



# OUTPATIENT DIAGNOSTIC APPROACH TO BLEEDING DISORDERS IN CHILDREN

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# References

- **SickKids Handbook of Pediatric Thrombosis and Hemostasis** 2nd, revised and extended edition
- [http://www1.wfh.org/docs/en/Resources/Assessment\\_Tools\\_ISTHBAT.pdf](http://www1.wfh.org/docs/en/Resources/Assessment_Tools_ISTHBAT.pdf).

CLINICAL GUIDELINES

 blood advances

 Check for updates

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

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

# Case

- 12 years old boy with recurrent epistaxis comes to your clinic
- No URI;
- No allergy
- No trauma or local problem
- Not related to seasons and climate conditions ,exercise, etc.
- Normal BP
- Laboratory evaluation :
  - Normal CBC & Platelet
  - BT=5`
  - PT=13`` PTT=40``

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# Main Problem

## Prevalent complaint

- Easy bruising or bleeding ,especially in children remains a challenge for the consulting hematologist to define a “significant bleeding history” :
  - mild underlying defects such as type 1 VWD or platelet function defects
- OR
- Normal population

## Limited Diagnostin tools

- the diagnostic limitations of available laboratory testing for mild bleeding disorders

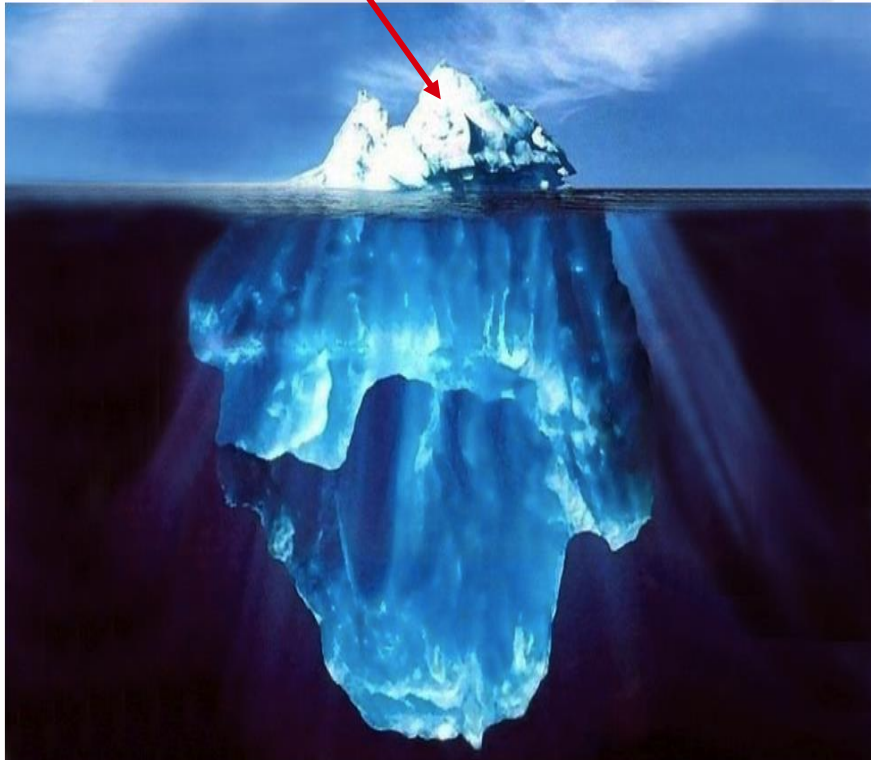
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## Iceberg of VWD

Expected incidence in IRAN for :

- all types of VWD is about 1/100
- bleeders is about 1/10000
- Sever bleeders is about 1/100000



## Normal population

- **Adults:** (<http://ds9.rockefeller.edu/RUBHPSR/>; accessed May 1, 2012)
  - 25% epistaxis,
  - 18% easy bruising,
  - 18% prolonged bleeding after a tooth extraction
  - 47% of women reported heavy menstrual bleeding.
- **Children:** (Nosek-Cenkowska B, et al.. *Thromb Haemost.* 1991;65(3):237-241).
  - 24% easy bruising
  - 39% epistaxis,

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## Von Willebrand disease type 1: a diagnosis in search of a disease

J. Evan Sadler

cause of symptoms is overlooked and untreated. Many of us have seen patients for whom the diagnosis of VWD type 1 has changed their self-image and caused them to limit activities for fear of bleeding or concern about transmitting a genetic disease. They may have received desmopressin (DDAVP) or blood products for dental and surgical procedures, and some have been denied insurance coverage. However, on repeated testing their VWF level and bleeding time may be normal.<sup>35</sup> A detailed history may show they



## Low von Willebrand factor: sometimes a risk factor and sometimes a disease

J. Evan Sadler<sup>1</sup>

*Hematology* 2009

## Many Diagnoses of VWD Type 1 Are False Positives

The European VWD type 1 study suggests that past bleeding is a better guide to future bleeding than is laboratory testing for VWF. However, this study population

# Other Questions

- To distinguish carriers in family members
- To select the type of requested special tests(VWD types ;Platelet function tests; other RBDs ;etc.)
- Treatment decision: the cases who need prophylaxis, intensified treatment, etc.

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# The development of Bleeding Scores(BS)

- Original **Vicenza bleeding scores** :
  - study population included 42 type 1 VWD obligatory carriers and 215 control subjects

*Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. J Thromb Haemost. 2005;3(12):2619-2626*

- Molecular and Clinical Markers for the Diagnosis and Management of Type 1 (MCMDM-1) VWD :
  - 154 families with at least 2 family members affected by type 1 VWD vs control peoples (checked by PFA-100 and VWF:Ag;VWF:Rco)

*Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM- 1 VWD). J Thromb Haemost. 2006;4(4):766-773..*

- **CONDENSED MCMDM-1 VWD BAT:**
  - 6-page questionnaire that **requires 5-10 minutes** (in comparison with 40 minutes for 17 pages)

*Bowman M, et al. J Thromb Haemost. 2008;6(12):2062-2066*

- Asked about a multitude of bleeding symptoms
  - **Scoring**
    - **Vicenza:** from 0 to 3
    - **European MCMDM-1VWD:** -1 to 4
- Abnormal bleeding score was considered to be  $\geq 3$
- **2 most predictive symptoms** for the identification of VWD were
  - bleeding after tooth extraction or surgery
  - cutaneous bleeding (ecchymoses or hematomas).

