What the Good Fellow Should Know about von Willebrand Disease in the Age of Guidelines

Peter A. Kouides MD

Clinical Professor of Medicine, University of Rochester School of Medicine

Medical and Research Director, Mary M. Gooley Hemophilia Center, Inc., Rochester NY

peter.kouides@rochesterregional.org

Cell/text: 585-766-3980

Disclosures

- Past COI (pre-2018)-
  - investigator-initiated support from CSL Behring for heavy menses study in VWD, VWD-related PPH study, prophylaxis study in VWD; advisory board (CSL manufactures HUMATE P)
  - research support from Octapharma for surgical prophylaxis study in VWD; advisory board (Octapharma manufactures WILLATE);
  - research support from Takeda for FDA licensure study of VONVENDI; advisory board (Takeda manufactures VONVENDI);
  - DMSB for FDA licensure trial for LYSTEDA manufactured by Xanodyne Pharmaceuticals
- Present COI-No relevant COI
- Universal disclosures presently:

  consultant to Uniqure FIX gene therapy trial

  consultant to Tremeau Inc on a hemophiliac arthropathy trial
- Intellectual disclosure: member of 2018-2021 American Society of Hematology/International Society of Hemostasis and Thrombosis/National Hemophilia Foundation/World Federation of Haemophilia von Willebrand disease management guideline committee

2021 Von Willebrand disease guidelines

11 diagnosis recommendations covering-

- The role of bleeding assessment tools (BAT) in the assessment of patients suspected of VWD
- Diagnostic laboratory cut-offs for type 1 and type 2 VWD
- The role of genetic testing vs. phenotypic assays for types 2B and 2N
- The reconsideration, rather than simple removal, of a type 1 VWD diagnosis, should VWF levels normalize over time

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

Blood Advances 5(1) 280; open access 1/12/21

8 management recommendations covering-

- Prophylaxis for severe and frequent bleeds
- Desmopressin (DDAVP) trials to determine therapy
- Use of antithrombotic therapy (antiplatelet agents and anticoaguant therapy)
- Target VWF and factor VIII activity levels for major surgery
- Strategies to reduce bleeding during minor surgery or invasive procedures
- Management options for heavy menstrual bleeding
- Management of VWD in the context of neuraxial anaesthesia during labour and delivery
- Management in the postpartum setting with tranexamic acid

First some physiology to lead us to the pathology: VWF has 3 binding partners involved in the primary and secondary stage of hemostasis. Which of the following is not a binding partner?

A.Platelets

B.FVIII

C.Collagen

D.Fibronectin

.

The two steps involved in forming a clot

...And how a deficiency in a clotting protein can lead to bleeding

- Step 1: Formation of Platelet "Plug"
  - exposed collagen + VWF + platelets

N.B. VWF in simple terms is a binding protein and has three binding partners- collagen, platelet GpIb and FVIII

Deficiency of VWF leads to poor platelet plug formation= von Willebrand Disease

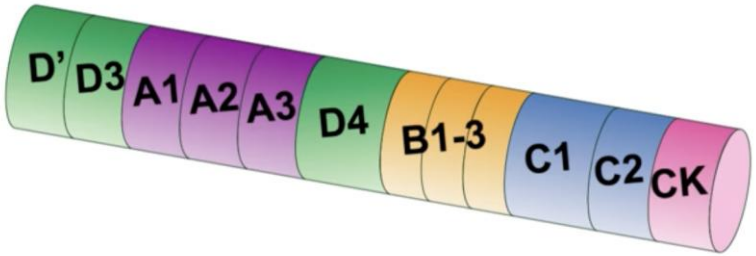
- Step 2: Formation of fibrin clot over platelets
  - platelets + cofactors V & VIII (IX) + the remaining coagulation factors

While major role of VWF is bridging subendothelial collagen to platelets; its secondary role is to protect FVIII from proteolytic cleavage- without VWF FVIII t½ is only 2 hrs. compared to 8-12 hrs normally!

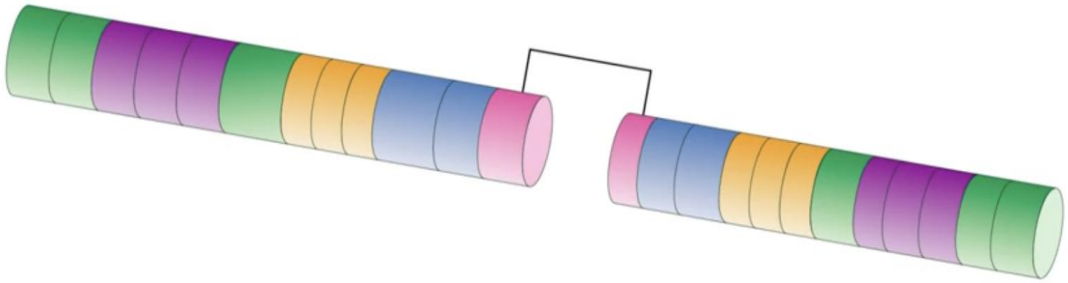
Deficiency of Factor VIII or IX leads to poor fibrin formation= Hemophilia (A,B)

From monomer to multimers, i.e. from non-sticky to sticky for platelets!

Within the Endothelial Cell
and megakaryocyte-

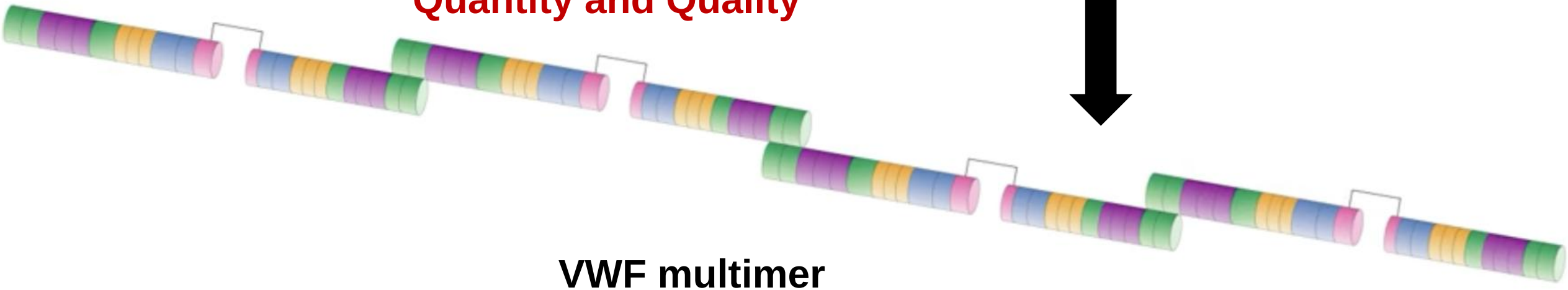


VWF monomer
(not sticky)



VWF dimer
(bit sticky)

Size and Function matters i.e.
Quantity and Quality



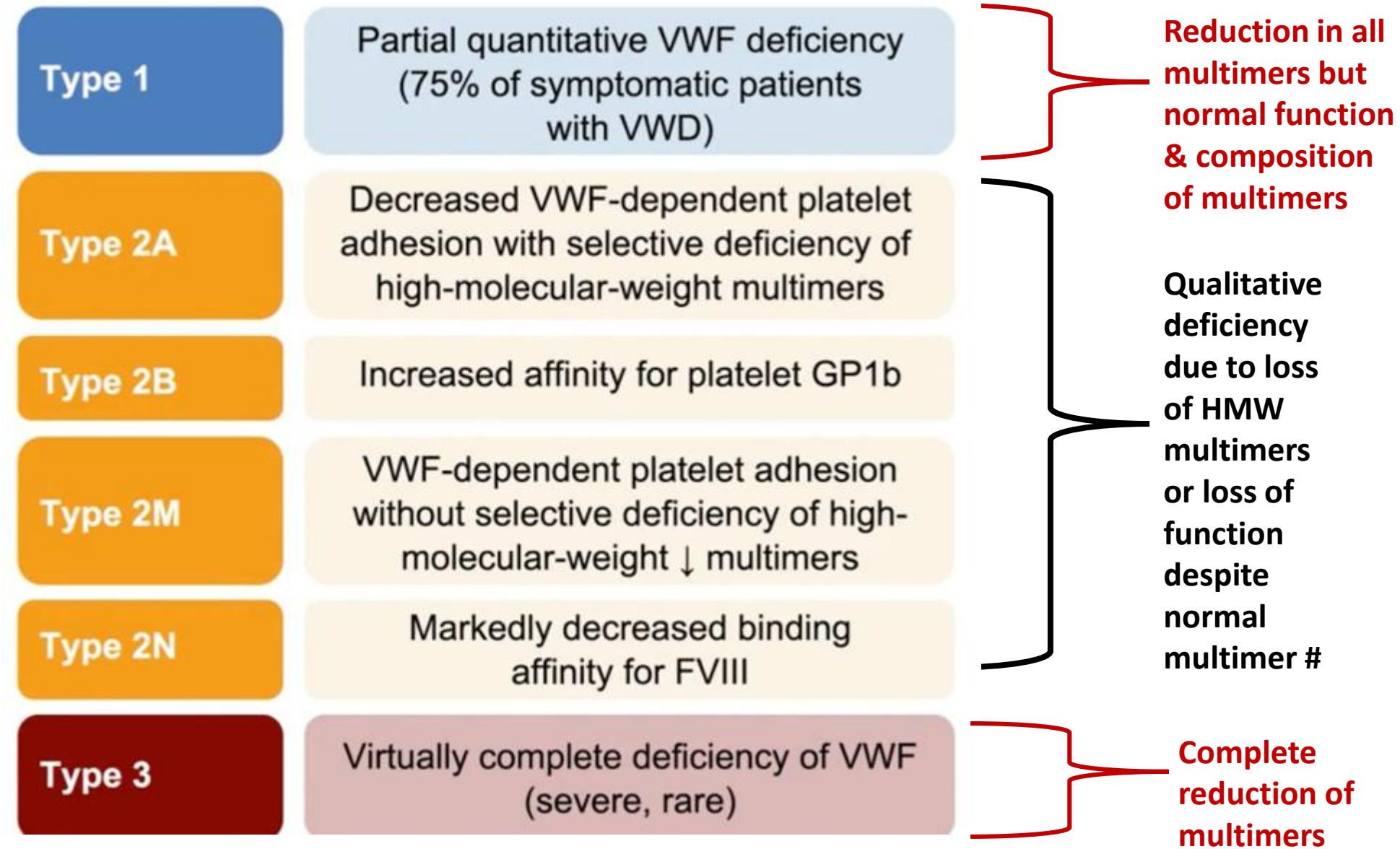
VWF multimer

the longer the string of monomers the more adhesive to platelets and collagen
i.e. Sticky to very sticky when unusually large VWF multimer state

More on VWD as a deficiency state of VWF binding……basis of classification-

Absolute or functional deficiency

i.e. Quantitative or Qualitative i.e.. Hypo/aprotienemia (Type1/3) or Dysproteinemia (Type 2)



Type 2 acronym by Dr. Roshni Kulkarni

- **A** = **A**bsent multimers
- **B** = increased platelets **b**inding
- **M**= **M**ad at the platelets
- **N** = No binding to factor VIII

Type 2 VWD; (VWF Rco: Ag < 0.7)

2A

- **A** = **a**bsent High and intermediate weight multimer leading to decreased platelet binding
- <u>Abnormal multimers</u>

2B

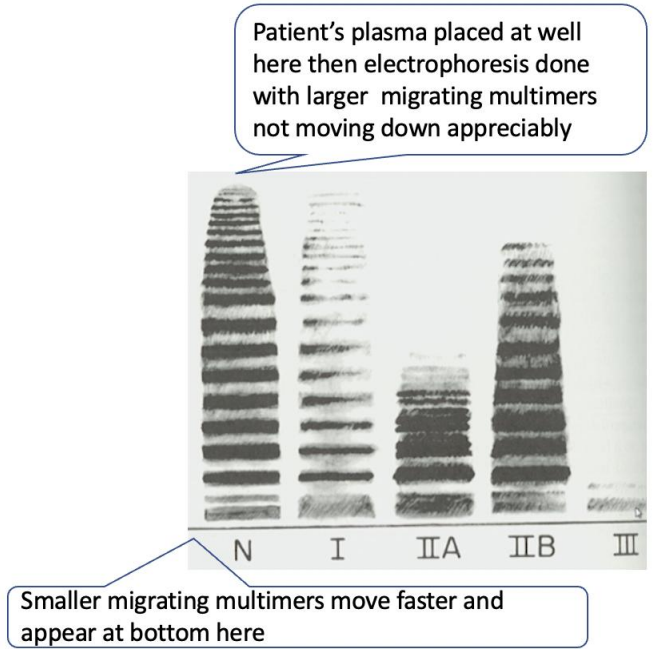
- **B** = increased platelet **b**inding
- Gain of function mutation
- <u>Abnormal multimers</u>
- <u>Thrombocytopenia</u>

