EHC Webinars

European von Willebrand Disease Community

Von Willebrand disease

Topic on focus

ERN-EuroBloodNet

Surgery in von willebrand disease

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EHC european haemophilia consortium

Advocating for people with haemophilia and congenital bleeding disorders

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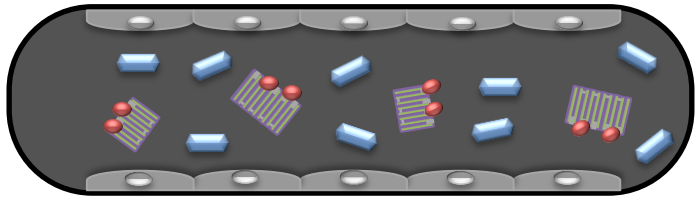
Conflicts of interest

Conflict	Disclosure
Research support	-
Director, Officer, Employee	-
Shareholder	-
Honoraria	-
Advisory committee	Biomarin, CSL Behring, Roche, Sanofi, SOBI
Educational meetings/Symposia	Takeda/Spark

Patients' learning objectives

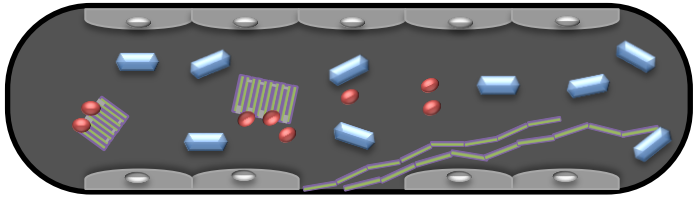
1. von Willebrand factor role in hemostasis
2. von Willebrand disease symptoms and diagnosis
3. Impact of incorrect diagnosis
4. Accessing factor cover before surgery
5. Post surgery recovery – International guidelines
6. Neuraxial anesthesia – International guidelines
7. Management of delivery in women with VWD

Role of VWF in primary haemostasis

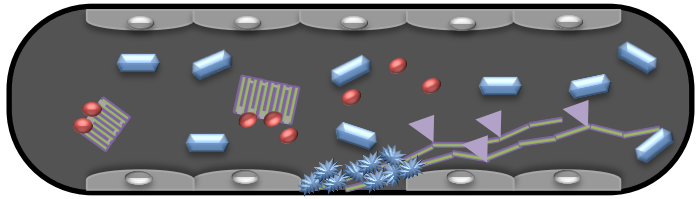


VWF circulates as a loosely coiled protein complex under **basal conditions of low shear stress**

VWF adheres to the site of vascular injury via exposed collagen, causing a conformational change of VWF

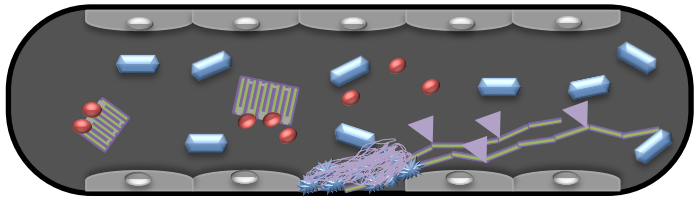


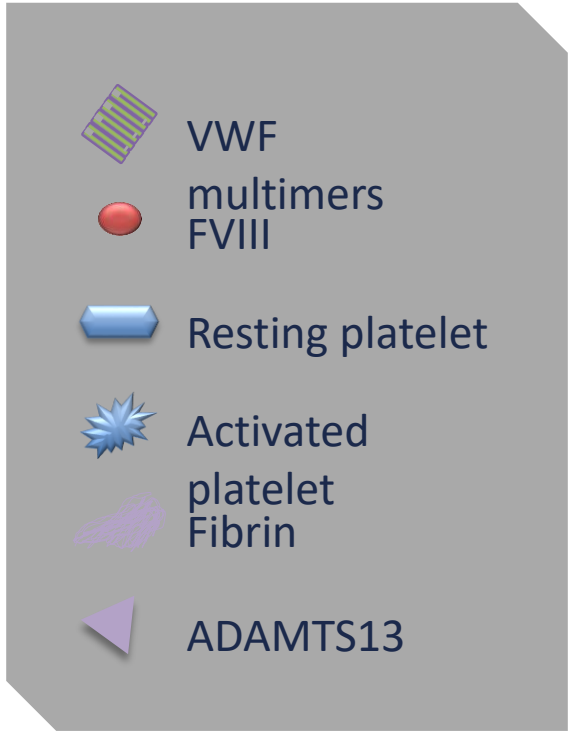
Vascular injury



Upon **unfolding of VWF**, binding sites for platelets and ADAMTS13 become accessible

