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von Willebrand Disease

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Table of contents

von Willebrand Disease

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1 Summary

Von Willebrand disease (VWD), the most common congenital bleeding disorder, is characterized primarily by mucocutaneous bleeding. It is caused by a quantitative or qualitative deficiency of von Willebrand factor (VWF). Diagnosing VWD is challenging due to varied clinical presentation. Specialized laboratory tests and the influence of various physiological processes on von Willebrand factor further complicate diagnosis. Approved therapeutic options include DDAVP, VWF concentrates, and adjuvant therapies such as antifibrinolytics.

Interdisciplinary collaboration and decision-making, including individualized care, are essential in the assessment and treatment of patients with VWD.

2 Basics

2.1 Definition and basic information

In 1926, Finnish physician Erik von Willebrand published a description of a new bleeding disorder that he observed in a family living on the Åland Islands in the Baltic Sea [1]. The index case was a young woman who bled to death during her fourth menstrual period; and many other family members also suffered from excessive bleeding. In the original report, the disease was initially referred to as "pseudohaemophilia"; however, it later became known as von Willebrand disease (VWD) [2, 3].

VWD is caused by a deficiency or disorder of von Willebrand factor (VWF), a multimeric glycoprotein that performs important hemostatic functions. These functions include the adhesion and aggregation of platelets to endothelial injuries and acting as a carrier protein (chaperone) for FVIII. Without binding to VWF, FVIII has a shortened half-life.

The VWF gene is located on the short arm of chromosome 12 (12p13.2-13.3). It is approximately 178 KBp, in size and consists of 52 exons. The primary VWF translation product is a 2,813 amino acid pre-pro peptide. VWF undergoes secondary modification and polymerization to form so-called multimers. The particularly large multimers are most active in primary hemostasis. FVIII binding is ensured by smaller multimers. VWF is synthesized exclusively in endothelial cells and megakaryocytes, released into the plasma, or stored in cell organelles.

The half-life of VWF in circulation is reported to be 12-18 hours [4].

There are different types of VWE.

Table 1: Classification of von Willebrand types

Type	Description	Functional effects
1	Quantitative reduction of VWF with consistent ratios between VWF/Ag, VWF/Act, and FVIII	VWF is functional but present in reduced quantities. Usually mild course.
1C	Increased clearance of VWF/Ag Increased VWF:pp compared to VWF/Ag	Usually mild course, DDAVP test (chapter 6.3.3) useful
2A	Reduced platelet-dependent VWF activity with loss of high-molecular-weight multimers	Impaired platelet adhesion due to lack of the largest, most effective multimers.
2M	Reduced platelet-dependent VWF activity with preserved multimeric pattern	VWF cannot bind platelets efficiently despite normal multimeric structure
2N	Reduced binding of FVIII	Clinically resembles mild hemophilia A, as factor VIII is rapidly degraded.
2B	Increased binding of VWF to GPIba, often leading to thrombocytopenia and loss of high molecular weight multimers	Excessive binding to platelets → possible thrombocytopenia (low platelet count).
3	Absence or near absence of VWF	Severe form with severely impaired hemostasis, spontaneous bleeding, and pronounced symptoms.

Legend:
VWF: von Willebrand factor, VWF/Ag: von Willebrand factor antigen, VWF/Act: von Willebrand factor activity, GPIba: glycoprotein Iba; pp: propeptide [5].

2.2 Epidemiology

The prevalence varies widely and is attributable to various criteria in the diagnosis of VWE. These include the complexity of the diagnosis, the variability of bleeding symptoms, the presence of external variables (blood groups, physiological factors such as physical activity, thyroid hormones, estrogens, and age), and insufficient knowledge about the clinical picture of VWD [6-8].

2.2.1 Distribution of Von Willebrand types

VWD type 1 is the most common form, followed by VWD type 2 and the least common type 3. Most studies and registries estimate the distribution of VWD types to be 60–70% type 1, 20–30% type 2, and 5–10% type 3 [9- 12].

2.2.1.1 Type 1 VWD

Type 1 VWD is the most common hereditary bleeding disorder affecting an estimated 0.1–1% of the general population [13] or 0.01% [14]. These large differences in the prevalence of type 1 VWD are due to the difficult diagnostic distinction between low normal VWF levels and a definitive diagnosis of VWD.

2.2.1.2 Type 2 VWD

The distribution of the various type 2 VWD patients was reported in a large Italian study of 321 patients as 35% 2M, 31% 2A, 26% 2B, and 8% 2N [15].

2.2.1.3 Type 3 VWE

The prevalence of VWE type 3 is very low, ranging between 0.1 and 5.3 per million people [16]. This rate varies by country and is influenced by the rate of consanguinity (recessive inheritance).

For example, a higher prevalence has been observed in Scandinavian countries (2.4–3.12 per million) [17], and the highest prevalence has been observed in Arab individuals (5.3 per million) [18].

2.2.2 Genetic prevalence

A genetic epidemiological, population-based study of 141,456 individuals estimated the global prevalence at 74 per 1,000 people for type 1, 3 per 1,000 for type 2A, 3 per 1,000 for type 2B, 6 per 1,000 for type 2M, 0.31 per 1,000 for type 2N, and 0.7 per 1,000 for type 3 [19].

These results suggest that von Willebrand disease (VWD) is underdiagnosed or that the bleeding phenotype is attenuated by unknown factors [8].

Age of diagnosis: The age of onset varies, with earlier onset associated with more severe VWF deficiency [20].

