Irish Centre for Vascular Biology

von Willebrand disorder – update on Treatment and Care

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Overview

1. Introduction to von Willebrand disorder
2. Best practise for VWD treatment and care – 2023
3. Important VWD questions we need to answer
4. New advances in VWD treatment – the future
5. Conclusions

Overview

1. **Introduction to von Willebrand disorder**
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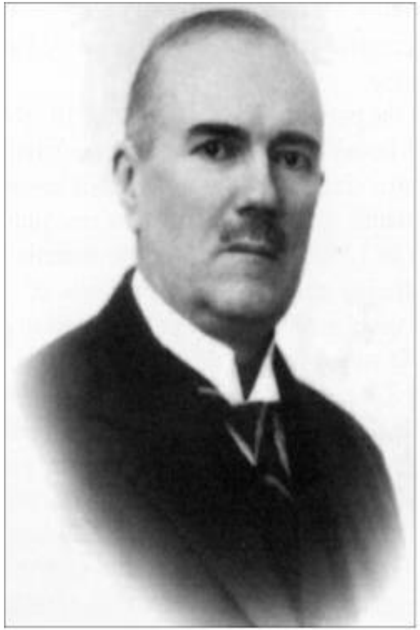
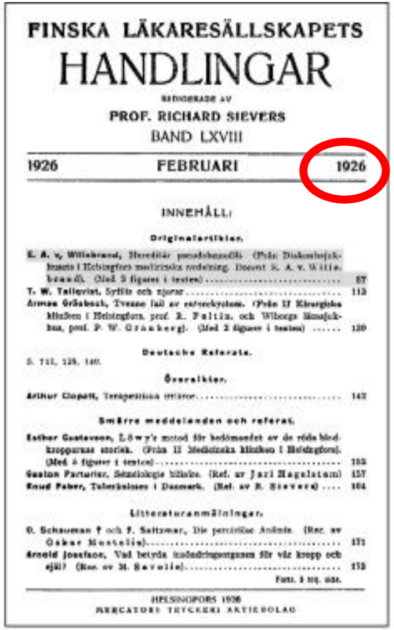
Dr Erik von Willebrand





FINSKA LÄKARESÄLLSKAPETS

HANDLINGAR

PROF. RICHARD SIEVERS

BAND LXVIII

1926 FEBRUARI 1926

INNEHÅLL:

Originalartiklar.

Deutsche Referate.

Översikter.

Smärre meddelanden och referat.

Litteraturanmälningar.

HELSINGFORS 1926

MERCATORS TRYCKERI AKTIEBOLAG

ORIGINALARTIKLAR.

Hereditär pseudohemofili.

Av

E. A. v. Willebrand.

(Med 3 figurer i texten.)

1. Sjukdomsbegrepp. Tidigare observerade fall.

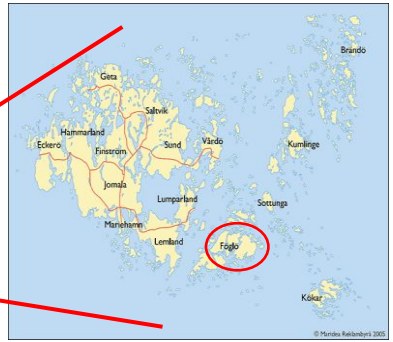
I sitt nya stora arbete över de hemorragiska diateserna framhåller E. Frank (Breslau), att den klassiska hemofilien är en så exkvisit hereditär—familjär anomali, att det kan ifrågasättas, huruvida över huvud sporadiska fall av sjukdomen existera. Däremot är, säger han, den klassiska trombopenien så utpräglat sporadisk, att man kan diskutera, om en familjär form av densamma alls förekommer. Med trombopeni avses här den sjukdom, som sedan gammalt bär namnet morbus maculosus Werlhofi eller purpura haemorrhagica och som på senaste tid av Frank och en del andra forskare betecknats såsom essentiell trombopeni.

Hittills har man velat betrakta ärftlig blödarsjukdom och hemofili såsom synonyma begrepp. Men om man genomögnar hithörande litteratur, skall man finna, om ock i ett fåtal fall, beskrivningar över en familjär form av hemorragisk diates, som redan därigenom skiljer sig från äkta hemofili att den även förekommer bland kvinnor och, såsom det tyckes, t. o. m. oftare än bland män. Men även i andra avseenden kan man draga en skarp gräns mellan ifrågavarande familjära lidande och hemofilien. Därom mera längre fram i kap. 6 om diagnosen.

Erik Adolf von Willebrand (1870-1949)

- 13 year old girl – fatal bleeding with 4th period
- Family with significant bleeding from Åland islands

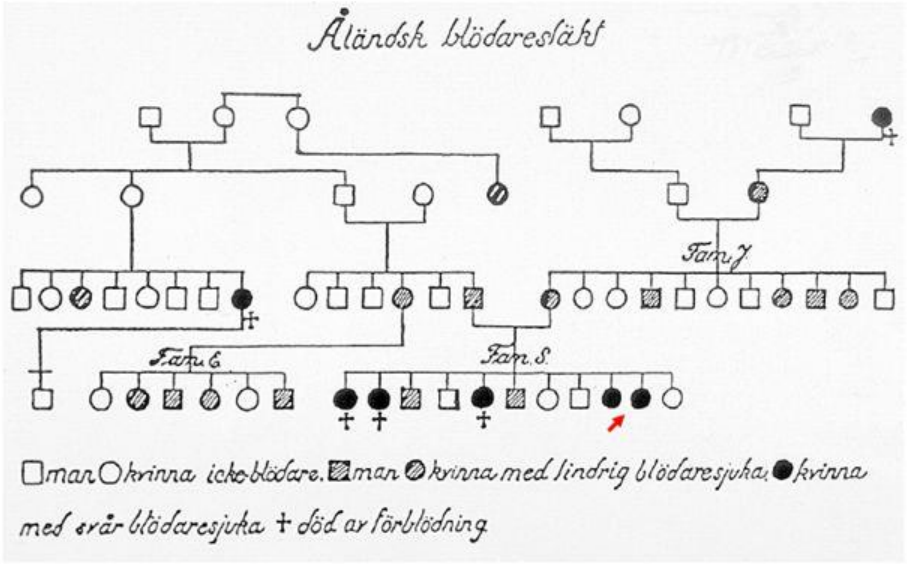
von Willebrand factor

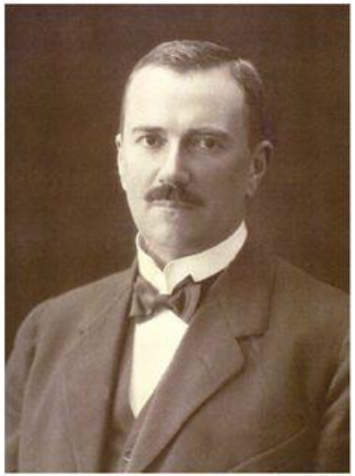


Åland archipelago consists of ~300 islands

- Autonomous region of Finland
- Language – Swedish
- Population 28,000

Von Willebrand disease



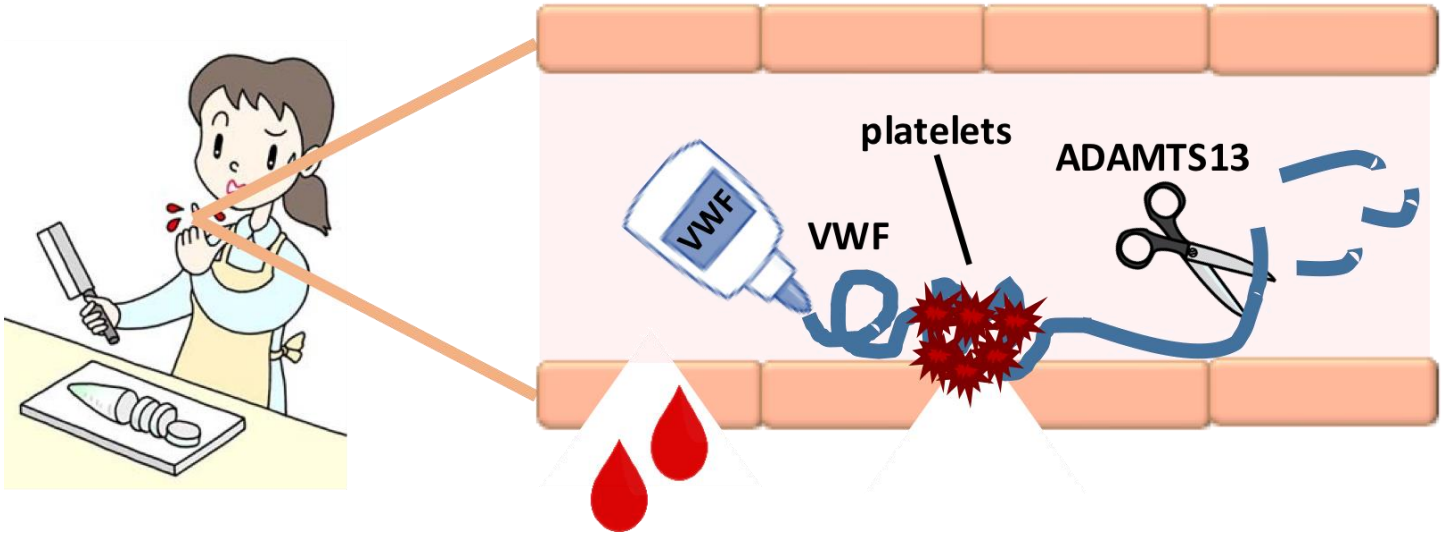


E. A. von Willebrand, *Finska Läkaresällskapets Handlingar* 1926; **68:** 7-112

. TROSSAËRT, DIU Lyon 2012

- **Interesting things - unlike haemophilia**
  - Both males and females affected
  - Heavy periods & nose bleeds rather than joint bleeding

What is von Willebrand factor ?