A **platelet-fibrin plug** is formed and bleeding ceases





Nichols WL, et al. Haemophilia. 2008;14:171–232; Denis CV, Lenting PJ. Int J Hematol. 2012;95:353–361

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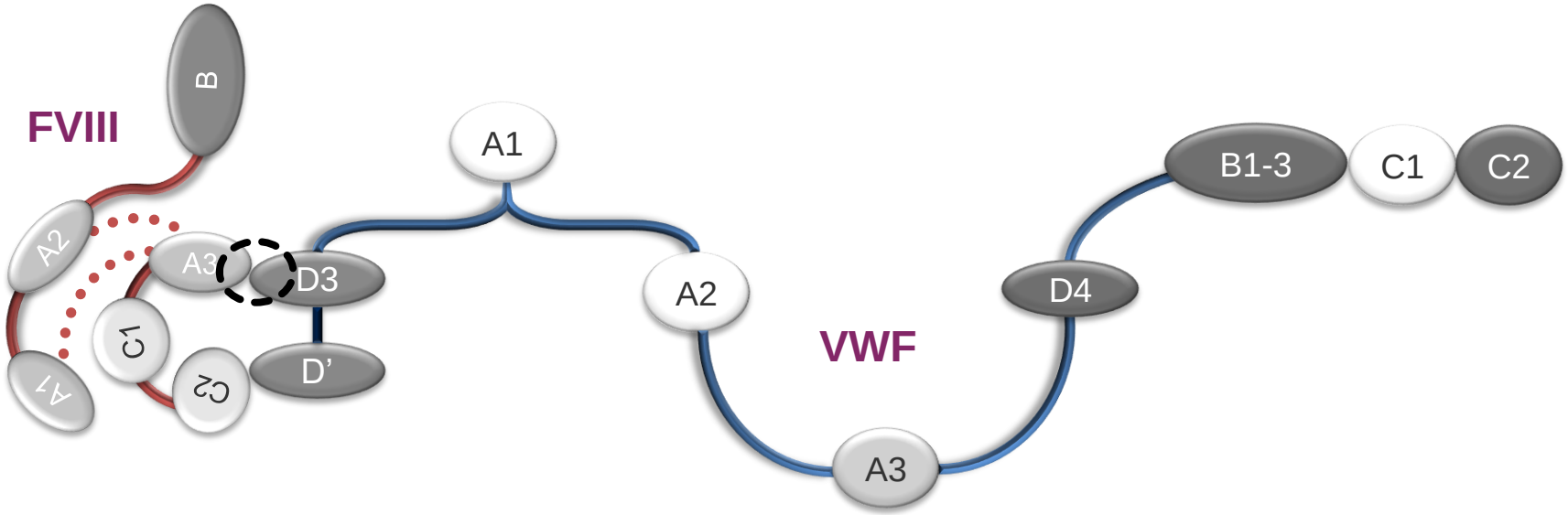
Role of VWF in secondary haemostasis

FVIII is noncovalently bound to the D'-D3 region of VWF (dotted lines)



VWF forms a complex with FVIII in circulation, which stabilises and protects FVIII from degradation and localizes it to the site of the platelet plug to bring about the formation of a clot

