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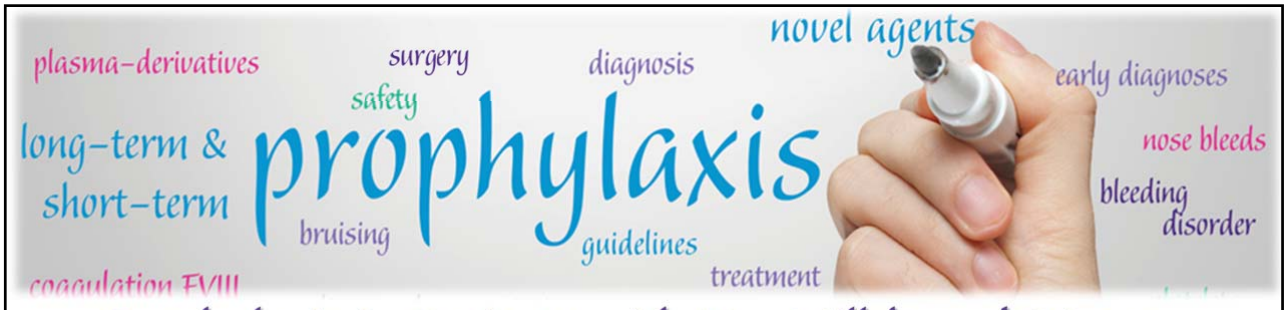

Prophylaxis in Patients with Von Willebrand Disease: Expert Perspectives and Shared Experiences

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- **Dr. Robert Sidonio, Jr.** has relevant financial relationships related to consulting from Bayer AG, Genentech, Inc., Grifols S.A., Guardian Therapeutics, Novo Nordisk A/S, Octapharma USA, Inc., Sanofi, Sobi, and Takeda Oncology, as well as investigator sponsored studies from Genentech, Octapharma, and Takeda.
- **Dr. Miguel Escobar** has relevant financial relationships related to advisory activities from CSL Behring, Genentech - A Member of the Roche Group, HEMA Biologics, LLC, LFB Biopharmaceuticals Limited, Novo Nordisk A/S, Pfizer Inc., Sanofi, Takeda Oncology, and uniQure N.V., as well as consulting from HEMA Biologics and LFB. He is on the speakers' bureau for Bayer AG, BioMarin Pharmaceutical Inc., and Kedrion, and has received research grant(s) from Genentech - A Member of the Roche Group, Novo Nordisk A/S, Sanofi, Takeda, and uniQure.
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Learning Objectives

- Outline recent guidelines concerning the use of short- and long-term prophylaxis in patients with von Willebrand Disease (VWD)
- Identify patient and disease characteristics that suggests a patient with VWD will benefit from long-term prophylaxis
- Summarize the safety and efficacy data from recent and ongoing trials investigating novel prophylaxis agents for VWD
- Outline factors that must be considered when identifying therapeutic strategies, doses and regimens for prophylaxis in patients with VWD

The Current Standard of Care in Von Willebrand Disease: Meeting Today's Challenges

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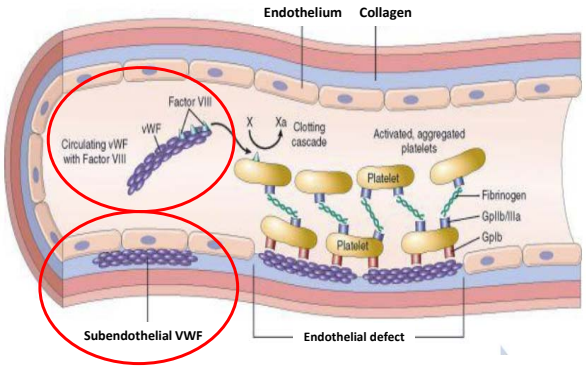
Von Willebrand Disease (VWD)

- Erik von Willebrand reported mucocutaneous bleeding and death among several members of a family living on the Åland islands the Baltic Sea
  - Both males and females were affected
  - Bleeding time was prolonged despite normal platelet counts
- Index case was a 5-year-old girl named Hjørdis
  - Hjørdis died after her 4th menstrual period
- At least 25k cases of VWD (many unrecognized as likely occurs in 1 in 1000 persons)

James PD, et al. *Genet Med*. 2011;13(5).; Soucie JM, et al. *Haemophilia*. 2021;27(3):445-453.

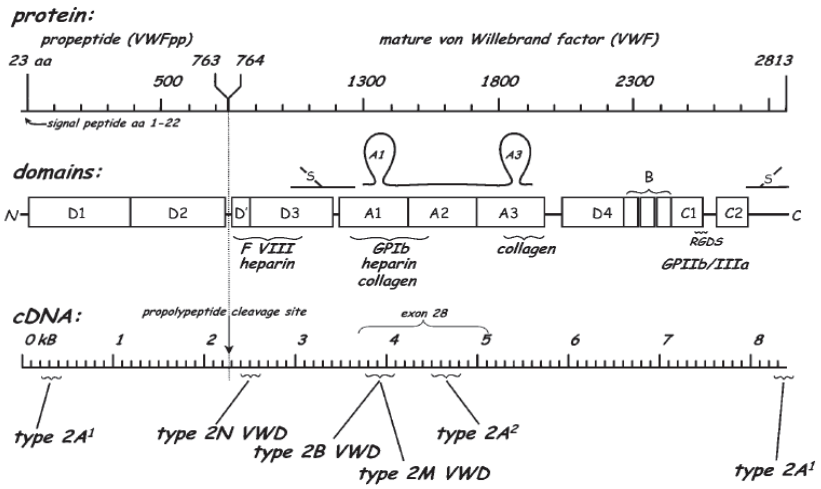
VWF Plays Two Important Roles



1. **VWF tethers the platelet to exposed collagen**
2. **VWF serves as a carrier protein for factor VIII**

VWF=von Willebrand factor
James PD, Goodeve AC. *Genet Med*. 2011;13(5).

VWF Genetics



The Diagnosis, Evaluation and Management of von Willebrand Disease. NBLI von Willebrand Disease Expert Panel. 2007.

VWD Classification

	Type 1	Type 2	Type 3
Definition	Below normal levels of VWF	Normal levels of VWF, but VWF fails to work properly	Total or near total quantitative deficiency of VWF
Severity	Mild-to-moderate	Mild-to-moderate	Severe
Prevalence (% of cases)	85%	13%	3%

- Type 2 includes four subtypes:
  1. Type 2A: Typically manifests as mild-to-moderate mucocutaneous bleeding
  2. Type 2B: Typically manifests as mild-to-moderate mucocutaneous bleeding that can include thrombocytopenia that worsens in certain circumstances
  3. Type 2M: Typically manifests as mild-moderate mucocutaneous bleeding
  4. Type 2N: Can manifest as excessive bleeding with surgery and mimics mild hemophilia A

Centers for Disease Control and Prevention (CCD). Von Willebrand Disease (VWD). https://www.cdc.gov/ncbddd/vwd/facts.html#Accessed. July 2022.

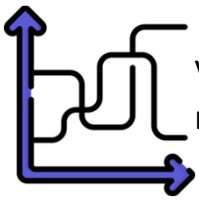
Hemophilia and VWD, Similar But Different…

HEMOPHILIA	VWD
The majority of bleeding is musculoskeletal	The majority of bleeding is mucocutaneous
The majority is moderate-to-severe deficiency	The majority of patients have mild deficiency
Largely consistent inheritance	At least half of VWD cases incompletely penetrant

Hemophilia ABR ≠ VWD ABR

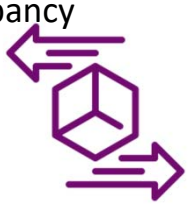
Goodeve A. *Hematology Am Soc Hematol Educ Program.* 2016;(1):678-682.; Miesbach W, et al. *Thromb Res.* 2021;199:67-74.

