- **HFXD is a rare bleeding disorder resulting in reduced plasma coagulation FX activity and potentially life-threatening symptoms.**
  - FX is a vitamin-K-dependent serine protease that plays a central role in blood coagulation in both the intrinsic and extrinsic pathways of the clotting cascade (Brown et al, 2008).
  - HFXD (also known as Stuart-Prower factor deficiency) is a rare bleeding disorder characterised by a reduced plasma concentration of coagulation FX activity (Menegatti and Peyvandi, 2016).
  - Delayed treatment or inadequate replacement of FX exposes patients to an increased risk of bleeding events and subsequent need for hospitalisation, which can ultimately result in developmental delays, musculoskeletal disabilities or death (Peyvandi et al, 2026; Tarantino, 2021).

- **HFXD is one of the most severe bleeding disorders, putting patients with severe FX deficiency at risk of life-threatening bleeds early in life.**
  - Patients with HFXD tend to have the most severe symptoms of the rare coagulation disorders and are often diagnosed in the first month of life due to spontaneous bleeding (Brown et al, 2008; Peyvandi et al, 2026).
  - HFXD manifests with varying degrees of severity, with lower FX activity associated with an increased risk of more severe bleeding complication (Brown et al, 2008; Peyvandi, Di Michele et al, 2012; Peyvandi, Palla et al, 2012)
  - Severe FX deficiency may present as neonates with circumcision or umbilical stump bleeding, intracranial or gastrointestinal haemorrhage, while moderate deficiency may present after surgery, trauma or menses. Mild deficiency may be diagnosed during routine screening or because of a positive family history (Brown et al, 2008)

- **HFXD affects females and males equally, although affected women and girls are more likely to experience bleeding and hence to be diagnosed** (Austin et al, 2016).
  - Women and girls with HFXD can suffer from further complications like menorrhagia and obstetric issues such as miscarriage, placental abruption and postpartum haemorrhage, leading to a higher rate of diagnosis than in males (Kulkarni et al, 2018; Peyvandi et al, 2021; Spiliopoulos et al, 2019).

1.1 Overview of hereditary factor X deficiency

Key takeaways

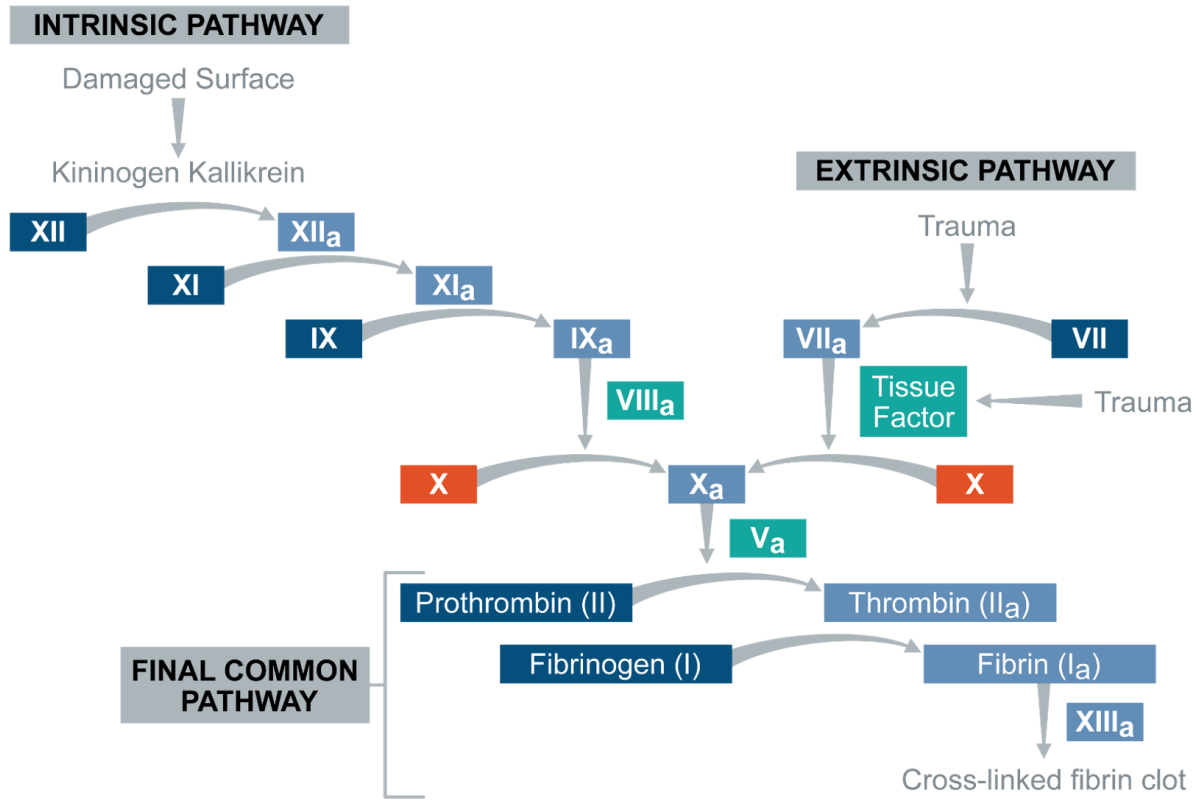
- Hereditary factor X deficiency (HFXD) is a rare bleeding disorder that results in reduced FX activity. (Menegatti and Peyvandi, 2009)
- Patients with severe FX deficiency commonly experience the most severe side effects of the coagulation disorders, similar to those of haemophilia A and B (FVIII and FIX deficiency), including hemarthrosis, haematomas and menorrhagia. (Brown et al, 2008)
- A variety of classification systems have been used in the literature. However, the consensus is that lower FX activity results in higher bleeding severity risk, although this may not be the case for all FX-deficient patients. (Brown et al, 2008; Peyvandi, Di Michele et al 2012; Peyvandi, Palla et al, 2012)
- While bleeding tendency may appear at any age, more severe patients (i.e. FX activity <1%) tend to present earlier in life with umbilical stump or CNS bleeding (Menegatti and Peyvandi, 2009)
- FX deficiency affects both males and females equally (Austin et al, 2016); however, females can also experience menorrhagia, obstetric issues and postpartum haemorrhage (Peyvandi et al, 2002), which often leads to a higher diagnosis rate than in males

1.1.1 Definition and clinical features

Factor X (FX) is a vitamin-K-dependent serine protease that plays a central role in blood coagulation in both the intrinsic and extrinsic pathways of the clotting cascade. (Brown et al, 2008)

Physiologically, FXa (the activated form of FX) is the most important activator of prothrombin for blood coagulation (Bolton-Maggs et al, 2004), being the first enzyme in the common pathway of thrombin formation (Figure 1) (Menegatti and Peyvandi, 2009).

