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Review

Diagnosis, therapeutic advances, and key recommendations for the management of factor X deficiency

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ABSTRACT

Factor X deficiency is a rare coagulation disorder that can be hereditary or acquired. The typology and severity of the associated bleeding symptoms are highly heterogeneous, adding to the difficulties of diagnosis and management. Evidence-based guidelines and reviews on factor X deficiency are generally limited to publications covering a range of rare bleeding disorders. Here we provide a comprehensive review of the literature on factor X deficiency, focusing on the hereditary form, and discuss the evolution in disease management and the evidence associated with available treatment options. Current recommendations advise clinicians to use single-factor replacement therapy for hereditary disease rather than multifactor therapies such as fresh frozen plasma, cryoprecipitate, and prothrombin complex concentrates. Consensus in treatment guidelines is still urgently needed to ensure optimal management of patients with factor X deficiency across the spectrum of disease severity.

1. Introduction

Factor X deficiency is a rare coagulation disorder that is either hereditary (i.e. an autosomal recessive condition) or acquired (usually due to amyloidosis) [1,2]. Given the rarity of the disorder, currently available reviews and guidance on the management of factor X deficiency generally form a relatively small component within larger publications addressing the diagnosis and management of multiple rare coagulation disorders [3–7]; indeed, a review of the literature uncovered only one authoritative factor X–focused review, published in 2008 [8], and only one publication in the past 5 years specifically concerned with the treatment of factor X deficiency [9].

We therefore sought to review the published literature on factor X deficiency and summarize current knowledge on the diagnosis and management of factor X deficiency, focusing in particular on hereditary disease. In addition, in view of the recent introduction of new treatments for factor X deficiency, we describe the evolution of treatments to manage factor X deficiency and discuss the advantages and disadvantages of each treatment type along with the treatment options in specific circumstances requiring special consideration. It is hoped that this exposition will help to bridge current gaps in our knowledge and highlight areas where further research is required, such as the minimum concentration of factor X required for hemostasis, as well as address the need for recommendations concerning the optimal management of factor X–deficient patients.

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2. Methods

A literature search was conducted in the US National Library of Medicine PubMed database for publications indexed for the major Medical Subject Headings (MeSH) term "Factor X Deficiency" and published in the English language since 1990. Additional relevant publications were identified from citations within relevant reviews and guidelines, such as the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guidelines on rare coagulation disorders [4]. This was supplemented by published abstracts presented at recent relevant conferences (annual meetings of the American Society of Hematology from 2015 to 2017 and the International Society on Thrombosis and Hemostasis from 2015 to 2018) that contain the phrase "factor X deficiency" or "FX deficiency."

Publications were manually selected from the search results that addressed key topics of interest: disease presentation/etiology/diagnosis; treatment (plasma, prothrombin, factor IX and X replacement, and prophylactic treatment); management under special situations, notably pregnancy, surgery, intracranial bleeding, and severe disease (bleeding within the central nervous system [CNS] or gastrointestinal [GI] tract); and other considerations (in particular, phenotype/genotype correlation and acquired factor X deficiency). In areas in which few publications were identified, additional searches without MeSH or date limitations were conducted as necessary to ensure that all topics of interest were adequately addressed.

3. Hereditary factor X deficiency: overview and diagnosis

3.1. Disease overview

Hereditary factor X deficiency is an autosomal recessive disorder of the *F10* gene that causes a variable reduction in plasma factor X coagulant activity (FX:C), in which decreasing FX:C activity is correlated with increasing bleeding severity [3,4,8,10,11]. In a cross-sectional study using data from the European Network of Rare Bleeding Disorders (EN-RBD), FX:C levels at which patients were asymptomatic or had grade 1, 2, or 3 bleeding were 56, 40, 25, and <10 IU/dL, respectively [10]. A similar classification has been proposed based on data from the EN-RBD registry, in which patients with factor X activity levels of >40, 10–40 and <10 IU/dL are classified as being largely asymptomatic, suffering minor spontaneous or triggered bleeding, or having a high risk of major spontaneous bleeding, respectively [12]. The disorder is sometimes further classified into type I disease (low coagulant activity and low immunological antigen levels) or type II disease (low coagulant activity and normal/borderline low antigen levels) [1,11,13].

The most severe form of the disease is rare, resulting from homozygous or compound heterozygous hereditary defects. The overall distribution of patients with factor X deficiency corresponds to approximately 8% of the total number of patients with rare blood disorders, yielding a worldwide prevalence of 1:1,000,000 [5,6,14]. However, in countries and regions in which consanguineous marriage is common, such as Iran, southern India, Pakistan, and Latin America, severe factor X deficiency occurs 8 to 10 times more frequently than in other regions [1,6,15–17]. While the heterozygous form of the disease is much more common (prevalence approximately 1:500 worldwide), it is associated with only a mild reduction in plasma FX:C (functional activity >30%) and is usually clinically asymptomatic [3].

Clinical manifestations are most commonly seen as mucocutaneous bleeds (particularly epistaxis), hemarthroses (soft tissue and joint bleeding), GI bleeding, and heavy menstrual bleeding [1,3–5,16,18–20]. In a review of 32 cases in Iran, these symptoms were reported in 72%, 69%, 38%, and 50% of patients, respectively, and in 61%, 77%, 66%, and 60% of those with severe factor X deficiency (FX:C levels of <10 IU/dL, n = 18), respectively [19]. Other symptoms seen in more severe cases include severe postoperative hemorrhage and CNS bleeding. Although CNS/intracranial hemorrhage occurs less frequently (being reported in 9%–21% of symptomatic cases of factor X deficiency [4,16,17,19]), it is a major concern, as it can be a presenting symptom of severe factor X deficiency at birth; patients may present at any age, but the most severe forms of disease become apparent at an early age, typically with umbilical stump or CNS bleeding in the newborn [1,5].

