Clinical presentation and diagnosis of von Willebrand disease

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INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Diagnosis can be challenging; some individuals with low von Willebrand factor (VWF) levels may not actually have VWD (or any bleeding disorder), whereas others who have never had a bleeding challenge or never been tested have a significant bleeding risk from VWD that would benefit from evaluation and counseling.

This topic reviews the clinical presentation, diagnosis, and differential diagnosis of VWD.

Separate topic reviews discuss the treatment and pathophysiology of VWD, the diagnosis and treatment of acquired von Willebrand syndrome (AVWS), and a general approach to bleeding disorders.

- Treatment of VWD – (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery" and "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care".)
- Diagnosis and treatment of AVWS – (See "Acquired von Willebrand syndrome".)
- Pathophysiology of VWD – (See "Pathophysiology of von Willebrand disease".)

- Approach to evaluating suspected bleeding disorders – (See "Approach to the adult with a suspected bleeding disorder".)

SUMMARY OF VWD TYPES

There are three major types of VWD (table 1) [1,2]:

- Type 1 is due to a quantitative reduction in von Willebrand factor (VWF) protein (both concentration and activity are decreased).
- Type 2 is due to dysfunctional VWF.
- Type 3 is due to absent or severely reduced VWF (a severe quantitative reduction).

Type 2 is divided into four subtypes that reflect the specific VWF function affected; the distribution of VWF multimers is also important for function and may be affected. The type and subtype have potential implications for bleeding risk, diagnostic testing, management, and genetic counseling.

The VWD types and subtypes are summarized in the table (table 1) and briefly below; the known genetic variants associated with each type and mechanisms by which they affect VWF quantity and function are discussed in more detail separately. (See "Pathophysiology of von Willebrand disease".)

Measures of VWF activity are discussed below. (See 'Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)' below.)

- **Type 1** – Type 1 VWD is characterized by reduced levels of VWF and variable degrees of bleeding. Type 1 is the most common type, accounting for approximately 75 percent of individuals with VWD. There is a concordant reduction in VWF activity and antigen, and all multimers are present in decreased amounts. Thus, the ratio of platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM) to VWF antigen (VWF:Ag) is normal (approximately 1:1). (See 'Derived ratios to aid classification' below.)

  Guidelines in 2021 recommended the official addition of category type 1C, which is characterized by a concordant reduction in VWF activity and antigen due to rapid clearance of VWD from the circulation [2]. The Vicenza variant is a type 1C variant [3-5]. Treatment may be impacted due to the shorter half-life of VWD [6,7].

- **Type 2** – Type 2 VWD is characterized by a dysfunctional VWF protein [8]. Different subtypes reflect which protein-protein interactions are affected. In some cases, reduced

binding to a physiologic binding partner may be caused by defective multimerization rather than a defect in a specific protein binding domain.

- **Type 2A** – Type 2A VWD involves loss of the platelet binding function of VWF and a reduction in the most functional high molecular weight (HMW) multimers. The loss of HMW multimers may be due to either decreased multimer assembly or to increased proteolysis [9,10]. The ratio of platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM) to VWF:Ag is decreased. This subtype accounts for 10 to 15 percent of VWD cases.

- **Type 2B** – Type 2B VWD involves increased platelet binding by VWF, especially by the HMW multimers, due to a gain-of-function mutation in VWF that enhances binding of VWF to platelet glycoprotein Ib (GPIb). This enhanced binding leads to accelerated clearance or sequestration of platelets and of the bound HMW VWF multimers, in turn causing thrombocytopenia and decreased VWF with abnormal VWF multimer distribution (loss of HMW multimers). The ratio of platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM) to VWF:Ag is decreased. This subtype accounts for approximately 5 percent of VWD cases.

  A platelet disease called platelet-type VWD involves enhanced platelet binding by VWF with accelerated platelet clearance and thrombocytopenia, a similar phenotype to type 2B VWD, but in the case of platelet-type VWD, the mutation resides in the platelet GPIb receptor rather than the VWF protein.

- **Type 2M** – Type 2M VWD involves reduced binding of VWF to platelet GPIb (similar to type 2A) or to collagen; these patients have reduced VWF levels. Unlike type 2A, the normal distribution of VWF multimers is preserved. Although the multimer distribution is normal, the ratio of platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM) to VWF:Ag is reduced, differentiating type 2M from type 1 (in those with abnormal collagen binding, testing with VWF:CB is needed). Type 2M is less common than types 2A or 2B.

- **Type 2N** – Type 2N (for Normandy) VWD involves reduced binding of VWF to factor VIII. As a result, the carrier function of VWF for factor VIII is disrupted, leading to low factor VIII levels and a low ratio of factor VIII activity to VWF:Ag. VWF platelet-dependent activity and antigen levels can be normal. Clinical manifestations include mucocutaneous bleeding but are otherwise similar to hemophilia A, with joint and muscle bleeding. Type 2N is uncommon. Homozygosity or double heterozygosity is required for symptomatic type 2N disease.

- **Type 3** – Type 3 VWD is characterized by absent (or undetectable) levels of VWF. This correlates with severely reduced VWF function and very low factor VIII levels, which contributes to a severe bleeding phenotype. Type 3 is rare.

- **AVWS** – Acquired von Willebrand syndrome (AVWS) is an acquired disorder characterized by low levels of VWF due to reduced production or enhanced removal of VWF from the circulation. It is distinguished from inherited VWD by a lack of prior personal bleeding, a negative family history of VWD, and a nongenetic cause. Often the patient has findings of a disorder associated with AVWS. (See "Acquired von Willebrand syndrome".)

Laboratory findings in the different types of VWD are discussed below. (See 'Additional testing to characterize (classify) the type of VWD' below.)

EPIDEMIOLOGY

Prevalence — VWD is the most common inherited bleeding disorder. In primary care, VWD that causes symptomatic bleeding has a prevalence of approximately 1 in 1000 (0.1 percent) [11,12]

Low von Willebrand factor (VWF) levels affect up to 1 percent of the population as assessed by random laboratory screening [13].

Of individuals diagnosed with VWD, the vast majority have type 1 (75 to 85 percent), followed by type 2A (10 to 15 percent) and type 2B (5 percent). (See 'Summary of VWD types' above.)

Inheritance patterns — All types of VWD are autosomal and thus affect males and females equally [14]. Females experience mucosal bleeding with menses and during the postpartum period and as a result may be diagnosed more commonly than males. (See 'Heavy menstrual bleeding' below.)

Most cases of VWD show autosomal dominant transmission; this includes:

- Type 1
- Type 2B
- Most cases of type 2A
- Most cases of type 2M

Autosomal recessive types include:

- Type 2N
- Type 3

- Some cases of type 2A
- Some cases of type 2M

VWD types are summarized above (see 'Summary of VWD types' above). The *VWF* gene and domain structure of the protein are discussed separately. (See "Pathophysiology of von Willebrand disease", section on 'Spectrum of pathogenic variants'.)

CLINICAL FEATURES

Types of bleeding presentations — Bleeding symptoms in VWD occur when plasma von Willebrand factor (VWF) is sufficiently decreased to affect hemostasis or when a qualitative defect in VWF impairs one of its hemostatic functions.

Affected females (adults) are usually symptomatic. Males and children may not have been exposed to sufficient hemostatic challenges to bring them to medical attention.

Many symptomatic individuals with VWD go undiagnosed, and studies have shown that females, in particular, have diagnostic delays of up to 16 years from the onset of bleeding symptoms. Systemic factors, including sexism, contributes to this [15,16].

In patients with mild VWD, use of aspirin, other nonsteroidal antiinflammatory drugs (NSAIDs), or other antiplatelet medications can precipitate bleeding that may not have occurred otherwise (table 2).

Patients with VWD can become symptomatic at any age. A typical history in a patient with mild to moderate disease includes epistaxis lasting longer than 10 minutes in childhood; lifelong easy bruising; heavy menstrual bleeding; and bleeding with (or following) dental extractions, other invasive dental procedures, or other forms of surgery. A typical presentation in a toddler may include oral mucosal bleeding or bleeding with circumcision; intracranial bleeding in infants has also been reported [17].

Although there is significant overlap in the bleeding symptoms experienced between the subtypes, in general, bleeding in type 3 VWD is the most severe, followed by type 2 VWD, followed by type 1 VWD [18]. The following findings (severity and sites of bleeding) are typical:

- Type 1 – Variable, from asymptomatic to serious bleeding; mucocutaneous
- Type 2A – Usually moderate to severe; mucocutaneous
- Type 2B – Usually moderate to severe; mucocutaneous
- Type 2M – Variable; usually moderate to severe; mucocutaneous

- Type 2N – Variable; usually moderate to severe; mucocutaneous but can include joint and muscle
- Type 3 – Severe; mucocutaneous and joint and muscle bleeding; often presents during infancy/childhood (eg, with circumcision)

In summary:

- Mild to moderate mucocutaneous bleeding is most common in types 1 and 2. Those without hemostatic challenges (especially adult males and children) may only come to medical attention after a family member is diagnosed with VWD. (See 'Bruising and mucocutaneous bleeding' below and 'Heavy menstrual bleeding' below.)

- Severe bleeding is more common with types 2 and 3. In type 3, the combination of reduced factor VIII levels with very low or absent VWF levels can lead to significant bleeding with the eruption of deciduous teeth, with minor trauma as the child begins crawling or walking, or with major or life-threatening hemorrhage at the onset of menstrual periods. (See 'Heavy menstrual bleeding' below and 'Gastrointestinal bleeding and angiodysplasia' below and 'Musculoskeletal bleeding' below.)

Bruising and mucocutaneous bleeding — Bruising and mucocutaneous bleeding are common, including:

- Easy bruising
- Cutaneous bleeding
- Prolonged bleeding from mucosal surfaces (eg, oropharyngeal, gastrointestinal, uterine)

These occur because there the normal initial VWF-dependent binding of platelets to sites of vascular injury is reduced, similar to primary platelet disorders.

These findings are typical in type 1 as well as types 2A, 2B, and 2M. Though mucocutaneous bleeding occurs in type 2N and type 3, type 3 is also characterized by additional muscle and joint bleeding.

In a series of 105 infants and toddlers diagnosed with VWD at age <2 years, 70 percent had a bleeding event [17]. Oral mucous membrane bleeding was the most common site, affecting one-third. Bleeding with circumcision affected 12 percent.

Heavy menstrual bleeding — More than half of females with VWD have heavy menstrual bleeding (as many as 60 to 90 percent in some studies) [19-22]. In one series, 20 percent of participants had undergone hysterectomy to treat severe menstrual bleeding [23].

The converse (the proportion of females with heavy menstrual bleeding diagnosed with VWD) depends on the population studied; systematic reviews report rates of approximately 10 to 15 percent [24,25]. (See "Abnormal uterine bleeding in nonpregnant reproductive-age patients: Terminology, evaluation, and approach to diagnosis" and "Causes of female genital tract bleeding", section on 'Coagulopathy (AUB-C)'.)

Postpartum bleeding — VWF levels generally increase during pregnancy; this can be protective against bleeding prior to and during delivery. However, VWF levels decline precipitously after delivery, and bleeding can occur during the peripartum period, often at or within hours of delivery and later at 5 to 15 days after delivery.

In one series involving 120 individuals with decreased VWF levels, 74 (62 percent) reported postpartum bleeding, and 22 percent required transfusion, critical care, or surgical/radiologic intervention [21]. A case-control study involving 62 deliveries in 33 individuals with VWD found a trend towards an increased incidence of primary postpartum hemorrhage (PPH), with a rate of 19 in those with VWD versus 13 percent in controls (adjusted odds ratio [OR] 1.31; 95% CI 0.48-3.60), and a series of 124 individuals with PPH determined that VWD was present in approximately half, most of whom had type 1 disease [26,27]. (See "Overview of postpartum hemorrhage", section on 'Coagulopathy or other bleeding diathesis' and "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Obstetric considerations'.)

Gastrointestinal bleeding and angiodysplasia — Bleeding from the gastrointestinal tract can also be seen in VWD, although this is less common than mucocutaneous bleeding.

Often, there may be a contribution of gastrointestinal angiodysplasia, which is common in VWD [28-32]. (See "Pathophysiology of von Willebrand disease".)

Musculoskeletal bleeding — Joint and muscle bleeding are not typical in most patients with VWD.

These types of bleeding are typically only seen with types 2N and 3, which have low factor VIII levels (<10 percent). Low factor VIII occurs because VWF is a carrier protein for factor VIII and prolongs the half-life of factor VIII in the circulation. (See "Pathophysiology of von Willebrand disease", section on 'Stabilization of factor VIII'.)

Factor VIII levels can be reduced if VWF does not bind to factor VIII properly (as in type 2N) or if VWF is markedly reduced or absent (as in type 3) [33-35]. (See 'Summary of VWD types' above.)

