Paradoxical Thrombosis in Rare Bleeding Disorders: Frequency, Clinical Contexts, and Outcomes in a Large Iranian Cohort

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- **Background**

Rare bleeding disorders (RBDs) are inherited deficiencies or dysfunctions of coagulation factors other than hemophilia A/B and von Willebrand disease. Traditionally, these disorders are viewed as **purely hemorrhagic**.

However, accumulated evidence over the last two decades demonstrates that **venous and arterial thrombosis can occur**, creating a clinically important paradox.

Rapid Classification of Thrombosis Risk in Rare Bleeding Disorders (RBDs)

Thrombosis Risk Level	***RBDs***
High risk	Dysfibrinogenemia; FID; FXIID
Moderate risk	Factor VII deficiency; Factor XI deficiency; Factor X deficiency; Factor II deficiency
Low risk	F XIIID;F VD deficiency; PAI-1D ; α2-Antiplasmin D

Disorder	Thrombotic risk	Key notes
Congenital fibrinogen disorders (FGI)	**Highest**	***Especially dysfibrinogenemia (intrinsic prothrombotic phenotype)***
Factor XI deficiency	Low–moderate	***Often perioperative or with replacement***
Factor VII deficiency	Low–moderate	***Usually treatment-related***
Factor XIII deficiency	Rare	***Mostly post-replacement, surgery, or pregnancy***
Factor V deficiency	Very rare	***Case reports only***
Combined deficiencies	Variable	***Depends on dominant defect and triggers***

- **Risk Factors of Thrombosis in Rare Bleeding Disorders (RBDs)**
- Thrombosis in RBDs is **multifactorial** and often **paradoxical**, resulting from the interaction between **intrinsic disease mechanisms**, **replacement therapy**, and **acquired clinical conditions**.

1. Disease-Related (Intrinsic) Risk Factors

Factor	Explanation
Dysfibrinogenemia	Structurally abnormal fibrin promotes clot stability and resistance to fibrinolysis [1–3]
Afibrinogenemia	Imbalance between thrombin generation and fibrin formation, leading to paradoxical thrombosis [1,4]
Factor XII deficiency	Impaired fibrinolysis despite absence of bleeding tendency [5]
Prothrombotic fibrin structure	Dense fibrin networks resistant to plasmin-mediated lysis [2,6]
Variable genotype–phenotype correlation	Thrombosis may occur at low or normal factor levels [1,7]
Chronic endothelial activation	Recurrent inflammation or vascular injury enhances thrombotic risk [8]

2. *Replacement-Therapy–Related Risk Factors*

Factor	Explanation
Supraphysiologic factor levels	Particularly FVIII, FIX, and fibrinogen; increased thrombin generation [9,10]
Repeated **high-dose bolus** therapy	Leads to extreme plasma peaks and transient hypercoagulability [10]
PCC	Contain activated vitamin K–dependent clotting factors [11]
rFVIIa	Strongly associated with arterial and venous thrombosis [12,13]
Long half-life factors (e.g., FXIII)	Risk of accumulation with frequent dosing [14]
Lack of ***trough-guided dosing***	Peak-oriented correction increases thrombosis risk [9]

3. Patient-Related Risk Factors

Factor	Explanation
Advanced age	Particularly relevant in FXI and fibrinogen disorders [15]
Obesity	Increased baseline thrombotic risk [16]
Pregnancy and postpartum period	Physiologic hypercoagulability [17]
Immobility	Hospitalization, fractures, neurologic disease [18]
Central venous catheters	Endothelial injury, especially in pediatric patients [19]
Smoking	Endothelial dysfunction and platelet activation [20]
Dehydration	Hemoconcentration and increased blood viscosity [21]

4. Genetic and Acquired Prothrombotic Conditions

Factor	Explanation
Factor V Leiden mutation	Adds synergistic thrombotic risk in RBDs [22]
Prothrombin G20210A mutation	Particularly relevant in FII-related disorders [23]
Antiphospholipid antibodies	Can override bleeding tendency [24]
Protein C / S deficiency	Reduced natural anticoagulation [25]
Malignancy	Tumor-associated procoagulant activity [26]
Chronic inflammatory disease	Cytokine-driven coagulation activation [27]

