

Clinical significance of slightly reduced von Willebrand factor activity

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KEY WORDS

low von Willebrand factor, threshold values, type 1 von Willebrand disease

ABSTRACT

Von Willebrand disease (VWD) is the most common congenital bleeding disorder, with a clinical presentation of mucocutaneous and surgical bleeding varying from mild to severe. It is inherited in an autosomal dominant or autosomal recessive manner. The disease is caused by quantitative or qualitative deficiency of the von Willebrand factor (VWF) and is classified as type 1, 2 (2A, 2B, 2M, 2N), and 3. Although type 1 VWD is the most common form of VWD, the formal cutoff for diagnosis remains a subject of debate. In our paper, we present results of studies regarding the clinical and laboratory importance of a new type of bleeding disorder called low VWF. The new guidelines for VWD diagnosis and management suggested that patients with historically type 1 VWD should be divided into 2 subsets: type 1 VWD with a VWF antigen level (VWF:Ag) of less than 30 IU/dl or less than 40 IU/dl, in which about 80% of patients exhibited *VWF* gene mutations, and low VWF with a VWF:Ag level of 30 to 50 IU/dl or 40 to 50 IU/dl, in which the causative mutation is detected in merely 40% of patients and in most families, inheritance is not dependent on the locus of VWF on chromosome 12. Previously, moderately reduced VWF levels (30–50 IU/dl) were considered a risk factor for bleeding, but not a true bleeding disorder, and this condition was named low VWF. Recently, it was documented in a large group of patients with type 1 VWD and low VWF that bleeding score does not correlate with VWF:Ag and bleeding symptoms in type 1 VWD (<30 IU/dl) and low VWF can change from infrequent and moderate to severe bleeds. Because the plasma concentration of VWF depends on many physiological and pathological factors that may mask the diagnosis of VWD, separation of the group of patients with low VWF (30–50 IU/dl) from those with type 1 VWD may delay or prevent them from receiving appropriate treatment. Diagnosis of VWD in each case, particularly those with a slight decrease in VWF (30–50 IU/dl), should be based primarily on the clinical manifestations and family history of hemorrhagic diathesis.

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Received: December 15, 2019.
Revision accepted: January 28, 2020.
Published online: January 28, 2020.
Pol Arch Intern Med. 2020;
130 (3): 225–231
doi:10.20452/pamw.15162
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Introduction Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is characterized mainly by mucosal bleeding and bleeding after surgery or trauma. It was described for the first time in 1926 by Eric von Willebrand.¹ The disorder is indicated by defective platelet adhesion and aggregation caused by either deficiency or dysfunction of the plasma glycoprotein von Willebrand factor (VWF).

Inheritance of von Willebrand disease The inheritance of VWD can be autosomal dominant or recessive. The *VWF* gene is located on the short arm of chromosome 12 (12p13.2), and its pseudogene corresponds to exons 23–34 of the *VWF*

gene at chromosome 22q11.2. The presence of the pseudogene *VWF* makes the molecular analysis of VWF more difficult.²

Biosynthesis of von Willebrand factor VWF is synthesized by endothelial cells and megakaryocytes as a pre-pro VWF consisting of a 22-amino acid signal peptide, 741-amino acid propeptide, and 20150-amino acid mature molecule.² After posttranslational modification (signal peptide cleavage, dimerization, glycosylation, sulfation, and multimerization) in the Golgi apparatus, VWF propeptide (VWFpp) is cleaved by the enzyme furin from a mature VWF molecule in the acidic compartment of trans-Golgi.

In the Weibel–Palade bodies of endothelial cells and platelet α granules, VWF and VWFpp form a noncovalent complex that is released into circulation by a constitutive and regulated pathway. After the release into circulation, complex VWF and VWFpp dissociate, and VWFpp circulates in plasma as a homodimer. Although 1 ml of normal plasma contains 1 μ g of VWFpp with a half-life of 2 to 3 hours and 10 μ g of VWF with a half-life of 8 to 12 hours, the stoichiometric ratio of VWFpp and VWF is 1:1.