In one large study from Iran involving 385 patients with type 3 VWD, 52 percent had muscle bleeding and 37 percent had joint bleeding [36]. Rates of epistaxis and oral bleeding were even

higher (77 and 70 percent, respectively).

Abnormalities in the CBC and coagulation tests — Many individuals with VWD have a normal complete blood count (CBC) and normal coagulation studies.

However, the following abnormalities may be seen:

- **Thrombocytopenia** – Individuals with type 2B VWD may have mild thrombocytopenia (platelet count 100,000 to 140,000/microL) due to increased binding between VWF and platelets that increases platelet clearance or sequestration [37]. (See 'Baseline hemostasis assessment' below.)

  Thrombocytopenia may worsen in these individuals when VWF levels increase, such as with stress, inflammation, or pregnancy. Administration of desmopressin (DDAVP) also increases VWF levels and can worsen thrombocytopenia in these individuals; this is the rationale for extremely careful use or avoidance of DDAVP in the treatment of patients with type 2B VWD. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'DDAVP trial'.)

- **Microcytic anemia** – Individuals with heavy menstrual bleeding or gastrointestinal bleeding may develop iron deficiency or iron deficiency anemia, with microcytosis. Ferritin level and/or an iron studies panel should be obtained to assess for iron deficiency if significant bleeding or microcytosis is present. (See "Microcytosis/Microcytic anemia", section on 'Approach to the evaluation'.)

- **Prolonged aPTT** – The activated partial thromboplastin time (aPTT) may be prolonged if the factor VIII level is significantly reduced. The factor VIII level below which the aPTT becomes prolonged depends on the sensitivity reagents and instrument used for the assay.

Changes with aging and pregnancy — VWF levels increase with age, by approximately 0.8 percentage points per year (approximately 8 percentage points per decade) [8]. An individual with a VWF level of 30 to 50 international units [IU]/mL and a bleeding history as a young adult who is retested years later may no longer have a VWF level below the threshold for diagnosis. Whether the increase in VWF levels in type 1 patients results in decreased bleeding symptoms is not established. Re-evaluation may be warranted if VWF levels increase into the normal range, but the diagnosis is not revised [38].

In a 2017 study that followed 26 individuals with type 1 VWD or low VWF for over 10 years, 28 percent had normalized VWF levels by the end of the study [39]. The age-related increase in VWF

levels may apply only to individuals with type 1 VWD and not to those with type 2 [40,41].

Estrogen stimulates VWF production; thus, VWF levels are higher with estrogen therapy and during pregnancy, and the bleeding risk may decrease prior to delivery. VWF levels increase by approximately three- to fivefold by the end of the third trimester. (See "Pathophysiology of von Willebrand disease", section on 'VWF protein'.)

Initial testing for the diagnosis of VWD is not ideally done during pregnancy; if an individual with suspected VWD has a borderline or normal level during pregnancy, it is appropriate to retest six weeks or more after delivery.

EVALUATION

Indications for evaluation — VWD should be considered in individuals with one or more of the following:

- Increased history of bleeding, especially mucocutaneous bleeding, abnormal bruising, nosebleeds, or abnormal uterine bleeding. (See 'Personal bleeding history and bleeding assessment tool (BAT)' below.)
- Positive family history of VWD or of a bleeding phenotype suggestive of VWD. (See 'Family history and transmission pattern' below.)
- Mild thrombocytopenia or mildly prolonged activated partial thromboplastin time (aPTT) without an explanation. (See "Approach to the adult with a suspected bleeding disorder".)
- Apparent hemophilia A (low factor VIII in the absence of a factor VIII inhibitor). (See 'Differential diagnosis' below.)

In general, the likelihood of VWD is higher in individuals with a significant personal and/or family history of bleeding (or a confirmed diagnosis of VWD in a family member) [42,43].

The role of screening for VWD in asymptomatic individuals is controversial; however, testing is often appropriate in someone with a clear family history. If the patient has not experienced a hemostatic challenge, the decision to test may depend on the patient's personal activities. As an example, we would be more likely to screen an individual prior to invasive procedures or in someone who participates in sports that are associated with an increased risk of injury, or if a parent/caregiver or patient has specific concerns about a bleeding disorder in a kindred.

Personal bleeding history and bleeding assessment tool (BAT) — An accurate bleeding history is essential to the evaluation of any suspected bleeding disorder, including VWD. (See "Approach to the adult with a suspected bleeding disorder", section on 'Patient history'.)

The bleeding history should address spontaneous bleeding and should specifically ask about bleeding challenges such as invasive dental procedures, tonsillectomy, circumcision, other surgical procedures (particularly involving mucous membranes), and menstrual and peripartum bleeding. The value of the history depends on the skill of the questioner and on the follow-up questions they use to evaluate the significance of the answers provided.

Details of the bleeding history can be documented using bleeding an assessment tool (BAT), which helps to quantify the severity, duration, and sites of bleeding, and whether treatment was needed. Guidelines from 2021 recommend using a BAT as the initial screening test for low-risk individuals seen in primary care, as a means of determining which individuals need VWD-specific laboratory testing [2]. However, for individuals with a high risk of VWD, such as a first-degree relative with VWD, laboratory testing should be done regardless of bleeding history. In these patients, the BAT may be helpful in assessing the severity of bleeding and in guiding therapy.

Some BATs have been validated in clinical practice, especially for females, and the International Society of Thrombosis and Haemostasis (ISTH) has created and validated the ISTH-BAT, which can be found online at the ISTH reference tools page [44,45]. A 2021 meta-analysis of BATs found the overall sensitivity for identifying VWD to be 75 percent (95% CI, 66 to 83 percent) and the overall specificity to be 54 percent (95% CI, 29 to 77 percent) [46]. Performance characteristics of several BATs are presented in the analysis. (See "Approach to the adult with a suspected bleeding disorder", section on 'Bleeding score'.)

A self-administered BAT (Self-BAT) for adults has also been used, and an online version has proven useful, especially in females [47,48]. Larger studies in individuals with and without VWD will be helpful in assessing the effectiveness of the self-administered tests. A separate pediatric BAT called the pediatric bleeding questionnaire (PBQ) and a self-administered pediatric version have also been designed, and both have been validated for clinical use [47,49,50].

We encourage the use of the ISTH-BAT or Self-BAT in individuals with suspected VWD because it provides an objective, quantitative picture of the bleeding history. The ISTH-BAT needs to be administered by a trained health care worker. In an analysis of data from 1040 adults and 328 children, the normal ranges were determined to be 0 to 3 for adult males, 0 to 5 for adult females, and 0 to 2 for children [44].

Other important aspects of the personal bleeding history include:

- Use of medications that may increase bleeding risk (table 2)
- Family history of bleeding symptoms (see 'Family history and transmission pattern' below)
- Medical conditions that could increase bleeding risk (see "Approach to the adult with a suspected bleeding disorder", section on 'Underlying medical conditions')
- Medical conditions associated with acquired von Willebrand syndrome (see "Acquired von Willebrand syndrome", section on 'Associated diseases')

The physical examination should include a search for ecchymoses and hematomas, documenting their size and location, and evidence for current or recent mucosal bleeding. A negative physical examination is common in patients.

Family history and transmission pattern — Family history is important in the evaluation for VWD. A positive family history is especially important for individuals who have not experienced a major bleeding challenge, since significant bleeding in a family member suggests the possibility of a serious bleeding disorder. In contrast, a negative family history cannot be used to eliminate the possibility of VWD because of the issues of missed/delayed diagnosis as well as incomplete penetrance and variable expressivity that affect type 1 VWD families.

The transmission pattern may be helpful in evaluating the likelihood of VWD (autosomal) rather than hemophilia A or B (X-linked). The transmission pattern (autosomal dominant versus recessive) may be helpful in suggesting the VWD subtype. (See 'Inheritance patterns' above.)

It is also very useful to have laboratory data on family members, including von Willebrand factor (VWF) levels and function, as well as specialized testing for the type of VWD and testing for other bleeding disorders. (See 'VWD screening tests' below and 'Additional testing to characterize (classify) the type of VWD' below.)

Recommendations for referral to a specialist — It is appropriate to refer patients to a hematologist with expertise in VWD for either of the following:

- When the personal bleeding history is abnormal or testing is borderline or difficult to obtain or interpret for diagnosis.
- When the family history is positive.
- When management requires clinical expertise, treatments, and timely testing beyond the ability of the local facility or clinicians.

LABORATORY TESTING

Baseline hemostasis assessment — Most patients will have a complete blood count (CBC) with platelet count and coagulation studies during the initial evaluation for excessive bleeding or bruising.

- Individuals with VWD can have a normal CBC and a normal platelet count. An exception is individuals with type 2B VWD, some of whom will have mild thrombocytopenia at baseline (platelet count 100,000 to 140,000/microL) [37]. Those with significant bleeding may have microcytic anemia.

- Individuals with VWD may have a normal or prolonged activated partial thromboplastin time (aPTT), depending on the degree of reduction in factor VIII activity. The prothrombin time (PT) is normal. (See 'Abnormalities in the CBC and coagulation tests' above.)

VWD screening tests — For initial testing for VWD, three screening tests that assess the quantity and function of von Willebrand factor (VWF) are recommended by guidelines jointly published by the American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), National Hemophilia Foundation (NHF), and World Federation of Hemophilia (WFH) [1,2,51]; these three tests usually establish whether the patient has VWD (algorithm 1).

- VWF antigen (VWF:Ag) – Quantitative measurement of VWF protein level (see 'VWF antigen' below)
- Platelet-dependent VWF activity (see 'Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)' below)
- Factor VIII activity (see 'Factor VIII activity' below)

These tests are performed on plasma, when the individual is at their baseline (not acutely ill; not pregnant). Interpretation is summarized in the table (table 3) and discussed below.

VWF antigen — Plasma von Willebrand factor antigen (VWF:Ag) measures the quantity of VWF protein in the plasma. Testing methods have evolved over time, and most testing is now done using an enzyme-linked immunosorbent assay (ELISA)-based method on microtiter plates or by other automated methods using latex beads coated with antibodies to VWF and patient plasma as the source of VWF [52,53]. The latter use a turbidimetric endpoint. Results of the latex bead assay compare favorably with the ELISA in most but not all instances. A potential problem is that rheumatoid factors can falsely elevate the VWF latex assay [54].

A VWF:Ag level <30 percent (<30 international units [IU]/dL) is consistent with VWD. Levels between 30 and 50 percent in a patient with a positive bleeding history also indicate VWD. Levels >50 percent are considered normal.

Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM) — VWF functional assays assess the ability of VWF to bind to its normal binding partners, platelet glycoprotein Ib (GPIb), collagen, and factor VIII (figure 1). The results of these tests are commonly referred to as "VWF activity." Unfortunately, confusion may result because some of the specific tests for measuring VWF binding to recombinant GPIb are themselves commercially labeled as "VWF activity."

- **Platelet (GPIb) binding** – VWF binding to platelet receptor GPIb allows VWF to recruit platelets to a site of vascular injury; it can be assayed by several methods:

  - **VWF:RCo (ristocetin cofactor)** – VWF:RCo is an assay that measures the ability of VWF to bind to platelet membrane receptor GPIb. It takes advantage of the ability of ristocetin (an antibiotic that is no longer in clinical use because it causes platelet agglutination) to bind to VWF and platelets and enhance their interaction [55-58]. In the VWF:RCo assay, ristocetin is added to patient plasma along with washed or formalin-fixed platelets, and the amount of functional VWF in the plasma that causes platelet agglutination is quantified using platelet aggregometry or a manual (tilt tube) method [59,60]. Using fixed platelets avoids the need to use fresh platelets for each assay and avoids the secondary aggregation reaction that occurs with fresh platelets [61].

    This test is limited by a high coefficient of variation and low reproducibility. A low value can be the result of VWF variants that affect ristocetin binding but do not affect VWF function or cause bleeding (ie, D1472, which is common in patients of African descent). As a result, the 2021 VWD Diagnosis Guideline suggests the use of the newer assays listed below (such as VWF:GPIbR or VWF:GPIbM) to measure platelet-dependent VWF function [2,62,63].

    VWF:RCo is different from ristocetin-induced platelet aggregation (RIPA); the RIPA tests aggregation of the patient's platelets in the patient's plasma (platelet-rich plasma) at low concentrations of ristocetin, and it does not measure VWF activity. Increased RIPA is seen in type 2B VWD. (See 'Ristocetin-induced platelet aggregation (RIPA)' below.)

  - **VWF:GPIbR** – VWF:GPIbR measures the ability of the patient's VWF to bind to a recombinant platelet GPIb receptor attached to a solid phase such as latex beads (in the place of platelets that contain membrane GPIb). Ristocetin is added to enhance binding, as done in the VWF:RCo assay. VWF:GPIbR is more sensitive than VWF:RCo and is automated [64,65].

