GUIDELINES

Management of von Willebrand disease. Recommendations of the Hemostasis Group of the Polish Society of Hematology and Transfusiology (2022)

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Summary

Recommendations of the Group on Hemostasis of the Polish Society of Hematology and Transfusiology are an update of the guidelines issued in 2008 [1]. In the absence of adequately designed randomized clinical trials for the diagnosis and treatment of von Willebrand disease, these recommendations are largely based on retrospective studies, expert opinions, series of case reports as well as guidelines published in other countries. In questionable cases, most conclusive for the final diagnosis of von Willebrand disease (VWD) is the physician's experience and his assessment of the patient's clinical picture.

Key words: von Willebrand disease, von Willebrand factor, bleeding disorders, guidelines

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Introduction

Von Willebrand disease (VWD) is the most common congenital bleeding disorder, first described in 1924 by a Finnish physician Erik von Willebrand. VWD is caused by quantitative or qualitative deficiencies in a plasma protein now called von Willebrand factor (VWF). VWF plays an essential role in primary and secondary hemostasis: it mediates platelet adhesion at sites of vascular injury and binds to and stabilizes factor VIII in circulation. The higher bleeding tendency in VWD is therefore associated with impaired primary hemostasis (platelet adhesion to the endothelium) as well as of secondary hemostasis (reduced factor VIII activity in plasma). In patients with VWD, the FVIII gene is normal and the FVIII deficiency is secondary to VWF which acts as stabilizer of FVIII in the circulation.

Von Willebrand factor is a large multimeric glycoprotein present in plasma. It is synthesized in the endothelial cells and bone marrow megakaryocytes and cleaved by ADAMTS13 metalloproteinase. VWF has a normal half-life of approximately 12 hours (9–15 hours). About 10–15% of the total amount of circulating VWF is in platelets.

VWD is inherited in an autosomal, dominant or recessive manner. Unlike hemophilia A and B, it affects males and females equally. The VWF encoding gene is located on the short arm of chromosome 12 (12p13.31). The location of the mutation within the VWF gene correlates well with the VWD subtype [2].

Penetrance and expression of VWD-related mutations is variable and the lack of detectable mutations in the VWF gene does not exclude VWD diagnosis. The disorder is underdiagnosed and its prevalence is estimated to affect 1:100 individuals in the general population, but the statistics approximated 1:1000 if bleeding was also taken into account [3]. Still, only some patients are properly diagnosed and referred to special treatment centers [2].

Classification of von Willebrand disease

The current classification of VWD was originally proposed in 1994 and updated in 2006 by the *International Society on Thrombosis and Haemostasis* (Table 1). There are three major types of VWD: moderate quantitative VWF deficiency (type 1, MIM: 193400; MIM, Mendelian Inheritance in Man), qualitative defect of VWF function (type 2, MIM: 613554) and undetectable VWF levels (type 3,

the most severe form, MIM: 277480). Type 2 is further divided into four subtypes, which differ with regard to VWF dysfunction. Identification of the type of VWD is pivotal for selection of optimal treatment and patient's care.

There are several limitations to the current classification of VWD. Assignment to a specific type or subtype of VWD is not always easy due to the large phenotypic heterogeneity of the disease, its complex pathogenesis and complicated quantitative and qualitative defects within the VWF molecule in patients with specific genetic mutations. There are no arbitrarily established threshold values for laboratory tests to enable a clear differentiation between VWD types (e.g., type 1 and 2, or subtype 2A and 2M). Furthermore, there is no easy access to some laboratory tests and sometimes only genetic testing allows for accurate diagnosis (type 2). The final interpretation of laboratory outcome and VWD classification should always be performed by a hematologist experienced in the management of bleeding disorders.

Type 1

Type 1 is diagnosed in as many as 75–85% of all symptomatic cases of VWD [4, 5]. Characteristic for this type of VWD is quantitative deficiency of VWF in the bloodstream measured with the VWF:RCo (ristocetin cofactor activity assay) or with alternative tests. Functionally the VWF molecule is normal. A low level of VWF may also mean a lower level of Factor VIII. No significant decrease in the number of large multimers is reported [6].

Type 1C

Type 1C VWD is characterized by enhanced VWF clearance. The disorder is confirmed by a desmopressin test with assessment of VWF activity 1 h and 4 h after cessation of drug infusion. Enhanced VWF clearance is confirmed when VWF activity after 4 h decreases by more than 30% compared to the maximum value. It is no longer recommended to calculate the ratio of VWF propeptide to plasma VWF concentration because the interpretation of the result is difficult (higher ratio indicates enhanced VWF clearance, but the normal value is no ground for exclusion). The ratio however, may be useful when the desmopressin test is contraindicated [7].

Type 2

The clinical picture of type 2 VWD varies. Bleeding symptoms are usually moderate, though they may be severe (e.g. recurrent gastrointestinal

Table 1. Classification of VWD (*Subcommittee on von Willebrand Factor of the International Society on Thrombosis and Hemostasis*)

Type	Description	Inheritance	Bleeding severity
1 (MIM: 193400)	Partial quantitative deficiency of VWF	Autosomal dominant	Mild or moderate
2 (MIM: 613554)	Qualitative deficiency of VWF	Autosomal dominant or recessive	Variable, usually moderate
2A	Qualitative variants with decreased platelet-dependent function associated with the absence of high--molecular-weight VWF multimers	Autosomal dominant or recessive	Variable, usually moderate
2B	Qualitative variants with increased affinity for platelet GPIba; some deficiency of high-molecular-weight VWF multimers	Autosomal dominant	Variable, usually moderate
2M	Qualitative variants with decreased platelet-dependent function not caused by the absence of high--molecular-weight VWF multimers	Autosomal dominant or recessive	Variable, usually moderate
2N	Qualitative variants with markedly decreased binding affinity for factor VIII	Autosomal recessive	Variable, usually moderate
3 (MIM: 277480	Virtually complete deficiency of VWF	Autosomal recessive	Severe bleeding

bleeding in patients with angiodysplasia). Differentiation between type 2 and type 1 is of great clinical significance as the treatment of some subtypes of the former differs from the management of type 1 VWD. Type 2 VWD is characterized by qualitative VWF deficiency which manifests with abnormal physiological functions. Differentiation between type 1 and type 2 is mainly based on VWF:CB/VWF:Ag ratio (ratio of VWF level and VWF activity). Type 2 VWD accounts for 20–35% of all VWD cases [5].

Subtype 2A

It is characterized by a smaller percentage of large VWF multimers either as result of their enhanced susceptibility to cleavage by ADAMTS13 or of impaired synthesis. VWF-dependent platelet adhesion is impaired. VWF concentration and the FVIII activity in plasma are normal or slightly lower, while VWF activity is markedly reduced. The deficiency of high-molecular-weight VWF multimers is responsible for higher bleeding tendency.

Subtype 2B

Mutations underlying subtype 2B VWD are responsible for pathological increase in the affinity of VWF for platelet glycoprotein Ib (GPIb). This intensifies proteolysis and removal of high-molec-ular-weight VWF multimers from the circulation. The mechanism is responsible for increased bleeding tendency. Moreover, the circulating platelets are bound to abnormal VWF molecules which may impede their adhesion at vascular injury.

Laboratory results for subtype 2A and 2B are similar, however type 2B individuals sometimes develop thrombocytopenia which may be further aggravated by surgery, pregnancy or stress. The most likely cause of thrombocytopenia is reversible sequestration of platelet and VWF aggregates in microcirculation. The aggregates are dissolved by ADAMTS13 that cleaves VWF to smaller forms. The diagnosis of subtype 2B is based on detection of pathologically increased low-dose ristocetin-induced platelet aggregation (LD-RIPA) or of the mutation responsible for this variant of VWD [7, 8].

Platelet-type von Willebrand disease (PT-VWD)

This is a rare autosomal dominant platelet disorder that affects approximately 15% of the patients diagnosed with type 2B VWD. The condition is caused by a gene mutation encoding for platelet glycoprotein iba (GPIba) conferring to GPIba enhanced affinity for VWF (as a result of a *gain of function* mutation in the GP1BA gene, MIM: 177820). The disorder presents with mucocutane-

ous bleeding as well as thrombocytopenia, increase in platelet size and loss of high-molecular-weight VWF multimers in laboratory assays. The LD-RIPA test shows enhanced platelet aggregation. Bleeding is however, not as severe as in type 2B VWD. The differential diagnosis of type 2B VWD and PT-VWD is a challenge [9].

Subtype 2M

This subtype of VWD presents with impaired VWF-mediated platelet adhesion not attributable to reduced amount of high-molecular-weight multimers. Mutations within the A1VWF domain weaken the interaction between VWF, GPIb and the connective tissue. The differential diagnosis between subtype 2M and 2A is based on the distribution of VWF multimers (which is normal in the 2M subtype).

Subtype 2N

The 2N subtype is characterized by a marked decline in the VWF binding affinity for FVIII (reduced binding of VWF to factor VIII). As result, FVIII activity in plasma is reduced (usually to 5–40%), while VWF concentration and activity are within normal range. This subtype of VWD may be misdiagnosed as mild hemophilia A. Unlike hemophilia A however, it is inherited in an autosomal recessive manner. The subtype is identified solely by an abnormal FVIII/VWF binding test (always normal in mild hemophiliacs or hemophilia A carriers) and/or genetic testing [10].

Type Vicenza von Willebrand disease

This type of VWD was introduced in response to the diagnostic difficulties caused by the complex mechanism of the disorder. The Vicenza type VWD was described with usually low VWF level in plasma (< 15 IU/dL) and VWF multimers that are larger than in physiological conditions (similar in size to ultra/supranormal VWF multimers in plasma). Lower VWF levels result from a missense mutation of p.Arg1205His (NM_000552.5: c.3614G> A) responsible for an app. 5-fold increase in VWF clearance and shorter VWF survival in plasma [7]. Accelerated VWF clearance seems to be the only explanation for the presence of ultra-large multimers which are not cleaved by ADAMTS13. The ratio of VWF activity to VWF level is usually normal. The Vicenza type is currently classified as either type 1 or subtype 2M of VWD, depending on how laboratory results are interpreted.

For patients with Vicenza-type VWD it is recommended to use desmopressin or FVIII/VWF concentrates contingent upon VWF half-life and patient's clinical picture [11].

