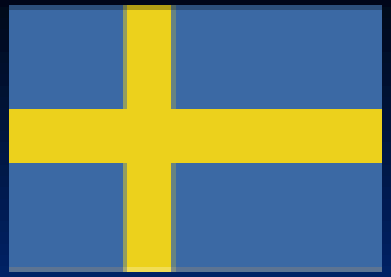
11th Hemostasis Seminar
1-2 October 2019, Bucharest, Rumenia

Clinical and Laboratory aspects of von Willebrand disease

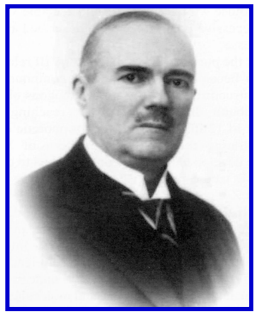
Giancarlo Castaman

Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy



SVEZIA

FINLANDIA



Family S, Föglö Island

Klas Oskar
78 y

Augusta
74 y

Dagny
2y

Anna
4 y

Thomas
31 y

Dagny
2 y

Harald
44 y

Sylvia
41 y

Runar
40 y

Hjördis
13 y

Greta
5 y

Gerda
34 y

Lars
29 y

Helga
17 y

Viking
10 y

Robert
17 y

Birgitta
15 y

Roger
13 y

Cecilia
10 y

Tage
9 y

Börje
6 y

Jan Uluf
1 y

Anders
8 y

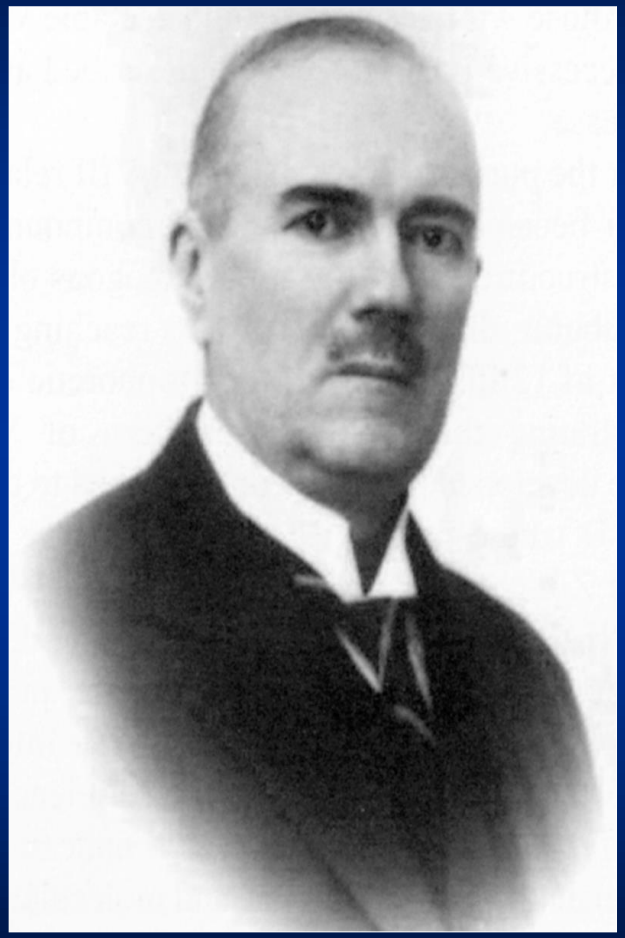
Monika
4 y

Lars-Uwe
1 y

Severe bleeding

Mild or dubious bleeding symptoms

Von Willebrand disease (VWD) is an inherited bleeding disorder due to a quantitative and/or qualitative deficiency of von Willebrand factor, first identified by E. von Willebrand in 1926



FINSKA LÄKARESÄLLSKAPETS
HANDLINGAR
REDIGERADE AV
PROF. RICHARD SIEVERS
BAND LXVIII
1926 FEBRUARI 1926

INNEHÅLL:

Originalartiklar.

E. A. v. Willebrand, Hereditär pseudohemofili. (Från Diakonissjukhusets i Helsingfors medicinska avdelning. Docent E. A. v. Willebrand). (Med 3 figurer i texten) 87
T. W. Tallqvist, Syfilis och njurar 113
Armas Gräsbeck, Tvenne fall av enterokystom. (Från II Kirurgiska kliniken i Helsingfors, prof. R. Faltin, och Wiborgs länssjukhus, prof. P. W. Granberg). (Med 2 figurer i texten) 130

Deutsche Referate.

S. 111, 128, 140.

Översikter.

Arthur Clopatt, Terapeutiska irrläror 142

Smärre meddelanden och referat.

Esther Gustavson, Löwy's metod för bedömandet av de röda blodkropparnas storlek. (Från II Medicinska kliniken i Helsingfors). (Med 5 figurer i texten) 152
Gaston Parturier, Séméiologie biliaire. (Ref. av Jarl Hagelstam) 157
Knud Faber, Tuberkulosen i Danmark. (Ref. av R. Sievers) 164

Litteraturanmälningar.

O. Schauman † och **F. Saltzman,** Die perniziöse Anämie. (Rec. av Oskar Mustelin) 171
Arnold Josefson, Vad betyda insöndringsorganen för vår kropp och själ? (Rec. av M. Savolin) 173

Forts. å följ. sida.

HELSINGFORS 1926
MERCATORS TRYCKERI AKTIEBOLAG

ORIGINALARTIKLAR.

(Från Diakonissjukhusets i Helsingfors medicinska avdelning.
Docent E. A. v. WILLEBRAND.)

Hereditär pseudohemofili.

Av

E. A. v. Willebrand.

(Med 3 figurer i texten.)

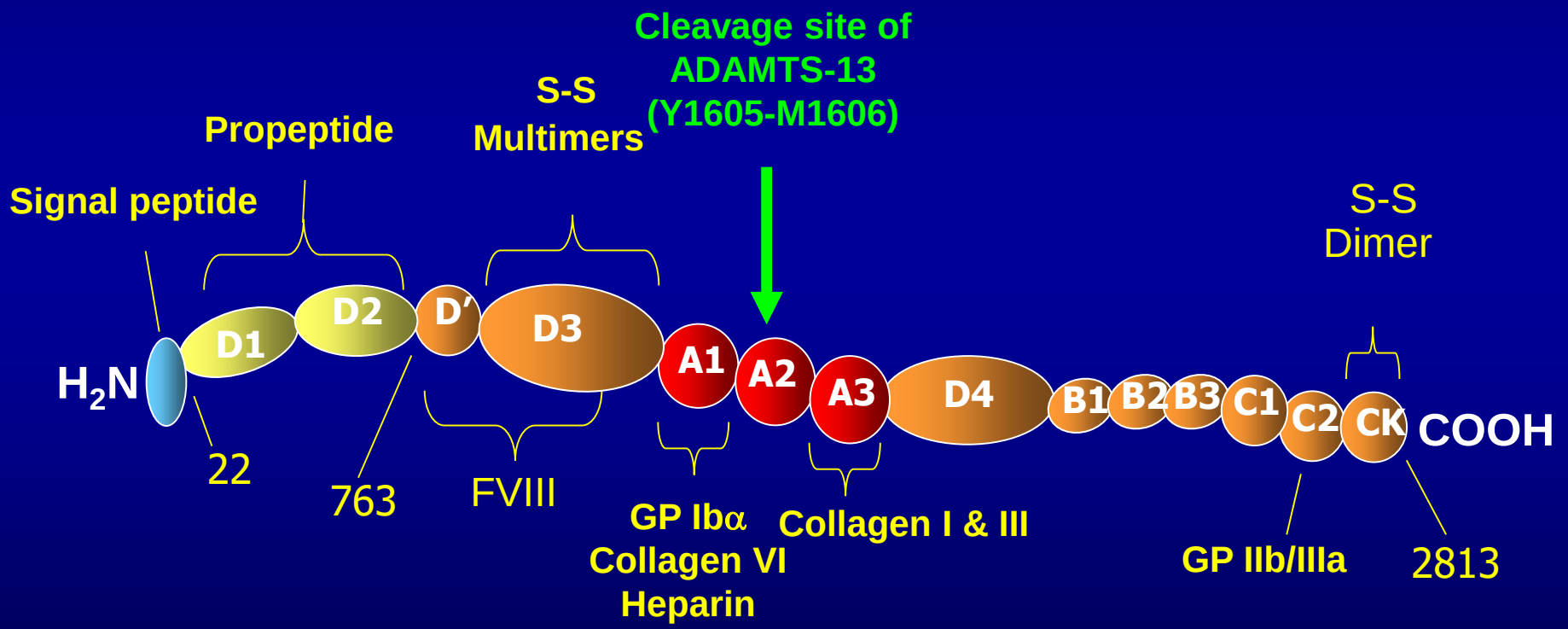
1. Sjukdomsbegrepp. Tidigare observerade fall.

I sitt nya stora arbete över de hemorragiska diateserna framhåller E. FRANK (Breslau), att den klassiska hemofilien är en så exkvisit hereditär—familjär anomali, att det kan ifrågasättas, huruvida över huvud sporadiska fall av sjukdomen existera. Däremot är, säger han, den klassiska trombopenien så utpräglat sporadisk, att man kan diskutera, om en familjär form av densamma alls förekommer. Med trombopeni avses här den sjukdom, som sedan gammalt bär namnet morbus maculosus WERLHOFI eller purpura haemorrhagica och som på senaste tid av FRANK och en del andra forskare betecknats såsom essentiell trombopeni.

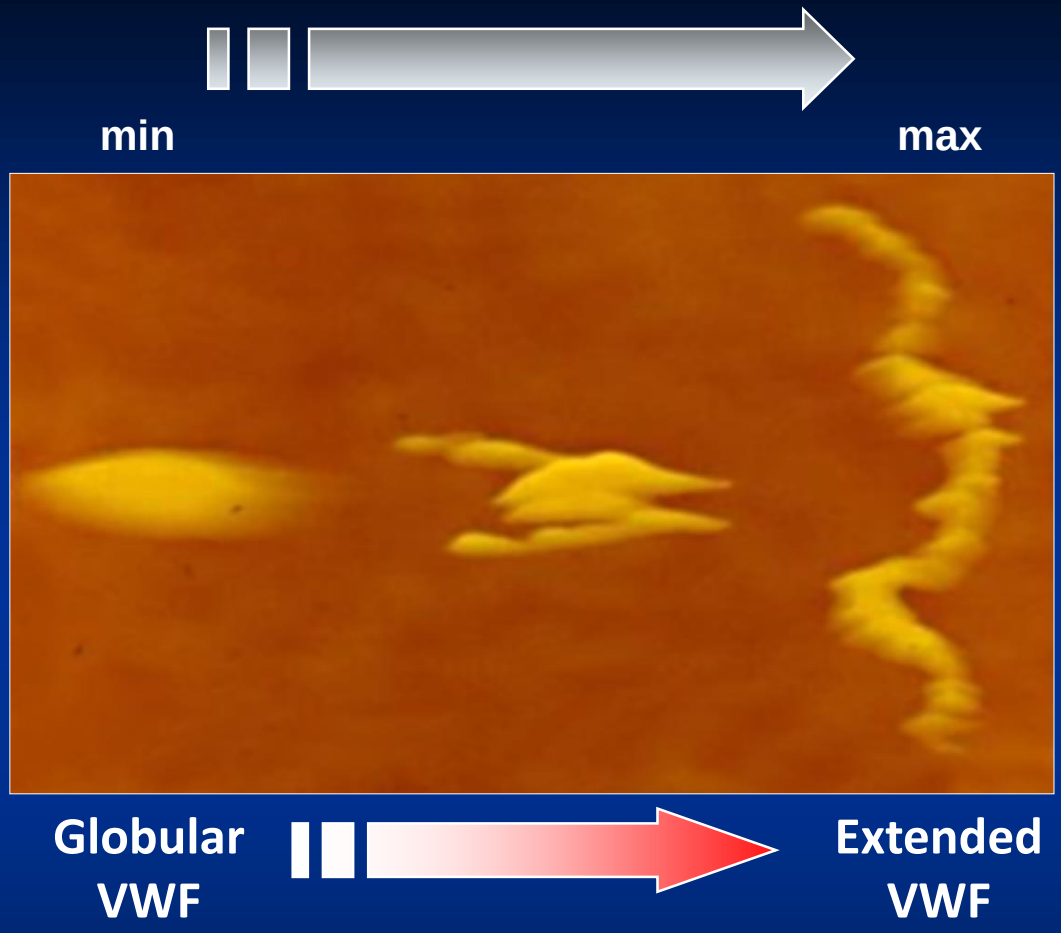
Hittills har man velat betrakta ärftlig blödaresjukdom och hemofili såsom synonyma begrepp. Men om man genomögnar hithörande litteratur, skall man finna, om ock i ett fåtal fall, beskrivningar över en familjär form av hemorragisk diates, som redan därigenom skiljer sig från äkta hemofili att den även förekommer bland kvinnor och, såsom det tyckes, t. o. m. oftare än bland män. Men även i andra avseenden kan man draga en skarp gräns mellan ifrågavarande familjära lidande och hemofilien. Därom mera längre fram i kap. 6 om diagnosen.

Erik Adolf von Willebrand
(1870-1949)

VON WILLEBRAND FACTOR (VWF):
The role of ADAMTS-13-dependent proteolysis



SHEAR STRESS FORCES OF THE BLOOD



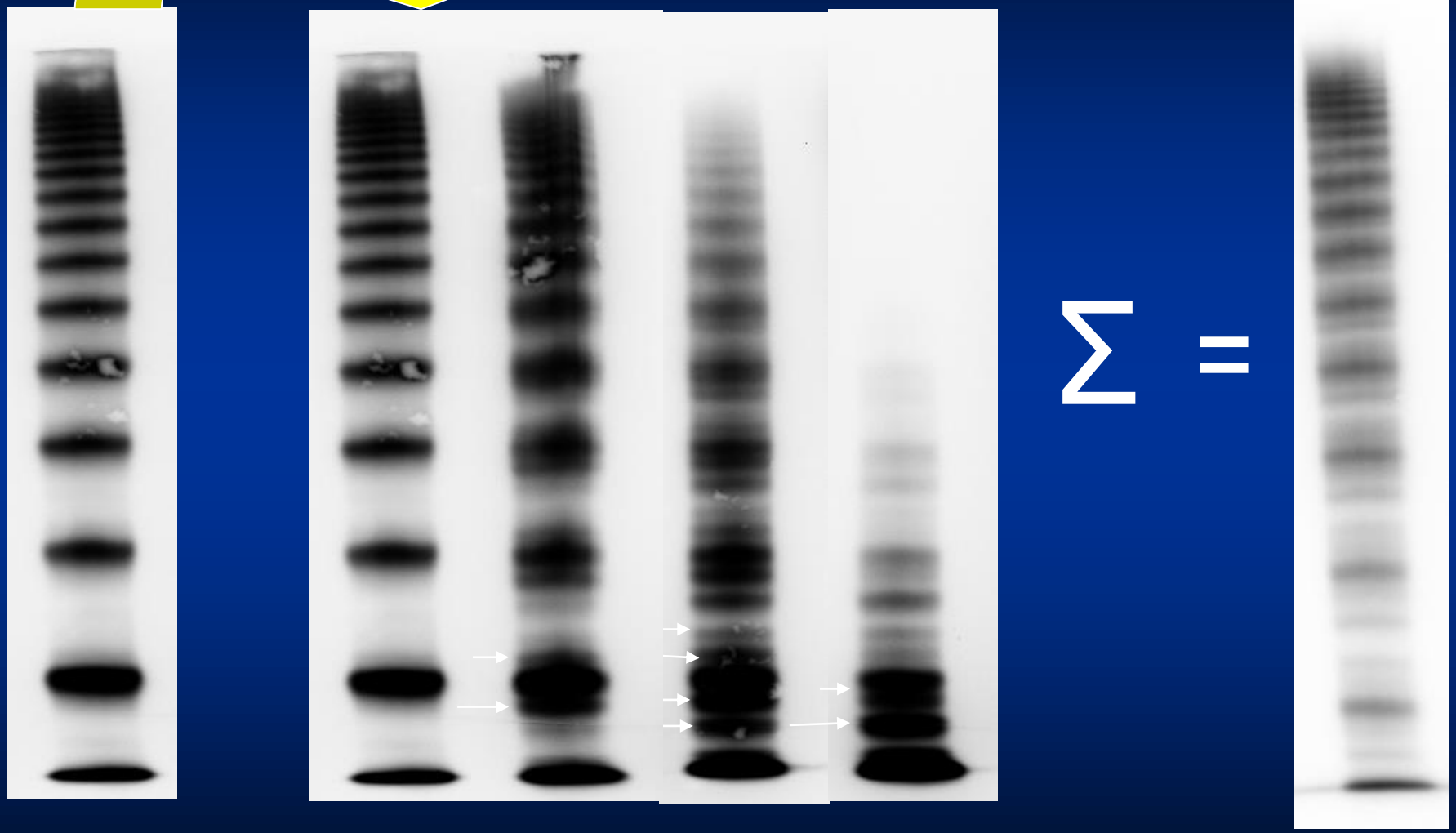
When shear stress is high enough to stretch VWF exposing the buried A2 domain, proteolysis is rapid (Dong et al, 2002)

Siedecki et al Blood 1996

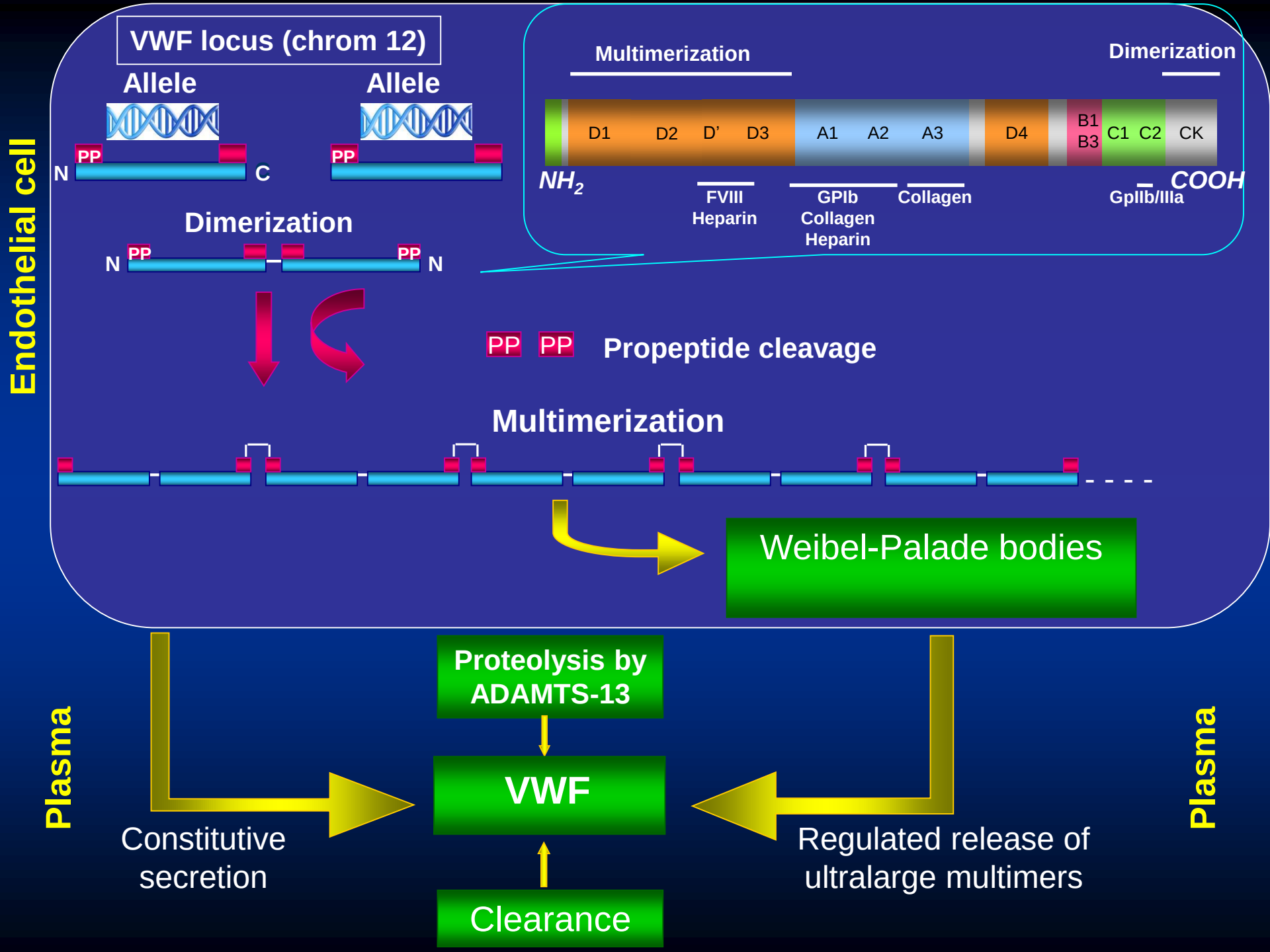
Synthesis

Proteolysis
(ADAMTS-13)

