

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Von Willebrand's Disease

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VON WILLEBRAND'S DISEASE IS AN INHERITED BLEEDING DISORDER characterized by defective platelet adhesion and aggregation. The disorder was first described in 1926 by Erik von Willebrand, who recognized that it differed from hemophilia and named it "hereditary pseudohemophilia."<sup>1</sup> The factor in plasma that corrects the disease was not identified until many years later and was called von Willebrand factor. It binds to collagen at sites of vascular injury, mediates platelet adhesion and aggregation, and serves as a carrier protein for coagulation factor VIII (Fig. 1).<sup>3</sup> Von Willebrand factor also has other functions and may be involved in such processes as inflammation and angiogenesis.<sup>4</sup>

Von Willebrand's disease is the most common inherited bleeding disorder and has an autosomal inheritance pattern. The disease is characterized mainly by mucosa-associated bleeding and bleeding after surgery and trauma. The diagnosis is based on a personal or family history of bleeding and laboratory evidence of abnormalities in von Willebrand factor, factor VIII, or both. Affected patients have reduced levels of functional von Willebrand factor, and various types of von Willebrand's disease can be distinguished on the basis of phenotypic characteristics. The goal of treatment is to increase von Willebrand factor levels by administering desmopressin or by the infusion of exogenous von Willebrand factor-containing concentrates. In this review, we discuss the latest findings regarding the pathophysiology, diagnosis, and treatment of von Willebrand's disease.

### EPIDEMIOLOGY AND CLASSIFICATION

On the basis of population studies, the prevalence of von Willebrand's disease is 0.6 to 1.3%.<sup>5,6</sup> Although the autosomal inheritance pattern would suggest an equal distribution of male patients and female patients, the disease is diagnosed in more females because of female-specific hemostatic challenges. Not all persons with low von Willebrand factor levels have clinically relevant bleeding symptoms. On the basis of referrals to specialized centers, the estimated prevalence of von Willebrand's disease is approximately 1 case per 10,000 persons.<sup>7</sup> The prevalence is strongly dependent on the diagnostic cutoff level for von Willebrand factor. The normal range is generally between 50 and 150 IU per deciliter. In several sets of guidelines, the diagnosis is based on a cutoff level for von Willebrand factor of 30 IU per deciliter, whereas the principles of care for von Willebrand's disease specify a cutoff level of 40 IU per deciliter.<sup>5,8-10</sup> In daily practice, clinicians do not always follow these guidelines, especially since the official classification of the International Society on Thrombosis and Haemostasis (ISTH) does not specify cutoff values.<sup>11</sup>

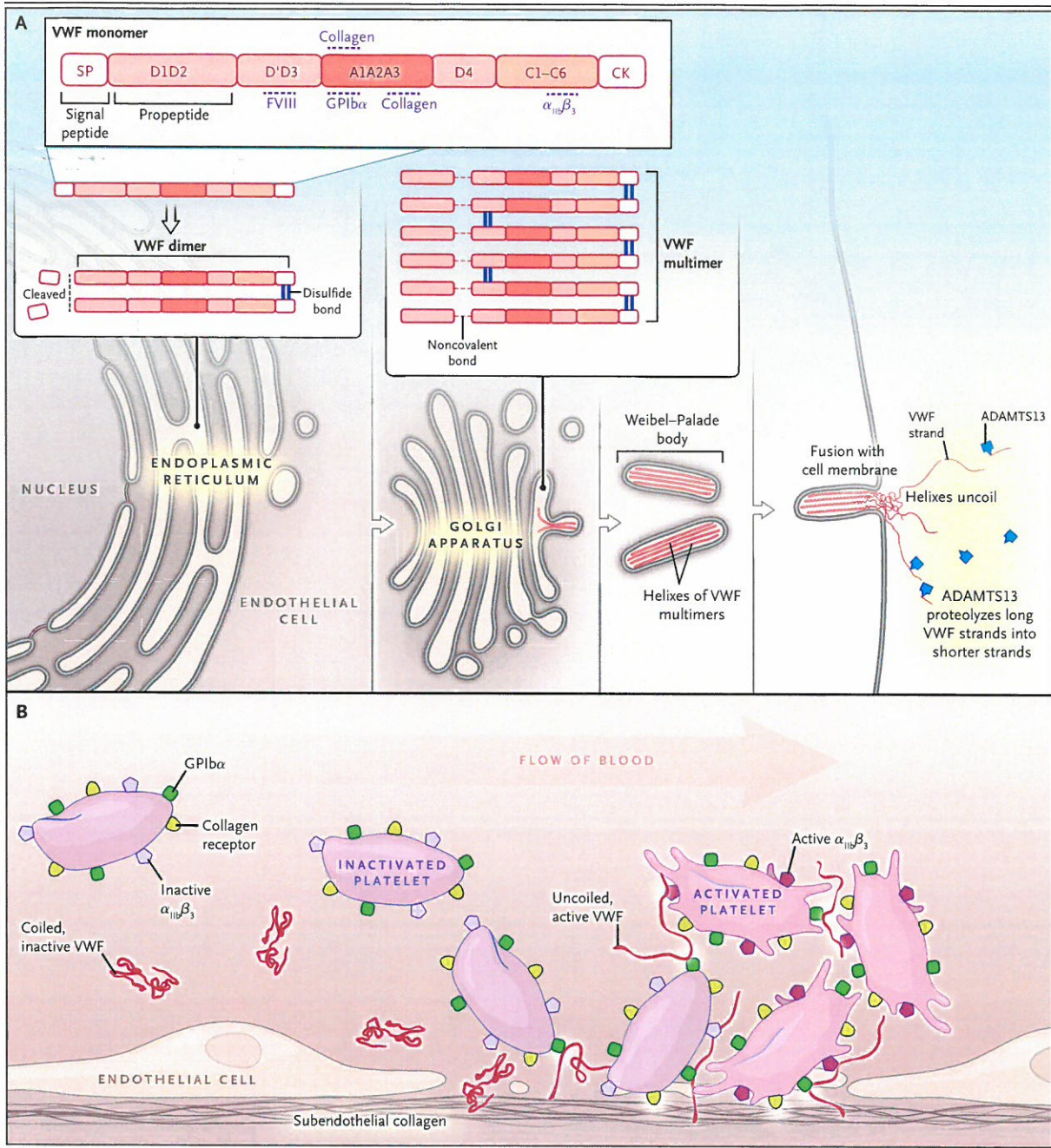
Von Willebrand's disease is subdivided into types 1, 2, and 3.<sup>11</sup> Type 1, which accounts for 70 to 80% of cases, is characterized by a quantitative deficiency of von Willebrand factor. Type 2, accounting for approximately 20% of cases, is