Type 3

The prevalence of type 3 VWD in the general population is estimated at 1:250.000––1:1.000.000 [2]. This accounts for less than 1% of all VWD cases [5]. Type 3 is the most severe form of VWD, which presents with virtually complete deficiency of VWF and extremely low FVIII activity (usually < 10 IU/dL). Type 3 VWD is mostly caused by nonsense or missense mutations although other mutations are also reported (large scale deletions and splicing mutations as well as insertions) which refer to different fragments of the VWF gene.

Type 3 VWD is inherited in an autosomal recessive manner. Heterozygous VWF mutations//deficiency usually manifest with no severe hemorrhagic symptoms [4].

Alloantibodies against von Willebrand factor

A small percentage of type 3 VWD patients develop anti-VWF alloantibodies in reaction to replacement therapy. The estimated frequency of such adverse reactions (ARs) is 5–10%. Recently alloantibodies have been reported in a 2B VWD patient which means that alloantibodies against VWF may also develop in other types of VWD. Alloantibodies, which are usually polyclonal and belong to the IgG class, shorten the survival and accelerate the clearance of infused VWF. The role of VWF in primary hemostasis is thereby reduced. Moreover, alloantibodies may be responsible for life-threatening allergic reactions caused by immune complex formation and complement activation. Factors predisposing to alloantibody formation are: large deletions in the VWF gene, VWF inhibitor in family history, and multiple VWF transfusions [12–14].

One constant feature of all described alloantibodies against VWF is the lack of hemostatic response to infused VWF concentrates which is a serious complication of VWD therapy. It is however possible to exercise indirect influence on the activity of factor VIII in plasma through interaction with the factor VIII-binding site of the VWF molecule [13].

Cases of antibody transmission through placenta and temporary reduction of VWF activity in newborns have been reported [15].

Acquired von Willebrand syndrome (AVWS)

In the course of such diseases as hematologic malignancies (particularly lymphoproliferative and myeloproliferative), cardiovascular disorders and autoimmune diseases (systemic lupus erythematosus), patients with no congenital VWD may present with bleeding disorders. Various mechanisms are implied in the pathophysiology of AVWS, the majority of them leading to the increased degradation or clearance of circulating vWF (presence of antibodies, cell adsorption, shear stress or increased proteolysis). Hypothyroidism may be associated with decreased synthesis of an otherwise qualitatively normal vWF. Cases of AVWS have also been reported following administration of medication such as alproic acid or cyproprofloxacin.

The distribution of VWF multimers may be normal or similar to that of type 2A VWD. The prevalence of AVWS has not yet been estimated. The clinical manifestations of congenital VWD and AVWS are similar, in the latter case however, the bleeding tendency is acquired and the family bleeding history is negative. The bleeding tendency is characteristic for a number of diseases which may coexist with AVWS and that only further complicates the diagnosis [16].

Clinical picture of von Willebrand disease

VWD patients usually experience skin and mucous membrane bleeding; the most common clinical manifestations are epistaxis, severe bleeding following tooth extractions, menorrhagia, bleeding gums. Bleeding is usually mild or moderate and requires no medical intervention or transfusion of packed red blood cells (RBCs). Life-threatening bleeding episodes (to the central nervous system, gastrointestinal tract) occur in patients with type 3 VWD, in some patients with type 2, and rarely in patients with type 1 VWD.

A common VWD symptom is bleeding from the gastrointestinal tract due to gastrointestinal angiodysplasia. Studies show that 4–6% of gastrointestinal bleeding in the general population is caused by age-related angiodysplasia, VWF deficiency (congenital or acquired), or renal failure [17]. Clinical and experimental data confirm that VWF deficiency may lead to pathological angiogenesis and vascular malformations in the gastrointestinal tract. The complication mostly affects type 2A, 2B or 3 VWD patients who suffer from the loss of high molecular VWF multimers [18].

Joint bleeds are rare but may occur in patients with severe FVIII deficiency, mainly type 3 VWD.

Recurrent hemorrhages may lead to arthropathy and the symptoms resemble those of hemophilia.

One of the major VWD symptoms in women is menorrhagia. VWD is reported in 5–20% of women who experience heavy menstrual bleeding and in 5–36% of teenagers who are less likely to have pathological organic causes of heavy hemorrhagic periods [19]. The diagnosis of VWD is delayed because the assessment of the bleeding intensity is largely subjective, and also because menorrhagia may also occur in other women of the same family.

Symptoms and signs of menorrhagia are: loss of more than 80 ml of menstrual blood per cycle, the presence of clots in the menstrual blood > 2.5 cm in diameter, soaking through a pad or tampon within 1h and ferritin levels below normal range [2].

The clinical course of VWD may be affected by comorbidities and medication. Non-steroidal anti-inflammatory drugs may exacerbate the symptoms while oral contraceptives reduce the bleeding tendency.

Laboratory diagnostics of von Willebrand disease

Figure 1 presents an algorithm for diagnosis of von Willebrand disease. There is no single sufficiently sensitive and specific screening test with low false-positive rate. Screening assays for hemostasis: platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT), plasma fibrinogen content or thrombin time (TT) are not sufficient to identify or exclude VWD. Nevertheless, the assays are helpful in differential diagnosis of hemorrhagic disorders, particularly as regards coagulation factor deficiencies and thrombocytopenia [7]. APTT is prolonged only in patients with markedly lower FVIII activity (< 30 IU/dL) and may be corrected to normal in a mixing study (mixture of patient's plasma with normal pooled plasma). APTT is normal in a large population of VWD patients, mainly types 1 and 2.

At some centers, the hemostasis screening panel includes also occlusion/closure time (CT) Platelet Function Analyzer PFA-100® or PFA-200®. Occlusion time is prolonged in most VWD patients (with the exception of type 2N), but the sensitivity and specificity of the assay is too low. The test however may be useful for exclusion of VWD, particularly when VWF activity tests are unavailable or the results are delayed. While interpreting test results, it is noteworthy that the CT may also be prolonged in patients with thrombocytopenia, thrombocytopathy or those who
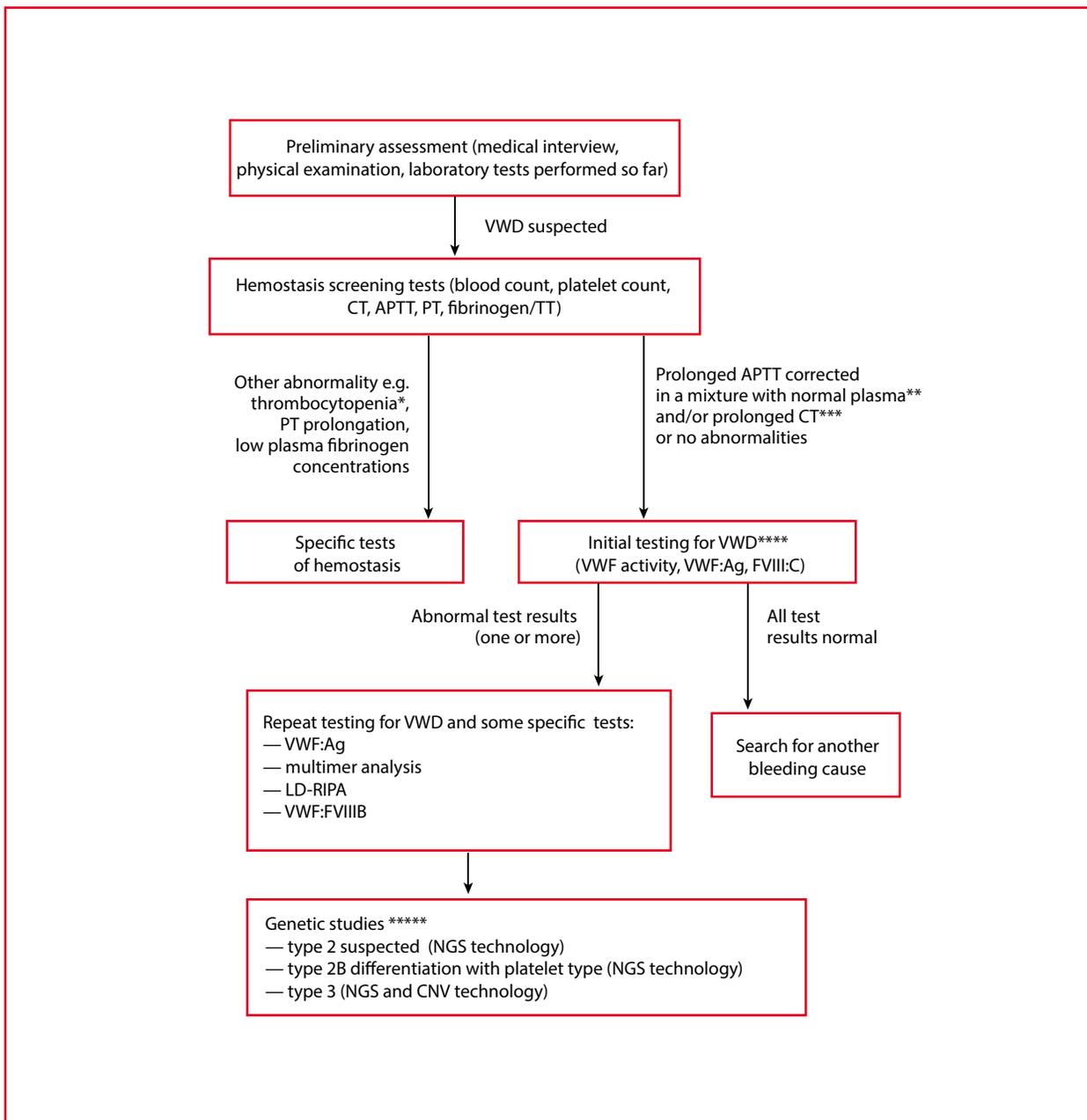
Figure 1. Diagnostic algorithm for von Willebrand disease (VWD)

*Thrombocytopenia may suggest subtype 2B VWD.

**APTT correction in a mixture with normal plasma excludes FVIII inhibitor and lupus anticoagulant as the cause of APTT prolongation. It is recommended to determine the activity of other factors of the intrinsic pathway.

***Prolongation of CT; recommended differentiation between von Willebrand disease and bleeding due to platelet dysfunction.

****Initial VWD testing may require multiple retesting due to the high biological variability of VWF and FVIII levels and interfering factors.