Patients with moderately severe disease (FX:C 1–5 IU/dL) are likely to bleed as a result of hemostatic challenge (e.g. trauma and surgery), while those with mild factor X deficiency may remain undiagnosed until they participate in routine screening or family studies [3]. Mild bleeding may occur in some heterozygous patients, typically after surgery, tooth extraction, trauma, or childbirth [17,21].

3.2. Genetic variants

As may be expected given the wide range in impact of the disease on FX:C levels, the genetic profile of factor X deficiency is varied [22–24]. The most common sites of mutation have been localized to the glutamic acid domain on exon 2 [8,22,24] and the catalytic site of factor X on exons 7 and 8, which are critically important in the functional activity of this protein [8,11]. Most mutations are reported to be missense mutations unique to a particular patient or family [1,8,11,13,22,25]. However, there is no clear link between the genotype/location of the mutation and the phenotypic expression of the disease [1,26,27]. Consistent with animal findings, complete absence of factor X is incompatible with life [11].

3.3. Assays for diagnosis

Prolongation of the prothrombin time (PT) and/or activated partial thromboplastin time (APTT) that can be corrected in a 50:50 mix with normal plasma are suggestive of either deficiency or an inhibitor of the final common pathway, and specific coagulation factor assays are necessary to determine which factors are deficient. The diagnosis of factor X deficiency may be confirmed by quantifying plasma FX:C through serial dilutions with factor X–deficient plasma [1,3,4,8]. Although such one-stage PT- or APTT-based clotting assays are sufficient to diagnose factor X deficiency, the corresponding degrees of prolongation may be influenced by differences in sensitivity between types of thromboplastin.

Additional methods available to support diagnosis include the dilute Russell Viper Venom (RVV) assay (a metalloproteinase that activates factor X directly and can therefore detect factor X deficiency in plasma samples), chromogenic assays (spectrophotometric detection of a substrate sensitive to activated factor X), and immunological assays (e.g. an enzyme-linked immunosorbent assay [ELISA] that measures factor X antigen) [3,4,8], though these assays cannot be used as screening tests for factor X deficiency given the false-normal values in patients with type II disease [1,3,8]. Cases of patients with factor X deficiency showing normal RVV assay results have also been reported [26,28,29]. This unexpected result was associated with a variety of genetic mutations and factor X dysfunction. While these methods may provide interesting or supportive information, measurement of factor X activity alone suffices to assess disease severity.

Concerns over the variability and reliability of test results, which depend on factors such as the type of anticoagulant used, sample shipping and centrifugation prior to analysis, the storing of reagents, equipment maintenance, and the use of internal/external quality control, have led to the development of laboratory standards [1]. Despite this, studies using both chromogenic and clotting assays have demonstrated differences between the two methods, depending on both the standard preparation used in the assay and the analytical method; however, the authors reporting these results have deemed this unlikely to be of clinical significance and noted that adjustments can be incorporated to accommodate any minor differences [30,31].

4. Evolution of treatment

Historically, bleeding episodes in patients with coagulation disorders were treated with whole blood replacement and later with fresh frozen plasma (FFP) products. More recently, with further elucidation of the role of specific coagulation factors and advances in technological abilities, a range of coagulation factor concentrates have been developed as replacement therapies [7]. For hereditary factor X deficiency, current therapeutic options include FFP, cryoprecipitate, prothrombin complex concentrates (PCCs), dual-factor therapy (factor IX/X), and human plasma–derived factor X concentrate (pdFX).

4.1. Plasma

Historically, hereditary factor X deficiency has been treated by plasma replacement therapy. Although virally inactivated FFP is now preferred to the native form, it is not universally available [1,7,9,32].

Typically, virally inactivated FFP is administered once daily (20 mL/kg then 3–6 mL/kg), aiming to maintain FX:C trough levels above 10–20 IU/dL [3]. Such levels are usually sufficient to treat hemarthrosis and soft tissue bleeding, but higher levels may be required for severe bleeding or surgery [33].

Concerns with this treatment include allergic reactions, the need for adequate pathogen inactivation, the increased risk of transfusion-related acute lung injury due to the unknown concentrations of other coagulation factors, delayed efficacy, physiologic differences in the hemostatic system of neonates and young children versus older patients, fluid overload due to the large volume required to achieve sufficiently high plasma FX:C levels, and the variable levels of vitamin K-dependent clotting factors in FFP, including FX [1,8,9,34–37]. Approaches to overcome some of these issues include antihistamine premedication in patients with a history of allergy; solvent-detergent processing for pathogen removal, though this may cause some loss of coagulation factors); the elimination of leukocyte antibodies that precipitate transfusion-related injuries by using plasma only from men, women who have not been pregnant, or women who have tested negative for human leukocyte antigen antibodies; and using slower infusion rates or diuretics to reduce the risk of fluid overload [38,39].

An additional concern is the substantial variability between plasma products, which may impact treatment efficacy [40]; substantial differences have been observed in the half-life of factor X when infused as FFP or plasma complex concentrates, with values ranging from 17 to 40 hours [41–43]. In addition, studies using FFP as the factor X source in two patients with undetectable levels of factor X showed considerable intra- as well as interindividual variation in apparent factor X half-life. However, there have been no reported cases of anti–factor X inhibitory antibodies developing in patients treated with FFP [8,41].

4.2. Cryoprecipitate

Early attempts to create improved factor VIII concentrates from pooled plasma in the early 1960s led to the discovery of cryoprecipitate, which is enriched in fibrinogen, factor VIII, von Willebrand factor, and factor XIII [44]. Cryoprecipitate is commonly prepared from thawed FFP (made from plasma processed within 8 hours of collection) or from whole blood processed within 24 hours of collection, which is then centrifuged to remove the supernatant and yield the insoluble precipitate [44,45]. Without viral inactivation, cryoprecipitate was viewed as an unacceptably high-risk product, able to transmit viral infection [46]. This led to its withdrawal from many European countries, although cryoprecipitate remains available for hemostatic therapy in several countries, including the United States and Canada [44]. The effectiveness of cryoprecipitate in achieving therapeutic levels of factor X may be limited [4,7], and the cost of virus-inactivated cryoprecipitate may actually be greater than that of specific factors in some countries. Therefore, if single-factor concentrate is available, it should be used rather than cryoprecipitate. However, where a single-factor concentrate is unavailable, cryoprecipitate that has been virus inactivated (e.g. by methylene blue treatment or solvent-detergent treatment) has potential value.