The reported prevalence was higher in women than in men ($p < 0.01$), although the gender distribution between men and women should actually be approximately equal [21].

Table 2: Summary of von Willebrand types*

Type	Mechanism	Inheritance	Genetic defect	Comments
1	Partial quantitative reduction in VWF	Autosomal dominant	Missense mutation (85–90%), null alleles (10–15%), variable penetrance	Includes VWF variants that cause rapid VWF clearance (e.g., VWF Vicenza) and requires a functional antigen ratio > 0.6.
2A	Reduced VWF-dependent platelet adhesion due to deficiency of high molecular weight VWF multimers	Autosomal dominant and recessive	Missense mutations, mainly in domains D3, A2, and CK; missense mutations in the propeptide; exons 5, 28, and 52	There is some controversy regarding the classification of VWF variants associated with a slight reduction in HMW multimers.
2B	Increased affinity of VWF for platelet GPIb	Autosomal dominant	Missense mutations in the A1 domain; exon 28	The phenotype is variable, and some cases with normal VWF multimers and normal platelet counts have been described.
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high molecular weight multimers	Autosomal dominant	Missense mutations in the A1 domain; exons 28, 45	May also include cases with isolated defect in VWF collagen binding.
2N	Reduced binding affinity of VWF to FVIII	Autosomal recessive	Missense mutation in the D and D3 domains, exons 5, 10, 18	To be distinguished from mild hemophilia A
3	Absence of VWF	Autosomal recessive	Frequent null alleles	Corresponds to <3 IU/dL in most assays

Legend:
VWF: von Willebrand factor, GPIb: glycoprotein Ib
**Adapted from [22]*

2.3 Pathogenesis

This guideline describes the congenital form of von Willebrand disease. There is also an acquired form—*see the Onkopedia guideline on acquired hemophilia and von Willebrand disease.*

Type 1 VWD is the most common form of VWD. It is characterized by low plasma VWF levels with normal VWF structure and function and autosomal dominant inheritance [23]. These patients are classified based on their plasma VWF levels into a low VWF phenotype (0.3-0.5 U/mL) and type 1 VWD (0.03-0.3 U/mL) [5], although these thresholds have long been controversial [24]. In fact, the recently revised guidelines for the diagnosis of VWD suggest that patients

with reduced VWF levels between 0.3-0.5 U/mL and bleeding should be classified as patients with type 1 VWD in order not to complicate access to treatment [25].

3 Prevention and early detection:

Von Willebrand disease is a congenital bleeding disorder [26. If VWD runs in the family, early diagnosis of affected family members is possible, This diagnosis can be made regardless of bleeding symptoms. Appropriate information should be provided to patients with VWD in hemostasis centers and help them to evaluate potentially affected family members and refer them for possible treatment.

The guideline team favors early detection through family screening [27] and clarification of VWD in cases of abnormal symptoms such as hypermenorrhea, iron deficiency, and postoperative bleeding. Tools such as the ISTH-BAT (bleeding assessment tool) are available for this purpose [28].

A research group was able to demonstrate the usefulness of the ISTH-BAT as a diagnostic tool in adolescents with heavy menstrual bleeding. Due to its standardized application and evidence of its predictive value, it would be desirable to use the ISTH-BAT routinely in clinical practice to promote the early identification of bleeding disorders in this age group [29].

Social media formats and patient organizations (e.g., IGH, DHG, ÖHG, SHG) are being used to raise awareness of VWD [30].

Current efforts to raise awareness seem to focus more on healthcare professionals and patient organizations than on comprehensive screening programs. A project to promote the emotional and social strengths of girls and boys, led by PD Dr. Susan Halimeh and Dirk Heinrich, has set itself the task of promoting the emotional and social strengths of young people and highlighting this in relation to the topics of heavy menstruation and puberty. A secondary endpoint of the project is the early detection of bleeding tendencies such as VWE.

This project is funded by the state of North Rhine-Westphalia (Startchancen-Programm) and is being carried out on behalf of Deutsche Bluthilfe e.V. (Startchancen-Programm – BMFTR; https://deutschebluthilfe.com/).

Efforts are underway to develop diagnostic tools using machine learning algorithms and improve diagnostics with these algorithms. The goal is to identify patients with potentially undiagnosed symptomatic vascular wall erosion (VWE). However, the authors conclude that further external validation using other VWE diagnostic databases is necessary [31].

4 Clinical picture

4.1 Bleeding symptoms

Typical bleeding symptoms are primarily mucocutaneous bleeding and bleeding in high-risk situations. Rare locations and severe bleeding are listed below, as each patient may have different symptoms.

- Bleeding of the mucous membranes of the mouth and nose
- Increased bleeding and tendency to hematomas in cases of minor trauma
- heavy menstrual bleeding (hypermenorrhea)
- Bleeding after dental procedures, bleeding gums
- Increased tendency to develop hematomas, with and without trauma

- Postpartal and postsurgical bleedings
- Prolonged bleeding after injury
- Urogenital bleeding
- Joint bleeding, especially in type 3, but also in severe forms of types 1 and 2
- Gastrointestinal bleeding
- Rare internal bleeding, e.g., intracerebral hemorrhage in 0.1–0.5% of cases, most common in type 3 VWD [32].
- Petechial bleeding and bleeding in unusual locations, e.g., the eye, also occur rarely [33].
- The signs of bleeding can vary among patients and within families. They can also change over time for the same patient. [34, 35].

