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Diagnosis and Individualized Management of von Willebrand Disease: Expert Perspectives on Synthesizing and Contextualizing the Evidence.

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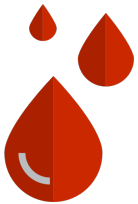
Learning Objective 1

Accurately diagnose VWD based on clinical assessments and laboratory tests

Von Willebrand Disease Background

Aland Islands, 1926:
Erik von Willebrand reported prolonged mucocutaneous bleeding and death among several members of a family, despite normal platelet counts. The index case was a 5-year-old girl named Hjørdis who later died after her 4th menstrual period.



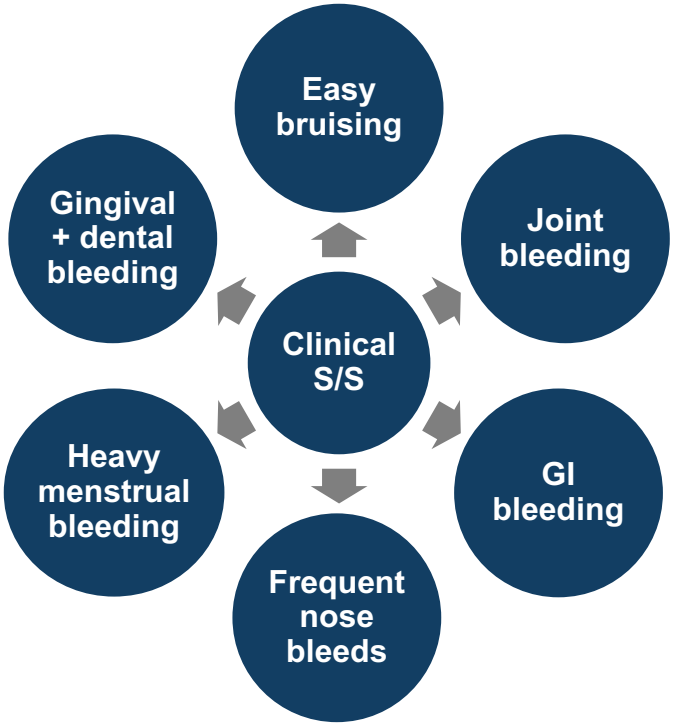
Characterized by abnormal quantity or quality of von Willebrand factor (VWF)

Most common inherited bleeding disorder

Occurs equally among genders and ethnic groups

May only become apparent upon hemostatic challenge

Severity from modest to major depending upon type



GI = Gastrointestinal. S/S = Signs and symptoms.

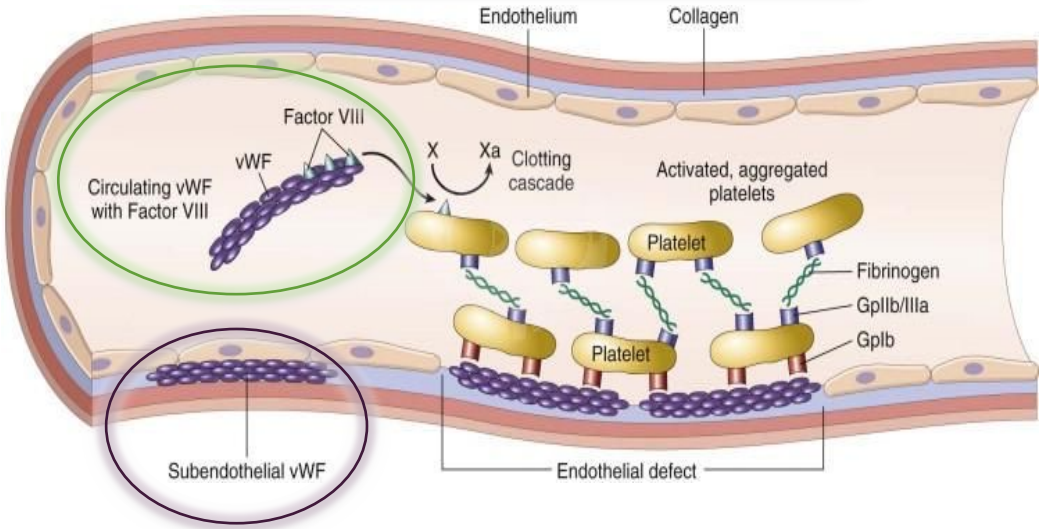
James PD, Goodeve AC. *Genet Med*. 2011;13(5):365-376. Von Willebrand Disease (VWD). Centers for Disease Control and Prevention Website. 2021. https://www.cdc.gov/ncbddd/vwd/. Accessed January 20, 2022. Map: Chino. Wikimedia Commons. https://commons.wikimedia.org/w/index.php?title=File:ArchipelagoSeaInBalticSea.png&oldid=483485784. Accessed January 20, 2022. Image: Flaticon.com.

Von Willebrand Factor (VWF)

VWF is

- a multimeric protein of dimeric building blocks
- stored in endothelial cells and megakaryocytes
- secreted into plasma for critical blood clotting roles

VWF plays 2 critical roles:



1) Tethers the platelet to exposed collagen

2) Serves as a carrier protein for Factor VIII

GpIIb/IIIa = Glycoprotein Iib-IIIa.

James PD, Goodeve AC. *Genet Med*. 2011;13(5):365-376. Ng C, et al. *Blood*. 2015;26:2029-2037.