# Likelihood ratio for VWD using Vicensa BATs

**Table 4. Diagnosis of von Willebrand's Disease Using the Bleeding Score**

Bleeding score	Likelihood ratio*	Post-test probability (%)
-3	0.00	0.0
-2	0.04	0.2
-1	0.10	0.5
0	0.13	0.7
1	1.60	8.0
2	2.20	10.0
3	3.00	13.0
4	16.00	43.0

NOTE: This table is based on a 5 percent pretest probability.

\*—Likelihood ratio with a 95% confidence interval.

Adapted with permission from Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results for a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. 2006;4(4):771.

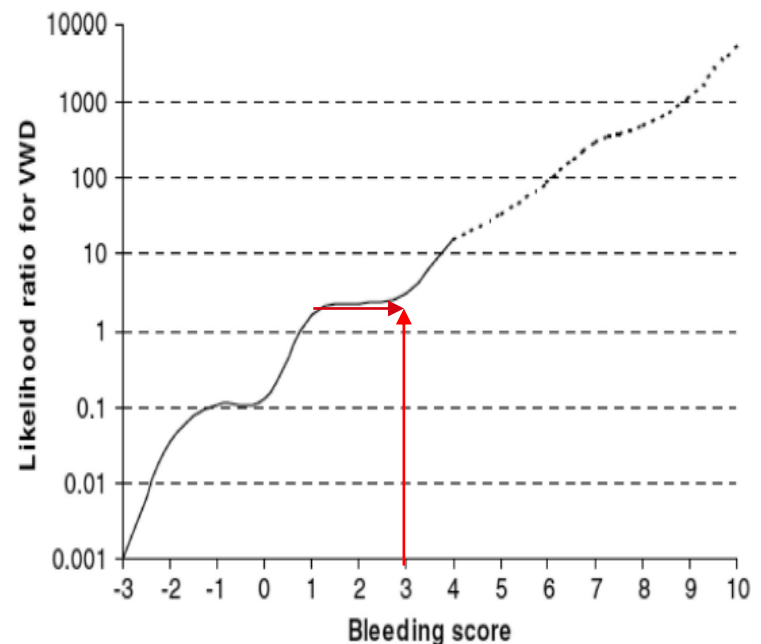


Figure 1. Likelihood ratios for VWD based on the Vicenza bleeding assessment tool (–1 version) and on data from the MCMDM-1 study. (Reprinted with permission from Tosetto et al.<sup>15</sup> Copyright 2007, Elsevier.)

**Table 2. Likelihood ratios for VWD at different levels of bleeding score**

Bleeding score	No. of investigated subjects		Likelihood ratio (95% CI)
	OCs	Controls	
0	3	158	0.097 (0.03-0.29)
1	2	20	0.51 (0.12-2.11)
2	2	14	0.73 (0.17-3.10)
3	4	9	2.28 (0.73-7.05)
4	6	11	2.79 (1.09-7.13)
5	5	2	12.8 (2.57-63.8)
6	4	1	20.5 (2.35-179)
6 or more	20	1	102 (14.1-742)

OC indicates obligatory carrier.

Blood 2008 111: 3998-4003 , Alberto Tosetto, Giancarlo Castaman and Francesco Rodeghiero

# The Pediatric Bleeding Questionnaire (PBQ) of MCMDM-1 VWD BAT

Bowman M, et al. *J Thromb Haemost.* 2009;7(8):1418-1421.

- Shorter life experience, children have fewer or no exposures to bleeding challenges
- Added “other” category, which has pediatric-specific bleeding symptoms to MCMDM-1 (such as umbilical stump bleeding, cephalohematoma, post-circumcision bleeding etc.)
- A “positive” bleeding score was therefore defined as  $\geq 2$  with high negative predictive value (99%) for VWD

# The ISTH/SSC Bleeding Assessment Tool

Rodeghiero F et al. , . *J Thromb Haemost* 2010; 8: 2063-2065 (plus supplementary material).

- In 2010, the ISTH/SSC Joint Working Group agreed to establish a single bleeding assessment tool (the BAT) to standardize the reporting of bleeding symptoms heavily based on the 0-3 Vicenza score
- **Used in children and adults to diagnose mild bleeding disorders** in patients who are being evaluated for a bleeding disorder **for the first time**
- **Overall utility: R/O VWD , Possible Platelet dysfunction**
- **Limitations: few validation studies, Requires a skilled professional to administer and 20 minutes**

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## Bleeding scores: are they really useful?

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- In the primary care setting, and even in the hematology setting, the **greatest clinical utility of bleeding scores lies in their high negative predictive value**, and perhaps their greatest value is in the **identification of patients for whom testing for VWD is not necessary**
- if the bleeding score is elevated and VWF levels are normal, this should be a sign for the hematologist to actively pursue alternate bleeding disorder diagnoses
- In a **young patient** with a **positive family history** of a bleeding disorder, some laboratory work-up will always be required to exclude a bleeding disorder

# Clinical approach

1. Is the bleeding significant ?
  1. Condense MCMDM-1
  2. PBQ
2. Local Vs Systemic ?
3. Platelet Vs Coagulation disorder ?
4. Inherited Vs Acquired ?

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Symptom	0 <sup>1</sup>	1 <sup>1</sup>	2	3	4
Epistaxis	No/trivial	>5/year	Consultation	Packing, cauterization, or	Blood transfusion or replacement
✓ R/O other local or systemic causes: seasonal occurrence , URI, Dusty dry air, High BP , etc. • Consultation only: the patient sought medical evaluation and was either referred to a specialist or offered detailed laboratory investigation					
Bl m	✓ petechiae when adequately described by the patient or relatives; or ✓ hematomas when occurring without trauma.				
Oral cavity	No/trivial	Present	Consultation	Surgical hemostasis or	Blood transfusion, replacement
➤ <b>tooth eruption : when requires assistance</b> or supervision by a physician, or lasts at least <b>10 minutes</b> ➤ <b>bites to lip and tongue,:</b> at least <b>10 minutes</b> or causes a <b>swollen tongue or mouth</b> .					
➤ Permanent teeth ➤ occurring after leaving the dentist's office and requiring a new, unscheduled visit PBQ: ➤ Any report of bleeding stopped <ul style="list-style-type: none"> <li>➤ without consultation : 1</li> <li>➤ With consultaion only:2</li> </ul>					
	none	intervention	procedures, no intervention <sup>3</sup>		

