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Review article

Rare inherited coagulation disorders and thrombosis

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Abstract

The traditional clinical paradigm of rare inherited coagulation disorders (RICDs) implies that reduced levels of coagulation factors increase the bleeding tendency, although the relationship between factor activity and clinical phenotype is often variable and disease-related. However, emerging evidence suggests a more complex coagulation balance in RICD, so that a few inherited factor deficiencies predispose patients to arterial thrombosis and venous thromboembolism (VTE). By synthesizing data from international registries, clinical trials and biochemical studies, this review explores the molecular and clinical mechanisms underlying the thrombotic risk in RICDs, including deficiencies of factors II, V, VII, XI, XII, XIII and fibrinogen disorders. We show how some molecular variants disrupt the interplay between procoagulant, anticoagulant, and fibrinolytic pathways. For instance, while FXII and FXI deficiencies are increasingly viewed as protective against thrombosis, in some dysprothrombinemias and dysfibrinogenemias the impairment of anticoagulant regulatory mechanisms lead to increased thrombin generation. In disorders such as FXIII deficiency and afibrinogenemia, mechanical clot instability and loss of thrombin sequestration are proposed as potential mechanisms contributing to an increased risk of thrombotic events. This increased risk is often triggered or exacerbated by replacement therapies, co-inherited thrombophilia, or acquired factors. Understanding the underlying molecular mechanisms is essential to manage patients at risk for both life-threatening hemorrhage and thrombosis. Ultimately, a personalized approach is required to optimize bleeding prophylaxis and as well as episodic treatment.

Introduction

The traditional conceptualization of rare inherited coagulation disorders (RICDs) relies on an interpretation of the coagulation system so that the degree of deficiency of a procoagulant protein results in a proportional and predictable hemorrhagic phenotype. This simplified model, however, fails to account for the complex, feedback mechanisms that maintain coagulation balance.[1] While the traditional cascade linear model effectively reflects *ex vivo* clotting in static plasma assays as the prothrombin time (PT) and activated partial thromboplastin time (APTT), *in vivo* hemostasis relies on a dynamic, cell-based model governed by cellular surfaces (e.g., tissue factor-bearing cells and activated platelets) and feedback loops.[2] Accordingly, the poor correlation between isolated factor levels measured through standard assays and the actual bleeding phenotype accounts for a paradox emerging in hematology clinical practice: some RICDs, involving the various stages of the coagulation system, predispose patients to both arterial and venous thromboembolism (VTE).[3-6]

This review provides an update into the molecular and clinical evidence regarding this seemingly paradoxical risk. By evaluating data collected from international registries, clinical trials and biochemical studies, we aim to elucidate the mechanisms by which a bleeding genotype may manifest as a thrombotic phenotype, with the ultimate goal to guide hematologists toward the proper management of these cases. This review is focused on rare inherited coagulation factor defects other than hemophilia A and B reported to present sometime with an unexpected thrombotic phenotype (Figure 1). Thrombotic events in inherited platelet function defects, such as Glanzmann thrombasthenia and Bernard Soulier syndrome, will not be evaluated. By the same token, factor X inherited deficiency is not mentioned because no report of thrombosis was found in the literature review. Table 1 summarizes the main characteristics of RICDs associated with an increased thrombotic risk.

The contact phase

RICDs of the contact phase of blood coagulation with a potential risk of thrombotic complications include FXII and FXI deficiencies (Figure 2).

Factor XII deficiency

FXII, historically known as Hageman factor, represents a fascinating anomaly in hematology. While indispensable for initiating blood coagulation in the context of laboratory tests, its absence in human plasma does not result in a bleeding disorder. This unique characteristic has shifted the focus from its role in coagulation to broader roles in inflammation and thrombosis.[7,8] Despite lack of bleeding symptoms, deficient people exhibit a prolonged activated partial thromboplastin time (APTT), a laboratory finding that often leads to confusion and unnecessary concern in the frame of pre-operative screenings.[7]

The discovery of FXII dates back to 1955 with the report of the first case John Hageman, who died from the thromboembolic consequences of trauma.[9] Thus, researchers investigated for decades whether or not FXII deficiency increases the risk of thrombosis, but clinical evidence remains controversial. An historical retrospective series suggested that up to 5% of cases with FXII deficiency experienced VTE,[10] but more recent cohort studies failed to find a link between low FXII and increased risk of VTE or arterial thrombosis.[11-13] Furthermore, a systematic review and meta-analysis, including six studies including 5,003 participants, failed to support an association between the deficiency and the risk of venous or arterial thromboembolic events.[14] Notably, the finding that knockout mice (genetically engineered to lack FXII) do not bleed abnormally after injury but are protected from the formation of clots in arteries and veins paved the way to the evaluation of anticoagulant drugs targeting FXII.[15,16]

