von Willebrand disease

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The „wanted poster" of von Willebrand disease (VWD)

- Most frequent inherited bleeding disorder worldwide
- Hereditary or acquired, affecting both sexes
- Quantitative and/or qualitative VWF defects
- Variable clinical phenotype
- Diagnosis and classification based on laboratory tests

- First described 1926 by E. A. von Willebrand
- Family from Föglö (Åland islands) with bleeding diathesis
  - 5 y girl with bleeding (as many siblings), died with 13 y from heavy menstrual bleeding (as 4 sisters before)
  - suspected form of haemophilia (but autosomal inheritance) → "hereditary pseudo-haemophilia“
  - prolonged bleeding time, normal coagulation time and platelet count

From: Berntorp E. Von Willebrand's disease. Haemophilia 2012

1953 Prolonged bleeding time + low FVIII → combination of FVIII deficiency + vasopathia?

1957 Plasma fractions containing partially purified FVIII → normalisation of bleeding time and FVIII deficiency

1957 Normalisation of haemostatic defect and bleeding time by blood from patients with haemophilia A (but not normal platelets)

→ VWD and haemophilia are different

1971 Immunologic identification of VWF (FVIIIR:Ag)

1972 Heterogeneity of VWD (quantitative vs. qualitative)

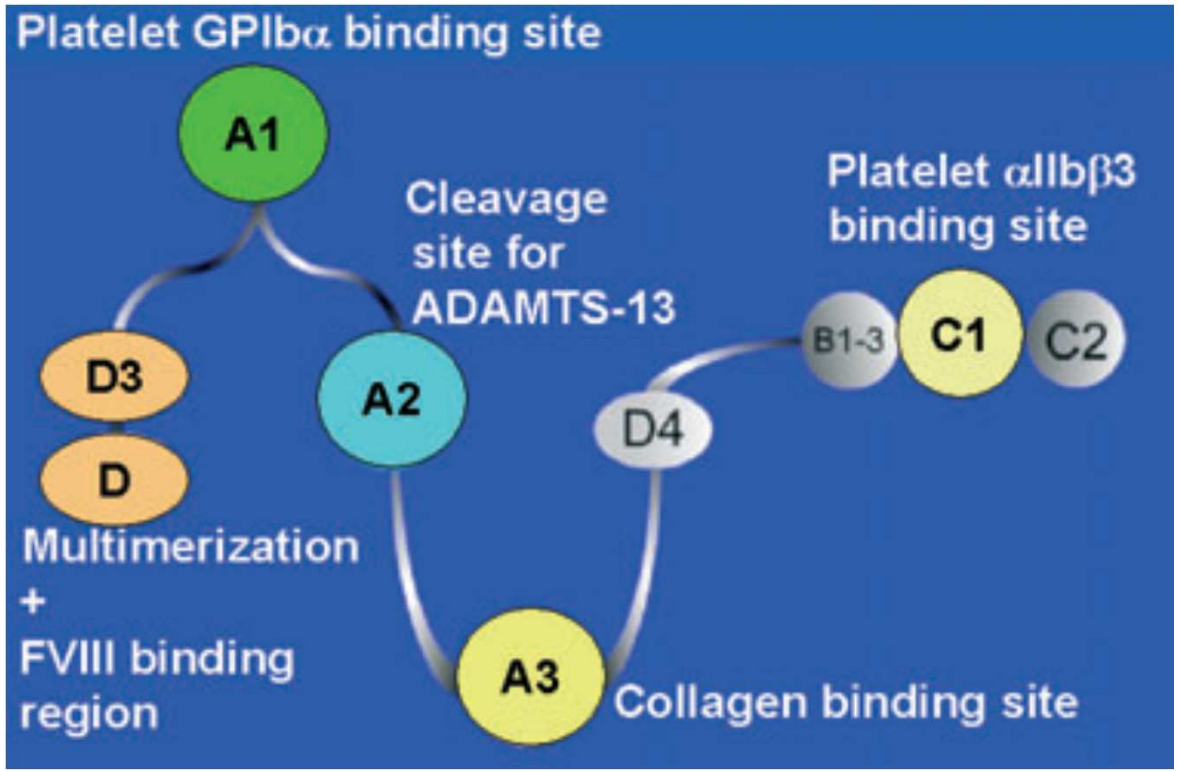
1980 VWF and FVIII circulate as a non-covalent complex

1985 FVIII and VWF → separate proteins, genes, chromosomes

- VWF, large (20 kDa) adhesive protein with multimeric structure; size regulated by ADAMTS-13 (A2 domain)
- Synthesis in endothelial cells (→ Weibel Palade bodies) and megakaryocytes (→ alpha granules); constitutive and stimulated secretion

