von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care

AUTHOR: Paula James, MD, FRCPC
SECTION EDITOR: Lawrence LK Leung, MD
DEPUTY EDITOR: Jennifer S Tirnauer, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2024.**
This topic last updated: **Sep 11, 2023.**

INTRODUCTION

von Willebrand disease (VWD) is the most common inherited bleeding disorder. Management can vary widely depending on the type of VWD, severity and location of bleeding, and need for invasive procedures.

This topic reviews the management of VWD in less serious bleeding situations, including treatment of minor bleeding and minor surgical procedures and use of DDAVP (1-deamino, 8-D arginine-vasopressin, also called desmopressin), including how to conduct a DDAVP trial.

Separate topics discuss the treatment of bleeding, pregnancy, diagnosis, pathophysiology, and acquired von Willebrand syndrome (AVWS):

- **Treatment of major bleeding, chronic GI bleeding, and major surgery** – (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery".)
- **Heavy menstrual bleeding and pregnancy** – (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)
- **Diagnosis** – (See "Clinical presentation and diagnosis of von Willebrand disease".)
- **Pathophysiology** – (See "Pathophysiology of von Willebrand disease".)

- **Diagnosis and treatment of AVWS** – (See "Acquired von Willebrand syndrome".)

GENERAL PRINCIPLES OF CARE

The following general principles apply to the care of individuals with VWD:

MedicAlert bracelet — We recommend MedicAlert bracelets and/or wallet cards for newly diagnosed patients and counseling on the risk of high-impact, high-velocity sports and other activities.

Reducing bleeding risk — In general, we advise patients to avoid (or to only use sparingly) medications that have a risk of bleeding such as NSAIDs. We also encourage regular dental care. (See "Preventive dental care and counseling for infants and young children".)

Screening for iron deficiency — Patients with chronic bleeding, such as those with heavy menstrual bleeding, GI bleeding, or recurrent epistaxis, should be evaluated for iron deficiency and iron deficiency anemia with a complete blood count (CBC) and ferritin level. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults" and "Treatment of iron deficiency anemia in adults".)

Planning for minor procedures (DDAVP trial) and pregnancy

- **Plan for surgery; DDAVP trial** – Planning for elective surgery and treatment of bleeding, including performing a DDAVP trial when the patient is not bleeding and ensuring close consultation among the surgeon, anesthesiologist, hematologist, and other clinicians involved in the patient's care. (See 'DDAVP trial' below and 'Minor bleeding and minor surgery' below.)

- **Obstetrics and gynecology** – Planning and treatment for menstrual blood loss, obstetric considerations, and evaluation for iron deficiency. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)

- **Education and counseling** – Counseling about the diagnosis, including the type of VWD, bleeding risk, when to seek medical attention, and implications for counseling and testing of relatives. (See "Clinical presentation and diagnosis of von Willebrand disease" and 'Testing and counseling of relatives' below.)

Individuals who require antithrombotic therapy — Individuals with VWD may have cardiovascular or venous thromboembolic (VTE) disease that warrants systemic antithrombotic therapy (eg, anticoagulation, antiplatelet agents) [1,2]

In general, patients with VWD who have an indication for antiplatelet and anticoagulant therapy should receive these treatments [3].

Important considerations in decisions regarding treatment include the following:

- Prior bleeding phenotype (the frequency and severity of historical bleeding, responses to past treatment, and von Willebrand factor [VWF] and factor VIII activity levels)
- Indication for antithrombotic therapy
- Properties of available anticoagulants (eg, availability of reversal agents)

Treatment decisions must be individualized and involve the input of experts in bleeding disorders as well as cardiovascular or thrombotic diseases. VWF concentrate may be required in patients with severe VWD to facilitate anticoagulant therapy.

Testing and counseling of relatives — First-degree relatives of an individual with documented VWD should have a thorough bleeding history taken and potentially be tested, particularly those with a positive bleeding history and/or when the disease in the index patient is moderate or severe.

Preconception testing and counseling is discussed separately. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Reproductive counseling'.)

MINOR BLEEDING AND MINOR SURGERY

Overview (minor bleeding and minor surgery) — Minor bleeding is generally defined as bleeding that causes <2 g/dL decrease in hemoglobin and/or leads to transfusion of <2 units of whole blood or red blood cells, is non-life threatening, and is located in non-critical areas or organs.

For most patients undergoing surgery or being treated for bleeding, von Willebrand factor (VWF) platelet-dependent activity levels should be increased to >0.50 international units/mL (with DDAVP or a VWF concentrate), and an antifibrinolytic agent should be added [3]. In patients with mild VWD undergoing minor mucosal procedures, antifibrinolytic therapy alone can often be used. (See 'Antifibrinolytic agents' below.)

- **DDAVP versus VWF concentrate** – The main options for increasing VWF levels for surgical prophylaxis and treatment of bleeding are DDAVP (desmopressin) and VWF concentrates.

(See 'DDAVP' below and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)

In the majority of type 1 VWD patients with minor bleeding or undergoing minor procedures, DDAVP is usually effective and can generally be used, provided the individual has demonstrated an adequate response in a DDAVP trial. (See 'DDAVP trial' below.)

For those who do not have an adequate response to DDAVP, VWF concentrates should be given, with close access to a facility able to monitor VWF and factor VIII levels. Patients with type 3 and severe types 1 and 2 VWD never/seldom have an adequate response to DDAVP and usually require VWF concentrates. For bleeds or urgent/emergency procedures in individuals with low baseline factor VIII levels, factor VIII may also be indicated. (See 'VWF concentrates and factor VIII for minor bleeding' below.)

