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webinar

HEALTH PROFESSIONALS

Topic on Focus on Rare Coagulation Disorders

An overview of inherited fibrinogen disorders with a focus on laboratory diagnosis

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ISLH
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Disclosures / Conflicts of Interest

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An overview of inherited fibrinogen disorders with a focus on laboratory diagnosis

Inherited fibrinogen disorders are rare bleeding or thrombotic conditions caused by quantitative or qualitative defects in fibrinogen. This webinar will provide an overview of the molecular and clinical characteristics of these disorders, with an emphasis on the role of laboratory testing in diagnosis and classification. We will also discuss diagnostic challenges, available assays, and interpretation of results to guide patient management.

- Describe the types and genetic basis of inherited fibrinogen disorders.
- Understand the principles and limitations of laboratory assays used to evaluate fibrinogen.
- Interpret laboratory findings to differentiate between quantitative and qualitative fibrinogen deficiencies.
- Identify the clinical manifestations and summarize recommendations for treatment

Outline

- Diagnosis of hereditary fibrinogen disorders (HFDs)
- Genotype
- Clinical features
- Management
- Conclusions

Types and subtypes of HFDs

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8-15:1000 (?)

8-15:1000 (?)

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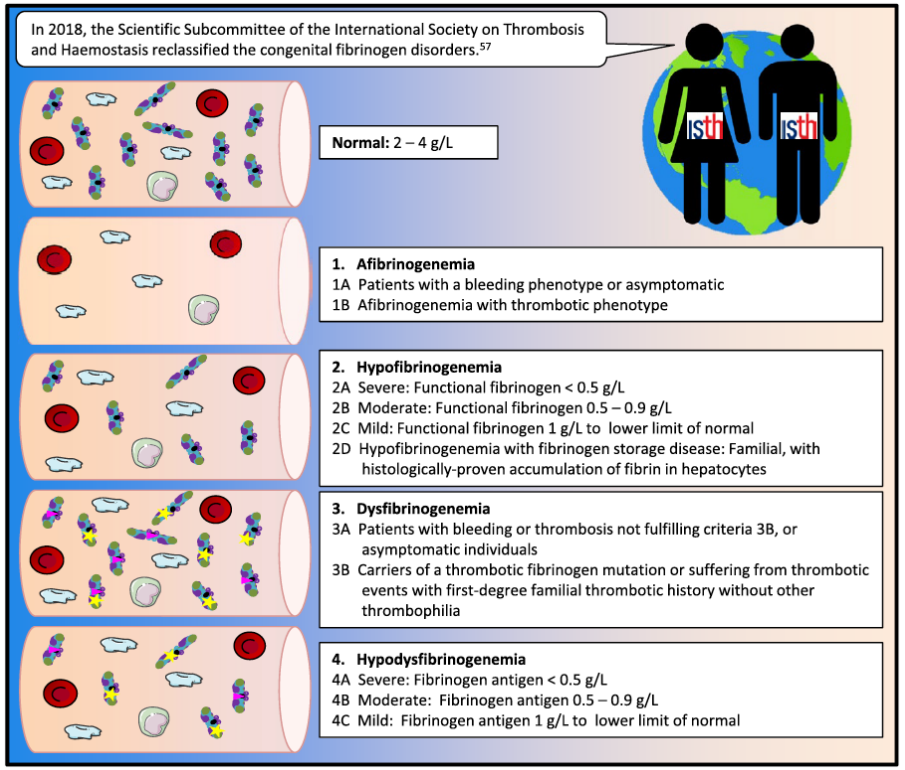
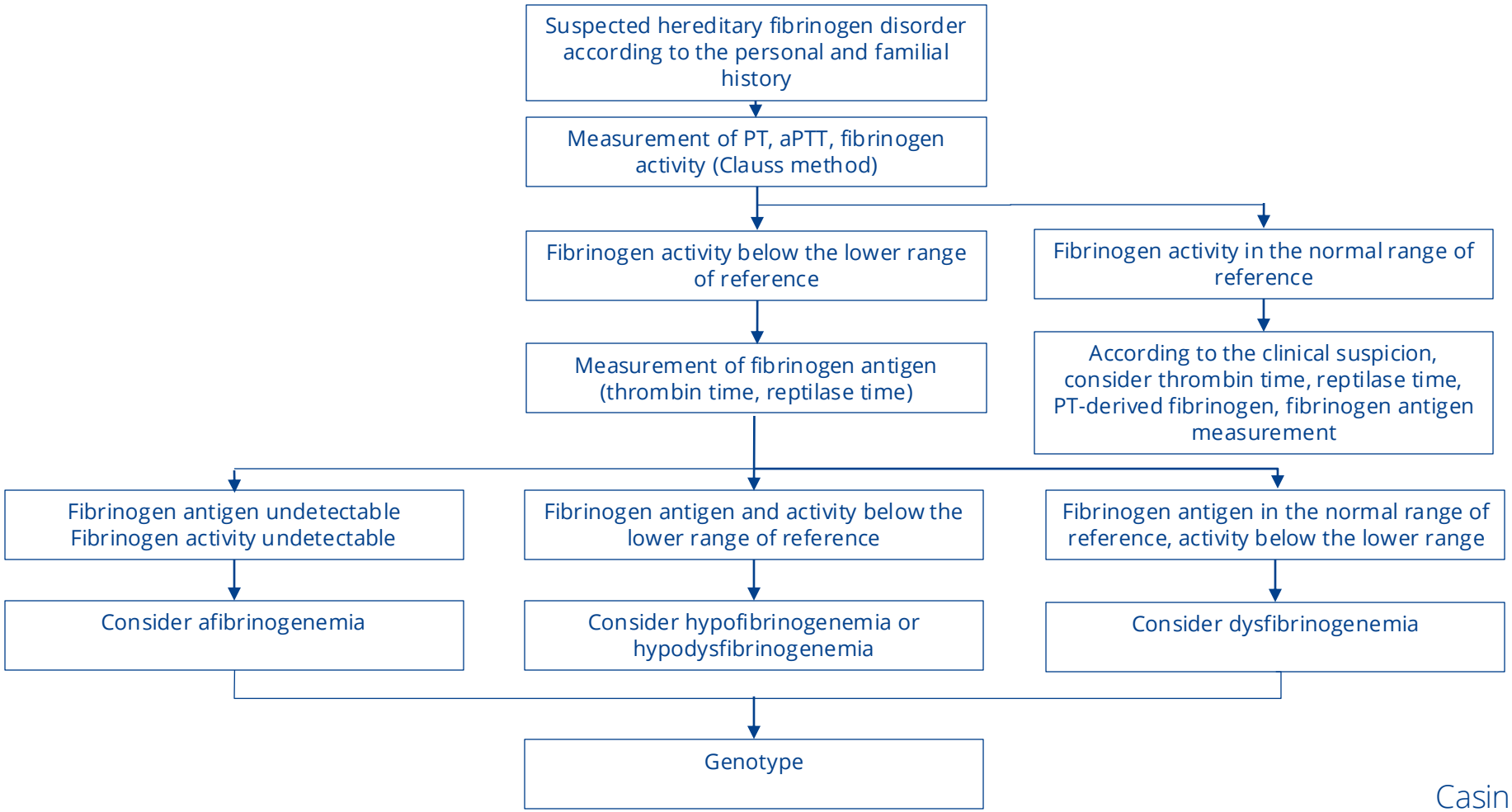


Quantitative deficiencies

Qualitative deficiencies

Couzens A et al. *Hamostaseologie* 2025
Pieters M et al. *Res Pract Thromb Hamost* 2019

Diagnosis of HFDs



Casini A et al. *Blood* 2021

When to suspect an HFD?

- Incidental discovery of low fibrinogen levels
- Unexplained tendency to bleeding
- Thrombosis, especially in young and positive familial history, without more common thrombophilia
- Pregnancy morbidity
- Familial history or screening
- No causes of acquired fibrinogen disorder

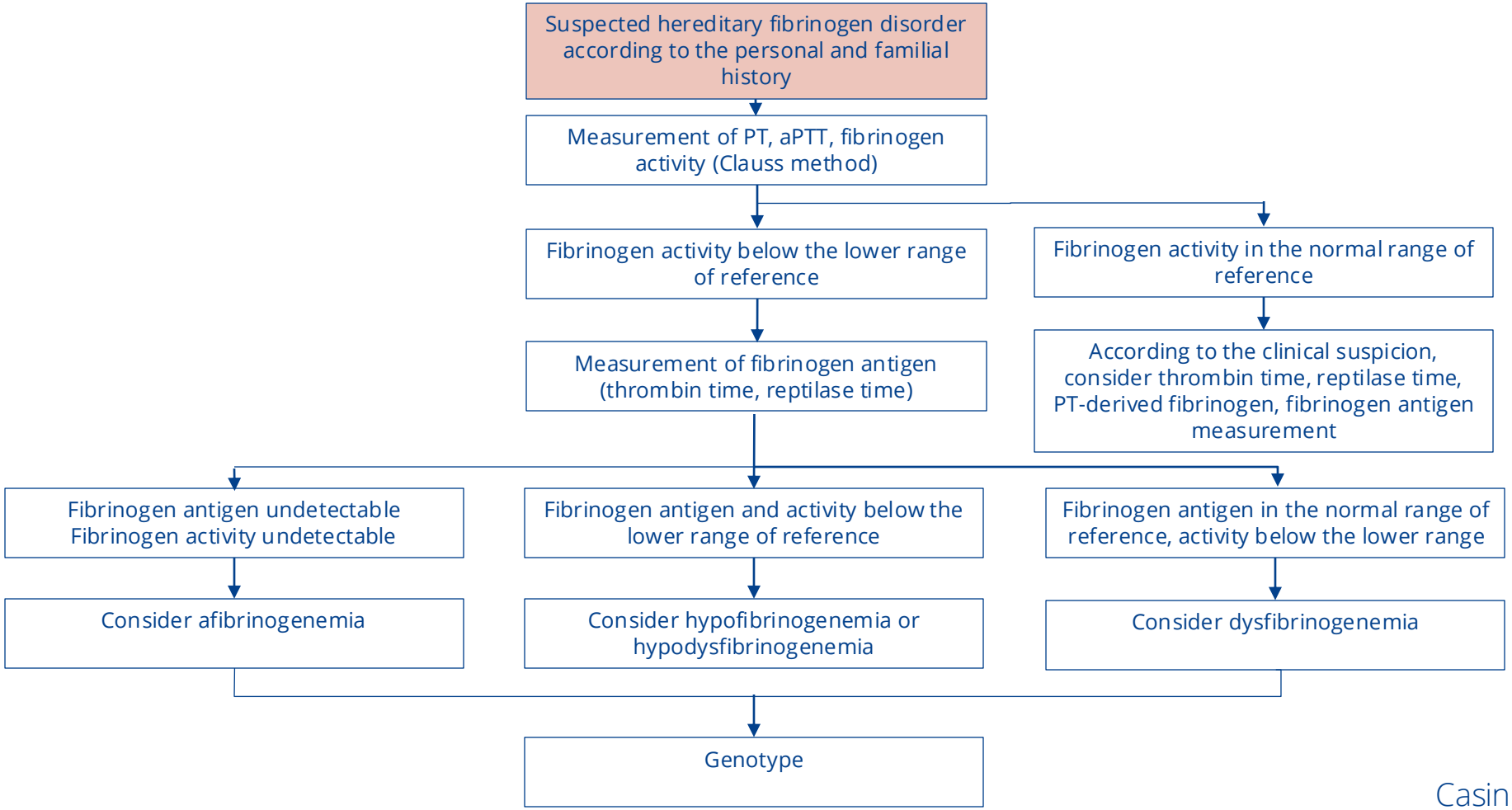
Acquired fibrinogen disorders

Condition	Mechanism	Examples of causes
Hypofibrinogenaemia	Decreased fibrinogen synthesis	Liver disease
	Increased fibrinogen consumption	Sepsis, DIC, thrombolytic therapy
	Haemodilution	Massive transfusion
Dysfibrinogenaemia	Protein modification	Abnormal sialylation
	Autoantibodies	Autoimmune disease, myeloma, drug-induced
	Interfering substances	Heparin, DTI

Tocilizumab
Tygecline
Alteplase
Asparaginase
Dexamethasone

Wen X et al. *Int J Clin Pharm* 2025
Mackie I et al. *Int J Lab Hematol* 2024

Diagnosis of HFDs



Casini A et al. *Blood* 2021

Tests available for fibrinogen investigations

Screening/ Standard tests	
Thrombin clotting time (TT) and Clauss assay	Initial screening test for functional fibrinogen Great reagent variability in TT Higher concentration thrombin is added to diluted plasma in Clauss assay Thrombin inhibitors influence the results (TT is more sensitive than Clauss assay)
PT-Fg assay	Measurement of fibrinogen estimates Not recommended for initial screening test Should be avoided under anticoagulation therapy Overestimate fibrinogen amount in qualitative fibrinogen anomalies
Reptilase time	A snake venom, Batroxobin is used Cleavage fibrinogen to release fibrinopeptide A Not inhibited by thrombin inhibitors
Viscoelastic method	Fibrinogen function can be assessed if suitable reagents/parameters are used Available for emergency assessment (e.g., major trauma or cardiac surgery)
Clot waveform analysis	A novel approach for differential diagnosis of fibrinogen abnormalities Available on certain analysers
Fibrinogen antigen	ELISA or immunoturbidimetric assays are generally used Necessary for diagnosing fibrinogen disorders
Specialist techniques	Total clottable protein assays Fibrinopeptide release Fibrin monomer polymerisation Clot permeability Rheometry Microscopy

Mackie I et al. *Int J Lab Hematol* 2024

Common problem faced by laboratories

Measurement of fibrinogen antigen is mandatory to distinguish:

- Hypofibrinogenemia from dysfibrinogenemia
- Hypofibrinogenemia from hypodysfibrinogenemia

Measurement of fibrinogen antigen is not widely available

- Most of laboratories do not assess antigen
- The diagnosis is often “hypofibrinogenemia”

Pitfalls in the diagnosis of quantitative HFDs

Low detection limit:

Afibrinogenemia
vs
Severe hypofibrinogenemia?