Hemophilia and VWD: What This Has Led To…



Variability in management

Discrepancy in care



Limited VWD trials

Frustration by patients…

…on lack of consensus

Hemophilia and Prophylaxis

Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B (Review)[1]

2006

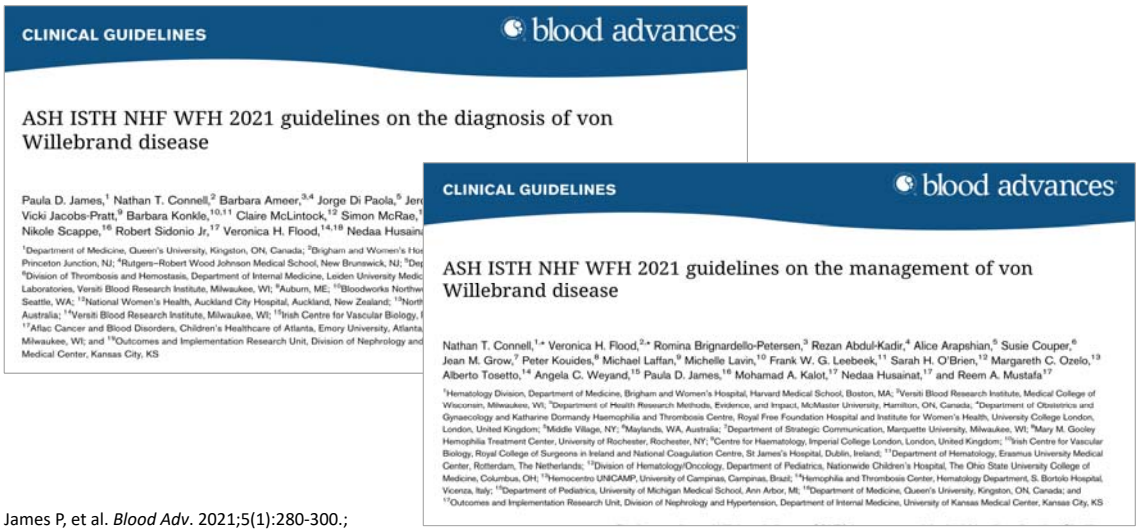
There is insufficient evidence from RCTs to determine whether prophylactic CFCs decrease bleeding and bleeding-related complications in hemophilia A or B…

2011

There is strong evidence from RCTs and observational trials that prophylaxis preserves joint function in children with hemophilia…

1. Iorio A, et al. *Cochrane Database Syst Rev.* 2011;(9):CD003429.

International Effort to Develop the 2021 VWD Guidelines



James P, et al. *Blood Adv*. 2021;5(1):280-300.;
Connell N, et al. *Blood Adv.* 2021;5(1):301-325.

Prophylaxis

Definition in Hemophilia

- *Primary:* Before the second clinically evident large joint bleed
- *Secondary:* After the second joint bleeding and before initiation of joint disease
- *Tertiary:* Treatment started after the onset of joint disease

Proposed Definition in VWD

- A period of at least 3 to 6 months of treatment consisting of VWF concentrate administered at least once weekly, or for women with HMB, use of VWF concentrate administered at lease once per menstrual cycle

Connell N, et al. *Blood Adv.* 2021;5(1):301-325.

Treat Recurrent Bleeding in VWD with Prophylaxis

Recommendation 1

In patients with VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks:

- Bleeding symptoms and the need for prophylaxis should be periodically assessed

*The recommendation is likely to be strengthened by future research. The majority of would want the suggested course of action.

Connell N, et al. *Blood Adv.* 2021;5(1):301-325.

Available VWF Concentrates

Product Name	Ratio of VWF:RCo to FVIII:C	Half-life (h)	Regulatory Approval
Alphanate (antihemophilic factor/VWF complex [human])	1.3:1	VWF:RCo 7.67 ± 3.32 FVIII:C 17.9 ± 9.6	Yes: surgery and/or invasive procedures; except Type 3 (not indicated for severe type 3 undergoing major surgery) No: prophylaxis
Humate-P (antihemophilic factor/VWF complex [human])	1.8-2.4:1	VWF:RCo 10.5 (2.8-33.6) FVIII:C 12.2 (8.4-17.4)	Yes: bleeding and surgery prophylaxis No: prophylaxis
Wilate (VWF/coagulation factor VIII complex [human])	1:1	VWF:RCo 15.8 ± 11 FVIII:C 19.6 ± 6.9	Yes: bleeding and surgery prophylaxis No: prophylaxis
Vonvendi [VWF (recombinant)]	N/A	VWF:RCo 19.1 ± 5 (No FVIII content)	Yes: on-demand bleeding, perioperative management of bleeding Yes: prophylaxis for severe Type 3 VWD receiving on-demand therapy

ALPHANATE® (antihemophilic factor/VSF complex [human]). Los Angeles, CA: Grifols Biologicals LLC. Revised June 2018. Alphanate Prescribing Information Patient.pdf. Accessed August 8, 2022, 2022.; HUMATE-P® (antihemophilic factor/von Willebrand factor complex [human]). Marburg, Germany: CSL Behring GmbH. Revised June 2020. Package-Insert---Humate-P-1.pdf. Accessed August 8, 2022.; WILATE® (von Willebrand factor/coagulation factor VIII complex [human]). Vienna, Austria: Octapharma Pharmazeutika Produktionsges.m.b.H. Revised March 2020. Package Insert - Wilate.pdf. Accessed August 8, 2022.; VONVENDI® (von Willebrand factor [recombinant]). Lexington, MA: Baxalta US Inc. Revised 1/2022. Package-Insert---VONVENDI.pdf. Accessed August 8, 2022.

Prophylaxis in VWD

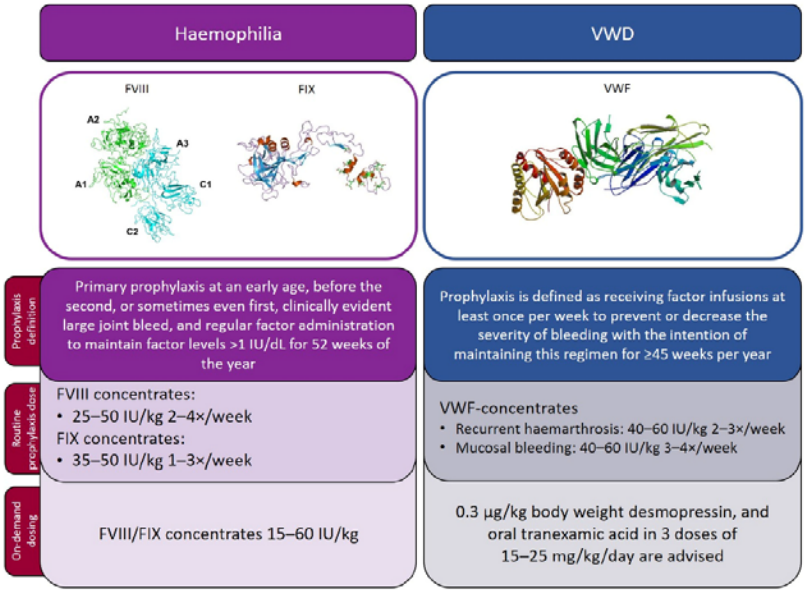
Dose escalation prospective study design part of the VWD prophylaxis network

- n=105 (90 retrospective; 10 prospective)
  - Type 1 VWD(<20 VWF levels) (13)
  - Type 2A/2M/2B VWD (38)
  - Type 3 VWD (54)

Indication	N	Prior to prophylaxis, median (IQR) prophylaxis	During prophylaxis, median (IQR)	Median rate change (IQR)	Median percentage change (IQR)
Epistaxis	28	11.1 (6.0 to 48.0)	3.8 (0.21 to 16.8)	-6.1 (-42.0 to -1.5)	-86.7 (-95.5 to -49.8)
GI bleeding	18	9.3 (6.0 to 21.6)	6.0 (3.6 to 7.1)	-3.0 (-6.0 to 0.0)	-44.3 (-72.2 to 0)
Joint bleeding	25	11.9 (6.0 to 18.0)	0.8 (0.0 to 3.2)	-8.5 (-12.0 to -4.2)	-86.9 (-100.0 to -52.5)
Menorrhagia	9	9.6 (8.4 to 12.0)	0.0 (0.0 to 0.4)	-9 (-9.3 to -6.0)	-100.0 (-100.0 to -95.8)

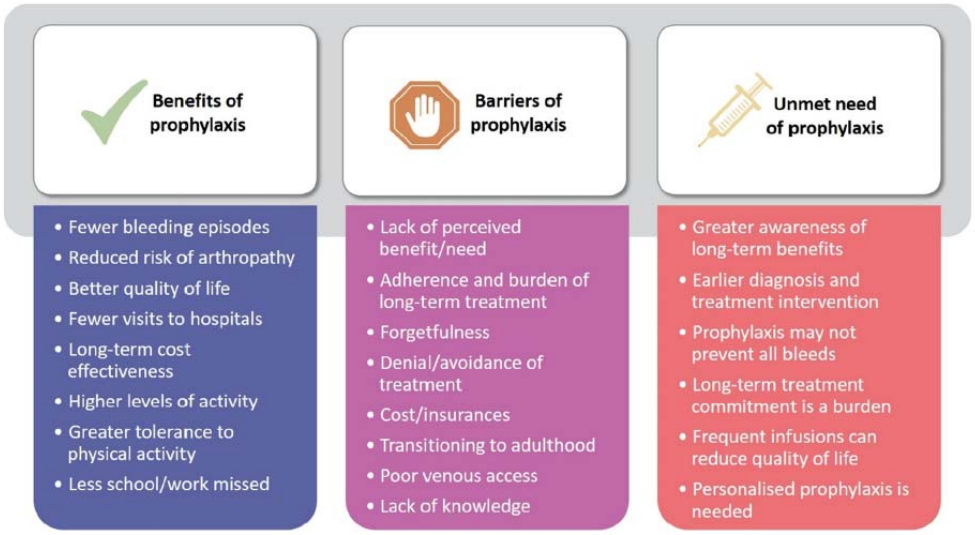
IQR=in quartile range
Holm E, et el. *Blood Coagul Fibrinolysis.* 2015;26(4):383-388(6).

