blood advances

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.

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]

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Data for the Evidence-to-Decision frameworks will be publicly available via Web links from the online version of the document.

The full-text version of this article contains a data supplement.

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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 ⊕⊕○○).

Remarks:

- 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 ⊕○○○).

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 ⊕○○○).

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 (eg, 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 (eg, gelatin sponges or fibrin glue, tranexamic acid rinse) as part of an individualized procedural plan.

Gynecology: heavy menstrual sleeding. 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 ⊕○○○).

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 (eg, 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 (eg, 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.

Introduction

Aim of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations on the management of VWD. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations that will improve access to appropriate treatments and facilitate individualized therapy when appropriate. Through improved provider and patient education on the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision making that will result in increased access to quality care for patients with VWD.

The target audience includes patients, hematologists, general practitioners, internists, obstetricians, gynecologists, surgeons, anesthesiologists, maternal-fetal medicine experts, other clinicians, and decision makers. Policy makers who may be interested in these guidelines include those involved in developing local, national, or international plans with the goals of implementing effective care management protocols and improving outcomes for patients with VWD. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem

VWD is the most common inherited bleeding disorder, originally described by Erik von Willebrand in 1926.[13] Current best estimates obtained from the primary care setting suggest that VWD affects 1 in 1000 individuals.[14] Despite this, many practitioners remain unaware of how to diagnose or treat affected patients. VWF plays a key role in coagulation, because it serves as a carrier protein for FVIII[15] and facilitates platelet binding to exposed collagen at sites of injury.[16] VWD occurs when there are either quantitative or qualitative defects in VWF. Difficulties in diagnosis are compounded by the existence of 3 major subtypes of VWD (Table 1).[17]

Diagnostic thresholds and criteria for the diagnosis and classification of VWD are covered in the concurrent guideline, "ASH ISTH NHF WFH 2020 Guidelines on the Diagnosis of von Willebrand Disease."[18] Types 1 and 3 are quantitative defects, with type 1 VWD representing a mild to moderate deficiency in the VWF protein and type 3 VWD representing the more severe form, with near-complete absence of VWF. The recently described type 1C subtype of VWD is characterized by a shortened VWF half-life, which requires potential management changes as compared with type 1 VWD.[19] Type 2 VWD includes variants with a qualitative defect in 1 of VWF's main functions, either forming of multimers (types 2A and 2B), platelet binding (type 2M), or FVIII binding (type 2N). The mechanism of type 2B VWD is important, because it represents a gain-of-function defect, with increased platelet binding leading to clearance of both VWF and platelets.[20]

The major symptoms of VWD include mucocutaneous bleeding, such as epistaxis, easy bruising, prolonged bleeding from minor cuts, and heavy menstrual bleeding, as well as surgical bleeding, particularly in the setting of dental extractions. Patients with type 3 VWD may experience joint bleeds similar to those seen in hemophilia.[21] Heavy menstrual bleeding is of particular concern in women because of its monthly occurrence, affecting their quality of life as well as their overall health.[22,23] Many women experience iron deficiency and anemia resulting from the presence of unrecognized or inadequately treated heavy menstrual bleeding.[24] Complications resulting from PPH are also more frequent in women with VWD.[25,26] Appropriate treatment is a major challenge for affected patients.

Existing guidelines have focused on expert opinion, with little room for patient preference or critical examination of the evidence for specific recommendations, resulting in the potential for increased costs to patients and families, ineffective therapies, or lack of consideration of effective therapies.

The scope of this guideline has been informed by areas of concern for patients and providers alike, which include treatment options for women with VWD, treatment options for surgery, testing during invasive procedures, use of desmopressin, and prophylaxis as highlighted by an international survey on VWD spearheaded by partner organizations.[27] These considerations informed the panel's deliberations, with a high value placed on patients' desire for appropriate treatment and providers' desire to provide the highest quality of care.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[4-10] The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external reviews, and organizational approval, was guided by policies and procedures derived from the G-I-N-McMaster Guideline Development Checklist[28] and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[1-3,29]

Organization, panel composition, planning, and coordination

These guidelines were developed as a collaboration by the American Society of Hematology (ASH), the International Society of Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH). The work of the panel was coordinated by ASH and the Outcomes and Implementation Research Unit at KUMC (funded by the collaborating organizations, under a paid agreement). KUMC subcontracted with the McMaster University GRADE Centre for part of the work. Project oversight was provided by the ASH Guideline Oversight Subcommittee, which reported to the ASH Committee on Quality. All 4 collaborating organizations made nominations, with ASH vetting all individuals appointed to the guideline panel. The Outcomes and Implementation Research Unit vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process, including the use of the GRADE approach. The membership of the panels and the systematic review team is described in supplemental Data 1.

The panel included adult and pediatric hematologists, obstetrician/gynecologists, internists, a dentist, and a nephrologist, all of whom had clinical and research expertise on the guideline topic, and 3 patient representatives. One cochair was a content expert; the other cochair was an expert in guideline development methodology.

Table 1. Classification of VWD: major types and subtypes

Type	Characteristic
1	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; normal multimer distribution
1C	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; increased VWF/pp compared with VWF/Ag
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 FVIII
2B	Increased binding to GPIbα, often leading to thrombocytopenia
3	Absence or near absence of VWF
Platelet-type VWD	Functional defect of platelet GPIbα, leading to excessive binding of platelets and VWF and subsequent thrombocytopenia and loss of high-molecular-weight multimers
Acquired von Willebrand syndrome	Decreased VWF and particularly loss of high-molecular-weight multimers as a result of either shearing from mechanical forces (eg, aortic stenosis resulting in Heyde syndrome), adsorption on tumors (eg, Waldenström macroglobulinemia or Wilms' tumors), or autoimmune inhibitor formation

Act, activity; Ag, antigen; GPIbα, glycoprotein Ibα; pp, propeptide.

The panel also included a clinical vice chair who served on both the management and diagnosis panels to ensure efforts were coordinated. All panelists were full and equal voting members with regard to the recommendations, with the exception of recusals as described in "Guideline funding and management of conflicts of interest."

In addition to synthesizing evidence systematically, the Outcomes and Implementation Research Unit at KUMC and McMaster GRADE Centre supported the guideline development process, including determining methods, preparing meeting materials, and facilitating panel discussions. The panel's work was done using Web-based tools (SurveyMonkey and GRADEpro) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by the 4 collaborating organizations: ASH, ISTH, NHF, and WFH. Organization staff supported panel appointments and attended meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings. The patient representatives received an honorarium of $200 each. Through the Outcomes and Implementation Research Unit at KUMC and the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies based on recommendations of the Institute of Medicine and the GIN.[3,30] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the guideline panel members, including the cochairs, had no such conflicts. None of the Outcomes and Implementation Research Unit at KUMC or the McMaster GRADE Centre researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was used to manage certain conflicts.[4,31-33] During deliberations about recommendations, any panel member with a current direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) or the direction or strength of the recommendation. The Evidence-to-Decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

Supplemental Data 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years before appointment; in part B, indirect financial interests; and in part C, not mainly financial interests. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplemental Data 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used online meetings to brainstorm recommendation questions and an in-person meeting to develop the questions outlined in Table 2.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[8] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision making following the GRADE approach.[8] While acknowledging considerable variation in the impact on patient outcomes, the panel considered the following outcomes as critical for clinical decision-making across questions:

Table 2. Summary of prioritized questions

Population	Intervention	Comparator	Outcome
1. Patients with VWD and history of severe and frequent bleeds	Periodic long-term prophylaxis with VWF concentrate	No concentrate (ie, on-demand therapy)	Major bleeding, serious adverse events, joint function, mortality, hospitalization
2. Patients with VWD	Treat based on results of desmopressin challenge	Not perform desmopressin challenge and treat with VWF concentrate and/or tranexamic acid Treat with desmopressin empirically	Major bleeding, serious adverse events
3. Patients with VWD and cardiovascular disease	Treat with antiplatelet agents or anticoagulant therapy as indicated	No treatment	Mortality, thrombotic events, serious adverse events, major bleeding, transfusion, hospitalization
4. Patients with VWD undergoing major surgery	Keep FVIII level ≥0.50 IU/mL for at least 3 d after surgery	Keep VWF activity level ≥0.50 IU/mL for at least 3 d after surgery	Mortality, major bleeding, need for additional surgical procedures, transfusion, serious adverse events, hospitalization, thrombotic events
5. Patients with VWD undergoing minor surgery or invasive procedures	Increase VWF activity level to ≥0.50 IU/mL with use of VWF concentrate or desmopressin	Tranexamic acid monotherapy Combination therapy by increasing VWF activity level to ≥0.50 IU/mL with use of VWF concentrate or desmopressin in conjunction with tranexamic acid	Major bleeding, need for additional hemostatic agents, need for additional surgical procedures, serious adverse events, mortality, hospitalization, transfusion, inability to perform surgery
6. Women with VWD with heavy menstrual bleeding	Tranexamic acid	Hormonal therapy (ie, levonorgestrel-releasing intrauterine system or hormonal contraceptives) Desmopressin	Menstrual blood loss and duration, absence from required activities, health-related quality of life, need for additional treatments, need for surgery and blood transfusion
7. Women with VWD who require or desire neuraxial anesthesia during labor (referring to spinal, epidural, or combined spinal-epidural procedures performed for surgical anesthesia for operative or pain relief)	Administer VWF concentrate to achieve VWF activity level of 0.50-1.50 IU/mL	Administer VWF concentrate to achieve VWF activity level >1.50 IU/mL	Major bleeding, serious adverse event in mother, spinal hematoma, ability to receive epidural anesthesia, mortality
8. Women with VWD in the postpartum period	Tranexamic acid	No treatment	Primary postpartum hemorrhage, secondary postpartum hemorrhage, serious adverse events in mother, need for other medical procedures, blood loss, mortality, transfusion, hospitalization

- Prophylaxis: major bleeding, serious adverse events, joint function, mortality, hospitalization
- Desmopressin challenge/trial: major bleeding, serious adverse events
- Anticoagulants/antiplatelet agents: mortality, thrombotic events, serious adverse events, major bleeding, transfusion, hospitalization
- Major surgery: mortality, major bleeding, need for additional surgical procedures, transfusion, serious adverse events, hospitalization, thrombotic events
- Minor surgery: major bleeding, need for additional hemostatic agents, need for additional surgical procedures, serious adverse events, mortality, hospitalization, transfusion, inability to perform the surgery
- Heavy menstrual bleeding: menstrual blood loss and duration, absence from required activities, health-related quality of life, need for additional treatments, need for surgery and blood transfusion
- Neuraxial anesthesia: major bleeding, serious adverse event in mother, spinal hematoma, ability to receive epidural anesthesia, mortality
- Postpartum hemorrhage: primary postpartum hemorrhage, secondary postpartum hemorrhage, serious adverse events in mother, need for other medical procedures, blood loss, mortality, transfusion, hospitalization

In addition, the panel considered that several other outcomes, including health equity, access to care, and cost, were important for decision making, and therefore, these were also considered when formulating the recommendations. Evidence for all outcomes was gathered through the systematic review process and presented to the panel. The panel also considered the implications when there was no evidence available for outcomes considered critical or important. The panel recognized the lack of standardized definitions for many populations (eg, major surgery and minor surgery), therapies (eg, prophylaxis), and outcomes (eg, desmopressin responsiveness) and opted to include populations, treatments, and outcomes based on how they were defined by the authors of the published studies to avoid limiting available evidence for consideration.

Evidence review and development of recommendations

For each guideline question, researchers at the Outcomes and Implementation Research Unit at KUMC and the McMaster GRADE Centre prepared a GRADE EtD framework using the GRADEpro Guideline Development Tool.[4,5,10] The EtD table summarized the results of systematic reviews of the literature that were performed for this guideline. The EtD table addressed effects of interventions, certainty in the evidence, patients' values and preferences (relative importance of outcomes), resource use (cost effectiveness), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, and after the guideline panel meeting and

provided feedback. To ensure that recent studies were not missed, searches in Medline (via OVID) and EMBASE (presented in supplemental Data 4) first conducted in December 2018 were updated in November 2019, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions.

Under the direction of the Outcomes and Implementation Research Unit at KUMC and the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions for conducting new systematic reviews of intervention effects. Risk of bias was assessed at the health outcome level using the Cochrane Risk of Bias 1.0 tool for randomized trials and the Risk of Bias Assessment of Non-Randomized Studies of Interventions for nonrandomized studies. When there was no evidence from randomized trials or comparative observational studies, we conducted systematic reviews of case series. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD framework.[4,5,10] Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels: very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and high (⊕⊕⊕⊕).[6-8]

During a 2-day in-person meeting, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly considered the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation) based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel *recommends*" are used for strong recommendations and "the guideline panel *suggests*" for conditional recommendations. Table 3 provides the GRADE interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 6 April 2020 for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public; 49 individuals submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. The ASH Guideline Oversight Subcommittee on 18 August 2020 and the ASH Committee on Quality on 26 August 2020 approved that the defined guideline development process was followed, and on 28 August 2020, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. On 28 August 2020, ISTH approved that the defined guideline development process was followed; on 27 August 2020, NHF approved that the defined guideline development process was followed; and on 25 August 2020, WFH approved that the defined guideline development process was followed. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

These guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions based on the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence become available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH, ISTH, NHF, and WFH do not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Recommendations

Prophylaxis

In patients with VWD with a history of severe and frequent bleeds, should routine prophylaxis with VWF concentrate or no routine prophylaxis (ie, treatment on demand) be used?

Recommendation 1

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

Remarks:

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

Table 3. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	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.
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.	Different choices will be appropriate for individual patients, and each patient must be helped to 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.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	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.
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.	The 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.

Summary of the evidence. We identified 3 bodies of evidence regarding prophylaxis in VWD: 1 randomized trial comparing prophylaxis with placebo,[34] 5 pre-post studies with an explicit comparison between time periods for prophylaxis vs no prophylaxis reported in 9 publications,[35-43] and 8 pre-post studies with an implicit comparison between time periods for prophylaxis vs no prophylaxis reported in 11 publications.[36,38,43-51] The effect of prophylaxis was assessed for the following outcomes: spontaneous bleeds (number of events per patient), bleeding episodes (events per month per patient), time to first bleeding in days, bleeding episodes lasting >2 days, serious adverse events, epistaxis episodes, gastrointestinal hemorrhage, and hemarthrosis. For the purpose of this question, major bleeding was defined as bleeding requiring hospital admission, requiring surgical intervention, requiring blood transfusion (of at least 2 units), resulting in a drop of ≥2 g/dL in hemoglobin, or resulting in symptoms involving critical areas (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome). Prophylaxis was defined as a period of at least 6 months of treatment consisting of VWF replacement administered at least once weekly. In the single randomized controlled trial evaluating prophylaxis, frequent bleeds were defined as "≥5 bleeding episodes in the last 12 months, or ≥3 episodes of haemarthrosis at the same joint or ≥2 episodes of gastrointestinal haemorrhage either unexplained or in association with underlying gastrointestinal angiodysplasia with requirement of [VWF concentrate] therapy."[34(p392)]

The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/JLMHIOqdI3E.