Circulating variant:

Hypofibrinogenemia
vs
Hypodysfibrinogenemia?

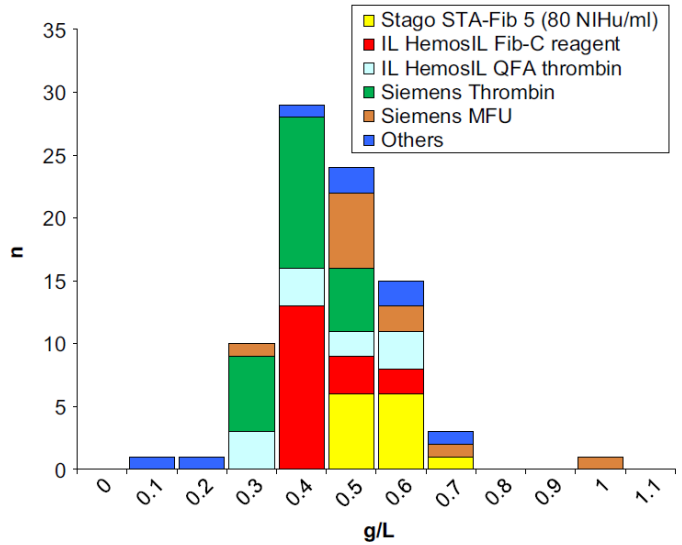
Mass spectrometry
Protein expression

} research

Genotype

Brennan SO et al. *Thromb Haemost* 2014
Asselta R et al. *Thromb Haemost* 2015

Pitfalls in the diagnosis of dysfibrinogenemia



Depends on reagent and method

	FB14:01 Dysfibrinogenaemia (γ p.Arg301Cys)				FB14:02 Fgn Longmont (Bβ 166Arg3Cys)			
	n	Median	Range	CV (%)[a]	n	Median	Range	CV (%)[a]
PT (ratio)	75	1.35	1.00-1.80	14.7	74	1.00	0.86-6.00	6.9 (71.8)
APTT (ratio)	86	1.03	0.75-1.25	8.5	86	0.96	0.87-3.75	7.1 (40.8)
Clauss Fibrinogen (g/L)	84	0.45	0.13-7.45	24.8 (145)	66	4.54	0.10-12.8	59.6
Derived fibrinogen (g/L)	22	3.84	1.54-5.30	25.2	20	1.02	0.35-2.14	43.7
Thrombin time (ratio)	74	2.15	1.68-6.75	8.4 (28.2)	73	1.29	0.81-1.88	16.4
Reptilase Time (ratio)	45	2.20	1.62-5.34	29.1	52	1.10	0.73-2.11	21.7
Fibrinogen antigen (g/L)	27	2.44	0.37-3.19	30.5	26	3.55	2.41-5.26	18.3

Depends on variant and method

Jennings K et al. *Int J Lab Hematol* 2017

PT-derived method in dysfibrinogenemia

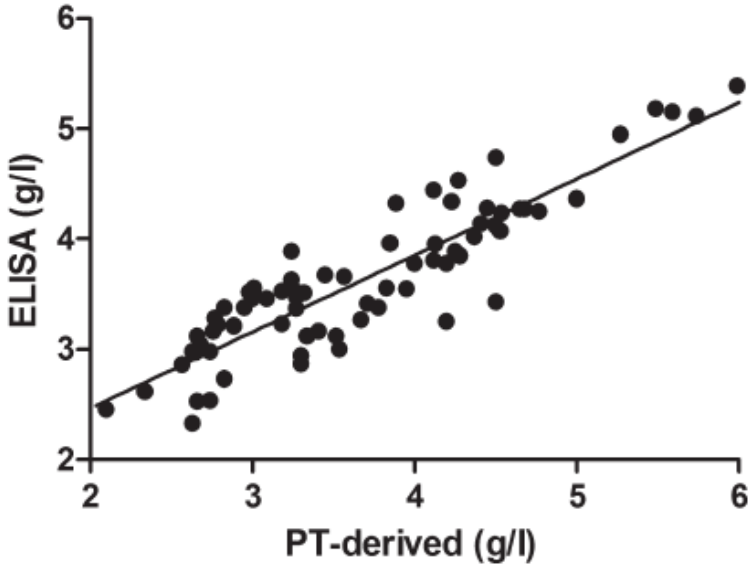
	Clauss assay		Prothrombin (PT) derived assay		Immun.	Heat
Patient	STA FIB-C g/l	ACL-Top FIB-C g/l	STA Fib PTder g/l	ACL-Top Fib PTder g/l	g/l	g/l
1	<0.60	<0.30	2.12	1.97	1.40	1.50
2	<0.60	0.35	2.64	2.52	3.12	3.00
3	<0.60	0.39	3.04	2.63	3.12	3.00
4	<0.60	<0.30	2.58	2.41	1.40	1.80
5	<0.60	0.37	2.91	2.56	3.12	3.00
6	<0.60	0.34	2.79	2.32	4.08	3.00
7	0.78	0.71	1.89	1.51	1.30	1.20
8	<0.60	<0.30	1.50	1.34	1.02	1.20
9	<0.60	<0.30	2.58	2.35	2.50	1.80
10	<0.60	0.37	2.46	2.36	2.50	2.40
11	<0.60	<0.30	2.23	1.97	1.92	1.50
12	<0.60	0.34	2.15	2.09	2.15	2.40
13	<0.60	0.35	2.68	2.50	3.26	2.50
14	<0.60	0.40	2.76	2.68	3.12	3.70
15	0.92	1.00	1.38	0.97	1.11	120
16	0.77	0.50	3.46	3.55	3.66	4.30
17	<0.60	0.41	2.81	2.51	2.74	2.40
18	1.57	1.08	4.39	4.87	4.23	5.60
19	<0.60	0.37	3.21	2.81	3.12	3.70
20	0.73	0.49	3.19	2.99	3.00	6.25
21	<0.60	0.50	2.12	1.80	1.40	1.80
22	0.81	0.57	3.82	3.87	3.94	5.00
23	2.20	1.08	4.10	3.63	Nd	3.70
24	<0.60	0.42	2.46	2.06	Nd	3.00
25	1.97	2.07	2.51	2.14	Nd	1.80
26	0.70	0.51	3.28	3.16	2.74	6.25
27	1.43	1.55	1.80	1.70	Nd	1.40
Median	0.60	0.40	2.64	2.41	2.74	2.50
Range	0.60–2.20	0.30–2.07	1.38–4.39	0.97–4.87	1.02–4.23	1.20–6.25
Normal range	1.5–4.5	2.67–4.37	2.0–4.0	1.84–4.8	2.05 –4.39	2.0–4.0

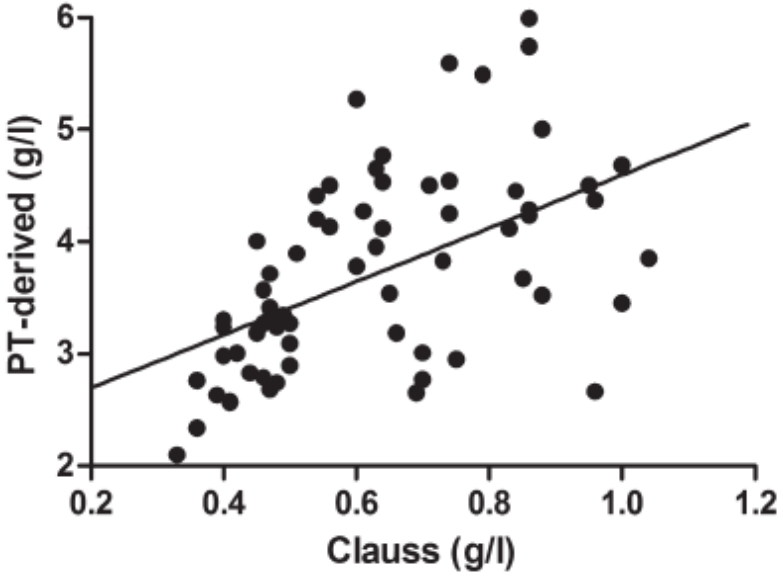
PT-derived overestimates functional fibrinogen levels

PT-derived method similar to antigen measurement

Miesbach K et al. *Thromb Res* 2010

PT-derived fibrinogen versus Clauss



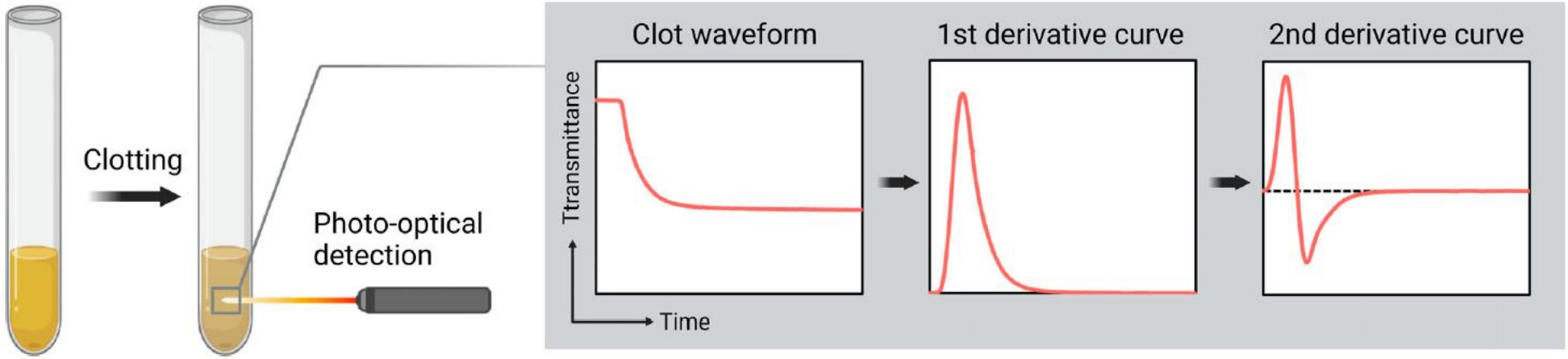


Dysfibrinogenemia, n=73
Cut-off ratio PT-derived / Clauss >1.43

- 100% specificity and sensitivity

Xiang et al. *Int J Lab Hem* 2018
Luo M et al. *Thromb Res* 2020

Clauss-CWA



The minimum value of the 1st derivative curve correlates with fibrinogen antigen (Min1)