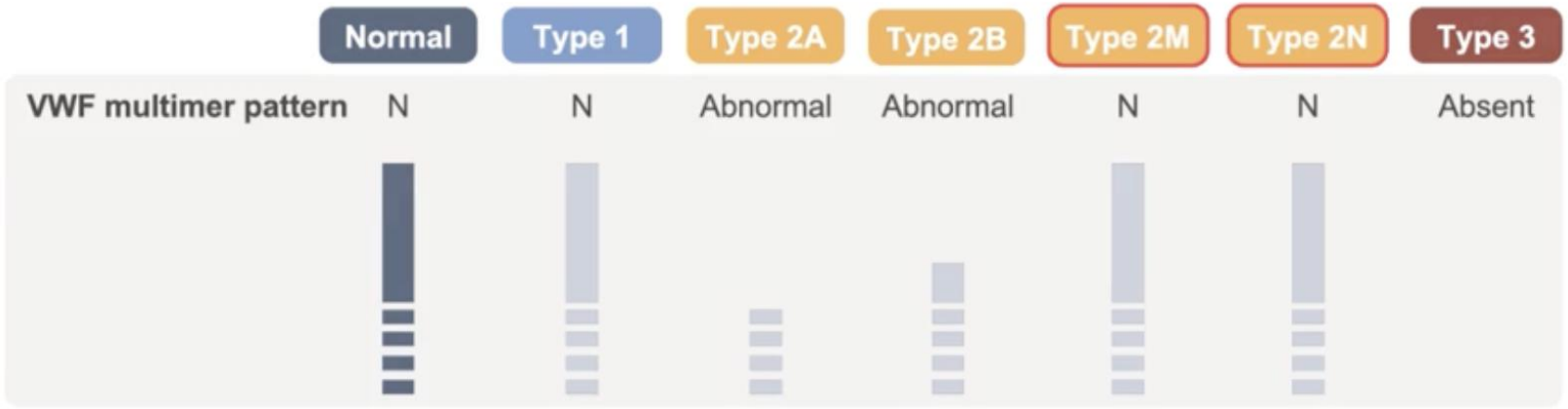
2M

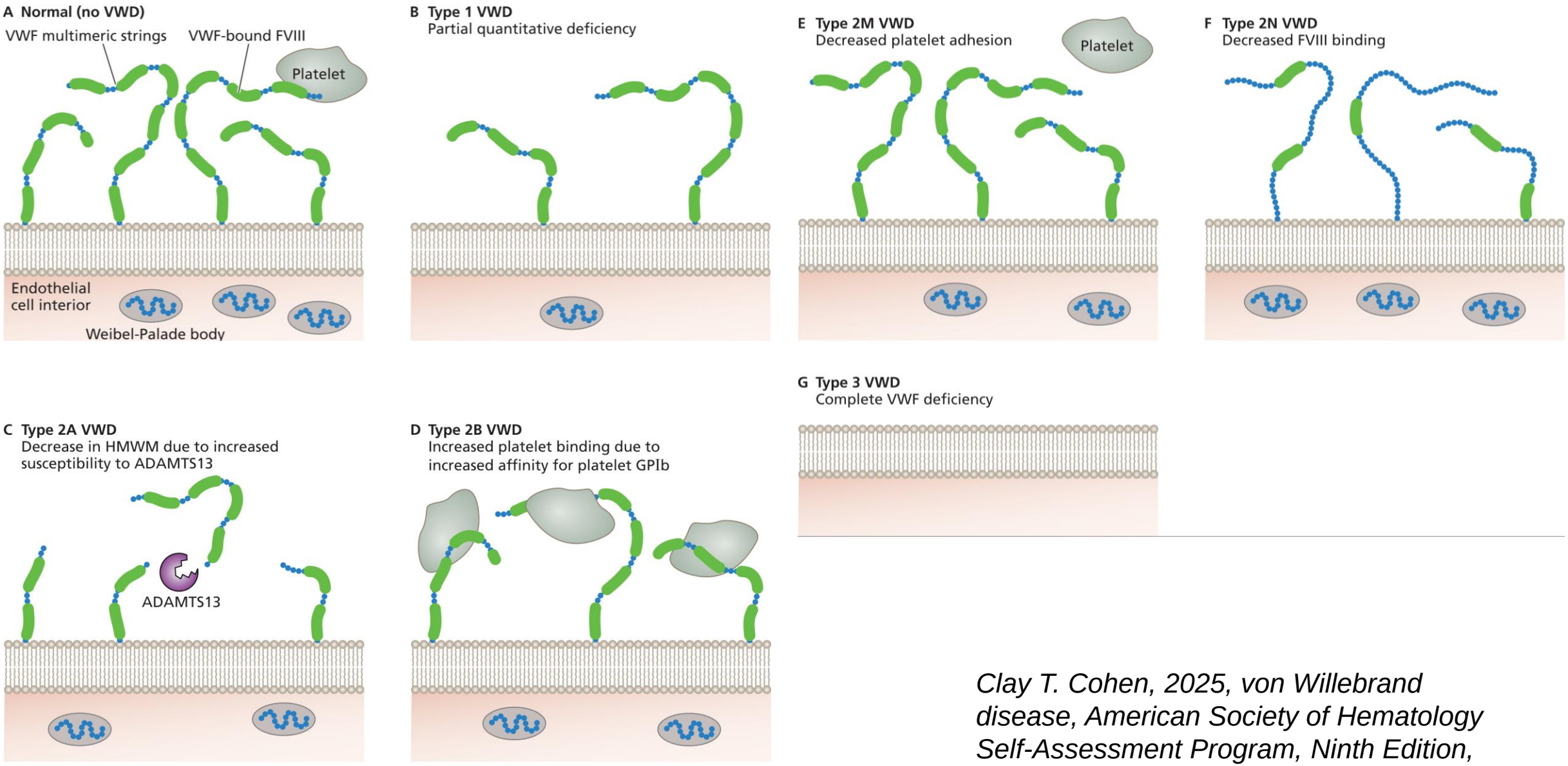
- M = decreased platelet & collagen binding
- Loss of function mutation in GP1b alpha binding site
- <u>Normal multimers</u>

2N

- N = no binding to FVIII
- Manifest similar to <u>hemophilia</u>
- <u>Normal multimers</u>



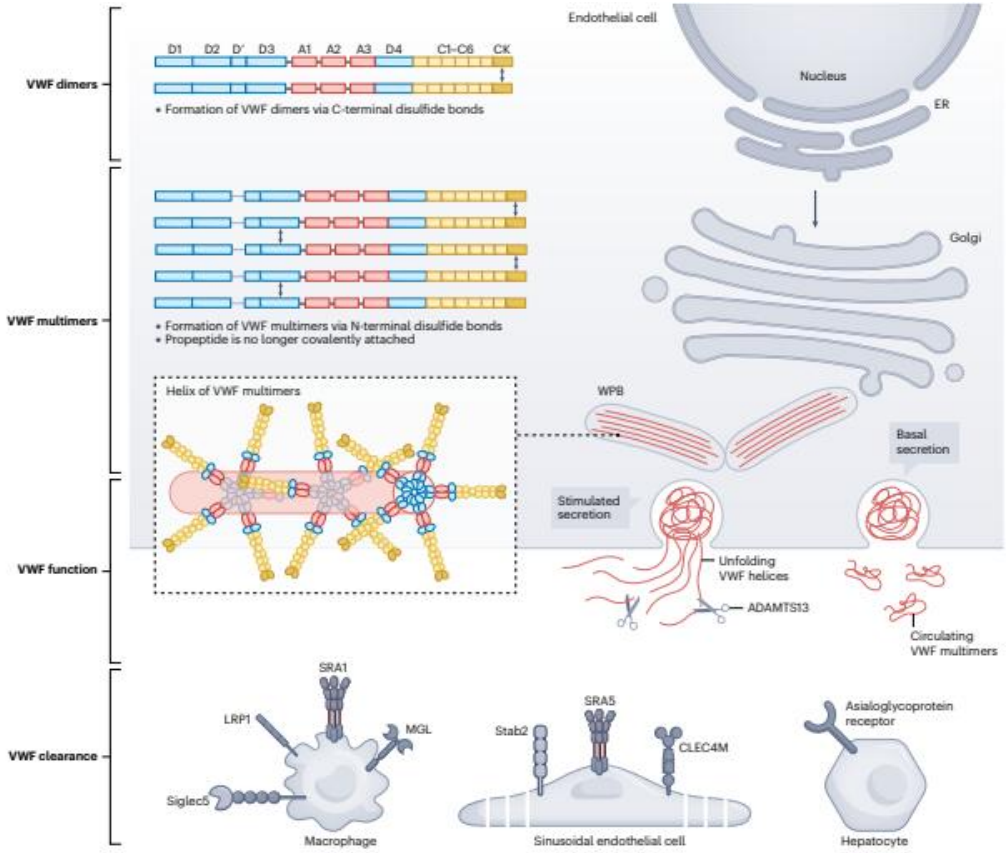




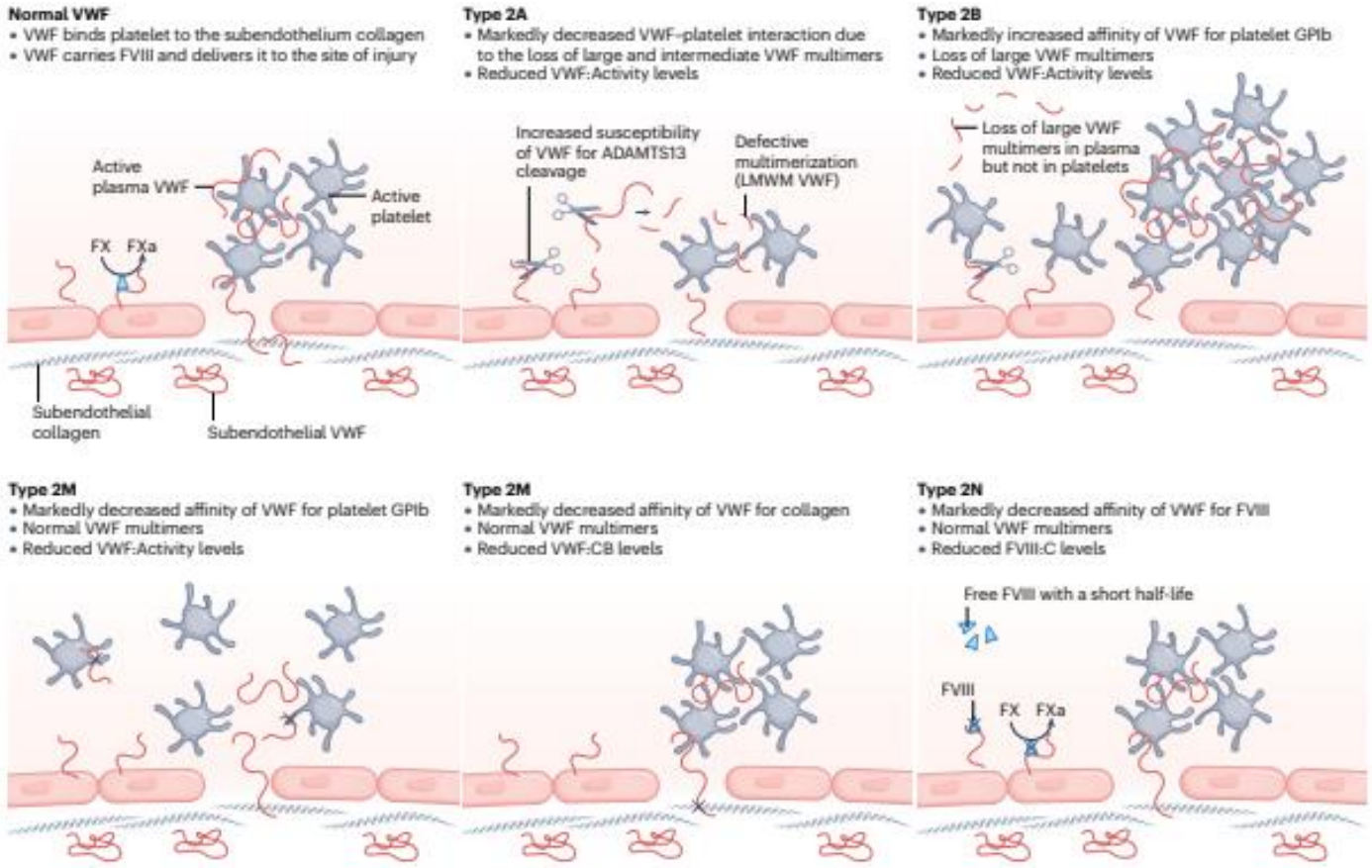
Clay T. Cohen, 2025, von Willebrand disease, American Society of Hematology Self-Assessment Program, Ninth Edition, Figure 20-2

Understanding the physiology of VWD will lead to understanding the pathology..

Type 1 d/t defect in synthesis or secretion or clearance, Type 3 in synthesis-



Type 2 d/t functional defect involving platelet or FVIII interaction-



REQUIRED READING- great review on laboratory and clinical aspects of VWD!!: *Seidizadeh O, Eikenboom JCJ, Denis CV, Flood VH, James P, Lenting PJ, Baronciani L, O'Donnell JS, Lillicrap D, Peyvandi F. von Willebrand disease. Nat Rev Dis Primers. 2024 Jul 25;10(1):51. doi: 10.1038/s41572-024-00536-8. PMID: 39054329.*

A 15 year old female is referred from the Emergency Room for suspected VWD after presenting with epistaxis requiring packing. She also reports heavy menses changing her sanitary pad every 90 minutes since menarche at age13 . She also reports “easy” bruising throughout childhood and prolonged bleeding from cuts. What is her bleeding score per the ISTH Bleeding Assessment Tool?

A. 3 points

B. 5 points

C. 8 points

D. 10 points

Answer C:

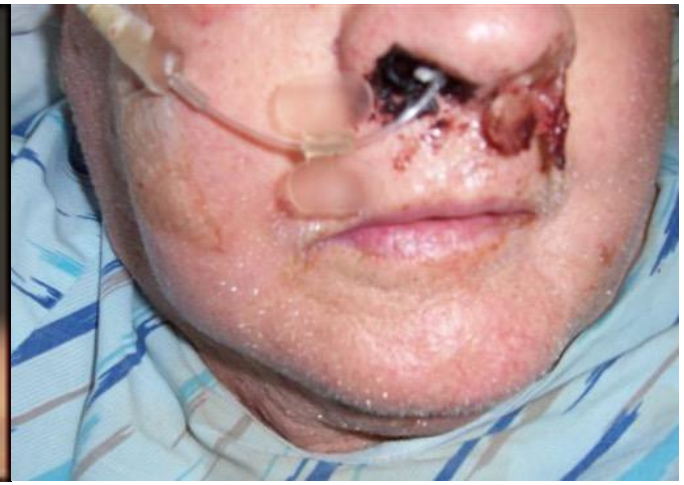
- Bleeding score can be calculated as follows:
  - ❑1 point for easy bruising,
  - ❑1 point for prolonged bleeding from cuts,
  - ❑3 points for epistaxis requiring packing,
  - ❑3 points for heavy periods since menarche.

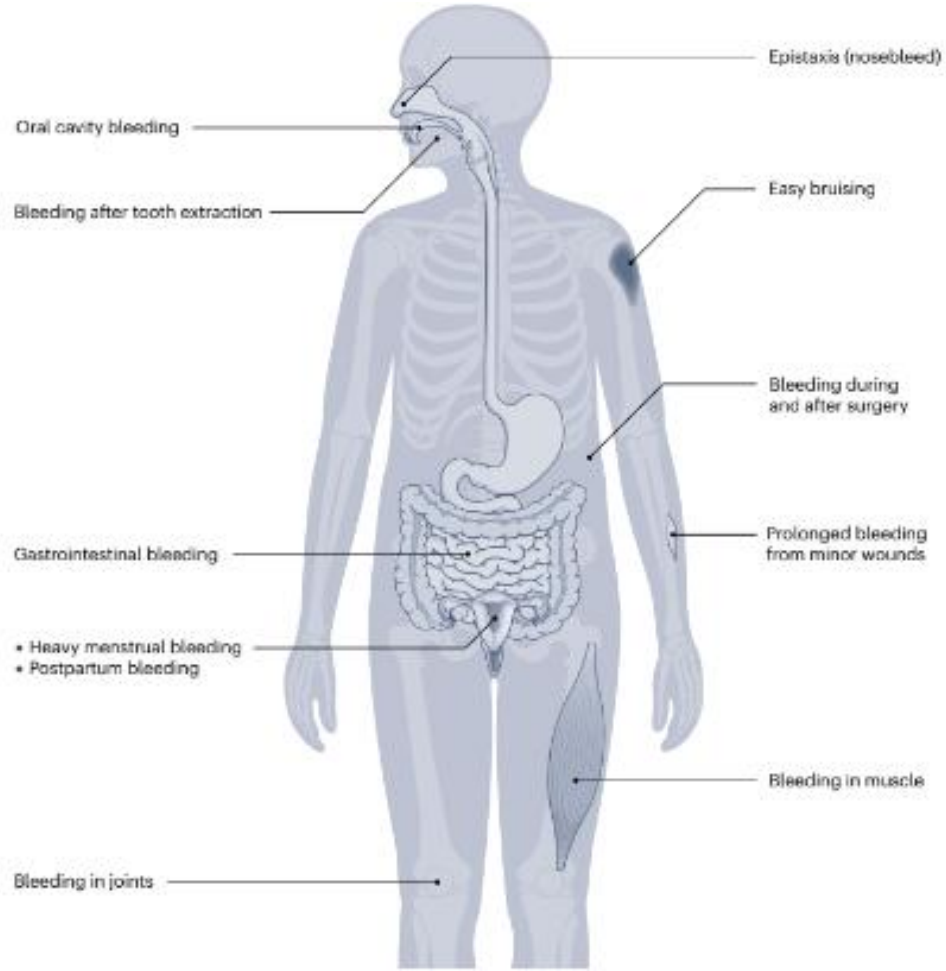
Normal bleeding score for adult females is 0-5.