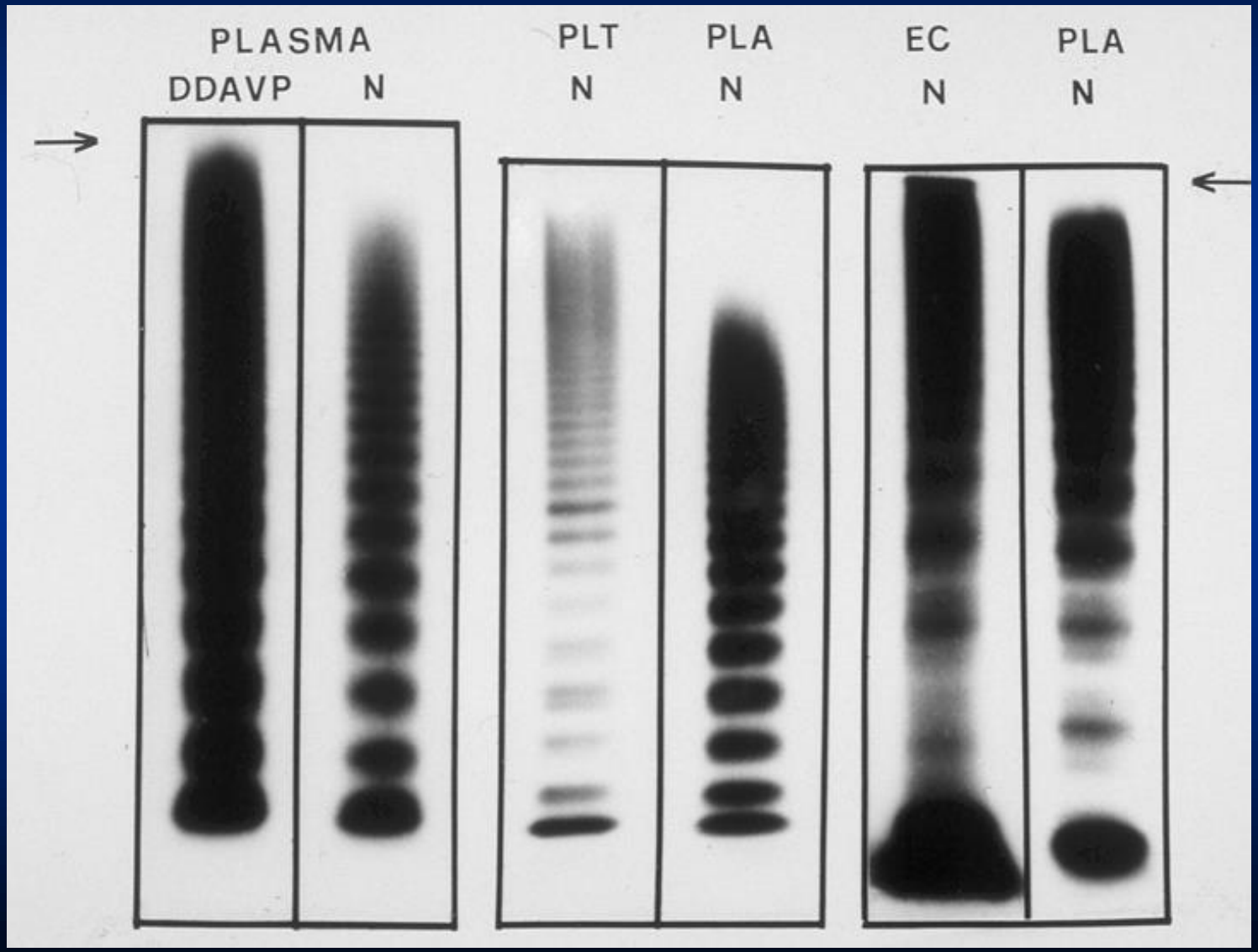
Steady state
(Normal Plasma)



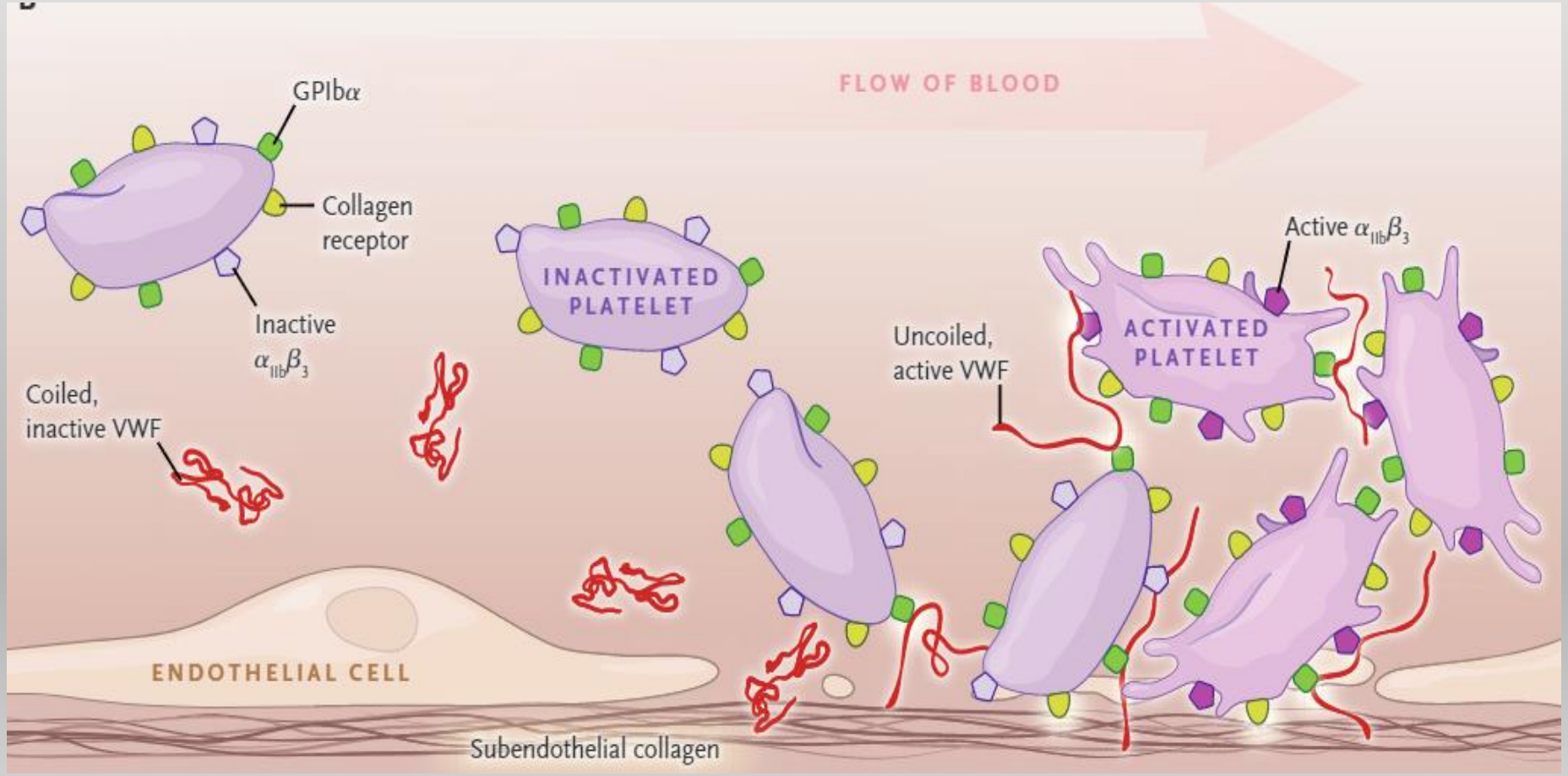
EC → Plasma


VWF locus (chrom 12)
Allele
Allele
PP
N
C
PP
Multimerization
Dimerization
D1
D2
D'
D3
A1
A2
A3
D4
B1
B3
C1
C2
CK
NH2
COOH
FVIII
Heparin
GPIb
Collagen
Heparin
Collagen
GpIIb/IIIa
Dimerization
N
PP
PP
N
PP
PP
Propeptide cleavage
Multimerization
Endothelial cell
Weibel-Palade bodies
Proteolysis by
ADAMTS-13
VWF
Clearance
Plasma
Constitutive
secretion
Regulated release of
ultralarge multimers
Plasma

The multimeric composition of VWF



VWF Journey: From Inactive Globular Form to Activation of Platelets



Leebeek FWG, Eikenboom JCJ. N Engl J Med 2016;375:2067-80.

Von Willebrand Factor

- Multimeric, adhesive protein, composed of a series of dimers of mature subunits up to 20,000 Kd (multiplicative effect of binding activities)

- **Carrier of FVIII**: localization and prevention of inactivation by the Protein C system

- **Platelet adhesion** to the subendothelium at high shear stress flow (via Gp Ib, $\alpha_2\beta_1$)

- **Platelet-to-platelet cohesion and aggregation** in cooperation with fibrinogen (via Gp IIb/IIIa, $\alpha IIb\beta_3$)

Von Willebrand disease

- Bleeding disorder due to a quantitative or qualitative defect of VWF
- Depending on the particular defect the disease may be inherited either in a dominant or recessive manner
- The spectrum of clinical symptoms is greatly influenced by a wide variation in expressivity and penetrance

VWD is an inherited bleeding disorder due to a quantitative or qualitative defect of VWF

Bleeding disorder → Bleeding risk in
- propositus
- family members

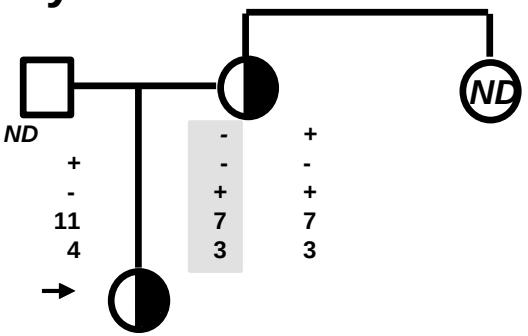
VWF deficiency → Quantity VWF:Ag (Type 1, 3)
Quality VWF:RCo/Ag (Type 2)
FVIII/VWF:Ag
Multimeric composition

Inheritance → Proven or inferred

GROUP A: Autosomal dominant inheritance, high penetrance and expressivity

(C1130F; Castaman et al, BJH 2000)

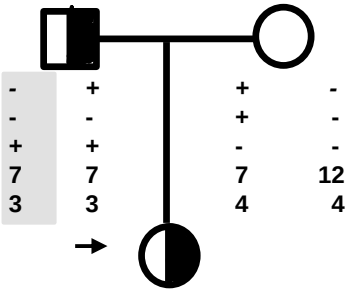
Family A



Rsa I	ND				-	+			
Rsa I	-	+			-	-			
Hph I	-	-			+	+			
VNTR I	10	11			7	7			
VNTR II	4	4			3	3			

Rsa I	-	+							
Rsa I	-	-							
Hph I	+	-							
VNTR I	7	10							
VNTR II	3	4							

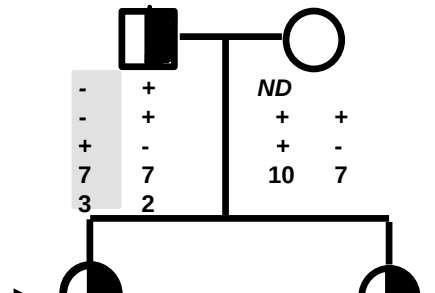
Family B



Rsa I	-	+			+	-			
Rsa I	-	-			+	-			
Hph I	+	+			-	-			
VNTR I	7	7			7	12			
VNTR II	3	3			4	4			

Rsa I	-	+							
Rsa I	-	+							
Hph I	+	-							
VNTR I	7	7							
VNTR II	3	4							

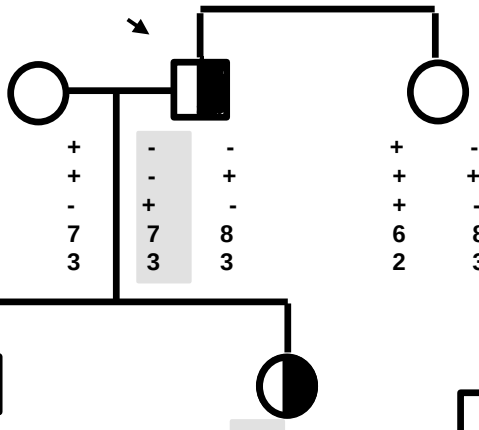
Family C



Rsa I	-	+			ND				
Rsa I	-	+			+	+			
Hph I	+	-			+	-			
VNTR I	7	7			10	7			
VNTR II	3	2							

Rsa I	-	-			-	-			
Rsa I	-	+			-	+			
Hph I	+	-			+	-			
VNTR I	7	7			7	7			
VNTR II	3	2			3	2			

Family D

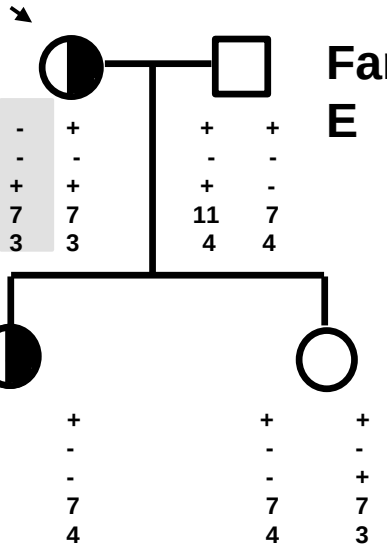


Rsa I	+	+	-	-	+	-			
Rsa I	+	+	-	+	+	+			
Hph I	-	-	+	-	+	-			
VNTR I	7	7	7	8	6	8			
VNTR II	3	3	3	3	2	3			

Rsa I	-	+			-	+			
Rsa I	-	+			-	+			
Hph I	+	-			+	-			
VNTR I	7	7			7	7			
VNTR II	3	3			3	3			

- Single *VWF* haplotype
- VWF ~ 10 U/dL
- BS > 5

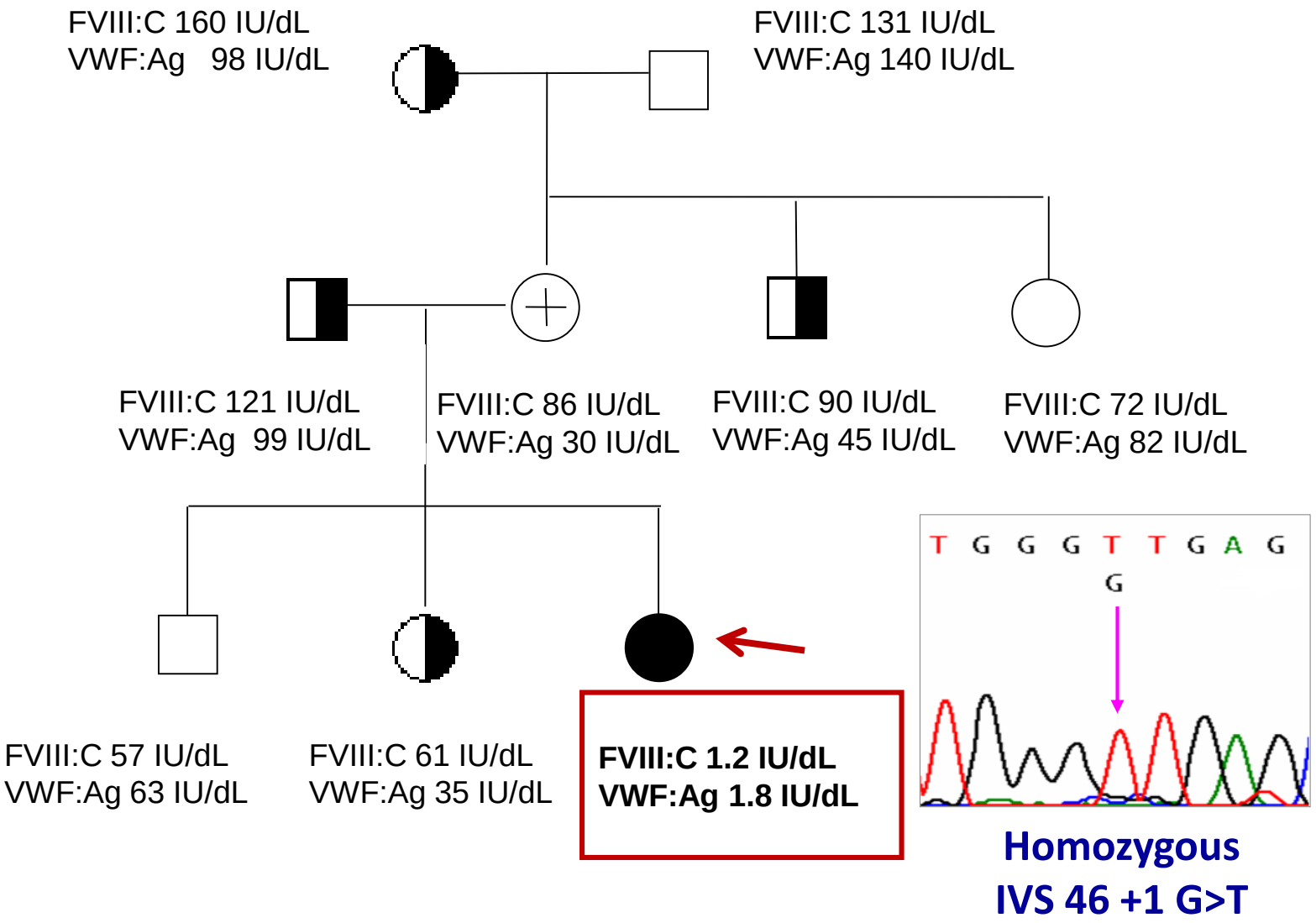
Family E



Rsa I	-	+			+	+			
Rsa I	-	-			-	-			
Hph I	+	+			+	-			
VNTR I	7	7			11	7			
VNTR II	3	3			4	4			

Rsa I	-	+			+	+			
Rsa I	-	-			-	-			
Hph I	+	-			-	+			
VNTR I	7	7			7	7			
VNTR II	3	4			4	3			

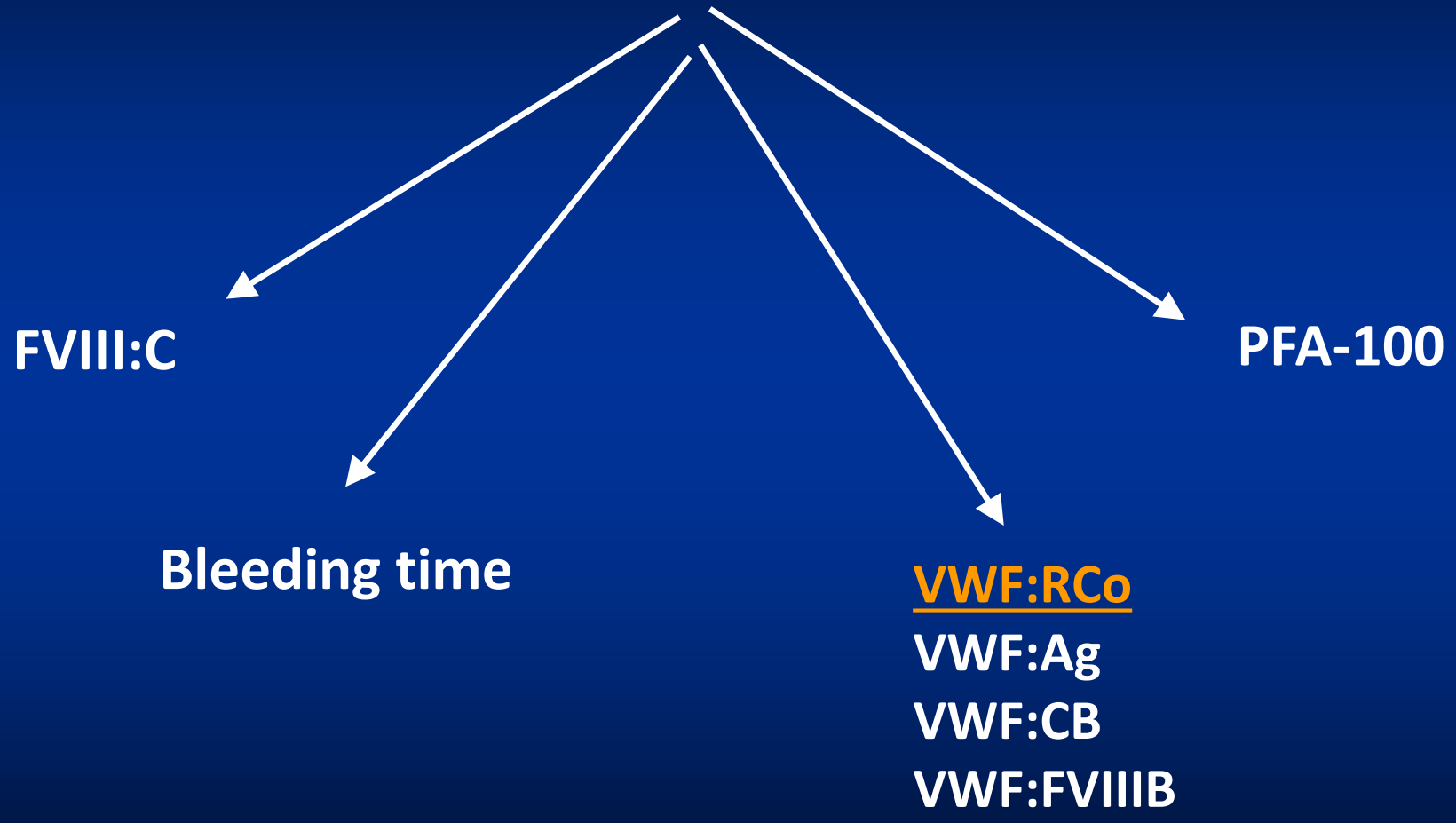
TYPE 3 VWD
(IVS46 +1, G>T n.7770+1)