VWD Classification

Type	VWF Defect	Severity	Frequency
Type 1* (majority dominant)	Partial quantitative deficiency	Mild-moderate	Most common
Type 2** (majority dominant)	Functional deficiency	Mild-moderate	Less common
Type 3 (recessive)	Virtually complete quantitative deficiency	Severe (clinically like hemophilia A)	Rare

*Includes 1 subtype

- Type 1C: VWF deficiency due to increased clearance; increased WWF/pp compared with VWF/Ag

*Includes 4 subtypes

- Type 2A: Decreased platelet-dependent VWF activity with loss of high-molecular-weight multimers
- Type 2B: Increased binding to GP1bα, often leading to thrombocytopenia
- Type 2M: Decreased platelet-dependent VWF activity with preserved multimer pattern
- Type 2N: Decreased binding of FVIII, often manifesting as excessive bleeding with surgery and mimics mild hemophilia A

Ag = Antigen. GP1bα = Glycoprotein 1b alpha. Pp = Propeptide.

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

International Effort to Develop the 2021 VWD Guidelines

blood advances

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]

blood advances

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

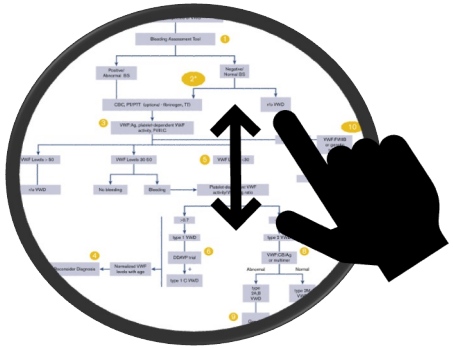
Nathan T. Connell,[1]* Veronica H. Flood,[2]* Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

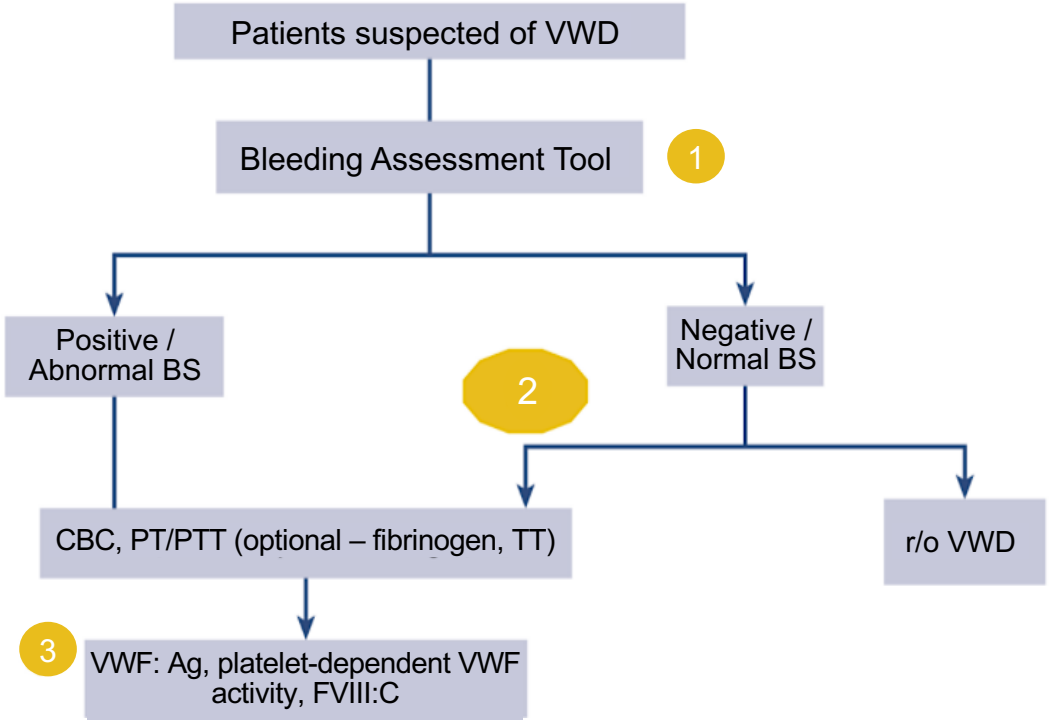
ASH = American Society of Hematology. ISTH = International Society on Thrombosis and Haemostasis. NHF = National Hemophilia Foundation. WFH = World Federation of Hemophilia.

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

ASH ISTH NHF WFH 2021 Diagnostic Guidelines

BATs and VWD Screening Tests





BATs = Bleeding assessment tools. BS = Bleeding score. CBC = Complete blood count. FVIII:C = Factor VIII coagulant activity. PT/PTT = Prothombin time/partial thromboplastin time. r/o = Rule out. TT = Thrombin time.

James PD, et al. *Blood Adv* 2021;5(1):280-300.

Use of Bleeding Assessment Tools

Probability of VWD	ASH ISTH NHF WFH 2021 Guidelines Recommendation on BATs
Low Ex: Patient seen in primary care settings	Panel *recommends* using a validated BAT as initial screening test to determine who needs specific blood testing[1] over nonstandardized clinical assessment; recommendation strongest for adult women.
Intermediate Ex: Patient referred to a hematologist	Panel *suggests against* relying on a BAT to decide whether to order specific blood testing.[2]
High Ex: Patient with affected first-degree relative	The panel *recommends against* relying on a BAT to decide whether to order specific blood testing.[2]

1. Specific blood testing for VWD refers to VWF antigen (VWF:Ag), platelet-dependent VWF activity (e.g., VWF glycoprotein IbM [VWF:GPIbM]), and factor VIII (FVIII) coagulant activity (FVIII:C)
2. Beyond their utility as a screening test, BATs can be used in the referral setting to assess and document the severity of bleeding and can be used in conjunction with specific blood testing as part of the initial diagnostic approach.

Vicenza Bleeding Questionnaire

MCMDM-1 VWD Bleeding Questionnaire

Condensed MCMDM-1 VWD

Pediatric Bleeding Questionnaire

ISTH-BAT

Self-BAT

MCMDM-1 = Molecular and clinical markers for the diagnosis and management of type 1.

