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Bleeding Disorders

Living with von Willebrand disease

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Understanding von Willebrand disease[1]

Von Willebrand disease (VWD) is a hereditary bleeding disorder characterized by bleeding from the skin and mucous membranes (e.g., mouth, nose, throat, gastrointestinal tract). The most common symptoms of von Willebrand disease are easy bruising, prolonged nosebleeds, heavy or prolonged menstrual periods (lasting more than 7 days), and prolonged bleeding following injury, surgery, dental procedures, or childbirth. Gastrointestinal bleeding can also occur.

This bleeding disorder is named for Dr. Erik Adolph von Willebrand (pronounced von WILL-uh-brawn) of Finland who first diagnosed it. Von Willebrand disease differs from hemophilia because it affects both males and females equally. It is the most common inherited bleeding disorder. About one percent of the population is affected.

WHAT HAPPENS WHEN YOU HAVE VON WILLEBRAND DISEASE?

Normally, when a blood vessel is injured, the wall of the vessel narrows or constricts to reduce blood flow. Blood platelets, small disc-shaped cells in blood, stick to the injured site and to each other, forming a platelet plug. Then a series of blood proteins, referred to as clotting factors, weave together to form a fibrin clot. After the fibrin clot forms, bleeding usually stops, and the body can repair the injured blood vessel.

People with von Willebrand disease have a deficiency or defect of a blood clotting protein called von Willebrand factor (VWF). This is a glue-like protein that helps platelets in the blood stick together to form a platelet plug and helps protect factor VIII as it circulates in the bloodstream. Since people with VWD do not form a complete platelet plug, it is weak and does not last very long. Bleeding then continues for a longer period of time.

WHAT ARE THE DIFFERENT TYPES OF VON WILLEBRAND DISEASE?[1]

There are several different types of von Willebrand disease that are determined by diagnostic blood tests. Since the type determines treatment, it is important for individuals to know the type of von Willebrand disease they have.

Type 1 is the most common type of VWD, accounting for approximately 90 percent of all cases. People with this type have reduced levels of von Willebrand factor. Bleeding symptoms are usually mild.

Type 2 includes subtypes 2A, 2B, 2M, and 2N. People with this type have a defect in the von Willebrand factor they produce, so it does not work properly. People with type 2 von Willebrand disease usually have mild to moderate symptoms. Each subtype is treated differently, so knowing the exact subtype is important.

Type 3 occurs when there is an absence or very low levels of von Willebrand factor and factor VIII. People with type 3 VWD often have severe bleeding symptoms. This rare type of von Willebrand disease can cause frequent bleeding, including in the joints and muscles, similar to hemophilia.

HOW IS VON WILLEBRAND DISEASE TRANSMITTED?

Von Willebrand disease is a genetic disorder that can be passed down from one generation to the next in different ways.

The most common way von Willebrand disease is inherited is called “classical inheritance pattern” or “autosomal dominant.” This occurs when one parent has von Willebrand disease. Each of the parent’s male or female children has a 50 percent chance of inheriting the bleeding disorder. Type 1 and most type 2 cases are inherited by this pattern.

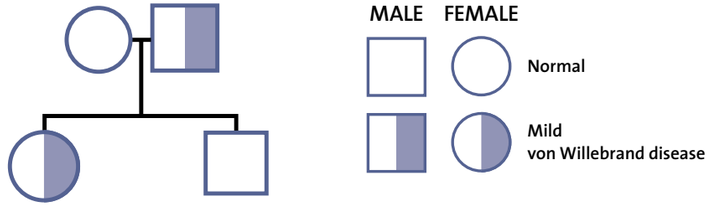
Type 3 and type 2N von Willebrand disease are the most severe forms of the disorder and are inherited in a less common way called “severe inheritance pattern” or “autosomal recessive.” This occurs when an individual inherits two genes for VWD, one from each parent.

HOW IS VON WILLEBRAND DISEASE DIAGNOSED?