Such patients should undergo VWF testing.

Improving the significance/specificity of bleeding symptoms

- Summing the symptoms/cumulative score
- Grading the symptom based on degree of intervention





Epistaxis	
0	No or trivial (<5)
1	>5 or more than 10
2	CONSULTATION ONLY
3	Packing or cauterization or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

Oral Cavity	
0	No
1	Reported at least one
2	CONSULTATION ONLY
3	Surgical hemostasis or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

Surgery	
-1	No bleeding in at least 2 surgeries
0	Not done or no bleeding in 1 surgery
1	Reported in <25% of all surgeries
2	Reported in >25% of all surgeries, no intervention
3	Surgical hemostasis or antifibrinolytics
4	Blood transfusion or replacement therapy or desmopressin

Muscle Hematoma	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Cutaneous	
0	No or trivial (<1 cm)
1	>1 cm and no trauma
2	CONSULTATION ONLY

GI Bleeding	
0	No
1	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia
2	Spontaneous
3	Surgical hemostasis or blood transfusion or replacement therapy or desmopressin or antifibrinolytics

Menorrhagia	
0	No
1	CONSULTATION ONLY
2	Antifibrinolytics or pill use
3	Curettage or iron therapy
4	Blood transfusion or replacement therapy or desmopressin or hysterectomy

Hemarthrosis	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Bleeding From Minor Wounds	
0	No or trivial (<5)
1	>5 or more than 5
2	CONSULTATION ONLY
3	Surgical hemostasis
4	Blood transfusion or replacement therapy or desmopressin

Tooth Extraction	
-1	No bleeding in at least 2 extractions
0	Not done or no bleeding in 1 extraction
1	Reported in <25% of all procedures
2	Reported in >25% of all procedures, no intervention
3	Resuturing or packing
4	Blood transfusion or replacement therapy or desmopressin

Postpartum Hemorrhage	
-1	No bleeding in at least 2 deliveries
0	No deliveries or no bleeding in 1 delivery
1	CONSULTATION ONLY
2	Curettage or iron therapy or antifibrinolytics
3	Blood transfusion or replacement therapy or desmopressin
4	Hysterectomy

CNS Bleeding	
0	Never
1	—
2	—
3	Subdural, any intervention
4	Intracerebral, any intervention

Evolution of the ISTH Bleeding Assessment Tool (BAT)

https://bleedingscore.certe.nl/

Also available in MedCalc

1 pt= symptom (rigorously defined) → **2 pts= sought provider attention** → **3 pts= underwent provider intervention** → **4 pts= underwent transfusion or surgery**

Rodeghiero et al, JTH 2005; 3:1-9

Role of BAT before VWF testing

	Pre-test probability	Utility of BAT
Primary Care setting	Low (~3%)	Yes
Referral to Hematology Clinic b/c of personal bleeding history	Intermediate (~20%)	No- test regardless of score
Referral to Hematology Clinic b/c of family history of bleeding	High (~50%)	No- test regardless of score

2021 VWD guideline panel:For patients with a low probability of VWD (eg, seen in the primary care setting), the panel recommends using a validated BAT as an initial screening test to determine who needs specific blood testing over nonstandardized clinical assessment (strong recommendation based on moderate certainty in the evidence from diagnostic accuracy studies

James PD Blood Adv. 2021 Jan 12;5(1):280-300. PMID: 33570651

Initial evaluation of patient 1: clinical pearls

- Be able to do bleeding score in your sleep
  - And short version in parents and sibs
- Ask for s/s in consideration of Hypothyroidism
  - Low thyroid hormone can decrease VWF biosynthesis
- Take good history for superimposed medications/OTCs causing platelet dysfunction

"A > H"

- **A**SA
- **B**eta lactams
- **C**lopidogrel
- anti-**D**epressants
- Vitamin **E**
- **F**lavinoids
- **G**ingko
- and other **H**erbs: garlic, birberry, ginger,ding quai, ginseng, turmeric, meadowsweet, willow
  - Besides anti-platelet meds and herbs, know about coumarin containing herbs- motherwort, chamomile, horse chestnut,red clover, fenugrek

What should be your initial “core” tests of someone with suspected VWD?

A. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FII, FV, FVIII, closure time

B. CBC, PT, PTT, fibrinogen, VWF:RCo , VWF antigen, FVIII, bleeding time

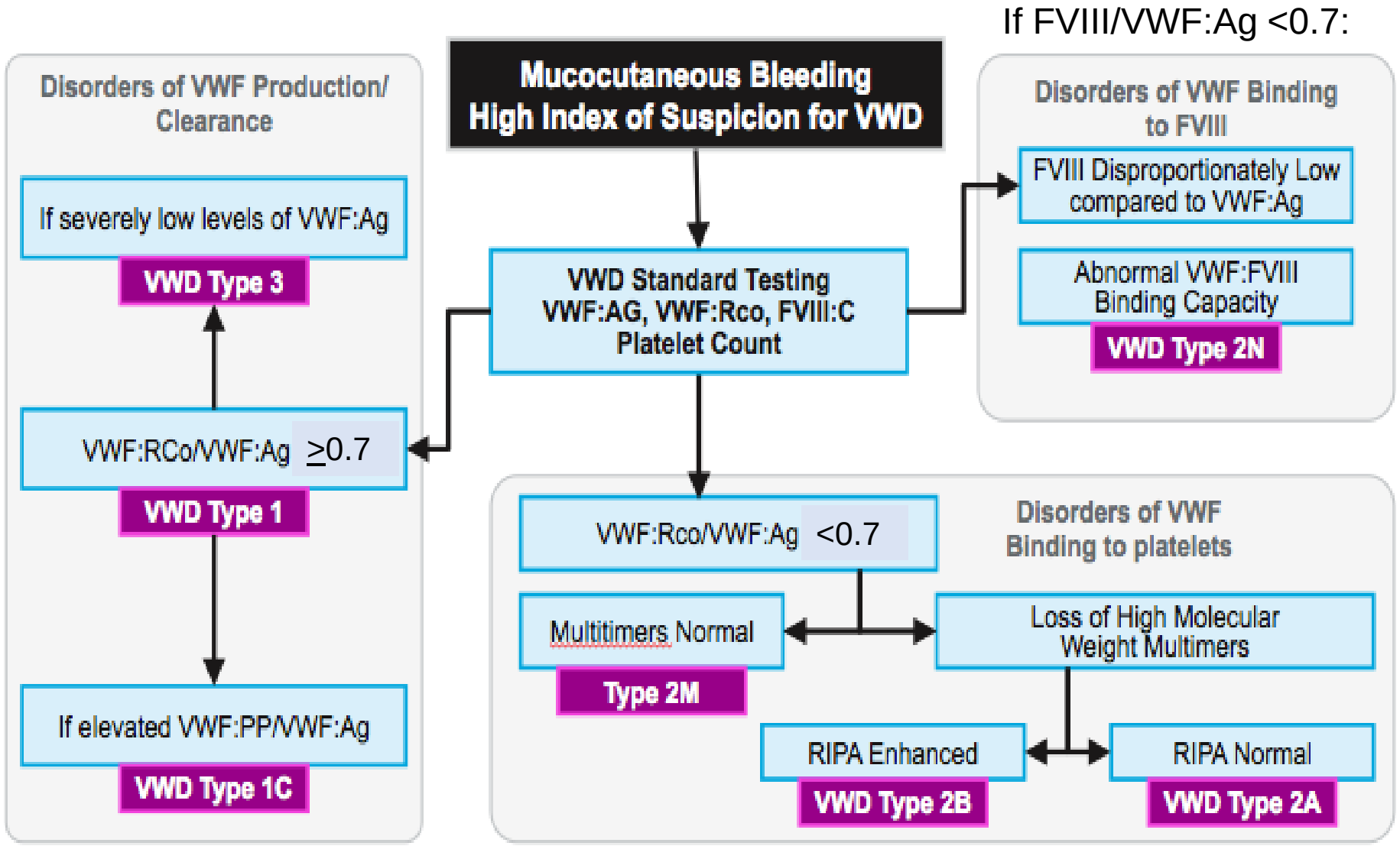
C. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FVIII, closure time

D. CBC, PT, PTT, fibrinogen, VWF:RCo, VWF antigen, FVIII, closure time, VWF multimers

My laboratory approach for suspected VWD….

1. Patients referred to me in consideration of an underlying bleeding disorder warrant a VWF panel (VWF activity by GP1R [GP1M best but not NYS approved yet] + VWF antigen + FVIII) besides CBC, PT, PTT, Fibrinogen and an extra blue top in case VWF panel WNL then run -
   - FIX, FXI, quantitative FXIII and if testing WNL-
   - then platelet aggregation and release studies
   - if the BAT is increased but the VWF panel returns normal, we will repeat testing if the levels are below 100%. based on 5 recent studies that an initial level ≥ 100% reliably excludes the laboratory diagnosis of VWD without need for repeat testing
2. If the VWF panel is subnormal x 2 sets, I then calculate VWF activity/VWF antigen ratio and if <0.7 (calculate FVIII/VWF Ag ratio too & if <0.7 send out VWF-FVIII binding assay to r/o 2N)-
   - Do on-site Ristocetin-induced platelet aggregation (RIPA) (decreased in 2A and increased in 2B) and send out for multimers and VWF:CBA (VWF:CBA/VWF Ag usually normal in 2M) to a reference lab then-
   - Have them reflex sample further based on those results in terms of tests like 2B binding assay and exon 28 analysis if abnormal multimers or if reduced CBA with normal multimers for 2M
3. In anticipation of any future procedure, per the 2021 VWD management guidelines we would do a DDAVP trial with sampling not only at 60 minutes but at 4 hours in consideration of type 1C VWD wherein there should be a 30% fall 4 hrs. post DDAVP from peak VWF levels-
   - though typically the baseline VWF activity is below 15%
   - if results suggest 1C will send out VWF propeptide/Ag ratio to confirm 1C

One algorithmic approach to laboratory testing- if VWF level < 50% then calculate 2 ratios- VWF act(RCo or Gp1bM)/ VWF:Ag and FVIII/VWF:Ag…



Adapted from Ng and DiPaola Blood. 2015;125:2029-2037

VWD Phenotypic Testing Panel

Designation	Property and assay available	Assay application
First-level assays		
VWF:Ag	The amount of VWF protein. Evaluated using ELISA, automated LIA or automated CLIA	Antigen levels <50 IU/dl are indicative of VWD. A level <3 IU/dl is indicative of type 3 VWD
VWF:Activity	The capacity of VWF to interact with the platelet GPIbα receptor. Evaluated using platelet aggregometer (VWF:RCo), coagulation analysers (VWF:RCo, VWF:GPIbR and VWF:GPIbM) or CLIA (VWF:GPIbR)	VWF:Activity levels <50 IU/dl are indicative of VWD. A VWF:Activity-to-VWF:Ag ratio <0.7 is indicative of a dysfunctional VWF variant (that is, type 2) due to loss of HMWM or variants in the A1 domain. A ratio ≥0.7 is normal or indicative of type 1 VWD
FVIII:C	The coagulant activity of FVIII. Evaluated using the one-stage clotting assay, the two-stage clotting assay or the chromogenic assay	A FVIII:C-to-VWF:Ag ratio <0.7 is indicative of a type 2N VWD or mild haemophilia A
Second-level assays		
VWF multimer analysis	Evaluates the distribution of the different molecular weight molecules of VWF. Evaluated using an electrophoresis, with an agarose/SDS gel, under non-reducing conditions	In patients with a VWF:Activity-to-VWF:Ag ratio <0.7 (that is, type 2), the assay discriminates type 2M from types 2A and 2B (loss of HMWM). In types 1, 2M and 2N VWD, a full multimer pattern is present
VWF:CB	The capacity of VWF to bind to collagen. Usually evaluated using ELISA methods. An automated CLIA is also available	A VWF:CB-to-VWF:Ag ratio <0.7 is usually indicative of loss of HMWM (types 2A or 2B). Less often, a ratio <0.7 is due to type 2M variants with specific collagen-binding defect
RIPA	RIPA evaluates the affinity of VWF to the GPIbα receptor. It is usually measured using an aggregometer and establishing the threshold value of ristocetin able to induce 30% of platelet agglutination in a PRP sample (normal range: 0.8–1.2 mg/ml of ristocetin)	An enhanced RIPA (ristocetin concentration <0.8 mg/ml) is typical of type 2B variants. Less often, this is due to the gain-of-function variants in the GPIbα receptor (that is, platelet-type VWD). Type 2A and 2M variants present a decreased RIPA (ristocetin concentration >1.2 mg/ml)
VWF:FVIIIB	The capacity of VWF to bind to FVIII. Evaluated using ELISA methods	Among patients with FVIII:C-to-VWF:Ag ratio <0.7, the assay discriminates between type 2N VWD and mild haemophilia A
VWFpp	The amount of VWFpp protein. Evaluated using ELISA methods	An increased VWFpp-to-VWF:Ag ratio is indicative of VWF variants with shorter half-life (for example, type 1C)