Figure 1: Activation of prothrombin for blood coagulation (adapted from Palta et al., 2014)



HFXD (also known as Stuart-Prower factor deficiency) is a rare bleeding disorder characterised by an autosomal recessive inheritance. Patients with FX deficiency have a reduced coagulant activity of FX (Menegatti and Peyvandi, 2009). In this respect, it can be regarded as similar to haemophilia A and B, which are caused by deficiencies of factor VIII (FVIII) and FIX, respectively.

As an autosomal recessive disorder, FX deficiency usually requires two defective genes to show phenotype. This means both parents must pass on the dysfunctional gene F10, which lies on the long arm of chromosome 13 (Menegatti and Peyvandi, 2009), to the offspring. However, an occasional bleeding phenotype has also been reported in heterozygotes (Uprichard and Perry, 2002).

FX deficiency is one of the most severe bleeding disorders with the third highest proportion (23.5%) of patients with grade III bleeding, following factor XIII (FXIII) and fibrinogen deficiencies (Figure 2). Patients with severe FX deficiency also commonly experience the most severe side effects of the coagulation disorders, similar to those of haemophilia A and B (FVIII and FIX deficiency) (Table 1) (Brown et al, 2008).

Figure 2: Distribution of clinical bleeding severity within the different rare bleeding disorders (Peyvandi, Palla et al, 2012)

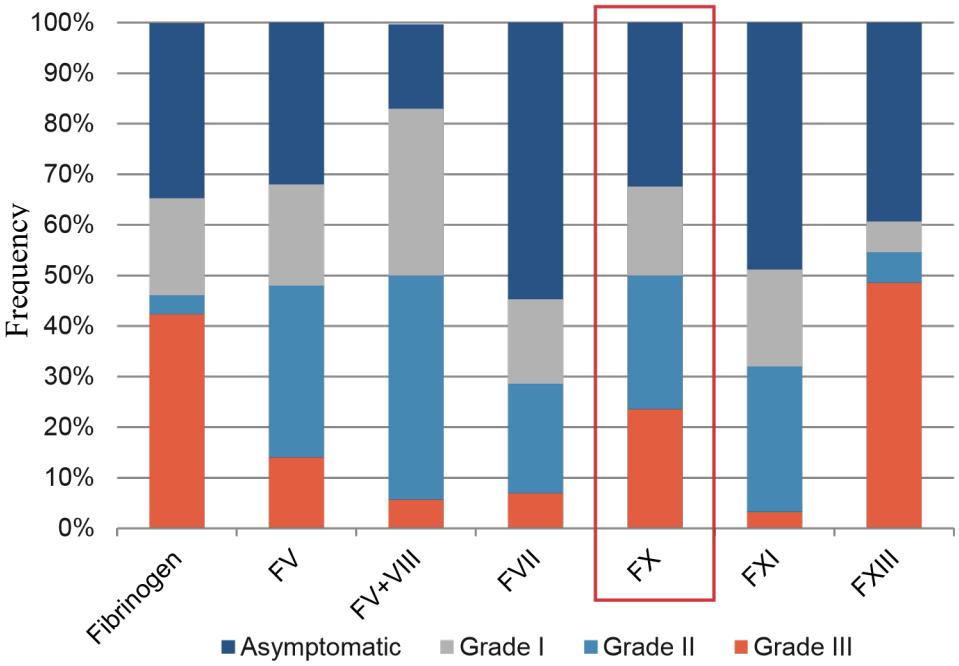


Table 1: Symptoms associated with different severities of FX deficiency (Menegatti and Peyvandi, 2009; Peyvandi, Di Michele et al, 2012)

Classification	Commonly associated symptoms
Severe	Epistaxis, hemarthrosis, haematomas, GI and umbilical cord bleeding, haematuria, CNS bleeding, menorrhagia
Moderate	Epistaxis, bleeding after haemostatic changes (i.e. trauma or surgery)
Mild	Epistaxis, bleeding after haemostatic changes (i.e. trauma or surgery)

CNS = central nervous system; GI = gastrointestinal.

1.1.2 Classification of hereditary FX deficiency

The classification of FX deficiency is based on the results of both immunologic and functional assays. In patients with Type I deficiency, a mutation in the FX gene leads to the production of truncated proteins, resulting in a reduction of both FX activity (FX:C) and antigen (FX:Ag) levels. Type II deficiency occurs when FX:C is reduced while antigen levels remain near normal, resulting in a qualitative defect. While more complex classification has been suggested, from a clinical standpoint, measurement of FX:C by routine laboratory prothrombin time (PT)- and activated partial thromboplastin time (aPTT)-based tests is usually sufficient for a correct diagnosis of FX deficiency (Menegatti and Peyvandi, 2009).

Caution has been raised about categorising patients according to their endogenous levels of FX as the clinical phenotype of FX deficiency does not necessarily correlate well with the laboratory phenotype. However, a strong inverse correlation between FX coagulant activity level and clinical bleeding severity has been noted. While there is general consensus that lower FX:C results in higher bleeding severity

risk, discrepancies exist in terms of defining each severity classification. Table 2 provides a summary of potential classification systems reported in the literature that are based on clinical datasets.

Table 2: Proposed bleeding severity classifications

Study	Study description	Bleeding severity classification
Peyvandi, Palla et al., 2012	Cross-sectional study using data from 489 HFXD patients registered in the European Network of Rare Bleeding Disorders	Asymptomatic: No documented bleeding episodes Grade I bleeding: Bleeding that occurs after trauma or drug ingestion (antiplatelet or anticoagulant therapy) Grade II bleeding: Spontaneous minor bleeding: bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis and menorrhagia Grade III bleeding: Spontaneous major bleeding: haematomas, hemarthrosis, CNS, GI and umbilical cord bleeding
Peyvandi, Di Michele et al., 2012	Classification based on two different sets of data: A detailed review of the available literature Overview of data on the association between the laboratory phenotype and clinical bleeding characteristics from the EN-RBD, UKHCDO, NARRBD and Indian registries (N=4,359 patients affected with RBDs)	Severe deficiency: coagulant activity associated with spontaneous major bleeding (coagulant activity: <10%) – suggesting this as a target level for prophylaxis Moderate deficiency: coagulant activity associated with mild spontaneous or triggered bleeding (coagulant activity: 10–40%) Mild deficiency: coagulant activity associated with a mostly asymptomatic disease course (Coagulant activity: >40%)
Menegatti and and Peyvandi, 2009	Review of the literature	Type I: low coagulant activity and low immunological antigen levels Type II: low coagulant activity and normal/borderline low antigen levels
Peyvandi et al., 1998	Review of the literature	Based on FX:C activity measurements: Severe deficiency: coagulant activity <1% Moderate deficiency: coagulant activity 1–5% Mild deficiency: coagulant activity 6–10%

CNS = central nervous system; EN-RBD = European network of rare bleeding disorders; FX:C = FX activity; GI = gastrointestinal; HFXD = hereditary factor X deficiency; N = total number of participants; NARRBD = North American Registry of Rare Bleeding Disorders; RBD = rare bleeding disorder; UKHCDO = United Kingdom Haemophilia Centre Doctors' Organisation

According to the most recent classification system detailed by Peyvandi et al. (2012) above, the proportions of patients with mild, moderate and severe FX deficiency are 50.0%, 26.5% and 23.5% respectively (Peyvandi, Palla et al, 2012).

