Webinars

Constitutional thrombocytopenia

EuroBloodNet

Constitutional thrombocytopenia and bleeding risk

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Perugia –Italy

05 June 2024

Co-funded by the Health Programme of the European Union

CRPP MHEMO

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

None

Inherited platelet disorders (IPD)

- A heterogeneous group of rare congenital hemorrhagic disorders with reduced platelet number (inherited thrombocytopenias, IT) and/or altered platelet function (inherited platelet function disorders, IPFD)
- Mucocutaneous bleeding diathesis of very variable severity
- Large heterogeneity in terms of molecular/genetic defect (for some forms not yet identified)
- Diagnosis of many forms is cumbersome and sometimes requires complex assays

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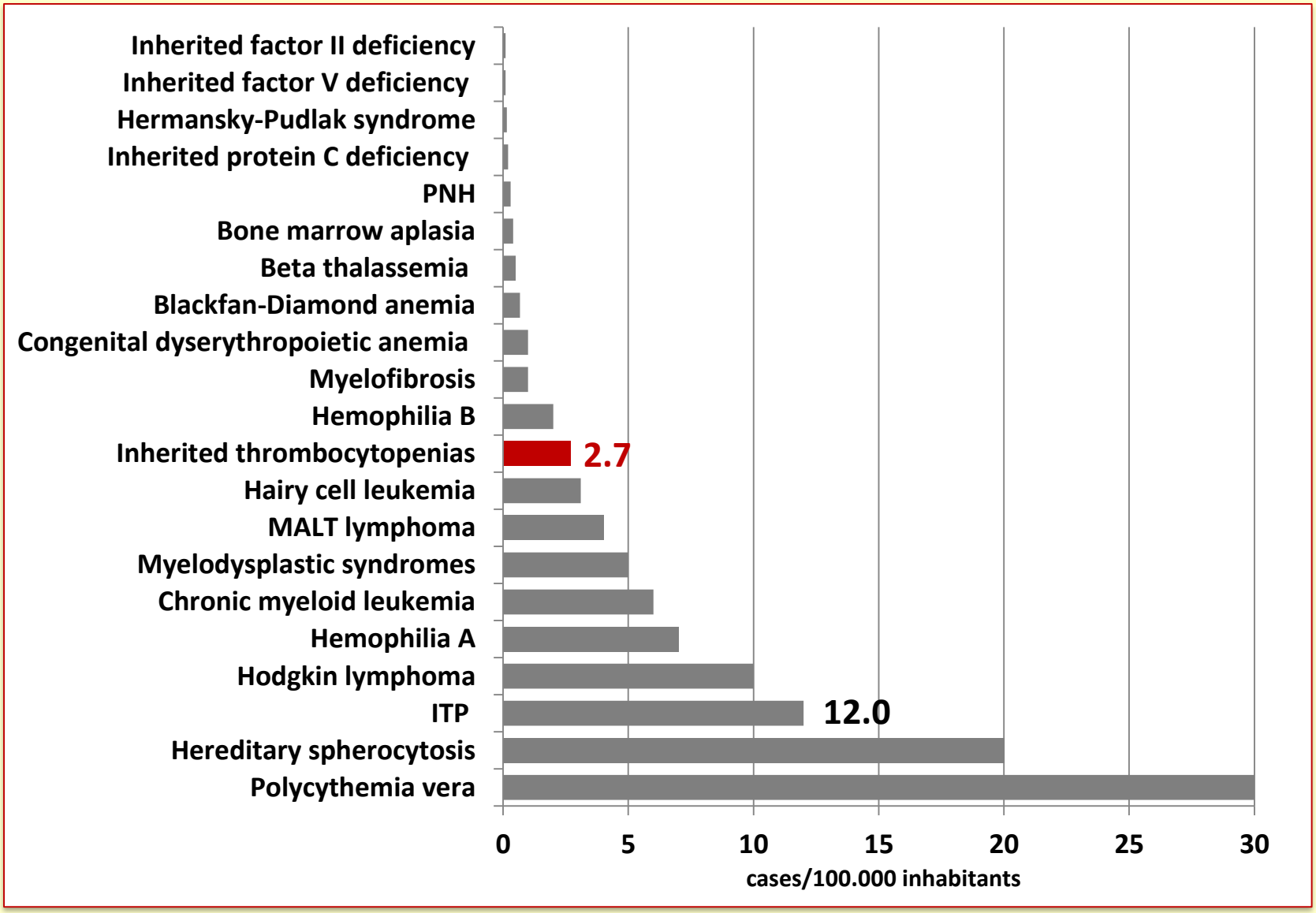
Inherited thrombocytopenias

prevalence compared with other rare blood disorders



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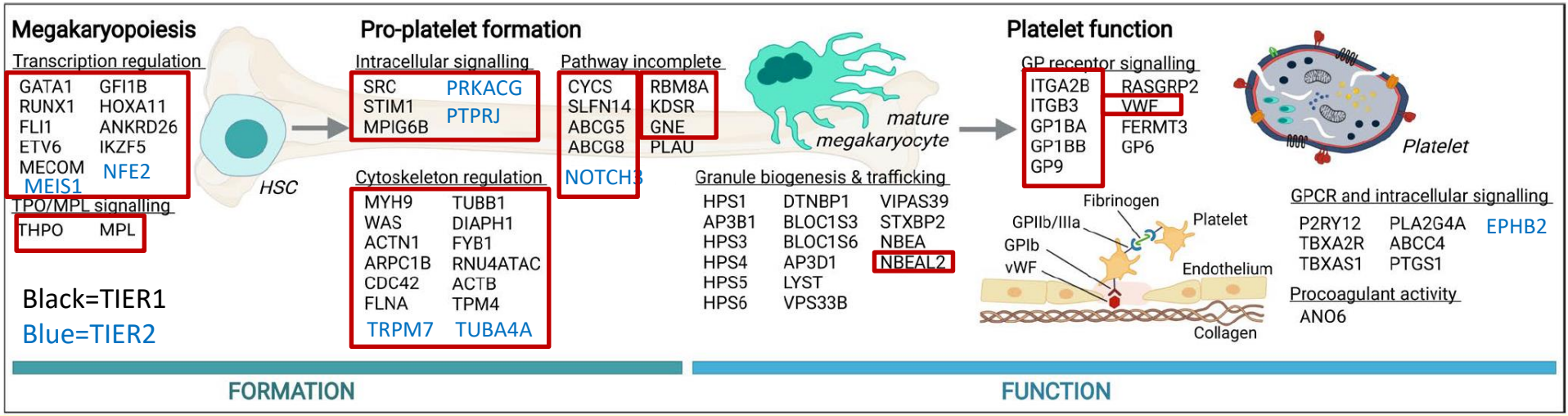
(from Balduini CL, *Hamostaseologie* 2012;32:259; Orphanet 2014)

Gene variants associated with platelet disorders

76 genes causing inherited platelet disorders

47 genes causing inherited thrombocytopenias



Gene list updated annually by the ISTH Scientific and Standardization Committee for Genomics in Thrombosis and Hemostasis (ISTH SSC-GinTH) (https://www.isth.org/page/GinTh_GeneLists)

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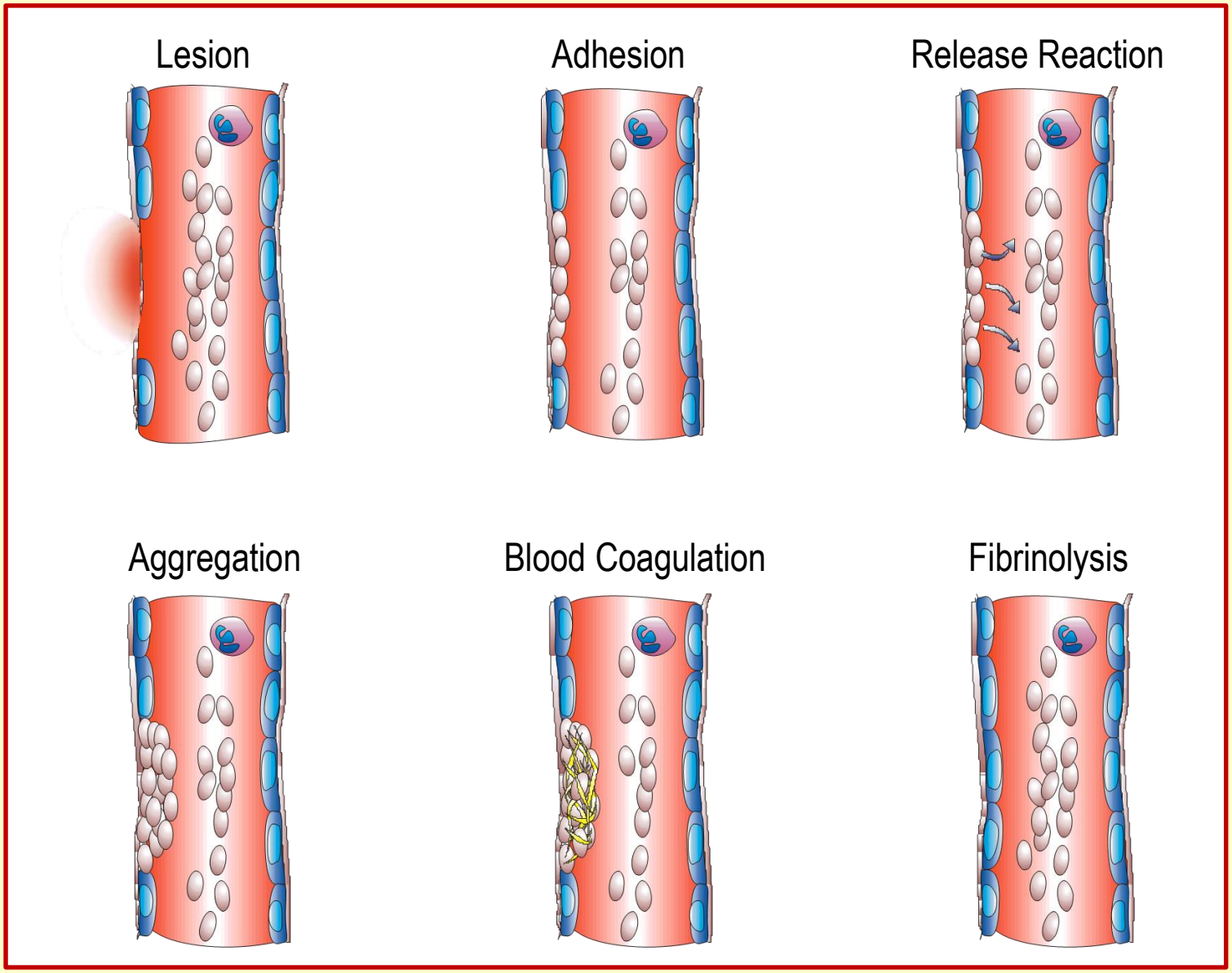
UPDATED from Ver Donck F et al, Res Pract Thromb Haemost. 2021;5:e12637

Platelets in Hemostasis



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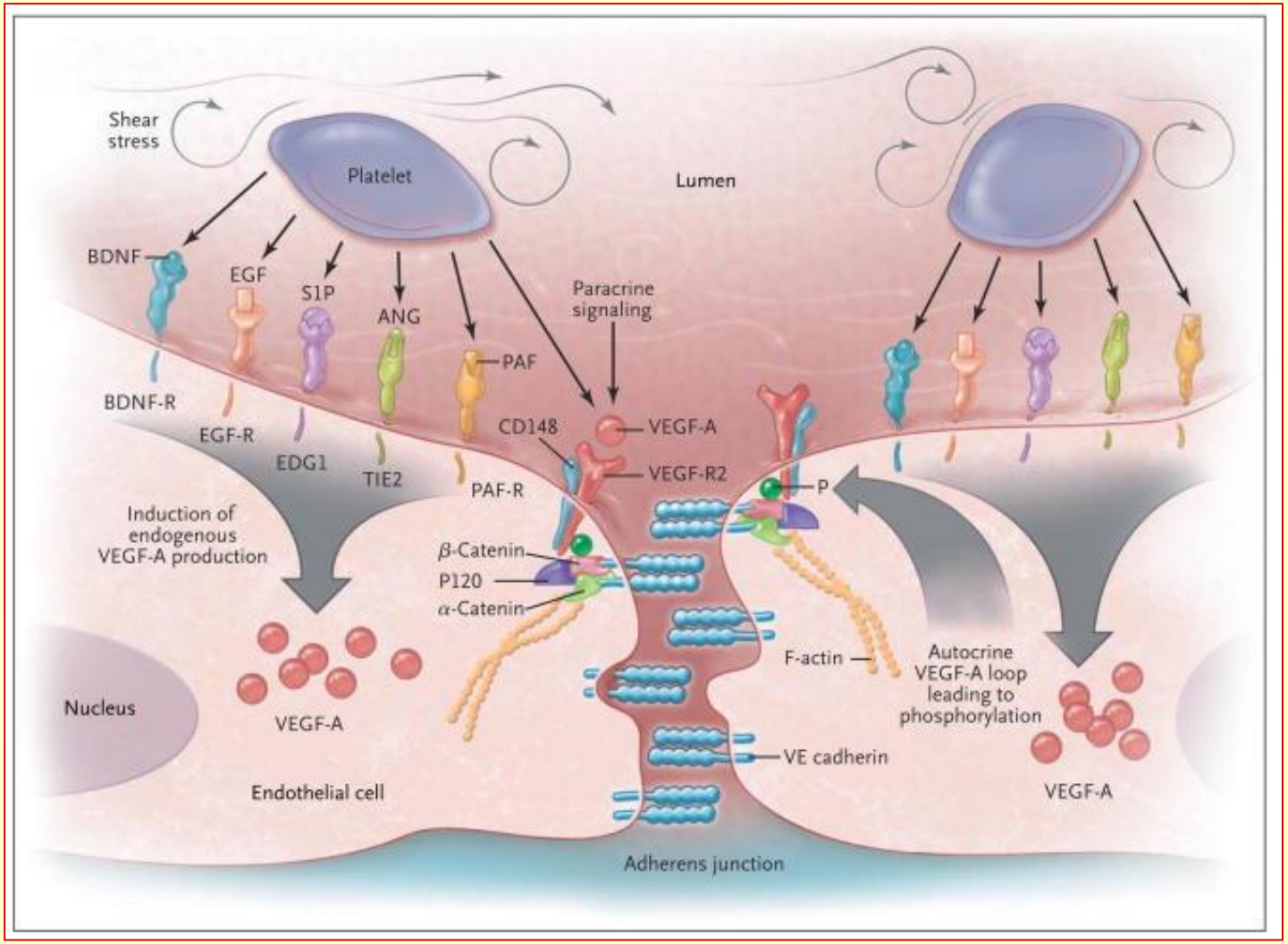
Platelets exert a trophic effect on the endothelium



Nachman RL & Rafii S, N Engl J Med 2008, 359:1261.

