EHC Webinars

European von Willebrand Disease Community

Von Willebrand disease

Topic on focus

ERN-EuroBloodNet

Von Willebrand Disease is not hemophilia

Prof Jeroen Eikenboom (Leiden University Medical Center, the Netherlands)
Baiba Ziemele (Latvia Hemophilia Society, EHC VWD, WFH VWD, ERN-EuroBloodNet ePAG).

Co-funded by the Health Programme of the European Union

European von Willebrand Disease Community

EHC european haemophilia consortium
Advocating for people with haemophilia and congenital bleeding disorders

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Name: Jeroen Eikenboom

Affiliation: Leiden University Medical Center

☐ I have no potential conflict of interest to report

☑ I have the following potential conflict(s) of interest to report

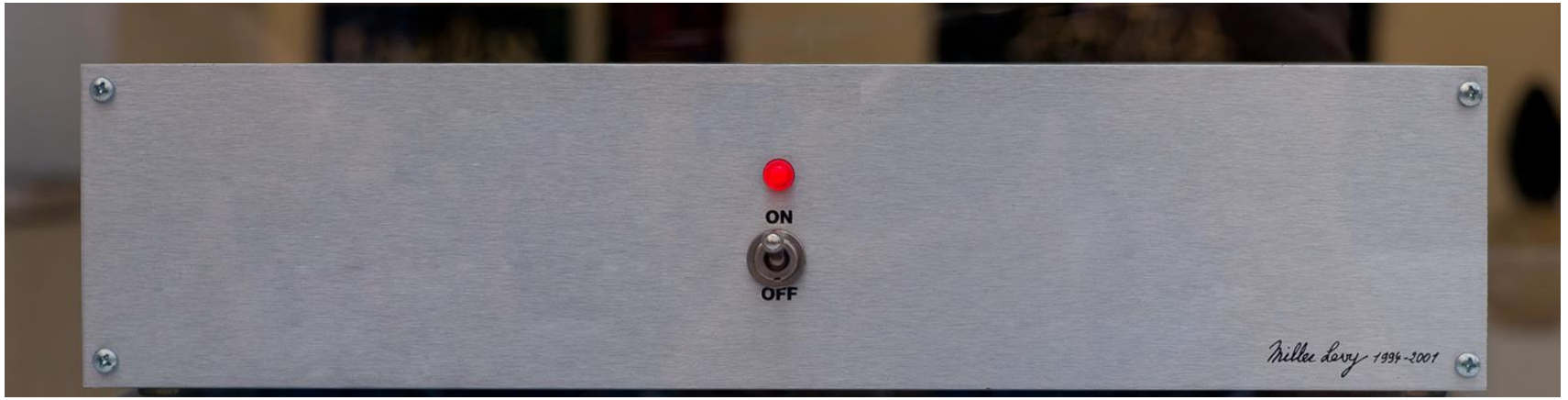
Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	CSL Behring
Receipt of honoraria or consultation fees:	-
Participation in a company sponsored speaker's bureau:	-
Stock shareholder:	-
Other support (please specify):	-
Scientific advisory board	-

Patients' learning objectives

Von Willebrand Disease is not hemophilia

1. **Shortly about coagulation cascade: various bleeding disorders**
2. **von Willebrand disease: what it is and how it differs from other bleeding disorders**
3. **Different VWD types**
4. **Variety of symptoms**
5. **Phenotype - the range between mild and severe expression of disease**
6. **VWD guidelines on diagnosis and on management**
7. **How to get diagnosis correctly? When and what tests to take?**
8. **What are the treatment options?**

Introduction Blood Coagulation - Hemostasis



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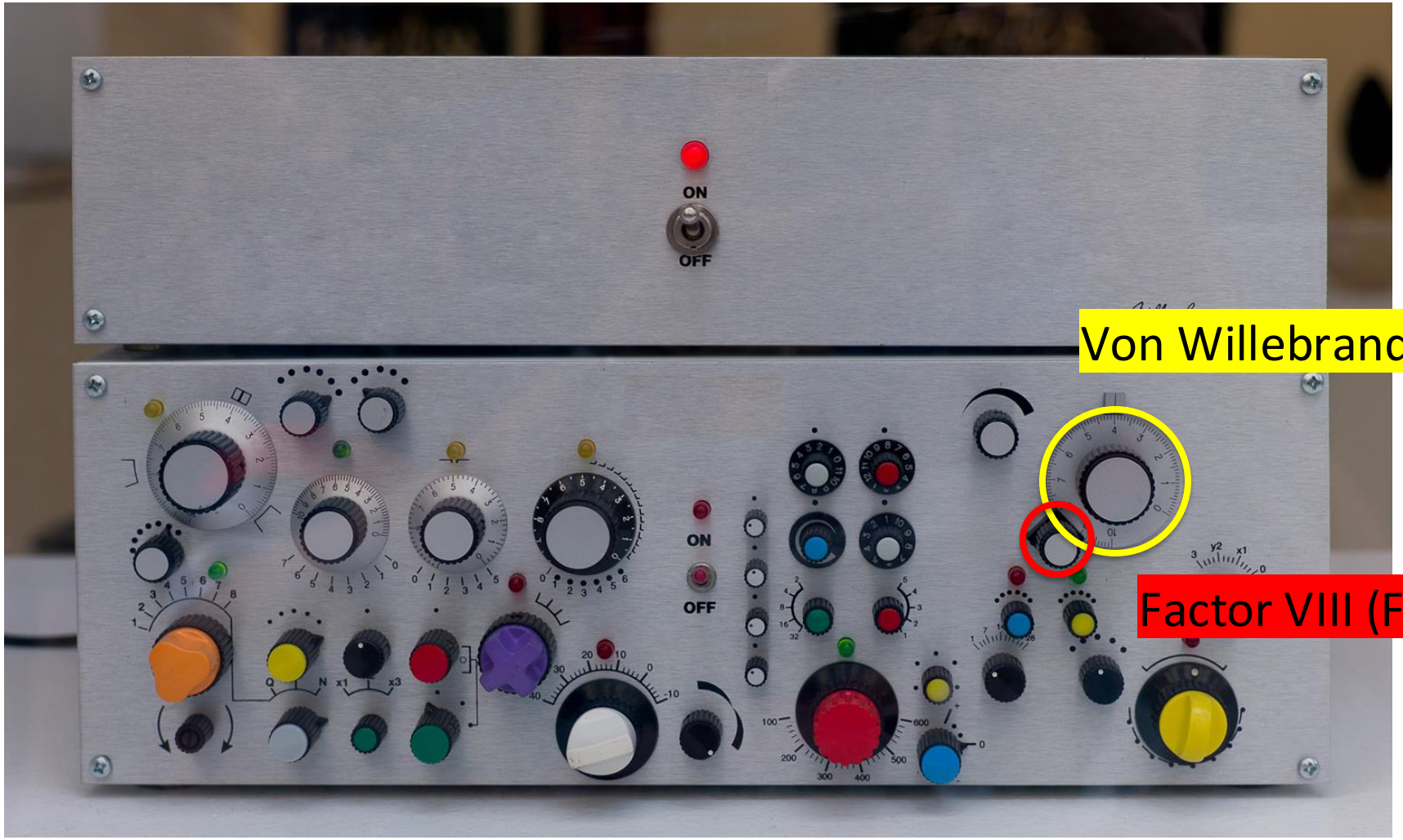
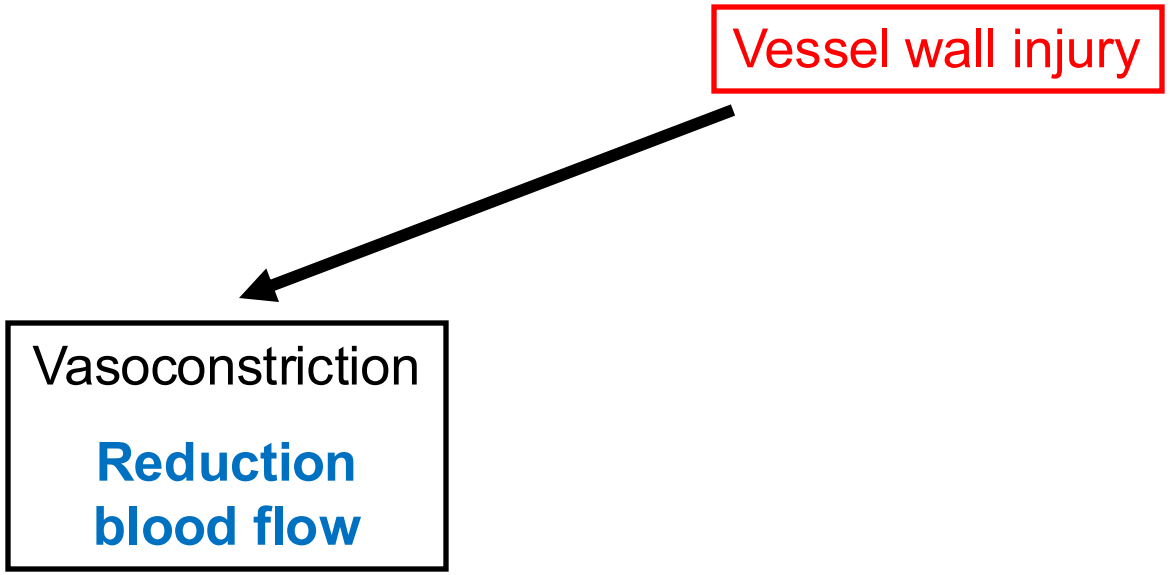