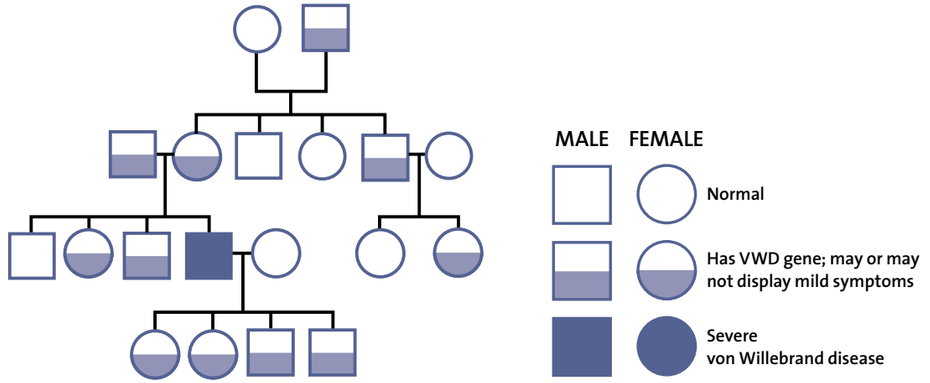
Since von Willebrand disease is a hereditary disorder, there is usually a strong family history of bleeding symptoms in other family members. Therefore, it is common to find grandparents, aunts, uncles, and cousins who have the disorder. Once von Willebrand disease is suspected, an individual usually undergoes a series of blood tests to diagnose von Willebrand disease. These tests check how long it takes for the blood to clot, the level of von Willebrand factor in the blood, and how well the von Willebrand factor in the blood is working. These tests include[1]:

- **Von Willebrand factor antigen (VWF:Ag)** — This test measures the amount of von Willebrand factor in your blood.
- **Ristocetin (ris-to-SEE-tin) cofactor activity (VWF: RCof)** — This test shows how well the von Willebrand factor works.
- **Factor VIII clotting activity** — Some people with von Willebrand disease have low levels of factor VIII, while others have normal levels.
- **Von Willebrand factor multimers** — This test is used to evaluate abnormal results of the tests listed above and shows the makeup or structure of the von Willebrand factor. This test helps your doctor diagnose what type of von Willebrand disease you have.
- **Platelet function test** — This test measures how well your platelets and von Willebrand factor work together.

VWD DOMINANT INHERITANCE TYPE 1, 2A, 2B, 2M



VWD RECESSIVE INHERITANCE TYPE 3, 2N



Since clotting factor levels may vary, diagnosis of von Willebrand disease may be difficult, requiring tests to sometimes be repeated. This is because different situations can affect von Willebrand factor and factor VIII levels in each individual at different times. Some examples include:

- Stress, exercise, smoking, and use of alcohol cause level fluctuations.
- Menstrual cycle affects testing due to hormonal fluctuation. In women, the best time for testing is during the first 3 days of the menstrual cycle. This is when hormone levels are the lowest.
- Medications, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral contraceptives (birth control pills), may affect test results.
- Different blood types (A, B, AB, and O) may also affect results. For example, individuals with type AB blood tend to have elevated VWF levels, while those with type O blood have lower VWF levels on average.
- It is difficult to diagnose VWD during pregnancy because hormones stimulate factor VIII and von Willebrand factor production.[2]

HOW IS VON WILLEBRAND DISEASE TREATED?[3]

Once the type of von Willebrand disease is diagnosed, your doctor will determine a treatment plan based on the severity and type of von Willebrand disease and the clinical situation. Following your treatment plan and seeing your doctor regularly are important. Contact your doctor if you have any questions or concerns.

Most cases of von Willebrand disease are mild and often don't require treatment. Treatment may only be needed to prevent or treat bleeding associated with surgery, tooth extraction, or an accident.[1]

Recommended treatments for von Willebrand disease include:

- Desmopressin products
- Plasma-derived factor concentrates that contain von Willebrand factor (VWF) and factor VIII
- Recombinant von Willebrand factor concentrates
- Antifibrinolytic agents

What is desmopressin?

Desmopressin is a synthetic agent. Following administration, it stimulates the release of factor VIII and von Willebrand factor stored in the lining of the blood vessels.

