EDUCATIONAL QUIZ WITH VOTING ON VWD TOPIC

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Aland Islands from Space: 6,500 islands

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Classification of von Willebrand disease

*Sadler JE, Thromb Haemost 1994; 71: 520-525

*Sadler JE, JTH 2006; 4: 2103-2114

- type 1 – partial quantitative deficiency, AD
- type 2 – qualitative defects, AD, AR
  - 2A – decreased VWF-dependent platelet adhesion and deficiency of HMW multimers, AD
  - 2B – increased affinity for platelet GPIb, AD
  - 2M – decreased VWF-dependent platelet adhesion without selective deficiency of HMW multimers, AD
  - 2N – decreased binding affinity for FVIII, AR
- type 3 – virtually complete deficiency of vWF, AR

Diagnosis of von Willebrand disease (SSC ISTH Subcommittee on vWF, 1996)

- **confirm:** a) mucocutaneous bleeding
  b) family history
  c) laboratory tests

  VWF: RCo, VWF:Ag < 2 SD (BG 0, non-0)

  MCMDM-1vWD cut off for percentil 2,5 (n=1166):
  - BG 0:
    - VWF:RCo 43%
    - VWF:Ag 44,4%
  - BG non-0:
    - VWF:RCo 54%
    - VWF:Ag 54%
- **possible:**
  - without a) or b)

*Sadler JE, J Thromb Haemost 2005; 3: 775-777

Acquired determinants of plasma VWF level

- Elevation:
  - Infections
  - Endothelial demage (DM)
  - Physical activity
  - Hyperthyroidism
  - Pregnancy, OC, HRT
  - Age (1-2% per 1 year)
- Reduction:
  - Hypothyroidism
  - Valproat

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Grades of bleeding severity

*Tosetto A.Haemophilia 2008;14:415-22

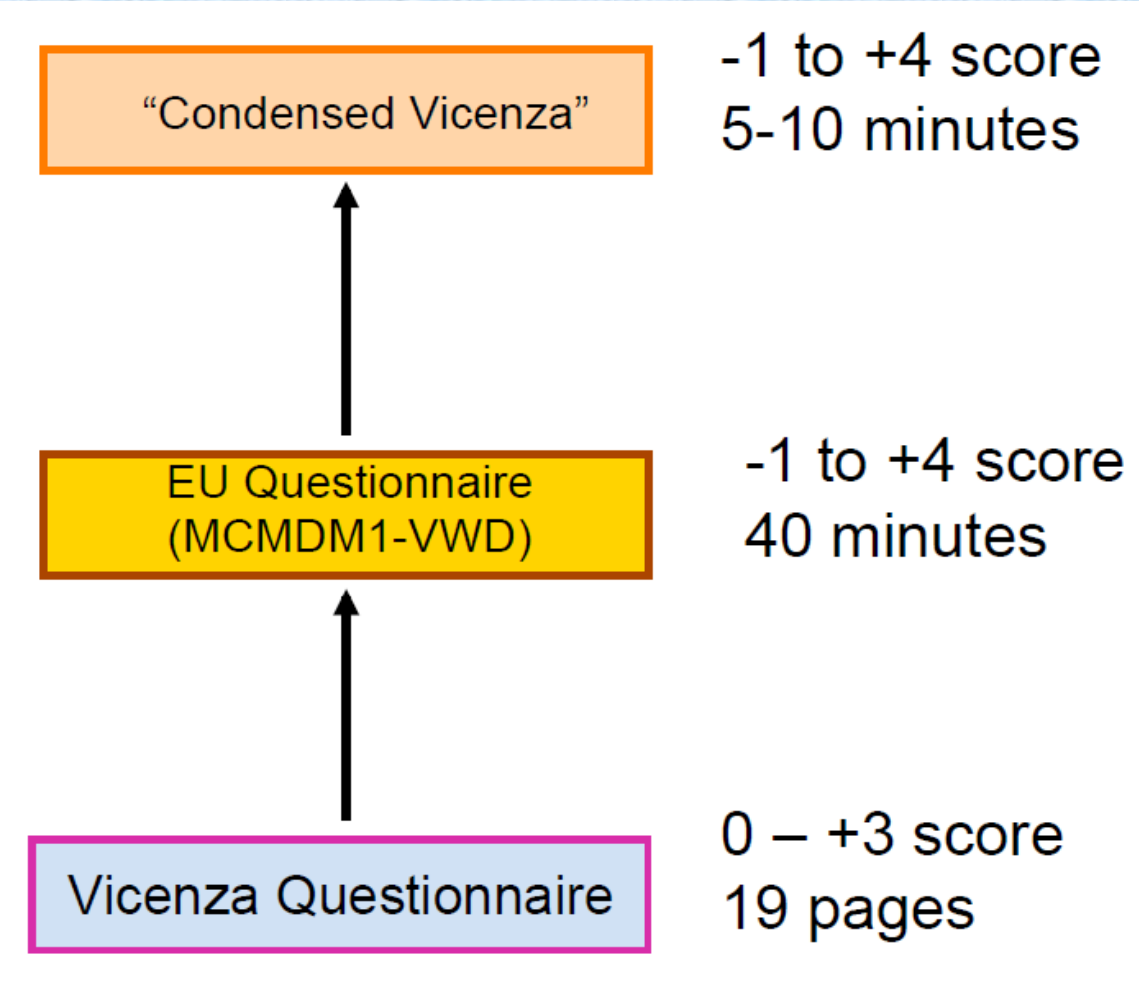
Symptom	Score 0	1	2	3
Epistaxis	No or trivial	Present	Packing, cauterization	Blood transfusion or replacement therapy
Cutaneous	No or trivial	Petechiae or bruises	Haematomas	Consultation
Bleeding from minor wounds	No or trivial	Present (1–5 episodes per year)	Consultation	Surgical haemostasis
Oral cavity	No or trivial	Present	Consultation only	Surgical haemostasis/blood transfusion
GI bleeding	No or trivial	Present	Consultation only	Surgery/blood transfusion
Tooth extraction	No or trivial	Present	Suturing or packing	Blood transfusion
Surgery	No or trivial	Present	Suturing or resurgery	Blood transfusion
Menorrhagia	No or trivial	Present	Consultation, pill use, iron therapy	Blood transfusion, hysterectomy, dilatation and curretage
Postpartum haemorrhage	No or trivial	Present, iron therapy	Blood transfusion, dilatation and curettage, suturing	Hysterectomy
Muscle haematomas	No or trivial	Present	Consultation only	Blood transfusion, surgery
Haemarthrosis	No or trivial	Present	Consultation only	Blood transfusion, surgery

