Leiden University
Medical Center

Low Von Willebrand Factor and diagnostic threshold

12th ECAT Participants' Meeting

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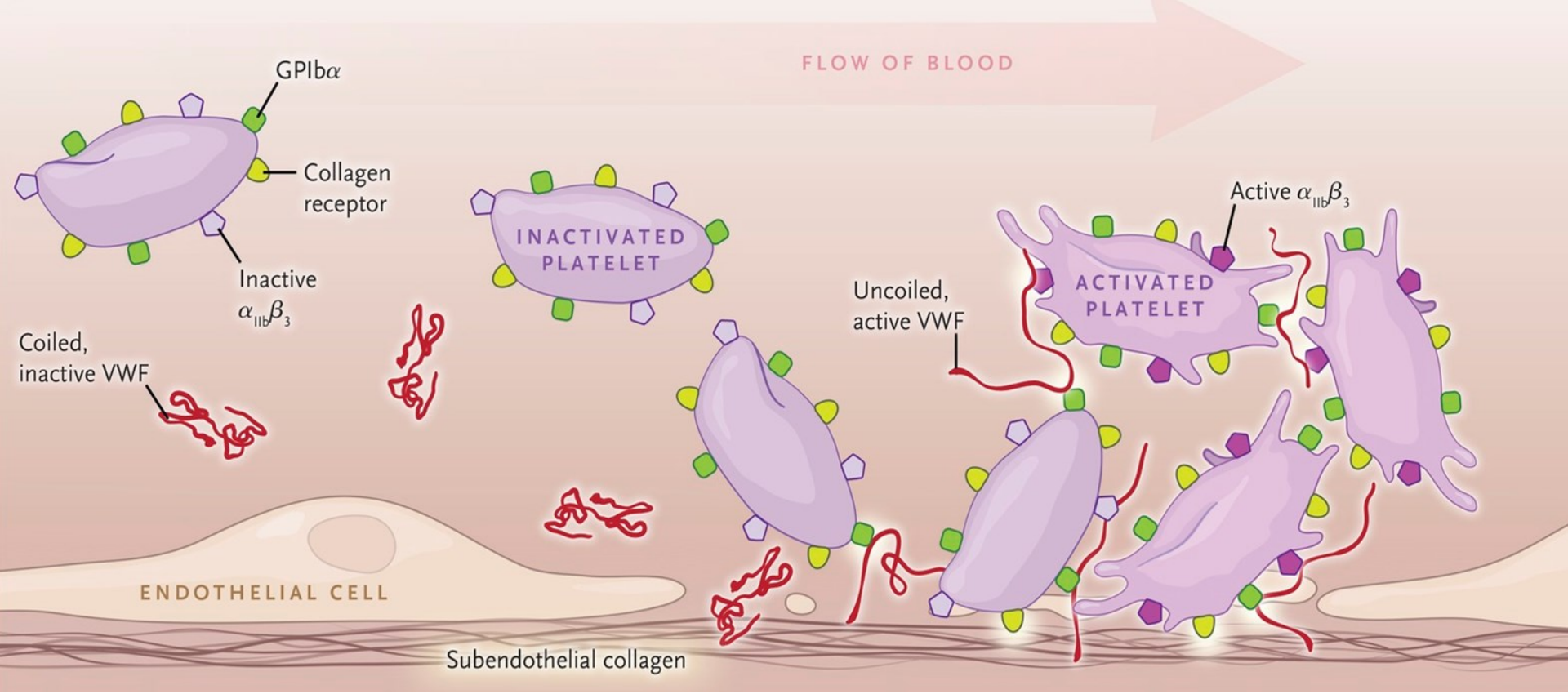
Thrombosis and Hemostasis
LEIDEN

Disclosures for Jeroen Eikenboom

Disclosures	Companies
Shareholder	-
Grant / Research Support	CSL Behring research funding
Consultant	-
Employee	-
Paid Instructor	-
Speaker bureau	Roche, educational ASH review

