Understanding von Willebrand disease in the age of guidelines- A Fellow Primer

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Disclosures

- Joint effort of 4 major organizations- American Society of Hematology/ISTH/NHF/WFH with a new standard for patient involvement in guideline development with each panel comprised of a quarter of VWD patients
- Last U.S based VWD guideline effort in 2007; different methodology employed this time-Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

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

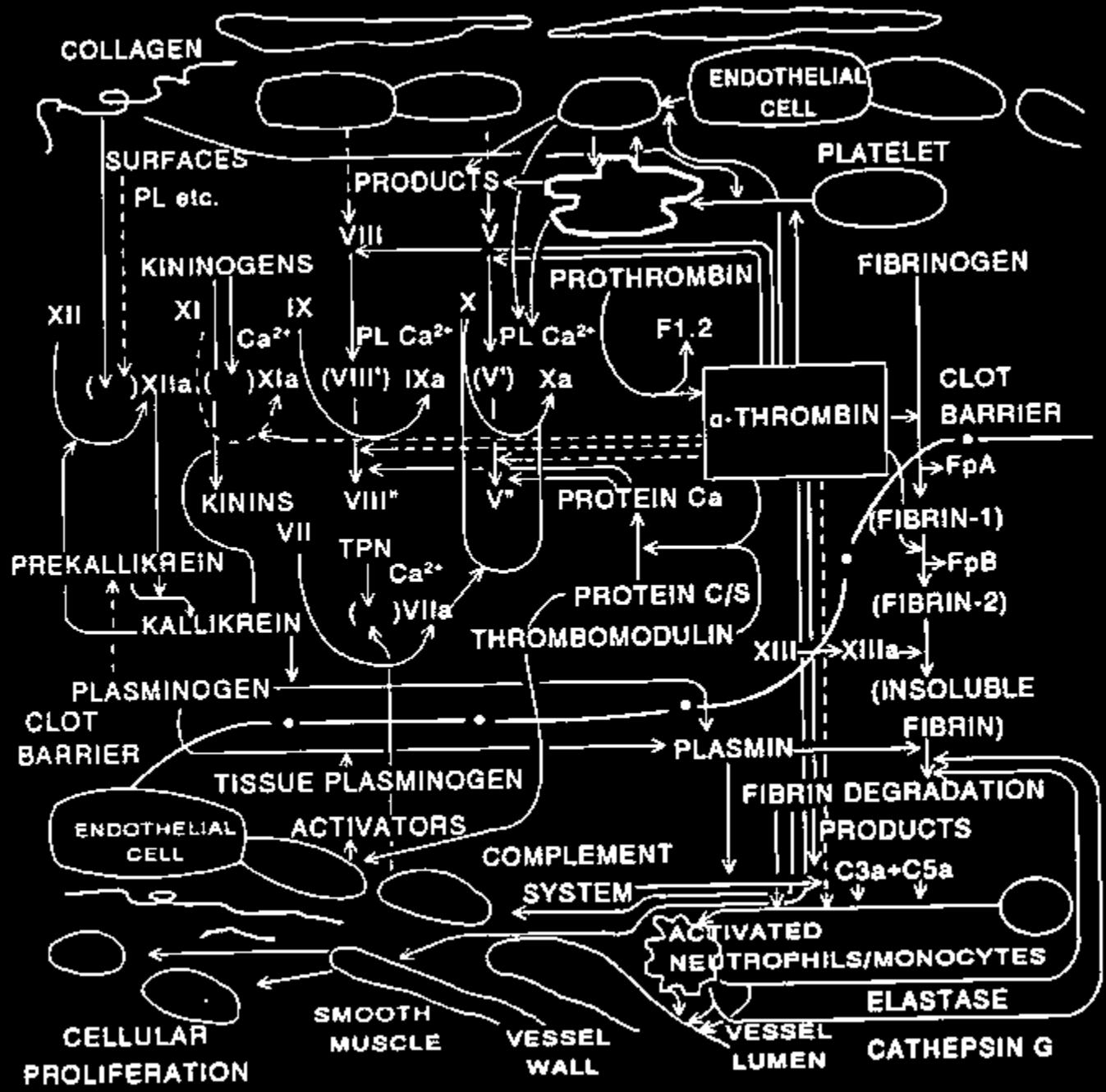
Blood Advances 5(1) 280; open access 1/12/21

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

Outline

1. The pathophysiology of hemostasis
2. History and laboratory approach to the bleeding patient
   a) The bleeding assessment tool
   b) Step-wise approach of lab testing
3. Von Willebrand disease (VWD), old and new concepts
4. New issues in VWD testing
   a) New and improved activity assays
   b) New subtype of VWD
   c) Impact of send out testing
   d) Impact of ageing
5. New management issues in VWD


COLLAGEN
ENDOTHELIAL CELL
SURFACES
PL etc.
PRODUCTS
PLATELET
VIII
V
KININOGENS
PROTHROMBIN
FIBRINOGEN
XII
XI
IX
X
Ca2+
PL Ca2+
PL Ca2+
F1.2
(V')
Xa
α-THROMBIN
CLOT BARRIER
FpA
KININS
VIII"
V"
PROTEIN Ca
(FIBRIN-1)
FpB
PREKALLIKREIN
VII
TPN
Ca2+
PROTEIN C/S
(FIBRIN-2)
KALLIKREIN
THROMBOMODULIN
XIII
XIIIa
PLASMINOGEN
(INSOLUBLE FIBRIN)
CLOT BARRIER
PLASMIN
TISSUE PLASMINOGEN
FIBRIN DEGRADATION PRODUCTS
ENDOTHELIAL CELL
ACTIVATORS
COMPLEMENT SYSTEM
C3a+C5a
ACTIVATED NEUTROPHILS/MONOCYTES
ELASTASE
SMOOTH MUSCLE
VESSEL WALL
VESSEL LUMEN
CATHEPSIN G
CELLULAR PROLIFERATION

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

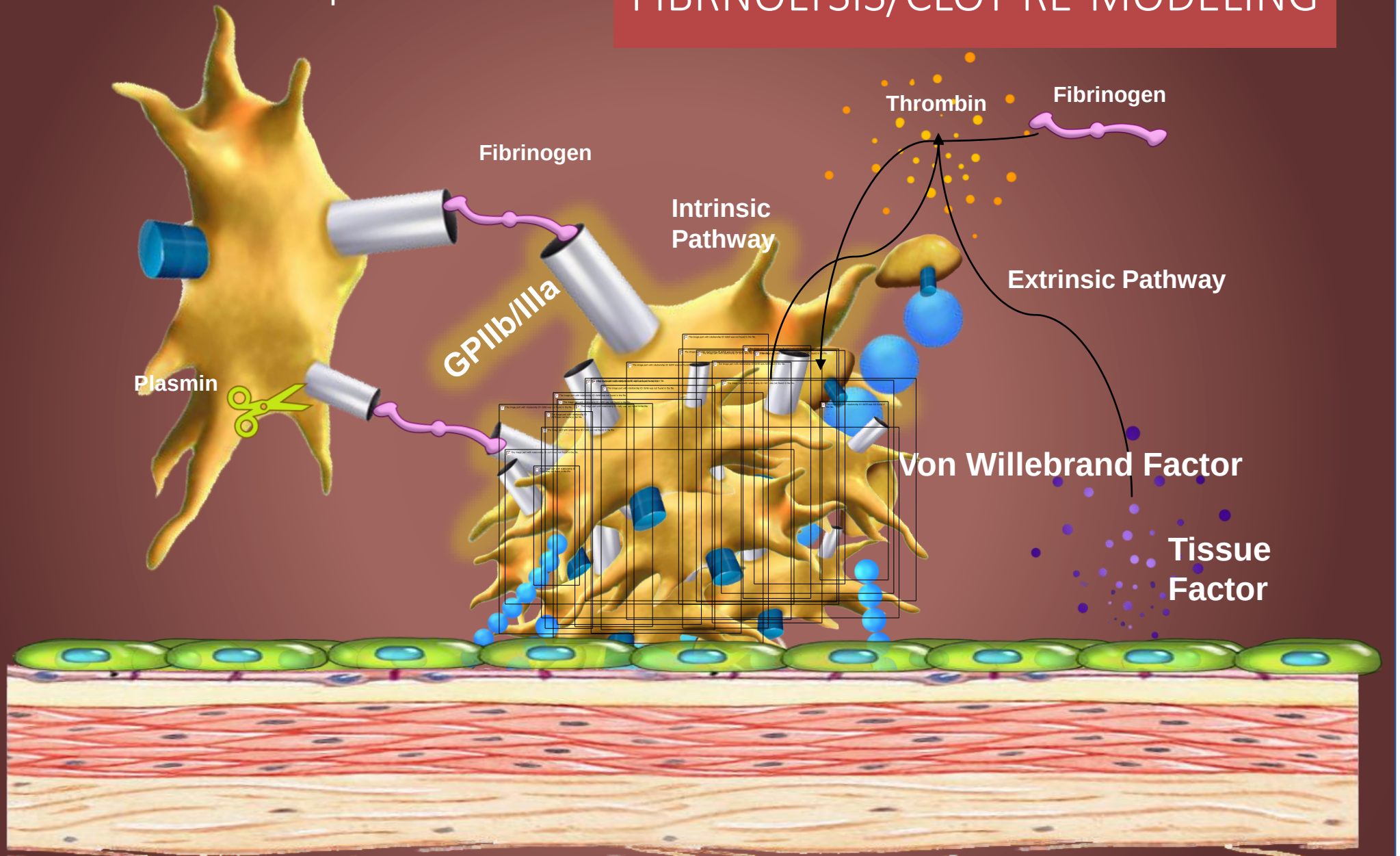
- Step 2: Formation of fibrin clot over platelets
  - platelets + cofactors V & VIII (IX) + the remaining coagulation factors

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)

In the beginning- the steady state- we do not bleed in a vacuum- MUST BE VESSEL INJURY- to lead to first step of hemostasis

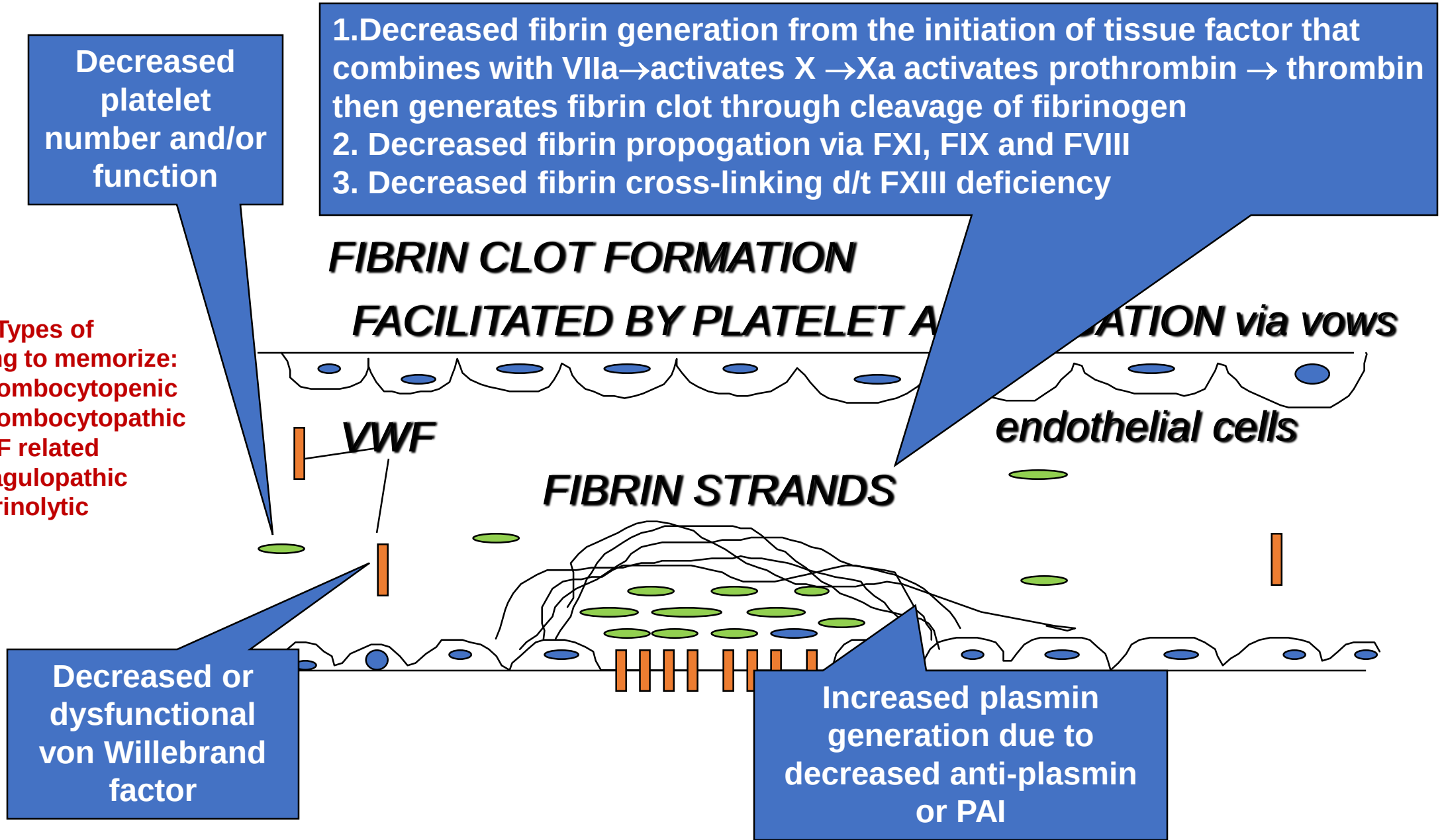
TERTIARY HEMOSTASIS- FIBRNOLYSIS/CLOT RE-MODELING



Where/why someone bleeds

Just 5 Types of bleeding to memorize:

- Thrombocytopenic
- Thrombocytopathic
- VWF related
- Coagulopathic
- Fibrinolytic



My patient

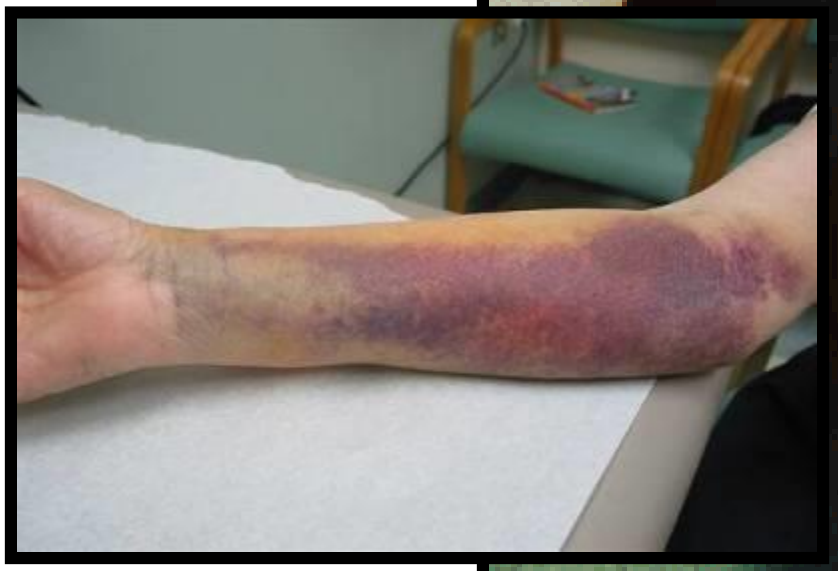
- A 14 year old female referred to our Hemophilia Treatment Center by her mother, a nurse who wanted her tested for VWD in setting of prolonged excessive bleeding since menarche a year ago changing her sanitary pad every 90 minutes.

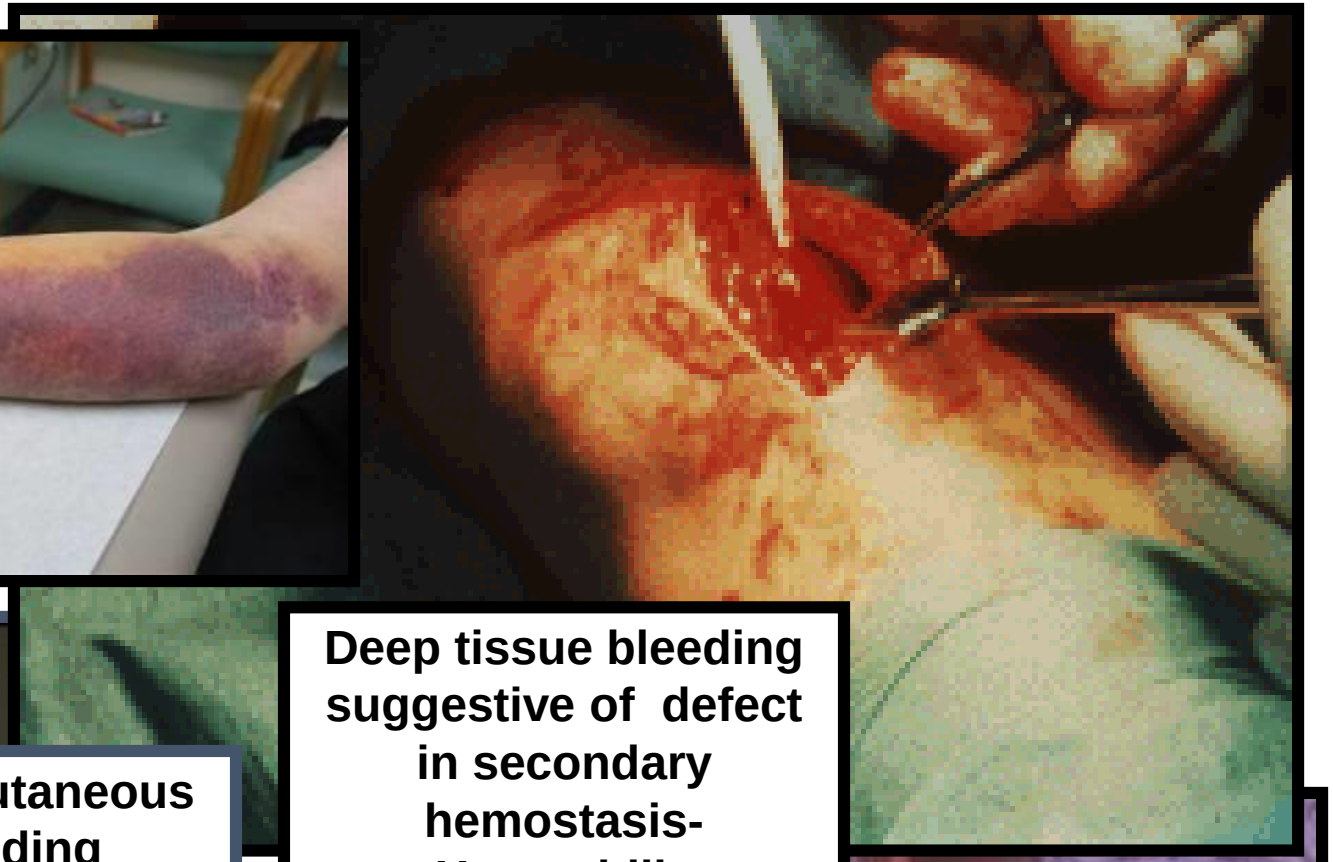
- Initially evaluated by her pediatrician who advised combined oral contraceptive.

- Mother was very uncomfortable with her daughter “going on the pill” and researched further causes/treatments of heavy menses and came across our HTC website raising awareness for VWD testing in the setting of heavy menses.

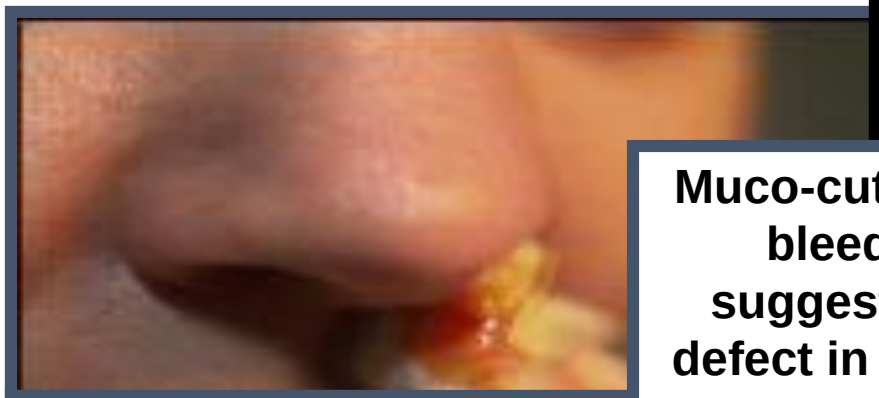
- Her past medical history included “easy” bruising throughout childhood, prolonged bleeding from cuts and an emergency department visit for epistaxis requiring packing.

- **How would you characterize her bleeding?**

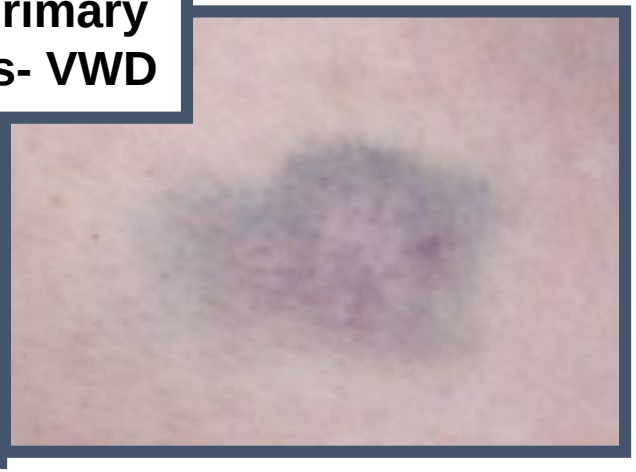


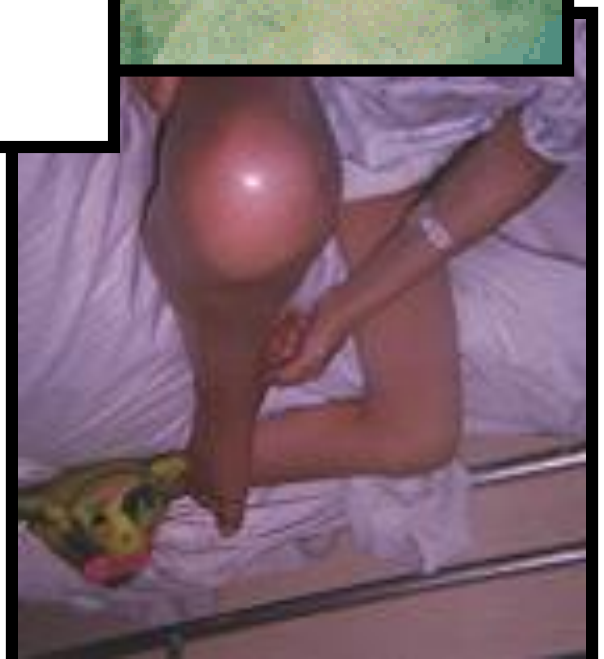


Deep tissue bleeding suggestive of defect in secondary hemostasis- Hemophilia



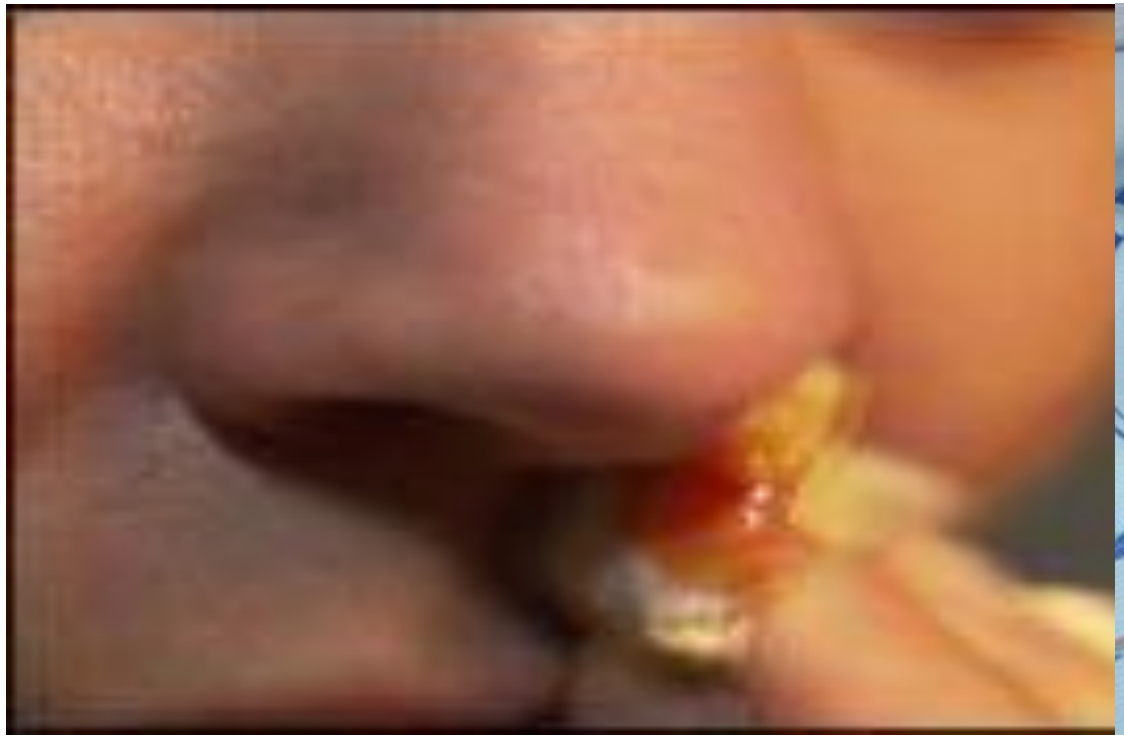
Muco-cutaneous bleeding suggestive of defect in primary hemostasis- VWD

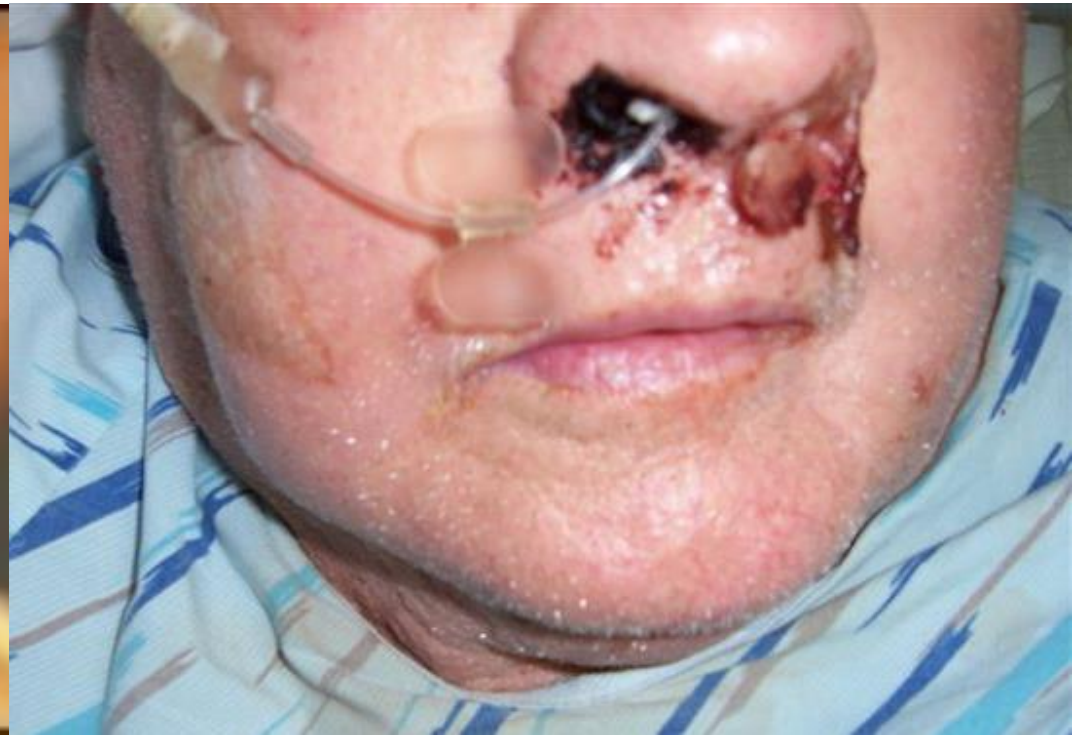




Improving the significance/specificity of bleeding symptoms

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





Bleeding assessment in VWD-ISTH multi-center study

- Previously, criteria defining a significant bleeding history have been suggested but never validated as to their sensitivity and specificity for the diagnosis of VWD

- To avoid selection bias, 42 obligatory carriers (OC) of type 1 VWD were identified from a panel of 42 families with type 1 VWD enrolled by 10 expert centers
  - she/he had at least an affected offspring (younger affected) and at least another affected first degree relative (either father/mother or brother/sister, older affected).