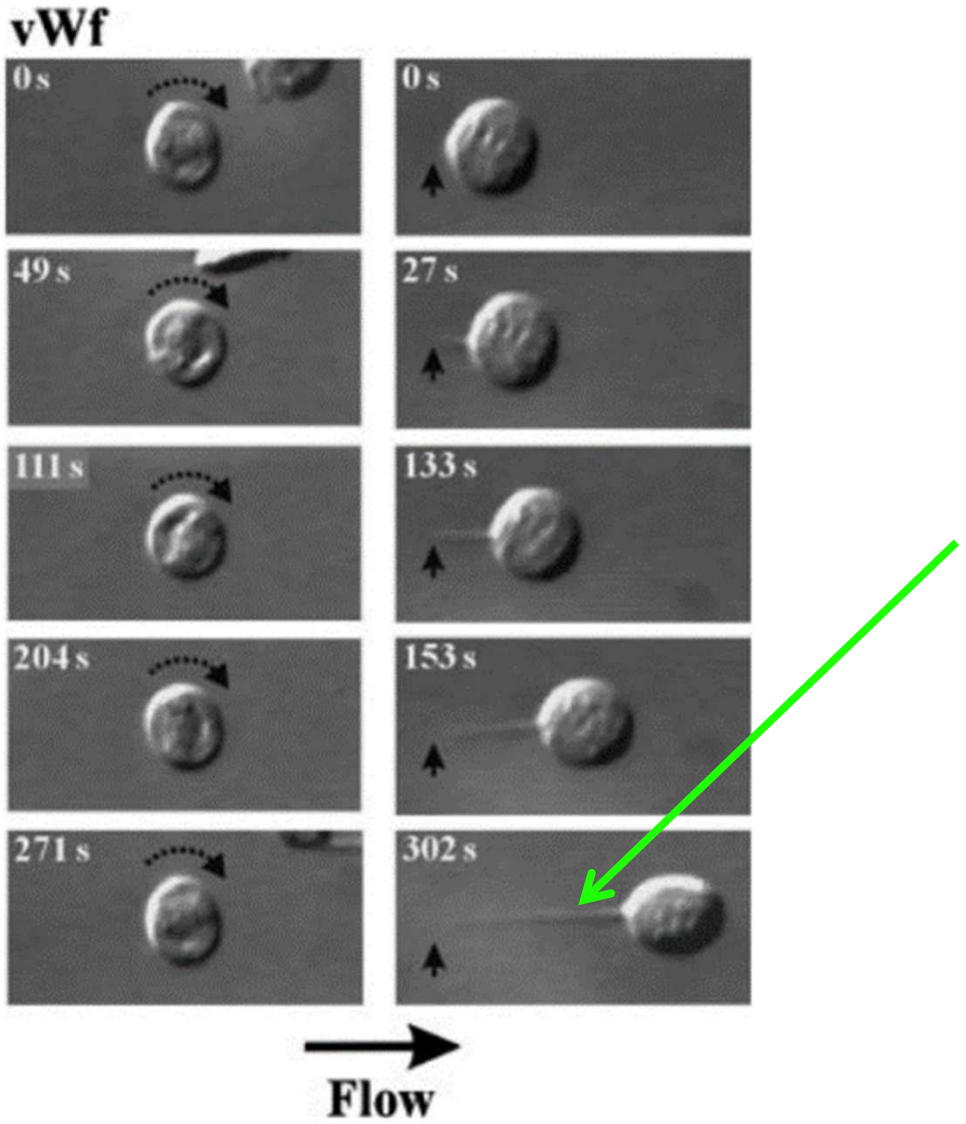
VWF has multiple domains and functions

- Binding to platelet receptors (A1 domain) and subendothelial collagen (A3 domain) → initial platelet adhesion
- Interacting with platelet GPIIbIIIa → platelet aggregation under high shear stress
- Binding of FVIII (D', D3 domain) → circulating complex protecting FVIII of premature removal

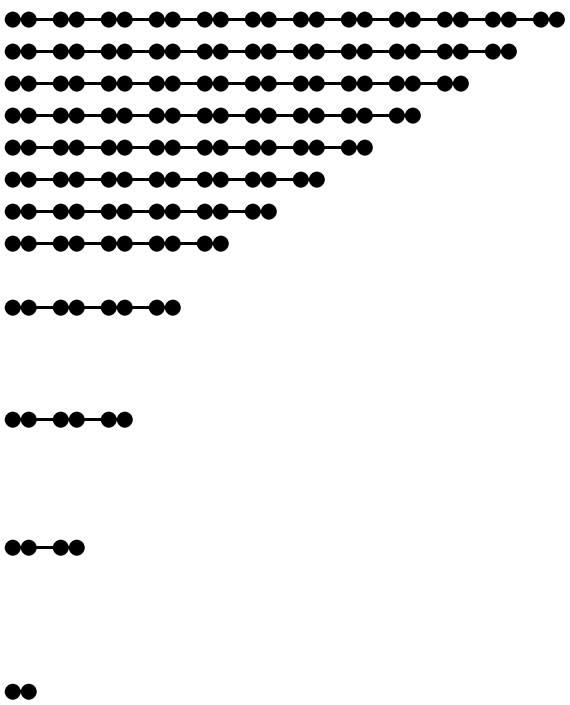


Mature VWF subunit with binding and cleavage sites

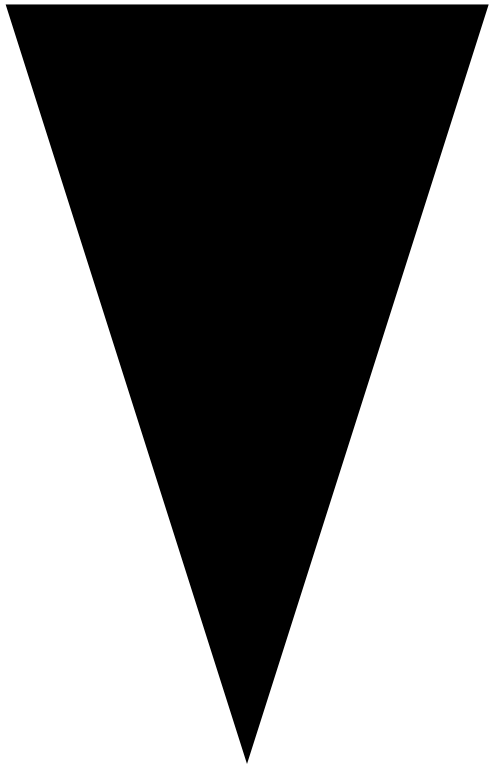
(from: Reininger A. Haemophilia 2008)



Tethering of platelets by VWF (from: Dopheide S. Blood 2002)



multimer size



adhesive function (interaction with platelets, collagen)

Epidemiology

- VWD most frequent hereditary bleeding disorder worldwide
- Laboratory constellation up to ~ 1% of population
- Clinically significant 1/5000-10000; variable clinical phenotype

  → prevalence dependes on criteria of patient identification

- Symptomatic patients as registered by centers in different countries → prevalence 0.002 - 0.01%
- Population screening → higher prevalence 0.8 - 1.3%
  - Scandinavia ~ 125/1 mio
  - screening of Italian school children ~ 8000/1 mio