Primary hemostasis summarized



Leebeek and Eikenboom; N Engl J Med 2016;375:2067-80

Von Willebrand Disease

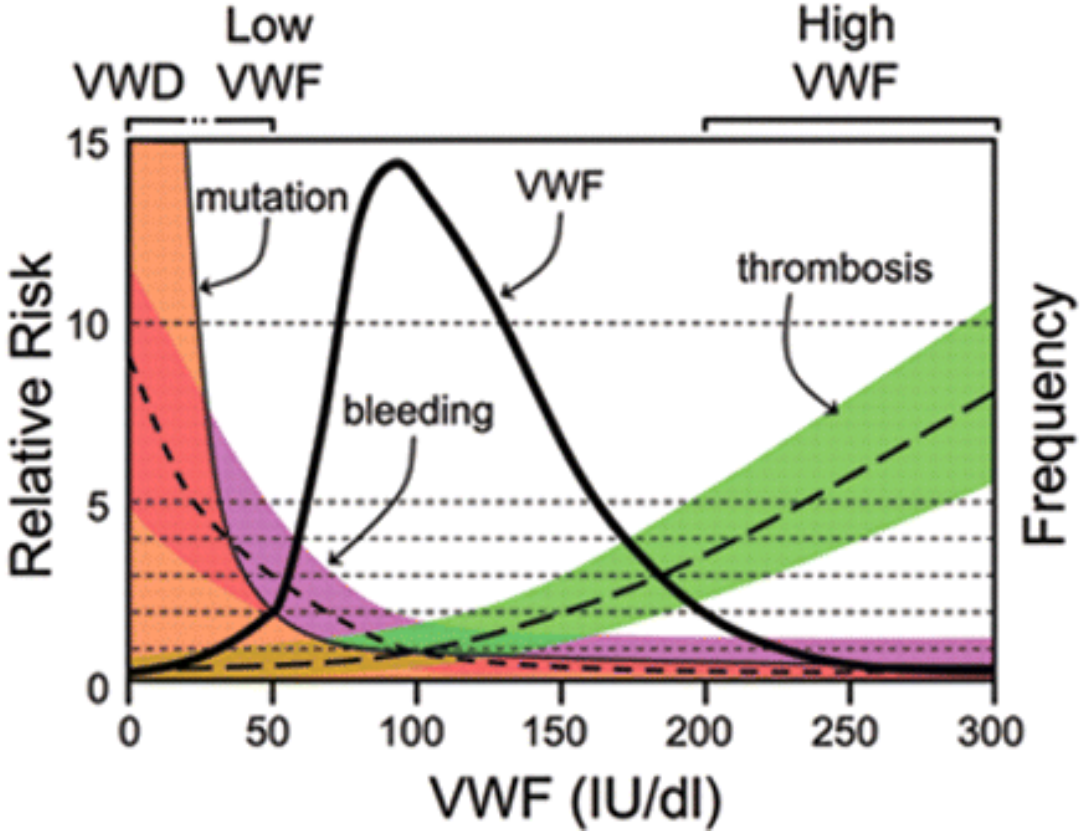
Definition

- Bleeding disorder caused by inherited defects in the concentration, structure, or function of von Willebrand factor (VWF)

- VWF levels
- Bleeding symptoms

VWF levels

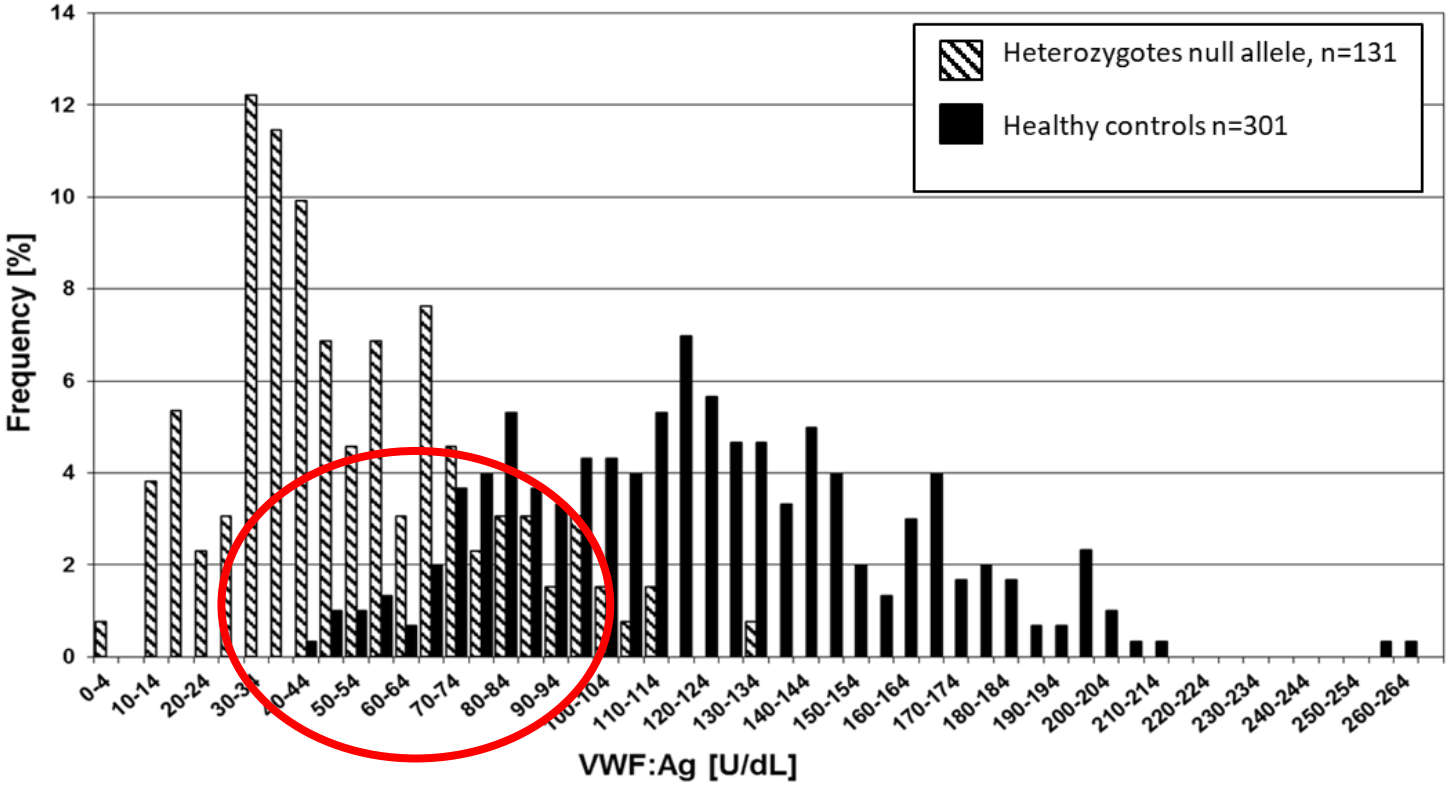
VWF levels versus risk of bleeding



Can the problem be solved by genotyping *VWF* ?