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

Evolution of the ISTH Bleeding Assessment Tool (BAT)

https://bleedingscore.certe.nl/

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

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

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

Patient 1 continued

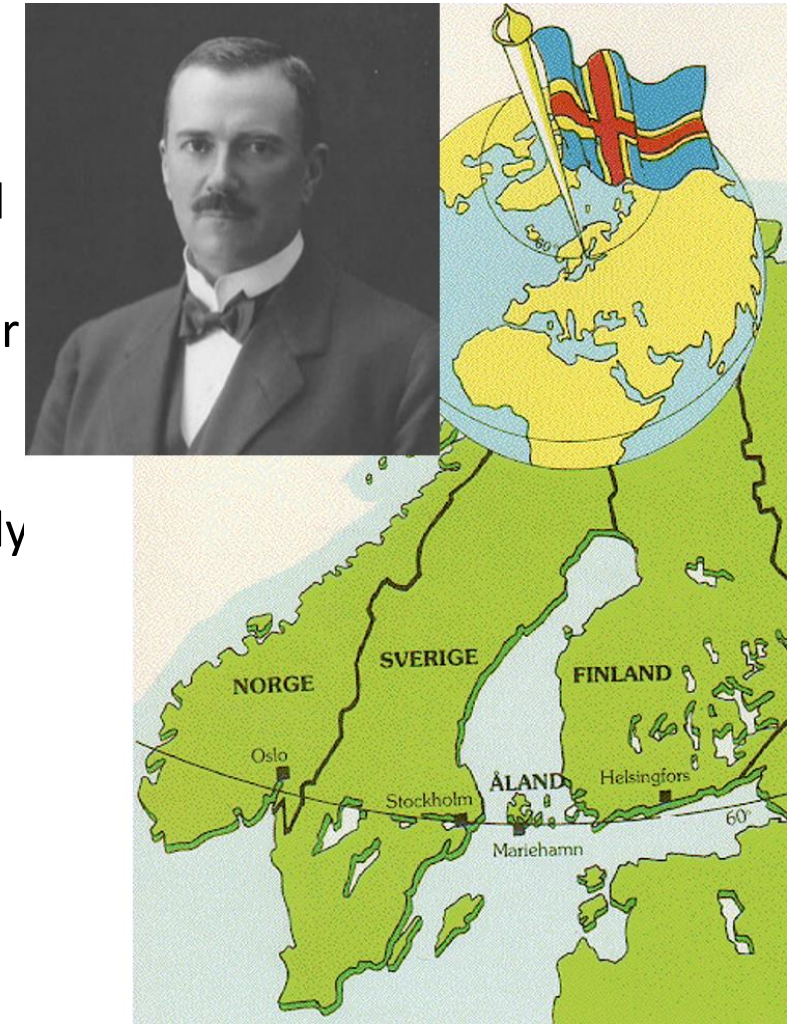
- BAT score-**8 points** (normal 0-5 in women): 1 pt. easy bruising + 1 pt. prolonged bleeding from cuts + 3 points epistaxis requiring packing + 3 points heavy menses since menarche

- 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).

Women and VWD- “The Silent majority”

- Although women and men are equally likely to be affected, women with VWD are more likely to suffer from bleeding symptoms due to the high prevalence of heavy menstrual bleeding (HMB) and risk of PPH known since the original description:
  - in 1924, Von Willebrand was consulted about a 5-year-old girl named Hjördis Sundblom with bleeding from the nose, lips, gums and skin.
  - Hjördis was the ninth of 11 children, and six of her siblings had similar bleeding. Three of her sisters had died due to the condition.
  - majority of affected kindred were females-
    - 23 (16 women and 7 men) of 66 members of her extended family
    - Hjördis died eight years later Hjördis died after her 4th period
- Subsequently, studies of women with VWD show that > 80% experience HMB.
- Conversely, studies of women with HMB show that between 5-24% have VWD
- Management is challenging and the diagnosis is delayed in many women, with an average of 16 years from onset of symptoms to diagnosis



Kirtava A: Haemophilia. 2004 Mar;10(2):158-61

The Muco-cutaneous symptoms of von Willebrand disease

Symptom	Frequency
Epistaxis	50%
Surgical-related	50%
Dental-related	50%
Easy bruising	80%
Menorrhagia	80%
Post-partum hemorrhage	30%

Childhood

Adolescence and on

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

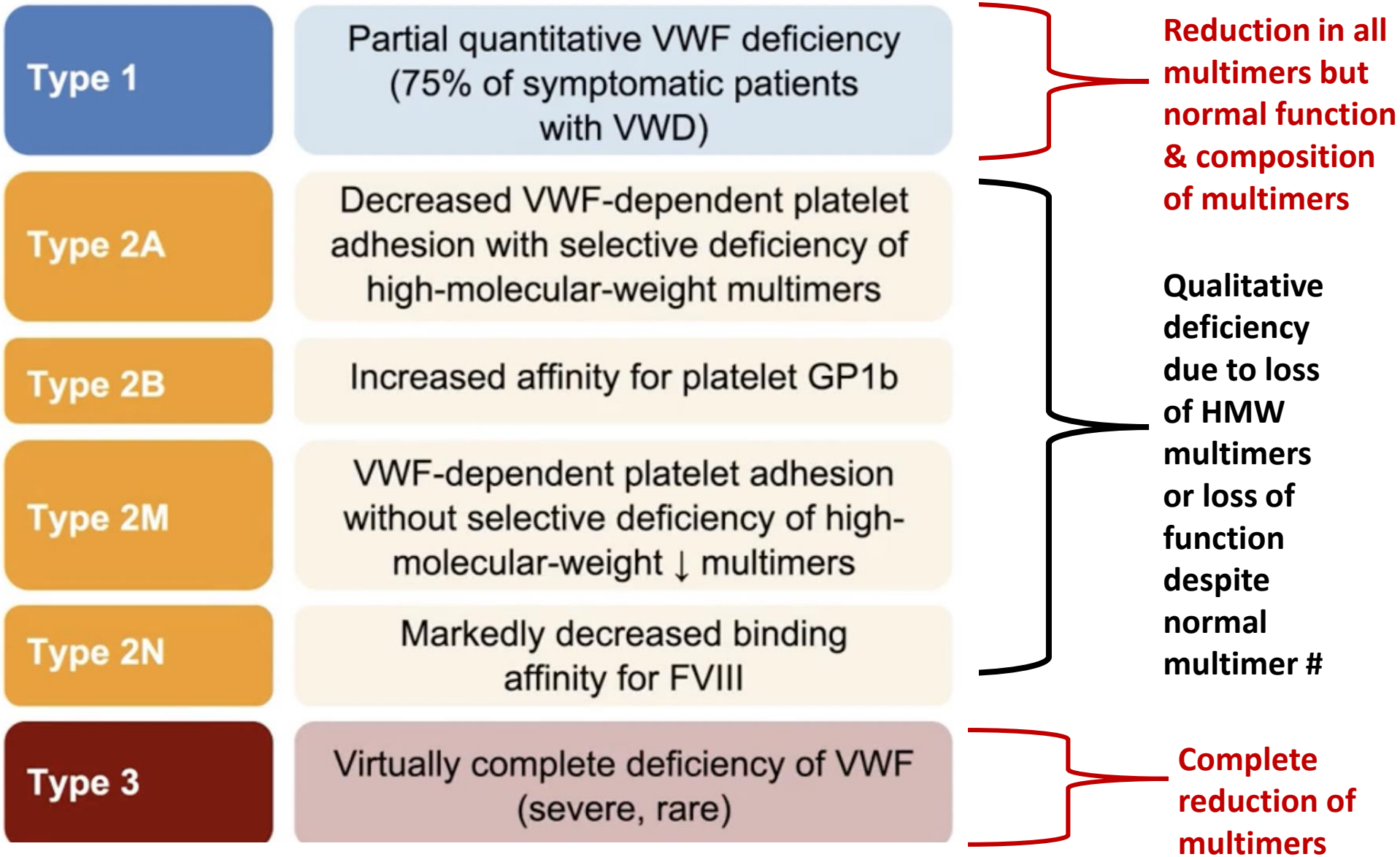
- Iron deficiency anemia
- Increased rate of surgical interventions: D&C, hysterectomy

How common is Patient 1's diagnosis?

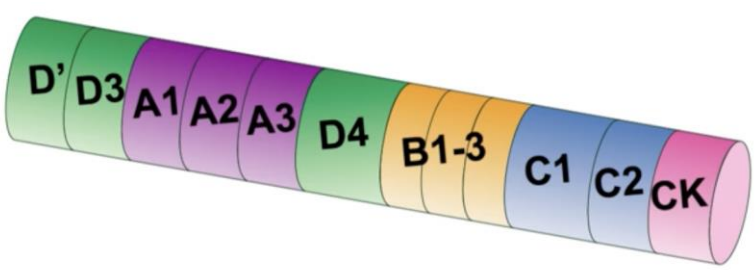
- Not one prevalence size fits all-
  - 1/100 in terms of laboratory diagnosis
    - Related to fact 40% of people are blood type O and can have 25% lower VWF levels
  - 1/1000 in terms of symptomatic prevalence
    - If using Bleeding assessment tool
- Know inheritance pattern-
  - What to tell people about risk of transmission in family vis a vie Type
- Is genetic testing always revealing and necessary?
  - Likelihood of mutation is inversely proportional to the VWF level
- Know how to explain the cause-
  - Quantitative or qualitative deficiency of VWF

How do we classify patient 1?

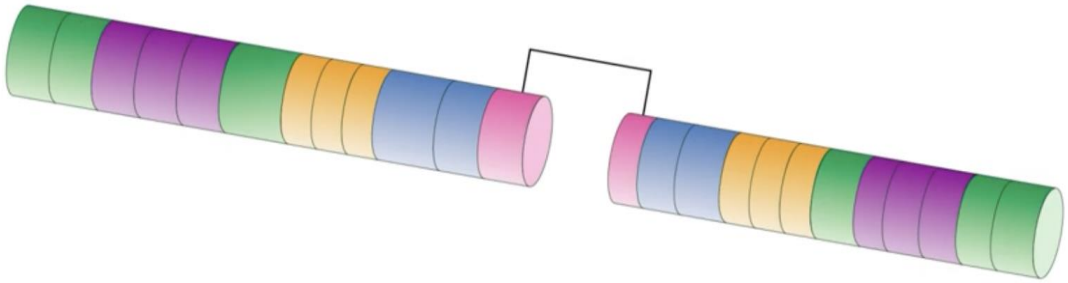
Absolute or functional deficiency i.e. Quantitative or Qualitative i.e.. Hypo/aprotienemia (Type1/3) or Dysproteinemia (Type 2)



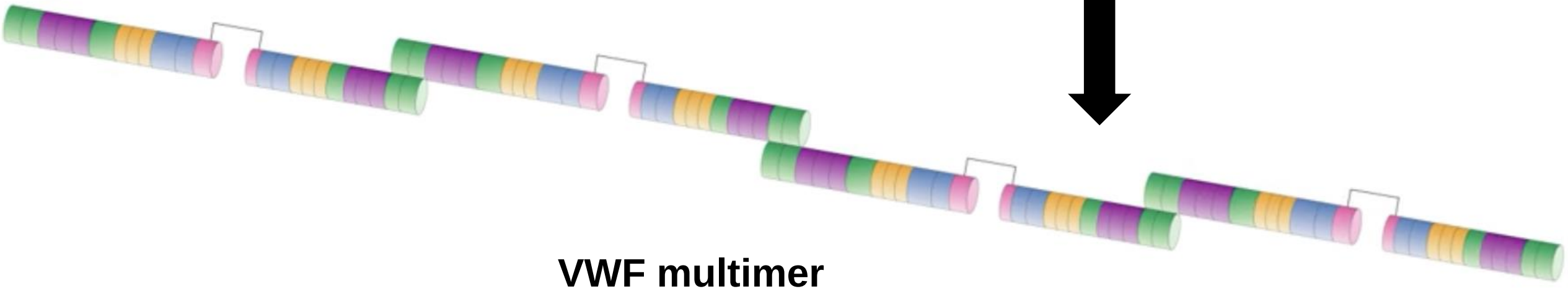
Within the Endothelial Cell (and megakaryocyte)