# Pediatric Bleeding Questionnaire (PBQ)

Score Symptom	-1	0	1	2	3	4
Epistaxis	-	No or trivial ( $\leq 5$ per year)	$>5$ per year OR $>10$ minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	-	No or trivial ( $\leq 1$ cm)	$>1$ cm AND no trauma	Consultation only	-	-
Minor wounds	-	No or trivial ( $\leq 5$ per year)	$>5$ per year OR $>5$ minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Oral cavity	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Post-partum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
Muscle hematoma	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
Other *	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin

Symptom	0 <sup>1</sup>	1 <sup>1</sup>	2	3	4
Muscle hematomas	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
CNS bleeding	Never	–	–	Subdural, any intervention	Intracerebral, any intervention
Other bleedings <sup>5</sup>	No/trivial	Present	Consultation only <sup>2</sup>	Surgical hemostasis, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin

- Spontaneous or Repeated abortion(?)
- Delayed wound healing (?)
- Their presence in infancy requires detailed investigation independently from the overall score. Include:
- **Umbilical stump bleeding, cephalohematoma, cheek hematoma caused by sucking during breast/bottle feeding, conjunctival hemorrhage, or excessive bleeding following circumcision or venipuncture.**

# Menorrhagia points(ISTH-BAT)

- Severity : more than 80 ml/period
  - More than 30 of tampons/pads used for a typical menstrual cycle
  - Hourly (0.5–2.0 h) change of tampon/pad on the heaviest day of menstrual period
  - use a tampon and a pad at the same time OR a super-absorbent tampon or pad
  - Clot >1 cm or flooding
  - frequently stain through clothes during menses
  - pictorial blood loss assessment chart (PBAC) >100
- Duration: More than 7 days ; Present since menarche and > 12 months
- Needs to treatment : OCP; Antifibrinolytics;DDAVP; anaemic or low in iron;Transfusion;surgical intervention
- lost time from work or school  $\geq 2$  times in the past year because of heavy periods (



# Postpartum hemorrhage

- ✓ uterine discharge (lochia) that lasts for more than 6 weeks
- ✓ judged by the obstetrician as abnormally heavy or prolonged
- ✓ Frequency
- ✓ Needs to treatment

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Menorrhagia	No/trivial	Consultation only <sup>2</sup> or Changing pads more frequently than every 2 h or Clot and flooding or PBAC score >100 <sup>4</sup>	Time off work/school >2/year or Requiring antifibrinolytics or hormonal or iron therapy	Requiring combined treatment with antifibrinolytics and hormonal therapy or Present since menarche and >12 months	Acute menorrhagia requiring hospital admission and emergency treatment or Requiring blood transfusion, replacement therapy, desmopressin or Requiring dilatation and curettage or endometrial ablation or hysterectomy
Postpartum hemorrhage	No/trivial or no deliveries	Consultation only <sup>2</sup> or Use of syntocin or Lochia >6 weeks	Iron therapy or Antifibrinolytics	Requiring blood transfusion, replacement therapy, desmopressin or Requiring examination under anesthesia and/or the use of uterine balloon/package to tamponade the uterus	Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery ligation, uterine artery embolization, uterine brace sutures)

Symptom-specific bleeding scores for menorrhagia (Pictorial Blood Loss Assessment Chart) and epistaxis are useful for describing the severity of the specific bleeding symptom

# Pictorial Blood loss Assessment Chart (PBAC)




## Menstrual chart and scoring system



Date of start 

day	month	year

 Score 

--

Towel								
	1 point for each lightly stained towel							
	5 point for each moderately soiled towel							
	20 point for each completely soiled towel							
Clots/flooding <small>Clots: size</small>	1 point for <1cm , 5 points for >1cm clots							

Tampon	1	2	3	4	5	6	7	8
								
								
Clots/flooding <small>Clots: size</small>								

## Scoring system

### Towels

**1 point** for each lightly stained towel  
**5 points** for each moderately soiled towel  
**20 points** if the towel is completely saturated with blood

### Tampons

**1 point** for each lightly stained tampon  
**5 points** for each moderately soiled tampon  
**10 points** if the tampon is completely saturated with blood

### Clots

**1 point** for small clots  
**5 points** for large clots

A score  $\geq 100$  has a sensitivity and specificity for a diagnosis of menorrhagia of  $\geq 80\%$ ,

Source: U.K. Haemophilia Society, A Guide for Women Living with von Willebrand's

**Table 2.** Epistaxis scoring system [9]

Component	Score <sup>1</sup>
Frequency	
5–15/year	0
16–25/year	1
>25/year	2
Duration	
<5 min	0
5–15 min	1
>15 min	2
Volume	
<15 ml	0
15–30 ml	1
>30 ml	2
Epistaxis history/age <sup>3</sup>	
<33%	0
33–67%	1
>67%	2
Site	
Unilateral	0
Bilateral	2

- Sum of scores for all components: mild = 0–6; severe = 7–10
- Estimation of average blood loss per episode, based on fractions or multiples of teaspoons, tablespoons, or cups.

# Key points

- **a positive family history** increases the risk of a bleeding disorder
- Circumcision (with cutting methods) and ear ring replacement as a haemostatic challenge ?
- History of Renal, Liver or Hematological disease
- Drug history
- Distinction between 0 and 1 is of critical importance

# Pre-operative recommendations

- The European Society of Anaesthesiology :
  - Recommends the use of a structured patient interview or questionnaire before surgery or invasive procedures.
- The British Committee for Standards in Haematology :
  - Recommends a bleeding history be taken in **all patients preoperatively and prior to invasive procedures**
  - Bleeding history may be negative in paediatric patients due to lack of haemostatic challenges. Therefore, if a **positive family history** exists, some laboratory workup will be required to confirm or exclude a bleeding disorder
- 1. Chee YL, Crawford JC, Watson HG and Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. British Journal of Haematology, 2008;140:496–504.
- 2. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30:270–382.





