von Willebrand sykdom:

- Diagnostikk og håndtering

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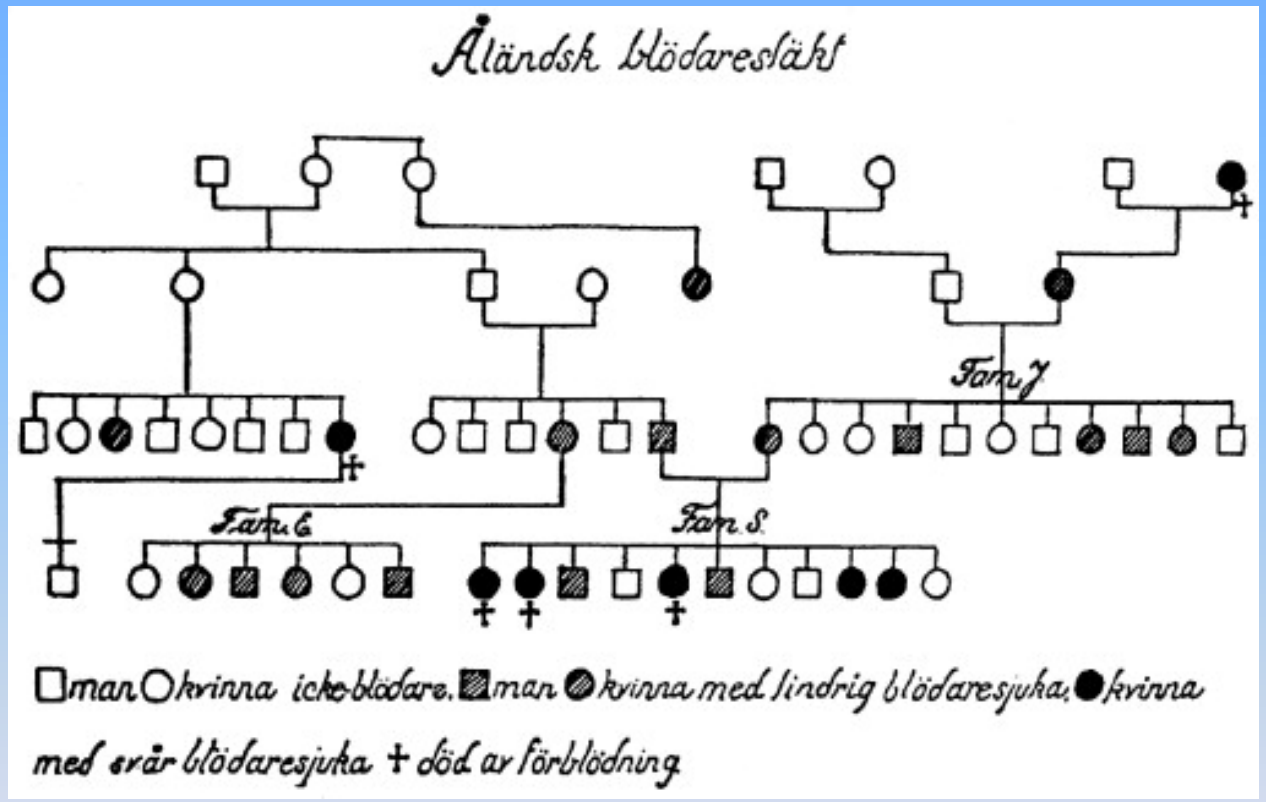
von Willebrand sykdom



1926- Pseudo hemofili - Erik A von Willebrand

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von Willebrand sykdom

Den vanligste arvelige blødningssykdommen.