The concentrations of VWFpp and VWFpp/VWF:Ag ratio are important biomarkers of the synthesis, secretion, and clearance of VWF. What is important, in spite of VWF, the VWFpp level is not influenced by the ABO blood group.³ This can be useful in VWD subtype discrimination to identify patients with acquired VWD and to identify those with reduced survival of VWF.^{4,5} After proteolysis by a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), VWF appears in circulating blood as a series of multimers, and their weight ranges from 500 to 10 000 kDa. In circulating blood, VWF plays an essential role in both primary and secondary hemostasis. In primary hemostasis, it mediates platelet adhesion and aggregation at sites of vascular damage; in secondary hemostasis, it serves as the carrier protein for coagulation factor VIII (FVIII; cofactor), protecting it from proteolytic degradation, prolonging its half-life in plasma, and preventing its premature clearance from blood.²

Epidemiology of von Willebrand disease Epidemiological investigations have shown that VWF deficiency occurs in about 1% of the general population, but only about 0.01% of the population develops a significant bleeding as a manifestation of VWD.^{6,7} Despite the autosomal inheritance of VWD, the distribution of male and female patients is not equal because of female physiology. The results of epidemiological investigations are strongly dependent on the diagnostic cutoff level for VWF. The historically normal range for VWF was 50 to 150 IU/dl, but since 2008, several guidelines have suggested a cutoff level of 30 to 40 IU/dl.⁸⁻¹³

Diagnosis of von Willebrand disease The diagnosis of VWD is based on a personal history of the bleeding disorder, family bleeding history, and reduced VWF activity confirmed by basic and discriminating laboratory assays, such as ristocetin cofactor (VWF:RCo), VWF antigen (VWF:Ag), and collagen binding (VWF:CB), as well as activity of coagulation FVIII (FVIII:C), low ristocetin-induced platelet aggregation, VWFpp assay, VWF multimer analysis, binding of FVIII:C to VWF, and molecular testing. For excluded hemostatic defects other than VWD, platelet count, activated partial thromboplastin time (APTT), and closure time (platelet function analyzer 100) should be measured.^{2,6,9}

Clinical manifestation of von Willebrand disease

Clinical manifestations most commonly associated with VWD are mucosal bleeding (epistaxis, especially during childhood), gingival bleedings, bruising, menorrhagia, prolonged bleeding time following (most frequently) dental extractions, and bleeding after injury, trauma, and surgery and from gastrointestinal and urinary tracts. Excessive menstruation lasting longer than 7 days may be the only manifestation of VWD in women. Bleeding into the muscles and joints rarely occurs, mainly in type 3 VWD.^{2,9,10,14-16} Spontaneous bleedings are very rare, even in patients with severe VWF deficiency.¹⁰

For assessment of bleeding disorders and the standardization of bleeding episodes, special questionnaires are administered, such as the bleeding assessment tool.¹⁷⁻¹⁹ These are then used to calculate a BS (>4 for men, >6 for women, and >3 for children according to Eltabarny et al,¹⁹ or >3 for men and >5 for women according to Federici et al,¹⁴ though further VWD-directed examinations are required). A low BS in combination with a normal APTT may be suggestive of no bleeding disorder.^{9,20}

Classification of von Willebrand disease

The current classification of VWD includes 6 types: type 1 VWD, which accounts for 60% to 80% of all cases; type 2 VWD (further divided into 2A, 2B, 2M, and 2N), which accounts for 25% to 30% of all cases; and type 3 VWD, which accounts for 1% to 2% of all cases.² In types 1 and 3 VWD, the VWF defect is quantitative. In type 1 VWD, it consists of partial VWF deficiency, and in type 3 VWD, there is almost complete deficiency of VWF in the plasma and platelets. In types 2A, 2B, 2M, and 2N VWD, the defect is qualitative. In type 2A VWD, decreased platelet-dependent function (aggregation with ristocetin) is associated with the absence of high- and intermediate-molecular-weight VWF multimers. Type 2B VWD is characterized by an increased affinity for platelet glycoprotein Ib (increased aggregation induced with ristocetin) and the absence of high molecular multimers. In type 2M VWD, impaired platelet aggregation is induced by ristocetin in the presence of normal VWF high-molecular-weight multimers. Impaired binding of FVIII characterizes type 2N VWD.