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caused by dysfunctional von Willebrand factor, resulting in a normal or reduced von Willebrand factor antigen concentration but a large reduction in von Willebrand factor function. Type 2 is further subdivided on the basis of specific phenotypic characteristics (Fig. 2). Type 3 von Willebrand's disease is rare (accounting for <5% of

cases), is the most severe form, and is caused by the absence of circulating von Willebrand factor.

In rare cases, von Willebrand's disease is acquired, rather than inherited, by means of various mechanisms that result in rapid degradation or clearance of von Willebrand factor. The acquired syndrome is not discussed here because

**Figure 1 (facing page). Biosynthesis and Function of von Willebrand Factor.**

Von Willebrand factor (VWF) is synthesized in endothelial cells and megakaryocytes and is stored, respectively, in Weibel–Palade bodies (WPBs) and  $\alpha$ -granules. Panel A shows the process of biosynthesis in endothelium. VWF is synthesized as a propolypeptide in the endoplasmic reticulum and is composed of several structural domains; domains A through D and the respective binding sites are indicated. After cleavage of the signal peptide (SP), the VWF subunits dimerize in the endoplasmic reticulum through intermolecular disulfide bridges at the C-terminal cystine knot (CK) domain. When the VWF dimers arrive in the Golgi, the acidic pH and high  $\text{Ca}^{2+}$  level stimulate the formation of VWF multimers through disulfide bridges between D3 domains. The propeptide is cleaved but remains noncovalently bound to the forming VWF multimer, facilitating the disulfide bond formation. The growing VWF multimer organizes into a right-handed helix, thereby folding itself into a tubular conformation for storage in the WPBs. When the WPBs fuse with the endothelial membrane, the pH in the WPBs rises to 7.4 and the VWF multimers lose their tubulated conformation, unfurling into long VWF strings. After secretion, the ultralarge VWF multimers are proteolyzed by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) into the smaller multimers that circulate in plasma. (The biosynthesis of VWF is reviewed in detail by Springer.<sup>2)</sup> FVIII denotes factor VIII, and GPIb $\alpha$  glycoprotein Ib $\alpha$ . As shown in Panel B, VWF circulates in plasma in a globular, inactive form and does not interact with platelets. With vascular damage and exposure of subendothelial collagen, VWF binds to collagen and uncoils in adhesive strings. In uncoiled VWF, the binding site for GPIb $\alpha$  in the A1 domain becomes exposed and allows the binding of platelet GPIb $\alpha$ . Platelets are not yet firmly attached and still roll in the direction of flow. In addition, the platelet collagen receptors bind to collagen. Together with the VWF–GPIb $\alpha$  interaction, the platelets adhere and are activated, leading to a conformational change in platelet integrin  $\alpha_{\text{IIb}}\beta_3$ . The activated platelets become irregularly shaped. VWF and fibrinogen bind to the activated integrin  $\alpha_{\text{IIb}}\beta_3$ , leading to aggregation of the activated platelets.

it requires diagnostic strategies and treatment that differ from those used for the inherited disease.<sup>12</sup>

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#### CLINICAL PRESENTATION

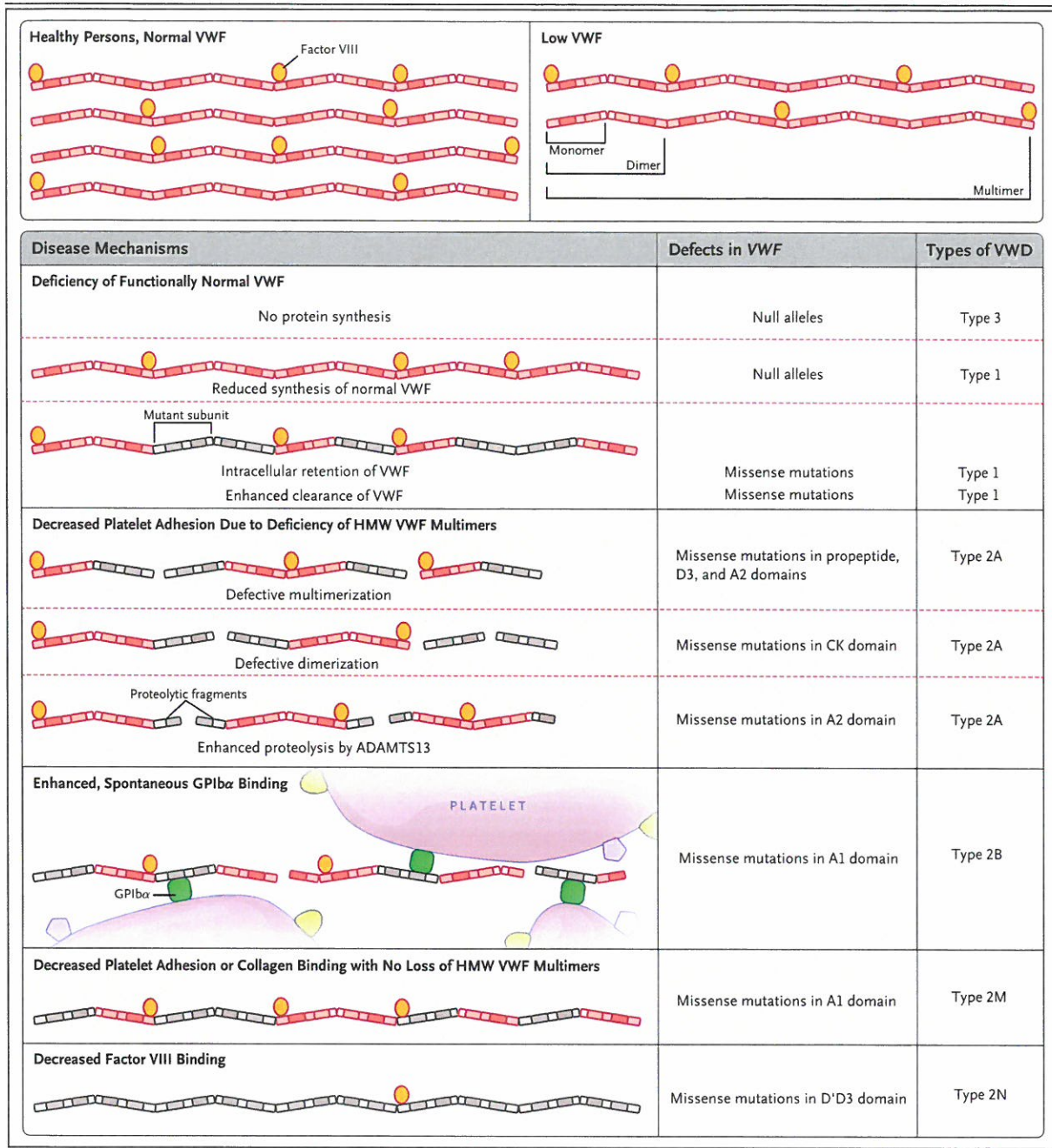
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The symptoms of von Willebrand's disease vary among patients, depending on the level of residual von Willebrand factor activity, the disease