*****The search for causative mutations in the VWF gene is particularly useful for type 2B and 2N VWD and for type 3

VWD — von Willebrand disease; VWF — von Willebrand factor; APTT — activated partial thromboplastin time; PT — prothrombin time; TT — thrombin time; CT — occlusion time measured in platelet function analyzer (PFA); VWF:Ag — VWF plasma concentration; FVIII:C — factor VIII activity; LD-RIPA — low dose ristocetin induced platelet aggregation; CNV — copy number variation analysis; NGS — next generation sequencing

take antiplatelet drugs or in the presence of VWF antibodies [20].

Screening tests for VWD

In cases of severe bleeding, screening tests for VWD may be considered even at the first visit. The assay panel should be available at all hematology centers and include: VWF activity in plasma, VWF concentration (VWF:Ag) and factor VIII coagulant activity (FVIII:C). If any of the parameters is abnormal, the patient should be referred to a special treatment center for repeat assays and further, in depth testing.

The higher content of VWF and FVIII in plasma may be caused by numerous factors such as age, stress, exercise, surgery, inflammatory mediators or oral contraceptives. The outcome of laboratory tests may also be affected by techniques used for sample collection as well as conditions of storage, transport and processing (see frame 1). During pregnancy, the VWF and F VIII parameters increase (the level and activity of VWF increase 2–5 fold in the third trimester), not only in healthy women, but also in women with type 1 VWD. All the above should be considered when interpreting test results. Frequently, the final VWD diagnosis is reached only after the assays are performed several times.

Diagnosis of type 1 VWD is extremely difficult when plasma VWF levels are reduced to below normal (normal range is 30–50 IU/dL). Decrease of VWF level is not always indicative of a pathogenic mutation. The likelihood of VWD correlates with the decrease of VWF content (if < 30 IU/dL, the VWD diagnosis is practically certain).

All three preliminary markers (VWF:Ag, VWF:RCo, FVIII:C) present high variability (up to 30%). The reasons for the decrease of plasma levels of VWF in patients who are not diagnosed with VWD, still remain unclear. A significant genetic factor which determines VWF level in plasma is the ABO blood group. Group O-individuals have lower plasma VWF levels than non-O subjects (about 25 IU/dL lower). It is not advisable however, to differentiate VWF activity and levels by blood types since it has been demonstrated that the risk of bleeding correlates with plasma levels of VWF and the blood group is an independent risk factor.

According to some experts, there is rationale for diagnosing VWD when VWF level in plasma (regardless of the testing method) falls below 30 IU/dL [7] or 40 IU/dL [21]. When the values are within the 30–50 IU/dL range, it is suggested to diagnose "borderline VWF activity" [2, 22–24] or to rely on the observed clinical symptoms [7]. Literature reports also imply "borderline VWD" when VWF plasma levels are within the 40–60 IU/dL range [25]. This is consistent with observations that individuals whose results are slightly above 50 IU/dL may also present bleeding symptoms which are unaccounted for by other causes or abnormalities in other tests of hemostasis.

The authors of these guidelines recommend to recognize VWD at VWF levels in plasma < 30 IU/dL. If the values are within the 30–50 IU/dL range, it is recommended to rely on the observed clinical symptoms or — as in the children and individuals never subjected to procedures burdened with bleeding-risk — on information of a first-degree relative affected with VWD. If the clinical criterion is not met, we recommend to diagnose "borderline VWF activity" as the potential bleeding risk. The 50–60 IU/dL VWF activities may be considered clinically significant only if there is severe bleeding in interview and other causes of bleeding have been excluded.

While interpreting test results, it is recommended to consider the relationship between VWF levels in plasma and the patient's age and comorbidities. In healthy individuals VWF activity in plasma increases by about 15–17 IU/dL per decade and in type 1 VWD, by about 3.5 IU/dL; while the tendency to bleeding does not decrease [24, 26––28]. No such tendency is observed in types 2 and 3 VWD [28]. The authors share the opinion that if a reliable VWD diagnosis had once been made, it should be supported despite no opportunity of confirming VWF deficiency due to time lapse (age) or other significant factors that affect test results (stress, pregnancy, inflammatory mediators) [7].

Diagnosis of VWD type 3 and type 2 usually causes no problems and relies on the measurement of VWF level and activity as well as FVIII activity in plasma. Type 2 VWD subtypes are differentiated in specific tests which include analysis of VWF multimers.

The Von Willebrand Factor Antigen (VWF:Ag) is an important diagnostic assay which evaluates the total protein amount in plasma. The most common immunological methods used in clinical laboratories are: ELISA (enzyme-linked immunosorbent assay), LIA (latex immunoassay) or chemiluminescent method. The LIA has the detection threshold of 10 IU/dL, insufficient for confirming type 3 VWD diagnosis. The detection thresholds for chemiluminescent and ELISA methods are 1.0 and 0.5 IU/dL, respectively [22].

Frame 1. Specimen collection and processing [56–59]

1. When drawing the specimen, avoid contaminating the sample with tissue thromboplastin as this may affect results. Venipuncture must be clean with no trauma, and the application of the tourniquet should be as short as possible. Do not use glass tubes.
2. Minimize patients' stress, crying, anxiety and physical effort which increase FVIII and VWF activity (this is particularly important for children). Acute and chronic inflammatory diseases, pregnancy and oral contraceptives increase FVIII and VWF levels in plasma.
3. Collect blood into test tubes with 3.2% sodium citrate (9 volumes of blood: 1 volume of sodium citrate). Massive hemolysis and clots affect test results; blood should be collected again. It is important to adjust the volume of citrate based on the patient's hematocrit (especially at high hematocrit values — >55%).
4. Store and transport whole blood specimens at room temperature (18–25°C). To obtain platelet poor plasma (PPP), centrifuge specimens at room temperature for 15 minutes at min. 1700 g. Store PPP at 20–25°C until the test is performed, no longer however than 4 hours of blood collection.
5. Do not store whole blood or PPP samples at 2–8°C as to avoid factor VIII inactivation and decrease in FVIII activity.
6. Perform tests of hemostasis and factor VIII and VWF activity assays within 4 hours of blood collection. In case of delay, PPP samples may be stored at ≤ –35°C for up to 3 months or at ≤ –70°C for up to 6 months. Thaw plasma at 37°C water bath for 5 minutes. Perform screening and coagulation factor tests in PPP.
7. Perform Closure Time (PFA–100/200) screening assay in whole blood (3.2% sodium citrate) within 4 hours of sample collection.
8. Perform Ristocetin-induced platelet aggregation tests in platelet rich plasma (PRP).
9. PRP is obtained from whole blood (3.2% sodium citrate) centrifuged for 10 minutes at 200 g at room temperature. The test is contraindicated if signs of increased hemolysis and lipemia are observed in PRP sample.
10. Store PRP at room temperature (18–25°C). The test should be performed within 4 hours of blood collection.

VWF ristocetin cofactor (VWF:RCo) assay measures the ability of a plasma sample to agglutinate platelets in the presence of ristocetin, an antibiotic from *Nocardia lurida*, which in vitro mediates VWF binding to platelet Ib glycoprotein. The assay does not accurately assess VWF activity under physiological conditions. Typically, it has a relatively high coefficient of variation with 20–30% differences between laboratories and even within the same laboratory. At low VWF activity (< 10 IU/dL), the assay sensitivity is insufficient, nevertheless it is widely used for diagnosis of VWD and classification into VWD types and subtypes [6, 29, 30].

The collagen binding assay [VWF:CB] measures the capacity of VWF binding to collagen. The immunoenzymatic ELISA method is used. The diagnostic value and sensitivity of the VWF:CB assay largely depends on the source and type of collagen used, therefore confirmed utility tests are recommended [29, 31]. It should be emphasized that the VWF:CB and VWF:RCo tests evaluate different biological properties of VWF. In some cases, only collagen binding defects are detected in the VWF molecule, so the VWF:RCo value is normal and VWF:CB test confirms the diagnosis [31]. Several clinical trials demonstrate that inclusion of VWF:CB assays in the VWD screening panel may markedly contribute to differentiating types 1 and 2 (2A, 2B and 2M) since lower VWF:CB correlates best with the loss of high-molecular-weight VWF multimers [29].

Assays for direct evaluation of VWF-platelet-binding are a new class of assays which measure spontaneous binding of VWF to GPIb alfa in a ristocetin-independent test. This new class of tests includes the VWF:Ab assay (latex particles coated with monoclonal antibodies specific for VWF A1 epitope domain, which binds to GPIb alpha) and VWF:GPIbM (latex particles conjugated with recombinant glycoprotein, changed with *gain-of-function* mutation to spontaneously bind VWF) as well as VWF:GPIbR based on both ristocetin and latex particles or magnetic beads conjugated with

recombinant GPIb alfa. These tests are easy to perform, correlate well with VWF:RCo, have low variability, lower detection threshold (especially VWF:GPIbM) so they are used interchangeably with VWF:RCo and gradually gain popularity [6, 30, 32, 33].

Factor VIII clotting assay (FVIII:C) is the basic laboratory test for diagnosis of hemophilia A. In the context of von Willebrand disease, it measures VWF capacity to bind FVIII and maintain its correct level in plasma. FVIII activity is measured by 1-stage APTT-based factor assay or, less frequently, a chromogenic method. Normal FVIII: C does not exclude VWD. Low FVIII: C activity at normal or only slightly reduced VWF: RCo and VWF:Ag is suggestive of 2N VWD type.

VWF:Ag, VWF:RCo and FVIII:C measurements are usually expressed in International Units per deciliter (IU/dL) or as percentage of normal. 1 IU expresses the activity of a coagulation factor in 1 ml of normal plasma prepared from blood mixed with 3.2% sodium citrate (9:1). For healthy individuals, plasma VWF:Ag, VWF:RCo and FVIII:C are within the 0.5–1.5 IU/ml range (which corresponds to 50–150 IU/dL or 50–150% of normal).

Coagulation factor levels vary and test results may be underestimated due to biological variation, environmental factors and laboratory limitations (conditions of blood collection, transport or sample handling).

Specific tests

Analysis of VWF multimers is a qualitative test performed to evaluate the size distribution of VWF multimers. There are three multimer fractions in plasma: high molecular weight (HMW), intermediate (IMW) and low (LMW). The assay is performed using electrophoresis and other detection techniques (radiolabeling of antibodies or Western blot and immunofluorescence). Semi-automated VWF multimer assays are currently available such as agarose gel serum protein electrophoresis (SPEP) and immunofixation (IFE). The methods help to differentiate the types of VWD (mostly types 1 and 2; Fig. 2). Abnormal distribution of VWF multimers which is characterized by the decrease in the number of large multimers, occurs in subtypes 2A, 2B and platelet-type VWD. The Vicenza type on the other hand, is marked by the presence of ultra large high molecular weight multimers (UL-HMW) at reduced VWF level [11].

