



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

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Background Von Willebrand disease (VWD) is a common inherited bleeding disorder. Significant variability exists in management options offered to patients.

Objective These evidence-based guidelines from the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and health care professionals in their decisions about management of VWD.

Methods ASH, ISTH, NHF, and WFH formed a multidisciplinary guideline panel. Three patient representatives were included. The panel was balanced to minimize potential bias from conflicts of interest. The University of Kansas Outcomes and Implementation Research Unit and the McMaster Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre supported the guideline development process, including performing and updating systematic evidence reviews (through November 2019). The panel prioritized clinical questions and outcomes according to their importance to clinicians and patients. The panel used the GRADE approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results The panel agreed on 12 recommendations and outlined future research priorities.

Conclusions These guidelines make key recommendations regarding prophylaxis for frequent recurrent bleeding, desmopressin trials to determine therapy, use of antiplatelet agents and anticoagulant therapy, target VWF and factor VIII activity levels for major surgery, strategies to reduce bleeding during minor surgery or invasive procedures, management options for heavy menstrual bleeding, management of VWD in the context of neuraxial anesthesia during labor and delivery, and management in the postpartum setting.

Subjects [Clinical Guidelines, Thrombosis and Hemostasis](#)

Topics [Desmopressin, eustachian tube disorders, guidelines, hemorrhage, menorrhagia, surgical procedures, operative, tranexamic acid, von willebrand disease, international society of thrombosis and haemostasis, neuraxial anesthesia](#)

Reference: Connell NT, Flood VH, 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. doi: <https://doi.org/10.1182/bloodadvances.2020003264>

Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the Outcomes and Implementation Research Unit at the University of Kansas Medical Center (KUMC). The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (G-I-N).¹⁻³ The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.⁴⁻¹⁰

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Multiple subtypes exist and require individualized treatment based on specific diagnosis, bleeding phenotype, and specific clinical context.¹¹ Major symptoms include mucocutaneous bleeding, including epistaxis, easy bruising, and heavy menstrual bleeding, as well as provoked bleeding in the setting of surgery and other invasive procedures. Major therapies include use of desmopressin to induce endothelial release of stored von Willebrand factor (VWF) and factor VIII (FVIII) and use of VWF concentrates, including both plasma-derived and recombinant products, as well as adjuvant therapies, such as antifibrinolytic tranexamic acid. Management remains challenging because of wide variability in individual patient bleeding symptoms, wide variability in clinical practice, and lack of high-certainty evidence to guide decision making.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong (“the guideline panel *recommends*”) or conditional (“the guideline panel *suggests*”) and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: 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.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.

Conditional recommendation

- For patients: a majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on if an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of good practice statements

As described by the GRADE Working Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.¹² Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Prophylaxis.

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 ⊕⊕○○).

Remark:

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

Desmopressin challenge/trial and administration.

RECOMMENDATION 2A.

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 (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 2B.

In these patients, the panel *suggests against* treating with desmopressin in the absence of desmopressin trial results (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- This recommendation does not apply to patients for whom desmopressin is not a reasonable treatment option (e.g., those with type 3 VWD). Desmopressin is contraindicated in type 3 VWD because of a lack of efficacy and in type 2B VWD because of increased platelet binding with subsequent thrombocytopenia.
- Many patients with type 2 VWD do not respond to desmopressin and require other modes of treatment. However, a desmopressin trial may be helpful to confirm diagnosis, and desmopressin may still be useful in some instances of mild bleeding for type 2 VWD patients.
- Patients undergoing major surgery, including in sites where even a small amount of bleeding may result in critical organ damage (e.g., central nervous system surgery), should not receive desmopressin as sole therapy.
- It is optimal to confirm desmopressin responsiveness before using desmopressin for therapeutic interventions, but because this may not always be practical, adult patients with type 1 VWD whose baseline VWF levels are ≥ 0.30 IU/mL can be presumed to be desmopressin responsive. Although they can receive desmopressin without requiring a trial, it is reasonable to obtain VWF levels to confirm response after administration. Patients with type 1 VWD and VWF levels of < 0.30 IU/mL may not respond to desmopressin, hence the recommendation for a trial.
- This recommendation does not address the choice between treating with tranexamic acid and VWF concentrate.

Good practice statements.

The administration of desmopressin to patients with type 2B VWD is generally contraindicated, because this may cause thrombocytopenia as a result of increased platelet binding.

Furthermore, desmopressin is generally contraindicated in patients with active cardiovascular disease (e.g., coronary heart disease, cerebrovascular disease, and peripheral vascular disease), patients with seizure disorders, patients age < 2 years, 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. IV 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.

Patient counseling about desmopressin should include strategies to mitigate risks associated with hyponatremia (e.g., free water restriction and education about signs and symptoms of hyponatremia that should lead to prompt medical evaluation) and cardiovascular disease.