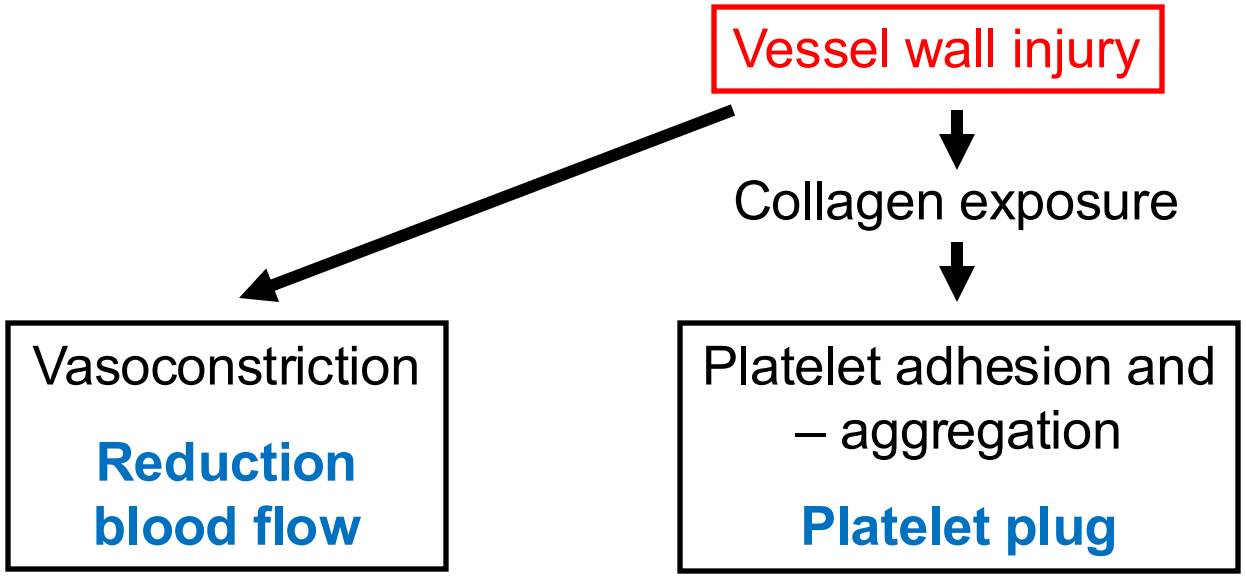
Mechanism of hemostasis

Vessel wall injury

Mechanism of hemostasis



Mechanism of hemostasis



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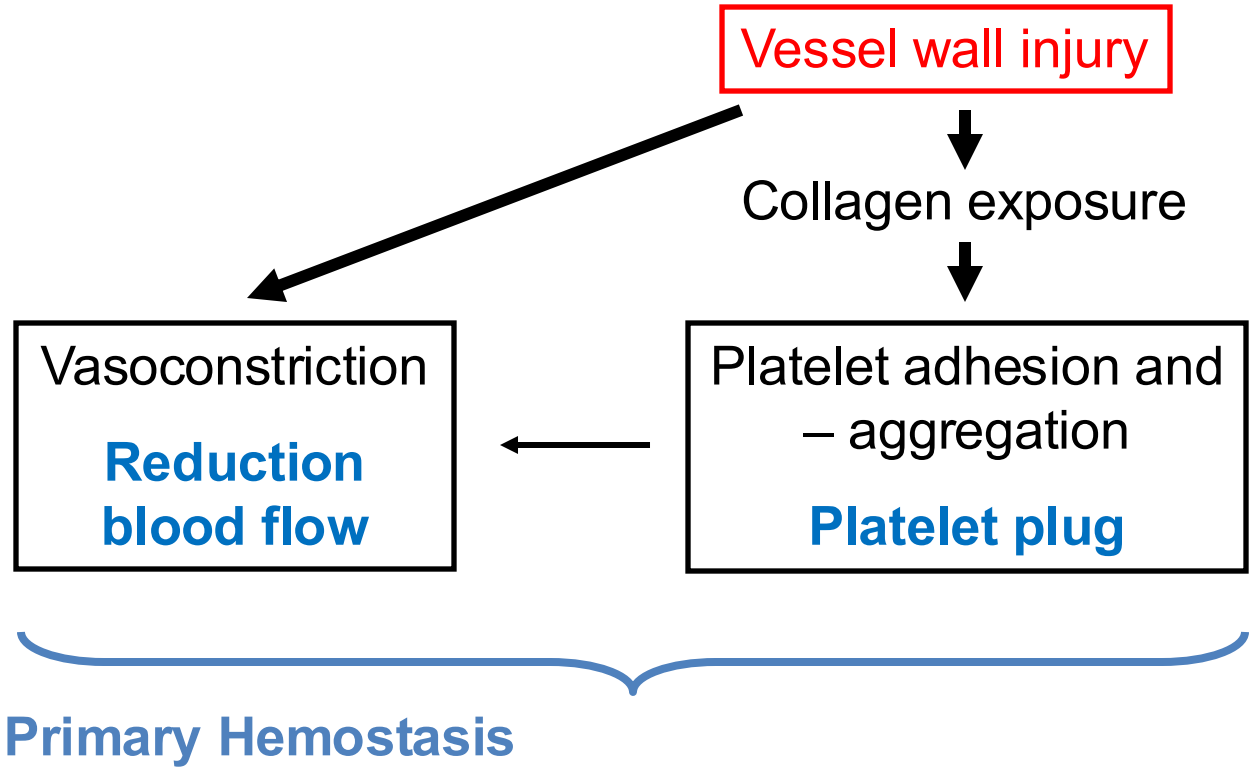

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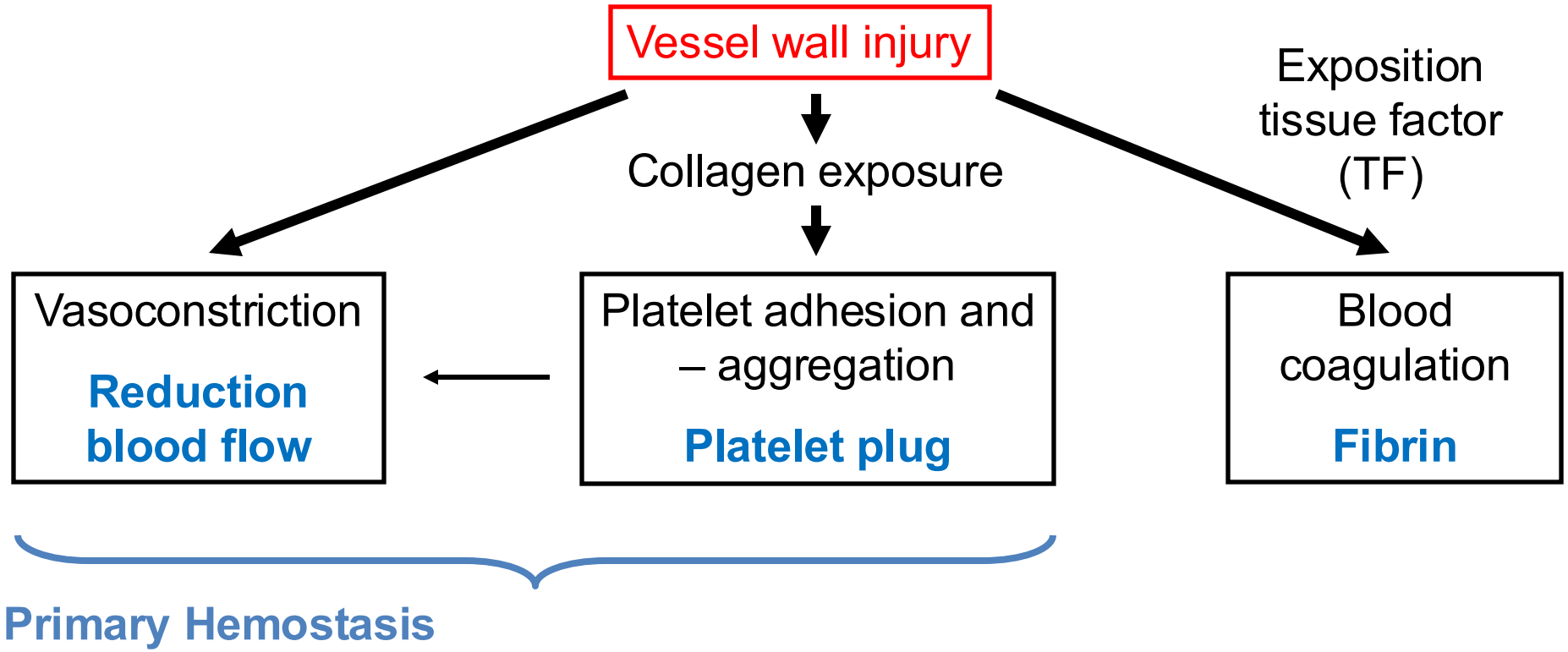