There are two forms of desmopressin: one that is administered through intravenous injection and one that is a highly concentrated nasal spray, *Stimate*®

It is important for your doctor to determine your response to *Stimate*. A test dose should be administered while in a nonbleeding state. Following a test dose, factor VIII and VWF levels are measured at predetermined times to determine response.[4] The test dose should be given several days before surgery because many people experience a diminished response to intravenously injected desmopressin with repeated doses.

Intravenously injected desmopressin is an effective treatment for most people with type 1 von Willebrand

disease. Some people with type 2 von Willebrand disease can be treated with it if they have been shown by trial to be responsive.

While both methods of desmopressin administration are considered safe, users must be aware that desmopressin is a potent antidiuretic agent; therefore, it can cause fluid retention and a deficiency of sodium in the blood (hyponatremia). To minimize risk, the following precautions should be observed when using this drug at home:

- It should be administered no more than once every 24 hours.
- It should be used for no more than 3 consecutive days, unless directed by your doctor or hemophilia treatment center medical staff.
- It should not be used in children under the age of 2 years.
- It should be used with caution in the elderly and in individuals with a history of heart disease, high blood pressure, or stroke.
- If a patient is treated with it before surgery, the anesthesiologist should be advised to avoid fluid overload and the lack of sodium that results in blood.
- It should be used with extreme caution in pregnant women and immediately after childbirth.

What are plasma-derived VWF-containing factor VIII concentrates?

Factor concentrates that contain both factor VIII and von Willebrand factor are used to treat von Willebrand disease. This treatment is recommended in certain types of VWD that do not respond to desmopressin, such as type 2B and type 3 VWD. Factor is also recommended for the treatment of people with VWD who are unresponsive to desmopressin or have contraindications to its use. Factor may also be used to curb severe bleeding.[5]

Humate-P®, *Alphanate®*, and *Wilate®* are the plasma-derived products that are FDA-approved for the treatment of von Willebrand disease. All three are made from human plasma collected from donors who are rigorously screened for viruses such as HIV, and hepatitis A, B and C. The final products are also treated to inactivate any viruses that are potentially present in human plasma.

What are recombinant von Willebrand factor concentrates?[6]

The first FDA-approved recombinant von Willebrand factor concentrate became available in 2016. It is produced without any addition of human or animal proteins. In contrast to the plasma-derived products, *Vonvendi* contains only von Willebrand factor. It does not contain any factor VIII; therefore, a dose of factor VIII concentrate may be prescribed by your doctor to be administered with the first *Vonvendi* dose used to treat a bleed.

How is your dose of von Willebrand factor determined?

When treating von Willebrand disease, factor doses are calculated using ristocetin cofactor activity (RCof). A unit of RCof is a measure of the activity of VWF in the factor concentrate and helps determine the appropriate dose to treat VWD. *Humate-P, Alphanate*, *Wilate* and *Vonvendi* list the RCof units contained on the vial. Your doctor will determine your dosage based on your type of VWD and what type of bleed or surgery you are having.

Factor concentrates can be infused by intravenous injection by a nurse or a caregiver. The patient may also self-infuse. Any of these scenarios allow people with von Willebrand disease to treat in the home.

What are antifibrinolytic agents?

Antifibrinolytic agents are substances that prevent blood clots from dissolving. These drugs are used mainly to stop or prevent bleeding following minor surgery, tooth extraction, or an injury. They may be used alone or together with desmopressin acetate, epsilon aminocaproic acid, tranexamic acid, or replacement therapy.[1]

Cryoprecipitate not recommended

In the past, cryoprecipitate, a fraction of blood rich in factor VIII, was the preferred agent for replacement of von Willebrand factor. However, because it has not undergone any viral inactivation steps, cryoprecipitate should not be used to treat patients with VWD except in life- and limb-threatening emergencies when VWD-containing factor VIII is not immediately available.

WHAT ARE GENERAL RECOMMENDATIONS FOR VON WILLEBRAND DISEASE?