1. James PD, et al. *Blood Adv* 2021;5(1):280-300. 2. Rydz N, James PD. *J Thromb Haemost*. 2012;10(11):2223-2229.

Bleeding Assessment in Low VWF

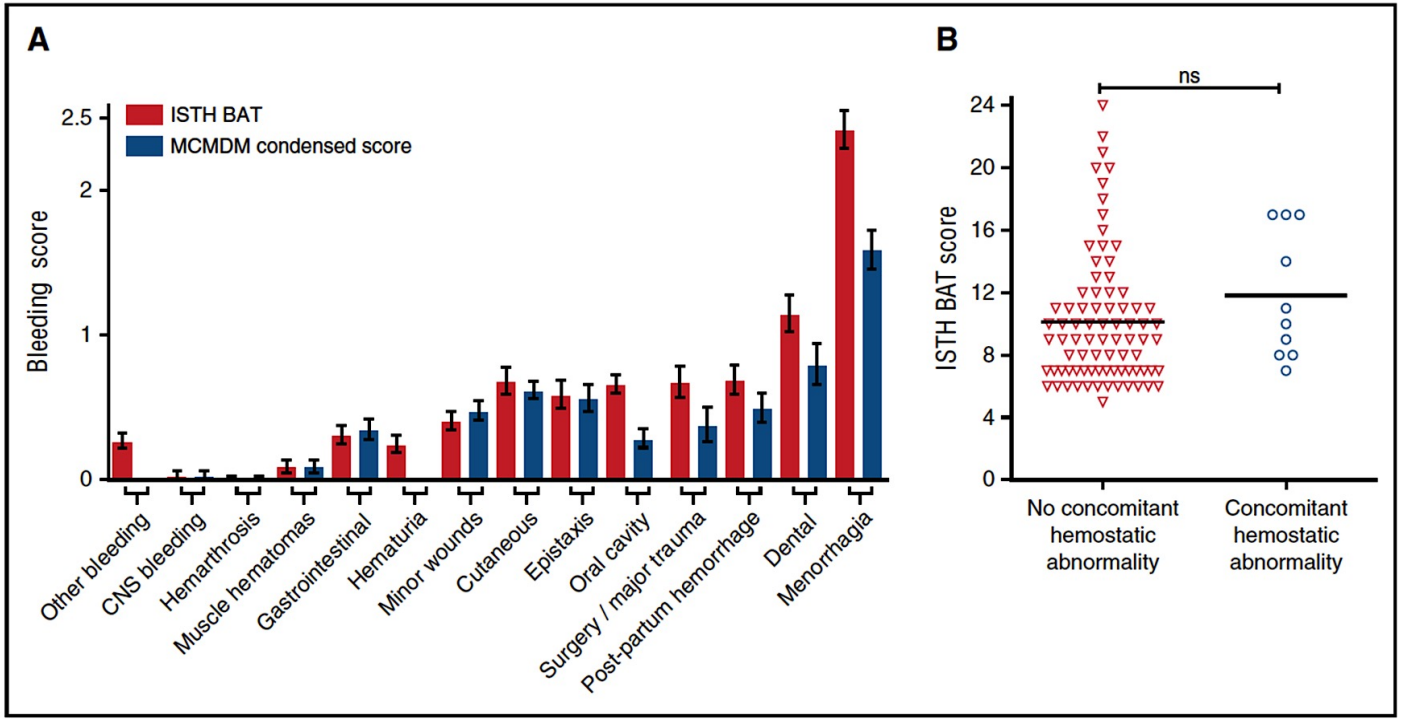


Figure: Bleeding in low VWF is not explained by concomitant bleeding disorders.

(A) comparison of ISTH BAT scores (red bars) and condensed MCMDM-1 VWD scores (blue bars) for all patients (N = 126) according to individual bleeding subdomains. Data are represented as mean ± standard error of the mean of bleeding scores.

(B) ISTH BAT scores were not significantly different for LoVIC patients with concomitant coagulation disorders (circles, n = 10) compared with those without (triangles, n = 81) (median scores 10.5 vs. 9.0; p = .15).

CNS = Central nervous system. LoVIC = Low VWF Ireland Cohort.
Lavin M, et al. *Blood* 2017;130(21):2344-2353.

Case Study

Daryl, a 9-year-old male with a personal history of bleeding and no family history of bleeding disorders, presents to his primary care physician.

__X___ Epistaxis requiring cautery with associated hx of anemia

__X___ No early life bleeding

__X___ Easy bruising

__X___ No prolonged skin bleeding

__X___ No surgeries

__X___ Oozing with dental extraction requiring tea bags and repacking

How should Daryl's PCP evaluate his bleeding?

Hx = History. PCP = Primary care physician.

Audience Response

How should Daryl's PCP evaluate his bleeding?

A. Use a Bleeding Assessment Tool
B. Refer Daryl to a hematologist
C. Order VWF genetic testing
D. Daryl's bleeding is not severe enough to warrant further evaluation.

Case Study

Daryl, a 9-year-old male with a personal history of bleeding and no family history of bleeding disorders, presents to his primary care physician.

__X___ Epistaxis requiring cautery with associated hx of anemia

__X___ No early life bleeding

__X___ Easy bruising

__X___ No prolonged skin bleeding

__X___ No surgeries

__X___ Oozing with dental extraction requiring tea bags and repacking

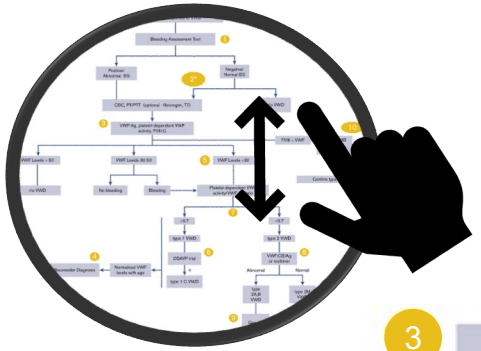
How should Daryl's PCP evaluate his bleeding?