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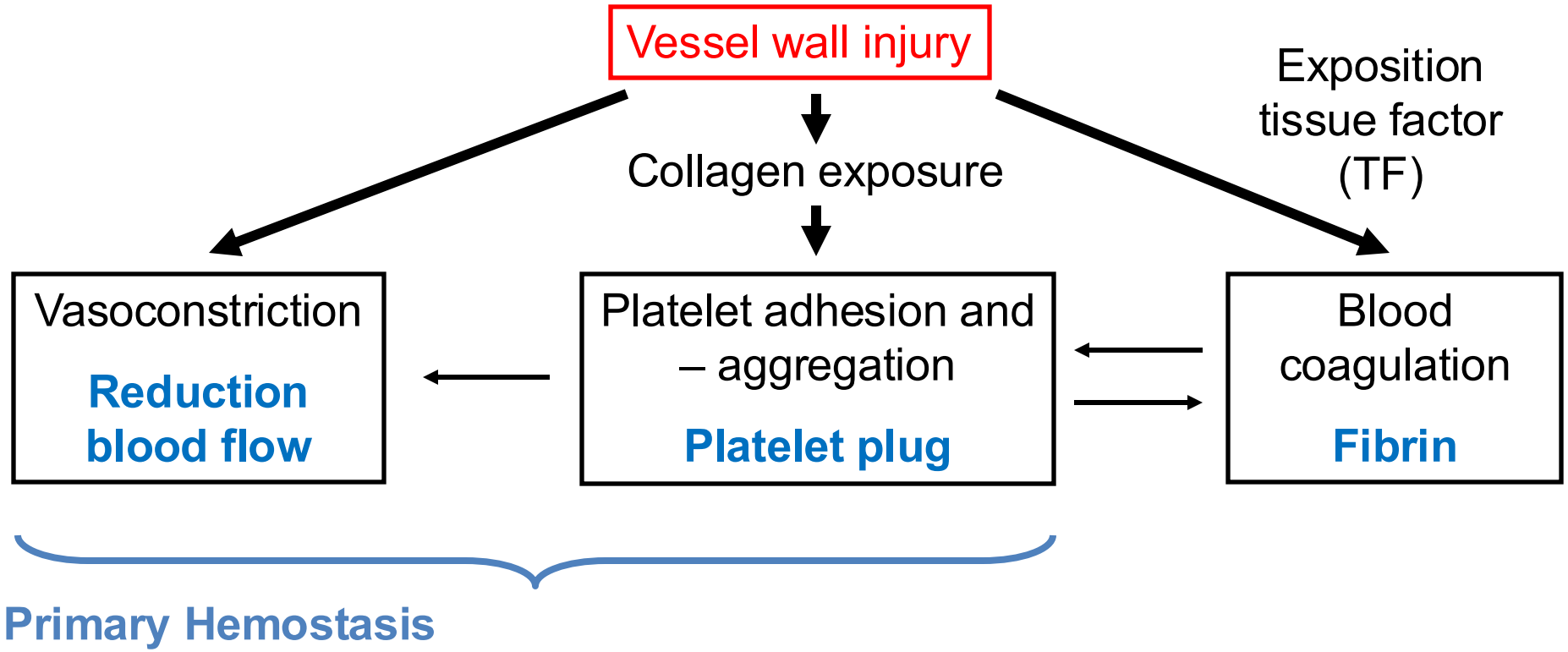

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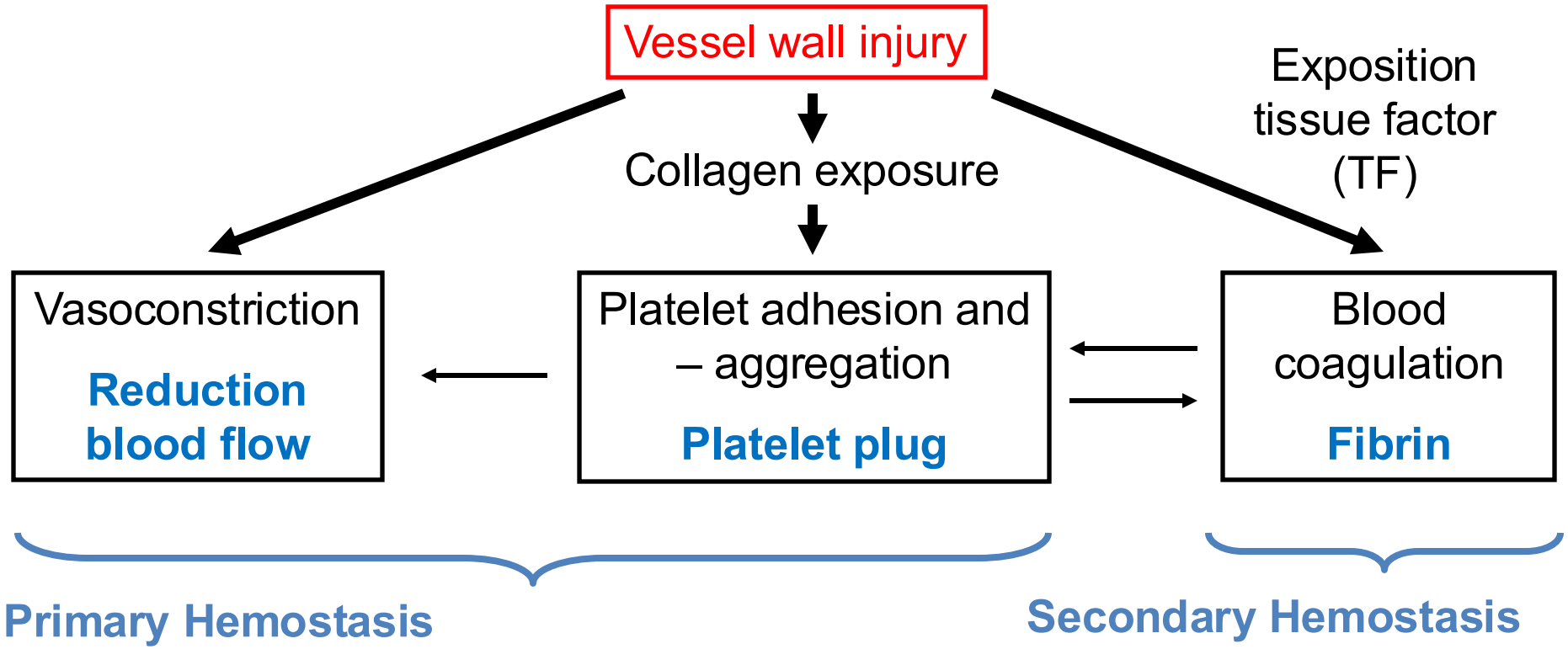