Personer med von Willebrands sykdom i Norge

Grad	*Antall*	*Totalt*
Alvorlig grad	38	
Øvrige tilfeller a)	813	
		851

Dvs ca 0,018% av den norske befolkningen

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von Willebrand disease (VWD) is the most frequent inherited bleeding disorder[1]

Prevalence:

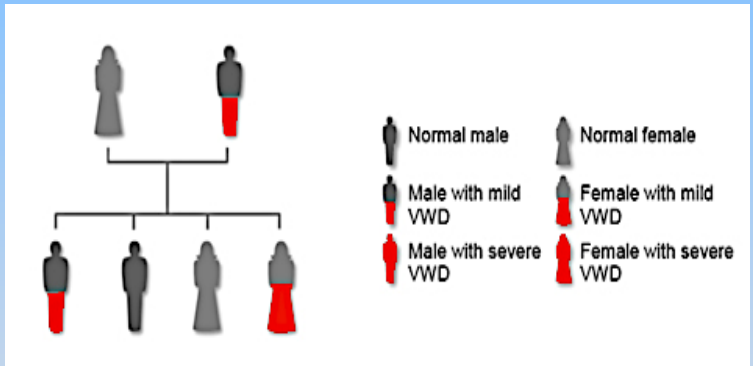
- All forms: Up to 0.6–1.3%[2]
- Symptomatic VWD: ~0.01%[3]

Inheritance:[4]

- The gene for VWF is located on the short arm of chromosome 12[5]

Autosomal dominant (not sex linked)

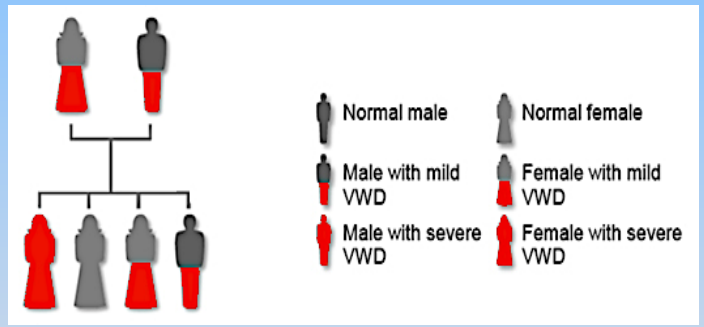
- Type 1 and Type 2 (except Type 2N)



- 50% probability of inheritance

Autosomal recessive (not sex linked)

- Type 3 and Type 2N (and some type 2A subtypes: 2A/IIC or 2A/IID)



- 25% probability of inheritance

VWD, von Willebrand disease; VWF, von Willebrand factor

1. Bolton-Maggs PHB, et al. Haemophilia. 2008;14(Suppl. 3):56–61; 2. James AH. Obstet Gynecol Surv. 2006;61:136–145; 3. Bowman M, et al. J Thromb Haemost. 2010;8(1):213–216;
4. Centers for Disease Control and Prevention website. http://www.cdc.gov/ncbddd/vwd/inherited.html. Accessed August 30, 2018;
5. Reininger AJ. Haemophilia. 2008:14(Suppl 5);11–26

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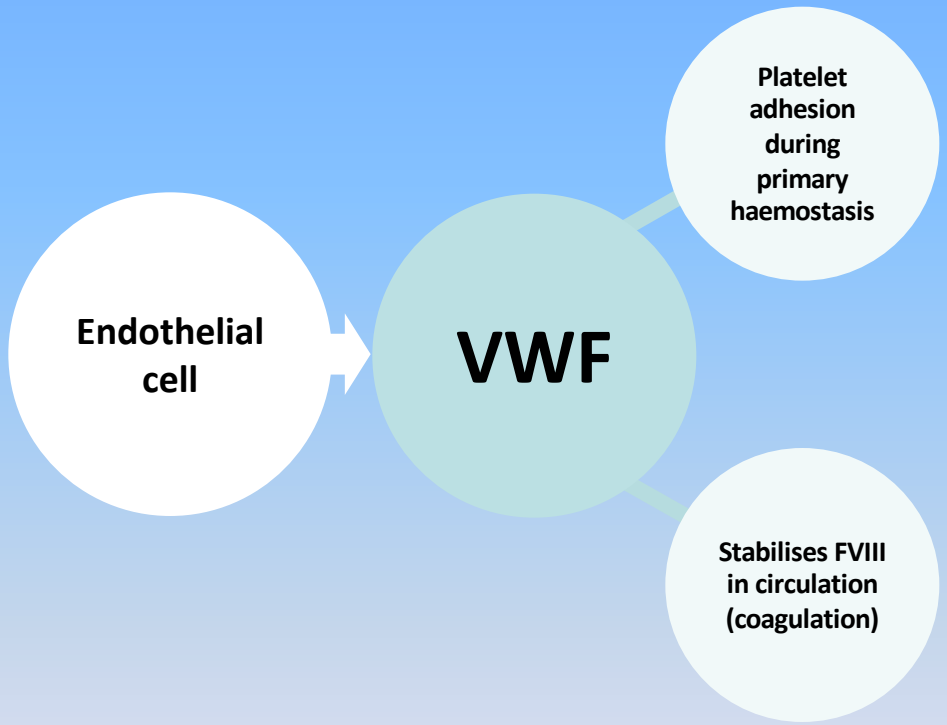
von Willebrand factor (VWF) plays an important role in haemostasis[1,2]