DDAVP is not used in children <2 years of age (due to concern about serious side effects) or in any VWD type 3 patients (due to lack of response); moderate (and severe) type 2 patients may not have an adequate response. DDAVP is generally considered to be contraindicated in type 2B VWD patients because of possible thrombocytopenia induced by DDAVP in these individuals. (See 'DDAVP' below.)

- **Antifibrinolytic and topical therapies** – An antifibrinolytic agent to stabilize the clot or a topical agent (table 1) may be appropriate, either alone or in addition to DDAVP, for selected clinical scenarios such as epistaxis, other mucosal bleeding, or surgery in the oropharynx or urogenital tract. Input from the patient and their primary clinician about which agents have been effective in the past may be especially helpful. (See 'Antifibrinolytic agents' below.)

  Use of antifibrinolytic therapy for heavy menstrual bleeding is discussed separately. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Heavy menstrual bleeding'.)

  Topical agents are most often used for nasal or oral bleeding. (See 'Topical therapies' below.)

- **Planning** – Elective procedures should not be performed until the individual has the diagnosis of VWD confirmed (and the type defined) or excluded. This includes newborn infants. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Obstetric considerations'.)

The patient should generally have a trial of DDAVP prior to its use to be certain that they will have an adequate response. (See 'DDAVP trial' below.)

VWF concentrates should be available for use in patients whose bleeding is not controlled by DDAVP, those who do not have an adequate response, and/or those who require prolonged treatment (more than three to five days). (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)

Patients undergoing cardiac procedures such as coronary angiography and/or stenting should be discussed with an expert in bleeding disorders to develop an individualized care plan that balances the risk of bleeding with the risk of harm from different treatments.

Attention should be paid to the other conditions and medications that might aggravate bleeding, including agents that affect platelet function. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'Overview of approach'.)

DDAVP

DDAVP indications and contraindications — Benefits of using DDAVP include decreased exposure to plasma-derived VWF concentrates and release of the most hemostatically active VWF monomers.

- **Appropriate use** –DDAVP (desmopressin) is appropriate for treating minor bleeding or for minor surgical procedures in individuals >2 years of age with VWD (typically mild to moderate type 1 and some type 2) and who have previously demonstrated an adequate response in a DDAVP trial. (See 'DDAVP trial' below.)

  DDAVP response requires an increase of at least >2 times the baseline VWF activity level and a sustained increase of both VWF and factor VIII activity levels (FVIII:C) >0.50 international units/mL for at least four hours [4].

- **Contraindications** – DDAVP is **not** used in the following:

  - Children <2 years, due to serious side effects in this age group
  - Individuals with type 3 VWD, due to lack of response
  - Individuals with lack of response in a DDAVP trial (See 'DDAVP trial' below.)
  - Individuals with cardiovascular disease, due to an increased risk of thrombosis

- **Areas of concern** – Great care should be taken if administering DDAVP to the following individuals:
  - Those >65 years old, due to the increased risk of thrombosis. Some individuals >65 years who have no cardiovascular or thrombotic risk factors may be able to receive DDAVP.
  - Those with a seizure disorder, due to the potential risk of hyponatremia.
- **Pregnancy** – DDAVP has been widely used during pregnancy and delivery with good effectiveness and safety in appropriate VWD patients, but it should be avoided in those with preeclampsia or cardiovascular disease [3]. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Pregnancy'.)
- **Serious bleeding** – DDAVP is **not** appropriate for serious or life-threatening bleeding because it rarely produces a sufficient increase or duration of VWF (or factor VIII), and the increase in VWF may take an hour or more to take effect; these individuals should be treated with VWF concentrates. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)

DDAVP trial

When to do the DDAVP trial — A DDAVP (desmopressin) trial is used to determine whether DDAVP can be used in that patient to reduce surgical bleeding with minor procedures or to treat minor nonsurgical bleeding. DDAVP promotes the release of endogenous VWF from endothelial storage sites; thus, it is most effective in individuals with sufficient baseline VWF levels to allow release of stored VWF. General experience has shown that patients with type 1 VWD are more likely to benefit from DDAVP than those with type 2 VWD.

We recommend a trial of DDAVP in most patients ≥2 years of age who have type 1 VWD and many who have type 2 VWD. Exceptions include adults with type 1 VWD and von Willebrand factor (VWF) levels ≥0.30 international units/mL, who can be presumed to be desmopressin-responsive, and selected patients for whom DDAVP is expected not to be effective, as discussed below. In patients with type 1 VWD who have VWF ≥0.30 international units/mL, it is recommended that clinical use of the medication be accompanied by testing of VWF levels to confirm response after DDAVP administration [3].

The DDAVP trial is performed when the person is not bleeding and not acutely ill; it should be done shortly after diagnosis to assess the response prior to its actual need. The goal is to

determine the effectiveness of DDAVP in the future should it be needed for minor surgery or non-life-threatening bleeding. (See 'Minor bleeding and minor surgery' above.)

We do **not** perform a DDAVP trial in the following patients (see 'DDAVP indications and contraindications' above):

- Children <2 years of age, in whom DDAVP can cause serious side effects and is not recommended for use in this age group.
- Type 3 VWD patients (absent VWF), who lack endogenous stores of VWF and do not have a response.
- Type 2B VWD, because it can cause or worsen thrombocytopenia [3].
- Patients with severe forms of type 1 and type 2 VWD often do not have an adequate response to DDAVP; the decision of whether to perform a trial in these patients should be made individually.
- Patients with cardiovascular disease.

Great care should be taken if administering DDAVP to individuals with a seizure disorder due to the potential risk of hyponatremia.