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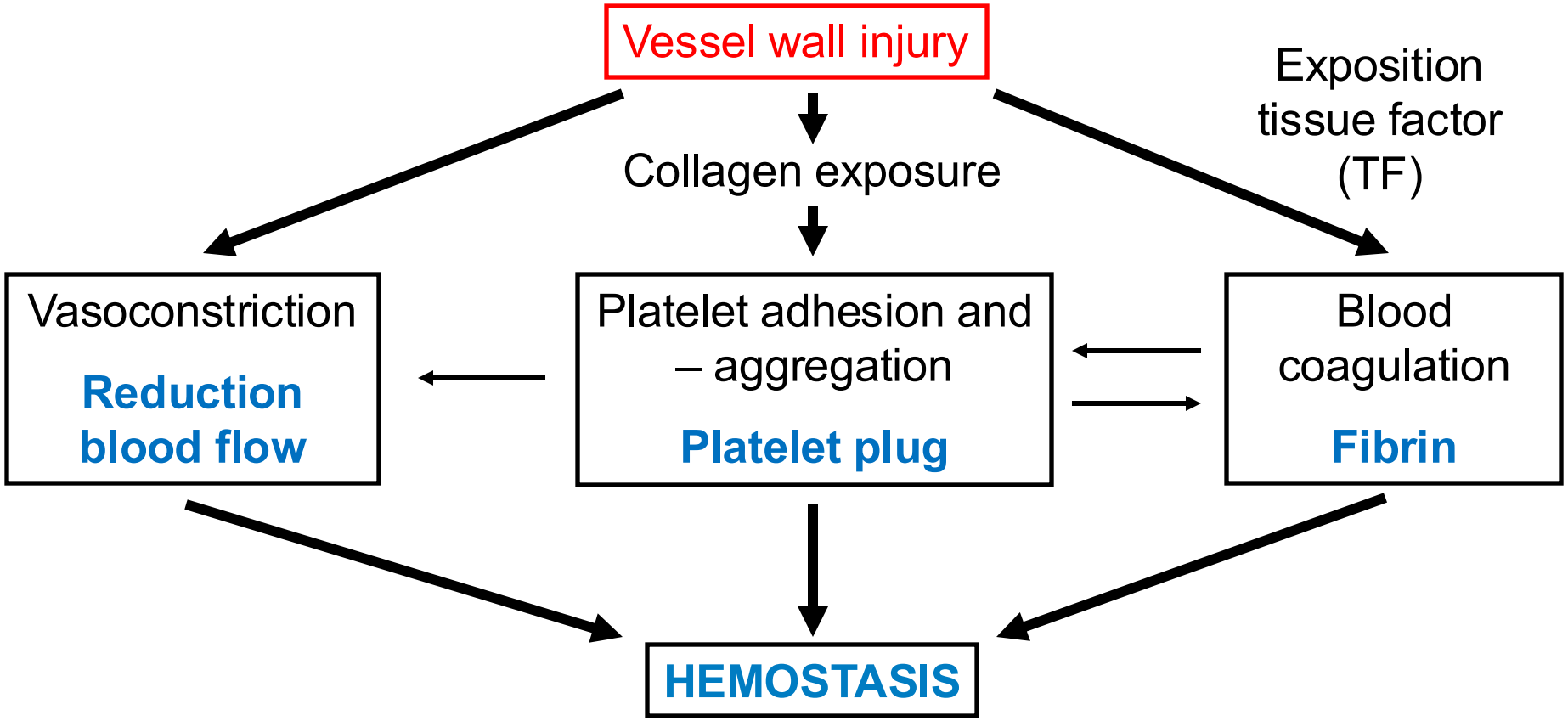
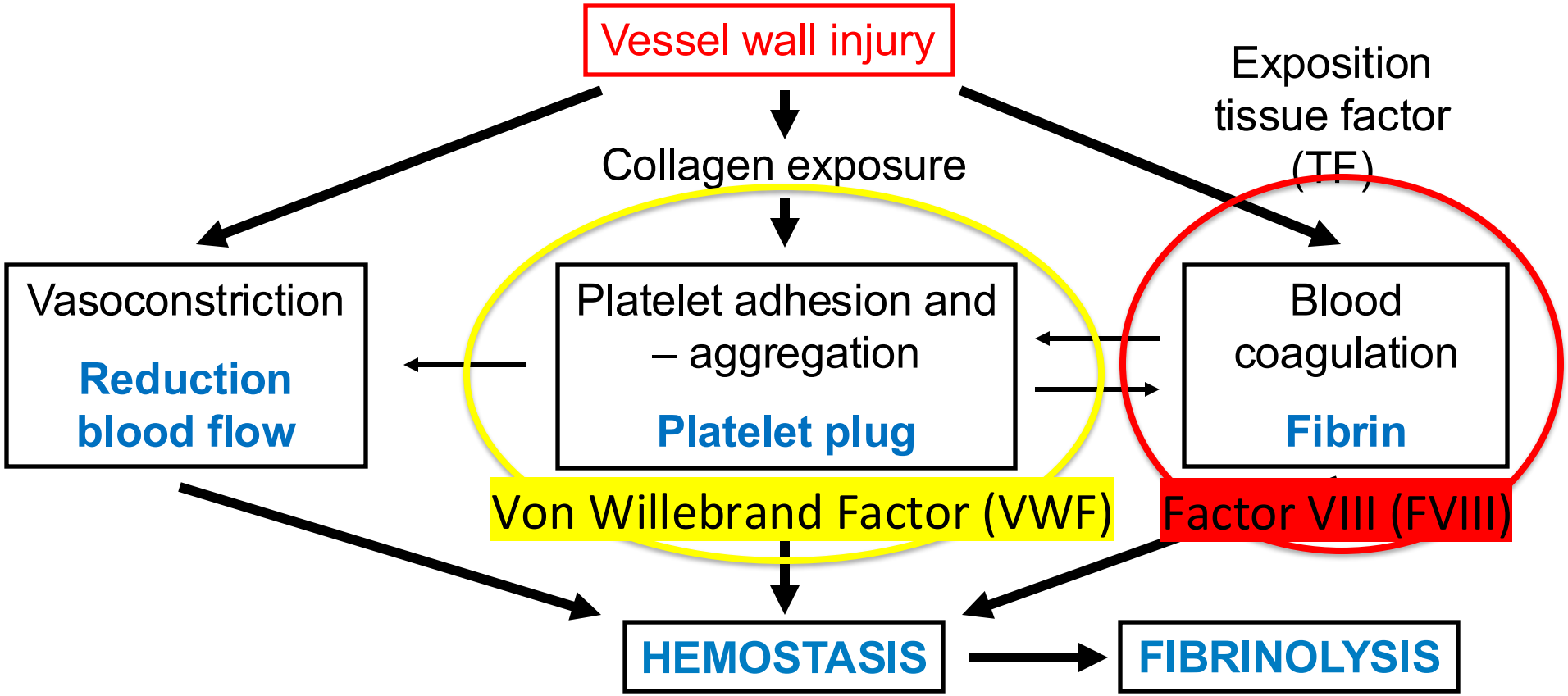


Mechanism of hemostasis



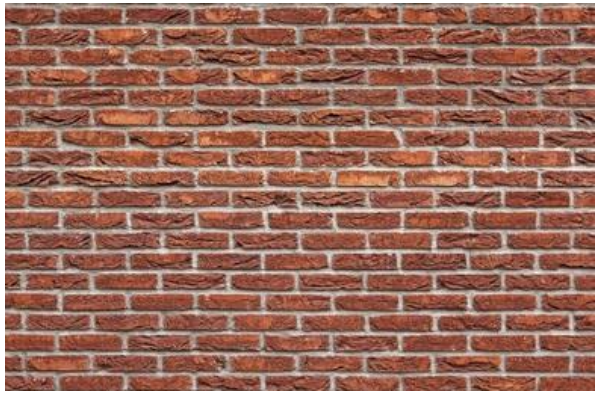
What is Von Willebrand disease (VWD)?

Platelets

+

VWF

→



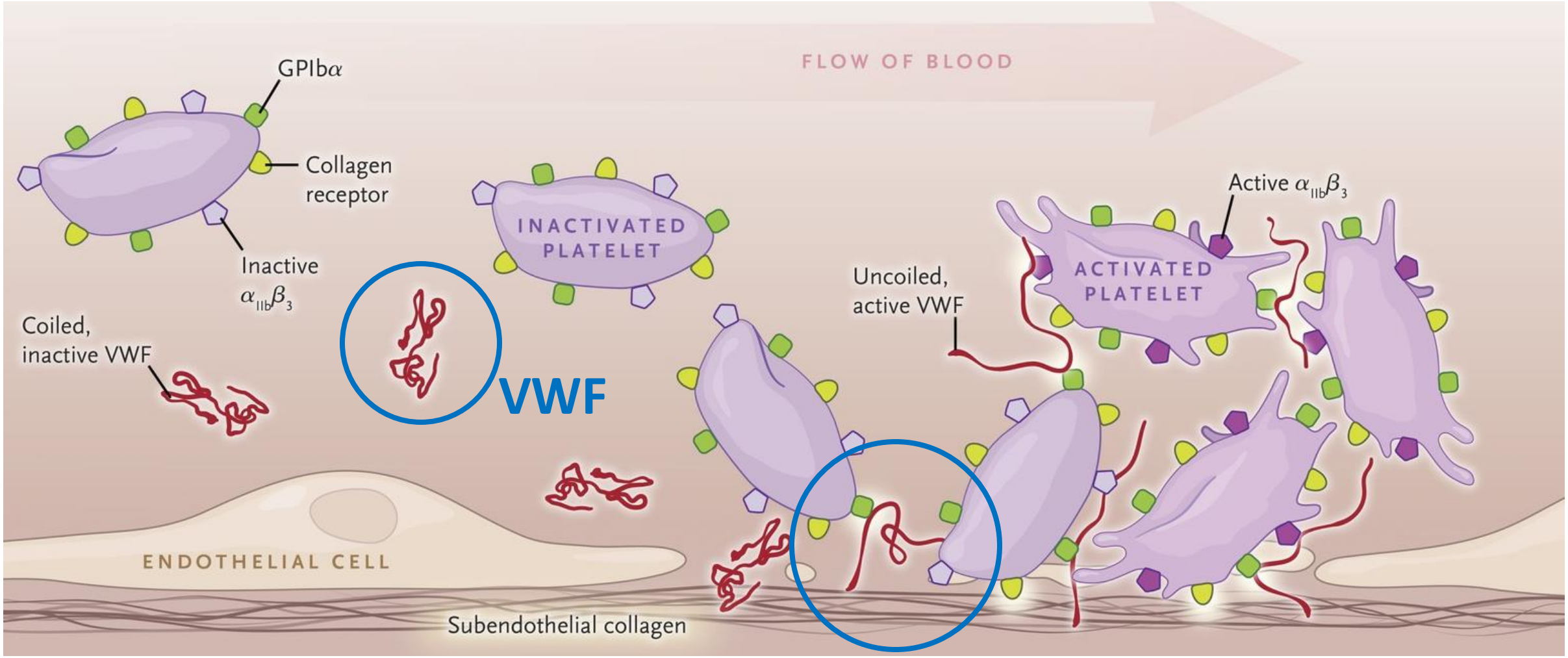
Platelet Plug

VWD
Insufficient VWF

- quantity
- quality

→

What is Von Willebrand disease (VWD)?