HOW TO DIAGNOSE

VON WILLEBRAND DISEASE

The pleiotropic effects of von Willebrand factor



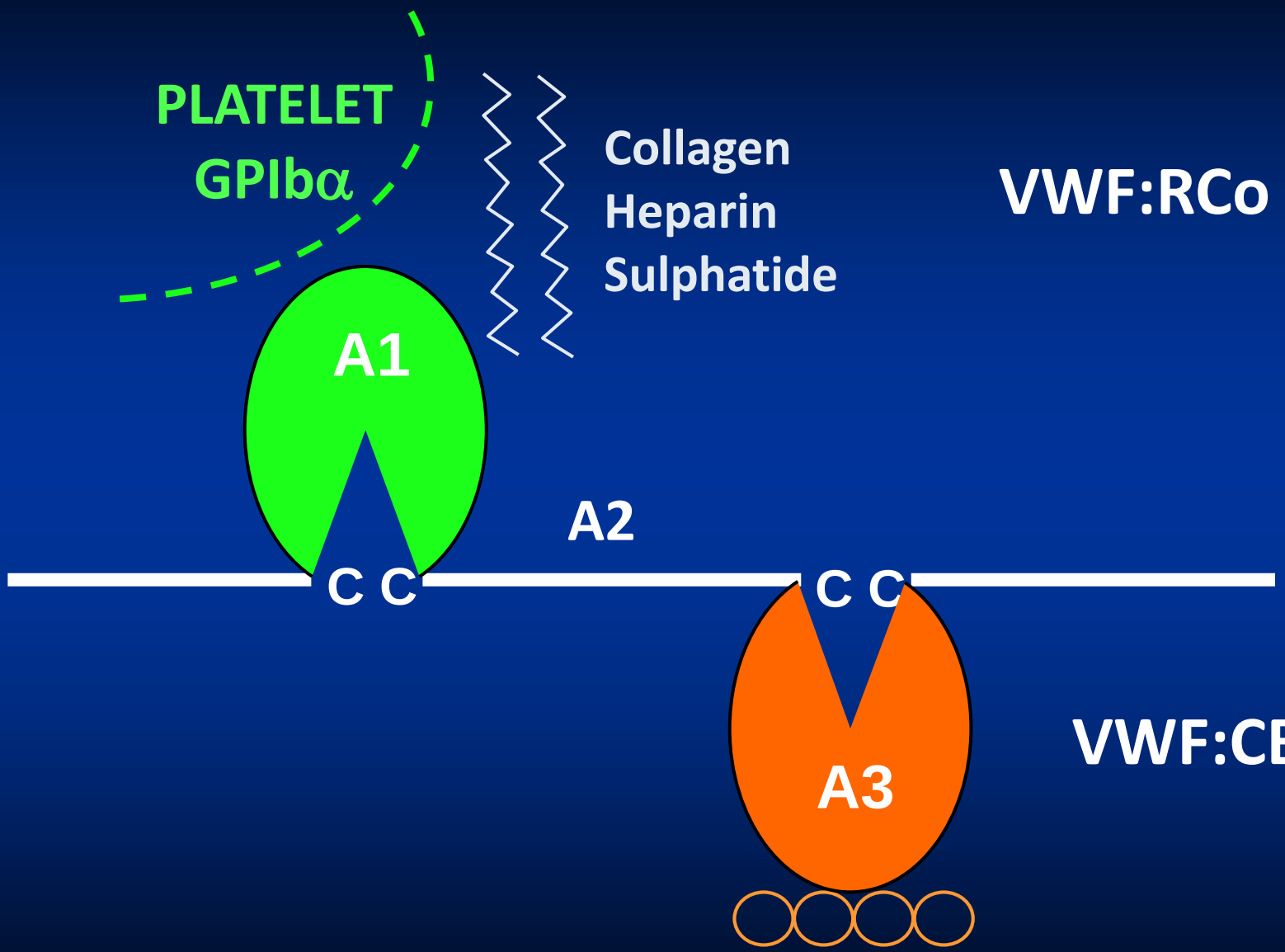
No single test reflects the whole spectrum of VWF activities

PHENOTYPIC DIAGNOSIS OF VWD

Tests in Use

- **Basic Tests**
  - –Platelet count
  - –BT (PFA-100)
  - –RIPA
  - –VWF:Ag
  - –VWF:RCo
  - –VWF:CB
  - –FVIII:C
- **Advanced tests**
  - –VWF/FVIII binding
  - –Platelet VWF assessment
  - –Multimer profile

ADHESION ACTIVITIES OF VWF



Why VWF:RCo as screening test for von Willebrand disease ?

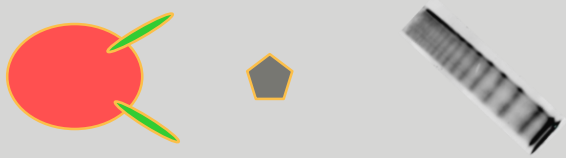
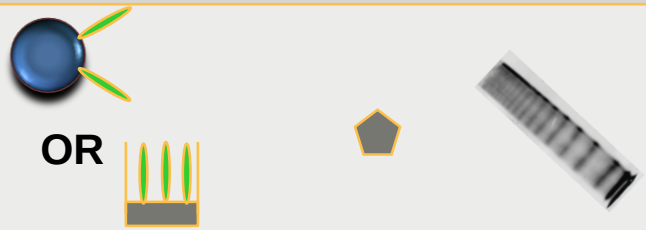
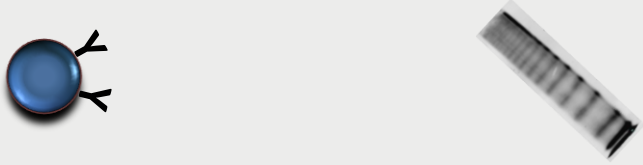
- Time-honored surrogate test to explore interaction with platelet GpIb

- Greater diagnostic sensitivity compared to classic tests for diagnosis of VWD

BUT

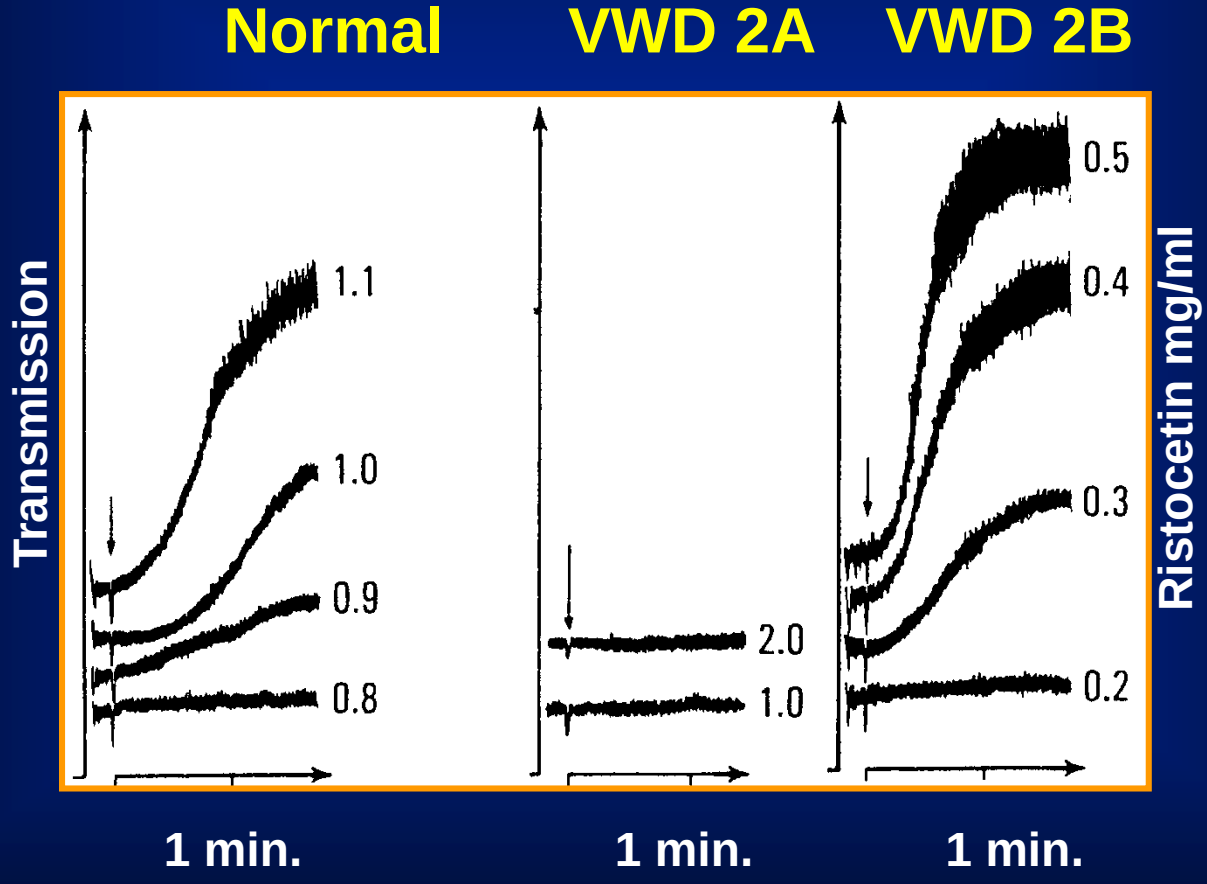
It does not reflect a true physiologic VWF function

Platelet-dependent VWF Activity: Nomenclature

Abbreviation	Description	Principle
VWF:RCo	Ristocetin cofactor activity: "traditional" assays that use ristocetin to induce binding to platelets	 Platelet + ristocetin + VWF
VWF:GPIbR	Assays based on ristocetin-induced binding of VWF to recombinant wild-type GPIb fragment	 OR rWT-GPIb + ristocetin + VWF
VWF:GPIbM	Assays based on spontaneous binding of VWF to gain-of-function mutant GPIb fragment	 OR Gain-of-function rGPIb +VWF
VWF:Ab	Assays based on binding of a monoclonal antibody to a VWF A1 domain epitope	 Anti-A1 MoAb + VWF

VON WILLEBRAND FACTOR: RIPA

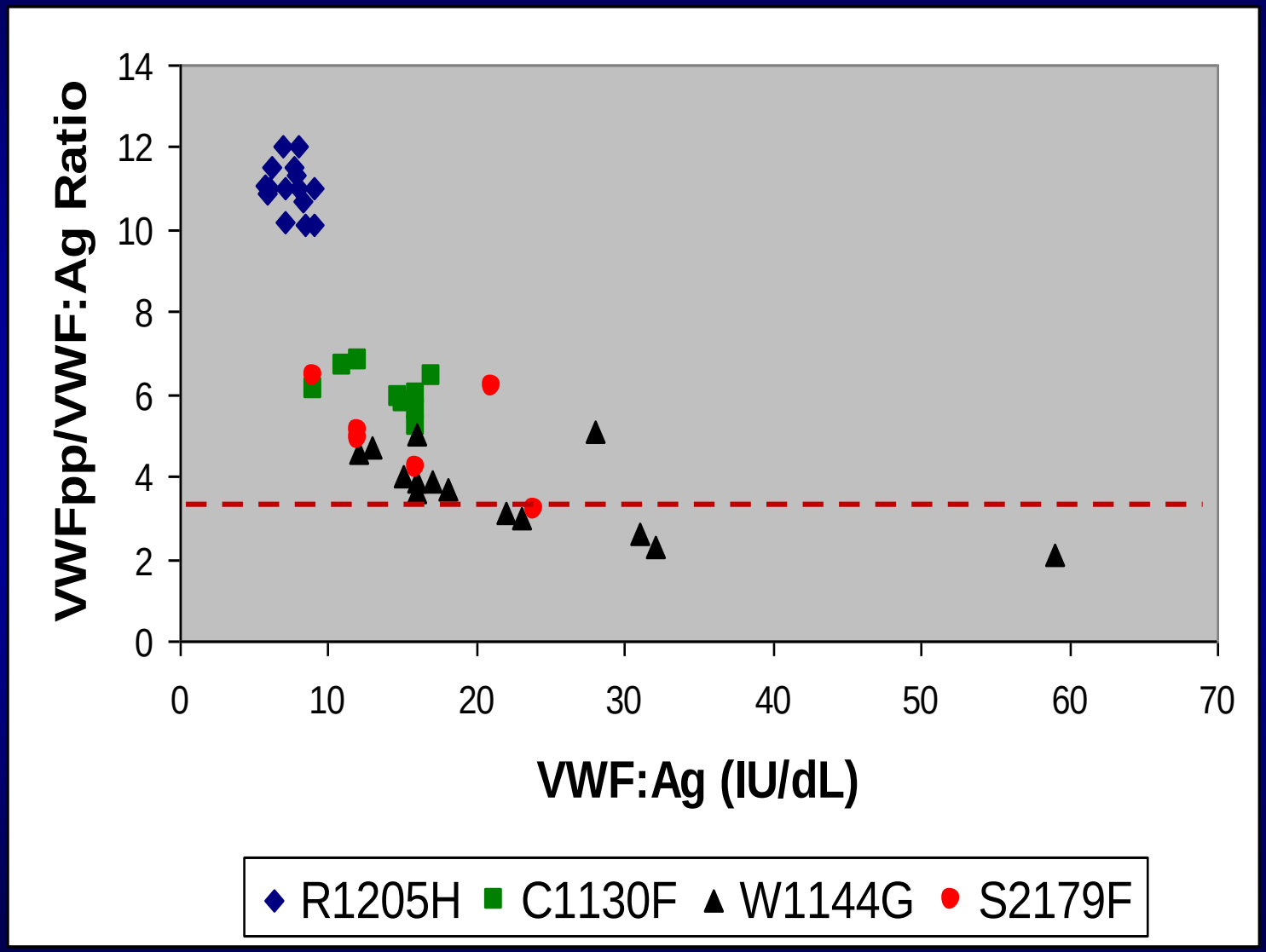
Ristocetin induced platelet agglutination



Platelet Rich Plasma from Patients + **RISTOCETIN [0.2-2.0 mg/ml]**

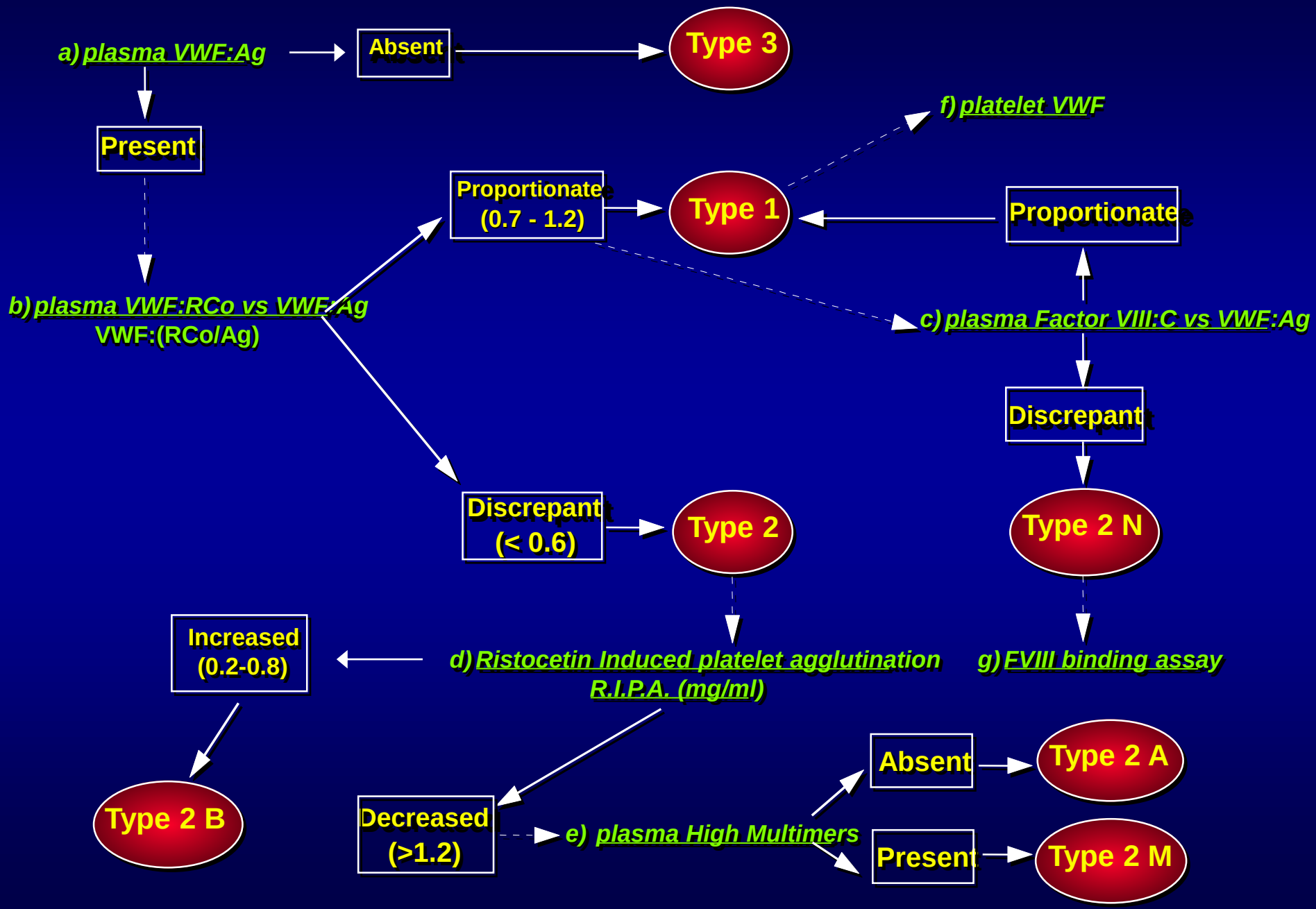
Test	Pathophysiologic significance	Diagnostic significance
Binding of VIII:C to VWF	Interaction of normal FVIII with patient plasma VWF	Allows the identification of type 2 N, characterized by low binding values and suspected in case of reduced VIII:C/VWF:Ag
Closure time PFA-100	Simulates primary hemostasis after injury to a small vessel	More sensitive than BT in screening for VWD; not tested in bleeding subjects without specific diagnosis; specificity unknown; poor sensitivity to mildly reduced VWF levels
Propeptide assay	Measures the amount of VWFpp released in plasma	Increased VWFpp/VWF:Ag ratio identifies patients with shortened VWF survival after desmopressin; still for research purposes

INCREASED VWF CLEARANCE: A SINGLE LABORATORY PHENOTYPE ?



Modified from Haberichter, 2008; Castaman, 2009

FLOW CHART FOR THE DIAGNOSIS OF A PATIENT WITH VWD:



Classification of von Willebrand disease

Quantitative deficiency *(RCo/Ag 0.6 – 1.2)*

- ***Type 1***: partial quantitative deficiency (~ 60-70 % of cases)
- ***Type 3***: virtual absence (~ 1-2 % of cases)

Qualitative deficiency*(RCo/Ag < 0.6; FVIII:C/VWF:Ag < 0.5)*

- ***Type 2***: dysfunctional VWF (~ 25-30 % of cases)

  - **A**: loss of high molecular weight multimers
  - **B**: increased affinity for platelet Gp Ib
  - **M**: normal multimers with low activity
  - **N**: reduced VWF-FVIII binding

VWD is a very heterogeneous bleeding disorder
Bleeding severity increases from type 1 to 3
and treatment differs

BLEEDING RISK IN VON WILLEBRAND DISEASE

Clinical phenotypes of VWD*

	Severe VWD (group A)	Intermediate VWD (group B)	Mild VWD (group C)
Symptoms	Manifest bleeding	Intermediate	Mild or very mild
Cosegregation (linkage) of symptoms with low VWF/haplotype	Invariable	Variable	Inconsistent
VWF levels	About 10 IU/dL or less	About 30 IU/dL	30–50 IU/dL
Diagnosis	Easy	Repeated testing needed	Not always possible; not clinically useful in most cases
Epidemiologic ascertainment	Referral-based: appropriate	Referral-based: underestimated	Cross-sectional: overestimated

*Castaman & Rodeghiero in «Textbook of Hemophilia», 2013

Patients with “low” VWF: >30 & <50 IU/dL

- More frequently O blood type
- Mostly type 1 VWD pattern
- Probands more symptomatic than relatives
- Genetic segregation and putative mutations less likely

Quantifying the bleeding history

- The presence of bleeding symptoms is mandatory for the diagnosis of VWD

- The use of a standardized questionnaire has allowed quantification of the bleeding history into a quantitative bleeding score (BS)