Benefits, harms, and burden. In the single available randomized controlled trial (n = 19), routine VWF concentrate prophylaxis in patients with severe VWD reduced the risk of bleeding episodes (rate ratio [RR], 0.24; 95% confidence interval [CI], 0.17-0.35), improved the time to first bleeding event (mean difference, 31.4 days longer; 95% CI, 8.44-54.36 days), and reduced epistaxis (RR, 0.38; 95% CI, 0.21-0.67).[34] Prophylaxis also probably reduced the number of spontaneous bleeds (RR, 0.62; 95% CI, 0.37-1.04) and hemarthrosis (RR, 0.50; 95% CI, 0.06-4.50), although this did not reach statistical significance. In the randomized controlled trial, prophylaxis seemed to result in more bleeding episodes lasting >2 days (RR, 45.69; 95% CI, 11.09-188.21) and more gastrointestinal hemorrhage (RR, 13.87; 95% CI, 1.84-104.46)[34]; however, the guideline panel noted that a majority of these events occurred in a single patient, possibly leading to overestimation of harm. Other forms of major bleeding, joint function, mortality, heavy menstrual bleeding, health-related quality of life, need for transfusions, and absence (from school, work, or other required activities) were not reported.

In observational studies with explicit comparative data,[35-43,52] VWF concentrate prophylaxis reduced the risk of bleeding episodes (RR, 0.34; 95% CI, 0.25-0.46), hospitalizations (RR, 0.64; 95% CI, 0.44-0.93), and heavy menstrual bleeding (median change in episodes, −9; interquartile range [IQR], −9.3 to −6.0). VWF concentrate prophylaxis probably reduced the need for blood transfusion, but the estimate was imprecise, and the CI did not exclude the possibility of no difference.

In observational studies without explicit comparative data,[36,38,43-51] the pooled rate of bleeding episodes per patient per year when the patient was receiving prophylaxis was 3.20 (95% CI, 1.96-5.24). The hemostatic efficacy was rated as excellent or good by providers and/or patients for 100% of patients in 3 of the studies and 99.7% of patients in another study. Effects on joint function, mortality, hospitalization, heavy menstrual bleeding, health-related quality of life, transfusions, and absence (from school, work, or other required activities) were not reported.

There were no harms reported with prophylaxis in observational studies with either explicit or implicit comparative data.[35-52] There is very low certainty in the estimate of the risk of adverse effects because of risk of bias and imprecision. There is a hypothetical risk of thrombosis, allergic reaction, or development of an inhibitor to VWF. These were not reported in the available studies. Overall, the certainty of these estimated effects is low because of risk of bias and concerns about imprecision of the estimates (evidence profile provided in supplemental Data 5). Although the evidence is very low certainty for many of the outcomes, and the direction and strength of the observed effect seemed heterogeneous for specific symptoms, the overall direction of the effect of the interventions on the outcomes in the included studies was consistent, prompting the panel to choose "low" for overall certainty of the evidence.

Table 4. VWF concentrate administration

VWF concentrate option	Description
VWF/FVIII concentrate (plasma derived)	Plasma-derived concentrate containing both VWF and FVIII; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg
VWF concentrate (plasma derived)	Plasma-derived concentrate containing VWF alone; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg; if used for emergency treatment, may require addition of FVIII concentrate in patients with low baseline FVIII
VWF concentrate (recombinant)	Recombinant concentrate containing VWF alone; administered IV; typical dosing: 40-80 VWF/RCo activity units per kg; if used for emergency treatment, may require addition of FVIII concentrate in patients with low baseline FVIII

RCo, ristocetin cofactor.

Other EtD criteria and considerations. In a survey of guideline panel members, all panelists suggested that patients are likely to place high value on reducing the risk of bleeding and that the consequences of bleeding for quality of life may play a role in decision making. The frequency and severity of the bleeding events, age of patient, and input from family members and other caregivers will affect decision making by an individual patient. Patients with a higher rate of bleeding are more likely to place a higher value on preventing such bleeding episodes than on avoiding adverse events, whereas those without a significant bleeding history place a lower value on prophylaxis. Most panel members highlighted the importance of discussing the risks and benefits of the various treatment strategies with the patient. Based on this, the panel judged that there is possibly important uncertainty or variability in patients' values and preferences. The panel highlighted the importance of educational materials for patients who are candidates for prophylaxis to help them understand the potential benefits and harms of this treatment strategy. Prophylaxis is associated with high costs because of the expense of VWF concentrate. Additionally, there is a lack of cost-effectiveness studies to assess the overall net health benefit. The panel agreed that prophylaxis was probably acceptable to most individuals, especially in the setting of limited access to emergency/acute care facilities for treatment of acute bleeding episodes. For some events, such as gastrointestinal bleeding, more intensive therapy may be required.[53] Lack of large numbers of women in the cited studies raised questions about the applicability of prophylaxis for heavy menstrual bleeding, but no inherent differences between men and women were observed for other types of bleeds. Specific recommendations for heavy menstrual bleeding are discussed in "Gynecology: heavy menstrual bleeding." Applicability will also vary in pediatric populations because of challenges with venous access and tolerability of injections.

Another important consideration is the use of prophylaxis to prevent joint bleeds and joint damage. Primary prophylaxis is commonly performed in severe hemophilia patients, but this is less common in VWD, although patients with severe VWD can still experience significant joint damage,[54] which may affect quality of life, because physical activity may be limited as a result of bleeding or fear of bleeding.[55]

Conclusions and research needs for this recommendation. The guideline panel determined that there is low-certainty evidence for a net health benefit of using long-term prophylaxis in patients with VWD and a history of severe and frequent bleeds. Based on the body of available evidence, it is likely that long-term prophylaxis reduces the risk of developing recurrent bleeding episodes, such as epistaxis and possibly also the development of spontaneous bleeding and hemarthrosis. There is very low certainty that long-term prophylaxis has an effect on other outcomes. However, because of low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist. The high costs were considered to be worth this net benefit by both clinicians and patients on the panel. Long-term prophylaxis is likely to be acceptable and feasible to implement, and this recommendation is likely to increase equity. Therefore, the desirable consequences are greater than the undesirable consequences. VWF concentrate administration is outlined in Table 4.

The panel identified the following additional research needs: (1) large randomized controlled trials on the use of prophylaxis versus on-demand therapy, particularly in patients with mucosal bleeds; (2) studies on the use of prophylaxis for heavy menstrual bleeding; (3) studies on the use of prophylaxis in gastrointestinal bleeding; (4) studies on the impact of prophylaxis on quality of life; (5) studies on the use of plasma-derived vs recombinant VWF concentrate for prophylaxis; (6) the role of concurrent antifibrinolytic therapy with prophylaxis for mucosal bleeding (eg, epistaxis, heavy menstrual bleeding, and gastrointestinal bleeding); and (7) the role of concurrent antiangiogenic therapies with prophylaxis for gastrointestinal bleeding.

Desmopressin challenge/trial and administration

In patients with VWD, should health care providers perform a desmopressin challenge and choose a treatment of bleeding depending on its results, not perform the desmopressin challenge and treat with VWF concentrate and/or tranexamic acid, or not perform the desmopressin challenge and treat with desmopressin empirically?

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 (eg, 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 in type 2 VWD patients.
- Patients undergoing major surgery, including in sites where even a small amount of bleeding may result in critical organ damage (eg, 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 the 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.[56] Furthermore, desmopressin is generally contraindicated in patients with active cardiovascular disease (eg, 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.[57-59]

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 (eg, free water restriction and education about signs and symptoms of hyponatremia that should lead to prompt medical evaluation) and cardiovascular disease.

Summary of the evidence. We did not find any comparative studies directly addressing the question. We conducted 3 systematic reviews of case series, 1 for each of the intervention arms. We included 21 case series: 8 in which patients underwent a desmopressin trial and were treated based on results,[60-67] 9 in which patients did not undergo a desmopressin trial and were treated with VWF concentrate or tranexamic acid,[26,38,45,68-73] and 4 in which patients did not undergo a desmopressin trial but were treated with desmopressin empirically.[74-77] The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/fnGuafOe504.