  - **VWF:GPIbM** – VWF:GPIbM measures the ability of the patient's VWF to bind to a recombinant mutated GPIb receptor attached to latex beads. Ristocetin is not needed

due to the gain-of-function mutation in the recombinant GPIb reagent. The test is more sensitive than VWF:RCo and is automated [64].

VWF activity of <30 percent (<0.30 international units [IU]/mL) confirms the diagnosis of VWD, regardless of bleeding history; VWF activity <50 percent (<0.50 IU/mL) confirms the diagnosis of VWD in someone with a positive bleeding history [2].

Though the VWF:RCo assay has been the "gold standard" for the platelet binding activity of VWF, the automated tests listed above are generally more reproducible and are more sensitive in the lower range; they are becoming widely used [64,66]. When compared with the VWF:RCo, the VWF:GPIbR, and VWF:GPIbM function well in most instances and are more sensitive below 10 IU/dL; however, a few VWF variants have not been identified correctly [64,65,67].

The VWF:Ab assay may be available but is not recommended [51,64].

Flow cytometry has also been used to measure VWF-platelet binding, but it is not widely available.

- **VWF:CB (collagen binding)** – Another functional assay evaluates the ability of the patient's VWF to bind to collagen. VWF binding to collagen allows VWF to be localized to the subendothelial matrix, bringing bound platelets to the site of vascular injury. Assays for collagen binding are performed using ELISA plates coated with collagen (typically collagen types I and III) [68,69]. Collagen binding assays are not used as frequently as platelet binding assays in the United States, but some laboratories are using it, and it measures a different function of VWF from the other VWF:Act assays [68,69]. Decreased collagen binding is also used by some laboratories as a surrogate test for decreased high molecular weight (HMW) multimers of VWF, but this has not been favored in the United States [70]. The 2021 VWD Diagnosis Guideline suggests the use of either the VWF:CB or VWF multimers [2].

- **Standards for reagents** – The VWF reagents used in VWF activity assays should always be related to the World Health Organization (WHO) standard for VWF, and the results should be reported in IU/dL or IU/mL, where 100 percent equals 100 IU/dL or 1 IU/mL.

As noted below, a VWF functional test showing activity <30 percent (<30 IU/dL) is consistent with VWD. (See 'Clinical considerations and evolution of guidelines' below.)

As in individuals with a VWF:Ag <30 IU/dL or in a patient with a bleeding history and activity of 30 to 50 IU/dL, further testing should be done to categorize the type of VWD. (See 'Additional

testing to characterize (classify) the type of VWD' below.)

Factor VIII activity — Decreased factor VIII activity may indicate reduced or dysfunctional VWF, as VWF acts as a carrier for factor VIII that protects it from proteolysis, increasing its plasma half-life. Significant reduction in VWF can lead to a decrease in factor VIII sufficient to prolong the aPTT. The level below which this occurs is highly dependent on the reagents and instruments used at each institution.

- Factor VIII activity is in the low normal range in many cases of mild VWD or only moderately decreased in type 1 and types 2A, 2B, and 2M.
- Factor VIII activity is low in type 2N VWD (impaired binding of VWF to factor VIII; factor VIII activity 5 to 15 percent) and in type 3 VWD (absent VWF; factor VIII activity 1 to 10 percent) [1,35,71].

In cases with low factor VIII activity, it is important to distinguish VWD from mild hemophilia. This is done using tests for VWF binding to normal factor VIII and/or by genetic analysis of the VWF binding site for factor VIII. (See 'Differential diagnosis' below.)

If the levels are discordant with the clinical picture (eg, if there is a high index of suspicion for VWD in the face of normal or equivocal initial results), testing should be repeated when the patient is at baseline. It is also appropriate to refer the patient to a hematologist with expertise in VWD in this setting.

Diagnostic testing is not recommended when the individual has any acute illness, pregnancy, other physiologic stress, or other estrogen exposure. (See 'Repeat testing in individuals with borderline or discordant clinical and laboratory findings' below.)

Other screening tests — The following tests are sometimes used in initial screening:

- **Platelet function analyzer (PFA) assay** – The PFA-100 assesses platelet plug formation in citrated whole blood exposed to shear stress [72]. The plug forms on a membrane with a central aperture that is coated with collagen and another platelet agonist, either ADP or epinephrine. The time to closure of the aperture as the platelet plug forms is measured. The closure time is dependent upon both VWF and intrinsic platelet function.

  This instrument has been used to screen for VWD due to its high sensitivity [73-75]. However, it lacks specificity, leading many to question its role in screening; the PFA-100 is not included in the recommended diagnostic assays by VWF guidelines [1,2,76]. (See "Platelet function testing", section on 'PFA-100'.)

- **Bleeding time (BT)** – The BT is an in vivo measure of the interaction of platelets with the blood vessel wall. It is performed by making a small, standardized cut on the skin and determining the time for bleeding to stop. The BT is no longer routinely used because it is time consuming, highly operator dependent, and does not correlate well with bleeding risk or with any specific assay of VWF function [77,78]. The BT may be abnormal in some individuals with VWD, but a normal BT does not eliminate the possibility of VWD.

Repeat testing in individuals with borderline or discordant clinical and laboratory findings — A number of things affect VWF levels. Thus, in patients who are deemed likely to have a bleeding disorder (especially if they have a positive personal or family history and borderline laboratory results), repeat diagnostic testing should be undertaken, reducing the stress-related elevation of VWF [79].

Conditions that can affect VWF levels include the following:

- VWF and factor VIII are acute phase reactants, and their levels can increase two to five times over baseline during exercise, adrenergic stimulation (stress), and inflammatory processes [80-85]. (See "Acute phase reactants".)

- VWF levels increase with estrogen exposure (eg, estrogen-containing oral contraceptives, menopausal hormone therapy). Pregnancy is associated with a two- to fivefold increase in VWF levels [80]. (See 'Changes with aging and pregnancy' above.)

- VWF levels decrease in hypothyroidism. (See "Clinical manifestations of hypothyroidism", section on 'Hematologic' and "Acquired von Willebrand syndrome", section on 'Hypothyroidism'.)

- VWF levels can be affected by age, ethnicity, ABO blood type, and genes unrelated to VWF [86].

The mechanisms of these effects are discussed separately. (See "Pathophysiology of von Willebrand disease", section on 'Clearance and control of plasma VWF levels'.)

Additional testing to characterize (classify) the type of VWD — If one of the VWF:Ag or platelet-dependent VWF activity tests is <30 percent, or <50 percent in a patient with a bleeding history, indicating a diagnosis of VWD, additional assays should be completed to determine the type of VWD (table 3). Use of this testing to classify the type of VWD is illustrated in the algorithm (algorithm 2).

Derived ratios to aid classification

- **Platelet-dependent VWF activity to VWF antigen** – Laboratories make use of the ratio of platelet-dependent VWF activity to VWF:Ag as a means of helping to identify patients with type 2 VWD (dysfunctional VWF; qualitative defect). (See 'Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)' above.)

  The following cutoffs are recommended by the 2021 guideline [2]:

  - **Ratio >0.7** – Individuals with type 1 VWD generally have good concordance between VWF activity and protein levels, leading to a ratio of platelet-dependent VWF activity to VWF:Ag close to 1.0. A ratio >0.7 is generally considered concordant and consistent with type 1 VWD. The ratio is also close to 1.0 in individuals with normal VWF levels.

  - **Ratio <0.7** – Types 2A, 2B, and 2M VWD all have decreased platelet-dependent VWF activity or VWF:CB out of proportion to the reduction of VWF protein in the circulation; thus, a low ratio of platelet-dependent VWF activity to VWF:Ag may be used to predict these type 2 patients. A ratio of <0.7 is considered discordant, consistent with type 2 VWD.

  The ratio is not applicable to rare type 3 VWD patients who have extremely low or undetectable platelet-dependent VWF activity and VWF:Ag.

  A meta-analysis from 2022 showed that a ratio of platelet-dependent VWF activity to VWF:Ag of <0.7 has moderate sensitivity and very low specificity for the diagnosis of type 2 VWD [38]. The same analysis found that a ratio of <0.7 was superior to ratios of <0.6 or <0.5, though these results are based on fewer patients.

  There is an increased frequency of the D1472H *VWF* polymorphism in some African Americans, which leads to slightly lower measured VWF:RCo levels even though the actual platelet-dependent VWF function is normal [62]. This is a limitation of the VWF:RCo assay and may result in some individuals with type 1 VWD being erroneously classified as having type 2M.

  Distinction among the subtypes of types 2A, 2B, and 2M VWD is made using results of VWF multimer analysis (or VWF:CB) and ristocetin-induced platelet aggregation (RIPA).

- **Factor VIII activity to VWF antigen** – The ratio of factor VIII activity to VWF:Ag is low in type 2N VWD and is helpful in directing the evaluation to a VWF:factor VIII (VWF:FVIIIB) binding assay. (See 'VWF binding to factor VIII (VWF:FVIIIB)' below.)

VWF multimer analysis — We perform VWF multimer analysis in newly diagnosed patients with VWD. The VWF multimer assay is a qualitative visual assessment of the size spectrum and

the banding pattern of VWF multimers that can be seen on gel electrophoresis (picture 1) [87].

Patient plasma is used to provide the source of VWF for analysis; patient platelets can also be examined, although this is not widely available. The proteins are separated by agarose gel electrophoresis, and multimers of different sizes are detected using anti-VWF reagents after transfer to a membrane (eg, Western blotting with chemiluminescence detection) [88].

Multimer distribution is assessed visually and can be quantified using densitometry of the bands. Often, the clinician will be provided only with the interpretation (without the actual gel image).

VWF multimer analysis is used to identify variants of type 2 VWD that lack the largest multimers (types 2A and 2B; in lanes 3 and 4 of the gel image (picture 1)), or those that have unusually large multimers or other qualitatively abnormal "bands" that indicate an abnormal VWF structure (table 1).

Ristocetin-induced platelet aggregation (RIPA) — The RIPA assay can be performed in all newly diagnosed patients with established VWD and abnormal ratios of platelet-dependent VWF activity to VWF:Ag. RIPA measures the affinity with which VWF binds to the platelet receptor GPIb. The end-point of this assay is platelet aggregation, using the patient's platelet-rich plasma (PRP) as a source of VWF and platelets and low concentrations of ristocetin.

The RIPA test is different from the ristocetin cofactor activity (VWF:RCo) described above (see 'Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)' above), because RIPA evaluates binding of VWF to platelets using suboptimal concentrations of ristocetin and patient PRP, and it does not quantitate VWF.

The RIPA test is performed by placing the patient's PRP in a series of test tubes and sequentially adding lower concentrations of ristocetin to each tube, using a range of concentrations from 0.4 to 1.2 mg/mL. The presence or absence of platelet aggregation is noted at each concentration of ristocetin. PRP from patients with normal VWF does not aggregate at concentrations of ristocetin that are lower than approximately 0.6 to 0.8 mg/mL, but PRP from patients with type 2B VWD will usually aggregate at concentrations of ristocetin of 0.4 to 0.5 mg/mL.

The RIPA test is most useful for identifying enhanced VWF binding to platelets due to a gain-of-function mutation that is characteristic of type 2B VWD, in which the RIPA is increased. (See 'Summary of VWD types' above.)

- RIPA increased – Consistent with type 2B VWD.

- RIPA decreased – Consistent with types 1 (if severe), 2A, 2M, and 3.
- RIPA normal – Consistent with mild types 1, 2A, 2M, and type 2N.

The 2021 VWD guideline suggests targeted genetic testing over the RIPA to determine if a patient has type 2B VWD [2]. Both the RIPA test and genetic testing are sensitive for distinguishing type 2B.

In addition to type 2B VWD, the RIPA test can also be abnormal in some primary disorders of platelet function:

- **Platelet-type VWD** – In platelet-type VWD, RIPA is increased similarly to type 2B VWD. However, the increase is caused by a gain-of-function mutation in the patient's platelet GPIb rather than a variant in *VWF* [37,89,90].

- **Bernard-Soulier syndrome (BSS)** – In BSS, RIPA is absent (table 4). BSS platelets are dysfunctional due to a pathogenic variant in *GPIb* that reduces its function and/or abundance on the platelet surface [91]. These individuals have thrombocytopenia with giant platelets and a bleeding phenotype that is greater than expected based on their platelet count. (See "Inherited platelet function disorders (IPFDs)", section on 'Bernard-Soulier syndrome'.)

Distinction of these conditions from VWD is discussed below. (See 'Differential diagnosis' below.)