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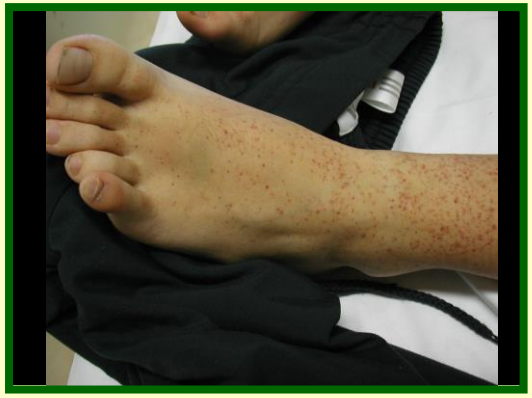
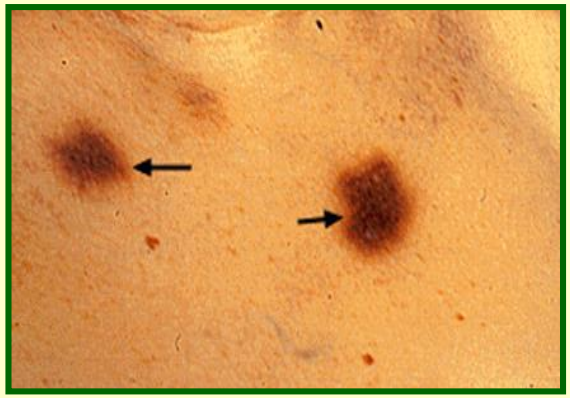
Thrombocytopenia: clinical presentation

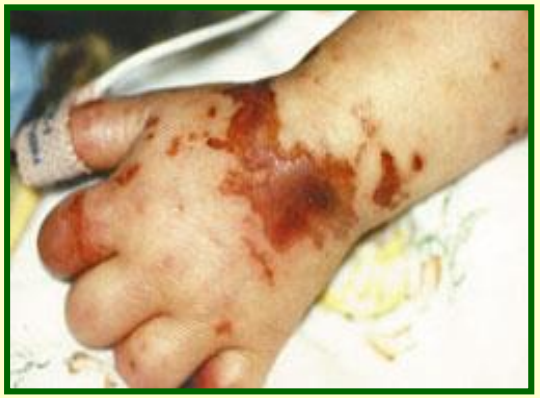
- Petechiae
- Ecchymoses/bruises
- Purpura
- Gum Bleeding
- Epistaxis
- Meno-metrorrhagia, GI bleeding
- ICH
- Surgery/trauma–related bleeding



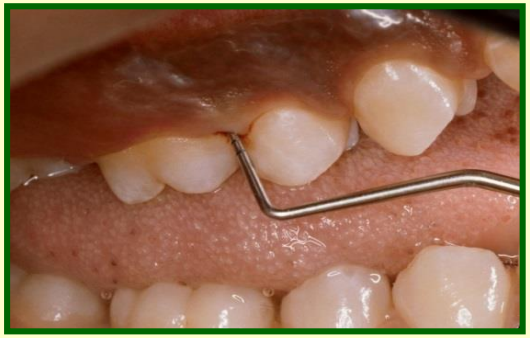
Petechiae



Ecchymoses

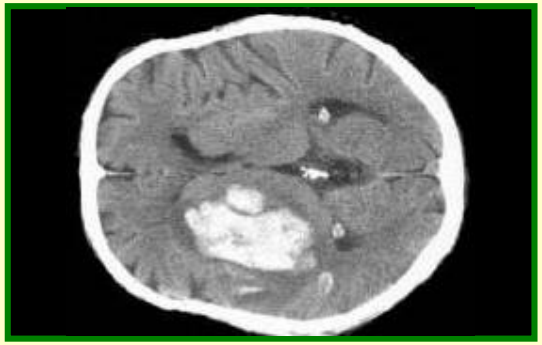


Purpura



Gum bleeding

Epistaxis



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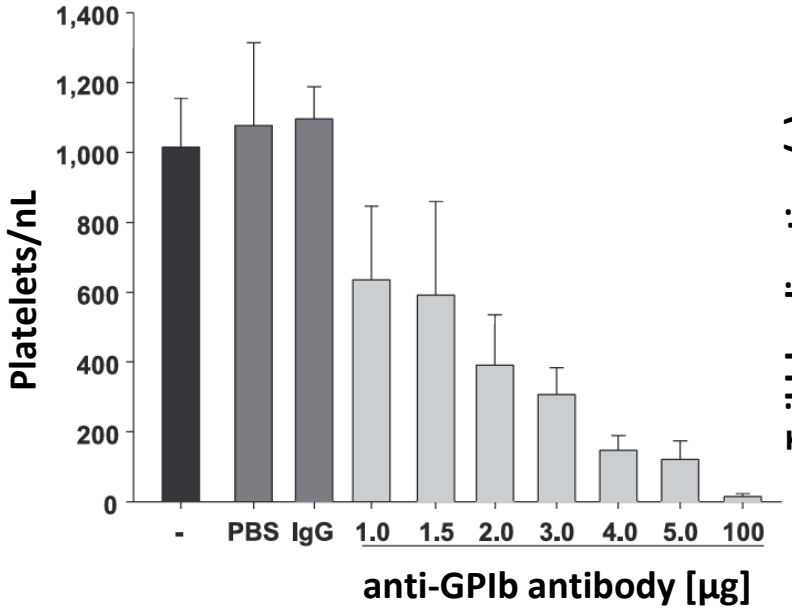
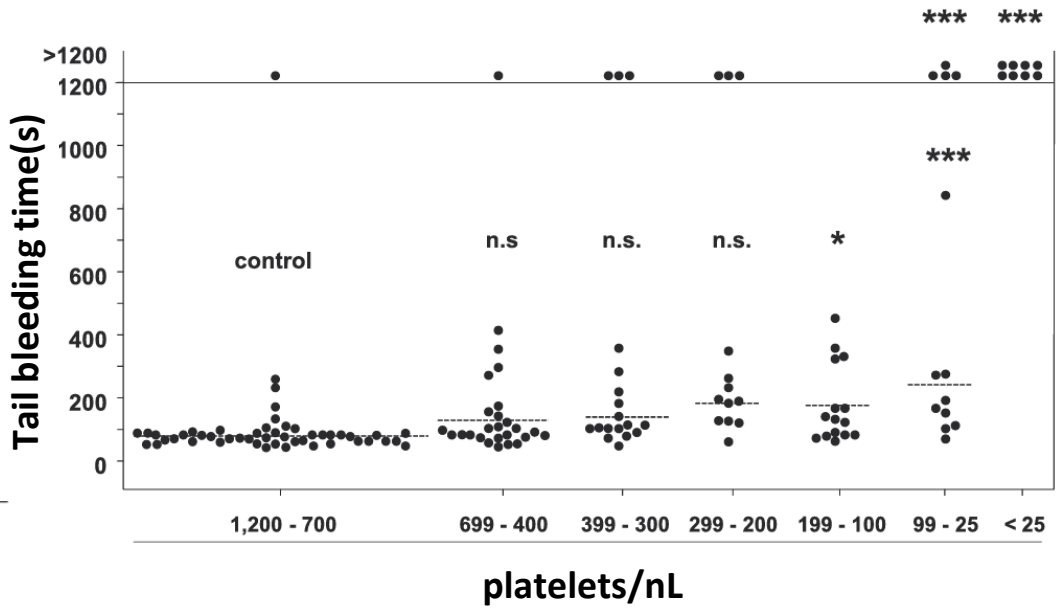
Only severe thrombocytopenia results in bleeding in mice





Morowski M et al, Blood 2013; 121:4938-47.

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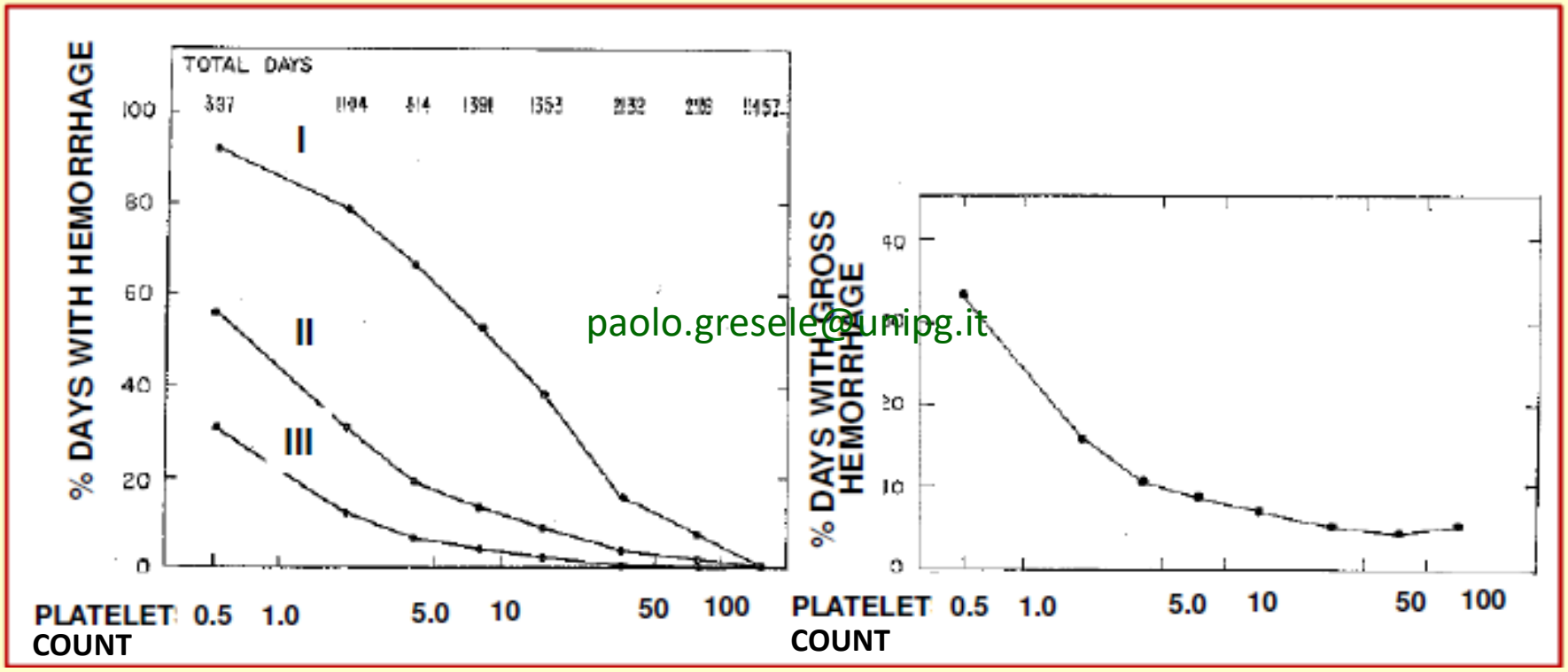
Relation between platelet count and incidence of hemorrhage in patients with acute leukemia



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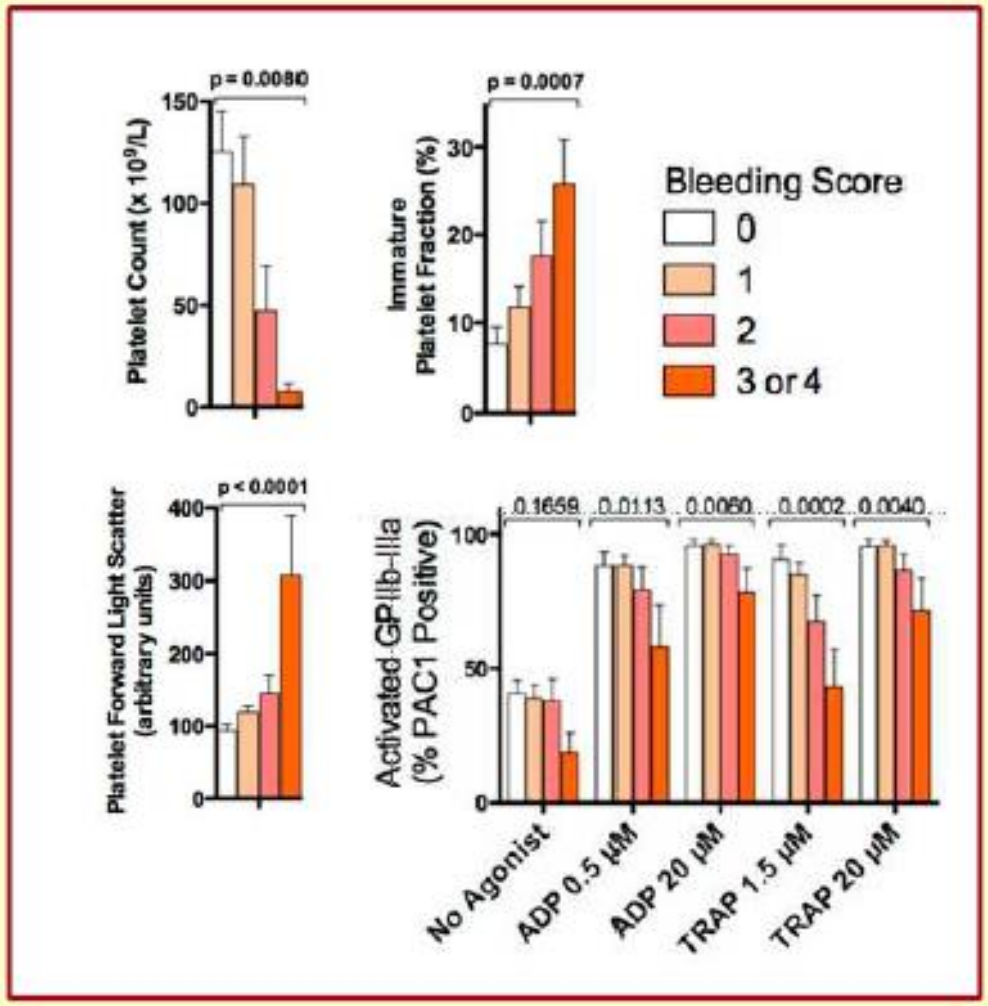
I =all hemorrhage
II =without skin/epistaxes
III=only grossly visible

Gaydos LA et al., NEJM 1962; 266:905

Platelet dysfunction correlates with bleeding in ITP

A study in 57 pediatric patients



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Frelinger AL et al., Blood 2015;126:873

Inherited thrombocytopenias can associate with platelet dysfunction

Without platelet dysfunction		With platelet dysfunction	
ABCC4	MECOM	ANKRD26 (5'-UTR)	SLFN14 (GOF)
ABCG5	MEIS1	ANO6	SRC (GOF)
ABCG8	MPIG6B	ARPC1B	STIM1 (GOF)
ACTB	MPL	ETV6	VWF (GOF)
ACTN1	MYH9	FLNA	WAS
CDC42	NFE2	GATA1	
CYCS	NOTCH3	GFI1B	
DIAPH1 (GOF)	RBM8A	GP1BA (GOF and biallelic)	
FYB1	RNU4ATAC (non coding)	GP1BB (biallelic)	
GNE	THPO	GP9 (biallelic)	
GP1BA (LOF and monoallelic)	TPM4	IKZF5	
GP1BB (monoallelic)	TRPM7	ITGA2B (GOF)	
GP9 (monoallelic)	TUBA4A	ITGB3 (GOF)	
HOXA11	TUBB1	NBEAL2	
KDSR		PRKACG	
		PTPRJ	
		RAP1B (GOF)	
		RUNX1	

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Assessment of the bleeding severity of hemorrhagic disorders

- Measurement of history of spontaneous or provoked hemorrhage by bleeding assessment tools
- Systematic evaluation of the prevalence of excessive bleeding during invasive procedures

