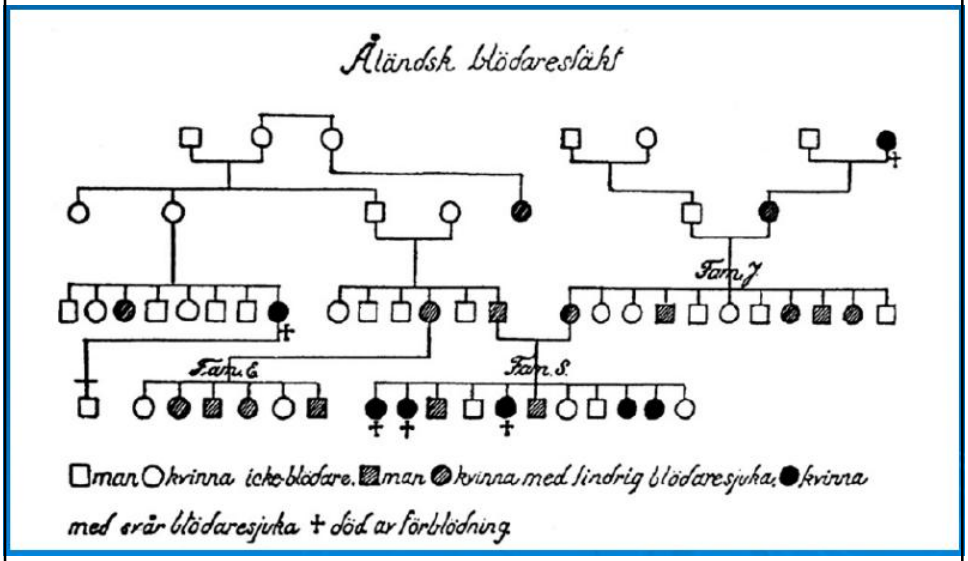
von Willebrand Disease
- Past, Present and Future

15 Sept 2018

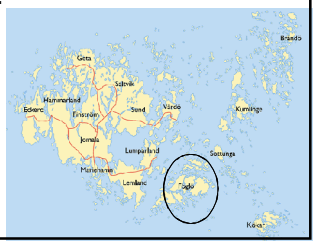
Elina Lehtinen, Adj. Prof.
Coagulation Disorders Unit
Helsinki University Hospital
Hematology, Comprehensive Cancer Center

HUS



Hjördis Sundblom

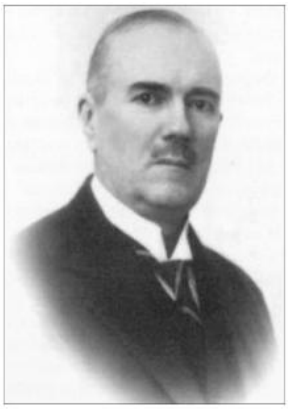
- In 1924 5-yo Hjördis from island of Föglö, part of the Åland Islands, was brought to see a doctor in Helsinki due to unusual bleeding symptoms.
- She suffered from recurrent mucous membrane bleeds.
- At age 3 she bled from her upper lip wound for 3 days and was in the hospital for 10 weeks.
- Hjördis was ninth of 11 children in the family. Three of her younger sisters had died from bleeding and 4 others had bleeding symptoms.
- Many family memebers from both father's and mother's side had bleeding symptoms.
- She was found to be otherwise a healthy and clever girl in good nutritional status.



Erik Adolf von Willebrand

- Finnish doctor
- Born 1870 in Vaasa
- Graduated highschool in 1890
- Studied in the University of Helsinki
- Spent summers of1894 ja 1895 on the Åland Islands as a spa doctor
- 1897, after graduation, workd as an assistant doctor at the Diaconess Hospital in Helsinki

- Publication in 1926 Erik von Willebrand:”Hereditär pseudohemofili”
- Finska Läkaresällskapets Handlingar




FINSKA LÄKARESÄLLSKAPETS
HANDLINGAR
PROF. RICHARD SIEVERS
BAND LXVIII
1926 FEBRUARI 1926
INNEHÅLL:


ORIGINALARTIKLAR.
Hereditär pseudohemofili.
E. A. v. Willebrand.
Sjukdomshegrepp. Tidigare observerade fall.

