Guideline on Von Willebrand Disease

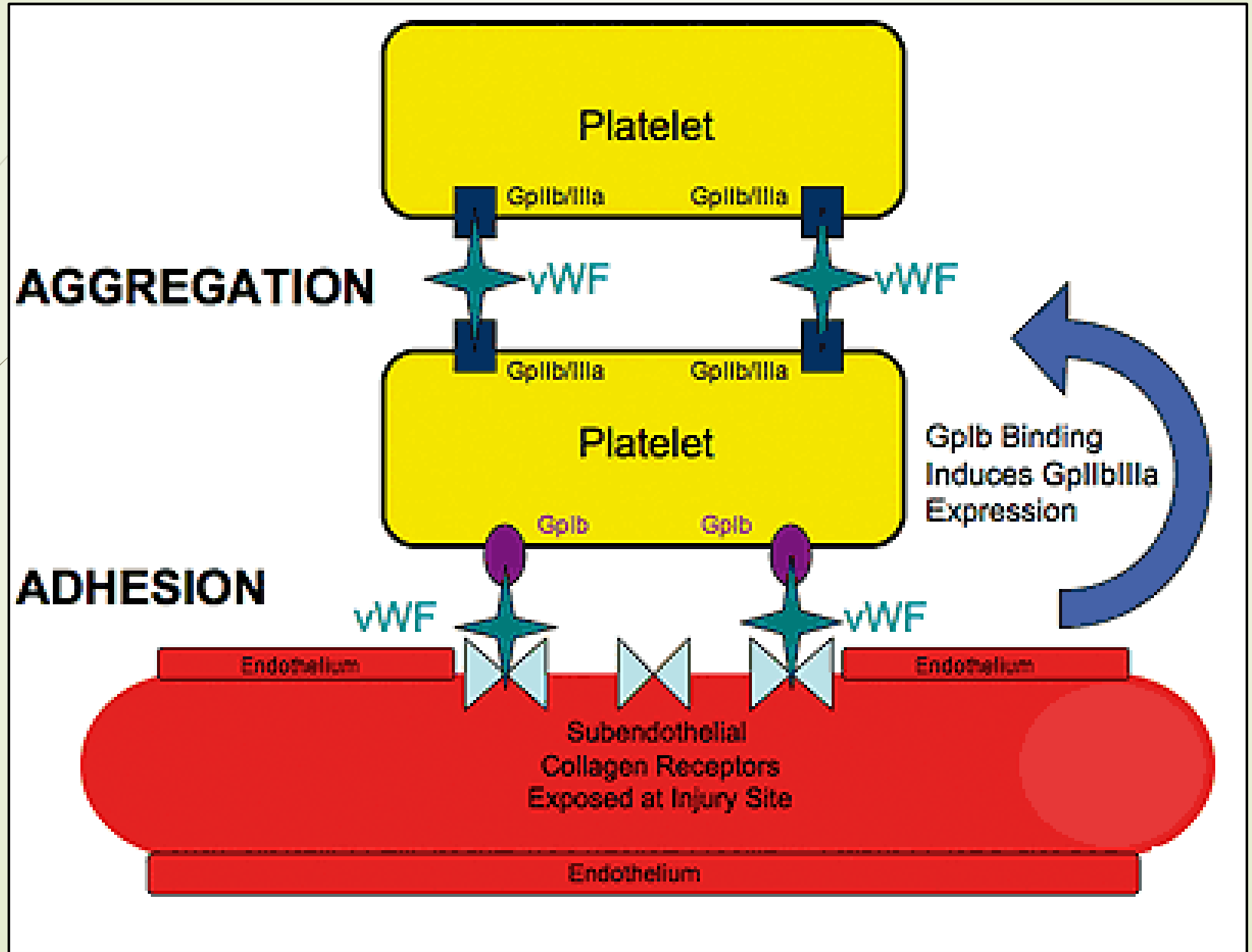
Assoc. Prof Nalini Pati

Haematologist, Canberra Hospital

Plan of my presentation

- Overview of VWD
- Overview of the guidelines
- Bleeding Assessment Tool
- Desmopressin Prophylaxis
- Desmopressin Trial
- Management of major and minor surgery
- Management of Menorrhagia
- Obstetric management