Minimaly diagnostic criteria for clinicaly useful diagnosis of VWD - BS

- **bleeding score:**
  - > 3 in men
  - > 5 in women
  - requirement for high BS is less stringent in children

*Rodeghiero F.2009;51st Congress of ASH,New Orleans

Effort into simplification of bleeding score questionnaire



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ISTH-BAT Standing Committee

- The Scientific and Standardization Executive Committee of ISTH has established it in October 2011
- The system is available to all investigators
- But requires an IRB-approved protocol
  - participants' informed consent
- Investigate the clinical phenotype of inherited bleeding disorders in a wide range
- https://bh.rockefeller.edu/bat/

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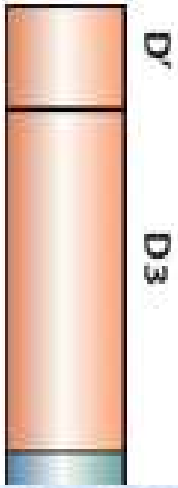
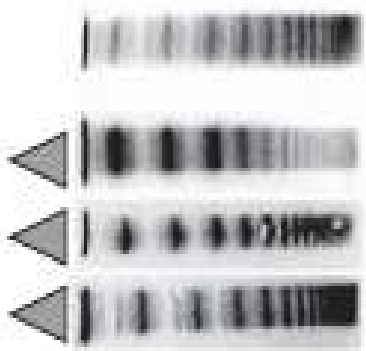
Role of the VWFpp/Ag ratio

- VWFpp is released after VWF secretion
- half-life:
  - VWFpp: 2-3 h
  - VWF:Ag 8-12 h
- diagnosis of increased clearence:
  - in VWD
  - in acquired VWF defects