VWF binding to factor VIII (VWF:FVIIIB) — Abnormal binding of VWF to factor VIII specifies VWD type 2N. This can be determined by genetic testing and/or a binding assay. *VWF* mutations in the binding site for factor VIII cause decreased binding of VWF to factor VIII and lead to low levels of factor VIII and low ratios of FVIII:VWF:Ag.

- The binding assay is usually performed in an ELISA format, using the patient's plasma VWF to coat the wells and recombinant factor VIII as the added binding protein. The ability of the patient's plasma VWF to bind factor VIII is compared with that of a normal plasma pool [35].

- Genetic testing can also be diagnostic for type 2N, and the 2021 guideline points out that it can provide information beyond the diagnosis with regard to the inheritance (eg, homozygous versus doubly heterozygous) for genetic counseling [2]. If genetic testing is negative, however, the VWF:FVIIIB should definitely be obtained.

Response to DDAVP — The response to a desmopressin (DDAVP) trial may reveal or confirm a diagnosis of type 1C or type 2N when the four-hour post-DDAVP VWF level falls by >30 percent over peak, or if the rise in factor VIII activity after DDAVP is short-lived. The results can also be

used to guide management. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'DDAVP trial'.)

Specialized tests for VWD

VWF propeptide (VWF:pp) — The VWF:pp is a protein sequence that is part of VWF when it is initially synthesized; it is cleaved during the release of VWF into the circulation, and it circulates independently with its own half-life. As such, it is a marker for the amount of newly synthesized and released VWF [92-94]. When VWF has a short half-life (as in rapid clearance of VWF due to any cause), the ratio of VWF:pp to VWF:Ag is elevated (ratio >3). This assay has been used as a surrogate measurement for a shortened VWF half-life, and the VWF:pp to VWF:Ag ratio can be helpful in the diagnosis and follow-up of acquired von Willebrand syndrome [95]. (See "Acquired von Willebrand syndrome".)

The 2021 guideline suggests that VWF:pp not be used for the diagnosis of VWD type 1C, since a DDAVP trial is important for management and yields similar information about half-life [2].

Genetic testing — Genetic testing is not required for the diagnosis of VWD, but it may be useful in selected settings [67,96].

It can be useful in the following settings:

- Diagnosis or confirmation of type 2N
- Distinguishing type 2N from mild hemophilia A in males
- Distinguishing type 2N from hemophilia A carrier status in female carriers of hemophilia A
- Diagnosis or confirmation of type 2M
- Diagnosis or confirmation of type 2B
- Distinguishing type 2B from platelet-type VWD
- Diagnosis or confirmation of type 2A
- Prenatal testing for type 3 VWD

Further details of the *VWF* gene structure and mechanisms by which different mutations affect VWF function are discussed separately. (See "Pathophysiology of von Willebrand disease".)

The *VWF* gene is very large and has not been completely characterized [97]. Some variants that were previously classified as disease causing (eg, M740I) were subsequently determined to be common in the general population, for example, in African Americans [67,97]. New mutations in mRNA processing are being studied and some may be causal [98]. Importantly, as noted above, a significant portion of individuals with type 1 VWD (as many as one-third) do not have an apparent *VWF* mutation, suggesting that variants in other genes that control VWF levels or that

control other proteins important in hemostasis may be responsible. Caution should be used in interpreting results of genetic testing that reveals new mutations; these may be normal variants.

Assays under development — A number of groups are working to develop assays that provide diagnostic information using platforms that can be automated or that can test the multiple physiologic roles of VWF in the same setting. As examples:

- **ELISA assay for classification** – An assay has been reported that uses enzyme-linked immunosorbent assay (ELISA) plate technology for discriminating between VWD types 1 and 2, including assignment of each type 2 [99]. The multi-well format and computer-based statistical analysis allow testing of patient plasma across multiple reagents including GPIbM, GPIb plus ristocetin, collagen, and factor VIII. In a sample of 160 previously diagnosed patients with VWD, the accuracy was greater than 88 percent. Larger studies using this approach are needed.

- **Assays using flow (shear stress)** – Several assays have been published that incorporate shear stress into the assay as a means of promoting VWF binding to platelet GPIb [100,101]. Shear stress is the physiologic stimulus for VWF-platelet binding; high shear stress causes unfolding of the VWF molecule to expose GPIb binding sites in vivo. In contrast, ristocetin binding is based on a non-physiologic means of activating the binding reaction. Shear-based assays have not been adopted on a large scale.

We do not use testing such as thromboelastography (TEG) because the results may be non-specific, and there appears to be significant overlap between individuals with type 1 VWD and unaffected individuals.

INTERPRETATION AND DIAGNOSIS

Clinical considerations and evolution of guidelines — The diagnosis of VWD is a clinical and laboratory diagnosis that incorporates the personal bleeding history, family history, and results of laboratory testing (algorithm 1).

There are no confirmatory genetic tests available for the diagnosis of most cases of type 1 VWD, which comprise the vast majority of VWD cases [102]. It is uncommon that the diagnosis of VWD would be made in an individual with a negative personal and family history of bleeding.

The results of laboratory testing are a continuum, and the diagnostic cutoffs for platelet-dependent von Willebrand factor (VWF) activity and antigen (VWF:Ag) levels for the diagnosis of

VWD are controversial.

- Guidelines in 2008 set the levels for a definitive diagnosis as <30 international units [IU]/dL and created a category of "low VWF" for individuals with levels of 30 to 50 IU/dL (this category of patients may have VWD, an undiagnosed platelet disorder, another unrecognized bleeding disorder, or no disease) [1]. This change in diagnostic limits also took into account the observations that VWF levels are affected by several common physiologic conditions and by variants of certain genes such as *ABO*, *STXBP5*, or *CLEC4M*, which can alter VWF levels [86]. There was, however, a danger that true VWF patients with VWF levels of 30 to 50 IU/dL would be missed and not be diagnosed as having VWD.

- A 2021 guideline from the American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), National Hemophilia Foundation (NHF), and World Federation of Hemophilia set the cutoff level for diagnosing VWD at <30 IU/dL (<0.3 IU/mL; <30 percent) regardless of bleeding [2].

  It also recommended that patients with a history of bleeding and VWF levels of 30 to 50 IU/dL (or levels between 30 and the lower limit of normal range in the local laboratory) be given the diagnosis of VWD. This definition errs on the side of not missing a diagnosis of VWD and access to further health care; it applies mainly to VWD type 1, since other testing would confirm the diagnosis in type 2 VWD, and type 3 VWD would have very low levels of VWF. Individuals with VWF values in the range of 30 to 50 IU/dL who do not have bleeding would not be designated as having VWD. Exceptions to this may include individuals (often, children) who have not had bleeding challenges).

Diagnosis — Diagnosis is as follows:

- **VWF <30 percent** – Individuals with platelet-dependent VWF activity (VWF:RCo or VWF:GPIbR) or VWF:Ag <30 IU/dL (<30 percent) are diagnosed with VWD regardless of bleeding history. Tests to determine the type of VWD are appropriate since the type has implications for bleeding risk and management. (See 'Additional testing to characterize (classify) the type of VWD' above.)

- **VWF 30 to 50 percent (or the lower limit of normal range in the local laboratory), and positive personal bleeding history** – Individuals with a positive personal history of bleeding and platelet-dependent VWF activity or VWF:Ag of 30 to 50 percent are given the diagnosis of VWD (providing the VWF levels are not spuriously elevated due to stress, inflammation, or other stimuli that increase VWF). These individuals usually have had repeat testing with plans for careful and non-stressful baseline testing. (See 'Repeat testing in individuals with borderline or discordant clinical and laboratory findings' above.)

- **VWF levels of 30 to 50 percent and negative personal bleeding history** – Individuals with a negative personal bleeding history (providing they have had bleeding challenges) and platelet-dependent VWF activity or VWF:Ag of ≥30 to 50 percent are not diagnosed with VWD.

Other contributing factors:

- VWF levels tend to be lower in individuals with type O blood (approximately 25 to 30 percent lower than in individuals with type A, B, or AB) [103-105]. Approximately 80 percent of individuals in the United States with levels of 30 to 50 IU/dL have blood type O [1]. This is significantly higher than the overall prevalence of type O in the United States population. (See "Pathophysiology of von Willebrand disease", section on 'Clearance and control of plasma VWF levels'.)

- VWF levels tend to be lower in White individuals than in many African American individuals or individuals of African ancestry, although there is substantial overlap. In a series of 310 participants in an unrelated study in South Africa, VWF:Ag was 102 IU/dL in White South Africans, 118 IU/dL in Zulu Africans, and 105 IU/dL in individuals from the Durban region of South Africa, with predominantly Indian ancestry [106].

A meta-analysis of 21 studies concluded that platelet-dependent VWF activity and VWF:Ag levels <0.3 IU/dL (<30 percent) are reasonable for diagnosing VWD, as are levels of 0.30 to 0.5 IU/dL (30 to 50 percent) in individuals with a personal history of bleeding, although certainty is very low [38]. The analysis also showed that pathogenic variants in the *VWF* gene are more likely to be found when VWF levels are <0.3 IU/dL (pathogenic variants found in 75 to 82 percent) than with VWF levels of 0.3 to 0.5 IU/dL (pathogenic variants found in 44 to 60 percent).

Considering the VWF levels across the general population, there are many more people with VWF levels of 30 to 50 IU/dL who do not have bleeding symptoms than those who have bleeding symptoms. It is possible that these lower VWF levels contribute partly to any bleeding these patients may have and that additional factors besides low VWF also contribute [107].

If an individual has a VWF level of 30 to 50 percent and the bleeding history is uncertain, it is appropriate to refer such individuals to a VWD specialist who can evaluate the bleeding history, perform additional testing to detect rare VWD subtypes, and perform other coagulation and platelet testing in patients with apparently normal initial testing. (See 'Repeat testing in individuals with borderline or discordant clinical and laboratory findings' above and 'Additional testing to characterize (classify) the type of VWD' above.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of VWD includes inherited and acquired bleeding disorders, as well as the possibility that an individual does not have a bleeding disorder.

Mild hemophilia A — Like hemophilia A (factor VIII deficiency), VWD types 2N and 3 usually have significantly low factor VIII levels and can share similar symptoms. Points of differentiation and tests to distinguish these conditions include:

- **Severity of bleeding** – In hemophilia A, bleeding can be severe and presents early in life, but bleeding may be mild and may present at an older age. In VWD type 2N, bleeding is variable but may be severe. In VWD type 3, bleeding is usually severe.

- **Type of bleeding** – In hemophilia A, bleeding occurs in joints and muscles. In VWD type 2N, bleeding can be mucocutaneous but also into joints and muscles. In VWD type 3, bleeding occurs in both mucocutaneous sites and joints and muscles.

- **Inheritance and sex distribution** – Hemophilia A is X-linked recessive; males are generally more severely affected (female carriers [heterozygotes] may be affected). VWD types 2N and 3 are autosomal; males and females are equally affected.

- **Laboratory testing** – In hemophilia A, platelet-dependent von Willebrand factor (VWF) activity, VWF antigen (VWF:Ag), and factor VIII binding are normal. In VWD type 2N, platelet-dependent VWF activity and VWF:Ag can be normal, but binding of the patient's VWF to factor VIII is low. In VWD type 3, platelet-dependent VWF activity and VWF:Ag are undetectable or extremely low. (See "Clinical manifestations and diagnosis of hemophilia".)

Inherited platelet disorders — There are several inherited platelet disorders that may present with similar bleeding patterns as VWD (eg, mucosal or skin bleeding). In addition, there are two inherited platelet disorders that produce abnormal results on the ristocetin-induced platelet aggregation (RIPA) test. (See 'Ristocetin-induced platelet aggregation (RIPA)' above.)

- **Bernard-Soulier syndrome (BSS)** – BSS is characterized by thrombocytopenia and giant platelets; it is due to a mutation that causes a low concentration of glycoprotein Ib (GPIb) in platelets. Like moderate to severe VWD types 1, 2A, 2M, and 3, BSS is associated with reduced RIPA. Unlike VWD, in BSS the VWF:Ag and platelet-dependent VWF activity are normal.

- **Platelet-type (pseudo) VWD** – Platelet-type VWD has a very similar phenotype to type 2B VWD; it is due to a gain-of-function mutation in platelet *GPIb* that enhances VWF binding to

platelets, leading to increased platelet clearance and thrombocytopenia. Like type 2B VWD, platelet-type VWD is associated with increased RIPA. Unlike VWD, platelet-type VWD has normal VWF multimers and normal VWF genotype. These and other inherited platelet disorders are discussed separately. (See "Inherited platelet function disorders (IPFDs)" and "Approach to the child with bleeding symptoms".)