Factor XI deficiency

Factor XI plays a dual role in the coagulation process, functioning as a procoagulant that sustains thrombin generation (through the activation of FIX) but also as an antifibrinolytic moiety, that

achieves this role by activating the thrombin-activatable fibrinolysis inhibitor (TAFI), that in turn modifies the fibrin mesh by increasing its resistance to fibrinolysis. This dual capability ensures that after its formation a clot remains stable enough to facilitate tissue repair.[17] Clinically, FXI deficiency is a rare genetic disorder (population prevalence 1 in 1,000,000) traditionally associated with Ashkenazi and Iraqi Jewish populations, even though it is described in all ethnic groups.[18] Similarly but more strikingly than for other RICD, there is no association between the measured plasmatic activity of factor XI and severity of clinical bleeding. Thus, even people with such relatively high levels as 30 to 40% may experience significant hemorrhage but on the other hand people with very low plasma levels may be fully asymptomatic. Bleeding occurs more commonly following trauma or surgery in tissues endowed with high fibrinolytic activity, such as the oral and nasal cavities and the prostate. Women often report heavy menstrual bleeding or post-partum hemorrhage, but bleeds into joints or muscles are rare.[19]

Spontaneous thrombosis in FXI deficiency is rare. In contrast, the therapeutic administration of plasma-derived FXI concentrates is associated with a clinically significant thrombotic risk, due to coagulation activation and enhanced thrombin generation. [20-23] Therefore, thrombotic complications related to FXI replacement should be regarded as a treatment-associated rather than an inherent risk. Interest has shifted in recent years toward the protective effect of low FXI levels against thrombosis. Animal models have consistently shown that severe FXI deficiency provides a defense against arterial thrombosis without impairing hemostasis.[5] In humans, severe deficiency appears protective from ischemic stroke and deep vein thrombosis (DVT) but not from acute myocardial infarction.[24-26] A cohort of 115 Israeli patients older than 45 years of age with FXI deficiency (< 15%) was compared with the general population.[24] After correction for common risk factors, the expected incidence of ischemic stroke in the general population was strikingly higher than in the FXI deficient group. Another Israeli study involving 10,193 individuals, in whom FXI levels were obtained over a 12-year period, showed that low FXI was associated with a reduced risk of VTE (adjusted hazard ratio [HR]

0.26, 95% CI 0.08-0.84): none of the people with FXI <30% developed VTE. Similarly, FXI deficiency was associated with an approximately halved risk of major cardiovascular events (composite of stroke, transient ischemic attack, and myocardial infarction).[25] This finding is likely to be explained by the fact that a reduction in FXI leads to lower thrombin generation, resulting in a fibrin meshwork with an altered structural integrity that makes it more susceptible to endogenous fibrinolysis. Accordingly, FXI inhibition has been proposed as a target for the development of anticoagulant drugs aimed at reducing the risk of VTE and ischemic stroke.[27,28] Conversely, high circulating levels of FXI above the 90th percentile are a risk factor for thrombosis.[29] Individuals with high levels are twice as likely to develop DVT, a risk that follows a linear dose-response relationship.[30,31] As forementioned, the risk of thrombosis is further highlighted by the finding that replacement therapy with plasma-derived FXI concentrates has been linked to thrombotic events due to suddenly enhanced thrombin generation.[20] To reduce their thrombogenic potential, antithrombin and/or heparin have been added to these products.[21]

The extrinsic pathway

Factor VII deficiency

Inherited FVII deficiency is the most frequent RICD, with an estimated prevalence of 1 in 500,000.[32-34] While traditionally classified as a bleeding diathesis that ranges from asymptomatic presentation to life-threatening intracranial hemorrhages poorly correlated with FVII coagulant activity, this autosomal recessive condition does not confer protection from thrombosis[34]. Approximately 3 to 4% of cases with FVII deficiency, including those with severe disease, experienced venous or arterial thrombotic events.[35,36] According to the largest series of patients published and international registries, alongside traditional sites of venous thrombosis (i.e., lower limbs and pulmonary embolism), some atypical localizations have been reported, including portal, splenic, central retinal and cerebral veins. Thrombosis was also described in arteries such as the aortoiliac axis and

cerebral.[37-42] This occurrence is frequently associated with acquired risk factors rather than being spontaneous. Common precipitants include surgical interventions, the administration of replacement therapies, particularly those containing activated factors (i.e., recombinant activated FVII [rFVIIa] or activated prothrombin complex concentrate [aPCC]), the presence of co-inherited gain-of-function gene variants such as FV Leiden as well as acquired conditions as the antiphospholipid syndrome.[43] Albeit rarely, thrombotic events with no associated risk factors occurred in FVII deficiency, and a few FVII gene variants appear to have an association with hypercoagulability.[34] The p.Arg304Gln (FVII Padua) and p.Ala294Val variants are more prevalent in FVII-deficient patients with thrombosis than in the general FVII-deficient population.[44] These variants may alter the conformation of the FVII protein, resulting in a higher affinity for tissue factor (Figure 2).[4,34]

Managing these patients requires a balance between preventing hemorrhage and mitigating the risk of thrombosis, especially in the perioperative setting. Clinical insights suggest that thromboprophylaxis should be individualized on the basis of the FVII plasma levels and presence or not of additional thrombosis risk factors.[45] Thus, prophylaxis may be considered even for cases with mild (FVII >20%) or moderate deficiencies (10-20%) but with a history of thrombosis. Conversely, thromboprophylaxis is generally not recommended for patients with severe deficiency.[34] All in all, the occurrence of cases of VTE and ischemic stroke emphasizes that FVII deficiency is not a naturally anticoagulated condition, but a complex condition in which the potential for thrombosis should be considered.