- Hjördis kuoli 14 vuotiaan elämänsä 4. kuukautisiin

1957 **Inga Marie Nilsson** from Sweden with her research group visited the Åland Islands to study 15 members of the original family
→She discovered that bleedings were due to a missing plasma factor which was present in both hemophilia A patients and normal individuals

1971 Americans Zimmermann and Stites found FVIII associated protein, wich was named von Willebrandin factor

1985 von Willebrand disease gene was discovered from chromosome 12

Von Willebrand Disease

- Incidence ~1 : 100
  - Rodeghiero, Blood 1987; Werner J Pediatr 1993
- Symptomatic ~1 : 1000
  - Bowman JTH 2010; Bowman Ped Blood and Cancer 2010
- 80% Type 1 – dominant inheritance
  - VWF levels can vary
  - Symptoms can vary within the same family

Nordic Guidelines
(*www.nordhemophilia.org*)

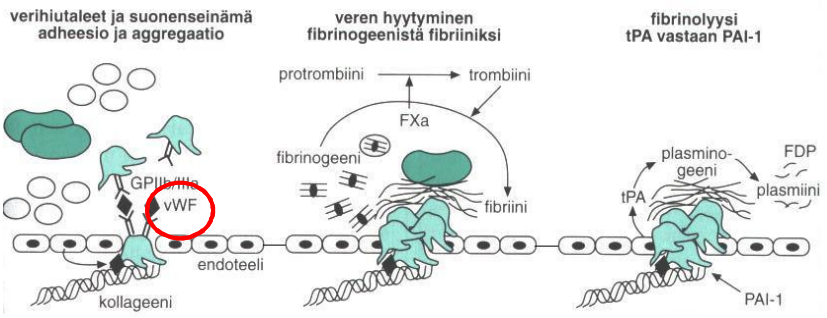
- Diagnostic criteria
- Bleeding symptoms
- Laboratory measurements:
  - **VWF:RCo / VWF-Act**
  - **VWF:CB**
  - **VWF:Ag**
  - **FVIII:C**
  - VWF subtypes (VWF:Ag, RIPA, Multimers)
  - ABO blood group: type O – appr 30% lower levels

- **Reduced platelet function**, suggestive of VWD
- Platelet number normal (except 2B)