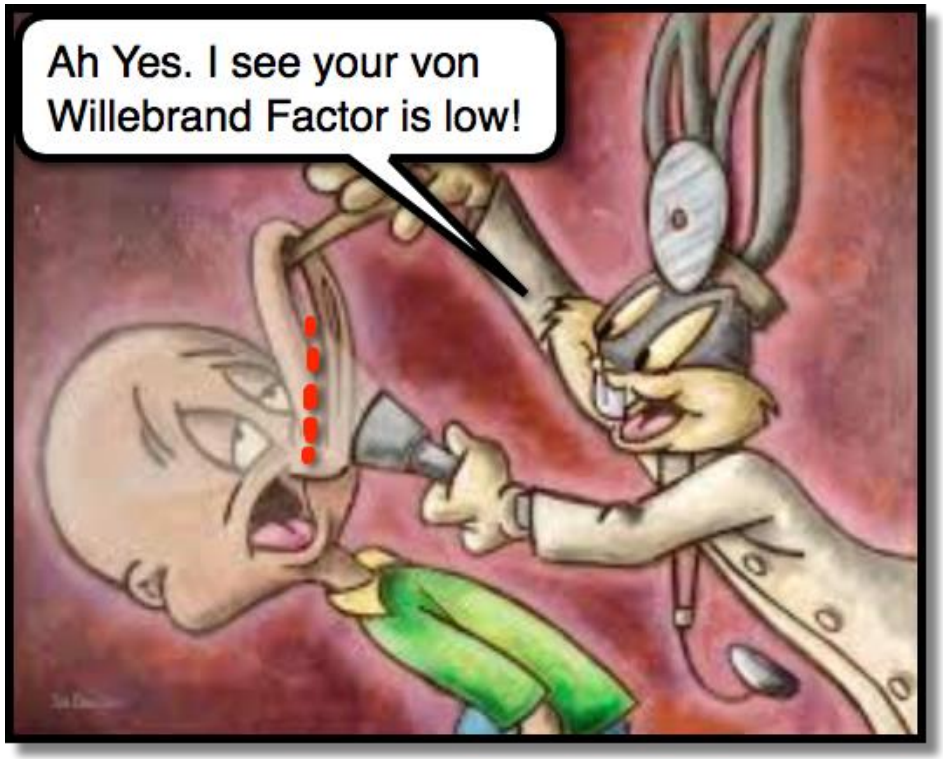
von Willebrand Disorder

Definition:

A defect in VWF that causes a bleeding tendency

- a reduced amount of VWF in the blood;
- a VWF protein that does not work properly in clotting

Patients with VWD are at increased risk for bleeding



Why is VWD important ?

Commonest inherited bleeding disorder

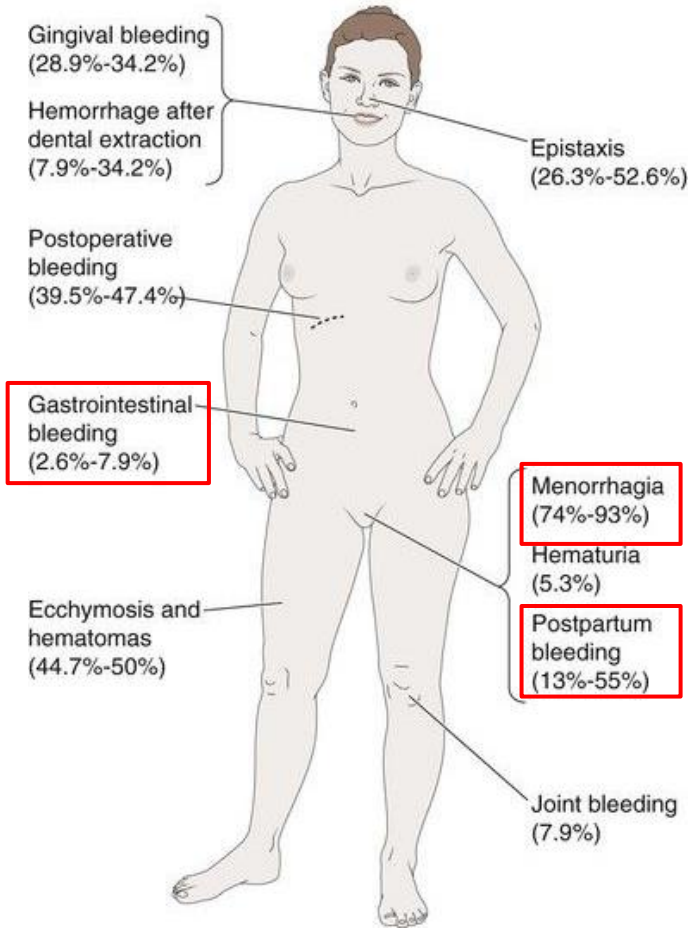
- 1 in 1000 people have low VWF levels and significant bleeding
- **Males & females equal chance of inheriting**
- **All races affected**

Bleeding in VWD

- **Characterised by muco-cutaneous bleeding**
  - Nose bleeds / gum bleeding
  - Easy bruising
  - Menorrhagia
  - Bleeding after trauma / dental / surgery

- **Rare patients with type 3 VWD**
  - Joint & muscle bleeds

Bleeding in VWD



bleeding disorders aren't just  for boys.

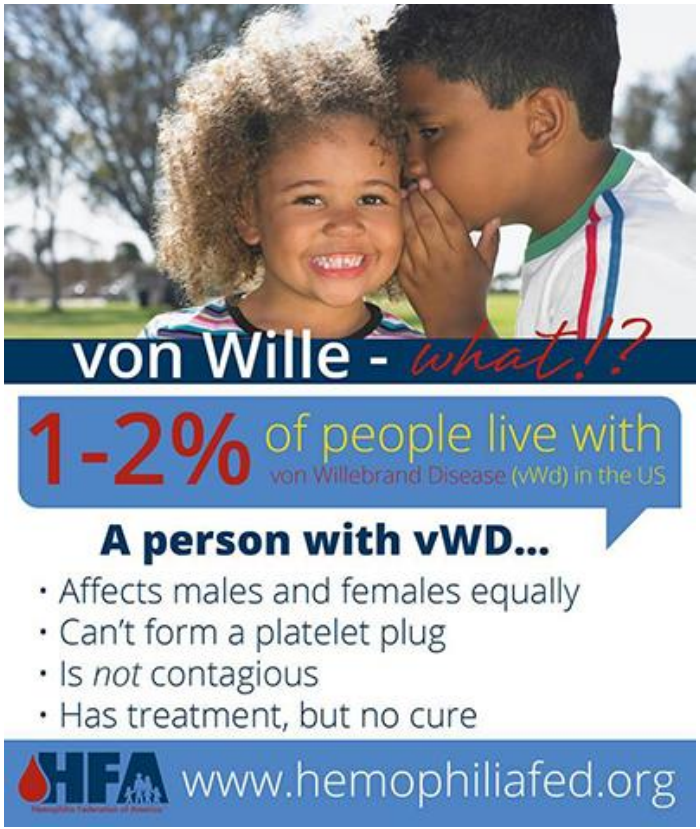
[girls bleed too]

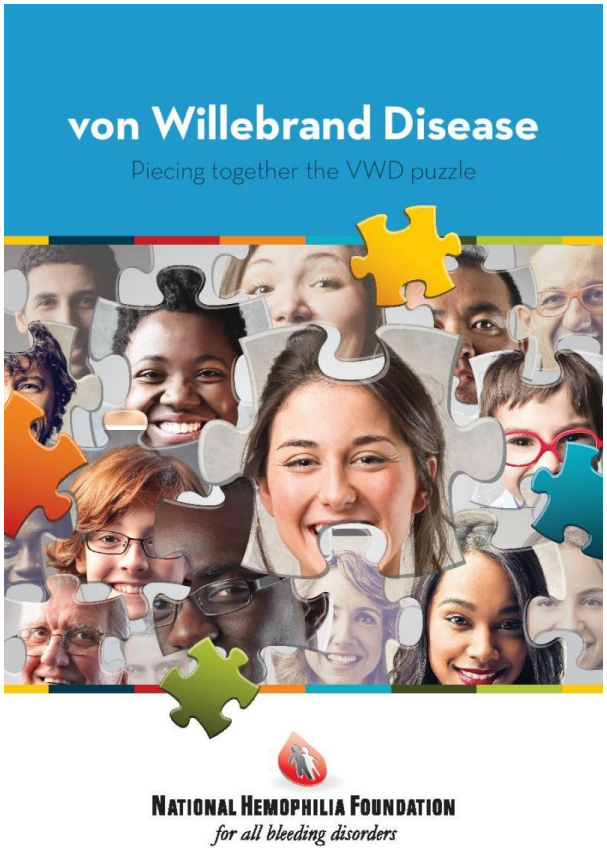
I went 26 years without knowing I had a bleeding disorder.

- Woman with von Willebrand Disease

HFA
Hemophilia Federation of America

In spite of its importance – VWD isn't well known !





Diagnosis of VWD can be difficult

Plasma VWF levels vary widely in normal population –

Influenced by variety of factors

- Age
- Ethnicity
- Stress
- Exercise
- Infection
- Inflammation
- Malignancy
- Pregnancy

ABO blood group influences VWF levels

ABO type	VWF levels
O	74 %
A	106 %
B	117 %
AB	123 %

VWD classification overview

VWD sub-classified as either quantitative or qualitative

Quantitative VWD accounts for ≈ 75% cases

– Proportionate VWF protein and function

Quantitative VWD sub-classification

- Normal plasma VWF:Ag levels 50 – 150 IU/dL

Quantitative VWD	
1. Type 1 VWD	More significant reduction in plasma VWF:Ag levels (< 50 IU/dL)
2. Type 3 VWD	Virtually complete deficiency of VWF (<3 IU/dL)

VWD Classification 2019

Qualitative VWD accounts for ≈ 25% cases

- Characterized by production of a dysfunctional VWF molecule
    - Disproportionate reduction in VWF function compared to protein

Qualitative VWD sub-classification

- Subdivided on the basis of specific phenotypic characteristics

Qualitative VWD	
Type 2A	Qualitative VWF variants with reduced platelet adhesion and loss of HMW multimers
Type 2M	Qualitative VWF variants with reduced platelet adhesion not caused by loss of HMW multimers
Type 2B	Qualitative VWF variants with increased affinity for platelet GpIbα
Type 2N	Qualitative VWF variants with decreased affinity for FVIII

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VWD studies in recent years

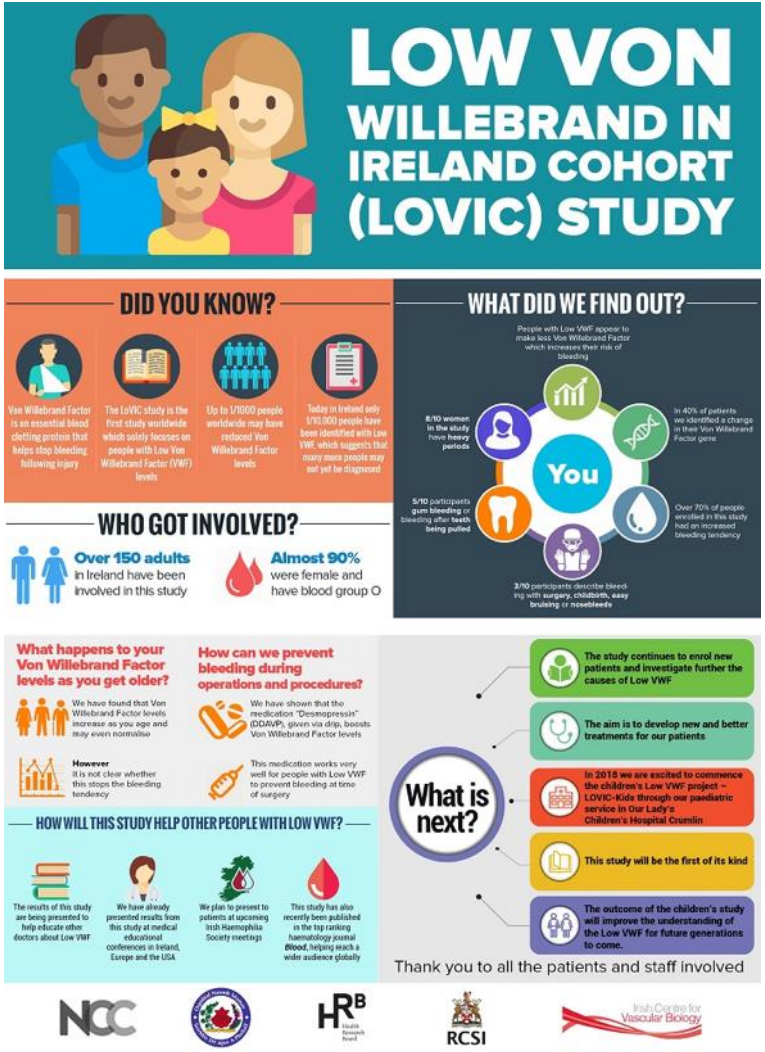
VWD studies

- EU MCMDM-1VWD
- UK-HCDO
- Canada
- Italy
- USA - Zimmerman program
- Willebrand in the Netherlands (WiN) study
- **Ireland - LoVIC study**