Types 2 and 3 VWD have been extensively explored and described, whereas the mechanisms involved in the pathogenesis of type 1 VWD have been poorly understood. This has recently begun to change due to several studies involving large cohorts of type 1 VWD patients.^{8,21-25}

Von Willebrand disease in Poland

There is still no general registry of VWD in Poland. In the register of patients with hemophilia and hemorrhagic diathesis held at the Institute of Hematology and Transfusion Medicine in Warsaw, there are 1849 patients with VWD (data from 2018), which represents 0.0048% of the general

TABLE 1 Current guidelines for the diagnosis of type 1 von Willebrand disease^{8,9,11-13}

Guidelines	Type 1 VWD	Low risk of bleeding	Reference
United States National Heart, Lung, and Blood Institute	VWF:RCo <30 IU/dl and/or VWF:Ag <30 IU/dl	VWF:RCo or VWF:Ag, 30–50 IU/dl Low VWF	Nichols et al ¹²
Polish Society of Hematologists and Transfusionists	VWF:RCo <30 IU/dl and/or VWF:Ag <30 IU/dl	VWF:Ag, 30–50 IU/dl	Zdziarska et al ⁹
European group on VWD disease	VWF:RCo <40 IU/dl or VWF:CB <40 IU/dl	–	Castaman et al ¹⁰
United Kingdom Haemophilia Centre Doctors Organization	VWF:RCo <30 IU/dl	VWF:RCo, 30–50 IU/ml Low VWF	Laffan et al ¹¹
Zimmerman Program for the Molecular and Clinical Biology of VWD	VWF:RCo <40 IU/dl or VWF:Ag <40 IU/dl	VWF:RCo, 40 IU/dl Low VWF	Flood et al ⁸

Abbreviations: VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen level; VWF:CB, collagen-binding von Willebrand factor; VWF:RCo, Von Willebrand ristocetin cofactor

population in Poland. Type 1 VWD (VWF <50 IU/dl) is most common, being reported in 1420 patients (76.7%).

The Polish Society of Hematologists and Transfusiologists⁹ recommendations regarding the principles of diagnostic evaluation in VWD were published in 2018. They include clinical criteria for VWD, namely, medical history, family history, and physical and laboratory examinations, that is, hemostatic screening, basic tests for VWD, and detailed tests enabling the identification of subtypes of this highly heterogeneous hemorrhagic disease, as well as treatment.

Von Willebrand disease type 1 vs threshold von Willebrand factor values Type 1 VWD is most common and occurs in 60% to 80% of the patient population. Historically, this category includes patients with VWF activity of less than 50 or 60 IU/dl and that is rather heterogeneous. Type 1 VWD is diagnosed in patients with lower VWF:RCo, a comparable decrease in VWF:Ag, and a VWF:RCo-to-VWF:Ag ratio higher than 0.6 or 0.7. Although type 1 VWD is the most frequent type of VWD, extensive studies on its molecular background did not begin until 2000.^{11,12,17,18,26} VWF gene mutations are detected in about 70% of patients with type 1 VWD (historical range); in about 82% of patients with type 1 VWD and VWF:Ag of less than 30 IU/dl, and in about 44% of patients with type 1 VWD and VWF:Ag higher than 30 IU/dl.^{8,21,27} VWF gene mutations are detected in about 70% of patients, and VWF of less than 30 IU/dl is more common than the values of 30 to 50 IU/dl. Although mutations are mostly of the heterozygous missense type, small deletions, insertions, splice sites, and nonsense mutations have been reported. Mutations can be dispersed throughout the whole VWF molecule and may decrease VWF synthesis and secretion,

impair intracellular transport of VWF subunits, or increase VWF clearance.^{21,22,28,29}

Until recently, the accepted threshold value for the diagnosis of type 1 VWD was VWF:RCo and/or VWF:Ag of 50 IU/dl. In recent years, several guidelines have suggested that only a VWF level below 30% is diagnostic for VWD, while a level of 30% to 50% is considered a mild risk of bleeding.

According to current guidelines of the United States National Heart, Lung, and Blood Institute,¹² Polish Society of Hematology and Transfusion Medicine,⁹ the European Group on VWD,¹⁰ and the United Kingdom Haemophilia Centre Doctors Organization,¹¹ patients with type 1 VWD (historical range) should be divided into 2 distinct subsets: type 1 VWD (<30 IU/dl) and low VWF levels (30–50 IU/dl). In addition, according to the Zimmerman Program for the Molecular and Clinical Biology of VWD, they should be divided into type 1 VWD of less than 40 IU/dl and low VWF with VWF:RCo from 40 IU/dl to the lower end of the normal range⁸ (TABLE 1). Independent of the guidelines, the cutoff varies widely in practice and some authors use the lower limit of the normal range (50 IU/dl).^{12,13,30}