The common pathway

Two RICDs of the common pathways have been linked to an increased thrombotic risk: FV and FII deficiency (Figure 2).

Factor V deficiency

FV deficiency is a rare autosomal recessive coagulopathy characterized phenotypically by a spectrum ranging from mild to moderate mucosal bleeding (i.e., epistaxis, oral cavity bleeding, hematemesis, melena, hematuria and heavy menstrual bleeding) to life-threatening hemorrhages (i.e., gastrointestinal and intracranial hemorrhage).[46-48] Approximately 80% of FV circulates in plasma, 20% is located within the platelet alpha granules. This intra-platelet pool is released locally at sites of vascular injury and often helps to maintain hemostasis even when plasma levels are undetectable.[46] However, FV deficiency has been sometime associated with arterial and, more frequently, venous thrombosis, despite its predominantly hemorrhagic phenotype.[40,49-54] The mechanistic basis for thrombosis is multifactorial and often stems from a disrupted balance between the procoagulant and anticoagulant pathways. A primary driver is the concomitant inheritance of gain-of-function gene variants, notably FV Leiden [c.1691G>A (P.(Arg506Gln))] resulting in pseudo-homozygosity, that is the presence of a single Leiden allele together with a null FV allele making the total circulating FV pool resistant to activated protein C inactivation. Furthermore, since FV acts as a cofactor for protein S in the inactivation of activated FVIII, its deficiency impairs the natural anticoagulant system, leading to a hypercoagulable state. Clinical management requires a tailored approach, because the administration of fresh frozen plasma to control hemorrhage may trigger thrombosis by altering the delicate hemostatic balance in these patients.[52]

Factor II deficiency

FII (prothrombin) deficiency is the rarest RICD, with an autosomal recessive inheritance and prevalence of approximately one in two million.[55] The disease spectrum is broadly divided into type I deficiency (hypoprothrombinemia), defined by a concomitant plasmatic reduction in both functional activity and antigen levels, and type II deficiency (dysprothrombinemia), with near normal antigen levels contrasting with severely reduced coagulant activity.[56] Prothrombin is a vitamin K-dependent zymogen that, upon activation by the prothrombinase complex (activated FX and FV, phospholipids and calcium), undergoes proteolytic cleavage to generate thrombin, the downstream effector of clot

formation. While the complete absence of prothrombin is considered incompatible with life, activity levels as low as 1% are consistent with survival, often in association with mucocutaneous bleeding and post-surgical hemorrhage.[55] However, the relationship between FII activity levels and clinical phenotype is inconsistent in dysprothrombinemia, because a laboratory defect in the procoagulant function does not invariably translate into a bleeding diathesis and may paradoxically predispose to VTE.[57-60] Indeed, a recent study from the American Thrombosis and Hemostasis Network (ATHN) found that among RICD, the highest rate of VTE occurred in cases with prothrombin deficiency, reaching 19%.[4]

The molecular basis underlying thrombotic complications often resides in gene variants affecting specific functional domains of thrombin. In particular, the p.Arg382His variant makes prothrombin unable to bind adequately fibrinogen to form a stable clot. Besides a dramatic loss of coagulant activity (~1%), this mutant prothrombin demonstrated when compared to wild-type thrombin a profound defect in the activation of protein C (600-fold reduction) and of the thrombin-activatable fibrinolysis inhibitor (TAFI) (2500-fold reduction).[55,56] This dual defect creates a condition that makes the patient poorly protected against hyperfibrinolysis due to impaired TAFI activation and leads to bleeding. At the same time, lack of the essential APC-mediated anticoagulant regulatory mechanisms can trigger thrombosis in the presence of concomitant hypercoagulability risk factors.[58] Clinical evidence of this hemostatic conundrum is illustrated by patients who experienced both severe bleeding and thrombotic events. For instance, cases with the p.Arg382His variant developed spontaneous abortions and pregnancy-related hemorrhages followed by postpartum pulmonary embolism and deep vein thrombosis.[61] Furthermore, other variants, such as those at residue Arg596 (including p.Arg596Leu, p.Arg596Gln, and p.Arg596Trp), represent a distinct class of dysprothrombinemia primarily characterized by resistance to the anticoagulant effect of antithrombin (Figure 2). These cases often present with no bleeding history but with recurrent venous thrombosis.[55] Thus, inherited prothrombin deficiency must not be simply viewed as a bleeding disorder, but as a

complex disruption of the hemostatic balance, with the site of the molecular variant determining whether the clinical phenotype is hemorrhagic, thrombotic, or a combination of both.