VWD papers

- **PubMed search on ‘VWD’ ≈ 14,000 papers**

Low VWF Irish Cohort (LoVIC) study



LoVIC

Low Von Willebrand in Ireland Cohort study

June 2015

Prospective longitudinal cohort study

> 250 patients with mild to moderate reductions in plasma VWF levels

LoVIC

Low Von Willebrand in Ireland Cohort study

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels

Michelle Lavin,[1,2,*] Sonia Aguila,[2,*] Sonja Schneppenheim,[3] Niall Dalton,[2] Kenneth L. Jones,[4] Jamie M. O'Sullivan,[2] Niamh M. O'Connell,[1] Kevin Ryan,[1] Barry White,[1] Mary Byrne,[1] Marie Rafferty,[1] Mairead M. Doyle,[1] Margaret Nolan,[1] Roger J. S. Preston,[5] Ulrich Budde,[3] Paula James,[6] Jorge Di Paola,[4] and James S. O'Donnell[1,2]

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Increased galactose expression and enhanced clearance in patients with low von Willebrand factor

Sonia Aguila,[1,*] Michelle Lavin,[1,2,*] Niall Dalton,[1] Sean Patmore,[1] Alain Chion,[1] George D. Trahan,[3] Kenneth L. Jones,[3] Catriona Keenan,[2] Teresa M. Brophy,[2] Niamh M. O'Connell,[2] Kevin Ryan,[2] Mary Byrne,[2] Margaret Nolan,[2] Anjali Patel,[1,2] Roger J. S. Preston,[1] Paula James,[4] Jorge Di Paola,[3] Jamie M. O'Sullivan,[2] and James S. O'Donnell[1,2]

REGULAR ARTICLE

blood advances

Significant gynecological bleeding in women with low von Willebrand factor levels

STIMULUS REPORT

blood advances

Enhanced VWF clearance in low VWF pathogenesis: limitations of the VWFpp/VWF:Ag ratio and clinical significance

Dearbhla Doherty,[1,2] Michelle Lavin,[1,2] Mary Byrne,[1] Margaret Nolan,[1] Jamie M. O'Sullivan,[2] Kevin Ryan,[1] Niamh M. O'Connell,[1] Sandra L. Haberichter,[3-5] Pamela A. Christopherson,[3] Jorge Di Paola,[6] Paula D. James,[7] and James S. O'Donnell,[1,2,8] on behalf of the Zimmerman Program Investigators

ORIGINAL ARTICLE

jth

Management of elective procedures in low von Willebrand factor patients in the LoVIC study

Dearbhla Doherty[1,2] | Michelle Lavin[1,2] | Jamie M. O'Sullivan[2] | Kevin Ryan[1] | Niamh M. O'Connell[1] | Alison Dougall[1,3] | Mary Byrne[1] | Marie Rafferty[1] | Mairead M. Doyle[1] | Jorge Di Paola[4] | Paula D. James[5] | James S. O'Donnell[1,2,6]

blood

How I Treat

How I treat low von Willebrand factor levels

Michelle Lavin and James S. O'Donnell

Zimmerman Program on von Willebrand disease biology

National Heart, Lung, and Blood Institute

Project Program Grant (PPG) award
Total funding: $12,000,000

Principal Investigators
Prof. Bob Montgomery – Blood Center Wisconsin, USA
Prof. David Lillicrap – Queens University, Kingston, Canada
Prof. James O'Donnell - RCSI


thank you
danke
謝謝
gracias
merci
obrigado
bedankt
dziękuję
hvala
mauruuru
sukriya
kop khun krap
go raibh maith agat
teşekkür ederim
ngiyabonga
tapadh leat
mochchakkeram
dakujem
arigatō
grazie
terima kasih
sagolun
спасибо
рахмат
Баярлалаа
dank je
merci
ευχαριστώ
감사합니다
ধন্যবাদ
merci

Expert guidelines on VWD

US NHLBI 2008

GUIDELINES

von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA)[1]

W. L. NICHOLS,* M. B. HULTIN,† A. H. JAMES,‡ M. J. MANCO-JOHNSON,§
R. R. MONTGOMERY,¶ T. L. ORTEL,** M. E. RICK,†† J. E. SADLER,‡‡ M. WEINSTEIN§§
and B. P. YAWN¶¶

EUVWD 2013

Principles of care for the diagnosis and treatment of von Willebrand disease

Giancarlo Castaman,[1] Anne Goodeve,[2] and Jeroen Eikenboom,[3] on behalf of the European Group on von Willebrand disease (EUVWD)

[1]Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [2]Haemostasis Research Group, Department of Cardiovascular Science, University of Sheffield, United Kingdom; [3]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

UKHCDO 2014

The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology

Mike A. Laffan,[1] Will Lester,[2] James S. O'Donnell,[3] Andrew Will,[4] Robert Campbell Tait,[5] Anne Goodeve,[6] Carolyn M. Millar[1]and David M. Keeling[7]

Joint initiative to update VWD guidelines

- Clinicians / scientists interested in VWD assembled into 2 panels
- Strong patient input into both panels

ORIGINAL ARTICLE

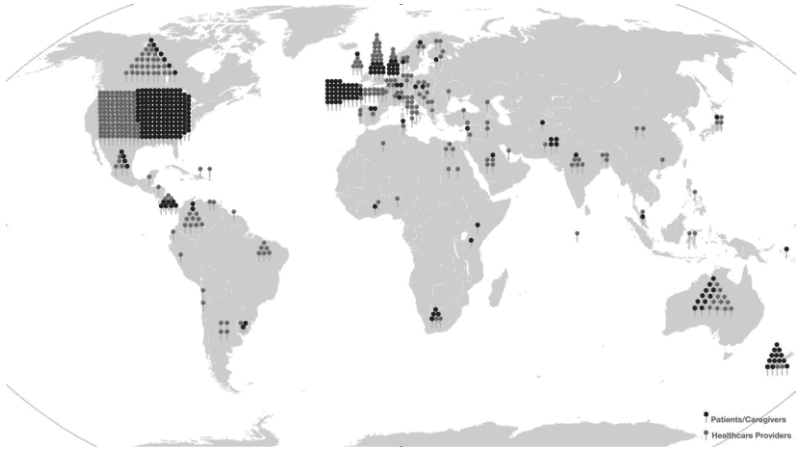
Haemophilia WILEY

An international survey to inform priorities for new guidelines on von Willebrand disease

Mohamad A. Kalot[1] | Mohammed Al-Khatib[1] | Nathan T. Connell[2] | Veronica Flood[3] | Romina Brignardello-Petersen[4] | Paula James[5] | Reem A. Mustafa[1,4] | For the VWD working group

Survey to identify topics of highest importance to stakeholders

- 601 responses



- 49% patients / caregivers
- 51% healthcare providers

Haemophilia 2020; 26:106-116

VWD guidelines methodology

Highest priority topics identified were:

- Diagnostic criteria / classification
- Bleeding assessment tools
- Treatment options for women and surgical patients

Based on survey responses - developed a series of PICO questions

- 10 questions addressed by Diagnosis panel
- 12 questions addressed by Management panel

Systematic review of evidence

- strict methodology led by University of Kansas

CLINICAL GUIDELINES

blood advances

Check for upd

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]

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]

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of VWD

Rec 1 - Panel recommend use of BAT in primary care.
Rec 2 - Panel suggest no need for BAT in patients referred to specialist centre.
Rec 3 - Panel suggest no need for BAT in patients with a family history.

Rec 4 - Panel suggest newer VWF activity assays (VWF:Gp1bM / R) over VWF:RCo.
Rec 5 - Panel suggest reconsidering diagnosis where VWF levels normalize with age.
Rec 6 - Panel recommend type 1 VWD diagnosis of VWF < 30 or VWF 30-50 IU/dl with bleeding.

Rec 7- Panel suggest desmopressin trial with 1 and 4 hour tests rather than VWFpp/VWF:Ag ratio.
Rec 8 - Panel suggest VWF:Ac/VWF:Ag ratio cut off of 0.7 for type 2 VWD subtyping.
Rec 9 - Panel suggest either multimer analysis or VWF:CB/VWF:Ag for type 2 VWD.

Rec 10 - Panel suggest genetic testing over low dose RIPA for type 2B VWD.
Rec 11 - Panel suggest wither VWF:FVIIIB or genetic testing for type 2N VWD.

James *et al*, Blood Adv 2021; 5:280

ASH ISTH NHF WFH 2021 guidelines on the management of VWD

Rec 1 - Panel suggest use of long term prophylaxis for patients with severe frequent bleeds.
Rec 2 - Panel suggest performing a desmopressin trial in VWD patients.
Rec 3 - Panel suggest antiplatelet or anticoagulant therapy for VWD with CVD.

Rec 4 - Panel suggest target FVIII & VWF:Ac > 50 IU/dL for min 3 days after major surgery.
Rec 5 - Panel suggest desmopressin or concentrate and TA for minor surgery.
Rec 6 - Panel suggest OCP / Mirena coil / TA over desmopressin for HMB.

Rec 7- Panel suggest target VWF:Ac 50-150 IU/dL for neuraxial anesthesia.
Rec 8 - Panel suggest postpartum TA in type 1 VWD.