Primary hemostasis

Coagulation system

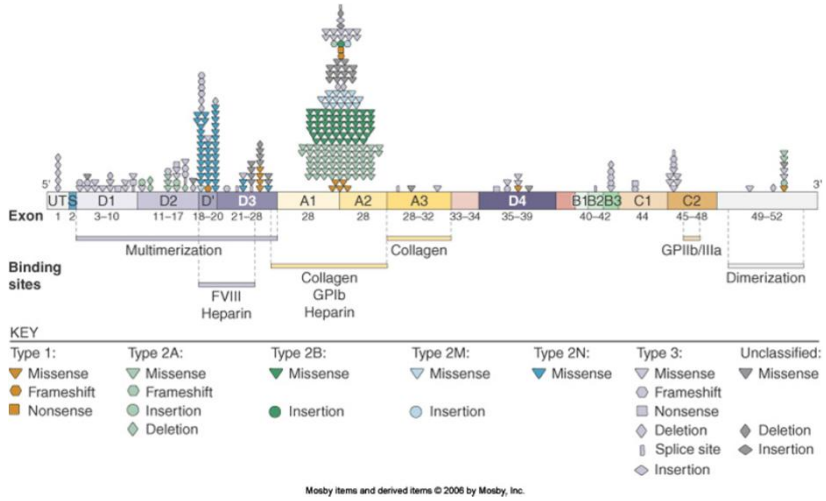
Fibrinolysis



FII, FV, FVII, FVIII,
FIX, FX, FXI, (FXII)
FXIII

VWF = von Willebrandin tekijä; F = faktori, hyytymistekijä

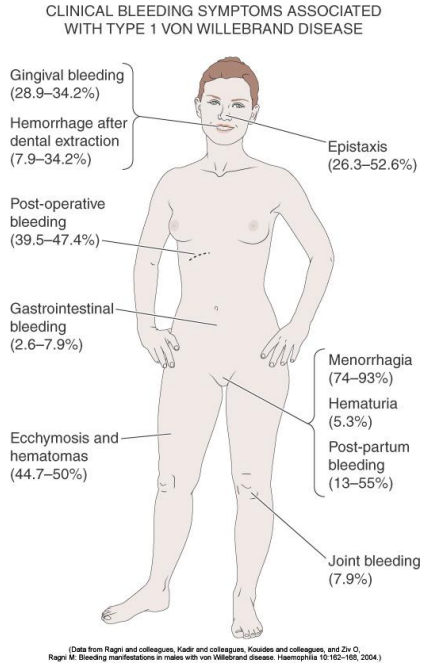
Protein Structure and Mutations



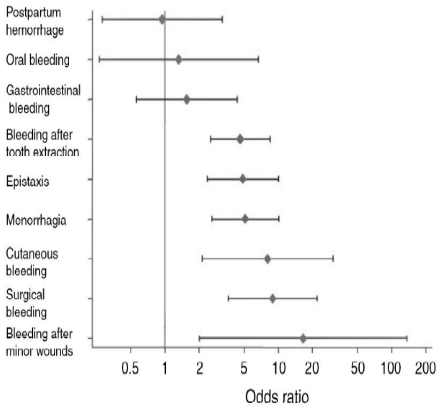
From N.S. Young, S.L. Gerson and K.A. High
CLINICAL HEMATOLOGY, Mosby Inc 2006

Types of VWD

VWD Type	Description	Inheritance	Prevalence
1	Partial VWF deficiency Mild to moderate	Autosomal dominant	70–80 %
2A	VWF dysfunction Moderate to severe	Autosomal dominant	10–15 %
2B	VWF dysfunction Increased GPIb-recepor binding of VWF Thrombocytopenia Moderate to severe	Autosomal dominant	~ 5 %
2M	VWF dysfunction Normal multimer distribution	Autosomal dominant	Rare
2N	VWF dysfunction Decreased binding to FVIII Phenotype as in mild hemophilia A	Autosomal dominant	Rare
3	Complete VWF deficiency Severe	Autosomal recessive	Rare



Symptoms



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Epistaxis	
0	No or trivial (less than 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 transf

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 ther -apy 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 (less than 5)
1	> 5 or more than 5'
2	CONSULTATION ONLY
3	Surgical hemostasis
4	Blood transfusion or Replacement therapy or Desmopressin

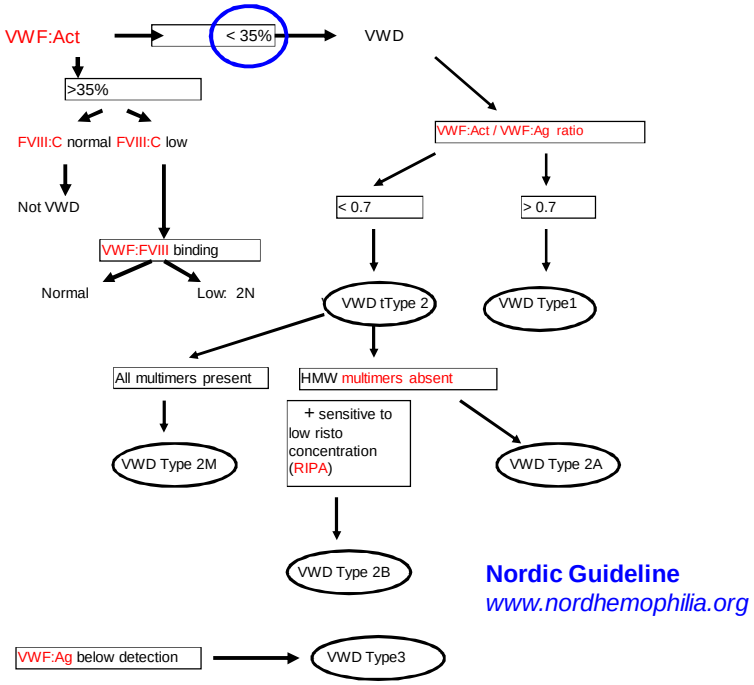
Tooth extraction	
-1	No bleeding in at least 2 extractions
0	Not done or no bleeding in 1 extraction
1	Reported in <25% of all procedures
2	Reported in >25% of all procedures, no intervention
3	Resuturing or Packing
4	Blood transfusion or Replacement therapy or Desmopressin

