

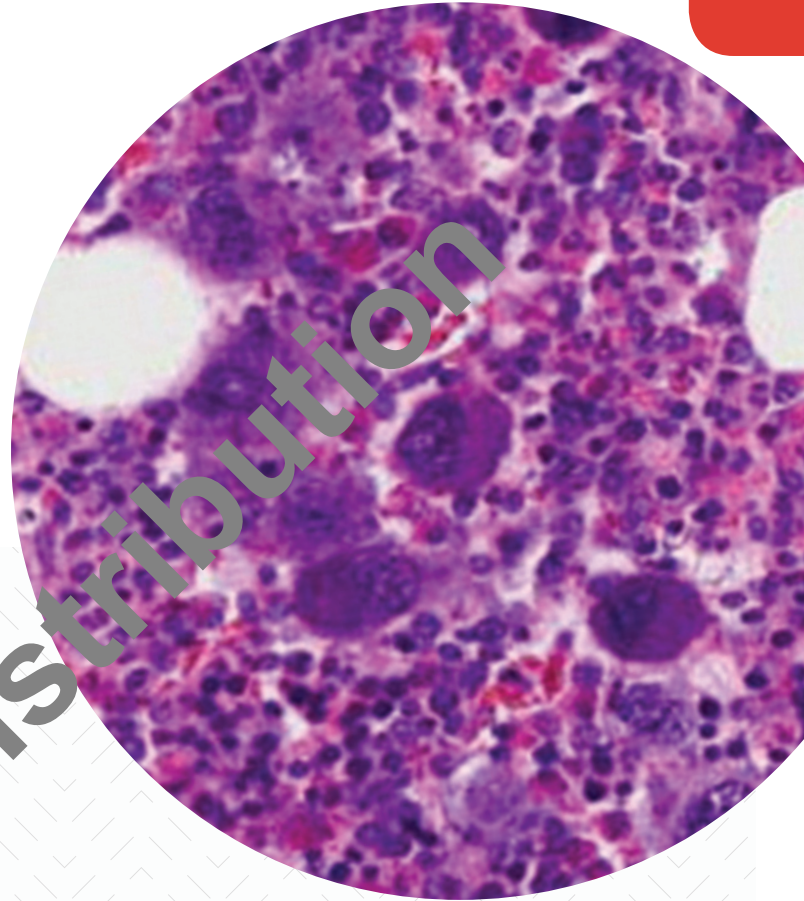


**ASH CLINICAL PRACTICE GUIDELINES  
VON WILLEBRAND DISEASE (VWD)**

# Diagnosis and Management of von Willebrand Disease

**A POCKET GUIDE FOR THE CLINICIAN  
SEPTEMBER 2022**

Not For Distribution



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The recommendations in this guide are based on the ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of von Willebrand Disease



## Context

VWD is characterized by excessive mucocutaneous bleeding, such as heavy menstrual bleeding, epistaxis, easy bruising, prolonged bleeding from minor wounds and the oral cavity, and gastrointestinal bleeding, as well as bleeding after dental work, childbirth, and surgery, with musculoskeletal bleeding, including joint bleeding, seen in more severe cases.

VWD is the most common congenital bleeding disorder known in humans and of autosomal inheritance making it equally prevalent in men and women. However, women are more likely to come to medical attention because of gynecologic and obstetrical bleeding.

**Table 1. Classification of VWD – major types and subtypes**

Type	Characteristics
1	Quantitative decrease in VWF with preserved ratios between VWF:Ag <sup>1</sup> , platelet-dependent VWF activity (e.g., VWF:GPIbM), and factor VIII. Normal multimer distribution.
1C	Quantitative decrease in VWF with preserved ratios between VWF:Ag, and factor VIII. Increased propeptide (VWF:pp) <sup>1</sup> compared to VWF:Ag. Initial VWF response to DDAVP challenge, followed by decrease of >30% from peak at four-hour timepoint.
2A	Decreased platelet-dependent VWF activity with loss of high-molecular weight multimers
2M	Decreased platelet-dependent VWF activity with preserved multimer pattern
2N	Decreased binding of VWF to FVIII
2B	Increased binding to glycoprotein Iba (GPIba), often leading to thrombocytopenia. Multimer pattern normal or absence of high molecular weight multimers.
3	Absence or near absence of VWF
Platelet-type VWD	Functional defect of platelet GPIba, leading to excessive binding of platelets and VWF and subsequent thrombocytopenia and loss of high molecular-weight multimers
Acquired von Willebrand syndrome	Possibly including decreased VWF and/or loss of high molecular weight multimers due to either shearing from mechanical forces (e.g., aortic stenosis resulting in Heyde syndrome), adsorption on tumors (e.g., Waldenström macroglobulinemia or Wilms' tumors), or autoimmune inhibitor formation.