A DDAVP trial may reveal a shortened half-life of factor VIII, as seen in type 2N, or a shortened half-life of both VWF and factor VIII, as in type 1C, where the VWF-factor VIII complex is cleared rapidly. If the patient is known to have a VWD type with shortened VWF survival, DDAVP may not be useful, and it is not recommended in the setting of surgery in these patients [3]. A clinical decision should be made about the usefulness of DDAVP depending on the situation [5].

DDAVP trial procedure — The trial is usually performed when an individual is well and not bleeding, to determine whether DDAVP can be used for minor bleeding or minor surgery. It is important to consider possible contraindications, cautions, and adverse effects. (See 'DDAVP indications and contraindications' above and 'Adverse effects of DDAVP' below.)

Given that absorption can be variable with different routes of administration, the DDAVP trial should be performed using the route most likely to be used for that patient.

- **Intravenous** – For an intravenous DDAVP trial, dosing is based on body weight. A dose of 0.3 mcg/kg (maximum 20 mcg), is given in 50 mL of saline over 20 to 30 minutes [3]. Blood samples for VWF:Ag, VWF platelet-dependent activity (VWF:RCo or VWF:GPIbM), and factor VIII activity are obtained before DDAVP administration and at one and four hours after the

infusion. These time points are used to assess the increase in levels of VWF and factor VIII and the duration of the effect.

- **Intranasal** – If intranasal use is planned, the intranasal formulation should be used for the trial. Intranasal DDAVP is administered using one puff in each nostril for individuals weighing ≥50 kg (total dose, 2 puffs, 300 mcg) or one puff only in individuals weighing <50 kg (total dose 150 mcg). Blood samples for testing are obtained as above.

  The intranasal formulation of DDAVP for use in VWD and other bleeding disorders (concentration 1.5 mg/mL) is much greater than the formulation for enuresis, which has a lower DDAVP concentration (0.1 mg/mL), and care should be taken to use the correct formulation.

DDAVP increases the risk of hyponatremia, and patients should be fluid-restricted to maintenance levels only for 24 hours after DDAVP administration.

An effective response to DDAVP requires an increase of at least >2 times the baseline VWF activity and a sustained increase of both VWF and factor VIII activity to >0.50 international units/mL for at least four hours [4]. Once an adequate response is documented in a trial, DDAVP can be used for subsequent bleeding episodes or invasive procedures without further trials.

The DDAVP trial in VWD should not be confused with the DDAVP stimulation test used to evaluate for Cushing syndrome (excess adrenocorticotropic hormone [ACTH]).

DDAVP administration and dosing — DDAVP (desmopressin) is generally used after a previous trial demonstrates efficacy. (See 'DDAVP trial' above.)

For those with a demonstrated response, DDAVP can be administered by several routes (intravenous or subcutaneous injection or intranasal spray) (table 2). The subcutaneous preparation is available in the United States but not FDA-approved; it has been used successfully in Europe and in a small number of patients in the United States [6,7]. In general, the DDAVP trial should be done using the route of administration most likely to be used for that patient.

DDAVP increases the risk of hyponatremia, and patients should be fluid-restricted to maintenance levels for 24 hours after administration. (See 'Adverse effects of DDAVP' below.)

The intranasal formulation of DDAVP (Stimate) was voluntarily recalled in mid-2020 due to packaging issues that affected potency. It is predicted to be available again in the second half of 2023. The intravenous and subcutaneous forms of DDAVP were not affected by the recall.

The table summarizes the dosing and adverse effects of DDAVP (table 2). Important considerations include:

- **Goal of therapy** – The goal is an increase of at least >2 times the baseline VWF activity level and a sustained increase of both VWF and FVIII >0.50 international units/mL for at least four hours.

- **Intravenous dosing** – Intravenous dosing is usually used at the onset of minor bleeding or approximately one hour prior to minor procedures and when intravenous access is already available for other reasons.

  The intravenous DDAVP dose is 0.3 mcg/kg (maximum 20 mcg), diluted in 50 mL of normal saline and infused over 20 to 30 minutes [8]. The dose maximum of 20 mcg is commonly used in the United States due to concerns about increasing toxicity (especially hyponatremia) and diminishing efficacy at higher doses.

  The half-life of the released VWF will correspond to the particular half-life of the patient's own VWF protein [9-11].

  A repeat dose may be given at 12 hours if clinically indicated. Subsequent doses can be given once-daily for an additional one to three days, for a total of three to five days of therapy [12,13]. Patients should be monitored for hyponatremia when more than three to four doses are given, particularly if intravenous fluids are used. (See 'Adverse effects of DDAVP' below.)

- **Subcutaneous dosing** – Subcutaneous DDAVP preparations are not approved for use for VWD in the United States, but subcutaneous use is approved in various countries (Canada, countries in Europe), using the same dosing as the intravenous route.

- **Intranasal dosing** – Intranasal administration of DDAVP is a reasonable option for patients who prefer to avoid a hospital or clinic visit (such as for heavy menstrual bleeding) or those who need treatment prior to a planned minor invasive procedure such as dental work or skin biopsy. The VWF and factor VIII responses may not peak until after approximately one and a half to two hours rather than at 30 to 60 minutes as seen after intravenous administration, and the peak level of VWF reached is similar to a lower intravenous dose of 0.2 mcg/kg [14].

  The intranasal DDAVP dose is 150 mcg (one puff) for individuals weighing <50 kg and 300 mcg (2 puffs, one puff into each nostril) for individuals weighing ≥50 kg [8].

Patients (and parents or caregivers) should be instructed to make sure to use the DDAVP formulation for bleeding disorders, which has a concentration of 150 mcg/spray, **not** the formulation for enuresis, which has a much lower concentration (eg, 1 to 10 mcg/spray); the lower dose formulation is not sufficient for VWD treatment.