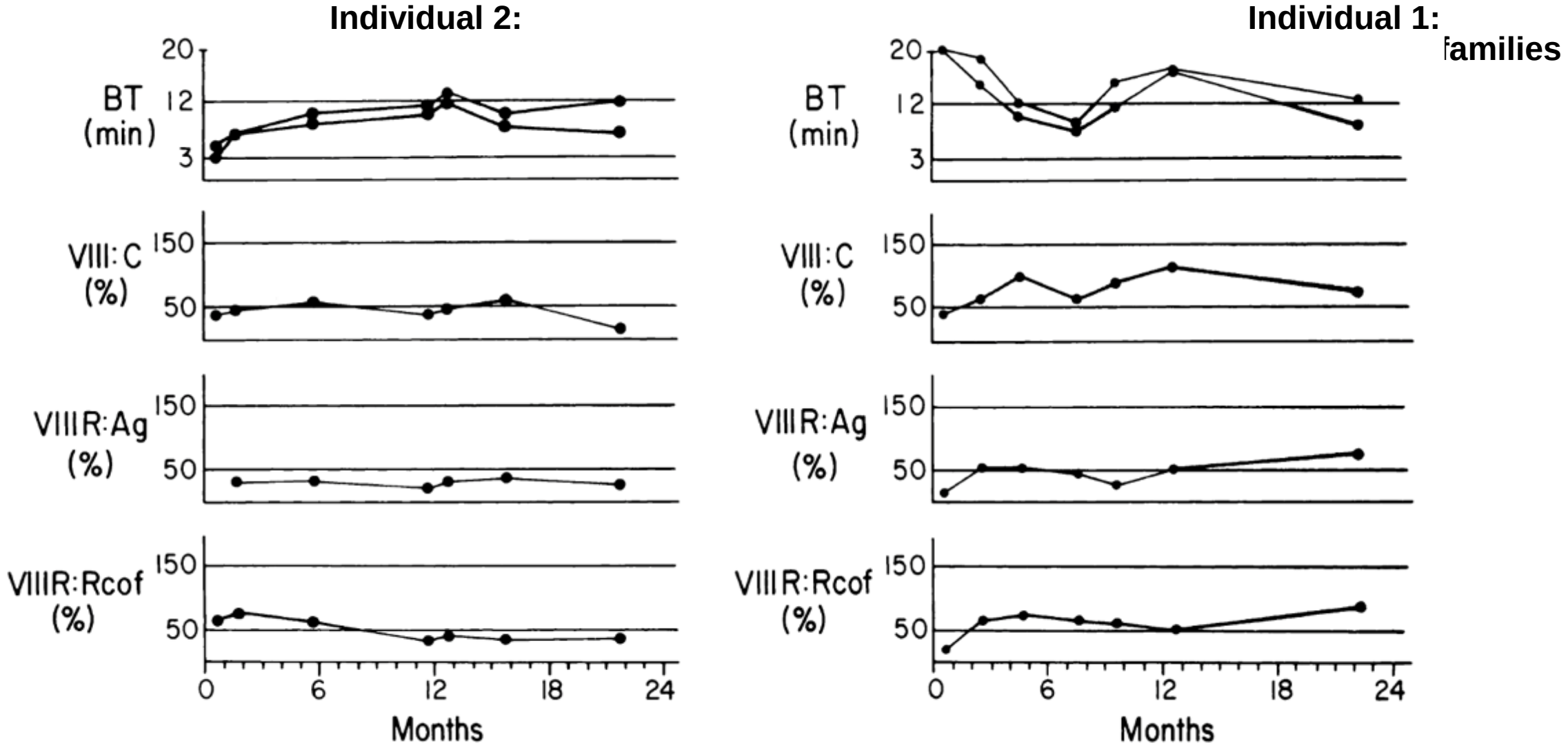
Seidizadeh O Nat Rev Dis Primers. 2024 Jul 25;10(1):51. PMID: 39054329.

Case 1 continued- 15 y/o with BAT of 8 presenting to ED with epistaxis needing packing and heavy menses since menarche

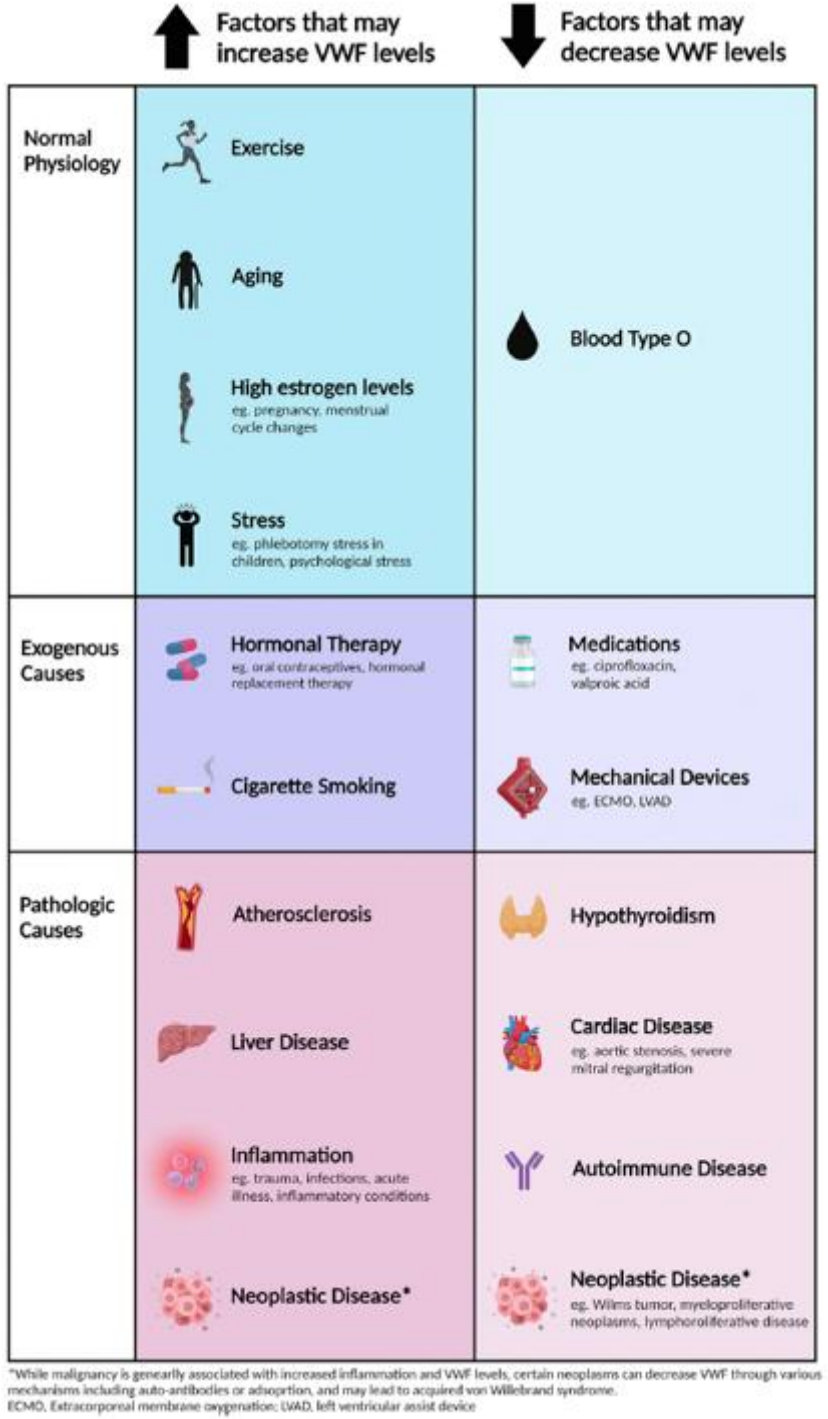
- The patient undergoes testing for VWD:
  - Ristocetin cofactor AKA VWF activity = 26% (normal 40%-120%)
  - VWF antigen = 28% (normal 50%-150%)
  - FVIII level = 47% (normal 50%-150%).
  - VWF multimers are slightly reduced but in normal pattern.

- A presumptive diagnosis of Type 1 VWD was made (definitive diagnosis was then made when a second set of levels returned subnormal).
- Why do we check levels at least twice?

When the “V” in Von Willebrand stands for variable …from pathologic variables to physiologic variables



Abildgaaard C Blood,Vol.56,No.4(October),1980



Abou-Ismail MY J Thromb Haemost. 2023 Feb;21(2):204-214. PMID: 36700502.

The many variables driving VWF levels up or down

	Increasing VWF level	Decreasing VWF level
Non-gender specific	• Advancing age ➢ Rotterdam, Kingston, Rochester, Dublin Milan have all shown up to a third can normalize levels over 5-20 years; appears to occur even in childhood to adolescence • Exercise ➢ 2-5-fold increase • Inflammation, i.e., high CRP related: ➢ e.g., ASHD, cancer, CLD, COVID-19, rheumatological diseases	• Acquired von Willebrand Syndrome (Cardiac devices, Hypothyroidism, MGUS, Wilms) • Blood type O ➢ Levels 25-30% lower • Medications- cipro, valproic acid • Pre-analytical variables (send-out to national laboratory) ➢ Send out levels 30-50% lower then testing at on-site laboratory at HTC ***Jaffray J, Am J Hematol. 2020; 95(9)1022-1029.***
Women and girls specific	• High dose estrogen in HRT or high dose COC (not low dose) • Pregnancy ➢ 2-5-fold increase in 3rd trimester ➢ Iron deficiency with heavy menses	• Follicular phase of menses • Hypothyroidism presenting as heavy menses ***Simoneau J et al. Association between hemoglobin values and VWF assays: a multicenter investigation. Blood Adv. 2024 Mar 12;8(5):1152-1154. PMID: 38295284***

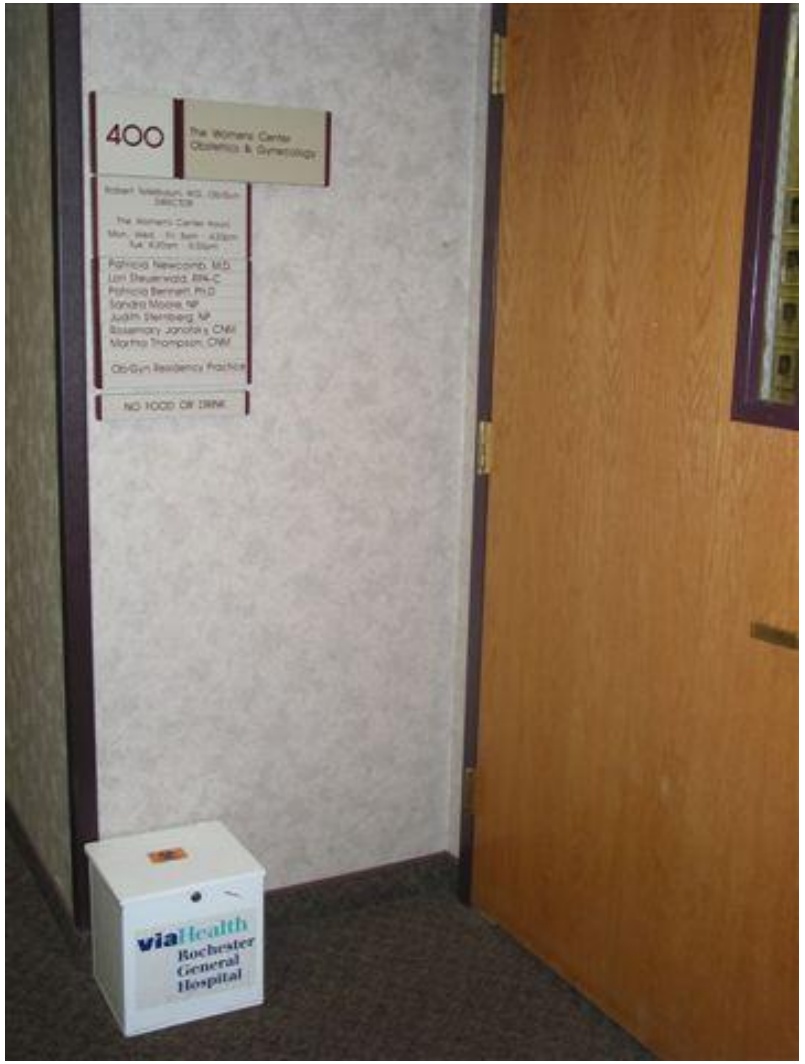
Increased VWD testing…. now sent by primary care physicians and obstetrics/gynecologists

- Is this a good thing that more primary care doctors and ob/gyns are thinking about VWD??

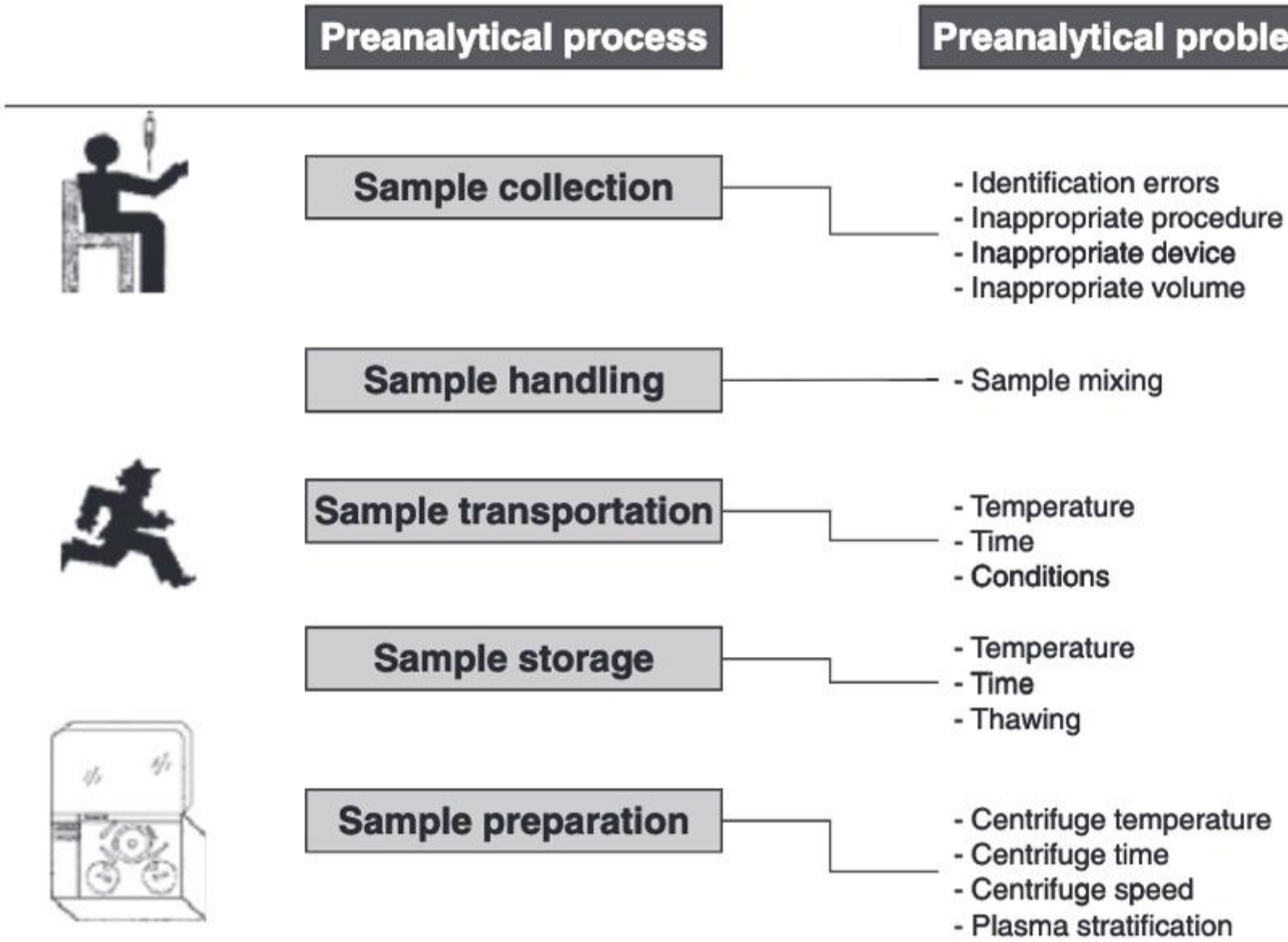
Yes and No

- Important to diagnose and identify women with VWD given 11-16% prevalence of VWD in chronic heavy menses with normal gyn exam
- But, more and more health insurance companies are contracting with large national laboratories to perform off-site hemostasis testing
- VWD testing is very sensitive to many pre-analytical variables:
  - Delay in centrifuging the sample
  - Heat or cold inactivation