<sup>1</sup> VWF:Ag – von Willebrand Factor Antigen.  
<sup>2</sup> VWF:pp – von Willebrand Factor Propeptide

## Diagnosis

**Table 2. Bleeding Assessment Tools (BATs)**

Beyond their utility as a screening test in the primary care setting, BATs can be used in the referral setting to assess and document the severity of bleeding and can be used in conjunction with specific blood testing as part of the initial diagnostic approach. Specific blood testing for VWD refers to VWF:Ag, platelet-dependent VWF activity (e.g., VWF:GPIbM), and FVIII:C.

Probability Level of VWD	Recommendation
Low	The panel <b>recommends</b> using a validated bleeding assessment tool (BAT) as an initial screening test to determine who needs specific blood testing over non-standardized clinical assessment. <sup>1</sup> ✓
Intermediate	The panel <b>suggests against</b> relying on a bleeding assessment tool (BAT) to decide whether to order specific blood testing. <sup>2</sup> ⚠
High	The panel <b>recommends against</b> relying on a bleeding assessment tool (BAT) to decide whether to order specific blood testing. <sup>3</sup> ✓

<sup>1</sup> This recommendation applies predominantly to adult women, as the data supporting the use of a BAT as a screening tool is strongest in this patient group. The quality of non-standardized clinical assessment will vary among the users of these guidelines.

<sup>2</sup> This recommendation addresses patients with an intermediate VWD pretest probability (~20%) corresponding to those typically referred for hematology evaluation because of an abnormal personal bleeding history or abnormal initial laboratory tests (e.g., prolonged aPTT) (including men and children).

<sup>3</sup> This recommendation addresses patients with a high VWD pretest probability (~50%) corresponding to those typically referred for hematology evaluation because of an affected first-degree relative regardless of their bleeding symptoms or initial laboratory tests (including men and children).

The panel **suggests** newer assays that measure the platelet binding activity of VWF (e.g., VWF:GPIbM, VWF:GPIbR) over the VWF ristocetin cofactor assay (VWF:RCo) (automated or nonautomated assay) for the diagnosis of VWD. ⚠

### Good practice statement

VWF activity assays should be performed in a lab with appropriate expertise.

The panel **recommends** a VWF activity level<sup>1</sup> of <0.30 IU/mL regardless of bleeding, and in patients with abnormal bleeding, a VWF level of <0.50 IU/mL<sup>2</sup> to confirm the diagnosis of type 1 VWD.<sup>3</sup> ✓

<sup>1</sup> VWF level(s) refers to VWF:Ag and/or platelet-dependent VWF activity (e.g., VWF:GPIbM).

<sup>2</sup> The lower limit of the normal range as determined by the local laboratory should be used if it is less than 0.50 IU/mL. ABO specific reference ranges are not required.

<sup>3</sup> VWF is an acute phase reactant that increases in response to a variety of stimuli (e.g., bleed, trauma, pregnancy). VWD diagnostic testing should be performed when patients are at a baseline state of health.

### VWF LEVELS THAT NORMALIZE WITH AGE

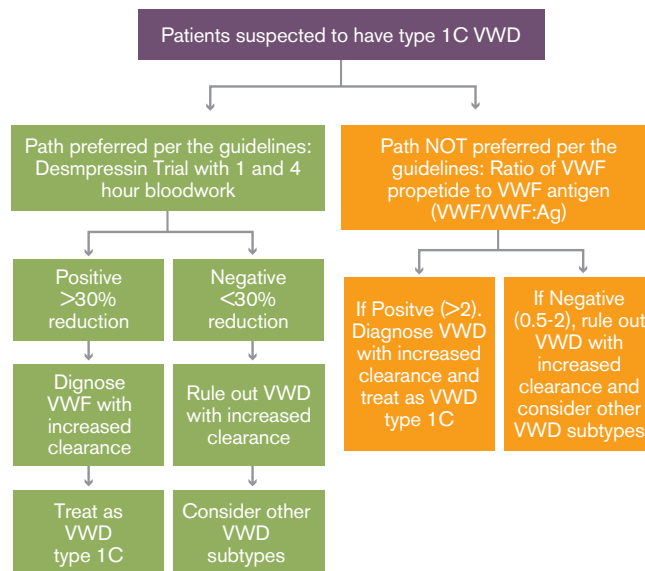
Reconsidering (as opposed to removing) the diagnosis would allow clinicians to consider and test for a concomitant bleeding disorder (e.g., a platelet function disorder), particularly if this testing was not done at the time of the type 1 VWD diagnosis. Reconsidering the diagnosis requires a detailed discussion and may not completely avoid the issue of loss of insurance coverage, which is a reason to consider when reconsidering or removing the diagnosis.