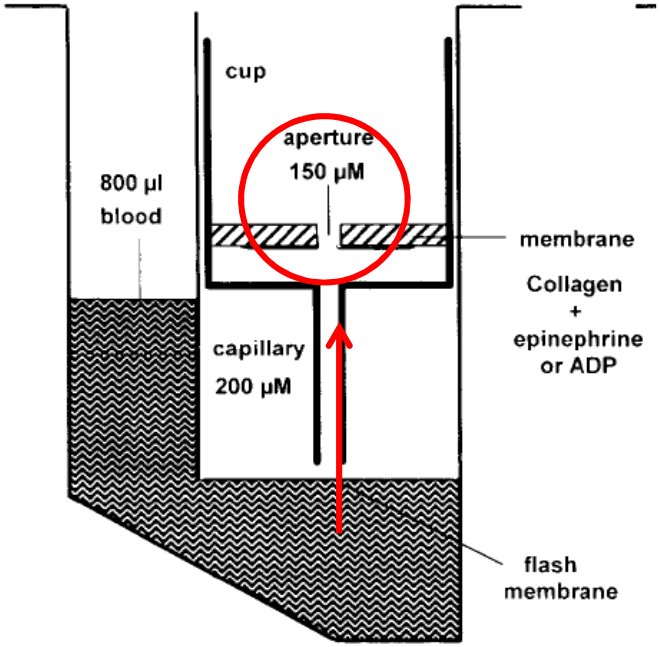
Diagnostic workup

Patient with hitherto undiagnosed bleeding disorder

- Bleeding history (patient, family, inheritance pattern)
- Clinical presentation (asymptomatic $\rightarrow$ severe bleeding; predominantly mucocutaneous)
- Specific laboratory work up (despite normal screening tests)

Initial screening

- History (validated questionaire, e. g. ISTH BAT)
  - including family history
- "Global" test of primary haemostasis
  - *in vivo* bleeding time: variable, often unspecific
  - PFA closure time



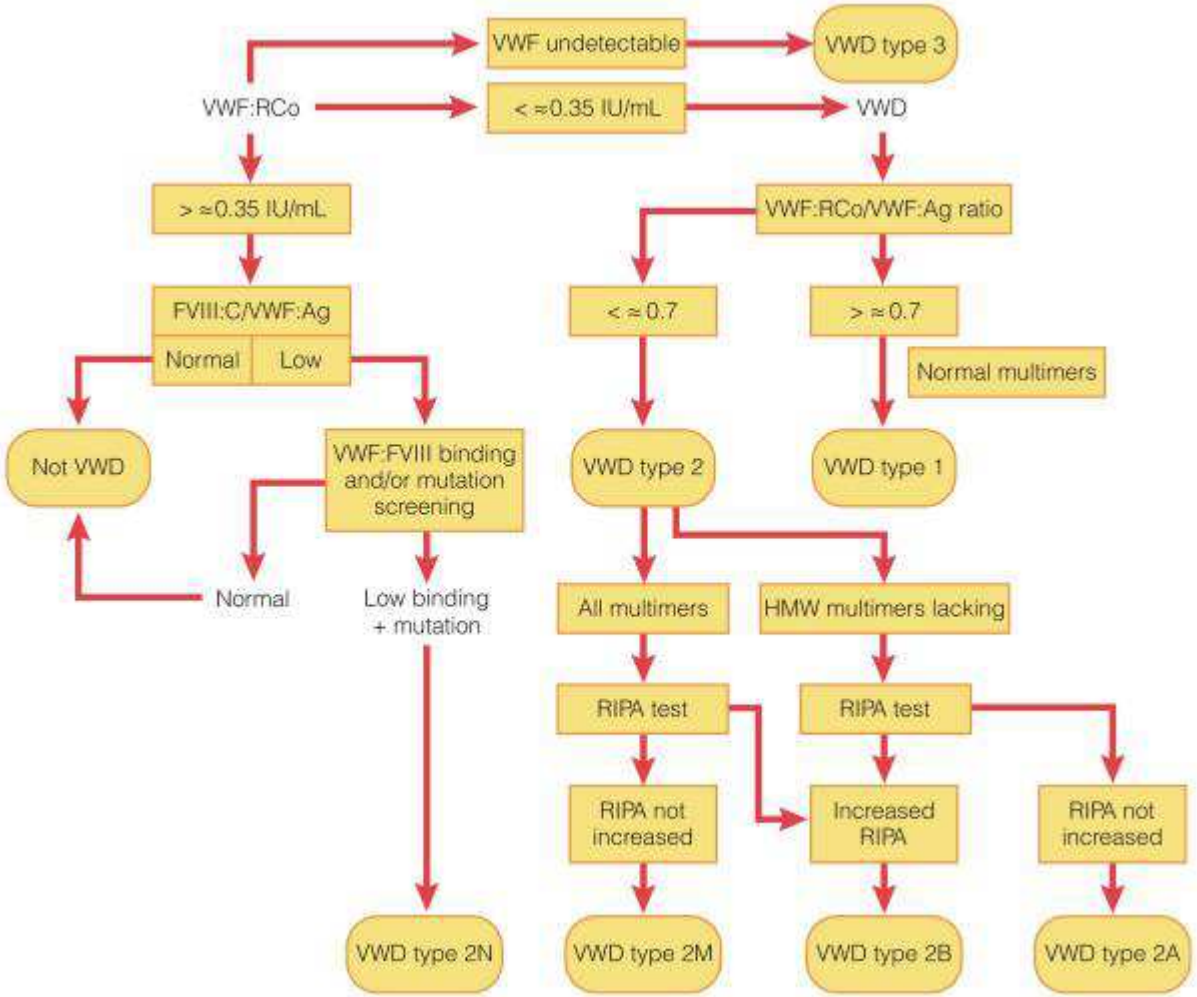
Platelet Function Analyzer

(from: Madan M. Am Heart J 2001)

	gesamt	Typ 1	Typ 2A	Typ 2B	Typ 2N	Typ 2M	Typ 3	Erw	Plttyp
	[%]	[%]	[%]	[%]	[%]	[%]	[%]	[%]	[%]
Col/ADP	86,3	79,5	100,0	93,0	0,0	97,6	100,0	100,0	100,0
Col/ EPI	90,0	85,8	100,0	93,0	0,0	97,6	100,0	100,0	100,0

