Von Willebrand disease (vWD)

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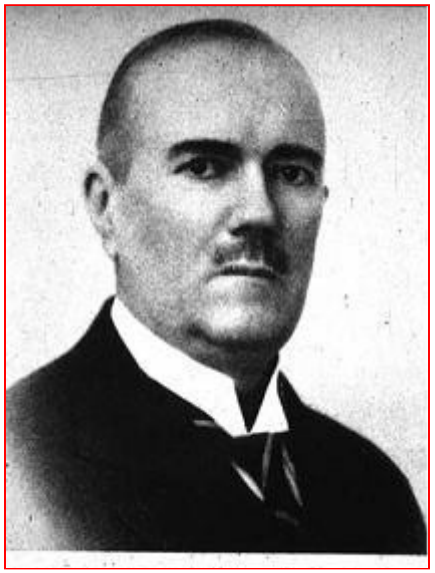
vWD is the *most common hereditary coagulation abnormality* described in humans, *prevalence:* 1-2 % of the population.

vWD is named after Erik von Willebrand, a Finnish pediatrician (1870–1949). He described the disease in 1926 in several members of one same family in the Finnish Åland islands.



The newly identified bleeding disorder differed from classic hemophilia:

- *bleeding was primarily mucocutaneous* (rather than the hemarthroses or deep muscle hematomas seen in hemophilia)

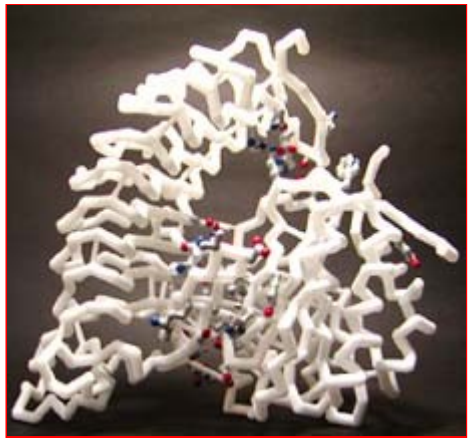
- *inheritance was autosomal dominant* → involved both sexes (rather than X-linked in hemophilia)

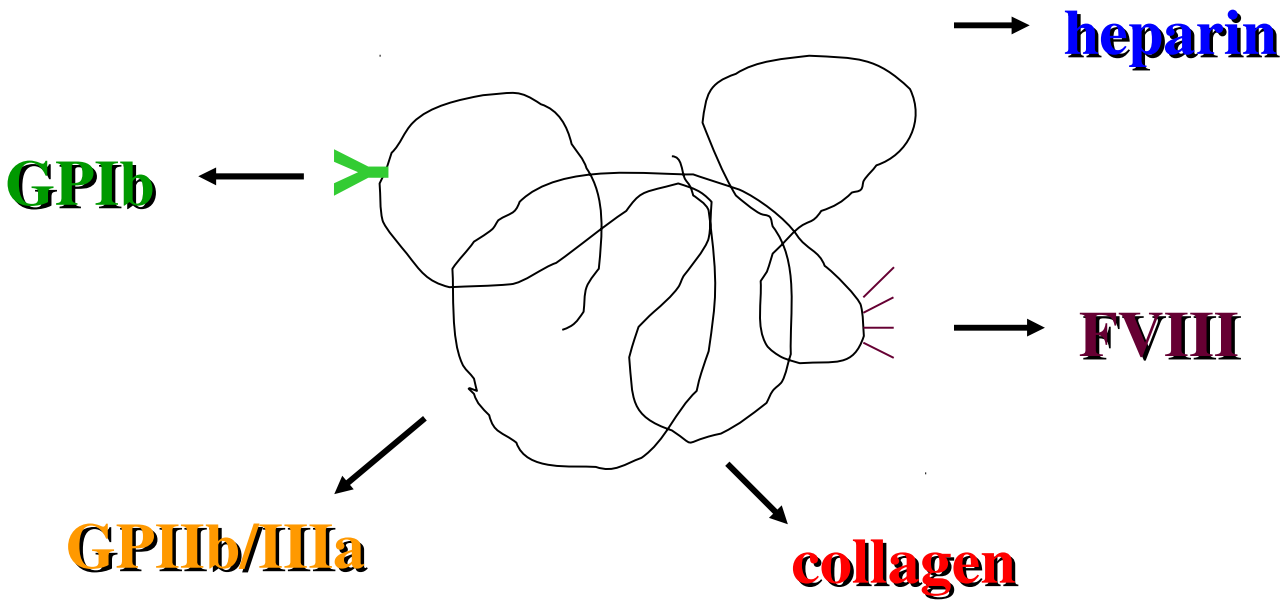
- *bleeding time was prolonged* (rather than the normal bleeding time seen in hemophilia)