Sports and activities — Choice of sports and activities for people with von Willebrand disease depends on the clinical severity of their bleeding problems. Some safe exercises or activities are swimming, biking, and walking. Football, hockey, wrestling, and weight lifting (heavy weights) are not safe activities if you have had certain kinds of bleeding problems. Always check with your doctor before starting any exercise program.[1]

Adjunctive therapies — Some minor injuries may respond to RICE. The letters stand for rest, ice, compression, and elevation. This complementary treatment helps an injured area heal more quickly.

Medical identification — All people with von Willebrand disease should wear medical identification jewelry and carry other information with them so prompt and appropriate treatment can be administered in emergencies, if needed.

Hepatitis vaccines — The American Academy of Pediatrics recommends hepatitis A and B vaccines for all children. In people with bleeding disorders, this immunization is particularly important, and primary immune response should be documented. Please discuss vaccination schedules with your hematologist and/or pediatrician.[7]

HIV concerns — The last transmission of HIV by an American-produced factor concentrate occurred in 1987.[5] It is advisable for all people who have received blood products in the past to be tested for transmissible viral infections, such as hepatitis A, B, C, and HIV. HIV-positive individuals should be encouraged to seek appropriate counseling, support, and medical follow-up.

Pain management — People with von Willebrand disease should not take nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, without talking to their doctor.[8] People who have VWD can take acetaminophen for pain relief because it does not inhibit platelet function.[9] Use caution when using over-the-counter medications. Aspirin can also be listed as ASA or acetylsalicylic acid in the active ingredient section.[10] Before using over-the-counter medications, consult with your pharmacist, doctor, or hemophilia treatment center.

Disclosure — If your child has von Willebrand disease that is severe enough to pose a significant risk of bleeding, your doctor may advise you to inform your child's caretakers or school personnel about the disorder. For example, the school nurse, teacher, daycare provider, coach, or any leader of after-school activities may need to know your child has von Willebrand disease. This information will help them handle the situation if your child has an injury.[1]

FREQUENTLY ASKED QUESTIONS

I have heavy periods. What can I do?

Excessive menstrual bleeding is a common symptom in women with von Willebrand disease. Women whose mothers have had heavy menstrual periods due to VWD may think their menstrual periods are normal. Doctors who are not familiar with the disorder often misdiagnose it. Women with heavy, prolonged periods caused by VWD are sometimes given unnecessary hysterectomies.[11] All women with VWD should consult a gynecologist regularly. Your gynecologist should keep in touch with your hematologist in order to coordinate therapy. To treat excessive menstrual bleeding, a gynecologist will usually recommend oral estrogens, such as birth control pills. Desmopressin acetate and factor concentrates containing von Willebrand factor have been used successfully to treat heavy menses. They are given during the period to decrease the flow. Occasionally, both forms of therapy may be used.

Will I have trouble having a baby?

Women with von Willebrand disease can get pregnant and have healthy babies. In women with type 1 VWD, the von Willebrand factor tends to normalize during pregnancy due to a rise in hormones. In women with type 2 and type 3 VWD, the values do not normalize, and treatment during childbirth is usually needed. Women with von Willebrand disease are also at risk of postpartum hemorrhage, particularly delayed postpartum hemorrhage.[4] It is important to consult a hematologist early in the pregnancy to monitor your bleeding disorder.

I have lots of nosebleeds. What should I do?

Nosebleeds are a common symptom of von Willebrand disease. To slow the bleeding, pinch the nose at the bridge, close to where glasses might sit. Tilt the head down, and put an ice pack on the nose. Many people have good results using an over-the-counter topical powder that retards bleeding when applied directly to the nostril with a special swab. To prevent nosebleeds from occurring, you may want to use saline nasal spray or gel once a day and use a humidifier year-round.[12]

Is von Willebrand disease curable?

No, von Willebrand disease is an inherited, lifelong bleeding disorder.

How should I prepare for emergencies?

Since emergency room staff may not be familiar with VWD, you should carry a letter from your doctor or wallet card about your bleeding disorder and treatment. It is also important to provide the telephone numbers of your hematologist and hemophilia treatment center. The letter should indicate choice of product and dose. Wear a medical identification bracelet or necklace to notify healthcare providers of your bleeding disorder in case you are unable to speak for yourself.