Translating the Success of Prophylaxis in Hemophilia to VWD



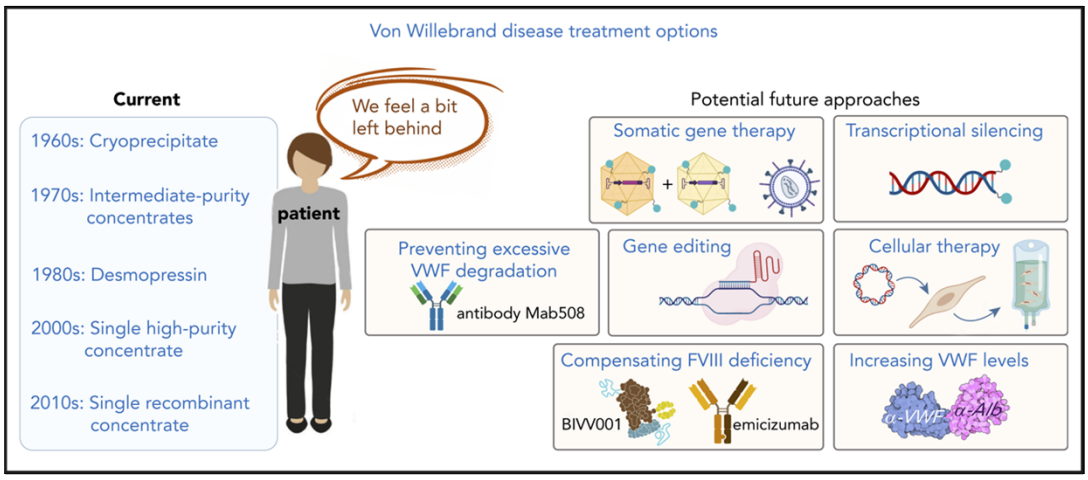
Miesbach W, et al. *Thromb Res.* 2021;199:67-74.

Benefits and Barriers…

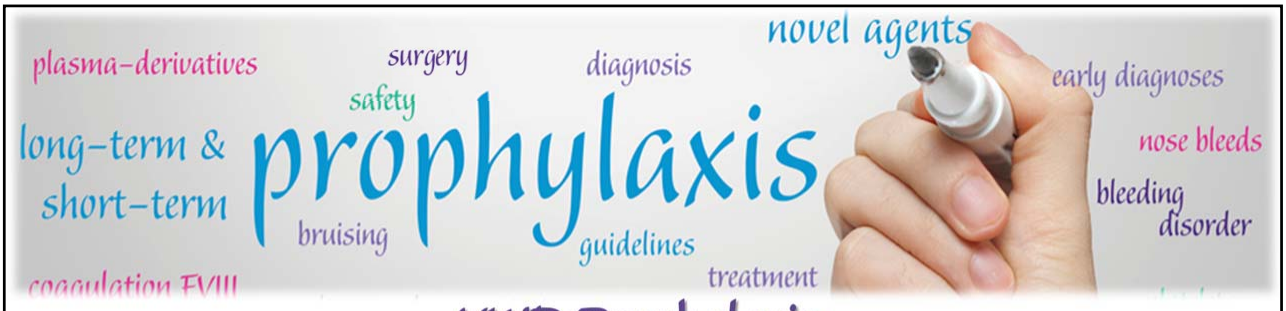


Miesbach W, et al. *Thromb Res.* 2021;199:67-74.

The Future of VWD?



Denis CV, et al. *Blood.* 2021;137(17):2299-2306.



VWD Prophylaxis: Applying Guidelines to Clinical Practice

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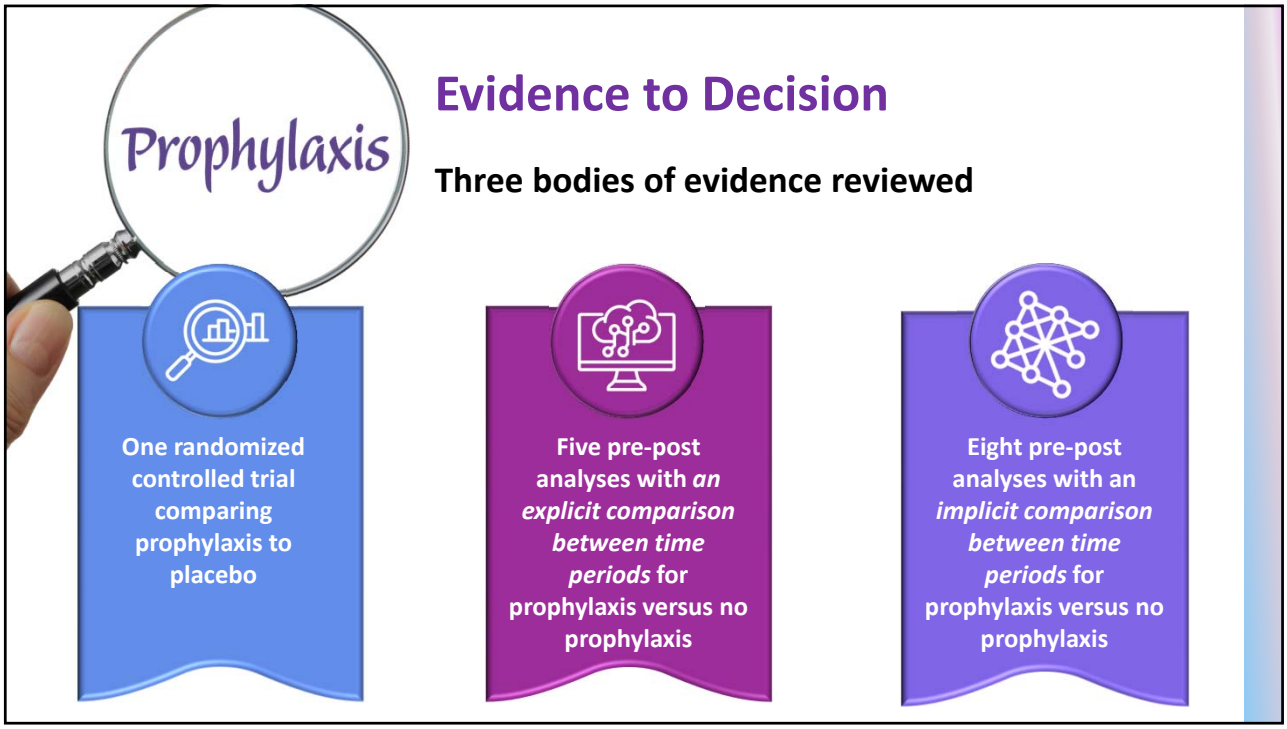
Management: Prophylaxis

In patients with VWD with a history of severe and frequent bleeds, should routine prophylaxis with VWF concentrate or no routine prophylaxis (ie, treatment on demand) be used?

Recommendation 1. In patients with VWD with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis.

Conditional recommendation based on low certainty in the evidence of effects

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.