VWF monomer



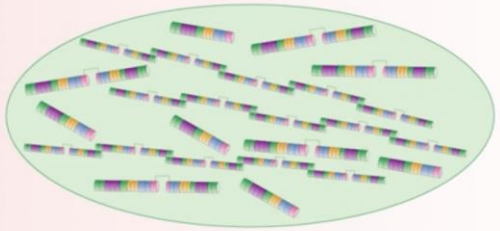
VWF dimer



VWF multimer

the longer the string of monomers the more adhesive to platelets and collagen

Endothelial cell



Weibel-Palade body

Endothelial cell

ADAMTS-13 cleaves unusually large multimers of VWF

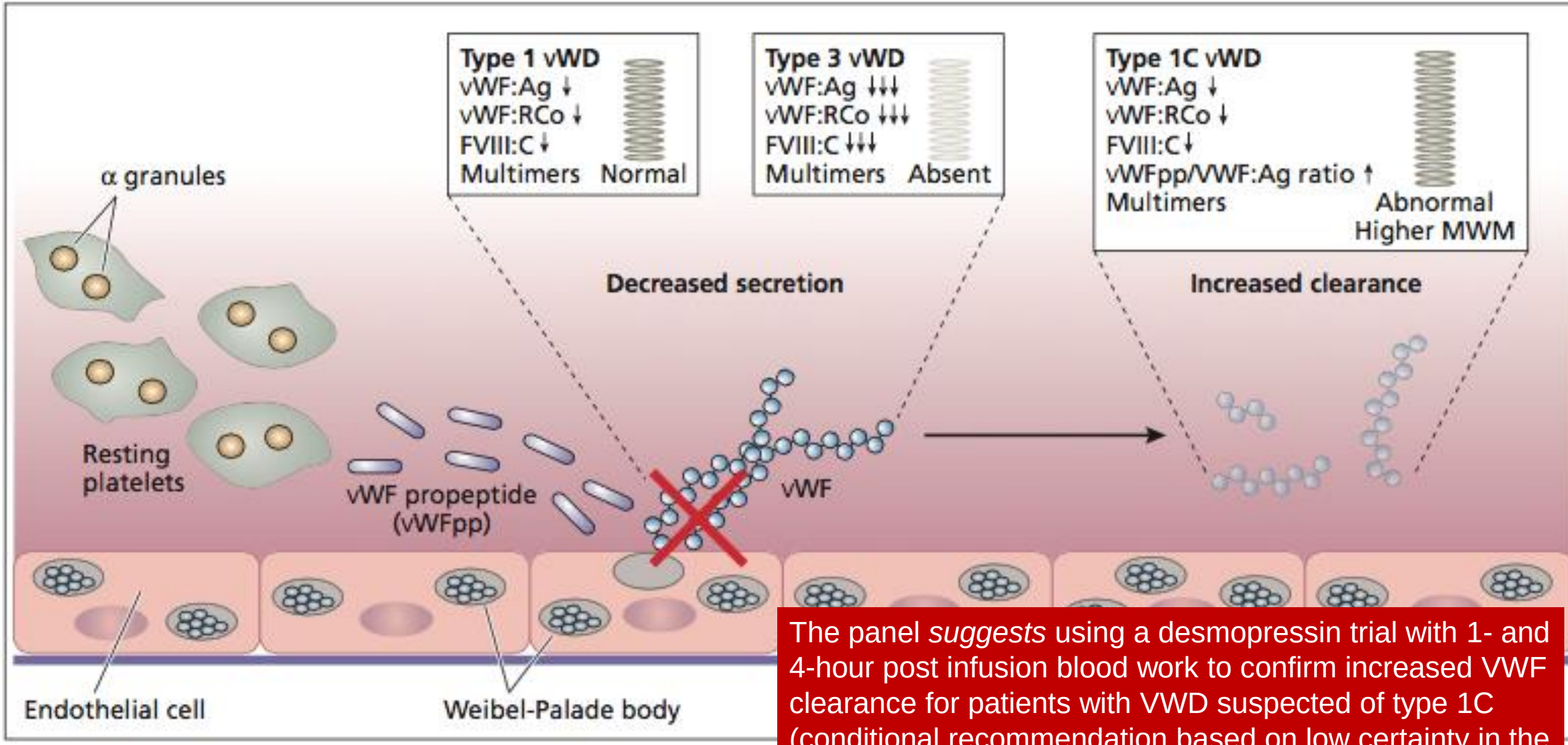
ADAMTS-13

ADAMTS-13

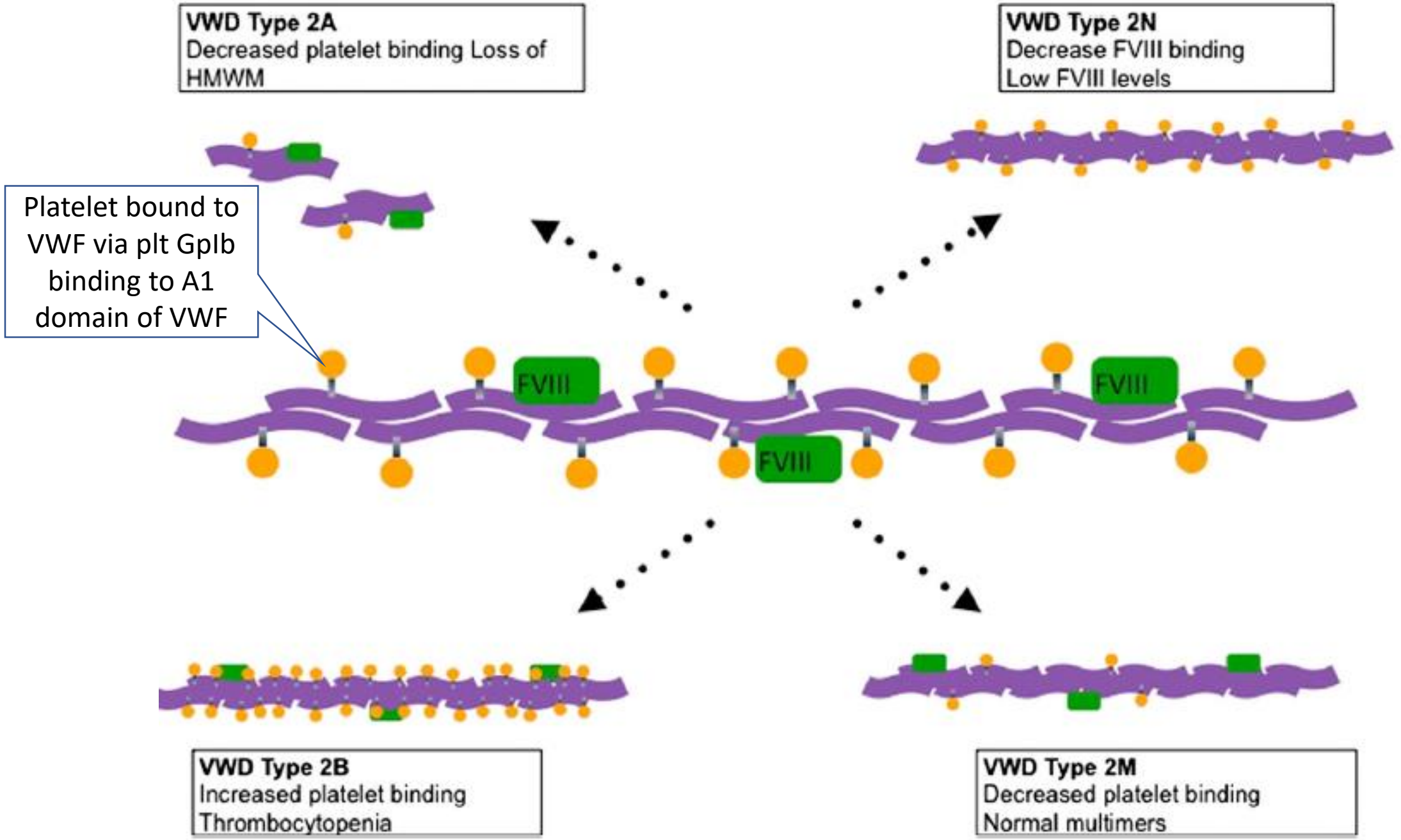
Endothelial cell

Endothelial cell

Defect in Type 1 VWD – synthesis, secretion and clearance



The panel *suggests* using a desmopressin trial with 1- and 4-hour post infusion blood work to confirm increased VWF clearance for patients with VWD suspected of type 1C (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies ⊕⊕◯◯).



Slide courtesy of Dr. Amro Elshoury Roswell Park

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 < 0.6)

2A

- **A** = **a**bsent High and intermediate weight multimer leading to decreased platelets binding
- Abnormal multimers

2B

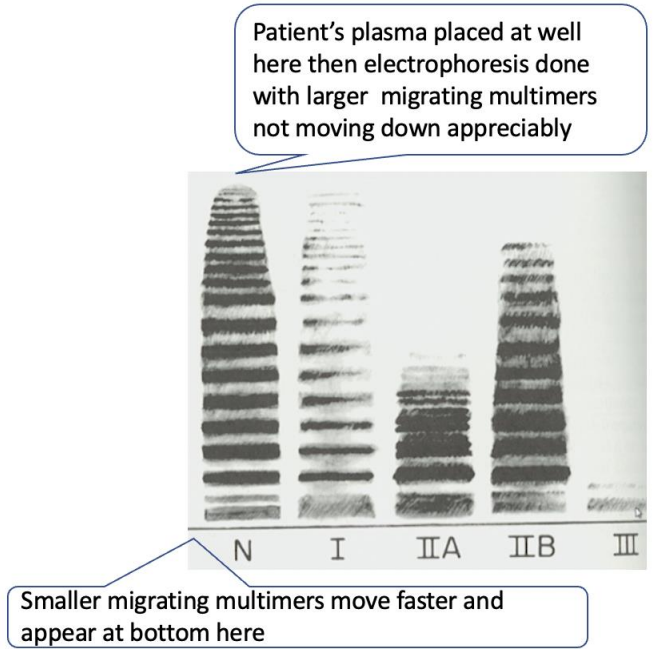
- **B** = increased platelets **b**inding
- Gain of function mutation
- Abnormal multimers
- Thrombocytopenia

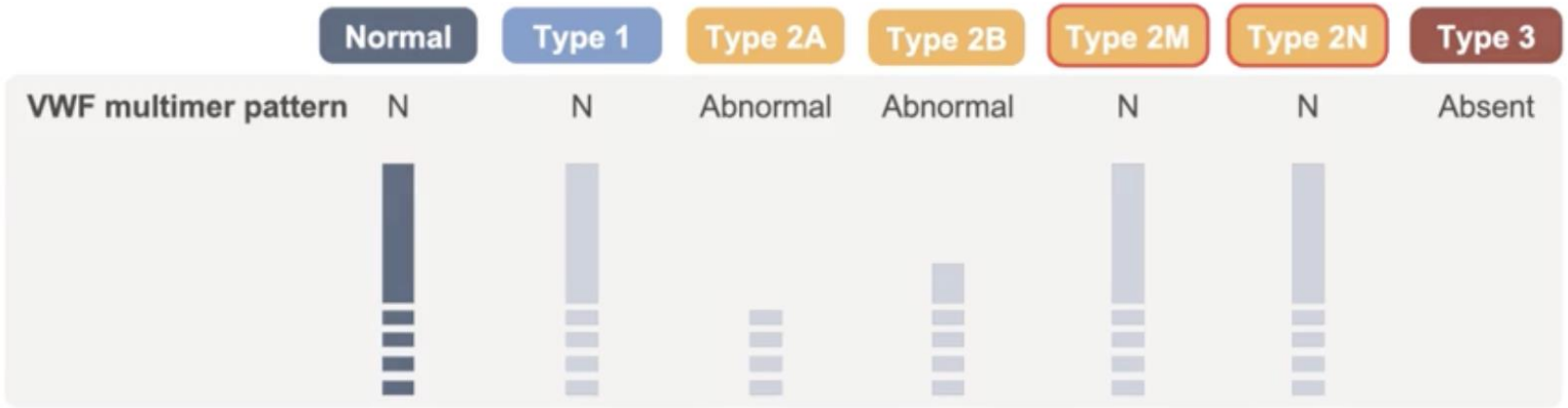
2M

- M = decreased platelets binding
- Loss of function mutation in GP1b alpha binding site
- Normal multimers

2N

- N = no binding to FVIII
- Manifest similar to hemophilia
- Normal multimers





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 Hypothyroidsm
  - Low thyroid hormone can decrease VWF biosynthesis
- Take good history for superimposed medications/OTCs causing platelet dysfunction