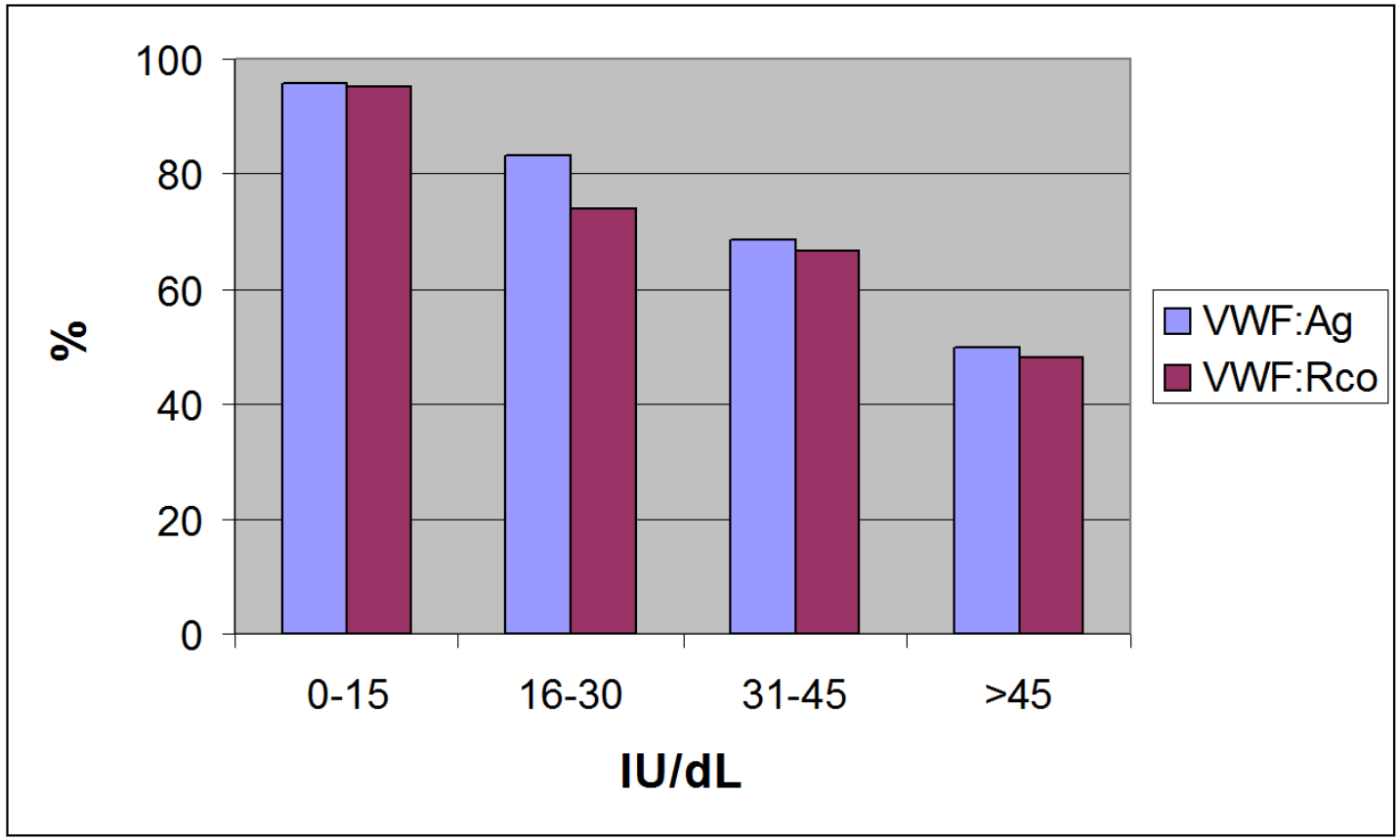
Sadler, Hematology Am Soc Hematol Educ Program. 2009:106-12