Low ristocetin-induced platelet aggregation (LD-RIPA) assay is performed on an aggregometer and it measures platelet aggregation in the platelet-rich plasma after adding ristocetin. The ristocetin concentration usually is no higher than 0.6 mg/ml. Under the described conditions, there is little or no platelet aggregation in the plasma of healthy patients (at 0.5 mg/ml ristocetin concentration, transmission of light increases < 30%). The test result is positive (≥ 30%) for subtype 2B VWD patients.

Increased platelet aggregation is also observed in platelet type VWD which can be differentiated from subtype 2B by the LD-RIPA mixing test or the VWF platelet binding test (VWF: PB), which evaluates VWF binding to normal platelets by the flow cytometry method [9]. None of these tests however is available in clinical practice, so genetic tests are required.

Standard ristocetin-induced platelet aggregation (RIPA) test: in type 3 VWD patients the aggregation is weaker at 1.1–1.3 mg/ml doses of ristocetin. The test however, is not sensitive enough for diagnosis of other types of the disease.

The VWF FVIII binding test (VWF: FVIIB) determines the VWF binding capacity to exogenous FVIII. It is used for diagnosis of 2N subtype VWD. The amount of bound FVIII was measured with ELIZA (enzyme-linked immunosorbent assay).

The VWF:RCo/VWF:Ag ratio is helpful for differentiation between type 1 and 2 VWD. In various sources the VWF:RCo/VWF:Ag value below 0.5–0.7 is accepted as criterion for VWF dysfunction (type 2), although the exact cut-off point remains controversial. The value of 0.7, recommended lately in the guidelines of the American Society of Hematology seems to have no strong advantage over the lower values [7]. Some clinicians draw attention to a high percentage of incorrect type 2M diagnoses in patients with type 1 VWD and recommend a cut-off value of 0.6, as reflected in the guidelines of national and international expert groups [21, 23, 34, 35, 36].

The role of VWF:CB/VWF:Ag ratio is similar but its sensitivity for detecting types 2A and 2B is higher than that of the VWF:RCo/VWF:Ag ratio [29]. The diagnosis needs to be confirmed by additional tests (e.g. LD-RIPA test, VWF multimer analysis or molecular tests).

The authors of these guidelines recommend to determine both ratios (if VWF:CB test is available) and 0.6 is suggested as the cut-off value for type 2 VWD.

It is also possible to measure VWF level in platelets (VWF:RCo, VWF:CB, VWF:Ag and VWF multimer analysis). No correlation however is

Gray line — control sample (healthy individuals)
Blue line — tested sample (patients with von Willebrand disease)

Gray line — control sample (healthy individuals)
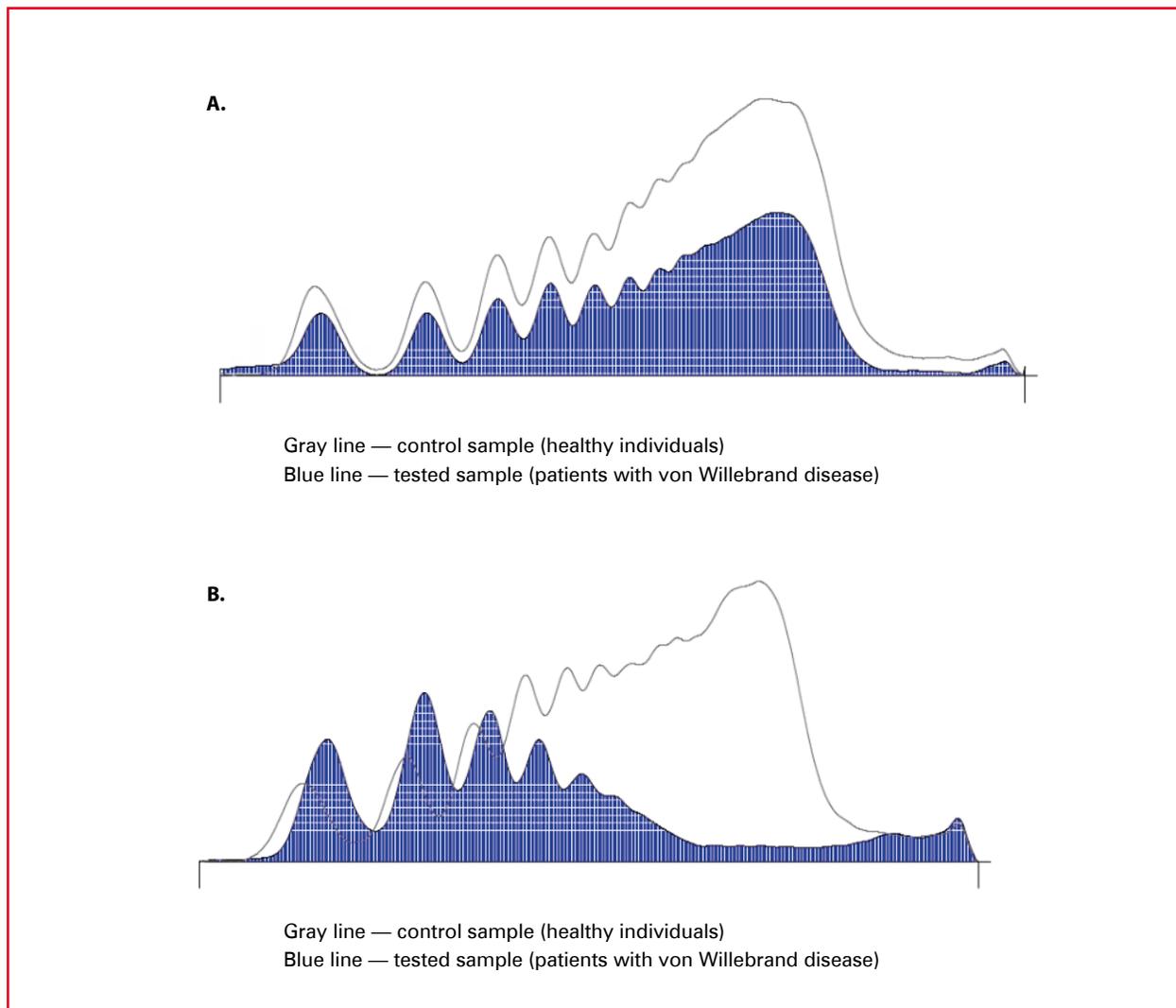Blue line — tested sample (patients with von Willebrand disease)

Figure 2. Von Willebrand factor multimer analysis in different types of von Willebrand disease. **A.** Normal distribution of von Willebrand factor multimers in healthy individuals and in von Willebrand disease type 1, type 2M and 2N; **B.** Loss of high molecular weight multimers and slight decrease in intermediate molecular weight multimers, typical for von Willebrand disease type 2A and 2B

observed between VWF level in platelets and the phenotype of bleeding disorder [24]. The clinical/ /diagnostic value of platelet VWF is under investigation; most likely the measurements may contribute to better understanding of VWD biology and prediction of the response to desmopressin [24].

Genetic testing is recommended due to structural gene variation as well as manner of inheritance. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Genetic tests should be performed in special laboratories experienced in parallel assays of point mutations (preferably with next generation sequencing technology, NGS or

Sanger sequencing), and identification of deletions and insertions in the VWF gene (e.g. high-density single-nucleotide polymorphism, SNP or other techniques for evaluation of copy-number variations in human genomes). Genetic tests are most useful in the diagnosis of type 2 VWD subtypes and type 3 VWD. In type 2A VWD, mutations are mostly located in the A1 and A2 domains, less frequently in the D2 and D3 domains. The 2B subtype mutations are mostly located in the A1 domain, 2M mutations — in the A1 domain and less frequently A3, while 2N mutations — in the D' and D3 domains. When multimer synthesis is disrupted, mutations may affect different regions of the VWF gene. In the diagnosis of subtypes 2 VWD, gene mutations

are identified in < 90% of patients. Identification of VWF gene mutation is recommended in diagnostics of type 2B and 2N VWD alongside functional tests. If type 2B is suspected, it is also recommended to perform a simultaneous test (the advantage of NGS technology) for platelet type von Willebrand disease, i.e. point mutations in the GP1BA gene.

Genetic testing in type 3 VWD is justified in terms of clinical utility and their significance for genetic counseling and prediction of development of anti-VWF alloantibodies. Risk factors for development of alloantibodies are biallelic nonsense mutations, frame-shift mutations caused by a deletion or insertion in a DNA sequence.

The genetic basis of type 1 VWD is not yet fully understood and research is ongoing. In this type of VWD, genetic testing is not recommended due to the low probability of identifying the causative mutation (< 40%).

Tables 2 and 3 present the expected results of screening tests and specific laboratory assays in VWD types and subtypes as well as differentiation with the platelet-type VWD.

Alloantibodies against von Willebrand factor

There are reasonable grounds to suspect anti-VWF alloantibodies if VWD patients infused with VWF present a range of symptoms, from lack or loss of hemostatic response up to anaphylactic reactions [12,14]. The evaluation of VWF pharmacokinetics may prove helpful.

There is no standardization of laboratory methods for identification and characterization of alloantibodies against von Willebrand factor (VWF). The available assays are based on the principle of a mixing study to demonstrate the inhibition of the platelet-dependent function of VWF (the baseline VWF activity is compared with the activity of the protein in the mixture). The anti-VWF antibodies do not demonstrate time and/or temperature

dependence and the assay is typically performed at 37°C with an incubation time of 15 minutes to 2 hours. The antibody titer is reported in Bethesda units, like for anti-factor VIII/IX inhibitor titer in hemophilia patients. Negative results of mixing studies do not necessarily rule out the presence of an anti-VWF antibody, because it may be directed against nonfunctional epitopes. More recently, some laboratories have used an enzyme-linked immunosorbent assay (ELISA) approach and, although these assays are highly sensitive, there is concern about the rate of false positivity [13, 14].

Based on these issues, a strong case can be made for centralized testing in an experienced laboratory familiar with both the screening ELISA and the functional mixing studies [13].

Diagnostics of the acquired von Willebrand syndrome (AVWS)

AVWS occurs in persons with no personal or family history of bleeding and is often associated with a variety of underlying diseases, most frequently lymphoproliferative, myeloproliferative and cardiovascular disorders.