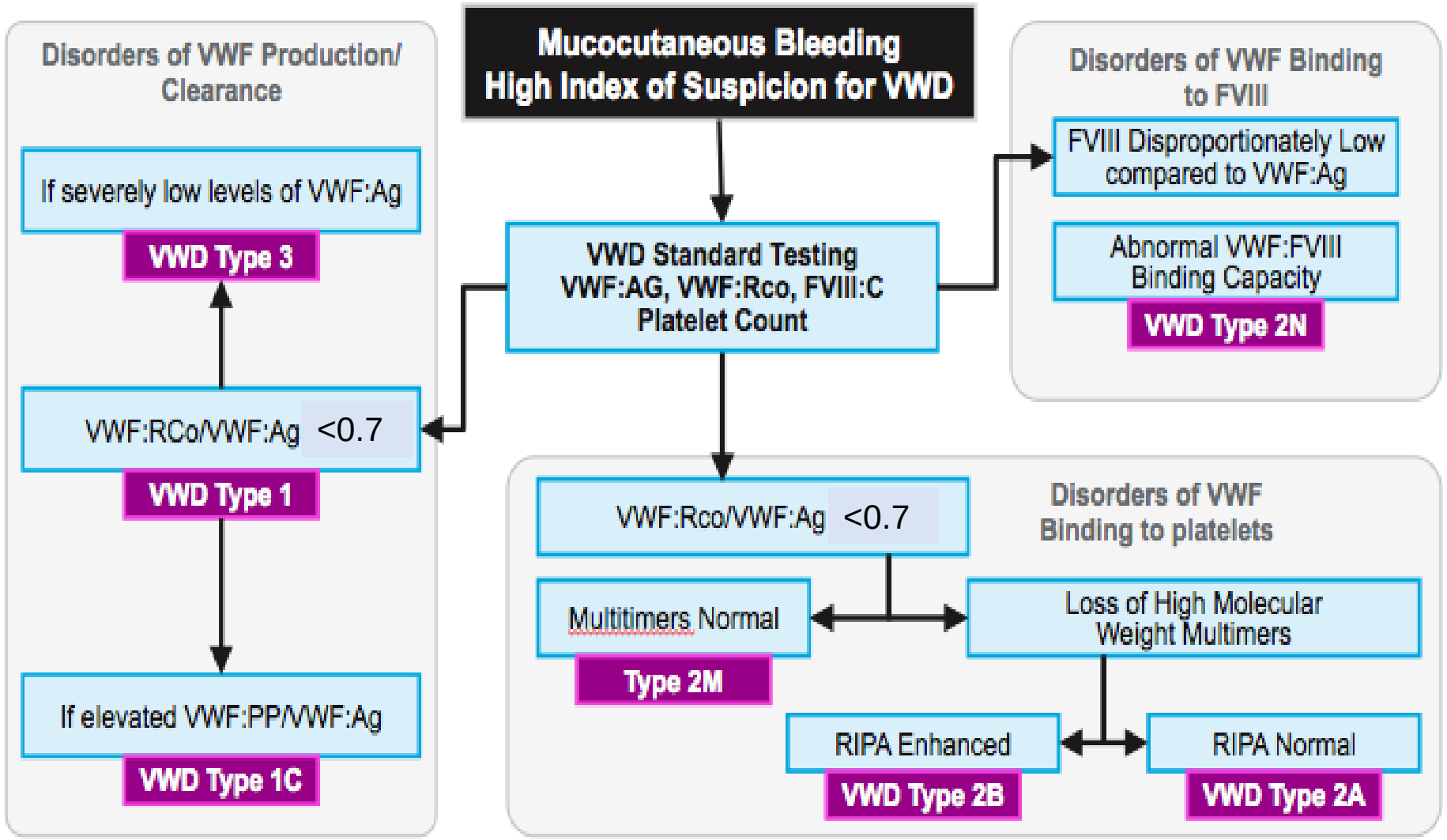
"A > H"

- **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

My laboratory approach for suspected VWD

1. Patients referred to me in consideration of an underlying bleeding disorder warrant a VWF panel (VWF activity + VWF antigen + FVIII)
   - besides CBC, PT, PTT, Fibrinogen, FIX, FXI, FXIII and platelet aggregation and release studies as bleeding can be multifactorial
2. If the BAT is increased but the VWF panel returns normal, we will repeat testing if the levels are below 100%.
   - This is based on 2 recent studies that an initial level $\geq$ 100% reliably excludes the laboratory diagnosis of VWD without need for repeat testing
3. If the VWF panel is subnormal x 2 sets, I then calculate the VWF activity/VWF antigen ratio and if <0.6-
   - send out for multimers and VWF:CBA to MCW-Milwaukee reference lab (Versiti) 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
4. 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-
   - 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…



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

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
VWF:Ag	N	L, ↓, or ↓↓	↓ or L	↓ or L	↓ or L	N or L	Absent
VWF:Rco	N	L, ↓, or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or L	Absent
FVIII	N	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	1-9 U/dL
RIPA	N	Often N	↓	Often N	↓	N	Absent
LD-RIPA	Absent	Absent	Absent	↑↑↑	Absent	Absent	Absent
PFA-100 CT	N	N or ↑	↑	↑	↑	N	↑↑↑
BT	N	N or ↑	↑	↑	↑	N	↑↑↑
Platelet count	N	N	N	↓ or N	N	N	N

Test

- D1472H polymorphism
- VWF activity GP1b immunoassay
- VWF propeptide
- VWF collagen-binding assay
- VWF FVIII-binding assay
- VWF 2B-binding assay
- Exon 28 and GP1b genotyping

Laboratory testing…the "new"

Test	Indication
VWF activity Gp1b immunoassay	Increased reproducibility and sensitivity compared to assessing activity by ristocetin platelet agglutination
D1472H polymorphism	When African American has reduced VWF:Rco activity with normal VWF Antigen
VWF propeptide	When considering Type 1C VWD (~10-15% of Type 1 VWD), VWF:Ag usually <15%, VWF:pp to VWF:Ag ratio >2 up to >10
VWF Collagen binding assay	When VWF act/Ag < 0.7; particularly helpful in the diagnosis of Type 2M
VWF FVIII binding assay	To confirm 2N
VWF 2B Binding assay	In lieu of ristocetin induced platelet agglutination (RIPA) or as confirmation
Exon 28 and GP1b genotyping	To distinguish VWD 2B and Platelet type VWD- All 2B VWD mutations have been identified between amino acid residues 1266–1461 encoded by exon 28 of VWF while PT-VWD mutations are encoded by the central region of GP1BA exon

2021 VWD Diagnosis Panel highlights

- Preferred coagulation test for VWF activity-
  - Out with the Ristocetin cofactor test
  - In with the newer assays that measure the platelet-binding activity of VWF (eg, VWF:GPIbM, VWF:GPIbR) but these tests are not yet FDA approved and setting up local range is laborious and costly!!
- Type 1 VWD no longer requires cutoff of 30%-
  - If increased bleeding score the VWF cutoff is higher at 50% (no longer using term “Low VWF”)
  - If no bleeding but level < 30%, the diagnosis of Type 1 VWD can be made as in screening family members
- Use a lower ratio of VWF activity to VWF antigen when diagnosing Type 2 VWD of 0.7 instead of 0.5 or 0.6
- In turn , use VWF multimer analysis or VWF collagen binding (VWF:CB)/VWF:Ag (the ratio of VWF collagen binding to antigen)
  - to diagnose type 2 VWD for patients suspected of type 2A, 2B, or 2M in need of additional testing
- For diagnosis of Type 2B VWD targeted genetic testing over low-dose ristocetin-induced platelet agglutination (RIPA)
  - to diagnose type 2B VWD for patients suspected of type 2A or 2B in need of additional testing

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

When the FVIII level is low with normal VWF levels: Type 2N VWD and Mild hemophilia

- Patients with a prior diagnosis of mild hemophilia who do not respond well to FVIII infusions or belong to families for whom the inheritance appears to be autosomal dominant (??) should be evaluated for VWD type 2N

- Specific FVIII binding assays are also available

- **Think of this when evaluating a female with a mildly or moderately reduced FVIII level and no FH/O hemophilia**

The 2021 panel *suggests* using either VWF FVIII binding (VWF:FVIIIB) or targeted genetic testing (when available) for patients with suspected type 2N VWD in need of additional testing

Slide courtesy of Dr. Amro Elshoury Roswell Park

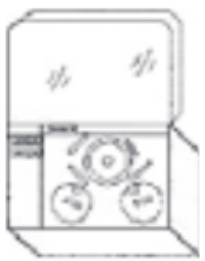
Why did we check Patient 1's VWF levels twice?

Variables driving levels up

- Traumatic blood draws, struggling/crying children, agitation of collected samples or extremes of temperature can alter results.
- Inflammation, stress, exercise as VWF is an acute phase reactant leading to 2-5 fold rise
- High levels of estrogen exposure (high dose OCs, HRT w estrogen, pregnancy- increase 2-5x during late pregnancy)
  - However present low dose estradiol in COCs do not appreciably raise levels
- Advancing age

Variables driving levels down

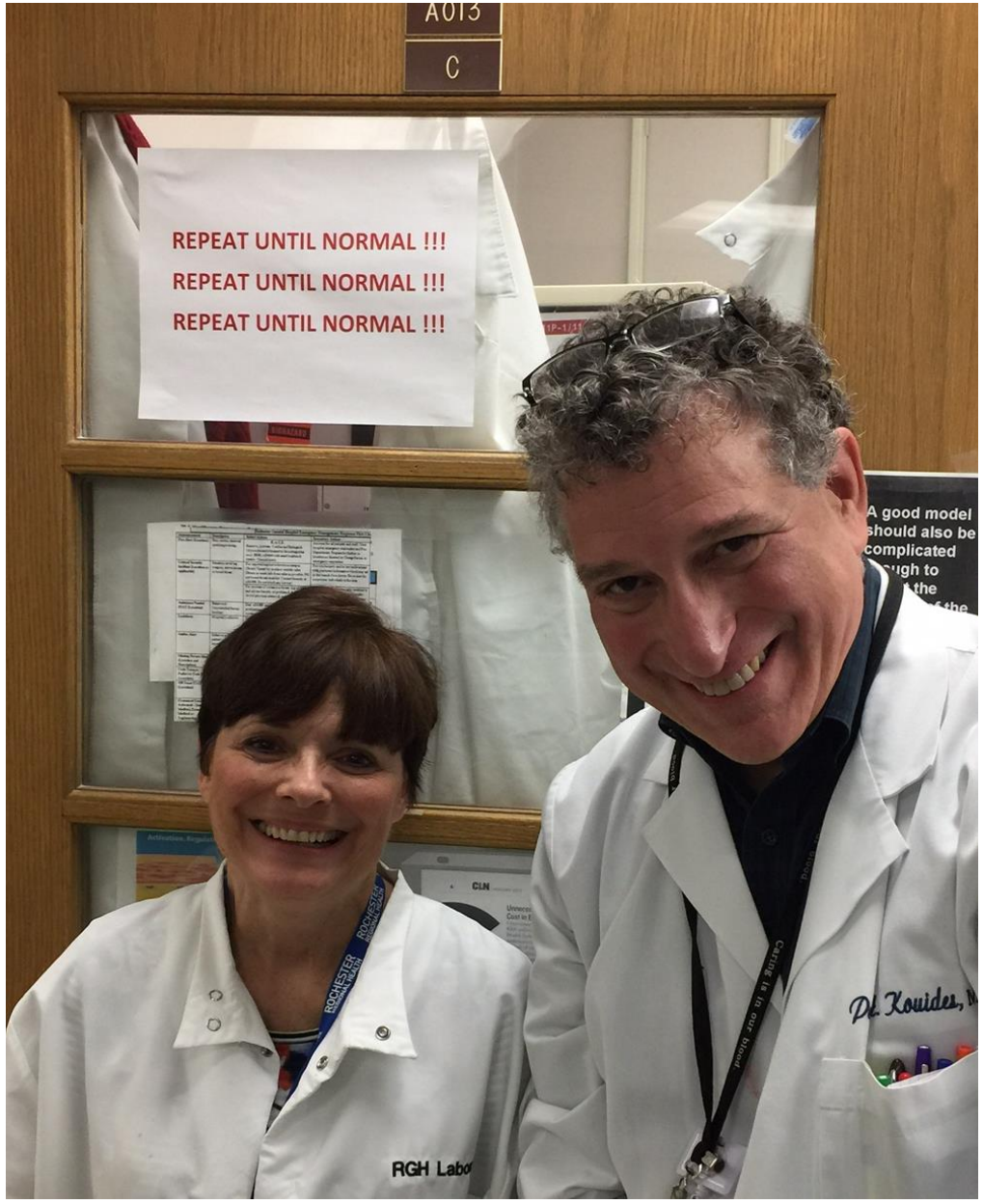
- Blood type O-VWF levels are lower in pts with blood group O by ~25-30%.
- Hypothyroidism
  - should always check TSH when doing VWF testing in setting of heavy menses as it can cause acquired VWD and lead to heavy menses in itself apart from VWD
- Specimen sampling and processing- be suspicious of referrals for VWD based on send out testing a problem you will see often in training!
  - Assays increased to within the normal range in 30% to 50% of subjects when retested at on-site laboratories
    - *Jaffray J: Am J Hematol. 2020 Sep;95(9):1022-1029*

Preanalytical process	Preanalytical problem
 Sample collection	- Identification errors - Inappropriate procedure - Inappropriate device - Inappropriate volume
Sample handling	- Sample mixing
 Sample transportation	- Temperature - Time - Conditions
Sample storage	- Temperature - Time - Thawing
 Sample preparation	- Centrifuge temperature - Centrifuge time - Centrifuge speed - Plasma stratification

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

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

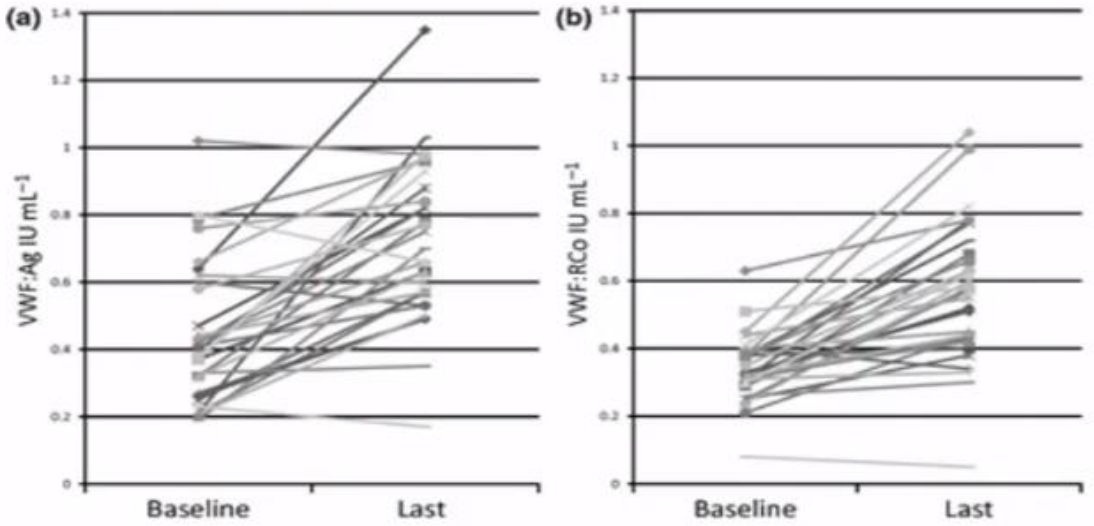


VWF and ageing

- **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

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.