4.3. Prothrombin complex concentrates

The therapeutic options available for treating factor X deficiency increased with the approval of plasma-derived, virally inactivated PCCs, at which point PCC treatment quickly came to be preferred over the use of FFP, at least in the United States and Canada [3,8,9,20,47]. Several PCC products are now available, as summarized in Table 1. However, in the European Union, the use of PCCs for factor X deficiency has been limited to the treatment of bleeding and perioperative prophylaxis in congenital deficiency of vitamin K–dependent factors II and X when a purified specific coagulation factor product is not available. PCCs typically include three or four coagulation factors (factors II, IX, and X, with or without factor VII), and most also include one or more other factors with anticoagulant activity, such as heparin, antithrombin, protein C, protein S, and/or protein Z [9,47,48]. The various products differ in the relative content of each coagulation factor, and there may also be variability between product batches [1,9]. This variability poses a particular risk for patients with severe symptoms, who require frequent infusions [1,47–50].

As PCCs were originally developed for the treatment of factor IX deficiency (hemophilia B), the focus in product labelling and dosing guidelines is on the concentration of factor IX. Most PCC products have approximately equivalent factor IX and X activity and increase plasma levels by approximately 1.5%/IU/kg body weight; a typical 20–30 IU/kg dose of factor IX is expected to increase plasma FX:C activity by 40–60 IU/dL [4,8]. PCCs do not generally require daily administration due to the long half-life of factor X (approximately 30 hours) [4,8], though there is substantial variability in the half-life of factor X infused as PCCs.

The efficacy of PCC administration has been reported in several small case series for various uses in patients with FX deficiency, including prophylaxis in patients with severe factor X deficiency, control of minor bleeding episodes, and hemostatic cover during surgical procedures, but in patients with recurrent intracranial hemorrhage, outcomes have varied depending on the plasma factor X levels achieved [1,3,8,20]. This has led to PCC dosing guidance indicating that 20–30 IU/kg (factor IX) should increase plasma factor X activity by 40–60 IU/dL, with further infusions required daily or every 2 days if sustained treatment is required [1,4]. However, there remains a lack of consensus among evidence-based recommendations regarding PCC use in different countries, as well as insufficient evidence to establish differences in efficacy and safety between three- and four-factor PCCs [47].

Concerns associated with PCC administration for factor X deficiency include the unknown concentrations of factors II, VII, and X and the increased risk of thrombosis [1,9,51]. The risk of thrombosis with PCCs appears be related to differences in product quality, the dose administered, infusion rates, and/or patient characteristics/risk profile, with thrombotic events associated with PCC administration observed more frequently among patients with acquired hemostatic disorders than in those with hereditary coagulation deficiencies [9,48,51]. Increased levels of factors VII, IX, and/or X do not appear to influence total thrombin generation; rather, evidence suggests that the most likely determinant of this thrombotic risk is the accumulation of prothrombin (factor II) due to its long half-life, along with the balance between this coagulation factor and coagulation inhibitors [48]. Since the half-lives of the different coagulation factors differ widely (from 6 hours for factor VII to 20 hours for factor IX, 30 hours for factor X, and 60 hours for factor II), repeated dosing can lead to accumulation of factors II and X. Consequently, care should be exercised during repeated or long-term PCC administration, and the inclusion of coagulation inhibitors such as protein C, protein S, and protein Z or antithrombin should be considered, particularly for patients with liver disease [48]. The

Table 1
Overview of PCC products previously or currently available in Europe, the United States, or Canada [1,4,47–50,96–109].[a]

Product name, content	Manufacturer or marketing authorization holder	Purification	Factor X content (IU relative to factor IX)	Coagulation proteins and other antithrombic additions
FEIBA NF or VH, PCC [108]	Baxalta US Inc./Shire/Baxter Healthcare Corporation	Vapor heat, nanofiltration, DEAE-Sephadex adsorption	NA	None
Proplex-T, 4-factor PCC [109]	Baxter Healthcare Corporation	Dry heat	100	Antithrombin, heparin
Prothromplex Total, 4-factor PCC [96]	Baxter Bioscience, Baxalta Innovations GmbH, Shire Pharmaceuticals Ltd	Vapor heat	100	Antithrombin, heparin
Prothromplex TIM3, 3-factor PCC	Baxter SpA		100	
Beriplex® P/N, 4-factor PCC [99–101]	CSL Behring	Pasteurization, nanofiltration	110–190	Antithrombin, heparin, proteins C, S, and Z
Confidex, 4-factor PCC [110]	CSL Behring GmbH	Pasteurization	100–200	Antithrombin, heparin, proteins C and S
Prothrombinex® VF, 3-factor PCC [102]	CSL Behring (Australia) Pty Ltd., CSL Bioplasma	Dry heat, nanofiltration	100	Antithrombin, heparin, low levels of factors V and VII
Profilnine®, 3-factor PCC [103]	Grifols Biologicals Inc.	Solvent detergent, nanofiltration	100	Antithrombin, low levels of factor VII
Uman Complex DI, 3-factor PCC	Kedrion SpA	Solvent detergent, dry heat	80	Antithrombin, heparin, proteins S, C, and Z
Kaskadil, 4-factor PCC [107]	LFB Biomedicaments	Solvent detergent	160	Heparin, proteins S and C
Kanokad, 4-factor PCC [104]	LFB Biomedicaments		56–140	Proteins S and C
Octaplex®/Ocplex®/Pronativ® 4-factor PCC [105]	Octapharma Limited	Solvent detergent, nanofiltration	72–120	Heparin, proteins C, S, and Z; low activated factor VII
Cofact, 4-factor PCC [106]	Sanquin Plasma Products BV	Solvent detergent, nanofiltration	56–140	Antithrombin, proteins C, S, and Z
Kcentra®, 4-factor PCC [111]	CSL Behring	Heat, nanofiltration	125–165	Antithrombin, heparin, proteins S and C

Three-factor PCC products contain factors II, IX, and X; 4-factor PCC products contain factors II, VII, IX, and X.
NA, not available; PCC, prothrombin complex concentrate.
[a] Not all products were/are available in all markets.