Use a BAT

Hx = History. PCP = Primary care physician.

ASH ISTH NHF WFH 2021 Guidelines

VWD Specific Blood Tests



10

FVIII < VWF

VWF:FVIIIB or genetic testing

3

VWF: Ag, platelet-dependent VWF activity, FVIII:C

Confirm type 2N VWD

VWF Levels > 50

VWF Levels 30-50

5

VWF Levels < 30

r/o VWD

No bleeding

Bleeding

Platelet-dependent VWF activity / VWF:Ag ratio

James PD, et al. *Blood Adv* 2021;5(1):280-300.

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VWD Specific Blood Tests

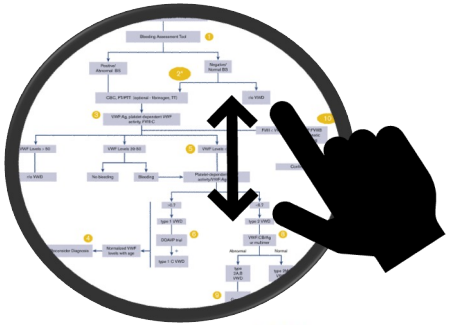
VWF:Ag	Assessment of **plasma VWF protein level** Screens for VWD Type 1 and Type 3 Only measures VWF presence not function
VWF:Rco	Assessment of **VWF to platelet GPIbα binding** ability, in vitro Screens for VWD Type 2A, Type 2M, and Type 2B Limited by VWF sequence variations, detection of low levels, and high variation
VWF:GPIbM	Ristocetin independent measure of **platelet binding** *limited availability* Improved precision and limit of detection over VWF:RCo
FVIII:C	Assessment of FVIII activity → Indicates **VWF to FVIII binding** ability Screens for Type 2N and Type 3
VWF activity / VWF:Ag	Assessment of **VWF platelet binding to VWF protein level ratio** Screens for Type 2A, Type 2B, and Type 2M

RCo = Ristocetin cofactor activity.

Roberts JC, Flood VH. *Int J Lab Hematol*. 2015;37:Suppl 1:11-17.

ASH ISTH NHF WFH 2021 Guidelines

VWD Confirmatory Tests



DDAVP = Desmopressin. VWF:CB = VWF-collagen binding activity.

James PD, et al. *Blood Adv* 2021;5(1):280-300.

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VWD Confirmatory Tests

VWF:CB

- Screen for variant VWD and specific collagen binding defects

VWD Multimer Distribution

- Performed when VWF activity / VWF:Ag decreased
- Abnormal distribution suggests Type 2A or 2B, normal suggests Type 2M

VWF:PB

- Spontaneous binding of commercial platelets and patient plasma
- Increase suggests Type 2B

LD-RIPA

- Spontaneous aggregation to low-dose ristocetin
- Decrease suggests Type 2B or platelet-type VWD

VWF:FVIIIB

- Patient plasma binding to rFVIII
- Confirmatory for Type 2N

VWFpp

- Increased VWFpp/VWF:Ag suggestive of Type 1C

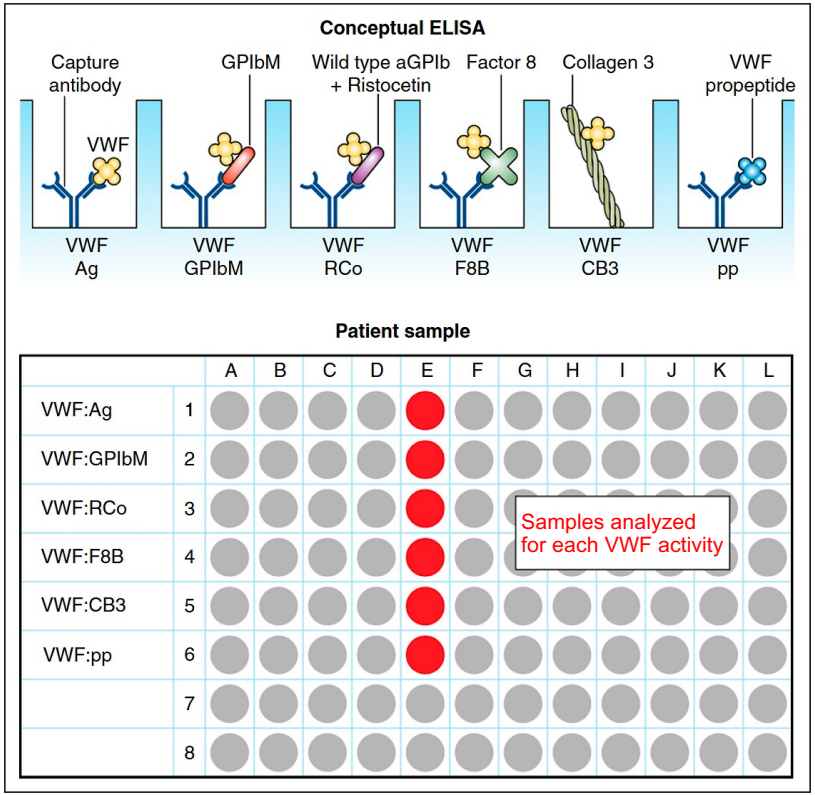
VWF gene sequencing

- Limited utility as a diagnostic test
- Most helpful in Type 2 variants

LD-RIPA = Low-dose ristocetin-induced platelet aggregation. rFVIII = Recombinant FVIII. VWF:PB = VWF-platelet binding.

Roberts JC, Flood VH. *Int J Lab Hematol*. 2015;37:Suppl 1:11-17.