The final phase

Two RICDs involving the final phase of blood coagulation may be associated with an increased thrombotic risk: fibrinogen disorders and FXIII deficiency (Figure 2).

Fibrinogen disorders

Fibrinogen is a hexameric glycoprotein synthesized by hepatocytes and composed by two sets of three polypeptide chains (Aα, Bβ, γ).[62,63] It is the ultimate substrate of the coagulation system, converted by thrombin into fibrin monomers that polymerize to form the structural scaffold of the clot. This protein also mediates platelet aggregation by binding to the integrin $\alpha_{IIb}\beta_3$. The three polypeptide chains are linked by disulfide bonds and are encoded by the gene cluster *FGA*, *FGB*, and *FGG* located on chromosome 4.[64] Inherited abnormalities of fibrinogen, with an estimated prevalence of one in million, may be classified as quantitative or qualitative.[65] The former include afibrinogenemia and hypofibrinogenemia, the latter including qualitative fibrinogen defects referred to dysfibrinogenemia.[65,66] More than 400 unique gene variants have been identified in inherited fibrinogen disorders.[67,68] Laboratory results of functional fibrinogen levels (measured in plasma by the Clauss method) and antigenic fibrinogen (measured by ELISA or immunonephelometry) permit to differentiate between afibrinogenemia/ hypofibrinogenemia (both tests are reduced in plasma) and dysfibrinogenemia (defined by a functional-to-antigenic fibrinogen ratio < 0.7), but definite diagnosis requires genotyping of *FGA*, *FGB*, and *FGG*.[66]

Although inherited fibrinogen disorders are usually associated with a bleeding tendency, in some cases they may cause thrombotic phenotypes, and both venous and arterial thromboembolism has been reported.[69] Some of these cases have other concomitant risk factors, such as coinherited thrombophilia, surgery, trauma, immobilization, pregnancy or fibrinogen replacement therapy,[69] that

contribute to transform inherited fibrinogen disorders from bleeding disorders into complex thrombophilic states.

Pertaining to afibrinogenemia, there is a high prevalence of thrombosis with this condition.[70] Reported rates vary across studies, ranging from 4% to 44%, and including traditional as well as unusual sites. Data from a 2016 systematic review documented 48 cases of thromboembolism, both arterial and venous.[71] These events typically first manifested around a median age of 31, spontaneously or precipitated (half of the cases) by such external triggers as trauma or systemic infections. While most patients responded well to fibrinogen replacement (sometimes in association with anticoagulants or antiplatelets), severe complications occasionally needed major surgical intervention, such as bowel resection following a mesenteric infarction.[71] Several mechanisms have been proposed to explain the predisposition to thrombosis. They include:

- Fibronectin uptake: in the absence of fibrinogen, the $\alpha_{IIb}\beta_3$ receptor (which usually transports fibrinogen into the platelet alpha-granules) may instead take up fibronectin, that may in turn induce platelet aggregation.[72]
- von Willebrand factor (VWF)-mediated platelet aggregation: in the absence of fibrinogen, platelet aggregation remains possible through VWF-mediated interaction between platelets, platelet membrane receptors and subendothelial structures, potentially acting as a substitute for fibrinogen.[72]
- Procoagulant imbalance: the concomitant increase of other coagulation factors may contribute to a prothrombotic phenotype.[72]
- Increased thrombin generation: under physiological conditions, fibrin sequesters thrombin, preventing its free circulation. This antithrombin role of fibrin is impaired in the absence of fibrinogen. Excessive thrombin may in turn promote platelet activation through protease-activate receptor-1 (PAR-1) signaling, thereby contributing to arterial and venous thrombosis.[69]

Although some patients with dysfibrinogenemia bleed, both arterial and venous thromboembolic disease have been observed in association with specific fibrinogen structural variants, predominantly located in the C-terminal domain of the Aα-chain and the thrombin cleavage site of the Bβ-chain.[73] These variants may impair the thrombin binding site on fibrinogen as well as the binding of profibrinolytic proteins to fibrin.[69] Data from 101 patients with inherited dysfibrinogenemia revealed a significant history of thrombosis, with 20 cases of VTE and 8 arterial events such as myocardial infarction, stroke, and mesenteric ischemia.[74] Furthermore, a 2024 analysis of the RICD database found that 6% of cases (3 out of 55) with inherited dysfibrinogenemia developed thrombosis, both arterial and venous.[75] According to a 1995 report by the International Society on Thrombosis and Haemostasis (ISTH) focusing on 27 cases with high-risk variants, the average age for an initial thrombotic event was 27 years, but occurrences were documented in individuals ranging in age from 12 to 50.[76] Two mechanisms have been proposed to explain thrombosis associated with dysfunctional fibrinogens:

- Thrombin sequestration: the abnormal fibrinogen fails bind thrombin efficiently, thus resulting in higher levels of free thrombin in blood and associated hypercoagulability.[77] For example, fibrinogen Naples (*FGB*, p.Ala98Thr) was associated with impaired thrombin sequestration.[78]
- Resistance to fibrinolysis: clots formed with dysfunctional fibrinogens may be structurally resistant to lysis, with reduced sensitivity to plasmin during tissue-type plasminogen activator (t-PA)-mediated fibrinolysis.[77] Therefore, impaired fibrin-mediated enhancement of fibrinolysis may contribute to an increased thrombotic tendency.[79] For example, fibrinogen Dusart (*FGA*, p.Arg573Cys), Bordeaux (*FGA*, p.Arg458Cys), and Caracas V (*FGA*, p.Ser551Cys) have been associated with impaired fibrinolysis and delayed clot lysis.[80,81]

The management of thrombotic events in inherited fibrinogen disorders is challenging and should be individualized according to the bleeding and thrombotic risk profiles.[69] Thus, while cases with milder

forms of hypofibrinogenemia or dysfibrinogenemia may receive antithrombotic therapy with no need for fibrinogen replacement, those with severe hypofibrinogenemia or afibrinogenemia may require replacement (a target plasma fibrinogen level of >1.0 g/l is recommended) in order to reduce both the bleeding risk and enhanced thrombin generation.[69,82] The intensity and duration of anticoagulation should be individually tailored.

FXIII deficiency

Factor XIII (FXIII) deficiency is a very rare autosomal recessive bleeding disorder, affecting approximately one in two million individuals.[83] Factor XIII, also known as fibrin-stabilizing factor, is a transglutaminase that circulates in blood as a heterotetramer consisting of two catalytic A subunits (FXIII-A) and two carrier B subunits (FXIII-B). It plays a critical role in the final phase of coagulation by cross-linking fibrin chains, which increases the mechanical strength of the blood clot and protects it against premature lysis (FXIII incorporates into the clot antifibrinolytic proteins, such as alpha 2 - plasmin inhibitor).[84,85] Most cases of severe deficiency are caused by variants in *F13A1*, leading to an absence of the A subunit. The clinical presentation of severe deficiency (<10%) is often dramatic at the time of birth, with umbilical cord bleeding occurring in up to 80% of affected neonates. Intracranial hemorrhage is the most devastating complication that occurs in approximately 30% of cases, being a leading cause of mortality.[86] Other common symptoms include delayed wound healing, recurrent miscarriages, and soft tissue hematomas.[83] Diagnosis is challenging because standard coagulation screening tests, such as the prothrombin time (PT) and APTT, are normal, necessitating specific FXIII activity assays.[87]

While primarily characterized by bleeding, a risk of thrombosis (predominantly VTE) has been shown in inherited FXIII deficiency.[88] The underlying molecular mechanism resides in the mechanical instability and vulnerability of the blood clots formed.[89] In the absence of sufficient FXIIIa-mediated cross-linking, clots may appear morphologically intact and yet exhibit a reduction in their ability to resist physical rupture under the mechanical stress of flowing blood, with an increased likelihood of

fragmentation and embolization.[90-92] In addition, acquired prothrombotic risk factors, such as replacement therapies (i.e., plasma-derived or recombinant), surgical procedures or concomitant inherited thrombophilia may play a role in triggering thrombotic events. Thus, the management of these patients requires a balanced and personalized approach: while lifelong bleeding prophylaxis with FXIII concentrates is the standard of care to prevent hemorrhage in severe deficiency, anticoagulant therapy becomes necessary if a thrombotic event occurs. In the latter case, however, concomitant prophylactic factor replacement is recommended (and should be adapted to the intensity of the anticoagulation), in order to ensure that the patient maintains enough fibrin stability to prevent breakthrough bleeding.[90]

Conclusions

The exploration of RICDs through the lens of thrombosis reveals a profound complexity. For decades, the coagulation system has been viewed as a linear pathway where a missing factor inevitably leads to a failure of clot formation. However, evidence synthesized in this review demonstrates that the coagulation system is a finely tuned, interconnected network where the absence of a single protein can trigger a cascade of compensatory pathological responses. The prothrombotic shift observed in some patients is not a singular phenomenon but rather a reflection of various molecular disruptions that affect thrombin generation, natural anticoagulant pathways, and the mechanical stability of the fibrin meshwork.

A primary issue emerging from current clinical and molecular data is that the site and type of gene variant may sometime predict the clinical phenotype more accurately than plasma factor levels alone. For example, in dysprothrombinemia the p.Arg382His variant creates a catastrophic double-edged sword: impaired activation of the protein C pathway that predisposes to thrombosis coupled with a failure to activate TAFI, that predisposes to bleeding. Similarly, in fibrinogen disorders, the loss of the protein role as antithrombin leads to an excess of free circulating thrombin. These complexities

highlight the inadequacy of traditional screening tests as the PT and APTT in capturing the thrombotic risk, so that the adoption of tools such as molecular genotyping is essential for accurate individual risk stratification.