Grading of each bleeding symptom

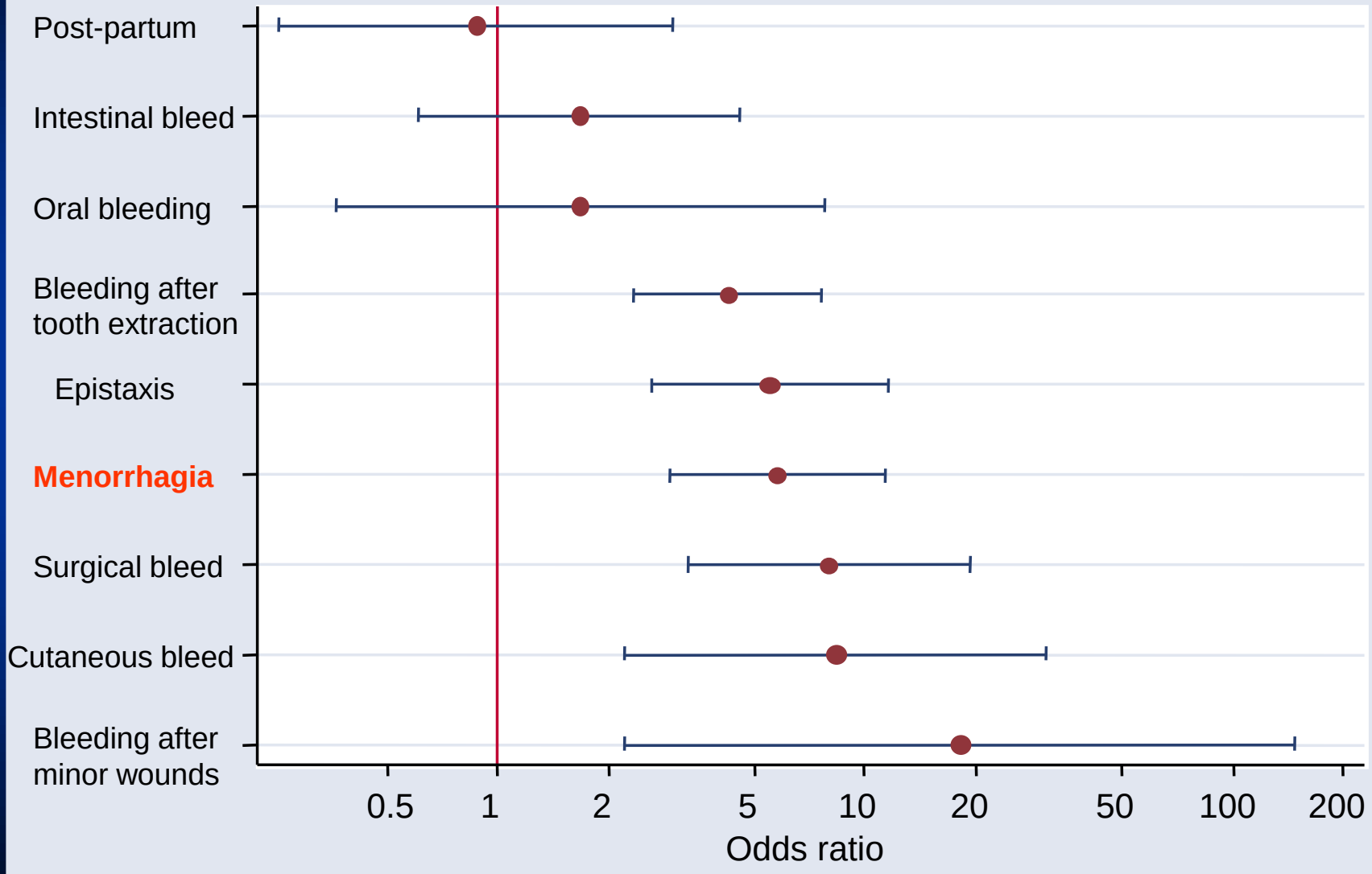
	SCORE					
Symptom	**-1**	**0**	**1**	**2**	**3**	**4**
Epistaxis	-	No or trivial (less than 5)	> 5 or more than 10'	Consultation only	Packing or Cauterization or Antifibrinolytic	Blood transf or Replacement therapy or Desmopressin
Cutaneous	-	No or trivial (<1 cm)	> 1 cm and no trauma	Consultation only		
Bleeding minor wounds	-	No or trivial (less than 5)	> 5 or more than 5'	Consultation only	Surgical hemostasis	Blood transf or Replacement therapy or Desmopressin
Oral cavity	-	No	Referred at least one	Consultation only	Surgical hemostasis or Antifibrinolytic	Blood transf or Replacement therapy or Desmopressin
GI bleeding	-	No	Associated with ulcer, portal hyp., hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, Blood transf, Replacement therapy, Desmopressin, Antifibrinolytic	
Tooth extraction	No bleeding in at least 2 extraction	None done or no bleed. in 1 extraction	Referred in <25% of all procedures	Referred in >25% of all procedures, no intervention	Resuturing or packing	Blood transf or Replacement therapy or Desmopressin
Surgery	No bleeding in at least two surgeries	None done or no bleed. in 1 surgery	Referred in <25% of all surgeries	Referred in >25% of all procedures, no intervention	Surgical hemostasis or Antifibrinolytic	Blood transf or Replacement therapy or Desmopressin
Menorrhagia	-	No	Consultation only	Antifibrinolytics, Pill use	D & C, Iron therapy	Blood transf or Replacement therapy or Desmopressin or Hysterectomy
Post-partum hemorrhage	No bleeding in at least two deliveries	No deliveries or no bleeding in 1 delivery	Consultation only	D & C, Iron therapy, Antifibrinolytics	Blood transf or Replacement therapy or Desmopressin	Hysterectomy

Tosetto et al JTH 2006

Validated in 300 healthy subjects and 753 patients with VWD type 1 Enrolled into the European Study:

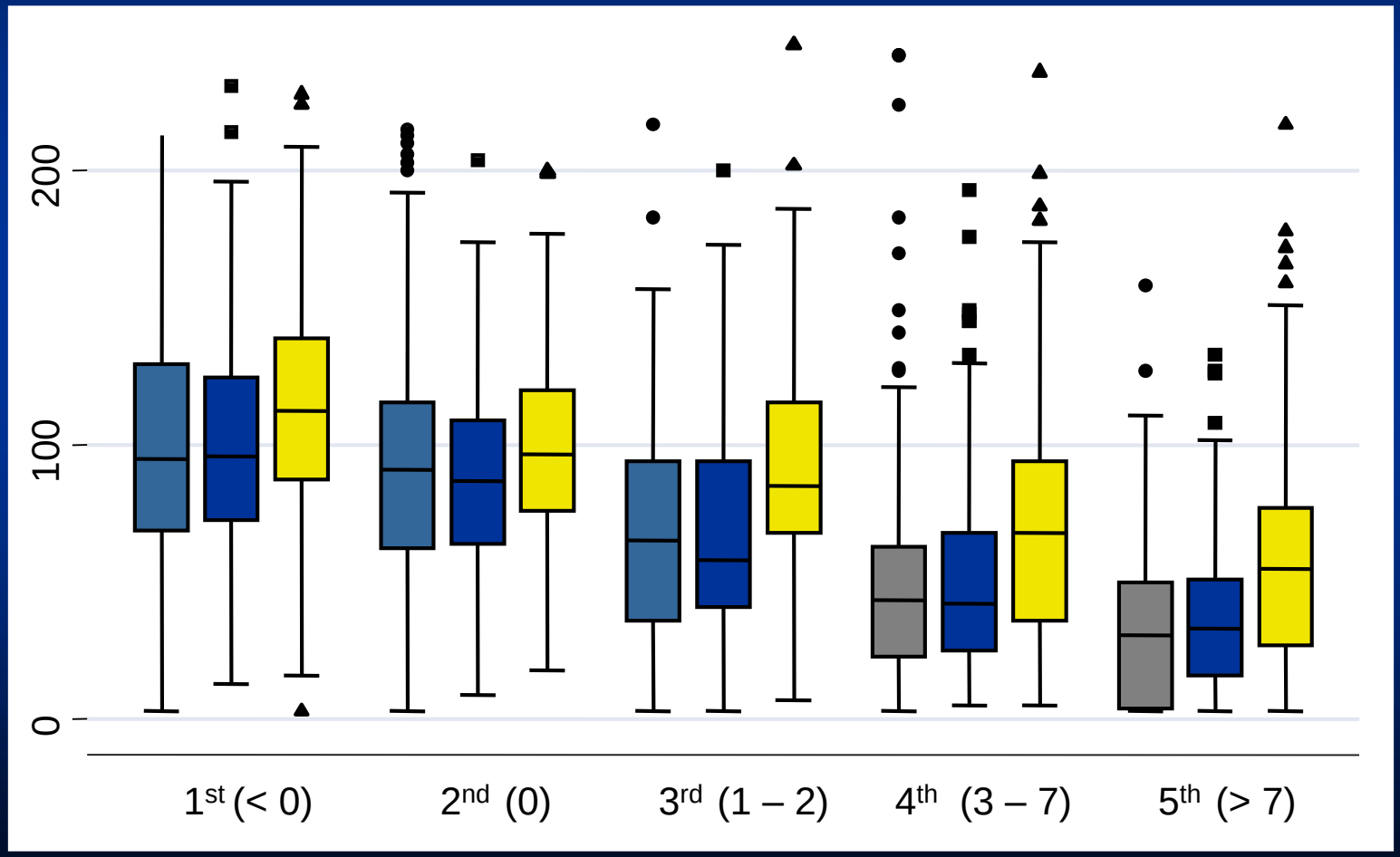
Bleeding Severity Score in Normals = -1/ 0

Association between bleeding symptoms in type 1 VWD vs normal relatives (MCMDM-1 VWD, JTH 2006)



Odds-Ratio (VWD vs. non affected family members)

The bleeding score correlates with VWF/FVIII:C levels (MCMDM-1VWD)



WiN (Willebrand in Netherlands)

Bleeding score according to type of VWD

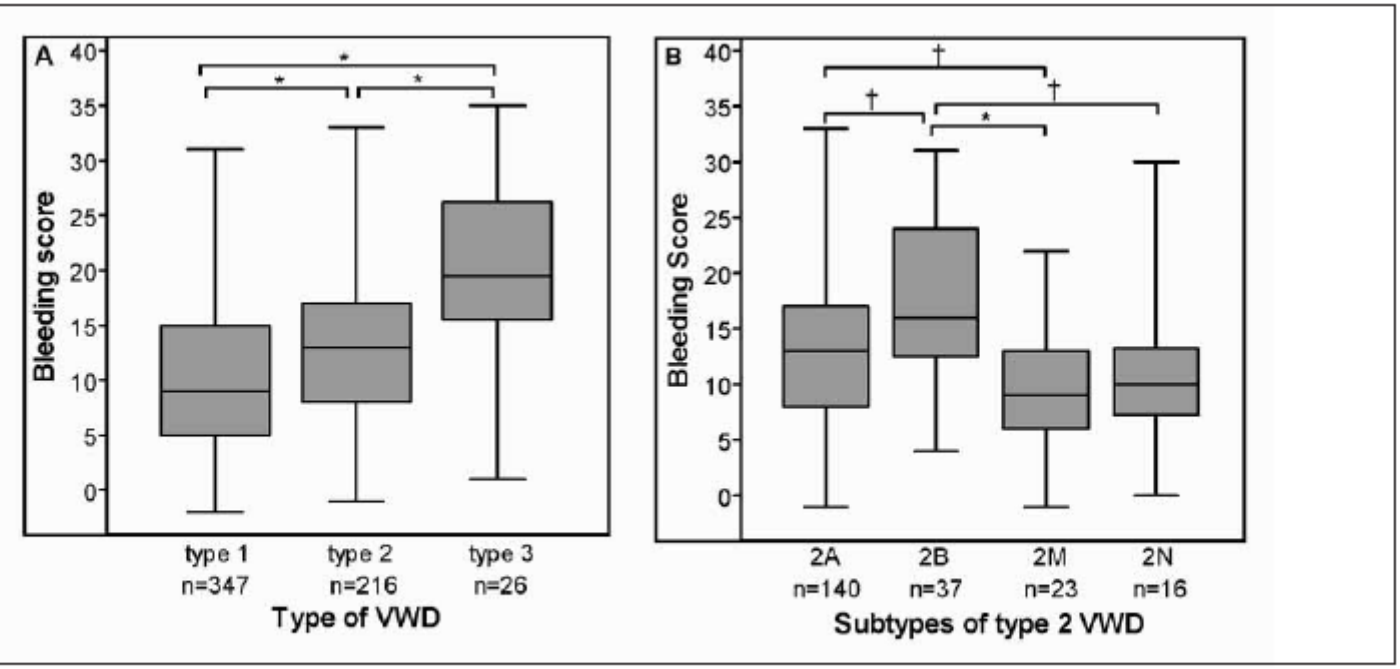
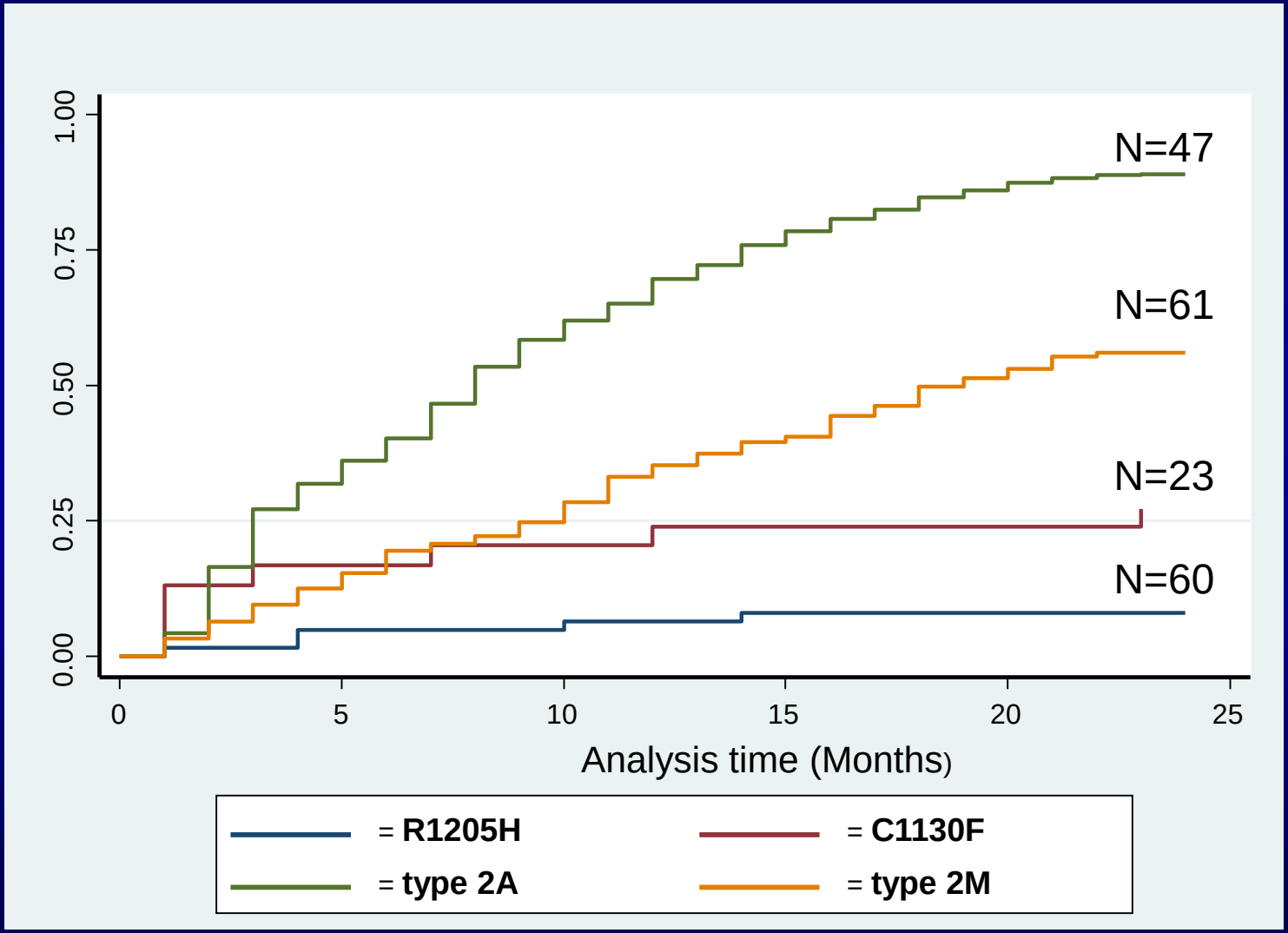


Figure 2: Bleeding score according to type of VWD. A) Bleeding score according to type of VWD. B) Bleeding score according to type 2 variants in patients with VWD. * $p<0.001$; † $p<0.01$.

De Wee et al, 2011

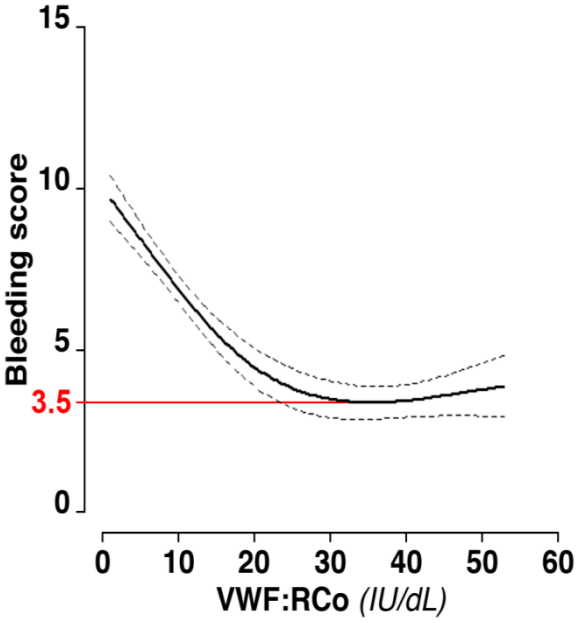
Cumulative risk of spontaneous hemorrhage is greater in type 2 than in type 1 VWD



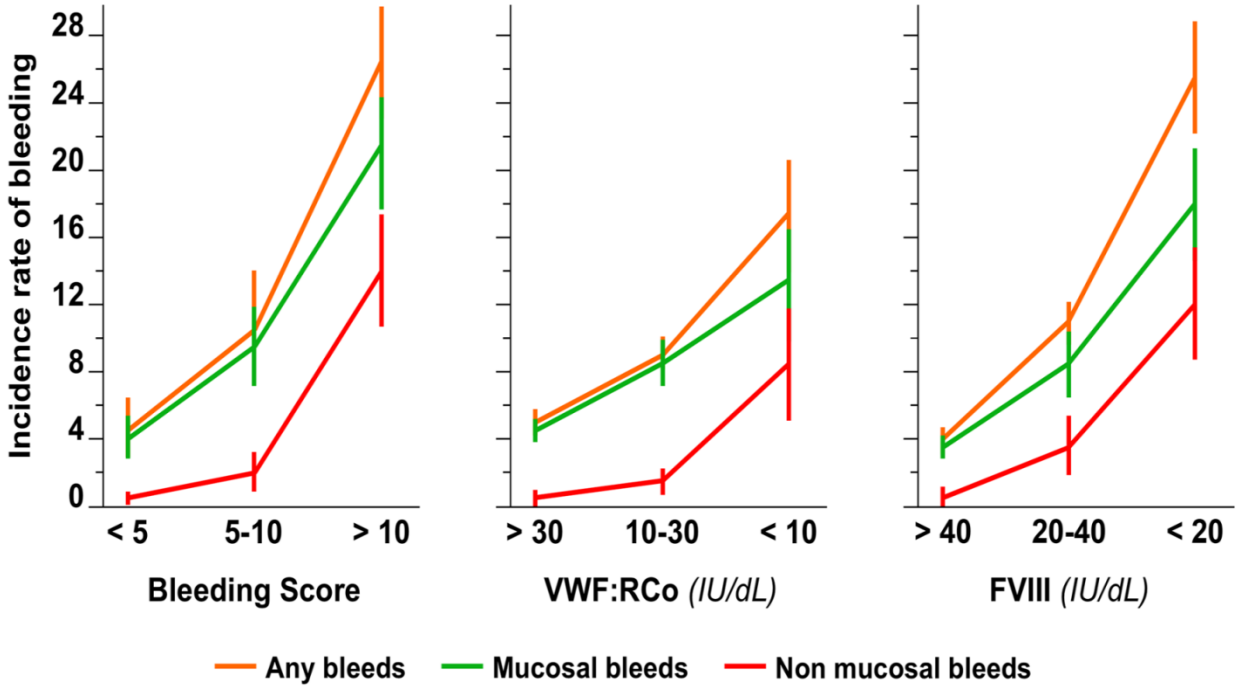
Castaman et al, JTH & TH 2011; 2012

Bleeding Phenotype in VWD
Evidence-Based Methods

Restricted Cubic Spline Curve



Cox's Proportional Hazard Model



Federici AB et al, Blood 2014; 123: 4037-4044

(Minimal) criteria for a clinically useful diagnosis of VWD

– BS > 3 male; > 5 female
(less stringent criteria for pediatric age or in young subjects with few hemostatic challenges)

– VWF:RCo < 40 IU/dL

Odds of VWD against normal ~ 4 (80%)

+

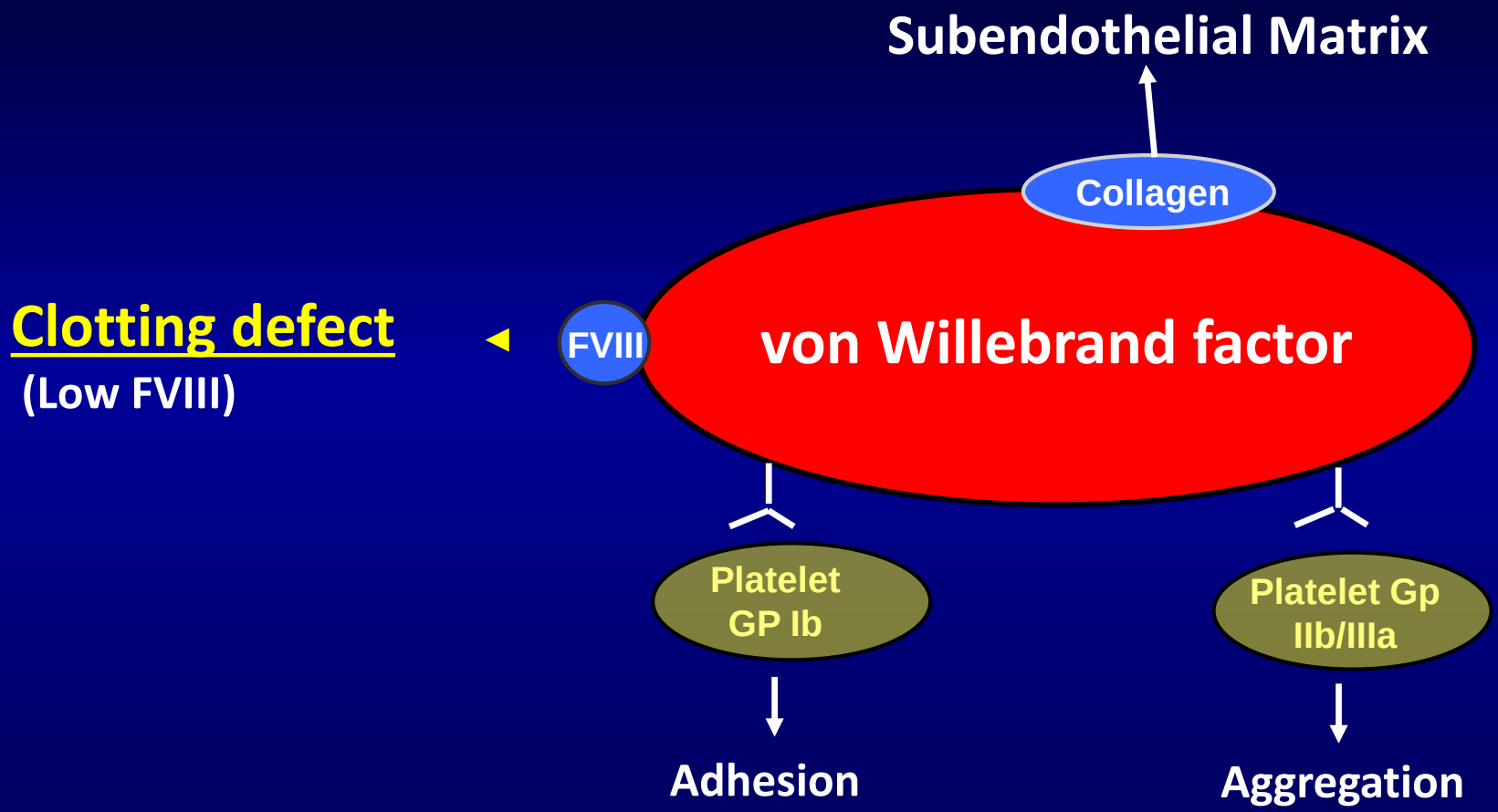
- Another family member with VWF:RCo < 40 IU/dL:

Odds of VWD > 15

HOW TO TREAT

VON WILLEBRAND DISEASE

Why does VWD patient bleed ?