→Leads to falsely low VWF or FVIII levels



- *Lipton R Misdiagnosis by Milkbox Haemophilia (2003), 9:235-236*
- *Jaffray J, Laboratory misdiagnosis of von Willebrand disease in post-menarchal females: A multi-center study Am J Hematol. 2020; 95(9)1022-1029.*

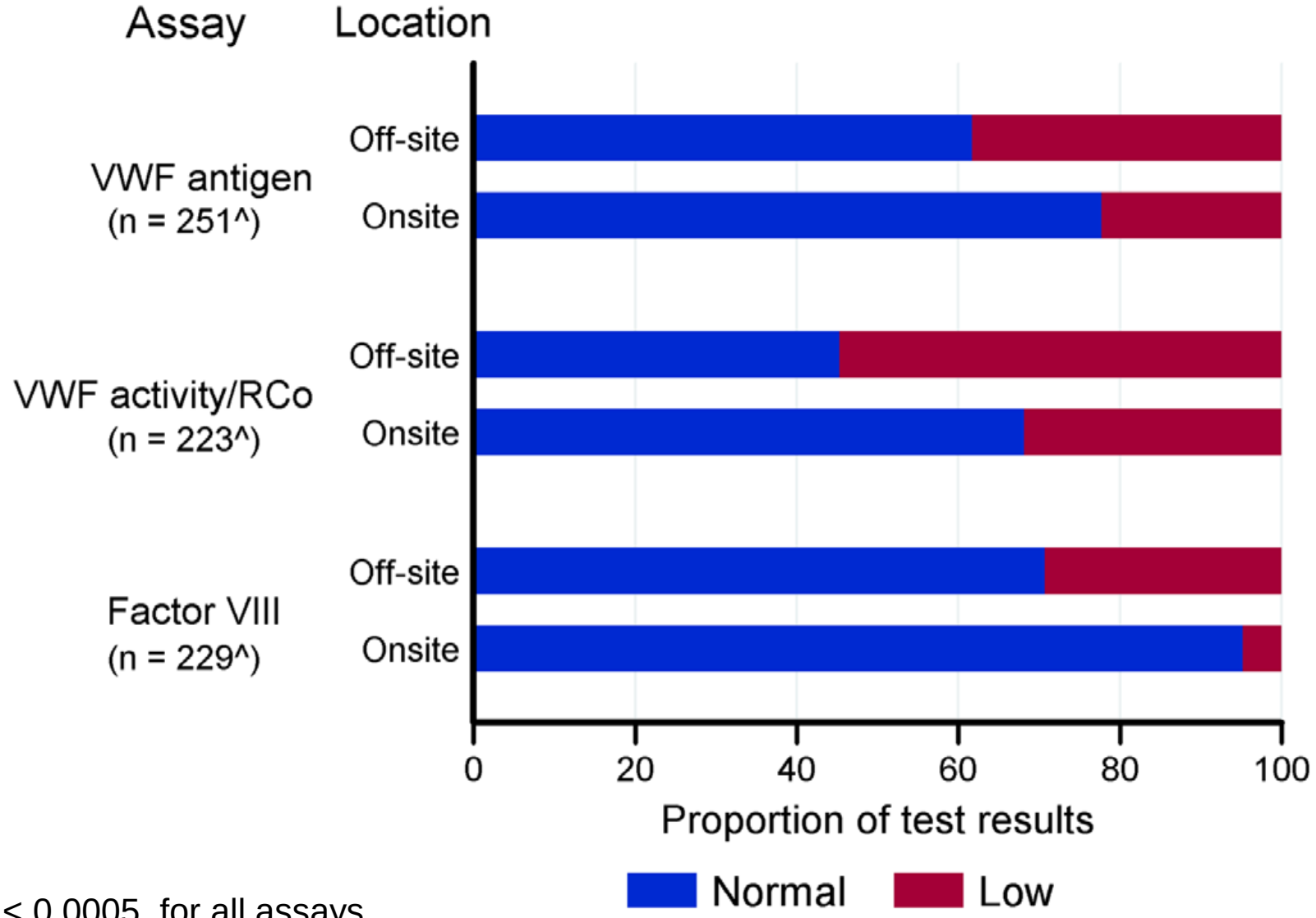


Preston et al, Quality issues in laboratory haemostasis, Haemophilia 2010; Favaloro et al., Am J Clin Pathol 2004; Favaloro et al, Semin Thrombo Hemost 2008

Multi-center study comparing off-site to on-site VWF phlebotomy and processing

Lower levels of VWF assays at off-site labs, n=236 patients

Assays increased to be within the normal range in 30% to 50% of subjects when retested at on-site laboratories

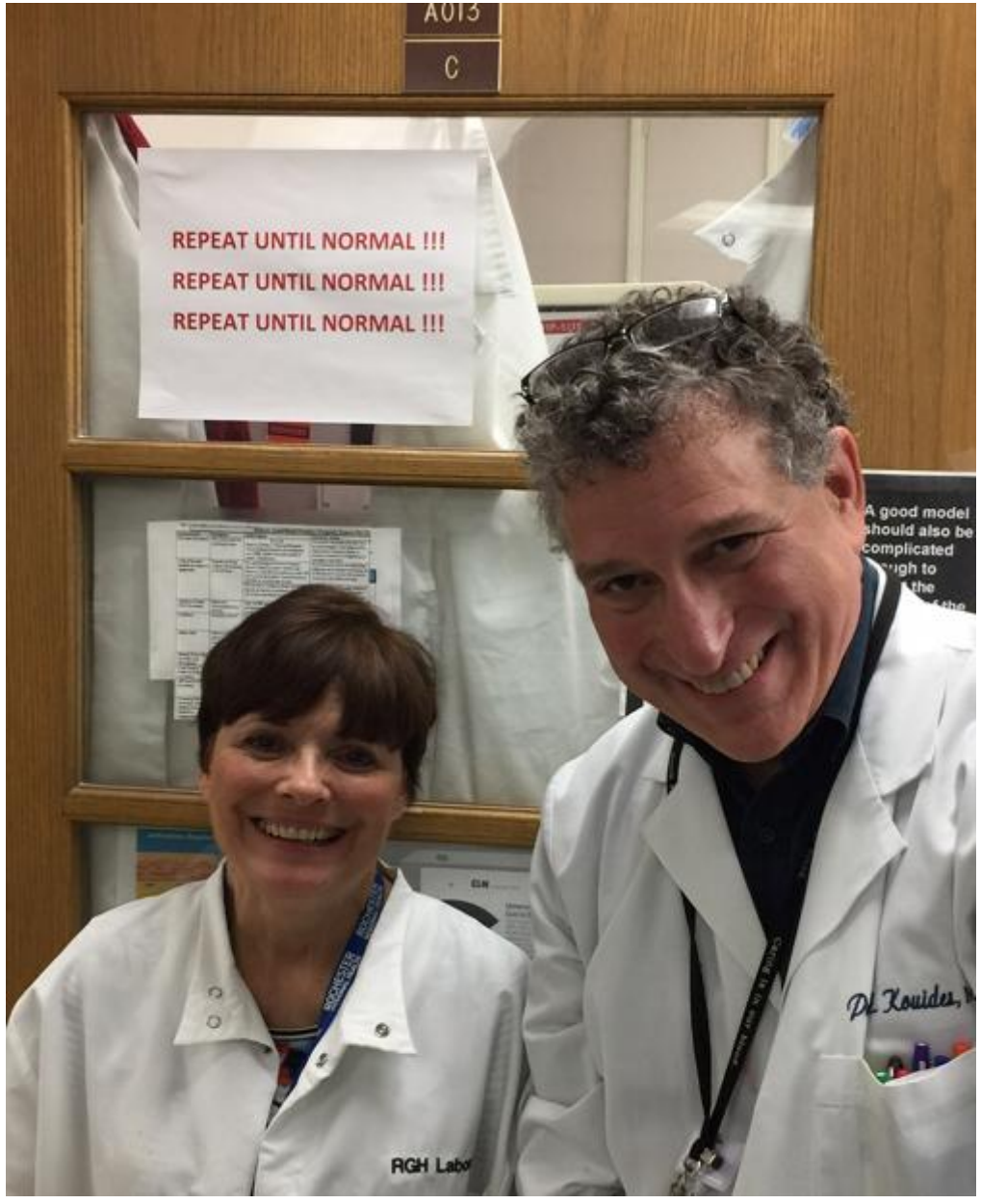


McNemar's test p-value < 0.0005, for all assays

Jaffray J: Am J Hematol. 2020 Sep;95(9):1022-1029. PMID: 32419248.

Ideal VWD testing environment- On-site Coagulation Lab

- Phlebotomy, processing and analysis occurring in a timely manner
  - **Most important aspect is prompt processing**
- Most insurers necessitate testing be performed at outside laboratories
  - Increased likelihood of inappropriate processing
  - False positive VWD diagnosis
- Consequences of misdiagnosing VWD-
  - Inappropriate interventions
  - Inadequate therapy
  - Increased healthcare costs
  - Unnecessary stress to patients and families
  - Repetitive VWD testing



Back to case 1, 15 y/o female

- How common is VWD (more then one answer!):

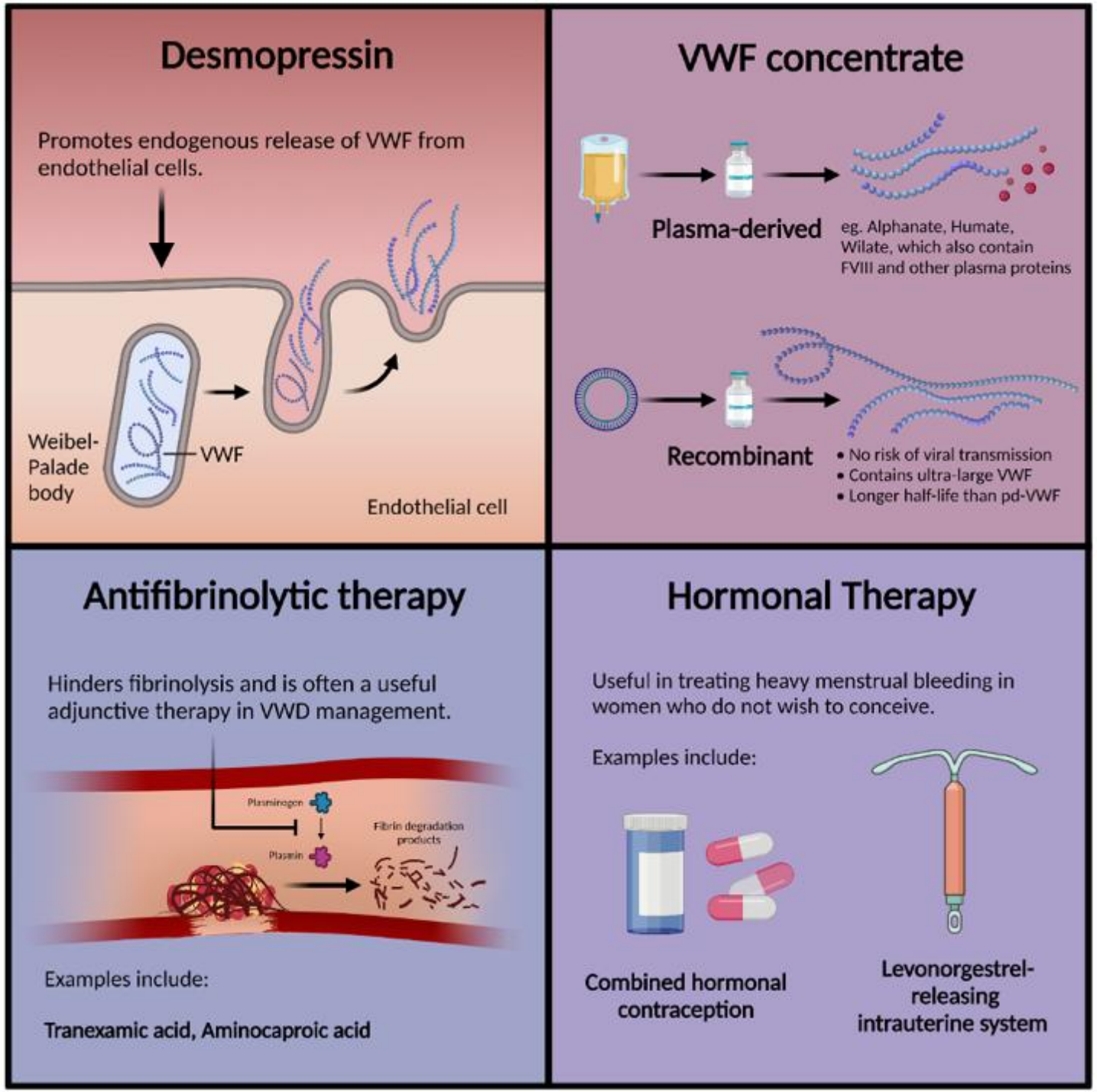
A. 1:100 in terms of laboratory prevalence