Peyvandi F, et al. Blood Transfus. 2011;Suppl 2:S3–S8

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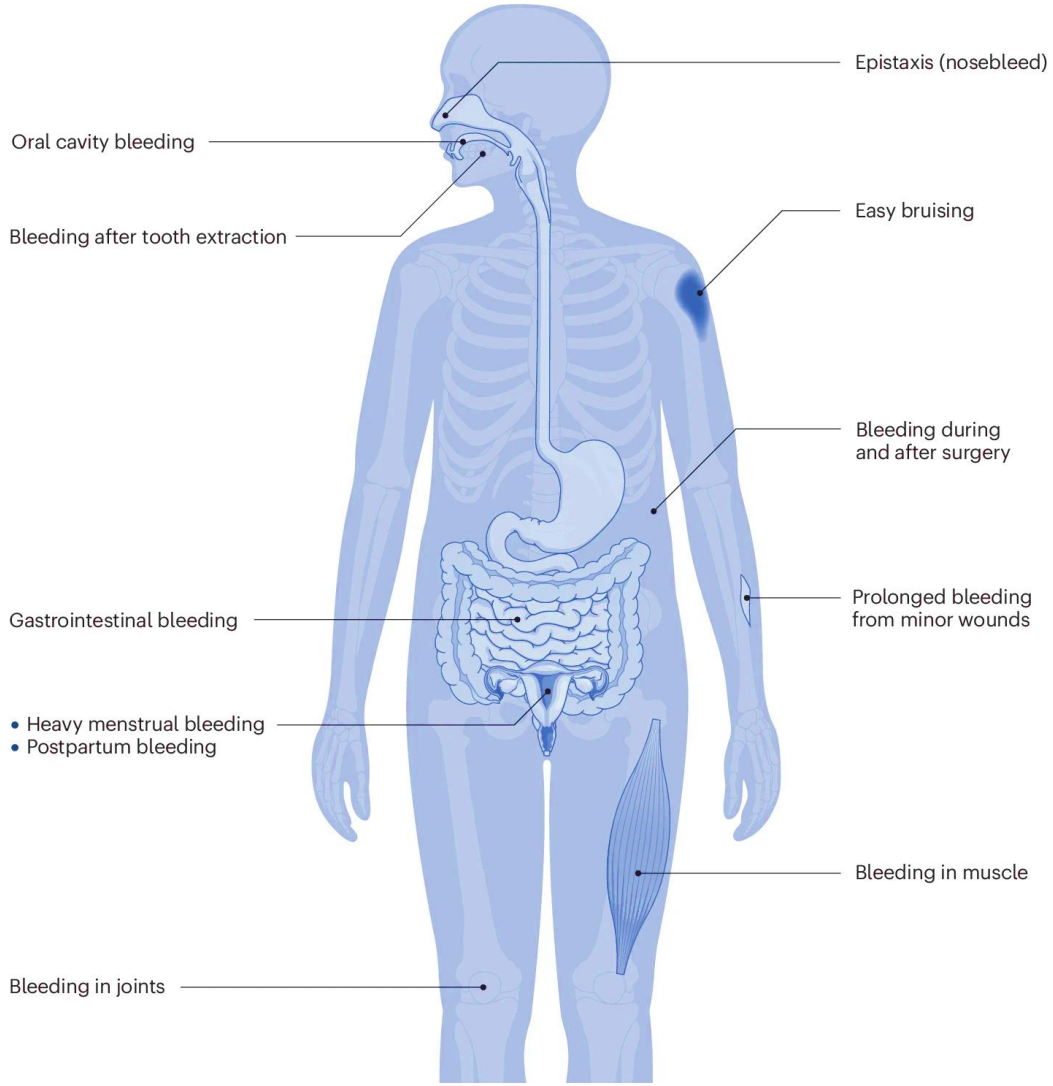
von Willebrand disease (VWD) symptoms