4.1.1 Hemarthrosis

Joint bleeding (hemarthrosis) occurs particularly in severe forms of VWD, such as type 3. These bleeds are less common than in hemophilia but can also lead to hemophilic arthropathy. Hemarthrosis is very rarely observed in VWD types 1 and 2, but can occur post-traumatically [36, 37].

As with severe hemophilia, prophylactic treatment may be advisable in patients with a severe VWD who experience spontaneous bleeding events. One recommendation for prophylaxis is substitution with a VWF/VWF-VIII concentrate at a dosage of 40–60 IU 2–3 times per week intravenously [10].

4.1.2 Angiodysplasia

Patients with VWD have an increased risk of angiodysplasia. The association between angiodysplasia and gastrointestinal (GI) bleeding in patients with VWD was first described in 1976 by Ramsey et al. [38].

One explanation for the occurrence of angiodysplasia may be the influence of VWF on angiogenesis. A deficiency of functional VWF can lead to dysregulation of angiogenesis with increased formation of large-lumen and thin-walled vessels, as vascular stabilization and maturation are reduced in favor of proliferation and migration [39- 42].

In the gastrointestinal tract, angiodysplasia occurs most frequently in the appendix and ascending colon, but has also been found throughout the gastrointestinal tract and is characterized by a fragile vascular network [43, 44].

The incidence of angiodysplasia varies depending on the VWE subtype. Angiodysplasia was found in 2% of patients with VWE type 2 and in 4.5% of patients with VWE type 3 [45].

Angiodysplasia may be associated with anemia and life-threatening gastrointestinal bleeding requiring transfusions [46- 49]. Although gastrointestinal bleeding caused by angiodysplasia also occurs in the general population, it is rare (prevalence 0.092–0.83%) and the lesions are usually small and have a low risk of bleeding [50, 51].

In a retrospective study of VWE patients with occult or angiodysplastic bleeding in the VWE prophylaxis network, angiodysplasia was confirmed as the cause of gastrointestinal bleeding in only one-third of the patients [52].

The management of angiodysplasia poses significant challenges due to the complexity of the condition and the absence of effective surgical or endoscopic treatment options. The high

recurrence rate of this condition further complicates therapeutic efforts. In addition to endoscopic and surgical interventions, treatment encompasses the substitution of VWF and VWF/factor VIII concentrates, along with therapeutic trials involving statins, tamoxifen, thalidomide, and VEGF inhibitors, among others, in cases of acute severity. It is also recommended that patients receive prophylaxis [40, 53].

Recurrent bleeding events due to angiodysplasia can lead to a deterioration in quality of life in patients with VWE.

4.1.3 Iron deficiency (anemia)

Iron deficiency anemia or iron deficiency can be an initial indication of VWE. General symptoms of anemia such as exhaustion, fatigue, dizziness, and even depressive disorders, which lead to an impairment of quality of life, may occur. In women and girls with VWE, iron deficiency (anemia) / may be caused by menorrhagia.

Regular hemoglobin checks are recommended for patients with VWE, and oral or intravenous iron treatment may be initiated as needed [54- 57].

4.1.4 Habitual abortions

The abortion rate in patients with VWE is reported to be 7% to 25% based on retrospective studies or databases.

A recently published study evaluated the frequency of miscarriage in women with VWE compared to women with a similar mucocutaneous bleeding phenotype ("bleeding disorder of unknown cause" – non-VWE) and control subjects without bleeding disorders.

No statistically significant difference was found between the two patient groups and the normal collective (odds ratio 0.94) in a total of 1,193 pregnancies examined. At least one live birth was documented in >90% of participants and in 95% of patients with VWE and non-VWE.

Finally, a comparative study showed that patients with VWE (with VWF-Ag and VWF-Act values < 50%) do not have an increased risk of miscarriage compared to the normal population. In addition, a German group was able to show that there were no differences in outcome between patients with and without VWE after reproductive medicine measures [58, 59].

4.2 General morbidity

Another underestimated issue in patients with VWE is morbidity Subjects diagnosed with VWE exhibited a 2.0-fold (SD 1.5–2.5) increase in the frequency of inpatient hospitalizations compared to the control group.. The most common causes for hospital stays were gastrointestinal (GI) bleeding (n = 232 as primary diagnosis), menorrhagia (n = 198), and epistaxis (n = 192). Outpatient visits per year were also twice as frequent in individuals with VWE. An excerpt from the Scandinavian registry with 105 patients showed the following distribution: VWE type 3, 52.4%; type 2A, 22.9%; type 1, 12.4%; and other types, 3.9%) [60].

The **quality of life** of those affected is significantly impaired by the bleeding (see chapter 6.9 Quality of life).

4.3 Prognosis

Patients with VWE have a life expectancy comparable to that of healthy individuals.

There is no cure for the hereditary form of the disease. For information on acquired forms, see the Onkopedia guideline on acquired hemophilia and VWD *(guideline to be published shortly).*

Gene therapy is not currently available.

5 Diagnosis

5.1 Diagnostic criteria

5.1.1 Introduction and summary

The diagnosis of von Willebrand disease is a multifaceted process, characterized by a series of obstacles that must be overcome. Patients present with a broad spectrum of symptoms, ranging from mild to severe manifestations, which complicates the diagnostic process. A detailed medical history, including family history, is therefore important. A special feature of the diagnosis is the variability of von Willebrand factor levels due to acute phase reactions such as stress, physical exertion, infections, pregnancy, and acute illnesses, but also due to age and blood type. Nicotine abuse and air pollution also have an influence [61].

