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# von Willebrand disease: A guide for the internist

## ABSTRACT

von Willebrand disease (VWD), the most common inherited bleeding disorder, results when patients either do not make enough von Willebrand factor (VWF) or make defective VWF. The pathophysiology of this disorder is complex but needs to be understood to interpret the diagnostic tests. Most patients have mild to moderate symptoms and can be adequately counseled and managed by a general internist, but some need to consult a hematologist. We review the pathophysiology of VWD, its subtypes, common presentations of each subtype, diagnostic testing, and management of mild as well as severe clinical manifestations of VWD.

## KEY POINTS

VWD is seen in both inpatients and outpatients. Most patients present with mild to moderate bleeding symptoms and can be adequately managed by a general internist, but in some cases referral to a specialist should be considered.

Specialized diagnostic tests are difficult to interpret and require knowledge of the underlying mechanisms of VWD and its various subtypes.

Treatment of VWD should be tailored to the acuity and severity of the clinical presentation.

VON WILLEBRAND DISEASE (VWD) is an inherited bleeding disorder caused by low levels of or defects in von Willebrand factor (VWF), a key molecule in clotting. It is the most common inherited bleeding disorder and is estimated to affect approximately 1% of the general population.[1] However, only some of those affected ultimately develop clinically significant disease, and many never receive a formal diagnosis. VWD occurs with equal frequency in men and women, although women are more likely to experience symptoms because of increased bleeding during menstruation and pregnancy and after childbirth.[2]

Acquired von Willebrand syndrome is much rarer and occurs when secondary processes lead to a functional impairment of VWF,[3] by either decreasing its quantity or interfering with the hemostatic pathway. Its exact incidence is unknown, but it has been associated with several disease states, including autoimmune disease, hematologic malignancies, solid tumors, metallic heart valves, and high-vascular flow states, such as in patients with ventricular assist devices or receiving extracorporeal membrane oxygenation.[4,5]

Clinical presentations of both acquired and inherited VWD can range from mild mucocutaneous bleeding to severe subcutaneous or intra-articular bleeding. Its diagnosis and management rely on taking an accurate history and interpreting complex diagnostic tests.

This review discusses in detail the clinical, diagnostic, and management considerations for VWD and its various subtypes.

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**TABLE 1**
**International Society of Thrombosis and Haemostasis classification of von Willebrand disease**

| Type | VWD type 1 | | VWD type 2 | | | | VWD type 3 |
|---|---|---|---|---|---|---|---|
| Subtype | Classic | 1C | 2A | 2B | 2M | 2N | |
| Frequency | Common (70% of cases) | | Uncommon (25% of cases) | | | | Rare (5% of cases) |
| Pathophysiology | Mutations result in partial quantitative deficiency of functionally normal VWF | | Qualitative defects in VWF | | | | Almost complete quantitative deficiency of VWF |
| Specific mechanism | Decreased synthesis of VWF due to various genetic mutations | Increased clearance of available VWF in circulation | Mutations result in fewer glycoprotein Ib binding sites and less effective platelet clot formation | Mutations increase affinity of glycoprotein Ib binding site and clearance of high-molecular-weight multimers | Mutations decrease affinity of glycoprotein Ib site or decrease VWF-collagen interaction | Mutation in factor VIII binding site decreases affinity of VWF for factor VIII | |
| Inheritance | Autosomal dominant | Autosomal dominant | Autosomal dominant | Autosomal dominant | Autosomal dominant | Autosomal recessive | Autosomal recessive |
| Clinical phenotype | Mild to moderate mucocutaneous bleeding | Mild to moderate mucocutaneous bleeding | Moderate to severe mucocutaneous bleeding | Moderate to severe mucocutaneous bleeding | Severe mucocutaneous bleeding | Hemophilia-like bleeding | Severe mucocutaneous and hemophilia-like bleeding |
| Response to desmopressin | Very effective in treating minor bleeding episodes | Used to diagnose type 1C (> 30% decrease in VWF 4 hours after infusion)<br><br>Ineffective in treatment of type 1C VWD | May respond to desmopressin<br><br>Recommend challenge before therapeutic administration | Desmopressin usually contraindicated due to thrombocytopenia | May respond to desmopressin<br><br>Recommend challenge before therapeutic administration | May respond to depression<br><br>Recommend challenge before therapeutic administration | Recommend avoiding desmopressin |

VWD = von Willebrand disease; VWF = von Willebrand factor

Data adapted from reference 13.