VWF Multiplex Activity Assay



- ELISA platform
- Linear Discriminant Analysis: statistical algorithm used to make variant VWD phenotype assignments
- Correctly assigned variant VWD phenotype in 124 of 134 (92.5%) subjects
- Jackknife resampling technique: cross-validation method predicts assay application to a general population
- Jackknife LDA: correctly assigned variant VWD phenotype in 118 of 134 (88.1%) subjects

ELISA = Enzyme-linked immunosorbent assay. LDA = Linear discriminant analysis.

Roberts JC, et al. *Blood*. 2016;127(20):2472-2480.

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Learning Objective 2

Individualize the management of VWD.

Treatment Strategies in VWD

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

- **Replacement therapy:** Increase plasma concentration of VWF by replacing with human plasma-derived, virus-inactivated concentrates or recombinant VWF (rVWF)
- **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

On-Demand | Perioperative | Prophylaxis

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

VWD Treatment Options

Type	Treatment	Alternative or Add-on Antifibrinolytic Therapy
Low VWF†	Desmopressin • IV: 0.3 µg/kg • Intranasal: total dose = 300 µg (> 50 kg) • SubQ: 0.3 µg/kg	Tranexamic acid 1 g, 3 or 4 times daily (10 mg/kg/dose TID in children)
1	Desmopressin (same dose)	Tranexamic acid 1 g, 3 or 4 times daily
2	Desmopressin (same dose) VWF–factor VIII or VWF concentrate‡	Tranexamic acid 1 g, 3 or 4 times daily
3	VWF–factor VIII or VWF concentrate	Tranexamic acid 1 g, 3 or 4 times daily

† Patients presenting with bleeding symptoms and VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having low VWF but not von Willebrand disease.

‡ Desmopressin is contraindicated in patients with type 2B disease.

G = grams. IU = International units. IV = Intervenous. Kg = Kilogram. µg/kg = Microgram per kilogram. SubQ = Subcutaneous. TID = three times a day.

Leebeek FW, Eikenboom JC. *N Engl J Med*. 2016;375:2067-2080.

Desmopressin (DDAVP) for VWD

DDAVP MOA: Triggers release of VWF + Factor VIII from endothelial storage

- Safety: Fluid and electrolyte balance must be monitored if dosed > 3x in 72 hours

DDAVP trials in Type 1 VWD

- "Low VWF" 30-50 IU/dL: Adults presumed 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** Will not respond

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, Atiq F. *Brit J Haematol.* 2019;187:418-430.

Replacement Therapy in VWD

Factor Concentrate Trade Name	VWF:Rco to FVIII:C Ratio	Half-Life (h)	Regulatory Approval
Alphanate® (human plasma-derived)	1.3:1	VWF:RCo 7.67 ± 3.32 FVIII:C 17.9 ± 9.6	Yes: perioperative except Type 3 No: on-demand and prophylaxis
Humate-P® (human plasma-derived)	1.8-2.4:1	VWF:RCo 10.5 (2.8-33.6) FVIII:C 12.2 (8.4-17.4)	Yes: on-demand and perioperative No: prophylaxis
Wilate® (human plasma-derived)	1:1	VWF:RCo 15.8 ± 11 FVIII:C 19.6 ± 6.9	Yes: on-demand and perioperative No: prophylaxis
Vonvendi® (recombinant)	N/A	VWF:RCo 19.1 ± 5 (No FVIII content)	Yes: on-demand, perioperative, and Type 3 prophylaxis* ***Approved for routine prophylaxis in Type 3 VWD on 1/28/2022, after this recording.**

VWF-containing concentrate is the treatment of choice for Type 3 and most Type 2 VWD.

- Most patients with VWD are believed to have an intact ability to produce FVIII that stabilizes when VWF levels are corrected by infusion.
- Replacement therapy with a high VWF:FVIII ratio will increase VWF proportionally more than FVIII.

Neff AT, Sidonio RF Jr. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):536-541. Mannucci PM. *N Engl J Med*. 2004;351:683-694. ALPHANATE® (antihemophillic factor/VSF complex [human]). Los Angeles, CA: Grifols Biologicals LLC. Revised June 2018. Alphanate Prescribing Information Patient.pdf. Accessed January 20, 2022. HUMATE-P® (antihemophilic factor/von Willebrand factor complex [human]). Marburg, Germany: CSL Behring GmbH. Revised October 2007. Package-Insert---Humate-P-1.pdf. Accessed January 20, 2022. VONVENDI® (von Willebrand factor [recombinant]). Lexington, MA: Baxalta US Inc. Revised 2022. Package-Insert---VONVENDI.pdf. Accessed February 3, 2022. WILATE® (von Willebrand factor/coagulation factor VIII complex [human]). Vienna, Austria: Octapharma Pharmazeutika Produktionsges.m.b.H. Revised September 2019. Package Insert - Wilate.pdf. Accessed January 20, 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			

*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:RCo infused per kilogram) and the target levels of both VWF:RCo and factor VIII activity. If high-purity or rVWF 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:RCo, should be monitored regularly in all patients undergoing surgical procedures and all patients with severe bleeding episodes. If measurement of VWF:RCo activity is not immediately available at a local laboratory, dosing should be based on factor VIII activity levels.

Leebeek FW, Eikenboom JC. *N Engl J Med*. 2016;375:2067-2080. Leebeek FWG, Atiq F. *Brit J Haemat* 2019;187:418-430.

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.