The diagnosis of VWE should be made when the patient is in a "basic state of health". Repeated measurements are therefore often useful.

In summary, the diagnosis includes [62, 63]:

1. Bleeding assessment tools (standardized questionnaires on
2. bleeding history),
3. Laboratory tests (including diagnosis-relevant threshold values)
4. special diagnostics for the diagnosis of subtypes
5. Genetic testing

5.1.2 Influence of age

VWF parameters may increase with age, leading to normalization of VWF levels [24]. In a study group (n=617) with a median age of 28 years and a mean observation period of 16 years, it was shown that VWF and factor VIII increased discreetly from the age of 20 and linearly from the age of 40. In type 2 vWE, only an increase in factor VIII was observed, while in type 1 vWE and patients with low vW levels, an increase in both vW activity and factor VIII was documented.

The authors observed an overall average increase in VWF of 22 IU/dl over a period of 10 years, accompanied by an increase in VWF propeptide (VWFpp), VWF:Ag of 6.9% over 10 years, and FVIII [64- 66].

5.1.3 Influence of blood type

VWF:Ag levels in individuals with blood group O are measured at 25-30% lower than in individuals with blood groups A, B, and AB. Individuals with blood group O are overrepresented among VWE patients (77% of all VWE patients), although they make up only 45% of the total European and American population. In addition to *ABO*, other modifying genes have been identified, including *CLEC4M, STXBP5*, and *STAB2*. Variants in the genes for the sinusoidal endothelial receptors "C-type lectin domain family 4 member M" (CLEC4M) and "Stabilin-2" are associated with plasma levels of VWF and/or FVIII in healthy individuals. The ability of these receptors to

bind, internalize, and remove the VWF-FVIII complex from the bloodstream [67- 69]. Blood groups ABO-adjusted reference ranges are not considered necessary according to the 2021 guidelines for the diagnosis of VWE [70].

5.1.4 Influence of subtypes

The existence of different VWD subtypes (e.g., type 1, type 2 with subtypes 2A, 2B, 2M, 2N, and type 3), which must be identified by different tests, also makes diagnosis complex, expensive, and time-consuming (e.g., multimer analyses or genetic testing).

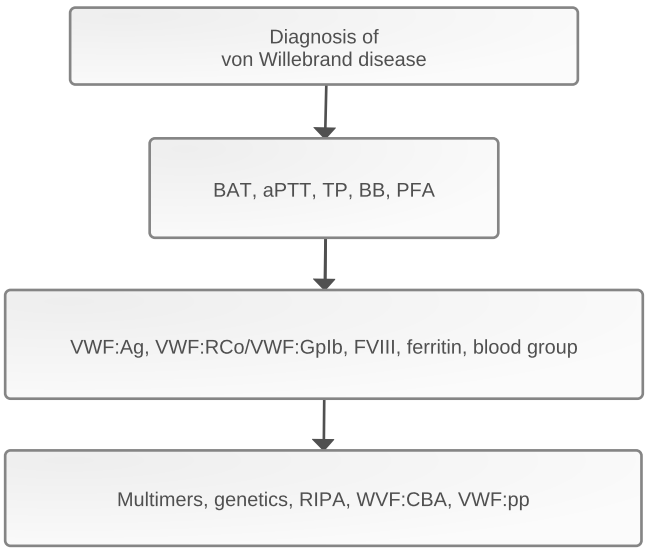
Furthermore, the optimal approach for managing patients who exhibit a propensity for bleeding in their daily lives and who fall within the borderline range of 50–70% remains to be elucidated [71, 72]. See chapter 5.3 Diagnostics.

5.1.5 Summary

The diagnosis of von Willebrand disease requires a combination of detailed medical history, including family history, a combination and, if necessary, repetition of specialized laboratory tests, and a differentiated interpretation of the results. Prothrombin time (Quick, PT) and partial thromboplastin time (aPTT) have been determined to be unreliable screening tests for diagnosing VWD are not reliable tests for screening for the diagnosis of VWD. Although the aPTT may be prolonged in certain types of VWD, such as type 3 or type 2N (as a proxy for the degree of factor VIII activity), it is not traditionally used as a screening test for VWD because it is normal in most cases [73].

Figure 1 below shows a significantly simplified diagnostic scheme. Further explanations follow in chapter 5.2.

Figure 1: Simplified diagnostic scheme for VWD



Legend:
BAT: bleeding assessment tool, VWF:Ag: von Willebrand factor antigen, VWF:Rco: von Willebrand factor ristocetin, GpIb: glycoprotein I b, BB blood count, PFA: platelet function analyzer
TP: thromboplastin time, aPTT: activated partial thromboplastin time; pp: propeptide; CBA: collagen binding assay

5.2 Diagnostics in detail

5.2.1 Screening with a standardized medical history questionnaire (BAT)

For the initial screening examination in cases of suspected VWE, the use of a validated bleeding assessment tool (ISTH-BAT) is recommended [30]. BATs can be helpful in documenting the severity of bleeding and can be used in combination with laboratory tests for initial diagnosis. A standardized medical history questionnaire has been shown to be more accurate than individual interviews conducted by individual practitioners. It should be noted that BAT is most effective in adult women. In patients with a high probability of VWD (e.g., those with affected first-degree relatives), the decision to perform specific tests should not be based on BAT alone [28].