Platelet count was normal → Willebrand hypothesized that a qualitative disorder of platelet function existed.

Pathogenesis:

The disease is due to a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein.
It is synthesised by the endothelial cells and megakaryocytes.





vWF offers multiple sites for contact with various ligands present in the circulation and injured vascular wall.

vWF serves two roles:

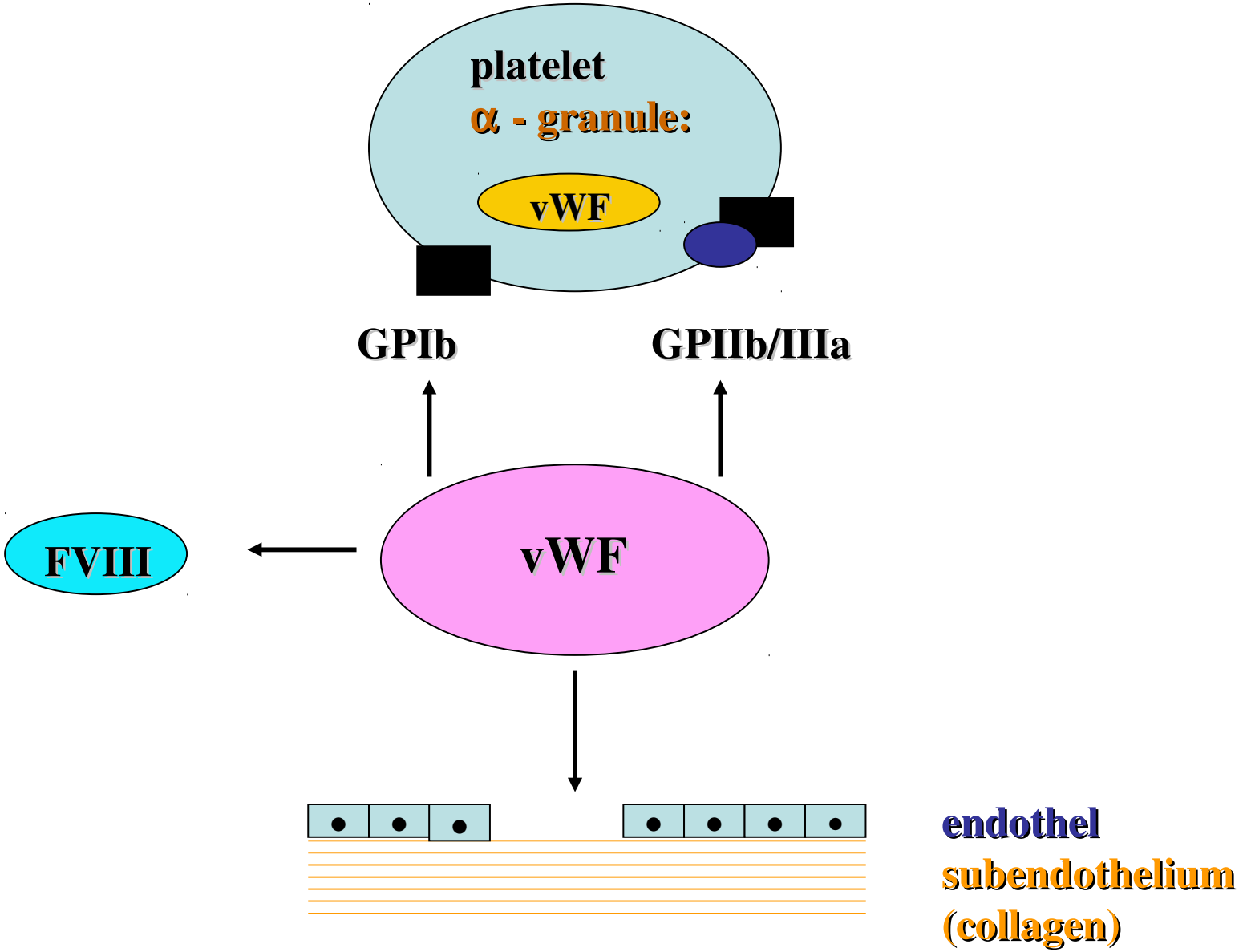
1. *It allows platelets to adhere to the injured vascular wall* (through binding sites for platelet GPIb and collagen from the endothelium).