VWF domain	Multimers	Mutation	FVIII:C	VWF:Ag	VWF:RCo	VWF:RCo/ VWF:Ag	VWF:pp/ VWF:Ag	VWD type
		WT	78–135	71–119	62–113	0.93	1.0	–
		C1130R	13–15	12–22	7–13	N/↓	2–4	I/2E
		W114G	24	31	12	N/↓	2–4	I/2E
		R1205H	7–19	5–10	3–10	±1	>10	I/Vicenza

**Gadisseur A.Acta Haematol 2009;121:128-38*

VWF:RCo – automated assay

- Monoclonal antibody against epitope of VWF which interacts with platelet GPIbα:
  - False normal results in some VWD2A
    - *Favaloro EJ, Thromb Haemost 2000; 84: 541-547*
- rf-GP Ibα:
  - Good correlation with classic VWF:Rco
    - *Vanhoorelbeke K, Thromb Haemost 2000; 83: 107-113*
- gain-of-function r-GPIb:

	RCo / Ag:	**IbCo / Ag:**
• 2A:	0,61	0,49
• 2B:	0,63	2,17
• platelet VWD	0,39	0,41

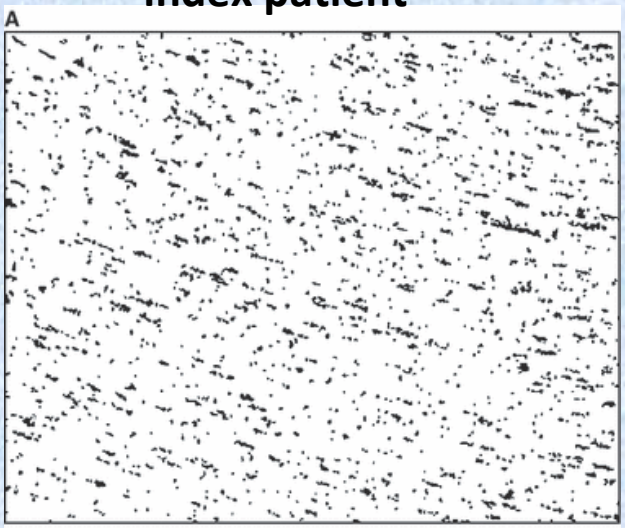
  - *Flood VH, ISTH 2009, Boston*
  - *Flood VH, JTH 2009, 7: 1832-1839*
- Plasma glykokalcin:
  - Good correlation with classic VWF:Rco
    - *Vanhoorelbeke K, Thromb Haemost 2005; 93: 165-171*

Limitations of the ristocetin cofactor assay in measurement of von Willebrand factor function

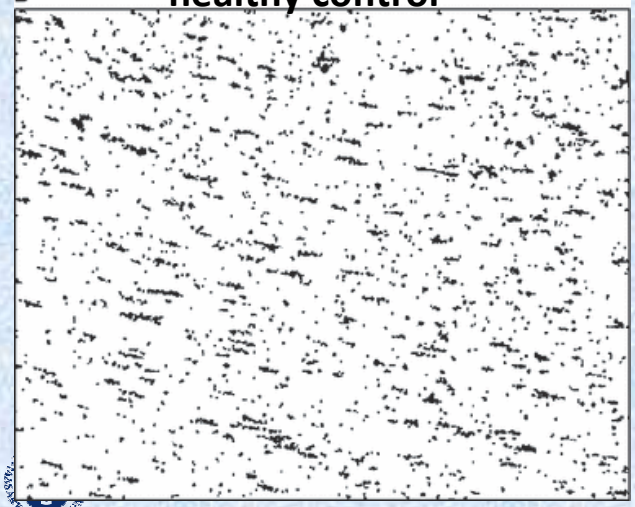
V. H. FLOOD*, K. D. FRIEDMAN†, J. C. GILL*†, P. A. MORATECK†, J. S. WREN†, J. P. SCOTT*† and R. R. MONTGOMERY*†
* * J Thromb Haemost 2009;7:1832-9