Achieving common definitions between different parties alongside longitudinal data collection would help to (Haghpanah et al 2017):

- Determine the haemostatic level of FX to help distinguish patients who may require a specific treatment only during surgery, from those with a potential for major spontaneous bleeding that requires prophylactic treatment
- Design clinical trials
- Establish future management guidelines or update current recommendations
- Inform genotype-phenotype analysis.

1.1.3 Assessment and diagnosis

The diagnosis of FX deficiency is based on the measurement of FX:C using prothrombin time (PT) and activated partial thromboplastin time (aPTT), Russel viper venom time (RVVT) or a chromogenic assay and the measurement of plasma FX:Ag by immunoassay (Menegatti and Peyvandi, 2009).

If both PT and aPTT are abnormal and subsequently correct with a 1:1 mix with normal plasma, FX deficiency is typically suspected. FX:C is measured by performing serial dilutions with FX-deficient plasma. However, PT reagents may vary in sensitivity to FX deficiency and it is possible for a congenital variant to present with normal PT and aPTT.

RVV is a metalloproteinase which activates FX directly and will detect deficiency of FX if FX-deficient plasma is used as substrate. Immunological assays (e.g. enzyme-linked immunosorbent assay) measure FX:Ag. Chromogenic assays use an FXa-sensitive chromophoric substrate that can be detected spectrophotometrically. However, immunological and chromogenic assays may omit cases of dysfunctional FX so are not recommended as diagnostic tests for FX deficiency.(Brown et al, 2008)

At birth, FX levels are low and should be compared with age- and gestational age-matched normal ranges before a deficiency is diagnosed in the neonate. Mean FX levels in healthy full-term infants are approximately 0.40 (±0.14) international units (IU)/mL and do not reach adult values until after 6 months of age (Brown et al, 2008). Due to the fact that FX is synthesised in the liver, liver disease will result in low levels of FX, along with the other liver-produced factors: prothrombin, FV, FVII and FIX. As with haemophilia A and B (FVIII and FIX deficiency), vitamin K deficiency and warfarin use also result in low levels of FX (Brown et al, 2008).

The events leading to diagnosis of FX deficiency have been investigated in an analysis of registry data from the North American Registry of Rare Bleeding Disorders (NARRBD), which reported the most common diagnostic events for homozygous patients (n=19) as nonsurgical bleeding (82% of patients), followed by positive family history (14% of patients) and postoperative bleeding (4% of patients) (Acharya et al, 2004).

1.1.4 Causes and risk factors

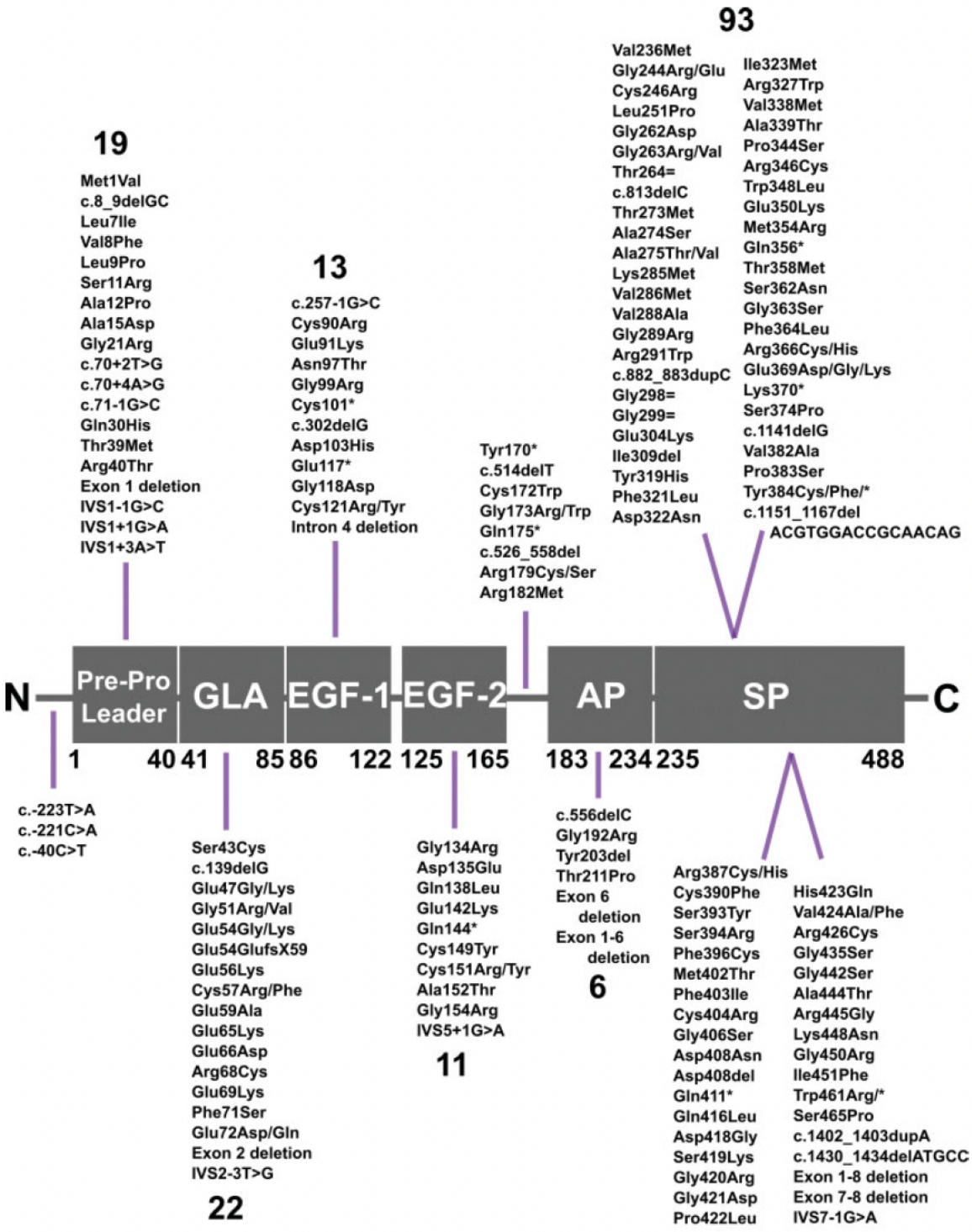
HFXD is a haemorrhagic disorder which is inherited as an autosomal recessive trait. A total or partial deficiency of FX results in impaired clot formation, leading to haemorrhagic disease which manifests with bleeding symptoms of varying severity (Menegatti and Peyvandi, 2009).