The clinical picture is sometimes complex and does not facilitate differential diagnosis with inherited VWD. The differential diagnosis with milder forms of inherited VWD is important given the difference in therapeutic approach.

In the absence of a family history of bleeding, the diagnosis of AVWS is usually based on the same laboratory tests that are used to diagnose inherited VWD.

Management of von Willebrand disease

General information

Bleeding therapy and prophylaxis in VWD patients consists in either desmopressin-stimulated endogenous VWF and FVIII release from endothelial cells, infusion of exogenous plasma-derived

Table 2. Typical results of screening tests in VWD types and subtypes

Type of VWD	VWF:RCo	VWF:Ag	FVIII:C	Ratio VWF:RCo//VWF:Ag
Type 1	↓	↓	↓ or normal	> 0.6
Subtype 2A	↓	↓ or normal	↓ or normal	< 0.6
Subtype 2B	↓	↓ or normal	↓ or normal	< 0.6
Subtype 2M	↓	↓ or normal	↓ or normal	< 0.6
Subtype 2N	↓ or normal	↓ or normal	↓/↓↓	> 0.6
Type 3	Undetectable	Undetectable	↓↓↓	Not applicable

Table 3. Expected laboratory test results in various VWD types; differential diagnosis with platelet-type VWD (PT-VWD)

Assay	Healthy individuals	Type 1	Subtype 2A	Subtype 2B	Subtype 2M	Subtype 2N	Type 3	PT-VWD
VWF:Ag	N	↓ or ↓↓	N or ↓	N or ↓	N or ↓	N or ↓	Undetectable	↓
VWF:RCo	N	↓ or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or ↓	Undetectable	↓↓
FVIII:C	N	N or ↓	N or ↓	N or ↓	N or ↓	↓/↓↓	↓↓↓	N or ↓
RIPA	N	often N	↓	often N	↓	N	↓↓↓	often N
LD-RIPA	< 30%	< 30%	< 30%	≥ 30%	< 30%	< 30%	< 30%	≥ 30%
CT (PFA-100 or PFA-200)	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
Number of platelets	N	N	N	↓ or N	N	N	N	↓
Distribution of VWF multimers	N	N	Abnormal	Abnormal	N	N	Brak	Abnormal

N — normal value; CT — closure time; VWD — von Willebrand disease

pathogen inactivated VWF with or without FVIII or administration of hemostatic drugs which do not affect VWF levels in the plasma but improve local hemostasis and support wound healing. The abovementioned drugs: desmopressin (DDAVP), VWF-FVIII plasma-derived products, and products containing only VWF (plasma-derived or produced by recombinant DNA technology) are the best treatment regimen for short-term prophylaxis and can be used together, at a schedule and dosage related to type of disease and bleeding intensity.

VWD patients require prophylactic treatment much less frequently than hemophilia patients, but home treatment may be necessary. Every VWD patient should carry an ID card with information on the type of disease, VWF and FVIII activity, recommended medication and contact to the care center (preferably phone number).

Desmopressin

Desmopressin (1-deamino-8-d-arginine vasopressin (DDAVP)) is a synthetic analogue of the antidiuretic hormone 8-arginine vasopressin. DDAVP stimulates the vasopressin V2 receptor, which causes water retention and the release of FVIII and VWF from endothelium. DDAVP also enhances release of tissue plasmin activator (tPA) which is quickly inactivated by the plasminogen activator inhibitor type1 (PAT-1) to prevent premature clot lysis [12].

After intravenous injection of DDAVP to healthy individuals, VWD patients or mild hemophilia A patients, the FVIII and VWF levels in plasma increase at least 2–5 fold. In children below 2nd year of age, the response is poorer. Intravenously DDAVP is administered at a dose of 0.3 μg//kg body weight in 30–100 ml of saline, infused over

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Frame 2. Laboratory assays in VWD

Screening tests of hemostasis
1. Platelet count from peripheral blood smear
2. Closure/Occlusion time (CT, PFA-100/200)
3. APTT
4. PT
5. Fibrinogen or Thrombin Time (TT)

Screening tests for VWD
1. Ristocetin cofactor activity (VWF:RCo) or (alternatively) VWF collagen binding test (VWF:CB) or VWF direct binding test to GPIb alpha
2. VWF concentration (VWF:Ag)
3. Activity FVIII (FVIII:C)

Specific tests
1. VWF multimer analysis
2. Low-dose ristocetin-induced platelet aggregation (LD-RIPA)
3. VWF to FVIII binding test (VWF:FVIIIB)
4. Genetic testing (Next Generation Sequencing, and microarray genotyping)

Recommendations for VWD diagnosis

1. VWD diagnosis is based on clinical criteria and laboratory outcome.
2. Clinical criteria include medical history, family history, and physical examination.
3. Medical history assesses the patient's bleeding risk. In the absence of strict criteria and clinical rating scales, it may be accepted that the likelihood of bleeding disorders (VWD included) increases with the number of bleeding symptoms and of features indicative of bleeding history in the physical examination.
4. Screening tests for hemostasis include peripheral blood with platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen concentration
5. Closure time (CT) on the PFA 100/200 may help to exclude VWD if it is more accessible than the VWF activity assay; which does not mean that CT and VWF tests are interchangeable.
6. Further diagnostics depends on medical history, physical examination and outcome of hemostasis tests.
7. Abnormalities (other than prolongation of APTT, bleeding history or physical examination), indicate the need to begin diagnostics for bleeding disorders (other than VWD) as well as for comorbidities. (NOTE: in subtype 2B VWD, the platelet count may additionally be permanently or temporarily lower).
8. If prolonged occlusion time is determined in the differential diagnosis, other platelet defects should be considered (eg.thrombocytopathies).
9. Screening tests for VWD are to be considered even at first visit if symptoms of mucocutaneous bleeding are severe.
10. In the absence of hemostatic abnormalities (in tests), prolongation of the occlusion time and/or an isolated prolongation of APTT that normalizes in the mixture of patient's plasma with normal plasma, it is recommended to perform screening tests for VWD unless other causes of bleeding are identified, or VWD seems unlikely.
11. Laboratory tests are to be performed in optimal conditions when the influence of external factors (stress, inflammatory mediators, pregnancy) have the least chance to affect the results of laboratory tests. Preparation and transport of blood/plasma samples are also of utmost significance (Frame 1).
12. Screening for VWD includes three measurements: VWF:RCo, VWF:Ag and FVIII:C. If possible/ /available, VWF:CB should also be included in the Screening Panel. Currently, tests that directly evaluate VWF-GPIb interactions (VWF binding to the GPIb receptor on platelets) are more common and used interchangeably with VWF:RCo.
13. If any test result is abnormal, the patient is referred to a hematology center, where the tests are repeated and specific tests are ordered, including:
a. VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag (another test of VWF activity can be used instead of VWF:RCo)
a. Analysis of VWF multimers
b. Platelet aggregation at different ristocetin concentrations (RIPA, LD-RIPA)
c. VWF collagen binding test (VWF: CB)
d. Genetic tests in reference laboratories (NGS technology and microarray)
e. Anti-VW detection tests
14. If FVIII activity is too low in relation to the VWF antigen and the clinical symptoms are suggestive

of type 2N VWD, it is recommended to perform a VWF to FVIII binding assay (VWF: FVIIIB). A genetic test may be helpful.

15. Differentiation between type 1 and type 2 VWD as well as initial differentiation between type 2 VWD subtypes, is based on the VWF:RCo/VWF:Ag ratio. The threshold value of 0.6 is recommended as criterion for type 2 VWD.

16. Typical laboratory parameters are presented in Table 3. In clinical practice, not all VWD cases fall within these value-ranges. Interpretation of laboratory assays requires clinical experience and some tests must be repeated several times.

17. The normal range for VWF: RCo and VWF: Ag is 50–150 IU/dL. The VWD diagnosis is certain if plasma VWF is < 30 IU/dL. In the range of 30–50 IU/dL, it is recommended to rely on clinical symptoms or VWD diagnosed in the 1st degree relative (for children and people never subjected to procedures burdened with bleeding risk). If the clinical criterion is not met, it is suggested to recognize/identify "threshold VWF activity" as a potential bleeding risk. **The threshold VWF activity of 50–60 IU/dL is considered clinically significant only if the patient's bleeding history is severe and other causes of bleeding have been excluded.**

a period of 30 minutes. The FVIII and VWF peak is observed 30–90 minutes following infusion [2]. Intranasal DDAVP at a dose of 150 μg/body weight below 50 kg or 300 μg/body weight above 50 kg may be effective for treatment of minor bleeding, however, the intravenous route is preferred for major bleeding associated with surgical procedures. DDAVP may also be administered in subcutaneous injections of commercially available 4 or 15 μg//ml products (the latter is currently unavailable). A maximum volume of a single subcutaneous bolus injection should not exceed 2–2.5 ml.

The production of nasal DDAVP at a dose effective for management of bleeding disorders (150 μg of DDAVP per dose) was temporarily suspended in 2020. DDVAP (oral route) is ineffective for treatment of bleeding disorders, as is the nasal form used to treat diabetes insipidus (merely 10 μg of DDAVP per intranasal dose).

The clinical efficacy of DDAVP largely depends on the increment of VWF or FVIII activity.

Prior to therapy, patients must be tested for response to desmopressin (in the absence of active bleeding). The test consists in measuring baseline VWF:RCo and FVIII:C and repeating the measurement 1 hour after intravenous or subcutaneous DDAVP bolus of 0.3 μg/kg bw., or intranasal DDAVP bolus of 150 μg/bw < 50 kg or 300 μg/bw > 50 kg). Poor responders are recommended to have the VWF:RCo and FVIII:C measurements repeated 4 hours after desmopressin application to determine the persistence of the positive response (some patients have elevated VWF clearance: type 1C VWD). Most type 1 VWD patients respond well to DDAVP (except for type 1C patients who present short-term response to the drug). After DDAVP

application to type 2 VWD patients they present higher VWF levels, but they still present functional abnormalities. That is why DDAVP is effective just in some 2A and 2M VWD patients. The response to treatment is monitored by checking the VWF:RCo correction. In the 2N subtype VWD, FVIII half-life is much shorter (up to 2 hours). After administration of DDAVP, the increase in VWF:RCo is lower in 2B subtype VWD patients than in type 1 individuals, and the VWF half-life is shorter. Transient thrombocytopenia may also occur, but is not usually associated with bleeding. In 2B subtype patients, DDAVP may be considered for minor bleedings given the risk of thrombocytopenia [37, 38]. In type 3 VWD, DDAVP is not effective [8].