Presence of *VWF* variant ≠ disease



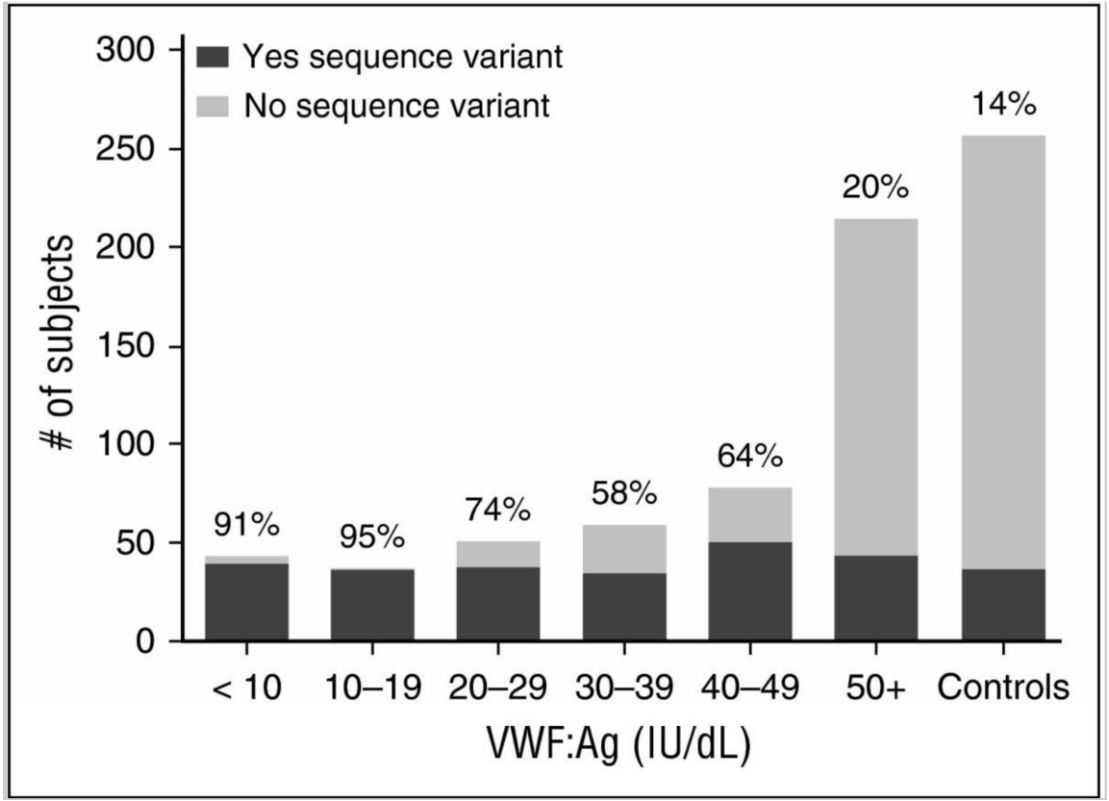
Eikenboom *et al*. Thromb Haemost 2002;87:252-7; Ned Tijdschr Hematol 2004;2:54-59

Prevalence of *VWF* mutations in type 1 VWD



Data from MCMDM-1VWD

Sequence variants at VWF levels

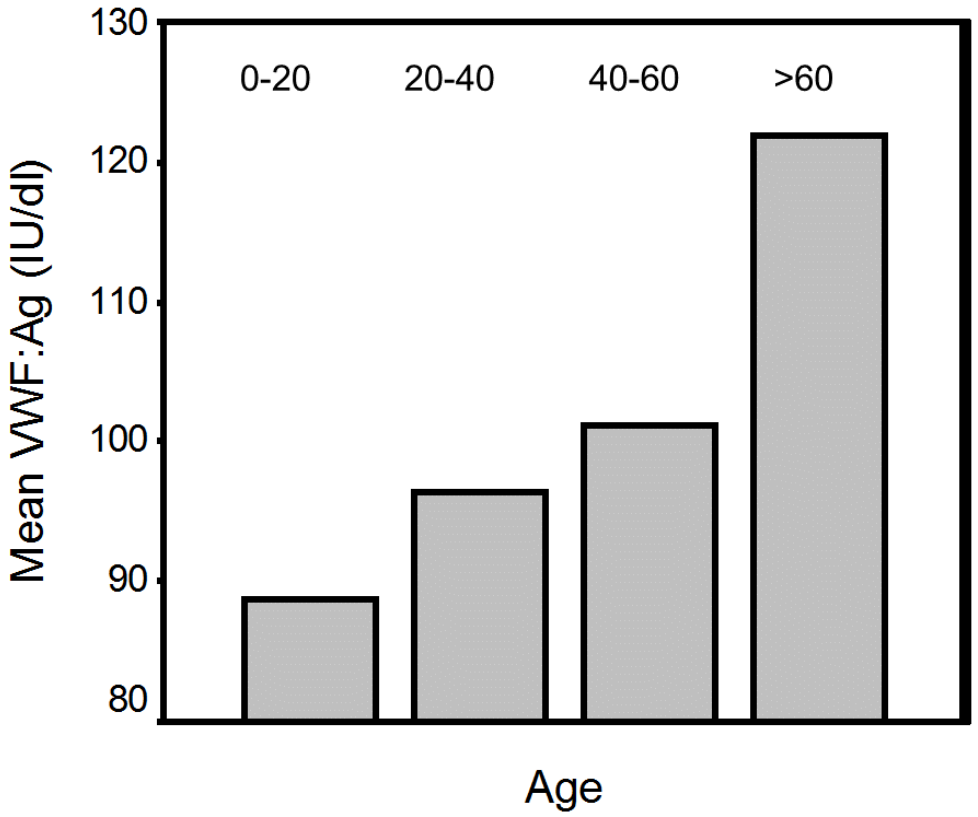


Flood *et al*., Blood 2016;127:2481-2488

Genotyping in VWD type 1

Country of study	Cases (n)	Variants identified (%)	References
Europe	150	70	Goodeve *et al.*, Blood 2007;109:112-21
Canada	123	63	James *et al.*, Blood 2007;109:145-54
United Kingdom	32	63	Cumming *et al.*, Thromb Haemost 2006;96:630-41
Sweden	54	56	Johansson *et al.*, Ann Hum Genet 2011;75:447-551
Spain	155	89	Batlle *et al.*, Thromb Haemost 2016;115:40–50
Total	**514**	**72**	