	Proband	Brother	Mother	Father
Age	19	16	49	50
FVIII	111	151	127	127
VWF:Ag	116	150	98	145
VWF:RCo	11	24	59	26
Blood type	O	A	O	A
Bleeding score	-1*	0	-1	-1
Genetics	C4399T	C4399T	No mutation	C4399T

index patient



healthy control



Cone and platelet analyzer Impact-R

- no difference in platelet adhesion

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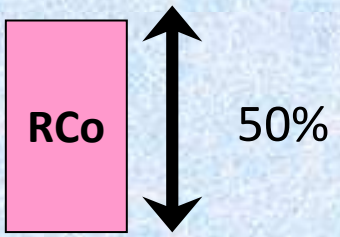
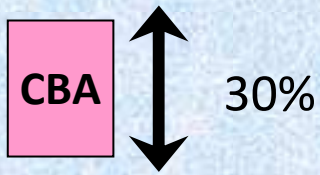
Collagen binding assay - VWF:CBA

- more sensitive for HMW multimer deficiency
  - type 2A,2B: vWF:CBA / vWF:Ag < 0,5
- dependent on collagen type:
  - mixture type I/III (equine or bovine tendon) is preferred
  - human-derived type III bind VWF too well:
    - do not show discrimination of HMW multimers
- 2006: 50% Australasian, 25% EU, 10% UK, < 5% USA laboratories used VWF:CBA





*Favaloro EJ.Semin Thromb Hemost 2006;32:456-71
*Favaloro EJ.Semin Thromb Hemost 2006;32:566-76

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A summary of the routine laboratory findings in the various types of VWD

type	RIPA	RCo	Ag	FVIII	RCo/Ag	CBA	CBA/Ag
1	N↓	↓	↓	N↓	N	↓	N
2A	↓↓	↓↓	N↓	N↓	↓< 0,6-0,7	↓↓	↓< 0,5
2B	N↑	↓	N↓	N↓	↓<0,6-0,7	↓↓	↓ < 0,5
2M	N↓	↓(N)	N↓	N↓	↓<0,6-0,7	N ↓	N ↓
2N	N	N ↓	N↓	↓	N	N	N
3	↓ ↓	↓ ↓	↓ ↓	↓ ↓	N↓	↓ ↓	N ↓

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Need for more physiologically relevant assays of VWF function

Studies under physiological flow conditions are needed to define:

- interaction with collagen
- interaction with platelets
- efficacy of different VWF-containing concentrates

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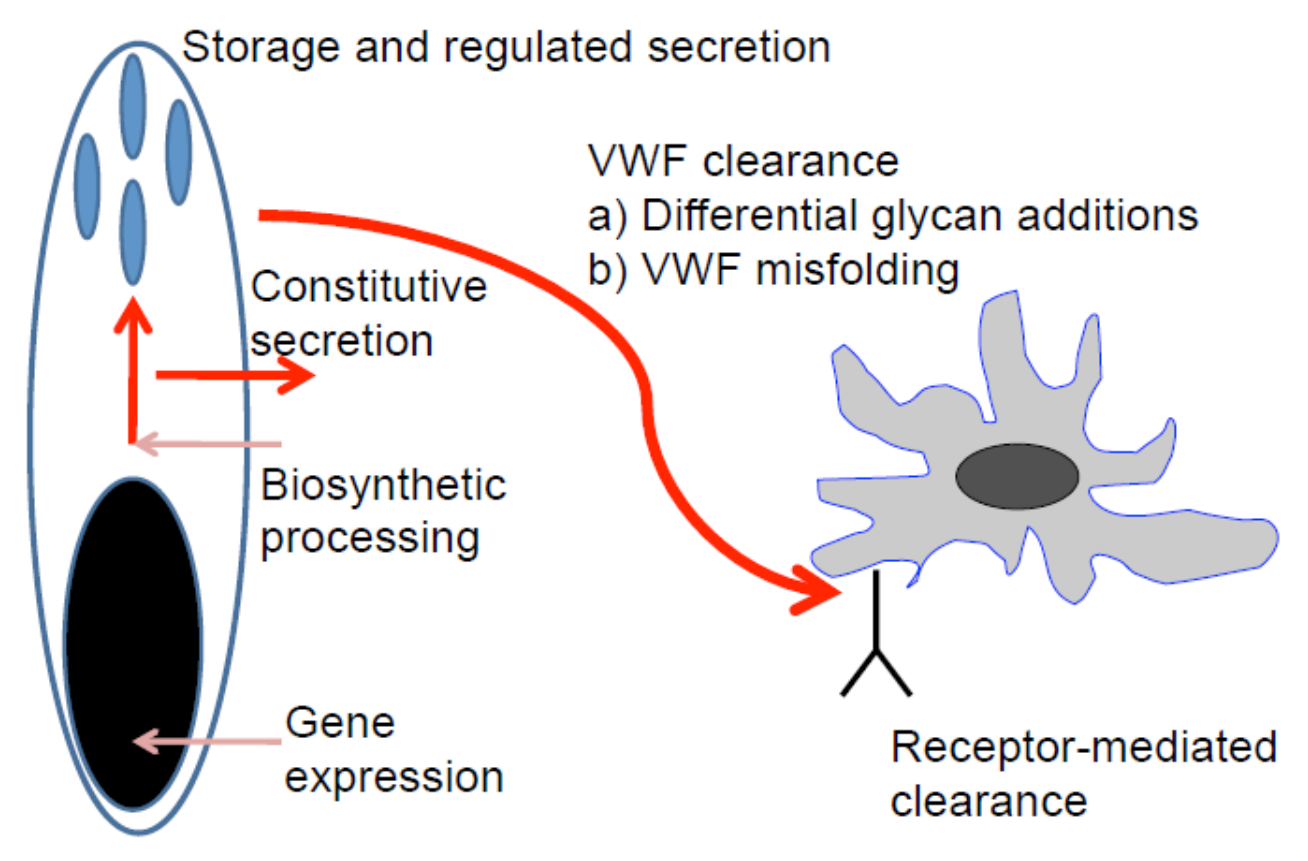
Results from the recent type 1 VWD studies