If you require treatment with factor products or *Stimate*, be sure to take a supply with you when you travel because many hospitals do not maintain a supply of these products.

Glossary of commonly used terms

Antifibrinolytic drugs — Medications that help prevent the breakdown of clots that form at bleeding sites. Available in both tablet and liquid forms.

Arthropathy — Joint disease. Repeated bleeding into the joints may cause arthropathy.

Autosomal dominant — An inheritance pattern where a parent with the gene passes it to a child. Also known as classical inheritance pattern.

Autosomal recessive — An inheritance pattern that occurs when the child receives the gene from both parents.

Bleeding episode (bleed) — A collection of blood at a site inside or on the surface of the body that occurs when the person with a bleeding disorder is actively bleeding.

Blood vessel — The part of the body that carries blood to and from all body areas. An artery carries oxygen-rich blood from the heart to the body's tissues; a vein carries blood from the body's tissues back to the heart and lungs to receive more oxygen.

Butterfly needle — A type of needle used to infuse factor or other medications into a vein. It has a small metal needle connected to plastic tubing and wings that are used to hold the needle during insertion.

Chronic — Long-lasting or lifelong.

Clot — A jelly-like substance made of a protein called fibrin interacting with blood cells called platelets. A clot forms to stop bleeding from a damaged blood vessel.

Coagulation — The process in which liquid blood changes into a jelly-like semisolid to seal an injured blood vessel and stop bleeding.

Desmopressin acetate — A synthetic agent of the natural pituitary antidiuretic hormone, 8-arginine vasopressin. When given to people who have the capability of producing some factor VIII or von Willebrand factor, the drug causes a rapid, transient increase in factor VIII and VWF.

Factor concentrate — A freeze-dried powder product that contains measured amounts of a particular clotting factor, such as factor VIII or factor IX. To treat VWD, clotting factor should also list ristocetin cofactor activity (RCof) units.

Hematologist — A doctor who specializes in the treatment of diseases of the blood.

Hemophilia treatment center (HTC) — A nationwide network of specialized treatment facilities where a team of healthcare providers (doctors, nurses, social workers, physical therapists, and other disciplines) work together to deliver comprehensive care for people with bleeding disorders and their families.

Homecare pharmacy — A company that provides factor products and infusion supplies to support home treatment of bleeding disorders. Homecare pharmacies may also provide other services to assist patients in adhering to the treatment plan prescribed by their doctor or HTC.

Home therapy — Administration of treatment products in the home by the caregiver or the patient.

Inflammation — The body's defensive reaction to injury or irritation. Symptoms include swelling, heat, redness, and pain. In people with a bleeding disorder, inflammation may occur in response to a bleeding episode.

Intravenous infusion — Giving a medicine or solution into a vein.

Joint — A place in the body where two or more bones come together.

Joint bleed — When a bleed occurs in a joint. Also called hemarthrosis.

Multimers — A part of the structure of the VWF molecule. High molecular weight multimers are needed to help form blood clots.

NSAID — Abbreviation for non-steroidal anti-inflammatory drugs that include aspirin and ibuprofen.

Plasma — Liquid portion of the blood containing clotting proteins.

Platelet — Disc-shaped blood cells needed for clotting.

RICE — Complementary treatment for bleeding episodes used in addition to factor therapy. The letters stand for rest, ice, compression, and elevation of the injured area.

Ristocetin cofactor — A unit that measures the activity of VWF.

Synthetic — Pertains to compounds formed by chemical reaction in a laboratory instead of those of natural origin.