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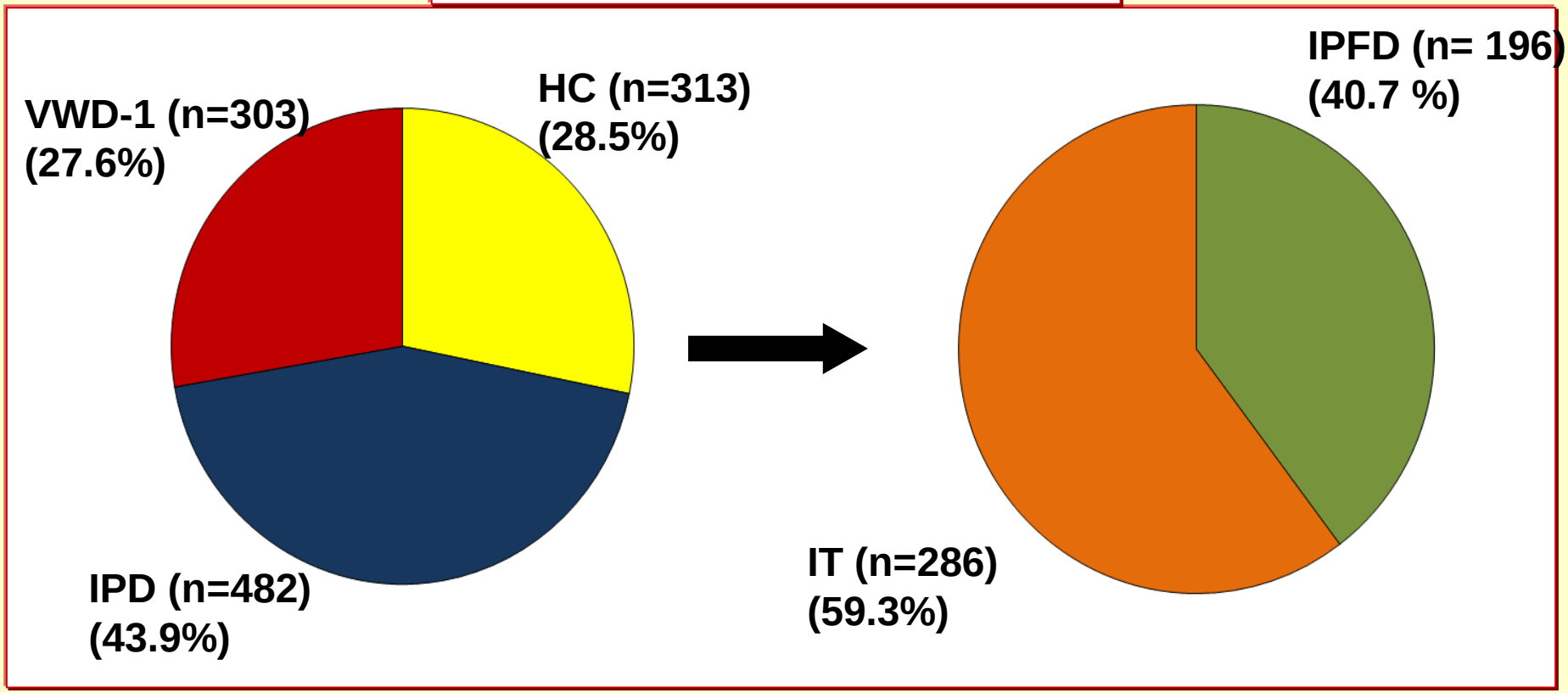
BAT-VAL (ISTH-BAT in IPD evaluation) study

Subjects enrolled according to group

43 centers enrolling; 1,098 subjects enrolled



Subjects enrolled according to groups			
	HC	VWD-1	IPD
Females (%)	60.13	59.15	57.41
Median age (y)	40	38	38.5
Pediatrics (<16y)(%)	7.40	10.46	15.02

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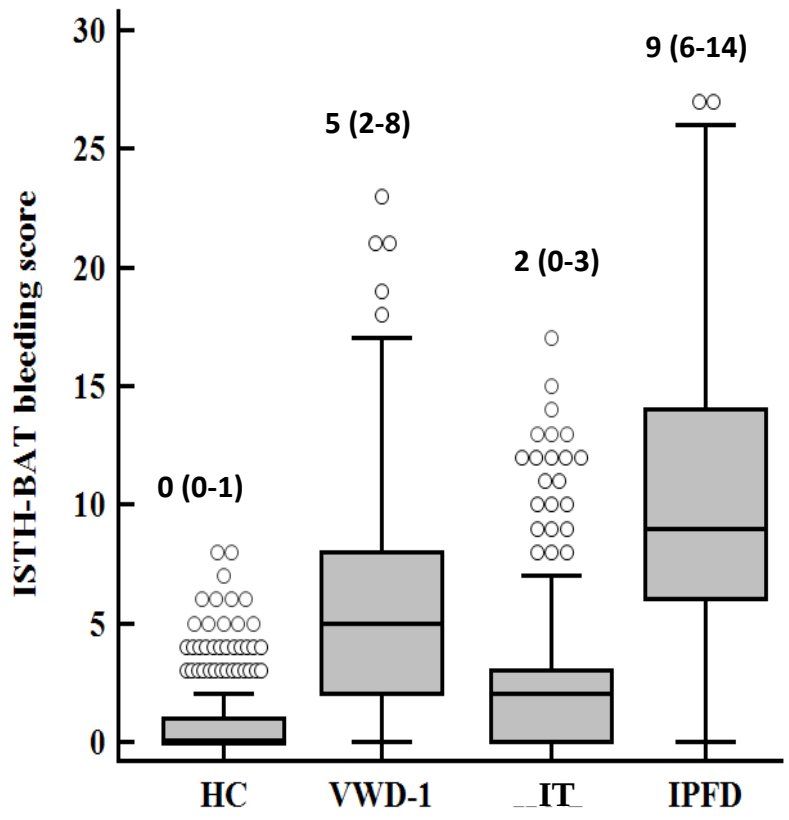
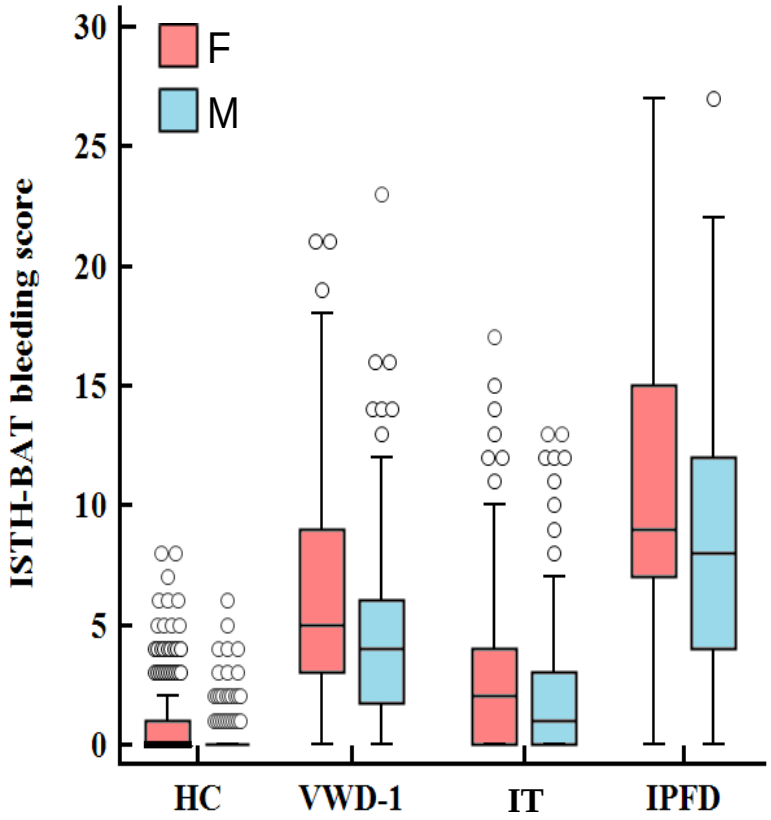
Gresele P et al., J Thromb Haemost 2020, 18:732

Validation of the ISTH/SSC bleeding assessment tool for inherited platelet disorders

The BAT-VAL Study





For each group p<0.05 M *vs* F

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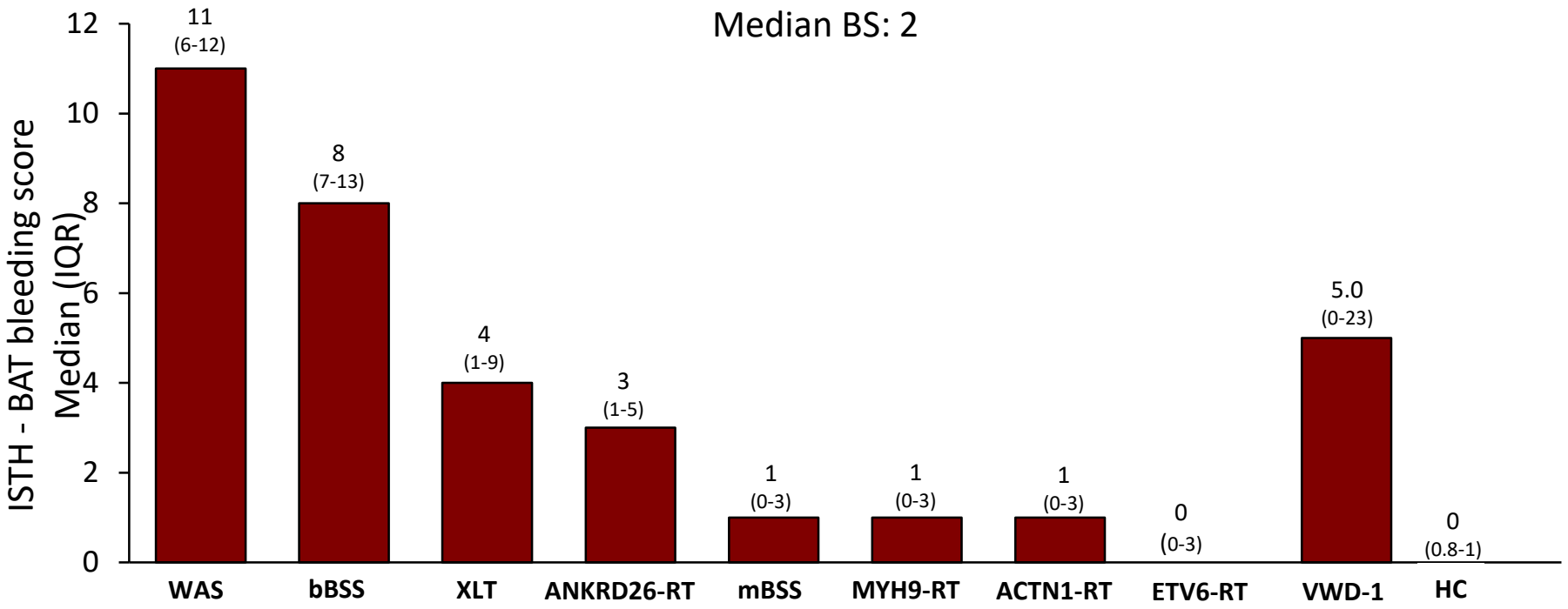
Gresele P et al., J Thromb Haemost 2020, 18:732

BAT bleeding score in ITs
by principal diagnoses



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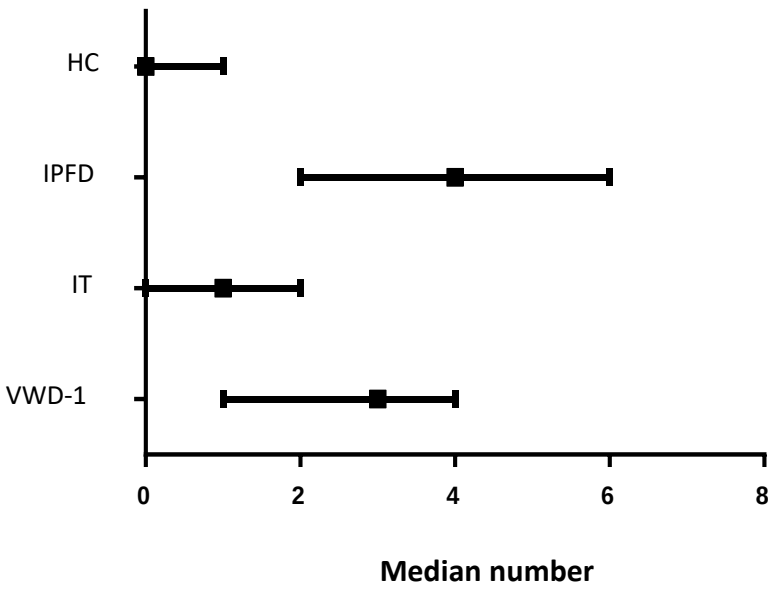
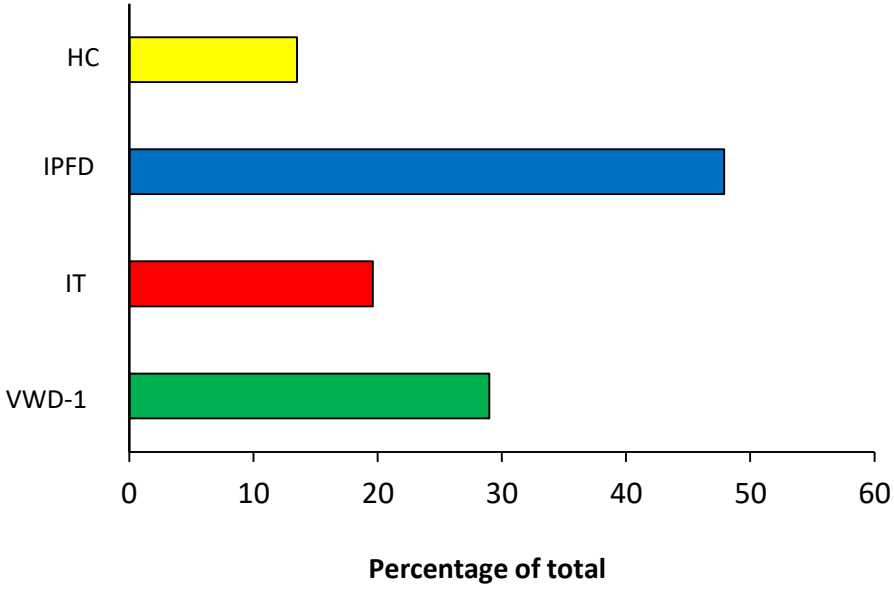
Gresele P et al., J Thromb Haemost 2020, 18:732

The BAT-VAL Study

Median number (IQR) of hemorrhagic symptoms



Percentage of clinically relevant symptoms



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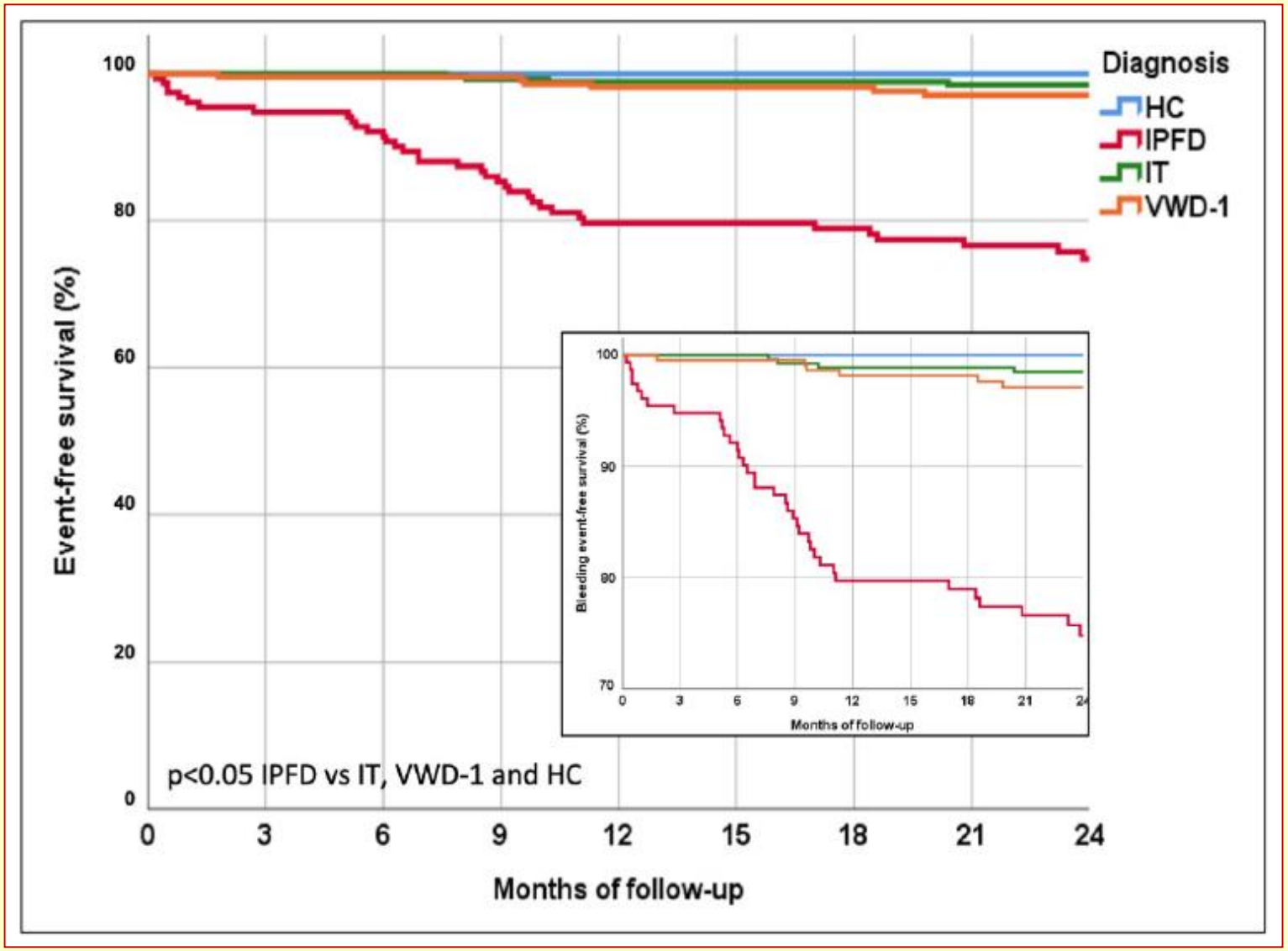
Gresele P et al., J Thromb Haemost 2020, 18:732