**James PD, Am.J.Hematol 2012,87: 4-11*

- Dominant trait
  - Varible penetrance and expresivity
- Oligogenic
  - VWF, ABO, other loci
- Candidate VWF mutations in 65% of index cases
- Missence mutations are the most frequent
- 15% of cases have > 1 mutation

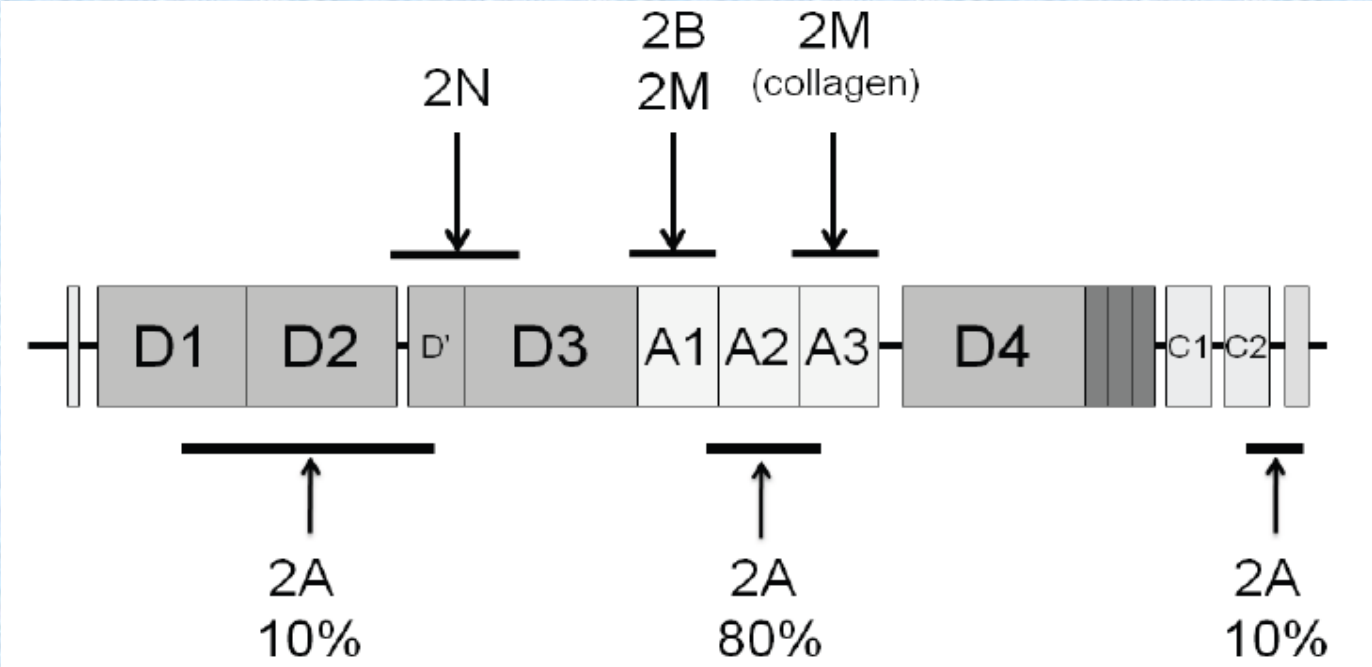
Pathogenic mechanism which results in a reduction of plasma VWF level