Single DDAVP applications for epistaxis, tooth extraction or heavy menstrual bleeding, usually require no laboratory monitoring. If required, maintenance/subsequent doses are administered every 12–24 hours. Repetitive administration of the drug (over a period of several days) results in reduced response to therapy, most likely due to depletion of tissue coagulation factors (tachyphylaxis) [38].

In surgery and major bleeding it is necessary to monitor VWF:RCo and FVIII:C. Patients should be treated in centers which perform such tests on a daily basis. If therapy lasts longer than 3–5 days, FVIII/VWF concentrate infusions are required.

Common adverse reactions following DDAVP include hot flushes, transient hypertension, and headache but the drug is rarely discontinued. The drug may cause hyponatraemia and water retention, therefore it is recommended to restrict fluid intake and sometimes to monitor electrolyte levels in serum. Hyponatraemia-induced seizures have been reported, mainly in children. DDAVP

Table 4. Suggested duration of replacement therapy for various surgical procedures

Major surgery (7–10 days)*	Minor surgery (1–5 days)*	Small, uncomplicated invasive procedures (single drug dose)
Cardiac surgery	Biopsy (breast, cervix)	Uncomplicated tooth extractions
Cesarean section	Complicated tooth extractions	Endoscopic treatments (not biopsies)
Hysterectomy	Placement of a central catheter	Cardiac catheterization
Cholecystectomy (laparotomy)	Laparoscopic treatments	Cataract surgery

*In individual cases, the treatment time may vary depending on the severity of the disease and type of surgery.

is not recommended for children under 2 years of age. Rare cases of myocardial infarction have been reported in haemophilia A patients treated with DDAVP, therefore DDAVP should be used with caution in individuals (especially the elderly) at risk of cardiovascular disease. DDAVP is to be avoided during neuro-ophthalmic and cardiovascular procedures because of the reported adverse reactions. Pregnancy is no contraindication for DDAVP, because of its negligible effect on uterus contractility [8, 38].

Replacement therapy

Replacement therapy for VWD is based on infusion of plasma-derived FVIII concentrates with VWF and purified VWF concentrates (either plasma-derived or recombinant). FVIII concentrates without VWF are not effective in the management of congenital VWD (except some cases with anti-VWF alloantibodies). Concentrates differ with regard to the quantitative ratio of VWF to FVIII, as well as the number of large VWF multimers, therefore their dosage and clinical effectiveness are not identical (see the current Summary of Product Characteristics). Coagulation/clotting factor concentrates are used in the prophylaxis and management of spontaneous and traumatic bleeding in VWD children and adults who are not responsive to DDAVP or when there are contraindications to DDAVP. They are also used in the management of major bleeding and surgical procedures of type 2 and 3 VWD patients as well as type 1 patients who require prolonged hemostasis.

The doses of FVIII/VWF concentrate should be based on VWF:RCo and (or) FVIII:C values/ /units. Injection of 1 IU of VWF:RCo per kg bw increases the VWF activity in plasma by an average of 1.5 IU/dL. On average, the injection of 1 IU of FVIII per kg bw increases plasma FVIII:C by 2 IU/dL [12]. The dosage and treatment time depend on the type of bleeding and timing of wound healing. The replacement therapy usually continues until the wound is healed (major surgeries require treatment for a minimum of 7–10 days, minor — for 1–5 days, while some procedures require no more than a single dose prior to procedure; see Table 4) [12]. FVIII/VWF concentrates are mostly administered 1–2 times daily in a bolus, but continuous infusion is also used [12].

For minor mucosal resections in type 1 VWD patients with VWF activity > 30% and mild bleeding phenotype, tranexamic acid in monotherapy is allowed [8].

Treatment efficacy is to be monitored by measuring VWF and FVIII activity (there is no need to control VWF and FVIII activity if FVIII/ /VWF concentrate is administered in single doses on outpatient basis or at home). Prior to any surgical procedure, approximately 30 minutes after administration of FVIII/VWF (or DDAVP), it is recommended to check that FVIII and VWF plasma levels have reached the required values. Table 5 presents the dosage of FVIII/VWF concentrates in various clinical situations.

Patients who require frequent infusions of FVIII/VWF concentrates should be qualified in special centers for home treatment and also educated in proper storage and self-infusion of these products.

In the past, von Willebrand disease and hemophilia A were treated with cryoprecipitate and fresh-frozen plasma but due to the low VWF content and the risk of pathogen transmission these products are now used only in situations when FVIII/VWF concentrates are unavailable.

In some type 3 VWD and AVWS patients, pharmacokinetic tests should be considered prior to major surgery because of the risk of anti-VWF antibodies [2].

Long-term use of FVIII/VWF concentrate may lead to FVIII accumulation in circulation (following FVIII/VWF administration, the half-life of VWF:RCo is 8–10 hours, while the half-life of endogenous FVIII gradually increases, up to

Table 5. Average doses of FVIII/VWF concentrates (in FVIII:C or VWF:RCo units) for bleeding prophylaxis and therapy in patients with severe VWF and FVIII deficiency (VWF activity < 10 IU/dl and/or FVIII:C < 20 IU/dL) [12, modified]

Bleeding	Dose (IU/kg body weight)	Target values for VWF:RCo and FVIII: C (IU/dL)		Duration of therapy (days)
		day 1 (peak activity)	Consecutive days (min. values)	
Mild /moderate	20–40	> 50–80	> 30	1–3
Heavy	50	> 100	> 50	3–10
Major surgery	50–60	> 100	> 50	7–10
Minor surgery	30–60	> 50–80	> 30	1–5
Tooth extraction*	25	> 50	–	1
Delivery	40–50	> 100	> 50	3–5 for natural delivery, 5–7 for cesarean section

*for several consecutive days following extraction, use tranexamic acid (preferably as mouthwash)

24–36 hours). Thromboembolic events related to high FVIII activity have been reported [12]. It is recommended to avoid the maintenance of VWF:RCo and FVIII:C values above 150 IU/dL for longer periods of time in patients at higher risk of thrombosis. Routine antithrombotic prophylaxis should be applied [8, 38].

Table 6 lists FVIII/VWF concentrates, (both plasma-derived and recombinant), registered in the European Union (as for 01.2022). Excessive increase in FVIII plasma activity may be prevented by using concentrates of VWF:FVIII ratio > 2:1. Haemate P concentrate (VWF:FVIII = 2.4:1) is a gold standard used in bleeding therapy, in pre- and perioperative prophylaxis as well as long-term prophylaxis in all VWD subtypes. The content of high molecular weight VWF multimeter is comparable to that in plasma. Currently the European market offers one purified plasma-derived VWF concentrate (approved for therapy and prophylaxis of bleeding in patients unresponsive to desmopressin) and one recombinant VWF concentrate (approved in 2015 for bleeding therapy and perioperative prophylaxis in adult VWD patients). These concentrates induce rapid increase of VWF activity in plasma at slow increase of FVIII activity, as conditioned by the binding of endogenous FVIII to exogenous VWF. For this reason, in emergency as well as in the perioperative setting, patients with low basic FVIII activity may require simultaneous administration of FVIII concentrate or beginning replacement therapy on the previous day [4, 8, 12].

Recombinant VWF concentrate carries no risk of pathogen transmission and the risk of allergic reactions is lower than for plasma-derived concentrates. In the process of manufacturing, VWF is not exposed to ADAMTS13 enzyme, so high molecular weight VWF multimers are maintained (which is of particular importance for mucosal bleeding therapy) [12]. Recombinant VWF concentrate (Veyvondi) has been approved by the Food & Drug Administration (FDA) also for routine bleeding prophylaxis in type 3 VWD patients.

As additional source of VWF for type 3 VWD bleeding patients and patients with low levels of VWF, platelet concentrates (PC) were used with success. PC transfusion is to be considered when the patient is irresponsive to replacement therapy with FVIII/VWF concentrate [12].

PC transfusion is the procedure of choice in PT-VWD patients. If VWF activity decreases, FVIII/VWF concentrate is additionally infused. If bleeding is severe and life-threatening, it is recommended to administer recombinant activated factor VII at a standard dose of 90 μg/kg b.w. every 2 h [9].

Other drugs used in the management of VWD

Antifibrinolytic drugs inhibit the conversion of plasminogen to plasmin and thereby reduce the activity of the fibrinolytic system and contribute to the stabilization of clot formation. They are used with success in the treatment of mild mucosal bleeding and the administration route is oral, intravenous or topical (mouth rinse). Combined use of antifibrinolytic drugs and DDAVP or FVIII/VWF concentrate is effective in oral, gastro-intestinal or genitourinary bleeding.

Tranexamic acid is administered orally or intravenously, at a daily dose of 2–4 g to adults and

Table 6. FVIII/VWF factor concentrates approved in the European Union for VWD therapy (as for 01.2022) [6, 38, 40, 41]

Product name (manufacturer)	Activity ratio		Origin
	VWF:RCo/FVIII	VWF:RCo/VWF:Ag	
Haemate P (CSL Behring)	2.45 ± 0.3	0.59 ± 0.1	Plasma derivative
Voncento (CSL Behring)	2.4	0.87–0.95	Plasma derivative
Fanhdi (Grifols)	1.04 ± 0.1	0.47 ± 0.1	Plasma derivative
Koate-DVI (Kedrion Biopharma)	1.1	0.48	Plasma derivative
Wilate (Octapharma)	1.0	No data	Plasma derivative
Factor 8Y (Bio Products Laboratory)	0.81	0.29	Plasma derivative
Willfactin (LFB Biomedicaments)	~ 50	~ 0.95	Plasma derivative
Veyvondi (Takeda)	Purified von Willebrand factor	1.16 ± 0.25	Recombinant

to children at a dose of 10–15 mg/kg b.w. every 6–8 hours (up to 25 mg/kg b.w. every 8 hours) [21, 39]. Epsilon-aminocaproic acid is currently unavailable in Poland.

Doses of antifibrinolytics should be modified for patients with advanced renal failure. Both drugs may cause nausea and vomiting. They are contraindicated in: disseminated intravascular coagulation (DIC), active thromboembolism and bleeding from the kidneys or upper urinary tract (due to urinary tract obstruction). Color vision disturbances secondary to antifibrinolytic drug intake are indication for drug discontinuation and referring the patient to an ophthalmologist.

