Unmet Needs in VWD Management: Treatment Options in different Clinical Setting

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Current Challenges and Unmet Needs In VWD Management

- Make simpler diagnosis of VWD types
- Identify risk factors of bleeding in VWD
- Better diagnose & treat GI bleeding
- Monitor VWF concentrates in surgery
- Identify & treat anti-VWF antibodies
- Indications & protocols of prophylaxis

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jeroen Eikenboom,[6] Nicolas Giraud,[7] Sandra Haberichter,[8] Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[13] Robert R. Montgomery,[14] James S. O'Donnell,[15] Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husainat,[19] Mohamad A. Kalot,[19] and Reem A. Mustafa[19]

Background: von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans. Accurate and timely diagnosis presents numerous challenges.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and other health care professionals in their decisions about VWD diagnosis.

Methods: ASH, ISTH, NHF, and WFH established a multidisciplinary guideline panel that included 4 patient representatives and was balanced to minimize potential bias from conflicts of interest. The Outcomes and Implementation Research Unit at the University of Kansas Medical Center (KUMC) supported the guideline-development process, including performing or updating systematic evidence reviews up to 8 January 2020. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subsequently subject to public comment.

Results: The panel agreed on 11 recommendations.

Conclusions: Key recommendations of these guidelines include the role of bleeding-assessment tools in the assessment of patients suspected of VWD, diagnostic assays and laboratory cutoffs for type 1 and type 2 VWD, how to approach a type 1 VWD patient with normalized levels over time, and the role of genetic testing vs phenotypic assays for types 2B and 2N. Future critical research priorities are also identified.

Blood Adv. 2021 Jan 12;5(1):280-300.

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VWD classification

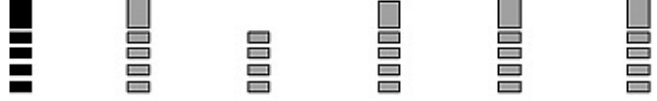
Type	Characteristic
1	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; normal multimer distribution
1C	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; increased VWF/pp compared with VWF/Ag
2A	Decreased platelet-dependent VWF activity with loss of high-molecular-weight multimers
2M	Decreased platelet-dependent VWF activity with preserved multimer pattern
2N	Decreased binding of FVIII
2B	Increased binding to GPIbα, often leading to thrombocytopenia
3	Absence or near absence of VWF
Platelet-type VWD	Functional defect of platelet GPIbα, leading to excessive binding of platelets and VWF and subsequent thrombocytopenia and loss of high-molecular-weight multimers
Acquired von Willebrand syndrome	Decreased VWF and particularly loss of high-molecular-weight multimers as a result of either shearing from mechanical forces (eg, aortic stenosis resulting in Heyde syndrome), adsorption on tumors (eg, Waldenström macroglobulinemia or Wilms' tumors), or autoimmune inhibitor formation

Act, activity; Ag, antigen; GPIbα, glycoprotein Ibα; pp, propeptide.

Blood Adv. 2021 Jan 12;5(1):301-325.

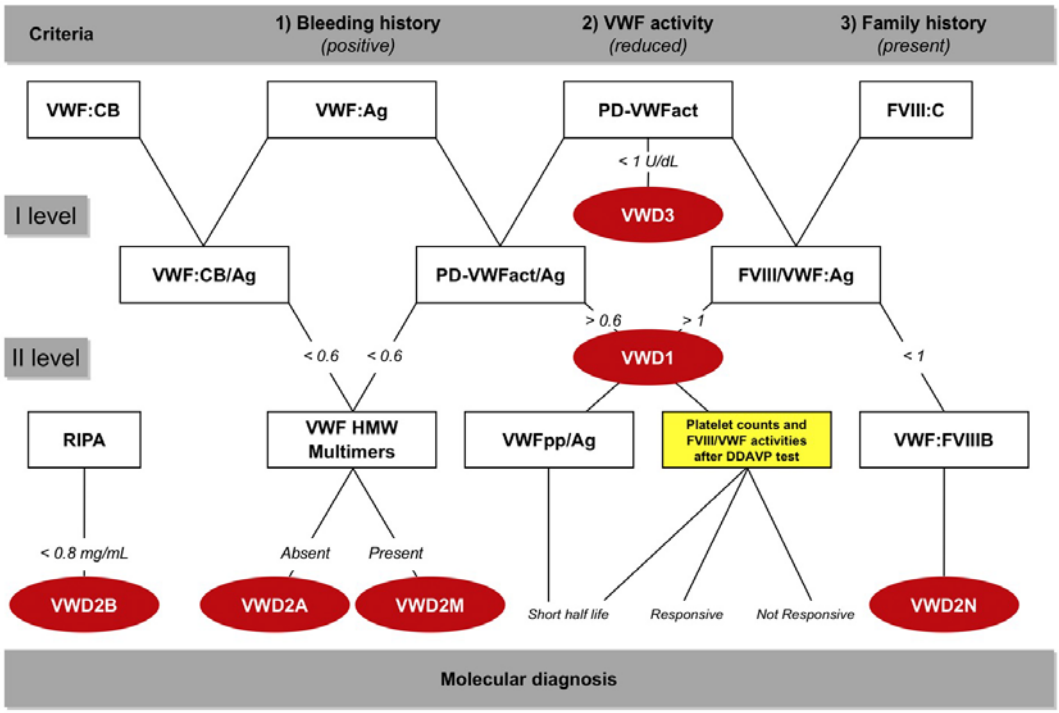
Classification of VWD types based on several assays