- **Duration of therapy** – DDAVP is effective for only short-term use (three to five days), since tachyphylaxis develops within a few days. Beyond this period it is generally no longer effective due to depletion of VWF stores, resulting in tachyphylaxis [15]. Additional therapies may be required if bleeding is prolonged for more than a few days. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding' and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'Other therapies'.)

- **Monitoring** – Once a DDAVP trial has shown efficacy, the DDAVP response is usually monitored clinically (assessment for ongoing bleeding). If clinically relevant bleeding occurs after DDAVP, VWF and factor VIII levels should be measured, and administration of a VWF concentrate may be required.

  Monitoring of serum sodium concentration is appropriate for hospitalized individuals, as well as those receiving more than three doses of DDAVP and/or those receiving intravenous fluids. (See 'Adverse effects of DDAVP' below.)

- **Fluid restriction** – DDAVP increases the risk of hyponatremia, and patients should be fluid-restricted to maintenance levels only for 24 hours after administration. Other adverse effects are listed below. (See 'Adverse effects of DDAVP' below.)

Adverse effects of DDAVP — Adverse effects of DDAVP include the following [16]:

- Hyponatremia
- Flushing (due to vasodilation)
- Headache (may be reduced by slowing the infusion rate)
- Nausea
- Hypotension (mild) or hypertension
- Tingling or weakness (may be related to hyponatremia)
- Potential for thrombosis (rare); for this reason, DDAVP is not recommended in patients who have known cardiovascular disease, and it should be used cautiously in a patient at risk of thrombotic complications.

Hyponatremia is due to the antidiuretic hormone activity of DDAVP. It can be severe enough to cause seizures or even death if measures are not taken to monitor for and mitigate it [17]. This

includes close monitoring and limiting of free water intake, both oral and intravenous.

A retrospective review of 107 children and adolescents with bleeding disorders who were treated with DDAVP perioperatively reported that 11 (10 percent) developed a serum sodium <130 mEq/L [18]. One child age 2 years developed seizures. Another study that used a fluid restriction protocol in children treated with DDAVP found that using two-thirds maintenance fluids was an effective strategy for reducing the risk of severe hyponatremia [19].

DDAVP should not be used in patients with known coronary or cerebral arterial vascular disease.

Evidence for efficacy — The efficacy of DDAVP in raising VWF levels and preventing or reducing serious bleeding has been established primarily from observational studies and clinical experience. The efficacy varies with the type and severity of VWD (table 3), as DDAVP causes release of only the patient's endogenous VWF from sites of synthesis, and if a patient has a qualitative defect, the abnormal VWF will also be released by DDAVP.

- **Type 1 disease** – Numerous observational studies in individuals with type 1 VWF and VWF activity above 10 percent have demonstrated good hemostasis when bleeding is treated with DDAVP [20-22]. Inadequate response to DDAVP has been noted in individuals with severe type 1 disease or in those with absent stores of VWF in platelets (rare, referred to as "platelet-low VWD") [21,23]. Platelet VWF (a surrogate marker for endothelial cell VWF) is not generally evaluated, and a DDAVP trial will identify individuals who do not benefit from DDAVP. (See 'DDAVP trial' above.)

- **Type 2 disease** – Good to excellent responses to DDAVP are less frequent in individuals with type 2 disease, but responses do occur in type 2 patients, especially those with mild disease [10,20,21,24-26]. DDAVP testing will help determine whether a specific patient is likely to benefit. (See 'DDAVP trial' above.)

  DDAVP is generally considered contraindicated in type 2B VWD (table 3) because the dysfunctional VWF in these individuals causes increased binding to platelets and can cause (or worsen) thrombocytopenia; this effect may be magnified after administration of DDAVP. However, some type 2B individuals have demonstrated a good response with inconsequential or no thrombocytopenia and no thrombotic complications [27-29]. (See "Pathophysiology of von Willebrand disease", section on 'Type 2 (dysfunctional protein; 2A, 2B, 2M, 2N)'.)

- **Type 3 disease** – Individuals with type 3 disease have absent VWF, including no VWF in storage granules, and thus these individuals are not expected to have a response to DDAVP [8].

VWF concentrates and factor VIII for minor bleeding — VWF concentrates (table 1) are appropriate for treating minor bleeding or surgery if DDAVP cannot be used (due to a poor desmopressin response) and/or if DDAVP fails to control bleeding sufficiently or if prolonged therapy (eg, more than three to five days) is needed. Patients with type 3 and severe types 1 and 2 VWD never/seldom have an adequate response to DDAVP and usually require VWF concentrates.

Individuals with very low VWF levels can also have low factor VIII activity because VWF stabilizes factor VIII and increases its half-life. Once functional VWF levels have been raised, factor VIII levels naturally rise as well, but this can take several hours. For type 2N VWD, the VWF is unable to bind and protect factor VIII; the platelet-related VWF functions are normal and the endogenous production of factor VIII is normal in these patients. (See "Pathophysiology of von Willebrand disease", section on 'Stabilization of factor VIII'.)