Evidence to Decision

Evidence showed routine VWF concentrate prophylaxis:

- **Reduced risk of bleeding**
- **Reduced epistaxis**
- **Improved time to first bleeding event**
- **Reduced risk of bleeding episodes, hospitalizations, and heavy menstrual bleeding**

- In the RCT, there was a question of increased bleeding episodes lasting >2 days and increased gastrointestinal hemorrhage
  - Majority occurred in a single patient possibly leading to overestimation of harm

Key Considerations

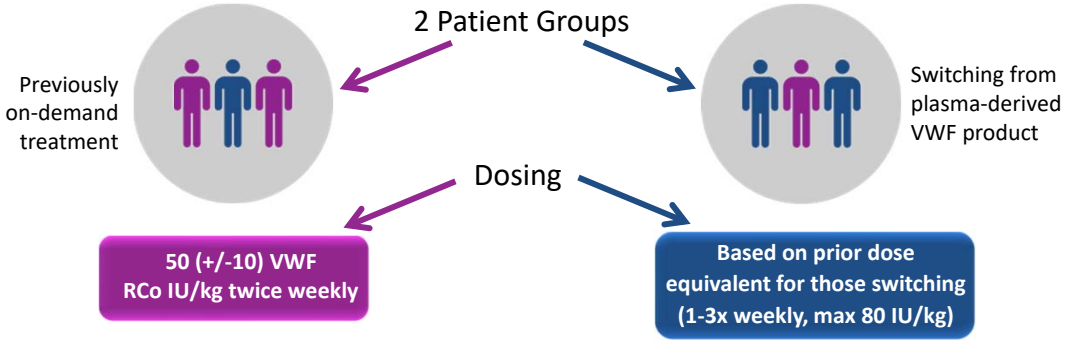
Themes from surveys and panel discussion

- Patients are likely to place ***a high value on reducing the risk of bleeding, particularly the effect of bleeding*** on quality of life
- ***Value depends on the frequency and severity*** of the bleeds
- Importance of ***shared decision making*** to review risks/benefits
- Likely ***variability in values and preferences amongst individual patients***
- Importance of the ***availability of educational material*** for clinicians and patients to highlight both the potential benefits and harms of long-term prophylaxis

Newer Evidence

Phase 3 adult, open-label, nonrandomized multicenter study of recombinant VWF product

Evaluated annualized bleed rate for treated spontaneous bleeding events relative to historical ABRs



Leebeek F, et al. *Blood.* 2022;140(2)89-98.

Phase 3 Open-label Study Results

Patient demographics and baseline characteristics

	Prior on-demand group* (n = 13)	Switch group† (n = 10)
Age, y		
Mean (SD) Median (range)	38.0 (17.6) 30.0 (20-67)	43.9 (21.8) 34.0 (18-77)
Sex, n (%)		
Male Female	5 (38.5) 8 (61.5)	7 (70.0) 3 (30.0)
Body mass index, kg/m²		
Mean (SD) Median (range)	23.3 (3.1) 23.6 (17.8-29.3)	23.3 (3.5) 23.7 (17.7-28.6)
VWD type, n (%)		
Type 1 Type 2A Type 2B Type 3	2 (15.4) 0 1 (7.7) 10 (76.9)	1 (10.0) 1 (10.0) 0 8 (80.0)
VWF:RCo, IU/dL		
Mean (SD) Median (range)	5.6 (10.7) 0 (0-27.8)	0.8 (2.6) 0 (0-8.3)
FVIII:C, IU/dL		
Mean (SD) Median (range)	25.9 (40.6) 3.0 (2-111)	10.3 (12.5) 3.5 (1-40)

Primary efficacy analysis: comparison of on-study sABRs with historical estimates

	Prior on-demand group (n = 13)	Switch group (n = 10)
Historical		
No. of treated spontaneous BEs	201	50
sABR mean (95% CI)**	6.54 (2.52 to 17.00)	0.51 (0.04 to 6.31)
rVWF prophylaxis (on-study treatment)		
No. of treated spontaneous BEs	9	18
sABR mean (95% CI)**	0.56 (0.15 to 2.05)	0.28 (0.02 to 3.85)
Comparison (rVWF prophylaxis vs historical sABR)		
sABR rVWF prophylaxis: historical ratio (95% CI)	0.085 (0.021 to 0.346)	0.550 (0.086 to 3.523)
sABR percentage change from historical (95% CI)††	−91.5% (−97.9% to −65.4%)	−45.0% (−91.4% to 252.3%)

Leebeek F, et al. *Blood.* 2022;140(2)89-98.

AEs in Patients Who Received rVWF Prophylaxis (Safety Analysis Set)*

	Prior on-demand group (n = 13) n (%)/events	Switch group (n = 10) n (%)/events	Total (n = 23) n (%)/events
AE† Mild Moderate Severe	10 (76.9)/26 7 (53.8)/18 1 (7.7)/5 2 (15.4)/3	7 (70.0)/15 4 (40.0)/12 2 (20.0)/2 1 (10.0)/1	17 (73.9)/41 11 (47.8)/30 3 (13.0)/7‡ 3 (13.0)/4§
Serious AE	1 (7.7)/1	2 (20.0)/2	3 (13.0)/3
AE considered related to rVWF	1 (7.7)/1	0	1 (4.3)/1
Serious AE considered related to rVWF	0	0	0
AE considered related to study procedures	0	0	0
Serious AE considered related to study procedures	0	0	0
AE leading to discontinuation of rVWF	1 (7.7)/1	0	1 (4.3)/1
Fatal AE	0	0	0
Life-threatening AE	0	0	0
AE of special interest‖	1 (7.7)/1¶	1 (10.0)/1**	2 (8.7)/2

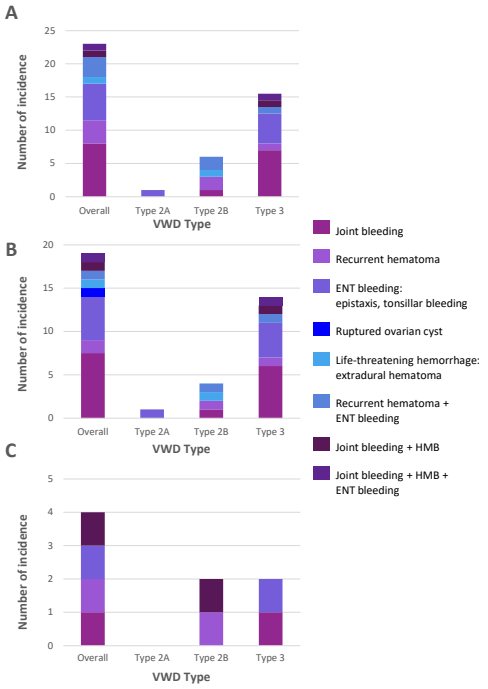
Leebeek F, et al. *Blood.* 2022;140(2)89-98.

Newer Evidence

Demographic characteristics of patients with VWD receiving LTP

	Total *n* = 23	Type 2A *n* = 1	Type 2B *n* = 6	Type 3 *n* = 16
Sex, *n* (%)				
Male	11 (47.8)	0 (0)	5	6
Female	12 (52.2)	1 (100)	1	10
Blood group O, *n* (%)	11 (47.8)	0 (0)	2 (33.3)	9 (56.2)
Age, years, median (range)[a]	16 (1–85)	4	7 (1–29)	20.5 (3–85)
Body weight, kg, median (range)	58 (15–84)	17	48 (15–72)	58 (21–84)

[a]Median age at the initiation of prophylaxis by Voncento®
Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.



Dose, frequency, duration of follow-up, and bleeding episodes in all patients receiving LTP with Voncento®

	Total *n* = 23	Type 2A *n* = 1	Type 2B *n* = 6	Type 3 *n* = 16
Dose, IU/kg	45 (33–109)	109	54.5 (33–100)	44 (35–62)
Weekly dose, IU/kg/week	96 (44–222)	109	100.5 (67–200)	90 (44–222)
Number of infusions per week	2 (1–3)	1	2 (1–3)	2 (1–3)
Duration of follow-up, months*	19 (5–48)	48	21 (17–27)	17.5 (5–46)
ABR	0.5 (0–7.2)	0.8	0.7 (0–2.9)	0 (0–7.2)
Effectiveness (Excellent/Good)[+]	9/10	0/1	3/3	6/6

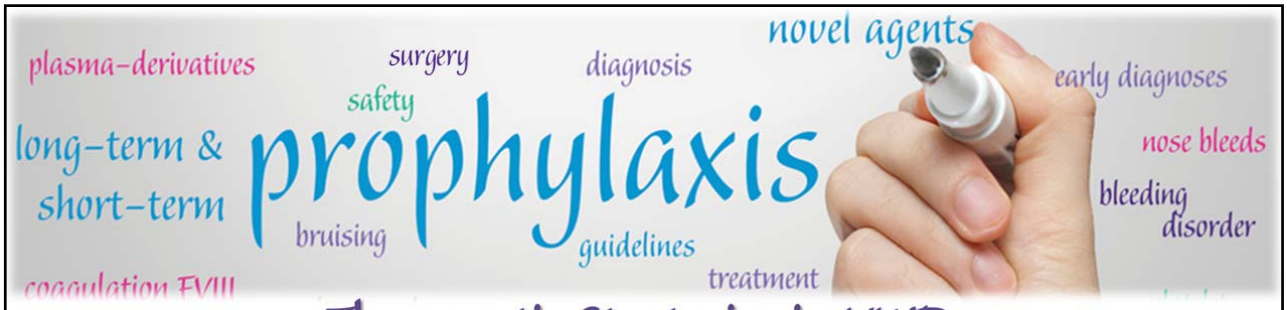
Comparison in terms of dose and bleeding episodes between initial prophylaxis and the prophylaxis by Voncento® (LTP group)

	Total *n* = 19	Type 2A *n* = 1	Type 2B *n* = 4	Type 3 *n* = 14
pdVWF**				
Dose IU/kg	42.5 (35–62)	46	44.5 (42–60)	40 (35–62)
Number of infusions per week	2 (1–3)	1	2 (2–3)	2 (1–3)
ABR	1 (0–6)	5	0 (0–6)	1 (0–4)
hFVIII/VWF concentrate (Voncento®)				
Dose, IU/kg	43.5 (33–109)	109	38.5 (33–50)	44 (33–96)
Number of infusions per week	2 (1–3)	1	2.5 (1.5–3)	2 (1–3)
ABR	0.3 (0–2)	0.8	0.6 (0–1.9)	0 (0–2)

Four patients switched from on-demand to LTP, ABR dropped from 0.5 to 0
Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.