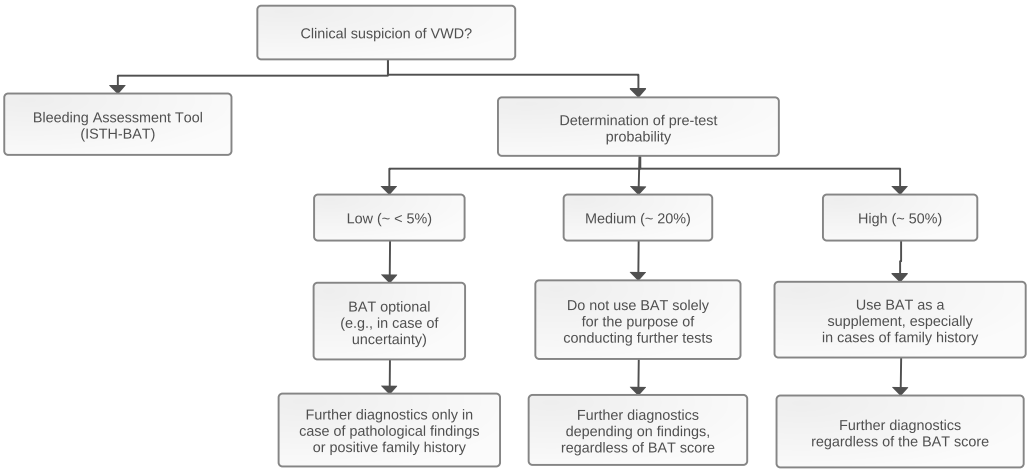
There are practical suggestions for the use of BAT [74]:

A: Use of BAT in cases of moderate VWE probability: For patients with a moderate probability of VWE (approximately 20%, often with a history of bleeding or abnormal initial tests), BAT alone should not be used to decide whether further tests are necessary.

B: BAT in cases of high VWE probability: Target group: Patients with a high pre-test probability of VWE (approximately 50%), often due to a family history, regardless of their own bleeding symptoms or initial laboratory tests.

The following is a diagnostic decision tree with explanations (Figure 2), adapted from the WFH/ISTH guideline [62], as well as another proposal from 2021 [63].

Figure 2: Use of the ISTH Bleeding Score



Legend:
Adapted from [75]

5.2.2 Further von Willebrand-specific laboratory methods

If VWD is suspected, specific tests such as VWF antigen (VWF-Ag), platelet-dependent VWF activity (e.g., VWF:GPIb), and factor VIII activity (FVIIIc) should be performed, ideally in conjunction with aPTT and PFA measurements (see chapter 5.2.3). Various reagents from different companies are available for determining von Willebrand parameters.

After determining these parameters, most laboratories automatically determine the VWF:Act / VWF:Ag ratio.

If the VWF:Act / VWF:Ag ratio is < 0.7, this indicates type 2 VWD.

5.2.3 Multimer analysis

Multimer analysis is particularly useful for differentiating between the various types of VWD: type 2. This is important because a reliable diagnosis of patients with types 2A, 2B, or 2M is essential for the prognosis and counseling of patients and their families. The analysis is performed by electrophoresis [76, 77].

5.2.4 Supplementary special tests (VWF:CBA and VWF:pp)

Other measurement methods include von Willebrand factor collagen-binding activity (VWF:CBA) and VWF:propeptide (VWF:pp).

Explanation: VWF: The functionality of von Willebrand factor (VWF) is assessed by the CBA, which involves testing the ability of VWF to bind to subendothelial collagen. The test is often performed using an enzyme-linked immunosorbent assay (ELISA) or chemiluminescence [78, 79].

The VWF:CBA test is helpful in distinguishing between different types of VWD. The ISTH guidelines recommend either VWF multimer analysis or the VWF:CBA/VWF:Ag ratio for the diagnosis of type 2 VWD in patients suspected of having type 2A, 2B, or 2M [62, 80].

Von Willebrand propeptide measurement (VWF: pp) was originally used to diagnose type 1C VWD. The propeptide is produced during the synthesis of von Willebrand factor (VWF) in the Weibel-Palade bodies and is released into the bloodstream in the same amount as VWF [81]. Due to its shorter half-life compared to VWF, the ratio of VWFpp to VWF:Ag (VWF:Ag) provides important insights into the synthesis, secretion, and degradation of VWF.

Increased degradation of VWF from the blood is reflected in a high VWF:pp/VWF:Ag ratio.

A normal VWF:pp/VWF:Ag ratio but low absolute values indicate reduced VWF synthesis [82]. This test is therefore useful for determining VWE type 1C. Unfortunately, the test is not yet widely available [83]. Alternatively, a DDAVP test can/should be performed if there are no contraindications. In the DDAVP test, the VWF levels that are elevated after one hour in VWE 1C already decrease again after 4 hours (see chapter 6.3.3) [62].