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
VWF:Ag	N	L, ↓ or ↓↓	↓ or L	↓ or L	↓ or L	N or L	absent
VWF:RCo	N	L, ↓ or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or L	absent
FVIII	N	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	1-9 IU/dL
RIPA	N	often N	↓	often N	↓	N	absent
LD-RIPA	absent	absent	absent	↑↑↑	absent	absent	absent
Platelet count	N	N	N	↓ or N	N	N	N
VWF multimer pattern	N	N	abnormal	abnormal	N	N	absent



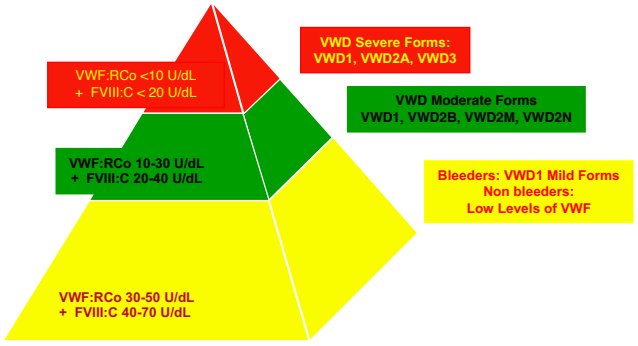
NIH US Guidelines

Flow chart for VWD Diagnosis: In Expert Laboratories (I)



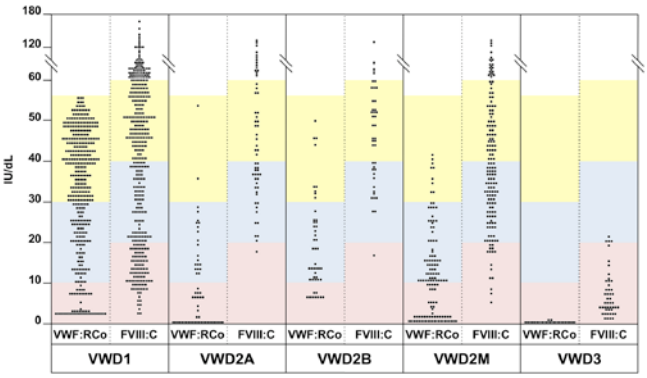
Heterogeneity of VWD Patients Based on Cohort Studies

Bleeders *versus* Non Bleeders



Diagnosed VWD: the tip of the iceberg?

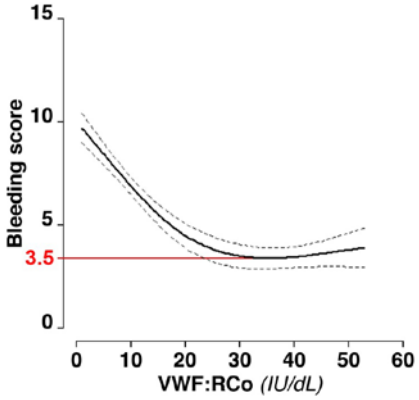
Heterogeneous VWD Cohort: Italian Registries (RENAWI)



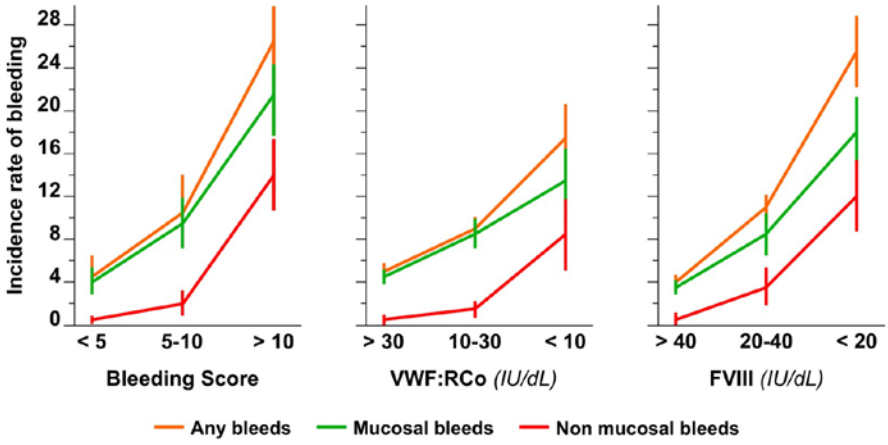
Federici AB et al, Blood 2014; 123: 4037-44.