Cut-off ratio Clauss / Min1 <0.65

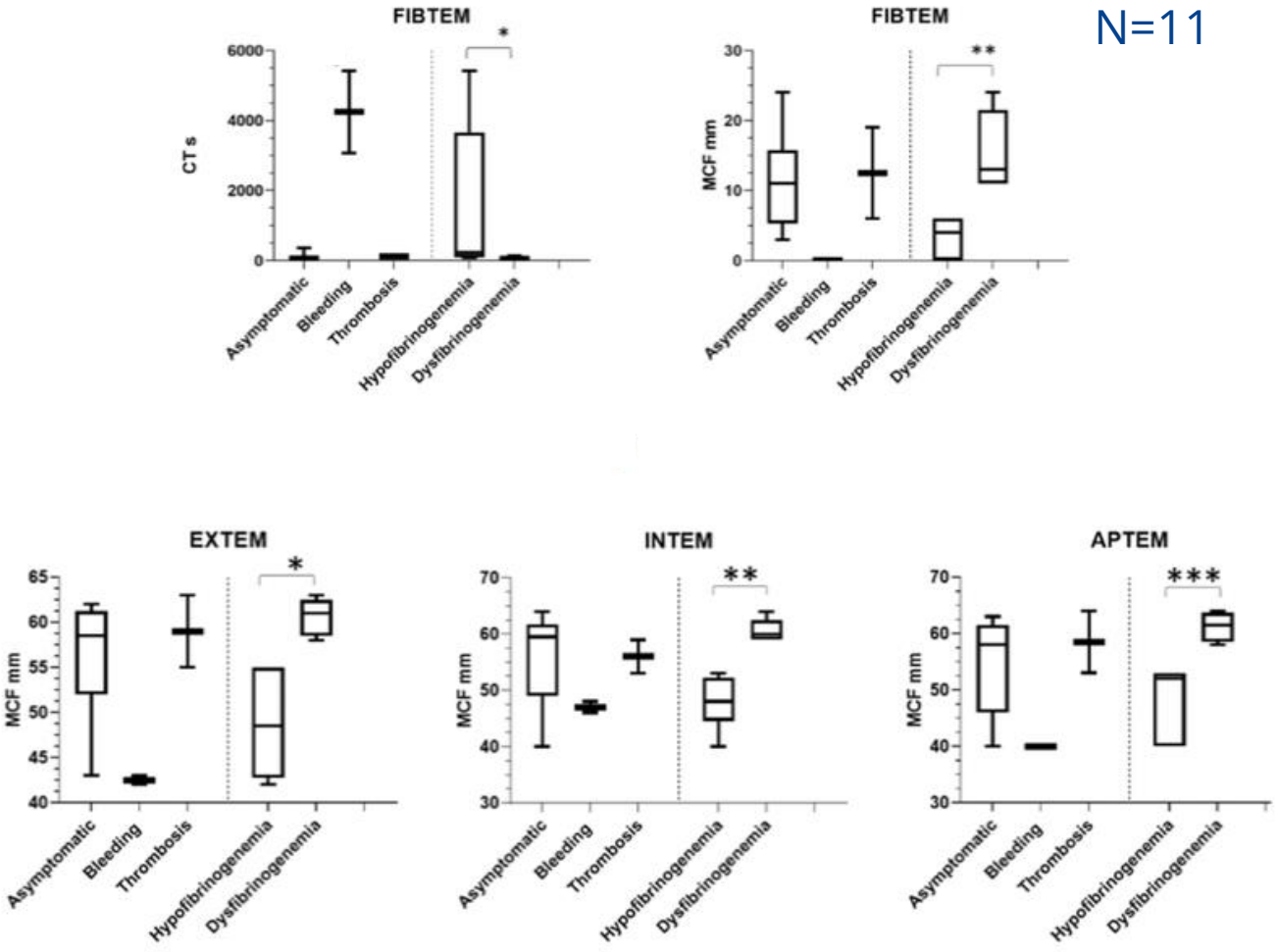
- 96% sensitivity and 100% specificity

Suzuki A et al. *Sci Rep* 2022

Arai S et al. *Int J Lab Hematol* 2021

Arai S et al. *Clin Chim Acta* 2021

Viscoelastic assays



N=11

Szanto T et al. *Int. J. Mol. Sci* 2021

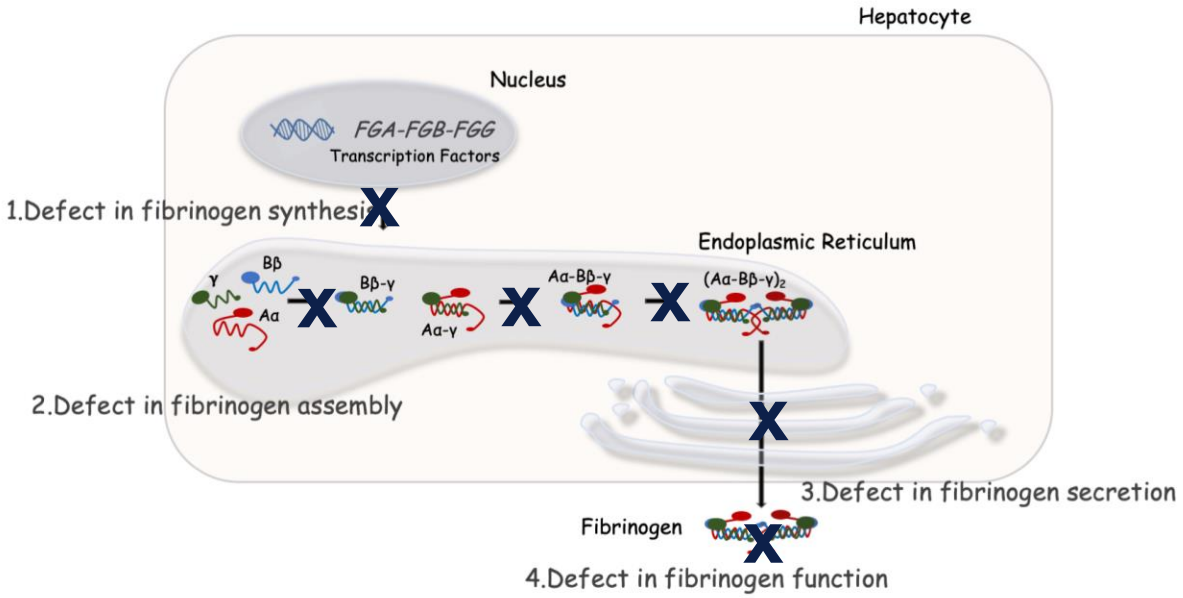
Conclusions 1

- To investigate fibrinogen disorders, it is essential to measure functional and antigen fibrinogen
- If antigen assessment is not available, indirect methods can be employed (PT-derived fibrinogen, Clauss CWA)
- The genotype is important in confirming the diagnosis

Outline

- Diagnosis of hereditary fibrinogen disorders (HFDs)
- Genotype
- Clinical features
- Management
- Conclusions

Monogenic disease



Quantitative disorder

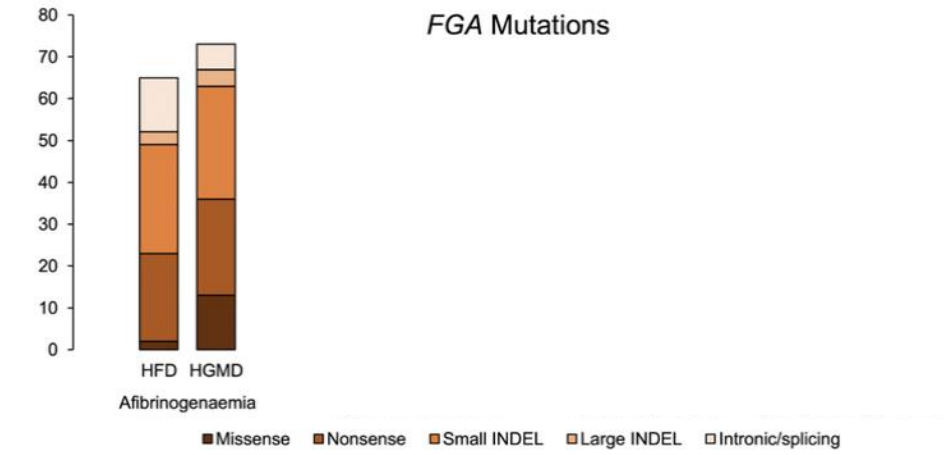
- Afibrinogenemia
- Hypofibrinogenemia

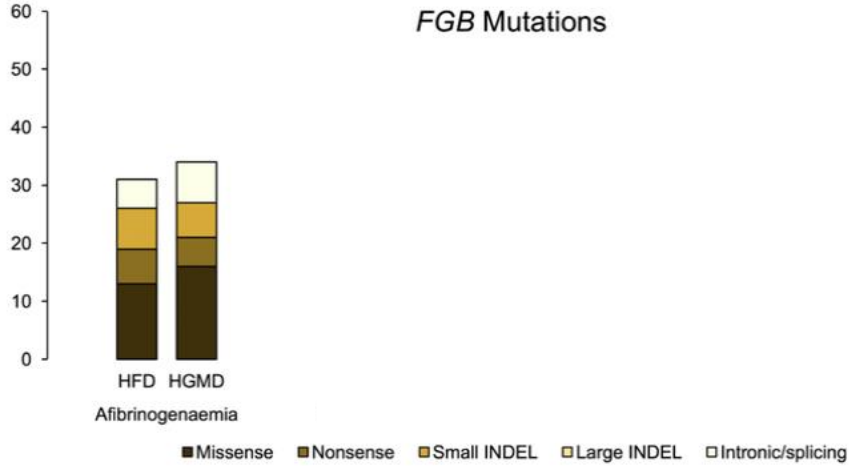
Qualitative disorder

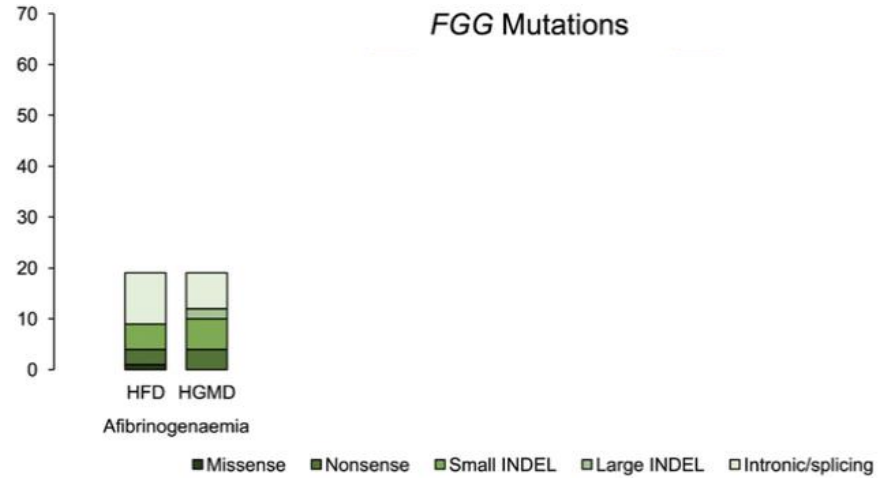
- Dysfibrinogenemia
- Hypodysfibrinogenemia