**James PD, Am.J.Hematol 2012,87: 4-11*

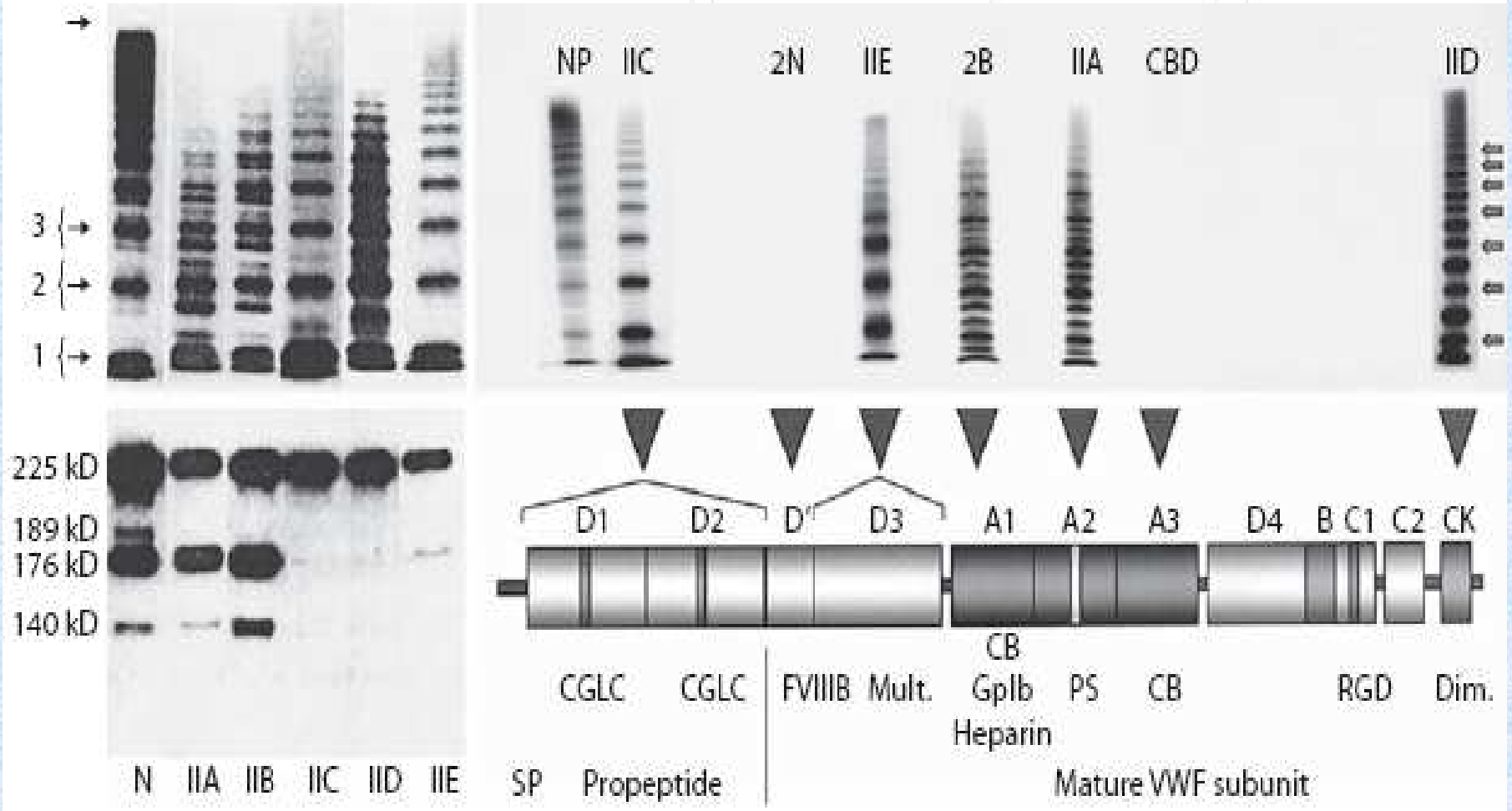


VWD type 2A, 2B, 2M, 2N

- Dominant traits (2N recessive)
- Monogenic – VWF gene
  - Missense mutations
- Fully penetrant