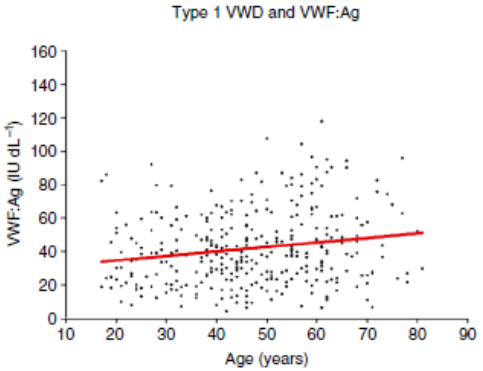
Age and increase in VWF level

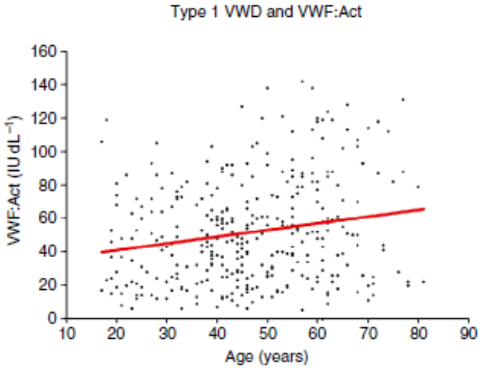


Healthy controls

MCMDM-1VWD study

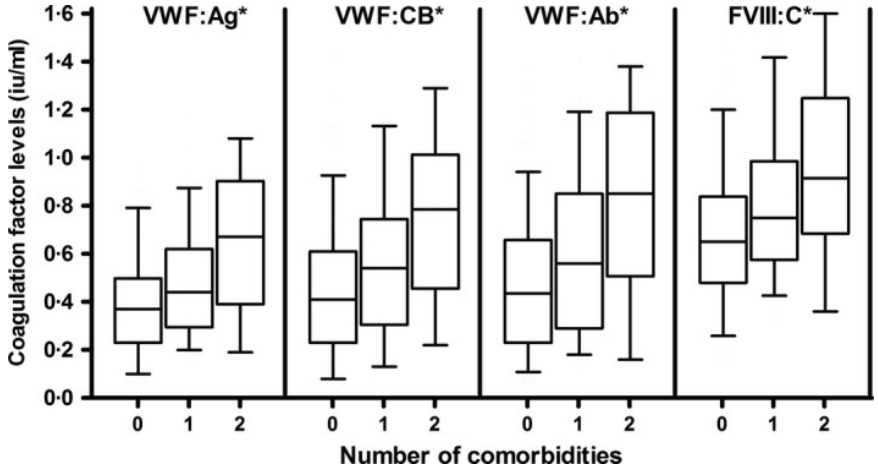
Age and increase in VWF level – VWD patients





Type 1 patients >65 yrs:

- A decade age increase associated with 3.5 U/dL VWF:Ag; 9.5 U/dL VWF:Act; 7.1 U/dL FVIII:C increase
- No mitigation of bleeding phenotype



Sanders *et al.,* J Thromb Haemost 2014;12:1066–75; Atiq *et al.*, Br J Haematol 2018;182:93–105

Bleeding symptoms

Assessment of bleeding history

Severity and likelihood of bleeding tendency

- Age at onset of bleeding symptoms
- Spontaneous versus traumatic
- Frequency of bleeding
- Bleeding at multiple sites
- Requirement for transfusion or intervention

Bleeding manifestations in VWD

Mucocutaneous bleeding

- Bruises and minor wounds
- Gum bleeds and epistaxis
- Menorrhagia
- Gastrointestinal bleeds

Bleeding after hemostatic challenges

- Surgery and tooth extraction
- Trauma
- Delivery

Bleeding assessment tools - BAT

- Structured questionnaire
- Severity score for each bleeding symptom
- Several modifications: self-BAT, condensed BAT, pediatric BAT