The BAT-VAL follow-up study
Bleeding event-free survival in the different groups



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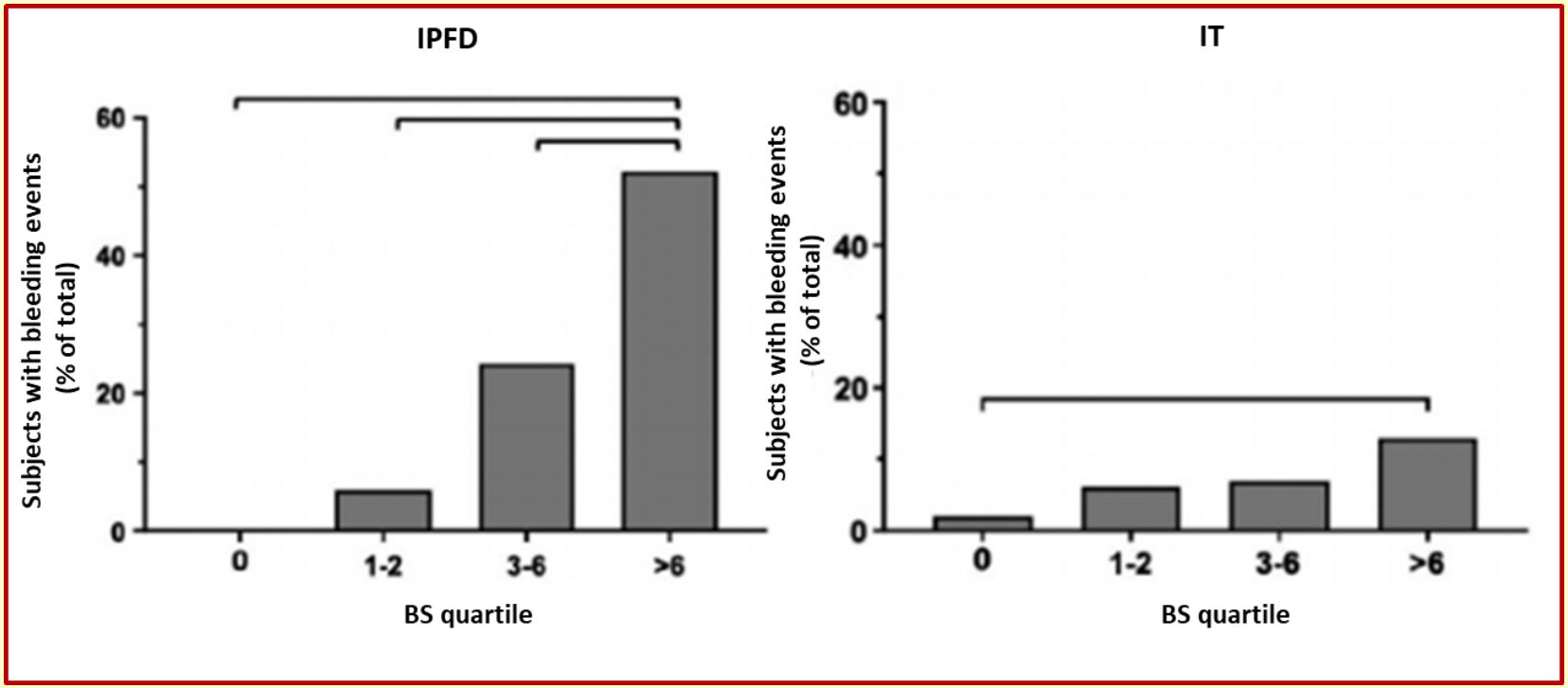
Gresele P et al., J Thromb Haemost 2021; 19(5):1364

The BAT-VAL follow-up study
The ISTH BAT BS predicts bleeding events in IPD



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Gresele P, et al., J Thromb Haemost 2021; 19:1364

Assessment of the bleeding severity of hemorrhagic disorders

- Measurement of history of spontaneous or provoked hemorrhage by bleeding assessment tools
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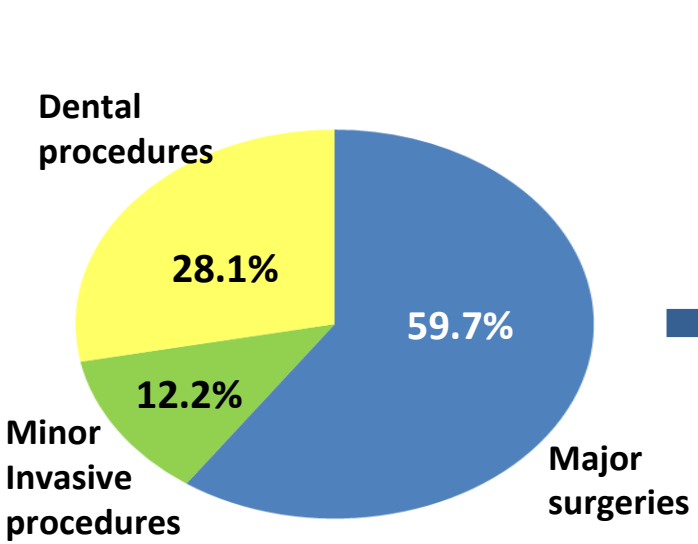
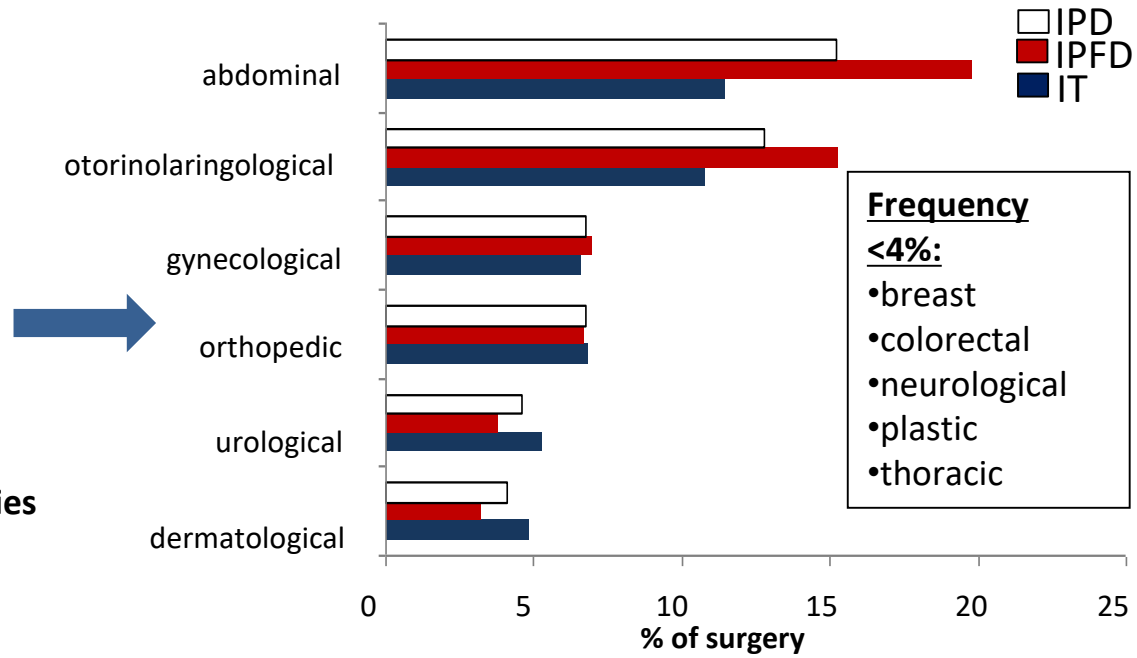
Surgery in Platelet disorders And Therapeutic Approach (SPATA)

Invasive procedures

829 procedures (355 in IPFD, 374 in IT)**.** Median age at surgery: 31 years (IQR 15-52)





Major: any procedure in which a body cavity was entered, a mesenchymal barrier was crossed, a facial plane was opened, an organ was removed or normal anatomy was altered;
Minor invasive: any operative procedure in which only skin, mucous membranes or superficial connective tissue were manipulated, gastroscopy, colonoscopy and similar;
Dental: extraction, abscess removal, apicectomy and similar

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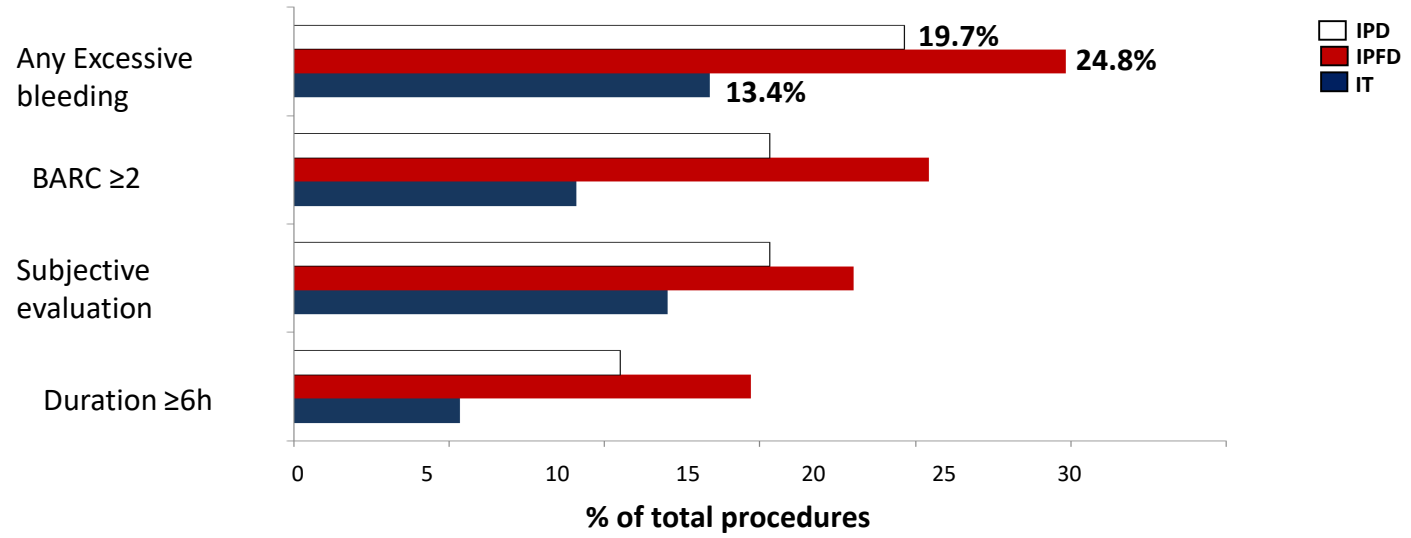
Orsini S et al., Haematologica 2017, 102:1192.

Frequency of excessive bleeding at surgery in IPD
The SPATA Study

49 centers, **17** countries.
829 procedures in 423 IPD patients (238 IPFD, 135 ITs)**, 16** forms of **IPFD and 9** forms of **IT**
Median age: 40 years (IQR 23.7-54). Women: 56%



In otherwise healthy subjects:
-From literature: 1.4-6 %
-Current study: 3%

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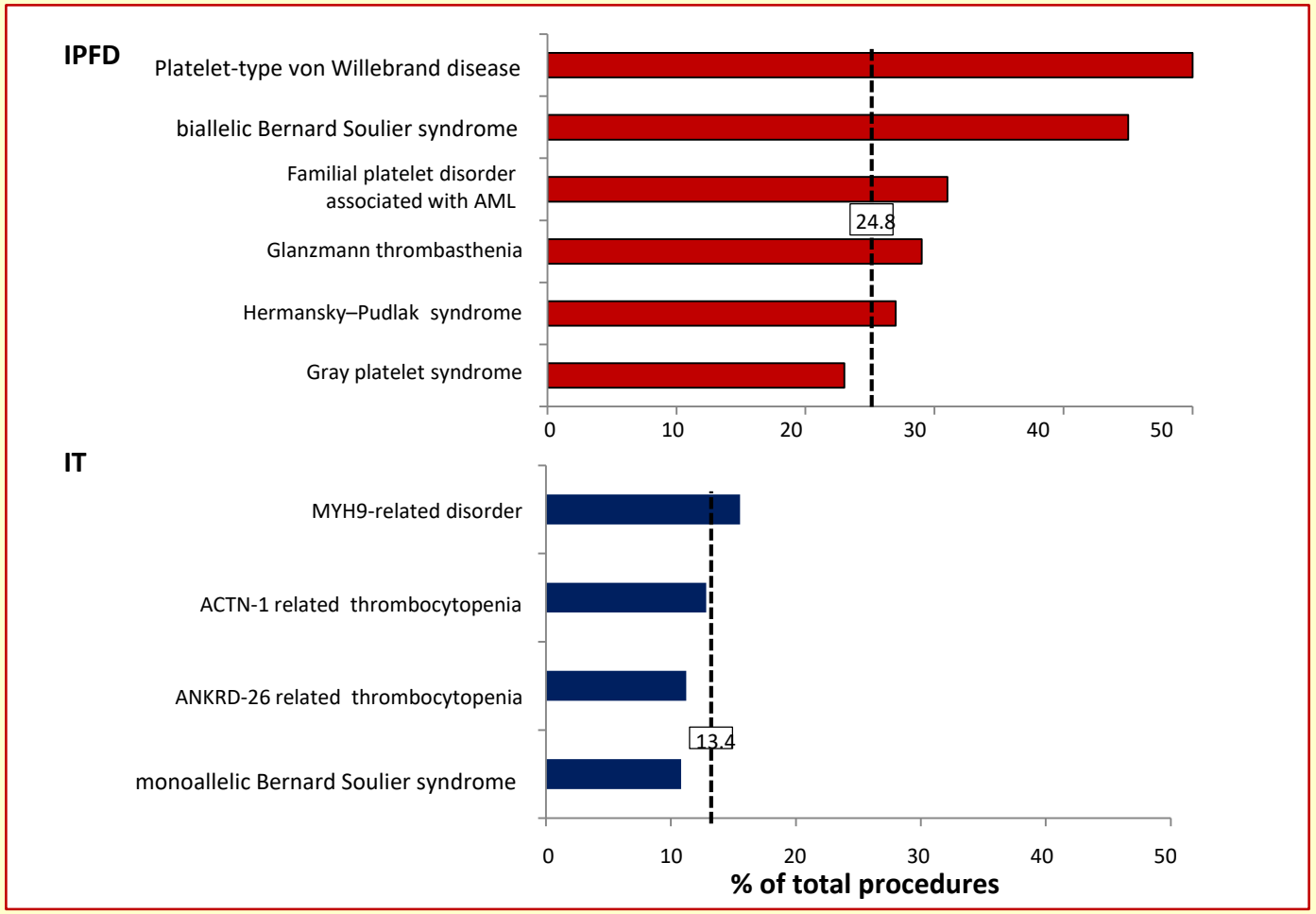
Orsini S et al., Haematologica 2017,102:1192.

Frequency of AEB at surgery according to diagnosis



Orsini S et al., Haematologica 2017, 102:1192.