The Rationale for Long-Term Prophylaxis in Clinical Practice

- Type 3 adult VWD patients
- Joint bleeding
- Gastrointestinal bleeding/angiodysplasia
- Severe, recurrent bleeding
- Heavy menstrual bleeding



Therapeutic Strategies in VWD: A Closer Look at the Use of Prophylaxis Treatment

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Professor of Medicine and Pediatrics
Director, Clinical Research Center
McGovern Medical School
The University of Texas Health
Science Center
Houston, Texas

Treatment Strategies in VWD

On-Demand | Perioperative | Prophylaxis

Goal: Prevent or control bleeding through improved platelet adhesion-aggregation and fibrin formation

- **Replacement therapy:** Increase plasma concentration of VWF by replacing with human plasma-derived, virus-inactivated concentrates or recombinant VWF
- **Non-replacement therapy:** Increase plasma concentration of VWF by stimulating the release of endogenous VWF stores
- **Adjunctive therapy:** Employ supportive agents that promote hemostasis and wound healing

Leebeek FWG, et al. *Brit J Haematol.* 2019;187:418-430.; Mannucci PM. *Blood Adv*. 2019;3(21):3481-3487.

Treatment Strategies in VWD

- Replacement therapy products
  - Are not all the same
  - Have different ratios of FVIII to VWF (Pd concentrates)
  - Should not be considered interchangeable
- All patients receiving replacement therapy should be monitored to:
  - Maintain hemostatic levels of VWF:RCo and FVIII
  - Avoid exceeding maximum recommended levels of VWF:RCo and FVIII
  - Assess thrombotic risk
  - Institute appropriate preventive strategies

National Heart, Lung and Blood Institute. *The Diagnosis, Evaluation, and Management of von Willebrand Disease*. National Institutes of Health; 2007
Mannucci PM. *Blood Adv.* 2019;21:3481-3487.

Desmopressin (DDAVP) for VWD

- **Mechanism of action:** triggers release of VWF + factor VIII from endothelial storage sites
  - Safety point: must monitor electrolyte and fluid balance
- **DDAVP trial in Type 1 VWD**
  - "Low VWF" 30-50 IU/dL: adults presumed to be responsive; children need trial
  - VWF <30 IU/dL (possible Type 1C): panel suggests performing a desmopressin trial and treating based on results

VWD	Type 1	Type 2		Type 3
Subtype	Omit Type 1C/non-responders	**2A, 2M, 2N**	**2B**	N/A
Use of DDAVP	**First line** on-demand and perioperative therapy if no contraindication	May have partial or shorter-lived response May be helpful for **minor bleeding**	**Contraindicated** May worsen low platelets	**Do not use** No response

IU/dL=International units per liter; MOA=mechanism of action
Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.; American Society of Hematology (ASH). *2012 Clinical practice guideline on the evaluation and management of von Willebrand disease (VWD).* ASH Website. 2012. Watermark-Von-Willebrand-Disease-Pocket-Guide-1.pdf. Accessed January 20, 2022.; Leebeek FWG, et al. *Brit J Haematol.* 2019;187:418-430.

Available VWF Concentrates

Product Name	Ratio of VWF:RCo to FVIII:C	Half-life (h)	Regulatory Approval
Alphanate (antihemophilic factor/VWF complex [human])	1.3:1	VWF:RCo 7.67 ± 3.32 FVIII:C 17.9 ± 9.6	Yes: surgery and/or invasive procedures; except Type 3 (not indicated for severe type 3 undergoing major surgery) No: prophylaxis
Humate-P (antihemophilic factor/VWF complex [human])	1.8-2.4:1	VWF:RCo 10.5 (2.8-33.6) FVIII:C 12.2 (8.4-17.4)	Yes: bleeding and surgery prophylaxis No: prophylaxis
Wilate (VWF/coagulation factor VIII complex [human])	1:1	VWF:RCo 15.8 ± 11 FVIII:C 19.6 ± 6.9	Yes: bleeding and surgery prophylaxis No: prophylaxis
Vonvendi [VWF (recombinant)]	N/A	VWF:RCo 19.1 ± 5 (No FVIII content)	Yes: on-demand bleeding, perioperative management of bleeding Yes: prophylaxis for severe Type 3 VWD receiving on-demand therapy

ALPHANATE® (antihemophilic factor/VSF complex [human]). Los Angeles, CA: Grifols Biologicals LLC. Revised June 2018. Alphanate Prescribing Information Patient.pdf. Accessed August 8, 2022, 2022.; HUMATE-P® (antihemophilic factor/von Willebrand factor complex [human]). Marburg, Germany: CSL Behring GmbH. Revised June 2020. Package-Insert---Humate-P-1.pdf. Accessed August 8, 2022.; WILATE® (von Willebrand factor/coagulation factor VIII complex [human]). Vienna, Austria: Octapharma Pharmazeutika Produktionsges.m.b.H. Revised March 2020. Package Insert - Wilate.pdf. Accessed August 8, 2022.; VONVENDI® (von Willebrand factor [recombinant]). Lexington, MA: Baxalta US Inc. Revised 1/2022. Package-Insert---VONVENDI.pdf. Accessed August 8, 2022.

Factor Concentrate Target Levels

Indication*	Dose †(IU/kg)	Target Levels‡	Duration (days)
Bleeding (on-demand)			
• Mild to moderate	20-40	Peak >50-80 on day 1; trough >30 after day 1	1-3
• Severe	50	Peak >100 on day 1; trough >50 after day 1	7-10
Intervention (perioperative)			
• Uncomplicated procedure	25	Peak >50 on day 1	1
• Minor surgery	30-60	Peak >50-80 on day 1; trough >30 after day 1	1-5
• Major surgery	50-60	Peak >100 on day 1; trough >50 after day 1	7-10
Safety parameters 1) Do not exceed VWF:RCo 200 IU/dL or FVIII 250-300 IU/dL, 2) Maintain hemostatic levels of VWF:RCo and FVIII, 3) Assess thrombotic risk, 4) Institute appropriate preventive strategies			

Leebeek FW, et al. *N Engl J Med*. 2016;375:2067-2080.; Leebeek FWG, et al. *Brit J Haemat.* 2019;187:418-430.

Phase 3 Study Comparing Secondary PRO vs ODT with VWF/FVIII Concentrates in Severe Inherited VWD

12-month, international, multicenter, randomized, open-label, parallel-group study (EudraCT 2006-001383-23)

Objective: Evaluate if prophylaxis with a VWF/FVIII concentrate was effective in preventing spontaneous bleedings in patients with severe VWD unresponsive to DDAVP when compared with ODT.

Number and incidence rate of bleeding episodes during the study according to treatment groups:

Type of bleeding episode	On-demand (N = 9)		Prophylaxis (N = 10)	
	N	*Rate*	*N*	*Rate*
Any type	172	1.41	32	0.34
Mucosal bleeding	164	1.34	17	0.18
Epistaxis	52	0.42	15	0.16
Other bleedings	112	0.92	2	0.02
Joint and muscle bleeding	7	0.05	2	0.02
Hemarthrosis	3	0.02	1	0.01
Muscle hematoma	4	0.03	1	0.01
Gastrointestinal hemorrhage	1	0.01	13	0.14

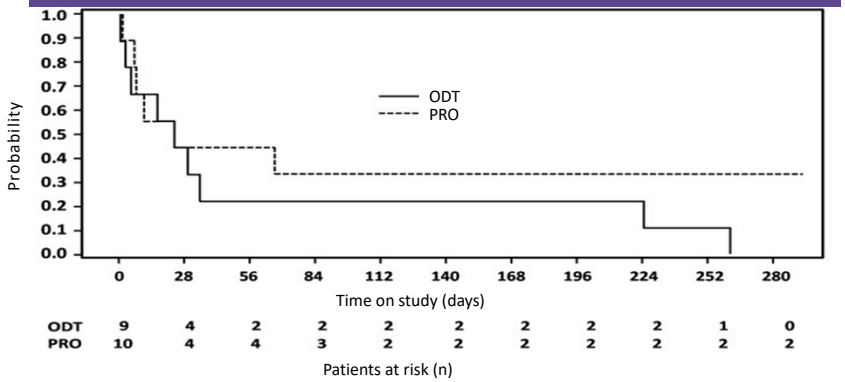
Safety: No clinical AEs attributed to study medication
PRO=long-term prophylaxis; ODT=on-demand treatment
Peyvandi F, et al. *Blood Transfus*. 2019;17(5):391-398.