5. Procedure-Related and Situational Factors

Factor	Explanation
Surgery (especially orthopedic or abdominal)	Marked thrombin generation [28]
Major trauma	Endothelial damage and tissue factor exposure [29]
Infections (e.g., sepsis, COVID-19)	Systemic coagulation cascade activation [30]
Perioperative overcorrection	Targeting “normal” levels instead of minimum effective levels [9,10]
Absence of thromboprophylaxis	When indicated but avoided due to bleeding concerns [31]

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RBD / Group	Type of evidence	Reported numbers / patterns	Clinical relevance	Key reference
RBDs overall	Critical review (case aggregation)	Large collection of arterial and venous thrombotic events; **arterial thrombosis only: 42 patients** (MI = 28, stroke = 4, arterial occlusion = 8, DIC = 2)	Highly informative for **counting cases and identifying clinical patterns**, but **does not provide population-based prevalence**	Girolami et al., 2006 (PubMed)
Congenital fibrinogen disorders (FGI)	Review (thrombotic paradox)	Emphasizes that in CFD—particularly **dysfibrinogenemia**—thrombosis may be **intrinsic and not merely trigger-related**	Represents the **highest thrombotic risk** among RBDs	Mohsenian et al., 2025 (RPTH)
FXIII deficiency – surgical cohort (Iran)	**Large case series**	**162 patients**; postoperative complications: **5 events** (2 bleeding + **3 thrombotic events**) → **thrombosis rate 1.85% (3/162)**	Provides **real-world perioperative thrombotic risk**; stronger epidemiologic value than isolated case reports	Naderi et al., J Thromb Haemost 2017
FXIII deficiency – recent cases	Case report	Recurrent VTE in severe FXIII deficiency with complex anticoagulation management	Demonstrates that FXIII deficiency can enter a **true VTE phenotype**, although extremely rare	Bounaix et al., 2024 (PubMed)
Factor VII deficiency	Review / overview	Dedicated discussion of thrombosis in RBDs with references to aggregated cases	Thrombotic events are usually **trigger- or treatment-related** (surgery, replacement therapy)	Ruiz-Sáez, 2012 (Semin Thromb Hemost)

Minimum Safe Trough

Disorder	Minimum Safe Trough	Comment
Hemophilia A/B	3–5%	Balance joint protection vs VTE
VWD	VWF ≥30%	Monitor FVIII
FXIII	3–5%	Long half-life
Fibrinogen	≥100 mg/dL	Dysfibrinogenemia is special
FVII	10–15%	Avoid frequent rFVIIa
FXI	15–20% (if needed)	Often no prophylaxis

Minimum and Maximum Coagulation Factor Levels and Thrombosis Risk in Rare Bleeding Disorders (RBDs)

RBD / Factor	Minimum Effective Level for Bleeding Prevention	***Maximum Safe Level***	Thrombosis Risk	Key Clinical Considerations
Factor XIII deficiency (FXIII)	**≥3–5%**	***<70–100%***	Low (rare)	Long half-life; avoid cumulative overdosing [1,2]
Afibrinogenemia	**≥50–100 mg/dL**	***<150–200 mg/dL***	**High**	Thrombosis reported even at low fibrinogen levels [3–5]
Hypofibrinogenemia	**≥100 mg/dL**	***<200 mg/dL***	Moderate	Careful balance between bleeding and thrombosis [3,4]
Dysfibrinogenemia	Individualized (phenotype-driven)	***Lowest effective level***	**High (intrinsic)**	Thrombosis may occur independent of fibrinogen level [3,6]
Factor VII deficiency (FVII)	**≥10–15%**	***Avoid repeated supraphysiologic peaks***	Moderate–High	rFVIIa strongly associated with thrombotic events [7,8]
Factor XI deficiency (FXI)	**≥15–20%** (if required)	***Avoid full correction***	Moderate	Many patients do not require prophylaxis [9,10]
Factor V deficiency (FV)	**≥10–20%**	***<50–60%***	Low–Moderate	Limited thrombotic data; individualized approach [11]
Factor X deficiency (FX)	**≥10–20%**	***<50–60%***	Moderate	Prothrombin complex concentrates (PCC) require caution [12]
Factor II deficiency (FII)	**≥20–30%**	***<50–60%***	Moderate–High	PCC-related thrombotic risk documented [12,13]
Factor XII deficiency (FXII)	Not required	—	**High (paradoxical)**	No bleeding phenotype; thrombosis reported [14]
PAI-1 deficiency	Symptomatic treatment	—	Low	Predominantly mucocutaneous bleeding [15]
α2-Antiplasmin deficiency	Episodic treatment	—	Low	Hyperfibrinolysis-driven bleeding [16]