Neerman-Arbez M et al. *Int J Mol Sci* 2018

Mutational epidemiology: afibrinogenemia

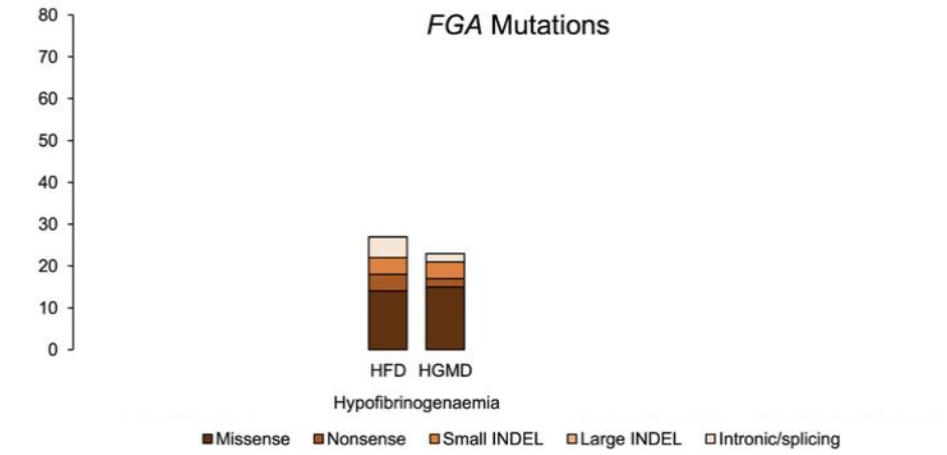


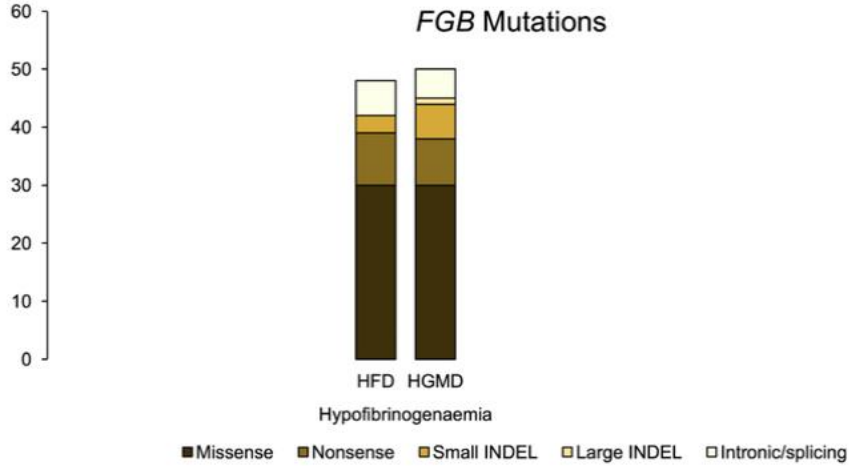


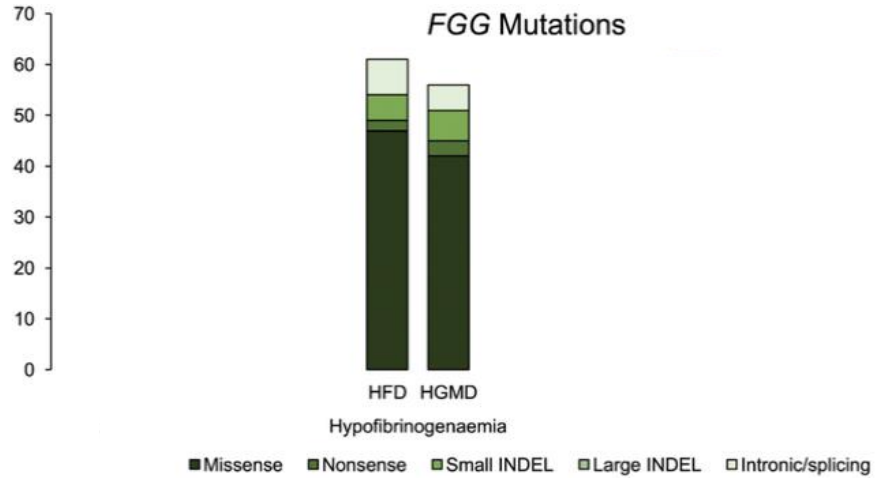


Ramanan R et al. *Br J Haematol* 2023

Mutational epidemiology: hypofibrinogenemia

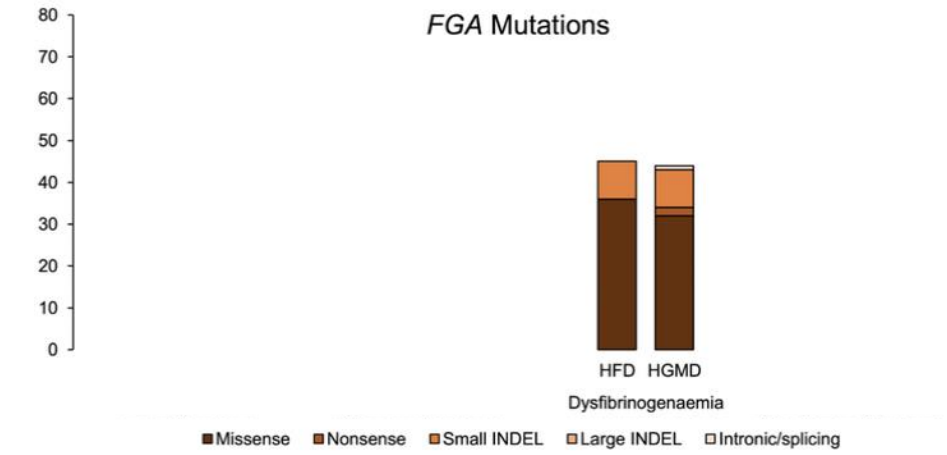


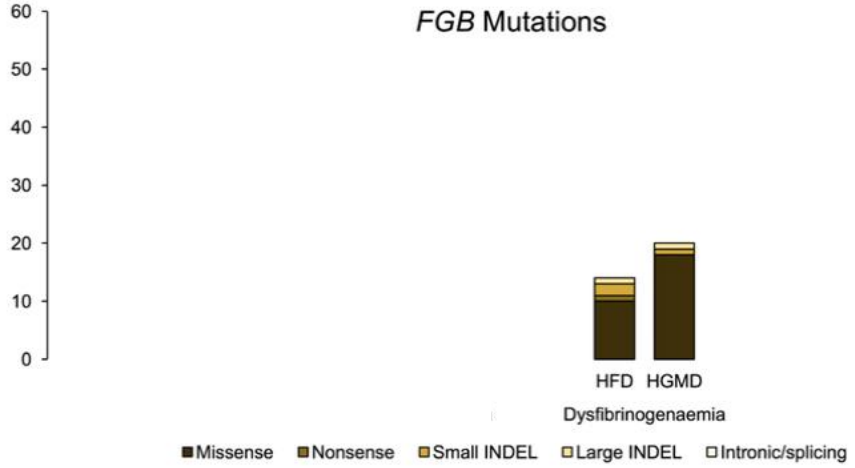


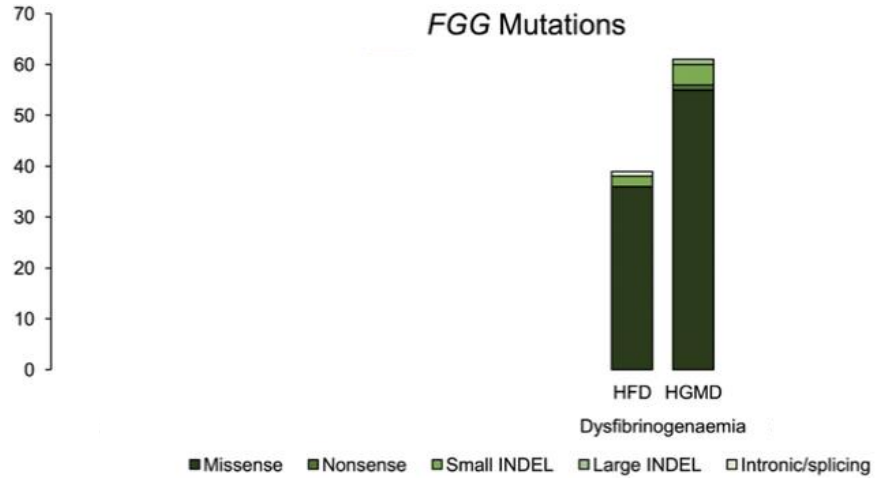


Ramanan R et al. *Br J Haematol* 2023

Mutational epidemiology: dysfibrinogenemia

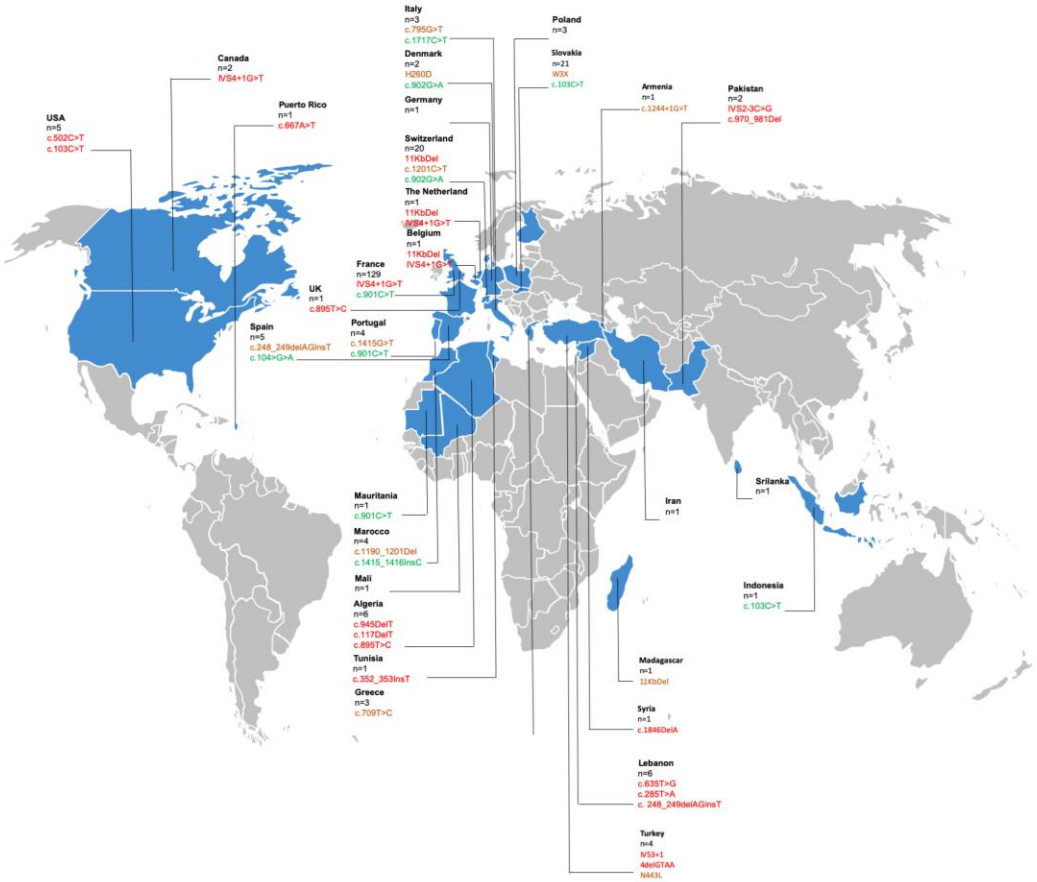






Ramanan R et al. *Br J Haematol* 2023

Hotspot mutations



Hotspot mutations

- *FGA* exon 2, p.Arg35
- *FGG* exon 8, p.Arg301

} >70%

- *FGA* 11Kb deletion
- *FGA* IVS4+1G>T

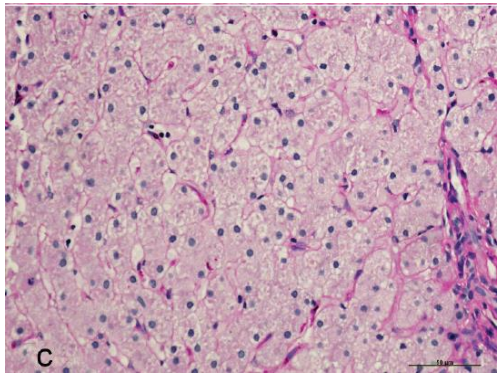
Regional clusters

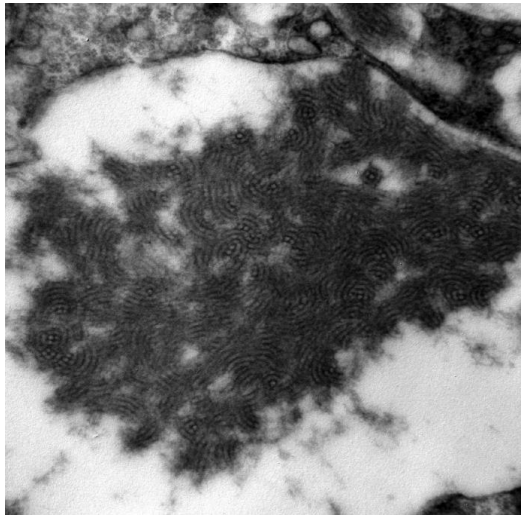
- Lebanon
- India
- Pakistan

Why genotype is important in HFDs?

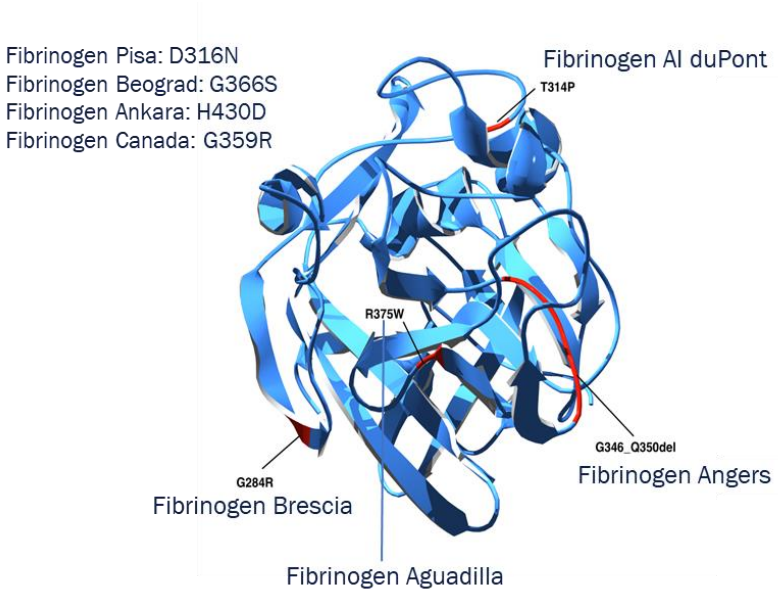
- Confirmation of diagnosis
- Distinguish between afibrinogenemia and severe hypofibrinogenemia, and between dysfibrinogenemia and hypodysfibrinogenemia
- Facilitate family screening and prenatal diagnosis
- Identify specific subtypes of HFDs

Hypofibrinogenemia type 2D: fibrinogen storage disease



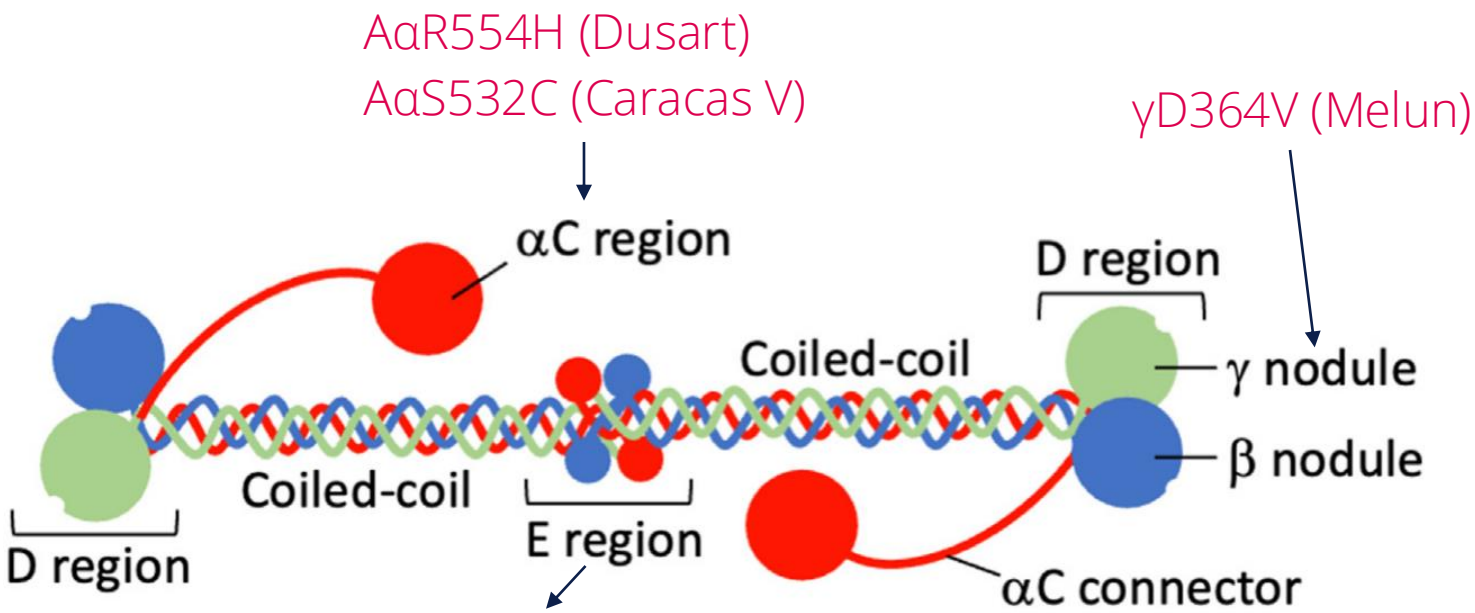


- Accumulation of fibrinogen aggregates in the hepatocellular endoplasmic reticulum
- Mutations clustered in exons 8 and 9



Asselta R et al. *Int J Mol Sci* 2020
Kehar M et al. *Ultrastruct Pathol* 2024

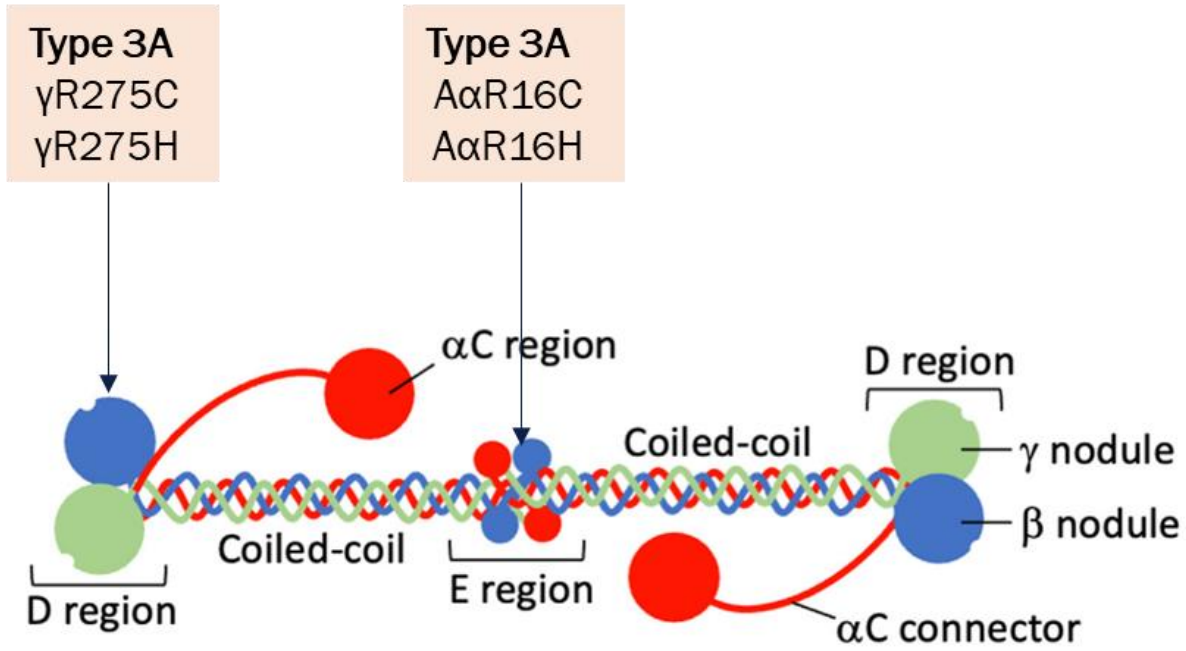
Thrombotic-related dysfibrinogenemia (type 3B)