Contents lists available at ScienceDirect

Thrombosis Research

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Full Length Article

## Establishment of a bleeding score as a diagnostic tool for patients with rare bleeding disorders



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Flora Peyvandi <sup>a,b</sup>, on behalf of the European Network of Rare Bleeding Disorders (EN-RBD) group

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<sup>b</sup> Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

- A large group of patients with RBDs enrolled in the EN-RBD database include fibrinogen, factor (F) II, FV, combined FV and FVIII (FV + VIII), FVII, FX, FXI, and FXIII deficiencies
- The predictive power of this BSS was also **compared with the ISTH-BAT** and examined for the **severity of RBDs based on coagulant factor activity**.
- Take **age and sex** as covariates into account their predictive effect on the probability of having a RBD.

<b>Epistaxis</b>	No = 0, Yes = 1
Frequency > 1/year	No = 0, Yes = 1
Spontaneous	No = 0, Yes = 1
On prophylaxis	No = 0, Yes = 1
Diffuse bleeding <sup>a</sup>	No = 0, Yes = 1
Bilateral	No = 0, Yes = 1
Requiring treatment with packing or cauterization or antifibrinolytics	No = 0, Yes = 1
Requiring treatment with blood transfusion or replacement therapy or desmopressin	No = 0, Yes = 2
<i>Epistaxis index score (Epi_In)</i>	<i>Total sum</i>

Diffuse bleeding:

- Bleeding lasting at **least 10 min** and/or **requiring medical attention** in case of epistaxis or oral cavity bleeding;

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### Oral cavity bleeding<sup>b</sup>

Frequency > 1/year

No = 0, Yes = 1

Spontaneous

No = 0, Yes = 1

On prophylaxis

No = 0, Yes = 1

Diffuse bleeding<sup>a</sup>

No = 0, Yes = 1

Involving tongue

No = 0, Yes = 1

Requiring treatment with surgical  
hemostasis or antifibrinolytics

No = 0, Yes = 1

Requiring treatment with blood  
transfusion or replacement therapy or  
desmopressin

No = 0, Yes = 1

No = 0, Yes = 2

*Oral cavity bleeding index score (Oral\_In)*

*Total sum*

Diffuse bleeding:

- Bleeding lasting at **least 10 min** and/or **requiring medical attention** in case of epistaxis or oral cavity bleeding;

The gum bleeding:

- Due to **toothbrush** should be **evaluated as normal**;
- Be considered significant when it causes **frankly bloody sputum**.

<b>Gastrointestinal bleeding</b>	No = 0, Yes = 1
Frequency $\geq 2$ times	No = 0, Yes = 1
Spontaneous <sup>d</sup>	No = 0, Yes = 1
On prophylaxis	No = 0, Yes = 1
Causing anemia	No = 0, Yes = 1
Requiring treatment with antifibrinolytics	No = 0, Yes = 1
Requiring treatment with surgical hemostasis, blood transfusion, replacement therapy or desmopressin	No = 0, Yes = 2
<i>Gastrointestinal bleeding index score (GI_In)</i>	<i>Total sum</i>

Any gastrointestinal bleeding that is not explained by the presence of a specific disease should be considered as spontaneous

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### **Hemarthrosis**

Frequency > 1

Spontaneous

On prophylaxis

Disabling<sup>c</sup>

Requiring treatment with replacement  
therapy or desmopressin

Requiring treatment with blood  
transfusion

*Hemarthrosis index score (Hemar\_In)*

No = 0, Yes = 1

No = 0, Yes = 1

No = 0, Yes = 1

No = 0, Yes = 1

No = 0, Yes = 1

No = 0, Yes = 1

No = 0, Yes = 2

*Total sum*

Disabling means that hemarthrosis has led to a compromised motility

<b>CNS bleeding</b>	No = 0, Yes = 1
Spontaneous	No = 0, Yes = 1
On prophylaxis	No = 0, Yes = 1
Diffuse bleeding <sup>a</sup>	No = 0, Yes = 1
Intracerebral bleeding	No = 0, Yes = 1
Requiring treatment with replacement therapy	No = 0, Yes = 1
Requiring treatment with surgery + blood transfusion or replacement therapy	No = 0, Yes = 1
<i>CNS bleeding index score (CNS_In)</i>	<i>Total sum</i>

Diffuse bleeding:

- when it is not possible to establish a localized lesion and define the hemorrhage volume in case of CNS bleeding.

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Parameter	Key	Value
<b>Menorrhagia</b>	No or Male = 0, Yes = 1	
Frequency $\geq 1/\text{year}$	No or Male = 0, Yes = 1	
Spontaneous	No or Male = 0, Yes = 1	
On prophylaxis	No or Male = 0, Yes = 1	
Pictorial chart $\geq 185$	No or Male = 0, Yes = 1	
Requiring treatment with antifibrinolytics, pill use, iron therapy or curettage	No or Male = 0, Yes = 1	
Requiring treatment with blood transfusion or replacement therapy or desmopressin	No or Male = 0, Yes = 2	
Requiring treatment with hysterectomy	No or Male = 0, Yes = 3	
<i>Menorrhagia index score (Meno_In)</i>	<i>Total sum</i>	

## Postpartum bleeding

Frequency > 1 time

Spontaneous<sup>e</sup>

On prophylaxis

Causing anemia

Requiring treatment with antifibrinolytics,  
iron therapy or curettage

Requiring treatment with blood  
transfusion or replacement therapy or  
desmopressin

Requiring treatment with hysterectomy

*Postpartum bleeding index score (PPH\_In)*

Never delivered or  
Male = 0, No = -1,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 1

Never delivered or  
Male = 0, No = 0,  
Yes = 2

Never delivered or  
Male = 0, No = 0,  
Yes = 3

*Total sum*

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## Bleeding during tooth extraction

Frequency > 1 time

On prophylaxis

For  $\geq 15$  min

Recurrence of bleeding

Requiring treatment with resuturing or packing or antifibrinolytics

Requiring treatment with blood transfusion or replacement therapy or desmopressin

Tooth extraction bleeding index score  
(Tooth\_In)

Never done = 0,

No = -1, Yes = 1

Never done = 0, No = 0,  
Yes = 1

Never done = 0, No = 0,  
Yes = 1

Never done = 0, No = 0,  
Yes = 1

Never done = 0, No = 0,  
Yes = 1

Never done = 0, No = 0,  
Yes = 1

Never done = 0, No = 0,  
Yes = 2

Total sum

## Bleeding during tonsillectomy<sup>8</sup>

On prophylaxis

Never done = 0,

No = -1, Yes = 1

Postoperative bleeding

Never done = 0, No = 0,  
Yes = 1

Requiring treatment with surgical  
hemostasis or antifibrinolytics

Never done = 0, No = 0,  
Yes = 1

Requiring treatment with blood  
transfusion or replacement therapy or  
desmopressin