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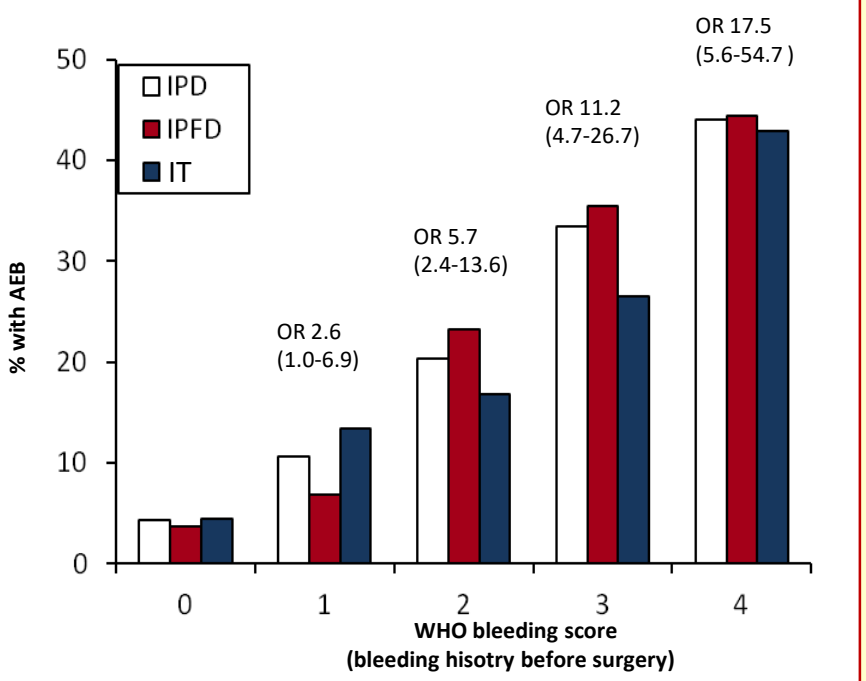
Predictors of post surgical bleeding

The SPATA Study



	IPFD (n=455)	IT (n=374)
	OR (95% CI)	OR (95%CI)
Female gender	1.8 (1.1-2.9)	-
Platelet count <68x10^9/L	-	2.04 (1.01-4.12)
Prophylaxis	0.38 (0.23-0.63)	-

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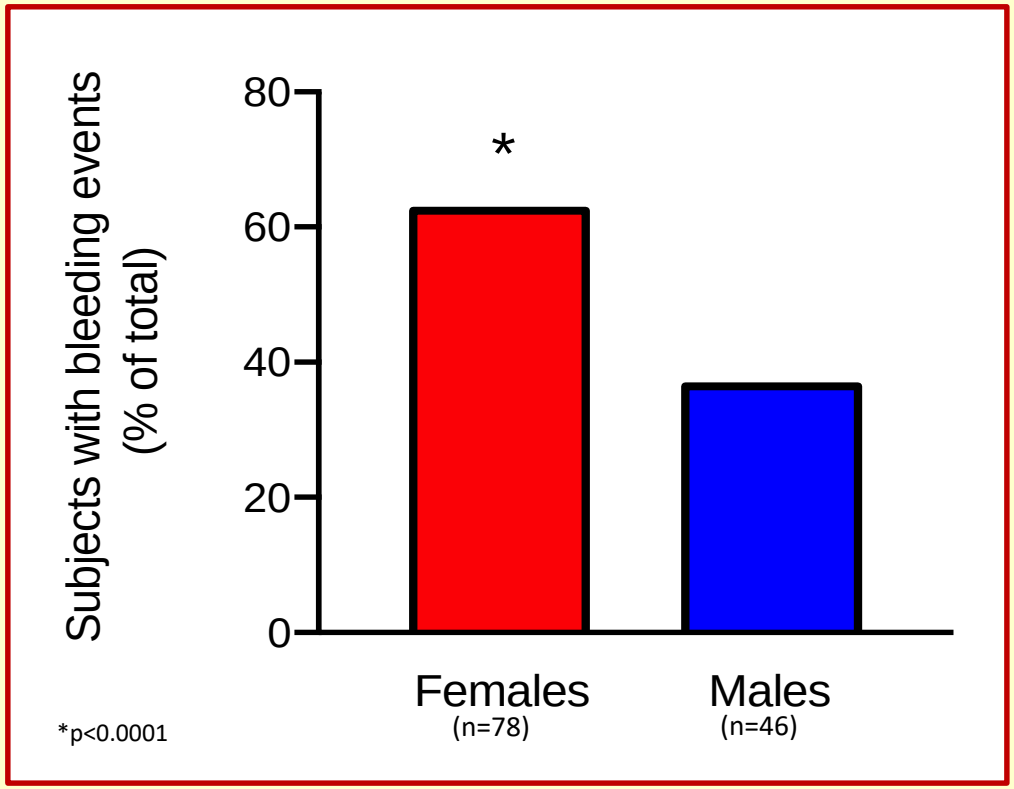
Orsini S et al., Haematologica 2017, 102:1192.

Bleeding events in an IPD population in a two-years follow-up



Median BAT of females with bleeding events: 9 (IQR 6-13)
Median BAT of males with bleeding events: 8 (IQR4-12)

Gresele P et al, J Thromb Haemost. 2021;19(5):1364-1371

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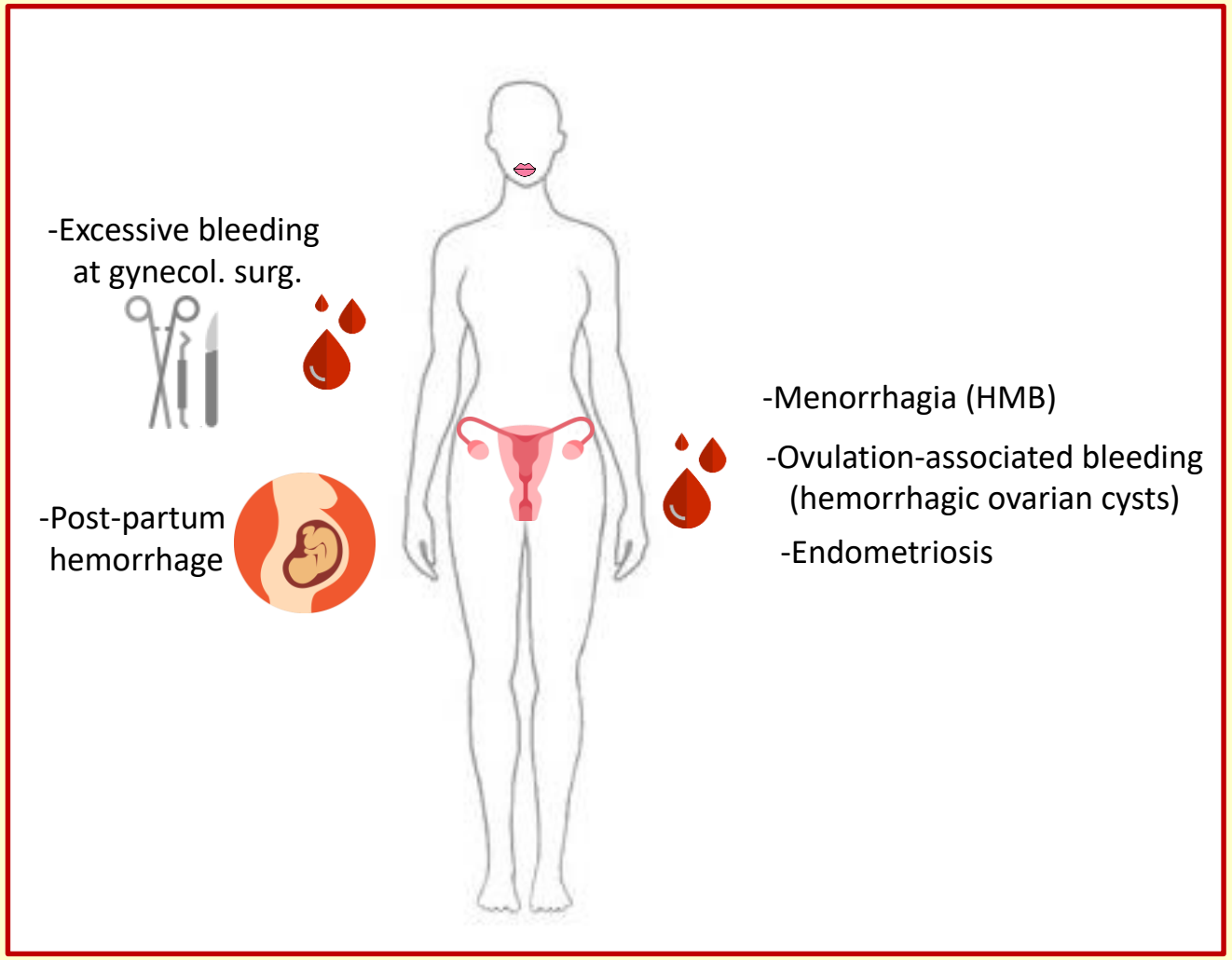
Female-specific hemorrhagic manifestations in IPD



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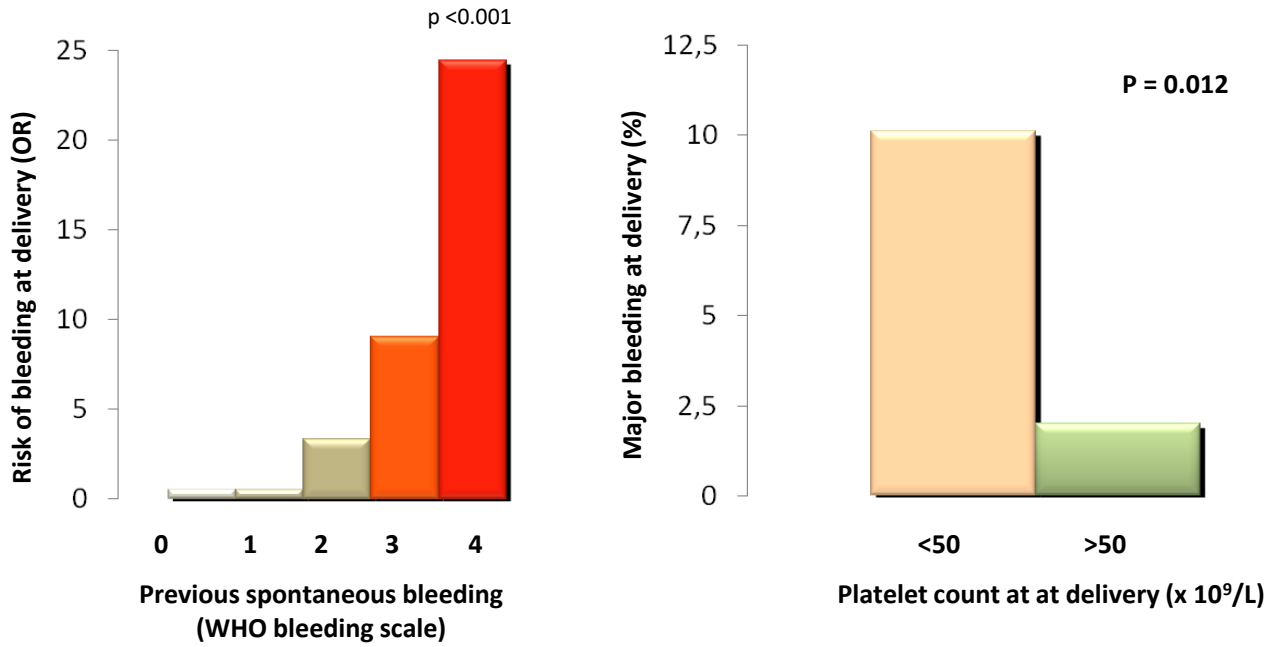
Gresele P et al., Thromb Res. 2019;181:S54-S59.

Post-partum hemorrhage in **Inherited Thrombocytopenias**
The PIPA Study

296 deliveries in 181 women with 13 different forms
Overall frequency of AEB at delivery: 14.2%
Overall frequency of major bleeding at delivery: 6.8%
Overall frequency of hemorrhage at delivery in healthy women: 3-7%

PREDICTIVE PARAMETERS



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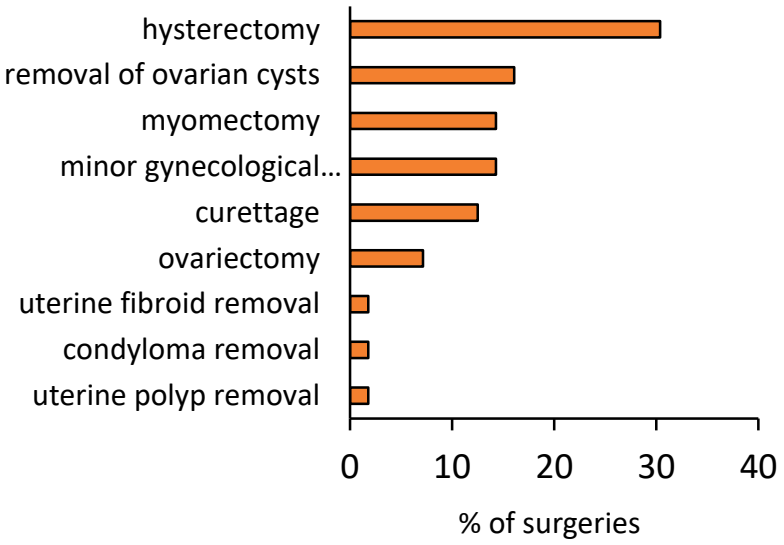
Noris P et al, Haematologica 2014;99:1387-94

Frequency of any excessive bleeding after gynecological surgery

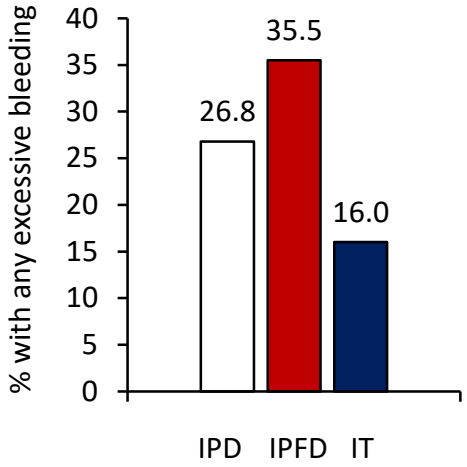
A sub-analysis of the SPATA Study

56 gynecological surgeries / 470 surgeries carried out in women (12%)

Type of surgery



Excessive bleeding at surgery



Gresele P et al., Thromb Res 2019;181 :S54-S59

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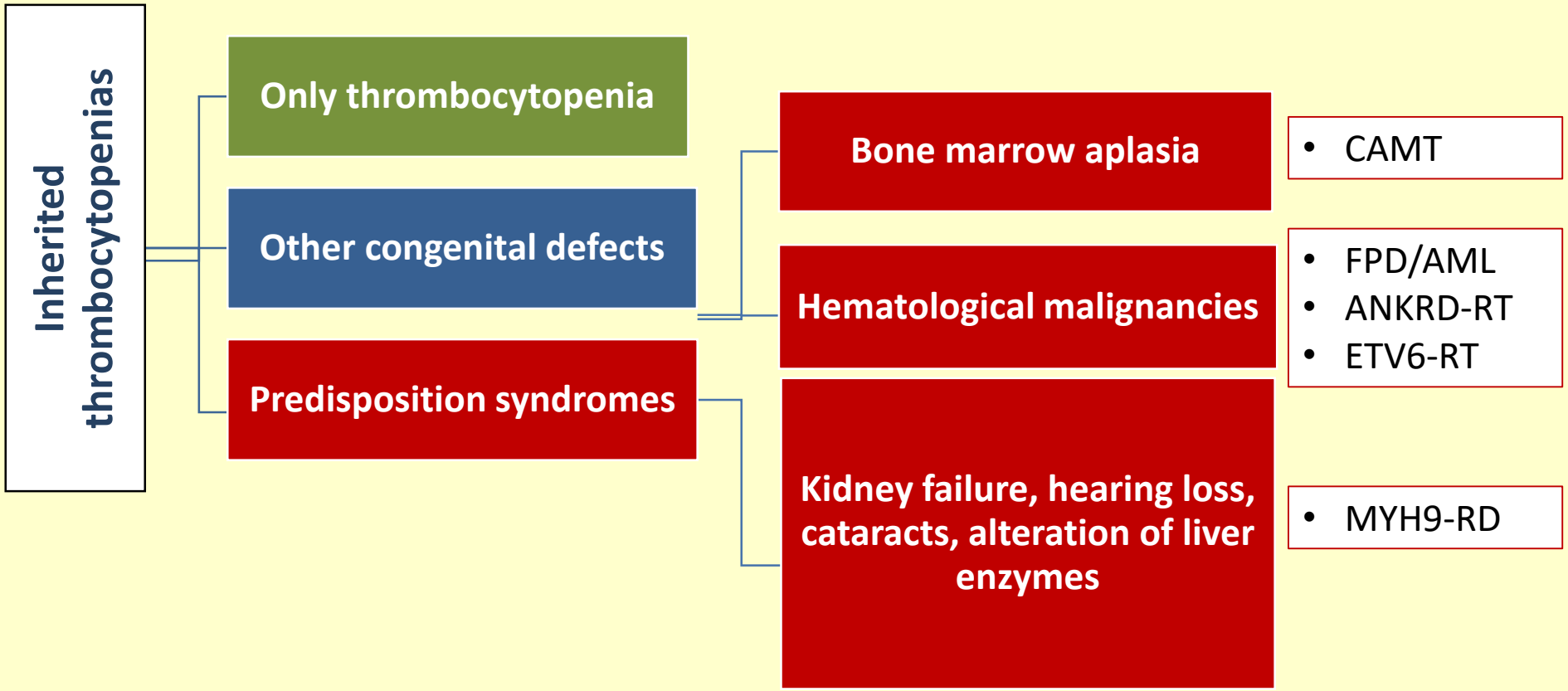
Inherited thrombocytopenias
Predisposition syndromes