First-degree familial thrombotic history (relatives with the same genotype) without any other thrombophilia

Wolberg A J *Thromb Haemost* 2023
Casini A et al. J Thromb Haemost 2015

Hotspots mutations in dysfibrinogenemia (type 3A)



Major bleeding

FGA Arg35 HR 0.8 (95%CI 0.1-4.1)

FGG Arg301 HR 1.2 (95%CI 0.4-4.1)

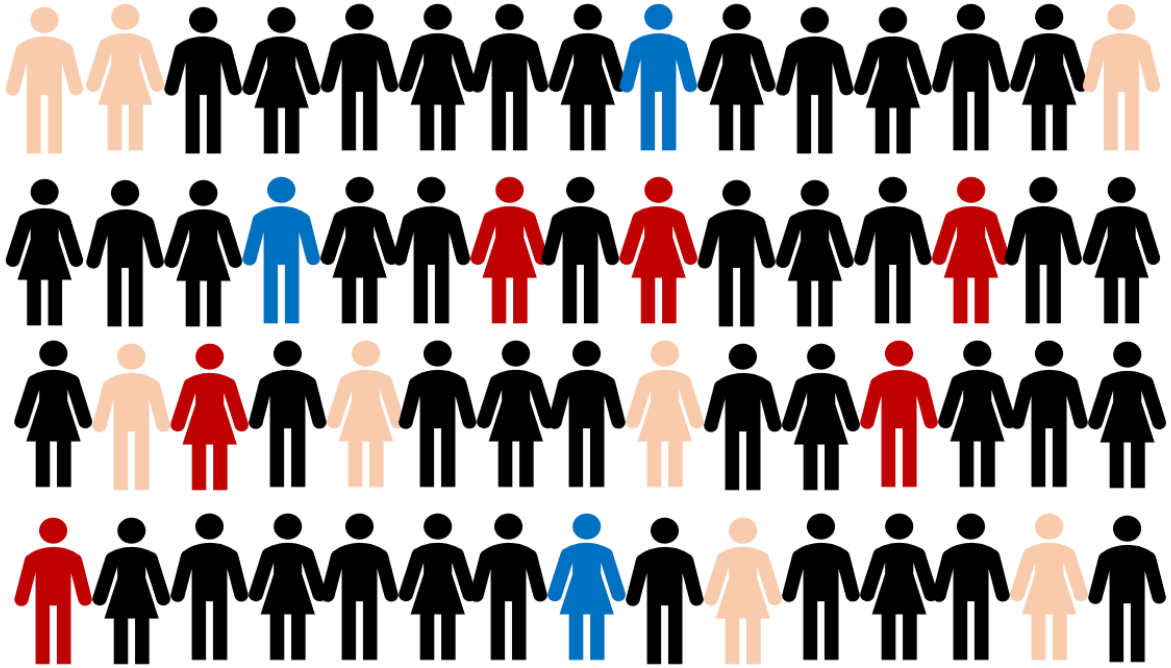
Thrombotic event

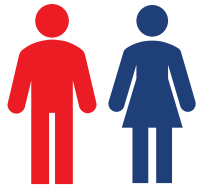
FGA Arg35 HR 0.8 (95%CI 0.3-2.4)

FGG Arg301 HR 1.1 (95%CI 0.5-2.6)

Casini A et al. *Blood* 2015

Genetic modifiers of the phenotype?



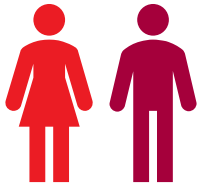


Polymorphisms

FGB Arg478

FGG Thr331

F13 Val35



Other coagulation imbalances

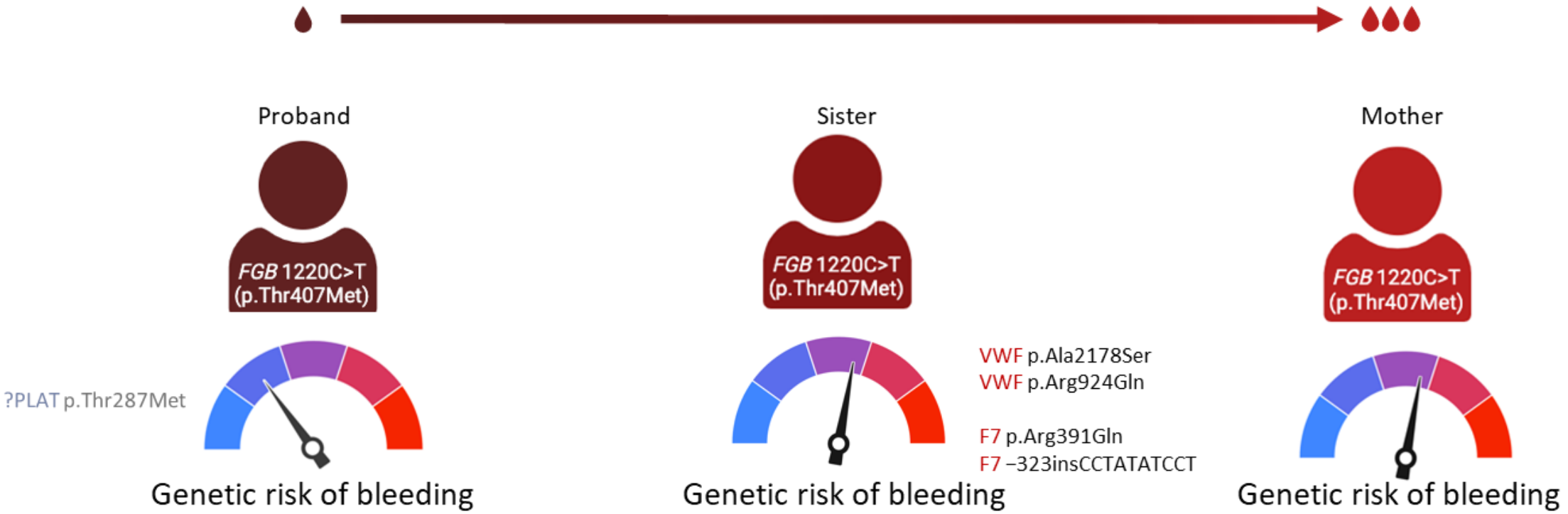
FV Leiden

FVII deficiency

Low FVW

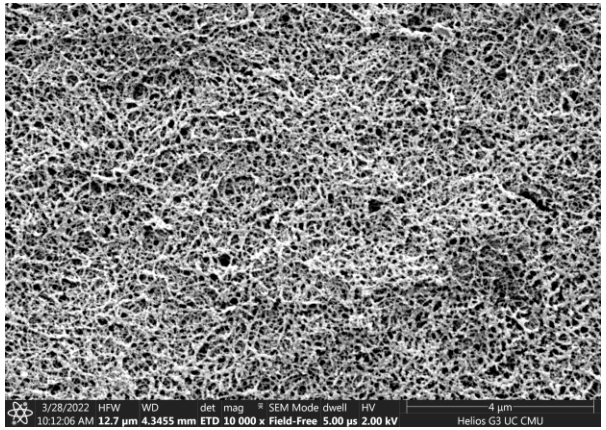
Blood group

Toward oligogenic traits in HFDs

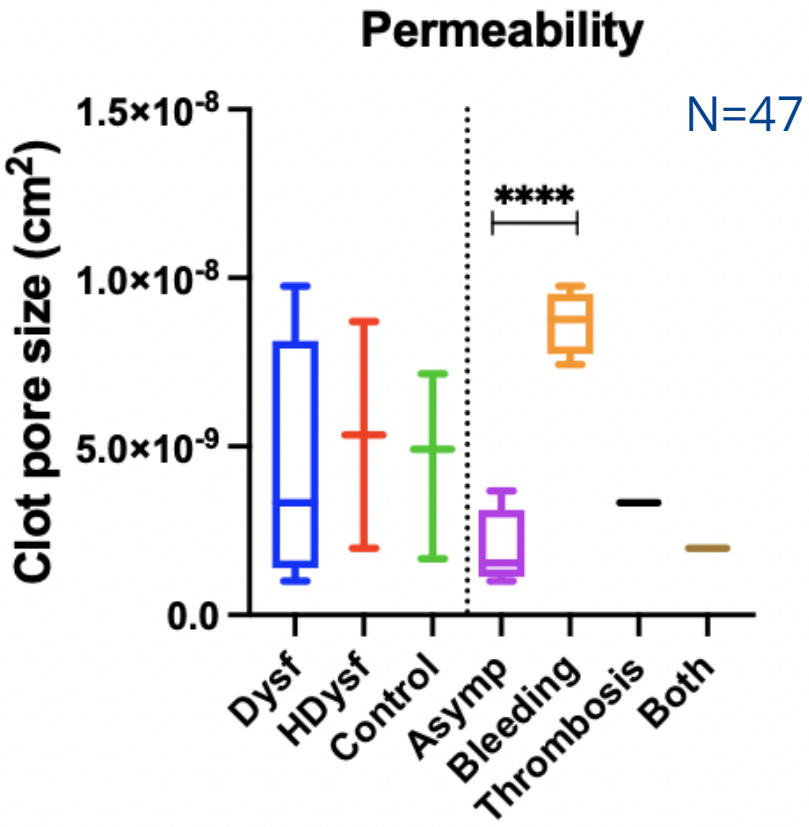


Courtesy of Alexander Couzens

Prediction of the clinical phenotype



Fibrinogen *FGA* c.1717C>G



Courtesy of Barbara Barath

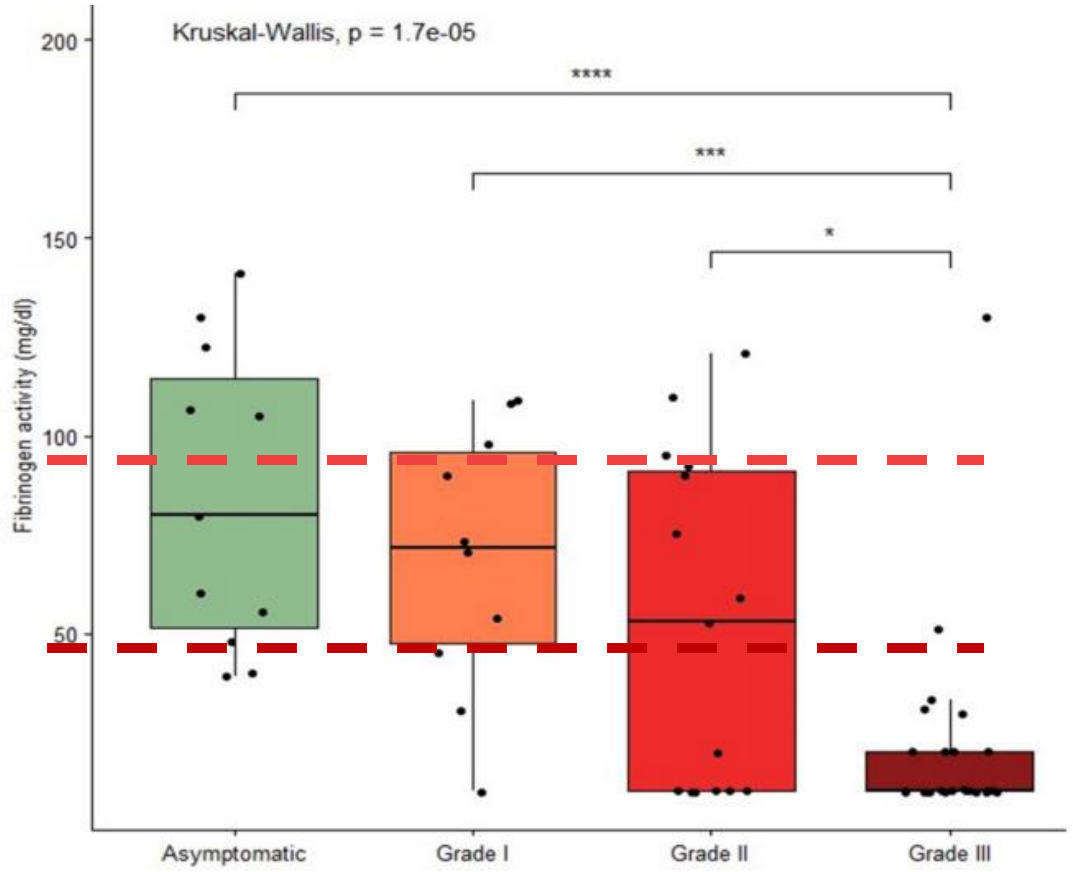
Conclusions 2

- Genotype is essential to confirm the diagnosis
- Mutations in exon 2 of *FGA* and exon 8 of *FGG* are frequent in dysfibrinogenemia
- Some fibrinogen variants are strongly associated with a clinical phenotype