## VWF IS KEY IN CLOTTING

VWF is a glycoprotein synthesized by megakaryocytes and endothelial cells. A disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS-13) modulates VWF by binding the "ultra-large" VWF multimers initially released from these cells and cleaving them into the normal-sized multimers observed in circulation. High-molecular-weight multimers are hemostatically the most effective conformation of VWF and are elevated in ADAMTS-13 deficiency, leading to formation of platelet thrombi. However, the VWF monomer is the major circulating form and has multiple domains that bind platelets, collagen, and factor VIII.

VWF plays an important role in clotting by binding platelets and subendothelial collagen, aiding in forming an initial platelet plug at the site of endothelial injury. Additionally, it binds and stabilizes coagulation factor VIII, which can activate the coagulation cascade at the site of endothelial injury and result in fibrin clot formation.[6–10]

VWD occurs when a quantitative or qualitative abnormality of VWF leads to defects in primary hemostasis and, depending on the type and severity, to a subsequent factor VIII deficiency similar to hemophilia.

## SEVERITY VARIES

Patients with VWD classically present with mild to moderate mucocutaneous bleeding, eg, epistaxis, gingival bleeding, excessive bleeding after dental extractions or minor wounds, easy bruising, abnormal postsurgical or postpartum bleeding, or menorrhagia. However, bleeding frequency and severity vary widely across and even within VWD subtypes (see below). Some

patients may bleed only with hemostatic challenges such as trauma or surgery, while others may have severe or spontaneous bleeding with minor provocation.[11,12]

## THREE MAIN TYPES, SEVERAL SUBTYPES

The types and subtypes of inherited VWD recognized by the International Society of Thrombosis and Haemostasis (**Table 1**)[13] are briefly described below, the better to understand the specialized tests done in reference laboratories to diagnose them.

### Type 1: Decreased production of VWF

Type 1 accounts for about 70% of all cases of VWD. It is caused by a mutation in the VWF gene that leads to not enough VWF being synthesized, and classically presents as mild mucocutaneous bleeding.[14] Most patients have autosomal dominant missense mutations with incomplete penetrance and variable expression.[15,16] The severity of bleeding is often inversely proportional to the VWF level.

### Type 1C: Increased clearance of VWF

Type 1C is a rare subset of type 1 in which there is not enough VWF in circulation because more of it is being cleared, as opposed to synthetic dysfunction.[17]

### Type 3: Total or near-total lack of VWF

Type 3 is the rarest and most severe type of VWD. As in type 1, VWF levels are low, but there is a total or near-total lack of the substance. It is typically inherited in an autosomal recessive or compound heterozygous pattern.[18] Patients with type 3 VWD are prone to severe bleeding that often mimics bleeding in hemophilia. Due to their lack of VWF, these patients have low factor VIII levels because factor VIII is not being stabilized in plasma by VWF.[19]

### Type 2: Defective VWF variants

In contrast to patients with type 1, type 1C, or type 3 VWD, those with type 2 have normal levels of VWF. However, their VWF has a qualitative defect and does not function as it should.

This is the second most common type of VWD, and it is divided into 4 subtypes (2A, 2B, 2M, and 2N) based on the specific defect.[20] All type 2 subtypes except for 2N have an autosomal dominant inheritance pattern. Notably, type 2N VWD affects the factor VIII binding site of VWF and causes a decrease in factor VIII levels and severe bleeding patterns that mimic hemophilia.

### Acquired von Willebrand syndrome

The clinical presentation of acquired von Willebrand syndrome is similar to that of inherited VWD, but patients do not have a family history of bleeding tendencies.[21] Several mechanisms exist, including decreased production of VWF (eg, in hypothyroidism), increased adsorption onto circulating cells (eg, in chronic lymphocytic leukemia), increased antibody-mediated clearance (eg, in lupus), high-flow states leading to increased circulatory clearance of VWF (eg, in patients on left ventricular assist devices), formation of complexes with circulating proteins (eg, in monoclonal gammopathies), and shear destruction (eg, in aortic stenosis).[22,23]

Heyde syndrome is a rare form of acquired von Willebrand syndrome consisting of a triad of aortic stenosis, recurrent gastrointestinal bleeding, and acquired VWF deficiency resulting from destruction of high-molecular-weight multimers of VWF under shear stress due to aortic stenosis.[24]