Clinical Pearls regarding diagnostic testing

- Be suspicious of referrals for VWD based on send out testing
  - Take home message (THM)- “repeat until normal”
- Even with normal on-site values, consider re-testing if VWF levels<100% but positive family history for VWD and/or increased bleeding score (if >100% >95% NPV)
  - THM- Don’t just focus on lab results but also history
- One set of subnormal levels is not sufficient- needs at least two subnormal sets ideally several months apart
  - THM- like APAS, document at least more then one set of abnormal values
- Present COC preparations do not “mask” the diagnosis of VWD
  - THM- its OK to test if on COC
- Up to 30% of Type 1 and LVWF patients ”outgrow” their laboratory diagnosis if re-tested (at least twice) 5-20 years later, studies on-going if they “lose” their bleeding phenotype
  - THM- repeat testing every few years and before surgery

Management of VWD

Three principles of treatment:

1) Increase (desmopressin) or replace (concentrates) VWF
   - Choice depends on VWD subtype and type of surgery

2) Replete FVIII

3) Stabilize clot with an anti-fibrinolytic agent

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)

Back to Patient 1

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

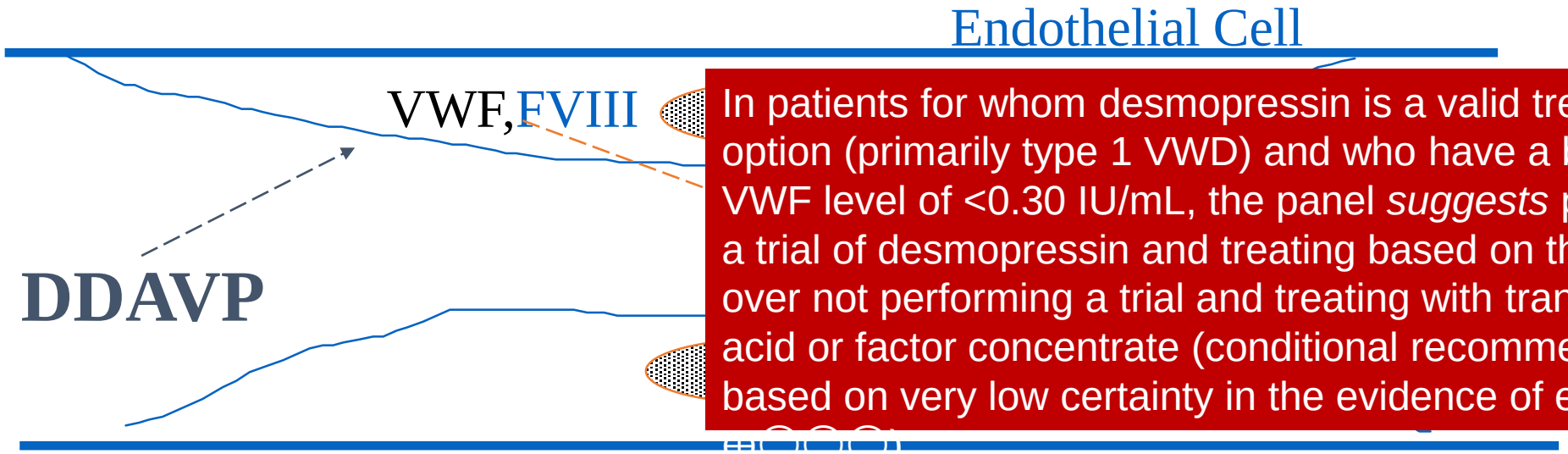
- Patient informed of positive response and instructed to use 1 puff to each nostril for first 3 days of menses
- Follow-up PBAC score showed decrease from 320 to 60

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

MARY M. GOOLEY
Hemophilia Center

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

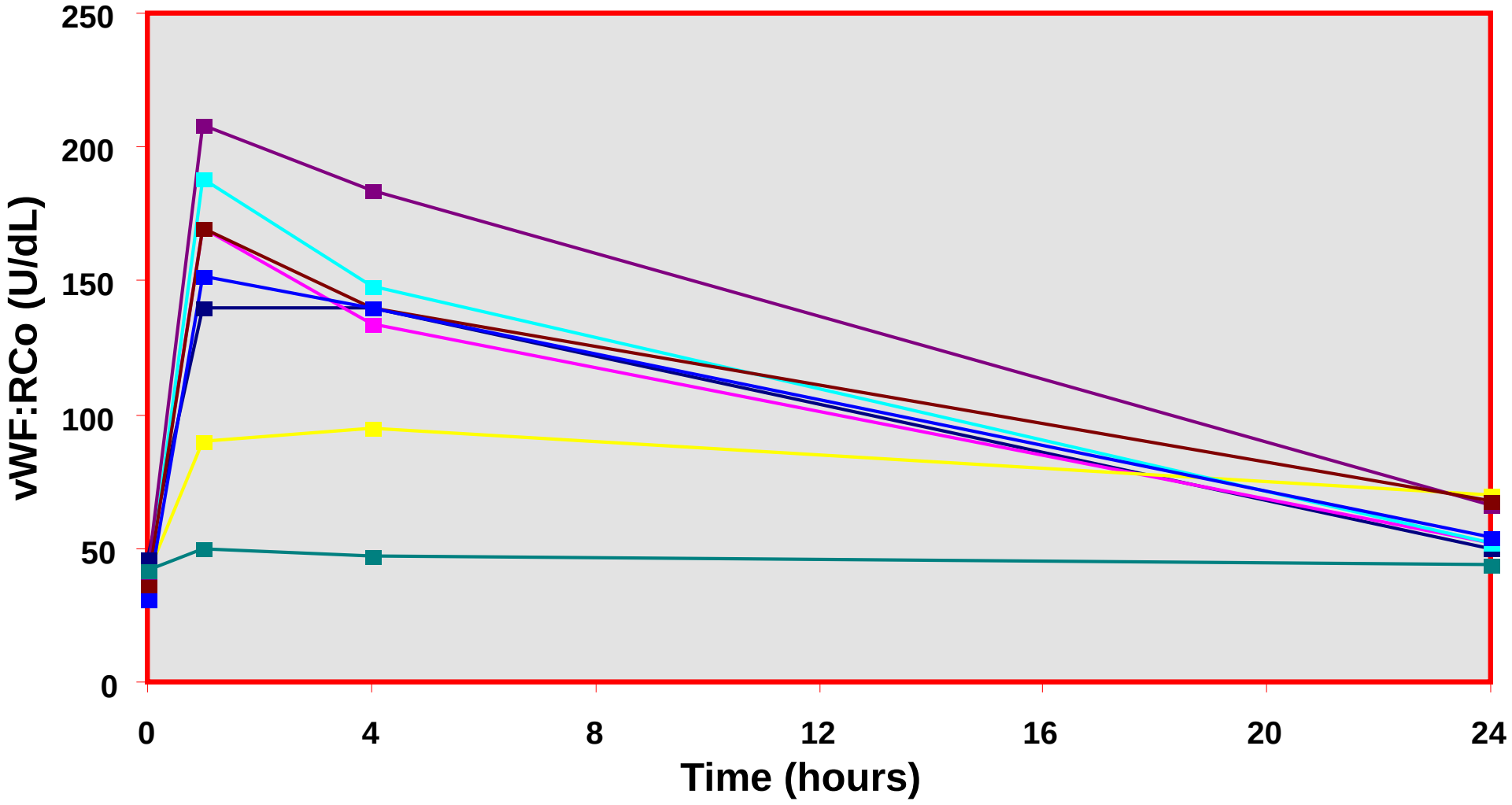
- releases pre-formed stores of FVIII and vWF from the endothelium
- effective in most patients with mild hemophilia as well as majority with von Willebrand disease
- Indications;
  - For minor surgery and dental procedures (NOT major surgeries)
  - WHY?.... Repeated dosing leads to tachyphylaxis and 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 2023 Q4



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

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

Response to IN DDAVP in Mild Type 1 von Willebrand Disease



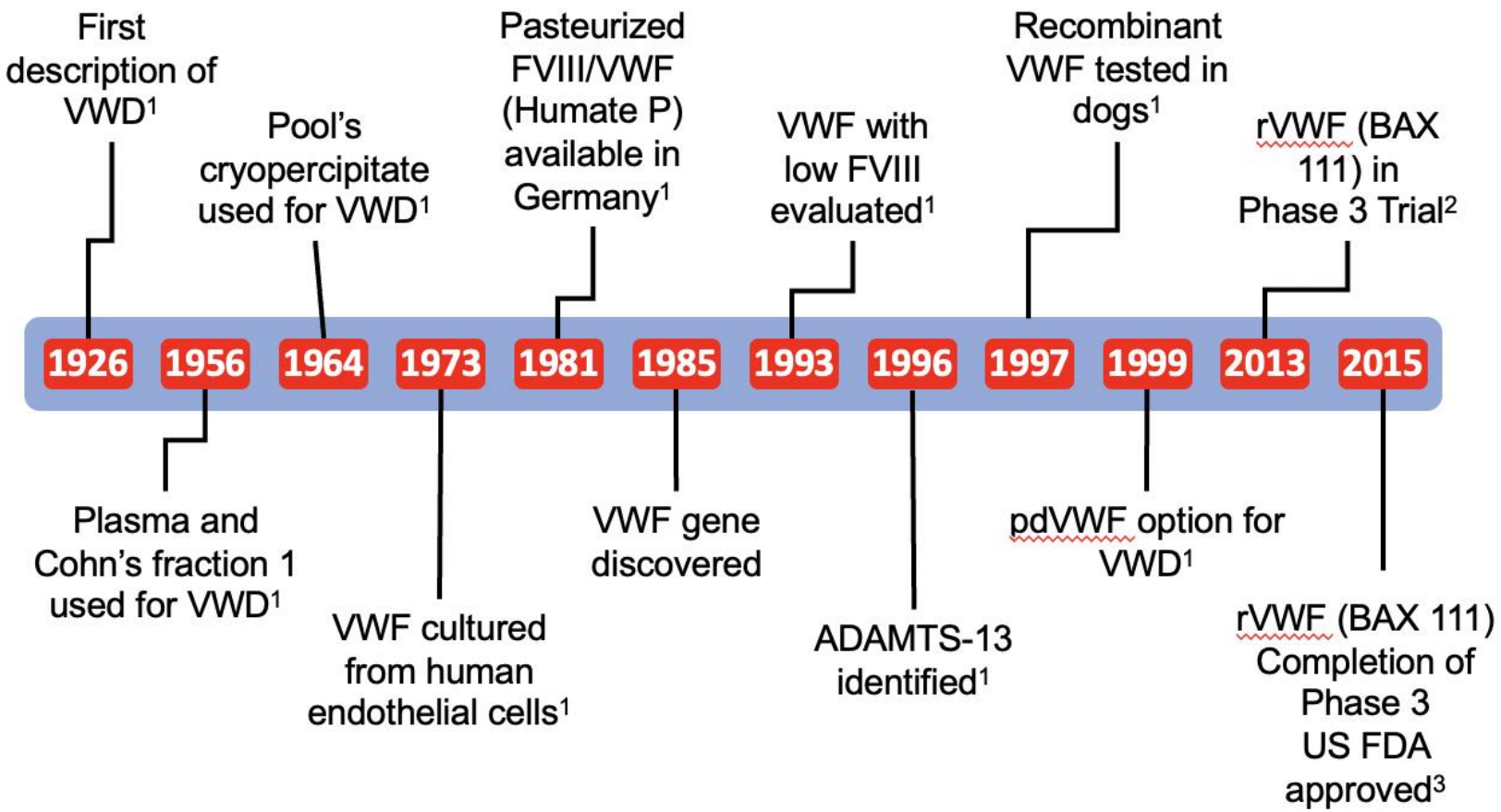
Gill JC, et al. *Jr Pediatr.* 2002;140:595-599.