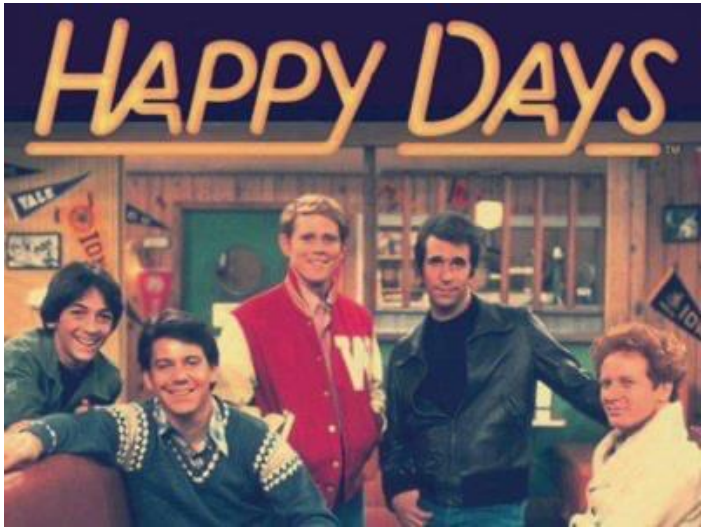
Connell *et al*, Blood Adv 2021; 5:301

State of the Art for VWD in 2023 …

ASH ISTH NHF WFH 2021 guidelines

- Exemplar model of how guidelines should be produced

Two new guidelines based on > 13,000 peer-reviewed publications



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Connell *et al*, Blood Adv 2021; 5:301

Interpretation of strong and conditional recommendations

	Strong recommendation *'The panel recommends…'*	Conditional recommendation *'The panel suggests…'*
For patients	Most individuals want the intervention	A majority of individuals would want the intervention but many would not.
For clinicians	Most individuals should follow the recommended course of action	Different choices will be appropriate for individual patients depending on values and preferences. Need for shared decision making.

James *et al*, Blood Adv 2021; 5:280

Guidelines serve to highlight the critical need for further research in the VWD field

	Strong recommendation *'The panel recommends…'*	Conditional recommendation *'The panel suggests…'*
For researchers	The recommendation is supported by credible research that make additional research unlikely to alter the recommendation.	The recommendation is likely to be strengthened by additional research - Helps to identify possible research gaps.

What are the key gaps in VWD understanding ?

James *et al*, Blood Adv 2021; 5:280

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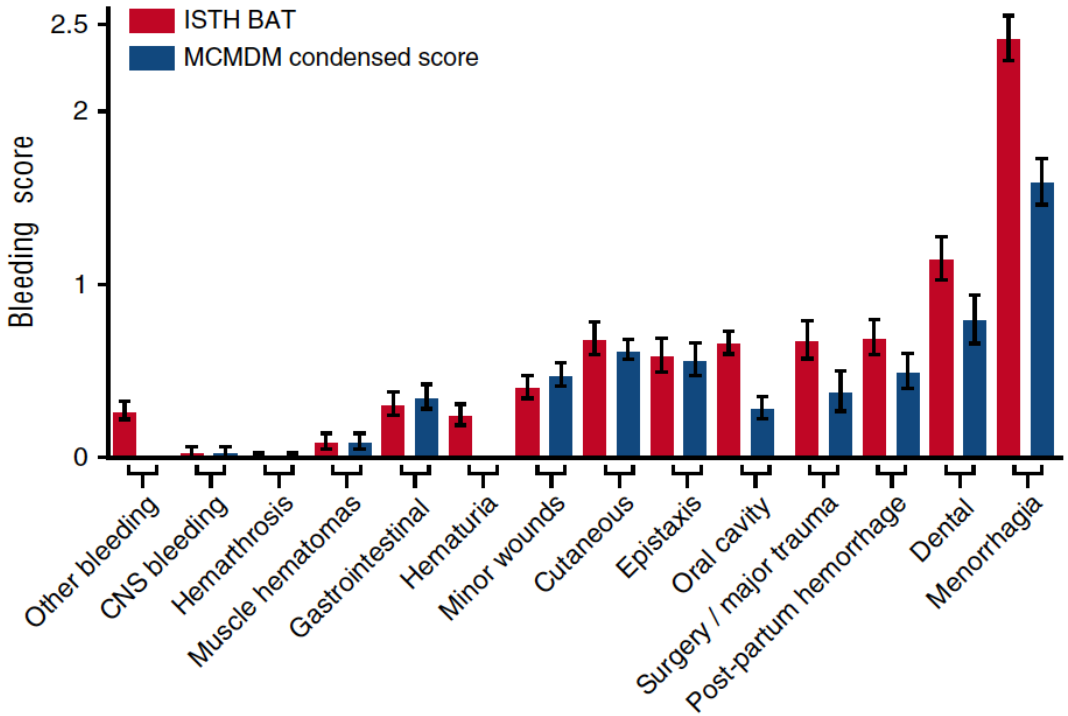
1. Why is heavy menstrual bleeding & post-partum hemorrhage such a problem in VWD ?

HMB and PPH in Irish women with mild to moderate reductions in VWF levels



LOVIC study, Blood 2017

HMB in women with Low VWF – clinical significance

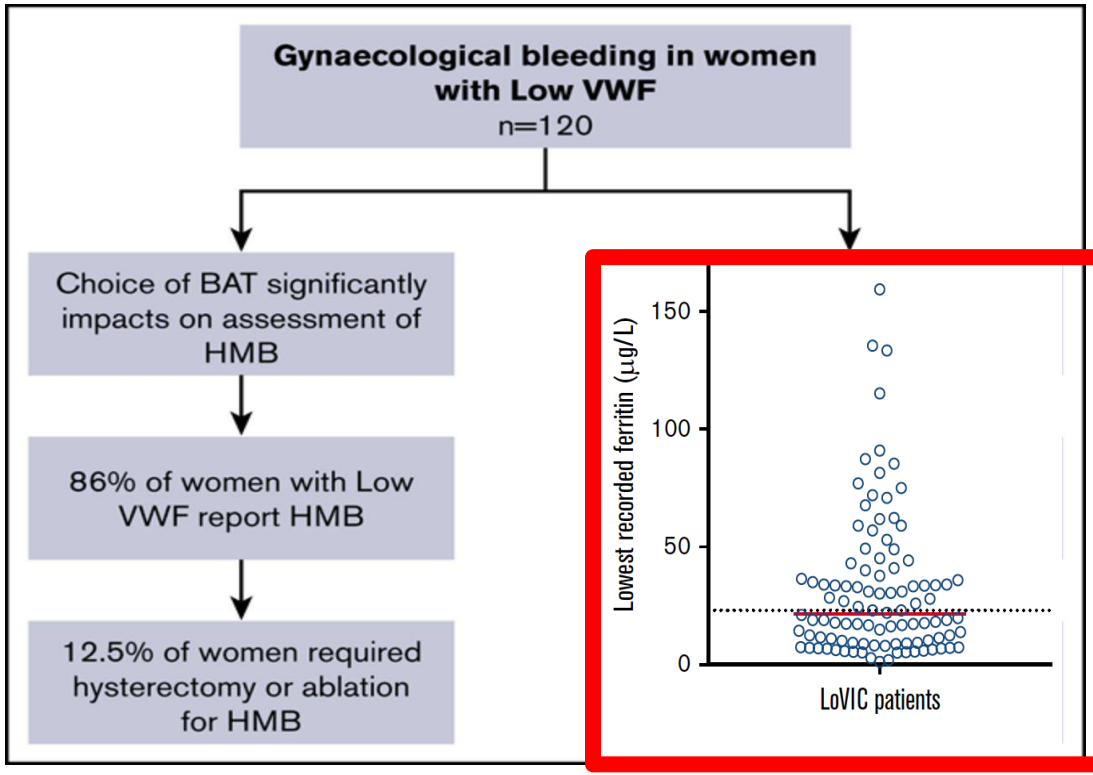
Of the LoVIC patients with menorrhagia

- 67% had been treated with hormonal therapy
- 36% had required treatment with iron

- 24% with significant menorrhagia underwent Dilation and Curettage (D&C)
- 8% had undergone a hysterectomy for menorrhagia

LOVIC study, Blood 2017

Menstrual bleeding in VWD is of clinical significance



Objective evidence

- Even <u>after</u> diagnosis and registration in Coagulation centre
- 46% LoVIC females had reduced ferritin
- 22% LoVIC females had iron deficiency anemia

LOVIC study, Blood 2017

HMB in Low VWF is of clinical significance

- 111 post-menarchal adolescent females – all aged < 21 years
- Low VWF levels 30-50 IU/dL

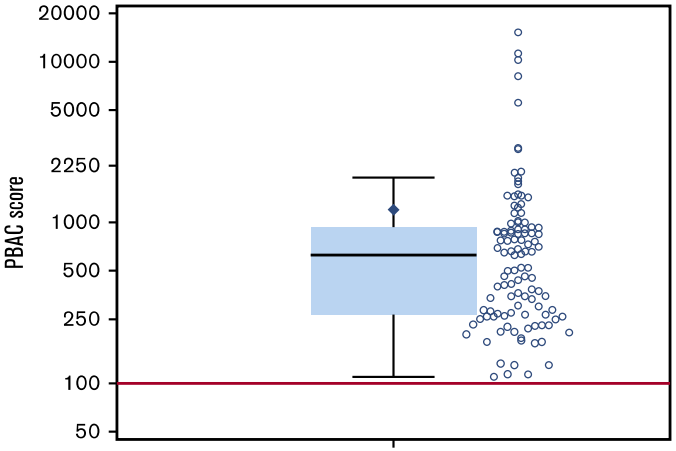
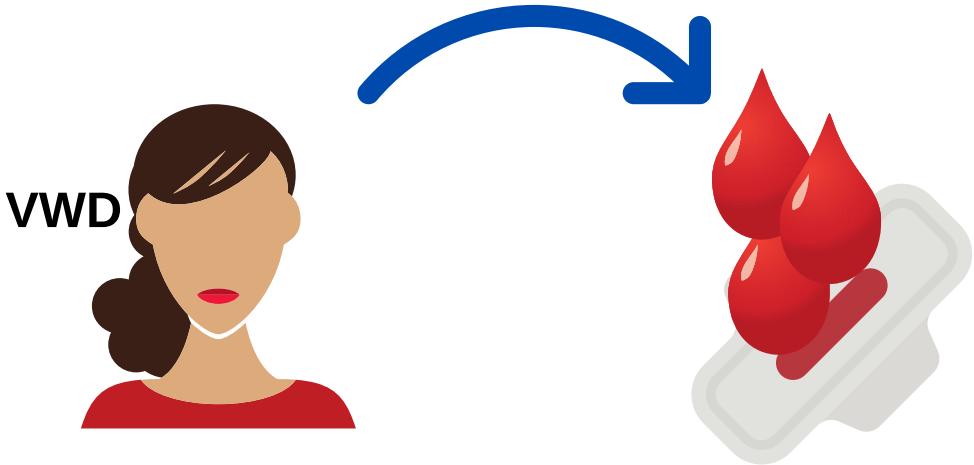


Table 2. Bleeding complications in adolescents with low VWF–associated HMB

Bleeding complication	n/N (%)
Iron deficiency (ferritin <20 ng/mL)	62/108 (60)
Anemia (hemoglobin <12 g/dL)	23/110 (21)
Red blood cell transfusion	13/108 (12)
Hospitalization for HMB	11/109 (10)