subtype, and to some extent, age and sex. In children with von Willebrand's disease, the most frequent presenting symptoms are bruising and epistaxis.<sup>13</sup> In adults, the most common symptoms are hematomas, menorrhagia, and bleeding from minor wounds. The majority of patients (60 to 80%) have bleeding after surgery or dental extractions.<sup>14</sup> Figure 3 shows the prevalence of self-reported bleeding symptoms derived from the large Willebrand in the Netherlands (WiN) study<sup>14</sup>; similar prevalences have been reported in other studies.<sup>5,17</sup>

A well-known, serious, and possibly life-threatening bleeding complication is gastrointestinal bleeding from angiodysplasia.<sup>18</sup> It is most common in elderly patients with type 2 or 3 von Willebrand's disease.<sup>14,18</sup> Intraarticular (joint) bleeding is a frequent complication in patients with hemophilia but has not been reported as a major problem in patients with von Willebrand's disease, although it may be a presenting symptom in those with type 2N (type 2 subtype Normandy) or type 3 disease.<sup>19</sup> It is now known that joint bleeding occurs in a considerable number of severely affected patients, potentially leading to arthropathy and reduced joint function.<sup>19</sup> The risk of joint bleeding is strongly dependent on the level of residual factor VIII, as well as the severity of von Willebrand's disease, and patients with type 3 disease who have very low factor VIII levels are at greatest risk.<sup>14,19,20</sup> A lower health-related quality of life for patients with von Willebrand's disease than for the general population is strongly associated with the bleeding phenotype.<sup>21</sup>

The majority of women with von Willebrand's disease have menorrhagia, which also impairs the quality of life (Fig. 3).<sup>22</sup> Conversely, von Willebrand's disease is diagnosed in 5 to 20% of women who present with menorrhagia. The link to menorrhagia accounts for the more frequent identification of von Willebrand's disease in women than in men.<sup>23,24</sup> In the WiN study, more than 80% of women with von Willebrand's disease reported excessive blood loss during the menstrual cycle, and more than 20% underwent hysterectomy, a proportion that is twice as high as in the general population.<sup>25</sup> Other reproductive tract symptoms also occur, including bleeding of an ovarian cyst, which should be considered in women with von Willebrand's disease who present with a sudden onset of severe abdominal pain.<sup>26</sup>



Primary and secondary postpartum bleeding also occurs frequently.<sup>25,27,28</sup>

As a result of the physiologic rise in von Willebrand factor levels throughout life, patients with type 1 von Willebrand's disease may have levels within the normal range when they become older.<sup>29</sup> It is still not known whether this rise results in fewer bleeding episodes. A recent

study showed that among patients with type 1 disease, bleeding symptoms occurred as frequently in patients who were older than 65 years of age as in those who were 18 to 65 years of age, which suggests that the age-dependent rise in von Willebrand factor levels does not lead to a mitigation of bleeding symptoms.<sup>30</sup> Even though von Willebrand factor antigen levels also

**Figure 2 (facing page). Pathophysiological Mechanisms and Classification of von Willebrand's Disease.**

In healthy persons, VWF circulates as high-molecular-weight (HMW) multimers carrying factor VIII. Some persons have mildly reduced VWF levels, which may contribute to a bleeding phenotype but are not necessarily caused by defects in the VWF gene. Persons with low VWF levels and a bleeding tendency are classified as having low VWF, rather than von Willebrand's disease (VWD). There is a partial deficiency of functionally normal VWF in type 1 VWD and a complete deficiency in type 3 disease. This deficiency can result from a reduction in protein synthesis, which is often caused by null alleles (large gene deletions, stop codons, frameshift mutations, or splice-site mutations) but may also be due to mutations in the promoter regions. Homozygosity or compound heterozygosity for these defects results in type 3 VWD. Some heterozygous carriers have mild symptoms and receive a diagnosis of type 1 disease. However, most cases of type 1 VWD are caused by heterozygous missense mutations that exert a dominant-negative effect because the mutant subunits are incorporated into the multimer together with the normal subunits, resulting in a disturbance of the entire multimer. Almost all cases of type 2 VWD are caused by missense mutations, which are usually restricted to specific functional domains. Inheritance of subtypes of type 2 disease is autosomal dominant, with the exception of type 2N, which has a recessive pattern of inheritance. Patients may be either homozygous for two type 2N mutations or compound heterozygous for a type 1 defect and a type 2N defect.

rise with age in patients with type 2 disease, von Willebrand factor activity remains low because of the functional defect in the protein. In these patients, an increase in bleeding symptoms is observed with increasing age.<sup>30</sup> These observations should be confirmed in larger prospective studies. An interesting finding in two recent studies is that the risks of cardiovascular disease and ischemic stroke are reduced among patients with von Willebrand's disease.<sup>31,32</sup>