UKHCDO guidelines note that PCCs should be used with caution, if at all, in patients with liver disease, large hematomas, major trauma, or antithrombin deficiency as well as in neonates [3].

As with FFP, PCC administration has not been associated with the development of inhibitory antibodies in patients with factor X deficiency [8], though antibody formation has been reported with other uses of PCCs [49].

4.4. Factor IX and X replacement

Freeze-dried concentrate containing specified amounts of human factors IX and X was developed in response to concerns about variability in coagulation factors in PCCs [1] and potential fluid overload or inability to maintain therapeutic levels with repeated administration [7]. Among the many factor IX products available, most contain multiple additional coagulation factors. However, available products also include a dual factor IX and factor X (Factor X P Behring [CSL Behring AG, Bern, Switzerland]) and several single-factor products. The two-factor product is a powder formulation containing 600–1200 IU human coagulation factor X and 600 IU human coagulation factor IX per vial, along with antithrombin III and heparin [52], and it is currently licensed only in Switzerland. Single-factor products include Immunine VH (Baxter AG, Vienna, Austria), a highly purified freeze-dried concentrate of virally inactivated pooled human blood coagulation factor IX also containing trace amounts of other coagulation factors (<0.02 IU of factors II, VII, and X per IU of factor IX) and heparin (<0.1 IU/mL) [53]. Another option is AlphaNine® SD (Grifols Biologicals, Inc., Los Angeles, CA, USA), a purified, virus-filtered lyophilized powder formulation of factor IX derived from human plasma that also contains trace amounts of factor VII (<0.04 U/IU factor IX), factor II (<0.05 U/IU), factor X (<0.05 U/IU), and heparin (<0.04 U/IU) [54].

The efficacy of dual-factor therapy in subjects with factor X deficiency has been reported in two studies. The most recent study followed 10 subjects with severe factor X deficiency who were given prophylactic therapy with Behring Factor X P (20 IU/kg administered weekly) for 1 year. The nine subjects who tolerated the treatment and remained on therapy for the full year all achieved factor X levels of ≥1 IU/dL and had no bleeding symptoms; one patient stopped treatment after the first infusion due to an anaphylactic reaction [55]. An earlier analysis of data from the Greifswald Registry showed that bleeding episodes in seven patients with factor X deficiency were well controlled using regular prophylaxis with another dual-factor product, Factor IX HS® (ZLB Behring [now CSL Behring]), a plasma-derived, pasteurized concentrate containing approximately 800 IU factor X and 1200 IU factor IX [56].

Of these factor IX/X products, only Behring Factor X P is approved for the treatment of factor X deficiency, and, as previously noted, this product is available only in Switzerland; at the time of licensing, no clinical trials had been performed with the product in subjects with factor X deficiency due to the rarity of the disease. Consequently, dosage recommendations are based on published information mainly derived from treatment of factor X–deficient patients with plasma or PCCs [52] plus the single study of Factor X P that has since been published [55].

Adverse events potentially associated with factor IX/X treatment include hypersensitivity reactions, thrombosis (which necessitates monitoring of factor IX levels and D-dimer), nephrotic syndrome, and the development of neutralizing antibodies [1,9,52,57].

4.5. Factor X replacement

Recognition of the advantages of single-factor concentrates over plasma or PCC replacement therapy for rare bleeding disorders [7,9,58] led to the development of Coagadex® (Bio Products Laboratory Ltd), a high-purity, high-potency pdFX formulation that represents the first and only available treatment specifically for hereditary factor X deficiency [59–61]. In Europe, pdFX is indicated in all age groups for the treatment and prophylaxis of bleeding episodes and for perioperative management of bleeding in patients with hereditary factor X deficiency [60]. In the United States, it has been approved for use in adults and children with hereditary factor X deficiency for routine prophylaxis to reduce the frequency of bleeding episodes, for on-demand treatment and control of bleeding episodes, and for perioperative management of bleeding in patients with mild and moderate hereditary factor X deficiency [59].

The approval of this product followed the successful outcomes of two pivotal phase 3 trials (designated TEN01 and TEN03; ClinicalTrials.gov identifiers NCT00930176 and NCT01086852, respectively) in a total of 18 subjects with mild to severe hereditary factor X deficiency [31,59,62–64].

In order to provide a more comprehensive understanding of the safety of pdFX, an analysis was conducted across the three prospective clinical trials, together with postmarketing data (spontaneously reported adverse reactions), with up to 4 years of follow-up [65]. Across the clinical trials, 18 subjects aged ≥12 years and 9 children aged <12 years received pdFX over a total of 2495 days of exposure, with six treatment-emergent adverse reactions (all nonserious) observed in two subjects. In the analysis of postmarketing data through September 16, 2017, an estimated 2925 pdFX infusions were administered over 105 patient-years; there were three case reports of nine nonserious adverse reactions, with no inhibitor development and no thromboembolic events, and the authors concluded the good safety profile of pdFX in clinical trials.

No cases of thrombosis or inhibitor development were reported with pdFX treatment in clinical studies, including with up to 4 years of treatment [62,63,66,67].