B. 1:1000 in terms of symptomatic prevalence

C. 1:10,000

D. 1:1,000,000 in terms of Type 3 VWD

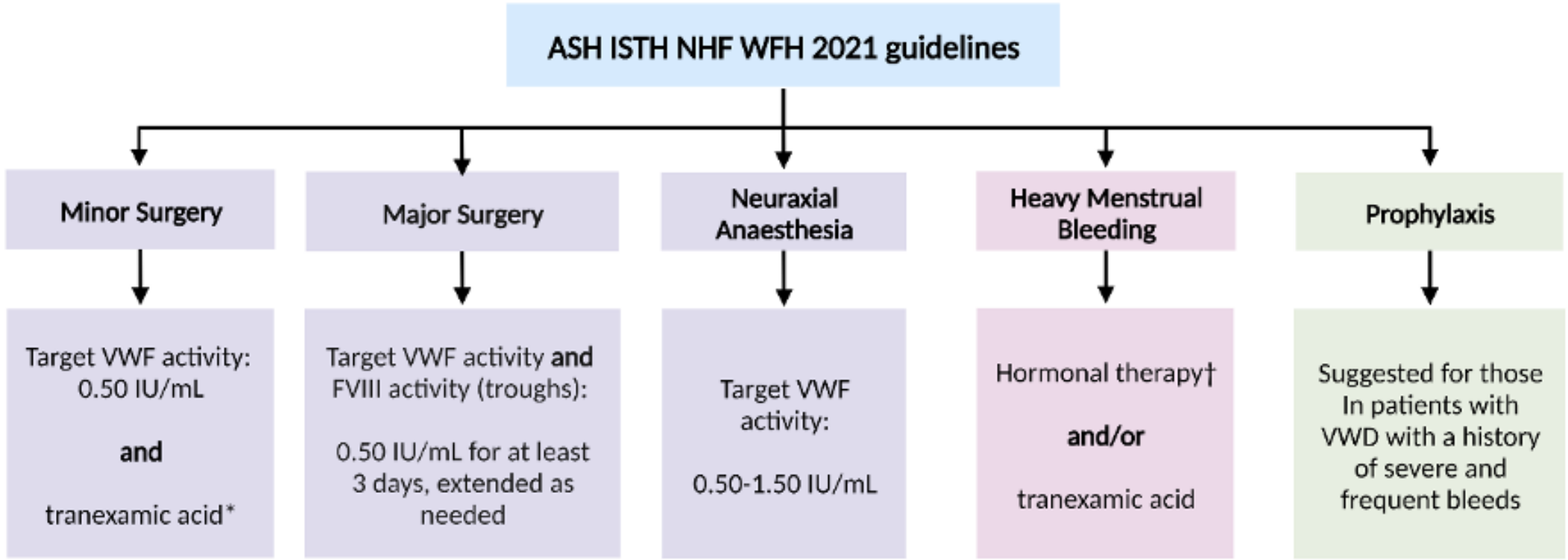
VWD Management Options



Management of VWD by subtype

Condition	Prevalence	Treatment (± Aminocaproic Acid or Tranexamic Acid for Mucosal Bleeding)
Type 1	75%-85%	Desmopressin usually works in majority of cases For major surgery, VWF replacement may be preferable
Type 2A	10%-15%	Desmopressin rarely effective Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2B	5%	Desmopressin maybe deleterious (may lower platelets, cause clots) Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2M	Rare	Desmopressin rarely effective Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 2N	Rare	Infuse VWF (plasma-derived FVIII concentrate or rVWF)
Type 3	1 in 1,000,000	Infuse VWF (plasma-derived FVIII concentrate or rVWF)

Management of VWD by guidelines



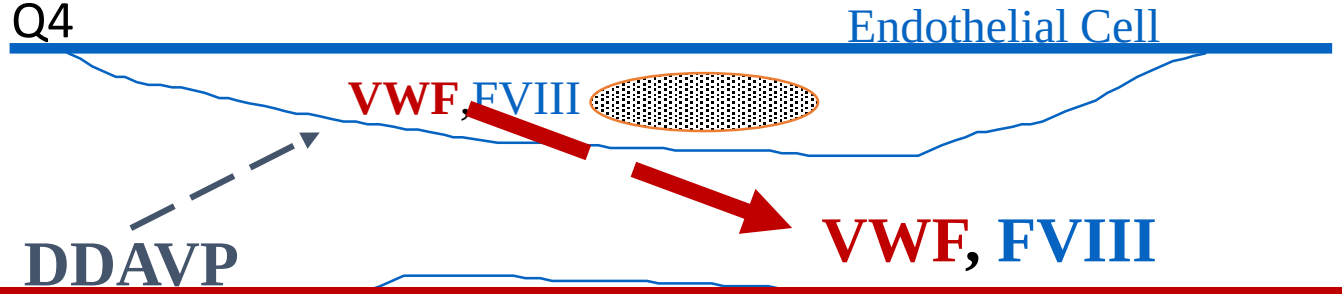
* Tranexamic acid alone can be considered for minor procedures in Type 1 VWD patients with baseline VWF activity levels of >0.30 IU/mL and mild bleeding phenotype.
† For those who do not wish to conceive.

ASH: American Soceity of Hematology, ISTH: International Society on Thrombosis and Haemostasis, NHF: National Hemophilia Foundation, WFH: World Federation of Hemophilia, VWF: von Willebrand Factor

Desmopressin-1-deamino-8-D-arginine vasopressin (DDAVP)

- releases pre-formed stores of FVIII and vWF from the endothelium
- effective in most patients with mild hemophilia as well as majority with von Willebrand disease
- Indications;
  - For minor surgery and dental procedure (NOT major surgeries)
  - WHY?.... Repeated dosing leads to tachyphylaxis and hyponatremia
  - Useful in type 1, some use/benefit in type 2 (2M, 2A).
  - *Do not use with type 2B or type 3*
- Intranasal form "STIMATE" due to manufacturing issue off

market till earliest 2025 Q4



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

2021 VWD guidelines panel-In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of <0.30 IU/mL, the panel *suggests* performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
In these patients, the panel *suggests against* treating with desmopressin in the absence of desmopressin trial results (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯)

Case continued 15 y/o Type 1 VWD

- **You counsel the patient and her parents on her new diagnosis. Which of the following is not a clinical manifestation/complication of VWD in females?**

A. Iron deficiency anemia
B. Increased rate of gynecological surgical interventions (dilatation and curettage, hysterectomy)
C. Decreased quality of life
D. Increased rate of miscarriage
E. Postpartum vulvar hematoma

Female with VWD

Kouides PA. Females with von Willebrand disease: 72 years as the silent majority. *Haemophilia* 1998; 4: 665–76.

Childbirth

Post-partum hemorrhage

Menstruation

Menorrhagia

Other menstrual issues:

- Increased prevalence of mid-cycle pain (Mittlesmerz) and dysmenorrhea
- Risk of hemoperitoneum
- ? Increased incidence of endometriosis, polyps, fibroids

Psychosocial complications (Quality-of-life impact)

- Increased prevalence of anxiety (-depressive) disorders
- 1/3rd to 1/2 have lost time from work/school in the past year
- In one study QOL impairment was equivalent to a HIV + severe hemophiliac

Medical and Surgical complications

- Iron deficiency anemia
- Increased rate of surgical interventions: D&C, hysterectomy

Case continued (15 y/o Type 1 VWD) The patient and her parents are informed that there are numerous treatment options for managing her heavy menses.

• All the following are front-line options to control heavy menses in this patient except?

A. Tranexamic acid (Lysteda TM) 1.3 gram po tid first 5 days of menses

B. MIRENA IUD

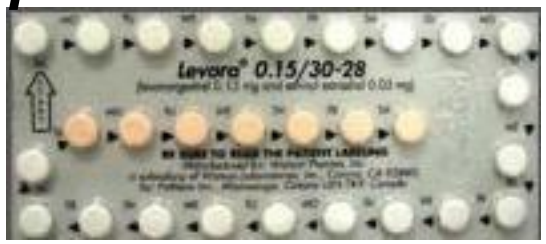
C. Combined oral contraceptive (COC)

D. Plasma-derived VWF containing FVIII concentrate

Armour

ANTI-MENORRHAGIC FACTOR GLANULES

Oral contraceptive



Levonorgestrel IUD

Endometrial ablation

Hemostatic Therapies:

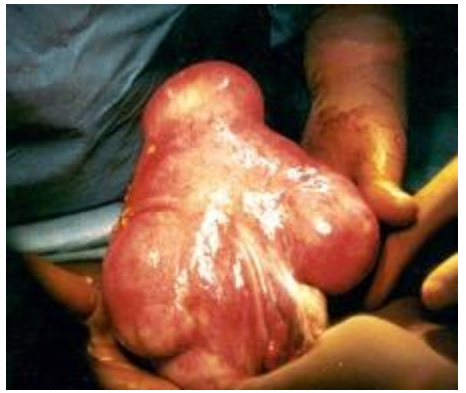
Intranasal DDAVP (Stimate®)

The panel suggests using either hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation)

VWF/FVIII concentrate

Antifibrinolytic therapy

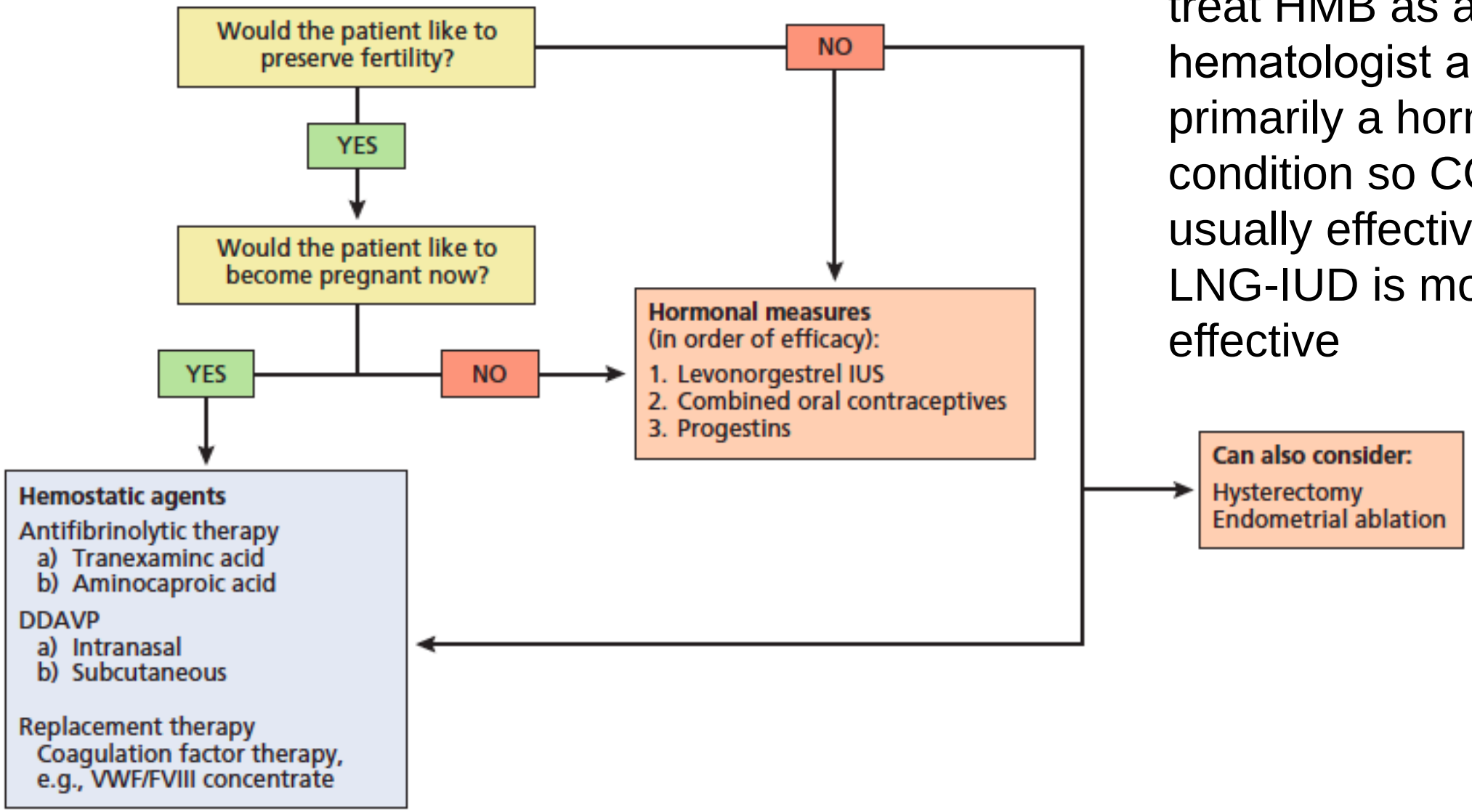
Hysterectomy



Brignardello-Petersen R et al : Blood Adv. 2021 Oct 21:Blood Advances. PMID: 34673921.

VWD-related Heavy Menses

- Try to avoid instinct to treat HMB as a hematologist as it's primarily a hormonal condition so COC usually effective- LNG-IUD is most effective



Suggested algorithm for management of bleeding disorder–related HMB. Adapted from James AH et al, *Am J Obstet Gynecol.* 2009;201:12 e1–12 e8.

Back to 15 y/o patient

- Patient undergoes DDAVP trial with robust response
- Parents opt for Intranasal DDAVP for daughter's heavy periods
- Follow-up PBAC score showed decrease from 320 to 60
- One year later, patient's pediatrician calls me and tells me that she is now pregnant
- Asks why did I not prescribe COC instead of IN DDAVP as she was sexually active then
  - A long silence ensued at my end of the phone call

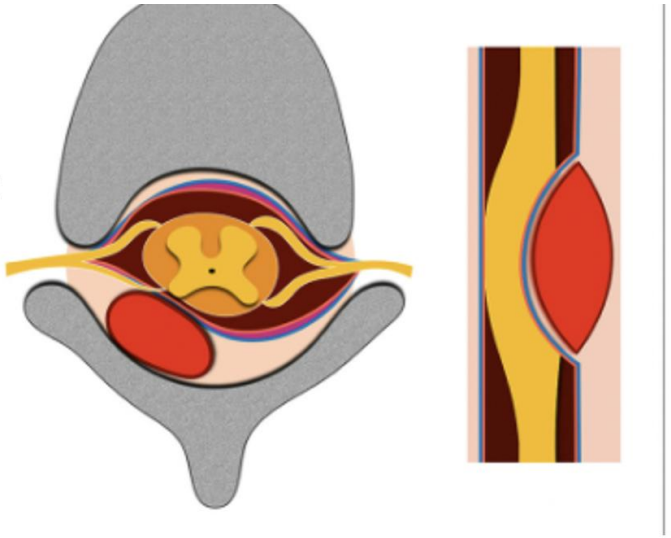
	Ristocetin cofactor (nl= 40% to 120%)	VWF antigen (nl = 50% to 150%)	Factor 8 level (nl = 50% to 150%)
Preintra-nasal DDAVP	20%	27%	52%
60 min postintra-venous DDAVP	103%	105%	185%
4 hr post	99%	100%	166%

N.B. She initially underwent 1 and 4 hr IV DDAVP trial with <30% decrease from the peak VWF level so ruling out Type 1C

Case continued- antepartum

- Patient age 16 now, chooses to keep pregnancy
- Patient very apprehensive about delivery and obstetrician asks for clearance for epidural
- Obstetrician also asks about prophylactic use of tranexamic acid

- Overall risk of epidural hematoma associated with neuraxial techniques in obstetric patients to be approximately 1:200,000
  - About 10 fold less then general population probably due to the protective hypercoagulable state of pregnancy
- 2017 Royal College of Obstetricians and Gynaecologists guidelines advise *"that neuraxial anesthesia be avoided unless VWF activity is more than 50% and the haemostatic defect has been corrected; this may be difficult to achieve in type 2 and central neuraxial anesthesia should not be given in cases of type 3"*



Pavord S. on behalf of the Royal College of Obstetricians and Gynaecologists. Management of Inherited Bleeding Disorders in Pregnancy. Green-top Guideline No. 71. BJOG 2017; 124:e263.