Post-partum 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

Total assigned score:

Bowman M, Mundell G, Grabell J, et al. Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. J Thromb Haemost.2008;6(12):2062-2066.



VWD – Diagnostic Challenge

- Criteria:
  - Low VWF-levels (<35-40%)
  - Bleeding symptoms
  - Family history
- Other influences:
  - VWF levels and bleeding symptoms correlate the best when VWF *<20-30-35%*
  - Age, stress, hormonal factors, medications, infection, inflammation, ABO blood group and other factors influence
  - Skin and mucous membrane bleeds also common with healthy people

Pre-analytical issues

Lab sampling

- Preferably after resing
- At rest
- Excersice, stress, infection, pregnancy recognized

Samples

- Carfeful centrifugation
- Should be frozen at -70C, if not immediately analyzed.
- Plasma samoles transported frozen
- No need to time with menstruation

Spectrum of Bleeding Disorders

Healthy → Patient

Bleeding tendency

Platelet function Possible/Probable VWD Carriers

Hemofilia
VWD Type 1, 2 ja 3
BSS, Glanzmann...

Clinical dg => goal is to find the ones with persistent disease / tendency

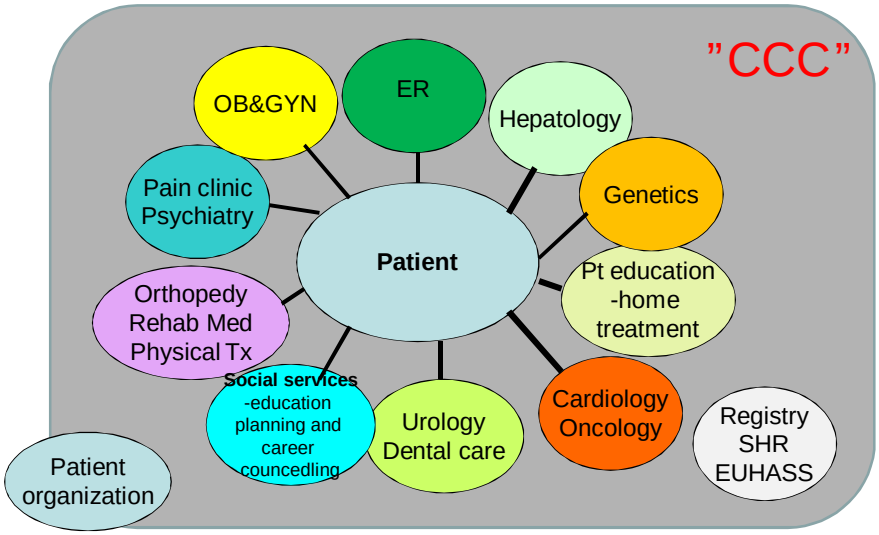
+

Lab dg => goal is to find the ones with abnormal results

⇒ Interpretation of the results
⇒ Correct diagnosis
⇒ Directed care
⇒ Treatment center and patient are informed

Modified from L. J-K

Centralized Care



Diagnosis and treatment card

- VWD dignostic criteria should be implemented to all cases
- → Re-evaluation is recommended
- Patient card is updated regularly to reflect the current situation

BLEEDING DISORDER • PATIENT CARD

Name:

Date of birth:

Dg: **D68.0 Von Willebrand disease**

Lab date:

VWF:RCo (%): VWF:Ag (%):

FVIII:C (%): VWF:CB (%):

Body weight (kg): Blood group:

DDAVP response: ☐ yes ☐ no (date):

Emergency replacement therapy:

Optional treatment:

Diagnosis date: *Card updated:*

Other diagnoses and information:

Hemophilia treatment centre:

ICE:

In case of acute bleed or trauma give treatment immediately!