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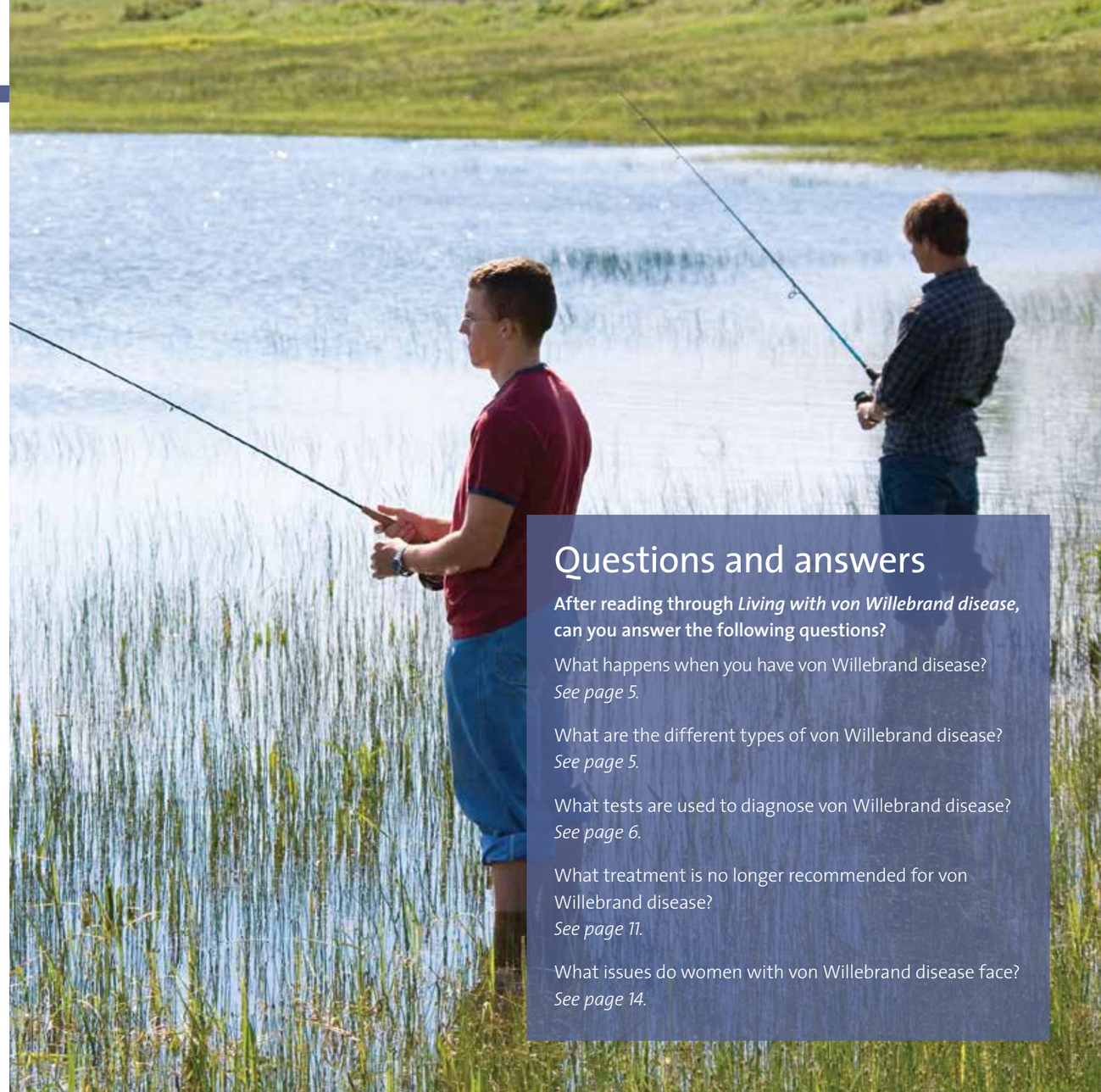

Questions and answers

After reading through *Living with von Willebrand disease*, can you answer the following questions?

What happens when you have von Willebrand disease?
See page 5.

What are the different types of von Willebrand disease?
See page 5.

What tests are used to diagnose von Willebrand disease?
See page 6.

What treatment is no longer recommended for von Willebrand disease?
See page 11.

What issues do women with von Willebrand disease face?
See page 14.

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This booklet contains general educational material and is not intended to constitute medical advice or the rendering of medical care. Accredo is not licensed to practice medicine. The diagnosis and treatment for bleeding disorders should only be undertaken by, or under the direction of, a qualified doctor. The patient's doctor should always be consulted with regard to the patient's medical treatment.

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