Srivaths *et al*, Blood Advances 2020

HMB is common in women with VWD

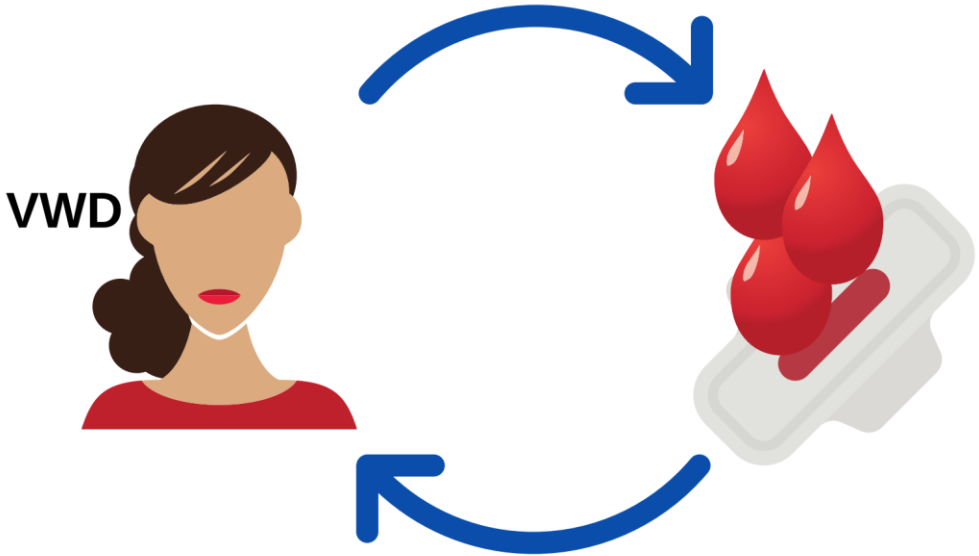


Up to 80% of women with VWD experience HMB[1,2,3]

~50% have depleted iron stores and iron-deficiency anemia[1]

1.Ragni *Am Soc Hematol Educ Program* 2019
2.Lavin et al, *Blood Advances* 2018
3. Byams et al, *Haemophilia* 2011

VWD is common in women with HMB



Adult HMB clinics
= 13% VWD[1]

Adolescents
=18[2] – 35%[3]

? hemostatic screening

1. Shankar et al. *Br J Obstet Gynae.* 2004
2. O'Brien et al, *J Pediatr Adolesc Gynecol,* 2019
3. Mikhail et al *Haemophilia* 2007

HMB – Socio-economic burden

USA alone

- 3 million GP visits per annum
- 1.8 million prescriptions per annum
- 125,000 hysterectomies per annum
- 35,000 EA procedures per annum (2000)
- **TOTAL direct costs > $1 billion pa (conservative !)**

HMB – Socio-economic burden

USA alone

- 3 million GP visits per annum
- 1.8 million prescriptions per annum
- 125,000 hysterectomies per annum
- TOTAL direct costs > $1 billion pa (conservative !)

Indirect costs

- HMB associated with 3.6 weeks fewer work per year
- Cost $1692 pa (2005)

- Lower estimate of prevalence (10%) = 7.2 million women with HMB in USA
  > $12 billion per year

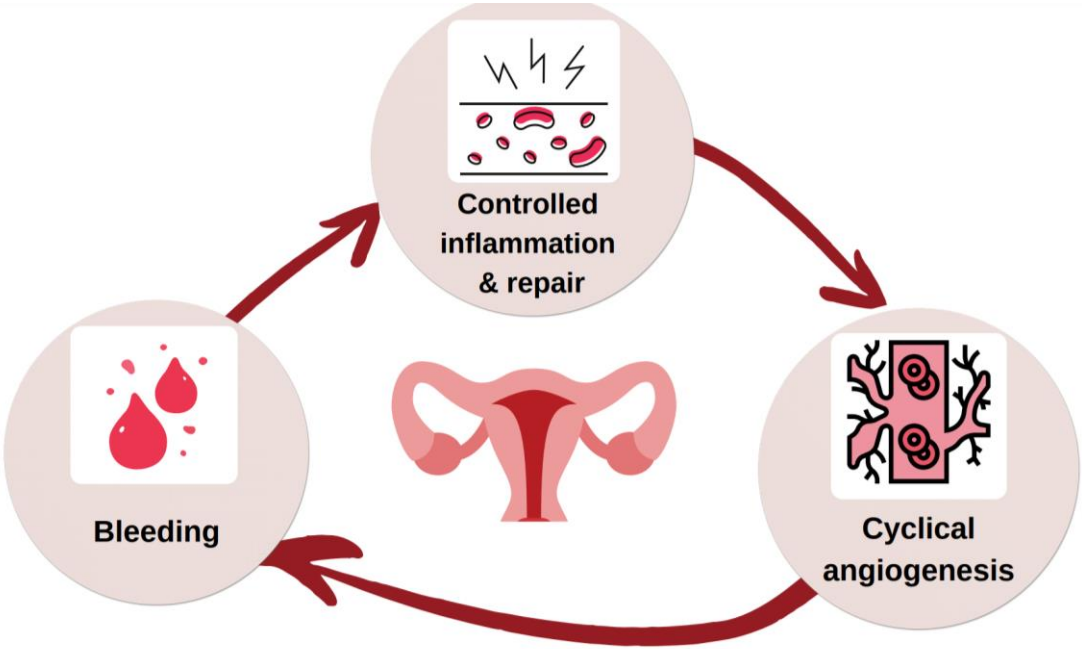
- Higher estimate of prevalence (30%) = 21.6 million women with HMB in USA
  > $36 billion per year

HMB is more common in women with VWD compared to other bleeding disorders

Bleeding disorder	VWD	Carriers < 40 IU/dL	Carriers > 40 IU/dL	Platelet function defect	Other bleeding disorder
Reported HMB	70%	51%	41%	57%	54%

Noone *et al*, Haemophilia 2019; 25:468

Heavy menstrual bleeding



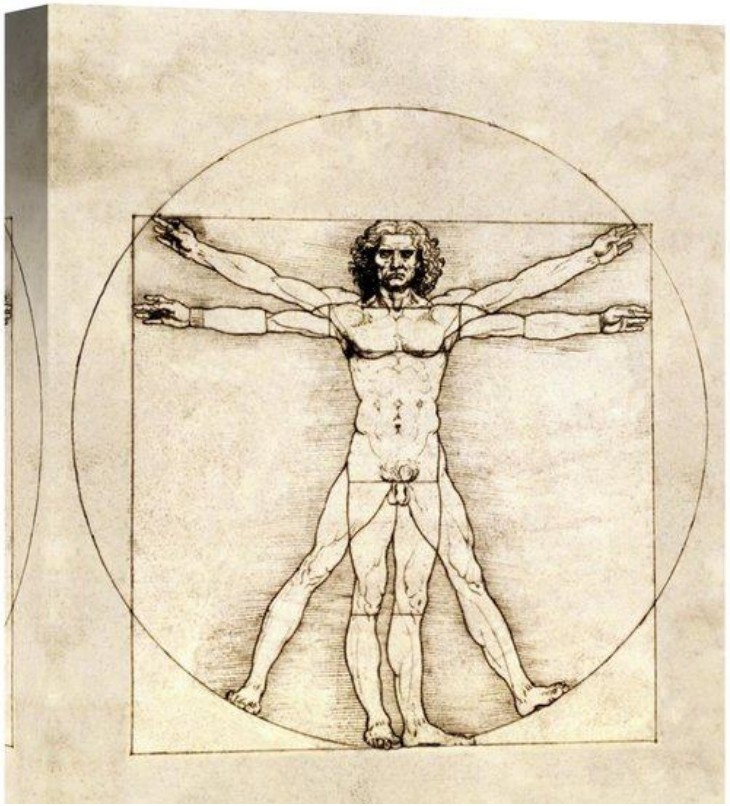
New biological roles for VWF beyond hemostasis

INFLAMMATION

ANGIOGENESIS

WOUND HEALING

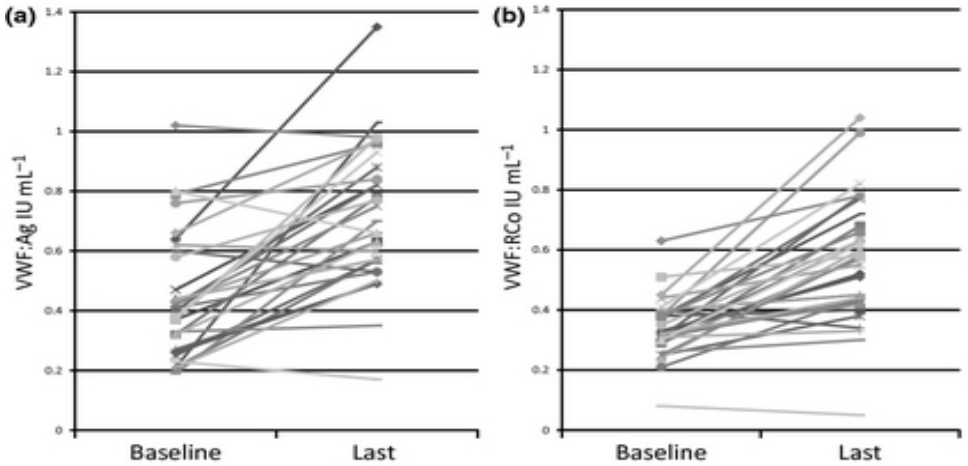
Cell proliferation



2. What happens as persons with VWD get older ?

Age influences plasma VWF levels

- Plasma VWF levels increase in normal population with age (> 10IU/dL per decade)



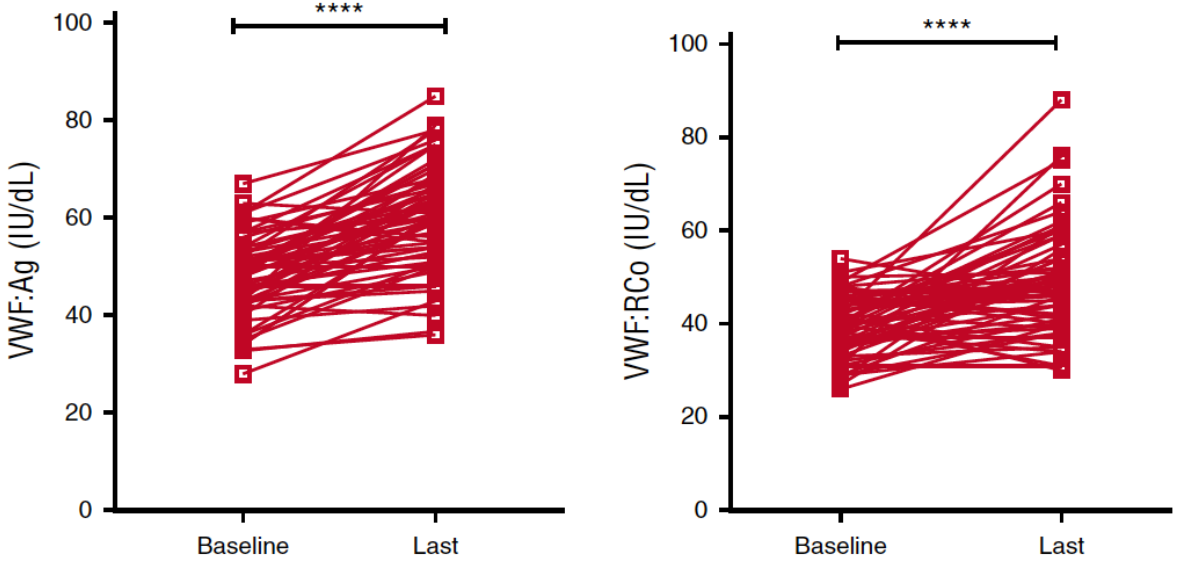
<u>Plasma VWF levels increase with age in some patients with VWD</u>