Never done = 0, No = 0,  
Yes = 1

*Tonsillectomy bleeding index score*  
(Tonsil\_In)

*Total sum*

# Thrombosis and Hemostasis

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**Bleeding during minor surgery<sup>f</sup>**

Frequency &gt; 1 time

On prophylaxis

Postoperative bleeding

Requiring treatment with surgical  
hemostasis or antifibrinolyticsRequiring treatment with blood  
transfusion or replacement therapy or  
desmopressin*Minor surgery bleeding index score*  
(Minor\_In)

Never done = 0,

No = -1, Yes = 1

Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 2*Total sum***Bleeding during major surgery<sup>f</sup>**

Frequency &gt; 1 time

On prophylaxis

Postoperative bleeding

Requiring treatment with surgical  
hemostasis or antifibrinolyticsRequiring treatment with blood  
transfusion or replacement therapy or  
desmopressin*Major surgery bleeding index score*  
(Major\_In)

Never done = 0,

No = -1, Yes = 1

Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 1Never done = 0, No = 0,  
Yes = 2*Total sum*ty of  
emostasis

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Table 1. Definitions for major and minor surgeries\*.

	Major surgery <sup>†</sup>	Minor surgery
Definition	An invasive operative procedure where one or more of the following occurred: <ul style="list-style-type: none"> <li>• A body cavity was entered</li> <li>• A mesenchymal barrier was crossed</li> <li>• A fascial plane was opened</li> <li>• An organ was removed</li> <li>• Normal anatomy was operatively altered</li> </ul>	An invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue was manipulated
Expected duration of surgery-related FVIII treatment	At least 7 days including the day of surgery <sup>‡</sup>	Less than 7 days including the day of surgery
Treatment	Bolus injection or continuous infusion	Bolus injection
Dose level	Dosing was determined by the investigator based on the local practice. The protocols recommended to aim for FVIII trough levels above 0.50 IU mL <sup>-1</sup> from the day of surgery through day 7 post surgery	Dosing determined by the investigator based on the local practice

\*The decision on whether a surgery was a minor or a major surgery was taken before the surgery was performed. Thus, in a few examples the criteria for treatment duration of major surgeries (at least 7 days) and minor surgeries (less than 7 days) do not apply. More details were collected for major surgeries, and the surgeries were therefore not reclassified based on the duration.

<sup>†</sup>Major surgery was not allowed in the paediatric trial (guardian™ 3).

<sup>‡</sup>Patients receiving bolus injections could be discharged before day 7 post surgery, but were to have daily assessments at least until that day.

$$\text{Bleeding Score (BS)} = 2.510 + (\text{Age in years} \times -0.029) + (-0.305 \text{ if Male}) + (\text{Epi\_In} \times -0.129) + (\text{Oral\_In} \times 0.197) + (\text{Bruis\_In} \times -0.342) + (\text{Hemato\_In} \times -0.040) + (\text{Hemar\_In} \times 0.618) + (\text{GI\_In} \times 0.490) + (\text{CNS\_In} \times 0.876) + (\text{Meno\_In} \times 0.073) + (\text{PPH\_In} \times 0.334) + (\text{Tooth\_In} \times 0.277) + (\text{Minor\_In} \times 0.270) + (\text{Tonsil\_In} \times 0.670) + (\text{Major\_In} \times 0.281).$$

$$\text{Probability of RBD} = 1 / (1 + e^{-[\text{BS}]})$$

- This BSS was able to differentiate patients with RBDs from healthy individuals with a bleeding score value of 1.5 having the highest sum of sensitivity (67.1%) and specificity (73.8%)
- there was a significant negative correlation between BS and coagulant factor activity level, which was strongest for fibrinogen and FXIII deficiencies.



# Drug History

**Table 5. Medications That Cause Bleeding and Bruising**

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**Common**

Aspirin  
Clopidogrel (Plavix)  
Heparin  
Nonsteroidal anti-inflammatory drugs  
Warfarin (Coumadin)

**Rare**

Cephalosporins  
Ginkgo biloba  
Gold  
Interferon  
Metaxalone (Skelaxin)  
Penicillins  
Propothiouricil  
Selective serotonin reuptake inhibitors  
Testosterone replacement  
Tricyclic antidepressants

# Drugs Proved or Suspected to Induce Drug-Dependent Antibody- Mediated Immune Thrombocytopenia

## Anti-inflammatory

Acetaminophen  
Acetylsalicylic acid  
Diclofenac  
Ibuprofen  
Indomethacin  
Meclofenamate  
Mefenamic acid  
Naproxen  
Oxyphenbutazone  
Phenylbutazone  
Piroxicam  
Sodium-p-amino salicylic acid  
Sulfasalazine  
Sulindac  
Tolmetin

## Antibiotics

### *Antituberculous drugs*

Ethambutol  
Isoniazid  
Para-aminosalicylic acid (PAS)  
Rifampin  
Streptomycin

### Penicillin group

Ampicillin  
Methicillin  
Penicillin  
Mezlocillin  
Piperacillin

## Cephalosporin

Cefamandole  
Cefotetan  
Ceftazidime  
Cephalothin  
Sulfonamides  
Sulfamethoxazole  
Sulfamethoxypyridazine  
Sulfisoxazole

## Other antibiotics

Amphotericin B  
Ciprofloxacin  
Clarithromycin  
Fluconazole  
Gentamicin  
Indinavir  
Nalidixic acid  
Novobiocin  
Pentamidine  
Sodium Stibogluconate  
Stibophen  
Suramin  
Vancomycin

## Antineoplastic

Actinomycin-D  
Aminoglutethimide  
Tamoxifen

## Anticonvulsants, sedatives, and antidepressants

Amitriptyline  
Carbamazepine  
Desipramine  
Diazepam  
Doxepin  
Haloperidol  
Imipramine  
Lithium  
Mianserin  
Phenytoin  
Valproic acid