Primary haemostasis

- Mediates platelet adhesion to damaged vascular subendothelium primarily collagen
- Binds to collagen and platelet receptors such as GPIbα and αIIbβ3

Secondary haemostasis

- Formation of non-covalently bound VWF-FVIII complex
- VWF prevents rapid clearance and proteolysis of FVIII which increases the half-life of FVIII

FVIII, factor VIII; VWF, von Willebrand factor

1. Reininger AJ. Haemophilia. 2008:14(Suppl 5);11–26; 2. Mannucci PM. N Engl J Med. 2004;351(7):683–694

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Clinical manifestations of VWD

The primary cause of VWD is deficiency or dysfunction of von Willebrand factor (VWF)[1]

- **Mucocutaneous bleeds** are frequently reported in patients with VWD[2]
- **Menorrhagia** is an important clinical issue among women with VWD[3,4]
  - In a study of 102 women with VWD and 88 women as controls, 95% reported menorrhagia, as did 61% of women without VWD[3]
  - Prevalence of VWD is 5–20% among women with menorrhagia[4]
- **GI angiodysplasia** is the most common vascular lesion of the GI tract and occurs in up to 11.7% of VWD patients[5,6]
- **Joint damage** in VWD is associated with joint bleeds[7,8]
- Joint bleeds occur most frequently in Type 3 VWD[2]

GI, gastrointestinal; VWD, von Willebrand disease; VWF, von Willebrand factor

1. Sadler JE, et al. J Thromb Haemost. 2006;4(10):2103–2114; **2.** Federici AB, et al. Ann Med. 2007;39(5):346–358; **3.** Kirtava A et al. Haemophilia. 2003;9(3):292–297; **4.** Kujovich JL. Am J Hematol. 2005;79(3):220–228; **5.** Starke RD, et al. Blood. 2011;117(3):1071–1080; **6.** Fressinaud E, et al. Thromb Haemost. 1993;70(3):546; **7.** Tjonnfjord GE. Haematologica reports. 2005;1:7–8; **8.** van Galen KPM, et al. Haemophilia. 2015;21(3):e185–e192

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VWD Subtyper

Type	Defekt	Arv
Type 1	Kvantitativ	Dominant Redusert penetrans
Type 2 (2A, 2B, 2M, 2N)	Kvalitativ	Dominant (Noen recessive)
Type 3	Kvantitativ (Fravær av vWF)	Recessiv