Of studies describing use of a desmopressin trial and subsequent treatment according to results, 4 observational studies reported hemostatic efficacy for surgical prophylaxis,[60,63,65,66] 4 observational studies reported postoperative bleeding,[61,62,64,67] 2 observational studies reported hemostatic efficacy for acute bleeding episodes,[60,66] and 2 observational studies reported adverse events of the treatment.[62,67] No studies reported major bleeding, mortality, heavy menstrual bleeding, hospitalization, transfusion, or thrombotic events.

Of studies describing empiric treatment with tranexamic acid or VWF concentrate for surgical prophylaxis without the results of a desmopressin trial, 4 observational studies reported bleeding episodes,[70,71,73,74] 4 observational studies reported hemostatic efficacy,[38,45,69,70] 4 observational studies reported adverse events of the treatment,[38,45,69,70] and 2 observational studies reported need for transfusion.[45,70] Of studies describing empiric treatment with tranexamic acid or VWF concentrate for bleeding episodes without the results of a desmopressin trial, 3 observational studies reported hemostatic efficacy.[38,45,69] Of studies describing empiric treatment with tranexamic acid or VWF concentrate for long-term prophylaxis without the results of a desmopressin trial, 1 observational study reported bleeding episodes and adverse events, and another study reported excessive postpartum bleeding. No studies reported major bleeding, mortality, heavy menstrual bleeding, hospitalization, transfusion, or thrombotic events.

Benefits. The strategy of performing a desmopressin challenge and using the results to determine therapy for surgical prophylaxis resulted in clinicians rating the hemostatic efficacy as excellent, good, or effective in 94% of 211 surgeries (95% CI, 81%-98%).[60,63,65,66] When used to treat bleeding episodes, this strategy resulted in clinician rating of hemostatic efficacy as good or effective for 97% of 29 bleeding episodes (95% CI, 79%-100%).[60,66]

The strategy of forgoing a desmopressin trial and treating empirically with VWF concentrate or tranexamic acid for surgical prophylaxis was udged to have excellent or good hemostatic efficacy in 97% of 205 procedures (95% CI, 88%-99%).[38,45,69,70] When used to treat bleeding episodes, this strategy resulted in clinician rating of hemostatic efficacy as good or effective for 96% of 132 bleeding episodes (95% CI, 91%-98%).[38,45,69] When used for long-term prophylaxis, the strategy of using tranexamic acid only reduced annual oropharyngeal bleeding episodes from 30 to 16.[68]

For the strategy of empiric treatment with desmopressin for surgical prophylaxis without the results of a desmopressin trial, 1 study reported that hemostasis was excellent in 93% of patients with mild type 1 VWD and 73% in patients with moderate type 1 VWD, with a mean hospitalization length of 6.3 days.[76] This strategy, when used to manage acute bleeding episodes, was judged to have excellent efficacy in 83% and good efficacy in 14% of 254 bleeding episodes in patients with mild type 1 VWD.[77] For moderate type 1 VWD, the efficacy was judged as excellent in 71% and good in 18% of 254 bleeding episodes. Mild or moderate VWD was defined

in the study as judged by clinicians based on a combination of laboratory values and bleeding phenotype; however, there were no strict cutoffs reported. In terms of efficacy for management of heavy menstrual bleeding, 1 study reported that 77% of 22 patients responded to the treatment, as measured by a pictorial blood loss assessment chart (PBAC) score of <100. Another study reported efficacy in 92% of patients with heavy menstrual bleeding for a single dose (excellent efficacy) or 2 doses (good efficacy) of desmopressin.[77]

Overall, the certainty in these estimated effects is very low, because of risk of bias in the studies (none of the studies included a control group to make inferences), lack of direct comparison, and imprecision of the estimates (evidence profile provided in supplemental Data 5).

Harms and burden. With a strategy of performing a desmopressin challenge and using the results to determine therapy for surgical prophylaxis, the proportion of surgical events in which patients experienced postoperative bleeding was 6% (95% CI, 0.02-0.14) across 199 surgical events.[61,62,64,67] One study reported that 10 of 41 patients experienced emesis, of whom 5 required hospital admission, and 1 patient developed hyponatremia.[67] In another study, which involved 37 children, all developed some degree of hyponatremia, which was usually mild, but 2 experienced severe hyponatremia and 1 of these patients developed seizures.[62]

With a strategy of forgoing a desmopressin trial and treating empirically with VWF concentrate or tranexamic acid for surgical prophylaxis, the pooled risk of bleeding episodes was 9% across 247 procedures (95% CI, 2%-34%).[70,71-73] Adverse events related to treatment were reported in 2% of 205 surgical procedures (95% CI, 0%-31%); none was deemed serious.[38,45,69,70] The need for transfusion was 11% across 55 surgeries (95% CI, 5%-22%).[45,70] In patients receiving tranexamic acid, headaches (60%), back pain (30%), and musculoskeletal pain (40%) were reported. Excessive postpartum bleeding occurred in 1 (6%) of 17 deliveries.

For the strategy of forgoing a desmopressin trial and treating empirically with desmopressin for surgical prophylaxis, hyponatremia was noted in 4% to 72% of patients, although the definition of hyponatremia varied across the 3 studies.[75,78,79] Empiric desmopressin therapy resulted in either headache (9%), facial flushing (9%), or both (4.5%). When desmopressin was used for surgical prophylaxis or treatment of acute bleeding, mild to moderate adverse events, such as headache, flushing, nausea, dizziness, asthenia, vomiting, and peripheral edema, were reported in 43% of patients with mild type 1 VWD and 14% of those with moderate type 1 VWD.[77]

There is very low certainty in the estimate of the risk of adverse effects because of lack of comparative studies, inconsistency of results, and small sample sizes. The guideline panel judged that the undesirable effects either of conducting a desmopressin trial with treatment based on results or of forgoing a desmopressin trial and treating with VWF concentrate or tranexamic acid are small but still important. The panel judged the undesirable effects of empiric use of desmopressin without a pretreatment trial to confirm response as moderate in comparison. The guideline panel was specifically concerned about the possibility of expecting an effect of therapy when actual response to that therapy is unknown and that of worsened thrombocytopenia in patients with type 2B VWD receiving desmopressin.

Other EtD criteria and considerations. The panel agreed there was possibly important uncertainty or variability in patient values, because there are patients who place a high value on the potential benefits of the desmopressin trial, whereas others place a high value on avoiding the adverse effects of desmopressin. According to judgments made by the panel, the approach of carrying out a desmopressin challenge and treating based on the results and that of forgoing a desmopressin challenge and treating with VWF concentrate or tranexamic acid are likely to be more effective and less harmful than empiric use of desmopressin with uncertain efficacy in an individual patient. Although performing the desmopressin trial requires additional resources, such as medication costs, laboratory testing, facility fees, and nursing administration costs, these costs are likely balanced by avoiding the high cost of VWF concentrate in patients for whom desmopressin is an appropriate therapy. Risks of severe adverse effects, such as myocardial infarction or hyponatremic seizures, are of greater concern when efficacy is in doubt. Desmopressin has been reported to be safely used during pregnancy in women with bleeding disorders and diabetes insipidus.[57,80,81]

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty in the evidence for a net health benefit of performing a desmopressin challenge and using the results to determine therapy and very low certainty in the evidence for a net health harm from treating with desmopressin in the absence of desmopressin trial results. Based on the body of available evidence, it is likely that a desmopressin trial reduces the risk receiving a treatment that may not be effective.

Practical considerations for performing a desmopressin challenge are outlined in Table 5.

The panel identified the following additional research needs: (1) evaluating the logistics and impact on patients of performing desmopressin challenges (eg, the need to take off a day from work or school or potential adverse effects experienced during desmopressin administration) and (2) evaluating the best time points for an intranasal trial vis-à-vis an IV trial.

Antithrombotic therapy

In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, should such treatment be provided?

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.