***It also promotes the aggregation of platelets to each other* (through its interaction with GPIIb/IIIa).**

The platelet-adhesive function of vWF is critically dependent on the presence of large vWF multimers.

2. *As the binding protein of FVIII, protects it from rapid proteolytic degradation,* resulting in significant prolongation of FVIII half-life in circulation.

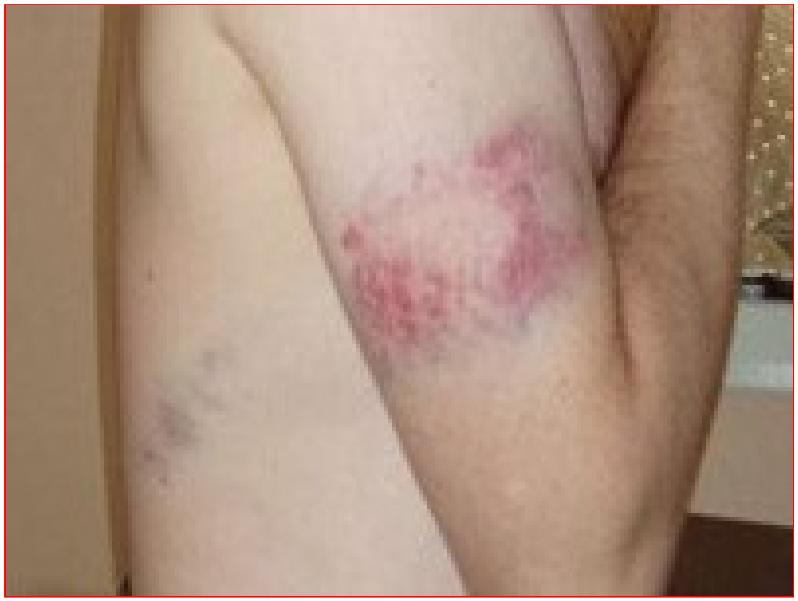
Two roles of vWF:

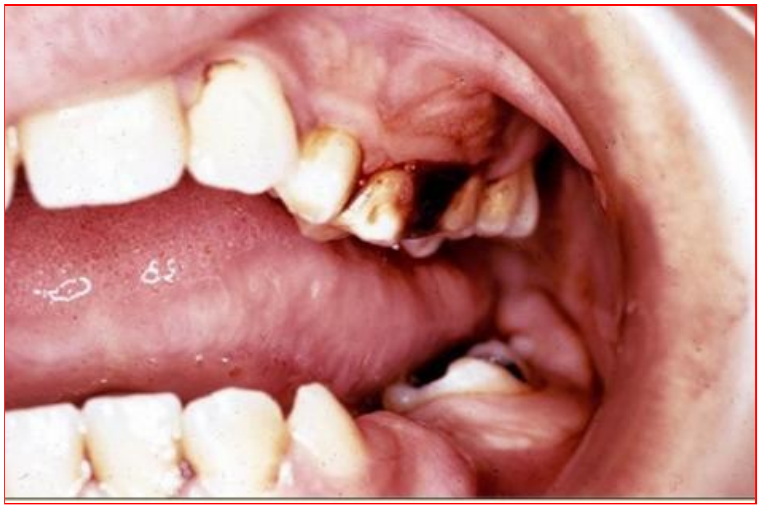


Clinical symptoms:

Most of the symptoms of vWD are „platelet-like” except in more severe vWD when FVIII level is low enough to produce symptoms similar to those found in hemophilia A.