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**PATHOPHYSIOLOGICAL FEATURES**


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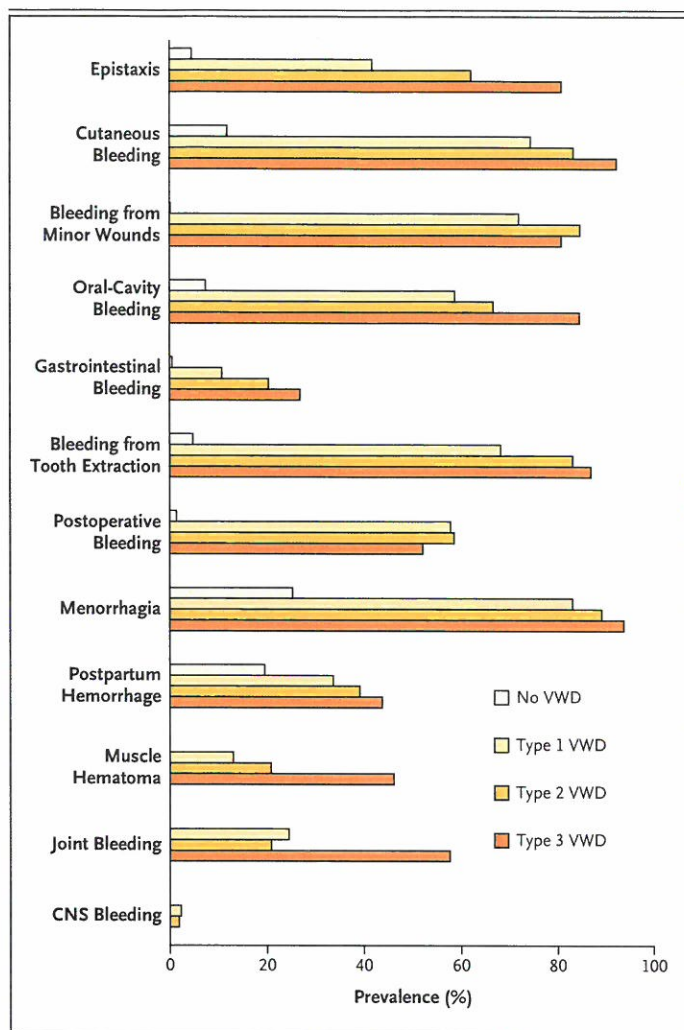
**VWF MUTATIONS**

The inheritance pattern for most types of von Willebrand's disease is autosomal dominant, but in some cases, the inheritance is recessive. In 80% of patients with type 3 von Willebrand's disease, the genetic defects in the VWF gene are null alleles, explaining the complete absence of von Willebrand factor<sup>17,33</sup> (mutation database, [www.vwf.group.shef.ac.uk](http://www.vwf.group.shef.ac.uk)). Most patients with type 3 disease are homozygous or compound heterozy-

gous. Codominant rather than recessive inheritance is observed in up to 50% of patients with type 3 von Willebrand's disease, with the heterozygous carriers having a mild type 1 disease phenotype.<sup>34</sup> Although null alleles might be expected in type 1 von Willebrand's disease, since it is also characterized by a quantitative deficiency of von Willebrand factor, the majority of the mutations are in fact missense mutations. Type 1 disease often shows variable expression and incomplete penetrance. The missense mutations in type 1 disease may lead to impaired intracellular routing, storage, and secretion of von Willebrand factor or to faster clearance (Fig. 2).<sup>9,17,35,36</sup> Missense mutations exert a dominant-negative effect on the normal allele as a result of the incorporation of mutant von Willebrand factor subunits, together with normal subunits, in von Willebrand factor multimers. This leads to a more severe phenotype than in the case of heterozygous null alleles (Fig. 2). In type 2 von Willebrand's disease, the phenotype is determined by specific functional defects or characteristics of the von Willebrand factor protein, and consequently, the mutations are usually dominant-negative missense mutations restricted to specific domains of von Willebrand factor. In contrast to type 1, the phenotype in type 2 disease is usually fully penetrant. Generally, the inheritance pattern of type 2 disease is autosomal dominant, with the exception of type 2N disease.<sup>33</sup>

**OTHER GENETIC DISEASE MODIFIERS AND PHYSIOLOGICAL FACTORS**

Even though many mutations causing type 1 von Willebrand's disease have been identified, no mutations are found in approximately 30% of patients.<sup>9,35-37</sup> Genetic modifiers outside the VWF gene and physiological factors probably play a role in reducing von Willebrand factor levels. One of the major genetic determinants of von Willebrand factor levels outside the VWF gene is the ABO blood group, with 25% lower von Willebrand factor levels in persons with type O blood than in those with other types.<sup>38</sup> Genomewide association studies have identified several other genetic loci that are associated with von Willebrand factor levels in healthy persons.<sup>39</sup> These studies have led to new insights into genetic loci that may be involved in clearance (e.g., CLEC4M [C-type lectin domain family 4, member M]) or exocytosis (e.g., STXBP5 [syntaxin-binding pro-



**Figure 3. Frequency of Bleeding Symptoms in Adults with von Willebrand's Disease.**

The prevalence of self-reported bleeding symptoms is shown for 664 adults with von Willebrand's disease (VWD), as compared with 500 healthy persons, in the Willebrand in the Netherlands (WiN) study.<sup>14-16</sup> Of all the patients with VWD, 59% had type 1, 37% had type 2, and 4% had type 3 disease. The respective prevalences of bleeding from tooth extraction, postoperative bleeding, menorrhagia, and postpartum hemorrhage are for patients who underwent tooth extraction (554 patients) or surgery (559) and for women who menstruated (423 women) or had given birth (314). Muscle hematoma was not assessed in healthy persons, and joint bleeding was not reported by any of the healthy persons; central nervous system (CNS) bleeding was not assessed in healthy persons and was not reported by the patients with type 3 VWD.