Von Willebrand Factor Pathway



Types of Von Willebrand Disease

- Classification
  - Type 1 Partial quantitative deficiency
  - Type 2 Qualitative deficiency
  - Type 3 Total quantitative deficiency
- Diagnostic tests:

	vonWillebrand type		
Assay	**1**	**2**	**3**
vWF antigen	⇓	**Normal**	⇓⇓
vWF activity	⇓	⇓	⇓⇓
Multimer analysis	**Normal**	**Normal**	**Absent**

Types of von Willebrand disease		
Quantitative defect in von Willebrand factor		
Type 1	Autosomal Dominant	Partial quantitative deficiency of vWF
Type 3	Autosomal Recessive	Virtually complete deficiency of vWF
Qualitative defect in von Willebrand Factor		
Type 2A	Autosomal Dominant	Point mutation leading to variant in vWF molecule with increased susceptibility to proteolysis by ADAMTS13
Type 2B		Mutations causing increasing affinity of vWF to platelet glycoprotein
Type 2M		Qualitative variant with decreased platelet dependent function
Type 2N		Qualitative variant with markedly decreased affinity for factors VIII

Clinical Presentation

- age at presentation
- sex
- familial history
- asymptomatic: prolonged bleeding after surgery
- primary hemostatic defects
  - mucosal bleeding, gastrointestinal bleeding (type 2A)
  - ecchymosis
  - hypermenorrhea
- secondary hemostatic defects
  - musculoskeletal bleeding
  - hemarthrosis is rare (type 2N and type 3)

Castaman G, et al. J Thromb Haemost.201

- Menorrhagia is seen in more than 70% of women with VWD and a half suffers from dysmenorrheal
- type 3 VWD have a severe internal and joint bleeding

Von Willebrand Disease

- Most common (1:10000) inherited disorder, yet very complex!
- Wide variability of presentation
- Many present late with complications
- Wide variability in practices
- Lack of high certainty evidence to guide decision making!
- Lack of Australian data
- Patients need to be treated with individualized approach including their own decisions on choices they have!

Hence the need for VWD guidelines

VWD Guidelines

CLINICAL GUIDELINES | JANUARY 12, 2021

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

Nathan T. Connell, Veronica H. Flood, Romina Brignardello-Petersen, Rezan Abdul-Kadir, Alice Arapshian, Susie Couper, Jean M. Grow, Peter Kouides, Michael Laffan, Michelle Lavin, Frank W. G. Leebeek, Sarah H. O'Brien, Margareth C. Ozelo, Alberto Tosetto, Angela C. Weyand, Paula D. James, Mohamad A. Kalot, Nedaa Husainat, Reem A. Mustafa

Blood Adv (2021) 5 (1): 301–325.

https://doi.org/10.1182/bloodadvances.2020003264

Article history

Connected Content

A related article has been published: ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

A related article has been published: Laboratory assays of VWF activity and use of desmopressin trials in the diagnosis of VWD: a systematic review and meta-analysis

Volume 5, Issue 1
January 12 2021

Previous Article
Next Article

Overview

- ASH, ISTH, NHF, and WFH formed a multidisciplinary guideline panel.
- Purpose of these guidelines is to provide evidence-based recommendations on the management of VWD.
- These guidelines are not intended to be served as a standard of care.
- Facilitate individualized therapy
- Primarily intended to help clinicians make decisions about diagnostic and treatment alternatives

What is new in these guidelines?

- Similar to previously published guidelines, with an emphasis on the treatment of bleeding in VWD.
- Specific recommendations about the diagnosis of VWD, including diagnostic thresholds, are provided in the concurrently published guidelines
- 2014 UK guidelines for diagnosis and management of VWD have many similar recommendations. However the **duration of treatment was not specified**.
- The 2008 US National Heart, Lung, and Blood Institute guidelines also recommended desmopressin trials, hormonal management for heavy menses, and VWF levels of >0.50 IU/mL for neuraxial anaesthesia.
- Balanced with presence of 3 patient representatives.
- Antifibrinolytics combined with desmopressin were recommended for oral surgery.
- After major surgery, it was recommended to keep both FVIII and VWF activity levels **>0.50 IU/mL for 7 to 10 days**.

What is new in these guidelines?