Key Clinical Messages

- **Minimum effective trough levels** are safer than full normalization.
- **Fibrinogen disorders**, particularly dysfibrinogenemia, represent the **highest paradoxical thrombotic risk** among RBDs.
- **PCC and rFVIIa** are the most thrombogenic replacement therapies in RBDs.
- Laboratory levels **do not reliably predict thrombosis risk** in several RBDs; ***phenotype dominates management decisions.***

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General Principles, management & treatment

- **1. *<u>Clinical Phenotype Takes Priority Over Factor Level</u>***
- Factors levels are **not reliable predictors** of thrombotic risk.
- This is particularly evident in:
  - Dysfibrinogenemia
  - Factor XI deficiency
  - Factor VII deficiency

2. Replacement Therapy Is the Most Common Modifiable Risk Factor

High thrombotic risk is associated with:

Prothrombin complex concentrates (PCC)

Recombinant activated factor VII (rFVIIa)

High-dose bolus infusions

Full factor normalization

“Full correction” ≠ “safe treatment”

- **3. Minimum Effective Level Is the Key Therapeutic Target**
- Not normal levels
- Not supraphysiologic peaks
- Not cumulative dosing
- The goal is the **lowest level sufficient for hemostasis**.
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- **4. Fear of Bleeding Should Not Prevent Thrombosis Treatment**
- Anticoagulation is **generally well tolerated** in most RBDs, provided that:
  - The appropriate agent is selected
  - Close clinical monitoring is performed
  - Excessive replacement therapy is avoided

Anticoagulant Selection in RBDs

Agent	Role in RBDs	Key Consideration
LMWH	First-line in most cases	Best balance between bleeding and thrombosis
UFH	Unstable patients / ICU	Rapid reversibility
Fondaparinux	Selected cases (e.g., HIT)	Limited evidence
DOACs	Highly selected patients only	Sparse data
Warfarin	Rarely used	INR monitoring unreliable

Low-molecular-weight heparin (LMWH) is the cornerstone of thrombosis treatment in RBDs.

Disorder-Specific Management of Thrombosis in Rare Bleeding Disorders (RBDs)

RBD / Disorder	*Main Thrombotic Context*	*Thrombosis Treatment*	*Replacement Therapy Strategy*	*Key Clinical Notes*
Congenital Fibrinogen Disorders (FGI) Afibrinogenemia / Hypofibrinogenemia / Dysfibrinogenemia	Intrinsic and replacement-related thrombosis	**LMWH**	Not routine Only if bleedingTarget: **80–100 mg/dL**Avoid **>150–200 mg/dL**	**Dysfibrinogenemia carries the highest intrinsic thrombotic risk**
Factor VII deficiency	Often **rFVIIa-related**	**LMWH**	Discontinue rFVIIa	Avoid concurrent rFVIIa and anticoagulation
Factor XI deficiency	Usually mild phenotype	**LMWH (reduced dose)**	Avoid full FXI correction	Many patients do not require prophylaxis
Factor X / Factor II / Factor V deficiency	Frequently **PCC-related**	**LMWH**	Discontinue PCCReplace only if active bleeding	PCC is a major modifiable risk factor
Factor XIII deficiency	Rare but reported	Standard anticoagulation	Adjust dosing interval to avoid accumulation	Long half-life increases accumulation risk
Factor XII deficiency	Paradoxical thrombosis	Standard anticoagulation	None required	Management identical to general population