- 31 VWD– followed for > 5 years (mean 11 years)
- 18/31 patients had VWF levels increased into normal range

- No age-related increase in type 2 VWD (Sanders *et al*, JTH 2014)

Rydz *et al,* Hphilia 2015; 21:636

Plasma VWF levels increase into the normal range with ageing in some Low VWF patients

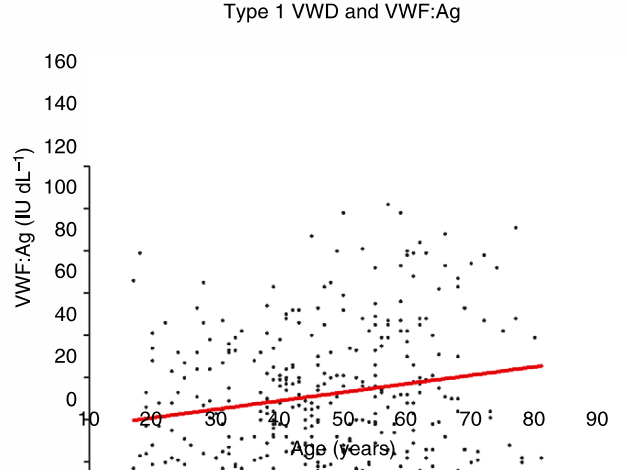


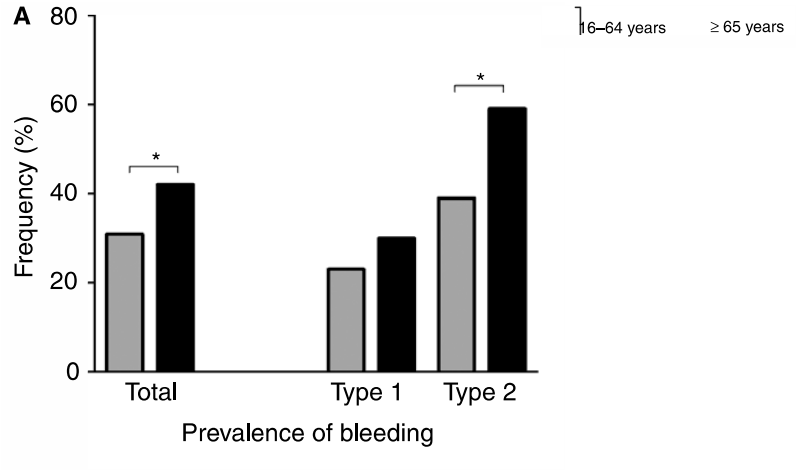
- 64 VWD patients with Low VWF – followed for > 5 years (mean 8.5 years)
- 29 patients corrected to within the normal VWF levels

LoVIC, Blood 2017

Bleeding phenotype is not necessarily corrected in VWD patients despite age-related *'normalization'* in VWF levels

- WiN study – patient reported bleeding episodes in the year preceding inclusion and during life

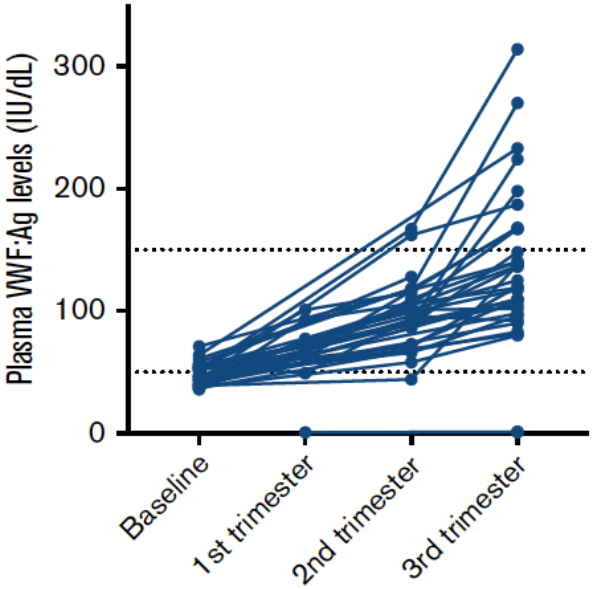




- Not necessarily associated with a correction in bleeding

Sanders *et al*, J Thromb Haemostas 2014

Plasma VWF levels increase into *'normal'* range during pregnancy in majority of LoVIC patients



PPH was self-reported in 63.5% of parous women

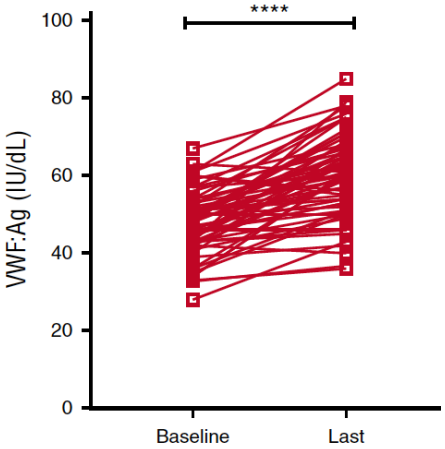
↓

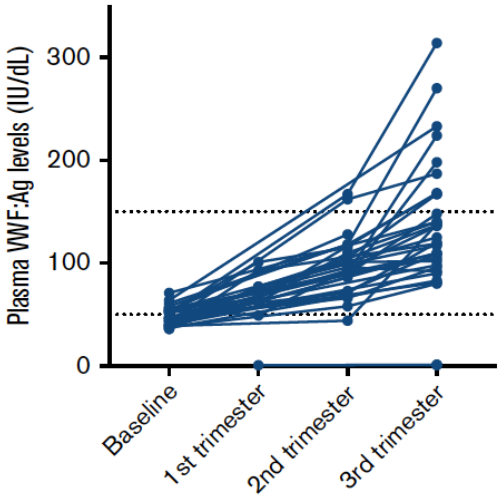
21.6 % required transfusion/ critical care/ intervention

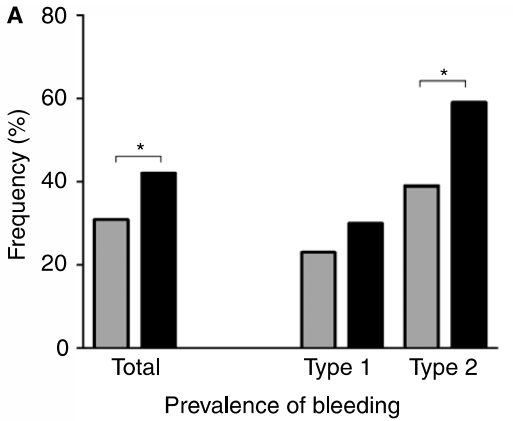
- Not necessarily associated with a correction in bleeding phenotype

LoVIC, Blood Advances 2018

Management of bleeding and hemostatic challenges following *'normalization'* of VWF levels ?







- How to define optimal therapeutic targets ?
- May differ for individual patients ?

LoVIC, Blood 2017; WIN, J Thromb Haemostas 2014

Overview

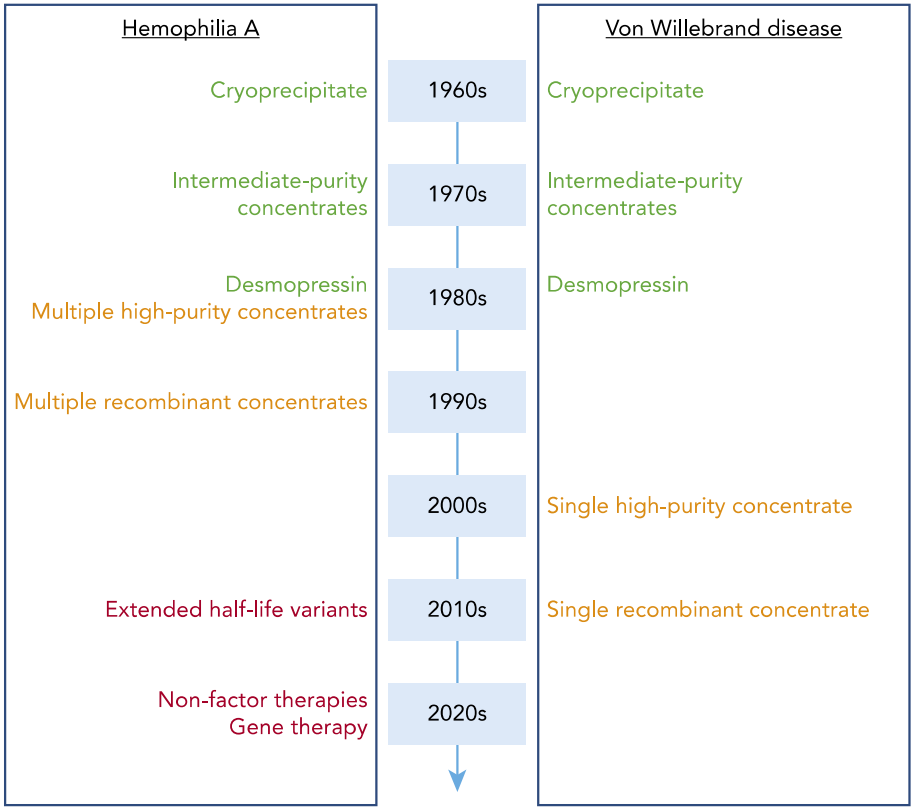
1. Introduction to von Willebrand disorder
2. Best practise for VWD treatment and care – 2023
3. Important VWD questions we need to answer
4. **New advances in VWD treatment – the future**
5. Conclusions

Treatment of patients with VWD

Options

1. Antifibrinolytics
   - Tranexamic acid / Aminocaproic acid
2. Desmopressin / DDAVP
3. Plasma-derived VWF containing concentrates
4. Platelet transfusion
5. Adjunctive therapies
   - Oral contraceptive / Intrauterine contraceptive
6. Recombinant VWF
   - VONVENDI® or VEYVONDI® – Takeda