The panel **suggests** reconsidering the diagnosis as opposed to removing the diagnosis in patients with previously confirmed type 1 VWD who now have VWF levels that have normalized with age. ⚠

### TYPE 1C VWD

The panel **suggests against** using the VWFpp/VWF:Ag (ratio of VWF propeptide to antigen) and rather using a desmopressin trial with 1- and 4-hour post infusion blood work to confirm increased VWF clearance in patients with VWD suspected of type 1C (see Figure 1). ⚠

**Figure 1. Patients suspected to have VWD with increased clearance**



### TYPE 2 VWD

The panel **suggests against** a platelet-dependent VWF activity/VWF:Ag ratio <0.5 cut-off, and rather using a higher cutoff of <0.7 to confirm type 2 VWD (2A, 2B, or 2M) in patients with an abnormal initial VWD screen.<sup>1</sup> ⚠

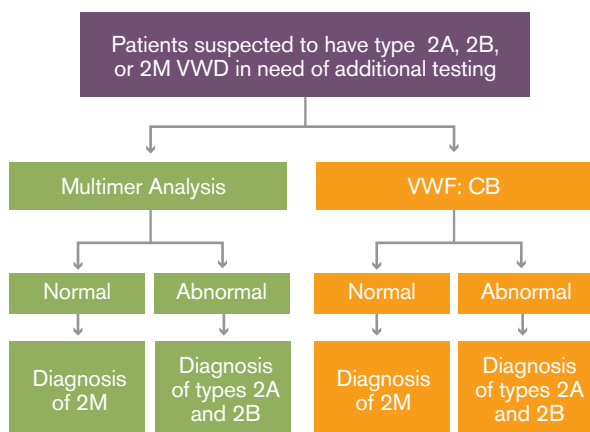
The panel **suggests** either VWF multimer analysis or VWF:CB/VWF:Ag (ratio of VWF collagen binding to antigen) to diagnose type 2 VWD in patients suspected of type 2A, 2B, or 2M in need of additional testing (see Figure 2).<sup>2</sup> ⚠

<sup>1</sup> Most labs that do the VWF:CB assay use type I and/or III collagen, which is known to be a surrogate for the presence of high molecular weight VWF.

<sup>2</sup> Some patients with type 2 VWD have normal VWF:Ag and platelet-dependent VWF activity but a low ratio of platelet-dependent VWF activity/VWF:Ag.

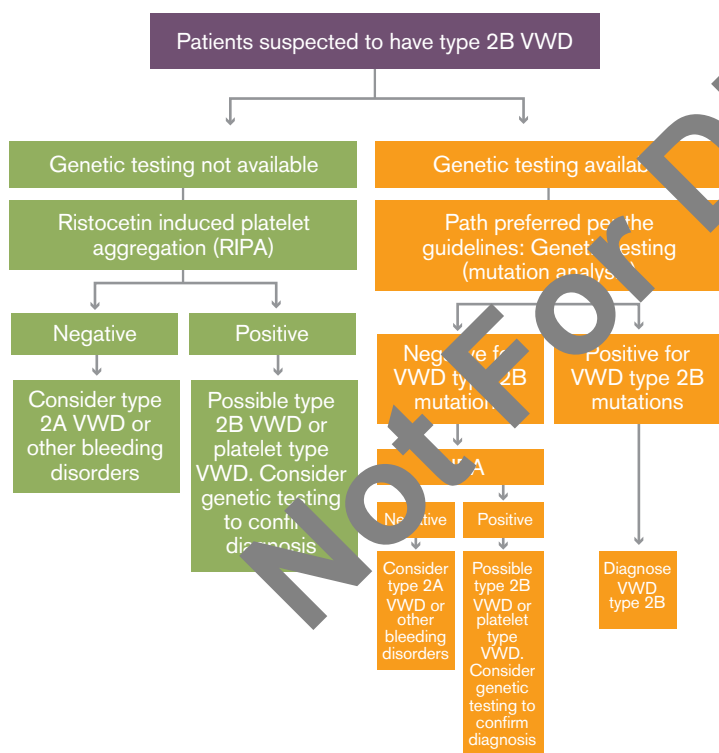
**Figure 2. Patients suspected of Type 2A, 2B or 2M VWD in need of additional testing**