Laboratory tests

- VWF plasma concentration (VWF:Ag)
  - normal plasma concentration ~10 μg/l
  - influenced by acute phase/inflammation, AB0 blood group, pregnancy, diabetes, liver disease, and many others
  - often requiring repetitive analyses
- Functional activitiy (VWF:RCo/VWF:Ac → GPIb, VWF:CB → Coll)
- Turnover/clearance (VWFpp)
- Binding of FVIII (VWF:FVIIIB)
- Structural integrity (VWF multimer analysis)
- Molecular diagnostics



Diagnostic work up in VWD (from: Berntorp E. Haemophilia 2012)

Assays for subclassification of VWD

- Multimer analysis crucial for diagnosing VWD 2A (↓ large multimers, structural alterations)
- Propeptide (VWFpp) → elevated turnover (e.g. acquired VWD)
- FVIII binding capacity (VWF:FVIIIB)
- Ristocetin-induced platelet aggregation (RIPA) → VWD 2A vs 2B
- Molecular genetics

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight VWF multimers
2B	Increased affinity for platelet glycoprotein Ib
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular-weight VWF multimers
2N	Markedly decreased binding affinity for factor VIII
3	Virtually complete deficiency of VWF

From: Sadler EJ. J Thromb Haemost 2006

Diagnosing VWD → always determine type/subtype

ISTH revised classification of VWD

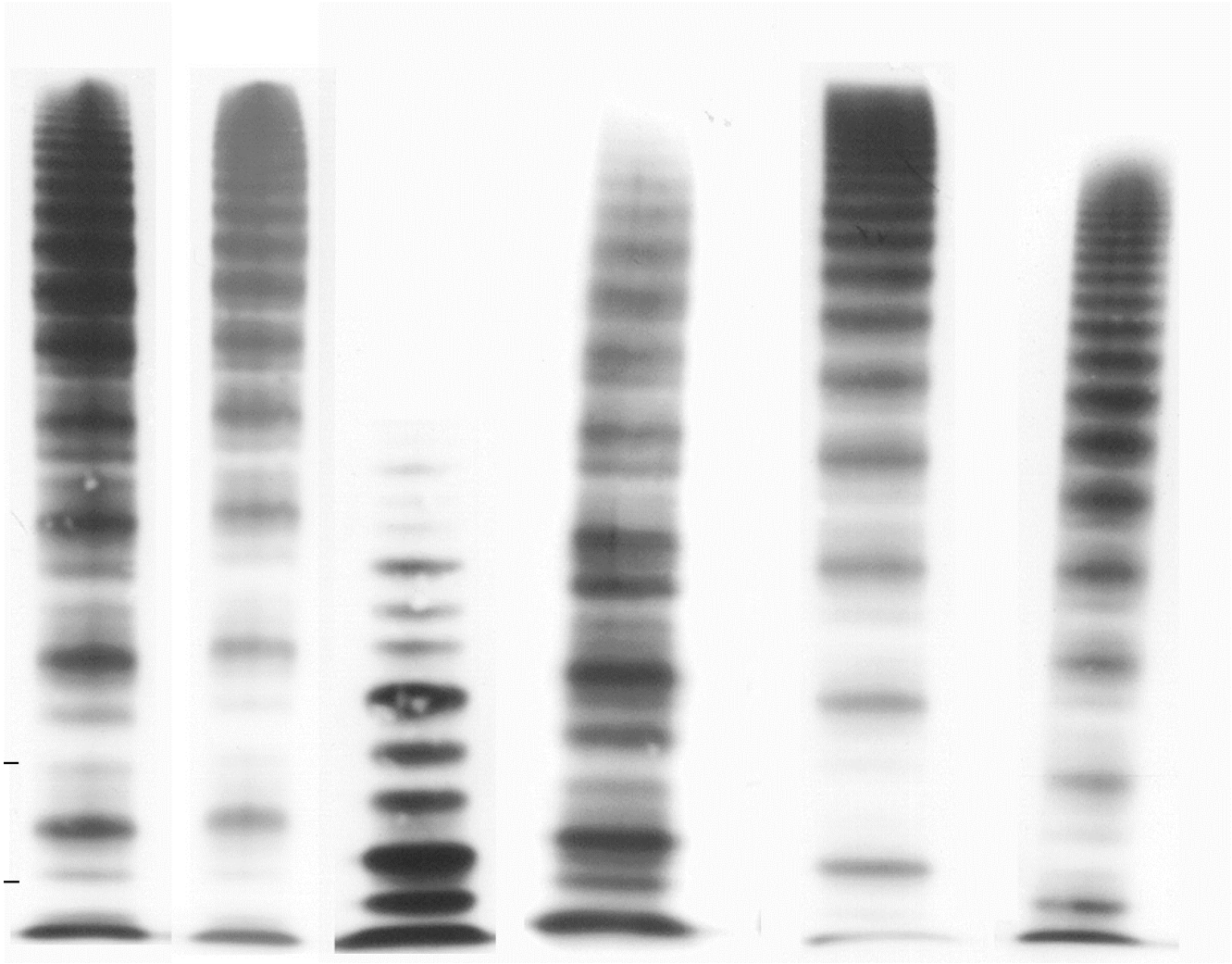
VWD 1 = quantitative deficiency of VWF (72%) (51%) * (29%) **

VWD 2 = qualitative defects

- 2A (~ 70%)
- 2B (~ 10%)
- 2M (~ 13%)
- 2N (~ 7%) (VWD „Normandy“)

VWD 3 = virtually complete deficiency of VWF (3%)

VWD 1 → depending on VWF:Ag cut off (50%), (40%) *, (30%) **



NP 1 2A 2B 2M 2N 3

VWD 1

- Mild VWD, most frequent subtype (up to 70%)
- Mostly autosomal-dominant inheritance
- VWF
  - reduced to ~ 20 to < 50% (reduced expression or secretion, increased clearance)
  - VWF functionally normal with all multimers present (VWF:RCo or VWF:Ac or VWF:CB = VWF:Ag)