Duration of Anticoagulation

Clinical Scenario	Suggested Duration
Replacement-related thrombosis	6 weeks – 3 months
Unprovoked venous thrombosis	≥3 months
Recurrent thrombosis	Individualized decision
Arterial thrombosis	Multidisciplinary (MDT) decision

Table 1: Summary of thrombotic events in RBD: sites, clinical contexts, and management outcomes

Age/Sex	Defect	Factor activity (%)	Type of thrombosis	Number of thrombosis	Morbidities	Risk factors	Replacement therapy	Thrombophilia profile
34/M	FXIII	<1%	DVT	1	Varicose veins	Surgery, Smoking, Obesity	FXIII Concentrate (Fibrogammin ®)	Neg
30/F	FXIII	<1%	DVT	1	Neg	Pregnancy	FXIII Concentrate (Fibrogammin ®)	Neg
15/F	FXIII	<1%	CNS thrombosis	1	Seizure disorder/epilepsy	Neg	FXIII Concentrate (Fibrogammin ®)	Neg
28/F	FXIII	<1%	DVT	1	Neg	Pregnancy second trimester	FXIII Concentrate (Fibrogammin ®)	Neg
18/F	FXIII	<1%	DVT	1	Neg	Pregnancy second trimester	FXIII Concentrate (Fibrogammin ®)	Neg
2/F	Afibrinogenemia	<30	Liver thrombosis	1	Neg	Gastroenteritis		Neg
3mo/M	Afibrinogenemia	<30	CVT	1	Seizure disorder/epilepsy	Neg		Neg
3mo/M	FVII	12%	CVT	1	Seizure disorder/epilepsy	Neg	rVIIa (AryoSeven ®)	Neg
20/F	FV	4%	CVT	1	Seizure disorder/epilepsy	Pregnancy third trimester	FFP	Neg
32/F	FV	3%	DVT	1	Neg	Neg	FFP	Neg
52/F	FII	15%	DVT	2	Varicose veins	Neg	PCC	Neg
13/M	FX	<1%	CVT	1	Seizure disorder/epilepsy	Neg	PCC	Neg

F: female, M: male, FXIII: factor XIII, DVT: deep vein thrombosis, CVT: cerebral venous thrombosis, Neg: Negative, PCC: Prothrombin concentrate complex.

Study Cohort Composition (Rare Bleeding Disorders)

RBD subtype	Total patients (n)	Proportion of cohort (%)
Factor XIII deficiency (FXIIID)	682	54.52
Factor VII deficiency (FVIID)	127	10.15
Factor X deficiency (FXD)	23	1.84
Factor V deficiency (FVD)	130	10.39
Factor II deficiency (FIID)	12	0.96
Afibrinogenemia	28	2.24
Other RBDs (not subclassified)	249	19.90
Total	**1,251**	**100.00**

Lifetime Thrombotic Events by RBD Subtype

RBD subtype	Patients with ≥1 thrombosis (n)	Total in subtype (N)	Proportion (%)
Factor XIII deficiency (FXIIID)	5	682	0.73
Factor V deficiency (FVD)	2	130	1.54
Afibrinogenemia	2	28	7.14
Factor X deficiency (FXD)	1	23	4.35
Factor II deficiency (FIID)	1	12	8.33
Factor VII deficiency (FVIID)	1	127	0.79
Other RBDs (not subclassified)	0	249	0.00
Overall	**12**	**1,251**	**0.96**

Associated Events

Analysis set	***Patients with ≥1 thrombosis (n)***	***Total cohort (N)***	***Proportion (%)***
Primary analysis (all events)	12	1,251	0.96
Sensitivity analysis (excluding pregnancy, surgery, PCC)	6	1,251	0.48

Interpretation (as stated): many thrombotic events occurred in **identifiable high-risk contexts**.

- Rarity is uncommon only in isolation; in total, it is frequent.

A Teacher of Ethics and the Art of Pediatrics

[***M H Marandian MD,1936-2023***]

- Although common observations stabilize scientific theories, **scientific progress is frequently initiated by rare, anomalous cases that challenge prevailing models**.