Hemostatic defect

(Low/abnormal VWF)

MANAGEMENT OF VWD

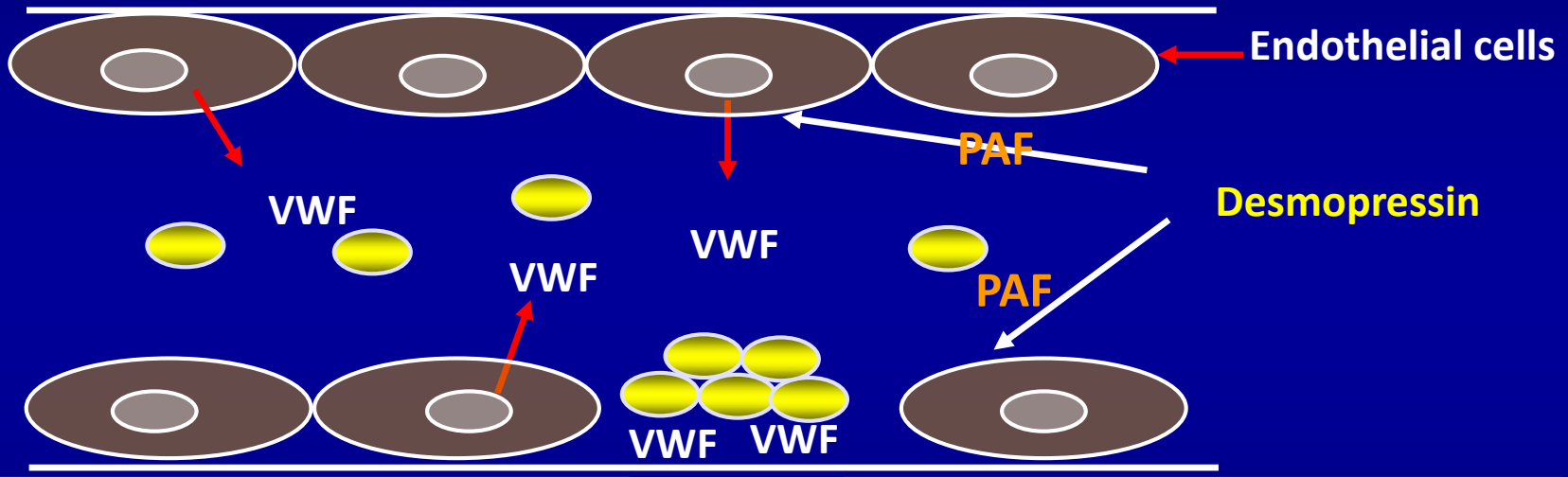
- **Desmopressin (DDAVP):** to be tested in type 1 & 2 (not in type 2B)

  DDAVP releases *endogenous VWF* from endothelial cells

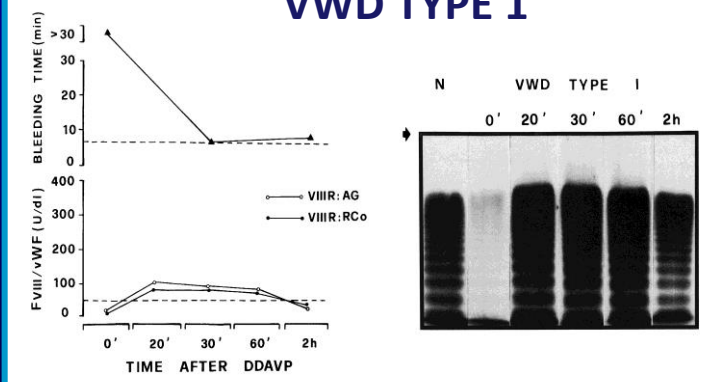
- **VWF Concentrates:** *exogenous VWF* to be used in VWD unresponsive to DDAVP (VWD 2 & 3, severe VWD 1)

How does desmopressin work

- Stimulates the release of VWF from endothelial cells
- Requires the presence of normal VWF in cells

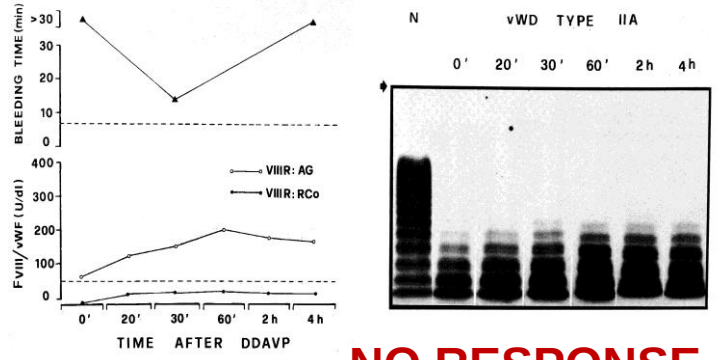


VWD TYPE 1



POSITIVE RESPONSE

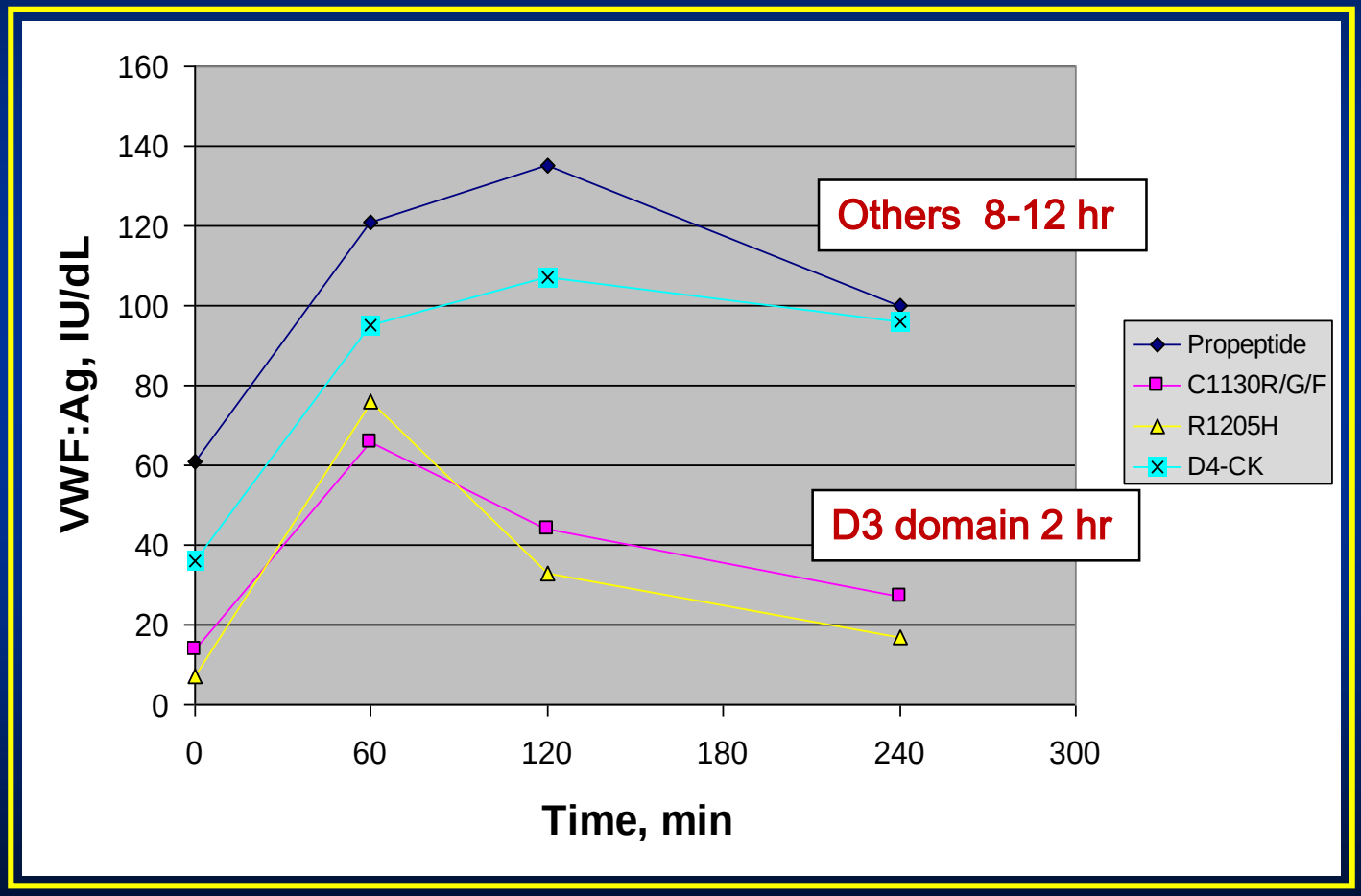
VWD TYPE 2A



NO RESPONSE

VWD type 1: evidence for heterogeneity of post-desmopressin VWF half-lives

Increased clearance in some D3 domain mutations



Usually identified by an increased VWFpp/VWF:Ag ratio

Castaman et al, Blood 2008

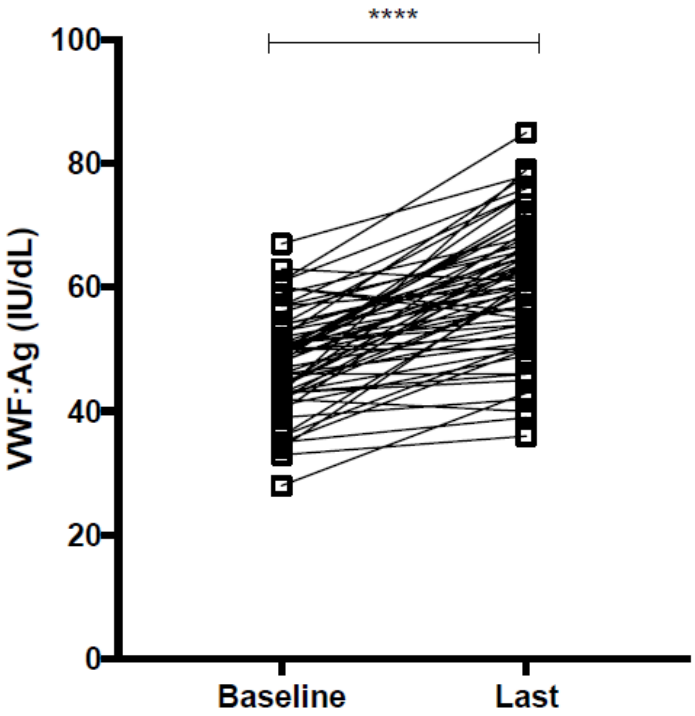
Correlates of BS and QoL in VWD

- BS correlates with QoL in VWD (SF-36)
- Nationwide (The Netherlands) investigation of 192 males and 317 females with VWD (WiN study cohort)
- VWD patients in the highest quartile (BS>17) had lower QoL:
  - Physical functioning
  - Role limitations due to physical functioning
  - Bodily pain
  - General health

De Wee et al, JTH 2010

In patients with “low” VWF, normalization of VWF is possible

- An increase of VWF levels is frequently observed
- Age-dependent effect
- Regression to the mean
- Need for repeated testing to avoid over-diagnosis



Lavin et al. Blood, 2017.

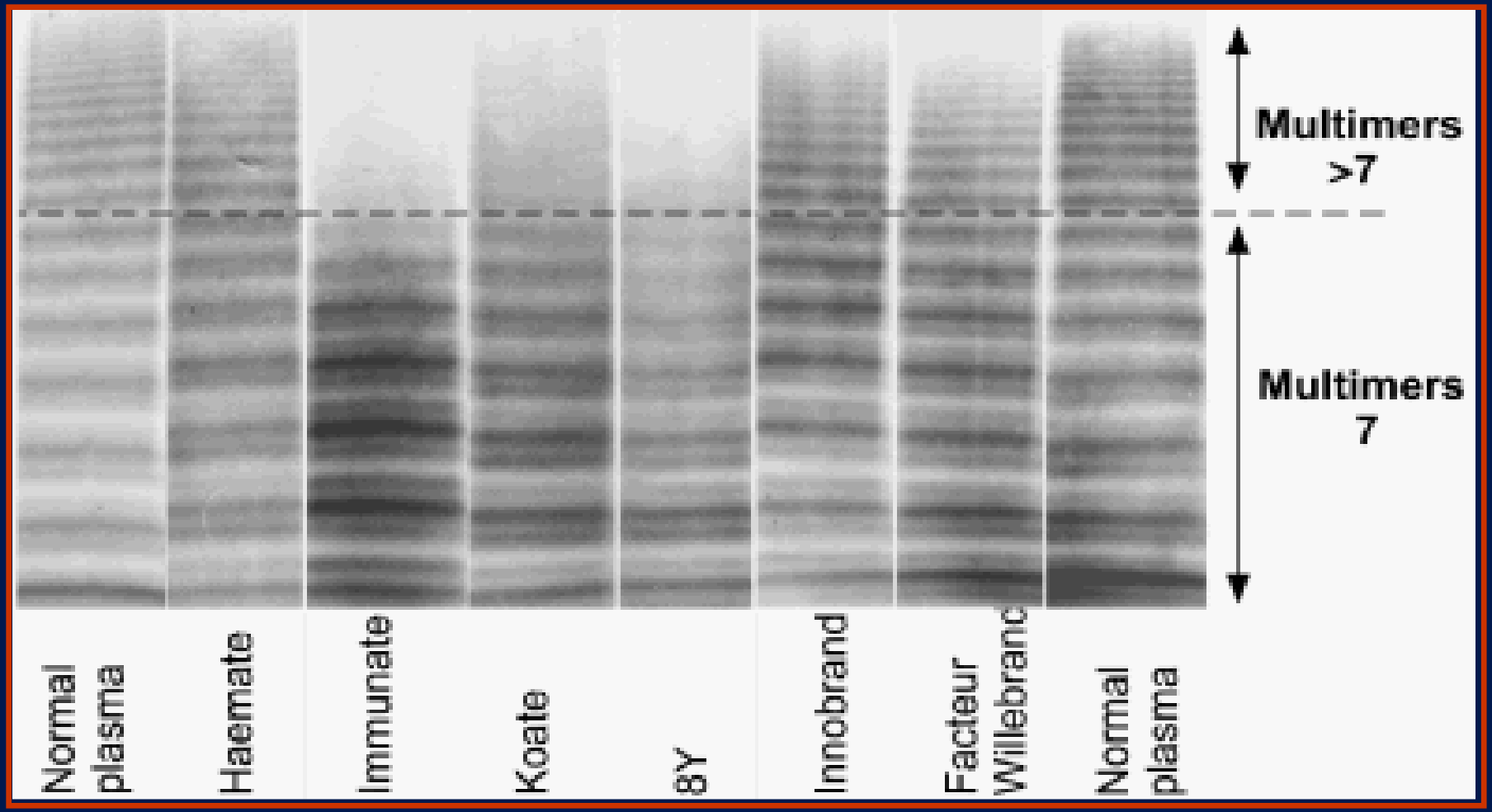
The response to desmopressin trial as a turning point in VWD management

- Who:
  - All intermediate/severe cases
- Who not:
  - Severe recessive (VWF:Ag < 3 IU/dL)
  - Enhanced responsiveness to RIPA
  - Mild (VWF:RCo > 30 IU/dL)
- How:
  - IV or SC injections (0.3 μg/kg) or intranasal (150 - 300 μg)
  - Monitor FVIII, VWF:RCo at least after 1 and 4 hours
- Response criteria (FVIII and VWF:RCo):
  - Between 30 - 50 IU/dL, partial response
  - ≥ 50 IU/dL, complete response
  - In type 2N half-life of released FVIII:C may be short and VWF:FVIII products could be required

Limitations to the use of desmopressin

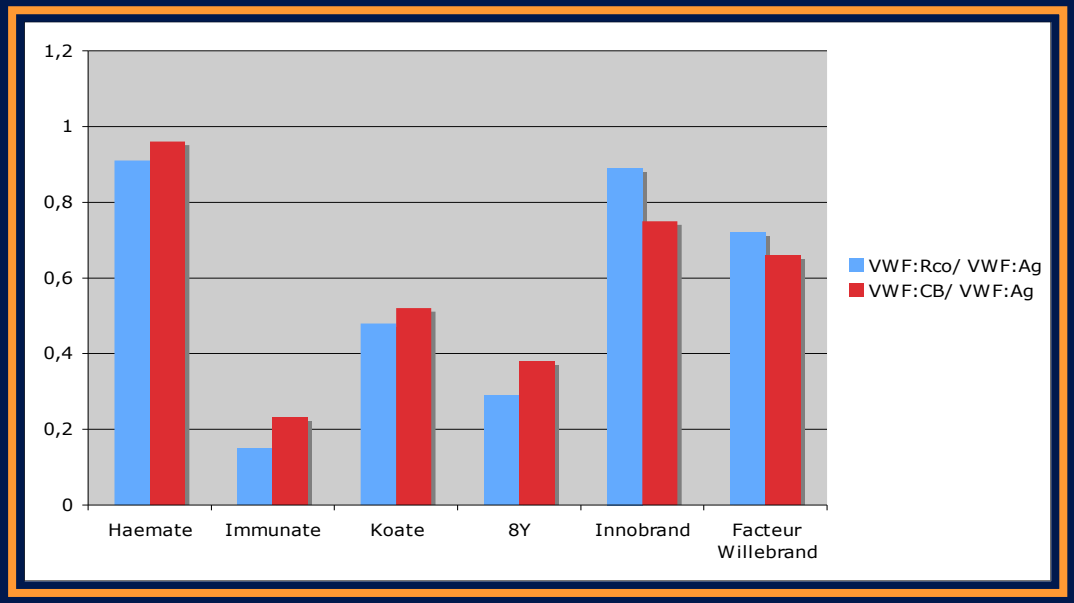
- Non-responders (type 3, most type 2 A)
- Short half-life of released factors (↑ clearance)
- Prolonged desmopressin treatment may be difficult:
  - Tachyphylaxis after 3 or more infusions at short intervals
  - Antidiuretic effect, other side effects
- Contraindications: overt cardiovascular disease, children <2 years, enhanced RIPA (type 2B)