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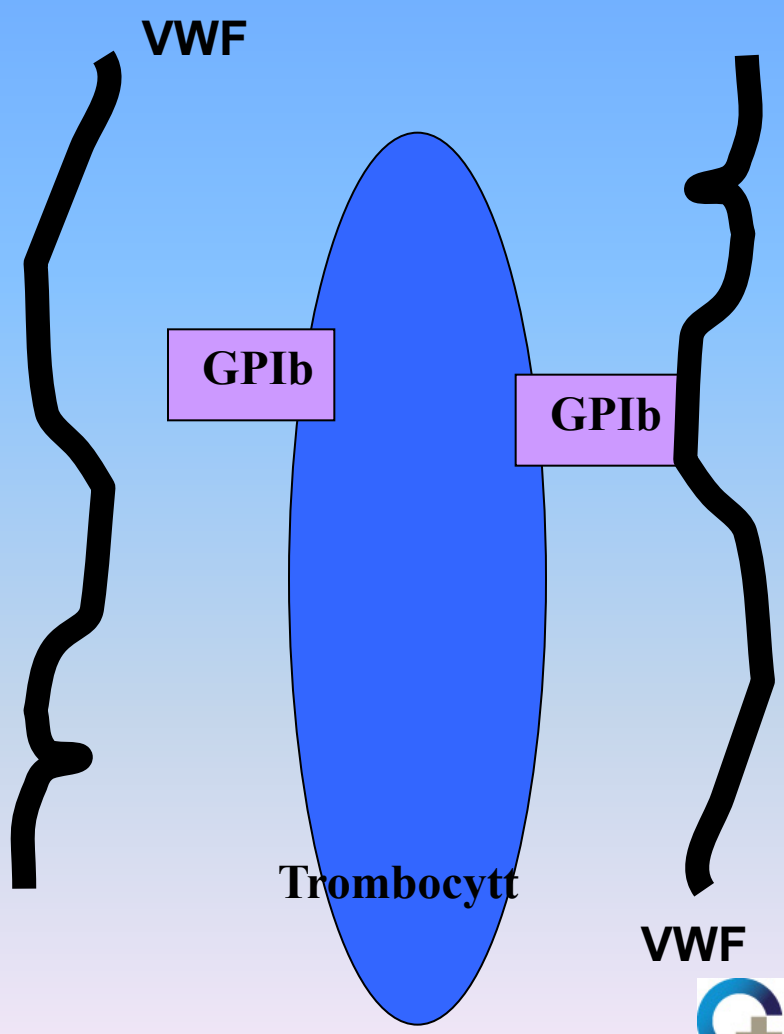
Type 2 vWD

Nedsatt binding til trombocytter

2A: Fravær av HMW vWF multimerer

2M: HMW vWF multimerer tilstede



Økt binding til trombocytter

2B: Fravær av HMW vWF multimerer Trc ↓

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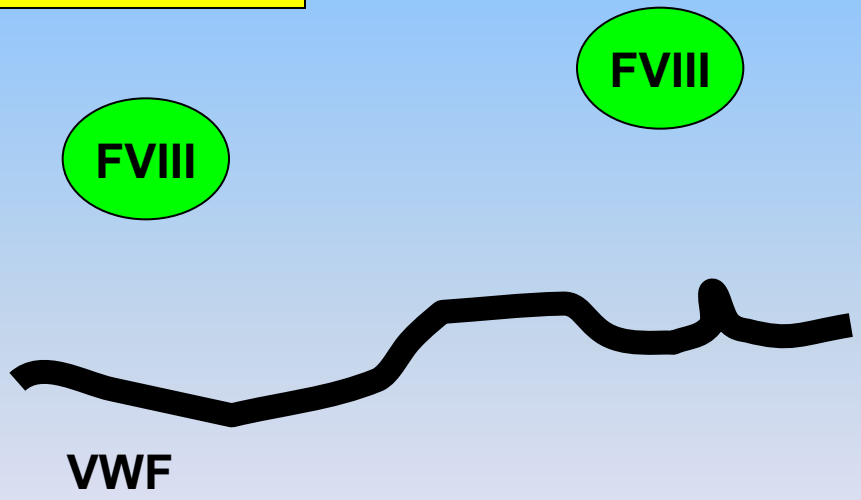
Type 2 vWD

2N: Nedsatt binding av FVIII til vWF



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von Willebrand sykdom

- **Diagnose**

  - **Symptomer**
  - **Familiær opphopning**
  - **Lab. tester**

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von Willebrand sykdom
Laboratorietester

- VWF mengde (VWF:Ag) ↓
- VWF aktivitet: (VWF:akt) ↓

- FVIII ↓
- INR -
- APTT- (↑)
- Blodplatetall
- Blodtype

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Laboratory procedures used for diagnosis and subclassification in von Willebrand disease.