- Strength of the evidence is discussed
- For many recommendations, choices are offered to include patient and family preferences when a clearly optimal treatment choice is lacking.
- This empowers patients and their providers to make decisions based on individual bleeding history, preferences, and values with the best information available at present.
- Focus on the most common inherited forms of VWD
- Highlights the guidelines on the diagnosis and management of platelet-type VWD from the ISTH Platelet Subcommittee
- Recent reviews on acquired von Willebrand syndrome

journal of thrombosis and haemostasis®

Brief Report | Free Access

The ISTH Bleeding Assessment Tool and the risk of future bleeding

M. R. Fasulo ✉, E. Biguzzi, M. Abbattista, F. Stufano, M. T. Pagliari, I. Mancini, M. M. Gorski, A. Cannavò, M. Corgiolu, F. Peyvandi, F. R. Rosendaal

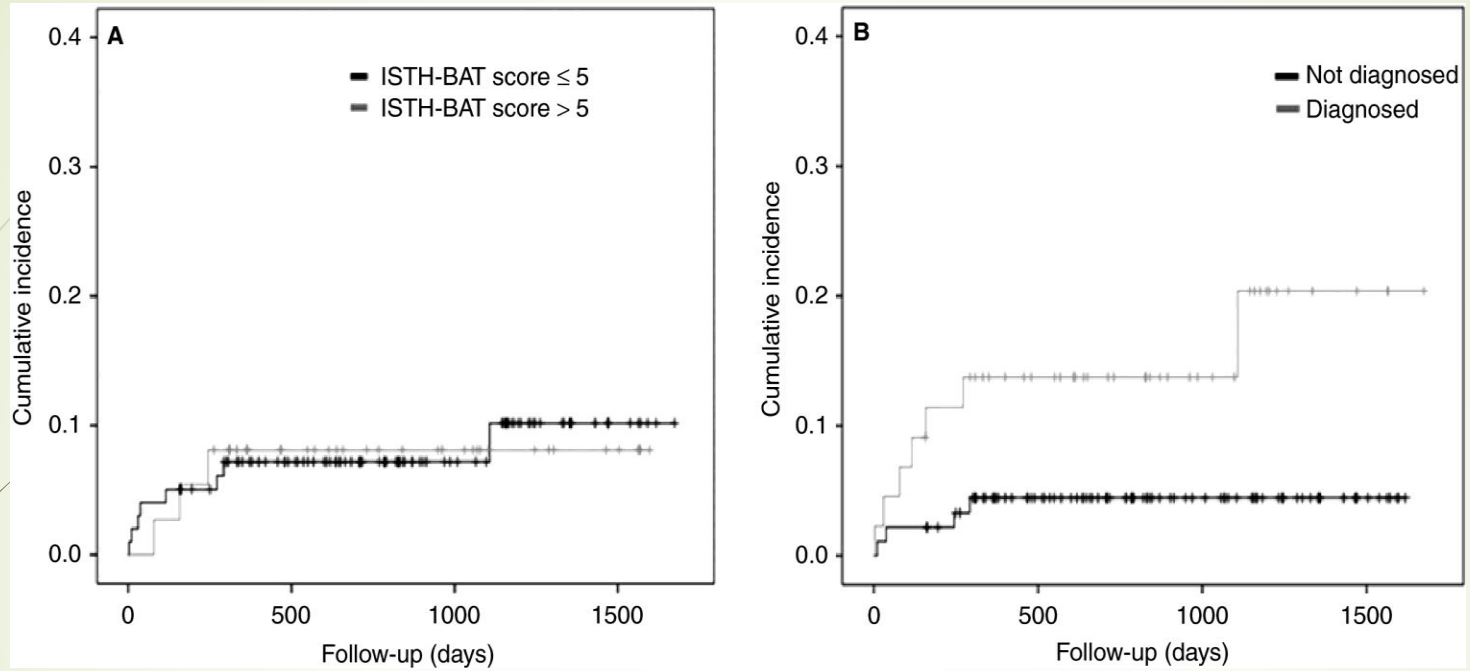
First published: 24 October 2017 | https://doi.org/10.1111/jth.13883 | Citations: 28

Manuscript handled by: M. Levi
Final decision: M. Levi, 2 October 2017

These results indicate that the ISTH-BAT bleeding score does not predict the risk of future bleeding, and is not useful for counselling subjects on their prognosis

Bleeding assessment tools were initially developed to triage the need for further laboratory tests.