Multimeric composition of the VWF in the different concentrates

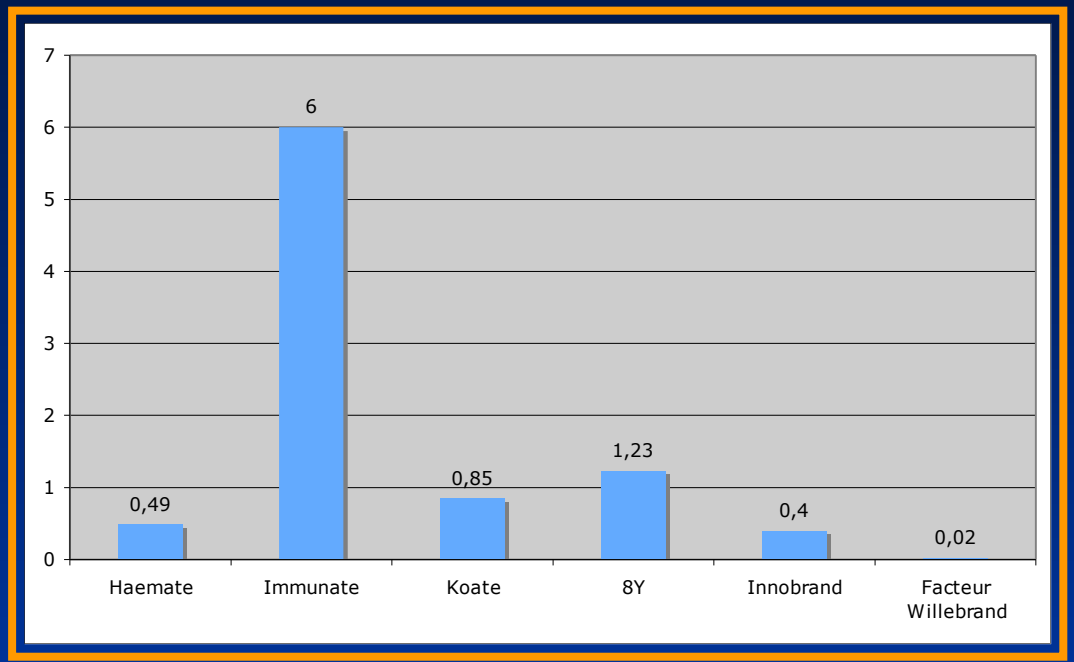


*Lethagen et al. Haemophilia 2004;*10: 243-249

VWF:RCo/VWF:Ag in FVIII/VWF concentrates

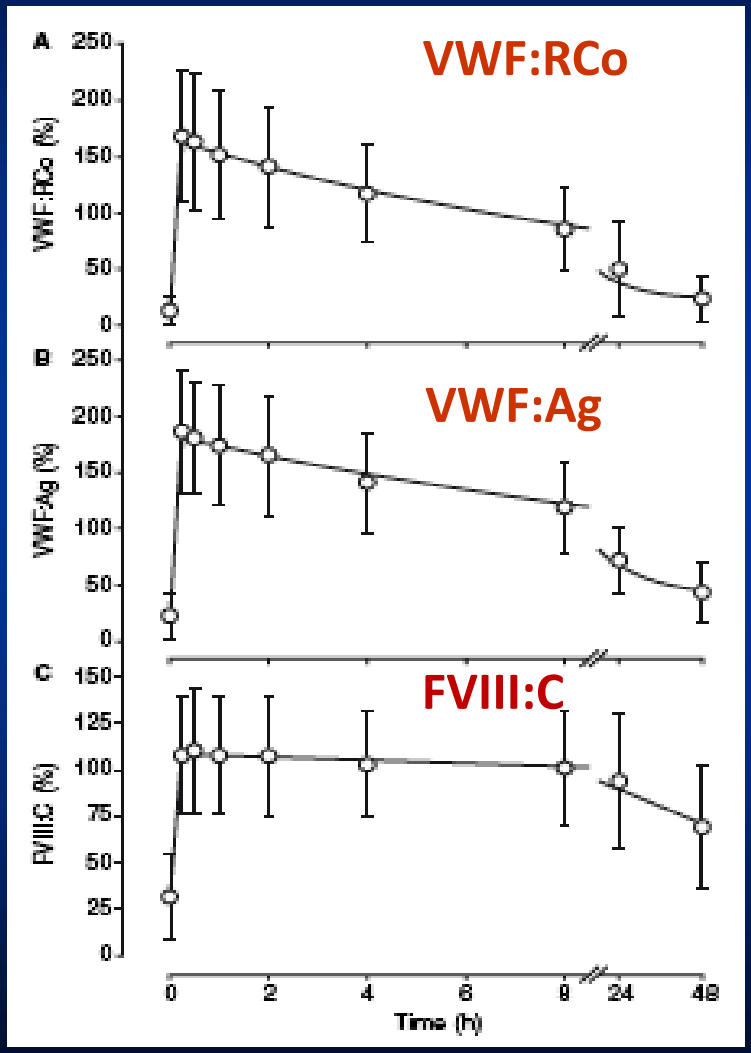


FVIII:C/VWF:RCo in FVIII/VWF concentrates



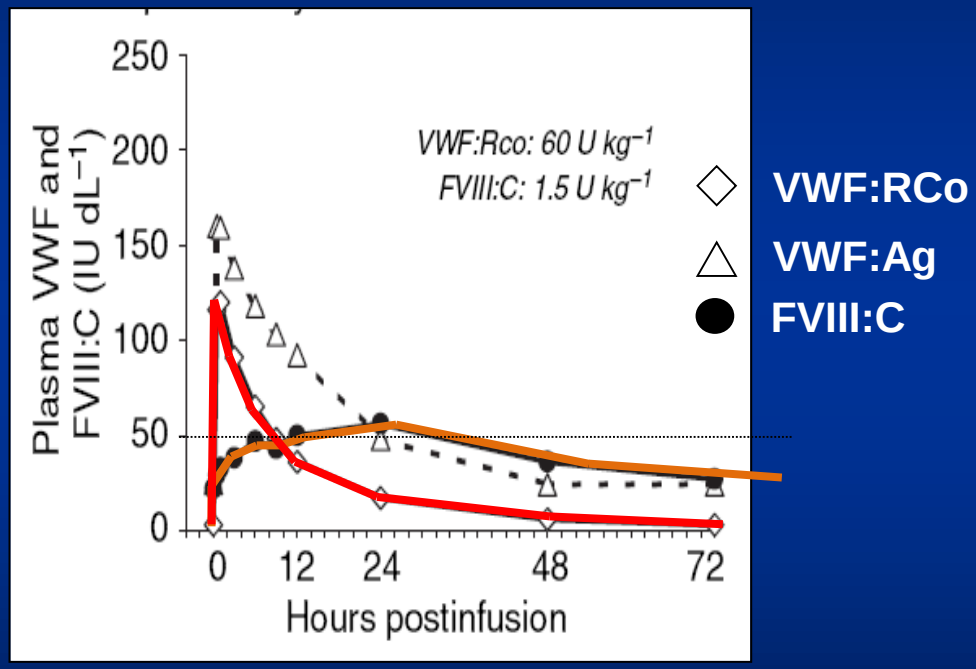
Lethagen et al. Haemophilia 2004;

Mean changes after VWF/FVIII ~ 2.4 (VWF:RCo ~70 U kg^{-1})



Lethagen et al, 2007

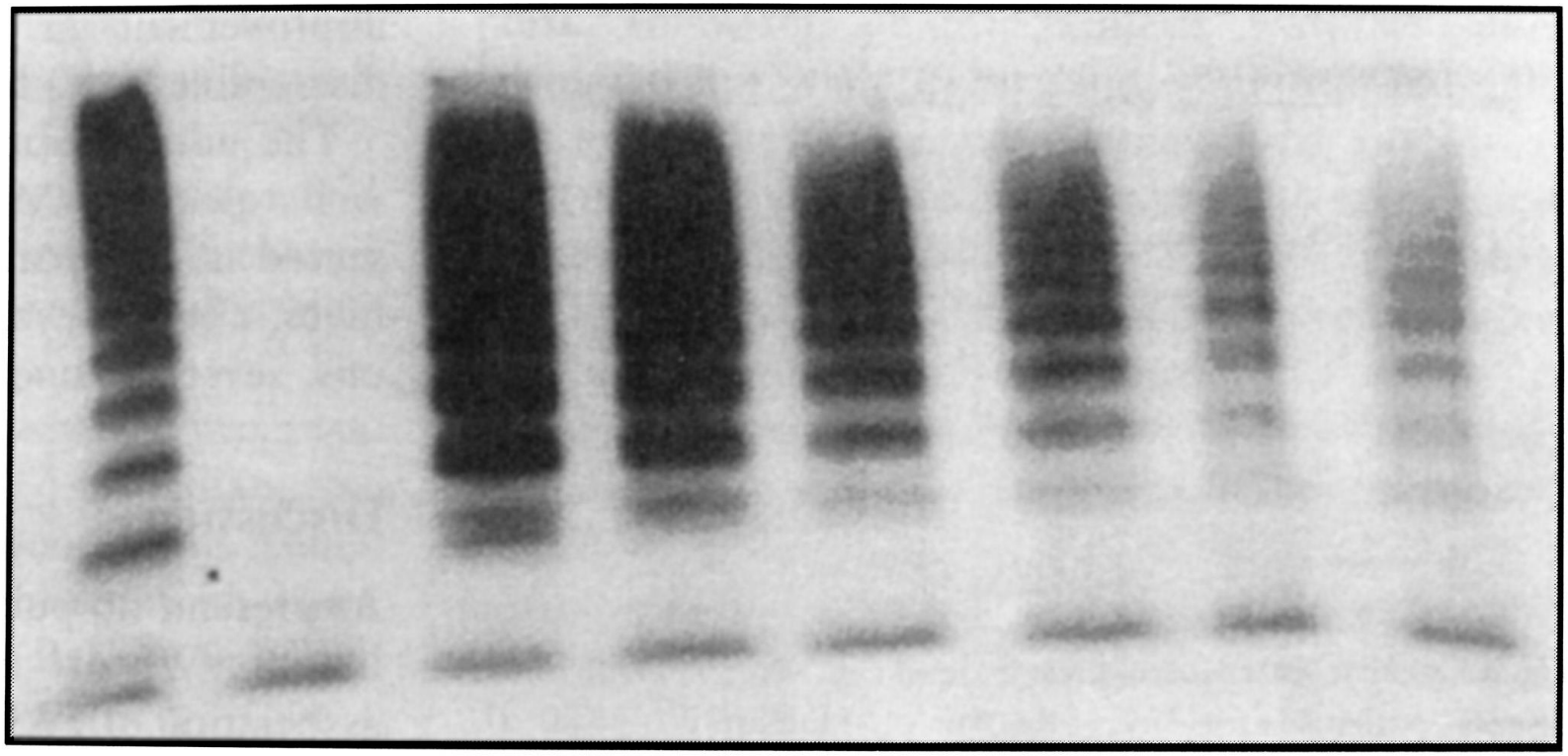
Mean changes after VWF/FVIII (~ 50 U *kg^{-1}*)



Goudemand et al, 2005

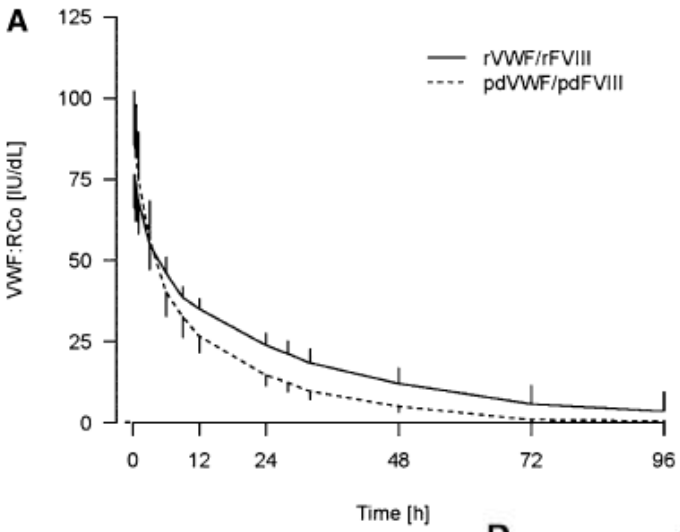
FVIII/VWF CONCENTRATES

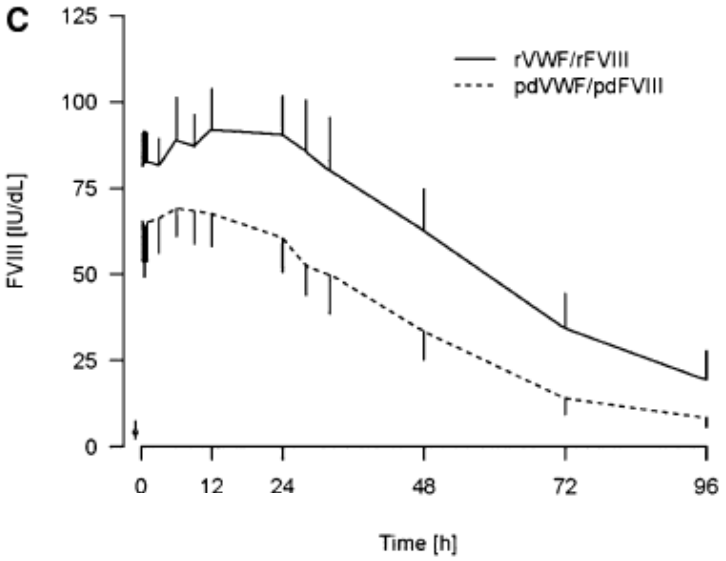
(Patient with VWD Type 3)

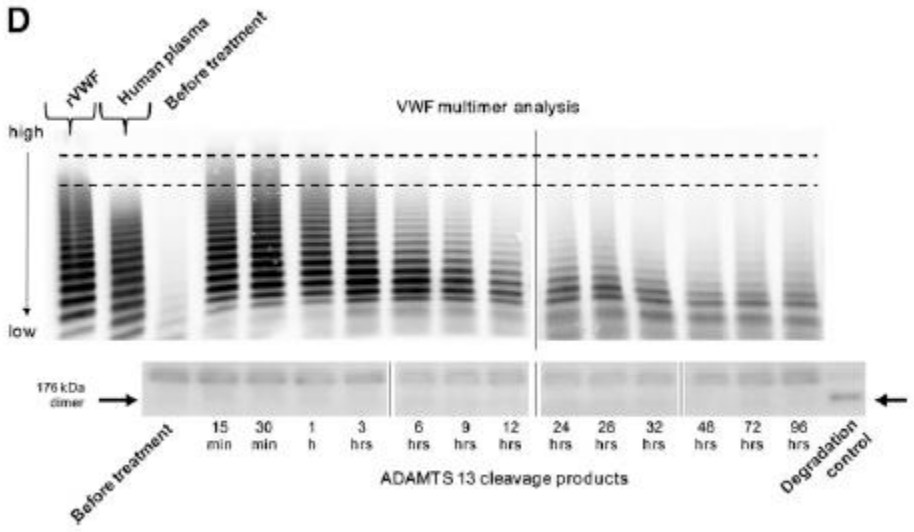


blood
2013 122: 648-657
doi:10.1182/blood-2013-01-479527 originally published online June 18, 2013

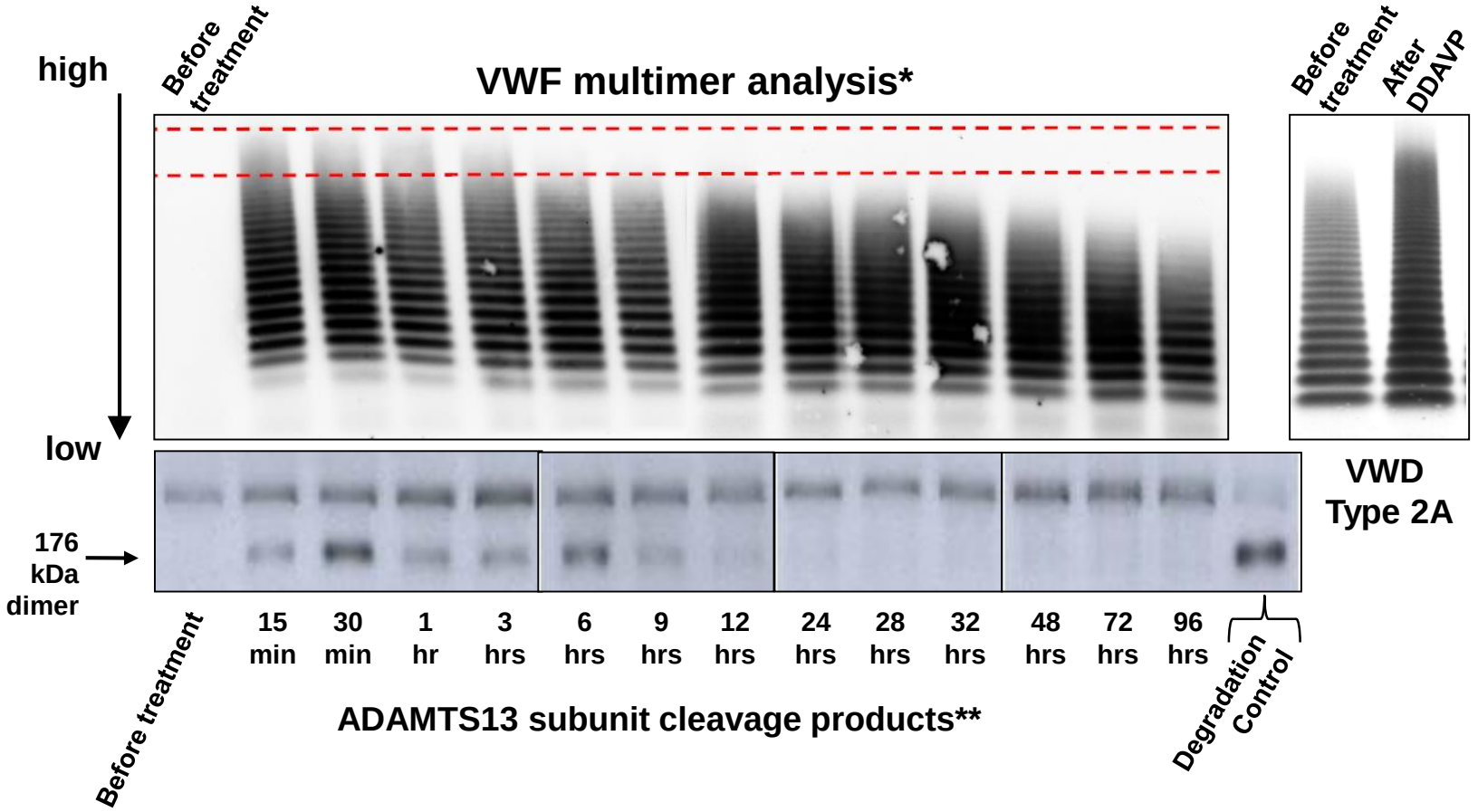
Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial







rhVWF multimers and ADAMTS13 cleavage



* Low resolution agarose (1% Seakem) / Samples adjusted to VWF:Ag content

** SDS-PAGE / Immunoblot with polyclonal anti-VWF Ab / Samples undiluted

Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease

Joan C. Gill,[1,2] Giancarlo Castaman,[3,4] Jerzy Windyga,[5] Peter Kouides,[6,7] Margaret Ragni,[8,9] Frank W. G. Leebeek,[10] Ortrun Obermann-Slupetzky,[11] Miranda Chapman,[11] Sandor Fritsch,[11] Borislava G. Pavlova,[11] Isabella Presch,[11] and Bruce Ewenstein[12]

Blood. 2015;126(17):2038-2046

- The treatment success rate (mean efficacy score of < 2.5) was **100%** (90% CI: 87.3 to 100.0) (n = 22: 17 type 3, 4 type 2A, 2 type 2N; 192 bleeds: 122 minor, 61 moderate, 7 major, 2 unknown).

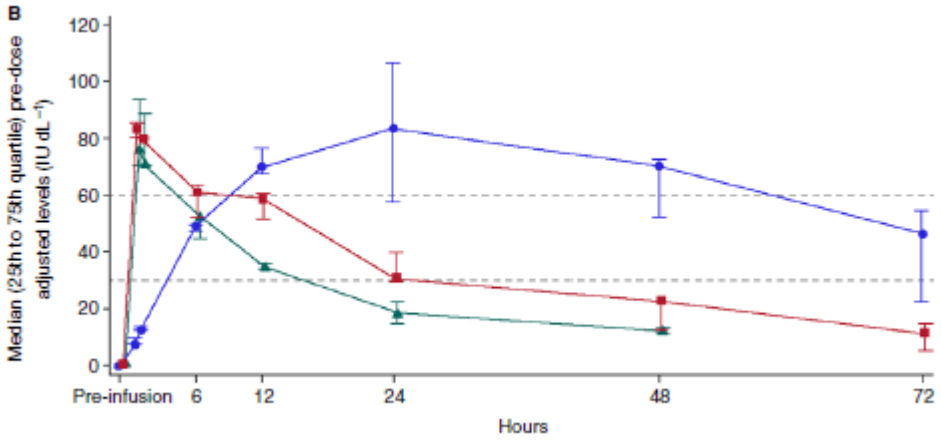
- Treatment was good (3.1%) or excellent (96.9%) in all bleeds

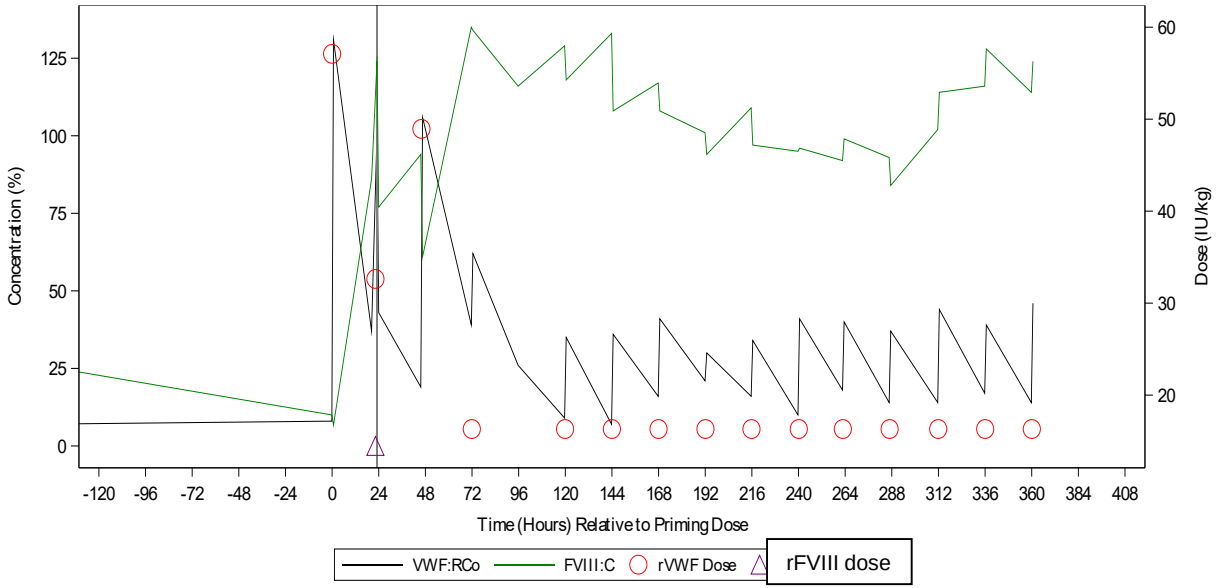
- The rVWF PK profile was unaffected by rFVIII (mean VWF:RCo terminal halflife = 21.9 h [rVWF] and 19.6 h [rVWF:rFVIII])

ORIGINAL ARTICLE

Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery

F. PEYVANDI,*† A. MAMAEV,‡ J.-D. WANG,§ O. STASYSHYN,¶ M. TIMOFEEVA,** N. CURRY,†† A. R. CID,‡‡ T. T. YEE,§§ K. KAVAKLI,¶¶ G. CASTAMAN*** and A. SYTKOWSKI†††





Session III • Pharmacological Treatment of VWD

Long-term prophylaxis in von Willebrand disease. Experience from Sweden

[haematologica reports]
2005;1(4):30-31

- 35 patients (28 type 3, 3 2B, 2 2A, 1 type 1 on prophylaxis for 11 yr (2 - 45)
- Once-thrice weekly infusions (25 U/Kg FVIII)
- 17 patients on prophylaxis for hemarthrosis had 1-4 episodes/year
- Most developed chronic arthropathy by clinical-radiologic evidences
- Improved QoL, no thrombosis