The management of these patients is a significant challenge for hematologists. Replacement therapies, while needed for preventing hemorrhages, introduces a new layer of risk. As seen particularly in inherited FVII and FXI deficiencies, the sudden surge in procoagulant activity following replacement therapy with plasma-derived or recombinant factor products may tip the balance toward thromboembolism, especially in the perioperative setting. This necessitates a highly individualized strategy where thromboprophylaxis is based on the comprehensive assessment of co-inherited thrombophilia, acquired risk factors, and the specific molecular defect. In FXIII deficiency, with the risk of thrombosis stemming from mechanical clot fragility and embolization, the simultaneous use of factor replacement and anticoagulation may be the only way to manage the patient. Notably, the protection from thrombosis observed in FXI and FXII deficiencies provides a new frontier for drug development. The observation that these patients are often protected from thrombosis without suffering from spontaneous bleeding paved the way for a generation of anticoagulants targeting this phase of the coagulation pathway.

The evidence synthesized in this article is the subject of important limitations. The rarity of RICDs means that available data are derived from small case series, registry studies and retrospective analyses, limiting robust conclusions. Publication bias is also a significant concern, because thrombotic events in patients with bleeding disorders are inherently unexpected and therefore more likely to be reported, inflating the apparent frequency. Finally, the concurrent presence of acquired triggering factors and co-inherited thrombophilia in a number of reported cases makes it difficult to attribute thrombosis solely to the factor deficiency.

In conclusion, the paradox of thrombosis in RICDs serves as a reminder that blood coagulation is an integrated system of checks and balances. The management of patients requires to move away from

generalized protocols toward a model of precision medicine. By integrating molecular biology with clinical evidence, hematologists can better navigate the delicate balance between hemorrhage and thrombosis. The goal of research should be to refine risk stratification tools, ensuring that each patient receives a therapeutic approach tailored to the complex reality of their bleeding genotype manifesting as a thrombotic phenotype.

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Table 1. Characteristics of thrombosis associated with rare congenital coagulation factor deficiencies.

Congenital defect	Coagulation phase	Prevalence (severe deficiency)	Type of bleeding	Type of thrombosis	Main thrombogenic mechanism(s)	Thrombosis trigger	References
Factor XII deficiency	Contact phase	1:1,000,000	No bleeding symptom also in the absence of FXII	No consistent evidence of an increased risk of arterial and venous thrombosis	N/A	N/A	10-14
Factor XI deficiency	Contact phase	1:1,000,000	No correlation between bleeding symptoms and FXI activity	Predominantly VTE associated with FXI replacement therapy. FXI deficiency protects against arterial and venous thrombosis	Excessive thrombin generation; impaired TAFI activation; reduced fibrinolysis susceptibility	Predominantly treatment-related (FXI concentrate)	24-26

Factor VII deficiency	Extrinsic pathway	1:500,000	Poor correlation between bleeding severity and residual FVII activity	Venous and arterial thrombosis, predominantly associated with acquired triggering factors	Gain-of-function variants (e.g., FVII Padua) increasing TF affinity; co-inherited thrombophilia (e.g., FV Leiden)	Predominantly treatment-related or with acquired triggers; rarely spontaneous	35-39, 42
Factor V deficiency	Common pathway	1:1,000,000	Predominantly mucosal bleeding	Predominantly VTE, mostly associated with concomitant risk factors (FV Leiden)	Pseudo-homozygosity for FV Leiden; impaired FV cofactor role in protein S-mediated FVIII inactivation	Predominantly treatment-related (FFP) or with co-inherited thrombophilia	50-54
Factor II deficiency (prothrombin)	Common pathway	1:2,000,000	Mucocutaneous bleeding (severe deficiency)	Predominantly venous thrombosis in dysprothrombinemia	Impaired protein C activation; antithrombin resistance (Arg596 variants); defective TAFI activation	Both spontaneous (gene variant-dependent) and treatment-related	57, 59-61

Fibrinogen disorders - **Afibrinogenemia** - **Dysfibrinogenemia**	Final phase	1:1,000,000 1:1,000.000 (probably underestimated)	Severe bleeding symptoms Only 25% of patients have hemorrhagic symptoms, usually mild to moderate	Arterial and venous thrombosis Arterial and venous thrombosis	Loss of thrombin sequestration by fibrin with excess free thrombin; VWF- and fibronectin-mediated platelet aggregation	Both spontaneous and treatment-related (fibrinogen concentrate)	70, 71 75, 78, 80, 81
Factor XIII deficiency	Final phase	1:2,000,000	Severe FXIII deficiency associated with early life-threatening bleeding	VTE	Mechanical clot instability with fragmentation and embolization	Both spontaneous and treatment-related	90-92