Acquired von Willebrand syndrome (AVWS) — AVWS refers to acquired deficiency or dysfunction of VWF, which is usually associated with various medical conditions that lead to immune or proteolytic destruction of VWF or to decreased VWF production. Examples include:

- Lymphoproliferative or myeloproliferative disorders
- Autoimmune disorders
- Cardiovascular disease
- Extracorporeal circulation that increases shear stress
- Hypothyroidism
- Certain medications

Like inherited VWD, AVWS presents with symptoms and laboratory results compatible with VWD. However, it generally presents later in life without a previous personal or family bleeding history, and it usually can be differentiated by finding an associated disease and often by measuring the ratio of VWF propeptide to VWF:Ag. (See 'VWF propeptide (VWF:pp)' above and "Acquired von Willebrand syndrome".)

SCREENING FAMILY MEMBERS

For first-degree relatives who are symptomatic, the evaluation is similar to that discussed above, with the exception that additional laboratory testing can be more focused if the propositus has a known *VWF* genotype.

For asymptomatic first-degree relatives, the decision to test for VWD may be based on the severity of VWD in family members, the likelihood of bleeding challenges (eg, planned surgeries, high-impact sports), and the patient's desire for testing.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: von Willebrand disease".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: von Willebrand disease (The Basics)")
- Beyond the Basics topics (see "Patient education: von Willebrand disease (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: von Willebrand disease".)

SUMMARY AND RECOMMENDATIONS

- **Classification** – Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Symptomatic disease affects 1 in 1000 people. There are three types (table 1). (See 'Epidemiology' above and 'Summary of VWD types' above.)

  - Type 1 (reduced von Willebrand factor [VWF]) is the most common
  - Type 2 (dysfunctional VWF), includes four subtypes
  - Type 3 (absent/undetectable VWF) is rare

  Transmission is usually autosomal dominant. Types 2N, 3 and some 2A and 2M are autosomal recessive.

Acquired von Willebrand syndrome (AVWS) is due to conditions that decrease VWF production or increase removal. (See "Acquired von Willebrand syndrome".)

- **Presentation** – Bruising, mucocutaneous bleeding, heavy menstrual bleeding, and postpartum bleeding are common. Gastrointestinal bleeding is less common; gastrointestinal angiodysplasia may contribute. Joint and muscle bleeding are not typical but can be seen with types 2N and 3. Some individuals have a normal complete blood count (CBC); many have normal coagulation studies. Some have a prolonged activated partial thromboplastin time (aPTT) due to low factor VIII. Some have thrombocytopenia (type 2B) or microcytic anemia (from iron deficiency). VWF levels increase with aging, inflammation, and estrogen. (See 'Clinical features' above.)

- **Evaluation** – VWD should be considered in individuals with bleeding (especially mucocutaneous), positive family history, mild thrombocytopenia, unexplained prolonged aPTT, or apparent hemophilia A. Accurate bleeding history is essential; a bleeding assessment tool (BAT) provides an objective picture. (See 'Evaluation' above.)

- **Diagnosis** – Initial testing includes CBC, platelet count, and coagulation studies. Screening tests for VWD include VWF antigen (VWF:Ag), platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM), and factor VIII activity (algorithm 1).

  Platelet-dependent VWF activity or VWF:Ag <30 percent confirms VWD. VWF is an acute phase reactant; individuals with VWF:Ag or platelet-dependent VWF activity of 30 to 50 percent should be retested. VWF level 30 to 50 percent in an individual with a bleeding history qualifies as VWD; with a negative bleeding history (provided bleeding challenges have occurred) it does not. (See 'Laboratory testing' above and 'Interpretation and diagnosis' above.)

- **Type** – After diagnosis, specialized assays are used to determine the type (table 3). The ratio of platelet-dependent VWF activity to VWF:Ag helps distinguish type 1 from type 2 (algorithm 2). VWF multimer analysis and ristocetin-induced platelet aggregation (RIPA) are also helpful. Concordant reduction of platelet-dependent VWF activity and VWF:Ag is consistent with type 1; discordant results suggest type 2A, 2B, or 2M; and absent/undetectable VWF suggests type 3. Low factor VIII activity and low factor VIII activity to VWF:Ag ratio suggests type 2N. Genetic testing is not helpful in most cases of type 1 but can be very helpful in certain type 2 and 3 patients. (See 'Additional testing to characterize (classify) the type of VWD' above.)

- **Differential diagnosis** – The differential diagnosis includes mild hemophilia, hereditary platelet disorders, and AVWS. (See 'Differential diagnosis' above and "Approach to the child

with bleeding symptoms" and "Approach to the adult with a suspected bleeding disorder".)

- **Treatment** – Separate topics discuss pathophysiology and treatment of VWD. (See "Pathophysiology of von Willebrand disease" and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery" and "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care".)

REFERENCES

1. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008; 14:171.
2. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv 2021; 5:280.
3. Ciavarella G, Ciavarella N, Antoncecchi S, et al. High-resolution analysis of von Willebrand factor multimeric composition defines a new variant of type I von Willebrand disease with aberrant structure but presence of all size multimers (type IC). Blood 1985; 66:1423.
4. Mannucci PM, Lombardi R, Castaman G, et al. von Willebrand disease "Vicenza" with larger-than-normal (supranormal) von Willebrand factor multimers. Blood 1988; 71:65.
5. Schneppenheim R, Federici AB, Budde U, et al. Von Willebrand Disease type 2M "Vicenza" in Italian and German patients: identification of the first candidate mutation (G3864A; R1205H) in 8 families. Thromb Haemost 2000; 83:136.
6. Haberichter SL, Balistreri M, Christopherson P, et al. Assay of the von Willebrand factor (VWF) propeptide to identify patients with type 1 von Willebrand disease with decreased VWF survival. Blood 2006; 108:3344.
7. Eikenboom J, Federici AB, Dirven RJ, et al. VWF propeptide and ratios between VWF, VWF propeptide, and FVIII in the characterization of type 1 von Willebrand disease. Blood 2013; 121:2336.
8. Swystun LL, Lillicrap D. How much do we really know about von Willebrand disease? Curr Opin Hematol 2016; 23:471.
9. Lyons SE, Bruck ME, Bowie EJ, Ginsburg D. Impaired intracellular transport produced by a subset of type IIA von Willebrand disease mutations. J Biol Chem 1992; 267:4424.

10. Gralnick HR, Williams SB, McKeown LP, et al. In vitro correction of the abnormal multimeric structure of von Willebrand factor in type IIa von Willebrand's disease. Proc Natl Acad Sci U S A 1985; 82:5968.
11. Bowman M, Hopman WM, Rapson D, et al. The prevalence of symptomatic von Willebrand disease in primary care practice. J Thromb Haemost 2010; 8:213.
12. Bowman M, Hopman WM, Rapson D, et al. A prospective evaluation of the prevalence of symptomatic von Willebrand disease (VWD) in a pediatric primary care population. Pediatr Blood Cancer 2010; 55:171.
13. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. Thromb Haemost 2000; 84:160.
14. Nilsson IM. Von Willebrand's disease--fifty years old. Acta Med Scand 1977; 201:497.
15. Atiq F, Saes JL, Punt MC, et al. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. EClinicalMedicine 2021; 32:100726.
16. Weyand AC, James PD. Sexism in the management of bleeding disorders. Res Pract Thromb Haemost 2021; 5:51.
17. Dupervil B, Abe K, O'Brien SH, et al. Characteristics, complications, and sites of bleeding among infants and toddlers less than 2 years of age with VWD. Blood Adv 2021; 5:2079.
18. Bowman M, Mundell G, Grabell J, et al. Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. J Thromb Haemost 2008; 6:2062.
19. Lukes AS, Kadir RA, Peyvandi F, Kouides PA. Disorders of hemostasis and excessive menstrual bleeding: prevalence and clinical impact. Fertil Steril 2005; 84:1338.
20. Ragni MV, Machin N, Malec LM, et al. Von Willebrand factor for menorrhagia: a survey and literature review. Haemophilia 2016; 22:397.
21. Lavin M, Aguila S, Dalton N, et al. Significant gynecological bleeding in women with low von Willebrand factor levels. Blood Adv 2018; 2:1784.
22. Byams VR, Kouides PA, Kulkarni R, et al. Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres. Haemophilia 2011; 17 Suppl 1:6.
23. De Wee EM, Knol HM, Mauser-Bunschoten EP, et al. Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease. Thromb Haemost 2011; 106:885.
24. Shankar M, Lee CA, Sabin CA, et al. von Willebrand disease in women with menorrhagia: a systematic review. BJOG 2004; 111:734.

25. James A, Matchar DB, Myers ER. Testing for von Willebrand disease in women with menorrhagia: a systematic review. Obstet Gynecol 2004; 104:381.
26. Chee YL, Townend J, Crowther M, et al. Assessment of von Willebrand disease as a risk factor for primary postpartum haemorrhage. Haemophilia 2012; 18:593.
27. Majluf-Cruz K, Anguiano-Robledo L, Calzada-Mendoza CC, et al. von Willebrand Disease and other hereditary haemostatic factor deficiencies in women with a history of postpartum haemorrhage. Haemophilia 2020; 26:97.
28. Ahr DJ, Rickles FR, Hoyer LW, et al. von Willebrand's disease and hemorrhagic telangiectasia: association of two complex disorders of hemostasis resulting in life-threatening hemorrhage. Am J Med 1977; 62:452.
29. Bush RW, Huff JW. Von Willebrand's disease and severe gastrointestinal bleeding. Report of a kindred. West J Med 1984; 140:781.
30. Sohal M, Laffan M. Von Willebrand disease and angiodysplasia responding to atorvastatin. Br J Haematol 2008; 142:308.
31. Hirri HM, Green PJ, Lindsay J. Von Willebrand's disease and angiodysplasia treated with thalidomide. Haemophilia 2006; 12:285.
32. Franchini M, Mannucci PM. Von Willebrand disease-associated angiodysplasia: a few answers, still many questions. Br J Haematol 2013; 161:177.
33. Tuley EA, Gaucher C, Jorieux S, et al. Expression of von Willebrand factor "Normandy": an autosomal mutation that mimics hemophilia A. Proc Natl Acad Sci U S A 1991; 88:6377.
34. Mazurier C, Dieval J, Jorieux S, et al. A new von Willebrand factor (vWF) defect in a patient with factor VIII (FVIII) deficiency but with normal levels and multimeric patterns of both plasma and platelet vWF. Characterization of abnormal vWF/FVIII interaction. Blood 1990; 75:20.
35. Nishino M, Girma JP, Rothschild C, et al. New variant of von Willebrand disease with defective binding to factor VIII. Blood 1989; 74:1591.
36. Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. Br J Haematol 2000; 111:1236.
37. Enayat MS, Guilliatt AM, Lester W, et al. Distinguishing between type 2B and pseudo-von Willebrand disease and its clinical importance. Br J Haematol 2006; 133:664.
38. Kalot MA, Husainat N, El Alayli A, et al. von Willebrand factor levels in the diagnosis of von Willebrand disease: a systematic review and meta-analysis. Blood Adv 2022; 6:62.

39. Abou-Ismail MY, Ogunbayo GO, Secic M, Kouides PA. Outgrowing the laboratory diagnosis of type 1 von Willebrand disease: A two decade study. Am J Hematol 2018; 93:232.
40. Sanders YV, Giezenaar MA, Laros-van Gorkom BA, et al. von Willebrand disease and aging: an evolving phenotype. J Thromb Haemost 2014; 12:1066.
41. Rydz N, Grabell J, Lillicrap D, James PD. Changes in von Willebrand factor level and von Willebrand activity with age in type 1 von Willebrand disease. Haemophilia 2015; 21:636.
42. Drews CD, Dilley AB, Lally C, et al. Screening questions to identify women with von Willebrand disease. J Am Med Womens Assoc (1972) 2002; 57:217.
43. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. J Thromb Haemost 2005; 3:2619.
44. Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project. Haemophilia 2014; 20:831.
45. https://c.ymcdn.com/sites/www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf (Accessed on February 09, 2016).
46. Kalot MA, Husainat N, Tayiem S, et al. Bleeding assessment tools in the diagnosis of VWD in adults and children: a systematic review and meta-analysis of test accuracy. Blood Adv 2021; 5:5023.
47. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia 2015; 21:e384.
48. Reynen E, Grabell J, Ellis AK, James P. Let's Talk Period! Preliminary results of an online bleeding awareness knowledge translation project and bleeding assessment tool promoted on social media. Haemophilia 2017; 23:e282.
49. Mittal N, Naridze R, James P, et al. Utility of a Paediatric Bleeding Questionnaire as a screening tool for von Willebrand disease in apparently healthy children. Haemophilia 2015; 21:806.
50. Casey LJ, Tuttle A, Grabell J, et al. Generation and optimization of the self-administered pediatric bleeding questionnaire and its validation as a screening tool for von Willebrand disease. Pediatr Blood Cancer 2017; 64.
51. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol 2014; 167:453.