A reduced plasma concentration of FX is the result of a dysfunctional gene *F10*, which lies on the long arm of chromosome 13. As of 2021, 180 mutations had been reported in *F10,* including (Harris et al, 2021):

- 128 missense mutations (representing 71.1% of all mutations)
- 10 nonsense mutations

- 10 splice site mutations
- 22 deletions
- 3 insertions
- 6 polymorphisms

Figure 3: Distribution of 180 variants identified in the *F10* gene (Harris et al, 2021)



1.1.5 Patient characteristics

It has been established that HFXD is one of the most serious rare bleeding disorders after factor XIII and fibrinogen deficiency and affects all ages (Peyvandi, Di Michele et al, 2012).

While bleeding tendency may appear at any age, more severe patients tend to present earlier in life with umbilical stump or CNS bleeding (Menegatti and Peyvandi, 2009). Females with FX deficiency can also experience menorrhagia and obstetric issues such as miscarriage, placental abruption and postpartum haemorrhage, which leads to a higher diagnosis in women compared with men (Kulkarni et al, 2018; Spiliopoulos and Kadir, 2019). However, unlike haemophilia A and B, both genders are equally affected by FX deficiency (Austin SK et al, 2016). According to an NARRBD assessment of homozygous FX-deficient patients on their registry (n=19), FX deficiency disease markers centre around bleeding symptoms, predominantly in the skin and mucous membranes (45%), followed by musculoskeletal (27%), intracranial (15%), gastrointestinal and genitourinary (4–9%) haemorrhage (Acharya et al, 2004).

NARRBD also mapped the most common complications of FX deficiency inpatients on the registry. As can be seen in **Error! Reference source not found.**, the homozygous type of FX deficiency presents substantially more complications than the heterozygous type, which is in line with the relative severity of each type.

Table 3: Complications of FX deficiency in NARRBD registered patients (Acharya et al, 2004)

Type of deficiency	Anaemia	Musculoskeletal	CNS	Other	None
Homozygous	34	7	22	0	37
Heterozygous	7	0	0	0	93

CNS = central nervous system; FX = factor X; NARRBD = North American Registry of Rare Bleeding Disorders

A systematic literature review conducted in 2019 shed light on the clinical implications and outcomes associated with FX deficiency in women and the need for further guidelines in this population (Spiliopoulos and Kadir, 2019). The review analysed 49 relevant articles, including 332 women with FX deficiency. The findings revealed that heavy menstrual bleeding affected 25% of women with FX deficiency, with 64% requiring blood products and 10% needing transfusions. Ovulation-related bleeding leading to hemoperitoneum occurred in 2.4% of cases, all necessitating transfusion and 75% requiring surgical interventions such as oophorectomy. Moreover, pregnancy outcomes were particularly challenging, with a 13% miscarriage rate, 30% preterm birth rate and an 11% neonatal death rate. Postpartum haemorrhage occurred in 22% of deliveries. Notably, antenatal prophylaxis significantly improved outcomes, with lower rates of preterm delivery and neonatal death. The review underscores the importance of collaborative management between haematology, obstetrics and gynaecology to address bleeding issues effectively in FX-deficient women, while also highlighting the need for definitive guidelines for prevention and treatment.

2 BURDEN OF HEREDITARY FACTOR X DEFICENCY

- **HFXD is an ultra-rare bleeding disorder with potentially life-threatening medical complications.**
  - FX deficiency corresponds to approximately 10% of all rare blood disorders (Menegatti and Peyvandi, 2009), with a global prevalence ranging between 1:500,000 and 1:1,000,000 (Brown et al, 2008; Peyvandi et al, 2016).
  - The estimated number of patients with FX deficiency worldwide in 2021 was 2,354, of which 14% were living in the UK (Spiliopoulos and Kadir, 2019).
  - Only a portion of FX-deficient patients experience bleeds which require treatment [NHS- Clinical Evidence review of human coagulation factor X for hereditary factor X deficiency (all ages)]

- **Patients with HFXD face substantial burden and healthcare utilisation due to bleeding events and the complexity of their rare disorder.**
  - As with other rare bleeding disorders, patients with HFXD experience substantial humanistic burden as bleeding events, along with the complications of heterogenous treatment pathways and the psychological stress of living with a rare disorder can have a negative impact on their physical, mental and social well-being (Elshinawry M and Elshinawry N, 2023; van Hoorn et al, 2022; Haghpanah et al, 2017).
  - Inherited rare bleeding disorders, including HFXD, have been found to result in substantial economic burden for patients due to the direct and indirect costs of diagnosis, treatment and complications, as well as the challenges and barriers in accessing adequate care (Burke et al, 2021; Lopez et al, 2022).
  - In bleeding disorders, including HFXD, and in addition to treatment costs, the healthcare system faces additional financial burdens from medical encounters, including clinic visits and hospitalisations (Burke et al, 2021; Lopez et al, 2022).

2.1 Epidemiology

Key takeaways

- FX deficiency is classified as an orphan indication and is estimated to have a worldwide incidence of 1:500,000 to 1:1,000,000 (Brown et al, 2008; Peyvandi et al, 2016).
- The estimated number of patients with FX deficiency worldwide in 2021 was 2,354 (WFH-report on the Annual Global Survey 2021).
- Only a portion of FX deficient patients experience bleeds that require treatment [NHS- Clinical Evidence review of human coagulation factor X for hereditary factor X deficiency (all ages)].