The panel **suggests** targeted genetic testing over low-dose RIPA (Ristocetin induced platelet agglutination) to diagnose type 2B VWD in patients suspected of type 2A or 2B in need of additional testing (see Figure 3). **C**

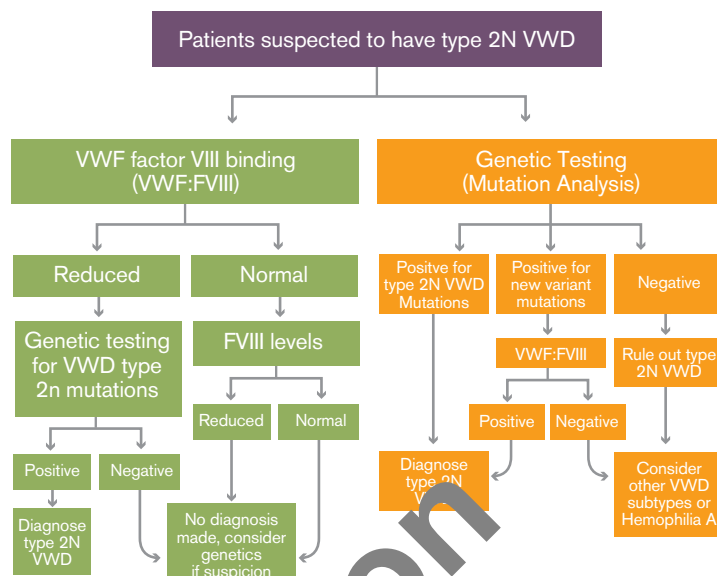


**Figure 3. Patients suspected to have type 2B VWD**

The panel **suggests** using either VWF:FVIII (between VWF and FVIII binding) or targeted genetic testing (when available) in patients with suspected type 2N VWD in need of additional testing (see Figure 4). **C**



**Figure 4. Patients suspected to have type 2N VWD**



## Management

### PROPHYLAXIS

In patients with VWD with history of severe and frequent bleeds, the guideline panel **suggests** using long-term prophylaxis rather than no prophylaxis. **C**

**Table VWF concentrate administration**

VWF concentrate options	Description
VWF/factor VIII concentrate (plasma derived)	Plasma-derived concentrate containing both VWF and factor VIII. Administered intravenously (IV). Typical dosing, 40–80 ristocetin cofactor (VWF:RCo) activity units/kg.
VWF concentrate (plasma derived)	Plasma-derived concentrate containing VWF alone. Administered IV. Typical dosing, 40–80 VWF:RCo activity units/kg. If used for emergency treatment, may require addition of factor VIII concentrate in patients with low baseline factor VIII.
VWF concentrate (recombinant)	Recombinant concentrate containing VWF alone. Administered IV. Typical dosing, 40–80 VWF:RCo activity units/kg. If used for emergency treatment, may require addition of factor VIII concentrate in patients with low baseline factor VIII.

<sup>1</sup>Bleeding symptoms and the need for prophylaxis should be periodically assessed. Prophylaxis in VWD is a period of at least 3 to 6 months of treatment consisting of VWF concentrate administered at least once weekly, or for women with Heavy Menstrual Bleeding (HMB), use of VWF concentrate administered at least once per menstrual cycle.