Patients with VWF levels of less than 30 IU/dl have a personal and family history of bleedings correlated with the presence of VWF gene mutations. A more difficult diagnostic challenge is patients with a VWF level of less than 30 to 50 IU/dl without a family history of bleedings and frequently without detected causative VWF gene mutation. It should be kept in mind that low VWF is quite common in the general population, but not all of these patients have bleeding symptoms that are significant enough for VWD diagnosis. Studies have demonstrated that a VWF level of 30 to 50 IU/dl is not sufficient for VWD diagnosis but indicates merely increased bleeding risk. It is suggested that patients with VWF levels of 30 to 50 IU/dl with no family history of bleeding should be classified as having a low bleeding risk and likely or low / threshold VWF levels.³¹⁻³⁴

Diagnostic problems in patients with von Willebrand factor levels of 30 to 50 IU/dl The VWF threshold values for the diagnosis of type 1 VWD have aroused numerous controversies.^{9,12,25} Historically, the threshold value of VWF:Ag was 50 IU/dl, and currently, 2 values 30 or 40 IU/dl are accepted.^{12,25} In 2008, the National Heart, Lung, and Blood Institute¹² published recommendations suggesting that type 1 VWD should only include patients with VWF:Ag or VWF:RCo of less than 30 IU/dl because in this group, this VWF level is correlated with the presence of VWF gene mutations and bleeding phenotype. Other patients should be classified as low VWF levels with low bleeding risk.^{12,16} Recommendations of the European Group on von Willebrand Disease issued in 2013 stated that the likelihood of VWD markedly increases in patients with a VWF level of less

TABLE 2 The frequency of abnormal bleeding score in patients with type 1 von Willebrand disease included in the Zimmerman Program³⁴

Diagnosis	VWF:Ag, IU/dl	Frequency of prevalence, %	
		Abnormal bleeding score	Normal bleeding score
Type 1 VWD	<30	76	24
Low VWF	30–50	64	36
Healthy control subjects	50–150	2	98

Abbreviations: see [TABLE 1](#)

than 40 IU/dl, while VWF levels of 40 to 60 IU/dl rarely confirm VWD diagnosis.²⁵

It is estimated that threshold VWD levels (30–40 IU/dl) occur in approximately 0.4% of the general population. In the United States alone, this applies to about 1.3 million people. No other type of VWD arouses such controversy as the categorization of patients with mucosal bleeding and VWF concentrations above the threshold value as low VWF. In a study of this population, VWF levels were inherited in only 25% to 32% of patients.³²

Molecular studies performed within the Zimmerman Program,⁸ which enrolled patients with low VWF, demonstrated causative mutations in 82% of patients with VWF levels of less than 30 IU/dl. However, in patients with VWF levels of 30 to 50 IU/dl, causative mutations were detected in 44% of the American population,⁸ 49% of the Canadian population,³² 51% of the European population, and 39.7% of the Irish population.²⁷

Diagnosis of low VWF is complicated by the variability of VWF, and it is dependent on numerous factors, both genetic and environmental. VWF plasma levels vary with age, are related to physical activity and infections, and increase during pregnancy. In addition, the clinical presentation of patients with low VWF levels is non-specific; similar bleeding may occur in patients with low VWF and in healthy people. It has been demonstrated that at least 1 nonspecific VWD symptom occurs in 23% of healthy people and in 88% of people with type 1 VWD. In healthy people, nosebleeds occur in 5% to 23% of the population, gum bleeding in 7% to 47%, easy bruising in 12% to 50%, bleeding after minor cuts in 0.2% to 33%, bleeding following dental extraction in 5% to 42%, bleeding following surgery in 1.4% to 28%, and postpartum bleeding in 6% to 23%. In patients with VWF levels of 30 to 50 IU/dl and bleeding history, the predictability of future bleeding is markedly higher, whereas in asymptomatic patients with VWF levels of 30 to 50 IU/dl, the risk of bleeding is considered rather low.^{12,31,32}

Clinical and laboratory characteristics of low von Willebrand factor Test results from various centers using large cohorts of patients suggest that in patients with VWF levels of 30 to 50 IU/dl, bleeding symptoms and VWF levels are most often

independently inherited.^{24,27,29,32} Bleeding score is high in most of these patients and does not correlate with VWF levels. Flood et al³⁴ presented the frequency of abnormal BS in type 1 VWD (<30 IU/dl) in comparison with low VWF (<30 IU/dl) and healthy controls ([TABLE 2](#)).