Method	Diagnostic and monitoring purposes
Ristocetin Cofactor activity (VWF:RCo)	The main functional VWF method. Sensitive to loss of high multimer VWF and measures the ability of the VWF to bind GPIb and, hence, cause agglutination of platelets or latex particles coated with recombinant GPIb protein.
VWF antigen (VWF:Ag)	Quantitation of VWF antigen. Used to differentiate between VWD type 1 and type 2.
Ristocetin induced platelet aggregation (RIPA) using patient's platelet rich plasma (PRP)	Detection of the sensitivity of platelets to ristocetin. Increased sensitivity at ristocetin concentration of 0.5 mg/ml or lower, is indicative of VWD type 2B. RIPA is absent in VWD type 3 and generally decreased in type 2A.
VWF collagen binding (VWF:CB)	Detects VWF multimer impairments as the VWF:RCo assay does but specifically assesses the collagen binding capacity of VWF. The assay is performed in the microplate (ELISA) format and the discriminatory power is dependent on type of collagen used.
VWF multimeric distribution and –pattern	Procedure essential for detection of VWF multimeric size distribution
FVIII coagulation activity (FVIII:C)	Determination of FVIII coagulation activity. A disproportionally reduced FVIII (compared to VWF) is found in VWD type 2 N.
FVIII binding capacity of the VWF (VWF:FVIIIB)	Determines the capacity of VWF to bind FVIII. Specific test for VWD type 2N.
von Willebrand factor propeptide (VWFpp)	

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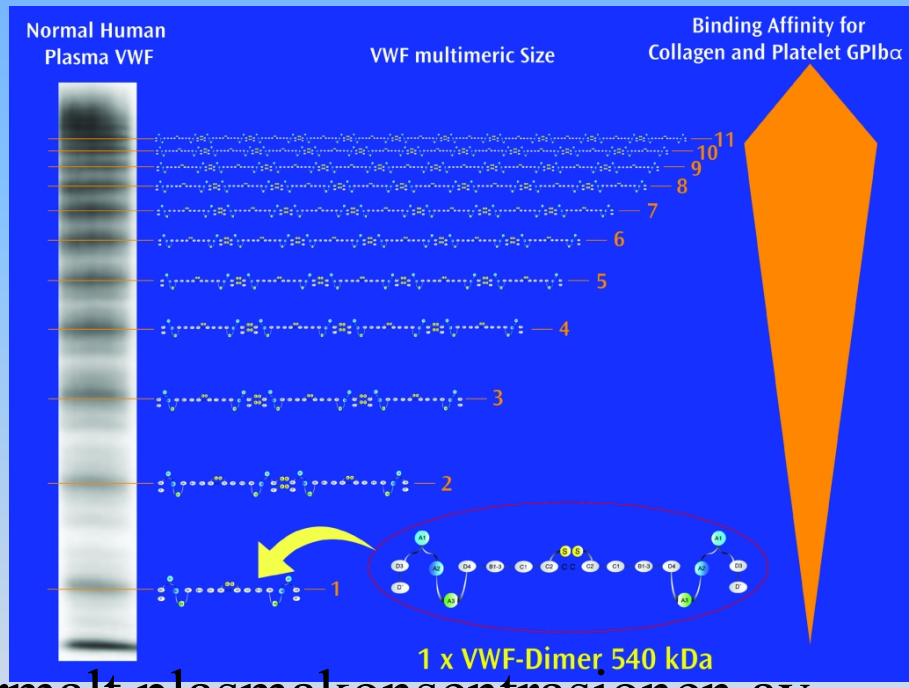
von Willebrand sykdom
Laboratorietester 2

- vWF:Ag Multimeranalyse



- Desmopressin –test

  - 0,3 µg/kg iv øker normalt plasmakonsentrasjonen av vWF/FVIII 2-5 x. Benyttes for å se hvorvidt pasienten får en tilfredsstillende stigning - som kan event utnyttes terapeutisk.