VWD guideline panel-In women with VWD for whom neuraxial anesthesia during labor is deemed suitable, the panel suggests targeting a VWF activity level of 0.50 to 1.50 IU/mL over targeting an activity level of > 1.50 IU/mL to allow neuraxial anesthesia

Case continued- regarding her pregnancy-

- **All the following statements are correct except:**

A. A VWF level > 50% in the third trimester would clear her for an epidural

B. The VWF levels can begin to fall 3 days post-partum placing the patient at risk of post-partum hemorrhage

C. Tranexamic acid can be prescribed prophylactically post-partum to reduce risk of hemorrhage

D. Patient should be advised to have an induction to reduce risk of PPH

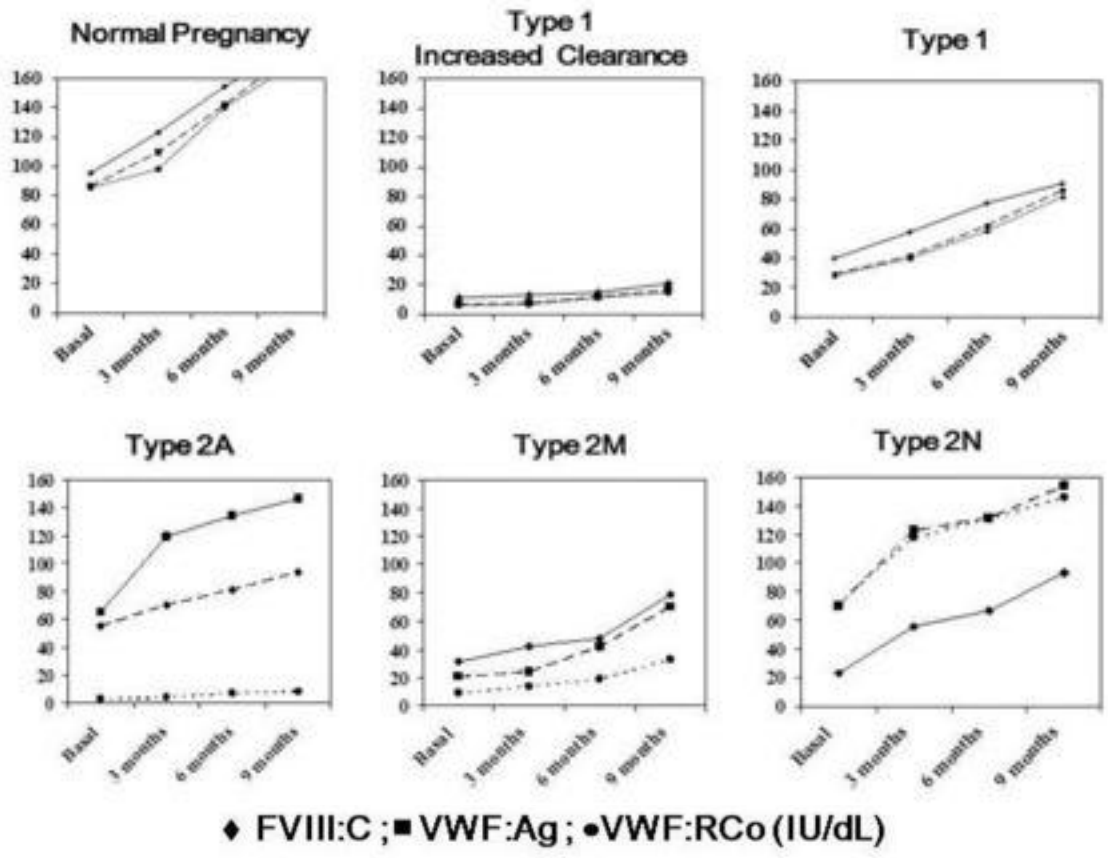
Pregnancy in VWD

- von Willebrand factor (VWF) and factor VIII (FVIII) levels increase in healthy pregnancy by 200-250%[1]
- VWF increases are much less pronounced (or absent) in pregnant women with VWD[2]
- Women with VWD have high rates of postpartum hemorrhage (PPH), even with treatment for VWD[3,4]
  - 5-40% prevalence of PPH compared to 2-10% prevalence in general population

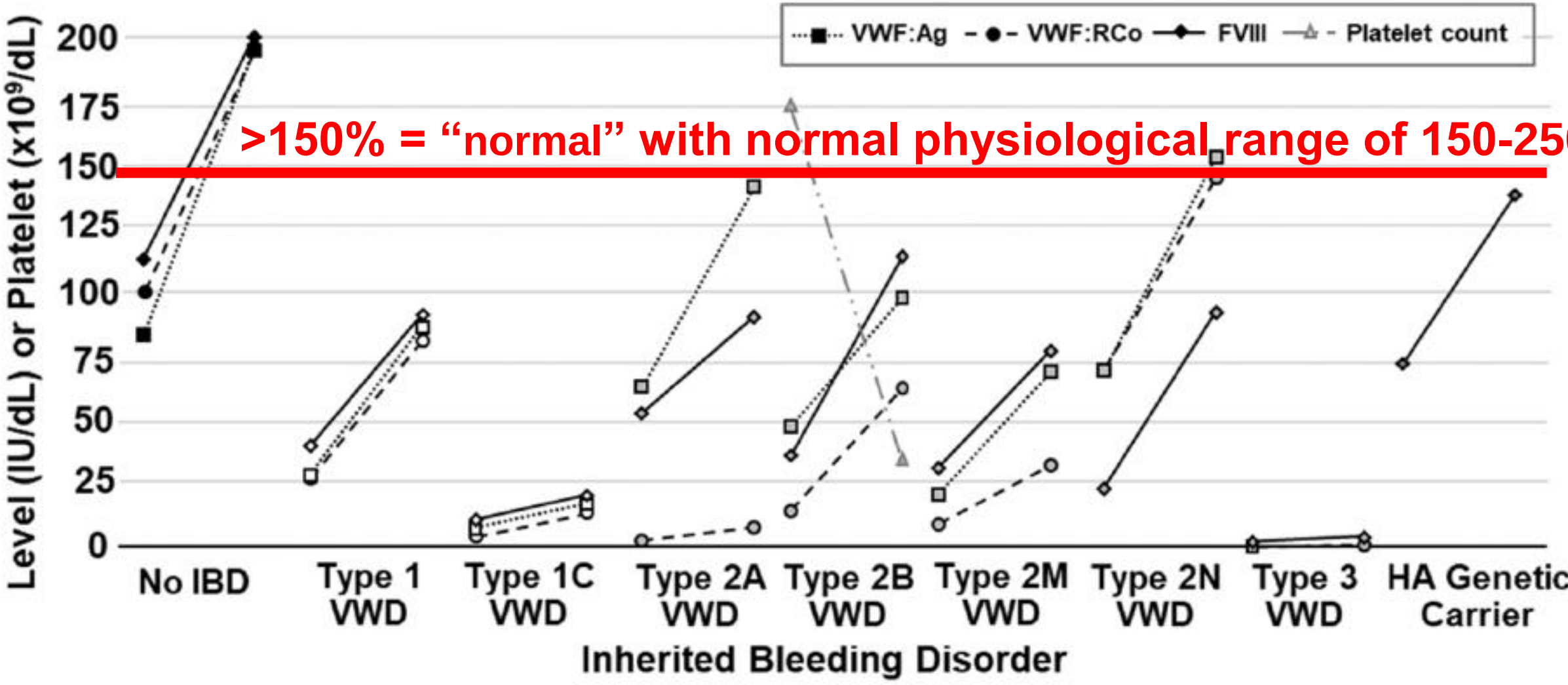
At minimum, sample VWF levels at 1st presentation of pregnancy and at 34-38 wks.; ideally 2 more times around 20 and 28 wks. to have data around times when complications can occur

In an analysis of U.S. insurance database, VWF levels were assessed in only 32% of women with VWD (n=2,238) in the 3rd tri with higher incidence of PPH in those whose plasma VWF levels were not reassessed (7.3 vs. 4.9%; p.0.023). *O'Brien SH et al JTH 2020 Mar;18(3):604-608*

VWF changes in pregnancy in normal patients and patients with VWD



[1] *Drury-Stewart et al. PLoS One. 2014 Nov 19;9(11):e112935;* [2]*Castaman G. Mediterr J Hematol Infect Dis. 2013; 5(1): e2013052;* [3]*James et al. Haemophilia. 2015 Jan;21(1):81-7;* [4]*Machin & Ragni. Blood Adv. 2020 Jul 28;4(14):3234-3238.*



1. How best to raise level in Type 1 VWD- DDAVP or VWF
2. ? Optimal target VWF level- >50% or > 100% or > 150%?
3. How long to maintain levels?
4. Role of tranexamic acid

DDAVP vs. VWF replacement at time of active labor in Type 1 VWD

- Historically, reluctance to use DDAVP peripartum was due to theoretical risk of inducing premature labor, maternal hypotension and neonatal hyponatremia
- But main reasons to avoid desmopressin are:
  1. Difficulty in precisely targeting levels
  2. Duration of effective DDAVP use (2-3 d) is much shorter than duration of bleeding because of tachyphylaxis
  3. Risk of hyponatremia being high due to fluids and oxytocic medications used
     - average fluid use 1500 ml/24 hrs i.e 50 oz. exceeding usual 32 oz. restriction

If, at time of active labor, DDAVP is used, it should be limited to a small number of doses:

1. With strict fluid restriction which is 32 oz only!!...that only about 1 liter……NOT realistic post delivery where they push fluids!!!!!
2. Only be given to patients with an established response

Johnsen JM, MacKinnon HJ. JTH. 2022;20(7):1568

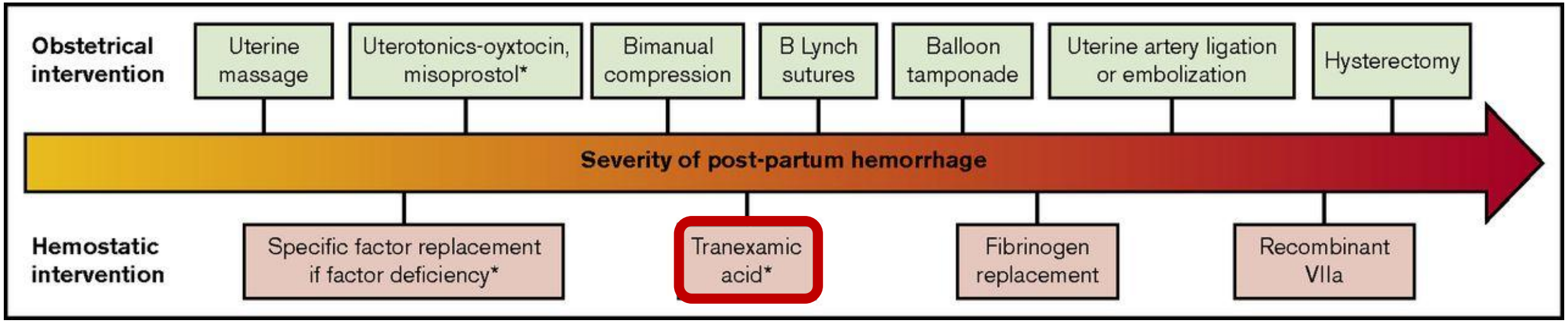
PPH prevention in VWD and Hemophilia carriers

- At time of active labor, we need to be more aggressive in terms of hemostatic therapy-
- Accruing data is suggesting we are undertreating many IBD women at time of active labor-
  - 2015 Netherlands study – review of 185 deliveries in 154 women with VWD or hemophilia carriership over a 9-year period
    - 1/3 primary PPH (500 mL) and 1/3 severe PPH (≥1000 mL) within 24 h post-partum
      - Inverse relationship between the incidence of PPH and third trimester factor levels
  - 2015 US multicenter study – 32 women with and 40 without VWD; 15/32 with VWD were treated
    - Mean estimated blood loss at delivery for treated women (615 mL) was significantly greater than for other women (448 mL) ($p < 0.05$)
  - 2020 Systematic review by Punt et al- found that the majority of articles followed a cut-off VWF level of 50% for delivery, with 34% of women experiencing bleeding complications.
  - 2021 VWD guideline expert panel systematic review of bleeding outcomes from 144 of their own pregnant VWD patients. Compared to patients with VWF levels >150%, patients with levels of 50 to 150 IU/dl were more likely to have:
    - major bleeding (2.7% vs. 0%)
    - serious adverse events in the mother (2.7% vs. 0%)
    - PPH (17% vs. 5.9%)
    - receive transfusion (10% vs. 0%).

"It is our practice to target VWF:Act 100-150%" for delivery
- Johnsen JM J Thromb Haemost. 2022;20:1568–1575

Stoof SC, et al. Haemophilia 2015; 21: 505–512.
James AH, et al. Haemophilia 2015; 21: 81–87.
Punt MC et al Blood Rev. 2020;39:100633.
Connell NT Blood Adv. 2021 Jan 12;5(1):301-325

Post-partum hemorrhage and the role of Tranexamic acid



Kouides PA Blood Adv 2017;1:699-702

Guidelines on tranexamic acid use post partum in VWD

	2017 Royal College of Ob Gyn Pa*vord S et al BJOG 2017*	**2018 Canadian Hemophilia Society (reaffirmed from 2005)-***Demers C et al J Obstet Gynaecol Can 2018;40(2):e91–e103*	**2021 ASH/ISTH/NHF/WFH guidelines-** *Connell NT Blood Adv. 2021 Jan 12;5(1):301-32*
Prophy-lactic use of Txa?	**Yes, qualified**	**No**	**Yes**
	Women with VWD should be considered for tranexamic acid for the postpartum period. *A standard dose is 1 g three to four times a day for 7–14 days. In some cases, prolonged use for 2–3 weeks or more may be necessary.*	*Should late postpartum hemorrhage occur, tranexamic acid and oral contraceptives are first-line therapy for its management.* *The risk of thrombosis might be a concern if antifibrinolytic agents are used postpartum, but the risk is probably reasonable in women without other risk factors.*	*The guideline 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) (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯)*

Back to our case- Her grandfather presents to the ER with substernal chest pain and shortness of breath. His EKG is notable for ST wave depressions. His vital signs and troponins are normal. His last known VWF testing from 6 years ago, prior to a colonoscopy, shows VWF:Ag = 0.46 IU/mL, VWF:RCo = 0.39 IU/mL, and FVIII

- **After discussing the case with you, the interventional cardiologist performs percutaneous coronary intervention which demonstrates 80% left anterior descending artery stenosis. What is the best next step?**

A. Bare metal stent and aspirin

B. Bare metal stent, aspirin and clopidogrel

C. Drug-eluting stent and aspirin

D. Drug-eluting stent, aspirin, and clopidogrel

E. B or D

F. A or C

VWD and cardiovascular disease

- In patients requiring percutaneous coronary intervention (PCI) and stenting, interventions that limit the duration of dual antiplatelet therapy (DAPT) should be considered.
- In general, bare metal stents (BMS) have been favored over drug-eluting stents (DES) in order to limit the duration of DAPT to one month
- However, more recent data suggest that newer-generation DES with bioresorbable polymers may allow one month of DAPT which was the approach recently reported in a case series of hemophilia patients undergoing PCI
- The multidisciplinary decision-making process should also factor:
  - individual coronary anatomy, risks of restenosis,
  - bleeding propensity like BAT score and additional bleeding risks like renal or hepatic disease, alcohol use, fall risk etc.