Table 5. Practical considerations for desmopressin trial/challenge and administration

Domain	Description
Route	Desmopressin trials may be performed with either IV or intranasal desmopressin, but intranasal desmopressin trials may not be successful because of issues with administration and/or absorption. Subcutaneous administration has also been used.
Dose	IV desmopressin is given as 0.3 μg/kg, with a maximum dose of 20 μg. The desmopressin 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 should be determined immediately before administration of desmopressin, ~30-60 min after administration of desmopressin, and ~4 h postadministration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	There are multiple definitions of desmopressin responsiveness.[128-130] The panel considered that 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 were required to consider the patient responsive to desmopressin. Desmopressin responsiveness does not guarantee, however, that the level achieved is adequate to prevent bleeding in all procedures (eg, higher levels may be indicated based on type of procedure).
Precautions	Because of the risk of hyponatremia, desmopressin should not be given on >3 concurrent days and is generally not administered to children age <2 y. In addition, tachyphylaxis occurs after repeated infusions. Caution is advised when desmopressin is used in patients with active cardiovascular disease. Additionally, desmopressin trials should be avoided in pregnancy.

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 (eg, 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 (eg, coronary heart disease, cerebrovascular disease, and peripheral vascular disease) and/or increased risk of thrombosis.

Summary of the evidence. We did not find any comparative studies addressing the question. We conducted a systematic review of case series of patients with VWD who received antiplatelet agents or anticoagulant therapy. We found 2 case series reported in 3 sources.[82-84] The guideline panel was surveyed to systematically collect panel members' experience in dealing with this issue. In addition, the panel discussed a case series of 19 patients with VWD who experienced an arterial thrombotic event and were treated with antiplatelet agents or anticoagulant therapy. This case series was not included in the original systematic review, because it did not meet inclusion criteria, but the panel considered that it provided important context for the discussion.[85] The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/DZVC2VsFcdI.

Benefits, harms, and burden. Because no studies directly compared treatment with antiplatelet agents or anticoagulant therapy vs no treatment, risk estimates for benefits are not available. In an 8-patient case series, 1 patient with hemophilia died after experiencing intracranial posttraumatic bleeding while on aspirin; however, this was after 11 years on therapy. Across 2 observational studies, none of 6 patients receiving low-molecular-weight heparin or warfarin experienced thromboembolic events.[83,84] In the 26 patients with VWD in the series, there was 1 major bleeding event. Serious adverse events, hospitalization, transfusion, health-related quality of life, and heavy menstrual bleeding were not reported. The desirable effects of anticoagulation in the setting of cardiovascular disease were judged to be large, whereas the undesirable effects were judged to be moderate, with variability in the latter resulting from type of anticoagulant and individual bleeding phenotype. Guideline panelists collectively reported their experience managing 65 patients with VWD who were recommended to receive antiplatelet agents or anticoagulant therapy for cardiovascular disease. In the 56 patients who received this therapy and in the 9 patients who did not receive therapy even though it was recommended, the median mortality, thrombotic events, serious adverse events, hospitalizations, and bleeding were low in both arms, and most patients were reported by their clinicians to have an acceptable health-related quality of life. Overall, the quality of the evidence for desirable and undesirable effects was judged to be very low because of serious risk of bias in case series (lack of a control group), small number of patients and events (imprecision), and lack of direct comparisons.

Other EtD criteria and considerations. Panel members emphasized the need for shared decision making with patients considering antiplatelet agents or anticoagulant therapy, and there was a perception among panel members that there is likely to be important variability among patients regarding how they perceive the tradeoff of risks and benefits of these therapies as well as variation in underlying bleeding risk. Strict adherence to optimal postoperative care is important to minimize bleeding risk. There may be important variability in patient values and in values of providers (eg, hematologists vs cardiologists).

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the evidence for a net health benefit from using antiplatelet agents or anticoagulant therapy in patients with VWD in whom these therapies are otherwise indicated for treatment of cardiovascular disease. Based on the body of available evidence, it is likely that antiplatelet agents and anticoagulant therapy reduce the risk of developing thromboembolic complications in cardiovascular disease. There is very low certainty that there is an effect of antiplatelet agents and anticoagulant therapy on other outcomes. However, because of low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

Given the potentially large benefits seen with these therapies in large studies of cardiovascular disease in patients without VWD but moderate harms in health outcomes as well as the important uncertainty and variability regarding how patients view the tradeoff of these outcomes, the panel judged that the balance

of effects probably favors the use of antiplatelet agents or anticoagulants. It is important to understand that the disease course for patients is dynamic, and the risk of complications for patients with cardiovascular disease increases over time. The panel highlighted the importance of the cardioprotective effects of therapy with antiplatelet agents and anticoagulant therapy, if otherwise indicated, and noted that a personalized treatment plan (eg, administration of VWF concentrate for prophylaxis) should be developed, along with patient education.

Consideration should be given to use of interventions that would limit the length of antiplatelet or anticoagulant therapy required (eg, non–drug-eluting stents). It should also be noted that bleeding is more of a risk in type 2 or type 3 VWD patients, as well as those with type 1 VWD in addition to another condition, such as FXI deficiency or a platelet function defect. Prophylaxis with VWF concentrate or addition of tranexamic acid may be required in patients with a severe bleeding phenotype to minimize bleeding.

The panel identified the following research priorities: (1) studies on the use of prophylaxis in VWD patients receiving antiplatelet agents or anticoagulant therapy; (2) studies on the incidence of cardiovascular disease in patients with VWD; and (3) in the setting of coronary artery stent placement, studies on the risks and benefits of a bare metal stent with a shorter course of antiplatelet therapy vs a drug-eluting stent and a longer course of antiplatelet therapy.

Major surgery

In patients with VWD undergoing major surgery, should the FVIII level be kept at ≥0.50 IU/mL for at least 3 days after surgery, or should the VWF activity level be kept at ≥0.50 IU/mL for at least 3 days after 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.

Summary of the evidence. We did not find any comparative studies addressing this question, so we conducted a targeted search for case series in which patients with VWD underwent major surgery, with researchers reporting both FVIII and VWF activity levels on postoperative day ≥3. The evidence synthesis contained 7 case series reporting data for patients with a variety of VWD types/subtypes and various procedures, including total hip and knee arthroplasty and vascular, obstetric/gynecologic, abdominal, and minor dental procedures.[37,45,46,86-89] The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/uhLux9nrMLM.

Benefits, harms, and burden. Because of the heterogeneity in reporting, we could not conduct metaanalyses. One series reported a mean FVIII activity level of 1.344 IU/mL and a mean VWF activity of 0.924 IU/mL, for which hemostatic efficacy was excellent in 92%, good in 4%, and poor in 4%.[46] There were no postoperative bleeding complications, adverse events related to therapy, or thrombotic events. Another series reported a median FVIII level of 1.15 IU/mL (IQR, 0.97-1.34 IU/mL) and a median VWF level of 0.85 IU/mL (IQR, 0.67-1.03 IU/mL), with hemostatic efficacy in 100% and without any thrombotic events.[45] No other studies reported significant adverse events.

Based on the limited available evidence, the panel could not make a judgment regarding the magnitude of the desirable or undesirable anticipated effects of maintaining a FVIII activity level of ≥0.50 IU/mL for at least 3 days after major surgery compared with maintaining a VWF activity level of ≥0.50 IU/mL for at least 3 days after major surgery. Overall, the certainty in the available evidence is very low, because there are no comparative studies addressing this question, and only case series were available as indirect evidence.

Other EtD criteria and considerations. The panel discussed the resources required to maintain these target levels. In a survey before the panel met to make recommendations, panelists estimated that the cost of maintaining an FVIII or VWF activity level of ≥0.50 IU/mL for 3 days was between US$5000 and US$12 000, depending on the weight of the patient. Many panelists were uncertain about the total costs, because they would also need to take into account other factors, such as laboratory monitoring. Because laboratory testing would be necessary in either scenario, the panel judged there to be no important difference in cost between the 2 interventions.