## DIAGNOSTIC APPROACH

The diagnosis of VWD can be nuanced because the clinical bleeding symptoms can vary, and specialized laboratory tests can be difficult to interpret. The diagnosis relies on both thoroughly assessing the bleeding and family history and accurately interpreting the test results. The general approach includes a clinical bleeding assessment, a preliminary laboratory evaluation, a quantitative assessment of VWD levels, a qualitative assessment of VWF function, and, if applicable, specialized tests to determine the subtype of VWD (**Table 2**).[13]

### Clinical bleeding assessment

The first step is to obtain an accurate and detailed history of bleeding in the patient and family members. This includes age at symptom onset, frequency of bleeding events, sites of bleeding, triggers for bleeding (spontaneous or after invasive procedures or trauma), exposure to medications associated with bleeding risk, and transfusion history.

Bleeding assessment tools have been developed and validated.[25–27] The 2 most studied are the following:

- The International Society for Thrombosis and Haemostasis Bleeding Score (https://bleedingscore.certe.nl/)
- The Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD Score (https://www.path.queensu.ca/labs/james/bq.htm).

An objective, quantifiable assessment of bleeding symptoms is certainly desirable, but numerous limitations of these tools have been noted in practice: they are time-intensive, they underdiagnose the disease in younger patients, and they rely on prior exposure to

**TABLE 2**
**Diagnostic laboratory criteria for each type of von Willebrand disease**

| Type | VWD type 1 | | VWD type 2 | | | | VWD type 3 |
|---|---|---|---|---|---|---|---|
| **Subtype** | **Classic** | **1C** | **2A** | **2B** | **2M** | **2N** | |
| **Ratio of VWF activity to VWF antigen** | Normal (about 1) | | < 0.6 | | | | Markedly low or undetectable VWF activity and antigen levels |
| **Factor VIII levels** | Normal or mildly low | Normal or mildly low | Normal or mildly low | Normal or mildly low | Normal or mildly low | Moderately low relative to VWF antigen | Very low |
| **VWF multimer analysis** | Full spectrum of multimers, but all at low level | Full spectrum of multimers, but all at low level | Absence of high- and intermediate-molecular-weight multimers | Absence of high-molecular-weight multimers | Normal multimer pattern | Normal multimer pattern | Minimal or complete absence of VWF multimers |
| **Specific testing to diagnose subtype** | None | Elevated ratio of VWF propeptide to VWF antigen<br><br>> 30% decrease in VWF 4 hours after infusion of desmopressin | Genetic testing | Increased ristocetin-induced platelet aggregation<br><br>Sensitivity to low-dose ristocetin<br><br>Genetic testing | Decreased ristocetin-induced platelet aggregation<br><br>Low VWF-collagen binding capacity<br><br>Genetic testing | Decreased binding of VWF to factor VIII<br><br>Prolonged partial thromboplastin time<br><br>Genetic testing | None |

VWD = von Willebrand disease; VWF = von Willebrand factor

Data adapted from reference 13.

hemostatic challenges such as trauma or surgery.[28,29] While acknowledging these limitations, recent guidelines recommend using a bleeding-assessment tool rather than a nonstandardized assessment in the primary care setting to screen patients with a low probability of VWD and to determine the need for specialized testing.[13]

## Preliminary laboratory evaluation

Preliminary laboratory testing should include a complete blood cell count, blood type and screen, prothrombin time with international normalized ratio, and partial thromboplastin time.[13] While the results of these tests are unremarkable in most forms of VWD, they help to ascertain the extent of bleeding in the patient and to distinguish VWD from other bleeding disorders. Of note, thrombocytopenia may be observed in type 2B VWD, and a prolonged partial thromboplastin time due to reduced factor VIII may be seen in type 2N or type 3.

## Specialized tests: preanalytic variables

Specialized tests for VWD require complex assays, and many preanalytic variables can affect their precision and accuracy, including patient age, sex, race, blood group, and comorbid conditions such as recent bleeding, infection, hepatic dysfunction, inflammatory conditions, and renal disease.[30] It is essential to use proper sample-collection technique and to avoid small-gauge needles, prolonged tourniquet application, and inappropriate tube-filling to avoid abnormal results that can be misinterpreted. It is generally recommended that at least 2 separate sets of samples be obtained at different times.