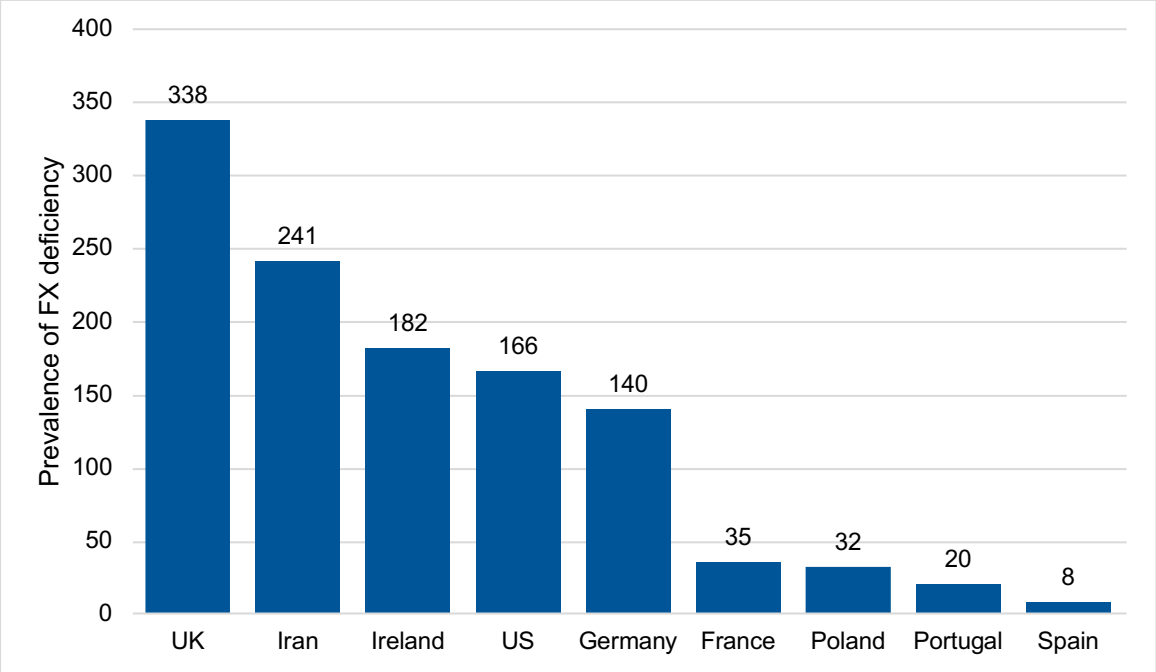
2.1.1 Prevalence

There is wide variation in the estimated prevalence of FX deficiency in the literature, which can be attributed to differences in the severity of the condition considered (mild, moderate and severe), reporting rates, consanguinity and the availability of national or international registries.

Patients with FX deficiency represent 10% of the total number of patients affected worldwide by rare bleeding disorders (Menegatti and Peyvandi, 2009). Recent data derived from the World Federation of Hemophilia (WFH) global survey show that of the countries reporting data from 2021 (79 countries in

total), there were 2,354 patients with FX deficiency worldwide with almost equal numbers of men (48%) and women (45%) (Spiliopoulos and Kadir, 2019). The highest prevalence was reported in the UK, where 338 people (14%) were living with FX deficiency in 2021 (**Error! Reference source not found.**). There were also high numbers of patients with FX deficiency in Iran (241 patients), Ireland (182 patients) and the US (166 patients) (WFH- report on the Annual Global Survey 2021). Data for Italy was not available in the latest report; however, the previous report indicated there were 118 patients with FX deficiency in Italy in 2020 (WFH- report on the Annual Global Survey 2020). Note that not all countries report to the WFH, and even those that do may utilise different criteria.

Figure 4: Prevalence of FX deficiency across a number of countries in 2021(WFH- report on the Annual Global Survey 2021)



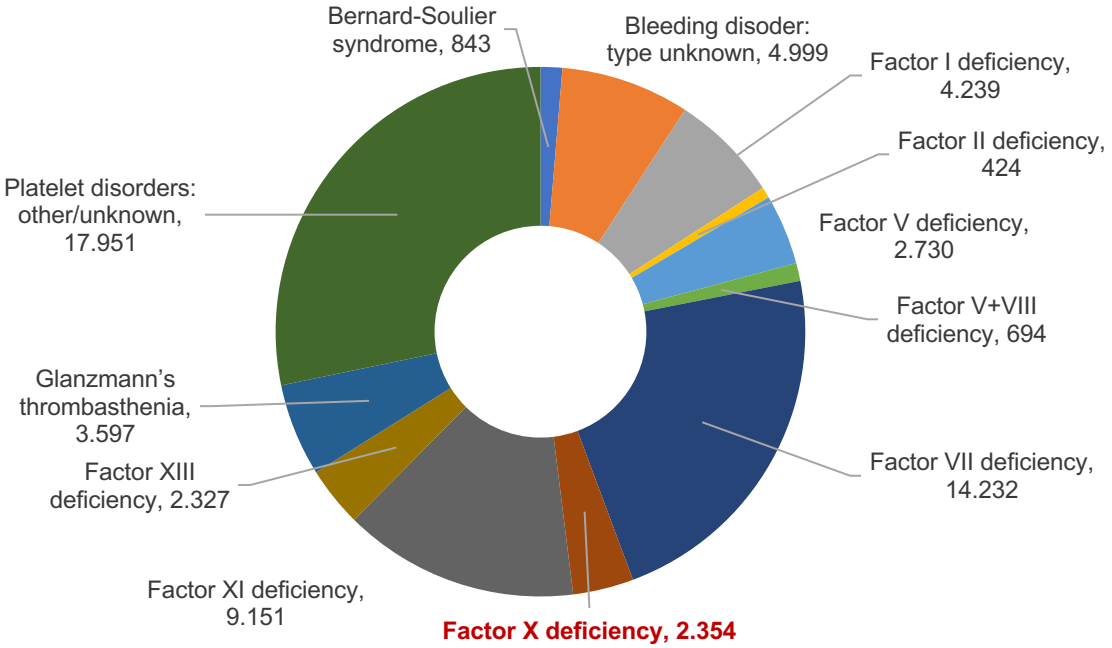
FX = factor X; UK = United Kingdom; US = United States.
Note: Data for Italy was not available in the latest report;[11] however, the previous report indicated there were 118 patients in Italy in 2020.[48]

The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) reported a total of 369 registered patients with FX deficiency between April 2022 to March 2023 and, of those, 37 (10%) have received treatment (UKHCDO Annual Report 2023 Bleeding Disorders Statistics for 2022/2023)

2.1.2 Incidence

The WFH presents FX deficiency as one of the least common other bleeding disorders (**Error! Reference source not found.**) (WFH- report on the Annual Global Survey 2021). Overall, FX deficiency is estimated to have a worldwide incidence of 1:500,000 to 1:1,000,000 and is therefore classified as an orphan indication (Brown et al, 2008; WFH- report on the Annual Global Survey 2021).