In the survey, panelists noted that some patients may feel uncertainty about maintaining only 1 level >0.50 IU/mL instead of both levels. There was considerable variability in opinion among panel members about whether this would be acceptable. Additionally, panel members highlighted the difference regarding the feasibility of testing across institutions (eg, FVIII activity, VWF/ristocetin cofactor, VWF/glycoprotein Ib, or other activity assays), with poor turnaround times for some laboratory testing options. Local availability of rapid results is critical for managing patients with VWD during the postoperative period, and recommending a test with limited availability at a particular hospital might result in decreased quality of care.

For the purpose of this question, major surgery was considered to include procedures requiring surgical opening into the large body cavities, procedures where severe hemorrhage was possible, interventions involving joints, third-molar extractions, and interventions where the patient's life was at risk. Minor surgery was considered to include procedures involving simple dental extractions and other outpatient procedures not otherwise specified under major surgery.

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty in the evidence for a net health harm from maintaining only FVIII activity at ≥0.50 IU/mL as a target for at least 3 days after major surgery and suggests maintaining both FVIII and VWF activity levels at ≥0.50 IU/mL for at least 3 days after major surgery. Even though maintaining only FVIII at ≥0.50 IU/mL is likely to be more feasible to implement, there are several threats to feasibility and acceptability that make it unlikely that clinicians would choose only 1 of the options. Although maintaining only the FVIII level >0.50 IU/mL for at least 3 days after surgery may be logistically easier, especially in centers with long VWF activity level assay turnaround times or limited access to VWF concentrate compared with FVIII preparations, administering only FVIII concentrate will not result in a sufficient increase in FVIII (because VWF serves as the carrier protein for FVIII) and will not address the underlying VWF defect. Maintaining VWF activity levels at ≥0.50 IU/mL allows VWF to participate in multiple physiologic roles in hemostasis and in most cases will simultaneously maintain FVIII activity levels at ≥0.50 IU/mL during the critical time in the perioperative setting. Patients with specific subtypes of VWD, such as type 2 and type 3, may not achieve adequate hemostasis if only FVIII levels are maintained after surgery. Therefore, the panel suggests keeping both the VWF activity level and FVIII activity level ≥0.50 IU/mL for at least 3 days in patients undergoing major surgery. It should also be noted that local measures during surgery may be helpful, including use of hemostatic gelatin sponges, fibrin glue, and/or local tranexamic acid application.[90] Some institutions have limited testing capacity, with no availability of real-time FVIII or VWF monitoring. In such cases, patient safety should be considered, and elective high-risk procedures may require alternate arrangements, such as moving the procedure to a different facility. Alternatively, a pharmacokinetic study using the planned preoperative dose can be performed in advance to determine the optimal dose at the time of the surgery.[91]

The panel identified the following additional research need: a randomized clinical trial to determine whether maintaining either the FVIII or VWF activity level at >0.50 IU/mL for at least 3 days after surgery leads to different outcomes, with particular attention to and stratification by type of procedure and associated bleeding risk. Furthermore, standardized definitions of major vs minor surgery and outcomes (eg, major and minor bleeding) as they apply to VWD patients will be critical to future research studies.

Minor surgery/invasive procedures

In patients with VWD undergoing minor surgery or minor invasive procedures, should the VWF level be increased to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin), should tranexamic acid monotherapy be used, or should combination therapy by increasing the VWF level to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin) in conjunction with tranexamic acid be used?

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 ⊕○○○).

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 ⊕○○○).

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 (eg, 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 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 (eg, gelatin sponges or fibrin glue, tranexamic acid rinse) as part of an individualized procedural plan.

Summary of the evidence. We found 2 randomized clinical trials comparing the use of factor concentrate with tranexamic acid vs factor concentrate alone and no randomized clinical trials or comparative observational studies addressing the other 2 comparisons of interest.[92,93] Although these 2 studies were performed in patients with hemophilia, the panel considered the studies as indirect evidence to assess benefits, harms, and risks of antifibrinolytic therapies in patients with a bleeding disorder. In addition, we found 8 case series in which patients received factor replacement therapy alone[94-102] and 4 case series in which patients received tranexamic acid alone.[103-106] Outcomes evaluated included major bleeding, need for additional hemostatic agents, need for additional surgical procedures, serious adverse events, mortality, hospitalization, transfusion, and inability to perform the surgery. The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/MQUjqirt10c.

Benefits, harms, and burden. Using factor concentrate or desmopressin alone to increase VWF levels to ≥0.50 IU/mL was associated with significantly higher risk of postoperative bleeding (n = 59; RR, 6.29; 95% CI, 2.12-18.65) compared with combination therapy consisting of tranexamic acid with either of these therapies.[92,93] The relative effect for major bleeding and adverse effects related to the treatment were not estimable. Mean operative blood loss was

84.1 mL (range, 4-323 mL) in those with an increase in FVIII activity to ≥0.50 IU/mL (n = 14) and 61.2 mL (range, 1-749 mL) in those with an increase in FVIII activity to ≥0.50 IU/mL in conjunction with tranexamic acid (n = 14; $P = .02$).

Evaluation of the strategy of increasing VWF levels to at least 0.50 IU/mL by any therapy without the use of tranexamic acid showed that bleeding complications occurred in 11% of 281 surgeries (95% CI, 6%-19%).[95,96,98,100-102] Hemostasis was judged by providers to be appropriate in 98% of procedures (95% CI, 91%-99%),[97,99,102] and the proportion of participants who required factor replacement postoperatively was 54% (7 of 13).[101] No thrombotic events were reported in the 3 studies that assessed for this outcome.[95,97,102] Approximately 2% of patients developed factor inhibitors (95% CI, 0%-21%).[98,99] Four studies reporting adverse events reported no allergic reactions, wound infections, or other adverse events, except for in a single patient with a vasovagal episode that required hospitalization for observation.[95,99,100,102]

For tranexamic acid alone, the pooled analysis demonstrated bleeding in 14% of surgeries (95% CI, 9%-20%), with a mean hospital stay of 4 days.[103-106]

Overall, the certainty of these estimated effects is very low because of risk of bias, indirect comparisons in the studies, and imprecision of the estimates (evidence profile provided in supplemental Data 5).

Other EtD criteria and considerations. The panel discussion reflected variability in how patients and clinicians view the tradeoff between potential adverse effects and benefits. The patients on the guideline panel placed a high value on avoiding adverse effects, whereas clinicians placed a high value on avoiding bleeding complications. Based on the likelihood of desirable effects on hemostasis and the potential for adverse effects, the panel ranked 2 interventions (increasing VWF level to at least 0.50 IU/mL with any intervention and tranexamic acid and increasing the VWF level to 0.50 IU/mL with any intervention) as having the best balance of effects.

When making the judgment of which treatment strategy would be most effective, the panel specifically considered patients with severe bleeding phenotypes. However, the panel noted that not all patients require an increase in VWF level to 0.50 IU/mL in conjunction with tranexamic acid to have good outcomes. The panel agreed that tranexamic acid has the least harmful undesirable effects in comparison with therapies used to increase VWF levels, which have the potential to induce inhibitor formation or hypersensitivity reactions during infusion.

The panel also discussed the possibility that when 2 interventions are prescribed, there may be an additive effect with regard to adverse effects. This led the panel to judge increasing the VWF level to 0.50 IU/mL with any intervention in conjunction with tranexamic acid as most harmful. However, the panel noted that none of the 3 treatment options are likely to result in frequent and important harms.

Although tranexamic acid was the primary antifibrinolytic considered by the panel, we recognize that ε aminocaproic acid is a reasonable alternative, particularly when used as an oral rinse in dental procedures or as a liquid administration in the pediatric population.