DDAVP…….Past and Present

Past	Present
Contraindicated in VWD 2B given reports of thrombocytopenia and rare cases of thrombosis	Can be used safely and effectively with certain genotypes associated with normal platelet count *(Kouides Blood 2008; Federici Blood 2009;113: 526-534)*
Contraindicated in Pregnancy due to theoretical concerns of premature labor, decreased placental flow, neonatal hyponatremia	Several case series of safe use in pregnancy (*Mannucci PM Blood 2001; 97:1915-1919; Sanchez-Luceros A et al Thromb Res 2007;120:387-390)*
Contraindicated in the very young (insert states not to use 0-3 mos.; most experts state 2-5 yrs.)	More case series of hyponatremia in older children and adults *(Sharma & Stein D J Ped Hematol Oncol 2014, 36:e371)*
Reports of thrombosis in patients with prothrombotic risk factors	Consider lower dosing in “high risk” patients (*Furqan F et al Am J Hem 2020; 95(10) EE285-E287)*
Intranasal DDAVP as main hemostatic therapy for heavy menses	Tranexamic acid appears to be more effective based on CDC cross-over study of TA and IN DDAVP (*Kouides et al Brit J Haem 2009; 145 (2):212-220*)

What if patient 1 had Type 3 VWD?

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.

VWF Concentrates; concepts and background

- Patients with VWD are deficient in both VWF and FVIII
- Different brands vary in their content of VWF relative to FVIII levels
- Be familiar with one or two brands in order to assure appropriate dosing

- General goal of replacement; VWF:Rco and FVIII trough level of 100 IU/dL, at least for the first 3 d, and a nadir of 50 IU/dL for both VWF:RCo and FVIII
- Levels of circulating FVIII greater than 150 IU/dL increase the risk of venous thrombosis
- The dose and duration of therapy depends on the haemostatic challenge e.g. wound eschar usually fall out around D10 post surgery

“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

Human plasma-derived VWF (Humate P), the old battle axe

- From 1982 to 2015, pharmacovigiilance data showed 670 post-marketing cases have been reported in relation to an estimated 25,000 patient years of exposure (5.2 billion units; 2.6 million standard doses)
- Of these cases, 343 involved ADRs considered important risks for this product-

Complication	N	
Hypersensitivity/allergic	110	
Inhibitor	97	→ Mostly in hemophilia A (24 cases high titer)
Thromboembolic	33	→ Mostly in patients undergoing surgery and/or other risk factors
Viral transmission, suspected	103	→ None confirmed to be associated with Humate P

Bottom line-

- More than 38 years of pharmacovigilance data continue to support the safety of this product.

Kouides et al Transfusion 2017 Oct;57(10):2390-2403

Recombinant VWF concentrate (no FVIII; “VONVENDI”)

- Purified von Willebrand factor (VWF) only
- No exposure to human protease ADAMTS13 during production process
  - Contains intact high molecular weight multimers (HMWMs) and ultra-large multimers
- Manufactured in the absence of animal or other human plasma proteins

Turecek PL, et al. Hamostaseologie. 2009; 29(Suppl 1):S32-S38.

Results (FDA licensure trial):hemostatic efficacy

- A total of 192 bleeding episodes were treated with rVWF
  - 122 minor, 61 moderate, 7 major/severe, 2 unknown severity
  - **In 157 bleeds, one infusion was adequate to treat the bleed (81.8%)**
- All participants (100%) reported successful treatment of bleeding episodes, with 96.9% of treated bleeds (N=192 bleeds in 22 patients) achieving an “excellent” efficacy rating, and 3.1% achieving a “good” efficacy rating
- Treatment was rated as excellent in 97.5% of minor bleeds and 96.7% of moderate bleeds
- A median of two infusions (range:1–3) were required to control major bleeds

SUMMARY

- 21.9 hour half-life of VWF:RCo after rVWF alone (12.8–15.8 hours for pdVWF)
- 100% treatment success, median of 1 infusion (2 for major bleeds)
- Enhanced FVIII stabilization that may be due to the high ultra large multimers (ULM) content in rVWF
  - suggests a potential for dosing independent of FVIII after the first infusion

Gill JC, et al. Blood. 2015;126(17):2038-2046.

Theoretical Advantages of recombinant VWF

May be preferable to the plasma derived concentrates in terms of:

1. Preventing viral transmission which would be an attractive option to parents of newborns with Type 3 VWD alleviating their worry about exposing their child lifelong to plasma.

2. In the obstetrics setting where the FVIII levels may be less likely to rise excessively so decreasing the risk of post-partum thrombosis.

3. The apparent extended half-life may also make its use attractive in the prophylaxis setting.

4. Ventricular assist device related bleeding where 100% of cases HMW multimers are lost with high acute phase reactant increase in FVIII > 200%

5. Enriched with unusually large multimers not present in plasma so may be more efficacious

Disadvantages- awkward to dose
for surgery (? give night before if FVIII <40%), Cost

Desprez D: Haemophilia 2021 Mar;27(2):270-276

What else may you prescribe Patient 1?
Anti-fibrinolytic Agents

- Tranexamic Acid : 10 mg/kg intravenously three times per day post op or oral form Lysteda 1.3 g po tid for heavy menses, oral bleeding….appears to more potent then-

- Epsilon Aminocaproic acid : 25 to 50 mg/kg orally (maximum 5 g dose) four times per day

- Prevent dissolution of the hemostatic plug that is formed, particularly in mucous membrane areas with naturally high fibrinolytic activity (eg, to decrease bleeding with dental procedures)

- These agents are contraindicated in the presence of gross hematuria, since un-lysed clots if bleeding lesion in the upper GU tract may lead to ureteral obstruction.

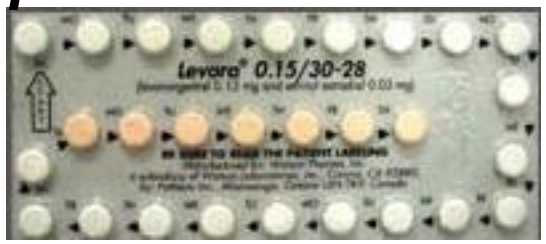
Back to Patient 1, type 1 VWD

- The patient and her parents are informed that she is a DDAVP responder
- They are also informed there are numerous treatment options for managing her HMB
- **What would you advise?**
  - **A. Intranasal desmopressin (IN-DDAVP)**
  - **B. Tranexamic acid (Lysteda TM) 1.3 gram po tid first 5 days of menses**
  - **C. MIRENA IUD**
  - **D. Estrogen-containing oral contraceptive (“COC”)**
  - **E. Plasma-derived VWF containing FVIII concentrate**

Armour

ANTI-MENORRHAGIC FACTOR GLANULES

Oral contraceptive



Levonorgestrel IUD

Endometrial ablation

Hemostatic Therapies:

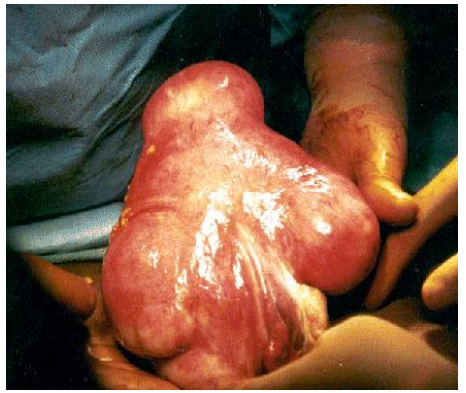
Intranasal DDAVP (Stimate®)

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

VWF/FVIII concentrate

Antifibrinolytic therapy

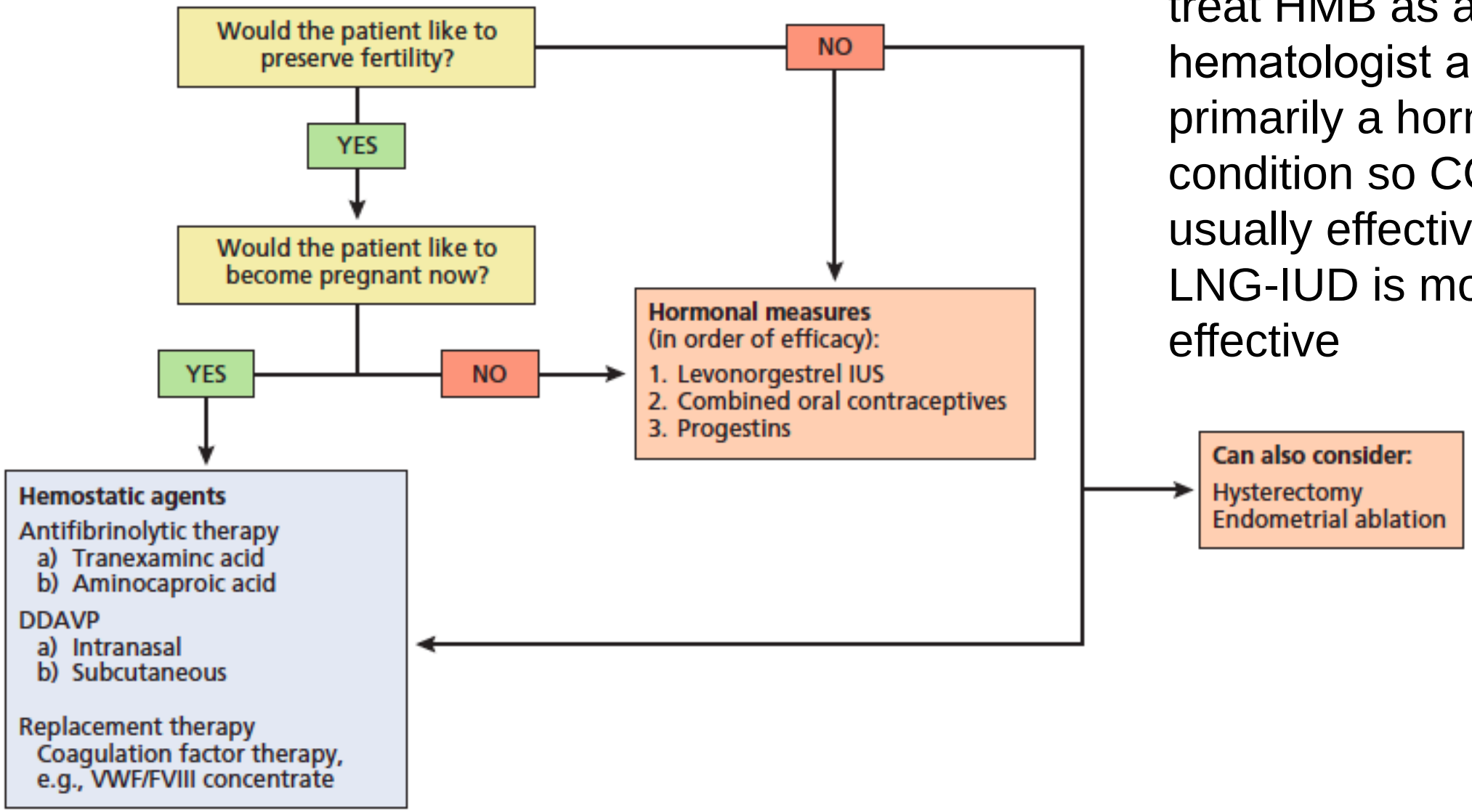
Hysterectomy



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

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.

European principles of care for women and girls with inherited bleeding disorders, 2021

"Consideration of the use of hormonal intrauterine devices (IUDs) is not dependent on age or parity as studies have identified these IUDs as an appropriate and effective treatment option for adolescents with HMB.

HTC/CCCs should offer treatment options, personalized according to age, fertility/pregnancy wishes, other gynaecological symptoms, patient's views and acceptance of treatment options and side effects, respecting cultural and psychological aspects"