## Cardiac and antihypertensive drugs

Acetazolamide  
Amiodarone  
Alprenolol  
Captopril  
Chlorothiazide  
Chlorthalidone  
Digoxin  
Digitoxin  
Furosemide  
Hydrochlorothiazide  
 $\alpha$ -methyldopa  
Oxprenolol  
Procainamide  
Spironolactone

## H2-antagonists

Cimetidine  
Ranitidine

## Cinchona alkaloids

Quinidine  
Quinine

## Miscellaneous

Antazoline  
Chlorpheniramine  
Chlorpropamide  
Danazol  
Desferrioxamine  
Diethylstilbestrol  
Etretnate  
Glibenclamide  
Gold salts  
Heparin  
Interferon- $\alpha$   
Iodinated contrast agents  
Isotretinoin  
Minoxidil  
Levamisole  
Lidocaine  
Morphine  
Papaverine  
Ticlopidine

## Foods

Beans

## Platelet Vs Coagulation disorder

Symptom	Platelet	Coagulation
Petechiae	Yes	No
Sites	Skin & Mucosa	Deep Tissue
Time	Immediate	Delayed
Ecchymoses /Hematomas	Yes	Yes

Note: Local pressure is effective in platelet bleeding but not in coagulation dis.



# Laboratory Approach

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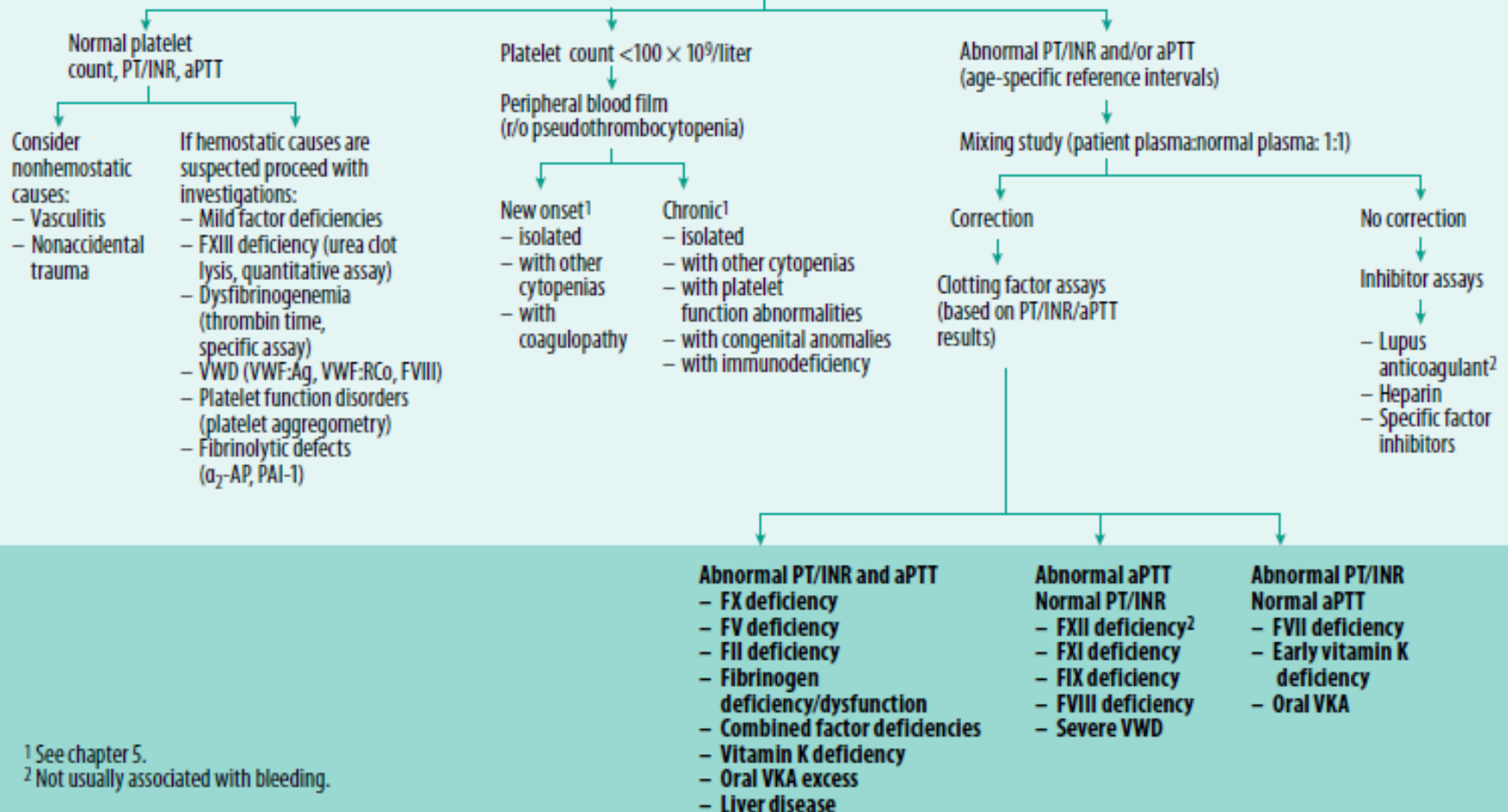
# AIMs

1. Demonstration of the defect
2. Identification of the defect(s)
3. Assessment of severity
4. Consequential studies eg. carrier detection
5. Monitoring of treatment

## Child with bleeding symptoms

Medical history: age, sex, past medical history, use of medications  
Bleeding history: standardized bleeding questionnaire  
Family bleeding history: standardized bleeding questionnaire, ethnicity  
Physical examination: hemodynamic status, pattern of bleeding, other findings (see text)

Initial laboratory tests: CBC, PT/INR, aPTT



<sup>1</sup> See chapter 5.

<sup>2</sup> Not usually associated with bleeding.