Summary

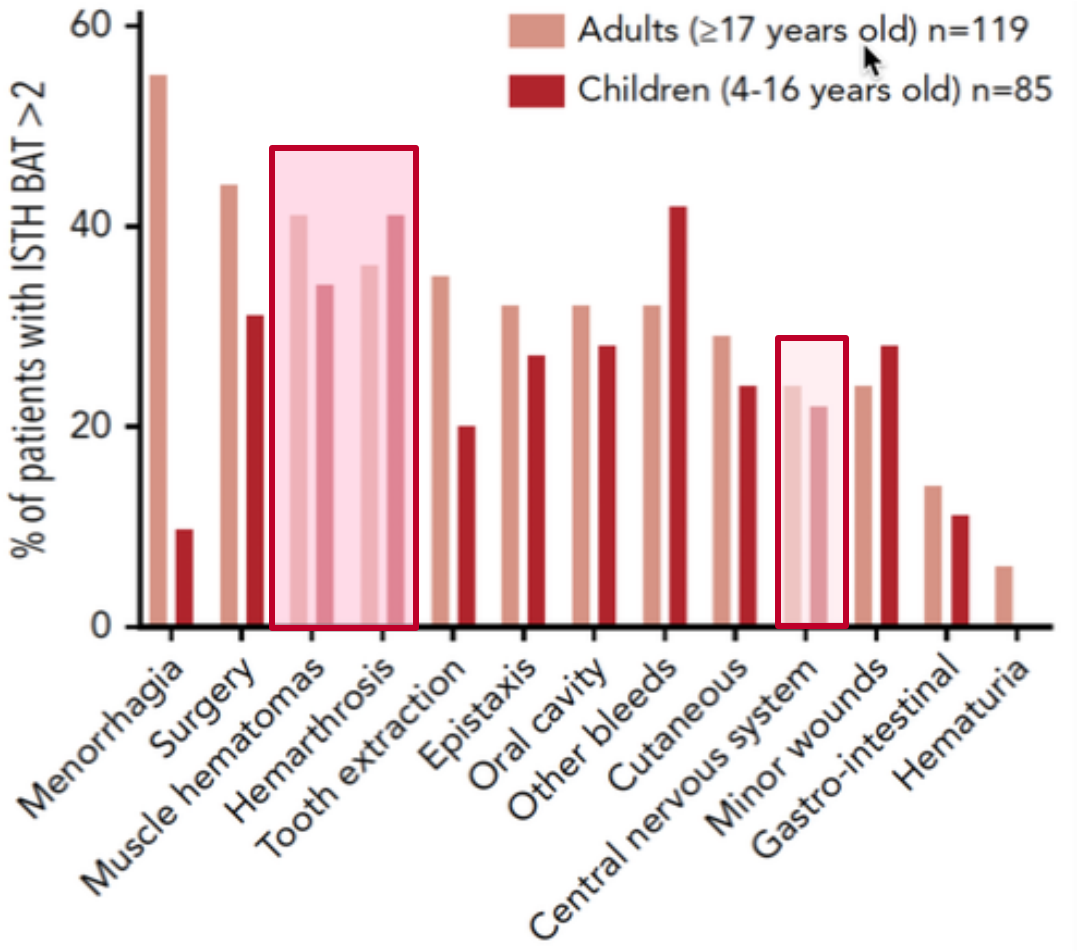
- Diagnosis of hereditary fibrinogen disorders (HFDs)
- Genotype
- Clinical features
- Management
- Conclusions

Bleeding risk depend on fibrinogen level in quantitative HFDs



Mohsenian S et al. *Blood Adv* 2024

Bleeding pattern in afibrinogenemia



Frequency of bleeding

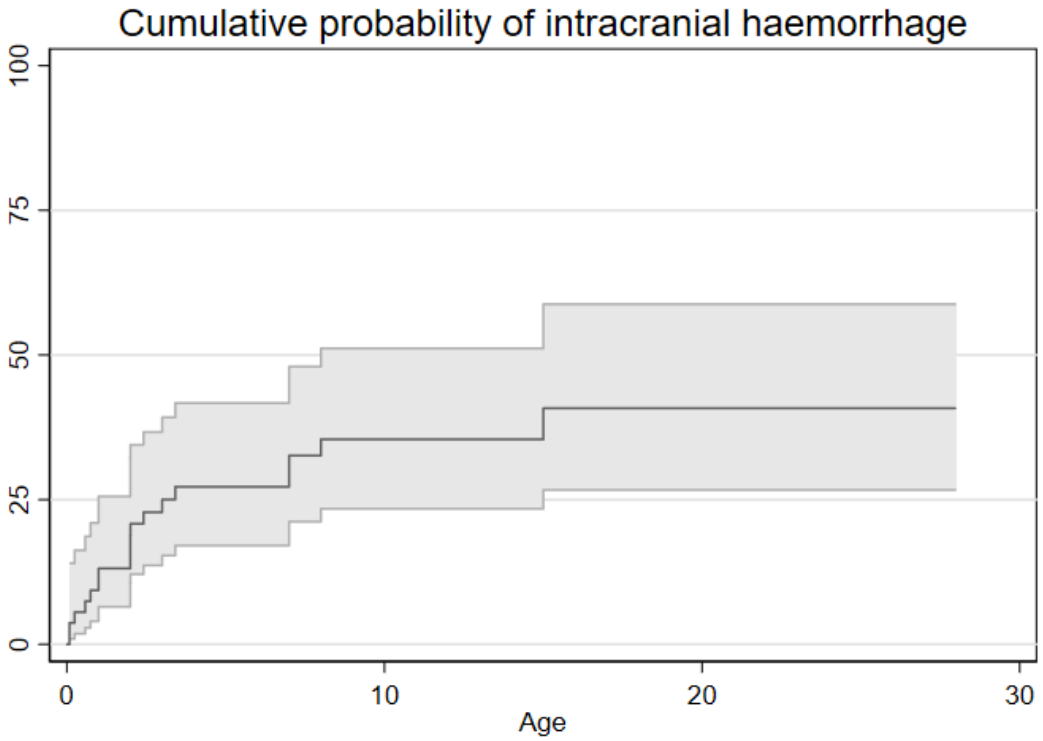
- 1% (0.5%) several time per day
- 8 (3.9%) several time per week
- 32 (15.7) several time per month
- 125 (61.3%) several time per year

Incidence bleeding per year

- 1 – 16.5 patients on demand

Casini A et al. *Blood* 2021
Peyvandi F et al. *J Thromb Haemost* 2006

Cerebral bleeding in afibrinogenemia



58 children from Egypt without prophylaxis

- 31% history of cerebral bleeding
- First episode at a median age of 1 year

Cumulative incidence

- 10 years 35% (95%CI 23-51)
- 20 years 40% (95%CI 26.7-58)

Abdelwahab M et al. *Haemophilia* 2023

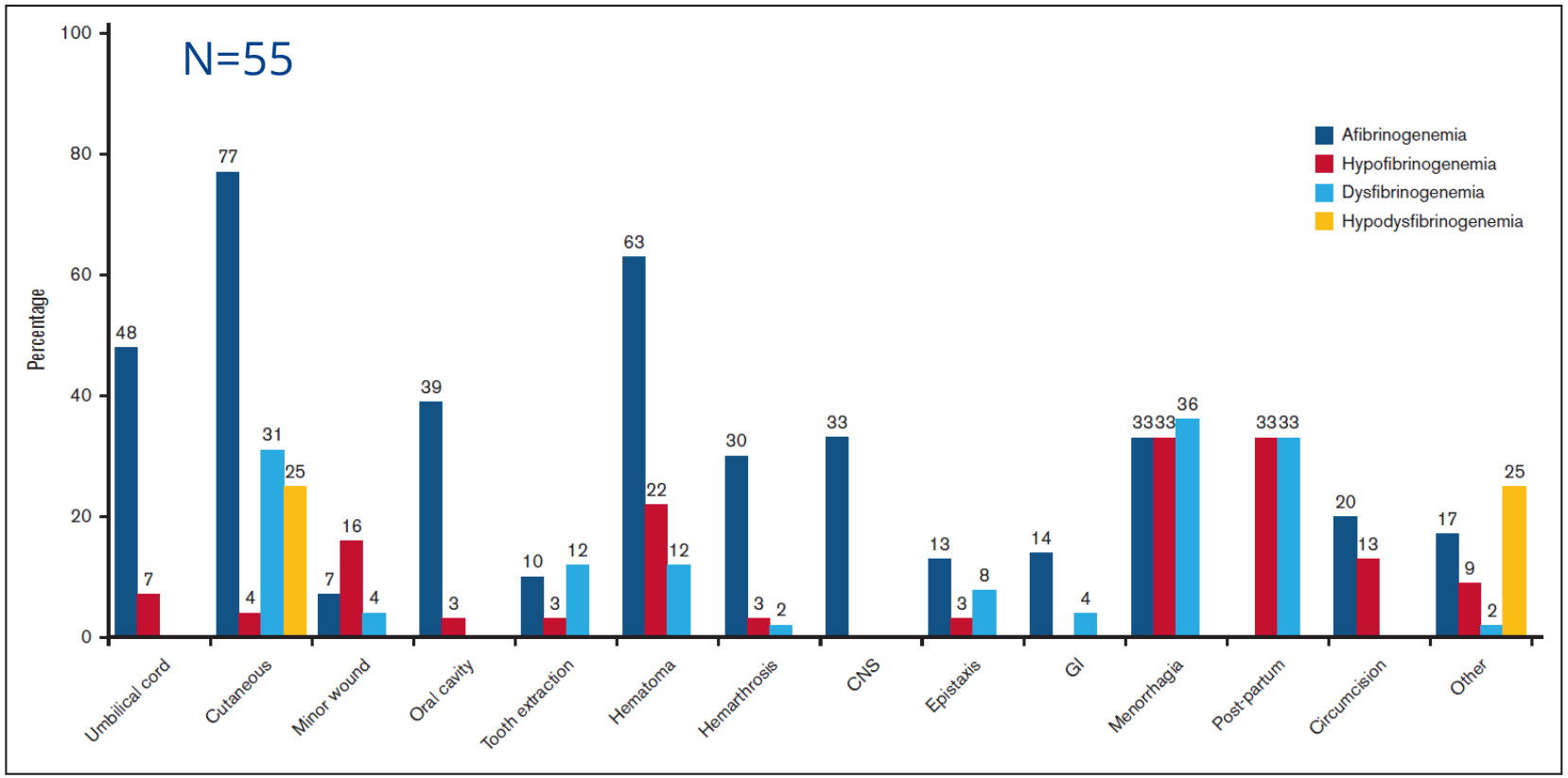
Thrombosis and other symptoms in afibrinogenemia

Variable	All patients N = 204	Adults (aged ≥17 y) n = 119	Children (aged 8-15 y) n = 62	Children (aged 4-7 y) n = 23
Thrombotic phenotype, no. (%)				
Total	37 (18.1)	31 (26.1)	4 (6.5)	2 (8.7)
Venous§	16 (43.3)	10 (32.3)	4 (100)	2 (100)
ArterialII	11 (29.7)	11 (35.4)	0 (0)	0 (0)
Both	10 (27)	10 (32.3)	0 (0)	0 (0)
Spontaneous spleen rupture, no. (%)	11 (5.4)	8 (6.7)	3 (4.8)	0 (0)
Bone cysts, no. (%)				
Yes	36 (17.6)	15 (12.6)	17 (27.4)	4 (17.4)
Unknown	3 (1.47)	0 (0)	1 (1.6)	2 (8.7)

- Splanchnic thromboses → frequent type of venous thrombosis
- Spontaneous spleen rupture → life-threatening events
- Bone cysts → especially in younger patients