Van Galen K: Haemophilia. 2021 Sep;27(5):837-84

Case continued

- 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

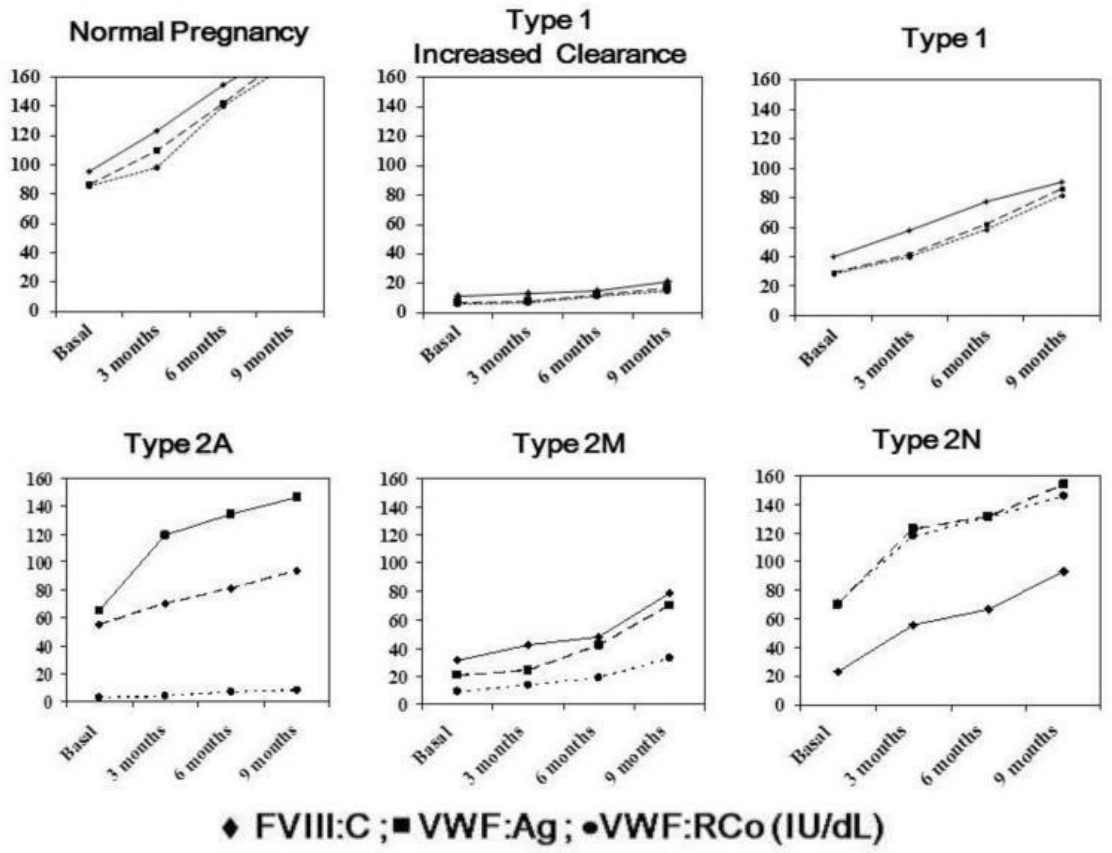
Case continued- antepartum

- Patient age 15, 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

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

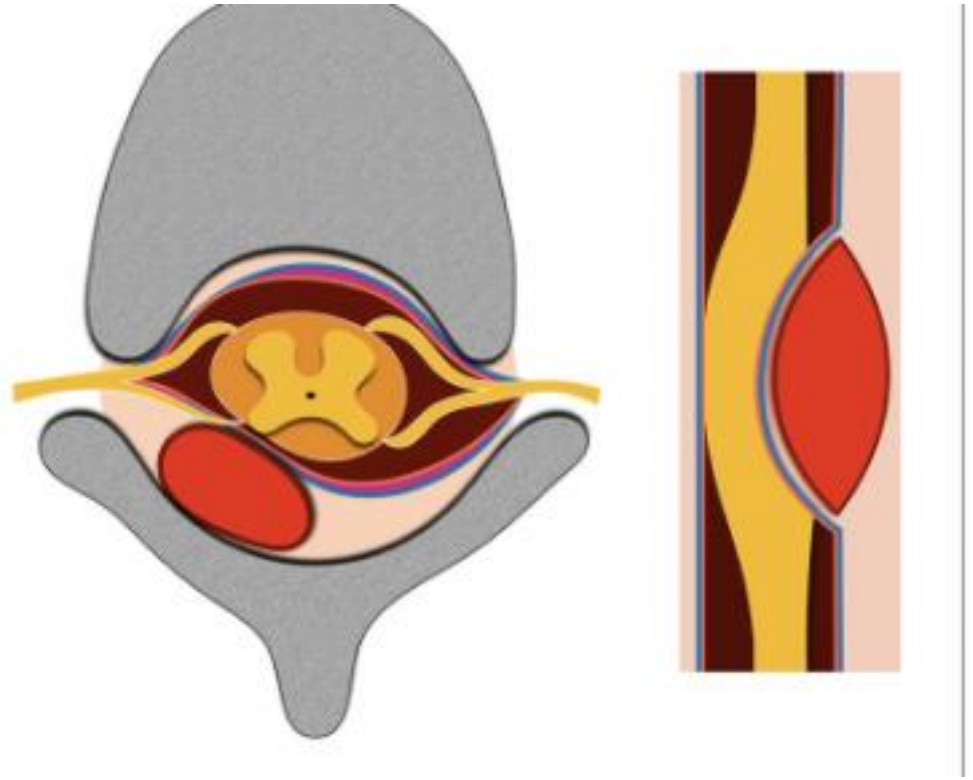
VWF changes in pregnancy in normal patients and patients with VWD



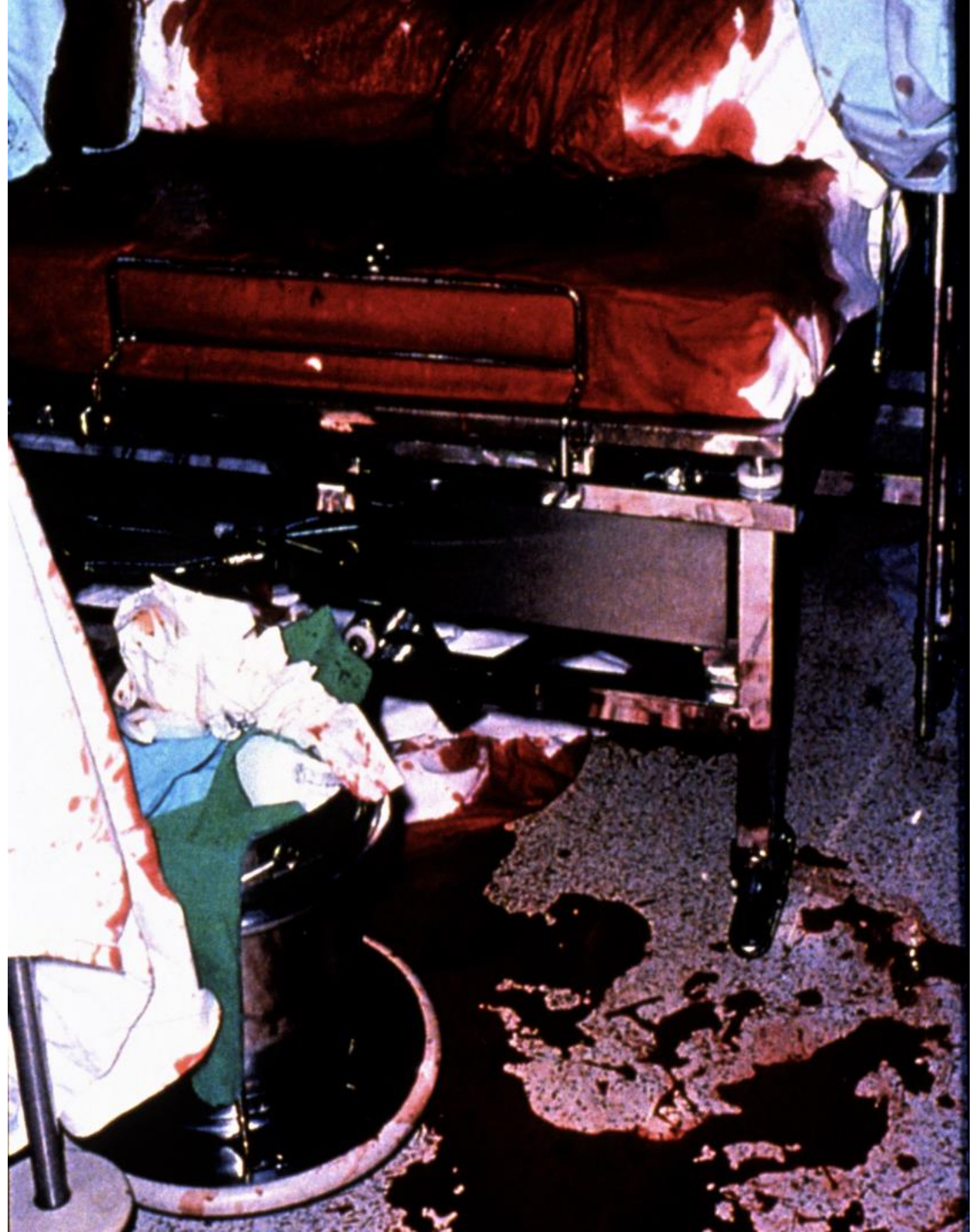
[1] Drury-Stewart et al. PLoS One. 2014 Nov 19;9(11):e112935; [2]Castaman G. Mediterr J Hematol Infect Dis. 2013; 5(1): e2013052; [3]James et al. Haemophilia. 2015 Jan;21(1):81-7; [4]Machin & Ragni. Blood Adv. 2020 Jul 28;4(14):3234-3238.

Risk of an epidural hematoma

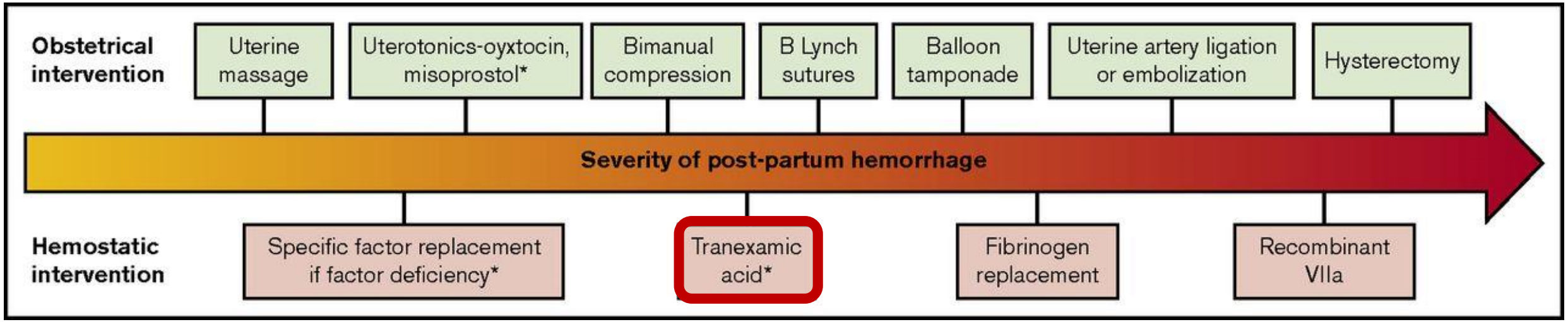
- Overall risk of epidural hematoma associated with neuraxial techniques in obstetric patients to be approximately 1:200,000
  - About 10 fold less then general population probably due to the protective hypercoagulable state of pregnancy
- 2017 Royal College of Obstetricians and Gynaecologists guidelines 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”*



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



Post-partum hemorrhage and the role of Tranexamic acid



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 ⊕⊕◯◯).

Kouides PA Blood Adv 2017;1:699-702

Chronic epistaxis-
What to do besides DDAVP and Amicar-

- Loratidine????
- QR powder???
- Salt pork anyone??
- Good old fashioned saline spray….
- In Type 2,3 have tried prophylaxis with VWF replacement

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

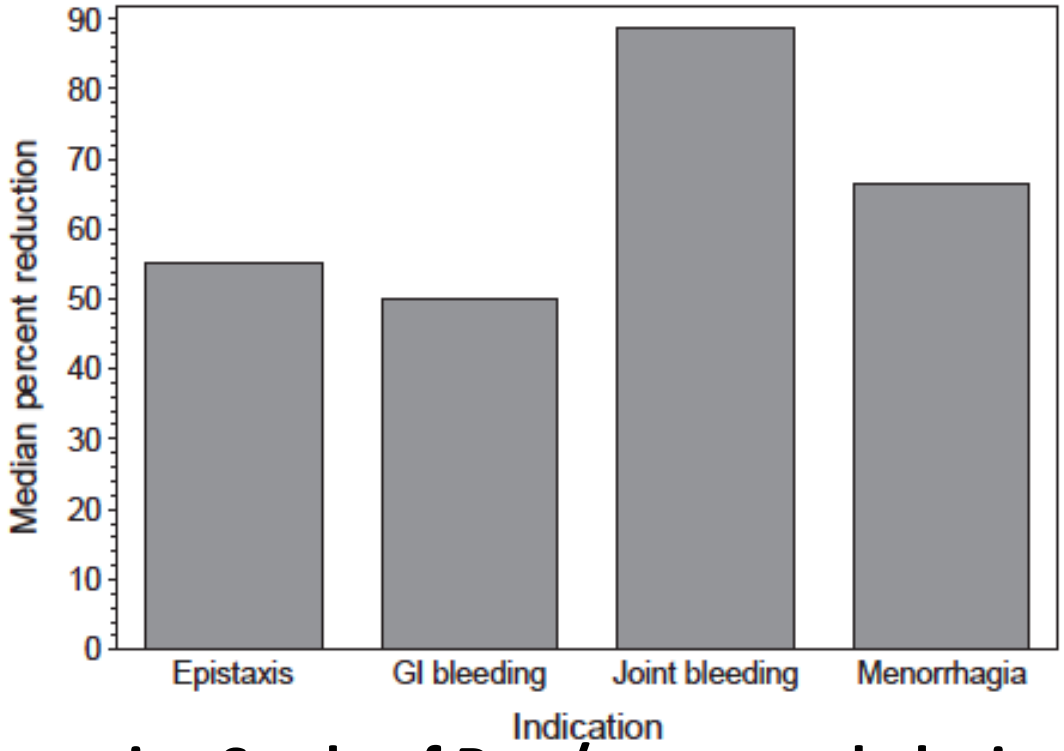
Back to Patient 1 if she had Type 3 VWD-Prophylaxis in VWD: VIP study group

1. Survey of 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 ⊕⊕◯◯).

Berntorp E & Abshire T – JTH 2006; 4: 2511
Abshire T Haemophilia 2013;19(1):76-81
Abshire T- JTH 2015; 13(9) 1585-9
Connell NT Blood Adv. 2021 Jan 12;5(1):301-325

2. Retrospective Study of Pre-/post-prophylaxis



3. Prospective Study of Pre-/post-prophylaxis

Final treatment level by VWD type and bleeding indication-

Treatment level 1 Weekly	
Type	Bleeding indication
2A	Epistaxis
2A	Epistaxis
3	Epistaxis
3	Epistaxis

Treatment level 2 2 x wk	
Type	Bleeding indication
2A	Epistaxis
3	GI bleeding
3	Joint bleeding

Treatment level 3 3 x wk	
Type	Bleeding indication
2A	Epistaxis
3	Joint bleeding
2A	GI bleeding

Escalated beyond level 3* qod	
Type	Bleeding indication
2A	GI bleeding

*Regimen escalated to one infusion (75 IU VWF:RCo/kg) every other day.

Thanks a clot ☺