52. Mazurier C, Parquet-Gernez A, Goudemand M. The assay of Factor VIII related antigen by an immuno-enzymatic method. Thromb Haemost 1980; 43:71.
53. Ingerslev J. A sensitive ELISA for von Willebrand factor (vWf:Ag). Scand J Clin Lab Invest 1987; 47:143.
54. Veyradier A, Fressinaud E, Sigaud M, et al. A new automated method for von Willebrand factor antigen measurement using latex particles. Thromb Haemost 1999; 81:320.
55. Coller BS, Gralnick HR. Studies on the mechanism of ristocetin-induced platelet agglutination. Effects of structural modification of ristocetin and vancomycin. J Clin Invest 1977; 60:302.
56. Weiss HJ, Hoyer LW, Rickles FR, et al. Quantitative assay of a plasma factor deficient in von Willebrand's disease that is necessary for platelet aggregation. Relationship to factor VIII procoagulant activity and antigen content. J Clin Invest 1973; 52:2708.
57. Howard MA, Sawers RJ, Firkin BG. Ristocetin: a means of differentiating von Willebrand's disease into two groups. Blood 1973; 41:687.
58. Scott JP, Montgomery RR, Retzinger GS. Dimeric ristocetin flocculates proteins, binds to platelets, and mediates von Willebrand factor-dependent agglutination of platelets. J Biol Chem 1991; 266:8149.
59. Strandberg K, Lethagen S, Andersson K, et al. Evaluation of a rapid automated assay for analysis of von Willebrand ristocetin cofactor activity. Clin Appl Thromb Hemost 2006; 12:61.
60. Salem RO, Van Cott EM. A new automated screening assay for the diagnosis of von Willebrand disease. Am J Clin Pathol 2007; 127:730.
61. Allain JP, Cooper HA, Wagner RH, Brinkhous KM. Platelets fixed with paraformaldehyde: a new reagent for assay of von Willebrand factor and platelet aggregating factor. J Lab Clin Med 1975; 85:318.
62. Flood VH, Gill JC, Morateck PA, et al. Common VWF exon 28 polymorphisms in African Americans affecting the VWF activity assay by ristocetin cofactor. Blood 2010; 116:280.
63. Flood VH, Friedman KD, Gill JC, et al. No increase in bleeding identified in type 1 VWD subjects with D1472H sequence variation. Blood 2013; 121:3742.
64. Bodó I, Eikenboom J, Montgomery R, et al. Platelet-dependent von Willebrand factor activity. Nomenclature and methodology: communication from the SSC of the ISTH. J Thromb Haemost 2015; 13:1345.
65. Boender J, Eikenboom J, van der Bom JG, et al. Clinically relevant differences between assays for von Willebrand factor activity. J Thromb Haemost 2018; 16:2413.

66. Higgins RA, Goodwin AJ. Automated assays for von Willebrand factor activity. Am J Hematol 2019; 94:496.
67. Sharma R, Flood VH. Advances in the diagnosis and treatment of Von Willebrand disease. Blood 2017; 130:2386.
68. Favaloro EJ. Detection of von Willebrand disorder and identification of qualitative von Willebrand factor defects. Direct comparison of commercial ELISA-based von Willebrand factor activity options. Am J Clin Pathol 2000; 114:608.
69. Riddell AF, Jenkins PV, Nitu-Whalley IC, et al. Use of the collagen-binding assay for von Willebrand factor in the analysis of type 2M von Willebrand disease: a comparison with the ristocetin cofactor assay. Br J Haematol 2002; 116:187.
70. Casonato A, Pontara E, Bertomoro A, et al. Abnormal collagen binding activity of 2A von Willebrand factor: evidence that the defect depends only on the lack of large multimers. J Lab Clin Med 1997; 129:251.
71. Rick ME, Krizek DM. Identification of a His54Gln substitution in von Willebrand factor from a patient with defective binding of factor VIII. Am J Hematol 1996; 51:302.
72. Mammen EF, Comp PC, Gosselin R, et al. PFA-100 system: a new method for assessment of platelet dysfunction. Semin Thromb Hemost 1998; 24:195.
73. Fressinaud E, Veyradier A, Truchaud F, et al. Screening for von Willebrand disease with a new analyzer using high shear stress: a study of 60 cases. Blood 1998; 91:1325.
74. Posan E, McBane RD, Grill DE, et al. Comparison of PFA-100 testing and bleeding time for detecting platelet hypofunction and von Willebrand disease in clinical practice. Thromb Haemost 2003; 90:483.
75. Castaman G, Tosetto A, Goodeve A, et al. The impact of bleeding history, von Willebrand factor and PFA-100(®) on the diagnosis of type 1 von Willebrand disease: results from the European study MCMDM-1VWD. Br J Haematol 2010; 151:245.
76. Quiroga T, Goycoolea M, Muñoz B, et al. Template bleeding time and PFA-100 have low sensitivity to screen patients with hereditary mucocutaneous hemorrhages: comparative study in 148 patients. J Thromb Haemost 2004; 2:892.
77. Ratnoff OD, Saito H. Letter: Bleeding in von Willebrand's disease. N Engl J Med 1974; 290:1089.
78. Peterson P, Hayes TE, Arkin CF, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. Arch Surg 1998; 133:134.

79. Abildgaard CF, Suzuki Z, Harrison J, et al. Serial studies in von Willebrand's disease: variability versus "variants". Blood 1980; 56:712.
80. van den Burg PJ, Hospers JE, van Vliet M, et al. Changes in haemostatic factors and activation products after exercise in healthy subjects with different ages. Thromb Haemost 1995; 74:1457.
81. Rickles FR, Hoyer LW, Rick ME, Ahr DJ. The effects of epinephrine infusion in patients with von Willebrand's disease. J Clin Invest 1976; 57:1618.
82. McGill SN, Ahmed NA, Christou NV. Increased plasma von Willebrand factor in the systemic inflammatory response syndrome is derived from generalized endothelial cell activation. Crit Care Med 1998; 26:296.
83. van der Poll T, van Deventer SJ, Pasterkamp G, et al. Tumor necrosis factor induces von Willebrand factor release in healthy humans. Thromb Haemost 1992; 67:623.
84. Bennett B, Ratnoff OD. Changes in antihemophilic factor (AHF, factor 8) procoagulant activity and AHF-like antigen in normal pregnancy, and following exercise and pneumoencephalography. J Lab Clin Med 1972; 80:256.
85. Sié P, Caron C, Azam J, et al. Reassessment of von Willebrand factor (VWF), VWF propeptide, factor VIII:C and plasminogen activator inhibitors 1 and 2 during normal pregnancy. Br J Haematol 2003; 121:897.
86. Desch KC. Regulation of plasma von Willebrand factor. F1000Res 2018; 7:96.
87. Hoyer LW, Shainoff JR. Factor VIII-related protein circulates in normal human plasma as high molecular weight multimers. Blood 1980; 55:1056.
88. Krizek DR, Rick ME. A rapid method to visualize von willebrand factor multimers by using agarose gel electrophoresis, immunolocalization and luminographic detection. Thromb Res 2000; 97:457.
89. Weiss HJ, Meyer D, Rabinowitz R, et al. Pseudo-von Willebrand's disease. An intrinsic platelet defect with aggregation by unmodified human factor VIII/von Willebrand factor and enhanced adsorption of its high-molecular-weight multimers. N Engl J Med 1982; 306:326.
90. Miller JL, Kupinski JM, Castella A, Ruggeri ZM. von Willebrand factor binds to platelets and induces aggregation in platelet-type but not type IIB von Willebrand disease. J Clin Invest 1983; 72:1532.
91. Savoia A, Kunishima S, De Rocco D, et al. Spectrum of the mutations in Bernard-Soulier syndrome. Hum Mutat 2014; 35:1033.

92. Haberichter SL, Christopherson PA, Flood VH, et al. Von Willebrand Factor (VWF) Propeptide and Factor VIII (FVIII) Levels Identify the Contribution of Decreased Synthesis and/or Increased Clearance Mechanisms in the Pathogenesis of Type 1 Von Willebrand Disease (VWD) in the Zimmerman Program. Blood 2016; 128:874.
93. Haberichter SL. von Willebrand factor propeptide: biology and clinical utility. Blood 2015; 126:1753.
94. Haberichter SL. VWF propeptide in defining VWD subtypes. Blood 2015; 125:2882.
95. Stufano F, Boscarino M, Bucciarelli P, et al. Evaluation of the Utility of von Willebrand Factor Propeptide in the Differential Diagnosis of von Willebrand Disease and Acquired von Willebrand Syndrome. Semin Thromb Hemost 2019; 45:36.
96. Rao ES, Ng CJ. Current approaches to diagnostic testing in von Willebrand Disease. Transfus Apher Sci 2018; 57:463.
97. Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. Blood 2015; 125:2029.
98. Borràs N, Orriols G, Batlle J, et al. Unraveling the effect of silent, intronic and missense mutations on VWF splicing: contribution of next generation sequencing in the study of mRNA. Haematologica 2019; 104:587.
99. Roberts JC, Morateck PA, Christopherson PA, et al. Rapid discrimination of the phenotypic variants of von Willebrand disease. Blood 2016; 127:2472.
100. Branchford BR, Ng CJ, Neeves KB, Di Paola J. Microfluidic technology as an emerging clinical tool to evaluate thrombosis and hemostasis. Thromb Res 2015; 136:13.
101. Lehmann M, Ashworth K, Manco-Johnson M, et al. Evaluation of a microfluidic flow assay to screen for von Willebrand disease and low von Willebrand factor levels. J Thromb Haemost 2018; 16:104.
102. Sadler JE. Von Willebrand disease type 1: a diagnosis in search of a disease. Blood 2003; 101:2089.
103. Gill JC, Endres-Brooks J, Bauer PJ, et al. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 1987; 69:1691.
104. O'Donnell J, Boulton FE, Manning RA, Laffan MA. Genotype at the secretor blood group locus is a determinant of plasma von Willebrand factor level. Br J Haematol 2002; 116:350.
105. Nitu-Whalley IC, Lee CA, Griffioen A, et al. Type 1 von Willebrand disease - a clinical retrospective study of the diagnosis, the influence of the ABO blood group and the role of the bleeding history. Br J Haematol 2000; 108:259.

106. Sukhu K, Poovalingam V, Mahomed R, Giangrande PL. Ethnic variation in von Willebrand factor levels can influence the diagnosis of von Willebrand disease. Clin Lab Haematol 2003; 25:247.

107. Lavin M, Aguila S, Schneppenheim S, et al. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. Blood 2017; 130:2344.

Topic 1307 Version 50.0

GRAPHICS

Classification of inherited von Willebrand disease (VWD)

Type	Clinical features	Laboratory findings	Comments on treatment
Type 1 (partial quantitative deficiency)	▪ Accounts for approximately 75% of individuals with VWD ▪ Variable bleeding severity from mild to severe ▪ AD inheritance	▪ VWF activity and antigen decreased concordantly ▪ Factor VIII activity normal or reduced ▪ RIPA decreased (may be normal in mild disease) ▪ Multimer electrophoresis: All multimers present and uniformly decreased ▪ In type 1C (increased clearance), the VWF level at 4 hours post DDAVP trial shows rapid reduction in VWF	▪ DDAVP* in most patients ▪ VWF concentrates in moderate, severe, and type 1C patients
Type 2 (qualitative variant)			
Type 2A (selective deficiency of HMW multimers, reduced binding to platelet GPIb)	▪ Accounts for approximately 10 to 20% of individuals with VWD ▪ Moderate to severe bleeding ▪ Mostly AD; occasional AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced ▪ RIPA decreased ▪ Multimer electrophoresis: Large multimers decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients ▪ Follow VWF levels
Type 2B (enhanced binding of HMW VWF multimers to platelet GPIb; may have	▪ Accounts for approximately 5% of individuals with VWD	▪ VWF activity decreased out of proportion to VWF antigen	▪ DDAVP* should be used with caution; it may be used to treat minor bleeding if a

decrease in circulating HMW multimers)	▪ Moderate to severe bleeding ▪ Thrombocytopenia ▪ AD inheritance	▪ Factor VIII activity normal or reduced ▪ Thrombocytopenia ▪ RIPA increased ▪ Multimer electrophoresis: Usually decreased large multimers	trial of DDAVP performed when the patient is not bleeding has demonstrated that the platelet count drop is temporary. Many experts will avoid DDAVP even for a temporary platelet count drop. ▪ VWF concentrates in moderate and severe patients
Type 2M (reduced binding of VWF to platelet GPIb)	▪ Uncommon ▪ Moderate to severe bleeding ▪ AD or AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or decreased ▪ RIPA decreased ▪ Multimer electrophoresis: All multimers present and uniformly decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients
Type 2N (reduced binding of VWF to factor VIII)	▪ Uncommon ▪ Clinically similar to hemophilia A with joint, soft tissue, and urinary bleeding ▪ AR inheritance	▪ VWF activity and antigen normal ▪ Factor VIII levels low (5 to 15%) ▪ RIPA normal ▪ Multimer electrophoresis: Normal	▪ DDAVP* ▪ VWF concentrates ▪ Monitor VWF and factor VIII levels
Type 3 (severe quantitative deficiency/absent VWF)	▪ Rare ▪ Clinically similar to hemophilia A with joint and soft tissue bleeding in addition to mucocutaneous bleeding ▪ AR inheritance	▪ VWF activity and antigen absent or markedly decreased ▪ Factor VIII levels low (1 to 10%) ▪ RIPA absent or very low ▪ Multimer electrophoresis:	▪ VWF concentrates ▪ Factor VIII replacement ▪ Do **not** use DDAVP to treat bleeding (will not be effective)

		Undetectable or too faint to visualize	

This table summarizes types of inherited VWD. Acquired von Willebrand syndrome (AVWS) is an acquired condition (not genetically transmitted) that mimics inherited VWD; AVWS has various underlying causes. Refer to UpToDate for additional details of the presentation, diagnosis, and management of VWD and AVWS.