Leebeek & Eikenboom, N Engl J Med 2016;375:2067-80

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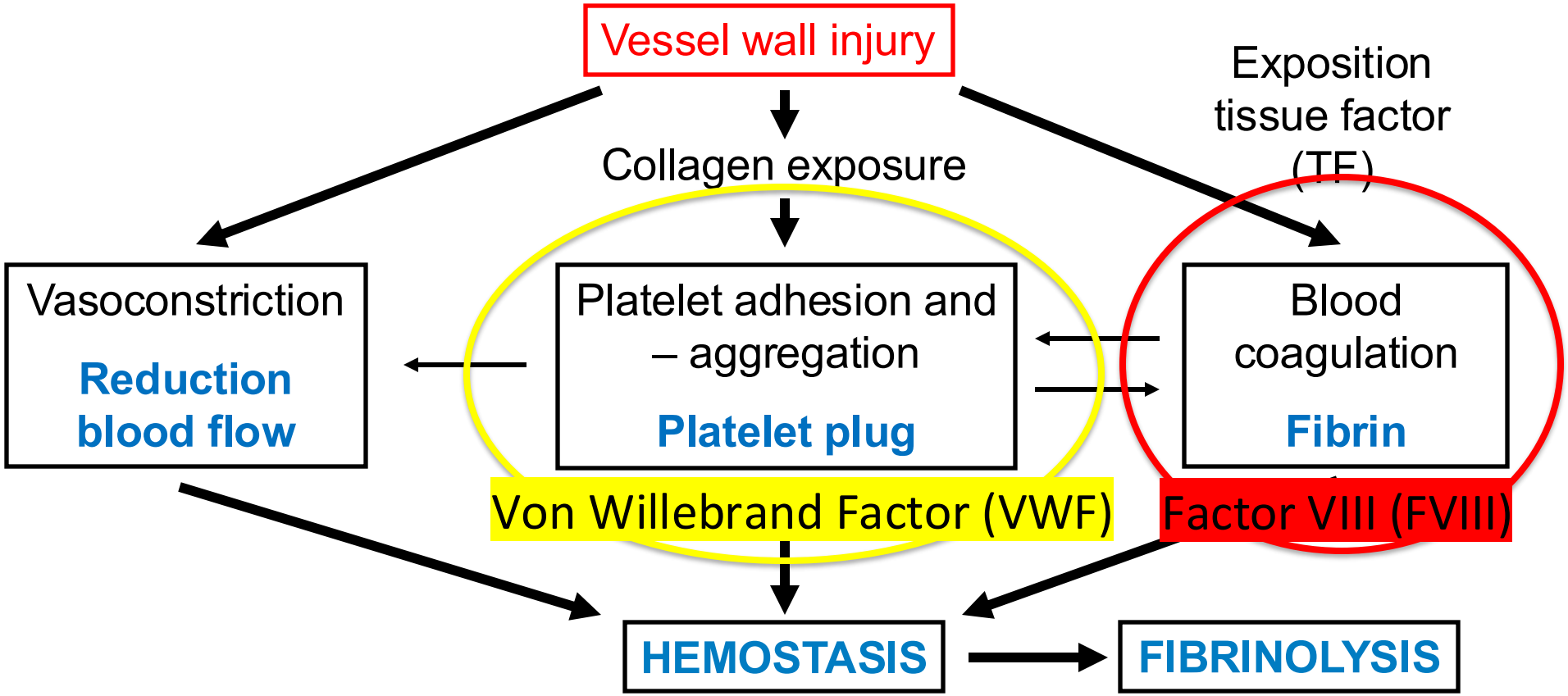
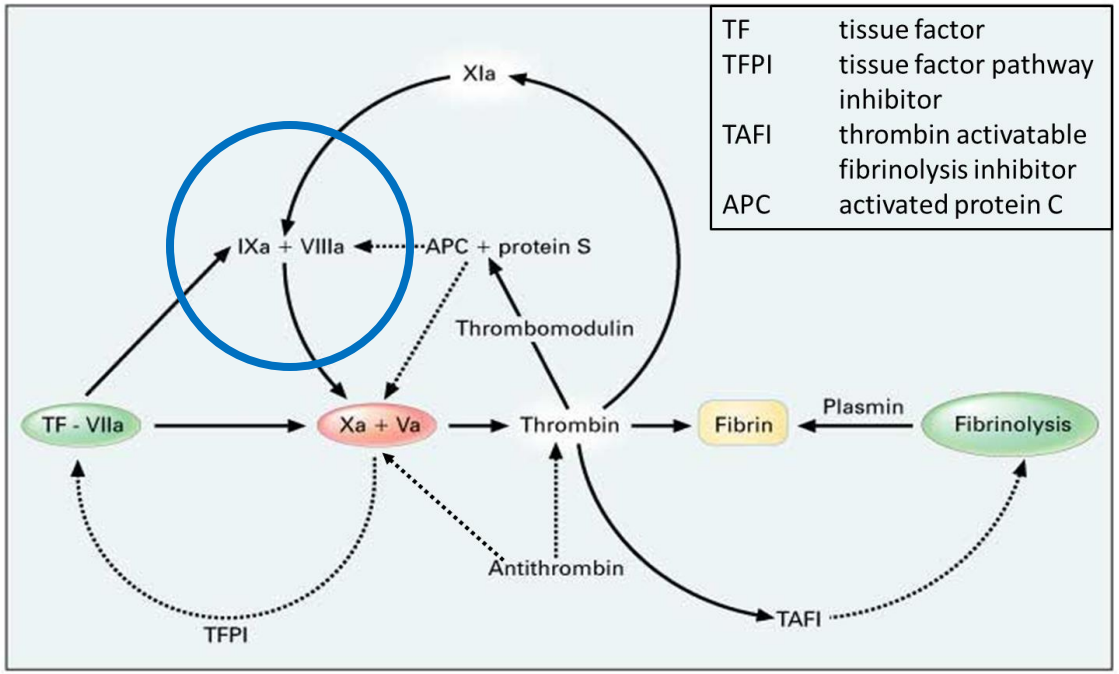
VWD ≠ Hemophilia



VWD ≠ Hemophilia

Hemophilia A - deficiency of FVIII
Hemophilia B - deficiency of FIX



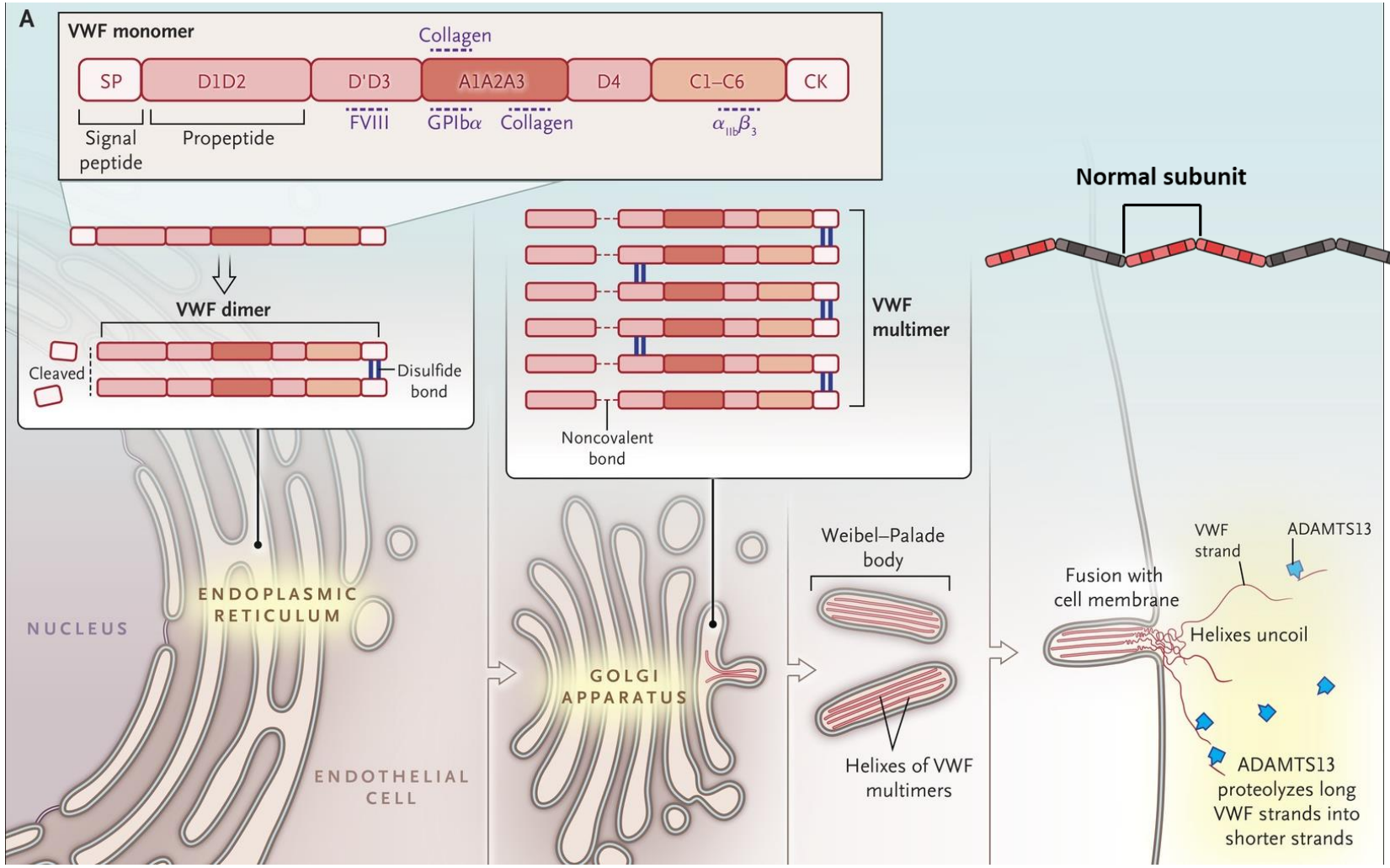
Adapted from Vandenbroucke et al., N Engl J Med 2001; 344:1527-35