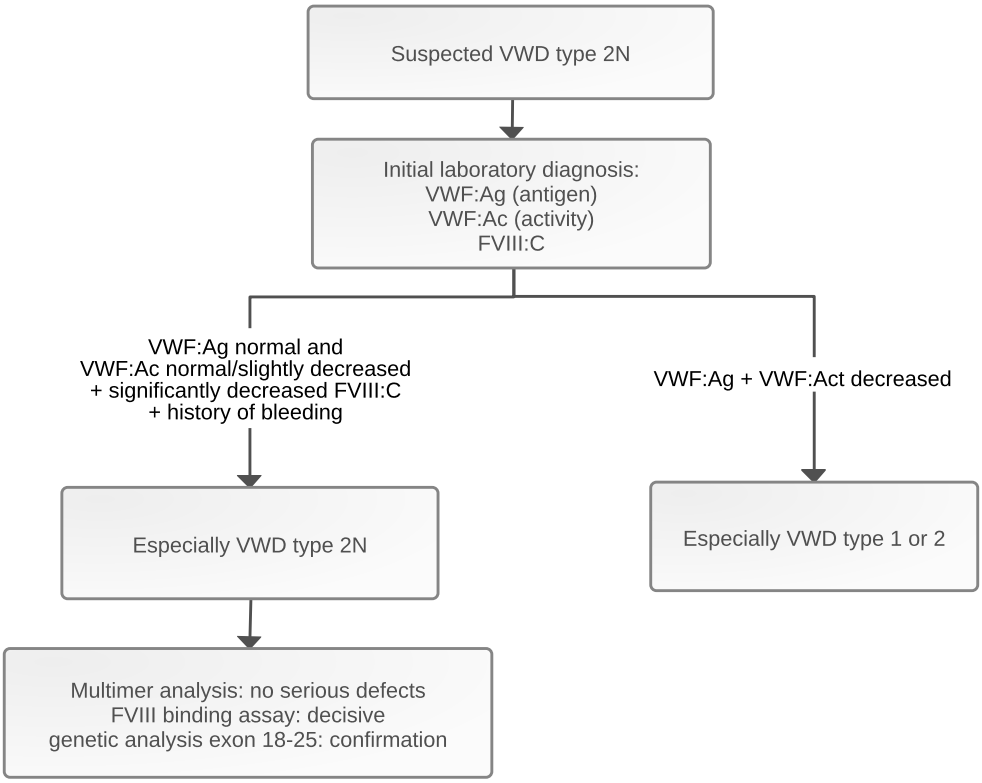
5.2.5 Tests to differentiate between type 2 VWE

If the multimeric analysis cannot be performed, is unclear, or if further diagnostic confirmation is desired, additional detailed examinations can be performed. The focus is on the difficult diagnosis of VWE type 2 B and VWE type 2 N. The diagnosis of the subtypes VWE type 2 B (RIPA) and type 2 N (VWF:FVIIIB) is particularly difficult. The following are explanations and suggestions for step-by-step diagnosis (Figure 3).

5.2.5.1 Explanation of type 2B diagnosis

Ristocetin-induced platelet agglutination (RIPA) is an in vitro test for examining the function and interaction of VWF with the GPIbα-V-IX complex of platelets. The test is performed with platelet-rich plasma (PRP) and measures agglutination at different ristocetin concentrations [84, 85]. A low ristocetin concentration (0.5 mg/ml) can distinguish type 2B (VWE 2B) from the platelet type (PT). At this concentration, platelet agglutination occurs, which is not triggered in normal individuals [86].

Figure 3: Clarification of VWE type 2B

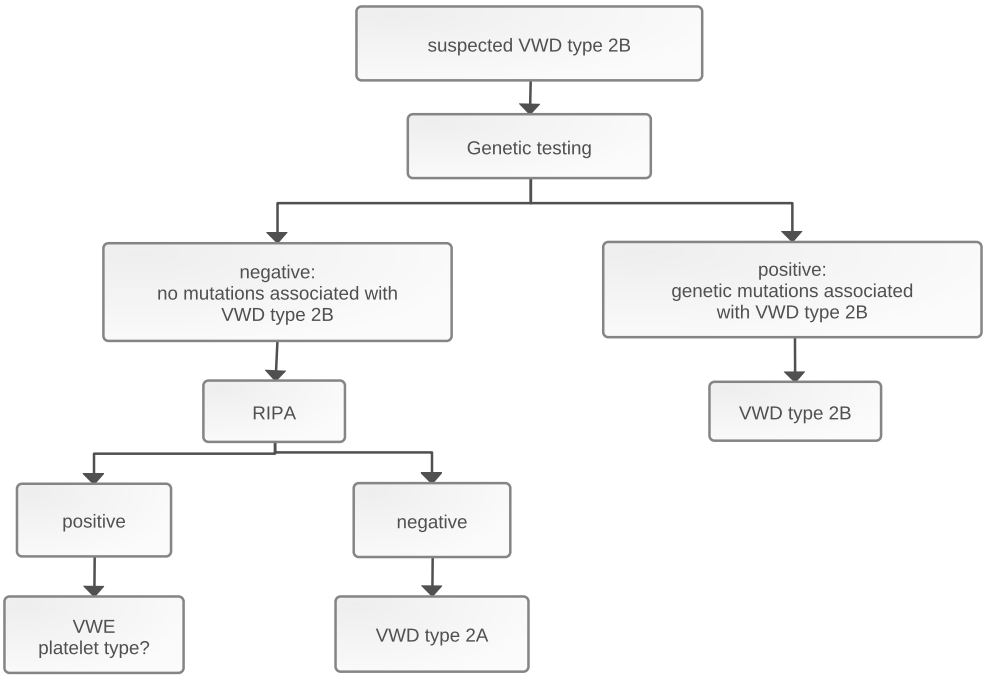


Legend:
VWF:Act von Willebrand factor activity, VWF:Ag: von Willebrand factor antigen

5.2.5.2 Explanation of type 2N diagnosis

The FVIIIC binding test, also known as the FVIII binding assay (VWF:FVIIIB), measures the ability of VWF to bind FVIII. This is an essential function of VWF, as it protects FVIII from degradation and supports its release at the site of injury. This test is used in particular to diagnose VWE 2N, which is characterized by a reduced FVIII binding capacity of VWF and is difficult to distinguish from mild hemophilia in individual cases. This test is particularly beneficial in circumstances where genetic testing is not an option and patients exhibit symptoms consistent with those associated with hemophilia A. A reduced ratio of VWF antigen (VWF:Ag) to FVIII binding activity (<0.7) indicates a defect in FVIII binding, which is typical of VWE 2N.