The ISTH Bleeding Assessment Tool and the risk of future bleeding



Kaplan–Meier curves of bleeding events according to ISTH Bleeding Assessment Tool (ISTH-BAT) cut off and clinical diagnosis. (A) reports cumulative incidence of bleeding events in subjects with ISTH-BAT ≤5 and >5. (B) reports cumulative incidence of bleeding

J of Thrombosis Haemost, Volume: 16, Issue: 1, Pages: 125-130, First published: 24 October 2017, DOI: (10.1111/jth.13883)

Received: 22 February 2019 | Accepted: 19 August 2019

DOI: 10.1002/rth2.12256

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Bleeding assessment tools to predict von Willebrand disease: Utility of individual bleeding symptoms

Jordan Spradbrow[1] | Sasha Letourneau[1] | Julie Grabell BA[1] | Yupu Liang PhD[2] | James Riddel RN, MS[3] | Wilma Hopman MSc[4] | Victor S. Blanchette MB BChir[5,6] | Margaret L. Rand PhD[7,8] | Barry S. Coller MD[9] | Andrew D. Paterson MD[10] | Paula D. James MD[1]

Most of the bleeding symptoms on BATs are significant predictors of VWD,
There is value in assessing multiple bleeding symptoms when eliciting a bleeding history.
Certain bleeding symptoms are more useful predictors than others.
Future BAT revisions may consider adding a relative weighting to each symptom.

Regular Prophylaxis

- VWD with a history of severe and frequent bleeds, the guideline panel *suggests* using long-term prophylaxis
- Bleeding symptoms and the need for prophylaxis should be periodically assessed

Clinical Trial > Blood Transfus. 2019 Sep;17(5):391-398. doi: 10.2450/2019.0183-18. Epub 2019 Feb 4.

A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease

Flora Peyvandi [1 2], Giancarlo Castaman [3 4], Paolo Gresele [5], Raimondo De Cristofaro [6], Piercarla Schinco [7], Antonella Bertomoro [8], Massino Morfini [9], Gabriella Gamba [10], Giovanni Barillari [11], Víctor Jiménez-Yuste [12], Cristoph Königs [13], Alfonso Iorio [14 5], Augusto B Federici [15 16]

- Patients on vWF/FVIII prophylaxis showed a reduction in bleeding risk and rate compared to on-demand treatment.

Desmopressin as prophylaxis

- Desmopressin trial results may be helpful to confirm diagnosis
- Desmopressin may still be useful in some instances of mild bleeding for type 2 VWD patients.
- Undergoing major surgery, should not receive desmopressin as sole therapy - even a small amount of bleeding may result in critical organ damage.
- No need for challenge test : adult patients with type 1 VWD whose baseline VWF levels are **≥0.30 IU/mL.**
- Type 1 VWD and VWF levels of **<0.30 IU/mL** – would need trial.

Desmopressin contraindicated in:

- Type 3 VWD
- Type 2B VWD - may cause thrombocytopenia as a result of increased platelet binding.
- Active cardiovascular disease
- coronary heart disease,
- cerebrovascular disease
- peripheral vascular disease
- seizure disorders
- age <2 years
- type 1C VWD in the setting of surgery
- Preeclampsia
- More precaution while using Oxytocin and IV Fluid

Hyponatremia in Desmopressin use

- Due to free water retention
- Should receive normal saline if IV fluid replacement is required
- Free water intake should be restricted
- Education about signs and symptoms of hyponatremia

PRINCIPAL DISPLAY PANEL - 5 mL Bottle Label

APOTEX CORP. NDC 60505-0815-0

Desmopressin Nasal Spray Solution USP, 0.01%

Rx Only

5 mL

Intranasal Spray

Benefits of the trial

- Excellent haemostatic efficacy in both surgical and medical setting: 94-97%
- Treatment of bleeding episode: efficacy -96%
- Avoid serious complications in Type2B VWD

Harms and burden of the trial

- Vomiting
- Hyponatremia (4-72%)
- Headache (9%), facial flushing (9%)
- Dizziness, asthenia and peripheral oedema (43%)

Desmopressin trial reduces the risk of not receiving a treatment that may not be effective.

Desmopressin as treatment option

- Desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of <0.30 IU/mL
- Recommendation: Trial of desmopressin and treating based on the results

› Thromb Haemost. 2010 Nov;104(5):984-9. doi: 10.1160/TH10-04-0220. Epub 2010 Sep 30.