Conclusions and research needs for these recommendations. Based on the body of available evidence, it is likely that tranexamic acid combined with achieving VWF levels of at least 0.50 IU/mL with desmopressin or factor concentrate reduces the risk of postoperative bleeding. There is very low certainty that there is an effect of this strategy on major bleeding or adverse effects related to treatment. However, because of low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

The evidence suggests that achieving VWF levels of at least 0.50 IU/mL by any therapy in conjunction with tranexamic acid would provide the most desirable effects with regard to hemostasis. Given that they have similar balances of effects, the recommendation for increasing VWF 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 places a high value on the synergistic effects of both VWF concentrate and tranexamic acid together, given the different mechanisms of action as well as the minimal adverse effect profile of tranexamic acid.

The recommendation for giving tranexamic acid alone vs increasing VWF levels to >0.50 IU/mL with any intervention in patients with type 1 VWD with levels of >0.30 IU/mL and a mild bleeding phenotype undergoing a minor mucosal procedure places a high value on the small amount of resources required, the feasibility of prescribing tranexamic acid in a scenario in which the likelihood of bleeding episodes is low, and the avoidance of the burden and costs associated with administering factor concentrate in these patients.

The panel identified the following additional research needs: (1) studies on the use of tranexamic acid vs no tranexamic acid in specific procedures and (2) studies to determine whether there are differences in outcome by procedure, anatomic site, tranexamic acid formulation, or VWD subtype.

Gynecology: heavy menstrual bleeding

In women with VWD with heavy menstrual bleeding, should tranexamic acid, hormonal therapy (ie, levonorgestrel-releasing intrauterine system or hormonal contraceptives), or desmopressin be prescribed?

Recommendation 6a

The panel *suggests* using either hormonal therapy (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 ⊕○○○).

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 (eg, 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.

Summary of the evidence. We found 2 comparative studies: 1 randomized clinical trial comparing tranexamic acid with desmopressin[107] and 1 observational study comparing hormonal therapy with desmopressin.[74] In addition, we found 5 case series about a levonorgestrel-releasing intrauterine system.[108-112] We also surveyed panel members to gather data on their experience. The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/2xCXJKkZZBI. This discussion centers on first-line treatment of heavy menstrual bleeding.

Benefits, harms, and burden. There were no comparative data for evaluating tranexamic acid vs hormonal therapy. A comparison of tranexamic acid and desmopressin showed that the mean difference in menstrual blood loss as measured by PBAC was 41.6 points higher with desmopressin than with tranexamic acid (19.6 vs 63.6).[107] Quality of life, as assessed through several instruments, was not explicitly compared between the groups. Although both quality-of-life domain and instrument scores went up with both interventions, this was not statistically significant. Comparative adverse effects were not estimable between tranexamic acid and desmopressin.

There was no difference between desmopressin and hormonal therapy as assessed by alleviation of symptoms (RR, 0.90; 95% CI, 0.66-1.23).[74] Menstrual flow as assessed by PBAC was 0.9 points higher in the desmopressin group than in the hormonal therapy group (95% CI, 9.89 lower to 11.69 higher). There were no adverse events reported.

Noncomparative data regarding a levonorgestrel-releasing intrauterine system suggested control of heavy menstrual bleeding as assessed by PBAC score, improved health-related quality of life, improvement in hemoglobin values, and shortened duration of menstruation.[110,111] The expulsion rate for a levonorgestrel-releasing intrauterine system was 15%, and the malposition rate was 10%.

Overall, the certainty of these estimated effects is very low because of risk of bias and indirect comparisons in the studies and imprecision of the estimates (evidence profile provided in supplemental Data 5).

Other EtD criteria and considerations. In a survey of panel members before the meeting, responses varied as to whether women with heavy menstrual bleeding would find all treatment options acceptable. Personal values and beliefs regarding hormonal therapy may make these more or less acceptable to some women. Adverse effects of desmopressin would lower its acceptability. The panel also discussed how early experiences with and potential adverse effects of hormonal contraception may affect acceptability. Quality of life may be most improved with hormonal contraception or a levonorgestrel-releasing intrauterine system. Many physicians are familiar with oral contraceptive pills and tranexamic acid but may be less familiar with a levonorgestrel-releasing intrauterine system. The panel discussed the possibility that the acceptability of tranexamic acid would be the greatest because it has the fewest adverse effects among the treatment options. However, in patients who bleed for a prolonged number of days or who have irregular bleeding, tranexamic acid may not be as desirable. In transgender patients, specific hormonal therapies may be less acceptable or contraindicated as part of their gender-affirming therapy plan. The potential for spotting with the etonogestrel implant, particularly in the setting of an underlying bleeding disorder, limited enthusiasm for this option. Specific recommendations regarding use of VWF concentrate for prophylaxis are addressed in "Prophylaxis."

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty in the evidence for a net health benefit of using either hormonal therapy (CHCs or levonorgestrel-releasing intrauterine system) or tranexamic acid to reduce heavy menstrual bleeding in women with VWD. Based on the body of available evidence, it is likely that either hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or tranexamic acid improves health-related quality of life, hemoglobin levels, menstruation duration, and absence from school, work, or other required activities. However, because of

low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

The panel judged tranexamic acid as having the least harmful undesirable effects in comparison with hormonal therapy and desmopressin. Based on the evidence and their experience, the panel agreed that an intrauterine device (IUD) and CHC are similar. IUDs are less likely to result in systemic adverse effects than CHC; however, IUDs require insertion, which might result in complications. When compared with those of tranexamic acid and desmopressin, the potential harms of an IUD and CHC were judged as intermediate. Even when it is properly positioned, expulsion of a levonorgestrel-releasing intrauterine system may occur more frequently in women with bleeding disorders, possibly because of increased menstrual bleeding during the first few periods after insertion. The evidence, however, suggests that the rate of expulsion is low. A potential adverse effect of hormonal IUDs is an increase in the risk of simple ovarian cysts, which are generally asymptomatic and self-limited, although some patients may require modification of therapy. CHC also reduces the risk of ovarian hemorrhage by suppressing ovulation. The panel discussed the fact that that even though the studies included are the only evidence available that may be relevant to inform this recommendation, they are indirect.

The recommendation for women who wish to conceive (Recommendation 6b) derives from the previous recommendation (Recommendation 6a), given that hormonal therapy is not an option for these women.

For patients with frequent and severe bleeding events, we refer to the evidence and recommendations in "Prophylaxis" as to whether prophylaxis should be considered part of an individualized therapy plan.

The panel identified the following additional research needs: (1) studies on the use of combined therapy vs single therapy (efficacy and safety of the combination of hormonal therapy with tranexamic acid), (2) studies assessing patients' values and preferences regarding the benefits and harms of various contraceptive methods, and (3) a prospective study of a levonorgestrel-releasing intrauterine system in terms of acceptability rates, spotting rate, and risk of expulsion or malposition.

Obstetrics: neuraxial anesthesia

In women with VWD who require or desire neuraxial anesthesia during labor, should VWF concentrate be administered to achieve a VWF activity level of 0.50 to 1.50 IU/mL or >1.50 IU/mL?

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 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 (eg, compression stockings or low-molecular-weight heparin) should be provided when needed.

Summary of the evidence. We did not find any comparative studies addressing this question. We included evidence from 5 case series.[113-117] In addition, we systematically collected the experience of panel members when facing this clinical scenario. The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/YAaXuhNm_Ac.

All studies reported the effect of neuraxial anesthesia on development of complications, including hypotension, dural puncture, inadequate analgesia, bloody tap, or failed block. No studies reported the risk of major bleeding, adverse events, spinal hematoma, thrombosis, or mortality.