Clinical diagnosis **is based on personal history and observation of bleeding symptoms:**
recurrent epistaxis, gingival bleeding, prolonged bleeding after superficial wounds, ecchimoses, superficial hematomas, menorrhagia, blood loss during childbirth .





The bleeding symptoms depend on the severity of the vWF deficiency.

Inheritance:

- autosomal dominant

- autosomal recessive

(Type 2N, Type 3)

The current *classification* of vWD consists of 6 distinct types (Sadler, 1994).

Types 1 and 3 result in a *quantitative* vWF deficiency, whilst the four type 2 variants cause *qualitative* vWF defects.

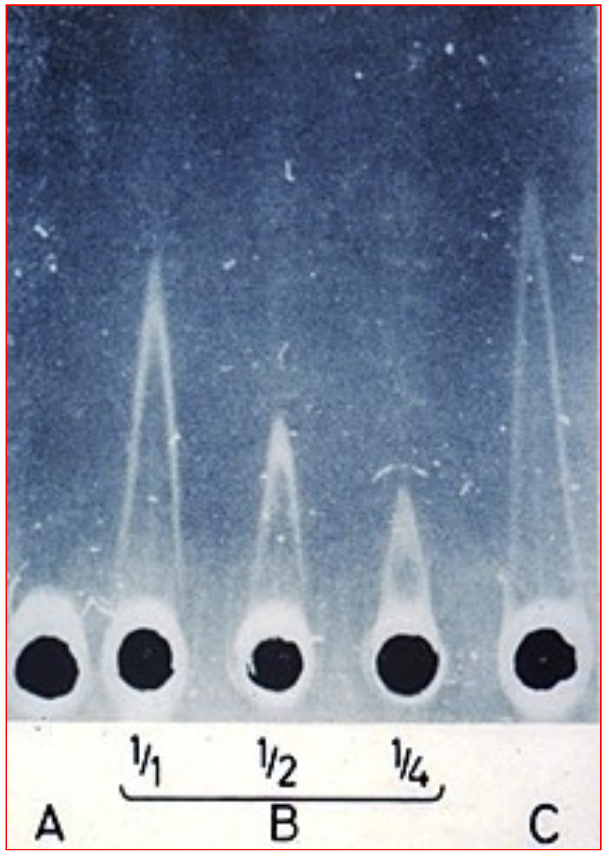
J. Evan Sadler

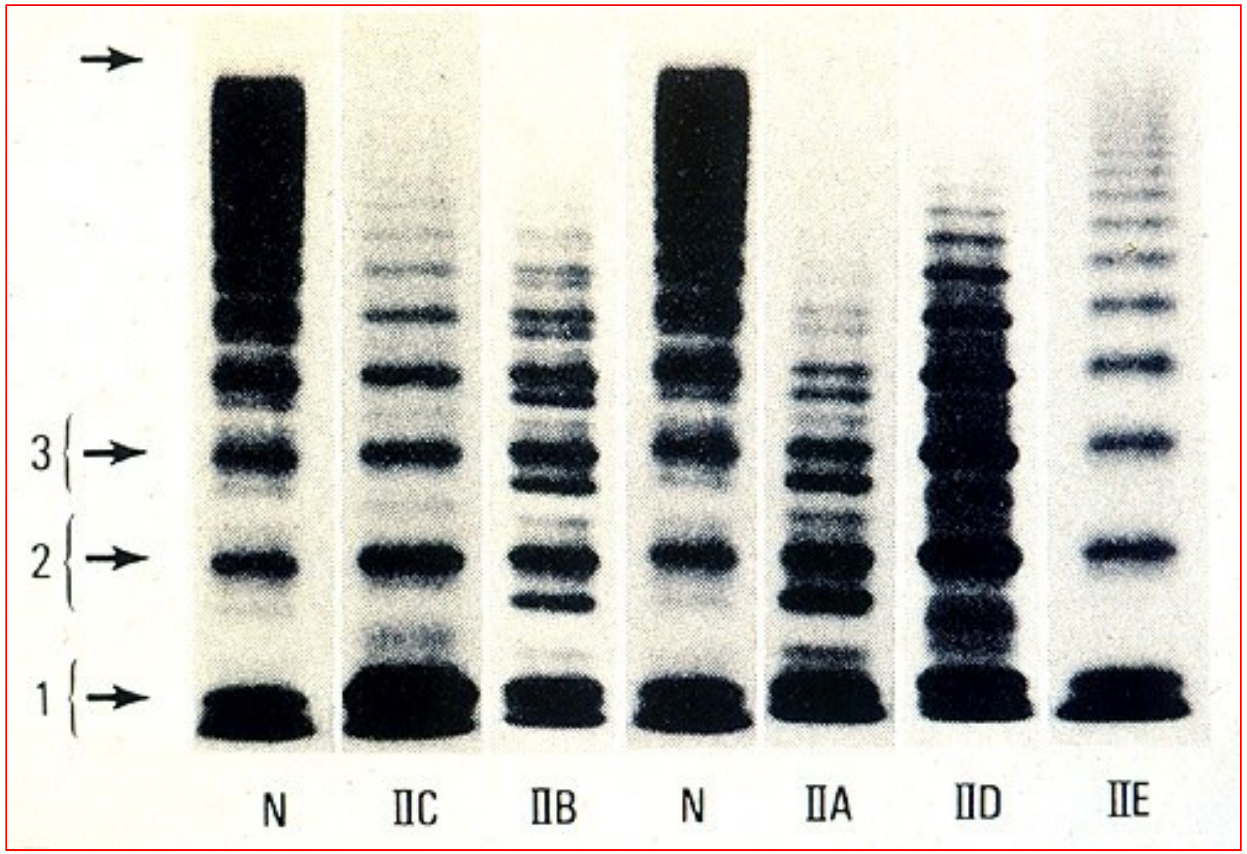
Classification of vWD:

- **Type 1: partial quantitative vWF deficiency**
  (70-80 % of cases)
- **Type 2: qualitative vWF deficiency (20-25 %)**
  - **2A: reduced vWF affinity for platelets, in association with absence of high molecular weight (HMW) multimers**
  - **2B: increased vWF affinity for platelets**
  - **2M: reduced vWF affinity for platelets, without HMW multimer abnormality**
  - **2N: reduced vWF affinity for FVIII**
- **Type 3: total quantitative vWF deficiency in association with consecutive FVIII deficiency**
  (<5% of cases)

Diagnosis of vWD:

Screening tests:	- Bleeding time - Closure time on PFA-100 - APTT - Platelet count
Specific tests: (confirmation tests)	- vWF:Ag - vWF:RCo assay (functional activity of vWF) - FVIII:C
Discriminatory and specialized tests: (to define the types of vWD)	- Platelet aggregation in the presence of various ristocetin concentration (RIPA) - vWF multimer distribution - vWF binding to GPIb, collagen, FVIII





vW antigen assay

(Laurell Rocket immunelfo)

vW multimer analysis

(SDS agarose gel elfo)

Platelet Function Analyser-100 /PFA-100/

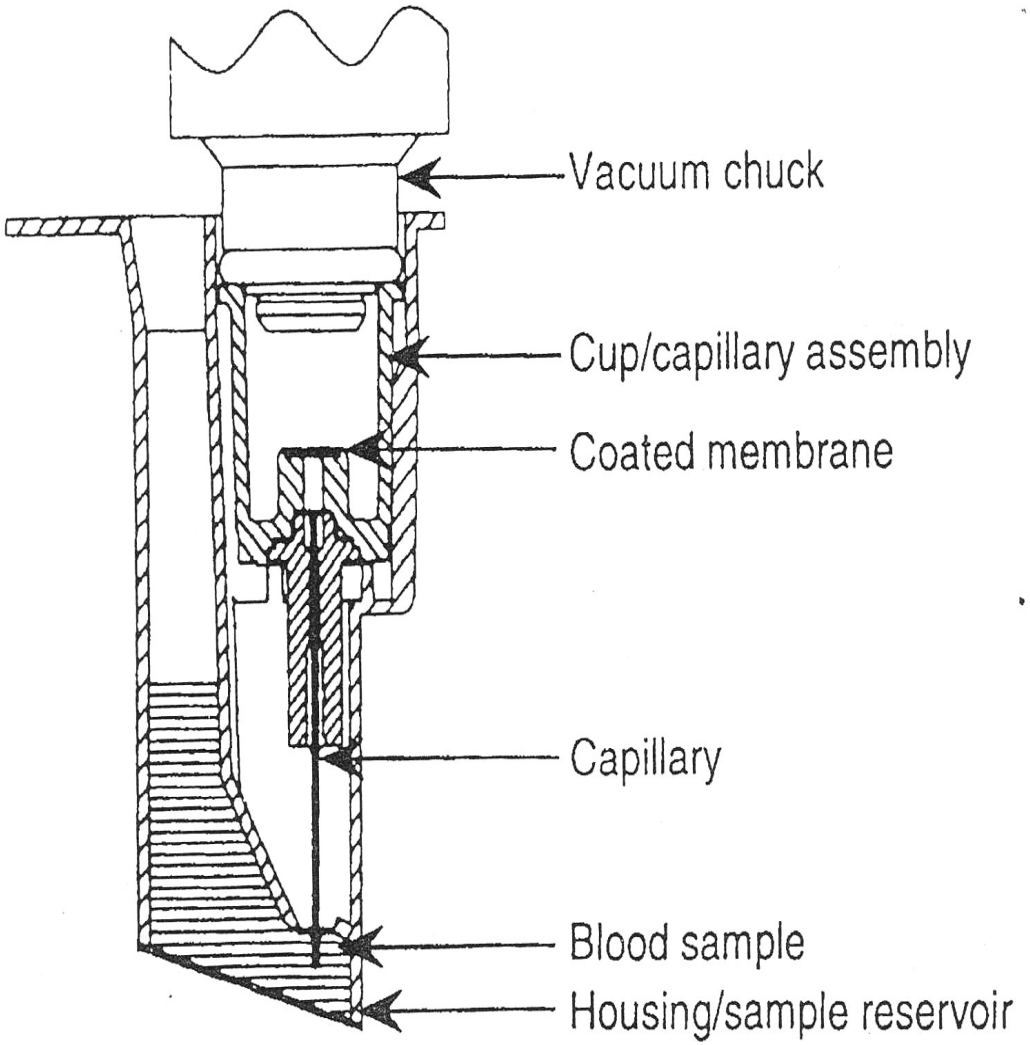
It is used to evaluate primary hemostasis in citrated blood. It measures ex vivo platelet binding to collagen/epinephrine or collagen/ADP in a high-share flow system.

It is more sensitive assay than the bleeding time.

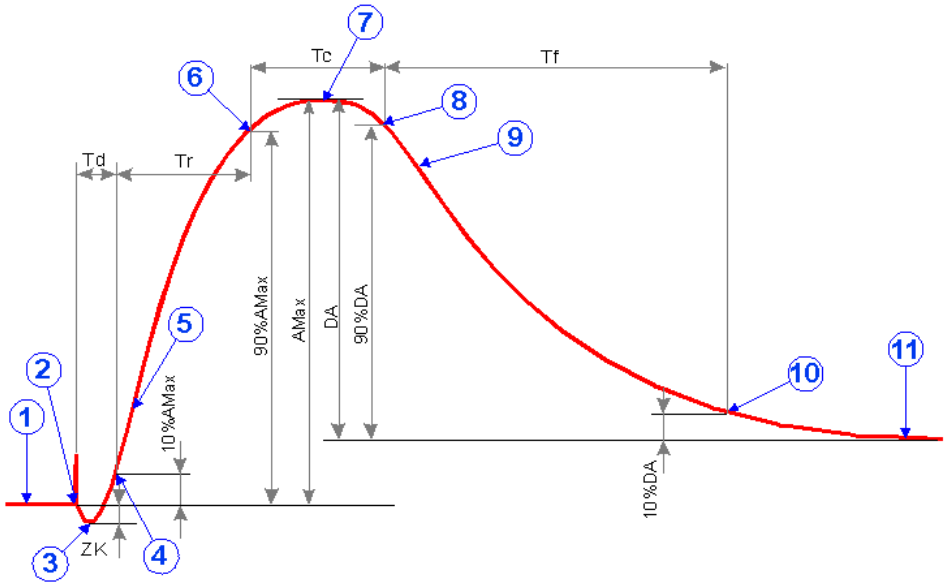
Citrated blood passes through a membrane with an aperture. The membrane is coated with collagen fibrils and one of activators (epinephrine or ADP)