Biological and clinical response to desmopressin (DDAVP) in a retrospective cohort study of children with low von Willebrand factor levels and bleeding history

Analía Sánchez-Luceros [1], Susana S Meschengieser, Adriana I Woods, Roberto Chuit, Karina Turdó, Alicia Blanco, María A Lazzari

Affiliations + expand

PMID: 20886181 DOI: 10.1160/TH10-04-0220

- **93.4% of whom showed good response**
- The treatment was effective with one **single dose of DDAVP in almost all patients**

Practical considerations for desmopressin trial/challenge and administration

Domain	Description
Route	Either **IV or intranasal desmopressin** (may not be successful because of issues with administration and/or absorption. SC route has also been used.
Dose	**IV** desmopressin: 0.3 µg/kg, maximum dose of 20 µg. **Nasal spray** (150 µg per spray) is given as 1 spray for individuals weighing <50 kg and 2 sprays for individuals weighing ≥50 kg.
Timing of laboratory testing	**VWF antigen, VWF activity, and FVIII activity levels:** immediately before administration of desmopressin, ~30-60 min after, and ~4 h post administration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	**Definitions:** An **increase of at least 2 times the baseline VWF level** and the ability to achieve both VWF and FVIII levels of **>0.50 IU/mL** Desmopressin responsiveness does not guarantee good haemostasis, Higher levels may be indicated based on type of procedure.
Precautions	Risk of **hyponatremia:** should not be given on >3 concurrent days and not administered to children age **<2 yr** **Tachyphylaxis** occurs after repeated infusions. Caution in patients with active **cardiovascular disease, pregnancy.**

Antithrombotic therapy

- Patients with cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel *suggests* **giving the necessary antiplatelet or anticoagulant therapy** over no treatment.
- Limit the length of antiplatelet or anticoagulant therapy as required
- Bleeding is more of a risk in type 2 or type 3 VWD
- Addition of tranexamic acid may be required in patients with a severe bleeding phenotype to minimize bleeding.

Management of Surgery:

Major Surgery

- **Targeting both FVIII and VWF activity levels of ≥0.50 IU/mL for at least 3 days** after surgery, as clinically indicated after the surgery
- Type of procedure, and bleeding history as well as availability of VWF and FVIII testing.
- WThe specific target levels should be individualized based on the patient, type of procedure, and bleeding history as well as availability of VWF and FVIII testing.
- Magnitude of the desirable or undesirable anticipated effects of maintaining a FVIII activity level of ≥0.50 IU/mL Vs VWF activity level of ≥0.50 IU/mL for at least 3 days after major surgery.
- Overall, the available evidence is very low.

Minor surgery/invasive procedures

- **Increasing VWF activity levels to ≥0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid**
- **Type 1 VWD: Tranexamic acid alone** rather than targeting VWF activity levels ≥0.50 IU/mL with patients with with baseline VWF activity levels of >0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures
- **Type 2 VWD** (including patients with type 2B VWD) will also require treatment with VWF concentrate rather than desmopressin
- **Type 3 VWD** will require VWF concentrate. Desmopressin is contraindicated
- For Dental procedures, may consider use of local haemostatic measures (eg, gelatin sponges

Biostate Presentations

Concentration	50 IU FVIII/mL / 120 IU VWF/mL		100 IU FVIII/mL / 240 IU VWF/mL	
Presentation	250 IU FVIII/ 600 IU VWF	500 IU FVIII/ 1200 IU VWF	500 IU FVIII/ 1200 IU VWF	1000 IU FVIII/ 2400 IU VWF
Active ingredients (IU/vial)				
FVIII:C	250	500	500	1000
VWF:Ac	600	1200	1200	2400
Reconstitution volume (mL)	**5**	**10**	**5**	**10**

[a] Nominal values.

FVIII:C – FVIII coagulation activity.

VWF:Ac – VWF to platelet glycoprotein Ib binding activity, equivalent to VWF:RCo.