SSC-ISTH classification of VWD 2A subtypes



**Schneppenheim R.Semin Hematol 2004;42:15-28*

**Gadisseur A.Acta Haematol 2009;121:128-38*

VWD – therapeutic weapons

- **release of endogenous VWF:**
  - DDAVP
  - IL 11
- **VWF substitution:**
  - pd concentrates containing VWF(FVIII)
  - platelet concentrates
- **other forms:**
  - antifibrinolytics
  - estragens

More than 30 years without effective treatment

- discovered by E. A. von Willebrand in April 1924
- published in 1926
- therapy with Cohn fraction by M. Blombäck and I. M. Nilsson in 1956

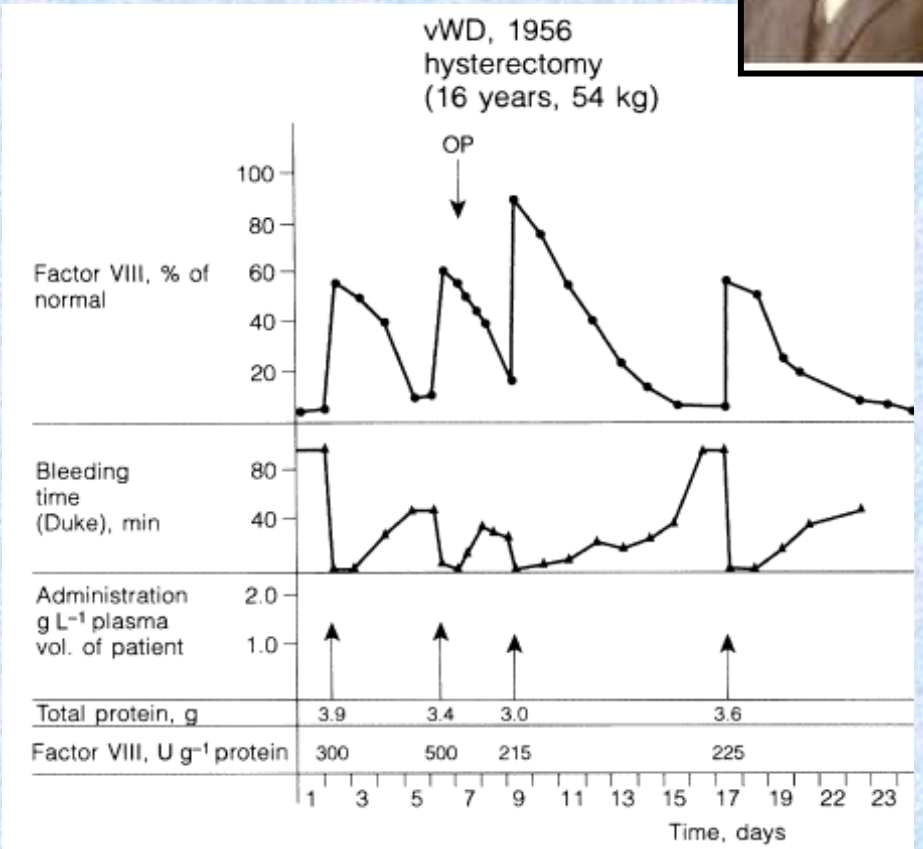
Cohn Fraction from fresh plasma

Extraction with mixture of
glycine 1M
ionic str. 0.3
ethanol 6.5%
pH 6.8
Temp -3%

Extract 1 discarded
Extract 2 discarded

I-0 precipitate

Fibrinogen (yield 96%)
(coagulability 88%)
Factor VIII (yield about 100%)
Bleeding time correcting factor (100%?)



*Cornu P. Rev Franc Etudes Clin Biol 1960; 5: 614-20

*Blombäck M. Haemophilia 2012; 18: 3-6.