Bleeding Phenotype in VWD
Evidence-Based Methods

Restricted Cubic Spline Curve

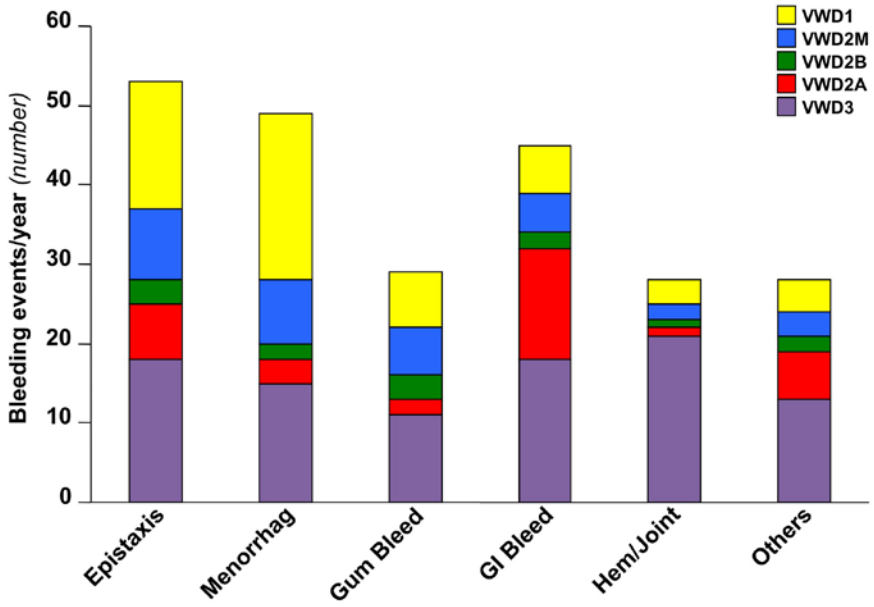


Cox's Proportional Hazard Model

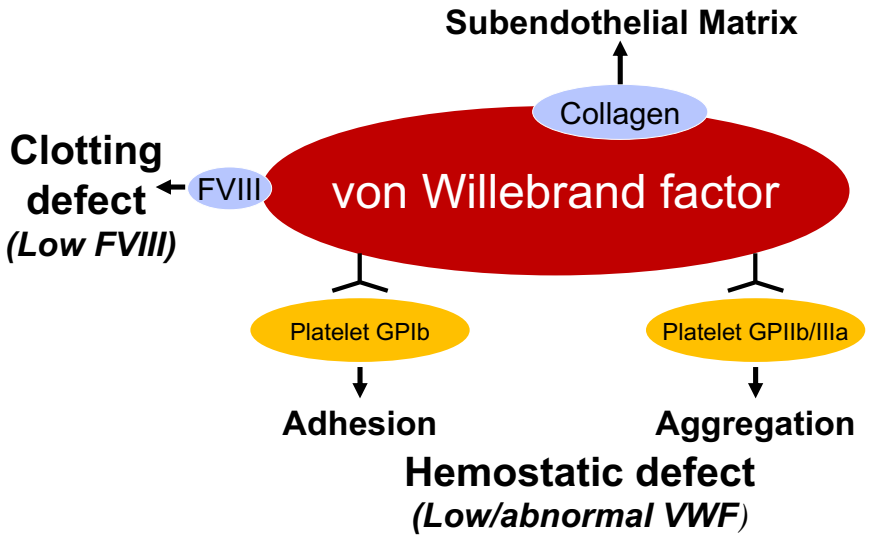


Federici AB et al, Blood 2014; 123: 4037-4044

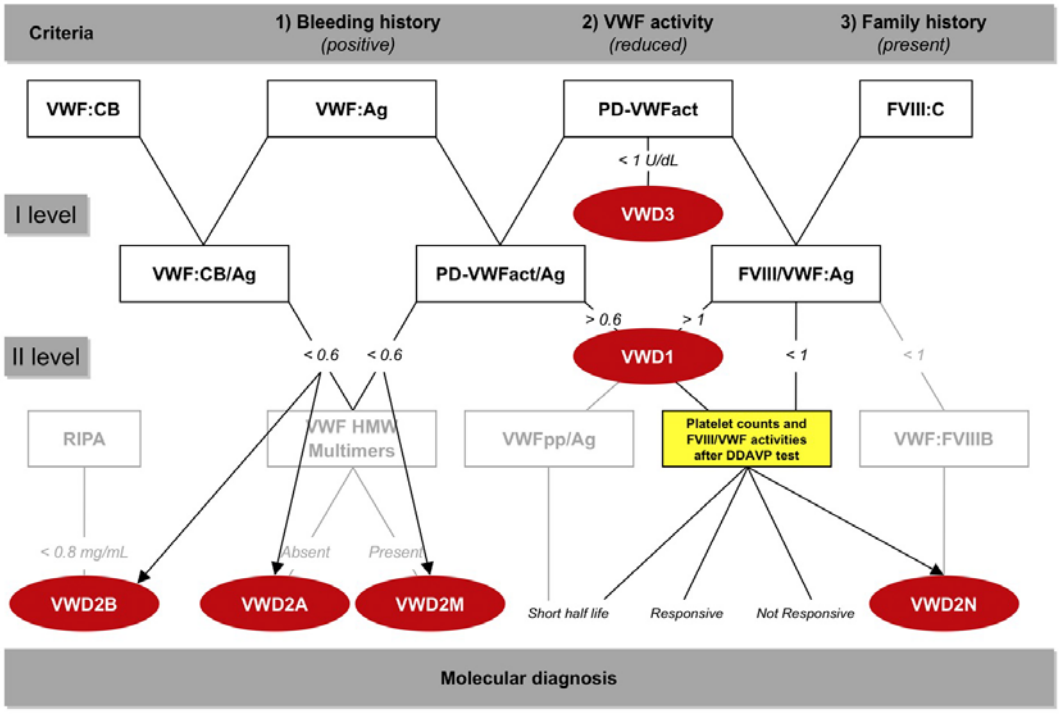
Bleeding Phenotype in VWD types
Type of Bleeding Symptoms