Local hemostatic agents play a supportive role during surgical procedures and in wound healing. They are usually in the form of gauze and membrane sheets, but also "self-propelling" particles such as sponge, foam or gel [42]. Glues that have long been in use may be of natural origin (fully biodegradable such as fibrin glues from human plasma, obtained either commercially or in laboratory setting as outcome of chemical precipitation or cryoprecipitation), or synthetic (cyanoacrylates, polyethylene) or semi-synthetic origin [43, 44]. Pork gelatin, oxidized cellulose, bovine collagen and plant-derived absorbable products should not be used for patients with coagulation disorders [45].

The indications for the use of aspirin, other cyclooxygenase-1 (COX-1) inhibitors and antiplatelet drugs in VWD patients must be considered on individual basis. Antiplatelet or anticoagulant therapy requires cooperation with a hematologist.

Paracetamol, COX-2 inhibitors as well as opioids (if required) may be administered to relieve pain.

In type 3 VWD, vaccinations should be subcutaneous or if not possible (as in COVID19), intramuscular and preceded by injections of FVIII/ /VWF concentrate. Mild forms of VWD are no contraindication to intramuscular vaccination.

Treatment of gastrointestinal angiodysplasia

Gastrointestinal angiodysplasia is reported in approximately 15% of VWD patients, almost exclusively type 2A, 2B and 3, in the course of which there is loss of high molecular weight VWF multimers [12]. It may also occur at a young age. Bleeding from the gastrointestinal tract often leads to chronic iron deficiency, anemia which may require transfusions of packed RBCs.

Acute gastrointestinal bleeding episodes require prompt administration of VWF/FVIII concentrate and local (endoscopic) treatment of the bleeding lesion [12]. Recurrent gastrointestinal bleeds indicate the need for implementation of long-term bleeding prophylaxis. For patients with high baseline factor VIII activity, infusion of purified VWF concentrate may be a safer option [40].

Attempts have been made to prevent gastrointestinal bleeding in the course of angiodysplasia with anti-angiogenic drugs (e.g. thalidomide), estrogens and octreotide [6, 40].

Treatment of menorrhagia in VWD women

Heavy menstrual bleedings are often the first symptoms of a bleeding disorder. More often however, they signal disorders of the reproductive system. A full gynecological evaluation is therefore recommended before the treatment can be started.

Heavy menstrual bleeding in VWD is treated with antifibrinolytic drugs (in Poland — tranexamic acid), oral hormonal contraceptives, DDAVP or levonorgestrel releasing intrauterine device. Menstrual bleeding can be treated with methods found effective for women with no bleeding disorders. An exception here are non-steroidal anti-inflammatory drugs (COX-1 inhibitors) which adversely affect platelet function. The therapeutical approach/option depends on age, concomitant gynecological disorders, and child-bearing plans.

Therapy usually starts with a loading dose of tranexamic acid or oral contraceptives. Sometimes however, DDAVP or FVIII/VWF concentrates are required.

Oral contraceptives have been reported to increase levels of fibrinogen, prothrombin, FVII, FVIII and/or VWF in plasma. It is not yet known whether this is the effect responsible for the clinical efficacy of the products, but they reduce menstrual blood loss and contribute to the increase of hemoglobin levels in anemic women. In general, long-term use of the products is safe for VWD female patients, with the exception of women with concomitant thrombophilia.

So far, no research has been made on the effects of transdermal hormonal contraceptives on hemostasis in VWD women, but the effects appear similar to those of oral contraception.

Another treatment option for severe menorrhagia in adolescent women with von Willebrand disease is a levonorgestrel-releasing intrauterine device. Levonorgestrel reduces menstrual blood loss by inhibiting estrogen-induced endometrial growth [12].

Sometimes surgical procedures are performed in the management of severe menorrhagia in VWD women. A dilation and curettage procedure (D&C) may be useful for diagnostic purposes but is ineffective for management of heavy bleeding periods. Endometrial ablation effectively reduces menstrual blood loss. In severe cases, hysterectomy is required.

Despite the risk of excessive bleeding in the perioperative period (even with support of replacement therapy), hysterectomy should be considered when other treatment options are ineffective. Elimination of heavy and prolonged menstrual bleeding markedly improves the woman's quality of life.

Ovarian hemorrhagic cysts

Ovarian hemorrhagic cysts are common in women with VWD. No significant bleeding occurs when ovulation proceeds normally but there is a risk of hemorrhage when the woman is diagnosed with a bleeding disorder; hemorrhage may lead to retroperitoneal hematoma or a hemorrhagic ovarian cyst. There are reports of the management of such conditions with tranexamic acid, surgical intervention and replacement therapy. Oral contraceptives are used to prevent relapses.

Pregnancy, childbirth and the postpartum period

The risk of bleeding in VWD women decreases during pregnancy. On the other hand, the risk of hemorrhage in the postpartum period is markedly higher than in the general population. Ambiguity of the data does not allow to estimate if the risk of miscarriage is higher in this population of women.

Before or during pregnancy, the woman should have the opportunity of genetic counseling and consultations with a pediatric hematologist as to the management of the newborn and VWD diagnosis in the offspring. VWD women should be under supervision of hemophilia treatment center as well as a department of pathology of pregnancy. Immediate access to VWD medication and special laboratory tests is of crucial importance. Prior to any invasive procedure (trophoblast biopsy, cerclage), VWF:RCo and FVIII:C levels should be determined and appropriate prophylactic treatment implemented. The tests should be repeated in the third trimester to plan actions in the perinatal period [12].

Data on the use of DDAVP during pregnancy are rather scarce. At lower doses of DDAVP administered to pregnant patients with diabetes insipidus, no adverse reactions were observed either in the mother or the fetus. The experimental model demonstrated no transfer of DDAVP through the placenta. Special attention should be paid to administration of DDAVP in the perinatal period as routine intravenous fluids combined with the antidiuretic action of oxytocin and DDAVP may cause fluid retention and life-threatening hyponatremia [8]. Some experts advise against using desmopressin prior to applying an umbilical cord clamp just to avoid the impact of the drug on the newborn [12].

There have been no eligible clinical trials to evaluate the bleeding risk during labor in relation

to FVIII and VWF activity. According to expert opinion, on delivery day, the activity of VWF and FVIII should be > 100 IU/dL, and then maintained at a level of > 50 IU/dL for at least 3 consecutive days following vaginal delivery and at least 5 days after cesarean section [12]. Combined spinal-epidural anesthesia (epidural blockade) is considered safe at VWF:RCo and FVIII:C levels > 50 IU/dL and hemostasis control. VWF activity should exceed 50 IU/dL during insertion and holding of the epidural catheter and for 6 hours after its removal [8]. Some experts however, advise against epidural blockade in women with type 2 and type 3 VWD even after injections of FVIII/VWF concentrate [12].

VWD women are at higher risk of postpartum hemorrhage. The frequency of perineal hematomas after natural delivery is also higher in this group of patients. In type 1 VWD women, the VWF activity and level (higher during pregnancy) return to baseline levels within 7–21 days after delivery. In type 2 VWD women, the increment in factor activity is slight and insufficient for normalization of hemostasis, while in type 3 VWD it does not occur at all [12]. The risk of late postpartum hemorrhage is 15–20 fold higher in VWD women than in healthy women. Late postpartum hemorrhage may occur despite prophylactic treatment, usually 10–20 days after delivery.

Women with type 2B VWD may develop thrombocytopenia during pregnancy. If the platelet count is low it may decrease still further. Platelet count should be monitored and raised to the value > 50,000/μl prior to delivery by way of PC transfusions [37].

Tranexamic acid helps to reduce the risk of obstetric hemorrhage and can safely be administered during pregnancy and lactation. Regardless of the type of von Willebrand disease and the type of delivery, tranexamic acid should be used as support in the perinatal period and for at least 7 days after delivery [12].

Von Willebrand disease and cardiovascular disorders

There are convincing data to demonstrate that VWD patients are at smaller risk of cardiovascular diseases, including myocardial infarction and stroke [1, 2]. Acute cardiovascular events are rare in VWD patients and occur most often in type 1, especially in the presence of such cardiovascular risk factors as smoking, diabetes or hypertension) [46, 47]. So far, no guidelines/recommendations have been de-

veloped for the management of such patients, and the available data come from case reports and case series [48]. Literature reports suggest that VWD patients with recognized myocardial infarction are to be treated like any other non-VWD patients [49], i.e. primary angioplasty with implantation of a new generation drug-eluting stents (bare metal stents are now rarely used). Hematoma at the injection site is the most common hemorrhagic complication in this group of patients. During invasive procedures, the VWF activity should be 80–100% and unfractionated heparin is preferrable as its effect can be reversed. This level of VWF activity should be maintained for a minimum of 48 hours. According to the current cardiological recommendations, patients at high risk for bleeding should be treated from the radial approach. Clopidogrel is the antiplatelet drug of choice for VWD patients with myocardial infarction or individuals subjected to angioplasty for chronic coronary artery disease. Ticagrelor and prasugrel should be avoided due to higher risk of hemorrhage. For dual antiplatelet therapy which is recommended after stent implantation, VWF activity should be maintained at 30 IU/dL or higher, usually with a proton pump inhibitor. The maximum VWF activity should not exceed 150%, because this may increase the risk of thrombotic complications also in the venous system. After a maximum of 3 months of dual antiplatelet therapy, a VWD patient (with the exception of type 3) may take only one antiplatelet drug (most often acetylsalicylic acid at a dose of 75–100 mg//day). VWD patients may be subjected to coronary artery bypass at VWF activity of 80–100%, as calculated from the pre-surgery period to healing of postoperative wound [50]. VWD patients who require anticoagulant therapy, most often for atrial fibrillation or venous thrombosis, may be treated with anticoagulants at VWF activity of 30 IU/dL or higher with vitamin K antagonist (VKA) or direct oral anticoagulant [50]; experts prefer drugs the reaction of which is quickly reversible i.e. VKA or dabigatran (in Poland) [50]. Currently the use of acetylsalicylic acid for stroke prevention in patients with atrial fibrillation is not recommended by cardiological guidelines, which also applies to patients with bleeding disorders. In view of scarce clinical evidence, it is recommended to approach the treatment of VWD patients with cardiovascular disorders individually and continue therapy under the supervision of a multi-professional teams.

Long term bleeding prophylaxis

Long-term prophylaxis for VWD is indicated if bleeding symptoms are frequent or severe. It may also be indicated in antiplatelet or anticoagulant therapy for patients with cardiovascular disorders. In type 3 VWD, secondary prophylaxis (rarely primary) is to be considered for prophylaxis of joint bleeds and arthropathy [8].