Analysis of test results for patients with type 1 VWD in the Zimmerman Program (741 patients and 256 donors) demonstrated that VWF gene mutations are more common in patients with VWF levels of less than 30 IU/dl than in those with VWF levels of 30 to 50 IU/dl, while BSs are similar regardless of the VWF level.³⁴ In patients with low VWF, the VWF levels did not always increase with age to a normal value. Increases in VWF levels to normal values in patients with low VWF levels enrolled in the Zimmerman Program were reported in 36% of the population, but for most of these patients, bleeding risk was not reduced.^{31,34-36}

In the low VWF Ireland Cohort study, Lavin et al²⁷ examined 126 patients, mostly women (n = 112; 89%), with threshold VWF levels. Diagnosis of low VWF levels was based on patient history, which included bleeding history and VWF level of 30 to 50 IU/dl assayed twice (in a 3-month interval). In the low VWF group, BS (according to the International Society of Thrombosis and Haemostasis Bleeding Assessment Tool) was high and in some cases markedly high, irrespective of a slight decrease in VWF plasma level. Flood et al³⁴ presented the frequency of abnormal BS with Zimmerman Program subjects: with type 1 VWD (VWF:Ag <30), low VWF (VWF:Ag 30–50 IU/dl), and VWF:Ag higher than 50 IU/dl in comparison with healthy controls. They showed that although the frequency of abnormal bleeding BS was higher in the type 1 VWD group, significant bleedings were also present in the low VWF group ([TABLE 2](#)).

In female patients with low VWF, as many as 77% had a BS of 6 or higher, and 37% had a BS of 10 or higher. No correlation between a VWF level of 30 to 50 IU/dl and severity of bleeding symptoms was determined. The highest BS was observed in the menorrhagia and dental domains. The most common symptom was increased menstrual bleeding; in 86 cases (6%), pads / tampons were changed more frequently than every 2 hours, clots and flooding were common, and bleeding lasted longer than 7 days.

Other studies³² have found that as many as 89% of women with VWF levels of 30 to 50 IU/dl reported symptoms of menorrhagia; furthermore, about 32.5% of women with low VWF levels required iron therapy, more than 30% needed surgical intervention (including curettage, endometrial ablation, or hysterectomy), and 66% needed hormonal therapy (contraceptive drugs or hormonal releasing intrauterine device in combination with antifibrinolytic agents).³⁷ Despite increased VWF levels during pregnancy, women with low VWF may experience severe postpartum bleeding within 24 hours of delivery or secondary bleeding within 6 weeks of delivery.³²

Laboratory characteristics of von Willebrand factor levels of 30 to 50 IU/dl

In an attempt to explain the clinical phenotype and pathophysiology underlying bleeding in patients with VWF levels of 30 to 50 IU/dl, Lavin et al²⁷ studied a cohort of 126 patients (including 112 women). This study and many others have demonstrated that for patients with low VWF:

- FVIII:C was lower than in the control group (although it was still within the reference range).^{27,38}
- FVIII:C-to-VWF:Ag ratio, which indicates impaired synthesis or VWF secretion, was markedly higher.^{27,38}
- VWFpp-to-VWF:Ag ratio was higher only in 6% of patients, which points to the small effect of VWF clearance on the reduction of VWF and the occurrence of bleeding symptoms.^{27,37-41}
- VWF:CB (collagen binding to VWF) and VWF:Ag were significantly lower compared to the control group.²⁷
- VWF increased with age but only reached normal levels for some patients.^{27,42}
- Low VWF was also reported in elderly people with a bleeding history.⁴³
- No correlation was observed between platelet VWF and intensity of bleeding disorder.²⁷

Pathogenesis of low von Willebrand factor A laboratory analysis performed by Lavin et al²⁷ demonstrated reduced VWF in the majority of patients; 3.2% of patients had reduced VWF high-molecular-weight multimers, and most lacked an additional hemostatic defect. Most of the patients had elevated FVII-to-VWF:Ag ratios, normal VWFpp-to-VWF:Ag ratio, and impaired collagen binding compared with the control group. This study strongly suggests that low VWF levels of 30 to 50 IU/dl are mainly due to impaired synthesis and/or VWF clearance.

Genetic background: mutations within the VWF gene Van Loon et al⁴⁴ performed a meta-analysis of data from 11 European populations totaling 31 149 persons and identified 5 genes associated with low VWF. In about 40% of cases, low VWF was caused by VWF gene mutations. Diversity in VWF levels also resulted from single nucleotide polymorphisms in the VWF gene. The most important is the single nucleotide polymorphism rs216303: T>C located within the intron. It is now widely believed that intronic variants not only regulate VWF plasma levels but also affect gene splicing and mRNA stability.^{21,44,45}

Contribution of deficiencies other than von Willebrand factor on hemostasis In a study of low VWF patients with high BS, only 11% had deficiency of a coagulation factor other than VWF, suggesting that the main cause of bleeding in this group of patients is a reduced VWF level.²⁷ However, it should be remembered that skin and mucosal bleeding, the most common symptoms of low VWF, are not very characteristic and can be caused or intensified by additional disorders, such as

abnormalities of primary hemostasis, generation of thrombin, or fibrinolysis.