- **VWF concentrates**
  - The initial dose for minor bleeding is 40 to 50 international units/kg intravenously, which is expected to raise the plasma VWF activity to ≥0.50 international units/mL.
  - Subsequent doses of approximately half the initial dose can be given every 12 to 24 hours to maintain VWF activity levels of >0.30 international units/mL, with measurement of plasma VWF activity. Patients with rapid clearance may require higher and/or more frequent doses.
  - Duration of treatment should be individualized considering the patient's bleeding phenotype and the procedure.
  - Information about different VWF concentrates (plasma-derived and recombinant), dosing, monitoring, duration of therapy, and adverse effects is presented separately. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)
- **Factor VIII**
  - **Target** – We target a factor VIII activity level >0.50 international units/mL.
  - **Presence of factor VIII in** plasma-derived VWF **concentrates** – Plasma-derived VWF concentrates contain factor VIII; a separate source of factor VIII is not required.
  - **Urgent procedure or bleeding** – If a procedure is urgent, or for a bleed, both VWF and factor VIII should be given, and levels should be checked.

- Plasma-derived VWF **concentrates** – Plasma-derived VWF concentrates contain both VWF and factor VIII in the same infusion.

- Recombinant VWF – Recombinant VWF concentrates do not contain factor VIII, and a separate factor VIII infusion is required. A typical dose of factor VIII is 50 international units/kg by intravenous infusion, which is similar to that given for a bleeding episode in a patient with hemophilia A (primary factor VIII deficiency). Only a single dose of factor VIII is needed, as endogenous factor VIII will become stabilized by the VWF.

- **Elective procedure** – If a recombinant VWF concentrate (not containing factor VIII) is given approximately 12 hours prior to a procedure, concomitant factor VIII may not be required because the factor VIII activity will naturally increase when VWF is present. However, a factor VIII activity level should be checked prior to the procedure to confirm that it is >0.50 international units/mL.

Antifibrinolytic agents — Antifibrinolytic agents (epsilon aminocaproic acid [EACA; Amicar] and tranexamic acid [TXA; Cyklokapron, Lysteda]) promote stability of the hemostatic plug by reducing fibrinolysis.

- **Indications and contraindications** – Antifibrinolytic agents can be used as an adjunct to other therapies or as standalone treatment, depending on the site and severity of bleeding and the individual's underlying VWF level. They are especially effective in areas with naturally high fibrinolytic activity such as the nose, oropharynx, or urogenital tract. Antifibrinolytic agents are generally considered to be contraindicated in the presence of upper urinary tract bleeding, since clots may lead to ureteral obstruction [30]. (See "Evaluation of gross hematuria in children" and "Etiology and evaluation of hematuria in adults".)

  We routinely add an antifibrinolytic agent to a VWF concentrate or DDAVP [3]. We sometimes use an antifibrinolytic agent alone (without a VWF concentrate or DDAVP) in individuals with mild bleeding; this is particularly useful with heavy menstrual bleeding, postpartum bleeding, epistaxis, and for selected dental, gynecologic, and other minor procedures [12,13,31]. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Heavy menstrual bleeding'.)

- **Dosing/administration** – Antifibrinolytic agents can be given orally or intravenously, with the route determined by the clinical situation (orally for an outpatient; intravenously for an inpatient who cannot take medications by mouth). Typical schedules are presented in the table (table 1).

- **EACA (epsilon** aminocaproic acid**)** – The usual oral dose in patients with VWD is 25 to 50 mg/kg per dose every six hours (maximum single dose 5 grams). Intravenous use is uncommon and not defined in congenital bleeding disorders.

- **TXA (**tranexamic acid**)** – The usual oral dose is 25 mg/kg per dose every six to eight hours. The usual intravenous dose is 10 mg/kg every eight hours.

Dosing must be adjusted for chronic kidney disease.

- **Duration** – The duration of therapy should be individualized depending on the patient's bleeding phenotype and the procedure.

- **Adverse effects** – Antifibrinolytic agents are generally well tolerated. Previous concerns regarding risks of thrombosis have largely been disproven in randomized trials [32,33].

Topical therapies — Topical agents are most often used for nasal or oral bleeding.

Supports such as Gelfoam or Surgicel can be soaked in topical thrombin and applied to local areas of bleeding [34]. It is recommended that human thrombin be used for this purpose. If human thrombin is not available, bovine thrombin can be used, although exposures to large amounts of topical bovine thrombin carry a risk of antibody formation against the bovine factor V in the preparation that can cross-react with human factor V and cause bleeding [35]. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Factor II (prothrombin) and IIa (thrombin) inhibitors'.)

Other available topical agents that may be used include micronized collagen (Avitene), which is available in strips for packing, and fibrin sealant (using human thrombin) [34]. (See "Fibrin sealants".)

Estrogens — We do not use estrogen therapy to treat VWD, but individuals who have other reasons for receiving estrogens, such as for contraception, treatment of acne, or menopausal symptoms, may notice a reduction in bleeding. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use" and "Menopausal hormone therapy: Benefits and risks".)

Combined oral contraceptives are commonly used for heavy menstrual bleeding in VWD if the patient does not want to become pregnant. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations", section on 'Heavy menstrual bleeding'.)

INVESTIGATIONAL THERAPIES

The following approaches are under investigation [36]:

Gene therapy or gene editing

- Gene therapy to express von Willebrand factor (VWF) in endothelial cells. The *VWF* gene is large and requires gene therapy vectors that can accommodate its size. For some types of VWD (type 2A and 2N), smaller portions of the gene may be used. (See "Overview of gene therapy, gene editing, and gene silencing", section on 'Inherited single gene disorders'.)

- Gene editing to allow transcriptional silencing of variant *VWF* alleles or to directly edit the patient's abnormal *VWF* gene. (See "Overview of gene therapy, gene editing, and gene silencing", section on 'Gene editing'.)

Autologous endothelial cells treated with gene therapy or gene editing constructs could be transduced or transfected ex vivo and transplanted into the recipient.

Increasing factor levels — Increasing factor VIII and VWF activity by increasing factor levels might reduce bleeding risk.