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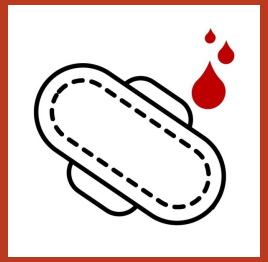
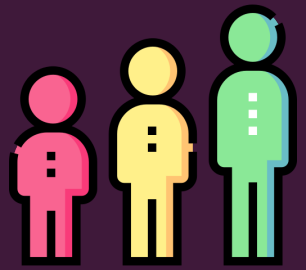
Management of VWD in Specific Populations



Heavy Menstrual Bleeding (HMB)

Pregnancy

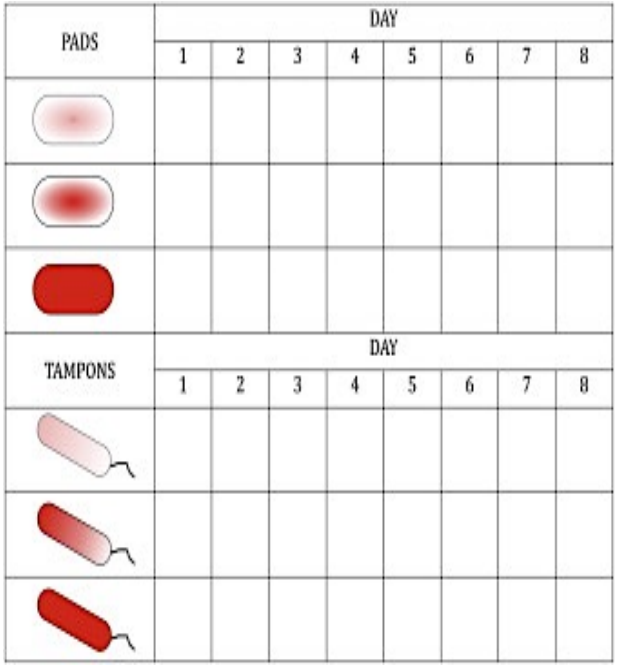


Aging

Images from: Flat icon

Heavy Menstrual Bleeding Defined

- Heavy menstrual bleeding
- Proposed definition:
  - Menstrual bleeding meeting any of the following criteria:
    - Lasting ≥ 8 days
    - Consistently soaks through 1 or more sanitary protections every 2 hours on multiple days
    - Requires use of > 1 sanitary protection item at a time
    - Requires changing sanitary protection during the night
    - Associated with repeat passing of blood clots
    - Pictorial Blood Assessment Chart (PBAC) score > 100



Menorrhagia Specific Screening Tool (Adapted for Ambulatory Use)

Available at: https://betteryouknow.org/i-want-to-know-for-women

Connell NT et al. *Blood Adv*. 2021;5(1):301-325. Hald K, Lieng M. *J Minim Invasive Gynecol*. 2014;21(4):662-668.

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.

Case Study

Shaina is a 25-year-old female who is planning to conceive. She has been followed in the hematology center since age 10 for heavy menstrual bleeding secondary to Type 1 VWD.

Patient History:

- Heavy menstrual bleeding associated with flooding, periods longer than 7 days, anemia
- No early life bleeding
- Easy bruising
- No prolonged skin bleeding
- No dental procedures
- Oozing and admission for post tonsillectomy bleed at 7 days

Labs

- VWF:Ag 45
- VWF:RCo 40
- FVIII 80

PBAC

- Score 575

What is the treatment of choice for managing Shaina's heavy menstrual bleeding?

Audience Response

What is the treatment of choice for managing Shaina's heavy menstrual bleeding?

A. Intranasal DDAVP
B. Tranexamic acid
C. VWF concentrate
D. Pharmacological treatment is not recommended.

Case Study

Shaina is a 25-year-old female who is planning to conceive. She has been followed in the hematology center since age 10 for heavy menstrual bleeding secondary to Type 1 VWD.

Patient History:

- Heavy menstrual bleeding associated with flooding, periods longer than 7 days, anemia
- No early life bleeding
- Easy bruising
- No prolonged skin bleeding
- No dental procedures
- Oozing and admission for post tonsillectomy bleed at 7 days

Labs

- VWF:Ag 45
- VWF:RCo 40
- FVIII 80

PBAC

- Score of 575

What is the treatment of choice for managing Shaina's heavy menstrual bleeding? Tranexamic Acid

ASH ISTH NHF WFH 2021 Guidelines

Management of VWD During Pregnancy and Delivery

During childbirth, women should achieve VWF:RCo and FVIII levels of *at least* 50 IU/dL before delivery, and those levels should be maintained for 3 to 7 days, with subsequent surveillance for delayed postpartum bleeding

In women with VWD for whom **neuraxial anesthesia during labor** is deemed suitable, the panel *suggests* targeting a VWF activity level of 50 to 150 IU/dL over targeting an activity level of > 150 IU/dL to allow neuraxial anesthesia.

To prevent postpartum bleeding, the panel *suggests* the use of **tranexamic acid** over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the postpartum period.

Leebeek FWG, Atiq F. *Brit J Haematol.* 2019;187:418-430. Connell NT, et al. *Blood Adv.* 2021;5(1):301-325.

ASH ISTH NHF WFH 2021 Guidelines

Management of VWD During Aging

Can you age out of VWD? The panel *suggests* **reconsidering** the diagnosis as opposed to removing the diagnosis for patients with previously confirmed type 1 VWD who now have VWF levels that have normalized with age.

- Bleeding risk should be reassessed throughout treatment.

How do you manage need for antithrombotic therapy in patients with VWD?

In patients with VWD and CVD who require treatment with antiplatelet or anticoagulant therapy, the panel *suggests* giving the necessary antiplatelet or anticoagulant therapy over no treatment.

- Severe bleeding phenotypes may require prophylaxis
- Desmopressin is generally contraindicated in CVD and/or increased risk of thrombosis

CVD = Cardiovascular disease.

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

CME OUTFITTERS

Learning Objective 3

Evaluate the evidence for long-term prophylaxis in patients with VWD.