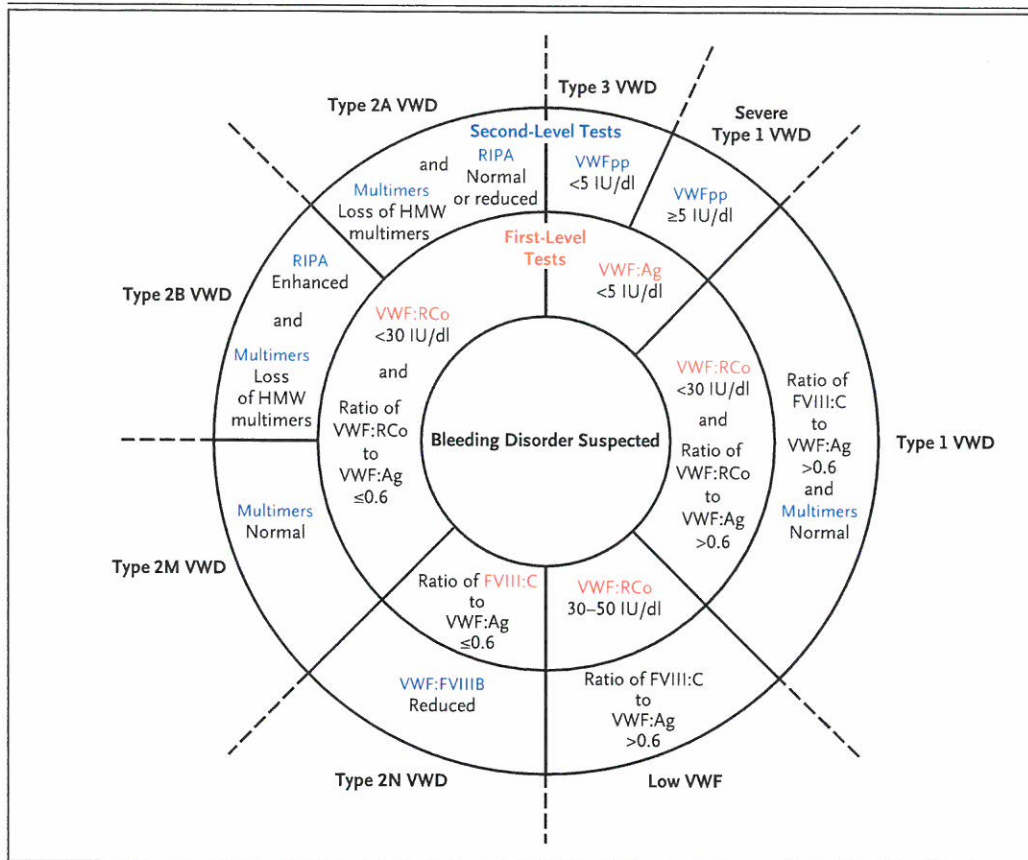
tein 5]) of von Willebrand factor.<sup>39</sup> Studies have confirmed that these genetic loci lead to variability in von Willebrand factor levels in patients with von Willebrand's disease, as well as in

healthy persons.<sup>40,41</sup> The newly recognized genetic loci may contribute to the variability in the von Willebrand's disease phenotype and may explain low levels of von Willebrand factor in affected patients who do not have a mutation in the VWF gene. Apart from genetic modifiers, physiological factors such as age and the response to exercise and the acute-phase response, as well as the menstrual cycle and pregnancy in women, also play a role in the variability of von Willebrand factor levels.

#### DIAGNOSIS

The diagnosis of von Willebrand's disease is based on a personal history of bleeding, a family history of bleeding, or both, in combination with laboratory tests showing abnormalities in von Willebrand factor, factor VIII, or both. The assessment of the bleeding phenotype starts with a detailed history of all bleeding symptoms in the patient and family members. The rating of the severity of bleeding symptoms in von Willebrand's disease has received considerable attention in recent years. Numerical scoring systems based on structured questionnaires, usually referred to as bleeding-assessment tools, have been developed and endorsed by the ISTH (<https://bh.rockefeller.edu/ISTH-BATR/>).<sup>42-44</sup> These tools have limited diagnostic use because they depend strongly on age and the number of previous hemostatic challenges. Diagnostic use of these tools is especially problematic in the case of young children, who have not yet undergone surgery or dental intervention. An additional limitation of the bleeding-assessment tools is that they use cumulative scoring, which means that once a patient has had a severe bleeding episode, the bleeding score will remain high even if bleeding does not recur.

The diagnosis of von Willebrand's disease is based on measurements of von Willebrand factor antigen; the level of von Willebrand factor-dependent platelet adhesion, historically measured with the use of the von Willebrand factor-ristocetin cofactor activity assay; and the coagulant activity of factor VIII (Fig. 4). When von Willebrand factor antigen is undetectable (or the level is <5 IU per deciliter, according to the latest disease classification), type 3 von Willebrand's disease is diagnosed.<sup>11</sup> However, the use of a cutoff level of 5 IU per deciliter means that patients with detect-



**Figure 4. Diagnostic Algorithm for von Willebrand's Disease.**

The diagnosis of von Willebrand's disease (VWD) begins with a relevant personal or family history of mucocutaneous bleeding. When VWD is suspected, the first level of testing comprises measurements of the VWF antigen (VWF:Ag) level, the platelet-binding activity of VWF (measured by means of a VWF-ristocetin cofactor activity [VWF:RCo] assay), and factor VIII activity (FVIII:C). (The VWF:RCo assay may be replaced by newer assays that measure the binding of VWF to a recombinant wild-type GPIb fragment with the use of ristocetin or the spontaneous binding of VWF to a gain-of-function recombinant mutant GPIb fragment.) When the results of all first-level tests are normal, VWD is ruled out; because of biologic variability, however, the tests should be repeated if values are at the low end of the normal range or if VWD is strongly suspected. If these first-level tests reveal definitive abnormalities, a diagnosis of VWD can be made; if the results are not conclusive, second-level tests are required. VWD can be subtyped on the basis of these second-level tests. A rare platelet defect due to a gain-of-function mutation in the GPIb $\alpha$  receptor, known as platelet-type VWD, has a phenotype similar to that of type 2B VWD; the two disorders can be distinguished with the use of genetic testing. RIPA denotes ristocetin-induced platelet aggregation, VWF:FVIII B VWF-FVIII binding activity, and VWFpp VWF propeptide. Persons with a bleeding tendency who have VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having "low VWF" or "possible type 1 disease" but are not classified as having definitive VWD.

able, although very low, von Willebrand factor antigen levels, who should actually be classified as having severe type 1 von Willebrand's disease, will instead be classified as having type 3 disease. Measurement of von Willebrand factor propeptide, a cleavage product formed during synthesis of von Willebrand factor (Fig. 1), helps discriminate between type 3 and type 1 disease.