## VWF antigen level

The next step is to measure the concentration of VWF protein (antigen) with an immunologic assay, most commonly an enzyme-linked immunosorbent assay or latex-enhanced immunoassay.[31–34] The normal range is between 50 and 200 IU/dL. VWD is diagnosed if the level is lower than 30 IU/dL, or if it is 30 to 50 IU/dL with a positive bleeding history.[13]

The VWF antigen level can be affected by factors such as age, menstrual cycle, contraceptive use, pregnancy, and comorbid conditions.[34] Of note, the

blood type can drastically affect VWF antigen levels. Specifically, patients with type O blood commonly have approximately 25% lower VWF antigen levels than those with type A.[35]

### Ristocetin cofactor assay

This test evaluates platelet-dependent VWF activity by assessing the ability of VWF to bind platelet glycoprotein Ib in the presence of the antibiotic ristocetin.[31] The normal range is 50 to 200 IU/dL.[13]

Although the ristocetin cofactor assay has been the gold standard for measuring VWF binding to platelets via glycoprotein Ib, several limitations have been noted, including laboratory variability, error at lower VWF antigen levels (limit of detection 10 IU/dL), and false-positive results associated with polymorphisms commonly found in the general population.[36] New assays have been developed to address these deficiencies, including assays for glycoprotein IbR, glycoprotein IbM, and VWF antibody. Some expert panels recommend these new assays over the ristocetin cofactor assay, but these are conditional recommendations based on low levels of evidence.[13]

### Ratio of VWF activity to VWF antigen

The VWF activity assay is a functional test that uses either the ristocetin cofactor assay (described above) or a monoclonal antibody that targets the region of the VWF molecule that binds to the glycoprotein Ib receptor as a measure of VWF activity. The VWF activity-to-antigen ratio helps distinguish quantitative vs qualitative deficiency of VWF (VWD type 1 vs type 2). In type 1 VWD, there is a concordant decrease in both VWF activity and VWF antigen, leading to a ratio greater than 0.7.[13] Type 2 VWD is characterized by a disproportionate reduction of VWF activity compared with VWF antigen levels, leading to a ratio less than 0.7. A notable exception is type 2N disease, in which the ratio is greater than 0.7. However, the joint guideline panel[13] gave this cutoff only a conditional recommendation based on very low certainty in the evidence from diagnostic studies.

### VWF multimer analysis

This is a qualitative assessment of the size distribution of VWF multimers in plasma, which helps distinguish the patient's subtype of VWD. The ability of VWF to bind platelets is related to size, with high-molecular-weight multimers showing the greatest activity. Under normal conditions, VWF multimers are distributed evenly across the various sizes. In types 1, 2M, and 2N VWD, all sizes of multimers are seen, while preferential loss of high-molecular-weight multimers is seen in type 2A and type 2B. Type 3 VWD is characterized by almost complete absence of VWF multimers.[37–39]

### Factor VIII coagulant assay

The factor VIII coagulant assay is typically used in patients with a substantial bleeding history that is suspicious for hemophilia. It is also integral to the workup of VWD, as a low factor VIII level may be seen with decreased or dysfunctional VWF, which is needed to stabilize factor VIII in plasma. In most types of VWD (1, 2A, 2B, 2M), factor VIII activity is moderately low. A more significant decrease in factor VIII activity suggests type 2N (factor VIII activity 5%–15%) or type 3 VWD (factor VIII activity 1%–10%).[40]

### VWF-factor VIII binding assay

This is an enzyme-linked immunoassay that evaluates the ability of VWF to bind recombinant factor VIII. An abnormal result confirms type 2N VWD and helps to distinguish it from hemophilia A.[41]

### Low-dose ristocetin-induced platelet aggregation

This assay also measures VWF's affinity for the platelet glycoprotein Ib receptor, but it uses less ristocetin than the ristocetin cofactor assay by exposing platelet-rich plasma from the patient to sequentially lower concentrations of ristocetin. Patients with type 2B VWD (characterized by increased VWF binding to platelet glycoprotein Ib) have platelet aggregation at much lower ristocetin concentrations (< 0.6 mg/mL).[13,42] This assay is also unique in that it can be used to distinguish type 2B VWD from a very rare platelet disorder known as pseudo-type or platelet-type VWD.

### VWF-collagen binding capacity

This assay measures the ability of VWF to bind collagen. Though less commonly used than other qualitative assays such as the ristocetin cofactor assay, the VWF-collagen binding capacity can help identify 2M subtypes characterized by defective collagen binding.[21,41]

### The VWF propeptide level, and the ratio of VWF propeptide to VWF antigen

This test measures the propeptide of VWF, which is normally synthesized and released in a 1:1 ratio with the VWF monomer.[43] Elevated VWF propeptide relative to VWF antigen suggests increased VWF clearance (type 1C VWD) and helps to distinguish it from complete quantitative deficiencies of VWF (type 3 VWD).