Seidizadeh O et al – Nature Reviews Disease Primers, 2024

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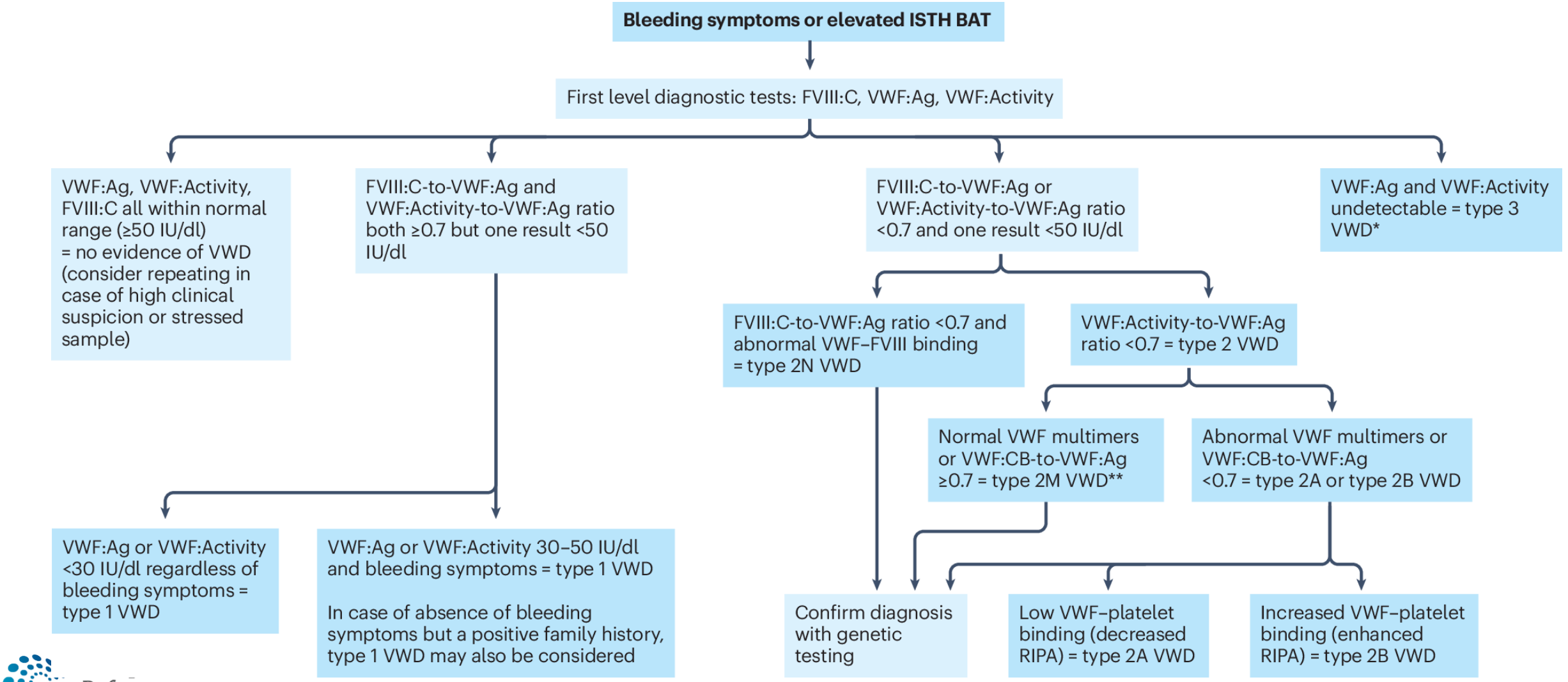
von Willebrand disease (VWD) diagnosis



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Von Willebrand disease– Nature Reviews Disease Primers, 2024

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Impact of incorrect diagnosis

Correct diagnosis is important for proper treatment and management of patients

1. **Appropriate management of patients**

- Differential diagnosis of type 2B vs PT-VWD: **VWF concentrate vs platelets**
- Differential diagnosis of type 2B vs 2A and 2M: **DDAVP is contraindicated**
- Differential diagnosis of type 2N vs hemophilia: **VWF concentrate vs FVIII concentrate**
- Type 1C VWD: **DDAVP may not be the proper therapy**

2. Genetic counseling

- Types 3 and 2N VWD are autosomal recessive disorders

  Usually genetic analysis is important in families with the severe form of the disease at risk of having an affected child with severe disorder

3. Quality of life

- Quality of life of patients with VWD changes significantly with an accurate diagnosis thus proper treatment

International guidelines

CLINICAL GUIDELINES

Blood Adv. 2021;5:301-325.
doi:10.1182/bloodadvances.2020003264

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

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Accessing factor cover before surgery

- It is always necessary to request haematological advice to establish:
  - Type of VWD
  - severity of the disease
  - presence of inhibitor
  - type of replacement therapy, dosage and frequency

Perioperative therapeutic strategies aim to:

- minimize bleeding
- maintaining hemostatic plasma FVIII and VWF levels throughout the postoperative period > 50IU until bleeding risk abates and healing is complete

Minor surgery – International guidelines

- Suggestion: increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate **WITH** the addition of tranexamic acid
- Suggestion: giving tranexamic acid alone in patients with type 1 VWD (baseline VWF activity of > 0.30 IU/mL and a mild bleeding phenotype) undergoing minor mucosal procedures

conditional recommendations (based on very low certainty in the evidence of effects)

Remarks:

- Individualized therapy plans are important for patients who may be overtreated when VWF activity is increased to ≥ 0.50 IU/mL by any therapy and addition of tranexamic acid
- Patients with type 3 VWD will require VWF concentrate to achieve any significant increase in VWF activity: desmopressin is contraindicated because of a lack of efficacy
- Many patients with type 2 VWD (including 2B VWD) require treatment with VWF concentrate rather than desmopressin
- For patients at higher risk of thrombosis, it may be desirable to avoid the combination of extended increased VWF and FVIII levels (> 1.50 IU/mL) and extended use of tranexamic acid
- In dental procedures, consider use of local hemostatic measures