Medicines increasing bleeding tendency,
ie. anti-platelet drugs (ASA, ADP- or GPIIbIIIa-blockers, dipyridamole, NSAIDs, certain antidepressive drugs), fibrinolytics, VKA, heparins, FXa or thrombin inhibitors, natural remedies
can only be used with the permission of the hematologist!

www.hematology.fi

Patient card

BLEEDING DISORDER • PATIENT CARD

Name:
Date of birth:
Dg: **D68.0 Von Willebrand disease**

Lab date:
VWF:RCo (%): VWF:Ag (%):
FVIII:C (%): VWF:CB (%):
Body weight (kg): Blood group:
DDAVP response: ☐ yes ☐ no (date):
Emergency replacement therapy:
Optional treatment:

Diagnosis date: *Card updated:*

Other diagnoses and information:

Hemophilia treatment centre:

ICE:

In case of acute bleed or trauma give treatment immediately!

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ie. anti-platelet drugs (ASA, ADP- or GPIIbIIIa-blockers, dipyridamole, NSAIDs, certain antidepressive drugs), fibrinolytics, VKA, heparins, FXa or thrombin inhibitors, natural remedies
can only be used with the permission of the hematologist!

Treatment

- Replacement ot the missing clotting factor intravenously
  - 'On demand'
  - Prophylactically 2-3 per week
- DDAVP / Octostim®
- Antifibrinolytic therapy
  - Tranexamic acid (Cyclokapron ® / Caprilon ®
- Local measures
  - Cooling
  - Immobilization
  - Rest
  - Pain medication

Octostim® intranasal spray

Indication: Treatment and prevention of bleeds
In VWD and mild hemophilia A
when response is known

Releases FVIII and VWF from endothelial cells
to increase levels.

Response testing recommended -> 2-3 x increase
Is considered adequate.

Also corrects platelet function.

TABLE 64–2. Treatment of VWD

vWD Type	Treatment: Minor Bleeding or Trauma*	Low-Risk Procedure†	Major Bleeding or Trauma‡	High-Risk Surgery§	Menorrhagia
Type 1	DDAVP	DDAVP	VWF concentrate (100% correction)	VWF concentrate (100% correction)	Estrogens DDAVP Antifibrinolytic
Type 2A	DDAVP VWF concentrate (50% correction)	DDAVP VWF concentrate	VWF concentrate (100% correction)	VWF concentrate (100% correction)	Estrogens DDAVP Antifibrinolytic
Type 2B	VWF concentrate (50% correction)	VWF concentrate	VWF concentrate (100% correction) Platelets	VWF concentrate (100% correction) Platelets	Estrogens Antifibrinolytic
Type 2M	DDAVP VWF concentrate (50% correction)	DDAVP VWF concentrate	VWF concentrate (100% correction)	VWF concentrate (100% correction)	Estrogens DDAVP Antifibrinolytic
Type 2N	VWF concentrate (50% correction)	VWF concentrate	VWF concentrate (100% correction)	VWF concentrate (100% correction)	Estrogens Antifibrinolytic VWF concentrate
Type 3	VWF concentrate (100% correction)	VWF concentrate	VWF concentrate (100% correction)	VWF concentrate (100% correction)	VWF concentrate Antifibrinolytic

*Epistaxis, mouth and gum bleeds, superficial lacerations, and skin bleeds.
†Dental cleaning, skin biopsy, vaccination, and local anesthesia injection.
‡Bleeding in the head, neck, throat, abdomen, pelvis, spine, iliopsoas, or hip; compartment bleeds; fractures or dislocations; deep lacerations; and serious trauma.
§Wisdom tooth extractions (when multiple or impacted); abdominal, thoracic, or spinal surgery; and neurosurgery.