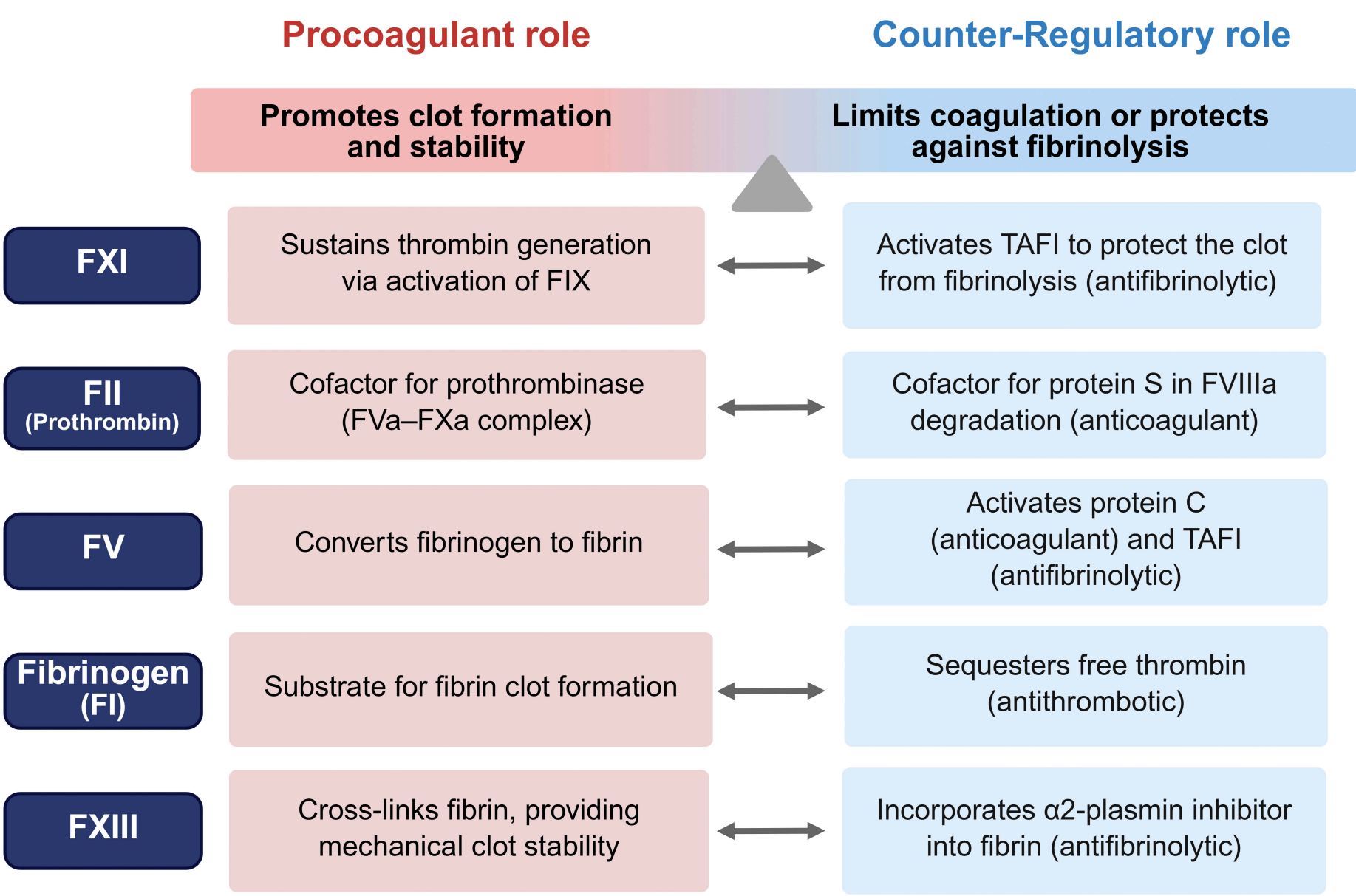
Abbreviations: Factor XII: FXII; Factor XI; FXI; VTE: venous thromboembolism; Factor VII, FVII; Factor V: FV; Factor XIII, FXIII.