# Screening Tests

1. Platelet count & morphology
2. Bleeding Time
3. Clotting Time?
4. Prothrombin Time
5. Activated Partial Thromboplastin Time
6. Thrombin Time
7. Clot lysis test

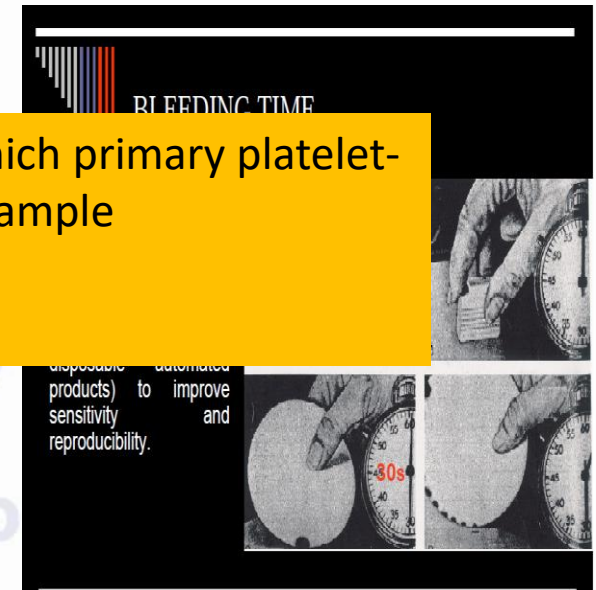
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# Bleeding time (Ivy Method)

- Inflate and Fix the pressure cuff on arm at 40 mmHg
- make a horizontal incision (1mm depth, 5 mm length) on volar surface of the forearm; 2 inches below the elbow line
- dry the bleeding border with drying paper every 30 Sec.
- No *PFA-100* ® and recently *PFA-200* ® are instruments in which primary platelet-related hemostasis is simulated with small volume blood sample
- ❖ Not available yet in Iran
- ❖ Bleeding time more than 9 min. means prolonged and seen in
  - ✓ platelet count less than 80000-100000 (some times less than 40000 in acute ITP)
  - ✓ Platelet dysfunction Dis.
    - Medication
    - Azotemia
    - VWD
    - Platelet aggregation



## Collection of blood sample

1. **Minimum circulatory stasis**
2. **Clean venous puncture**
3. **Proper anticoagulant**
4. **Proportion of blood to anticoagulant**
5. **Separation of plasma and storage**
6. **Effect of stress, pregnancy, drugs**
7. **Effect of PCV on the proportion of plasma to anticoagulant**

**SSC OFFICIAL COMMUNICATION**

## **Provisional criteria for the diagnosis of VWD type 1**

J. E. SADLER and F. RODEGHIERO\* ON BEHALF OF THE ISTH SSC SUBCOMMITTEE ON VON WILLEBRAND FACTOR

*Howard Hughes Medical Institute, Chevy Chase, MD and the Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; and \*Department of Hematology, Hemophilia and Thrombosis Center, San Bortolo Hospital, Vicenza, Italy*

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To cite this article: Sadler JE, Rodeghiero F on behalf of the ISTH SSC Subcommittee on von Willebrand Factor. Provisional criteria for the diagnosis of VWD type 1. *J Thromb Haemost* 2005; 3: 775–7.

.These criteria were approved at the 42nd Annual  
SSC Meeting held in Barcelona as provisional criteria,

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# Criteria for bleeding symptoms

- at least two symptoms in the absence of a blood transfusion history,

or

- one symptom requiring treatment with blood transfusion,

or

- one symptom recurring on at least three distinct occasions.

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# Criteria for family history

- at least one first-degree relative,  
or
- at least two second-degree relatives, have a personal history of significant mucocutaneous bleeding and laboratory tests compatible with VWD type 1

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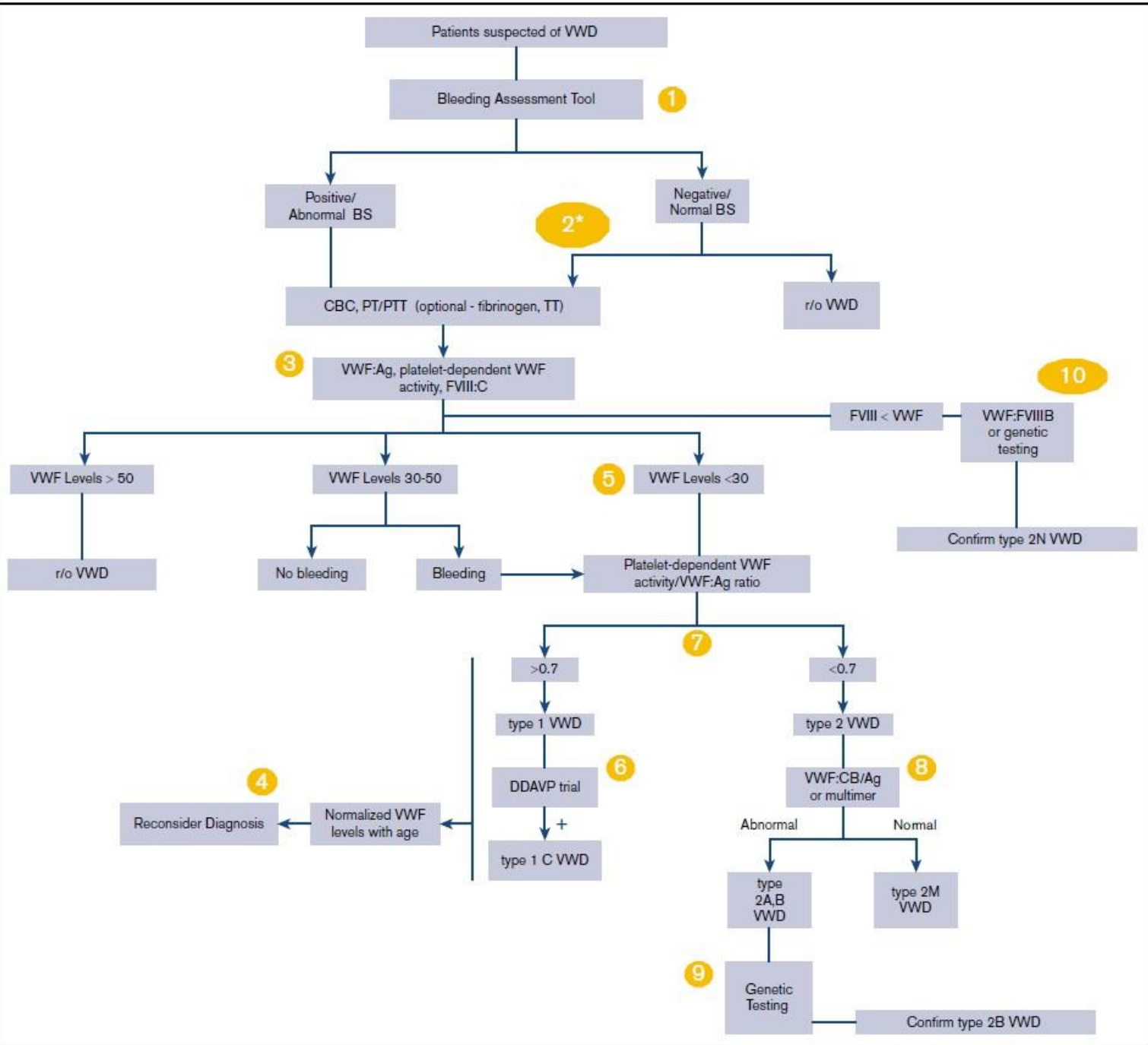
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# Criteria for laboratory tests