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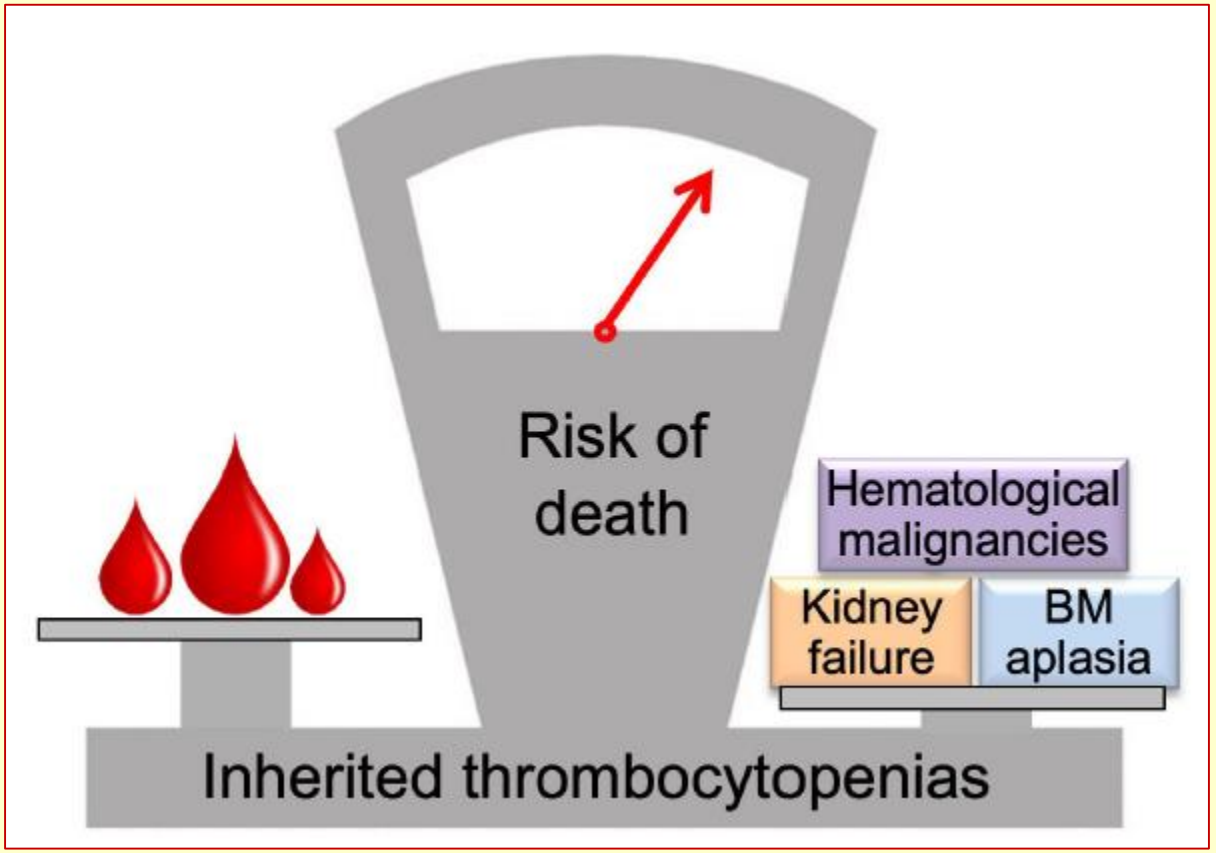
Relative weight in the risk of death of inherited thrombocytopenias of the bleeding and extra hemostatic manifestations



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Balduini A et al., Haematologica 2022; 107: 1268

Treatment goals in inherited thrombocytopenias

- **Prevention of bleeding**
  - Prohemostatic interventions
    - Antifibrinolytic agents (Tranexamic acid, EACA)
    - Desmopressin
    - Platelet transfusions
    - FVIIa
  - Increase of platelet count
    - Platelet transfusion
    - Splenectomy (WAS/XLT)
    - Eltrombopag
    - HSCT (CAMT, WAS, bBSS)
    - Gene therapy (WAS)
- **Treatment of other defects**
  - MYH9-kidney (proteinuria): ACE-I/ARB
  - MYH9-ear (deafness): cochlear implantation
  - MYH9-ocular (cataract): cataract surgery

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Treatment options for bleeding

- **Antifibrinolytic agents**: local or systemic; arrest/prevent epistaxis, gingival bleeding or menorrhagia; used for the prevention of bleeding for minor surgery
- **DDAVP:** i.v., s.c., nasal spray; efficacious in preparation to invasive procedures or surgery (contraindicated in PT-VWD; uncertain efficacy in some IPFDs)
- **Platelet transfusion:** treatment of acute bleeding or prior to surgery; should be used only when other agents have failed (alloimmunization and infectious risks)
- **rFVIIa:** approved for treatment of acute bleeding and for perioperative management of GT refractory to platelet transfusions; little or no informations for other IPFDs
- **Eltrombopag**: for some ITs

From Gresele P et al, Haemostaseologie 2016; 36:265

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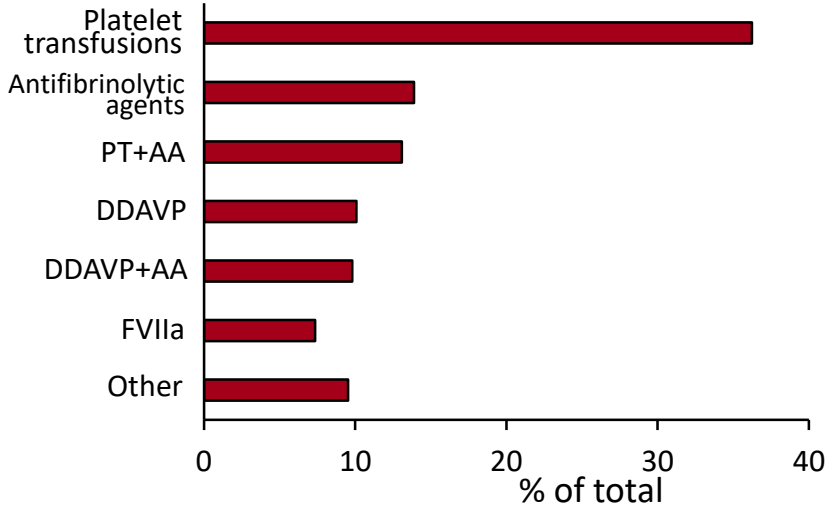
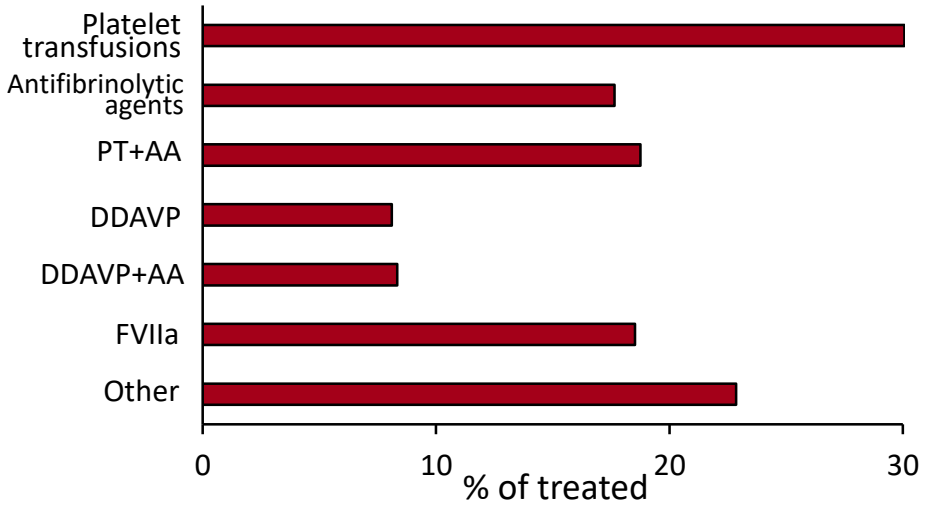
The SPATA Study

Prophylactic antihemorrhagic preparation and outcome

Antihemorrhagic pre-operatory prophylaxis



AEB depending on antihemorrhagic prophylaxis



OTHER: composition of two or more; cryoprecipitate; fibrin-glue, fibrinogen, FFP, IVIG, local hemostatic agent, suture, local tranexamic acid

-Prophylaxis given in 80.6% of procedures for IPFD and 20.6% for IT

-AEB in IPFD patients not receiving vs receiving prophylaxis (40.9% vs 21%, $p<0.01$).

-No difference in ITs (AEB 12.7% without, 14.9% with prophylaxis).

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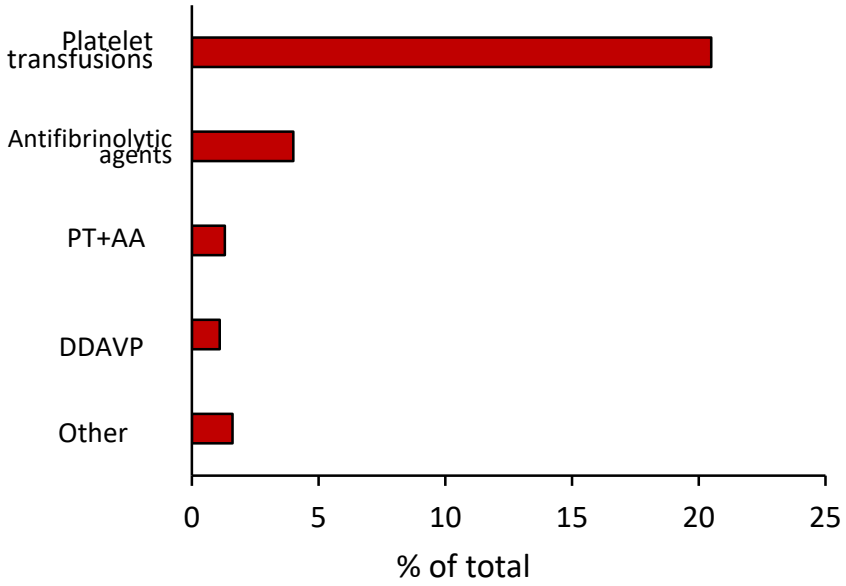
Orsini S et al., Haematologica 2017;102(7):1192-1203

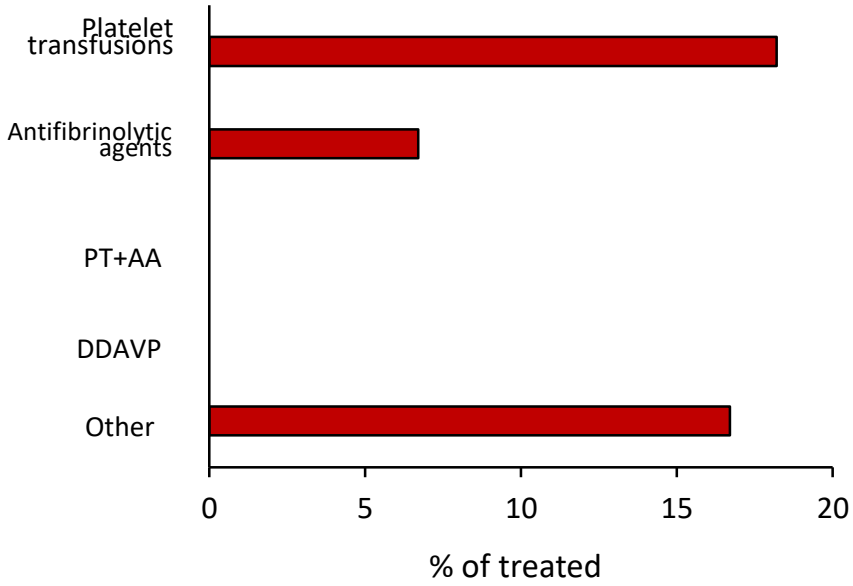
The SPATA Study: IT subgroup

Prophylactic antihemorrhagic preparation and outcome

Antihemorrhagic pre-operatory prophylaxis



AEB depending on antihemorrhagic prophylaxis



OTHER: composition of two or more; cryoprecipitate; fibrin-glue, fibrinogen, FFP, IVIG, local hemostatic agent, suture, local tranexamic acid

-Prophylaxis given in 20.6% for IPND

-No difference for AEB in IT patients not receiving vs receiving prophylaxis (12.7% vs 14.9%, p=ns).