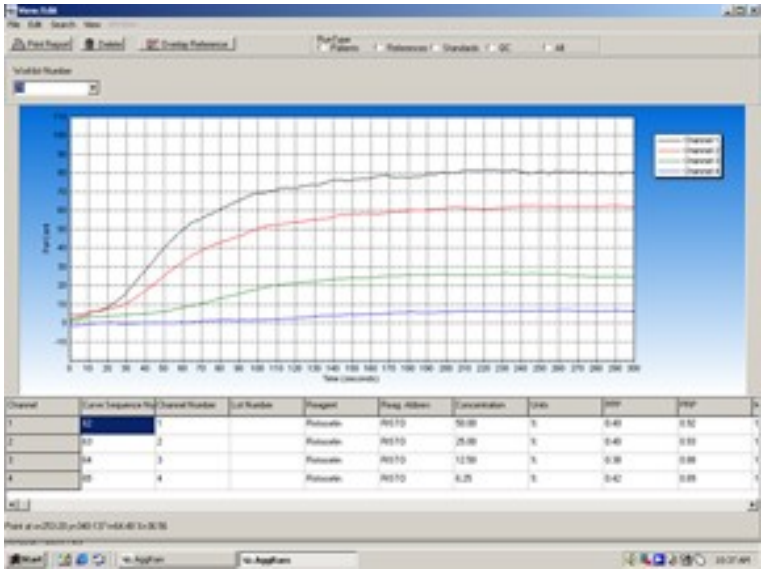
The platelet activation occurs as blood flows through the aperture. When citrated whole blood mixes with activators, platelets start to form aggregates.

The time taken for blood to form a platelet plug that occludes the aperture is an indication of platelet function and is referred to as the closure time (CT).



Aggregometer





Expected laboratory values in vWD (R.R. Montgomery)

	Type 1:	Type 2A:	Type 2B:	Type 2M:	Type 2N:	Type 3:
Bleeding time:	N or ↑	↑	↑	↑	N	↑↑↑
PFA-100 CT:	N or ↑	↑	↑	↑	N	↑↑↑
Platelet count:	N	N	↓ or N	N	N	N
FVIII:	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	↓
vWF:Ag:	↓ or ↓↓	↓ or L	↓ or L	↓ or L	N or L	absent
vWF:RCo	↓	↓	↓	↓	N or ↓	absent
RIPA:	often N	↓	often N	↓	N	absent
LD-RIPA:	absent	absent	↑↑↑	absent	absent	absent

L: 30-50 IU/dl, LD-RIPA: concentration of ristocetin ≤ 0,6 mg/ml

Treatment of vWD:
there are two main types of treatment

- **Desmopressin**

- **Replacement therapy** with factor VIII concentrates complexed to vWF.

The choice of treatment depends on the type of vWD, situation and degree of emergency.

In emergency situation: is not enough time to wait to vWF mobilization → factorconcentrate is necessary.

1. Desmopressin (DDAVP):

is a *synthetic analog* of vasopressin, that increases endogenous plasma FVIII and vWF levels by inducing their release from the endothelial cells (for periods 3-4 days).

It is effective in patients able to produce some vWF or FVIII.

DDAVP is effective in 80 % of patients with type 1 vWD, is ineffective in type 3, contraindicated in type 2B.

Advantage: no risk of transmitting blood-borne viruses.

A therapeutic test should be performed to obtain precise information about the efficacy.

Administration: *intravenous route* (D: 0,3 μg/kg in 50-100 ml fiz. NaCl infusion), *subcutaneous inj.* (D: 300 μg 1-2xdaily), *nasal spray*.

2. Factorconcentrate (FVIII complexed to vWF):

All type of vWD, when DDAVP treatment alone is ineffective or contraindicated (type 3, type 2B).

- **Major operation:** 40-60 IU/kg/day, for 7-10 days (FVIII/vWF level > 50%)
- **Minor operation:** 30-50 IU/kg/day, for 1-3 days
- **Tooth extraction:** 1x 20-30 IU/kg + antifibrinolytic agent /tranexamic acid)
- **Intracerebral, gastrointestinal bleeding:** 40-60 IU/kg 2x daily, for 10 days (FVIII/vWF level > 50%)
- Severe bleeding: rFVIIa.