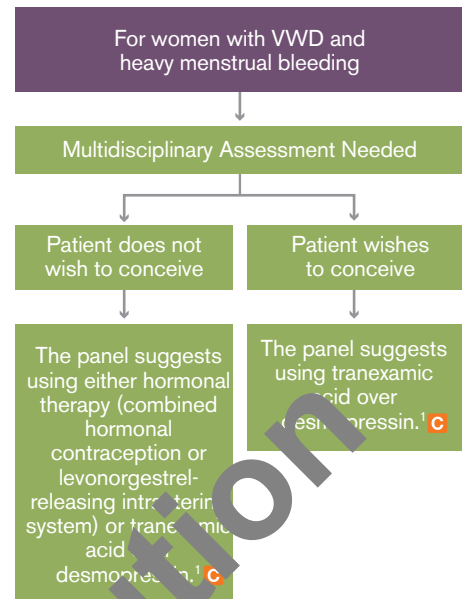
### DESMOPRESSIN CHALLENGE/TRIAL AND ADMINISTRATION

In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of < 0.30 IU/mL, the panel **suggests** performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate. **C** In these patients, the panel **suggests against** treating with desmopressin in the absence of desmopressin trial results. **C**



## HEAVY MENSTRUAL BLEEDING

Figure 5: Women with VWD and Heavy Menstrual Bleeding



<sup>1</sup> This recommendation does not imply that the interventions considered can be prescribed only as monotherapy. In some cases, multiple options can be combined, especially if control of heavy menstrual bleeding is less than optimal with the first therapy. Desmopressin is not effective in type 3 and many type 2 VWD patients and is contraindicated in type 3 VWD. Women may require additional treatment directed at bleeding symptoms for the first several menstrual cycles after placement of a levonorgestrel-releasing intrauterine system.

## Good Practice Statement

The administration of desmopressin to patients with type 2B VWD is generally contraindicated, as this may cause thrombocytopenia due to increased platelet binding. Furthermore, desmopressin is generally contraindicated in patients with cardiovascular disease (e.g., coronary heart disease, cerebrovascular disease, and peripheral vascular disease), patients with seizure disorders, patients under the age of 2, and patients with type 1C VWD in the setting of surgery. Desmopressin has been used safely in many women during pregnancy, including those with bleeding disorders and diabetes insipidus. It should be avoided in women with preeclampsia and those with cardiovascular disease. Fluid restriction and strict fluid balance are of paramount importance when desmopressin is used at the time of delivery. Intravenous fluid infusion and oxytocic medications are often used during labor and delivery, both of which increase the risk of desmopressin-induced hyponatremia. Patients receiving desmopressin are at risk for hyponatremia from free water retention; therefore, they should receive normal saline if IV fluid replacement is required, and oral free water fluid intake should be restricted to prevent hyponatremia.

## ANTITHROMBOTIC THERAPY

In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel **suggests** giving the necessary antiplatelet or anticoagulant therapy over no treatment.<sup>1</sup>

<sup>1</sup> It is important to reassess the bleeding risk throughout the course of treatment.

## Good practice statements

Patients considered for treatment require individualized analysis of the risks and benefits of the specific therapy plan in conjunction with a multidisciplinary team that includes cardiovascular medicine specialists, hematologists, and the patient.

Patients with type 2 or type 3 VWD may require prophylaxis with VWF concentrate to prevent bleeding while on antiplatelet or anticoagulant therapy; similar precautions may apply to patients with type 1 VWD and concurrent additional bleeding problems.

Desmopressin therapy is generally contraindicated in individuals with cardiovascular disease (e.g., coronary heart disease, cerebrovascular disease, and peripheral vascular disease) and/or increased risk of thrombosis.

## MINOR SURGERY/INVASIVE PROCEDURES

In patients undergoing minor surgery or minor invasive procedures, the panel **suggests** raising VWF activity levels to  $\geq 0.50$  IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to  $\geq 0.50$  IU/mL with desmopressin or factor concentrate alone.<sup>2</sup>

The panel **suggests** giving tranexamic acid alone over increasing VWF activity levels to  $\geq 0.50$  IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of  $>0.30$  IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures.<sup>2</sup>

<sup>2</sup> Individualized therapy plans should consider the variation in bleeding risk for the specific procedure in question.

## MAJOR SURGERY

The panel **suggests** targeting both factor VIII and VWF activity levels of  $\geq 0.50$  IU/mL for 3 days after surgery.<sup>3</sup>

The panel **suggests against** using only factor VIII  $\geq 0.50$  IU/mL as a target level for 3 days after surgery.<sup>3</sup>

<sup>3</sup> When it is possible to keep both trough levels at  $\geq 0.50$  IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only one), this should be the preferred option.

## Good Practice Statements

For some patients, there may be other benefits to use of hormonal therapy such as treatment of menstrual pain and management of endometriosis and polycystic ovary syndrome-related symptoms.