In circulation FVIII is bound in complex to VWF
Defects in VWF may also affect FVIII !

VWF versus Hemophilia A

	VWD	Hemophilia A
Sex	Males and Females equally affected	When having the affected gene: - Males patients - Females patients if FVIII below 40%
Inheritance	Autosomal dominant or recessive	X-linked recessive
Effect on hemostasis	Primary hemostasis	Secondary hemostais
Symptoms	Mucocutaneous bleeding Bleeding after trauma or surgery Recurring gastro-intestinal bleeding Rare joint and muscle bleeding	Joint and muscle bleeding Bleeding after (minor) trauma or surgery
Treatment	Usually on demand, sometimes long-term prophylaxis	Long-term prophylaxis in severe, on demand in all

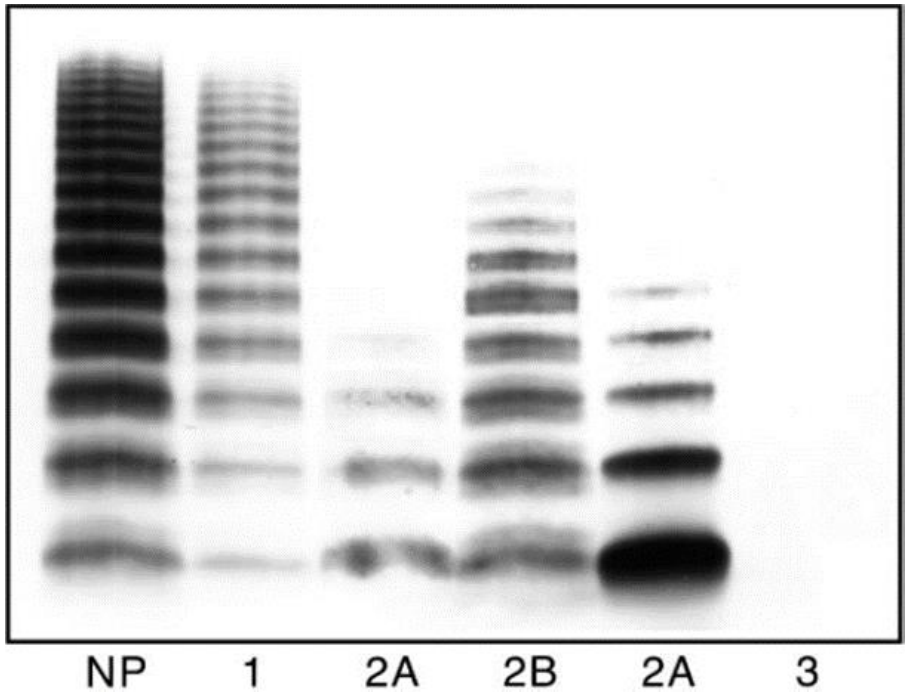
Synthesis of VWF



Leebeek & Eikenboom, N Engl J Med 2016;375:2067-80

Types of VWD

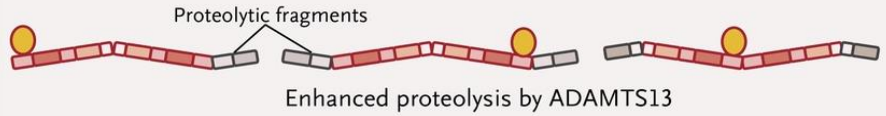
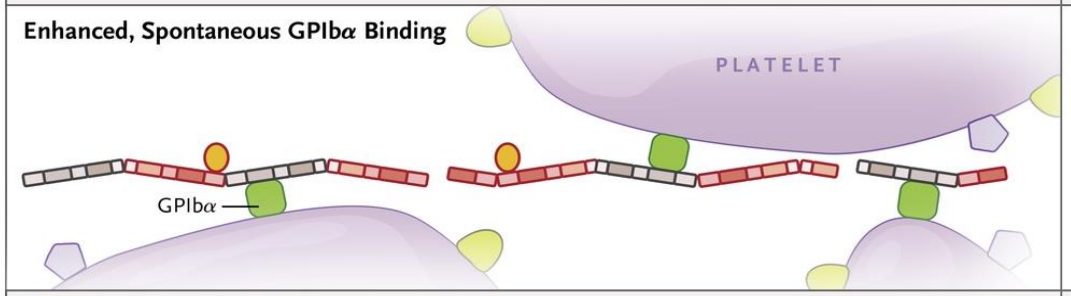
- **Type 1 (~75%)**
  - Less VWF, but normal function
  - Usually mild
- **Type 2 (~20%)**
  - Functionally or structurally abnormal VWF
  - Usually more severe than type 1
- **Type 3 (<5%)**
  - No VWF at all (and therefore also low FVIII)
  - Very severe



Types of VWD

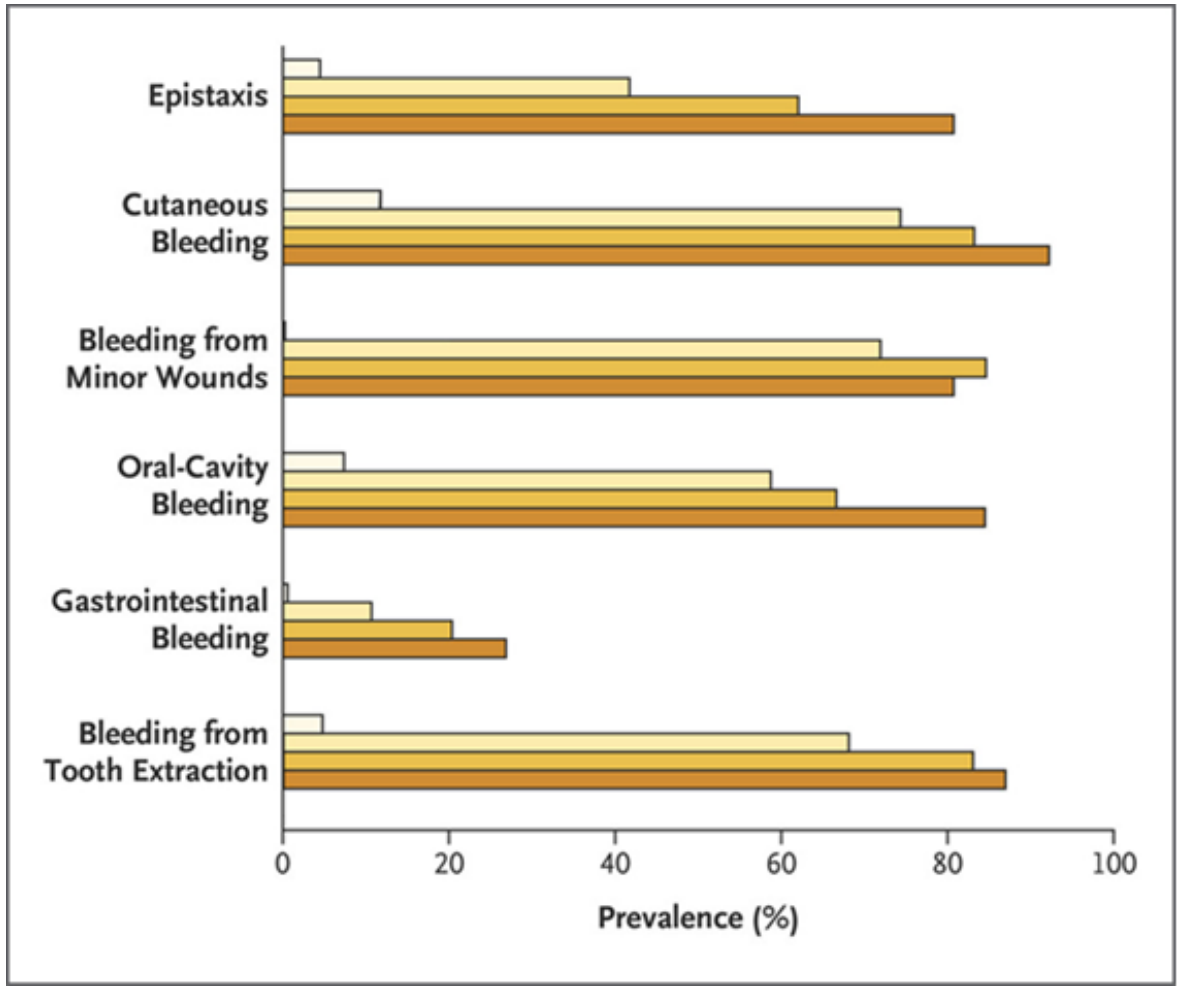
Type	Disease mechanism	Inheritance	Majority of genetic defects
1	Partial quantitative deficiency of VWF	Autosomal dominant	Missense mutations (85-90%), null-alleles (10-15%), variable penetrance
2A	Decreased VWF-dependent platelet adhesion due to a selective deficiency of high molecular weight (HMW) VWF multimers	Autosomal dominant Autosomal recessive	Missense mutations, mainly in D3, A2, and CK domains Missense mutations in propeptide
2B	Increased affinity of VWF for platelet GPIb	Autosomal dominant	Missense mutations in A1 domain
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of HMW VWF multimers	Autosomal dominant	Missense mutations in A1 domain
2N	Decreased binding affinity of VWF for factor VIII	Autosomal recessive	Missense mutations in D' and D3 domains
3	Virtually complete deficiency of VWF	Autosomal recessive	Mainly null-alleles, often consanguinity