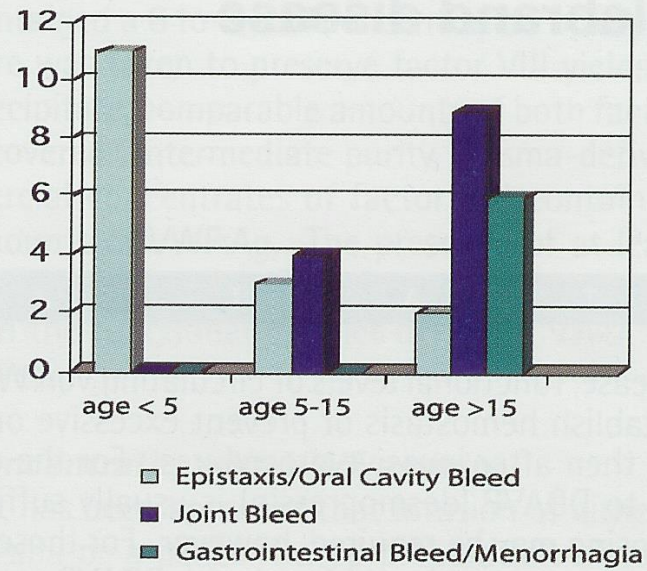
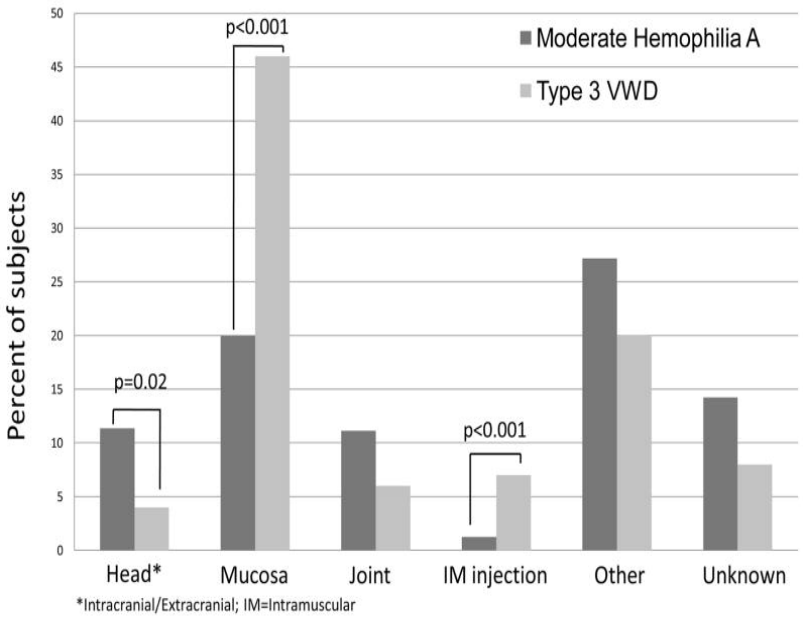
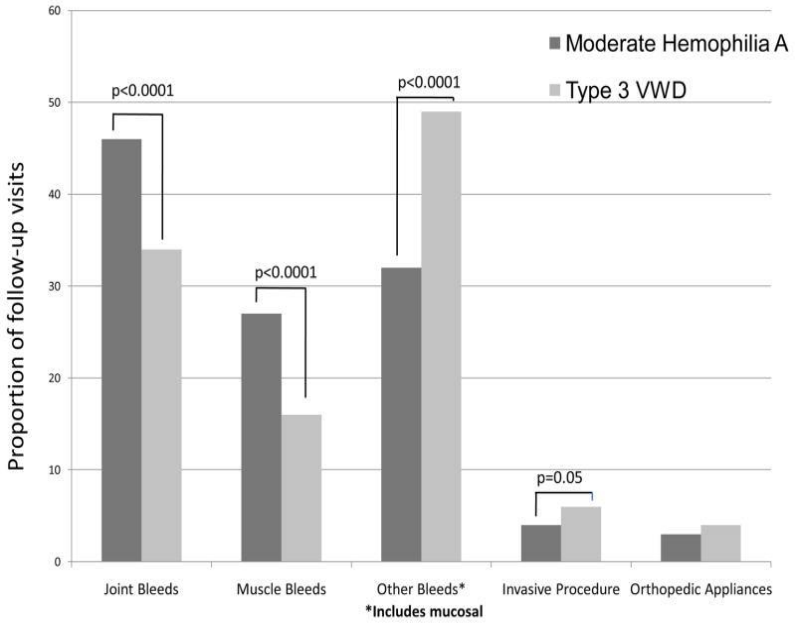


Figure 1. Clinical indication for prophylaxis by age at commencement of therapy.

Similar rates of joint function limitation between Type 3 VWD and moderate HA





- **No difference in joint ROM loss over time between individuals with VWD and moderate HA.**
- **Higher FVIII level was associated with preserved joint ROM (p < 0.001).**
- **Lower FVIII level correlated with a higher rate of joint (p< 0.001) and muscle (p< 0.001), but not mucosal bleeding (p=0.10).**

Sood et al., Haemophilia. 2013 Jul; 19(4): 595–601.

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2013), 19, 76–81 DOI: 10.1111/j.1365-2516.2012.02916.x

Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN)

T. C. ABSHIRE,* A. B. FEDERICI,† M. T. ALVÁREZ,‡ J. BOWEN,§ M. D. CARCAO,¶ J. COX GILL,** N. S. KEY,†† P. A. KOUIDES,‡‡ K. KURNIK,§§ A. E. LAIL,§ F. W. G. LEEBEEK,¶¶ M. MAKRIS,*** P. M. MANNUCCI,††† R. WINIKOFF‡‡‡ and E. BERNTORP§§§ FOR THE VWD PN

Retrospective, 59 patients

Median age at onset prophylaxis 22.4 yr

Δ bleeding rates pre vs post: P<0.0001

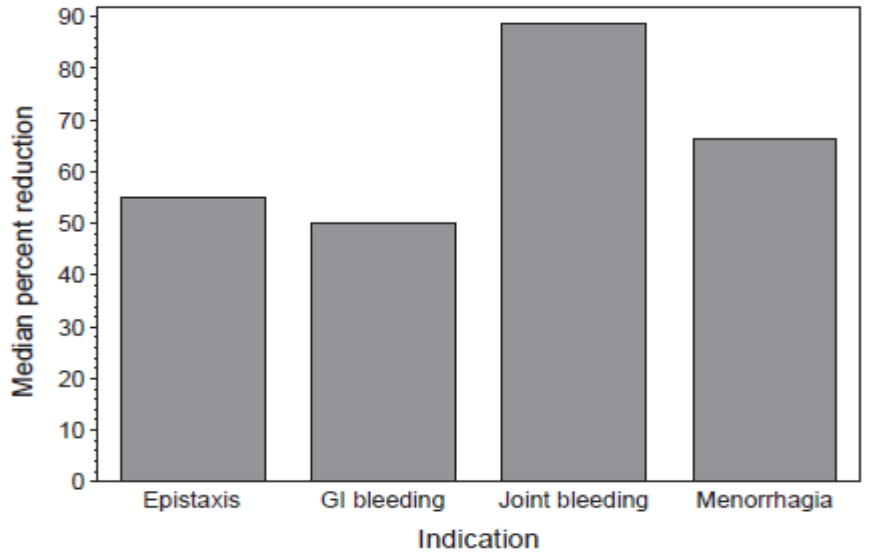
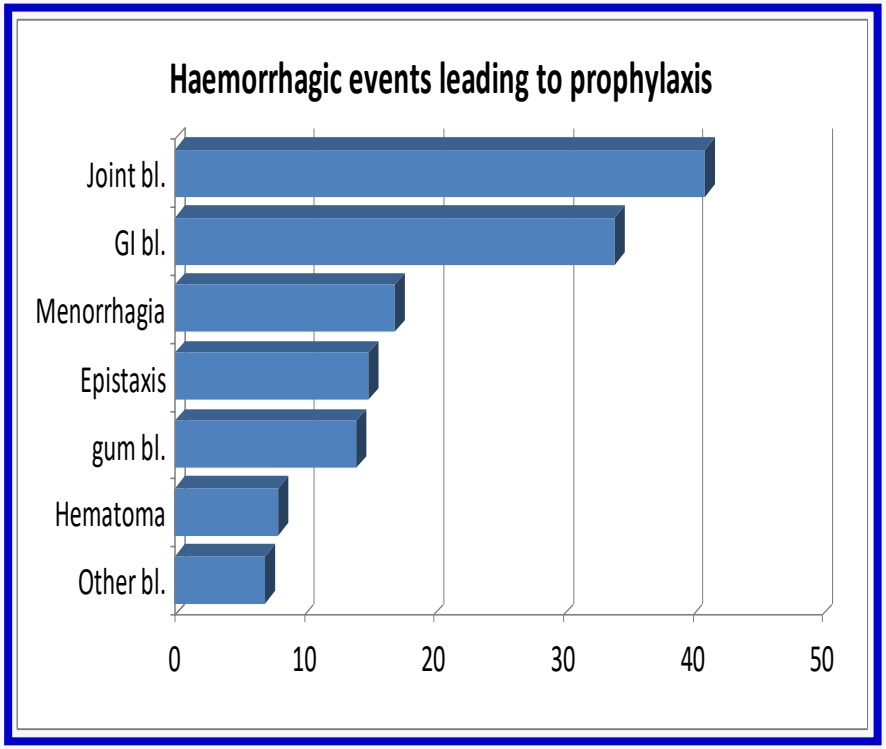


Fig. 1. Outcomes measured as percent reduction in bleeding within individuals during prophylaxis, according to primary indication for treatment.

WISH: Prospective Prophylactic treatment in 31 patients
Clinical Response: 93% Excellent & Good



Castaman et al, 2013

Clinical spectrum of VWD: implications for management

Minimal diagnostic criteria

VWD diagnosis: Increased BS and VWF:RCo<40 IU/dL

Assessment of VWD clinical severity

	Severe	Intermediate	Mild
Bleeding manifestations	Spontaneous bleeding, particularly mucocutaneous. High bleeding risk after minor challenges	Clearly increased BS, but spontaneous bleedings less frequent	Spontaneous bleeding uncommon; Frequently uneventful surgeries, even without prophylaxis
Indicative VWF:RCo levels	**<10 IU/dL** (All types)	**10 - 30 IU/dL** (Type 1 and 2)	**30 - 40 IU/dL** (Mainly type 1)
Desmopressin trial infusion	**Recommended**		**Not required**

Treatment

- FVIII/VWF concentrates if desmopressin unresponsive/contraindicated or at-risk surgery
- Desmopressin (if responsive)
- Counseling / antifibrinolytics

Conclusions

- Diagnosis relatively easy in severe cases, consider clinical history as a diagnostic starting point
- Bleeding risk in VWD variable according to types,
- Therapeutic agents safe and efficacious
- Prophylaxis in selected cases; cost-effective analysis still lacking; start ASAP in case of joint bleeding

EU Guidelines (Castaman et al, 2013)

- **Spontaneous bleeding episodes**: single or daily doses of 20-60 IU/kg of VWF to maintain FVIII:C levels > 30 U/dL until bleeding stops (usually 2-4 days)[1]
- **Major surgery:** daily doses of 50-60 IU/kg of VWF to maintain preoperative FVIII:C and VWF:RCo levels of 80-100 U/dL until 36 h postoperatively and then > 50 U/dL until healing is complete (usually 5-10 days)[1]
  - Measure plasma levels of FVIII:C (and VWF:RCo) every 12 h on the day of surgery, then every 24 h
  - Usual thrombo-prophylactic treatment with LMWH should be implemented in patients at high risk of venous thrombosis
- **Minor surgery:** daily or every other day doses of 30-60 IU/kg of VWF to maintain FVIII:C level > 30 U/dL until healing is complete (usually 2-4 days)[1]
- **Dental extractions or invasive procedures**: single dose of 30 IU/kg of VWF to maintain FVIII:C level > 50 U/dL for 12 h[1]
- **Delivery and puerperium**: daily doses of 50 IU/kg VWF to maintain FVIII:C level > 50 U/dL for 3-4 days

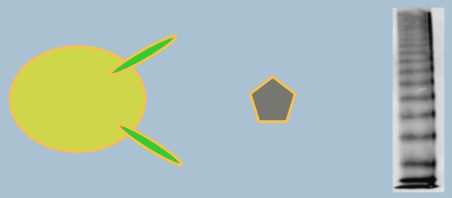
Dosing should be based on VWF:RCo content where this is available

[1] These doses are indicated for VWD patients with severely reduced FVIII:C/VWF:RCo levels (< 10 U/dL)

VWF:RCo – Pros and Cons

Advantages

- "Gold Standard" for measuring VWF activity
- Most data correlating VWF levels and DDAVP/replacement treatment related to VWF:RCo
- 3rd and 4th generation fully automated VWF:RCo assays widely available



Platelet + ristocetin + VWF

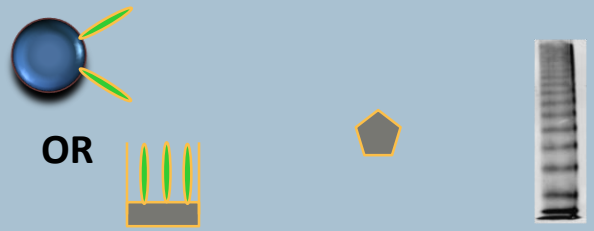
Disadvantages

- Poor sensitivity (LOD ≥ 10 IU/dL)
- Difficult to characterize patients with severe VWD
- VWF:RCo/VWF:Ag ratio is critical for subclassification; high CV may lead to false diagnoses in moderately severe VWD
- Not a physiologic measure of VWF activity
- VWF variants p.P1467S and p.D1472H cause spuriously decreased VWF:RCo (assay artifact)

VWF:GPIbR – Pros and Cons

Advantages

- First version was ELISA-based assay with much improved LOD and CV
- More recently available as latex or magnetic particle-enhanced automated assays
- Correlation with VWF:RCo reported to be excellent
- Automated assay applications allow for precise and sensitive detection of VWF activity



Disadvantages

- Not a physiologic measure of VWF activity
- Several assays available but with different GPIb capture, source of GPIb, and variable ristocetin source and concentration – variable results?
- Due to dependence on ristocetin for activation spuriously decreased activity may still exist for VWF variants p.P1467S and p.D1472H

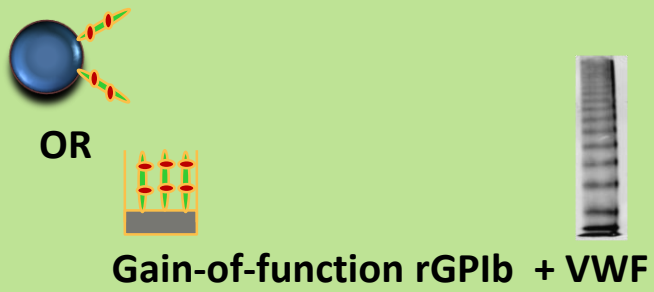
VWF:GPIbM – Pros and Cons

Advantages

- Gain of function GPIb allow for spontaneous binding of VWF
- Not subject to false low values when p.P1467S or p.D1472H present
- With ELISA application, may be possible to discriminate between types 2A and 2B VWD
- Automated applications of assay allow for precise and sensitive detection of VWF activity
- Consistently correlated with VWF:RCo

Disadvantages

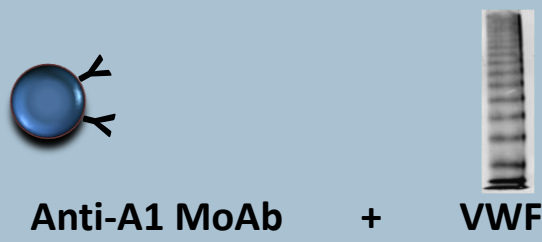
- Several assays available but with different GPIb capture, source of GPIb, GPIb mutations – variable results?
- Automated application may not discriminate between types 2A and 2B VWD



VWF:Ab – Pros and Cons

Advantages

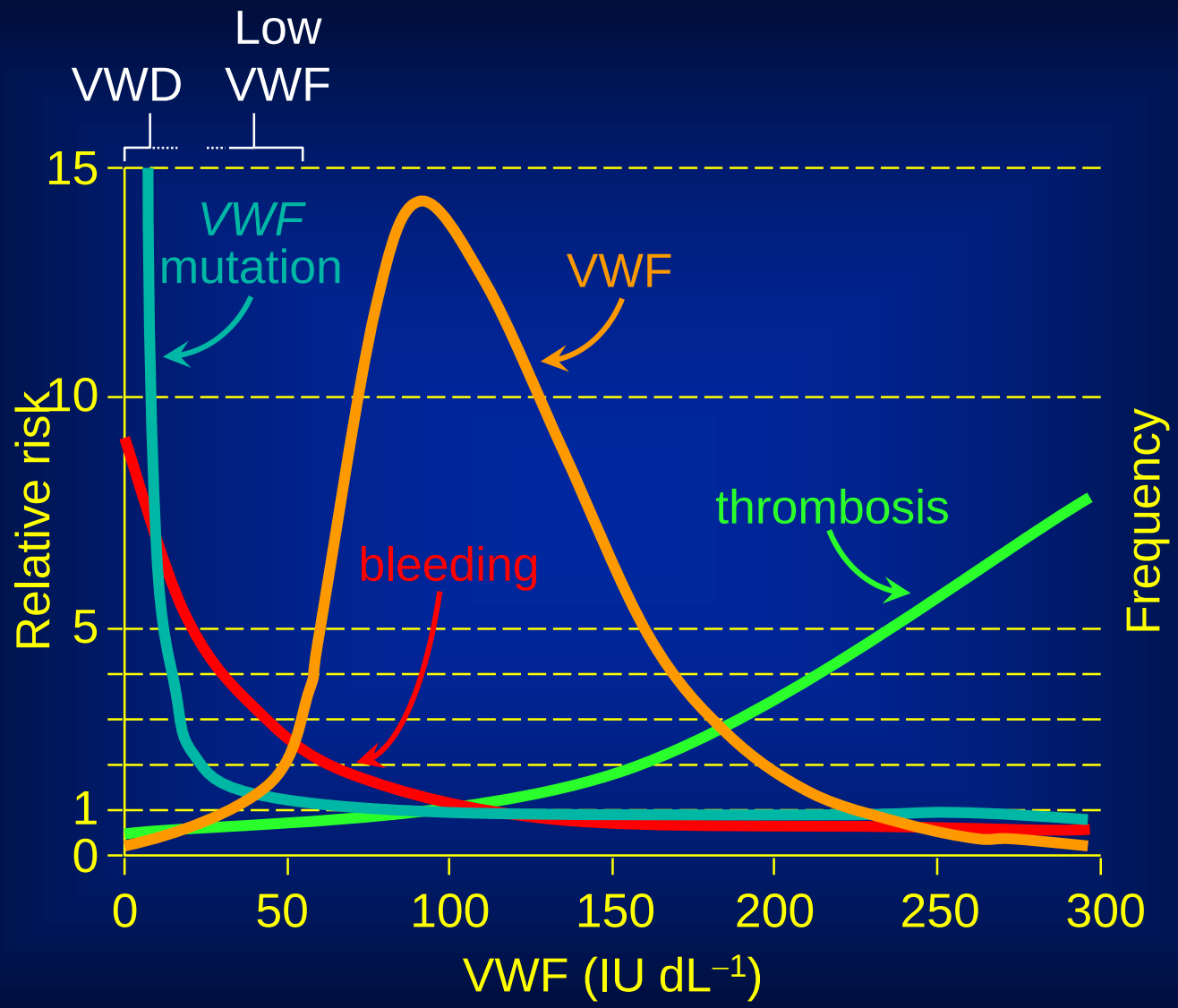
- Reports the binding of the VWF A1 domain to a mAb
- LIA version performed better than ELISA in discriminating subtypes
- User-friendly, applicable to several platforms, feasible for routine laboratories
- Good correlation with VWF:RCo



Disadvantages

- Does not provide information about the function of VWF
- Some VWD type 2M mutations (p.G1324A) are not detected
- No improvement in LOD (19 IU/dL) compared to VWF:RCo
- Acceptable role in screening of VWF patients when combined with other tests
- Not recommended as a replacement for VWF:RCo