4.6. Prophylactic treatment

Prophylactic therapy is recommended in patients with severe factor X deficiency, particularly those at risk for severe bleeding episodes such as CNS and GI bleeding, hematoma, and hemarthrosis [1]. This recommendation is based on beneficial effects observed across several case series using various prophylactic strategies. Data from the Greifswald registry showed that bleeding episodes in seven patients with factor X deficiency were reduced using Factor IX HS at doses of 15–20 IU/kg factor X weekly, while control of joint bleeding required treatment 2–3 times per week, and two patients received prophylaxis every other day [56]. Similarly, bleeding symptoms in 10 patients with severe factor X deficiency were significantly reduced in a study of prophylaxis using 20 IU/kg Behring Factor X P concentrate weekly [55]. In addition, prophylactic PCC therapy at FX doses of 50–70 IU/kg once or twice weekly achieved hemostasis in four neonates with severe factor X deficiency (with umbilical cord bleeding, intraperitoneal hemorrhage, and/or intracranial bleeding) [1,42] and three children with recurrent hemarthrosis and intracranial hemorrhage (described further in Sect. 5.3) [8,16,68]. Additional individual cases of successful use of PCC prophylaxis have also been reported, including an adult patient with severe factor X deficiency who received a dose of 30 IU/kg twice weekly to prevent joint bleeding [1,69]. In other reports, PCC doses providing 15–40 IU/mL factor IX 2–3 times weekly exhibited greater efficacy than doses delivering 20–70 IU/mL once weekly [4]. While the optimal dosing regimen for PCC remains to be confirmed, the higher risk of major spontaneous bleeding observed in the EN-RBD registry at factor X levels <10% suggest that factor X ≥ 10% is an appropriate target level for prophylaxis [12].

However, the most authoritative data on prophylactic therapy come from the results of a 6-month, open-label, multicenter, prospective phase 3 study of pdFX prophylaxis in 9 children aged <12 years with confirmed diagnosis of moderate to severe hereditary factor X deficiency (ClinicalTrials.gov identifier NCT01721681) [67]. Eight subjects with severe factor X deficiency (baseline FX:C < 1 IU/dL) and one with moderate factor X deficiency (baseline FX:C = 1 IU/dL) were enrolled to receive routine prophylaxis at a recommended dose of 40–50 IU/kg twice weekly to maintain trough FX:C levels >5 IU/dL (with peak levels ≤120 IU/dL). Incremental recovery was significantly lower at each time point in younger subjects (0–5 years) than in older subjects (6–11 years; $p < 0.05$). Following the first dose, mean incremental recovery was 1.45 in subjects aged 0–5 and 1.83 in subjects aged 6–11, both of which are lower than the mean incremental recover in subjects aged 12 or older (2.04) [59]. There were 10 bleeds during the study (6 minor, 3 major, and 1 of unrecorded severity) in 3 subjects, of which 4 bleeds in 2 subjects were treated with a single infusion of pdFX (mean dose ± standard deviation, 35.3 ± 7.2 IU/kg). The investigators rated the prophylactic efficacy of pdFX (primary endpoint) as excellent (defined as no minor or major bleeds during the study period or a lower frequency of bleeds than expected given the subject's medical/treatment history) for all subjects in the per-protocol population (those with ≥50 days of exposure and ≥26 weeks of treatment). The safety profile was consistent with previous studies conducted in subjects aged ≥12 years [65].

Further evidence of the efficacy of pdFX prophylaxis was also found in a retrospective analysis of 15 subjects with hereditary factor X deficiency who received pdFX on a compassionate-use basis (TEN05), which is described in Sect. 4.4. This study included seven subjects given pdFX for routine prophylaxis (defined as regular doses of 25 IU/kg at least once/week) and one subject who alternately received prophylactic and on-demand treatment [66]. Four of the eight subjects given routine pdFX prophylaxis experienced bleeds (mean, 2.1 bleeds per patient total and 0.09 bleeds per patient per month). This bleed frequency was lower than that among subjects given on-demand therapy, whereas the mean dose of pdFX given to treat the bleeds was slightly higher (26.7 vs 20.5 IU/kg, respectively) [66]. Like on-demand treatment, prophylactic therapy was not associated with any adverse drug reactions, safety concerns, infusion site reactions, tolerability issues, or inhibitor development [66].

5. Special situations

5.1. Women and girls with factor X deficiency

In addition to exhibiting the general bleeding symptoms associated with factor X deficiency, women and girls with this disorder may also experience heavy menstrual bleeding and complications associated with pregnancy and childbirth [70]. Therapeutic options for control of heavy menstrual bleeding have included antifibrinolytics, a levonorgestrel intrauterine system, oral and hormonal contraceptives, and clotting factor replacement, as well as surgical procedures such as endometrial ablation and hysterectomy [70]. In a post hoc analysis of the efficacy, safety, and pharmacokinetics of pdFX in 16 subjects from study TEN01 with moderate or severe factor X deficiency, pdFX treatment was effective at treating spontaneous bleeding as well as bleeding due to injury or menstruation in the 10 women and girls (aged 14–58 years); across 132 assessable bleeding episodes in women and girls (55.3% major bleeds, 43.9% minor, and 0.8% uncategorized), there was a 98% treatment success rate, defined as an investigator-rated response of "excellent" or "good" [71], with a total of 267 pdFX infusions (178 for on-demand treatment and 89 preventive infusions) administered. Women and girls received more infusions per month (2.48) than men and boys (1.62); treatment of bleeds required a mean of 1.58 infusions per month per woman/girl (vs 0.65 infusions per month for each man/boy) and an average dose of 30.5 IU/kg pdFX [71].