Phase 3 Study Comparing Secondary PRO vs ODT with VWF/FVIII Concentrates in Severe Inherited VWD

12-month, international, multicenter, randomized, open-label, parallel-group study (EudraCT 2006-001383-23)

Conclusion: The prophylactic use of VWF/FVIII concentrates appeared to be associated with a lower risk and frequency of bleeding episodes in severe VWD patients unresponsive to DDAVP, although more data are needed for GI bleeding.

Probability of remaining free of a first spontaneous bleeding episode during the study:



Peyvandi F, et al. *Blood Transfus*. 2019;17(5):391-398.

Summary of Reports on the Use of Long-term Prophylaxis in VWD

Author, year, study design	Product	# of prophylaxis/ overall pop.	Duration of f/u, mo	VWD Type 1/Type 2A-2B-2M/Type 3	Primary bleeding Indication *N* (%)	Dose FVIII:C or VWF:Rco (IU/kg) Median (range)	Frequency *N* time/week	ABR Median (range)	Outcome Excellent/ Good (%)
Dunkley, 2010 Prospective	Biostate®	4/23	12 (6–12)	5/2–6-1/6[c]	NA	23.4 (14–29.1)	NA	1 (1–17)	100
Castaman, 2013 Prospective	Haemate® P	31/121	24	9/1–5-0/16	GI = 34[b] Joint = 41[b] HMB = 17[b]	20	2–3	3 (1–11)	92.9
Abshire, 2015 Prospective	Haemate® Alphanate® Fandhi®	11	NA	0/6–0-0/5	GI = 3 (27) Joint = 2 (18) Epistaxis = 6 (54)	50	1, 2,3	4 (0–27.7)	n/a
Holm, 2015 Retrospective and Prospective	Haemate® Alphanate® Fandhi®	95–10/105	60	13/25–9-3/54[a]	GI (23.2) Joint (23) Epistaxis (32.7) HBM (4.1)	38–73[c]		3.8 (0.2–16.8) 6.0 (3–6-7.1) 0.8 (0–3.2) 0 (0–0.4)	Significant reduction of joint bleed, epistaxis, GI
Goudemand, 2020 Prospective	Wilfactin®	32/155	36	1/13/18	GI (40.6) Joint (43.8)[d] Others (15)	45.2 (22–55) 42.2 (26–76) 46.6 (27–53)		1.1 (0–11) 0.8 (0–5.4) 1.0	n/a
Lissitchkov,2021 Prospective	Voncento®	10/19	41	1/2/7	NA	42.8 (28.5–85.8)	1 (90%)	4.37 (0–25.9)	97.9
Sholzberg, 2021 Prospective	Wilate®	91/25	24	3/5–1–0-1/14	NA	55.4 (8.3–1441.4)	1 to (85%)	1.9 (0–27.0)	99
Berntorp, 2005 Retrospective	Humate-P® Haemate®P	35	12	1/2–4-0/28	GI = 3 (8) Joint = 13 (37) ENT = 16 (45.7) HMB =3 (8)	24 (12–50)	1 to 3	Joint =0.3 ENT = 0.4	n/a
Federici, 2010 Retrospective	Alphanate® Fandhi®	15/120	60	7/3–2-0/3	GI = 9 (61) Joint = 2 (13) CNS = 2 (13)	42 (17–74)	1 to 2	NA	87%
Halimey, 2011 Retrospective	Humate® P Wilate®	32	12	4/15/13	Joint GI Relevant anemia	40 (20–47)	2 to 4		Significant reduced BS
Howman, 2011 Retrospective	Biostate®	2/43	60	0/0/2	Joint Epistaxis	NA	NA		n/a
Abshire, 2013 Retrospective	Haemate® P Alphanate® Fandhi®	59	12	5/10–8-2–/34	GI = 13 (23.6) Joint = 12 (21.8) Epistaxis = 13 (23.6) HMB = 4 (7.3) Combined = 5 (9.1)	60 (47–60) 40 (30–50) 48 (40–60) 39 (38–40) 42 (33–49)	1.5 to 3	6 (3–6) 1.3 (0.3–3.2) 6 (2.9–12) 4 (1–9) 6 (1.2–12)	n/a
Miesbach, 2015 Retrospective	Haemate® P	3		0/1–0-0/2	GI = 3 (100)	50 to 74 18 to 20	2, 2 to 6		100
Leebeek, 2022 Prospective	Vonicog Alfa	23	12	3/1-1/18	17 oral/other mucosa 3 menorrhagia 1 other location 1 hemarthrosis 3 unknown	50±10 IU/kg prior on-demand group. 1-3 x week max 80 IU/kg Switch group based on prior prophylaxis dose	1-3	0.56 (0.15-2.05) prior on demand 0.28 (0.02-3.85) switch group	n/a

Rugeri L, et al. *Eur J Haematol.* 2022;109(1):109-117.

Phase 3 Trial Results: Prophylaxis with Recombinant VWF (Vonicog Alfa) in Patients with Severe VWD

12-month, prospective, open-label, single-arm, non-randomized, multicenter phase 3 study (NCT02973087; EudraCT 2016-001478-14)

Objective: To investigate efficacy and safety of rVWF prophylaxis in adults with severe VWD, including on-study vs. historical sABR and sABR intra-patient comparison.

Primary efficacy analysis: comparison of on-study sABR through month 12 vs historical sABR

Time period Statistic	Prior OD arm (n = 13)	Switch arm (n = 10)
Historical		
Number of treated spontaneous BEs	201	50
sABR (95% CI)	6.54 (2.52, 17.00)	0.51 (0.04, 6.31)
On-study (while receiving prophylactic rVWF)		
Number of treated spontaneous BEs	9	18
sABR (95% CI)	0.56 (0.15, 2.05)	0.28 (0.02, 3.85)
Comparison (on-study vs. historical sABR)		
sABR on-study:historical ratio (95% CI)	0.09 (0.02, 0.35)	0.55 (0.09, 3.52)
sABR percentage change from historical	91.5% reduction	45.0% reduction

Conclusion: rVWF prophylaxis can effectively reduce sABR in patients previously treated OD with VWF products and maintains at least the same level of hemostatic control in patients who switch from prophylaxis with pdVWF to rVWF, with a favorable safety profile.

Secondary efficacy analysis: sABR intra-patient comparison:

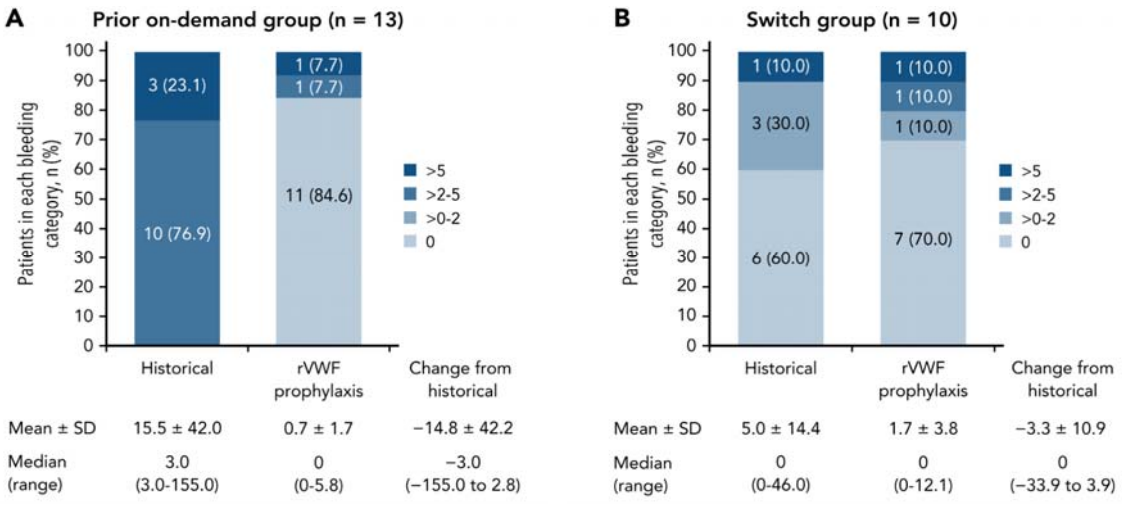
	n/N	95% CI	
sABR* reduction success (prior on-demand group)			
All VWD types	2/13	64.0-99.8	92%
VWD Type 3	9/10	55.5-99.7	90%
sABR preservation success (prior prophylaxis [switch] group)			
All VWD types	9/10	55.5-99.7	90%
VWD Type 3	7/8	47.3-99.7	88%

Safety: 1 AE (moderate headache) possibly related to study medication; no serious AEs; no inhibitors developed

ABR=annualized bleeding rates

Leebeek F, et al. *Blood.* 2022;140(2):89-98.