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von Willebrand sykdom
Diagnose Lab.tester

- **VWF mengde < 35% → vWD type 1**
- **VWF aktivitet < 35% → vWD type 1**
- **VWF:Akt/vWF:Ag > 0,7 vWD type 1**
  < 0,7 vWD type 2
- **Mangler vWF → type 3**

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von Willebrand sykdom
Diagnostiske kriterier type 1

- Signifikant blødningstendens

- VWF mengde < 35%
- VWF aktivitet < 35% målt ved 2 anledninger
- VWF:Akt/vWF:Ag > 0,7 VWD type 1

- Normalt multimermønster

- Positiv familieanamnese

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Diagnostiske problemer ved mild von Willebrand sykdom type 1

- Milde symptomer
- VWF nivåer varierer
  - -Menstruasjonssyklus
  - -Hypothyreose ↓
  - - Stress, betennelse, graviditet = VWF ↑↑
  - - Blodtype O → 30% reduksjon i VWF
  - - Alder – normalnivå ved 6 mnd.

Gjentatte analyser på 2 forskjellige tidspunkter bør tas for å stille diagnosen

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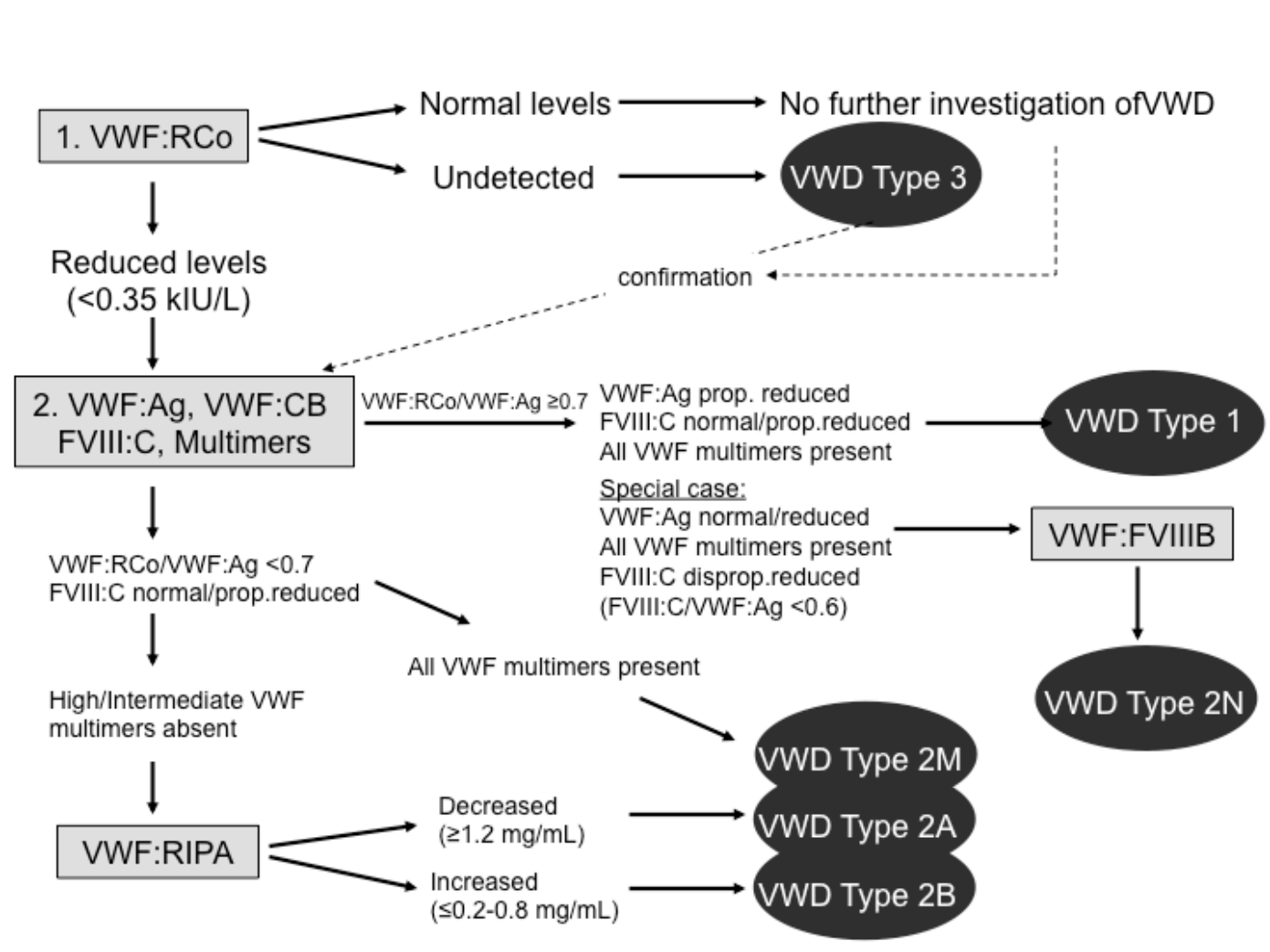
Laboratory algorithm for investigating suspected von Willebrand disease.