Figure 5: Proportional distribution of other bleeding disorders worldwide in 2021 (WFH- report on the Annual Global Survey 2021)



Other bleeding disorders include deficiencies of factor I, factor II, factor V, factor V+VIII, VII, X, XI and XIII, Glanzmann's thrombasthenia, Bernard Soulier syndrome, platelet disorders (other or unknown) and other hereditary bleeding disorders (type unknown).

FX deficiency is more common in populations in which consanguineous marriage is common, such as Iran, where the frequency is reported to be 1:200,000 (Brown et al, 2008; Peyvandi et al, 1998). For example, FX deficiency accounts for 1.3% of patients with inherited coagulation deficiencies in Iran, compared with 0.4% in Italy and 0.5% in the UK (Peyvandi, Palla et al, 2012; Peyvandi et al, 2002).

The UKHCDO reported the number of newly registered FX-deficient patients between April 2022 to March 2023 to be 18 (UKHCDO Annual Report 2023 Bleeding Disorders Statistics for 2022/2023), which translates to an incidence rate of nearly 3 per 10,000,000 across all disease severities, based on a total population of 67,026,292 (estimated UK population at mid-year 2021.ONS. Population estimates for the UK, England, Wales, Scotland and Northern Ireland: mid 2021).

The incidence of heterozygous FX deficiency, which is the carrier state of the disorder, is much higher than the severe form and may be as high as 1:500 (Brown et al, 2008).

The proportion of patients with FX deficiency who require treatment varies depending on the severity of the disease. According to the Haemophilia Society, approximately 14.5% of the patients diagnosed with FX deficiency experience bleeds and require treatment in the UK [NHS- Clinical Evidence review of human coagulation factor X for hereditary factor X deficiency (all ages)].

2.1.3 Mortality

Prognosis of patients with FX deficiency varies with the severity of defects. Due to the small number of cases reported, there is limited information available on the mortality associated with the disease. Fatal brain haemorrhage is a cause of death in early age. Mortality rates due to ICH have been reported to be 20% to 30% in patients with FX deficiency (Tarantino, 2021). FX activity levels of approximately 10% of normal (i.e. mild to moderate disease) are thought to be sufficient to ensure a reasonable quality of life; however, surgery, trauma, pregnancy or invasive diagnostic procedures are likely to increase the risk of fatal complications (Girolami et al, 2008).

2.2 Patient burden of disease

Key takeaways
• The most frequent bleeding symptoms are mucocutaneous: easy bruising, epistaxis and gum bleeding. Menorrhagia is also common among women with severe FX deficiency (Peyvandi et al, 2002)
• Other more serious symptoms of the disease include recurrent hemarthrosis, intracranial haemorrhage and miscarriage among pregnant women (Brown et al, 2008; Peyvandi et al, 1998; Nance et al 2012).
• Patients with the rare blood disease haemophilia report significantly lower scores ($p<0.001$) compared with healthy controls for the SF-36 scales measuring physical health (Solovieva et al, 2004).

2.2.1 Consequences or complications of disease

Due to the development of several registries, patient information on the symptoms and complications for FX deficiency has improved. Registries include the Greifswald Registry of Factor X Deficiency in Europe and Latin America, the Rare Bleeding Disorder Registry in North America and population registries of inherited bleeding disorders from the UKHCDO and the Haemophilia Surveillance System in Iran (Brown et al, 2008). The bleeding symptoms reported from these registries are summarised in **Error! Reference source not found.**.

Table 4: Bleeding symptoms reported in haemophilia registries (Brown et al, 2008)

Symptoms	Herrmann et al. (n=35)*	Acharya et al. (n=19)†	Peyvandi et al. (n=32)‡	Anwar et al. (n=20)§
Easy bruising	18 (51%)	(45%)	NR	9 (45%)
Epistaxis	12 (34%)	NR	23 (72%)	7 (35%)
Gum bleeding	12 (34%)	NR	NR	7 (35%)
Menorrhagia	9/12 (75%)	(4–9%)	4/8 (50%)	1/10 (10%)
GI bleeding	4 (14%)	NR	12 (38%)	2 (10%)
Haematuria	3 (9%)	NR	8 (25%)	1 (5%)
Haematomas	16 (46%)	(27%)	21 (66%)	NR
Haemarthrosis	14 (40%)	NR	22 (69%)	1 (5%)
ICH	9 (26%)	(15%)	3 (9%)	NR

Umbilical cord	NR	NR	9 (28%)	3 (15%)
Circumcision	NR	NR	NR	3/10 (30%)

FX = factor X; GI = gastrointestinal; ICH = intracranial haemorrhage; NR = not reported.
* Includes 28 homozygous and seven compound heterozygous patients
† Includes homozygous patients with FX levels of 0–13%.
‡ All patients have FX levels <10%.
§ FX levels were not reported.

In contrast to haemophilia A and B, the most frequent bleeding symptoms are mucocutaneous: easy bruising, epistaxis and gum bleeding.

In women with severe FX deficiency, menorrhagia has also been reported in 10 to 75% (Brown et al 2008; Peyvandi et al, 1998). FX levels increase in pregnancy of non-affected women, but FX-deficient women often experience complications during pregnancy, including uterine bleeding, foetal loss and postpartum haemorrhage (Spiliopoulos and Kadir, 2019). Among 14 reported pregnancies in women with homozygous FX deficiency, there were two instances of miscarriage and two of postpartum haemorrhage (Romagnolo et al, 2004). In a more recent review, out of 31 pregnancies in 19 women, there was a 13% miscarriage rate, 30% preterm birth rate (with 11% resulting in neonatal death for viable pregnancies), and 22% experienced postpartum haemorrhage (Spiliopoulos and Kadir, 2019).

Several patients with moderate to severe FX deficiency have been described as having recurrent hemarthrosis with development of haemophiliac arthropathy. Hemarthrosis occurred in 69% of Iranian patients with FX levels <10% (Peyvandi et al, 1998). Intracranial haemorrhage is reported in 9 to 26% of patients and is most common during the neonatal period. This is supported by the recent findings in a review of 50 publications on severe bleeding episodes in 197 patients with FX deficiency. This study found that spontaneous central nervous system (CNS) bleed was the most common type of severe haemorrhage in patients with FX deficiency, occurring in 82 patients (42%). Among the severe CNS bleeds, it was also reported that ICH was the most common and that infants are the most vulnerable population group to ICH. The mortality rate due to ICH in patients with FX deficiency was estimated to be 20% to 30% as this type of severe bleeding is likely to be spontaneous, occur early in life and recur (Tarantino, 2021).

