occurrence of thrombosis in almost all patients with congenital FVII deficiency. Critical review of the literature. *J Thromb Thrombolysis* 2010; **30**: 172–8
100. Syburra T, Siciliano RD, Hofer C, Genoni M. Mitral valve surgery in severe congenital factor VII deficiency. *Hematology* 2014; **19**: 49–51
101. Mathijssen NC, Masereeuw R, Holme PA, *et al*. Increased volume of distribution for recombinant activated factor VII and longer plasma-derived factor VII half-life may explain their long lasting prophylactic effect. *Thromb Res* 2013; **132**: 256–62
102. Frattini F, Bonfanti C, Piccoli P, *et al*. Triple coronary artery bypass graft surgery in a patient with factor VII deficiency: a case report. *Haemophilia* 2013; **19**: e268–9
103. Petersen LC, Karpf DM, Agerso H, *et al*. Intravascular inhibition of factor VIIa and the analogue NN1731 by antithrombin. *Br J Haematol* 2011; **152**: 99–107
104. Arellano-Rodrigo E, Gironella M, Nicolau I, Vila M. Clinical management of thrombosis in inherited factor VII deficiency: a description of two cases. *Thromb Haemost* 2009; **101**: 402–4
105. Vogler EA, Siedlecki CA. Contact activation of blood-plasma coagulation. *Biomaterials* 2009; **30**: 1857–69
106. Baglia FA, Walsh PN. Prothrombin is a cofactor for the binding of factor XI to the platelet surface and for platelet-mediated factor XI activation by thrombin. *Biochemistry* 1998; **37**: 2271–81
107. Oliver JA, Monroe DM, Roberts HR, Hoffman M. Thrombin activates factor XI on activated platelets in the absence of factor XII. *Arterioscler Thromb Vasc Biol* 1999; **19**: 170–7
108. Kravtsov DV, Matafonov A, Tucker EI, *et al*. Factor XI contributes to thrombin generation in the absence of factor XII. *Blood* 2009; **114**: 452–8
109. Muller F, Renne T. Platelet polyphosphates: the nexus of primary and secondary hemostasis. *Scand J Clin Lab Invest* 2011; **71**: 82–6
110. Choi SH, Smith SA, Morrissey JH. Polyphosphate is a cofactor for the activation of factor XI by thrombin. *Blood* 2011; **118**: 6963–70
111. Von Dem Borne PA, Bajzar L, Meijers JC, Nesheim ME, Bouma BN. Thrombin-mediated activation of factor XI results in a thrombin-activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. *J Clin Invest* 1997; **99**: 2323–7
112. Seligsohn U. Factor XI deficiency in humans. *J Thromb Haemost* 2009; **7(Suppl 1)**: 84–7
113. Mitchell M, Mountford R, Butler R, *et al*. Spectrum of factor XI (F11) mutations in the UK population–116 index cases and 140 mutations. *Hum Mutat* 2006; **27**: 829
114. Bolton-Maggs PH, Patterson DA, Wensley RT, Tuddenham EG. Definition of the bleeding tendency in factor XI-deficient kindreds—a clinical and laboratory study. *Thromb Haemost* 1995; **73**: 194–202
115. Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. Inheritance and bleeding in factor XI deficiency. *Br J Haematol* 1988; **69**: 521–8
116. Gomez K, Bolton-Maggs P. Factor XI deficiency. *Haemophilia* 2008; **14**: 1183–9

117. Gerhardt MA, Greenberg CS, Slaughter TF, Stafford Smith M. Factor XII deficiency and cardiopulmonary bypass: use of a novel modification of the activated clotting time to monitor anticoagulation. *Anesthesiology* 1997; **87**: 990–2
118. Koster A, Despotis G, Gruendel M, *et al*. The plasma supplemented modified activated clotting time for monitoring of heparinization during cardiopulmonary bypass: a pilot investigation. *Anesth Analg* 2002; **95**: 26–30
119. Davidson SJ, Burman JF, Rutherford LC, Keogh BF, Yacoub MH. High molecular weight kininogen deficiency: a patient who underwent cardiac surgery. *Thromb Haemost* 2001; **85**: 195–7
120. Bolton-Maggs PH, Perry DJ, Chalmers EA, *et al*. The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004; **10**: 593–628