- **Factor VIII**

  - Efanesoctacog alfa is a factor VIII-VWF fusion protein that does not require VWF for stabilization of factor VIII. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Efanesoctocog alfa (factor VIII-VWF fusion)'.)

  - Emicizumab is a bispecific antibody that mimics factor VIII function. It binds to factors IXa and X simultaneously, bringing these two molecules together and essentially substituting for the scaffold role of factor VIIIa as a cofactor for factor IXa in activating factor X. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab for hemophilia A'.)

- **VWF**

  - Interleukin 11 (IL-11) increases VWF production.
  - Nanobodies fused to albumin target VWF and extend its lifespan.

Increasing VWF half-life — Another approach involves preventing degradation of VWF and prolonging its half-life using antibodies that bind to susceptible sites on VWF and block its destruction by ADAMTS13.

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

- **Education** – We educate and counsel patients about the diagnosis and type of VWD (table 3), bleeding risk, importance of planning for surgery and pregnancy, and avoidance of antiplatelet agents in most cases. (See 'General principles of care' above.)

Most VWD is autosomal dominant. First-degree relatives should have a thorough bleeding history and may require testing, particularly if they have a positive bleeding history or when the index patient has moderate to severe disease. (See 'Testing and counseling of relatives' above.)

- **Minor bleeding/minor surgery** – The main options to increase VWF levels are DDAVP (desmopressin) and von Willebrand factor (VWF) concentrates (table 1). Antifibrinolytic agents should also be used. (See 'Minor bleeding and minor surgery' above.)

  - **DDAVP** – DDAVP is often effective in type 1 patients with minor bleeding or minor procedures, provided a response was demonstrated in a DDAVP trial. We perform a baseline DDAVP trial in most type 1 and many type 2 patients ≥2 years old. The table summarizes dosing, monitoring, and adverse effects (table 2). For individuals with type 1 VWD who have mild bleeding or minor surgery and have demonstrated a response, we suggest DDAVP (**Grade 2C**). Dose and route should generally match that used in the DDAVP trial.

    Some individuals with type 1 disease may use a VWF concentrate (those who have not demonstrated a prior DDAVP response; those with more severe bleeding or other concerns). Some individuals with type 2 disease may use DDAVP.

  - **VWF concentrates and factor VIII** – VWF concentrates (table 1) are appropriate for treating minor bleeding or surgery if DDAVP cannot be used (due to a poor desmopressin response) or if DDAVP fails to control bleeding. The initial dose for minor bleeding is 40 to 50 international units/kg intravenously, which is expected to raise the plasma VWF activity to ≥0.50 international units/mL. In patients with type 3 VWD, type 2N, and other severe type 1 and 2 who require urgent treatment and are receiving recombinant VWF, one dose factor VIII may be required. Subsequent dosing and duration of therapy are discussed separately. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)

  - **Antifibrinolytic agents** – Epsilon aminocaproic acid and tranexamic acid reduce fibrinolysis (clot breakdown). They are especially effective in areas with naturally high fibrinolytic activity such as the nose, oropharynx, or urogenital tract; they are generally considered to be contraindicated in upper urinary tract bleeding.

    - For more serious mucosal bleeding, we suggest adding an antifibrinolytic agent to a VWF concentrate or DDAVP (**Grade 2C**).

- For mild mucosal bleeding such as epistaxis, oral bleeding, or gynecologic bleeding, an antifibrinolytic agent can be used alone or with DDAVP.

- **More severe bleeding** – This is discussed separately. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery".)

- **Iron deficiency** – Individuals with chronic bleeding (epistaxis, GI, or heavy menstrual bleeding) should be evaluated for iron deficiency and treated if necessary. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults" and "Treatment of iron deficiency anemia in adults".)

- **Heavy menstrual bleeding and obstetric considerations** – These are discussed separately. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)

- **Antithrombotic therapy** – Antithrombotic therapy should be used if needed (acute coronary syndrome, venous thromboembolism). Close consultation with a hemostasis expert is essential. (See 'Individuals who require antithrombotic therapy' above.)

REFERENCES

1. Martin K, Key NS. How I treat patients with inherited bleeding disorders who need anticoagulant therapy. Blood 2016; 128:178.
2. Girolami A, Tasinato V, Sambado L, et al. Venous thrombosis in von Willebrand disease as observed in one centre and as reported in the literature. Blood Coagul Fibrinolysis 2015; 26:54.
3. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv 2021; 5:301.
4. Connell NT, James PD, Brignardello-Petersen R, et al. von Willebrand disease: proposing definitions for future research. Blood Adv 2021; 5:565.
5. 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.
6. Rodeghiero F, Castaman G, Mannucci PM. Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. Thromb Haemost 1996; 76:692.