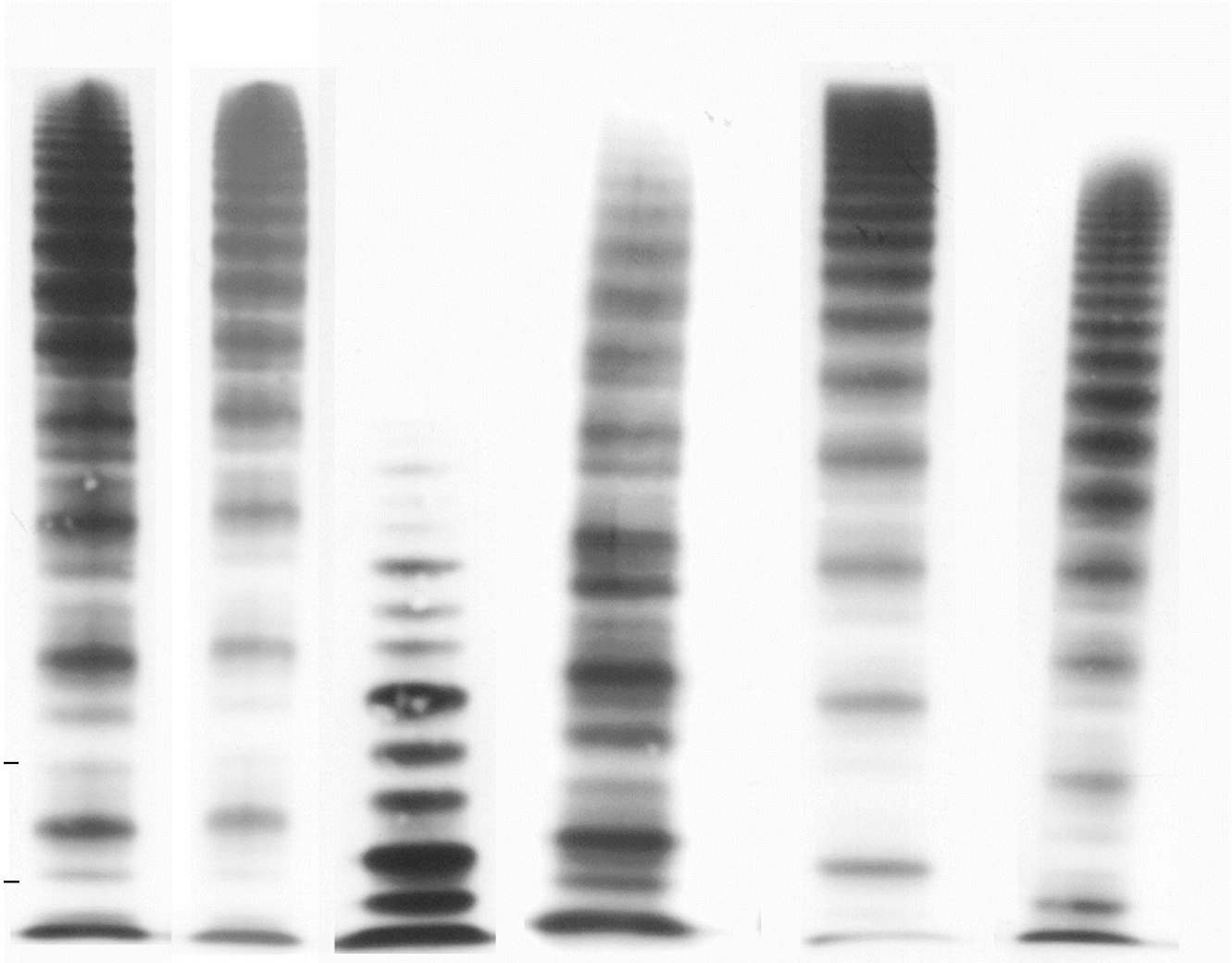
Diagnosing VWD 1 may be difficult

- Low normal vs. reduced VWF
- Variable clinical presentation, often asymptomatic without provocation

ISTH preliminary diagnostic criteria

- clinical symptoms (significant mucocutaneous bleeding)
- laboratory results
- inheritance
- „possible“ VWD 1 → laboratory results + bleeding or inheritance

Importance of bleeding history (Rodeghiero F. J Thromb Haemost 2005)