- Recombinant VWF: Vonicog alfa – Veyvondi- EU, US, Canada and Switzerland
- TGA approved for management of bleeding, surgical bleeding and surgical prophylaxis

		MINOR SURGERY	MAJOR SURGERY
	Dose (FVIII) **and interval**	30 IU/Kg every 24hrs	50 IU/kg every 12-24hr
	Pre-op target	FVIII:C and VWF:RCo >50 IU/dL	FVIII:C and VWF:RCo near 100 IU/dL
	Maintenance target	FVIII:C and VWF:RCo >30 IU/dL	FVIII:C and VWF:RCo >50 IU/dL
	Duration	1-5 days until bleeding risk has passed	5-10 days until bleeding risk has passed
Borderline	FVIII, VWF:Ag and RCo >30-50IU/dL.	No therapy DDAVP if response	DDAVP if response VWF concentrate
Mild-mod type 1	FVIII, VWF:Ag and VWF:RCo >15 IU/dL	DDAVP if response VWF concentrate	DDAVP if response VWF concentrate
Severe type 1	FVIII>10 IU/dL and VWF:Ag<15 IU/dL	DDAVP if response VWF concentrate	VWF concentrate
2A or M	VWF:RCo to VWF:Ag <0.6-0.7	DDAVP if response VWF concentrate	DDAVP if response VWF concentrate
2B	VWF:RCo to VWF:Ag <0.6-0.7 and enhanced low dose RIPA	VWF concentrate	VWF concentrate
2N	FVIII <40 IU/dL and FVIII:C to VWF:Ag <0.5. Low VWF:FVIIIB	DDAVP if responsive (t 1/2) VWF concentrate	VWF concentrate
3	FVIII <10 IU/DL and/or VWF:Ag <5 IU/dL	VWF concentrate (consider continuous infusion)	VWF concentrate (consider continuous infusion)

The addition of Tranexamic acid should be considered in all situations

Biostate Dosing Guide

Indication	Dose (IU/kg)		Dose frequency	Target FVIII/VWF (%) (IU/dL)
	FVIII:C	VWF:Ac[1]		
Spontaneous bleeding episodes	10–20	25–50	Initial	VWF peak level >50%, FVIII >30%
	10	25	Subsequent every 12–24 hours	VWF/FVIII trough levels of >30% until bleeding stops (usually 2–4 days)
Minor surgery	25	60	Daily	VWF/FVIII trough levels of >30% until healing is complete (usually 2–4 days)
Major surgery	25–35	60–80	Initial	VWF peak level >100%, FVIII >60%
	15–25	30–60	Subsequent every 12–24 hours	VWF/FVIII trough levels of >50% until healing is complete (usually 5–10 days)
Prophylaxis	10–15	25–40	1–3 times weekly	Trough >1

Menorrhagia

- **How we define?** >80mL, passing clots >2.5cm diameter, changing pad or tampon hourly or developing anaemia
- Should be managed with multidisciplinary approach.
- 73% good response to the combined oral contraceptive pill.
- Tranexamic acid orally 1g qid d1-4 of menstruation
- DDAVP may be used for a maximum of 3 days
- Intrauterine progesterone contraceptive device
- Iron supplementation should be considered if there is evidence of iron deficiency anaemia

Heavy menstrual bleeding

Should tranexamic acid, hormonal therapy (ie, levonorgestrel-releasing intrauterine system or hormonal contraceptives), or desmopressin be prescribed?

- Either hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin
- Multiple options can be combined, especially if control of heavy menstrual bleeding is less than optimal with the initial therapy with tranexamic acid.
- Desmopressin is **not effective in type 3** and many type 2 VWD patients and is **contraindicated in type 2B VWD**.
- Levonorgestrel-releasing intrauterine system
- Development of multidisciplinary clinics
- Other benefits with use of hormonal therapy
- Use of VWF concentrate in selective patients

Broaden the approach in management

- Rule out **common pelvic pathologies**, such as fibroids and polyps, especially those not responding to first-line treatment.
- Special consideration for those who are at high risk of endometrial hyperplasia/malignancies.
  - Women age >35 years
  - Polycystic ovaries
  - High BMI
  - Diabetes
  - Hypertension

Evidence:

- No comparative data for evaluating tranexamic acid vs hormonal therapy.
- No difference between desmopressin and hormonal therapy
- Menstrual flow was higher in the desmopressin group
- Levonorgestrel-releasing IUD helps
  - Better control of heavy menstrual bleeding,
  - Improved QOL,
  - Haemoglobin
  - Shortened duration of menstruation.
- The **expulsion rate** for a levonorgestrel-releasing IUD- **15%,** and the **malposition rate -10%.**
- Research needs: Comparative studies mono Vs Combined

  QOL improvement

  Lev containing IUD- acceptability, expulsion, spotting rates

Obstetric issues

VWF cover for neuraxial anesthesia during labor?
What should be the target VWF activity?