Antithrombotic therapy.

RECOMMENDATION 3.

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 (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Remark:

- It is important to reassess the bleeding risk throughout the course of treatment.

Good practice statements.

Patients considered for treatment require individualized analyses 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.

Patient education about the risks and benefits of using antiplatelet agents or anticoagulant therapy should be provided to inform shared decision making.

Patients with a severe bleeding phenotype (e.g., severe type 1, 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.

Major surgery.

RECOMMENDATION 4A.

The panel *suggests* targeting both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

RECOMMENDATION 4B.

The panel *suggests against* using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- When it is possible to keep both trough levels at ≥ 0.50 IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only 1), this should be the preferred option.
- The 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.
- The duration of the intervention can vary for specific types of surgeries.

Minor surgery/invasive procedures.

RECOMMENDATION 5A.

In patients undergoing minor surgery or minor invasive procedures, the panel *suggests* increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate alone (conditional recommendation based on very low certainty in the evidence of effects $\oplus\textcircled{0}\textcircled{0}\textcircled{0}$).

RECOMMENDATION 5B.

The panel *suggests* giving tranexamic acid alone over increasing VWF activity levels to ≥ 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 (conditional recommendation based on very low certainty in the evidence of effects $\oplus\textcircled{0}\textcircled{0}\textcircled{0}$).

Remarks:

- Individualized therapy plans should consider the variation in bleeding risk for the specific procedure in question. Individualized therapy plans are especially important for patients who may be overtreated when VWF activity is increased to ≥ 0.50 IU/mL by any therapy and addition of tranexamic acid (e.g., those undergoing cutaneous procedures, such as superficial skin biopsy).
- Patients with type 3 VWD will require VWF concentrate to achieve any significant increase in VWF activity levels. Use of desmopressin is contraindicated in this population because of a lack of efficacy.
- Many patients with type 2 VWD (including patients with type 2B VWD) will also require treatment with VWF concentrate rather than desmopressin.
- For patients at higher risk of thrombosis, it may be desirable to avoid the combination of extended increased VWF and FVIII levels (>1.50 IU/mL) and extended use of tranexamic acid.
- Dental proceduralists may consider use of local hemostatic measures (e.g., gelatin sponges or fibrin glue, tranexamic acid rinse) as part of an individualized procedural plan.

Gynecology: heavy menstrual bleeding.

RECOMMENDATION 6A.

The panel *suggests* using either hormonal therapy (combined hormonal contraception [CHC] or levonorgestrel-releasing intrauterine system) or tranexamic acid over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation based on very low certainty in the evidence of effects $\oplus\textcircled{0}\textcircled{0}\textcircled{0}$).

RECOMMENDATION 6B.

The panel *suggests* using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive (conditional recommendation based on very low certainty in the evidence ⊕○○○).

Remarks:

- 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 initial therapy.
- Desmopressin is not effective in type 3 and many type 2 VWD patients and is contraindicated in type 2B 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 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.

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

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

Both iron deficiency and anemia resulting from iron deficiency are associated with adverse outcomes, including diminished health-related quality of life. Patients with heavy menstrual bleeding should be regularly assessed and treated for iron deficiency and/or anemia.

Women with known bleeding disorders and heavy menstrual bleeding should undergo a standard gynecologic 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.

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

Obstetrics: neuraxial anesthesia.

RECOMMENDATION 7.

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 (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- Neuraxial anesthesia refers to spinal, epidural, or combined spinal-epidural procedures performed for surgical anesthesia for operative deliveries or pain relief during labor.
- 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 FVIII 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 after removal.
- The assessment of whether neuraxial anesthesia is appropriate for an individual patient is a complex decision that includes assessment of factors outside the scope of these guidelines. 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.
- Patients should also be assessed for thrombotic risk postdelivery, and prophylaxis (e.g., compression stockings or low-molecular-weight heparin) should be provided when needed.

Obstetrics: postpartum management

RECOMMENDATION 8.

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 types 2 and 3 VWD) during the postpartum period) (conditional recommendation based on low certainty in the evidence of effects ⊕⊕○○).

Good practice statements.

Tranexamic acid may be given systemically via the oral or IV route. 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.

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.

Values and preferences

Values and preferences for this guideline were considered from the patient's perspective, with input from all panel members, including patient representatives. The guideline panel rated mortality, major bleeding, serious adverse events, joint function, thrombotic events, inability to perform surgery, need for hospitalization, transfusion, additional surgical procedures or additional hemostatic agents, and primary or secondary postpartum hemorrhage as critical for decision making and placed a high value on these outcomes and on avoiding them with the interventions that were evaluated. These recommendations place a high value on ensuring access to treatment.

Explanations and other considerations

These recommendations take into consideration cost and cost effectiveness, resource requirements, impact on health equity, acceptability, and feasibility.

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