von Willebrand sykdom
Behandling

- Stimulere endogen hemostase

  Desmopressin (DDAVP) - Octostim

  - 0,3 µg/kg iv, sc. Kan også gis intranasalt
  - Kan gjentas etter 8-12 timer
  - Obs hyponatremi!
  - Nesten alle Type 1 svarer tilfredsstillende
  - Ingen effekt på Type 3
  - Ikke benyttes på Type 2B

  Traneksamsyre - Cyklokapron

  - Kan gis iv, po. Samt lokalt (som munnskyll)
  - 10 mg/kg x 3-4 iv , 25 mg/kg x 3-4 po
  - Alle typer vWD

  P-piller – kan gi god kontroll ved menoragi

Current treatments in VWD

		Mechanism of action	Route of administration	Use in practice	Potential side effects
Promote VWF production	**Desmopressin (DDAVP)***	↑ VWF and FVIII production and secretion[1]	IV, SC, intranasal[1]	Bleeding episodes and short-term use prior to minor surgery[2]	Antidiuretic, tachyphylaxis, facial flushing, hyponatraemia[1]
	Hormonal contraceptives	↑ FVIII and/or VWF production and secretion[1]	Various e.g. oral, intrauterine, SC[3]	Primary treatment option for menorrhagia in women not desiring pregnancy[1]	Generally well-tolerated, caution in women with thrombophilia[3]
VWF replacement	**Plasma-derived VWF/FVIII complex**	Temporarily replaces VWF and FVIII[2]	IV[2,4]	On demand, perioperative treatment and prophylaxis (varies by brand)[1]	Rare but life-threatening anaphylactic reaction, inhibitor formation, thromboembolic reactions[1]
	Plasma-derived VWF	Temporarily replaces VWF and stabilises endogenous FVIII[4]			
	Recombinant VWF	Temporarily replaces VWF, and stabilises endogenous FVIII[5]	IV[5]	On demand and perioperative treatment[5]	Thromboembolic and hypersensitivity reactions. Inhibitor formation[5]
Promote haemostasis	**Antifibrinolytics**	Inhibit fibrinolysis[1]	Oral or IV[1]	As adjunct to DDAVP or clotting factor concentrates in mucocutaneous sites (e.g. tonsillectomy, tooth extraction)[1]	Thrombosis, nausea and vomiting, DIC, urinary tract obstruction and bleeding[1]
	Topical agents	Enhance thrombus formation[1]	Topical[1]	Minor surface bleeding and adjunctive treatment in surgery[3]	Thrombosis, hypersensitivity reactions[3]

1. Neff AT & Sidonio RF. Hematology Am Soc Hematol Educ Program. 2014;536–541; **2.** Castaman G, et al. Haematologica. 2013;98(5):667–674; **3.** Nichols WL, et al. Haemophilia. 2008;14(2):171–232; **4.** Willfact Summary of Product Characteristics; **5.** VEYVONDI® EU Summary of Product Characteristics draft date August 2018

von Willebrand sykdom
Behandling

- Substitusjonsbehandling
  - VWF konsentrat m/FVIII
    (Octanate)
    Haemate
    Wilate
  - VWF konsentrat uten FVIII
    (Wilfact)
    Veyvondi- rekombinant

Ved alvorlige blødninger/kirurgi:
VWF aktivitet > 50% i 3-5 dager
VWF aktivitet ikke > 200%, eller FVIII > 250%

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von Willebrand sykdom Behandling

Type vWD	Profylakse/behandling
1	Desmopressin Traneksamsyre P-Pille ved menoragi
2	vWF konsentrat Traneksamsyre Desmopressin kan gis forutsatt respons- unntatt type 2B
3	vWF konsentrat Traneksamsyre