AD: autosomal dominant; AR: autosomal recessive; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; GPIb: platelet glycoprotein Ib; HMW: high molecular weight; RIPA: ristocetin-induced platelet aggregation; VWD: von Willebrand disease; VWF: von Willebrand factor.

* DDAVP should only be used after a therapeutic trial (when not bleeding) shows efficacy in raising VWF levels (or factor VIII levels in type 2N disease) to >50%.

Adapted from:

1. *Sadler JE, Budde U, Eikenboom JCJ, et al. Update on the pathophysiology and classification of von Willebrand disease: A report of the Subcommittee on von Willebrand factor. J Thromb Haemost 2006; 4:2103.*
2. *The National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation, and Management of Von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832, December 2007.*
3. *James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv 2021; 5:280.*

Graphic 71525 Version 15.0

Medications and other substances that may increase the risk of bleeding or bruising

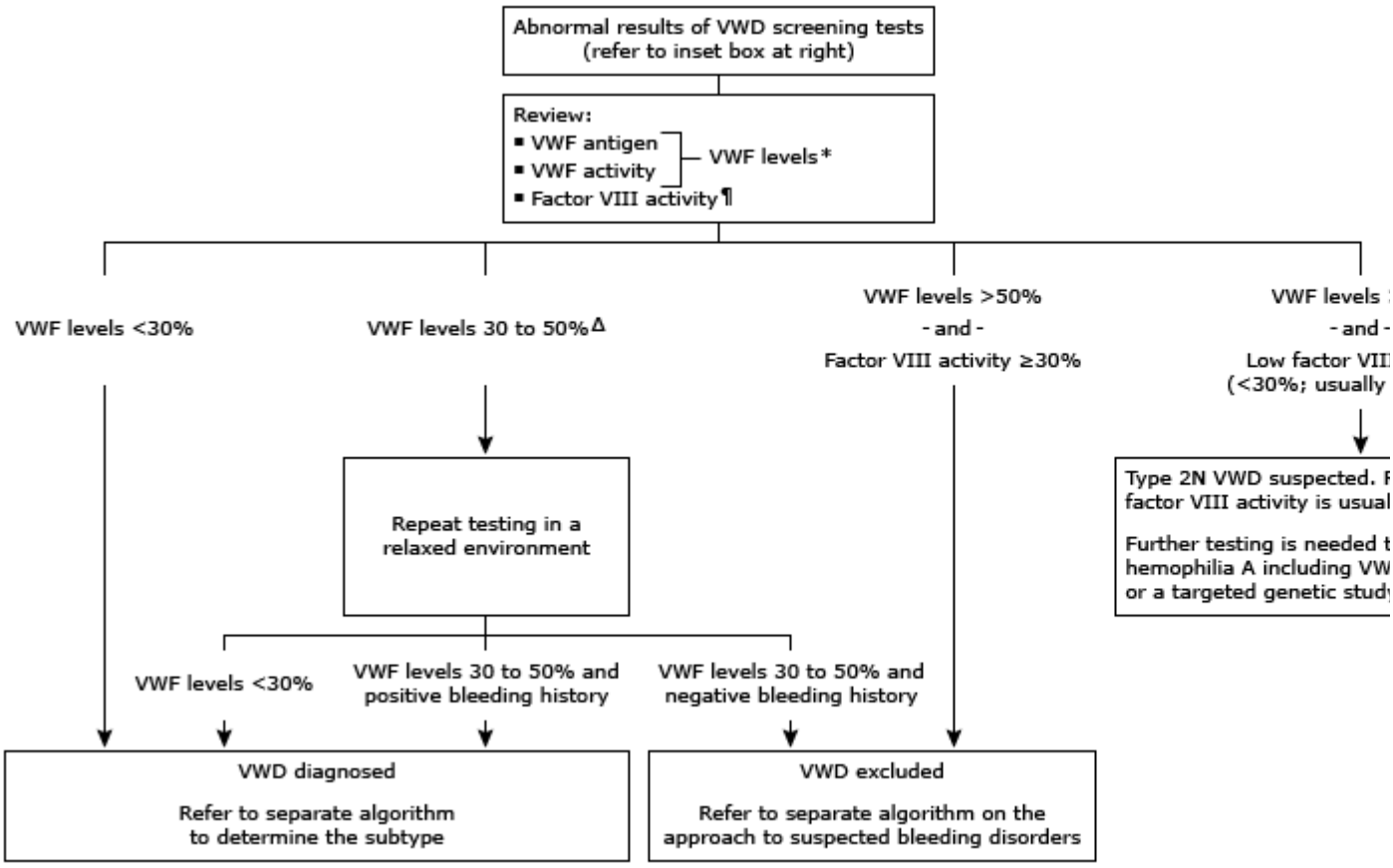
Drug class or substance	Mechanism
Anticoagulants	Interfere with clot formation (secondary hemostasis)
Antiplatelet agents, including NSAIDs	Interfere with platelet function (primary hemostasis)
Glucocorticoids	Interfere with vascular integrity
Antibiotics	Cause vitamin K deficiency, especially with longer use Some interfere with platelet function
SSRIs	Interfere with platelet function (primary hemostasis)
Alcohol	Complications of liver disease may affect clot formation and may cause thrombocytopenia May cause thrombocytopenia due to direct marrow toxicity
Vitamin E	Interferes with vitamin K metabolism in some individuals
Garlic	Interferes with platelet function in some individuals
Gingko biloba	Unknown

This is a partial list that does not include drugs used for cancer therapy or drugs that alter the metabolism of anticoagulants. The magnitude of increased bleeding risk depends on many factors including the patient's other bleeding risk factors and the specific drug, dose, and duration of use. Fish oil is often cited, but bleeding risk does not appear to be increased. Refer to drug information monographs and UpToDate topics for further information.

NSAIDs: nonsteroidal antiinflammatory drugs; SSRIs: selective serotonin reuptake inhibitors.

Graphic 120264 Version 2.0

Approach to VWD initial diagnosis



Diagnosis of VWD includes both clinical and laboratory features. The evaluation first determines whether VWD is present (as illustrated here) and then determines the subtype, which has implications for management (refer to separate algorithm in UpToDate). Screening may be performed by the primary clinician or hematologist. Secondary testing is generally done by the consulting hematologist or clinician with expertise in diagnosing VWD.

VWD: von Willebrand disease; VWF: von Willebrand factor; ELISA: enzyme-linked immunosorbent assay; GPIb: glycoprotein Ib; HMW: high molecular weight.

* "VWF Levels" includes VWF antigen (VWF:Ag) and/or VWF activity (VWF:Act). Concordant reductions in VWF:Ag and VWF:Act suggest type 1 VWD, or, if both are undetectable or extremely low, type 3 VWD; discordant reductions (VWF:Act lower than VWF:Ag) suggest type 2A, type 2B, or type 2M VWD.

¶ Factor VIII activity can be low in VWD because VWF is a carrier for factor VIII. Factor VIII activity is typically low-normal or moderately decreased in type 1, 2A, 2B, and 2M VWD. Factor VIII activity can be low in type 2N and type 3; in these cases, it is important to distinguish between VWD and mild hemophilia A using VWF levels, and, for type 2N, using additional testing listed in the box above.

Δ Individuals with 30 to 50% VWF levels require repeat testing, especially after recovery from an acute stress or after estrogen exposure (estrogen-containing contraceptives or pregnancy). Diagnosis of VWD in individuals with VWF levels of 30 to 50% is based on the bleeding history.

◇ A VWF:Ag to factor VIII activity ratio >3 is expected; if this does not occur, initial VWD screening should be repeated.

Graphic 131037 Version 2.0

Assays used for diagnosing von Willebrand disease (VWD)

Assay name	What it measures	Method
VWF activity		
VWF activity: Platelet binding	Ability of VWF to bind to:	Quantitate binding of plasma VWF to:
VWF:RCo (ristocetin cofactor activity)	Fixed normal platelets in the presence of ristocetin	Platelets; assess agglutination using dilutions of plasma to quantitate VWF
VWF:GPIbR (binding to platelet glycoprotein Ib)	Recombinant GPIb in the presence of ristocetin	Recombinant GPIb using an ELISA plate or latex or magnetic beads
VWF:GPIbM (binding to a platelet glycoprotein Ib mutant)	Recombinant mutated "gain-of-function" GPIb (GPIbM) in the absence of ristocetin	Recombinant GPIbM using an ELISA plate or latex or magnetic beads
Binding to a monoclonal antibody to the GPIb site)	Binding of a specific monoclonal antibody to the VWF binding site for GPIb	Antibody that is specific for the GPIb binding site in VWF
VWF activity: Collagen binding (VWF:CB)	VWF binding to collagen	Binding of patient plasma VWF to collagen-coated plates in an ELISA assay (usually type I or type III collagen)
VWF antigen (VWF:Ag)	VWF protein concentration measured by immunologic assays (does not imply functional activity)	Immunologic assay using ELISA, RIA, or latex beads
VWF multimer analysis	Distribution of VWF multimers as visualized in gels	Electrophoresis in low concentration agarose gel and visualization using a monospecific antibody to VWF
Ristocetin-induced platelet aggregation (RIPA)	Ability of patient's VWF to bind to platelets in the presence of suboptimal concentrations of ristocetin	Platelet aggregation using patient's platelet-rich plasma and low concentrations of ristocetin (less than required in VWF:RCo)
VWF activity:VWF antigen ratio (VWF:Act/VWF:Ag)	Comparison of functional activity of VWF with its protein concentration	Ratio of measured levels of VWF:Act to VWF:Ag (a ratio of <0.7 suggests type 2A, 2B, or 2M)
Factor VIII activity:VWF:Ag ratio (FVIII/VWF:Ag)	Comparison of factor VIII activity to VWF antigen	Ratio of measured levels of FVIII to VWF:Ag (a low level suggests

		type 2N)