Rational for Prophylaxis in VWD

Benefits of prophylaxis

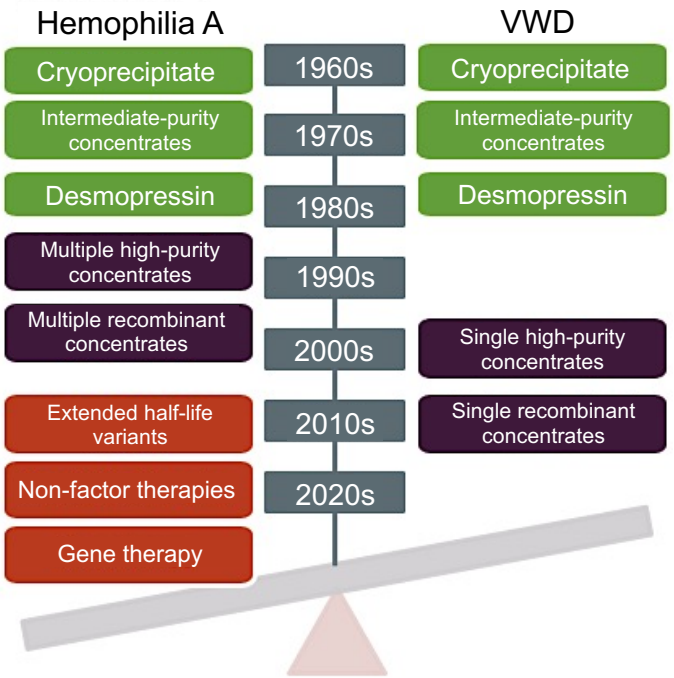
- Fewer bleeding episodes
- Reduced risk of arthropathy
- Better quality of life
- Fewer visits to hospitals
- Long-term cost effectiveness
- Higher levels of activity
- Greater tolerance to physical activity
- Less school/work missed

Barriers of prophylaxis

- Lack of perceived benefit/need
- Adherence and burden of long-term treatment
- Forgetfulness
- Denial/avoidance of treatment
- Cost/insurances
- Transitioning to adulthood
- Poor venous access
- Lack of knowledge

Unmet need of prophylaxis

- Greater awareness of long-term benefits
- Earlier diagnosis and treatment intervention
- Prophylaxis may not prevent all bleeds
- Long-term treatment commitment is a burden
- Frequent infusions can reduce quality of life
- Personalized prophylaxis is needed



Miesbach W, Berntorp E. *Thromb Res.* 2021;199:67-74.

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.

Phase 3 Trial Results: Prophylaxis with rVWF in Patients with Severe VWD

12-month, prospective, open-label, single-arm, non-randomized, multicenter 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

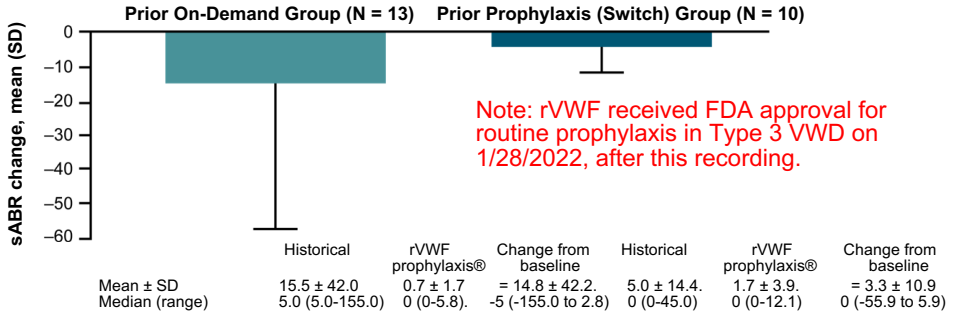
Time period Statistic	Prior OD arm (n = 13)	Switch arm (n = 10)
Historical		
Number of treated spontaneous BEs	201	50
sABR (95% CI)	6.54 (2.52, 17.00)	0.51 (0.04, 6.31)
On-study while receiving prophylactic rVWF		
Number of treated spontaneous BEs	9	18
sABR (95% CI)	0.56 (0.15, 2.05)	0.28 (0.02, 3.85)
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

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

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%



Note: rVWF received FDA approval for routine prophylaxis in Type 3 VWD on 1/28/2022, after this recording.

AE = Adverse event. BE = Bleeding event. CI = Confidence interval. OD = On-demand. pdVWF = Plasma-derived VWF. sABR = Spontaneous annualized bleeding rate. SD = Standard deviation

Leebeek F, et al. ISTH Virtual Conference; 2021. Abstract No. LPB0128. https://abstracts.isth.org/abstract/phase-3-trial-results-prophylaxis-with-recombinant-von-willebrand-factor-in-patients-with-

A Phase III Study Comparing Secondary Long-Term Prophylaxis vs. On-Demand Treatment 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.

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 gastrointestinal bleeding.

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

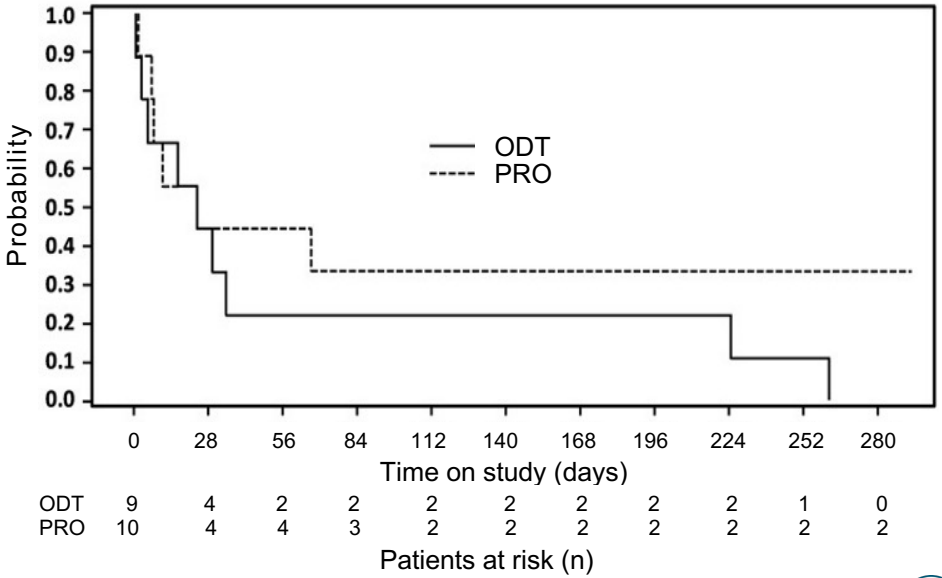
Type of bleeding episode	On-demand (N = 9)		Prophylaxis (N = 10)	
	N	*Rate*	*N*	*Rate*
Any type	172	1.41	32	0.34
Mucosal bleeding	164	1.34	17	0.18
Epistaxis	52	0.42	15	0.16
Other bleedings	112	0.92	2	0.02
Joint and muscle bleeding	7	0.05	2	0.02
Haemarthrosis	3	0.02	1	0.01
Muscle haematoma	4	0.03	1	0.01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