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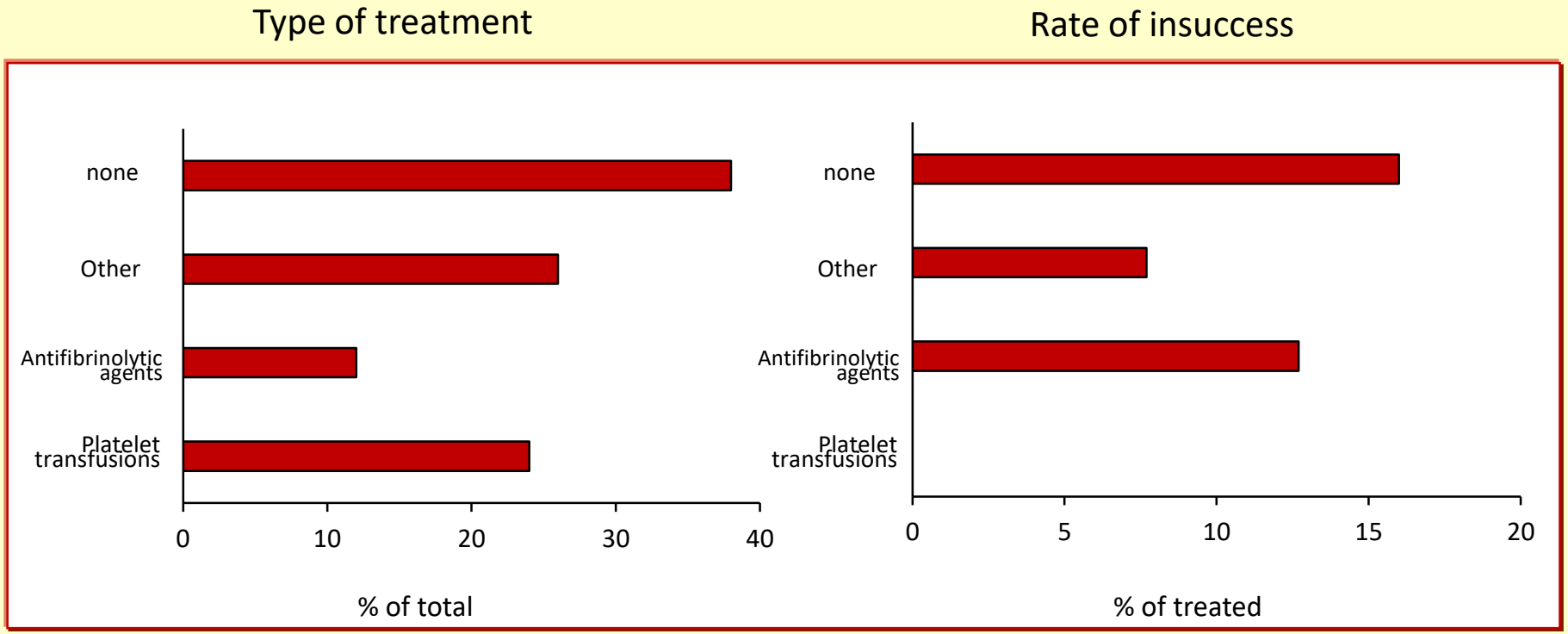
The SPATA Study: IT subgroup

Emergency treatment of surgery-associated bleeding



Other treatments: surgical hemostasis, packing, compression, stiches
Excessive bleedings requiring treatment: 31

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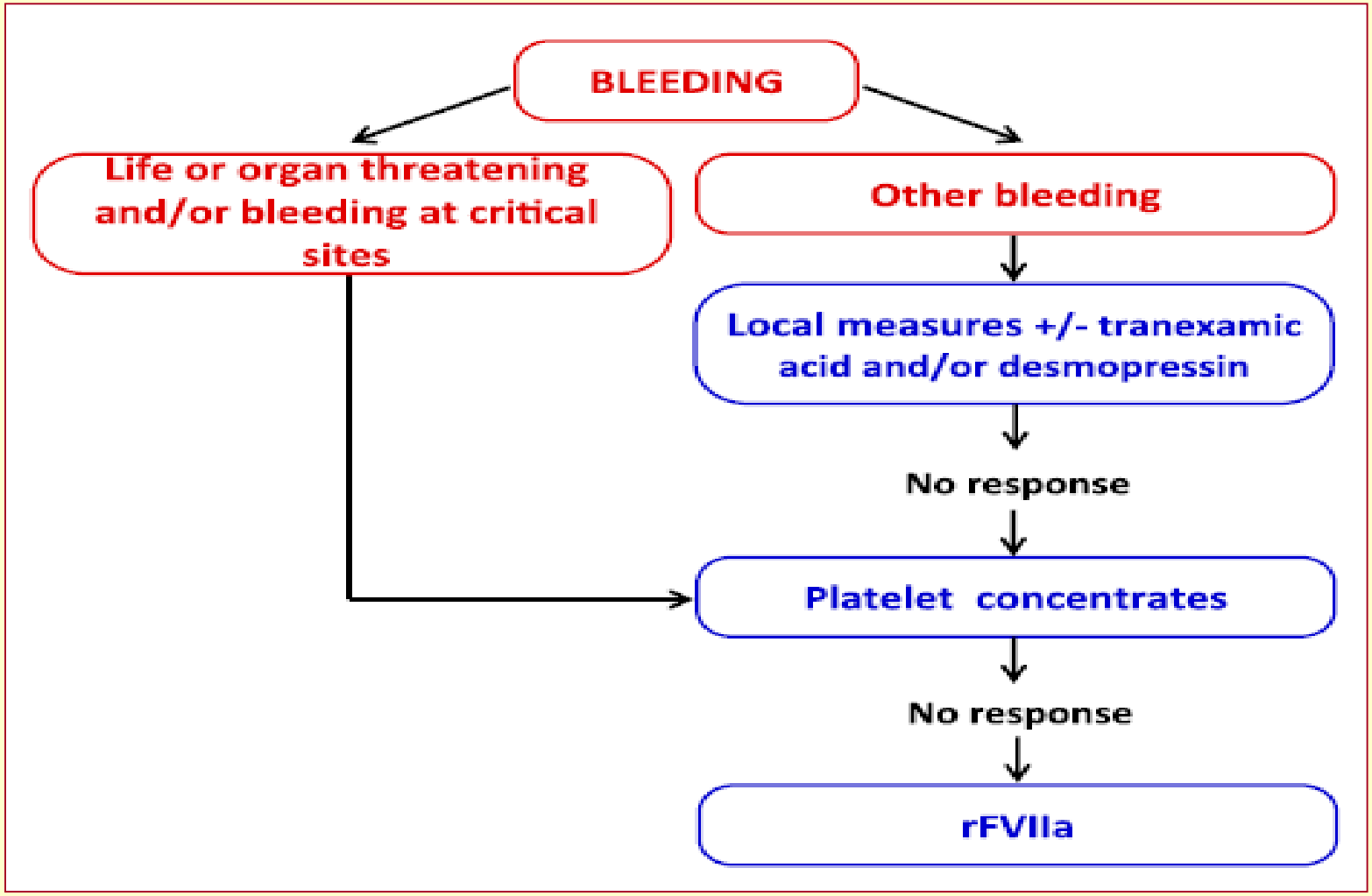
Approach to the management of bleeding episodes



Noris P et al, Haematology 2017, 1:385-399

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Conclusions

- Inherited thrombocytopenias are an heterogeneous and continuously expanding group of platelet disorders
- They may be asymptomatic, infrequently are severely haemorrhagic but some forms may be associated with bleeding during invasive procedures and childbirth
- ITs are rather often associated with syndromic manifestations which may severely affect prognosis
- Advances in treatment have made the management of these disorders more effective

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Acknowledgments

"Platelet Lab" – Perugia

- Loredana Bury
- Emanuela Falcinelli
- Giuseppe Guglielmini
- Annamaria Mezzasoma

ISTH SSC Platelet Physiology

Carlo Balduini and the

Registro Italiano della Malattia MYH9-correlata

William Ouwehand and Kathleen Freson for the Thrombogenomics and BRIDGE Consortia

Grant support:

TELETHON GMR22T1086 to PG

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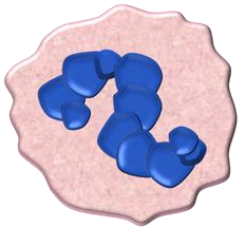
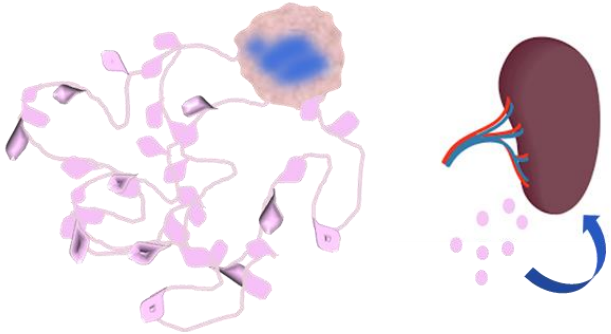
PATHOGENIC MECHANISMS OF INHERITED THROMBOCYTOPENIAS

Defective megakaryocyte maturation



ANKRD26, ETV6, FLI1, FYB, GATA1, GFI1B, HOXA11, MECOM, MEIS1, IKZF5, MPL, NBEAL2, NFE2, RBM8A, RUNX1, THPO

Defective platelet production / increased clearance



ACTB, ACTN1, ARPC1B, CYCS, DIAPH1, FLNA, GP1BA, GP1BB, GP9, ITGA2B, ITGB3, KDSR, MYH9, MPIG6B, PRKACG, STIM1, TRPM7, TPM4, TUBA4A, TUBB1, WAS

Unknown pathogenic mechanism

ABCG5, ABCG8, CDC42, GNE, NOTCH3, SLNF14, SRC, PTPRJ

TIER-1 genes
TIER-2 genes

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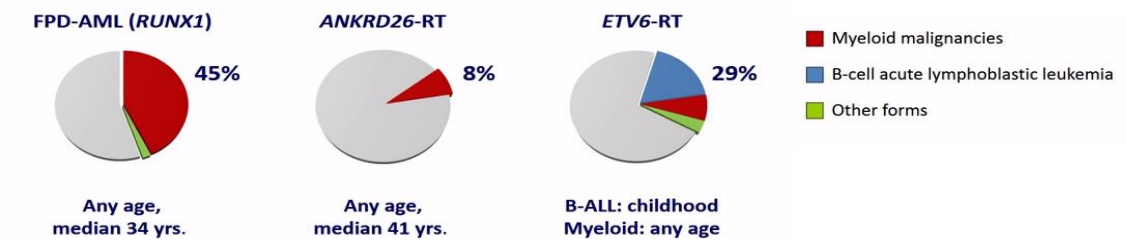
Bury L et al., J Clin Med 2021, 10:533

Inherited thrombocytopenias predisposing to hematological malignancies

- THC2: thrombocytopenia caused by variants at the 5'-UTR of *ANKRD26*
- Familial platelet disorder associated to acute myeloid leukemia (FPD/AML): variants in *RUNX1*
- Thrombocytopenia associated with variants in *ETV6*

	ANKRD26-RT	FPD/AML	*ETV6*-RT
Gene	*ANKRD26*	*RUNX1*	*ETV6*
Relative frequency (% of known forms)	18%	3%	5%
Transmission	AD	AD	AD
Thrombocytopenia	Mild/moderate	Mild/absent	Mild
Platelet size	Normal	Normal	Normal
Platelet function	Normal	Abnormal*	Normal
Bleeding tendency	Absent/mild	Absent/moderate	Absent/mild

* Heterogeneous abnormalities, most frequently delta-granule deficiency/release defect



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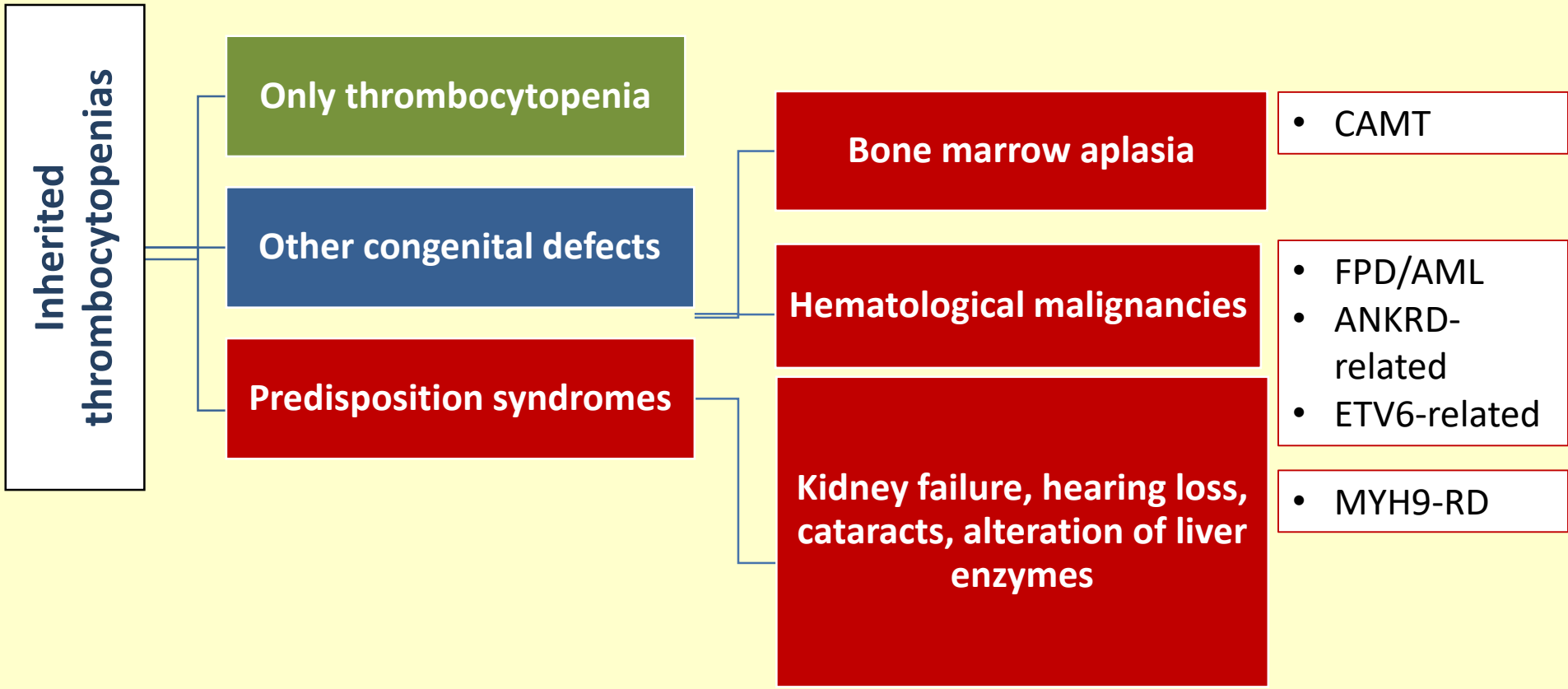
Inherited thrombocytopenias
Predisposition syndromes



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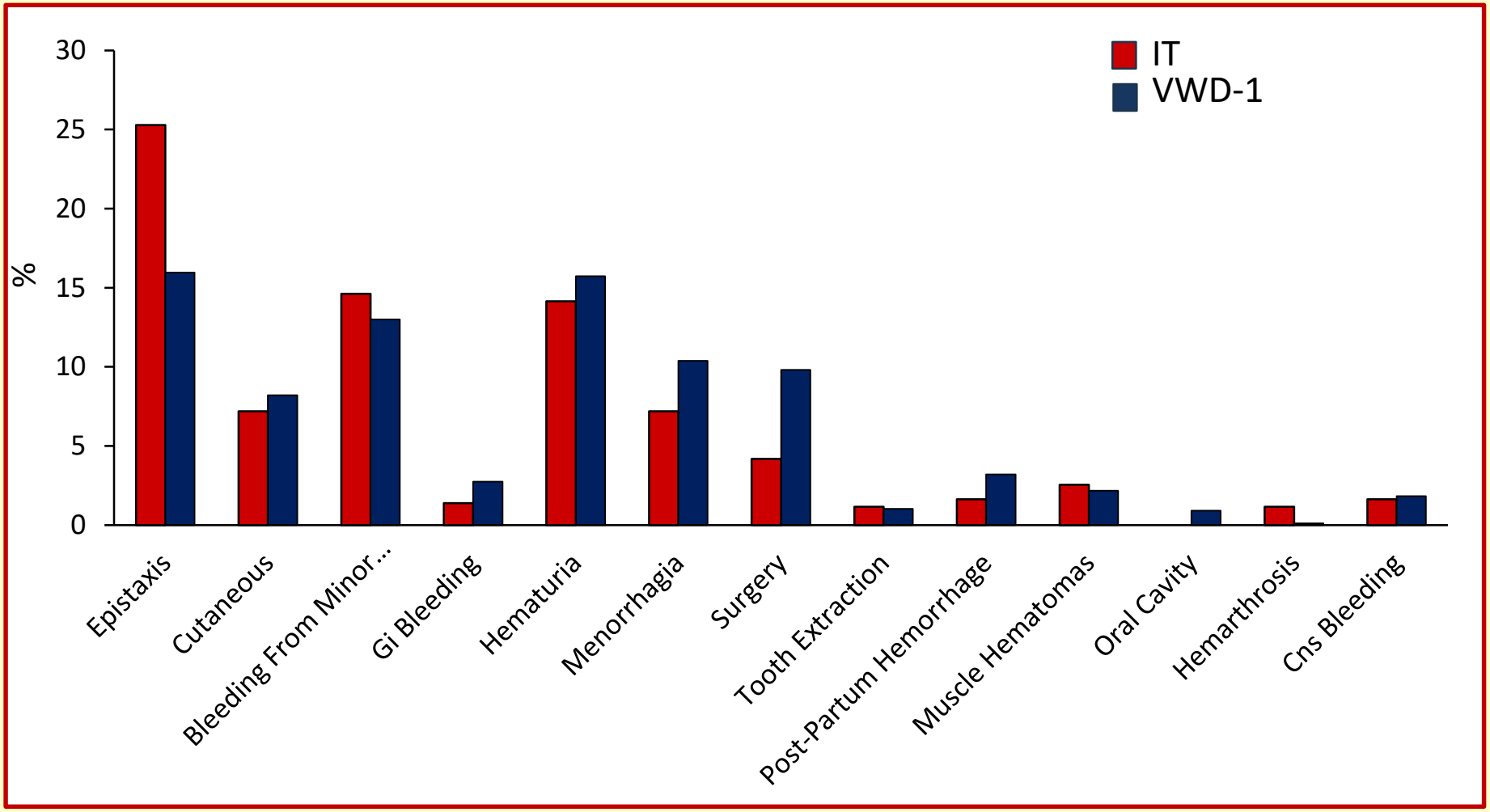
Frequency of clinically significant bleeding symptoms (score≥2) in ITs, and VWD-1