VWF in hemostasis and thrombosis

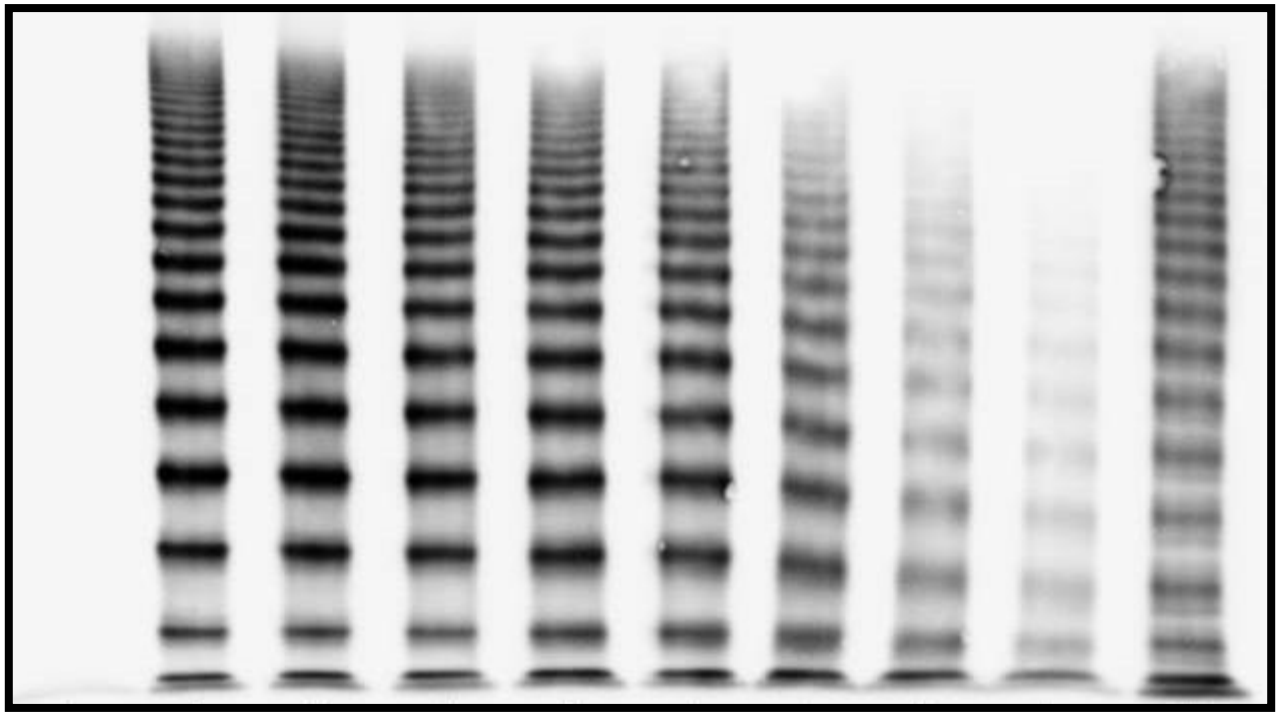


Sadler JE, J Thromb Haemost 2005; 3: 1702–9

Plasma VWF and VWFpp

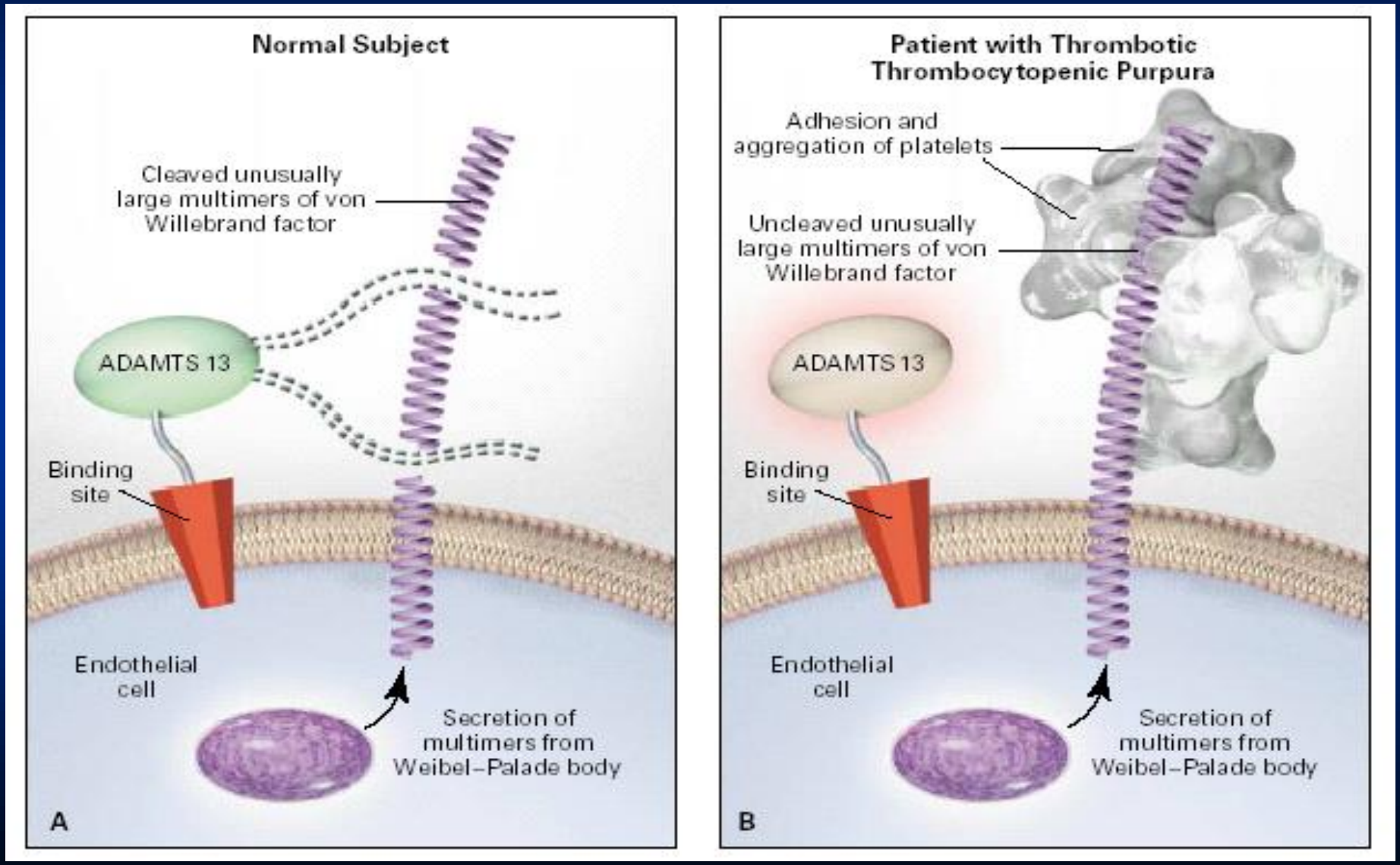
- VWF and VWFpp stored in Weibel-Palade bodies and platelet α-granules
- VWF and VWFpp circulate independently in plasma
- $t_{1/2}$ (VWF) = 8-12 hours; $t_{1/2}$ (VWFpp) = 2-3 hours in plasma
- 1 mL of plasma contains 1 unit each of VWFpp & VWF
- The ratio of VWFpp:VWF in plasma is ~ 1
- **VWFpp level as a measure of VWF synthesis and secretion**

VWF multimers and degradation products pre- and post-infusion of rVWF in a subject with type 3 VWD

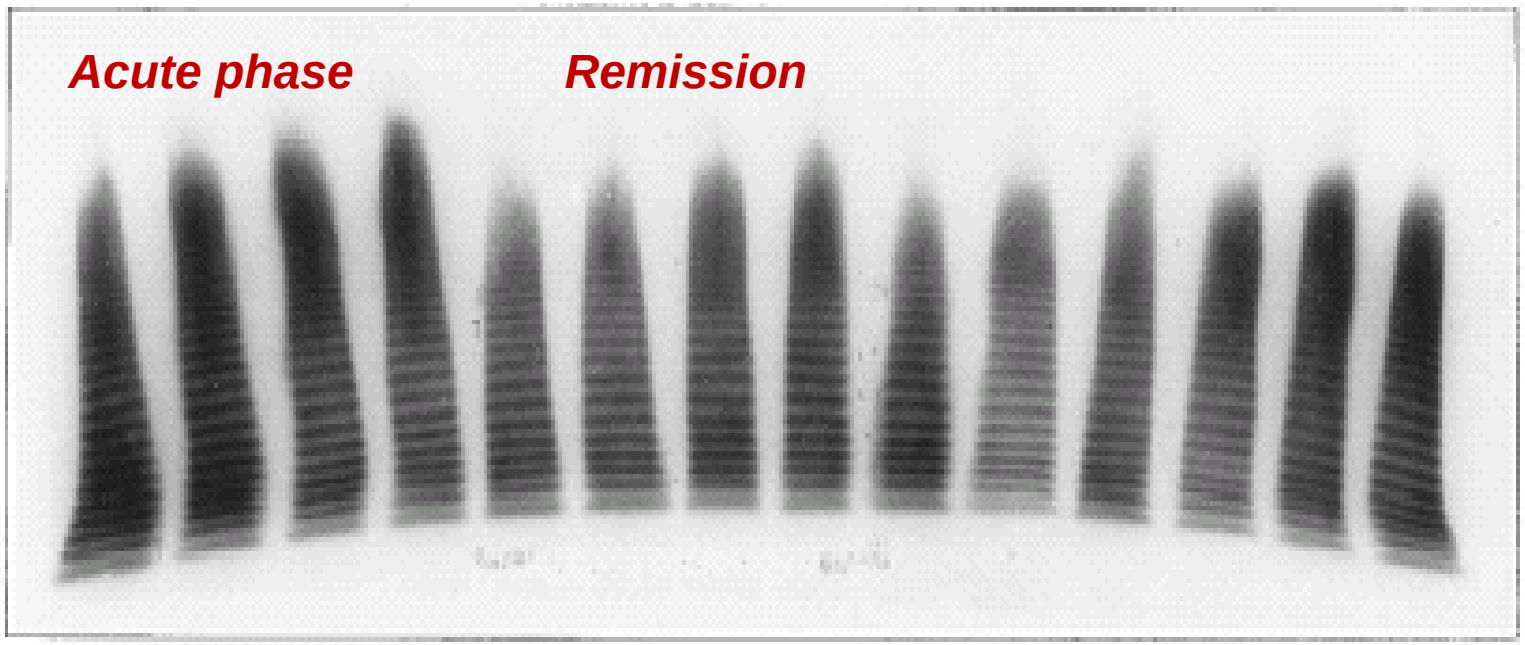


Hemostatic efficacy, safety and pharmacokinetics of a recombinant VWF in severe von Willebrand disease
JC Gill, G. Castaman, J Windyga, et al, Blood 2016

Deficiency or inhibition of ADAMTS-13 is responsible for Thrombotic Thrombocytopenic Purpura

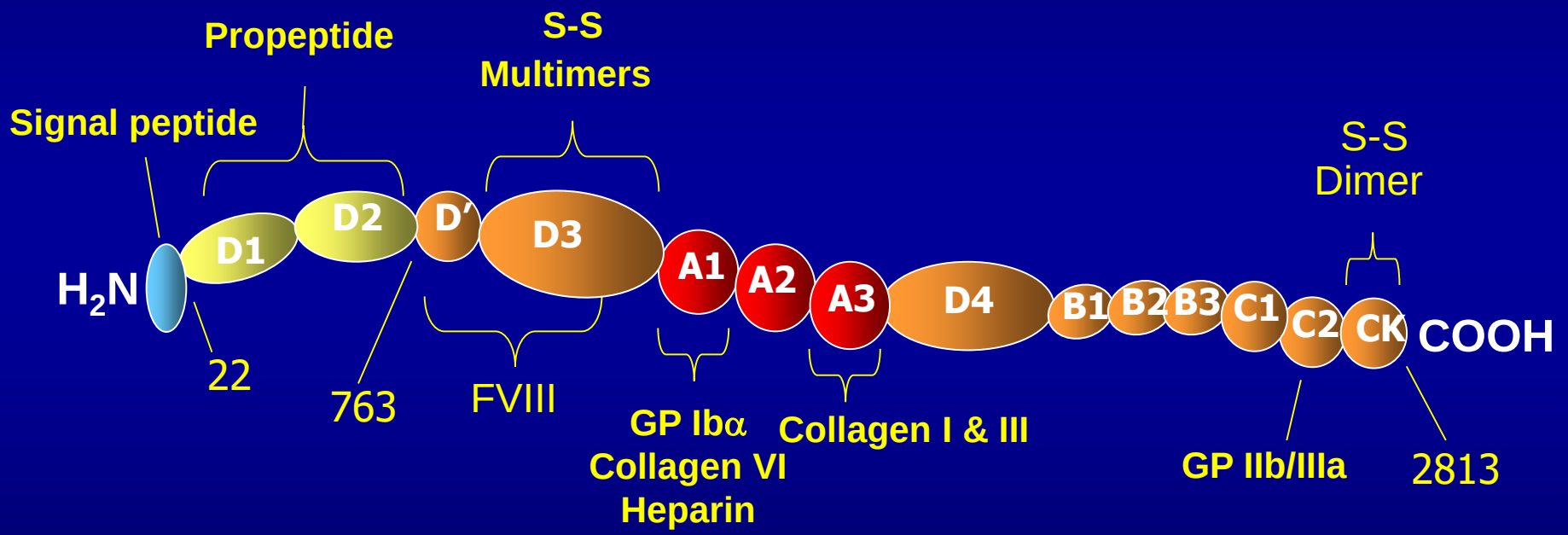


TTP: inherited deficiency or acquired inhibitors against ADAMTS 13 lead to an excess of supra-normal HMW VWF multimers



Subject	A1	A1	A2	A2	A3	A3	A4	A4	A5	NHP	B	B	C	C
Plasma sample	1	2	1	2	1	2	1	2	1	—	1	2	1	2

VON WILLEBRAND FACTOR (VWF)

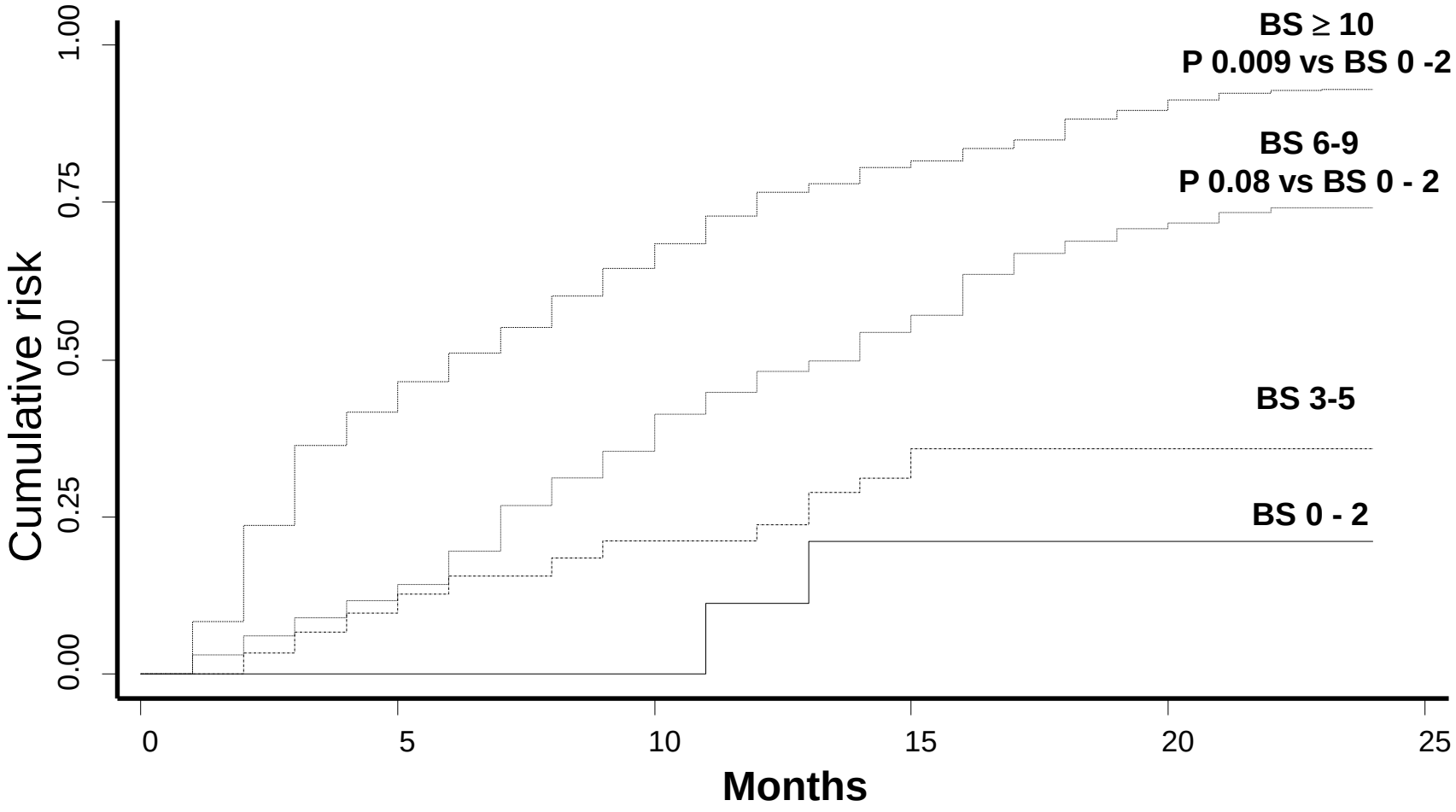


Number and types of bleeding episodes during 24-month follow-up

	Type 1 R1205H (n = 60)	Type 1 C1130F (n = 23)	Type 2 A (n = 46)	Type 2 M (n = 61)
Epistaxis	2	0	19	20
Menorrhagia	2	6	18	11
Oral	0	0	4	4
Hemorrhoidal	0	0	1	4
Gastrointestinal	1	0	53	7
Hematuria	0	0	0	3

Castaman et al, 2011; 2012

Cumulative risk of spontaneous bleeding according to baseline BS in type 2A and 2M VWD (age- and sex-adjusted)



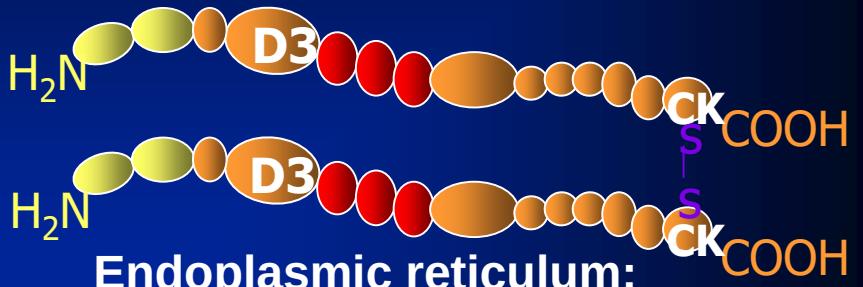
Castaman et al, 2012

Treatment summary of all bleeding episodes

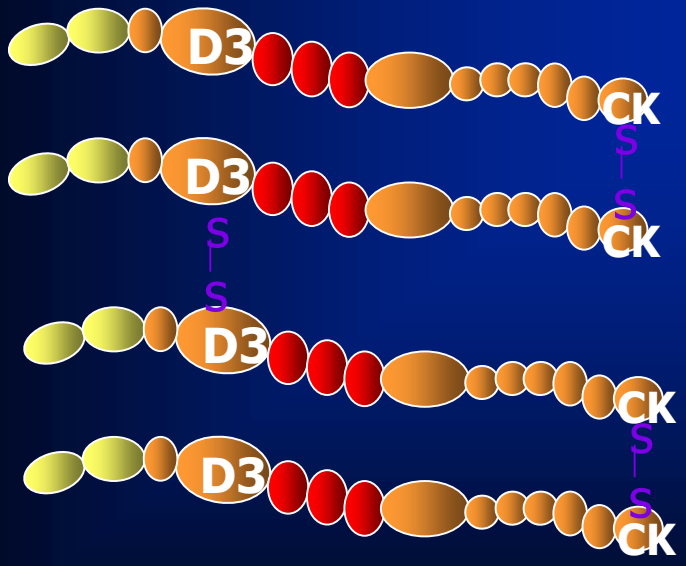
	No. bleeding episodes	Total no. infusions	Median (range) no. infusions/ bleed	Median (range) VWF:RCo dose (IU/kg)/ infusion	Median (range) rFVIII dose (IU/kg)/ infusion	% bleeds (N=192) rated* excellent or good (n excellent / good)
Subject VWF type						
Type 3	175	219	1 (1-4)	48.2 (23.8-184.9)	33.6 (16.6-129.3)	100% (171 / 4)
Type 2A	16	18	1 (1-2)	50.2 (32.9-90.2)	32.5 (23.7-38.6)	100% (14 / 2)
Type 2N	1	1	1 (1-1)	54.3 (54.3-54.3)	NA†	100% (1 / 0)
Bleed severity						
Minor	122	132	1 (1-3)	43.3 (25.2-158.2)	33.5 (17.6-86.2)	100% (119 / 3)
Moderate	61	89	1 (1-4)	52.7 (23.8-184.9)	36.9 (16.6-129.3)	100% (59 /2)
Major/severe	7	15	2 (1-3)	100.0 (57.5-135.0)	39.0 (25.0-42.3)	100% (6 / 1)
Unknown	2	2	1 (1-1)	33.4 (33.1-33.8)	23.3 (23.1-23.6)	100% (2 / 0)
Bleed site‡						
Joint	59	66	1 (1-3)	48.2 (23.8-139.6)	34.9 (16.6-129.3)	100% (57 / 2)
GI	6	10	1 (1-2)	60.0 (53.6-121.1)	33.2 (19.3 -49.4)	100% (5 / 1)
Mucosal	106	121	1 (1-4)	43.3 (23.8-184.9)	30.6 (16.6-61.3)	100% (103 / 3)
Other§	37	57	1 (1-4)	52.2 (25.2-184.9)	36.8 (17.6 -86.2)	100% (36 / 1)
Bleed cause						
Spontaneous	165	255	1 (1-4)	46.5 (23.8-184.9)	33.6 (16.6 -86.2)	100% (160 / 5)
Traumatic	26	30	1 (1-3)	51.9 (25.2-139.6)	35.8 (17.6-129.3)	100% (26 / 0)
Unknown	1	3	3 (3-3)	125.5 (125.5-125.5)	50.3 (50.3-50.3)	100% (0 / 1)

MULTIMERIZATION OF VWF

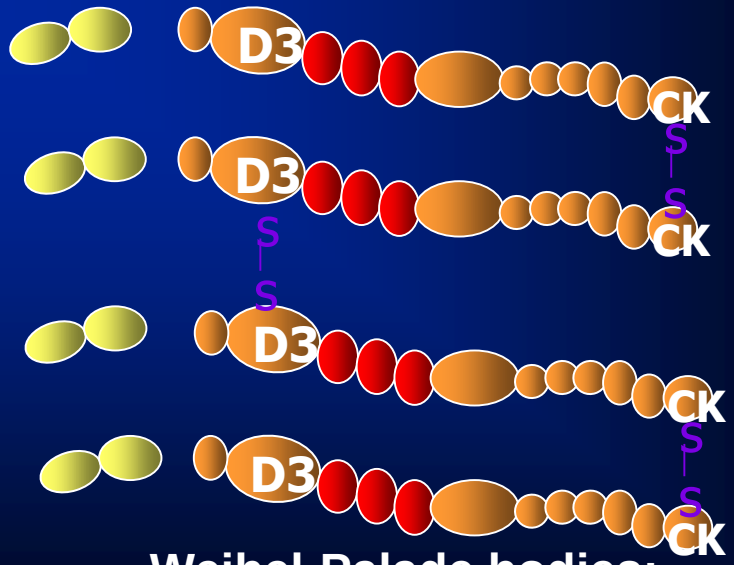
Monomer



Endoplasmic reticulum:
Dimerization e glycosylation



Golgi Apparatus:
Multimerization e glycosilation



Weibel-Palade bodies:
Cleavage of propeptide