Figure 4: Diagnosis of VWE type 2N



Legend:
VWF:Act von Willebrand factor activity, VWF:Ag: von Willebrand factor antigen

5.2.6 Diagnosis of von Willebrand type 1 Vicenza and type 1C

Von Willebrand disease type 1C and von Willebrand type Vicenza are not the same, even though they have some similarities. They are both characterized by low von Willebrand factor (VWF) levels, but they differ in cause and mechanism.

VWE 1C is a subcategory of type 1 VWE characterized by increased clearance of VWF from the bloodstream. This means that VWF is produced normally but is unstable and therefore breaks down faster than usual. It is characterized by certain known mutations (see chapter 5.2.8). Patients typically have low VWF levels, a reduced half-life of VWF (can be detected by the DDAVP test (chapter 6.3.3) and due to the high VWF:pp/ag ratio), and a tendency to bleed.

Von Willebrand disease type Vicenza is characterized by very low VWF levels (<10 IU/dl) and an exceptionally short half-life of circulating VWF. It is typically associated with the *R1205H* mutation in the VWF gene. This mutation causes VWF to be removed from the blood unusually quickly. The bleeding tendency can vary greatly. The Vicenza type was first described in the Vicenza region of Italy but is not limited to this region. The multimeric pattern shows ultra-large multimers.

VWE Vicenza is often considered a special case within type 1 disorders, with overlaps with type 1C (increased clearance) [87- 89].

5.2.7 Platelet function analyzer 100/200 (PFA)

The PFA-100/200 simulates the conditions of an injured endothelium under flow conditions and thus records, among other things, the function of VWF. The closure time (CT) is measured. One advantage of this method is that it can be performed quickly. PFA alone is not an adequate diagnostic tool for VWE [90- 92].

5.2.8 Genetic testing

Genetic analyses are becoming increasingly important in the diagnosis of VWD. In line with the British guidelines, genetic testing can be performed if patients have reduced VWF activity (as determined by any activity test) or VWF levels: antigen <30 IU/dL on two occasions and VWF levels between 30 and 50 IU/dL are detected, if no other causes for the bleeding phenotype have been identified [93].

In line with the WFH ISTH guidelines (James et al.), genetic testing should be preferred over RIPA for the diagnosis of VWE type 2B.

Genetic testing is also recommended for the determination of type 2N, if available. Alternatively, the FVIII binding test can be used.

Genetic testing can also be helpful in distinguishing between congenital and acquired forms [94]. Genetic testing is also helpful in the diagnosis of VWD type 3, type 1C, and type Vicenza [95].

Many mutations are already known. Most mutations that cause VWD type 1 are missense mutations (about 70%), followed by splice site mutations (about 9%), transcription mutations (8%), small deletions (6%), nonsense mutations (5%), and small insertion or duplication mutations (2%). Type 2 VWD can be explained genetically in a relatively simple manner, as mutations in specific areas of the VWF protein lead to defects in its function. Type 3 VWS is the most severe form: due to homozygosity or compound heterozygosity for zero alleles in the VWF gene, affected individuals produce virtually no von Willebrand factor (VWF). In addition, it has been demonstrated that copy number variants (CNVs) can cause all subtypes of VWE [96- 98].

In recent years, it has become increasingly evident that a more comprehensive genetic understanding of VWE also requires analysis outside the VWF gene. This is evident from the fact that not all patients with low VWF or type 1 VWS have characteristic mutations in the VWF gene, which highlights the genetic complexity of this disease. Specifically, no probable causative variant in the VWF gene has yet been identified in approximately 35% of patients with VWE type 1, and only 41% of families with VWE type 1 show linkage to the VWF locus [99].

The same applies to type 3 VWE: in one study, no null mutations in the VWF gene were detected in approximately 15% of type 3 patients, suggesting that other genes may also play a role in the disease. An increase in genetic testing is expected in the coming years [100- 104].

The authors believe that the recommendations will be adapted in the coming years. Next-generation sequencing (NGS) is a suitable method for this purpose.

This method enables more accurate and faster diagnosis, can identify variants that are not detected by the older test, and offers the possibility of updating or expanding the diagnosis at a later date when new findings become available [95, 105].

In general, before a person undergoes genetic testing, a declaration of consent must be obtained that also contains information about possible incidental findings. Not all physicians are allowed to order all genetic tests. The respective regulations of the federal states must be considered.

5.2.9 Summary of diagnostics

Table 3: Short version of typing

	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	Vicenza	Type 1C
aPTT	N (↑)	N (↑)	N (↑)	N (↑)	↑	↑	↑	N (↑)
FVIIIc	N (↓)	N (↓)	N (↓)	N (↓)	↓	↓↓	↓	N (↓)
VWF:Ag	↓	↓	N (↓)	N (↓)	N (↓)	<10%	N (↓)	N (↓)
VWF Act (e.g., VWF:GpIb	↓	↓	↓	N (↓)	N (↓)	↓↓	↓	↓
Ratio Act/Ag	1	<0.7	<0.7	<0.7	<0.7	nd	mostly 1	mostly 1
RIPA (0.9 mg/ml ristocetin)	N (↓)	N (↓)	↑	N (↓)	n	nd	n	N (↓)
Multimers	All bands	Reduction of high molecular weight bands	Reduction of high molecular weight bands	Normal/high molecular weight	All	nd	Partial reduction of high molecular weight	All bands
VWF:pp	n	n	n	n	n	nd	↓	n
Ratio to pp/Ag	n	n	n	n	n	nd	↓	n
VWF:FVIII	n		n	n	↓	n	n	n