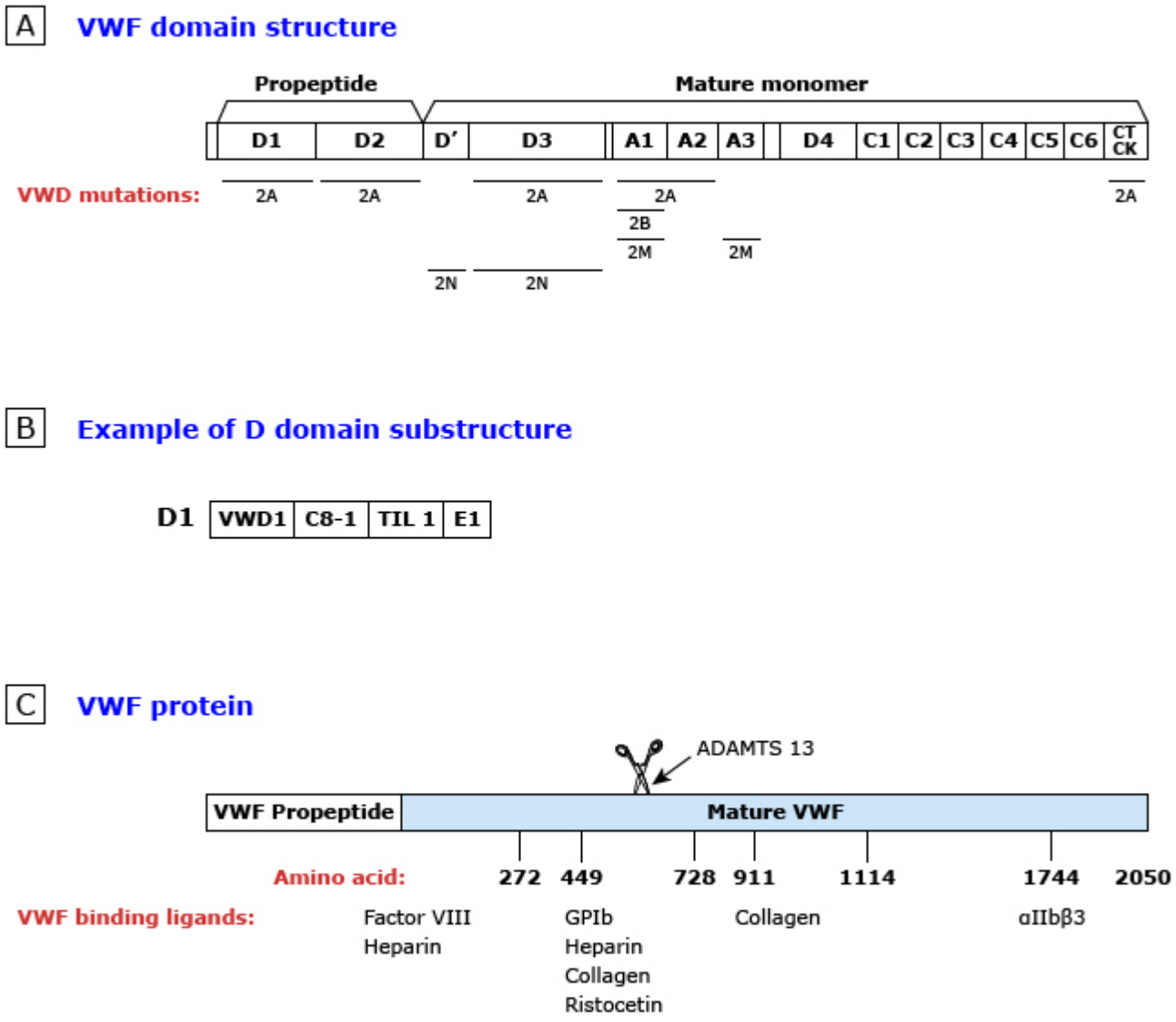
von Willebrand factor is a multimeric glycoprotein that promotes platelet adhesion to collagen and platelet aggregation. VWF also acts as a carrier protein for coagulation factor VIII in plasma. Ristocetin is an antibiotic (no longer in clinical use) that induces VWF binding to platelet glycoprotein Ib (GPIb), which in turn causes platelets to aggregate. Refer to UpToDate for information on how these tests are used and interpreted in the patient evaluation.

VWD: von Willebrand disease; VWF: von Willebrand factor; ELISA: enzyme-linked immunosorbent assay; RIA: radioimmunoassay.

Adapted from: The National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation, and Management of Von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832, December 2007.

Graphic 73391 Version 5.0

Structure of the *VWF* gene including common VWD-associated mutations and domain structure of the protein showing binding sites

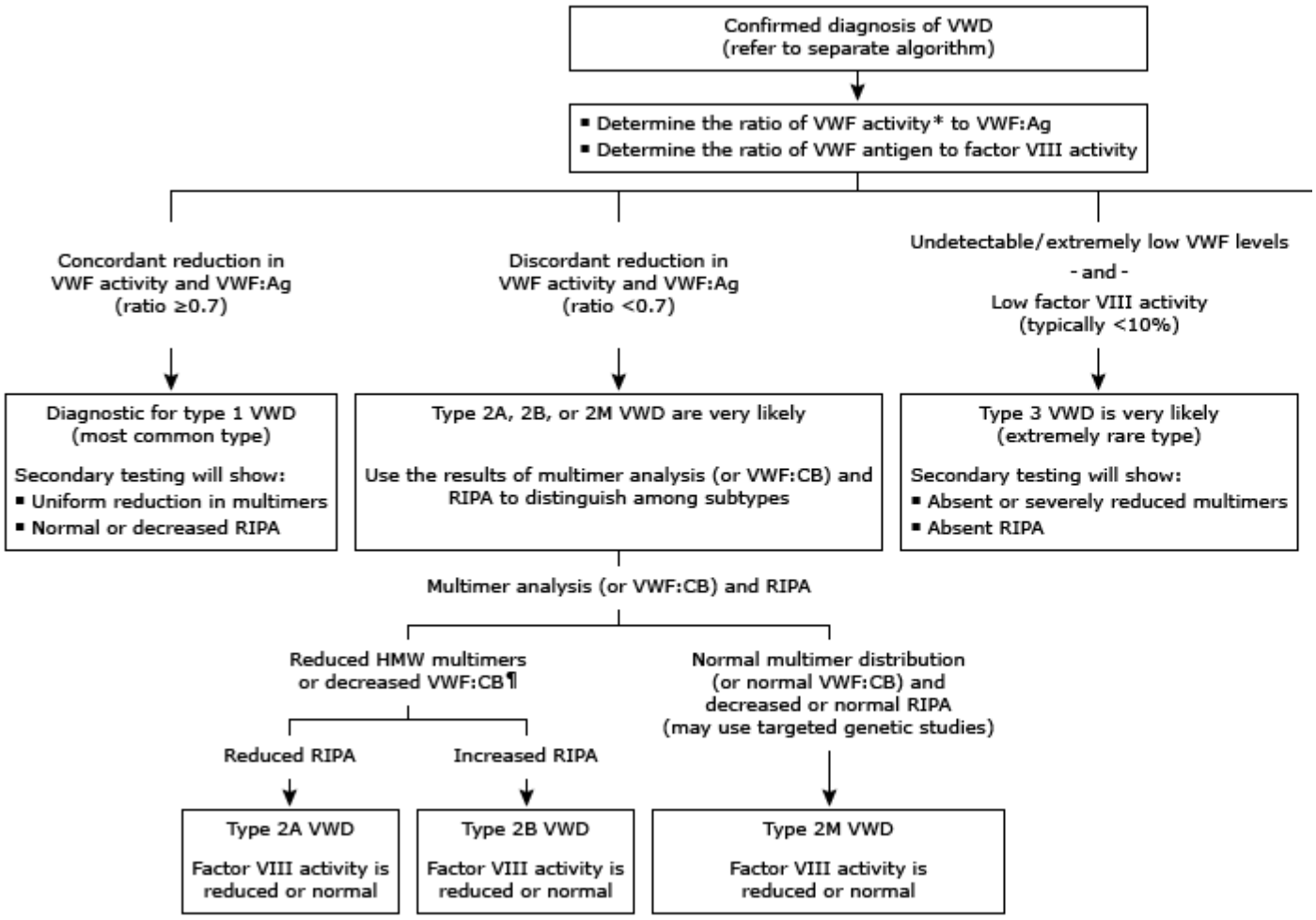


Types 1 and 3 VWD mutations are not shown in the figure because they are distributed widely throughout the VWF sequence. Refer to UpToDate for additional information about D domain assemblies.

VWF: von Willebrand factor; VWD: von Willebrand disease; TIL: trypsin inhibitor-like domain; GPIb: glycoprotein Ib.

Graphic 60152 Version 9.0

Approach to determining VWD subtype



Diagnosis of VWD includes both clinical and laboratory features. After determining whether VWD is present (refer to separate algorithm in UpToDate), one then determines the subtype, which has implications for management, as depicted here. Type 1 is the most common, affecting 75 to 85% of individuals. Type 2A affects approximately 10 to 15% of individuals and type 2B affects approximately 5%. Types 2M and 2N are less common, and type 3 is rare. The bleeding history, family history, and inheritance pattern are also important factors in making the diagnosis of VWD and in assigning the type. Screening may be performed by the primary clinician or hematologist. Secondary testing is generally done by the consulting hematologist or clinician with expertise in diagnosing VWD.

VWD: von Willebrand disease; VWF: von Willebrand factor; VWF:Ag: von Willebrand factor antigen; FVIII: factor VIII; RIPA: ristocetin-induced platelet aggregation.

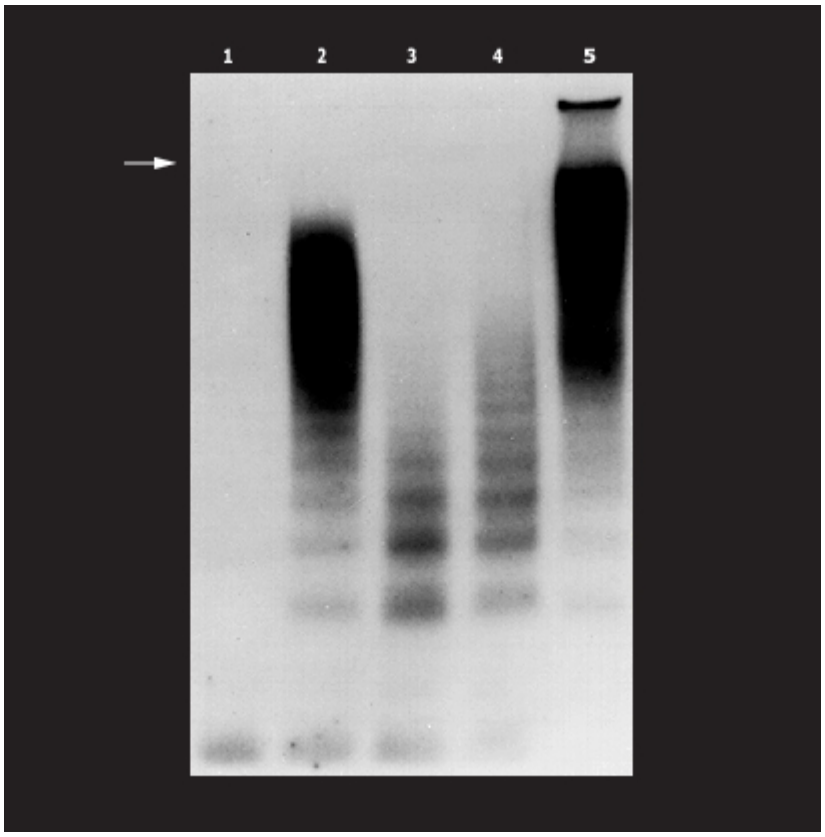
* VWF activity is measured using one of several assays including:
- VWF:RCo – Ristocetin cofactor activity (binding to platelet GPIb in the presence of ristocetin)
- VWF:GPIbR – Binding to recombinant GPIb in the presence of ristocetin
- VWF:GPIbM – Binding to recombinant mutated (gain-of-function) GPIb that does not require ristocetin

In rare cases where VWD is suspected, VWF activity is >50%, and factor VIII activity is <30%, additional testing is needed to distinguish type 2N VWD from mild hemophilia. Refer to inset box for details.

¶ Less commonly, cases of type 2B may have a normal multimer distribution.

Graphic 131040 Version 2.0

VWF multimer analysis



Agarose gel electrophoresis (1.0 percent) of plasma followed by fixation and exposure to a monospecific radiolabeled antibody to VWF. The highest molecular weight multimers of VWF are at the top of the gel (arrow). Lane 1 - severe vWD (type 3) plasma, lane 2 - normal pooled plasma, lane 3 - type 2A plasma, lane 4 - type 2B plasma, lane 5 - vWF extracted from platelets.

From Rick, ME, Diagnosis and management of von Willebrand's syndrome, Med Clin North Am 1994; 78:609.

Graphic 71943 Version 2.0

Patterns of platelet aggregation in selected disorders of platelet function and VWD

Disorder	Aggregation response				Other features
	Primary ADP	Secondary ADP	Collagen	Ristocetin	
VWD	++++	++++	++++	Highly variable	Platelet morphology normal; VWD panel is usually abnormal
Bernard-Soulier syndrome	++++	++++	++++	0	Giant platelets, thrombocytopenia VWD panel is normal
Glanzmann thrombasthenia	0	0	0	+++	Normal platelet morphology
Storage pool disease	++++	0 to ++	++	++	Platelet morphology normal (except in gray platelet subgroup); electron microscopy is abnormal
Secretion defect	++++	0 to ++	++	++	Normal morphology by light and electron microscopy

Expected aggregation responses in various disorders are illustrated. Refer to UpToDate for details. For inherited COX-1 defects or acquired interference with COX-1 function (eg, aspirin), testing can be done using arachidonic acid as the agonist. Results will show absent aggregation response to arachidonic acid as well as reduced secondary aggregation to ADP. Thromboxane receptor defects can be tested for using U-46619 in conjunction with this.

VWD: von Willebrand disease; ADP: adenosine diphosphate; COX-1: cyclooxygenase 1; ++++: normal response; +++: slightly reduced response; ++: reduced response; +: markedly reduced response; 0: no response.

Graphic 69518 Version 4.0