Although factor X levels are known to rise during pregnancy, women with severe factor X deficiency and a history of adverse outcomes (e.g. spontaneous abortion, placental abruption, or premature birth) usually require replacement therapy to maintain hemostasis at delivery, together with appropriate monitoring to minimize the risk of thrombotic complications (particularly in those given PCCs) [1,3,4]. The use of PCCs or FFP as factor X replacement therapy during pregnancy has also been reported, but with highly variable regimens, as described elsewhere [4,8,72]; in one series of 13 cases, the complication rate was relatively high, with two women experiencing postpartum hemorrhage, though there were no cases of thrombosis [8,73]. In addition to PCC use, one case of plasma exchange with FFP prior to cesarean delivery in a pregnant patient with severe factor X deficiency has been reported [72].

In another case report, the safe and effective use of pdFX treatment to maintain hemostasis during pregnancy and delivery was described in a patient with factor X deficiency (basal FX:C < 5 IU/dL) who had

participated in a phase 3 trial of on-demand/prophylactic pdFX use and was receiving 1500 IU pdFX (approximately 23 IU/kg) twice weekly under a compassionate-use program. Following four spontaneous abortions (three unconfirmed), the patient reported another pregnancy. The frequency of pdFX treatment was increased to three times weekly to prevent nose bleeds and protect the pregnancy, with twice-weekly administration resuming 3 weeks after healthy, uncomplicated delivery (spontaneous labor supported by an additional 1500 IU dose of pdFX) [74].

Published recommendations for this patient population include aggressive factor X replacement therapy in women with severe deficiency and a history of adverse outcome in pregnancy, and assaying of factor X levels in pregnant heterozygous women prior to delivery to assess the bleeding risk, followed by assaying of factor X levels in cord blood at birth for the neonate, with retesting at 6 months of age [3]. Antenatal prophylaxis should be considered in pregnancy in women with severe factor X deficiency and a history of recurrent bleeding or adverse pregnancy outcomes. Expert consensus UK guidance recommends the maintenance of factor X activity >30 IU/dL following delivery in women with low factor X levels and a history of bleeding, as well as in all women requiring cesarean section [74].

5.2. Surgery

The evolution of treatment for patients with severe factor X deficiency undergoing surgery followed the same pattern as that described in Sect. 4 above, with early cases managed using FFP, PCCs, and factor IX/X concentrate [32] prior to factor X concentrate becoming available. However, data associated with the use of PCCs and/or infusions of FFP are confined to individual case reports in which hemostasis during surgery was achieved with this treatment modality, maintaining postoperative factor X levels at 10–40 IU/dL [32,75–78].

The efficacy and safety of pdFX for perioperative bleeding management has been evaluated as part of two prospective, open-label phase 3 studies involving five subjects aged 14–59 years undergoing seven surgical procedures: two subjects participating in study TEN01 who each underwent two procedures and three subjects from study TEN03 who each underwent one procedure [63]. Factor X deficiency was severe (FX:C levels <1 IU/dL) in two subjects, moderate (FX:C ≥ 1 to <5 IU/dL) in one patient, and mild in two subjects (FX:C 6 and 8 IU/dL, respectively), all with a history of bleeding after surgery or spontaneous bleeding. All subjects were given pdFX infusion to raise plasma FX:C levels to 70–90 IU/dL 1–4 hours before surgery. For all surgeries (four major and three minor), no blood transfusions were required, the investigator evaluation of hemostatic efficacy was “excellent” (defined in terms of parameters similar to those in subjects without a bleeding disorder), and no additional pdFX infusions were given during surgery [63]. In this study, FX:C levels were maintained above 50 IU/dL until the subject was no longer considered to be at risk of postoperative bleeding. (This lower limit of 50 IU/dL is higher than that traditionally considered sufficient for hemostasis: FX:C levels of 0.1–0.2 IU/mL [10–20 IU/dL] are generally regarded as sufficient for subjects undergoing surgery, though this is based on very little evidence [3,32].) There were no adverse drug reactions, hypersensitivity reactions, thrombotic events, or evidence of inhibitor development [63].

In addition, the compassionate-use study described in Sect. 4.4 (study TEN05) included three subjects receiving pdFX as presurgical hemostatic cover [66]. Two subjects each underwent a dental procedure and received a single presurgical pdFX infusion (27.1 and 28.5 IU/kg), and one patient underwent a port-a-cath insertion and required six infusions to maintain hemostasis (72.8 IU/kg presurgically and five infusions of 48.5 IU/kg on postsurgical days 1, 2, 3, 5, and 15) [66]. These subjects were included together with others receiving compassionate use in the analysis of efficacy (rated as “excellent” or “good” for all subjects) and safety, as reported in section 4.5 [66].

5.3. Intracranial bleeding

Intracranial hemorrhage has been reported in 9%–26% of patients, most commonly in neonates, and seems to be associated with the occurrence of Gly380Arg mutation in particular [1,8,16,17,19]. Management following intracranial hemorrhage has primarily focused on PCC prophylaxis [8,16,68,79], though FFP has also been used with some success [78]. The findings of several cases reviewed by Brown et al. were variable, with no further bleeding seen in two reports in a total of five children with intracranial hemorrhage treated with PCC doses of 40–70 U/kg factor IX once or twice weekly [42,79], but inadequate efficacy observed in two other children treated with PCC weekly or twice weekly [43]. In addition, in a report of three cases of severe congenital factor X deficiency (FX:C < 1 IU/dL) in neonates with spontaneous life-threatening intracranial hemorrhage, FFP infusion was of limited benefit, and patients were treated with activated PCC prophylaxis at 50 IU/kg doses administered twice weekly for 10, 4, and 2 years, respectively, with no new bleeding episodes observed [68].

With the development of single-factor concentrates, a case has also recently been reported of a 20-year-old male with severe factor X deficiency who experienced a subdural hematoma that was effectively treated with 15 IU/kg pdFX. After recovery, the patient received weekly routine prophylaxis with 25 IU/kg pdFX [80].

Because of the high risk of intracranial hemorrhage in neonates with severe factor X deficiency, cranial ultrasound scanning has been recommended, together with prophylactic replacement therapy prophylaxis, though the authors warn that hemorrhage may still occur even with these measures [3].