In type 3 disease, both von Willebrand factor antigen and propeptide are absent or are present at very low levels, whereas in severe type 1 disease, the antigen level is very low, but the propeptide level is minimally reduced or normal (Fig. 4).<sup>45</sup>

When von Willebrand factor antigen is measurable, the level is considered in relation to the

results of the von Willebrand factor–ristocetin cofactor activity assay. Because of low sensitivity and precision, this assay is being replaced in an increasing number of laboratories by new assays measuring the binding of von Willebrand factor to a recombinant wild-type glycoprotein Iba fragment with the use of ristocetin or the spontaneous binding of von Willebrand factor to a gain-of-function recombinant mutant glycoprotein Iba fragment.<sup>46-48</sup> The results of these assays accurately reflect the platelet-binding activity of von Willebrand factor and correlate very well with results of the von Willebrand factor–ristocetin cofactor activity assay.<sup>48</sup> A proportional decrease in von Willebrand factor antigen and von Willebrand factor–ristocetin cofactor activity fits the diagnosis of type 1 von Willebrand's disease. A disproportional reduction in von Willebrand factor–ristocetin cofactor activity as compared with von Willebrand factor antigen (ratio of von Willebrand factor–ristocetin cofactor activity to von Willebrand factor antigen,  $\leq 0.6$ ) indicates type 2 disease. Further subtyping tests, such as assays of von Willebrand factor multimers and ristocetin-induced platelet aggregation, are then required to determine the phenotypic characteristics that define types 2A, 2B, and 2M von Willebrand's disease (Fig. 4).

Factor VIII activity is also measured as a first-line test because the level is frequently reduced in any type of von Willebrand's disease.<sup>20</sup> A reduction in factor VIII activity that is greater than the reduction in von Willebrand factor antigen (ratio of factor VIII activity to von Willebrand factor antigen,  $\leq 0.6$ ) may indicate type 2N von Willebrand's disease, which should be confirmed by measuring the binding of factor VIII to von Willebrand factor in order to rule out mild hemophilia A.<sup>49</sup>

The von Willebrand factor propeptide assay is not part of the official disease classification,<sup>11</sup> but it may identify von Willebrand factor variants that have increased clearance, on the basis of an increased ratio of propeptide to antigen.<sup>45,50</sup> Some authors have proposed that an increase in the ratio of von Willebrand factor propeptide to antigen warrants the designation of a specific subtype of type 1 von Willebrand's disease, characterized by increased clearance of von Willebrand factor (type 1C).<sup>50</sup> However, enhanced clearance is a characteristic of several subtypes of von Willebrand's disease, and this feature is probably

not specific enough to justify a separate classification.<sup>45</sup> Although measurement of the binding of von Willebrand factor to collagen is not widely used in the diagnosis of von Willebrand's disease, it may have added value for identifying cases of type 2M disease that have specific defects in collagen binding, which are usually associated with a mild bleeding phenotype.<sup>51</sup>

New assays that are faster and combine several functional aspects in a single approach are currently under development.<sup>48,52</sup> Genotyping of the VWF gene is not performed routinely in the diagnosis of von Willebrand's disease. In selected cases of suspected von Willebrand's disease, however, genetic analysis may be useful for diagnosing type 2N and type 2B disease. In families with type 3 disease, genetic analysis may be useful for counseling. Innovations in sequencing techniques (e.g., next-generation sequencing) have made genotyping easier to perform.<sup>9</sup>

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#### DIAGNOSTIC CONTROVERSIES

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With the use of the diagnostic algorithm shown in Figure 4, the diagnosis of types 2 and 3 von Willebrand's disease is quite straightforward. However, a definitive diagnosis of type 1 disease is more controversial. The phenotypic characteristic of type 1 disease is a partial reduction in the level of intrinsically normal von Willebrand factor, but it is difficult to determine an unambiguous cutoff level for von Willebrand factor. The lower the level, the more consistent the bleeding phenotype, the inheritance pattern, and the identification of VWF mutations.<sup>35,37</sup> Levels of von Willebrand factor–ristocetin cofactor activity below 30 IU per deciliter are considered to be diagnostic of von Willebrand's disease. According to several current guidelines, persons with a bleeding tendency who have von Willebrand factor levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having “low von Willebrand factor” or “possible type 1 disease” but are not classified as having definitive von Willebrand's disease, although they may require treatment before undergoing surgery or in the event of a bleeding episode. Some persons may actually have mutations in VWF, whereas in other persons, the von Willebrand factor level may be determined by other genetic loci, such as the ABO blood group.<sup>37</sup> A low von Willebrand factor level can be considered a bio-



**Table 1. Treatment of von Willebrand's Disease.\***

Disease Type	Treatment	Alternative or Additional Treatment
Low VWF†	Desmopressin, administered intravenously (0.3 µg per kilogram of body weight), intranasally (total dose, 300 µg [150 µg per nostril]; in patients with body weight <50 kg, only one dose of 150 µg), or subcutaneously (0.3 µg per kilogram)	Alternative or additional treatment: tranexamic acid (1 g, 3 or 4 times daily)
Type 1	Desmopressin, at same doses as above	Additional treatment: tranexamic acid, at same dose as above
Type 2	Desmopressin, at same doses as above, or VWF–factor VIII or VWF concentrate‡	Additional treatment: tranexamic acid, at same dose as above
Type 3	VWF–factor VIII or VWF concentrate	Additional treatment: tranexamic acid, at same dose as above

\* VWF denotes von Willebrand factor.