Treated Spontaneous ABRs



Leebeek F, et al. *Blood.* 2022;140(2):89-98.

ATHN 9: Severe VWD Natural History Study

A Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Severe Von Willebrand Disease (VWD)

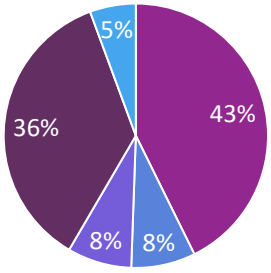
9

~54 U/kg/dose 2.3x per week for rVWF

~50 U/kg/dose 2.4x per week for pdVWF

Study Type	Longitudinal, Observational
Objective	To assess safety of VWF regimens for different indications in patients with clinically severe congenital VWD
Treatment	Regimen at discretion of participants' hemophilia provider
Duration	3 years (subjects followed up to 2 years from enrollment)
Procedures	Lab and genetic testing used; inhibitor testing available
Population	81/130 subjects with clinically severe VWD enrolled, majority characteristics: • White (81%) • Female (58%) • First bleeding event prior to age 10 years (51%) • Nasal cautery (26%) and dental extraction (18%) • Age range newborn to 75+ years

Medication Treatment Type



- Prophylaxis - Continuous (38)
- Prophylaxis - Event-based, short-term or intermittent (7)
- Prophylaxis - Menstrual bleeding (7)
- Episodic (32)
- Treatment Type Unknown (5)

American Thrombosis & Hemostasis Network (ATHN). *ATHN 9: A natural history cohort study of the safety, effectiveness, and practice of treatment for people with severe von Willebrand disease (VWD).* ATHN Website. 2022. https://athn.org/what-we-do/national-projects/athn9.html. Accessed July 2022.

ASH ISTH NHF WFH 2021 Guidelines

Surgery Management with Tranexamic Acid

- **For minor procedures,** the panel suggests increasing VWF activity levels to ≥50 IU/dL with **desmopressin or factor concentrate with the addition of tranexamic acid**
- The panel suggests giving **tranexamic acid alone** over increasing VWF activity levels to ≥50 IU/dL for:
  - Type 1 with baseline VWF activity levels >30 IU/dL
  - Mild bleeding phenotype
  - Minor mucosal procedures
- **For patients at higher risk of thrombosis,** avoid the combination of extended increased VWF and FVIII levels (>150 IU/dL) and extended use of tranexamic acid

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.; World Federation of Hemophilia (WFH). WFH Website. 2021. https://elearning.wfh.org/resource/ash-isth-nhf-wfh-guidelines-on-the-diagnosis-and-management-of-vwd/. Accessed January 20, 2022.

CLINICAL GUIDELINES

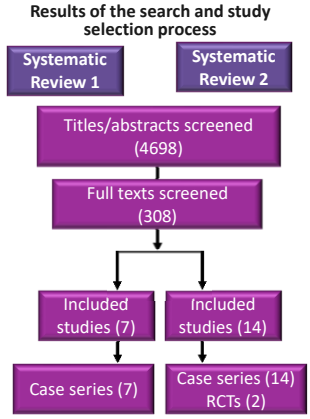
blood advances

Surgical Management of Patients with VWD:
Summary of 2 Systematic Reviews of the Literature

Given the low-quality evidence for guiding management decisions, a shared-decision model leading to individualized therapy plans will be important in patients with VWD who are undergoing surgical and invasive procedures

This systematic review directly informs clinical practice guidelines for the management of VWD and includes recommendations:

1. Target both FVIII and VWF activity levels of ≥0.50 IU/mL for at least 3 days after major surgery
2. Increase VWF activity levels to ≥0.50 IU/mL with desmopressin or VWF concentrate with the addition of TXA after minor surgery or invasive procedures, and
3. To give TXA monotherapy for minor mucosal procedures in patients with Type 1 VWD and baseline VWF activity levels >0.30 IU/mL and a mild bleeding phenotype



Bignardello-Petersen R, et al. *Blood Adv*. 2022;6(1):121-128.

Reminder!

- To participate in the case study audience response questions, get ready by typing ***"slido.com"*** into your browser on your mobile phone.
- You will then be prompted for a code: Please enter ***3793785***.
- Polls will appear when we reach the case study section.
- Don't forget to hit ***"send"*** after responding.

Case Study 1

Lina is a 25-year-old female with menorrhagia who has been managed by a primary doctor and OBGyn for the last 10 years. Took OCPs for a few years but stopped due to severe acne and headaches. Was told she "could have VWD." Mother with history of menorrhagia.

Patient History:

- Heavy menstrual bleeding associated with flooding, periods longer than 7 days, iron deficiency anemia
- Easy bruising
- No dental procedures
- Appendectomy at age 22 (laparoscopic) "without bleeding complications"

Labs

- VWF:Ag 37
- VWF:RCo 32
- FVIII 70

PBAC

- Score 550

What are the treatment options for managing Lina's heavy menstrual bleeding?

Audience Response

What are the treatment options for managing Lina's heavy menstrual bleeding?

A. Intranasal DDAVP
B. Tranexamic acid
C. VWF concentrate
D. Levonorgestrel IUD
E. Combination of the above

ASH ISTH NHF WFH 2021 Guidelines

Management of Heavy Menstrual Bleeding in VWD

The panel *suggests* using either **hormonal therapy** (combined hormonal contraception or levonorgestrel IUD) or **tranexamic acid** over desmopressin to treat women with VWD and heavy menstrual bleeding who **do not wish to conceive**

The panel *suggests* using **tranexamic acid** over desmopressin to treat women with VWD and heavy menstrual bleeding **who wish to conceive**

Note: *Prophylaxis with replacement therapy may be necessary in cases of on-demand treatment failure*

IUD=intrauterine device
Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.

ASH ISTH NHF WFH 2021 Guidelines

Role of prophylaxis in VWD

In patients with VWD with a history of severe and frequent bleeds, the panel *suggests* using long-term prophylaxis rather than no prophylaxis
- Bleeding symptoms and the need for prophylaxis should be periodically assessed

- **Justification**
  - Although the published evidence is limited, the large costs to patients with severe and frequent bleeds were considered to be worth the net benefit of this recommendation. **Long-term prophylaxis is likely to be acceptable and feasible to implement, and this recommendation is likely to increase equity.** Thus, the desirable consequences are greater than the undesirable consequences

Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.

Case Study 2

Eva is a 35-year-old female with history of VWD Type 1. Played competitive sports in HS and college (basketball, volleyball and softball) with multiple injuries to her knees. Underwent 3 knee laparoscopic surgeries with VWF concentrate without complications. Has severe pain of R knee affecting quality of life. Ortho recommends TKA. Works as an EMT. Sister and Father with VWD.

Patient History:
- Heavy menstrual bleeding with periods longer than 7 days, iron deficiency anemia
- Life-long easy bruising
- Responds to VWF concentrate and TXA

Labs
- VWF:Ag 19%
- VWF:RCo 18%
- FVIII 68%
- Multimers normal

What are the treatment options for undergoing total knee arthroplasty?

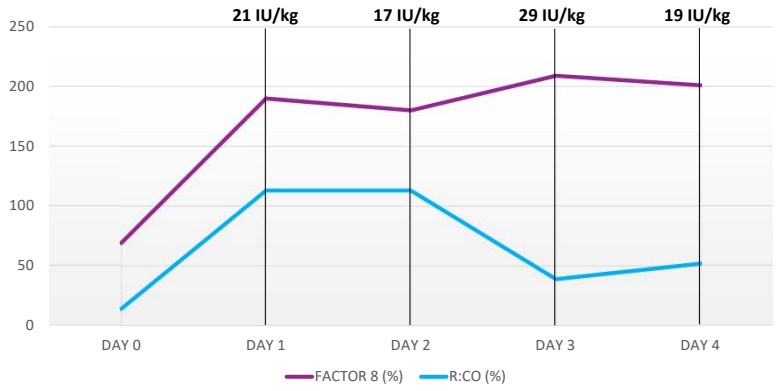
Audience Response

What are the treatment options for undergoing total knee arthroplasty?