7. Sharthkumar A, Greist A, Di Paola J, et al. Biologic response to subcutaneous and intranasal therapy with desmopressin in a large Amish kindred with Type 2M von Willebrand disease. Haemophilia 2008; 14:539.
8. Sutor AH. DDAVP is not a panacea for children with bleeding disorders. Br J Haematol 2000; 108:217.
9. Michiels JJ, van de Velde A, van Vliet HH, et al. Response of von Willebrand factor parameters to desmopressin in patients with type 1 and type 2 congenital von Willebrand disease: diagnostic and therapeutic implications. Semin Thromb Hemost 2002; 28:111.
10. Mazurier C, Gaucher C, Jorieux S, Goudemand M. Biological effect of desmopressin in eight patients with type 2N ('Normandy') von Willebrand disease. Collaborative Group. Br J Haematol 1994; 88:849.
11. Ferrari M, Galvanin F, Barolo M, et al. A Mechanistic Model to Quantify von Willebrand Factor Release, Survival and Proteolysis in Patients with von Willebrand Disease. Thromb Haemost 2018; 118:309.
12. Jiménez-Yuste V, Prim MP, De Diego JI, et al. Otolaryngologic surgery in children with von Willebrand disease. Arch Otolaryngol Head Neck Surg 2002; 128:1365.
13. Witmer CM, Elden L, Butler RB, et al. Incidence of bleeding complications in pediatric patients with type 1 von Willebrand disease undergoing adenotonsillar procedures. J Pediatr 2009; 155:68.
14. Lethagen S, Harris AS, Sjörin E, Nilsson IM. Intranasal and intravenous administration of desmopressin: effect on F VIII/vWF, pharmacokinetics and reproducibility. Thromb Haemost 1987; 58:1033.
15. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). Br J Haematol 1992; 82:87.
16. Dunn AL, Powers JR, Ribeiro MJ, et al. Adverse events during use of intranasal desmopressin acetate for haemophilia A and von Willebrand disease: a case report and review of 40 patients. Haemophilia 2000; 6:11.
17. Shepherd LL, Hutchinson RJ, Worden EK, et al. Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. J Pediatr 1989; 114:470.
18. Sharma R, Stein D. Hyponatremia after desmopressin (DDAVP) use in pediatric patients with bleeding disorders undergoing surgeries. J Pediatr Hematol Oncol 2014; 36:e371.
19. Mason JA, Robertson JD, McCosker J, et al. Assessment and validation of a defined fluid restriction protocol in the use of subcutaneous desmopressin for children with inherited

bleeding disorders. Haemophilia 2016; 22:700.

20. Federici AB, Mazurier C, Berntorp E, et al. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. Blood 2004; 103:2032.
21. Castaman G, Lethagen S, Federici AB, et al. Response to desmopressin is influenced by the genotype and phenotype in type 1 von Willebrand disease (VWD): results from the European Study MCMDM-1VWD. Blood 2008; 111:3531.
22. Castaman G, Tosetto A, Federici AB, Rodeghiero F. Bleeding tendency and efficacy of anti-haemorrhagic treatments in patients with type 1 von Willebrand disease and increased von Willebrand factor clearance. Thromb Haemost 2011; 105:647.
23. Mannucci PM, Lombardi R, Bader R, et al. Heterogeneity of type I von Willebrand disease: evidence for a subgroup with an abnormal von Willebrand factor. Blood 1985; 66:796.
24. Batlle J, Lopez Fernandez MF, Campos M, et al. The heterogeneity of type IIA von Willebrand's disease: studies with protease inhibitors. Blood 1986; 68:1207.
25. Mauz-Körholz C, Budde U, Körholz D, Göbel U. DDAVP treatment in a child with von Willebrand disease type 2M. Eur J Pediatr 1999; 158 Suppl 3:S174.
26. Nishino M, Nishino S, Sugimoto M, et al. Changes in factor VIII binding capacity of von Willebrand factor and factor VIII coagulant activity in two patients with type 2N von Willebrand disease after hemostatic treatment and during pregnancy. Int J Hematol 1996; 64:127.
27. McKeown LP, Connaghan G, Wilson O, et al. 1-Desamino-8-arginine-vasopressin corrects the hemostatic defects in type 2B von Willebrand's disease. Am J Hematol 1996; 51:158.
28. Casonato A, Steffan A, Pontara E, et al. Post-DDAVP thrombocytopenia in type 2B von Willebrand disease is not associated with platelet consumption: failure to demonstrate glycocalicin increase or platelet activation. Thromb Haemost 1999; 81:224.
29. Mauz-Körholz C, Budde U, Kruck H, et al. Management of severe chronic thrombocytopenia in von Willebrand's disease type 2B. Arch Dis Child 1998; 78:257.
30. Wymenga LF, van der Boon WJ. Obstruction of the renal pelvis due to an insoluble blood clot after epsilon-aminocaproic acid therapy: resolution with intraureteral streptokinase instillations. J Urol 1998; 159:490.
31. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999; 57:1005.
32. Lei T, Bingtao W, Zhaoqing G, et al. The efficacy and safety of intravenous tranexamic acid in patients with posterior operation of multilevel thoracic spine stenosis: a prospective

randomized controlled trial. BMC Musculoskelet Disord 2022; 23:410.

33. Devereaux PJ, Marcucci M, Painter TW, et al. Tranexamic Acid in Patients Undergoing Noncardiac Surgery. N Engl J Med 2022; 386:1986.
34. Hemophilia and von Willebrand's disease: 2. Management. Association of Hemophilia Clinic Directors of Canada. CMAJ 1995; 153:147.
35. Ortel TL, Charles LA, Keller FG, et al. Topical thrombin and acquired coagulation factor inhibitors: clinical spectrum and laboratory diagnosis. Am J Hematol 1994; 45:128.
36. Denis CV, Susen S, Lenting PJ. von Willebrand disease: what does the future hold? Blood 2021; 137:2299.