† Patients presenting with bleeding symptoms and VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having low VWF but not von Willebrand's disease.

‡ Desmopressin is contraindicated in patients with type 2B disease.

marker for an increased risk of bleeding.<sup>53</sup> It is also possible that other hemostatic defects, such as mild platelet-function disorders, contribute to the bleeding phenotype in these patients.<sup>54</sup>

A further diagnostic dilemma is posed by the physiologic increase in von Willebrand factor levels with age throughout life. This may have an effect on the diagnosis of von Willebrand's disease. In childhood, the physiologically lower levels may be erroneously interpreted as indicative of von Willebrand's disease. Elderly patients who met the diagnostic criteria when they were younger may no longer have a von Willebrand factor level below the lower limit of the reference range but may still appear to be at risk for bleeding.<sup>29,30</sup>

TREATMENT

Treatment of von Willebrand's disease is based on normalizing von Willebrand factor and factor VIII levels in case of bleeding or before an intervention. This can be achieved by increasing the endogenous factor levels with the use of desmopressin or by infusing exogenous coagulation factors in the form of a high-purity von Willebrand factor concentrate or a low-purity factor VIII–von Willebrand factor concentrate (Table 1).

DESMOPRESSIN

For most patients who have type 1 von Willebrand's disease or who are classified as having a low level of von Willebrand factor or possible type 1 von Willebrand's disease, and for some

patients with type 2 von Willebrand's disease, desmopressin can be given intravenously (0.3 µg per kilogram of body weight), intranasally (300 µg [150 µg per nostril] or, in a patient with a body weight of <50 kg, only one dose of 150 µg), or subcutaneously (0.3 µg per kilogram) to increase factor VIII and von Willebrand factor levels by two to four times. The use of a capped desmopressin dose of 15 or 20 µg (administered intravenously or subcutaneously) has been suggested, but this approach requires further study before it can be recommended.<sup>55,56</sup> The desmopressin dose can be repeated after 12 to 24 hours, depending on the individual response. Desmopressin is considered to be safe but may have mild side effects such as hypotension and flushing. More severe, rare side effects are cardiovascular complications and hyponatremia. The latter can be prevented by limiting fluid intake to 1500 ml for 24 hours after the administration of desmopressin.<sup>56,57</sup> Various factors influence the response to desmopressin, including the genotype and phenotype of von Willebrand's disease.<sup>58</sup> Therefore, a test-dose infusion is recommended to establish the magnitude and duration of the response to desmopressin.

FACTOR CONCENTRATE

In patients with type 3 von Willebrand's disease and in most patients with type 2 disease, von Willebrand factor–containing concentrate is the treatment of choice. Plasma-derived concentrates of factor VIII and von Willebrand factor are commercially available in various ratios.<sup>59</sup> Therefore,

**Table 2.** Indications for and Doses of Factor Concentrate in von Willebrand's Disease.

Indication for VWF–Factor VIII or VWF Concentrate*	Dose†	Target Levels for VWF–Ristocetin Cofactor Activity and Factor VIII Activity‡	Duration of Treatment
	IU/kg	IU/dl	days
<b>Bleeding</b>			
Mild to moderate	20–40	Peak, >50–80 on day 1; trough, >30 after day 1	1–3
Severe	50	Peak, >100 on day 1; trough, >50 after day 1	7–10
<b>Intervention</b>			
Dental extraction	25	Peak, >50 on day 1	1
Minor surgery	30–60	Peak, >50–80 on day 1; trough, >30 after day 1	1–5
Major surgery	50–60	Peak, >100 on day 1; trough >50 after day 1	7–10
Delivery	40–50	Peak >100 on day 1; trough, >50 after day 1	3–4

\* VWF–factor VIII or VWF concentrate is administered in patients with type 3 disease and in patients with type 1 or 2 disease who do not have a response to desmopressin or in whom it is contraindicated.

† The dose of factor concentrate depends on the type of concentrate used. If VWF–factor VIII concentrate is used, the dose of factor concentrate also depends on the brand of concentrate. The dose is based on an anticipated in vivo recovery (2 IU per deciliter for every unit of factor VIII activity infused per kilogram of body weight and 1.5 IU per deciliter for every unit of VWF–ristocetin cofactor activity infused per kilogram) and the target levels of both VWF–ristocetin cofactor activity and factor VIII activity. If high-purity or recombinant VWF concentrate is administered, a single dose of factor VIII concentrate should also be administered in order to achieve the target level of factor VIII immediately.

‡ Factor VIII activity, and preferably also VWF–ristocetin cofactor activity, should be monitored regularly in all patients undergoing surgical procedures and all patients with severe bleeding episodes. If measurement of VWF–ristocetin cofactor activity is not immediately available at a local laboratory, dosing should be based on factor VIII activity levels.

dosing is concentrate-dependent. Recommendations for the administration of von Willebrand factor concentrates are given in Table 2. High-purity von Willebrand factor concentrates with low amounts of factor VIII are also available.<sup>60</sup> Infusion of pure von Willebrand factor concentrate will normalize levels of von Willebrand factor instantaneously, without an immediate increase in factor VIII levels. However, factor VIII levels will gradually increase through the binding of endogenously synthesized factor VIII to the infused von Willebrand factor, which prevents the breakdown and increases the half-life of factor VIII. In the case of an acute bleeding episode or surgery, both of which require immediate normalization of von Willebrand factor and factor VIII levels, additional factor VIII concentrate should be infused together with the high-purity von Willebrand factor concentrate.<sup>60</sup>

In a patient who has a bleeding episode or is undergoing surgery, the aim is to normalize the levels of von Willebrand factor–ristocetin cofactor activity and factor VIII activity with the use of desmopressin or von Willebrand factor concentrate. During major surgery, both values should be higher than 100 IU per deciliter to ensure normal hemostasis. Trough levels should

be monitored regularly after the surgical procedure, with values maintained at a level above 50 IU per deciliter for 7 to 10 days in the case of major surgery and for 1 to 5 days in the case of minor surgery, depending on the specific intervention (Table 2).<sup>5,61</sup> Whether factor VIII levels or von Willebrand factor levels should be used to monitor the response to treatment is still debated, and until that question is answered, it is reasonable to measure both. Especially during treatment with low-purity von Willebrand factor concentrates, factor VIII levels may rise to supraphysiologic levels, potentially predisposing patients to thrombotic complications, although such complications have been reported only sporadically.<sup>61,62</sup>