Abnormal von Willebrand factor glycosylation Abnormal glycosylation of the VWF molecule may play an important role in VWD pathogenesis. Aguilí et al⁴⁶ demonstrated that in patients with low VWF, abnormal glycosylation in the final fragment of the VWF molecule (α 2-6 binding) could occur. Reduction of sialic acid at the N-terminus of the VWF chain results in increased exposure of galactose that correlates with a higher VWF clearance through binding to receptors on hepatocytes or macrophages. In patients with higher clearance, an inverse correlation was observed between VWF half-life and galactose exposure. Studies⁴⁶ suggest that modification in the VWF polysaccharide part may play an important role in VWD pathogenesis, particularly in low VWF pathogenesis in patients with an undetected causative mutation.

Genetic background: gene mutations other than VWD The activity of VWF is determined by blood type (O < A < B < AB). It is known that about 14% of healthy people with type O blood have a 25% lower VWF than those with other blood types.⁴⁷ The mechanism behind this is not fully understood. This is most likely due to the antigenic determinants of the ABO system (H-antigen) expressed on the N-linked VWF polysaccharide chains. It has been suggested that slight modification in the VWF structure containing these determinants affects proteolysis and VWF clearance.⁴⁸

It has been demonstrated that in a large proportion of patients with VWF levels of 30 to 50 IU/dl, the VWF threshold values are due to mutations/polymorphisms in genes other than VWF gene. Van Loon et al⁴⁴ performed a meta-analysis of genome-wide association results from 11 European populations (31 149 people in total), and they identified 3 additional genes (apart from ABO and VWF) that affect reductions in VWF levels. These were syntaxin binding protein 5 (STXBP5) 6q24, which is involved in the exocytosis of Weibel-Palade bodies; stabilin-5 (STAB5) 12Q23, which is a transmembrane protein receptor involved in endocytosis; and ubiquitin-fold modifier-1 (UFM1) 13q13, which is involved in cellular homeostasis.^{44,49-52} In a manuscript published in 2013, Rydz et al⁵¹ suggested a relationship between CLEC4M lectin gene polymorphisms (responsible for binding, internalizing, and increasing VWF clearance) and reductions in VWF plasma levels.

Treatment Treatment of patients with low VWF is the same as that of those with type 1 VWD, with management dependent on the intensity of bleeding symptoms. Antifibrinolytic agents, such as tranexamic or aminocaproic acid, desmopressin 1-desamino-8-D-arginine vasopressin (DDAVP), or VWF concentrates, should be administered.³¹ Patients with type 1 VWD have individual sensitivities to DDAVP.

Unlike patients with type 1 VWD, most of those with low VWF exhibit a strong and long-lasting response to DDAVP. For example, Lavin et al²⁷ found that for 88% of patients, the VWF levels increased above 100 IU/dl, and in 72%, they remained unchanged 4 hours after DDAVP administration.

Conclusion The 2008 guidelines of the National Heart, Lung, and Blood Institute suggested the distinction of 2 groups of patients with type 1 VWD. The first type is type 1 VWD with a VWF concentration of less than 30 IU/dl, in which almost all patients exhibit mutations of the VWF gene. Meanwhile, the second type is type 1 VWD with a VWF concentration of 30 to 50 IU/dl, named low VWF, in which the causative mutation is detected in merely 40% of patients and in most families, inheritance is not dependent on the locus of VWF on chromosome 12. The bleeding tendency in patients with low VWF is more severe than in healthy people, and the elevated BS is a risk factor for subsequent bleedings. Because the plasma concentration of VWF depends on many physiological and pathological factors that may mask the diagnosis of VWD, it is therefore suggested that patients with threshold VWF values and bleeding symptoms should be treated in the same way as patients with type 1 VWD, with management depending on the type and severity of bleeding. In our opinion, all patients with symptoms of bleeding, family bleeding history, and reduced VWF activity confirmed by basic and discriminating laboratory assays should be referred to a hematologist.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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HOW TO CITE Bykowska K, Ceglarek B. Clinical significance of slightly reduced von Willebrand factor activity. *Pol Arch Intern Med.* 2020; 130: 225-231. doi:10.20452/pamw.15162

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