Topic 122618 Version 31.0

GRAPHICS

Therapies that can be used to treat VWD and AVWS

Medication	Dose	Comments
DDAVP	▪ **Intravenous:** 0.3 mcg/kg (maximum dose, 20 mcg) in 50 mL saline over 20 minutes **or** ▪ **Nasal spray:** Weight >50 kg: 300 mcg (1 spray in each nostril); weight <50 kg: 150 mcg (1 spray in 1 nostril)	▪ Adequate response to a test dose is ideally established before use, but a patient with AVWS and acute bleedin may receive the first dose as a therapeutic trial ▪ Use caution when an antifibrinolytic agent is given concurrently due to risk of thrombosis ▪ Dose may be repeated after 12 hours and 24 hours ▪ Tachyphylaxis and hyponatremia may occur; monitor hemostasis and serum sodium ▪ Thrombocytopenia may worsen in some type 2B patients
VWF concentrates (these contain all VWF multimers)	▪ **Major bleeding or surgery:** Initial dose 40 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 24 hours to keep VWF level 50 to 100 international units/dL for 7 to 14 days, or as indicated clinically ▪ **Minor bleeding or surgery:** Initial dose 30 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 48 hours to keep VWF level >30 international units/dL for 3 to 5 days, or less as indicated clinically	▪ Dose and duration based on clinical experience ▪ Case reports have described the use of continuous infusion (2 to 15 international units/kg per hour) in cases of serious bleeding that does not respond to intermittent dosing ▪ Increased doses or more frequent administration may be necessary in AVWS
Recombinant VWF	▪ **Major bleeding or surgery:** Initial dose 50 to 80 international units/kg, followed by 40 to 60 international units/kg every 8 to 24 hours to keep the VWF level 50 to 100 international units/kg for 2 to 3 days or longer, as needed clinically	▪ In patients with less than 40% factor VIII activity, 1 dose of recombinant factor VIII is given (dose ratio of 1 to 1.3 for rFVIII to rVWF) within 10 minutes of the first dose of rVWF ▪ Published studies using rVWF are limited, and more data are needed to assess responses in patients of

	▪ **Minor bleeding or surgery:** Initial dose 40 to 50 international units/kg, followed by 40 to 50 international units/kg every 8 to 24 hours as needed clinically	differing ages and severities of VWD and in specific clinical settings
Antifibrinolytic agents	▪ Aminocaproic acid, 25 to 50 mg/kg per dose orally (maximum 5 g dose) 4 times per day **or** ▪ Tranexamic acid, 25 mg/kg per dose orally every 6 to 8 hours or 10 mg/kg intravenously 3 times per day	▪ Can be used alone or in conjunction with other therapies; use caution when combined with DDAVP ▪ Especially useful for mucosal bleeding (often used for dental procedures) ▪ Dose reduction may be required in patients with impaired kidney function
IVIG (only applies to AVWS)	▪ 1 g/kg intravenously once daily for 2 days*	▪ May be particularly helpful in monoclonal gammopathies ▪ May be used in conjunction with VWF concentrates and/or DDAVP, particularly when treating AVWS associated with autoimmune disease

Refer to UpToDate topics on the management of VWD and AVWS for additional information.

VWD: von Willebrand disease; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; VWF: von Willebrand factor; rFVIII: recombinant factor VIII; rVWF: recombinant VWF; IVIG: intravenous immune globulin.

* Divided doses may be required; refer to UpToDate topics on IVIG for details.

Adapted from: Rick ME. Diagnosis and management of von Willebrand's syndrome. Med Clin North Am 1994; 78:609. Copyright 1994 WB Saunders.

Graphic 75956 Version 16.0

Administration of DDAVP for hemostasis

Administration	Caveats and comments
Uses and limitations	▪ Adequate response to a test dose is ideally established before use, but a patient with AVWS and acute bleeding may receive the first dose as a therapeutic trial ▪ Do not use in children <2 years of age ▪ Avoid or use with extreme care in individuals with cardiovascular disease ▪ Avoid or use with extreme care in pregnant women
Dosing	▪ May be repeated once daily for 3 to 5 days. Beyond 5 days, tachyphylaxis renders it ineffective
Intravenous or subcutaneous	▪ Intravenous: 0.3 mcg/kg (maximum 20 mcg) diluted in 50 mL of normal saline and infused over 20 to 30 minutes ▪ Subcutaneous (not approved for use in the United States): 0.3 mcg/kg (maximum 20 mcg) subcutaneously
Nasal spray	▪ Use the formulation intended for hemostasis (concentration of 1.5 mg/mL; dose 150 mcg/spray), **not** the formulation for enuresis (concentration of 0.01%) ▪ Weight <50 kg: One spray in one nostril (total dose 150 mcg) ▪ Weight ≥50 kg: One spray in each nostril (total dose 300 mcg)
Adverse events	
Hyponatremia	▪ Avoid excess free water intake (oral or intravenous) ▪ Avoid NSAIDs ▪ Monitor serum sodium
Thrombotic events	▪ Especially of concern in individuals with pre-existing increased risk factors such as cardiovascular disease
Headache, flushing, hypotension, hypertension	▪ Usually alleviated by slowing the infusion

Administration of DDAVP causes release of stored von Willebrand factor and factor VIII from endothelial cells and platelets. Refer to UpToDate for details of the management of VWD, hemophilia, and uremic bleeding. Refer to Lexicomp drug information on desmopressin (DDAVP) for additional prescribing information.

AVWS: acquired von Willebrand syndrome; DDAVP: 1-desamino-8-D-arginine-vasopressin; NSAIDs: nonsteroidal antiinflammatory drugs; VWD: von Willebrand disease.

Graphic 110532 Version 9.0

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 decrease in	▪ Accounts for approximately 5% of individuals with VWD ▪ Moderate to severe bleeding ▪ Thrombocytopenia	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced	▪ DDAVP* should be used with caution; it may be used to treat minor bleeding if a trial of DDAVP performed when the

circulating HMW multimers)	▪ AD inheritance	▪ Thrombocytopenia ▪ RIPA increased ▪ Multimer electrophoresis: Usually decreased large multimers	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: Undetectable or too faint to visualize	▪ VWF concentrates ▪ Factor VIII replacement ▪ Do **not** use DDAVP to treat bleeding (will not be effective)

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