- ISTH-BAT endorsed by ISTH

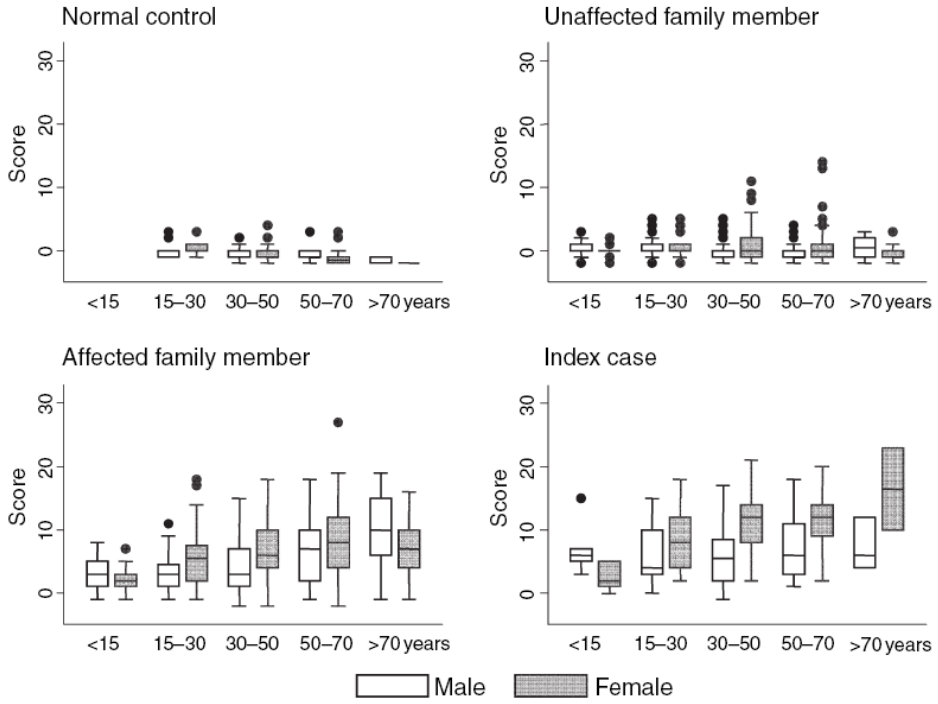
Rodeghiero *et al.,* J Thromb Haemost 2010;8:2063-5

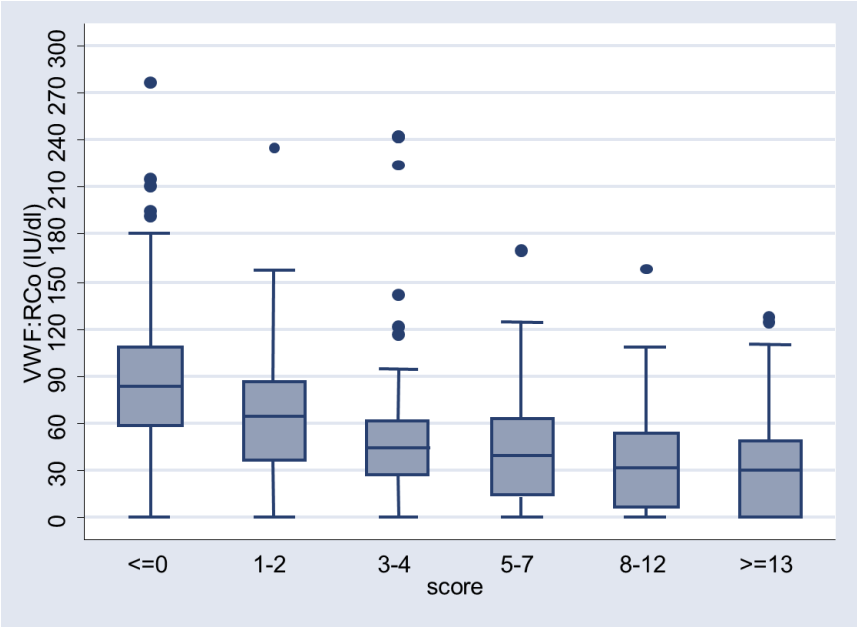
Table 1 Assigned score for each bleeding symptom

	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 transfusion or replacement therapy or desmopressin
Cutaneous	–	No or trivial (< 1 cm)	>1 cm and no trauma	Consultation only		
Bleeding from minor wounds	–	No or trivial (less than 5)	>5 or more than 5′	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity	–	No	Referred at least one	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding	–	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	
Tooth extraction	No bleeding in at least two extraction	None done or no bleeding in one extraction	Referred in <25% of all procedures	Referred in >25% of all procedures, no intervention	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least two surgeries	None done or no bleeding in one surgery	Referred in <25% of all surgeries	Referred in >25% of all procedures, no intervention	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin

Tosetto *et al*., J Thromb Haemost 2006;4:766-73

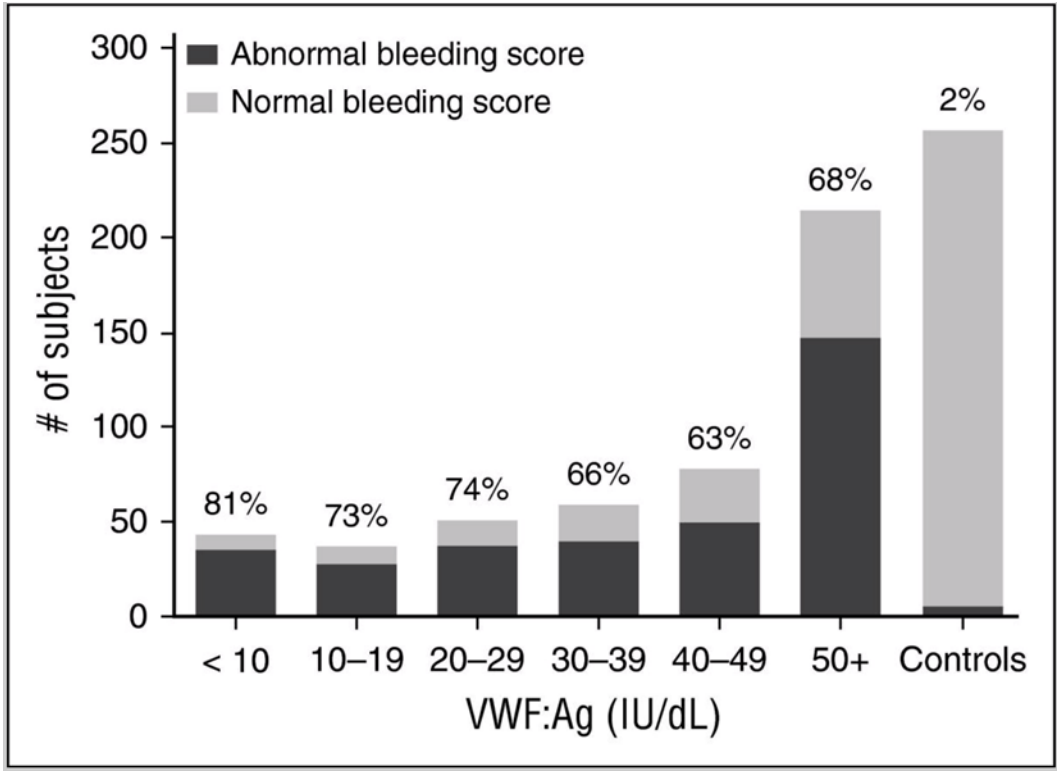
Tosetto bleeding score





Tosetto et al., J Thromb Haemost 2006;4:766-73

Bleeding rates at VWF levels

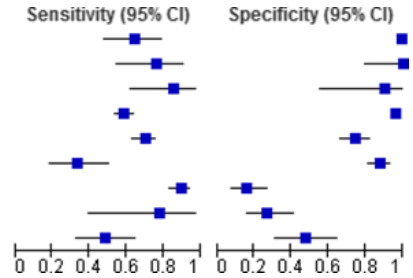


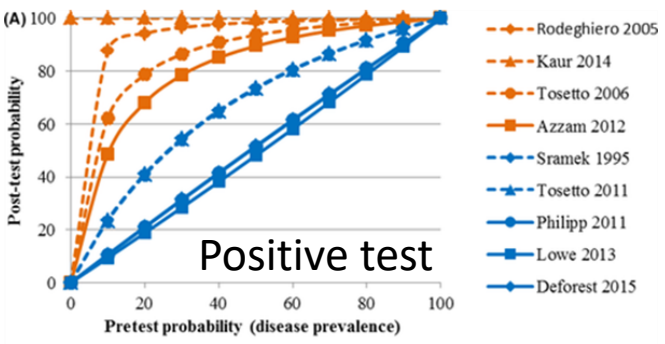
Flood *et al.*, Blood 2016;127:2481-2488

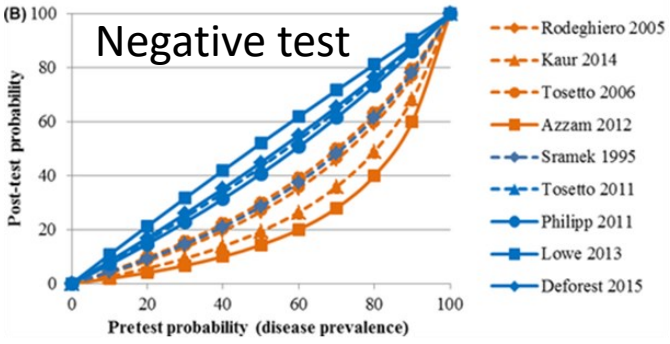
Diagnostic value of BAT limited

- Major variation in specificity and sensitivity among studies

Study	TP	FP	FN	TN	Questionnaire	Condition	Sensitivity (95% CI)	Specificity (95% CI)
Rodeghiero 2005	27	2	15	213	VICENZA BAT	VWD	0.64 (0.48, 0.78)	0.99 (0.97, 1.00)
Kaur 2014	19	0	6	16	e-cMCMDM-1VWD BAT	VWD	0.76 (0.55, 0.91)	1.00 (0.79, 1.00)
Azzam 2012	17	1	3	9	cMCMDM-1VWD BAT	MBD	0.85 (0.62, 0.97)	0.90 (0.55, 1.00)
Tosetto 2006	245	18	172	472	MCMDM-1VWD BAT	VWD	0.59 (0.54, 0.64)	0.96 (0.94, 0.98)
Sramek 1995	155	34	67	100	Sramek	MBD	0.70 (0.63, 0.76)	0.75 (0.66, 0.82)
Tosetto 2011	13	17	26	120	cMCMDM-1VWD BAT	MBD	0.33 (0.19, 0.50)	0.88 (0.81, 0.93)
Philipp 2011	137	53	17	10	screening tool	MBD	0.89 (0.83, 0.93)	0.16 (0.08, 0.27)
Deforest 2015	7	40	2	15	ISTH self-BAT	VWD	0.78 (0.40, 0.97)	0.27 (0.16, 0.41)
Lowe 2013	20	20	21	18	ISTH BAT	PFD	0.49 (0.33, 0.65)	0.47 (0.31, 0.64)