Why does the VWD patient bleed?



Flow chart for VWD Diagnosis
To be used in all Hemophilia Centers



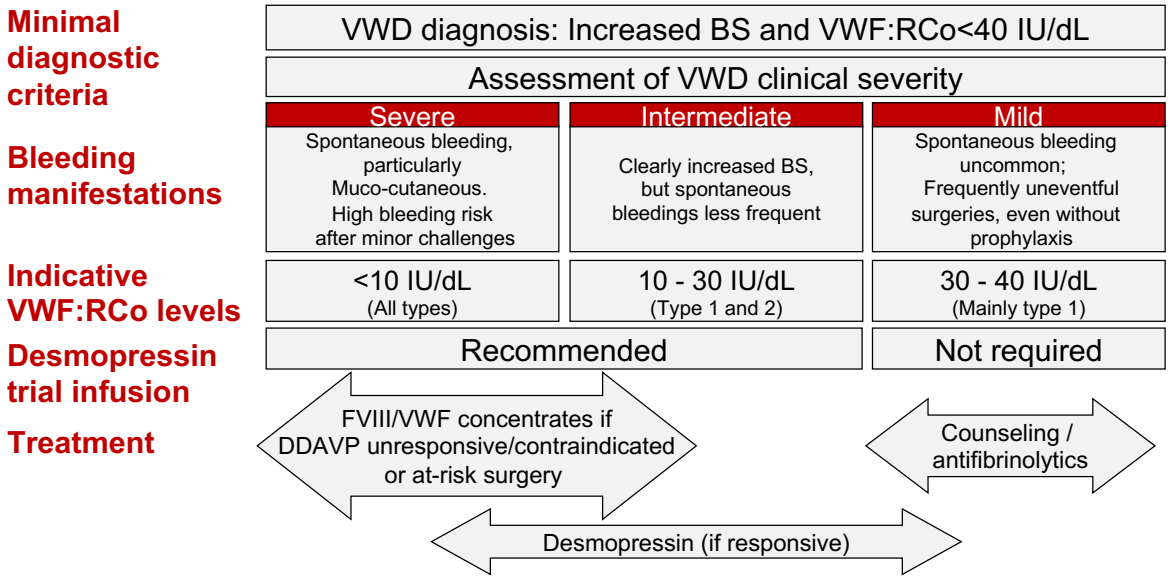
Aims of Treatments of VWD patients
Correction of the VWF defects

To correct the dual VWF defect present in patients with different VWD types:

A) Impaired Platelet adhesion to sub-endothelium and platelet-platelet interactions (PD-VWF ACT & VWF:CB)

B) Reduced levels of Factor VIII that are associated with reduced or abnormal VWF

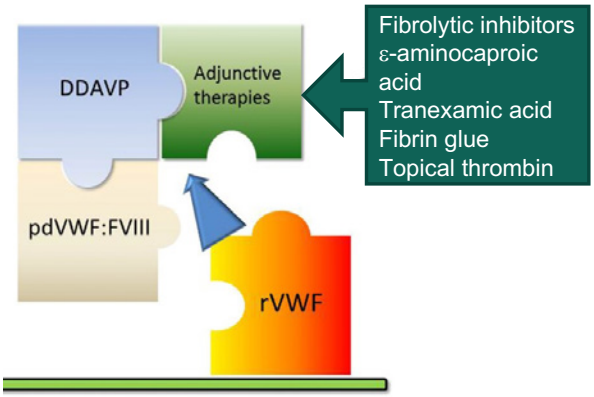
Clinical spectrum of VWD: implications for management



Rodeghiero F, Castaman G, and Tosetto A.
Hematology. 2009 2009:113-123; doi:10.1182/asheducation-2009.1.113

Therapeutic options in VWD patients

Treatment	Mechanism	For which patients?
Desmopressin (DDAVP)	Facilitates **endogenous VWF** release from endothelial cells	Test in type 1, type 2 (except 2B)
VWF Concentrates	**Exogenous VWF**	Unresponsive to DDAVP (type 2, type 3, severe type 1)



Metjihan AD. Blood 2015

Management of VWD patients
Three main factors

- Type and/or **severity of VWD patients: baseline VWF & FVIII levels**
- Clinical settings: acute bleeding
  surgery
  prophylaxis
- VWF Concentrates: VWF:FVIII ratios