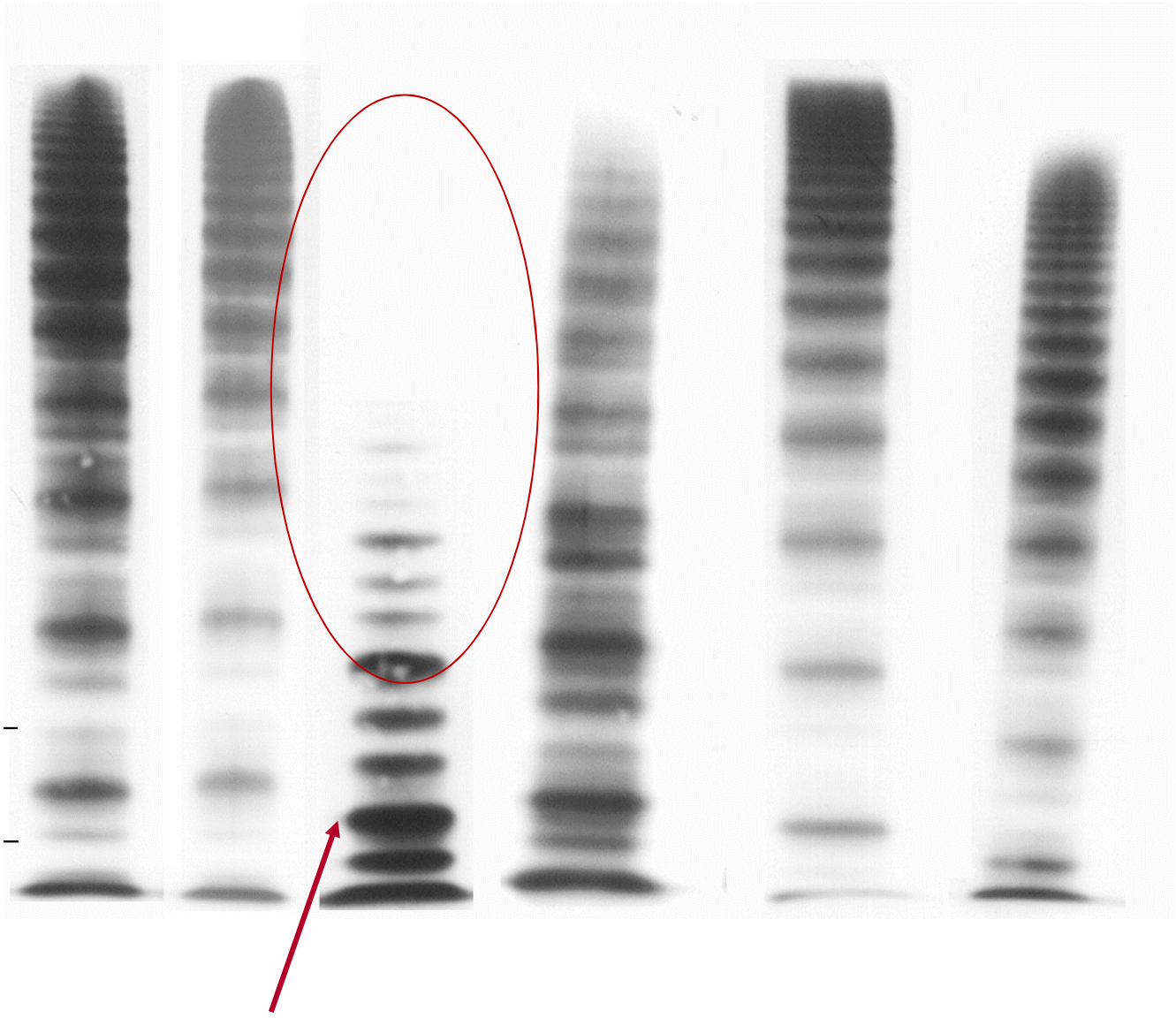
NP 1

VWD 2A

- ↓ interaction of VWF with platelets and subendothelium
- Caused by reduction or loss of large VWF multimers
- Heterogeneous, different pathomechanisms (e.g. defects of multimerisation, increased susceptibility to proteolysis)
- VWF → discrepant reduction of functional activity vs. antigen

e. g. VWF:Ac 11%, VWF ag. 35%, ratio 0.31 (≥ 0.7)

- Diagnosis of VWD 2A is confirmed by multimer analysis


NP
2A

VWD 2B

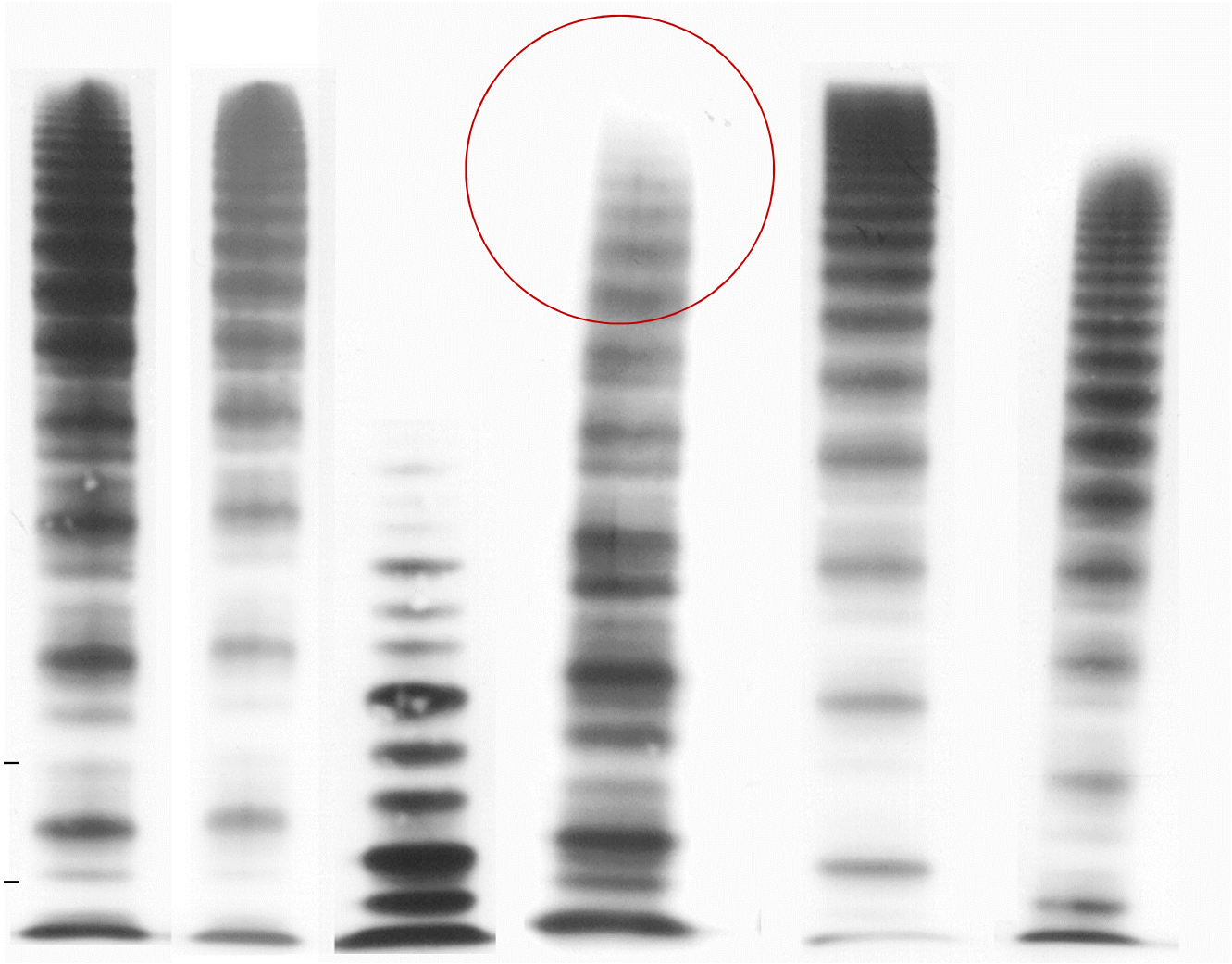
- Increased affinity of VWF to platelet GPIb (A1 mutations);