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Treatment with concentrates in clinical situations for patients with VWD

Clinical situation	Loading dose of VWF:RCo	No. of infusions and maintenance dose	Target plasma level
Major surgery/bleeding[1]	40-60 IU/kg*	20-40 IU/kg, every 8-24 h	>50 IU/dL; maintain levels for 7-14 days (VWF:Rco and FVIII)
Minor surgery/bleeding[1]	30-60 IU/kg*	20-40 IU/kg, every 12-48 h	>50 IU/dL for 1-4 days (VWF:Rco and FVIII)
Dental extractions or invasive procedures[2]	30 IU/kg	Single dose	>50 IU/dL for >12 h (FVIII:C)
Spontaneous bleeding[2]	20-60 IU/kg	One daily dose until bleeding stops. Monitor clinically	>30 IU/dL (~2-4 days) (FVIII:C)
Delivery and puerperium[2]	50 IU/kg	Once daily	>50 IU/dL; maintain levels for 3-4 days (FVIII:C)

*Loading dose is in VWF:RCo IU/dL.

FVIII:C=FVIII procoagulant activity; VWD=von Willebrand disease; VWF=von Willebrand factor; VWF:RCo=VWF ristocetin cofactor activity.

1. Nichols WL et al. *Haemophilia*. 2008;14:171-232.

2. Castaman G et al. *Haematologica*. 2013:98:667-674.

VWD- Pregnancy and delivery

Plasma levels of VWF and FVIII increase significantly and may even normalize in patients with mild type 1 VWD.

In type 3, VWF and FVIII do not increase and prophylactic treatment with VWF concentrates should be considered during pregnancy and delivery. Tranexamic acid is the first treatment option in case of mucocutaneous bleeds.

Generally, vaginal delivery is regarded as safe if VWF:RCo is > 0.40 kIU/L whereas for caesarean section the VWF:RCo level should be > 0.50 kIU/L.
The delivery should preferably take place at an obstetrical unit close to the hemophilia center.

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VWD- Pregnancy and delivery

Tranexamic acid

In mild cases (DDAVP responders), DDAVP is administered intravenously in a dose of 0.3 microgram/kg immediately after delivery. One dose is usually sufficient, but DDAVP may be repeated with 12- 24 h intervals if needed.

In DDAVP non-responders: VWF concentrate when the delivery starts. (50-60 IU VWF:RCo/kg i.v.)
In severe cases, treatment with a VWF concentrate about 3 times weekly, is continued over a period of two weeks postpartum.

Complications of treatment

- Alloantibodies[1,2]
  - Patients with VWD Type 3 can form alloantibodies to exogenously provided VWF
    - In rare cases, exposure to exogenous VWF can be dangerous and cause anaphylactic reactions
    - Recombinant FVIII (rFVIII) and/or rFVIIa can be used
- Thrombosis[2]
  - Sustained high plasma levels of FVIII:C may increase the risk of venous thrombosis
  - FVIII:C levels should be monitored to ensure they remain <150 IU/dL

FVIII:C=FVIII procoagulant activity; VWD=von Willebrand disease; VWF=von Willebrand factor.

1. Neff AT, Sidonio RF. *Hematology ASH Educ Program.* 2014;536-541.

2. Castaman G et al. *Haematologica*. 2013;98:667-674.

Akkvirert von Willebrand sykdom

•Mindre hyppig enn medfødt VWD
•Enten kvantitativt eller kvalitativt betinget.
• 50-60% forårsaket av lymfo-eller myeloproliferative sykdommer
•Lab funn er lik de med medfødt VWD, multimermønster kan være normalt, men ofte finner man nedsatt mengde av de høymolekylære multimerer som ved VWD type 2A.

3 mekanismer:
•Økt clearance eller antistoffer rettet mot VWF
•Økt shear indusert proteolyse av VWF
•Økt binding av VWF til plater eller andre celler.

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von Willebrand sykdom - Konklusjon

Diagnose bygger på 3 kriterier:

- Blødningstendens
- Familiehistorie
- Laboratoriedata

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