All in one single patient (106/112 bleeding gums). 9 in one single patient.

Safety: No clinical AEs attributed to study medication

ODT = On-demand treatment. PRO = Long-term prophylaxis.

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



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

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

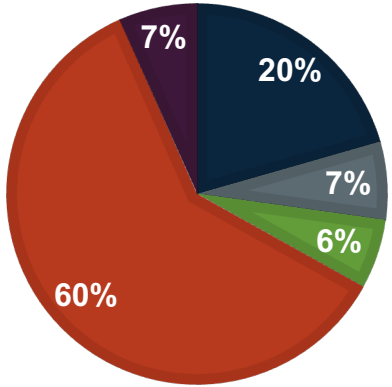
Robert Sidonio + Angela Weyand co-PIs

~58 U/kg/dose 2x per week for rVWF

~51 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

CURRENT TREATMENT TYPE



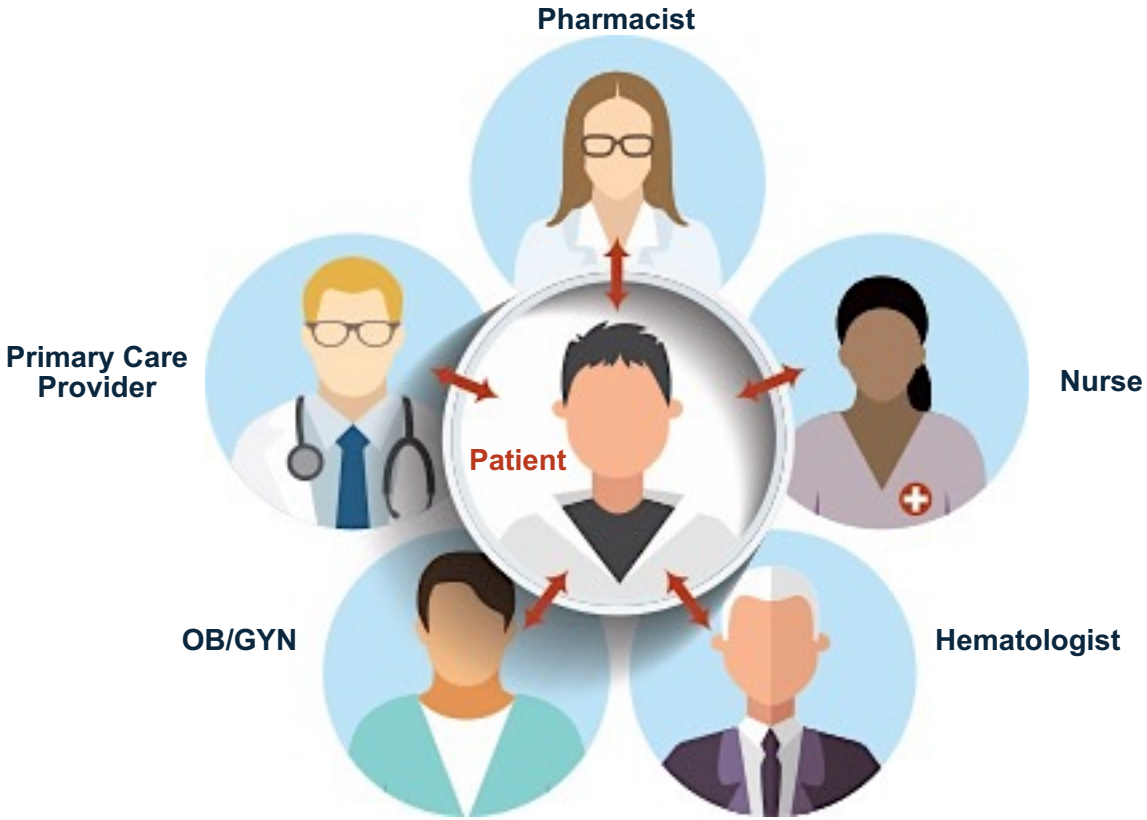
- Prophylaxis: continuous (28)
- Prophylaxis: event-based, short-term or intermittent (9)
- Prophylaxis: menstrual bleeding (8)
- Episodic (82)
- Other non-hemostasis medication (9)

PI = Principal Investigator.

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 January 20, 2022.

CME

Team-Based Approach for Management of VWD



SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Use validated clinical assessments and laboratory tests to accurately recognize, screen, refer, and diagnose patients with suspected bleeding disorders.
- Optimize patient outcomes by proactively incorporating an individualized, team-based approach to management of VWD.
- Use guideline recommended strategies to accurately identify candidates for long-term prophylaxis in patients with all VWD types.

CME Outfitters

AFTER THE SHOW

Questions & Answers

CME OUTFITTERS

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