- Management of pregnancies should occur in consultation with the nearest HTC centre and in an obstetric unit with appropriate facilities
- VWF and FVIII rise during pregnancy and should be repeated in the third trimester between **32-34 weeks.**
- Levels of FVIII and VF:Rco >50 IU/dL are considered adequate for delivery
- **VWF concentrate** should be used to achieve these levels
- If necessary maintain them for 5-7 days post partum
- Mode of delivery should be decided on obstetric grounds

Obstetric issues

- No comparative studies
- Complications of the epidural procedure was 6%
- Experience with 110 women whose VWF levels were increased to 0.50 - 1.50 IU/mL Vs 34 women whose levels were increased to >1.50 IU/mL. In both groups, 100% of women were able to receive the epidural procedure.
- Panel did not recommend targeting higher VWF levels due to lack of evidence.

Obstetrics: postpartum management

In women with VWD, should tranexamic acid be prescribed (or not) during the postpartum period?

- Tranexamic acid may be given systemically via the oral or IV route. The oral dose is 25 mg/kg (typically 1000-1300 mg) 3 times per day for 10 to 14 days or longer if blood loss remains heavy.
- **Safe while breastfeeding**
- Outcomes evaluated included vaginal hematoma, thrombotic complications, and blood loss.
- **No studies evaluated the risk of major bleeding**, need for other medical procedures, or mortality.
- **Reduced the risk of secondary postpartum haemorrhage**
- Tranexamic acid may also **reduce the risk of primary postpartum haemorrhage, Pr PPH, Need for Tx, vaginal haematomas**

Obstetrics: postpartum management

- Ideal VWF activity level to prevent PPH is not known
- Women without VWD often have VWF activity levels of >1.50 IU/mL by the time of delivery.
- Raises the question of whether women with VWD are at greater risk of postpartum haemorrhage if they do not achieve these same physiologic levels.
- **Additional research needs:**
  - *Efficacy of tranexamic* acid in the prevention and treatment of PPH in women with VWD, including the *optimal duration of therapy*
  - Clinical trial on *prevention of PPH*
  - Basic science research on *understanding fibrinolysis in the postpartum period.*

Platelet-type von Willebrand Disease (PT-VWD)

J Thromb Haemost. 2020 Aug;18(8):1855-1858. doi: 10.1111/jth.14827.

Guidance on the diagnosis and management of platelet-type von Willebrand disease: A communication from the Platelet Physiology Subcommittee of the ISTH

Maha Othman [1 2], Paolo Gresele [3]

Affiliations + expand

PMID: 32279414 DOI: 10.1111/jth.14827

Free article

- PT-VWD is a **rare autosomal dominant** platelet bleeding disorder. (55 pts).
- Frequently misdiagnosed and inappropriately treated.
- Currently, there are no clear guidelines for the diagnosis and management of PT-VWD pts.
- **Tests essential are:** platelet count and size, ristocetin-induced platelet agglutination with mixing studies, and sequencing of platelet GP1BA gene.
- Platelet transfusions and von Willebrand factor-rich concentrates (if VWF is low) are the most effective treatments.
- This consensus may help to avoid misdiagnosis and guide appropriate management of patients with this disease.

VWF inhibitors

- In multi-transfused patients with **type 3 VWD: Frequency 5–10%** but not seen in other VWD subgroups.
- Loss of response to VWF concentrate, occasional anaphylactic reaction.

Recommendations:

- **Traditional mixing studies are unreliable** method for inhibitor screening in type 3 VWD and *measurement of in vivo recovery should be considered* if an inhibitor is suspected.
- **Management:** High dose rVIII infusion, rVIIa, platelet transfusion and tranexamic acid.