Treatment for VWD has lagged behind advances in the hemophilia field



Denis *et al*, Blood 2021

Developing better therapies for treating VWD

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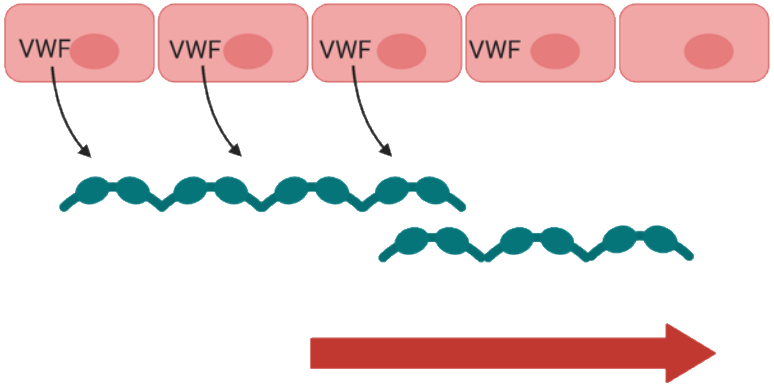
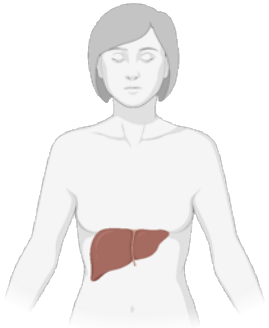
VWF lifecycle in normal individuals



Endothelial cells line the blood vessel wall

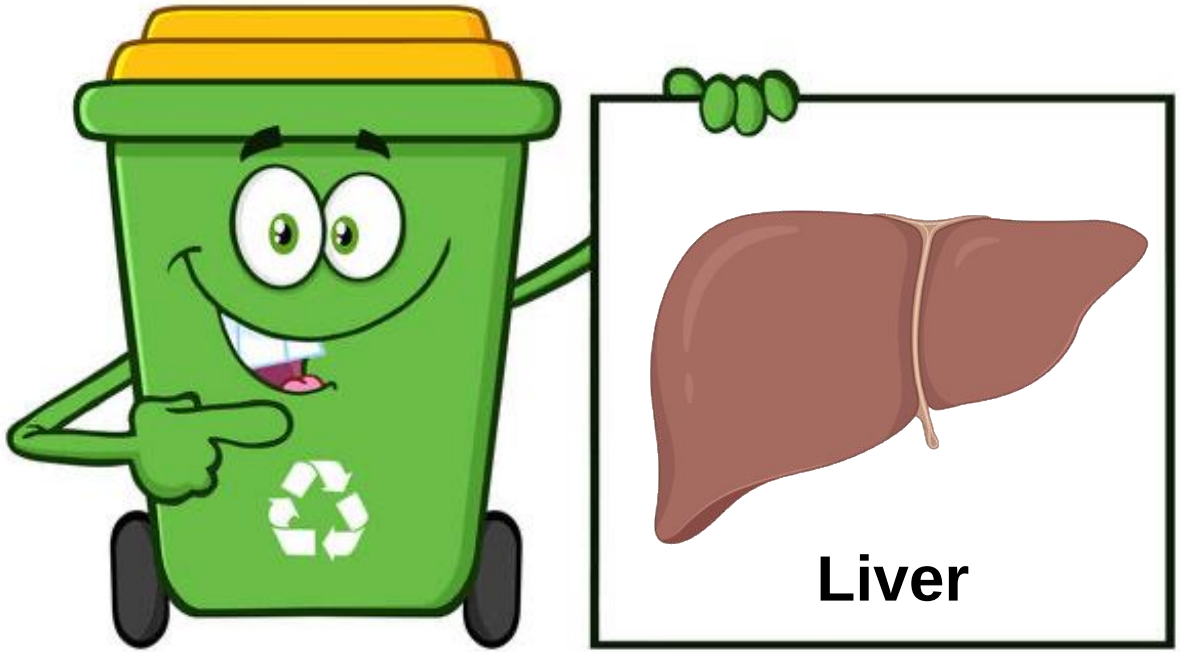
VWF is then secreted into the blood

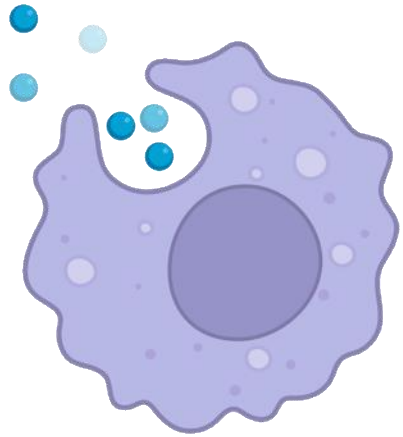
VWF circulates in blood



VWF is removed by liver after 12-18 hours

Macrophages are liver cells that clear VWF





Liver macrophage

Developing longer-lasting VWF therapies for treating VWD

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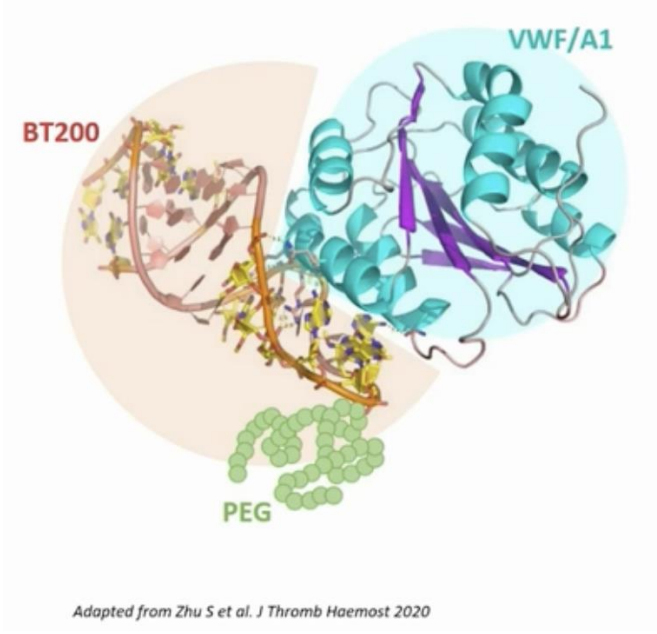
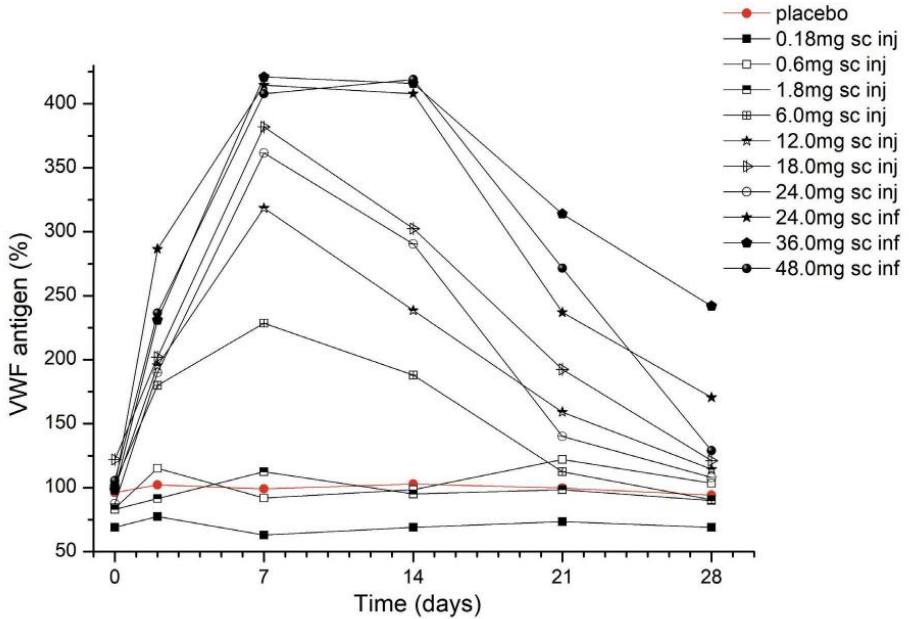
Rondoraptivon pegol (BT200) – pegylated aptamer to VWF



- **Synthetic molecule**
- **Long half-life 7-12 days**
- **Subcutaneous**

Developed as a VWF inhibitor to use as an anticoagulant in stroke

In human studies – single dose of BT200 causes a 3-4 fold increase in VWF levels



Kovacevic *et al* Haematologica 2022

In human studies – BT200 causes a 3-4 fold increase in plasma FVIII levels

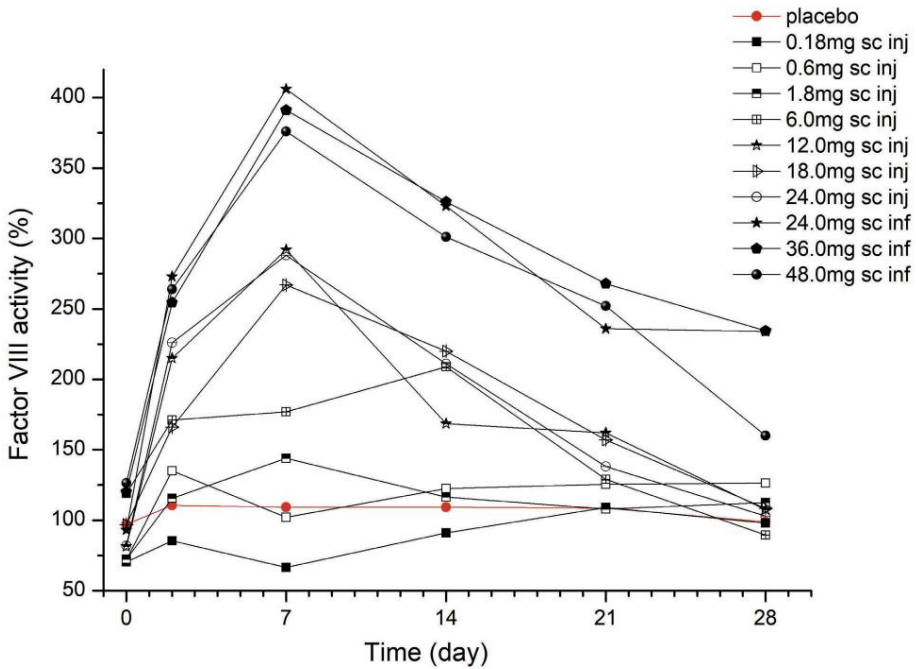


Figure 5. Factor VIII activity levels after single doses of BT200. Data are mean values without error bars for better visibility (n=6 for BT200 groups, n=20 for placebo). sc: subcutaneous; inj: injection; inf: infusion.