Casini A et al. *Blood* 2021

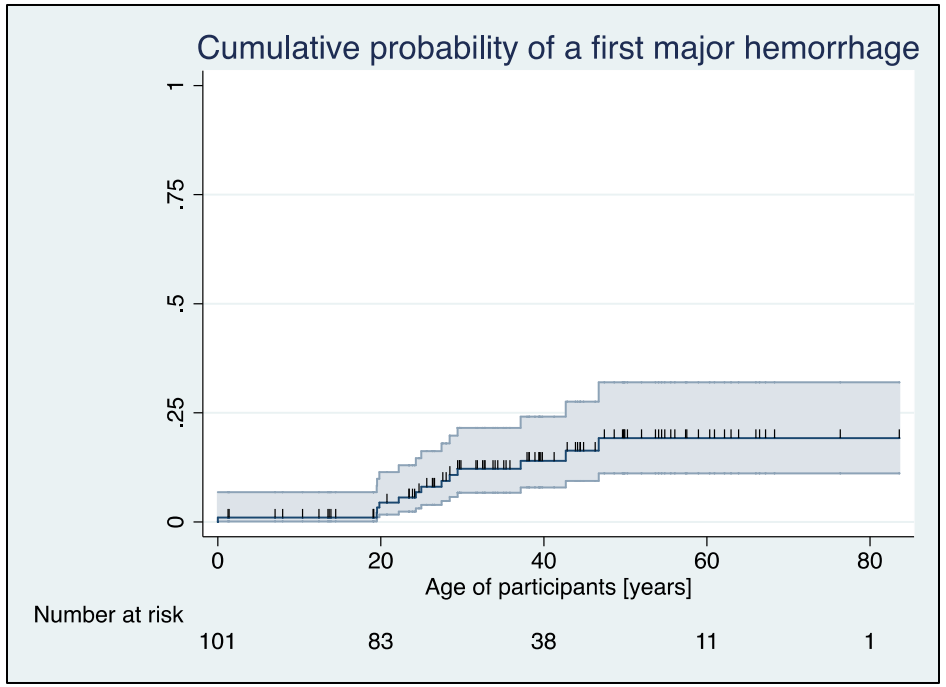
Bleeding pattern in dysfibrinogenemia

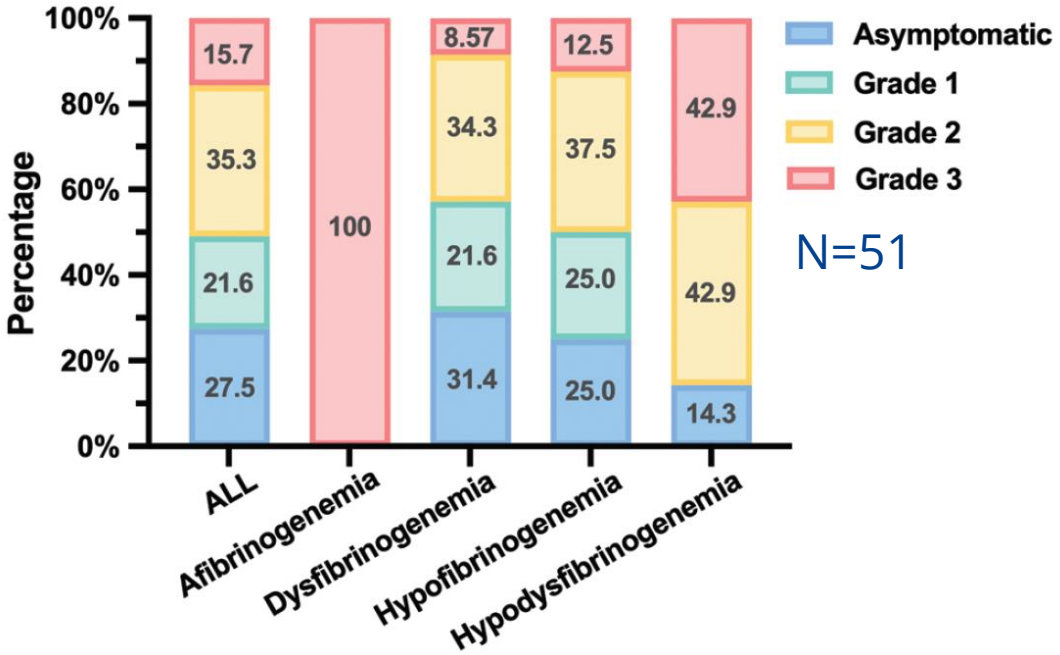


Mohsenian S et al. *Blood Adv* 2024

Risk of major bleeding in dysfibrinogenemia

N=101

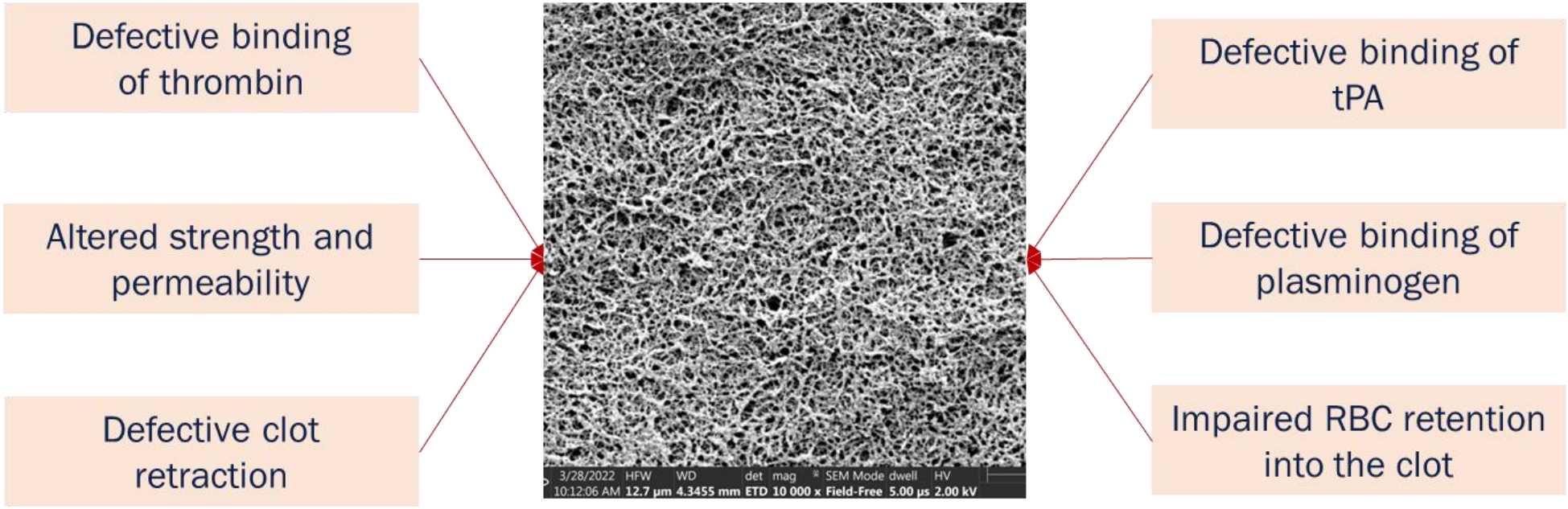




Cumulative incidence 50 years 19.2% (95%CI 11.1-31.9)

Casini A et al. *Blood* 2015
Cai Y et al. *Thromb Haemost* 2025

Thrombosis in dysfibrinogenemia



Cumulative incidence 50 years 30.1% (95%CI 20.1-43.5)

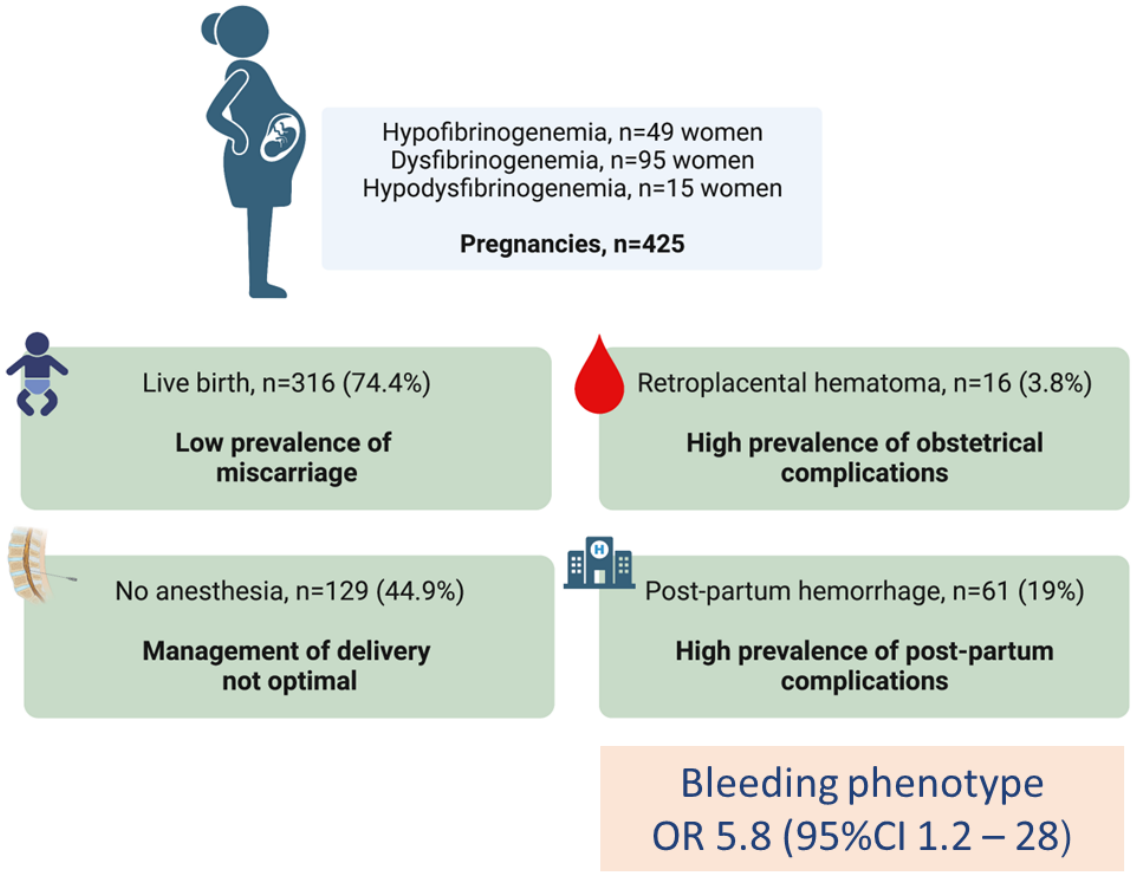
Casini A et al. *Blood* 2015

Pregnancy issues

- Miscarriages
- Stillbirth
- Placenta abruptio
- Intra-uterine growth retardation
- Vaginal bleeding
- Post-partum hemorrhage
- Thrombosis

In the absence of fibrinogen replacement

Obstetric outcomes



Hugon-Rodin J et al. *J Thromb Haemost* 2023

Conclusions 3

- In quantitative fibrinogen disorders the bleeding risk depends on the fibrinogen level
- Patients with HFDs are at risk of thrombotic events
- Pregnancy is high-risk clinical situation for all women with HFDs

Summary

- Diagnosis of hereditary fibrinogen disorders (HFDs)
- Genotype
- Clinical features
- Management
- Conclusions

Available sources of fibrinogen

Product	Standard posology	Formula to estimate the amount of fibrinogen to be administered
Fibrinogen concentrates*		
FibCLOT (Clottafact)	50-75 mg/kg	(Target fibrinogen activity [g/L] – measured fibrinogen activity [g/L]) × body weight (kg) × (1/incremental recovery)†
RiaSTAP (Haemocomplettan P)	50-75 mg/kg	
Fibryga	50-75 mg/kg	
Other sources		
Cryoprecipitate	10-20 units	(Target fibrinogen activity [g/L] – measured fibrinogen activity [g/L] × plasma volume) ÷ fibrinogen per unit of cryoprecipitate (mg)‡
Fresh frozen plasma	15-30 mL/kg	(Target fibrinogen activity [g/L] – measured fibrinogen activity [g/L] × plasma volume) ÷ fibrinogen per unit of fresh frozen plasma (mg)§

Casini A *Blood* 2025

Fibrinogen concentrate is the first option

- Predictable rise of fibrinogen
- Lower procoagulant factors
- Smaller reconstitution volume
- Lower risk of overload
- Low risk of transfusion complications
- No ABO specificity

Négrier C et al. *Vox Sang* 2016
Menegatti M et al. *Blood* 2019

Prophylaxis versus on demand ?

Questionnaire based study, n=100

- Incidence of bleeding 0.5 (0 – 2.6) on prophylaxis
- Incidence of bleeding 0.7 (0 – 16.5) on demand

Prospective study, n =22

- ABR 1.2 on prophylaxis
- ABR 0.8 on demand

Delphi study

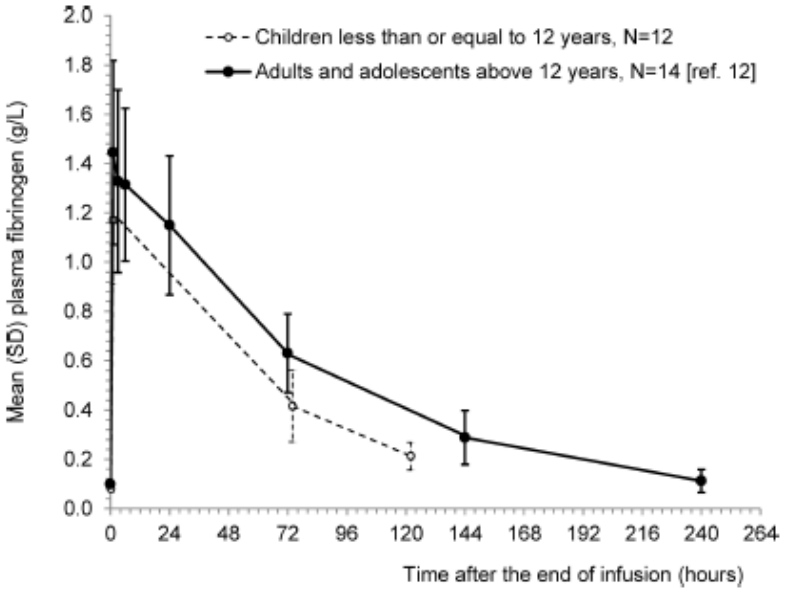
- Consensus on starting prophylaxis in case of life-threatening bleeding or recurrent bleeding

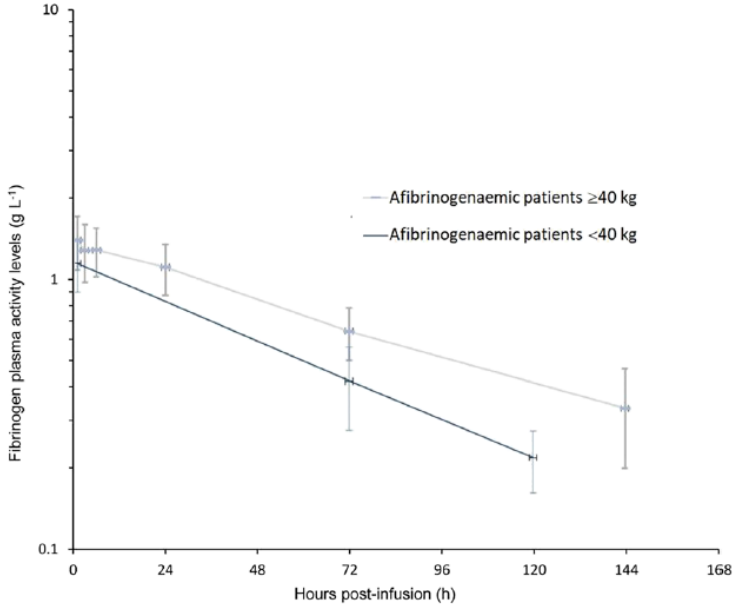
Peyvandi F et al. *J Thromb Haemost* 2006
Lasky J et al. *Res Pract Thromb Haemost* 2020
Casini at al. *Haemophilia* 2016

Multidisciplinary and tailored approach

- Personal and familial history of bleeding
- Availability of fibrinogen product
- Risk of catheter-related thrombosis and infection
- Repeated hospital visits or the administration of fibrinogen infusions in the home