Benefits, harms, and burden. The pooled proportion of complications of the epidural procedure was 6% (5 of 83 deliveries). In 4 studies, the types of complications were not reported. In 1 study, reported complications included hypotension, accidental dural puncture, inadequate analgesia, bloody tap with no additional complications, and failed block requiring general anesthesia. In the only series to report failed procedures, the rate was 2.4% (1 of 41 deliveries). Guideline panelists reported their collective experience with 110 women whose VWF levels were increased to 0.50 to 1.50 IU/mL and 34 women whose levels were increased to >1.50 IU/mL. In both groups, 100% of women were able to receive the epidural procedure. Compared with women achieving levels of >1.50 IU/mL, women who achieved levels of 0.50 to 1.50 IU/mL were more likely to

have major bleeding (2.7% vs 0%), serious adverse events in the mother (2.7% vs 0%), and postpartum hemorrhage (17% vs 5.9%) and to receive transfusion (10% vs 0%). There were no spinal hematomas, maternal deaths, or adverse events in the child reported in either group. Although the survey of guideline panelists' experience suggested better outcomes with a higher target VWF level, the panel did not feel it was substantial enough to justify recommending the higher target, given the lack of adequate published evidence available to make judgments about how the desirable effects and harms of the options compare (evidence profile provided in supplemental Data 5).

Other EtD criteria and considerations. The panel judged that there is possibly important uncertainty or variability in patient values and preferences, with some individuals placing a high value on avoiding bleeding and others a higher value on avoiding thrombotic complications. The panel also discussed the fact that values may vary in patients with more significant bleeding phenotypes and certain VWD subtypes, particularly types 2 and 3. Targeting a higher level would increase costs of therapy and result in potential delays if a specific VWF level were required before the procedure.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the evidence for a net health benefit for targeting VWF levels of 0.50 to 1.50 IU/mL in women with VWD for whom neuraxial anesthesia is deemed suitable during labor. Based on the body of available evidence, there is very low certainty that there is an effect of targeting VWF levels of 0.50 to 1.50 IU/mL on outcomes, such as major bleeding and spinal hematoma. However, because of low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

Given that there is no evidence to support a judgment on how the options compare with regard to their effects on epidural health outcomes, the recommendation for targeting VWF levels of 0.50 to 1.50 IU/mL over targeting a level of >1.50 IU/mL in women with VWD in labor who require or desire epidural treatment places a high value on increasing health equity and the lower cost of targeting levels of 0.50 to 1.50 IU/mL. Recent research suggests that targeting higher VWF levels may be beneficial in preventing PPH.[118] Moreover, although higher factor levels may reduce PPH, some indirect data suggest correlation between the presence of an epidural itself and higher risk of PPH. Women who have neuraxial anesthesia are more likely to have a longer second stage of labor, increased need for oxytocin, and higher rate of instrumental deliveries. There may be a larger potential risk of thrombosis when VWF levels are >1.50 IU/mL than when they are 0.50 to 1.50 IU/mL.

The panel identified the following additional research needs: (1) studies evaluating whether patients with type 2 or 3 VWD completely correct defects in hemostasis and whether there are differences in this correction between plasma-derived and recombinant VWF replacement therapies; (2) studies to determine the role of platelet-derived VWF in hemostasis during pregnancy, particularly in the settings of labor, delivery, and postpartum hemorrhage; (3) development and evaluation of clinical testing to ensure adequate primary hemostasis and determine whether therapy can be guided by these tests to improve outcomes; and (4) studies to directly compare delivery and neurologic outcomes in women with VWD who are treated to achieve different target VWF and FVIII levels, specifically evaluating the difference between a target level of ≥0.50 IU/mL and a target level of ≥1.50 IU/mL.

Obstetrics: postpartum management

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

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 25 mg/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.

Summary of the evidence. We found 2 studies that addressed this question, both retrospective cohorts.[118,119] 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. The EtD framework for this recommendation is available online at https://guidelines.ash.gradepro.org/profile/Z0HQ-0k8FJE.

Benefits, harms, and burden. Tranexamic acid reduced the risk of secondary postpartum hemorrhage (RR, 0.42; 95% CI, 0.20-0.91). Tranexamic acid may also reduce the risk of primary postpartum hemorrhage (RR, 0.25; 95% CI, 0.04-1.75), severe primary postpartum hemorrhage (RR, 0.36; 95% CI, 0.05-2.59), need for blood transfusion (RR, 0.24; 95% CI, 0.01-4.23), and vaginal hematoma (RR, 0.34; 95% CI, 0.02-6.39), but the estimates were imprecise, and CIs did not exclude the absence of an effect. Adverse events in the mother, such as thrombosis, were not estimable; however, given the available evidence, the guideline panel considered the risk of adverse effects to be most likely small.

Overall, the certainty of these estimated effects is very low because of risk of bias and inconsistency in the studies' findings and imprecision of the estimates (evidence profile provided in supplemental Data 5).

Other EtD criteria and considerations. In a survey of panel members before the meeting, all of them said they believed tranexamic acid is a treatment that patients would accept. It was judged that no important uncertainty existed around values. They noted that some women, however, may be concerned about potential adverse effects of tranexamic acid while breastfeeding as a major threat to acceptability and that patients need to be reassured that tranexamic acid is safe in this situation.[120,121]

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in the evidence for a net health benefit from using tranexamic acid. Based on the body of available evidence, it is likely that tranexamic acid reduces the risk of developing secondary postpartum hemorrhage

and possibly also the risks of developing primary postpartum hemorrhage, severe primary postpartum hemorrhage, and vaginal hematoma, and of requiring blood transfusion. There is very low certainty that there is an effect of tranexamic acid on other outcomes. However, because of low certainty in the evidence or no published information about other outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.

The recommendation for using tranexamic acid in women with VWD during the postpartum period places a high value on the benefits of prevention and treatment during significant life-threatening hemorrhages and the small harms of the intervention. The intervention is not costly, and it is acceptable to key stakeholders and feasible to implement.

The panel deliberated as to whether this recommendation should be a strong recommendation, given the possibility of preventing life-threatening bleeding in the setting of very minimal risk. However, a majority could not agree on a strong recommendation because of the lack of high-certainty evidence.

As noted in "Obstetrics: neuraxial anesthesia," the ideal VWF activity level to prevent postpartum hemorrhage is not known, but it is important to note that women who do not have VWD often achieve VWF activity levels of >1.50 IU/mL by the time of delivery, which raises the question of whether women with VWD are at greater risk of postpartum hemorrhage if they do not achieve these same physiologic levels.

The panel identified the following additional research needs: (1) research on the efficacy of tranexamic acid in the prevention and treatment of PPH in women with VWD, including the optimal duration of therapy (and assessing the benefit of tranexamic acid in relation to the prepartum bleeding phenotype); (2) a clinical trial on prevention of PPH; and (3) basic science research on understanding fibrinolysis in women during the postpartum period.

What are others saying, and what is new in these guidelines?

The VWD guidelines discussed here are 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.[18]

The 2014 UK guidelines for diagnosis and management of VWD have many similar recommendations to those stated here.[122] These include use of prophylaxis for all patients with significant bleeding, a desmopressin trial for patients with type 1 (or type 2A, 2B, or 2N) VWD, hormonal management for heavy menstrual bleeding, and use of neuraxial anesthesia with a VWF level of >0.50 IU/mL. In those guidelines, type 1 VWD was defined as a VWF level of <0.30 IU/mL. Desmopressin with or without tranexamic acid was recommended for minor surgery, such as dental work with an inferior dental block. FVIII levels of ≥0.50 IU/mL were recommended for the postoperative period and VWF activity levels of ≥0.50 IU/mL in the perioperative setting. The discussion in the UK guidelines highlights evidence for 6 days and for 7 to 10 days but does not ultimately comment on the specific number of days required. This may vary by type of surgery and requires attention to a specific patient's surgical and bleeding history.

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 anesthesia.[123] 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.

Our guidelines do differ from the UK and National Heart, Lung, and Blood Institute guidelines somewhat in that the strength of the evidence is discussed, and 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.

These guidelines focus on the most common inherited forms of VWD; however, we would like to highlight the recently published guidelines on the diagnosis and management of platelet-type VWD from the ISTH Platelet Physiology Subcommittee[124] and several recent reviews on acquired von Willebrand syndrome.[125,126]

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, the collaborating organizations will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions based on literature searches.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[127]

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Authorship

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