There has been a shift to using desmopressin challenge testing instead of the ratio of VWF propeptide to VWF antigen for patients with suspected type 1C

VWD. However, the guidelines give this a conditional recommendation based on a low level of evidence.[13]

### Desmopressin challenge testing

Desmopressin promotes excretion of stored VWF from endothelial cells into plasma. In desmopressin challenge testing, the VWF antigen, VWF activity, and factor VIII levels are measured 1, 2, and 4 hours after desmopressin administration.

An adequate increase in VWF antigen, ristocetin cofactor, and factor VIII levels is seen in most cases of type 1 VWD and in many of type 2. Conversely, in type 2N disease, an initial adequate response is seen but is not appropriately sustained in duration (< 4 hours) because of the increased clearance of factor VIII owing to the impaired stabilization function of VWF.

Desmopressin challenge testing can also be used to diagnose type 1C VWD, as a greater than 30% decrease in VWF from peak concentrations measured 4 hours after the infusion indicates increased VWF clearance, compatible with type 1C VWD.

Of note, desmopressin is contraindicated if type 2B VWD is suspected, as released VWF binds circulating platelets in type 2B, thereby worsening thrombocytopenia.[42,44]

### Genetic testing

Genotyping is not required to diagnose VWD and is done only in select clinical scenarios. Genetic analysis in VWD is complicated by the large size and incomplete characterization of the VWF gene as well as by significant genotypic and phenotypic variability. It is not widely available for types 1 and 3 VWD, and it is most useful for diagnosing type 2. Genotyping may be helpful in confirming VWD subtypes (including type 2B, 2M, and 2N disease) when results might affect therapeutic decisions.[21,42] Genetic testing may also be used to screen potential carriers of autosomal recessive forms of VWD.[20]

## TREATMENT

We recommend the following approach when treating a bleeding patient with VWD, depending on the acuity and severity of the clinical presentation.

### Referral to a hematologist

Though mild forms of VWD can be managed in the primary care setting, several situations may warrant referral to a hematologist or a center with expertise in VWD:

- An abnormal score on a bleeding assessment tool or positive family history
- Testing is not available, or results are needed quickly
- When testing provides results that are borderline, difficult to interpret, or positive for type 2 or type 3 VWD
- Persons with type 1 VWD with a bleeding history, or those with VWD undergoing a hemostatic challenge (ie, major surgery).

Most cases of VWD can be adequately comanaged by primary care physicians with the following treatment strategies.

## TREATING MINOR BLEEDING

### Local therapies

For minor nasal or oral bleeding, prolonged local pressure can be attempted as a first measure. Topical agents including topical human thrombin, micronized collagen, and fibrin sealants can also be used to control bleeding.[40,44]

### Antifibrinolytic agents

When topical agents are ineffective or not practical, antifibrinolytic agents are typically the next-line treatment for minor bleeding in VWD.[42] These drugs inhibit the enzymatic breakdown of fibrin, which cross-links and strengthens clots. Most commonly used are tranexamic acid and epsilon-aminocaproic acid.

These agents are particularly useful in mucocutaneous bleeding including epistaxis, oral bleeding, menstrual bleeding, and postpartum bleeding. They are safe to use in all forms of VWD. Tranexamic acid can be given as an oral capsule, mouthwash, or intravenously, and may be used alone or in combination with desmopressin or VWF-containing products.[42] Antifibrinolytics should be avoided in patients with a history of thromboembolic disease or significant hematuria due to the risk of clot formation and subsequent urinary obstruction.[44]

### Desmopressin

Desmopressin is a synthetic derivative of antidiuretic hormone that is useful in treating bleeding episodes in patients with type 1 VWD.[45] It works by inducing the release of endogenous VWF from endothelial cells through agonist activity at vasopressin 2 receptors. Desmopressin is readily available and inexpensive and can be given intranasally, subcutaneously, or intravenously.

Desmopressin is most effective in patients with type 1 VWD but is generally avoided in most patients with types 1C, 2, and 3. A desmopressin challenge should be performed in patients with a history of mild

or moderate bleeding and a diagnosis of VWD to confirm its effectiveness as a potential therapy.