121. Salomon O, Zivelin A, Livnat T, Seligsohn U. Inhibitors to Factor XI in patients with severe Factor XI deficiency. *Semin Hematol* 2006; **43**: S10–2
122. Petroulaki A, Lazopoulos G, Chaniotaki F, Kampitakis E, Pavlopoulos D, Chalkiadakis G. Factor XI deficiency and aortic valve replacement: perioperative management. *Asian Cardiovasc Thorac Ann* 2017; **25**: 450–2
123. Bolton-Maggs P, Goudemand J, Hermans C, Makris M, de Moerloose P. FXI concentrate use and risk of thrombosis. *Haemophilia* 2014; **20**: e349–51
124. Setty S, Reddell A, England A, Gomez K, Kadir R. The role of recombinant factor VIIa for obstetric block in women with severe factor XI deficiency. *Haemophilia* 2011; **17**: 906–9
125. Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr. Treatment of factor XI inhibitor using recombinant activated factor VIIa. *Haemophilia* 2005; **11**: 20–5
126. Valentino LA, Holme PA. Should anti-inhibitor coagulant complex and tranexamic acid be used concomitantly? *Haemophilia* 2015; **21**: 709–14
127. Rao VK, Lobato RL, Bartlett B, *et al*. Factor VIII inhibitor bypass activity and recombinant activated factor VII in cardiac surgery. *J Cardiothorac Vasc Anesth* 2014; **28**: 1221–6
128. Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. *J Thromb Haemost* 2012; **10**: 1478–85
129. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia* 2008; **14**: 1176–82
130. Mahmood S, Blundell J, Drebes A, Hawkins PN, Wechalekar AD. Utility of factor X concentrate for the treatment of acquired factor X deficiency in systemic light-chain amyloidosis. *Blood* 2014; **123**: 2899–900
131. Austin SK, Brindley C, Kavakli K, Norton M, Shapiro A. Pharmacokinetics of a high-purity plasma-derived factor X concentrate in subjects with moderate or severe hereditary factor X deficiency. *Haemophilia* 2016; **22**: 426–32
132. Escobar MA, Auerswald G, Austin S, Huang JN, Norton M, Millar CM. Experience of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency undergoing surgery. *Haemophilia* 2016; **22**: 713–20
133. Ni AF, Preston RJ, Jenkins PV, *et al*. Protamine sulfate downregulates thrombin generation by inhibiting factor V activation. *Blood* 2009; **114**: 1658–65
134. Gudmundsdottir BR, Francis CW, Bjornsdottir AM, Nellbring M, Onundarson PT. Critical role of factors II and X during coumarin anticoagulation and their combined measurement with a new Fiix-prothrombin time. *Thromb Res* 2012; **130**: 674–81
135. Beardell FV, Varma M, Martinez J. Normalization of plasma factor X levels in amyloidosis after plasma exchange. *Am J Hematol* 1997; **54**: 68–71
136. Knight RD, Barr CF, Alving BM. Replacement therapy for congenital Factor X deficiency. *Transfusion* 1985; **25**: 78–80
137. Kouides PA, Kulzer L. Prophylactic treatment of severe factor X deficiency with prothrombin complex concentrate. *Haemophilia* 2001; **7**: 220–3
138. Castoldi E, Simioni P, Tormene D, *et al*. Differential effects of high prothrombin levels on thrombin generation depending on the cause of the hyperprothrombinemia. *J Thromb Haemost* 2007; **5**: 971–9
139. Aleman MM, Walton BL, Byrnes JR, *et al*. Elevated prothrombin promotes venous, but not arterial, thrombosis in mice. *Arterioscler Thromb Vasc Biol* 2013; **33**: 1829–36
140. Nicolaes GA, Dahlback B. Factor V and thrombotic disease: description of a janus-faced protein. *Arterioscler Thromb Vasc Biol* 2002; **22**: 530–8
141. Mann KG, Kalafatis M. Factor V: a combination of Dr Jekyll and Mr Hyde. *Blood* 2003; **101**: 20–30
142. Monkovic DD, Tracy PB. Functional characterization of human platelet-released factor V and its activation by factor Xa and thrombin. *J Biol Chem* 1990; **265**: 17132–40
143. Bouchard BA, Chapin J, Brummel-Ziedins KE, Durda P, Key NS, Tracy PB. Platelets and platelet-derived factor Va confer hemostatic competence in complete factor V deficiency. *Blood* 2015; **125**: 3647–50