One in utero subdural haemorrhage occurring at 35 weeks of gestation in an affected foetus has been reported. Umbilical cord bleeding is also a common bleeding symptom in the neonatal period, having been reported in 28% of patients with FX levels <10% (Peyvandi et al, 1998).

2.2.2 Health-related quality of life

To date, limited evidence is available to indicate how FX deficiency affects health-related QoL or productivity of patients or their caregivers. Overall, humanistic burden among patients with FX deficiency is expected to be substantial compared with other rare bleeding disorders.

A prospective cross-sectional survey provided insights into the diagnosis experience, disease burden and QoL impact of HFXD on patients and caregivers in the US. A total of 30 patients (six were caregiver-assisted in their responses) and 38 caregivers completed the web-based survey. Over half (53.3%) of the patients were receiving single-factor replacement as monotherapy or in combination with other treatments, and 71.4% were receiving prophylaxis (Branchford et al, 2024).

The QoL and well-being scores indicated challenges for HFXD patients compared to the general population (**Error! Reference source not found.**) The mean 12-Item Short-Form Health Survey (SF-12) physical (45.3) and mental (48.8) QoL scores were below the US average (50.0). Patients also had reduced well-being based on the Haemophilia Well-being Index (HWBI) (20.04), where, on a scale of 0–32, higher scores indicate lower well-being. All patients either strongly agree (71.4%) or somewhat agree (28.6%) that treatment helps improve their own QoL, while most caregivers responded that

treatment helps to improve overall caregiver burden all of the time (47.4%) or most of the time (36.8%) (Branchford et al, 2024)

Table 5: QoL and well-being (patient survey) (Branchford et al, 2024)

Questionnaire and component		Mean score (SD)
SF-12	Physical component score (n=24)	45.13 (11.67)
SF-12	Mental component score (n=24)	48.79 (10.60)
HWBI	HWBI summary score (n=27)	20.04 (8.68)

HWBI = Haemophilia Well-being Index; QoL = quality of life; SD = standard deviation; SF-12 = 12-Item Short-Form Health Survey
The SF-12 is used to assess overall quality of life (Physical and Mental) and can be compared to the general population; higher scores (0–100) indicate greater functioning; overall patient QoL was lower when compared to the US average of 50.
The HWBI assesses patient well-being. Patients are asked about how their life has been negatively affected by haemophilia. Higher scores (0–32) indicate lower well-being.

Heavy menstrual bleeding was reported to limit physical and social activities for most female patients surveyed (66.7%, n=6/9), with five (55.5%) reporting that bleeding limited social and leisure activities at least moderately (Branchford et al, 2024).

Caregivers reported negative effects on burden but also positive aspects of caregiving like self-worth and inner strength. The mean burden score of 15.88 on a 35-point scale quantitatively demonstrated the negative impact HFXD has on caregivers. Overall, this survey provided valuable insights into patient and caregiver experiences and the substantial burden of this rare genetic bleeding disorder. The results highlight the need for better diagnosis, treatment, and support (Branchford et al, 2024).

Another cross-sectional study evaluated QoL in 52 children aged 4–18 years with rare bleeding disorders (RBDs) in Iran. FX deficiency was among the most common deficiencies in the study sample (n=7, 13.5%) and the total QoL score for the FX-deficient patients was 40.02 (± 12.75) evaluated using Haemo-QoL questionnaire. This was lower than the mean total QoL score (41.15 ± 14.27). Social domains like family and friends which depict the participant's relationship and interaction with their family members like parents and their friends, were found to be the most impaired. Bleeding severity, health status, and being bothered by the disease were significantly associated with QoL in children. The study also found that girls with rare bleeding disorders had lower QoL scores compared to boys. The findings further emphasise that FX deficiency poses challenges throughout childhood and adolescence and addressing the need for better treatment to alleviate disease-related concerns and bleeding severity is crucial to improving patient QoL (Haghpanah et al, 2017).

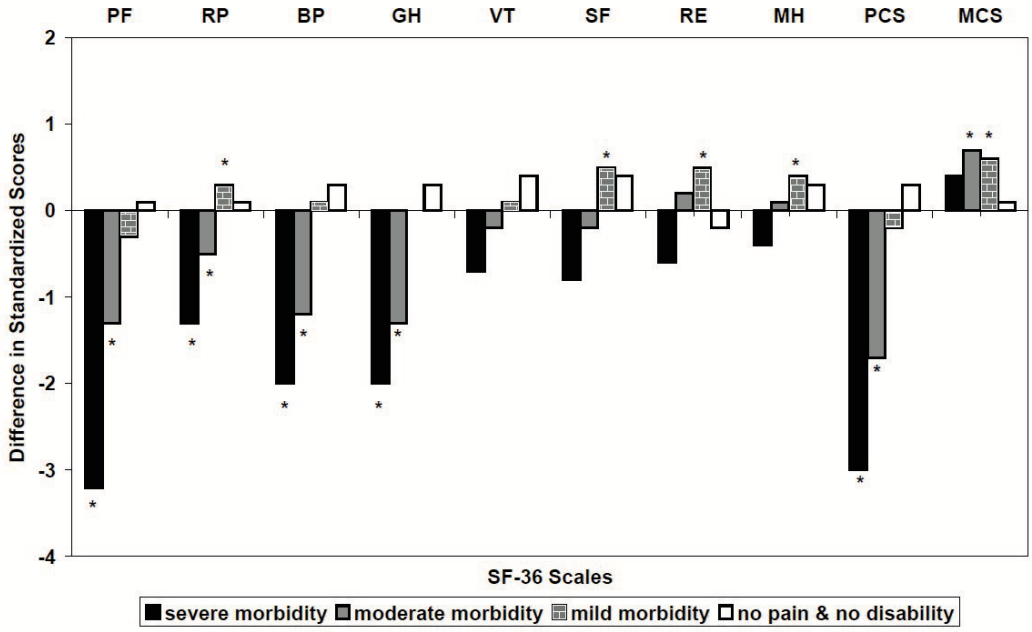
2.2.2.1 Evidence in other rare blood disorders

Rare bleeding disorders are lifelong, life-threatening diseases and therefore have a considerable impact on patients' QoL (Solovieva et al, 2004). The QoL of 164 patients on the Finnish Red Cross Blood Transfusion Service was compared with that of healthy controls in order to establish the impact of haemophilia on QoL. Participants' QoL was assessed using several established measures, including the 36-item Short-Form Health Survey (SF-36) (Solovieva et al, 2004).

To illustrate the effect of the disease, average standardised scores for each SF-36 scale were plotted (**Error! Reference source not found.**) in relation to the scores from healthy controls. Patients with severe and moderate musculoskeletal morbidity reported significantly lower scores ($p<0.001$) compared

with controls for the SF-36 scales measuring physical health. Patients who did not experience any pain problems or functional disability were not significantly different from healthy controls in any of the SF-36 scales (Solovieva et al, 2004).