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Clinical use of DDAVP

Domain	Description
Route	Desmopressin trials may be performed with either IV or intranasal desmopressin, but intranasal desmopressin trials may not be successful because of issues with administration and/or absorption. Subcutaneous administration has also been used.
Dose	IV desmopressin is given as 0.3 μg/kg, with a maximum dose of 20 μg. The desmopressin nasal spray (150 μg per spray) is given as 1 spray for individuals weighing <50 kg and 2 sprays for individuals weighing ≥50 kg.
Timing of laboratory testing	VWF antigen, VWF activity, and FVIII activity levels should be determined immediately before administration of desmopressin, ~30-60 min after administration of desmopressin, and ~4 h postadministration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	There are multiple definitions of desmopressin responsiveness.[128-130] The panel considered that an increase of at least 2 times the baseline VWF level and the ability to achieve both VWF and FVIII levels of >0.50 IU/mL were required to consider the patient responsive to desmopressin. Desmopressin responsiveness does not guarantee, however, that the level achieved is adequate to prevent bleeding in all procedures (eg, higher levels may be indicated based on type of procedure).
Precautions	Because of the risk of hyponatremia, desmopressin should not be given on >3 concurrent days and is generally not administered to children age <2 y. In addition, tachyphylaxis occurs after repeated infusions. Caution is advised when desmopressin is used in patients with active cardiovascular disease. Additionally, desmopressin trials should be avoided in pregnancy.

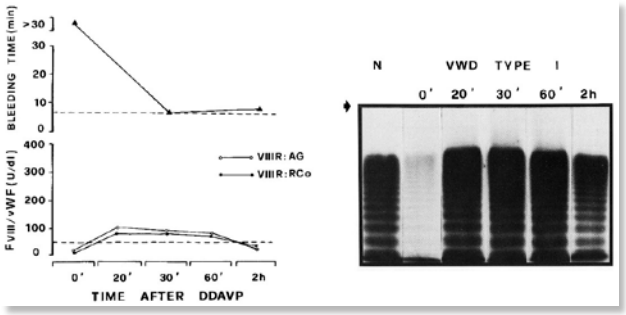
Blood Adv. 2021 Jan 12;5(1):301-325.

Summary on Desmopressin *(DDAVP: 1977-2021)*

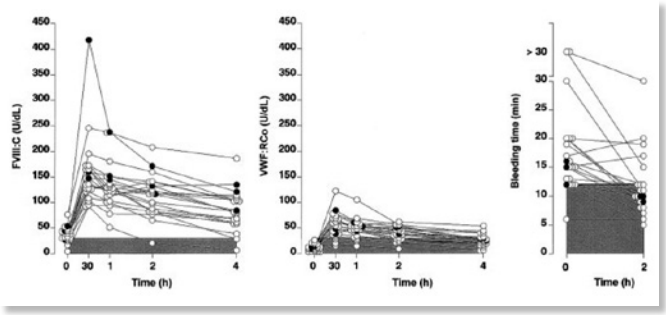
- **DDAVP is a long-acting V2 receptor-selective analog of AVP.**
- **DDAVP has complex effects on the coagulation process with both pro-hemostatic (dominant) and fibrinolytic effects (t-PA).**
- **Doses of DDAVP required for effects on coagulation are leading to peak plasma concentrations ~50-200 times above maximally anti-diuretic plasma concentrations.**
- **High intra-individual reproducibility of desmopressin-induced increase in FVIII plasma concentration.**
- **Tachyphylaxis of DDAVP-induced increase in FVIII and VWF plasma concentrations by daily dosing is moderate, limited, and do not lead to a clinically significant impairment of the hemostatic effects.**

Biological Response to DDAVP

VWD1

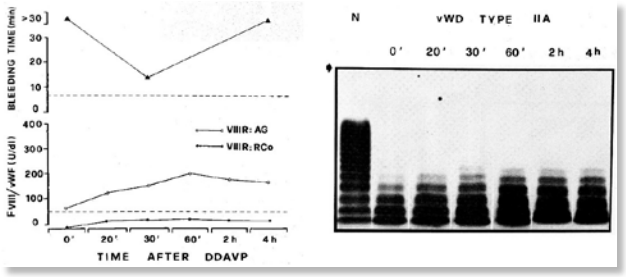


VWD2M



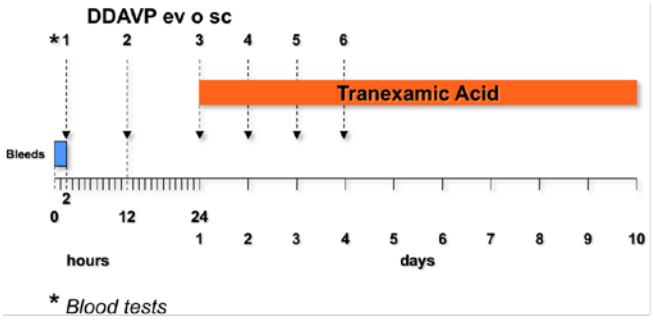
Federici et al, Blood 2004.