Patients with heavy menstrual bleeding should be assessed and treated for iron deficiency and anemia.

Special consideration is required in terms of side effects of therapy for those who are at high risk of endometrial hyperplasia/malignancies, such as women over 35 and those with polycystic ovaries, high body mass index (BMI), and comorbidities such as diabetes and hypertension.

## Good Practice Statements


When feasible, the panel encourages the development of multidisciplinary clinics in which gynecologists and hematologists see patients jointly to facilitate the management of heavy menstrual bleeding for patients with bleeding disorders.

Women with known bleeding disorders and heavy menstrual bleeding should undergo standard gynecological assessment that is recommended for women with heavy menstrual bleeding in the general population to rule out common pelvic pathologies such as fibroids and polyps, especially those not responding to first-line treatment.

Decisions regarding the use of the levonorgestrel-releasing intrauterine system should be made in a setting of shared decision-making with multidisciplinary input (e.g., gynecology professionals, hematology professionals, and patients).


## Neuraxial Anesthesia

Neuraxial anesthesia refers to spinal, epidural, or combined spinal-epidural procedures performed for surgical anesthesia for operative deliveries or pain relief during labor. The ultimate decision about whether it is appropriate for an individual patient to undergo these procedures lies with the obstetric anesthesiologist or other clinician performing the procedure. Decisions regarding anesthesia and delivery should be made in the context of a multidisciplinary discussion with input from anesthesia, hematology, and obstetrics and shared decision-making with the patient. These discussions should take place well in advance of the patient's due date.

In women with VWD for whom neuraxial anesthesia during labor is deemed suitable, the panel **suggests** targeting a VWF activity level of 0.50 to 1.50 IU/mL over targeting an activity level of  $>1.50$  IU/mL to allow neuraxial anesthesia.<sup>1</sup> 

<sup>1</sup> This recommendation focused on the outcomes of the anesthesia procedure itself and not on the effects of the VWF levels on postpartum hemorrhage (PPH), in which VWF activity levels of  $>1.50$  IU/mL may be advised in some situations. Individual risk assessment should be performed, taking into account patient diagnosis and history, and for this reason, the panel advocates a third-trimester visit where VWF and factor VIII activity levels can be checked, and a prospective plan formed for anesthesia and delivery. This recommendation is intended for women who desire or require neuraxial anesthesia and does not address suitability of neuraxial anesthesia itself. VWF activity levels should be maintained at  $>0.50$  IU/mL while the epidural is in place and for at least 6 hours following removal. Patients should also be assessed for thrombotic risk postdelivery, and prophylaxis (such as compression stockings or low-molecular-weight heparin) should be provided when needed.

## Obstetrics: Postpartum Management

The guideline panel **suggests** the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to type 2 and 3 VWD) during the postpartum period. 

### Good Practice Statements

Tranexamic acid may be given systemically via the oral or intravenous route. Treatment is generally given as 1,000 to 1,300 mg orally three times a day for 10 to 14 days or longer if blood loss remains heavy.<sup>1</sup>



Patients who intend to breastfeed should be provided education about the safety of tranexamic acid during breastfeeding in conjunction with its benefits in reducing bleeding.

<sup>1</sup> The oral dose is 25mg/kg (typically 1000-1300 mg) 3 times per day for 10 to 14 days or longer if blood loss remains heavy

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## Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in ASH ISTH NHF WFH 2021 Guidelines on the diagnosis and management of von Willebrand disease.<sup>1</sup>

Strength of Recommendation	
	<b>Strong recommendations</b> - Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
	<b>Conditional recommendations</b> - Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

## How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnosis and treatment alternatives. The information included in this guide is not intended to be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally through a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including, but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, these pocket guides may become obsolete. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

The complete ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of von Willebrand Disease<sup>1</sup> include additional remarks and contextual information that may affect clinical decision making. To learn more about these guidelines, visit [hematology.org/VWD-guidelines](https://www.hematology.org/VWD-guidelines).

Conflict of interest information for Drs. Ozelo, Elbaz, Woyand, and El Ekiaby may be found at [hematology.org/pocketguides](https://www.hematology.org/pocketguides).

<sup>1</sup> James P, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv* 2021; 5 (1): 280–290.

Connell NT, Flood V, Brignardello-Petersen R et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv* 2021; 5 (1): 301–325.



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