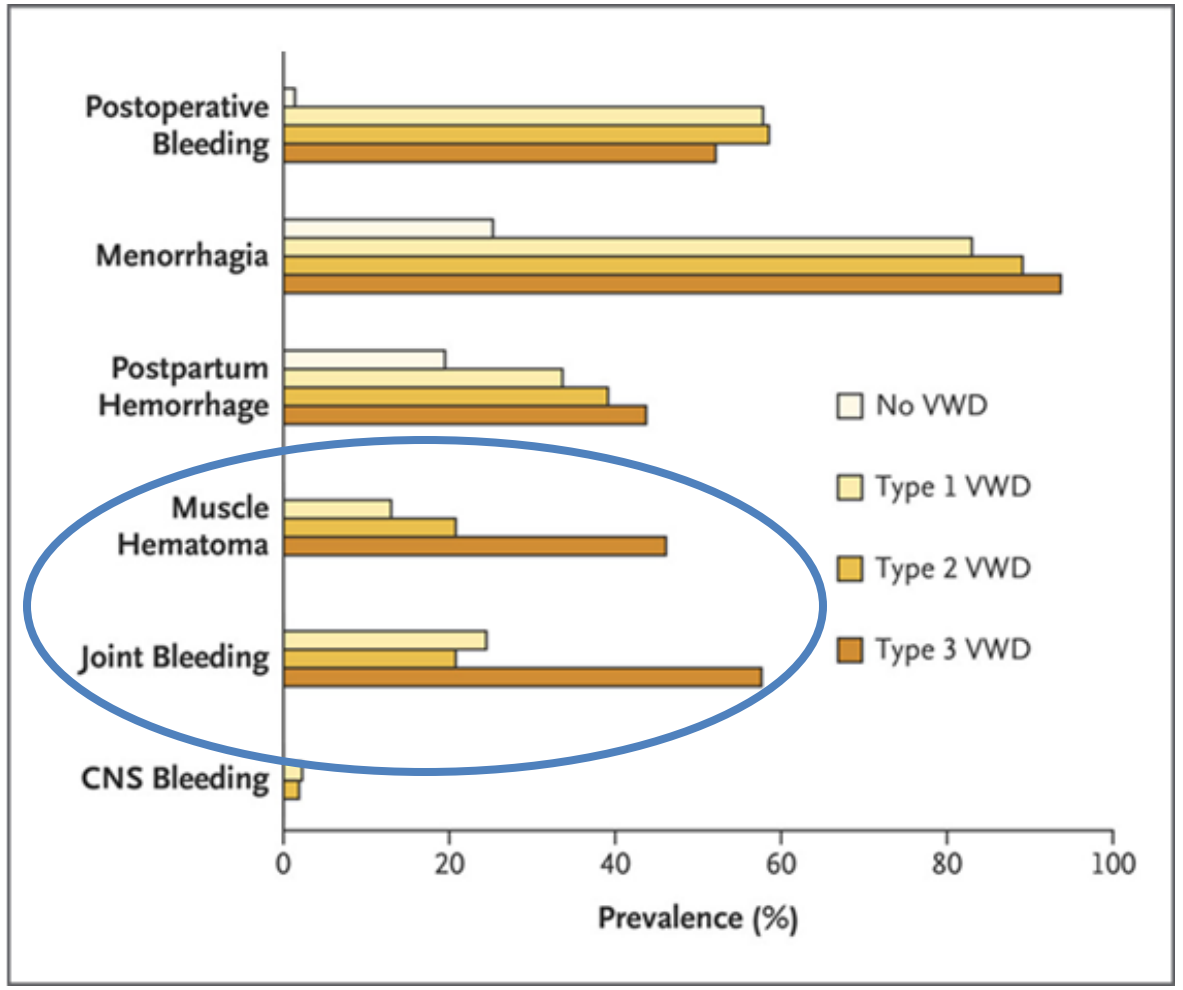
Subtypes of type 2 VWD

Disease Mechanisms	Defects in *VWF*	Types of VWD
Decreased Platelet Adhesion Due to Deficiency of HMW VWF Multimers 	Missense mutations in propeptide, D3, and A2 domains	Type 2A
	Missense mutations in CK domain	Type 2A
	Missense mutations in A2 domain	Type 2A
Enhanced, Spontaneous GPIbα Binding 	Missense mutations in A1 domain	Type 2B
Decreased Platelet Adhesion or Collagen Binding with No Loss of HMW VWF Multimers 	Missense mutations in A1 domain	Type 2M
Decreased Factor VIII Binding 	Missense mutations in D'D3 domain	Type 2N

Leebeek & Eikenboom, N Engl J Med 2016;375:2067-80

Symptoms of VWD





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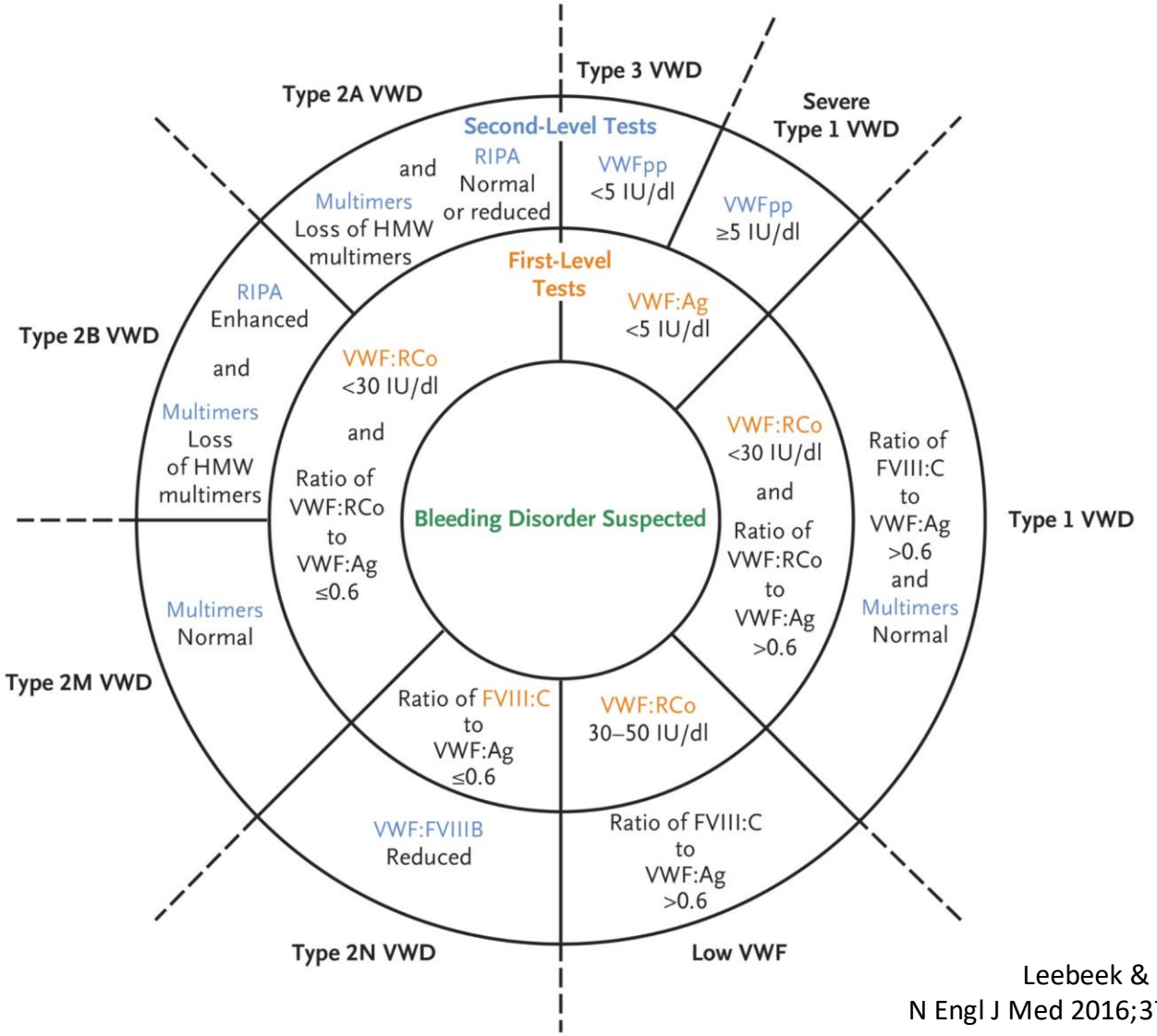
How to diagnose VWD ?