Patients with von Willebrand's disease who are treated with coagulation factor concentrate should be treated in centers that have extensive experience in the management of bleeding disorders and have access to a local hemostasis laboratory. This also applies to the counseling and care of women with von Willebrand's disease during labor.<sup>5,10</sup>

Recombinant factor concentrates may reduce the risk of transferred viral infections and allergic reactions. In recent years, a recombinant von

Willebrand factor concentrate has been developed. A phase 1 trial showed that it has increased specific activity, as compared with plasma-derived von Willebrand factor.<sup>63</sup> Infusion of recombinant von Willebrand factor together with a single dose of recombinant factor VIII was shown to have high efficacy as a treatment to stop bleeding, without significant side effects, in patients with severe von Willebrand's disease.<sup>64</sup> In 2015, recombinant von Willebrand factor was approved in the United States by the Food and Drug Administration for the treatment of bleeding episodes in adults with von Willebrand's disease.

#### PROPHYLACTIC TREATMENT

In contrast to patients with hemophilia, regular infusion of factor concentrate to prevent bleeding is not commonly used in patients with von Willebrand's disease, although beneficial results have been observed in several case series.<sup>65,66</sup> Recently, a prospective dose-escalating study evaluated prophylaxis in patients who had a severe bleeding phenotype of von Willebrand's disease.<sup>67</sup> Although only 11 patients were included in this study, which was stopped because of slow enrollment, a significant reduction in the number of bleeding episodes, including gastrointestinal bleeding, joint bleeding, and severe epistaxis, was observed in patients receiving regular prophylaxis. Most of the patients were treated with 50 IU of von Willebrand factor–ristocetin cofactor activity per kilogram two or three times a week.

#### TREATMENT OF GYNECOLOGIC BLEEDING

In women with von Willebrand's disease who have menorrhagia, gynecologic and hormonal abnormalities should be ruled out. Once they have been ruled out, treatment should be initiated with oral contraceptives containing both progestin and estrogen. In addition, antifibrinolytic treatment with tranexamic acid may reduce menstrual blood loss.<sup>68</sup> A levonorgestrel-releasing intrauterine device can be placed in patients who do not have a response to oral contraceptives.<sup>69</sup> Even more severe cases may benefit from desmopressin or von Willebrand factor concentrate.<sup>68</sup> If these approaches are not successful, endometrial ablation or hysterectomy can be performed.<sup>70</sup>

In healthy pregnant women, factor VIII and von Willebrand factor levels increase by a factor of 2 to 3 at the time of labor, and these increases are also seen in women with type 1 von Wille-

brand's disease. In women with type 2 disease, the level of von Willebrand factor antigen also rises; however, von Willebrand factor activity remains reduced as a result of the functional defect of the protein.<sup>71</sup> To prevent postpartum hemorrhage, women are treated with factor concentrates during labor if factor VIII or von Willebrand factor levels are less than 50 IU per deciliter in the third trimester of pregnancy. In such cases, the goal of replacement therapy is levels of von Willebrand factor and factor VIII that are higher than 100 IU per deciliter at the time of delivery, ensuring trough levels of more than 50 IU per deciliter. In patients with type 1 disease who do not have sufficiently high factor VIII or von Willebrand factor levels despite the physiologic rise in values during pregnancy, desmopressin can be administered, preferably after clamping of the umbilical cord. Tranexamic acid can be safely administered in the postpartum period. Despite these measures, women with von Willebrand's disease have more postpartum bleeding than women without von Willebrand's disease.<sup>27,28,71</sup>

#### ADDITIONAL TREATMENT

Fibrinolysis inhibitors, such as tranexamic acid and aminocaproic acid, are important as additional treatment of mucocutaneous bleeding. They can also be used to reduce bleeding and especially to prevent rebleeding in patients undergoing surgical or dental interventions, although evidence from randomized trials is lacking.<sup>72</sup> Besides systemic treatment for bleeding or surgery, local measures, such as use of tranexamic acid mouthwash or additional suturing, may be required. Protracted bleeding despite treatment with von Willebrand factor concentrate can sometimes be managed by platelet transfusion because von Willebrand factor is present within the transfused platelets.<sup>61</sup> An innovative treatment strategy is daily subcutaneous administration of interleukin-11, which increases von Willebrand factor and factor VIII levels by a factor of 1.3 to 2.0, presumably by increasing von Willebrand factor messenger RNA levels in patients with type 1 von Willebrand's disease that is unresponsive to treatment with desmopressin.<sup>73</sup> One trial showed that interleukin-11 reduced the severity of bleeding in women with menorrhagia.<sup>74</sup> Angiodysplasia-associated gastrointestinal bleeding episodes are frequently severe and not responsive to treatment with von Willebrand factor concentrate.

Antiangiogenic drugs may be beneficial in such cases. Several case reports have described the successful use of atorvastatin and thalidomide.<sup>18,75</sup> Interleukin-11, atorvastatin, and thalidomide have not yet been approved for use in von Willebrand's disease.

#### FUTURE PERSPECTIVES

In the past decade, new pathophysiological insights into von Willebrand's disease and improved diagnostic approaches and treatment options have emerged. Diagnosis will be further improved by the introduction of more reproducible and rapid assays of von Willebrand factor function. Next-generation sequencing will facilitate the routine identification of mutations in VWF. More widespread use of prophylactic treatment for severely affected patients seems warranted, considering the reported beneficial effects.

Prospective studies are needed to address the question of whether persons who have low von Willebrand factor levels and a bleeding tendency but do not meet the diagnostic criteria for von Willebrand's disease benefit from hemostatic treatment during surgical interventions. Similar studies are needed to determine whether treatment is warranted for elderly patients with von Willebrand's disease in whom von Willebrand factor has risen to levels within the normal range.

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