  sometimes, associated thrombocytopenia

- Large multimers frequently reduced; increased RIPA

- Similar to (but different) from pseudo/platelet VWD

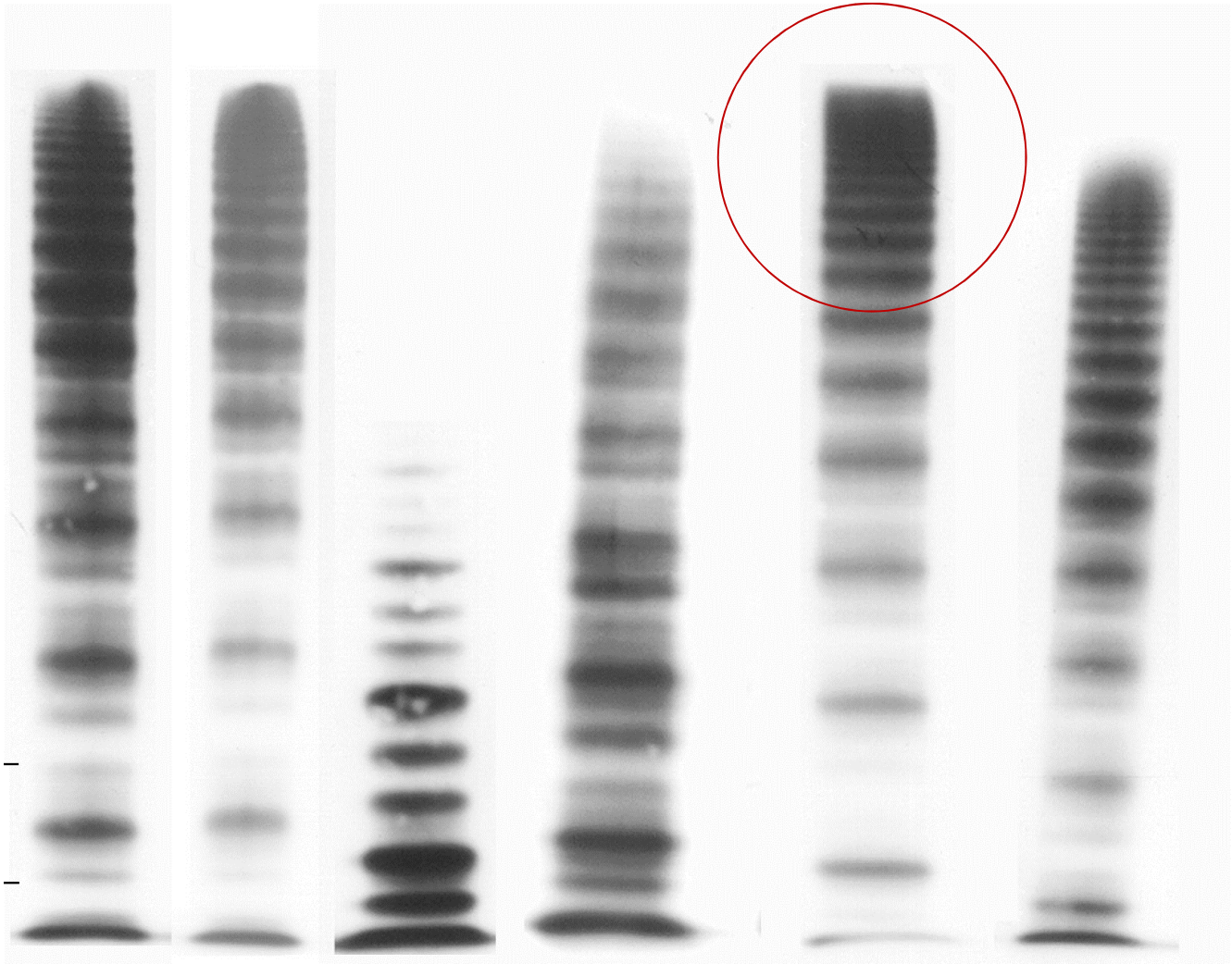
  (GPIb mutations)



NP 2B

VWD 2M (M for multimers)

- Variants with adhesive defect similar to VWD 2A
- Defect not due to loss of large multimers; some variants with larger-than-normal (supranormal) multimers
- Causal mutations in the GPIb (A1) or collagen binding domain (A3)