144. Cmolik BL, Spero JA, Magovern GJ, Clark RE. Redo cardiac surgery: late bleeding complications from topical thrombin-induced factor V deficiency. *J Thorac Cardiovasc Surg* 1993; **105**: 222–7; discussion 7–8
145. Donohoe K, Levine R. Acquired factor V inhibitor after exposure to topical human thrombin related to an otorhinolaryngological procedure. *J Thromb Haemost* 2015; **13**: 1787–9
146. Sallah AS, Angchaisuksiri P, Roberts HR. Use of plasma exchange in hereditary deficiency of factor V and factor VIII. *Am J Hematol* 1996; **52**: 229–30
147. Baron BW, Mittendorf R, Baron JM. Presurgical plasma exchange for severe factor V deficiency. *J Clin Apher* 2001; **16**: 29–30
148. Tholpady A, Monson J, Radovancevic R, Klein K, Bracey A. Analysis of prolonged storage on coagulation Factor (F)V, FVII, and FVIII in thawed plasma: is it time to extend the expiration date beyond 5 days? *Transfusion* 2013; **53**: 645–50
149. Cushing MM, Asmis L, Calabia C, Rand JH, Haas T. Efficacy of solvent/detergent plasma after storage at 2-8 degrees C for 5 days in comparison to other plasma products to improve factor V levels in factor V deficient plasma. *Transfus Apher Sci* 2016; **55**: 114–9
150. Chediak J, Ashenhurst JB, Garlick I, Desser RK. Successful management of bleeding in a patient with factor V inhibitor by platelet transfusions. *Blood* 1980; **56**: 835–41
151. Seligsohn U, Zivelin A, Zwang E. Combined factor V and factor VIII deficiency among non-Ashkenazi Jews. *New Engl J Med* 1982; **307**: 1191–5
152. Nichols WC, Seligsohn U, Zivelin A, *et al*. Mutations in the ER-Golgi intermediate compartment protein ERGIC-53 cause combined deficiency of coagulation factors V and VIII. *Cell* 1998; **93**: 61–70
153. Zhang B, McGee B, Yamaoka JS, *et al*. Combined deficiency of factor V and factor VIII is due to mutations in either LMAN1 or MCFD2. *Blood* 2006; **107**: 1903–7
154. Mansouritorghabeh H, Shirdel A. Desmopressin acetate as a haemostatic elevator in individuals with combined

deficiency of factors V and VIII: a clinical trial. *J Thromb Haemost* 2016; **14**: 336–9
155. Tang M, Wierup P, Terp K, Ingerslev J, Sorensen B. Cardiac surgery in patients with haemophilia. *Haemophilia* 2009; **15**: 101–7
156. Sun WY, Witte DP, Degen JL, *et al*. Prothrombin deficiency results in embryonic and neonatal lethality in mice. *Proc Natl Acad Sci USA* 1998; **95**: 7597–602
157. Xue J, Wu Q, Westfield LA, *et al*. Incomplete embryonic lethality and fatal neonatal hemorrhage caused by prothrombin deficiency in mice. *Proc Natl Acad Sci USA* 1998; **95**: 7603–7
158. Mann KG. Thrombin: can't live without it; probably die from it. *Chest* 2003; **124**: 1S–3S
159. Girolami A, Scarano L, Saggiorato G, Girolami B, Bertomoro A, Marchiori A. Congenital deficiencies and abnormalities of prothrombin. *Blood Coagul Fibrinolysis* 1998; **9**: 557–69
160. Lancellotti S, De Cristofaro R. Congenital prothrombin deficiency. *Semin Thromb Hemost* 2009; **35**: 367–81
161. Allen GA, Wolberg AS, Oliver JA, Hoffman M, Roberts HR, Monroe DM. Impact of procoagulant concentration on rate, peak and total thrombin generation in a model system. *J Thromb Haemost* 2004; **2**: 402–13
162. Downes KA, Wilson E, Yomtovian R, Sarode R. Serial measurement of clotting factors in thawed plasma stored for 5 days. *Transfusion* 2001; **41**: 570
163. Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. *Vox Sang* 2010; **99**: 251–60
164. Lance MD, Ninivaggi M, Schols SE, *et al*. Perioperative dilutional coagulopathy treated with fresh frozen plasma and fibrinogen concentrate: a prospective randomized intervention trial. *Vox Sang* 2012; **103**: 25–34

Handling editor: Christa Boer