Summary of the treatment of vWD:

Type:	Treatment:
1	DDAVP
2A	Factorconc. (DDAVP)
2B	Factorconc.
2M	Factorconc.
2N	Factorconc. (DDAVP)
3	Factorconc. + platelet conc. rFVIIa
„platelet type”	Factorconc. + platelet conc.

2B type: DDAVP is contraindicated!

Complementary („adjuvant”) treatment:

Antifibrinolytic therapy :

tranexamic acid or epsilon aminocapronic acid.

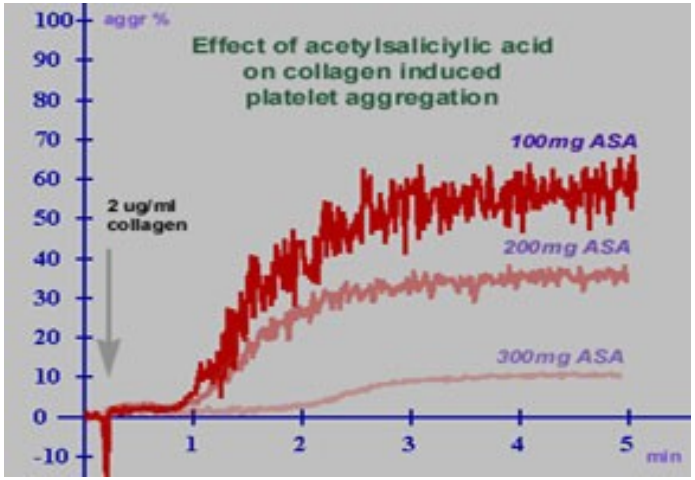
Is is an important therapy, either alone or in an adjunctive capacity, particularly for the prevention or treatment of mucosal bleeding.

These agents are particularly useful in prophylaxis for dental procedures, tonsillectomy, menorrhagia.

Contraindication: upper urinary tract bleeding (due to the risk of ureteral obstruction).

Medicinal products not recommended:

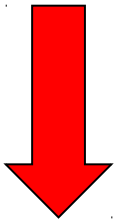
- All forms of acetylsalicylic acid (paracetamol is preferred)
- All forms NSAIDs (nonsteroidal anti-inflammatory drugs) and derivates
- Vitamins and multivitamins containing vitamin E (anti-platelet aggregation effect)
- Antidepressants that inhibit recapture of serotonin and noradrenalin
- Hydroxyethyl starch



Im. injections should be avoided!

Heavy menstruation *(menorrhagia)* or bleeding outside of the menstruation period *(metrorrhagia)* are common symptoms in women with vWD.

The prevalence of vWD in women with metrorrhagia is reported to be 13 %.



vWD requires special gynecological and obstetric management in women.

Gynecological management:

- for women with heavy menstrual bleeding the *combined oral contraceptive pill* may be effective in reducing bleeding or in reducing the length or frequency of periods.

- if OC is contraindicated, *DDAVP* (nasal spray), or *intrauterine devices that release levonorgestrel* may be a therapeutic option.

- *antifibrinolytic agents* (tranexamic acid): commonly used for the treatment of menorrhagia

- *replacement therapy* for severe menorrhagia

Obstetric management I:

Collaboration between the gynecologist, anesthesiologist, hemostasis specialist is necessary.

- type 1: FVIII, vWF levels increase (2-3 fold) during pregnancy, starting in the 10^{th}-11^{th} weeks.

- type 2: increase is the same, but vWF molecule remains abnormal (dysfunctional).

- type 3: vWF levels do not change

→ **replacement therapy is necessary in patients with type 2 and 3 vWD.**

Obstetric management II:

If FVIII and vWF levels < 50 IU/dl: replacement therapy at the beginning of labour.

Epidural anesthesia is contraindicated in women with type 2 and 3 vWD – due to the risk of bleeding complications.

Post-partum: the rapid drop in FVIII and vWF levels after delivery increases the risk of hemorrhage during the post-partum period → replacement therapy for 3-7 days.

Newborns with vWD are at a great risk of intracranial bleeding or hematomas on the scalp.