Per 2021 VWD management guidelines-in patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel suggests giving the necessary antiplatelet or anticoagulant therapy, and reassessing the bleeding risk throughout the course of treatment. This should be done in conjunction with a multidisciplinary team and discussion with the patient on the risks and benefits of using antithrombotic medications.

The same patient returns for follow-up 6 years later. He has been in good health and follows his cardiologist since the time of his stent placement. He has not had any recent bleeding symptoms, including when he was previously on DAPT. His primary care physician recommends a 10-year screening colonoscopy and requests your guidance. You repeat his VWF testing, which now reveals VWF:Ag = 65 IU/mL, VWF:RCo = 58 IU/mL, and FVIII:C = 75 IU/mL. Which of the following is correct?

A. Aging has been associated with normalization of VWF levels in most VWD patients

B. The diagnosis of VWD should be removed in patients who no longer fulfill the diagnostic laboratory criteria

C. Bleeding does not persist in patients with normalized VWF levels

D. A single dose of DDAVP should be given prior to colonoscopy

E. Fecal occult blood testing should be done in lieu of colonoscopy

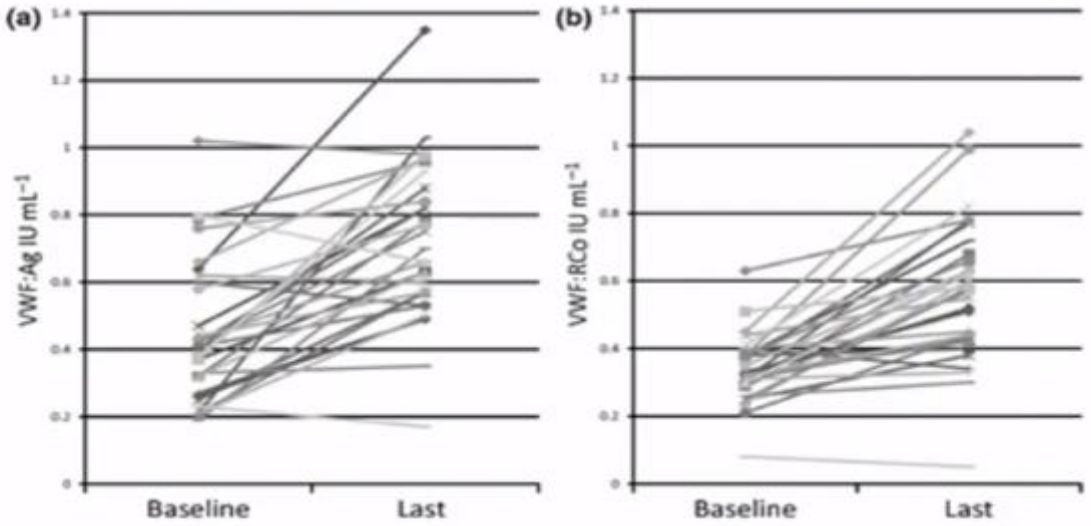
F. None of the above

VWF and ageing

- **Dutch study[1] - 71 patients**
  - VWF and FVIII levels increase with age in type 1 patients, not in Type 2.
  - In elderly type 1 patients, a decade age increase was associated with:
    - 3.5 U dL (95% CI, 0.6 to 7.6) VWF:Ag increase
    - 7.1 U dL 95% CI, 0.7 to 13.4) FVIII:C increase

- **Rochester HTC study[3]- 126 patients**
  - Approximately 30% of patients with Type 1 VWD have normalization of VWF levels over 5-20 years study.

Canadian study[2] - 31 patients



Plasma VWF levels increase with age in some patients with type 1 VWD
- 31 VWD– followed for > 5 years (mean 11 years)
- 18/31 patients had VWF levels increased into normal range

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 (conditional recommendation based on very low ertainty in the evidence of effects

1. Sanders Y *Journal of Thrombosis & Hemostasis* (2014).12 366—375
2. Rydz N *Haemophilia* (2015) 1—6
3. Abou-Ismail Am J Hematol. 2018;93:232–237.

A 28 year old female has Type 3 VWD. Both older siblings also are affected. The oldest expired from HIV due to transmission from cryoprecipitate while this patient and her remaining sibling are both HIV negative but HCV positive. Her FibroSure score is consistent with cirrhosis and her platelet count is in the 70,000/ml range. Her menstrual periods are heavy. She intermittently has severe epistaxis lasting 20-30 minutes. She is anemic in the 10 g/dl hemoglobin range with a ferritin of only 2 ng/ml. She also has intermittent right elbow pain and swelling due to chronic arthropathy

This patient would benefit from all the following measures except:

A. VWF/FVIII concentrate prophylaxis TIW

B. Periodic ultrasound imaging to screen for hepatocellular carcinoma

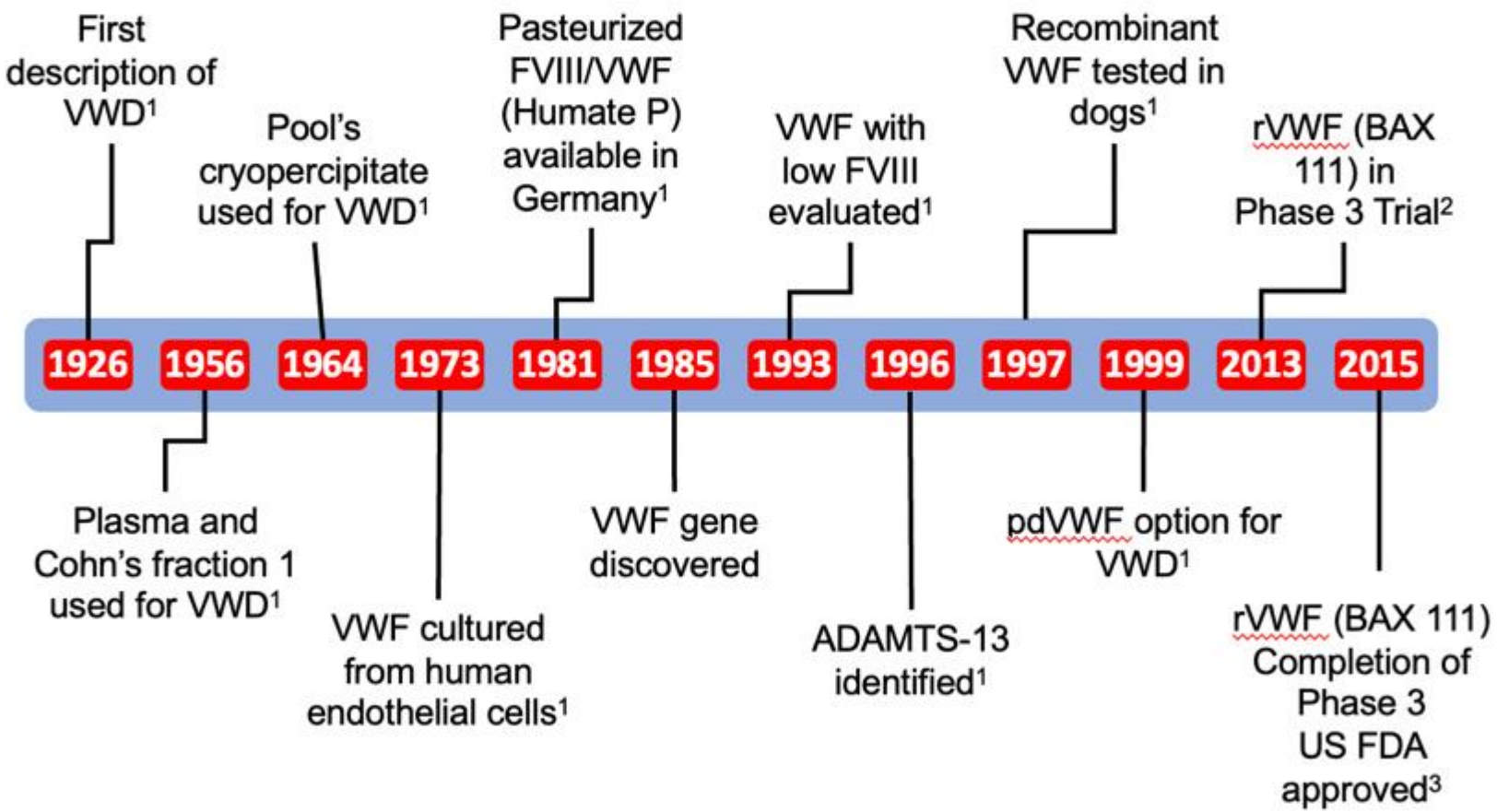
C. Digital capsule endoscopy

D. Total elbow arthroplasty

E. MIRENA IUD

Evolution of VWF replacement therapy

Beyond DDAVP: Milestones in VWF replacement therapy



1. Federici AB, et al. *Haemophilia*. 2006; 12:563-572; 2. Baxter. News Release; October 13, 2011. Available at: http://www.baxter.com/news-media/newsroom/press-releases/2011/10_14_11_bax111_rvwf.page; 3. FDA Press Release, December 8, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm476065.htm.

“Replacing VWF”

	Plasma-Derived VWF-Containing FVIII Concentrates				Recombinant VWF
	Humate	Alphanate	Wilate	Wilfactin	Vonvendi
Purification method	Multiple precipitation	Precipitation/ heparin ligand CT	Precipitation/ion exchange and size-exclusion CT	Ion exchange + affinity chromatography	Chinese hamster ovary cell line
Viral inactivation	Pasteurization	Solvent detergent, dry heat	Solvent detergent, dry heat	Solvent detergent, dry heat/35-nm filtration	Not required
VWF:RCo/VWF:Ag	0.91	0.43	0.9-1.0	0.95	1.16
VWF:RCo/FVIII:C ratio	2.88	0.82	1.0	50	No FVIII
Ultra-large multimers	Absent	Absent	Absent	Absent	Present
FDA approved	Yes	Yes	Yes	No	Yes

Singal M: Drugs of Today 2016;52(12)-653-664

After 6 months of therapy, the patient reports significant improvement in her bleeding symptoms, joint symptoms, and quality of life. She would like her 42 year-old brother, who also has type 3 VWD, to consider it. She recalls that he has had frequent bleeding and two hospitalizations for gastrointestinal haemorrhages in association with angiodysplasia

- Sister tells brother she is on prophylaxis and that he should go on it but he is reluctant as he has always used factor just on demand. Which is the following is true?

A. Prophylaxis definitely reduces recurrence of VWD-related GI bleeding

B. RCT data in support of prophylaxis in VWD is scant

C. Recombinant VWF is preferred agent for prophylaxis compared with plasma derived products like Humate P or Wilate

D. Concurrent use of tranexamic acid improves prophylaxis

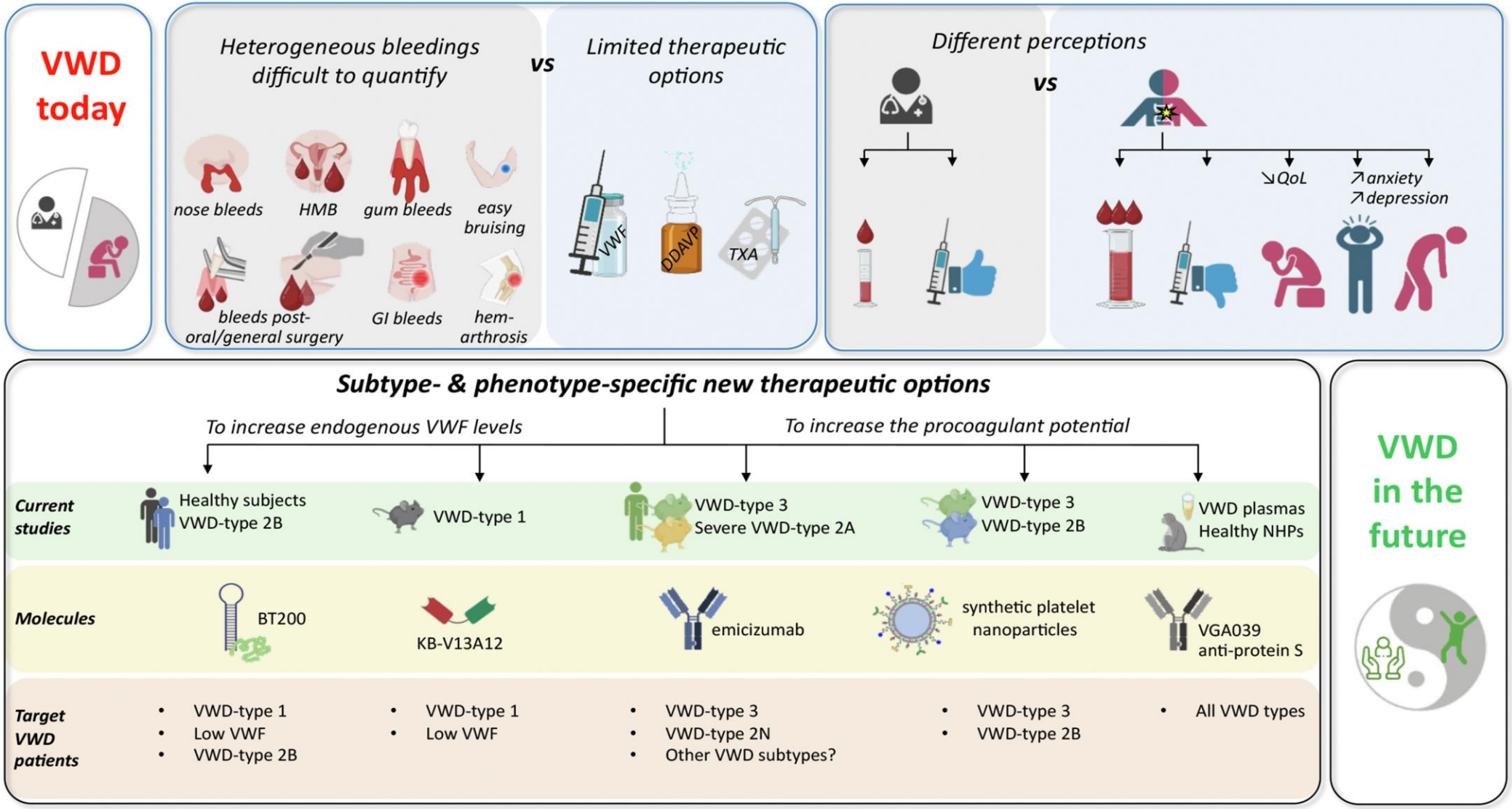
In patients with VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Chronic GI bleeding

- Very challenging situation!
  - Look hard for AVMs given association in Type 2,3 as loss of HMW multimers leads to loss of inhibition of angiogenesis
  - Tranexamic acid ATC
  - Prophylaxis by VWF replacement
  - Novel approaches-
    - Local injection of avastin
    - Lenalidomide
    - Losartan

Future is bright for VWD/WBD patients!!

- Greater awareness in screening women and girls that should improve QOL
- Guidelines offer a road map for present management and future research
- We are at the cusp of several exciting new therapeutics beyond studying yet another replacement product!



From Caterina Casari- google her name and *Illustrated State-of-the-Art Capsules of the ISTH 2023 Congress*