- **Bleeding symptoms**
  - Personal history
  - Family history
- **Laboratory testing**
  - VWF levels and function
    - VWF antigen
    - VWF-platelet binding
    - VWF-multimers
    - VWF-Factor VIII binding
    - VWF-Collagen binding
  - FVIII activity



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How to treat VWD ?

- **On demand**
  - Treatment at the time of a bleeding to stop and control the bleeding
  - May be at clinic or self-treatment at home

- **Prophylactic treatment**
  - Treatment to prevent bleeding
  - Before and after surgery / intervention
  - Long-term prophylaxis
    - Gastrointestinal bleeding
    - Joint bleeding (especially type 3 VWD)

Treatment options in VWD

- **VWD specific measures**
  - DDAVP (desmopressin)
  - VWF/(FVIII) concentrate
    - Plasma derived
    - Recombinant

- **General supportive treatment**
  - Antifibrinolytic drugs
    - Tranexamic acid
    - Aminocaproic acid
  - Oral contraceptive pill

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- 1-Deamino-8-D-Arginin VasoPressine
  - Induces secretion of VWF endothelial cells
  - VWF (and FVIII) will rise 2-4 times, peak after 1 hour
  - Administration: intravenous, subcutaneous, intranasal
  - Variable response, test infusion required
    - Usually effective in type 1
    - Usually not effective in types 2A, 2M and 2N
    - Not effective in type 3
    - Contra-indicated type 2B
  - Less effective after repeated administration
  - Risk of low serum sodium (water intake restriction)

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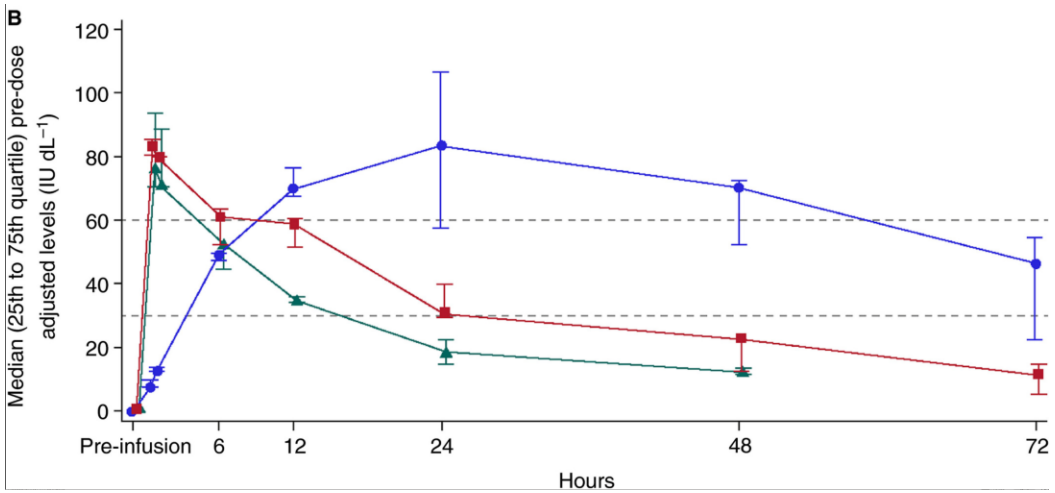
Product	Company	Source	VWF:RCo/ FVIII:C
Aphanate®	Grifols	Plasma	≈ 0,9
Fanhdi®	Grifols	Plasma	≈ 1
Haemate-P®	CSL Behring	Plasma	≈ 2,4
Veyvondi®	Baxalta	Recombinant	Only traces of FVIII
Wilate®	Octapharma	Plasma	≈ 0,9
Wilfactin®	LFB	Plasma	≈ 50



Peyvandi *et al.*
J Thromb Haemost
2019;17:52-62

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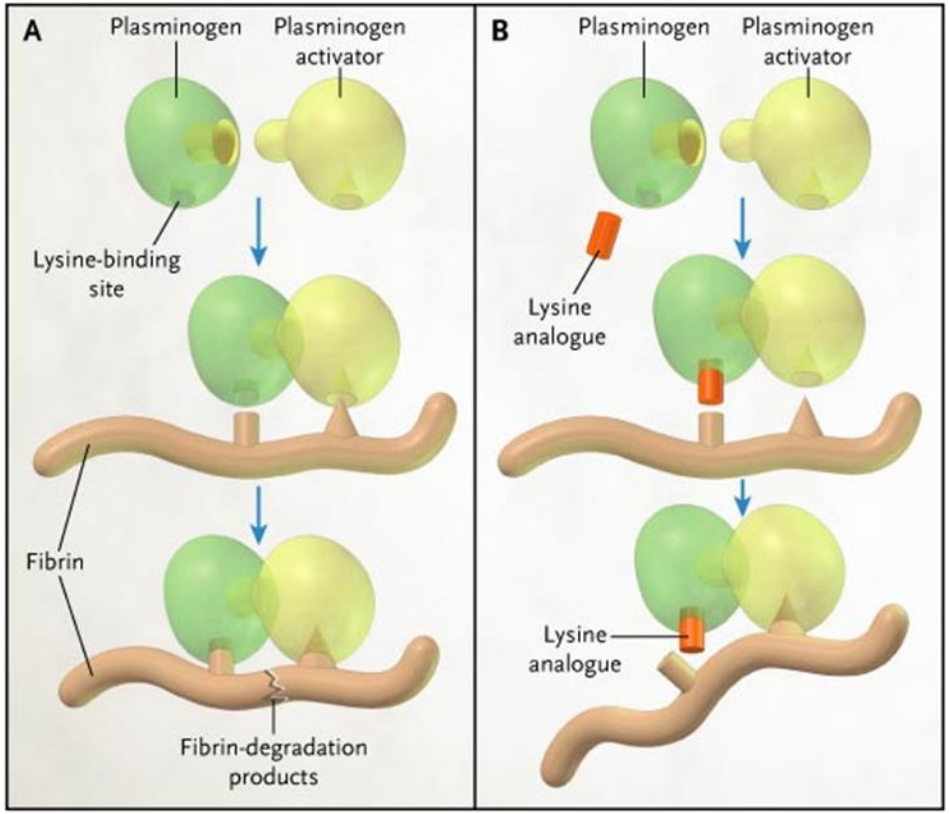

Mannucci, N Engl J Med 2007;356:2301-11

VWD guidelines

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

Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jeroen Eikenboom,[6] Nicolas Giraud,[7] Sandra Haberichter,[8] Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[13] Robert R. Montgomery,[14] James S. O'Donnell,[15] Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husainat,[19] Mohamad A. Kalot,[19] and Reem A. Mustafa[19]

James et al.
Blood Advances 2021;5:280-300

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

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

Connell et al.
Blood Advances 2021;5:301-325

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Questions ?

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VWD

Definition & Clinical Presentation:

- Bleeding disorder due to an inherited defect in VWF
- Defect in primary hemostasis with abnormal platelet plug formation
- Spontaneous bleeding and bleeding after trauma or surgery
- Major problem is heavy menstrual bleeding
- Treatment with DDAVP, VWF-concentrate, antifibrinolytics

www.ehc.eu

vwd@ehc.eu

@EHC_Haemophilia

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European Haemophilia Consortium

@EHCTVChannel EHC Youtube channel

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Eurobloodnet - European Reference Network on Rare Hematological Diseases

ERN-EuroBloodNet's EDUcational Youtube channel

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