6. Other considerations: acquired factor X deficiency

Acquired factor X deficiency can be caused by primary amyloidosis (occurring in up to 14% of patients with amyloidosis), severe liver disease, or vitamin K antagonist therapy (in association with other coagulation factor deficiencies) [2,8]. In addition, acquired inhibitors to factor X have been identified in patients with burns, respiratory infections, or exposure to topical thrombin [8]. The clinical characteristics, common comorbidities, and typical symptoms of patients with acquired factor X deficiency have been summarized in previous reviews [2,81], supplemented by more recent analyses (e.g. by Patel et al. [82]). In brief, bleeding manifestations resemble those in patients with hereditary factor X deficiency and show marked heterogeneity; however, bleeding tendency is not always correlated with FX:C levels in these patients, unlike those with hereditary factor X deficiency [2].

The presence of a specific inhibitor has been observed in some patients with acquired factor X deficiency [1,2], suggested by anomalous findings, such as factor X assays that are inconsistent with the extent of hemorrhagic symptoms. Testing for inhibitory activity typically involves mixing patient and normal plasmas and measuring factor X activity following dilution; additional tests may also include ELISA testing for immunoglobulin M and G antiphospholipid antibodies and platelet neutralization testing [83,84].

Unlike the hereditary form of the disease, acquired factor X deficiency appears to be short-lived, with some patients even demonstrating spontaneous normalization of coagulation tests; all of the cases described by Lee et al. [2] demonstrated a complete recovery, and none required long-term therapy for factor X deficiency. However, at least one case has subsequently been reported of fatal bleeding due to acquired factor X and IX deficiencies [85].

There is no standardized treatment for acquired factor X deficiency [2]. Limited, variable success has been achieved with vitamin K plus FFP, PCCs (with dosing frequency and disease severity each playing a role in treatment efficacy), dual-factor concentrate, or recombinant activated factor VIIa with oral corticosteroids [2,86–94]. Treatments targeting the underlying primary conditions have been successful for some patients, including patients with inflammatory bowel disease,

malignancy, or infections, along with removal of precipitant medications [2]. In addition, a few cases have been reported of improvement on treatment with various other treatment approaches: FFP and vitamin K; high-dose glucocorticoids; alpha amino-caproic acid or recombinant activated factor VII in conjunction with prednisolone; factor IX complex in combination with activated clotting factor, PCCs, and prednisolone; intravenous immunoglobulin; and therapy targeted at removing specific inhibitors and suppressing the immune system in patients with suspected inhibitors [2].

Recently, two cases have been reported of the successful treatment of acquired factor X deficiency in patients with systemic light-chain amyloidosis with pdFX; the findings indicated that higher and/or more frequent dosing may be required for hemostasis, with frequent monitoring of factor X levels to achieve target thresholds similar to those in patients with hereditary factor X deficiency (10–16 IU/dL for minor bleeding and 50 IU/dL for major bleeding, trauma, or surgery [95]. However, pdFX is not approved for the treatment of acquired factor X deficiency.

7. Conclusions and recommendations

Factor X deficiency is among the most serious of the rare bleeding disorders, particularly in neonates and small children with severe factor X deficiency, who are at risk of life-threatening bleeds within the first weeks and months of life. It is a highly heterogeneous disorder, both as a hereditary disease and as an acquired deficiency. The treatment of factor X deficiency has evolved over recent years, with the development of pdFX representing the most recent advance. While the patient numbers in clinical studies are limited due to the rarity of the disease, evidence to date indicates that single-factor therapy with pdFX provides advantages over previously used multiple-factor therapies such as FFP and PCCs, which may fail to achieve adequate hemostasis due to dose limitations associated with the risks of volume overload with FFP (especially in neonates and small children with severe deficiency and life-threatening bleeds), anaphylaxis, and thrombosis.

Current prescribing information for available therapies provides limited guidance on dosing in the treatment of factor X deficiency, whether hereditary or acquired. (See Table 2 for current guidance on dosing derived from various sources.) The most specific information is given in the prescribing information for pdFX for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment to control bleeding episodes, and peri- and postoperative management of bleeding, which includes recommendations of target plasma factor X levels of 70–90 IU/dL and 50 IU/dL for pre- and postoperative periods, respectively [59]. A minimum threshold of 10–20 IU/dL has been suggested to provide adequate hemostasis for bleeding prophylaxis and in the treatment of minor bleeding [3,32,95].

For pregnant women (or women wishing to conceive) who have severe factor X deficiency and a history of recurrent bleeding or adverse pregnancy outcomes, antenatal prophylaxis should be considered. The authors suggest prophylactic therapy with pdFX to maintain trough levels of factor X above 20 IU/dL until the end of pregnancy; this approach has been successful in four pregnancies to date in women with severe factor X deficiency ([74] and unpublished observations). In addition, expert consensus UK guidance recommends the maintenance of factor X activity above 0.3 IU/mL (or 30 IU/dL) following delivery in women with low factor X levels and a history of bleeding, as well as in all women requiring cesarean section.

8. Future considerations

Clearly, further research is necessary to define the optimal factor X threshold levels in other scenarios with all available treatment options. With the advent of new therapies and advances in the formulation of PCCs and other factor replacement therapies (including the use of additional constituents), there is now an urgent need to achieve

Table 2
Dosages of replacement therapies used in the treatment of severe factor X deficiency.