NP

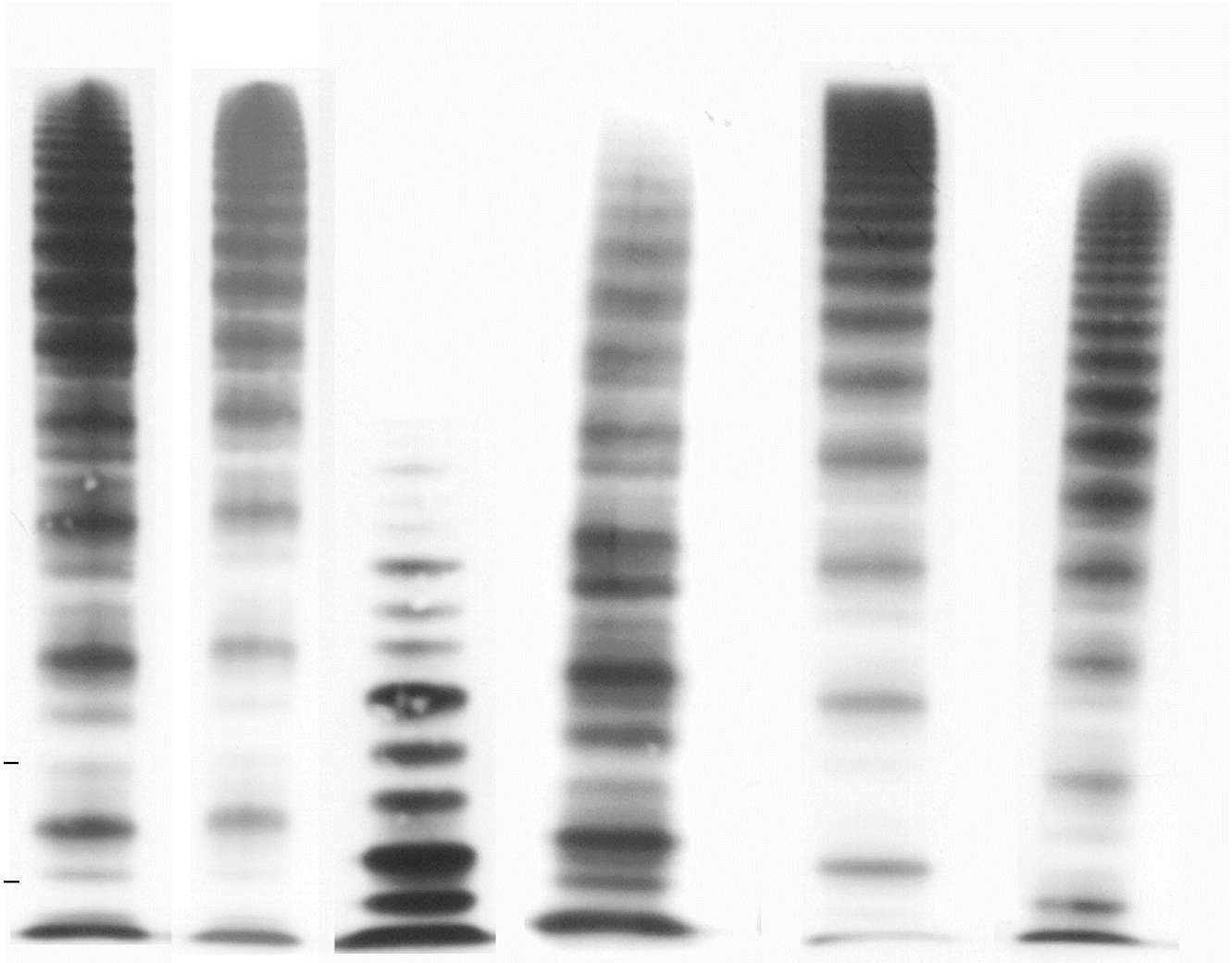
2M

VWD 2N (Normandy)

- VWF with normal adhesive function but reduced ability to bind FVIII
- Causal D domain mutations
- Reduced FVIII half-life despite normal synthesis
- Presenting like mild haemophilia A (→ important differential dg.)
- Recombinant FVIII concentrates are ineffective!

VWD 3 (severe VWD)

- Rare (1/mio), autosomal recessive inheritance
- Virtually complete deficiency of VWF in plasma and platelets
- Secondary FVIII deficiency (usually <10%)
- Combined defect of primary and secondary haemostasis



NP

3

Bleeding symptoms	Italian pts (n = 1286)			Irani VWD 3	Scandinavian pts
	VWD 1 (n = 944)	VWD 2 (n = 268)	VWD 3 (n = 74)		
Epistaxis	56	63	74	77	62
Menorrhagia	31	32	32	69	60
Bleeding after tooth extraction	31	39	53	70	51
Haematoma	14	19	31	nn	49
Bleeding from injuries	36	40	50	nn	36
Gingival bleeding	30	37	48	nn	35
Postop. bleeding	20	23	41	41	28
Postpartal bleeding	17	18	26	15	23
GIT bleeding	5	11	18	20	14
Petechiae	nn	nn	nn	nn	11
Joint bleeding	2	5	42	37	8
Haematuria	2	4	11	1	7
CNS bleeding	0,5	2	8	nn	nn

(Federici A. Haemophilia 2002; Lak M. Br J Haematol 2000; Silwer J. Acta Paediatr Scand 1973)

Treatment according to type and subtype of VWD

VWD	1	topical, hormones, antifibrinolytics, DDAVP (VWF concentrate)
	2	VWF concentrate (on demand) DDAVP not effective in many subtypes and contraindicated in VWD 2B
	3	FVIII/VWF concentrate (on demand or prophylaxis)

Faktor 8 (VIII, fkt.) #	%	50-200	70	70	136	137	119
von Willebrand Faktor (fkt.) #	%	50-200	* 18 (2)	* 25 (2)	* 46 (2)	* 45 (2)	* 40 (2)
von Willebrand Faktor (ag.)	%	50-200	* 18 (2)	* 25 (2)	* 42 (2)	* 46 (2)	* 40 (2)
Ratio vWF #		>0.7	1.00 (2)	1.00 (2)	1.10	0.98 (2)	1.00 (2)
von Willebrand Faktor (MM) #		normal	(3)				
vWF: Propeptid #	%	50-200	* 31 (4)				

Insufficient DDAVP effect in VWD 2M (→ 4 hrs)

Acquired VWD

- Quantitative and qualitative defects
- Presentation and laboratory resembling congenital VWD
- Associated with a variety of underlying diseases, e. g.
    - lymphoproliferative and myeloprolifereative (MW, ET)
    - cardiovascular (aortic valve stenosis)
    - autoimmune (SLE → first report 1968)
    - hypothyreoidism
- Different pathomechanisms, e. g. ↑ proteolysis or ↑ clearance
- Treatment includes DDAVP, VWF concentrate (less efficient in autoimmune disorders), rFVIIa, IVIG (e. g. IgG MGUS)
- Treatment of underlying disease

Summary

- VWD is (in comparison) frequent
- Relevant cause of unexplained bleeding
- Often mild and not recognised before provocation
- Congenital or acquired
- Identification of patients requires history, clinical presentation, and laboratory
- Prophylaxis and tretament of bleeding according to the type / subtype of VWD