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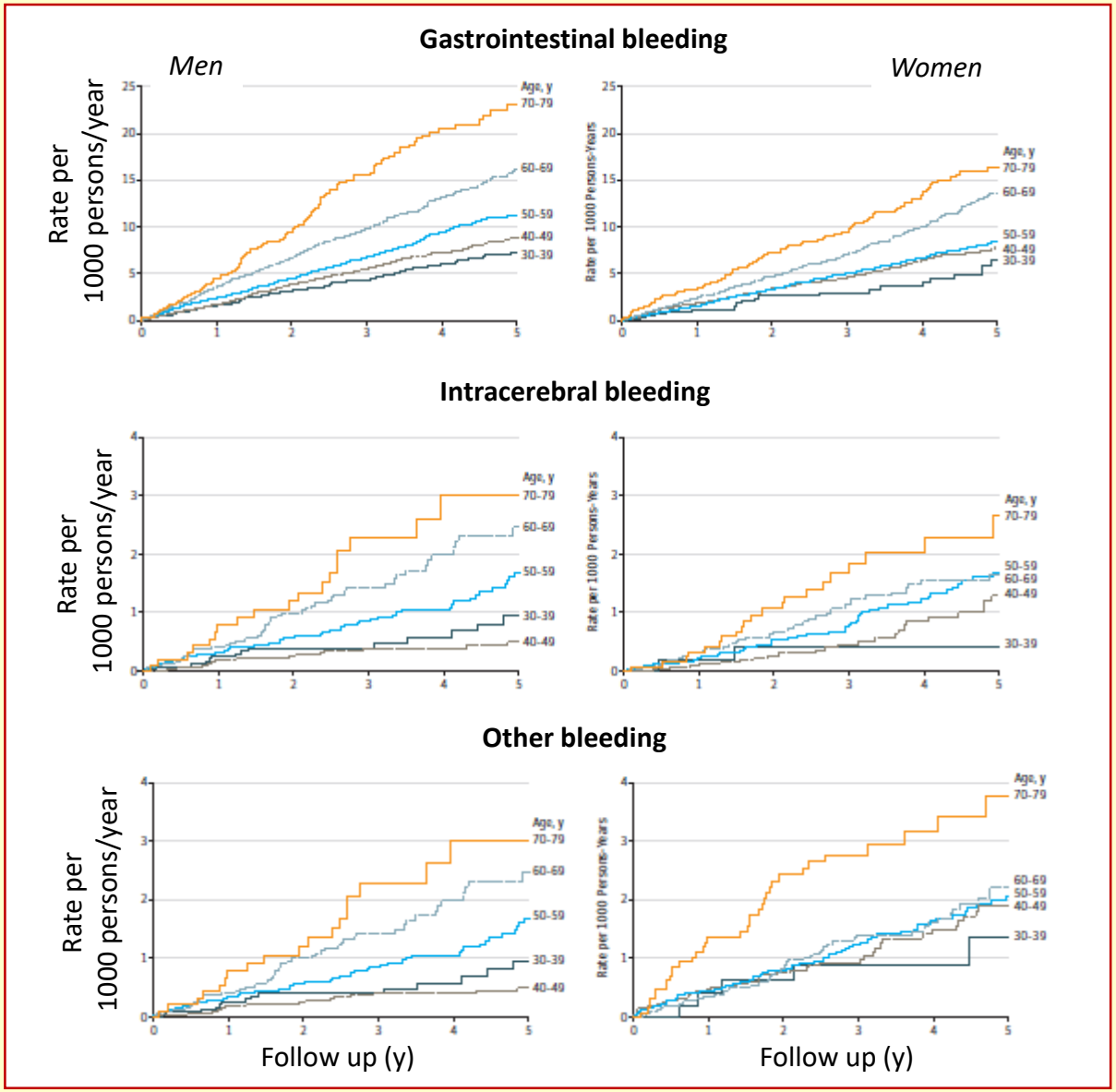
Gresele P et al., J Thromb Haemost 2020, 18:732

Annual risk of major bleeding among persons not receiving antithrombotic therapy



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Selak V et al., JAMA 2018; 319:2507

Prevalence of IPD

- Prevalence of ITs is at least 2.7/100,000 (Balduini C et al. *Hamostaseologie* 2012;32:259-270).
- Prevalence of IPFDs from 2/1,000,000 (Israels SJ et al. *Pediatr Blood Cancer* 2011; 56:975-83) to more than 1/100 (Quiroga T et al. *Haematologica* 2007;92:357).
- Annually at least 14,000 patients worldwide undergo investigations for a suspected IPFD and over 5,600 new diagnoses are made (Gresele P et al. J *Thromb Hemost* 2014;12:1562-9).
- Exome sequencing of 125,748 individuals (general population) from the GnomAD database shows that 0.329% have a clinically meaningful LOF variant of a platelet function gene (Oved JH, J Thromb Haemost 2021,19:248).
- Between 2007 and 2019 the number of patients with an IPD registered in the UK-haemophilia centers database rose by 165% (VWD +8%, haemophlia +11%) (Gomez Blood Review 2022; 56:100972)

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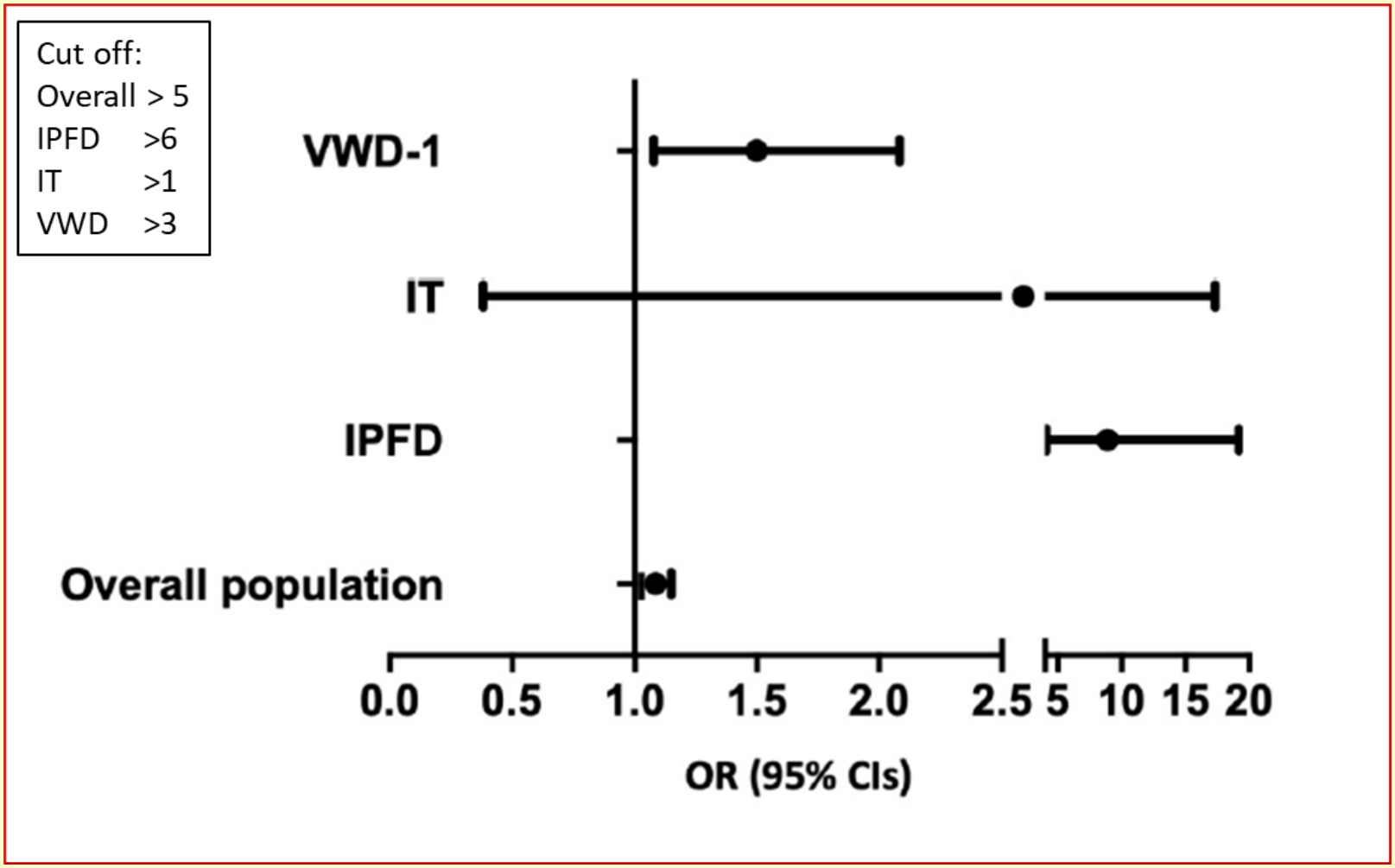
Likelihood to suffer a bleeding event on follow up for subjects with a BS above the identified cut-off values



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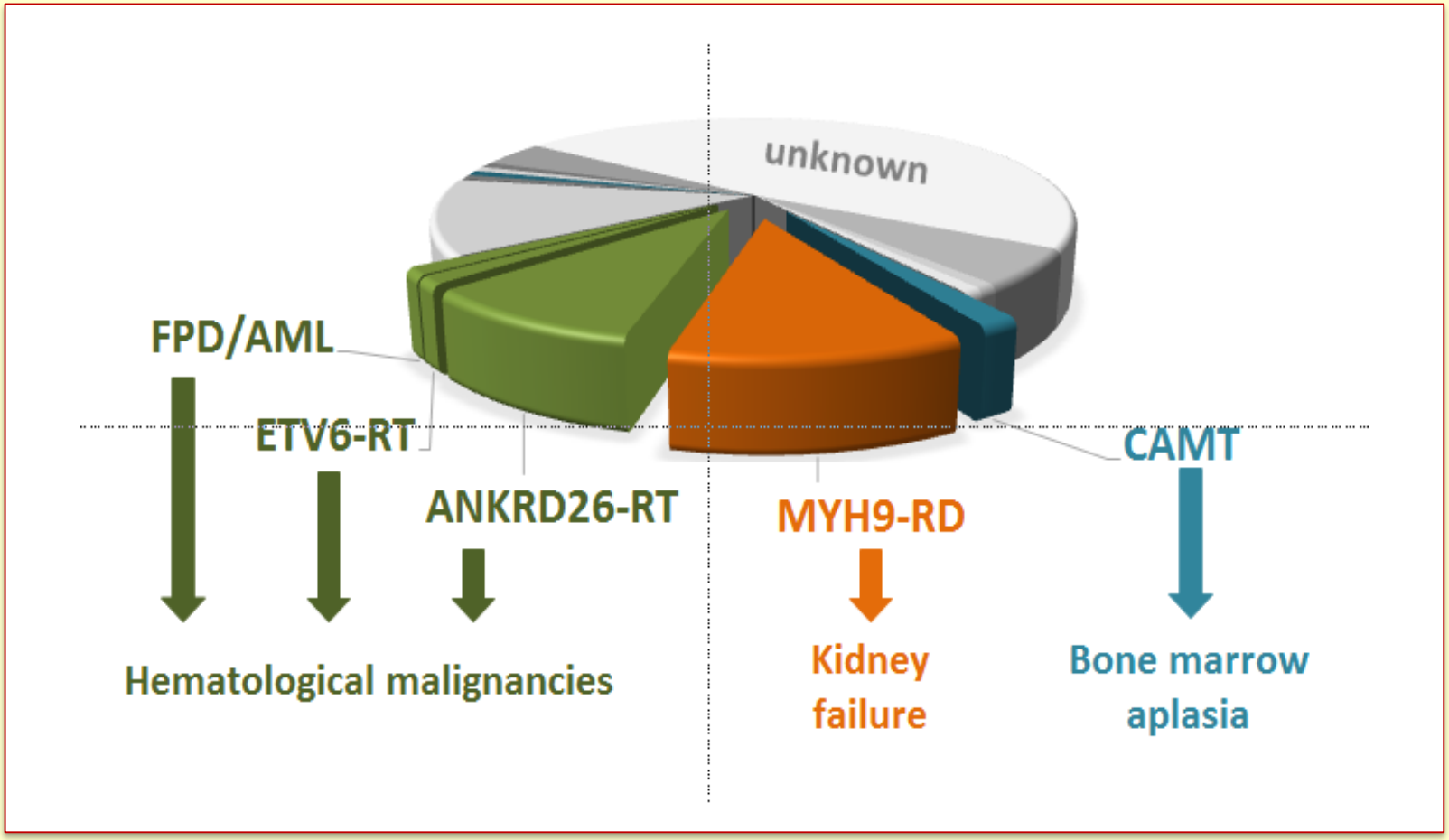
Gresele P et al., J Thromb Haemost 2021; 19(5):1364

50% of patients with known inherited thrombocytopenias are predisposed to acquire additional, severe disorders



We must recognize them because they require personalized follow-up and treatment

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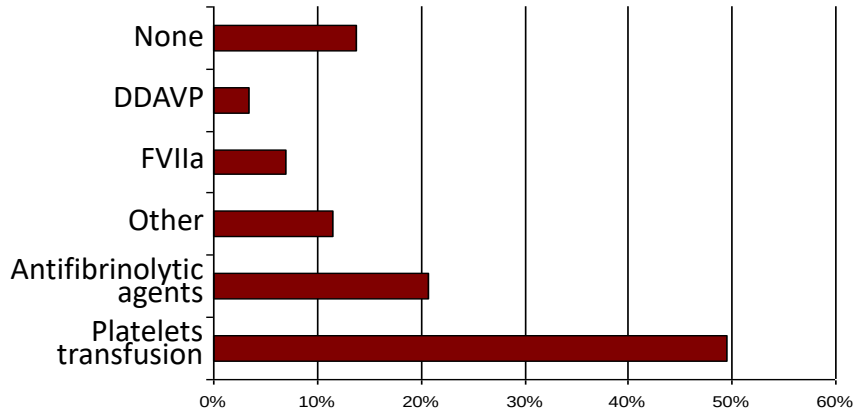
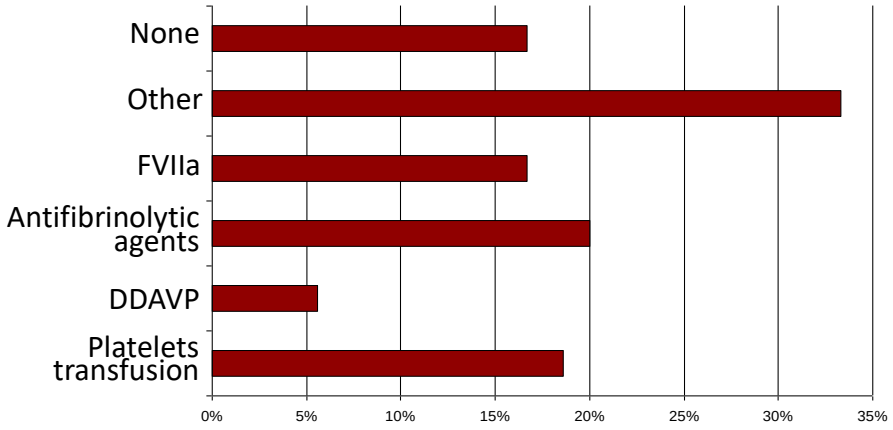
Emergency treatment of surgery-associated bleeding

Type of treatment



OTHER: cryoprecipitate (CYRO), Ice, Novoseven, Sandostatine IV, stitches, surgery, spontaneous resolution

Rate of insuccess



1 Glanzmann thrombastenia patient died

Excessive bleedings requiring treatment: **87**

Orsini S et al., Haematologica 2017;102(7):1192-1203

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