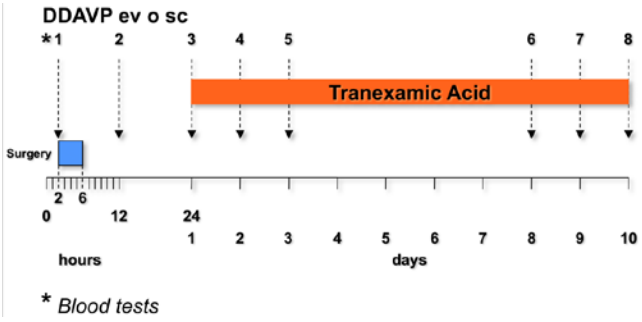
No Biological Response VWD2A

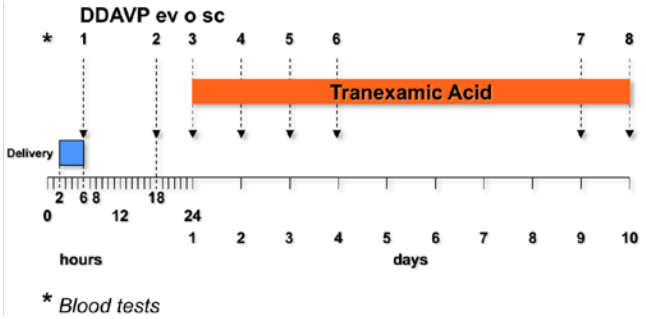


Ruggeri et al, Blood 1982.

Regimens of DDAVP administration In Bleeds, Surgery, Delivery







Limitations to the use of desmopressin

- **Non-responders *(VWD3, most VWD2A)***
- **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 *(VWD2B)***

Consider a VWF/FVIII concentrate

Mannucci PM; World Federation of Hemophilia. Desmopressin (DDAVP) in the treatment of bleeding disorders. http://www1.wfh.org/publication/files/pdf-1131.pdf. Published November 2012. Accessed July 28, 2017.
Emc+: DDAVP/Desmopressin Injection. https://www.medicines.org.uk/emc/medicine/659. Updated June 2011. Accessed July 28, 2017.

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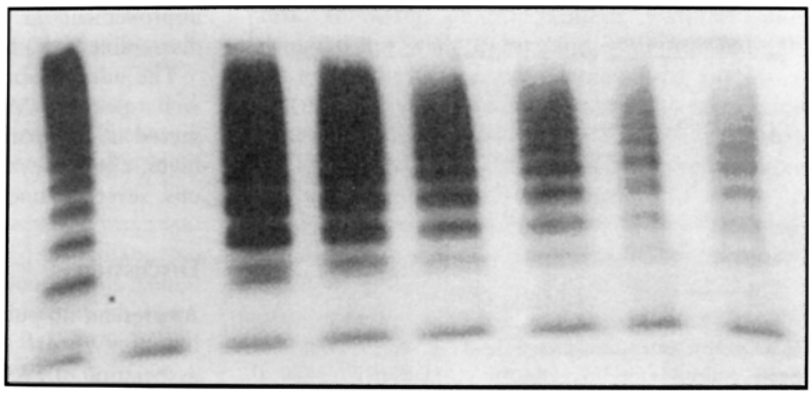
VWF concentrates with or without FVIII

VWF concentrate option	Description
VWF/FVIII concentrate (plasma derived)	Plasma-derived concentrate containing both VWF and FVIII; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg
VWF concentrate (plasma derived)	Plasma-derived concentrate containing VWF alone; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg; if used for emergency treatment, may require addition of FVIII concentrate in patients with low baseline FVIII
VWF concentrate (recombinant)	Recombinant concentrate containing VWF alone; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg; if used for emergency treatment, may require addition of FVIII concentrate in patients with low baseline FVIII

RCo, ristocetin cofactor.

Blood Adv. 2021 Jan 12;5(1):301-325.

VWF/FVIII Concentrates
In VWD3 patients



VWF:RCo =	**< 3**	**120**	**75**	**24**	**20**	**8**	**< 3**
VWF:Ag =	**< 3**	**165**	**90**	**78**	**45**	**28**	**10**
FVIII:C =	**7**	**85**	**95**	**90**	**82**	**61**	**35**

Variability in relative proportions and concentrations amongst VWF/FVIII concentrates

Table II - Summary of the major current VWF/FVIII concentrates: similarities and differences.