- the levels of both VWF:Rco and VWF:Ag are  $>2$  SD below the population mean and ABO type adjusted mean on  $>2$  determinations

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## Laboratory Values for VWD\*

Condition	Description	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:RCo/VWF:Ag Ratio
Type 1	Partial quantitative VWF deficiency	<30**	<30**	Low or Normal	>0.5-0.7
Type 2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2B	Increased affinity for platelet GPIIb; decreased platelets	<30**	<30-200**	Low or Normal	Usually <0.5-0.7
Type 2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2N	Markedly decreased binding affinity for FVIII	30-200	30-200	Very Low	>0.5-0.7
Type 3	Virtually complete deficiency of VWF	<3	<3	Extremely Low (<10 IU/dL)	Not applicable
"Low VWF"***		30-50	30-50	Normal	>0.5-0.7
Normal		50-200	50-200	Normal	>0.5-0.7

\*These values represent prototypical cases. Exceptions occur, and repeat testing may be necessary.

\*\*<30 IU/dL is designated as the level for a definitive diagnosis of VWD; some patients with type 1 or type 2 VWD have levels of VWF:RCo and/or VWF:Ag of 30-50 IU/dL.

**NOTE:** 30 IU/dL is recommended as the "cut-off" for the definite diagnosis of VWD for the following reasons: 1) high frequency of blood type O in the United States, which is associated with "low" VWF levels; 2) bleeding symptoms are reported by a significant proportion of normal individuals; 3) no abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels. This does not preclude the use of agents to increase VWF levels in those who have VWF:RCo of 30-50 IU/dL and who may be at risk for bleeding.

*For patients with an abnormal initial VWD screen (low VWF:Ag and/or platelet-dependent VWF activity) suspected of type 1 VWD, should the diagnostic cutoff be at VWF:Ag and/or VWF platelet-dependent activity <0.30 IU/mL or <0.50 IU/mL?*

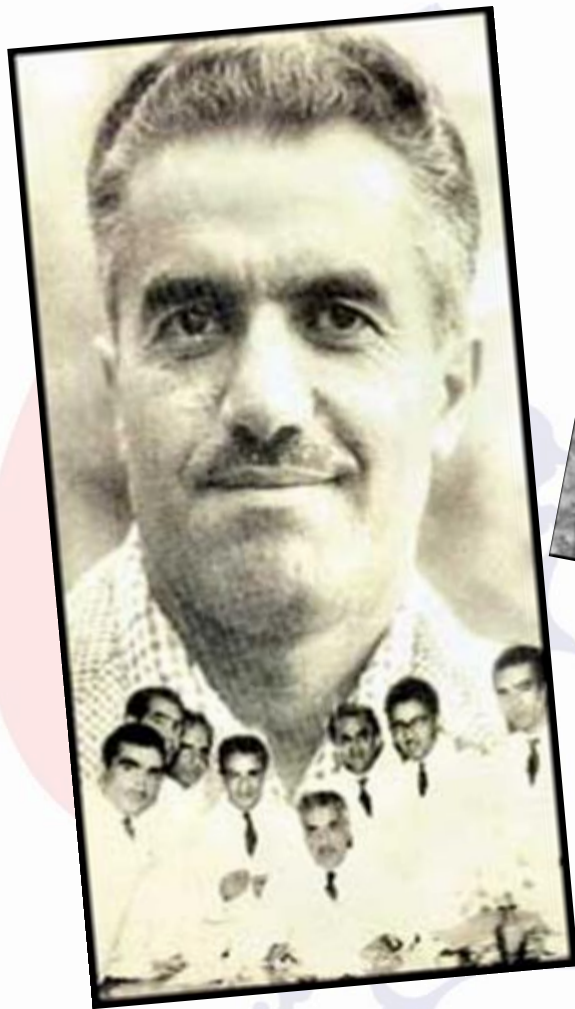
#### **Recommendation 6**

The panel *recommends* a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD (strong recommendation based on low certainty in the evidence of effects ⊕⊕○○).

#### **Remarks:**

- VWF level(s) refers to VWF:Ag and/or platelet-dependent VWF activity (eg, VWF:GPIbM).
- The lower limit of the normal range as determined by the local laboratory should be used if it is <0.50 IU/mL. ABO-specific reference ranges are not required.
- VWF is an acute-phase reactant that increases in response to a variety of stimuli (eg, bleed, trauma, pregnancy). VWD diagnostic testing should be performed when patients are at a baseline state of health.

- **Basic tests:**
  - Bleeding time
  - CBC;platelet
  - Prothrombin time(PT) & mixing test
  - Activated partial thromboplastin time (aPTT) & mixing test
  - BG
- **1<sup>st</sup> specific VWD diagnostic tests:**
  - Factor VIII clotting activity
  - vWF:Ag
  - vWF platelet dependent activity: GP1bM; Ristocetin cofactor activity
- **2<sup>nd</sup> specific VWD diagnostic tests:**
  - Collagen binding activity
  - F VIII binding activity
  - vWF: pp
  - LD-RIPA
  - Multimeric analysis (to define the type of VWD)
- **Other coagulation factor deficiency` s diagnostic tests:**
  - Coagulation factor assay ( one stage;chromogenic assay)
  - Clot lysis test ; Elisa ;etc.
- **Platelet function assay & diagnostic tests:**
  - RIPA
  - Platelet aggregation tests
  - Platelet secretion tests
  - FCM: CD<sub>41/61</sub> ; CD 42
- **Genetic tests**



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