Major surgery – International guidelines

- Suggestion: targeting both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery
- Suggestion against: using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery

conditional recommendations (based on very low certainty in the evidence of effects)

Remarks:

- Keep both trough levels (FVIII and VWF) at ≥ 0.50 IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only 1)
- The specific target levels should be individualized based on the patient, type of procedure, and bleeding history as well as availability of VWF and FVIII testing
- The duration of the intervention can vary for specific types of surgeries

Neuraxial anesthesia – International guidelines

refers to spinal, epidural, or combined spinal-epidural procedures performed for surgical anesthesia for operative deliveries or pain relief during labor

NEURAXIAL ANESTHESIA DURING LABOR
Suggestion: targeting a VWF activity level of 0.50 to 1.50 IU/mL

conditional recommendations (based on very low certainty in the evidence of effects)

Remarks:

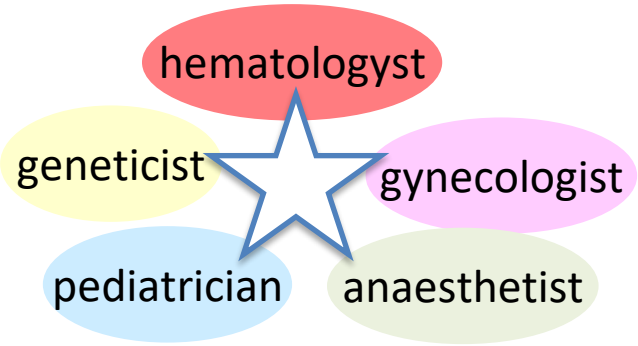
- Individual risk assessment performed on patient diagnosis and history: a third-trimester visit to check VWF and FVIII activity and plan anesthesia and delivery
- VWF activity levels should be maintained at > 0.50 IU/mL while the epidural is in place and for at least 6 hours after removal
- Decisions regarding anesthesia and delivery should be made in the context of a multidisciplinary discussion: obstetric anesthesiologist or other clinical performing the procedure and hematology, and obstetrics and shared decision with patient
- Discussions should take place well in advance of the patient's due date
- Patients should also be assessed for thrombotic risk postdelivery and prophylaxis should be provided when needed

Management of delivery in women with vWD

- **Pregnancy** is associated with a physiological rise in VWF and FVIII levels, however, in women with VWD type 3 there is lack of increase
- Clinically **relevant bleeding episodes** remain particularly rare in patients with VWD type 1 and women with VWF activities >50 IU/dL

Monitoring within the third trimester and ahead of the expected date of delivery should be taken into consideration

The risk of bleeding at delivery needs an experienced team



- **PPH**: Essential to determine the hemoglobin levels of the patients, and screen women for iron deficiency: anemia constitutes a risk factor and is associated with adverse fetal and maternal outcomes (appropriate therapy)

BLOOD LOSS IN PPH
Primary PPH: >1000 mL within 24h
Secondary PPH: heavier than normal between 24h and 6 weeks post delivery

Restrictive use of DDAVP: possible side effects. The risk of fetal hyponatremia, and the adverse effects of preeclampsia

- DDAVP interact with the oxytocin receptor and might promote uterine contraction
- DDAVP is practiced in the United Kingdom, both in pregnancy and at delivery

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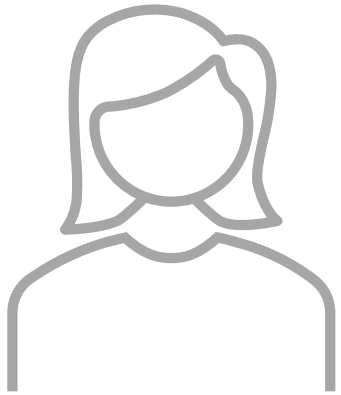
AK Malinowski, RA Kadir - Semin Thromb Hemost, 2023
E Fagr & W Miesbach - Hamostaseologie, 2022