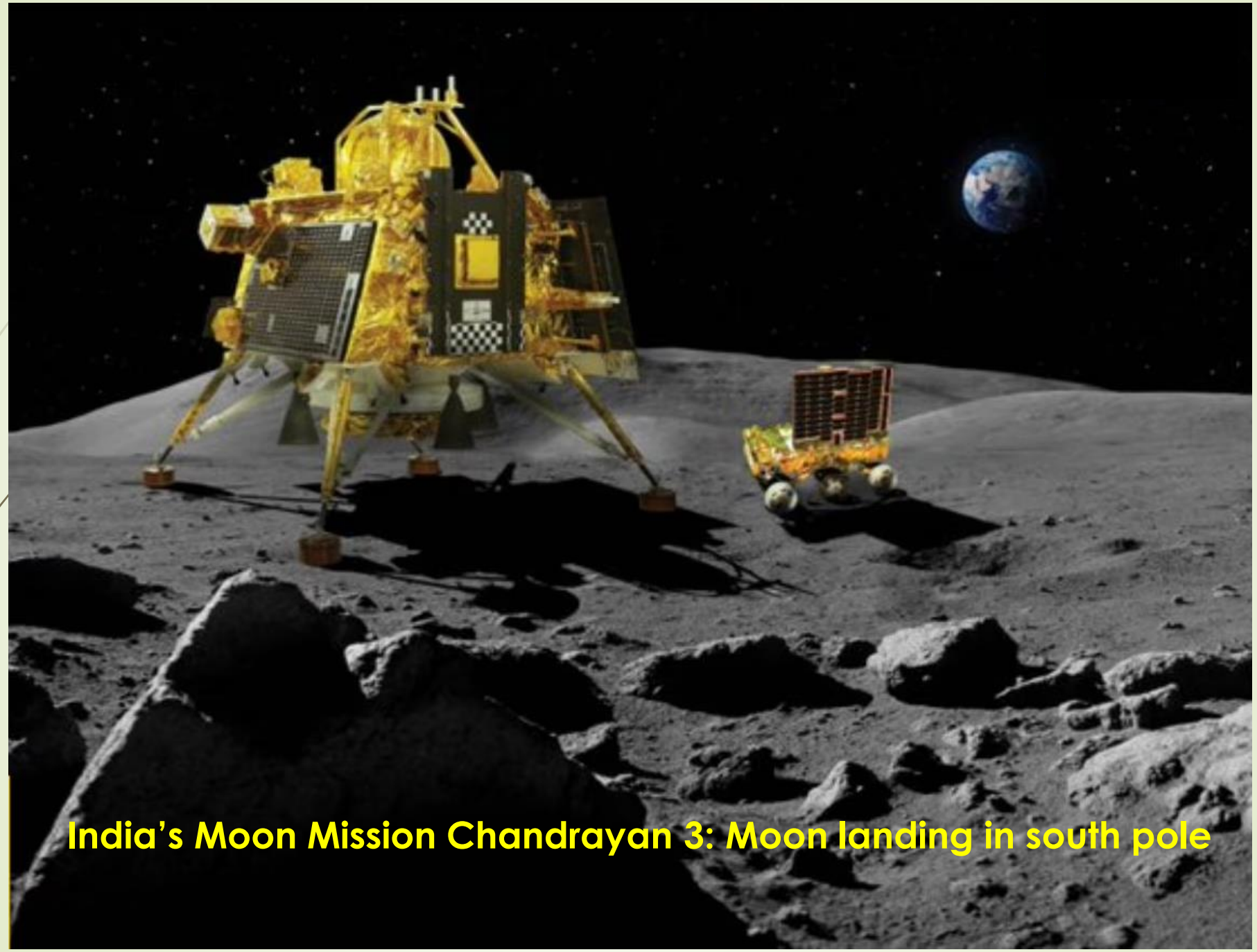
James et al, 2013; Mannucci, 2001

Limitations of these guidelines

- The limitations of these guidelines, still recommendations with low or very low certainty in the evidence.
- **Updating or adapting recommendations locally.**
- **Plans for updating these guidelines.**
- More collaborative work needed
- ongoing surveillance for new evidence, review by experts, and regular revisions.

Take Home Messages:

- Clear diagnosis of VWD is very important
- Prophylaxis for frequent recurrent bleeding pts
- Desmopressin trials to determine therapy is preferred
- Use of antiplatelet agents and anticoagulant therapy, in clinical context
- Target VWF and factor VIII activity levels for major surgery >.50IU/L
- Effective use of Tranexamic acid
- Management options for heavy menstrual bleeding – Hormonal IUDs are most useful
- Management of VWD in the context of neuraxial anaesthesia during labor and delivery
- Management in the postpartum setting tranexamic acid is safe.


India’s Moon Mission Chandrayan 3: Moon landing in south pole

Thanks !

Acknowledgements:
Thanks to my colleagues and patients at ACT Health, Australia.

Nalini.Pati@act.gov.au