A. Intranasal or IV DDAVP
B. Tranexamic acid
C. VWF concentrate
D. A and B
E. B and C

Patient Course of Treatment

- TKA was performed with von Willebrand factor (recombinant) coverage
- Initial dose of 55 IU/kg given one hour before procedure
- Discharged on Day 5 with 40 IU/kg 3 x week for 2 weeks



Approach to the Surgical Management of VWD Patients

- Characterization of VWD subtype and assessment of bleeding phenotype
- Preoperative assessments of plasma VWF levels/PK study
- Stratification of surgical risk (major and minor)
- Treatment options
  - Antifibrinolytic therapy
  - Desmopressin
  - pdVWF
  - Recombinant VWF
- Perioperative management
- Thromboprophylaxis

O'Donnell JS, et al. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):604-609.

Surgical Risk Stratification

Major	Minor	Single Treatment if Uncomplicated
Examples • Spinal/neurosurgical procedures • Laparotomy • Prostatectomy • Tonsillectomy • Hysterectomy • Orthopedic (eg, joint replacement or amputation • Caesarean section	**Examples** • Biopsy: breast, cervical • Complicated dental extractions • Gingival surgery • Laparoscopic procedures	**Examples** • Cataract surgery • Endoscopy (without biopsy) • Simple dental extractions

O'Donnell JS, et al. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):604-609.

Recommended Dosage Regimens of Concentrates of VWF/Factor VIII or VWF Only in Patients with VWD Undergoing Surgical Prophylaxis

Indication	Dose Regimen	Target plasma VWF:RCo/ FVIII:C level*
Major surgery	40-60 IU/kg once-daily until wound healing is complete	50-100 IU/dL maintain levels for 5-10 days
Minor surgery	30-50 IU/kg once-daily (may require for only 1-3 days)	>30 IU/dL
Dental extraction or other invasive procedure	20-30 IU/kg (usually a single dose prior to procedure)	>30 IU/dL for >12 h
*These dosages are indicated for patients with VWD with reduced factor VIII activity/VWF ristocetin cofactor levels <10 IU/dL)		

Franchini M, et al. *Ther Adv Hematol*. 2021;12: 20406207211064064.

Summary Points

- In patients with VWD with a history of severe and frequent bleeds, there is expert opinion to support using VWF prophylaxis
  - This includes reproductive tract bleeding
  - Bleeding response should be evaluated, and dosing adjusted
- Heavy menstrual bleeding often requires a multimodal approach and may include the use of VWF replacement
- The diagnostic approach and clinical management to VWD is different than hemophilia
  - Clinical research investigation needs to be tailored to the unique characteristics and bleeding patterns of VWD

Audience Discussion and Questions

Robert Sidonio, Jr., MD

Miguel A. Escobar, MD

Angela C. Weyand, MD

Don't Forget to Complete Your Evaluation!

- Symposium participants can complete their post-test and evaluation by accessing the electronic version available at ***surveymonkey.com/r/VWDeval***. This link is also located on the back of your workbook. Paper copies will also be available from team members in the room.
- Simulcast viewers can access the post-test and evaluation by clicking the link in your resources tab.
- Partial credit will not be awarded for this activity. Participants must receive a minimum score of 70% on the post-test to qualify for CE credit.
- Certificates will be emailed within 4 weeks to those who have successfully met the criteria for completion.

Additional Slide References, Footnotes and Abbreviations

Slide 31 - Phase 3 Open-label Study Results

*Pts treated on-demand with any VWF during12-mo period before enrolling in study. †Pts treated prophylactically with pdVWF for ≥12 mo before enrolling in study. **Estimated using generalized linear mixed-effects model for full analysis set thru month 12. Only BEs treated with VWF infusions included: 6 BEs unknown cause (4 historical [all in prior on-demand group], 2 on-study [switch group]) were counted as spontaneous BEs for this analysis. †† % change in sABR was calculated directly from sABR ratio (RR): 100 × (RR - 1).

Slide 32 - AEs in Patients Who Received rVWF Prophylaxis (Safety Analysis Set)*

Table displays the number and percentage of patients who had ≥1 AE and the number of AEs for a given parameter.

*AEs starting or worsening after the first dose of rVWF. †Patients were counted once for the highest severity. ‡Joint (shoulder) injury, supraventricular tachycardia, and ventricular extrasystoles (all in the same patient); joint (knee) injury; headache; arthralgia; gastroenteritis; all events resolved; includes events in 2 patients who also had severe events and so are listed in the severe category. §Fall and multiple injuries from fall (2 events in the same patient and requiring hospitalization); toothache; rheumatoid arthritis. All events resolved except rheumatoid arthritis. ‖AEs of special interest defined as thromboembolic events, hypersensitivity reactions (including allergic or anaphylactic reactions), the development of neutralizing or binding antibodies to VWF and FVIII, and binding antibodies to trace proteins in rVWF (Chinese hamster ovary immunoglobulin G [IgG], murine IgG, and human Furin IgG). ¶Purpura, which developed due to trauma, was classified as a thromboembolic event (per broad SMQ search); considered nonserious and nonsevere by investigator, and resolved with no action taken. **Rash pruritic was classified as a hypersensitivity reaction (per broad SMQ search); considered nonserious and nonsevere by investigator, and resolved with no action taken.

Slide 34 - Dose, frequency, duration of follow-up, and bleeding episodes in all patients receiving LTP with Voncento®

Note: Results are expressed as median (range).

ABR=annualized bleeding rate; LTP=long-term prophylaxis.

*One patient remained only for 5 months under LTP. +Effectiveness was not available for 4 patients. **Two patients (one Type 2B and one Type 3) received pdVWF + FVIII concentrates before inclusion in the study.

Additional Slide References, Footnotes and Abbreviations

Slide 41 - Factor Concentrate Target Levels

*VWF–factor VIII or VWF concentrate is administered in patients with Type 3 disease and in patients with Type 1 or 2 disease who do not have a response to desmopressin or in whom it is contraindicated. †Dose of factor concentrate depends on the type of concentrate used. If VWF–FVIII concentrate is used, the dose also depends on the brand of concentrate. The dose is based on an anticipated in vivo recovery (2 IU per deciliter for every unit of factor VIII activity infused per kilogram of body weight and 1.5 IU per deciliter for every unit of VWF ristocetin cofactor activity infused per kilogram) and the target levels of both VWF–ristocetin cofactor activity and factor VIII activity. If high-purity or recombinant VWF concentrate is administered, a single dose of factor VIII concentrate should also be administered in order to achieve the target level of factor VIII immediately. ‡FVIII activity, and preferably also VWF–ristocetin cofactor activity, should be monitored regularly in all patients undergoing surgical procedures and all patients with severe bleeding episodes. If measurement of VWF–ristocetin cofactor activity is not immediately available at a local laboratory, dosing should be based on factor VIII activity levels.

Slide 47 - Summary of Reports on the Use of Long-term Prophylaxis in VWD

BS=bleeding score; GI=gastrointestinal; CNS=central nervous system; ENT=ear, nose, throat; VWD=Von Willebrand disease; NA=not available.

a Type of VWD given for the overall population. b Number of bleeding events. c Means, expressed according to the frequency and type of bleeding. d Others: included epistaxis, Heavy Menstrual Bleeding (HMB), hematoma.

Dunkley S, et al. *Haemophilia.* 2010; 16(4): 615- 624.; Castaman G, et al. *Haemophilia.* 2013; 19(1): 82- 88.; Abshire T, Cox-Gill J, Kempton CL, et al. *J Thromb Haemost.* 2015;13(9):1585-1589.; Goudemand J, et al. *J Thromb Haemost.* 2020;18(8):1922-1933.; Sholzberg M, et al. *TH Open.* 2021;5(3):e264-e272. ; Berntorp E, et al. *Blood Coagul Fibrinolysis.* 2005; 16(Suppl 1): S23-S26.; Federici AB, et al. *Haemophilia*. 2010;16(1):101-110.; Halimeh S, et al. *Thromb Haemost*. 2011;105(4): 597-604.; Howman R, et al. *Haemophilia.* 2011;17(3): 463-469.; Abshire TC, et al. *Haemophilia.* 2013;19(1): 76-81.; Miesbach W, et al. *Thromb Res*. 2015;135(3): 479-484.