Individualized pharmacokinetics



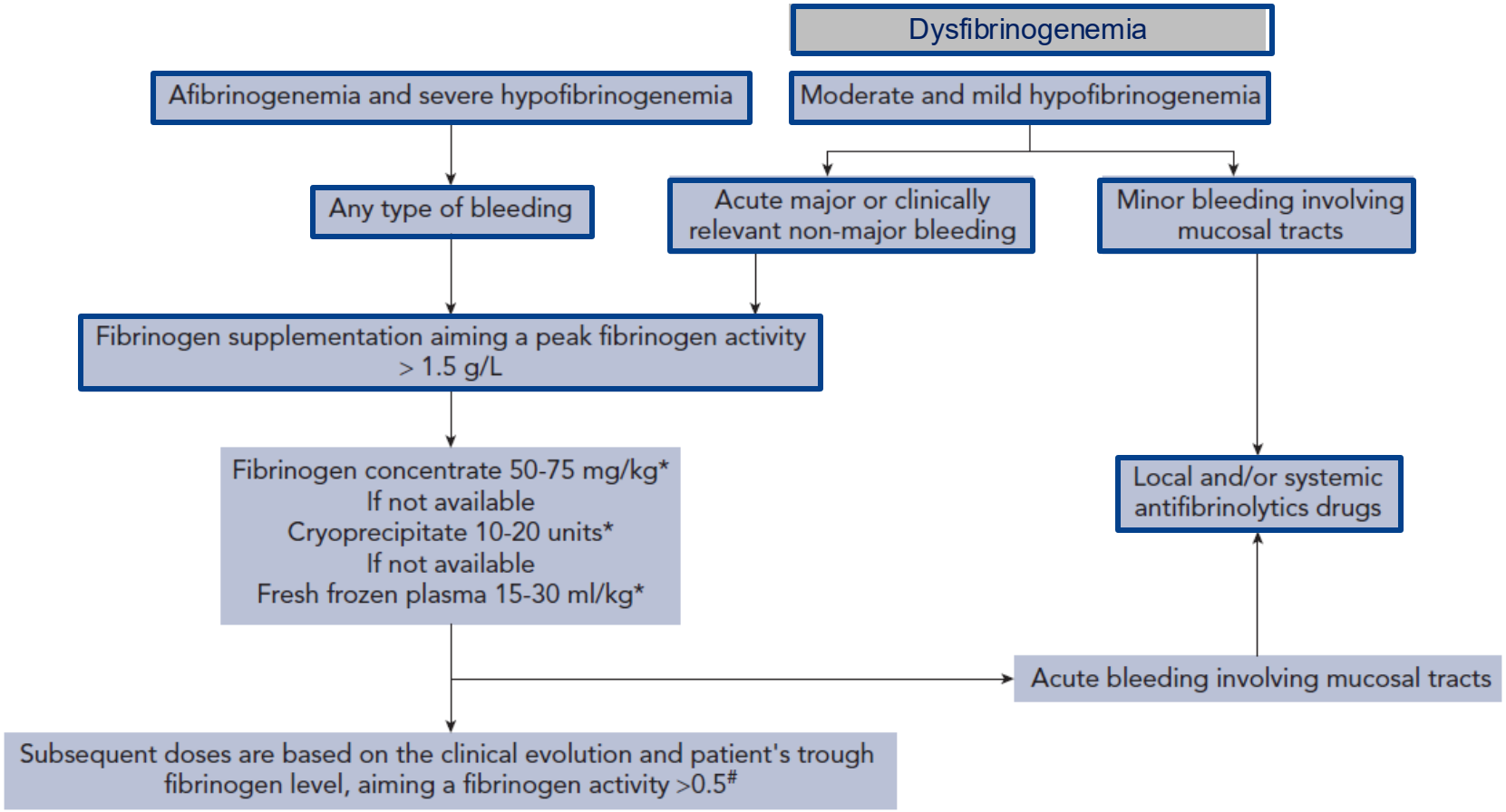


Target fibrinogen trough level >0.5 g/L

Once or twice injections per week or every two weeks

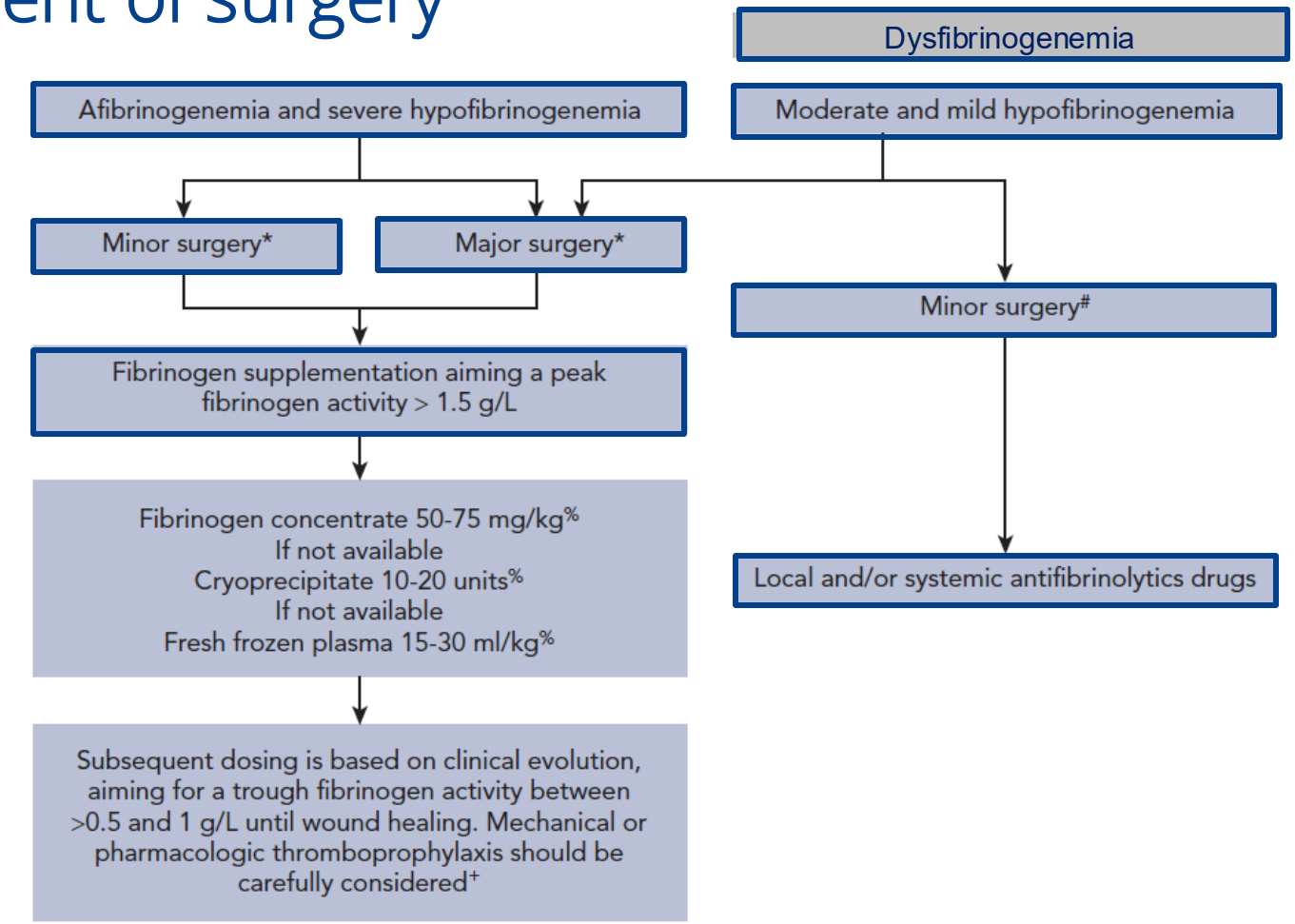
Khayat C et al. *Thromb Haemost* 2020
Bellon C et al. *Br J Clin Pharmacol* 2020

Management of acute bleeding



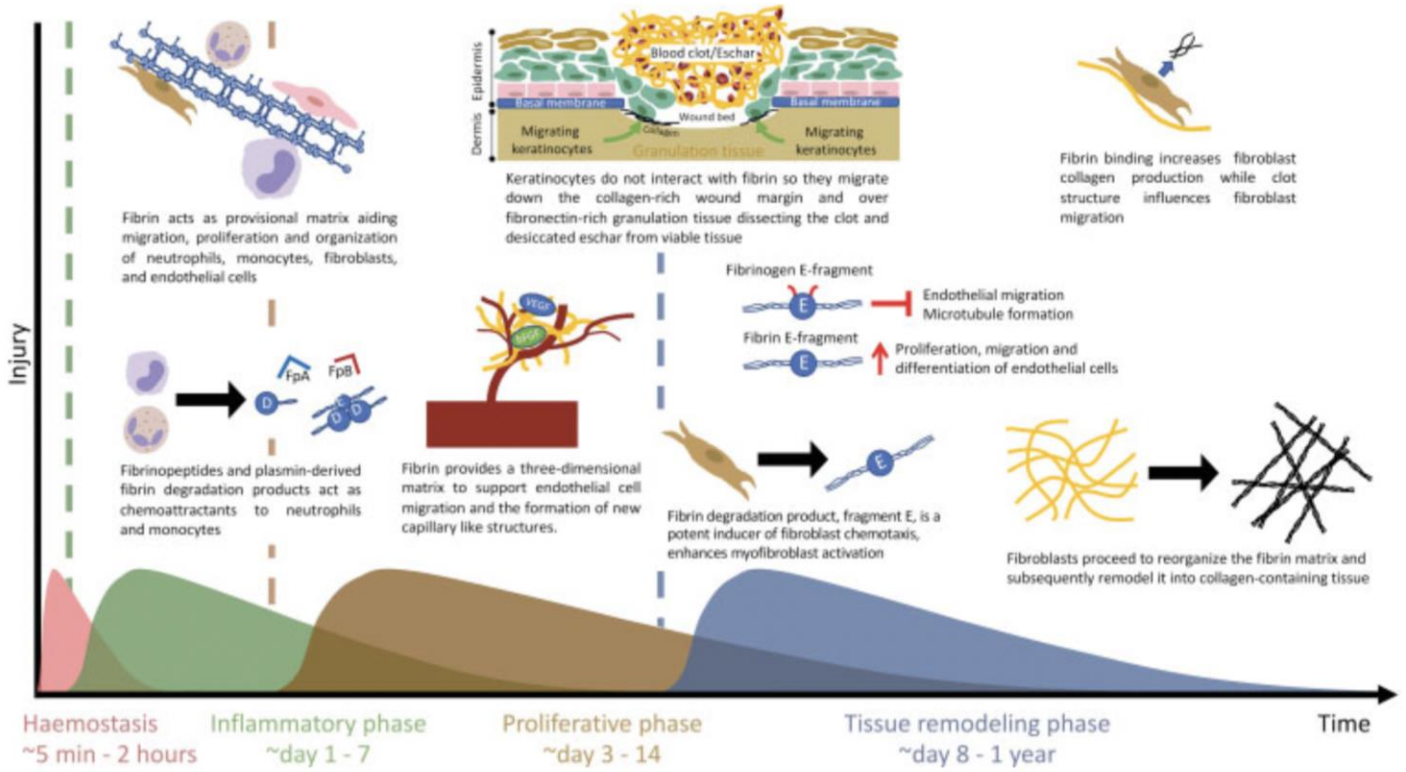
Casini A *Blood* 2025

Management of surgery



Casini A *Blood* 2025

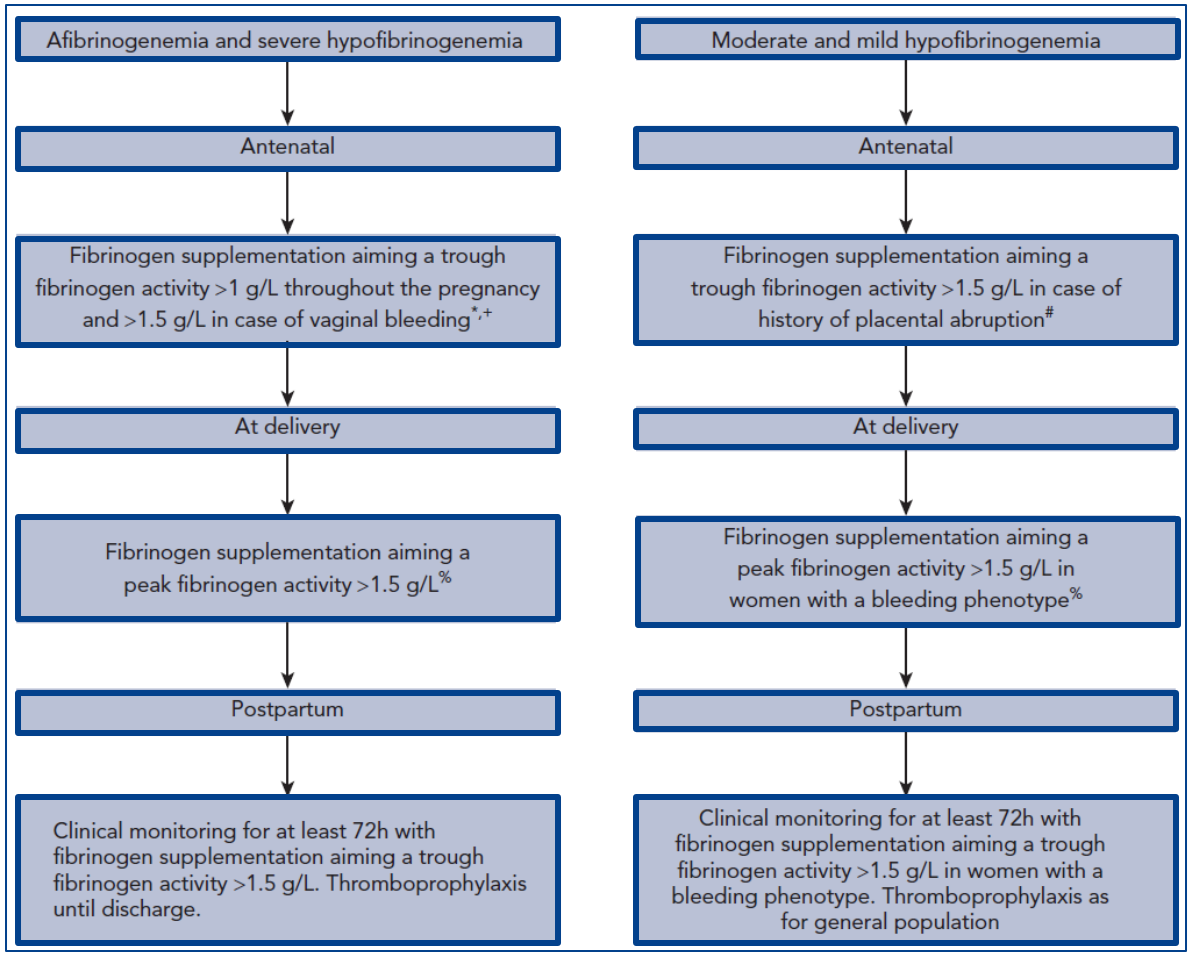
Until wound healing



Fibrinogen level >0.5 g/L

Kearney K et al. *Semin Thromb Hemost* 2022

Management of pregnancy



Casini A et al. *J Thromb Haemost* 2024

Conclusions

- HFDs encompass a large group of fibrinogen deficiencies with specific clinical features and bleeding and/or thrombotic risks
- The diagnosis is based on the measurement of functional and antigenic fibrinogen
- The genotype confirms the diagnosis and may help to predict the clinical phenotype
- Fibrinogen replacement is the mainstay of treatment for HFDs

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