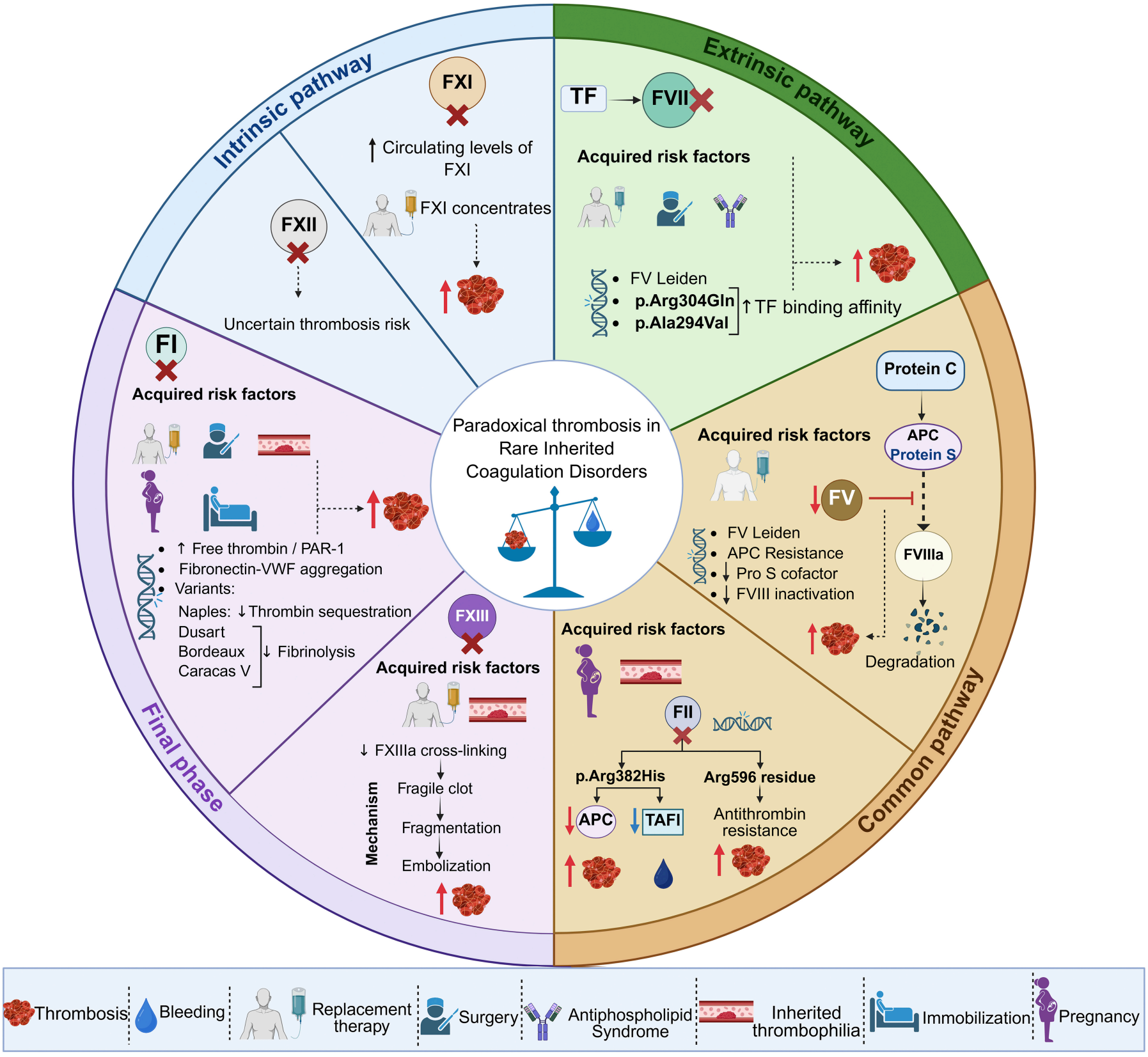
Legend.

Figure 1. Dual roles of some coagulation factors in hemostasis. Several factors participate in both procoagulant and regulatory pathways. Deficiency or dysfunction may therefore concomitantly impair multiple hemostatic mechanisms, contributing to both bleeding and thrombotic phenotypes. APC, activated protein C; TAFI, thrombin-activatable fibrinolysis inhibitor. Created with BioRender.com.

Figure 2. Mechanisms of thrombosis in rare inherited coagulation disorders. Created with BioRender.com.

Dual Roles of Coagulation Factors




Intrinsic pathway
Extrinsic pathway
Common pathway
Final phase
Paradoxical thrombosis in Rare Inherited Coagulation Disorders
FXI
↑ Circulating levels of FXI
FXI concentrates
FXII
Uncertain thrombosis risk
TF
FVII
Acquired risk factors
FV Leiden
p.Arg304Gln
p.Ala294Val
↑ TF binding affinity
Protein C
APC
Protein S
Acquired risk factors
FV
FV Leiden
APC Resistance
↓ Pro S cofactor
↓ FVIII inactivation
FVIIIa
Degradation
FII
Acquired risk factors
p.Arg382His
Arg596 residue
APC
TAFI
Antithrombin resistance
FXIII
Acquired risk factors
↓ FXIIIa cross-linking
Mechanism
Fragile clot
Fragmentation
Embolization
FI
Acquired risk factors
↑ Free thrombin / PAR-1
Fibronectin-VWF aggregation
Variants:
Naples: ↓Thrombin sequestration
Dusart
Bordeaux
Caracas V
↓ Fibrinolysis
Thrombosis
Bleeding
Replacement therapy
Surgery
Antiphospholipid Syndrome
Inherited thrombophilia
Immobilization
Pregnancy