Adverse effects of desmopressin include hyponatremia, headache, vasodilation, hypotension, tachycardia, flushing, and, rarely, thrombosis.[46,47] Another important clinical consideration when using desmopressin is tachyphylaxis, which develops within a few days due to depletion of VWF stores.[46] Desmopressin should be avoided in cases of serious or life-threatening bleeding, as the transient increase in VWF in response to desmopressin is generally insufficient to achieve adequate hemostasis.

**Other considerations.** Medications that affect platelet function, such as aspirin and nonsteroidal anti-inflammatory drugs, should be avoided in patients with VWD and a history of bleeding.

## MAJOR BLEEDING

Patients with severe bleeding or those with mild or moderate VWD undergoing major surgery will not achieve sufficient hemostasis with the aforementioned supportive therapies and should always be comanaged with a hematologist. These patients require exogenous replacement of VWF using plasma-derived or recombinant VWF products. As VWF causes an increase in factor VIII levels, separate factor VIII infusions may not be required depending on the subtype of VWD and the specific treatment used.

These 2 types of VWF products have never been compared head-to-head, though cross-trial comparisons of efficacy and safety do not show appreciable differences.[48] The decision on which product to use is often based on availability and cost.

### Plasma-derived VWF

The 3 plasma-derived VWF products approved in the United States—Humate-P, Alphanate, and Wilate—all contain VWF and factor VIII, but at different ratios. Plasma-derived products almost devoid of factor VIII (Wilfactin, Willfact) are available in Europe but not in the United States.

The package inserts for each product provide guidance for dosing. The target VWF level depends on the severity of bleeding if given for trauma, or the complexity of surgery if being used for surgical prophylaxis. In general, replacement is provided to initially reach a peak VWF activity level of 100 IU/dL with a trough of 50 IU/dL. Maintenance doses are then provided for 3 to 7 days depending on the amount of bleeding and patient response.[44]

An important consideration: because plasma-derived VWF products contain factor VIII, separate infusions of factor VIII are generally not required. Repeated dosing may lead to significant elevations of factor VIII (especially for products with a lower VWF-to-factor VIII ratio) and increased risk of thrombosis.[49] The incidence of thrombosis is thought to be relatively small and can be mitigated by closely monitoring factor VIII levels during therapy, with the goal of avoiding factor VIII levels above 150 U/dL.[50]

### Recombinant VWF

The first recombinant VWF was approved for adult patients in the United States in 2015 after publication of a landmark phase 3 trial in which it achieved excellent hemostatic efficacy in 97% of bleeding episodes.[50–52] This product contains ultra-large high-molecular-weight multimers, which are the most active form of VWF in attaining primary hemostasis.

Though recombinant VWF replacement will cause a delayed increase in endogenous factor VIII levels, the products themselves are almost devoid of factor VIII.[52] Therefore, factor VIII is often given with recombinant VWF to achieve hemostasis more rapidly, particularly in VWD subtypes with very low endogenous factor VIII levels (types 2N, 3, and severe type 1).

## PERIOPERATIVE MANAGEMENT

Careful risk stratification and perioperative management of patients with VWD is required to minimize bleeding risk. Risk stratification depends on the nature of the surgery, the severity of the patient's bleeding history, baseline plasma VWF levels, and responses to previous hemostatic challenges. We recommend a multidisciplinary discussion between the hematology consultant, surgical team, and patient before undertaking a surgical procedure, especially in the case of major surgery or severe VWD.

Consensus is still lacking as to the therapeutic target and assays to be monitored for in the postoperative period. In general, hemostatic levels are maintained until bleeding risk abates (usually 3 to 5 days), depending on the nature of the surgery and the patient's specific phenotype. As a general principle, for emergency surgery, VWF and factor VIII are given together, and for elective surgery, early infusion of VWF replacement therapy alone is sufficient.

## TAKE-HOME POINTS

- Despite recent advances, the diagnosis and management of VWD remain challenging.
- A thorough patient history and bleeding assessment are required for prompt diagnosis of VWD.

- Diagnostic testing is crucial to distinguish VWD from other bleeding disorders such as mild factor VIII deficiency and inherited platelet disorders.
- An understanding of the complex pathophysiology and diagnostic testing of VWD can aid in timely diagnosis and referral to a hematologist. Such referral should be considered based on severity of bleeding symptoms, type of VWD, and upcoming hemostatic challenges.
- Treatment of acute bleeding events associated with VWD should be tailored to the acuity and severity of the specific patient's clinical presentation.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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