Kovacevic *et al* Haematologica 2022

In human studies – multiple weekly doses of scut BT200

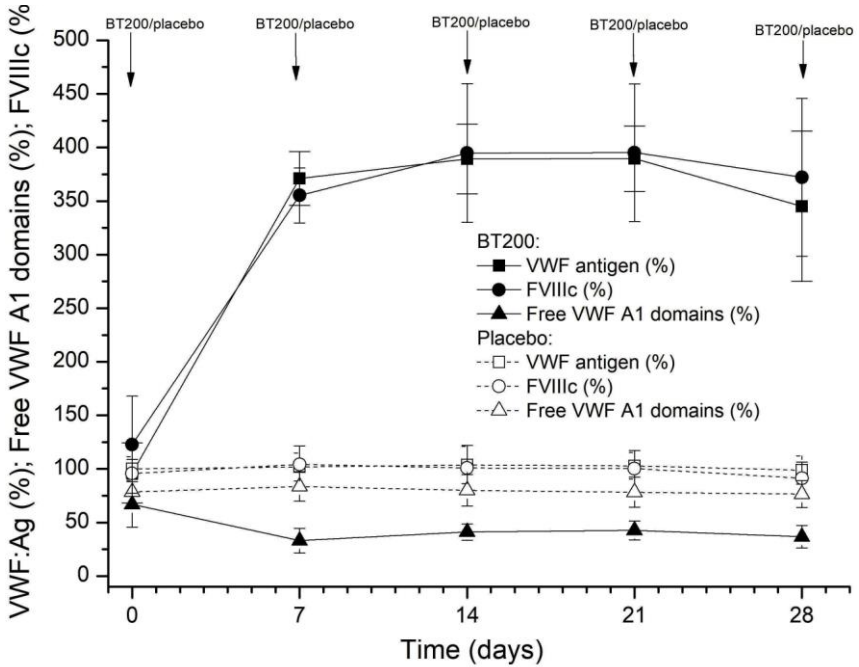
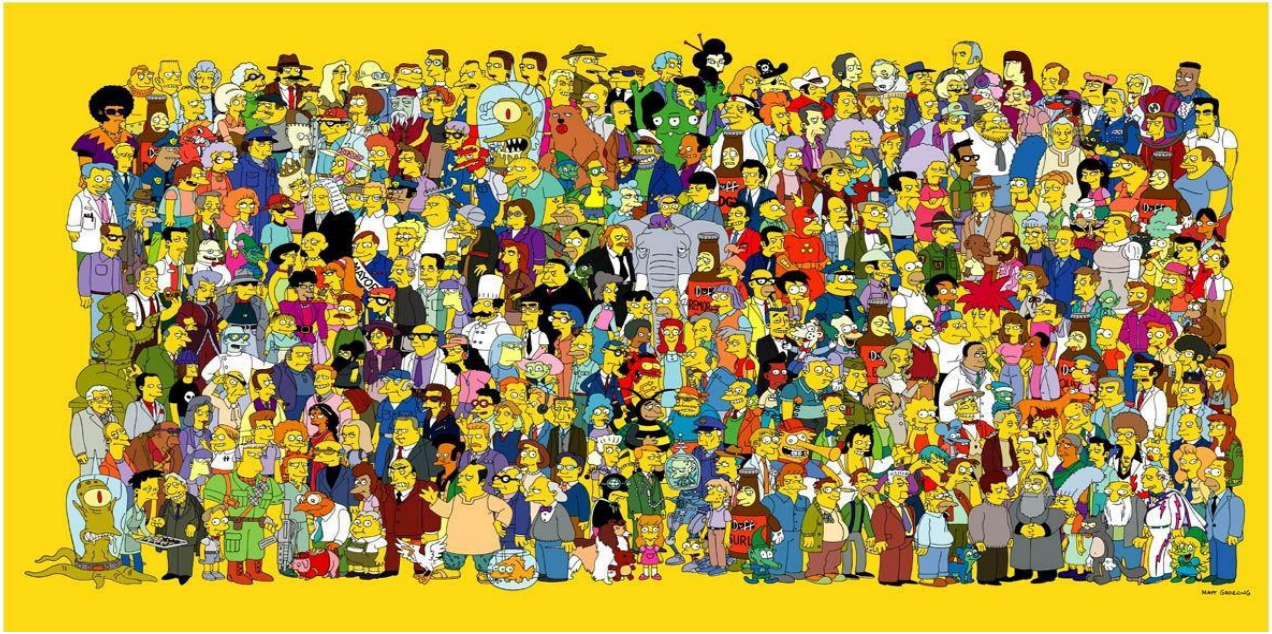


Figure 4. von Willebrand factor antigen levels, free A1-domains and factor VIII activity (%) after multiple doses of BT200. Subjects received 12 mg BT200 intravenously plus 12 mg subcutaneously on the first day and 12 mg subcutaneously weekly or placebo. Data are presented as mean values with 95% confidence intervals (n=6 for BT200 groups, n=20 for placebo). VWF: von Willebrand factor; Ag: antigen; FVIIIc: factor VIII activity.

Kovacevic *et al* Haematologica 2022

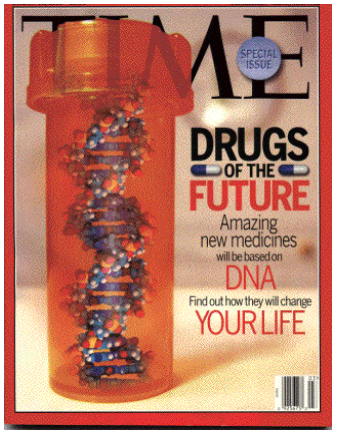
Patients with VWD are heterogeneous



One size treatment for VWD does not fit all …

Personalized Medicine in VWD

- **Treatment tailored specifically for individual patient**
  - Guideline recommendations
  - Patient-specific aspects



Personalized Medicine in VWD

- **Treatment tailored specifically for individual patient**
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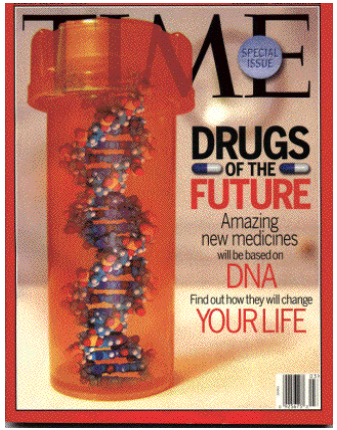

Patient preferences need to
be considered
– empowered to be actively involved
in decision making process

Prophylaxis in VWD

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Prophylaxis in VWD

Significant clinical experience of primary and secondary prophylaxis in patients with severe hemophilia

- Data on prophylaxis in VWD are limited

Retrospective studies - VWD Prophylaxis Network (VWD PN)

- Enrolled 61 patients from 10 countries
- > 90% type 2 or type 3 VWD

- Median age starting prophy = 22.4 years / median duration 2.2 years
- Typical VWF dose ~ 50U/kg given 2-3 times per week

- **Significant reduction in annualized bleeding rates (p<0.0001)**
  - Prophylaxis was more effective in preventing some types of bleeding (e.g. hemarthrosis) than others (e.g. gastrointestinal bleeding)

Abshire *et al,* Haemophilia 2013; 19:76

ASH/ISTH/NHF/WFH guidelines - prophylaxis in VWD

Recommendation 1

In patients with VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks:

- Bleeding symptoms and the need for prophylaxis should be periodically assessed.

Connell *et al*, Blood Adv 2021; 5:301

Prophylaxis in VWD

Recommendation 1

In patients with VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks:

- Bleeding symptoms and the need for prophylaxis should be periodically assessed.

Important unanswered questions:

- Selection of patients ?
- Optimal prophylaxis treatment regimen ?
- Personalized based upon PK ?
- Pharma-economic analysis ?

Need for future adequately powered clinical trials

'What got us to where we are today is not going to get us to where we need to go tomorrow'

Blake Mycoskie

- Small studies – inadequately powered
- Single centre
- Retrospective
- Non-randomized
- Hemophilia study end-points
- Limited science

‘What got us to where we are today is not going to get us to where we need to go tomorrow’

Blake Mycoskie

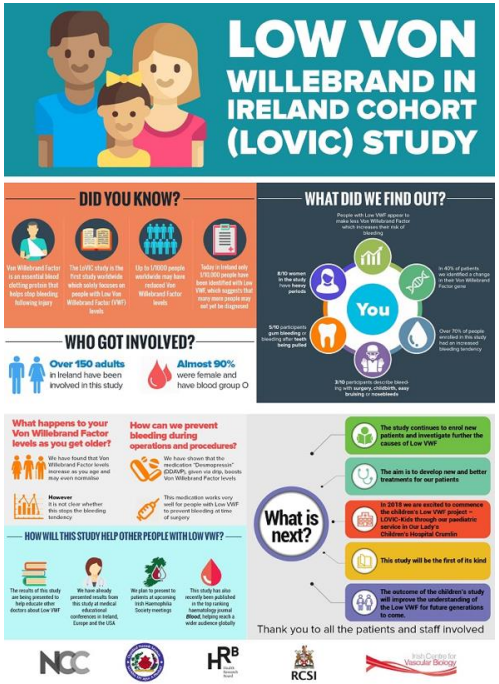
- Large international collaborative studies
- VWD is NOT a rare disorder
- Subgroup stratification and multivariate analyses
- Prospective and randomized
- State-of-the-art science
- Multiomic strategies
- Not solely dependent upon pharma funding

'What got us to where we are today is not going to get us to where we need to go tomorrow'

Blake Mycoskie

2005

Updates - 1



LoVIC

Low Von Willebrand in Ireland Cohort study

LoVIC Progress study

2024

Updates – 2

COMMENTARY

blood advances

TO THE EDITOR:

von Willebrand disease: proposing definitions for future research

Nathan T. Connell,[1,*] Paula D. James,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Barbara Ameer,[5,6] Alice Arapshian,[7] Susie Couper,[8] Jorge Di Paola,[9] Jeroen Eikenboom,[10] Nicolas Giraud,[11] Jean M. Grow,[12] Sandra Haberichter,[13] Vicki Jacobs-Pratt,[14] Barbara A. Konkle,[15,16] Peter Kouides,[17] Michael Laffan,[18] Michelle Lavin,[19] Frank W. G. Leebeek,[20] Claire McLintock,[21] Simon McRae,[22] Robert Montgomery,[23] Sarah H. O'Brien,[24] James S. O'Donnell,[19] Margareth C. Ozelo,[25] Nikole Scappe,[26] Robert Sidonio Jr,[27] Alberto Tosetto,[28] Angela C. Weyand,[29] Mohamad A. Kalot,[30] Nedaa Husainat,[30] Reem A. Mustafa,[30] and Veronica H. Flood[23]

'*Severe*' VWD ???????

Connell *et al*, Blood Adv 2021; 5:565

Conclusions

1. Significant advances in understanding of VWD

2. Key clinical questions remain to be addressed in terms of diagnosis and management.

3. Unmet clinical need – associated with significant global morbidity

4. VWD field has lagged behind recent advances in hemophilia

5. Recent ASH/ISTH/NHF/WFH guidelines highlight the issues

6. Finally, new treatments are in development

Acknowledgements

National Institutes of Health

Science Foundation Ireland

wellcome trust

Thank you

IRISH HAEMOPHILIA SOCIETY

Cumann Haemifile Na hEireann

Representing people living with haemophilia, von Willebrand's and other inherited bleeding disorders