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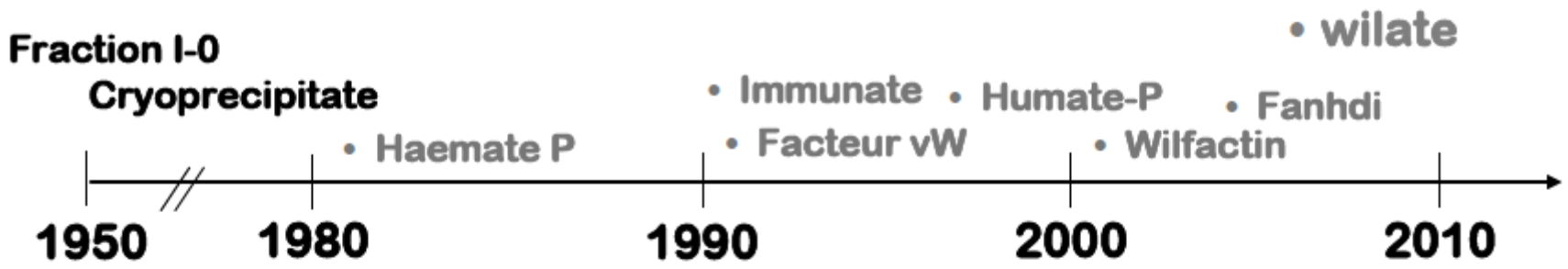
Plazma derived concentrates in treatment of VWD



	1980ies	1990ies	2000ies
1st indication	Haemophilia A	Haemophilia A / VWD	VWD / Haemophilia A
Purity [FVIII / total protein]	Intermediate 5 IU/mg	Intermediate 5-30 IU/mg	High >50 IU/mg
Albumin added as stabilizer	Yes	Yes	No
Virus inactivation	Single	Double (+)	Double

*Federici AB. Haemophilia 2006;12 (Suppl. 3):152-8.

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Plasma derived concentrates with content of VWF (FVIII) in Czech Republic

concentrate	VWF:RCo / FVIII	Recovery / IU / kg		t1/2 (hod.)	FVIII IU / 1 mg	VWF: RCo IU / 1 mg
		dosage	pharmacokinetic			
Haemate P®	2,4	2%	1,9%	7	2 - 6	3 - 17
Fanhdi®	1,2	2%	1,9%	14	2,5 - 10	3 - 12
Wilate®	0,9	1,5 - 2%	1,5%	18 - 34	≥ 60	≥ 53
Willfact®	≥ 10	2%	2,1%	8 - 14		≥ 50

Recommended level of VWF:RCo and FVIII:C

bleeding type	desired level		duration of substitution
	VWF:RCo	FVIII:C	
major surgery	> 50%	> 50%	until healing (7 - 10 days)
minor surgery	> 30-50%	> 30-50%	until healing (1 - 5 days)
dental extraction	> 50%	> 50%	for 12 h
	+ antifibrinolytics		5 -10 days
bleeding episodes	> 30-50%	> 30-50%	until bleeding stops (2 - 4 days)
vaginal delivery	> 40-50%	> 40-50%	3 - 4 days

**Mannucci PM.Blood Transfus 2009;7:117-26 *Nichols WL. Haemophilia 2008;14:171-232 *Nordic Guidelines on VWD 2008*

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Question 1

- E.A. von Willebrand discovered pseudohaemophilia (VWD) in what year?

  a) 1923

  b) 1924

  c) 1926

  d) 1956

Question 2

- In the recent type 1 VWD studies mutation in VWF gene has been found in?

  a) 90% index cases

  b) 80% index cases

  c) 65% index cases

  d) 50% index cases

Question 3

- The plasma level of VWF is influenced by?

  a) estragens

  b) viral nfections

  c) hypertyroidism

  d) all factors mentioned above

Question 4

- The ratio VWFpp/VWF is increased in VWD type?

  a) 1 - Vicenza

  b) 2E

  c) acquired

  d) in all types mentioned above

Question 5

- In what pd VWF / FVIII concentrate is the lowest ratio VWF:RCo / FVIII?

  a) Haemate P

  b) Willfact

  c) Fanhdi

  d) Wilate

Question 6

- In what pd concentrate is the highest ratio VWF:RCo / 1 mg protein?

  a) Haemate P

  b) Haemate P and Willfact

  c) Wilate

  d) Wilate and Willfact

Thank you for your kind attention!

Aland Islands flag

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