Concentrate	Biostate[§a]	Haemate P[§]/ Humate-P[§b]	Alphanate[§c]	Fanhdi[§d]	Immunate[§e]	Wilate[§f]	Wilfactin[§g]	Factor 8Y[§h]	Range
HMW VWF (% of NHP)	86	93.6	29.3	31.7	3.9	N/A	N/A	32.1	4-94
VWF:RCo/ VWF:Ag	0.73-0.99	0.91	0.43	0.69	0.38	0.9-1.0	0.95	0.6	0.4-1.0
VWF:CB/ VWF:Ag	0.72-0.95	0.89	0.49	0.47	0.21	N/A	N/A	N/A	0.5-1.0
VWF:RCo/ FVIII:C	2.00	2.88	0.82	1.29	0.67	1.0	>10	1.8	0.7->10
VWF:CB/ FVIII:C	2.53	2.28	0.68	0.80	0.16	N/A	N/A	N/A	0.2-2.5

[a]CSL Behring, Melbourne, Australia; [b]CSL Behring, King of Prussia, PA, USA; [c]Grifols, Los Angeles, CA, USA; [d]Grifols, Cambridgeshire, UK; [e]Baxter AG, Vienna, Austria; [f]Octapharma, Hoboken, NJ, USA; [g]LFB, Les Ulis, France; [h]BioProducts Laboratory, Hertfordshire, UK. FVIII:C: factor VIII coagulant activity; HMW: high molecular weight; N/A: not available; NHP: normal human plasma; VWF: von Willebrand factor; VWF:Ag: antigen; VWF:CB: collagen binding assay; VWF:RCo: ristocetin cofactor. Data collated from various references[35-44].

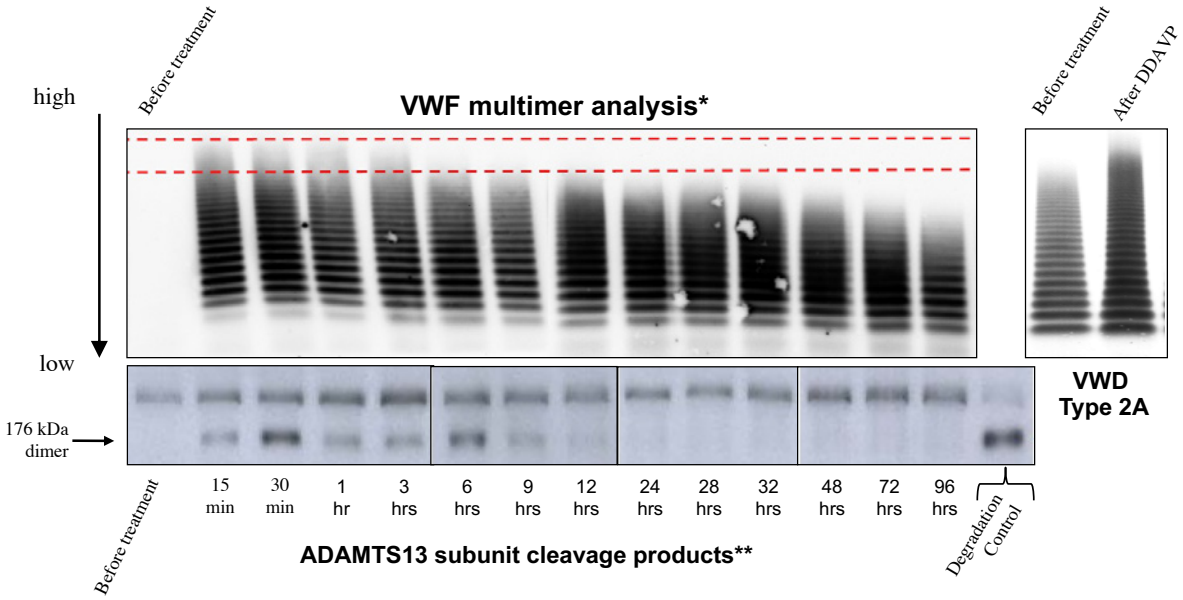
Favaloro EJ. Blood Transfus. 2016;14:262-76.

Limitations of VWF/FVIII concentrates

- Because of the qualitative, and quantitative VWF differences observed across VWD types, replacement therapy with VWF concentrates for many different clinical scenarios are needed.
- Since these are donor-derived concentrates, there is a possibility of allergic reaction, and a theoretical possibility of transmitting blood-borne viruses.
- Batches of the same concentrate can vary in VWF concentration and VWF/FVIII proportion (see next slide), possibly leading to variable plasma levels when administered to patients

Favaloro EJ. Blood Transfus. 2016;14:262-276.
Keeney S Clin Invest. 2012;2:755-757.
Gill JC et al. Blood. 2015;126:2038-2046.
Ofosu FA et al. Thromb Haemost. 2008;99:851-862.

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

How is recombinant VWF different from plasma/plasma-derived concentrates?

Specific VWF activities	Plasma/plasma-derived VWF	Plasma-derived VWF concentrates	rVWF
VWF:RCo/VWF:Ag	~1[a]	Variable, but typically <1	>1
VWF:CB/VWF:Ag	~1[a]	Variable, but typically <1	>1
VWF:RCo/FVIII:C	~0.5-1 (plasma)	Variable	>10[b]
VWF:CB/FVIII:C	~0.5-1 (plasma)	Variable	>10[b]

[a] Theoretical/relative/reference values;
[b] Recombinant VWF only contains trace amounts of FVIII, but can be combined with recombinant FVIII in variable quantities.

Favaloro EJ. Blood Transfus. 2016;14:262-76.