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Table 15. Initial Dosing Recommendations for VWF Concentrate Replacement for Prevention or Management of Bleeding

Major surgery/bleeding	
Loading dose:*	40–60 U/kg
Maintenance dose:	20–40 U/kg every 8 to 24 hours
Monitoring:	VWF:RCo and FVIII trough and peak, at least daily
Therapeutic goal:	Trough VWF:RCo and FVIII >50 IU/dL for 7–14 days
Safety parameter:	Do not exceed VWF:RCo 200 IU/dL or FVIII 250–300 IU/dL
May alternate with DDAVP for latter part of treatment	
Minor surgery/bleeding	
Loading dose:*	30–60 U/kg
Maintenance dose:	20–40 U/kg every 12 to 48 hours
Monitoring:	VWF:RCo and FVIII trough and peak, at least once
Therapeutic goal:	Trough VWF:RCo and FVIII >50 IU/dL for 3–5 days
Safety parameter:	Do not exceed VWF:RCo 200 IU/dL or FVIII 250–300 IU/dL
May alternate with DDAVP for latter part of treatment	

http://www.nhlbi.nih.gov/guidelines/vwd/4_managementofvwd.htm

VWF

- **HAEMATE® 1000* IU (10ml)**
  CSL Behring
  - **plasma FVIII 1000IU /VWF 2400 IU**
- **WILATE® 450* IU (5ml) 900* IU (10 ml)**
  Octapharma
  - **plasma FVIII/VWF 1:1**
- **WILFACTIN® 1000 IU (10 ml)**
  LFB BIOMEDICAMENTS / Sanguin
  - **plasma VWF**
- **Recombinant VWF** in clinical research

Towards Individualized Care

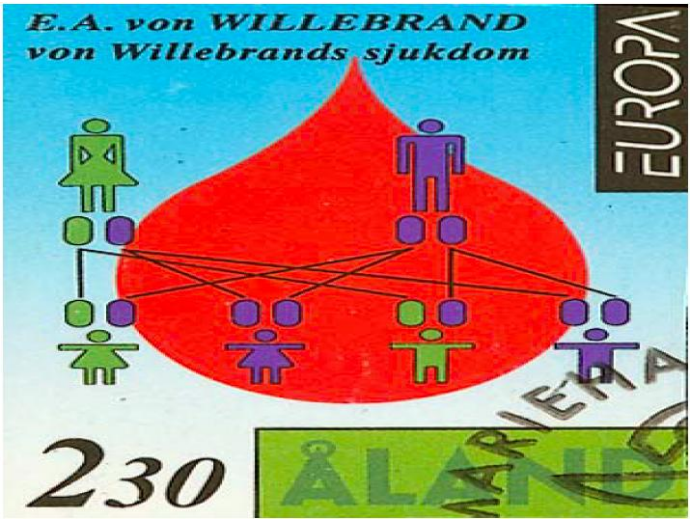
Summary of the major current VWF/FVIII concentrates: similarities and differences.

Concentrate	Biostate®[a]	Haemate P®/Humate-P®[b]	Alphanate®[c]	Fanhdi®[d]	Immunate®[e]	Wilate®[f]	Wilfactin®[g]	Factor 8Y®[h]	Range
HMW VWF (% of NHP)	86	93.6	29.3	31.7	3.9	N/A	N/A	32.1	4–94
VWF:RCo/VWF:Ag	0.73–0.99	0.91	0.43	0.69	0.38	0.9–1.0	0.95	0.6	0.4–1.0
VWF:CB/VWF:Ag	0.72–0.95	0.89	0.49	0.47	0.21	N/A	N/A	N/A	0.5–1.0
VWF:RCo/FVIII:C	2.00	2.88	0.82	1.29	0.67	1.0	>10	1.8	0.7–>10
VWF:CB/FVIII:C	2.53	2.28	0.68	0.80	0.16	N/A	N/A	N/A	0.2–2.5

Blood Transfus. 2016 May; 14(3): 262–276

VWD - Future

- **Development in treatments**
  - **recombinant VWF (Vonvendi)**
- **Genetic diagnosis**
- **Laboratory assay development**
- **VWF interactions in blood and tissues**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