Figure 6: Deviations of standardised SF-36 scores for haemophilia patients (Solovieva et al, 2004).



BP = bodily pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; VT = vitality.
* $p<0.001$.

Complications from haemophilia treatment can also impact QoL. The major complication associated with treatment is the development of inhibitor antibodies, resulting in poor bleeding control and the need for alternative treatments. Other complications may include adverse reactions to a coagulation factor, including anaphylaxis and nephrotic syndrome. This highlights a need for highly specialised treatments that reduce the risk of poor bleeding management and AEs (Dalton, 2015).

3 CURRENT MANAGEMENT OF HEREDITARY FX DEFICIENCY

- **HFXD is generally treated when patients present with a bleeding episode.**
  - HFXD is still underdiagnosed and undertreated in Europe and around the world.
  - Due to the extremely rare nature of HFXD and lack of US or European Union (EU) guidelines for preventive options, the clinical management of FX deficiency focuses on the symptomatic treatment of bleeds, leaving prophylaxis needs unaddressed (Peyvandi F et al, 2016).
- **Management of HFXD is directed by the FX deficiency severity, with preventive options reserved for high-risk patients.**
  - Management of patients is determined by the severity of FX deficiency and associated risk of bleeding, with those at a high risk often requiring prophylactic treatment and those at lower risk managed with on-demand treatment (Peyvandi F et al, 2016; Peyvandi F et al, 2021).
- **PCC or FFP is used in HFXD despite providing unquantifiable amounts of FX and the presence of other redundant factors.**
  - Current therapeutic options vary and include FFP, cryoprecipitate, PCCs, dual-factor therapy (factor IX/X), and human plasma-derived FX concentrate (pdFX), with the development of pdFX being the most recent advance (Peyvandi F et al, 2021).
- **Due to the lack of specific guidelines and licensed options, patients with HFXD may be treated with suboptimal treatment options.**
  - In the EU, pdFX is licensed for on-demand and prophylactic treatment of bleeding episodes as well as for perioperative management in patients with HFXD (Tarantino MD, 2021).
  - pdFX is the recommended product for replacement therapy in HFXD, as it allows for targeted and specific correction of the deficiency without exposing patients to unnecessary additional factors that are present in PCC or FFP, increasing the risk of thrombosis and creating the need for careful monitoring of other coagulation factors (Tarantino MD, 2021; Austin SK et al, 2016; Austin SK, Brindley C et al, 2016; Palla R et al, 2015).
  - Within the marketing authorisation of PCCs, the therapeutic indications state that the products are to be used in the 'treatment and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available' (Core summary of product characteristics for human prothrombin complex products - Scientific guideline | European Medicines Agency (europa.eu)).
  - Dual factor concentrate contains FX and factor IX but is currently only licensed in Switzerland and Saudi Arabia, and is not approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) (CSL Behring Products | CSL).
  - To the best of our knowledge, there are no published clinical trial data on the systematic utilisation of any PCC, FFP or double concentrate product for the treatment of bleeding episodes in HFXD.
  - National and international guidelines and expert consensus in bleeding disorders recommend the use of single-factor therapies wherever available (MASAC recommendations; EU directorate for the Quality of Medicines and Healthcare; National hemophilia Council NHC; Giangrande P et al, 2014).

3.1 Overview of treatment paradigms

Key takeaways

- HFXD is generally treated when patients present with a bleeding episode, focusing on symptomatic treatment of bleeds. Prophylactic needs are not well addressed (Peyvandi F et al, 2016).
- Management of HFXD is directed by the FX deficiency severity, with preventive options reserved for high-risk patients (Peyvandi F et al, 2016).
- Due to the lack of specific guidelines and licensed options, patients with HFXD may be treated with suboptimal treatment (Peyvandi F et al, 2016).
- Patients with HFXD need replacement therapy with a product that contains specific and adequate amounts of FX – FFP and PCCs used by default contain variable and often unspecified concentrations of FX (Austin SK et al, 2016).

3.1.1 Goals of therapy in hereditary FX deficiency

Current treatment of HFXD focuses on symptomatic treatment of bleeds. Prophylaxis needs are not well addressed, as few physicians prescribe prophylactic treatment and primarily in patients with higher risk of spontaneous bleeding. Patients with low bleeding risk are treated on-demand, as soon as possible after the onset of bleeding (Peyvandi F, Di Michele D et al, 2012). This can be dangerous as in some bleeding events such as ICH, reactive treatment may not be sufficient to stop the bleed before death (Mumford AD et al, 2014).

3.1.2 Current treatment options in hereditary FX deficiency

Minor bleeding symptoms can be adequately managed using a range of topical therapies and antifibrinolytic agents. Therapeutic options for control of menorrhagia can be medical (e.g. antifibrinolytics, hormonal suppressive therapy, levonorgestrel intrauterine device, clotting factor replacement) or surgical (e.g. endometrial ablation and hysterectomy if required) (Palla et al, 2015).

Replacement therapy is the mainstay of treatment for patients with HFXD who have more severe symptoms. This can be given as routine primary prophylaxis to prevent bleeds, secondary prophylaxis around surgeries or other high-risk events, or as on-demand therapy after an acute bleeding episode (Acharya et al, 2004).

There are no previously approved specific treatments for HFXD. Patients requiring replacement therapy are treated by default with either fresh frozen plasma (FFP) or a prothrombin complex concentrate (PCC), both of which contain variable and often unspecified concentrations of FX (Brown et al, 2008). Importantly, the EMA clearly states that PCCs should only be considered for the treatment of bleeding and perioperative prophylaxis when purified specific coagulation factor product is not available (Core Summary of product Characteristics for human Prothrombin Complex Products - CPMP/BPWG/3735/02).

A freeze-dried concentrate of human coagulation factors IX and X is also currently licensed in Switzerland and Saudi Arabia for the treatment and prophylaxis of bleeding in patients with haemophilia B and factor IX and/or FX deficiency; however, it has not been approved by the EMA.

Human coagulation FX was approved by the EMA on 16 March 2016 and by the FDA on 19 October 2015. Ultra-purified plasma-derived FX is the recommended product for replacement therapy in HFXD, given its precise correction of the deficiency without subjecting patients to extraneous factors present in PCC or FFP products, consequently minimising the risk of thrombotic events and obviating

the necessity for vigilant monitoring of other coagulation factors (Tarantino, 2021; Austin, Kavakli et al, 2016; Austin, Brindley et al 2016; Palla et al, 2015).

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