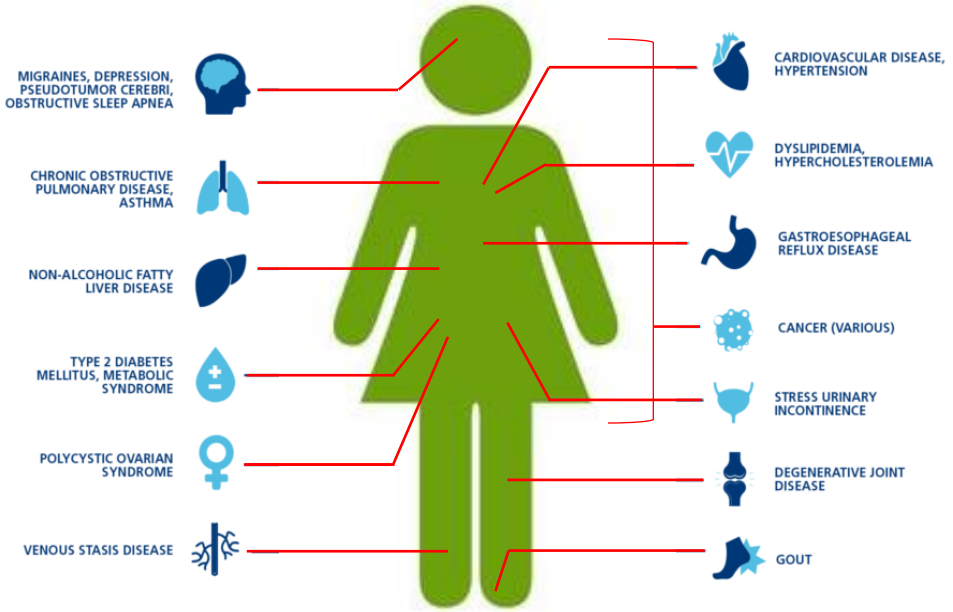
Clinical case:
Von Willebrand Disease and prophylaxis

Female patient, 47 years



- Family history of inherited bleeding disorder
- Diagnosis: VWD type 3
- Basal plasma levels:
  - **VWF:Ag <3%**
  - **VWF:RCo <6%**
  - **FVIII 1%**
- Normal BMI (19.5)

Comorbidities



- **Systemic lupus erythematosus** (significant skin involvement) → treated with low daily dose of prednisone
- **Psoriasis**
- **Gastroesophageal reflux** disease
- **Osteoporosis** treated with ibandronate monthly
- **Fibromyalgia** syndrome
- Active chronic **HCV+** hepatitis (mild steatosis at ultrasound; 4.4 kPa stiffness at fibroscan)

Clinical manifestations before prophylaxis

- Epistaxis, gum bleeding, and frequent bruising
- Menorrhagia leading to severe anaemia and blood transfusions
- Muscle and joint bleeding requiring episodic FVIII/VWF treatment
- **Recurrent GI bleeding leading to severe anaemia and blood transfusions**.
- **Two caesarean sections**, **dental extractions** and **endoscopic procedures** were performed with FVIII/VWF prophylaxis

Multiple upper GI tract endoscopy was performed:
→ angiodysplastic lesion of the duodenum treated with argon-plasma coagulation

On subsequent episodes a new endoscopy was performed:
→ duodenal bleeding without evident lesions (sine materia) treated with hemoclips

Treatment

Acute phase of GI bleeding:

- red blood cells transfusion
- supplementation with iron and folic acid
- haemostatic treatment with a VWF/FVIII plasmaderived concentrate, maintaining FVIII coagulant >50 IU/dL and VWF activity (VWF:RCo) >30 IU/dL in the first 7 days

Prophylactic regimen:
VWF/FVIII concentrate (50 IU/kg of FVIII 3 times/week) was started

[episode of acute GI bleeding, requiring 4 U of red blood cells and cycles of iron therapy for the following 2 years]

Reduction of prophylactic regimen:

- after 2 years: 50 IU/kg of FVIII twice/week
- after 2 additional years: 40 IU/kg of FVIII twice/week

The patient had no other episode of acute GI bleeding in the next 5 years and received no more iron therapy.
The patient is still on prophylaxis

Conclusions

- Prophylaxis is important for patients with type 3 VWD with a severe bleeding phenotype
- No evidence-based recommendation can be issued on the best timing to start/stop the prophylactic regimen nor on its dosing
- Our practice:
  - A prophylactic regimen (30-50 IU/kg of VWF 2-3 times/week) after the first episode of GI bleeding should be proposed to the patient
  - In cases of severe type 3 VWD characterized by low levels of FVIII:C (<5 IU/dL) and repeated joint bleeding prophylaxis should be started as soon as possible

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@EHCTVChannel EHC Youtube channel

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ERN-EuroBloodNet's EDUcational Youtube channel

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