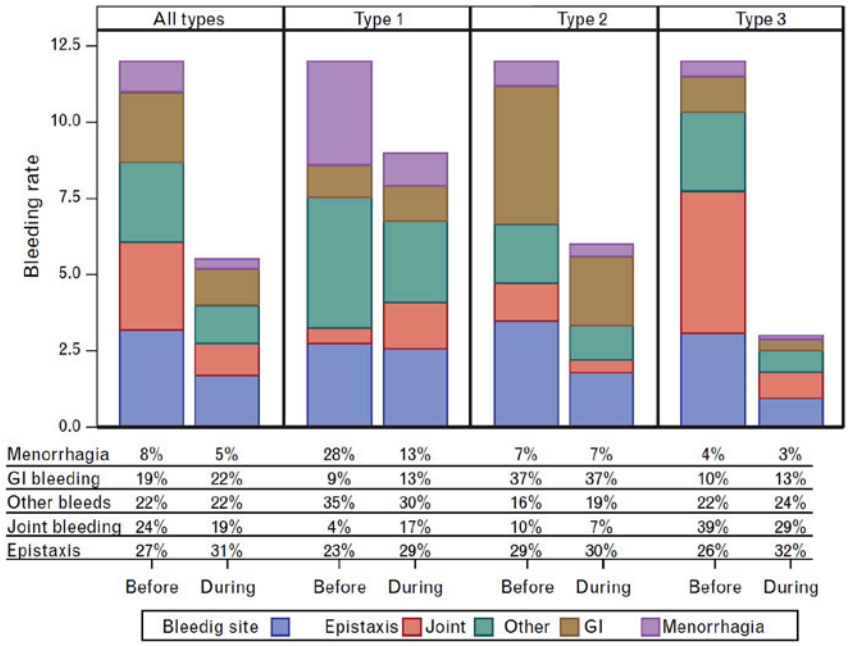
How is recombinant VWF different from plasma/plasma-derived concentrates?

- **Half life**
  - ***In a nonbleeding state, mean plasma VWF:RCo t1/2 for rVWF (19.6 hours) is considerably longer than that of pd-VWF (range, 12.8-15.8 hours)***
    - ➢ **May relate in part to differences in glycosylation profile**

- **rVWF does not contain significant amounts of FVIII**
  - **In the absence of rFVIII co-administration, infusion of rVWF in patients with type 3 VWD still leads to normalization in plasma FVIII:C levels as a result of stabilization of endogenous FVIII.**
  - **rVWF appears to be more effective in stabilizing endogenous FVIII compared with pd-VWF.**
    - ➢ **Related to longer plasma half-life? or increased high-molecular-weight multimers?**

Lavin M, O'Donnell JS. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):683-9.
Mannucci PM, et al Blood. 2013;122(5):648-57.
Gill JC, Blood. 2015;126(17):2038-46.

Changes in bleeding patterns in von Willebrand disease after institution of long-term replacement therapy: results from the von Willebrand Disease Prophylaxis Network



Holm E et al, Blood Coagul Fibrinolysis 2015;26:383-8.

Secondary Long-Term Prophylaxis in VWD

Italian Criteria for SLTP according to evidence-based data (1)

According to the prospective Italian Registry (RENAWI-2) evaluating 796 patients centrally confirmed for the predictors of spontaneous bleeds, high bleeding score (>10 IU/dL) together with low levels of VWF activities (< 10 IU/dL) are the most important parameters to predict clinical outcomes and replacement therapy with VWF concentrates in adult patients with VWD.

The main conclusions of RENAWI-2 were the following:

1. **Bleeding score helps to predict clinical outcomes in adult VWD.**
2. **High bleeding scores correlate with intensive on demand therapy and may identify cases requiring regular prophylaxis**

Federici et al, Blood 2014; 123: 4037-44.

Prophylaxis in patients with von Willebrand disease: who, when, how?

A. B. FEDERICI*†

Factor replacement therapy	Hemophilia A and B	von Willebrand disease
Episodic 'on-demand' replacement therapy	Replacement therapy given at the time of clinically evident bleeding	Replacement therapy when mucosal or non- mucosal bleeds occur
Regular replacement therapy	Replacement therapy given to prevent bleeding	Therapy used to prevent bleeding in surgery
Primary prophylaxis	Regular continuous* replacement therapy started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and age 3 years	Due to the late onset of the first bleeds in VWD this approach is currently not used in patients (*not applicable to VWD*)
Secondary prophylaxis	Regular continuous* replacement therapy started after two or more joint bleeds but before the onset of joint disease documented by physical examination and/or imaging studies	This approach can be used in patients with severe bleeding history and recurrent mucosal or non-mucosal bleeds (*secondary long-term prophylaxis*)
Tertiary prophylaxis	Regular continuous* replacement therapy started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints	This approach has not been reported yet in VWD due to the limited number of cases with an affected target joint (*not applicable to VWD*)
Intermittent 'periodic' prophylaxis	Replacement therapy given to prevent bleeding for periods not exceeding 45 weeks in a year	This approach can be used in VWD women with recurrent episodes of menorrhagia

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Clinical management of VWD: toward a more evidence-based approach

Questions?

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