It has been demonstrated that a dose of 50 IU VWF/kg body weight two or three times weekly markedly reduces the number of clinically significant bleeding episodes in severe VWD patients [12]. Various secondary and periodic prophylaxis regimens are used in clinical setting, individually adjusted to the patient's needs and bleeding phenotype (e.g. menorrhagia).

Management of VWD with anti-VWF alloantibodies

Anti-VWF alloantibodies are a rare though severe complication of VWD replacement therapy. They occur in about 5.8–9.5% of type 3 VWD patients [51].

For VWD patients who are at risk of developing alloantibodies, it is recommended to perform first FVIII/VWF concentrate infusions in hospital setting [14].

In type 3 VWD patients with alloantibodies, plasma-derived VWF concentrates are to be avoided due to the risk of life-threatening anaphylactic reaction [12, 14], unless the antibody titer is low or no allergic reactions following FVIII/ /VWF infusion occur [13]. Hemostatic treatment is based on recombinant activated factor VII (rVIIa) or recombinant FVIII with no VWF (or merely traces of VWF). It is recommended to administer FVIII concentrate in continuous infusion and at high doses (even 25 U/kg b.w./h) due to very short half-life of FVIII, which has no stabilizing effect of VWF (< 2 hours). FVIII activity in the plasma should be monitored [14, 52]. The rVIIa dose in this indication has not been determined. The recommended doses are similar as for hemophilia complicated by inhibitor and depend on the patient's clinical status (hemostasis) [14, 52]. A scheme is also suggested which consists in the administration of a preoperative loading dose of rVIIa 100–200 μg/kg b.w., and then maintenance doses of 90 μg/kg b.w. every 2 h or a continuous infusion of 20 μg/kg b.w./h. Successful attempts at sequential application of rVIIa and recombinant FVIII have been made [14].

Transfusion of platelet concentrate (PC) is another therapeutic option. The alpha granules of platelets contain normal VWF which is released not earlier than at the wound site and is thus protected against interaction with antibodies [14]. Intravenous immunoglobulin (IVIG) in combination with FVIII/VWF concentrate is still another option to consider [53].

A case of effective immune tolerance induction (ITI) has been described in a child who was administered FVIII/VWF concentrate (Haemate P) every other day for 3 months following premedication with methylprednisolone and hydroxyzine, in combination with monthly IVIG infusions [54].

Treatment of acquired von Willebrand syndrome (AVWS)

In some cases of AVWS (especially secondary to myeloproliferative neoplasms and autoimmune diseases), DDAVP administered intravenously or subcutaneously at a standard dose of 0.3 μg/kg b.w. was effective although the response to the drug was short term [16]. Nevertheless, DDAVP is sometimes used by many centers as first choice drug for the treatment of minor bleeding in patients with no contraindications to this form of therapy [55]. Likewise, the response to FVIII/VWF concentrate may be short-term (the reported dosage was within 30–100 U VWF:RCo/kg b.w.). The activity of VWF and FVIII should be monitored, particularly during surgery [16, 55].

In AVWS cases in the course of lymphoproliferative neoplasms, solid tumors and autoimmune diseases, the efficacy of high doses of IVIG was observed (1 g/kg b.w./d for 2 days or 0.4 g/kg b.w./d for 5 days). The therapy was particularly beneficial for monoclonal gammapathy of undetermined significance (MGUS) associated with IgG antibodies because the increase in FVIII and VWF activity was more persistent than after administration of FVIII/VWF concentrate or desmopressin. The effect is observed no earlier than 24–48 hours after administration, so for acute bleeding the effectivity of IVIG monotherapy is limited (FVIII/VWF concentrate or desmopressin should be administered supportively in the first days of treatment). There have however, been reports of prophylactic IVIG infusions every 3–4 weeks for the treatment of recurrent gastrointestinal bleeding [16, 55].

For treatment of bleeding in the course of IgM MGUS, when IVIG proved ineffective, plasmapheresis procedures gave good results, and eliminated autoantibodies and paraproteins from circulation [55]. Likewise, if desmopressin

and FVIII/VWF concentrates were ineffective, attempts were made to use rVIIa at a single dose of 90 μg/kg b.w. [16, 55]. For minor bleeding and as supportive treatment for major bleeding or surgery (particularly mucosal epithelium) it is recommended to administer tranexamic acid orally, intravenously or topically [16].

It is noteworthy that the treatment of the underlying disorder responsible for the symptoms of AVWS is of crucial importance is [16, 55].

Recommendations for VWD therapy

1. If VWD is suspected, laboratory tests are recommended to confirm the diagnosis and to determine the type of disease. This does not apply to emergency cases when treatment may be required despite lack of confirmed diagnosis.
2. Individuals with bleeding symptoms, VWF:RCo in the 30–60 IU/dL range and no confirmation of VWD diagnosis, may sometimes require therapy or bleeding prophylaxis.
3. Individuals with VWF:RCo > 10 IU/dL and FVIII:C > 20 IU/dL, require a DDAVP test in the absence of active bleeding. At lower VWF:RCo and FVIII:C values, the response to DDAVP is less likely, though the test may still be considered.
4. If bleeding continues despite attaining proper VWF:RCo and FVIII:C values, other bleeding causes should be considered (local injury).
5. Long-term bleeding prophylaxis may be indicated especially when bleeding is recurrent, life--threatening or requires antiplatelet/anticoagulant medication.
6. Genetic counseling should be provided.
7. Von Willebrand disease is not a contraindication to vaccination against hepatitis A and B. Type 3 VWD patients should be vaccinated subcutaneously or in intramuscular injections following administration of FVIII/VWF concentrate.
8. Once diagnosed with VWD, the patient should be instructed to avoid aspirin, other COX-1 inhibitors, and antiplatelet agents.
9. DDAVP-treated patients (especially children and the elderly) should limit fluid intake to reduce the risk of hyponatraemia and seizures.
10. Epistaxis, oropharyngeal and soft tissue bleeding as well as other minor bleeds can be treated with intravenous, subcutaneous or intranasal DDAVP (following DDAVP test). If increment of VWF activity is insufficient, it is recommended to administer FVIII/VWF concentrate.
11. During bleeding prophylaxis for minor surgical procedures, a VWF:RCo > 30 IU/dL should be attained and maintained for 1–5 days.
12. During DDAVP therapy for minor bleeding (e.g., epistaxis, menstrual bleeding, tooth extraction), there is no need to monitor laboratory parameters, provided fluid intake is restricted and no more than 3 DDAVP doses are administered within 72 hours.
13. For oral surgery and other mucosal bleedings in patients with mild to moderate VWD, it is recommended to use an antifibrinolytic drug or, if necessary, a combination of DDAVP and an antifibrinolytic agent. It is recommended to administer FVIII/VWF concentrate if DDAVP cannot be applied or if bleeding persists despite the use of DDAVP and an antifibrinolytic agent. The use of local hemostatic drugs may also be beneficial. After tooth extraction, alveolus sutures are to be considered.
14. For major surgery, it is recommended to adjust DDAVP or FVIII/VWF concentrate doses to FVIII:C activity and (if possible) VWF:RCo. Prior to surgery, approximately 30 minutes after administration of FVIII/VWF concentrate (or DDAVP), it is recommended to determine FVIII and/or VFW:RCo levels in plasma to make sure the required levels are attained. Whenever possible, major surgical procedures and management of major bleeds should be performed in centers which guarantee round the clock access to VWF:RCo and FVIII:C tests as well as counselling of hematologists experienced in the management of bleeding disorders.

15. For major bleeding (e.g. intracranial, retroperitoneal) and bleeding prophylaxis during major surgical procedures, it is recommended to maintain VWF:RCo and FVIII:C at screening test values > 100 IU/dL. It is recommended to maintain VWF:RCo and FVIII:C daily values at the minimum of > 50 IU/dL for at least 3–10 consecutive days.

16. To minimize the risk of thrombosis in the perioperative period it is recommended to maintain VWF and FVIII:C levels at < 150 IU/dL.

17. Before major surgery in some type 3 VWD patients it is recommended to consider pharmacokinetic tests following administration of FVIII/VWF concentrate since the increment in VWF activity may not be sufficient due to the presence of antibodies.

18. VWD women with menorrhagia or abnormal vaginal bleeding should be subjected to complete gynecological check-up prior to therapy.

19. Tranexamic acid or oral contraceptives are usually first choice therapy for menorrhagia in VWD women. Sometimes however, it is necessary to administer DDAVP or FVIII/VWF concentrates.

20. For hormonal treatment of menorrhagia in young women with VWD and no immediate plans for pregnancy, it is recommended to use oral contraceptives or a levonorgestrel-releasing intrauterine device (in women who qualify for an IUD).

21. Menorrhagia in VWD women who are planning pregnancy, should be treated with tranexamic acid, DDAVP or FVIII/VWF concentrates.

22. Dilatation and curettage (D&C) as the sole treatment option for severe vaginal bleeding in VWD women is usually ineffective.

23. VWD women who are planning pregnancy should be in the care of specialists experienced in the management of bleeding disorders — a hematologist and a gynecologist from the department of pregnancy pathology.

24. VWD pregnant women with VWF:RCo or FVIII:C < 50 IU/dL or history of major bleeding should be referred to a prenatal care facility. Prior to any invasive procedure, it is recommended to administer DDAVP or FVIII/VWF concentrates. On delivery day, VWF and FVIII levels should be increased to > 100 IU/dL and be maintained at the level of > 50 IU/dL for at least 3 consecutive days following vaginal delivery and 5 days after caesarean section.

25. Central blockade may be considered when VWF:RCo and FVIII:C > 50 IU/dL, VWF: RCo and FVIII: C can be determined and no additional blood coagulation disorders are reported.

26. As the VWF and FVIII levels return to baseline within 7–21 postpartum days, close monitoring is recommended.

27. To select optimal treatment strategy for patients with AWVS, presurgical pharmacokinetic analysis of FVIII and VWF: RCo is recommended following administration of DDAVP or FVIII/VWF concentrate.

28. If DDAVP and FVIII/VWF concentrate therapy for AVWS patients is unsuccessful, it is recommended to consider intravenous immunoglobulins, plasmapheresis, glucocorticosteroids or other immunosuppressive drugs. It is essential however, to focus on the treatment of the underlying cause of AVWS.

Conflict of interest

Joanna Zdziarska — participated in clinical trials and/or received remuneration for consultations and lectures from Amgen, CSL Behring, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, SOBI.

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