Treatment	Indication	Dosage
Single-factor pdFX therapy (Coagadex, Bio Products Laboratory) [60]	On-demand control of bleeding episodes	Children <12 years: 30 IU/kg Adults/adolescents ≥12 years: 25 IU/kg For all: repeat at intervals of 24 hours until the blead stops [59,60]
	Preoperative bleeding prophylaxis	Dose to target FX levels of 70–90 IU/dL[a] [59,60]
	Postoperative bleeding	Dose to target FX levels of 50 IU/dL[a] [59,60]
	Prophylaxis and control of minor bleeds	Children <12 years: 40 IU/kg twice weekly Adults/adolescents ≥12 years: 25 IU/kg twice weekly For all: monitor trough blood levels of FX targeting ≥5 IU/dL and adjust dosage to clinical response and trough levels. Do not exceed a peak level of 120 IU/dL [59,60]
Dual-factor IX/X therapy (Behring X P) [52]	Control of bleeding episodes	Dose to target FX levels of 10–40 IU/kg at 24-h intervals[b]
	Prophylaxis in infants/young children	Dose to target FX levels of 20–40 IU/kg once or twice weekly[b]
Multifactor replacement therapy (FIX HS, ZLB Behring) [56]	Prophylaxis in patients with severe bleeds	15–20 IU FIX/kg once weekly
	Control of joint bleeding	15–20 IU FIX/kg 2 or 3 times weekly
Multifactor replacement therapy (AlphaNine SD, Grifols Biologicals) [54]	Surgery	50–100 IU FIX/kg twice daily for up to 10 days
	Major hemorrhage	30–50 IU FIX/kg twice daily for up to 10 days
	Moderate hemorrhage	25–50 IU FIX/kg twice daily for 2–7 days
	Minor hemorrhage	20–30 IU FIX/kg twice daily for 1–2 days
3- or 4-factor therapy (PCC) [3]	Replacement therapy	Dose calculated based on empirical findings of 1.5% increase in FX per 1 IU FX/kg dose[c,d]
	Surgery	Dose to target 5–20 IU/dL
	Breakthrough bleeding during prophylaxis	30 IU/kg for up to 2 doses in 24 h or daily for 3 days
	Regular prophylaxis	30 IU/kg twice weekly
FFP [3]	Replacement therapy	Dose to target trough FX levels above 10–20 IU/d (20 mL/kg followed by 3–6 mL/kg twice daily)
	Surgery	35 IU/dL preoperatively and dose to target 5–20 IU/dL postoperatively

FFP, fresh frozen plasma; FIX, factor IX; FX, factor X; IU, international units; PCC, prothrombin complex concentrate; pdFX, plasma-derived factor X concentrate.

[a] The dose to achieve a desired in vivo peak increase in factor X level may be calculated using the following formula: for individuals ≥12 years: dose (IU) = body weight (kg) × desired factor X rise (IU/dL or % of normal) × 0.5; for young children (<12 years of age): dose (IU) = body weight (kg) × desired factor X rise (IU/dL) × 0.6.

[b] Required dose (IU factor IX) = body weight (kg) × desired rise in factor X (IU/dL) × 1.21.

[c] Recommendations from the UK Haemophilia Centre Doctors' Organization.

[d] Please refer to Table 1 for FX content of individual PCC products.

consensus in treatment guidelines to ensure optimal management of patients with severe and mild forms of the disease alike.

Practice points

- Factor X deficiency is a highly heterogeneous rare bleeding disorder, with serious and life-threatening consequences, particularly in neonates and small children.
- The treatment of factor X deficiency has evolved substantially, from plasma replacement therapy (fresh frozen plasma) to prothrombin complex concentrates (PCCs) to, most recently, the development and licensing approval of a high-purity, plasma-derived, specific single-factor concentrate (pdFX). While patient numbers are small, clinical studies have demonstrated the ability of pdFX therapy to improve hemostasis while limiting the safety concerns associated with earlier treatments such as volume overload (particularly in neonates and young children), anaphylaxis, and thrombosis.
- Given the rarity of the disease, there is limited guidance on optimal therapy and dosing across the spectrum of patient needs, i.e. for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment in the control of bleeding episodes, peri- and postoperative management of bleeding, special situations such as pregnancy, acquired factor X deficiency, and management of serious concerns such as intracranial hemorrhage.
- With the advent of new therapies, advances in the formulations or inclusion of additional constituents in PCCs and other factor replacement therapies, and the potential for new non-replacement therapeutic approaches, there is now an urgent need to achieve consensus in treatment guidelines to ensure optimal management of patients with severe, moderate, or mild forms of the disease in all scenarios.

Research agenda

- Thresholds of FX activity that can define severity of disease.
- Optimal treatment approaches across the spectrum of disease severity.
- Minimal amount of FX needed to prevent early bleeding.
- Optimization of prophylaxis.
- Optimization of treatment for women with FX deficiency in terms of preventing menorrhagia and of having a safe pregnancy.

Author contributions

Study conception/design: FP.

Analysis and interpretation of the literature: FP, GA, SA, RL, KK, MT, AR, CMM.

Manuscript preparation: FP.

Manuscript review and approval: FP, GA, SA, RL, KK, MT, AR, CMM.

Declaration of Competing Interest

FP has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Bioverativ, Grifols, Roche, Sanofi, Sobi, Spark Therapeutics, and Takeda and is a member of the Roche, Sanofi and Sobi Advisory Board.

GA has received honoraria for participating as a speaker at satellite symposia by BPL and CSL Behring and for attendance at congresses and advisory board meetings organized by Bayer, Grifols, and Novo Nordisk.

SKA has received honoraria for participating as a speaker and attendance at congresses and advisory board meetings organized by Novo Nordisk, Taketa, Amgen, BPL, Bayer, Sobi, Octapharma, LFB, Grifols, and Roche.

RL has been as a consultant and advisory board member for Baxalta, Bayer, Bio Products Laboratory, Novo Nordisk, Octapharma, Roche, and Sobi; has received honoraria from Baxalta Bayer, Novo Nordisk, Octapharma, Roche, and Sobi; and has been a research funding recipient and speakers' bureau participant for Baxalta, Bayer, Novo Nordisk, Octapharma, Roche, Sobi, and Sobi/Bioverativ.

KK has received honoraria for participating as a speaker and attendance at congresses and advisory board meetings organized by Bayer, Novo Nordisk, Pfizer, and Taketa.

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