Prevalence 1%
NPV% 99.2
Prevalence 20%
NPV% 84.1

Tosetto *et al.*,
J Thromb Haemost
2011;9:1143–8

Moenen *et al*., Haemophilia 2018;24:525-35

Low VWF versus VWD type 1

Table 1. Significant differences between low VWF and type 1 VWD

	Low VWF	Type 1 VWD
VWD type	Partial quantitative	Partial quantitative
Plasma VWF levels, IU/dL	30-50*	<30
Bleeding phenotype	Variable bleeding. Independent of plasma VWF levels. Significant HMB & PPH in some patients	Mucosal bleeding. Correlates inversely with residual plasma VWF levels.
Sex	Marked female predominance	Less female bias
ABO blood group	Group O+++	Group O+
VWF sequence variants	~40% patients. Pathological importance for many variants unclear.	Present in >80% cases
Pathophysiology	Multifactorial. Predominantly reduced biosynthesis. Subtle increased clearance in ~25% patients (VWFpp/VWF:Ag ~ 2).	Dependent upon *VWF* mutation. Reduced biosynthesis. Enhanced clearance in ~45% cases. Type 1C VWD (VWFpp/VWF:Ag >3).
VWF glycosylation abnormalities	Enhanced SNA binding, increased RCA-I binding, and reduced sialylation	Increased RCA-I binding, PNA binding, and T antigen expression and reduced sialylation
Platelet VWF levels	May be reduced or normal	May be reduced or normal
Abnormal angiogenesis	Unknown	Previously reported

+, mild increase in prevalence; +++, markedly more prevalent; PNA, peanut agglutinin; RCA-I, *Ricinus communis* agglutinin I; SNA, *Sambucus nigra* agglutinin; VWFpp, VWF propeptide.

*There are some differences between International Consensus guidelines for the optimal range.

O'Donnell *et al*., Blood Adv 2020;4:3191-3199

Guideline

Diagnostic threshold VWF

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. James *et al.*, Blood Advances 2021;5:280-300

For patients with an abnormal initial VWD screen (low VWF:Ag and/or platelet-dependent VWF activity) suspected of type 1 VWD, should the diagnostic cutoff be at VWF:Ag and/or VWF platelet-dependent activity <0.30 IU/mL or <0.50 IU/mL?

Diagnostic threshold VWF

- The panel recommends a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD

Diagnostic threshold VWF

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- Strong recommendation based on low certainty in the evidence of effects

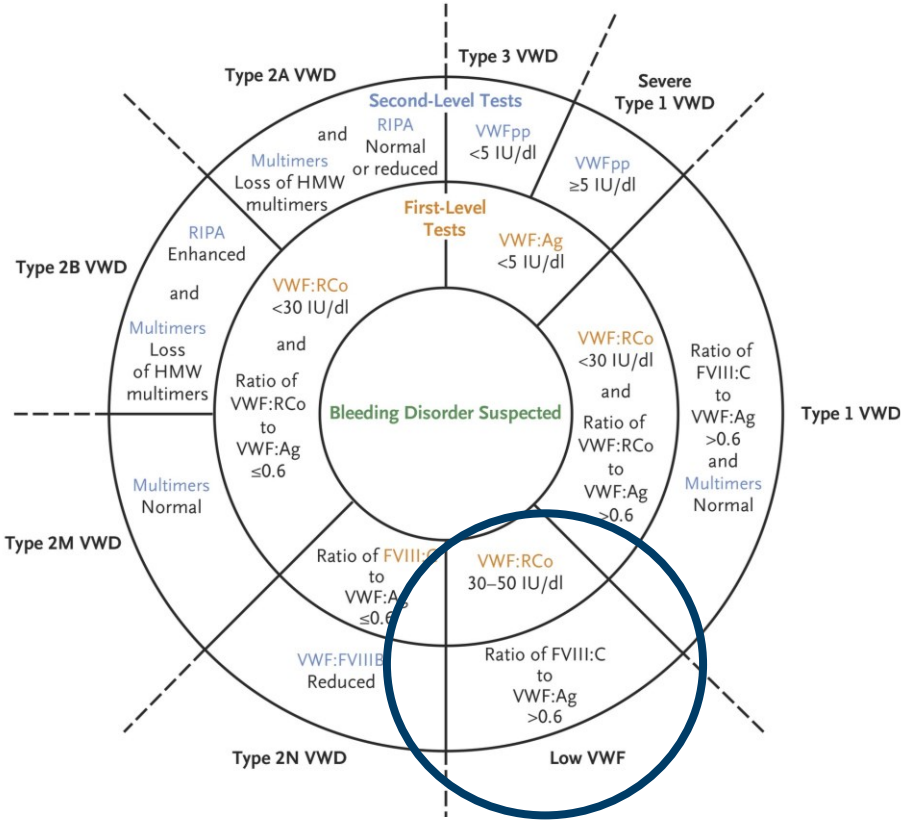
- Considerations for “strong recommendation”
  - not missing the diagnosis, avoiding overdiagnosis
  - explicit diagnosis to ensure access to care
  - international uniformity in diagnostic criteria, avoidance of center-specific thresholds based on a conditional recommendation

Diagnostic threshold VWF

- The panel recommends a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD
- Strong recommendation based on low certainty in the evidence of effects

- Remarks
  - Use lower limit of normal by the local laboratory if it is <0.50 IU/mL
  - ABO-specific reference ranges are NOT required
  - VWD diagnostics should be performed at a baseline state of health

Risk factor *versus* disease



Leebeek and Eikenboom, N Engl J Med 2016;375:2067-80

Castaman *et al*., Thromb Res 2010;126:227-31

VWF diagnosis

- Chose the right direction based on all lab and clinical information
- No fixation on thresholds, judgement of clinical context