Legend:
N normal, high molecular weight or all bands (multimer field)
↓ : decreased, ↑ : increased, nd: not relevant
VWF: PP: von Willebrand factor propeptide, RIPA: ristocetin-induced agglutination, GpIb: glycoprotein Ib, Act/Ag: ratio of von Willebrand factor activity to antigen

5.3 What pitfalls should be considered in the diagnosis?

5.3.1 Preanalytics

It is important to observe the preanalytical conditions; current recommendations are available.

Whole blood samples for coagulation tests should be stored at an ambient temperature of 18–25°C during transport and storage prior to processing. Refrigeration should be avoided.

The time between sample collection and testing (or freezing) of citrated plasma for VWE tests should not exceed twelve hours.

Before making a diagnosis of VWE, it is recommended that results that deviate from the normal values be confirmed at a specialised center with experience in performing the tests and interpreting the results. In addition, samples should be taken on site to check the preanalytics [93].

5.3.2 Borderline findings*

**see also chapter 5.1.4 Subtypes*

- 0.3–0.50 IU/mL and 0.5–0.7 IU/mL are diagnostically challenging.
- According to WFH guidelines: In cases of clinically relevant bleeding, the threshold value is < 0.50 IU/mL; if the lower normal limit of the local laboratory is below this, its reference values should be used.

- Patients with 0.5–0.7 IU/mL are **not** currently classified as having VWD, but require a careful bleeding history and, if necessary, control measurements, especially in older patients [62].

In a German cohort of patients with suspected VWD, 47 patients with a slight reduction in VWF at the lower end of the normal range (50-70 IU/dL) were examined to gain more insight into this specific cohort, which does not meet the official diagnostic criteria for VWD. Remarkably, approximately 70% (33 of 47) of these patients carried VWF variants associated with VWD. Most of the VWF variants identified in this group were also present in patients with a confirmed diagnosis of VWD type 1 [106].

5.4 Classification

VWD is classified according to typing (multimer composition) and clinical severity of bleeding (see Table 1 and Table 3).

5.4.1 Differential diagnosis

Once the diagnosis of von Willebrand disease has been confirmed, there are only a few differential diagnoses.

Thrombocytopenia in VWD type 2b can sometimes lead to a false diagnosis of isolated thrombocytopenia [12].

Type 2N can be difficult to distinguish from moderate hemophilia A. In this case, the FVIIIc binding test or genetic analysis are helpful and effective [107].

It is therefore most important to consider Von Willebrand disease in patients with a bleeding tendency and to investigate this possibility.

6 Therapy

6.1 Therapy structure

Treatment involves various mechanisms, which may vary depending on the type and severity of the disease:

- Increasing the body's own von Willebrand factor (VWF) in the blood
- Replacement of VWF
- Additional treatments.

A detailed description of the medication is provided in chapter 6.2.

In principle, the following treatment scenarios are distinguished for VWE [108, 109]:

- Treatments for acute bleeding (on demand)
- Preventive substitution of VWF , for example before surgical procedures (short-term prophylaxis)
- Long-term prophylaxis with regular factor infusions (long-term prophylaxis). Prophylaxis in VWD is defined as the administration of factor at least once a week to prevent or reduce the severity of bleeding. The definition also stipulates that this regimen must be maintained for at least 45 weeks per year.

Numerous factors must be taken into account when deciding on treatment:

- clinical bleeding tendency,
- von Willebrand factor levels,
- joint damage,
- previous course of the disease and bleeding history,
- side effects of therapy,
- consequences for education and career (avoiding occupational disability),
- age of the patient, comorbidities, concomitant medication (especially anticoagulants),
- access to outpatient and inpatient specialist care,
- Experience of the attending physician/clinic in the treatment of VWD
- Patient preferences, health literacy, psychosocial situation,
- In children and adolescents, there is a stronger urge to move, therefore special consideration must be given to the risk of injury in kindergarten, school, and leisure activities.

Shared decision making (SDM) promotes patient participation in treatment and, through active involvement, strengthens trust and adherence to therapy recommendations [74, 109].

6.2 Overview of therapeutic options

Antifibrinolytic therapy is considered the basic treatment, especially for mucosal bleeding. In Germany, only tranexamic acid is currently approved. The drug can be administered orally, intravenously, as a nasal ointment, or as a mouthwash.

Topical aids are also useful for minor injuries.

Desmopressin (DDAVP): This drug can be used in particular in type 1 VWD, but also in types 2A, 2M, and 2N, to stimulate the release of VWF and factor VIII from the endothelium.

VWF concentrates: These are used to replace VWF deficiency, especially in more severe forms of VWD or when desmopressin is ineffective or contraindicated The concentrates are available in two forms: plasma derived and recombinant. The concentration of FVIIIc varies between these forms.. There are also FVIII-poor or FVIII-free preparations.

Combination therapies: In some cases, such as in patients with inhibitors, a combination of different therapies may be necessary to achieve effective bleeding control.

6.3 Presentation of treatment options

See also approval status (German Version)

6.3.1 Local hemostatic agents

Local hemostatic agents are also available to support the daily lives of VWD patients.

Local hemostatic agents are applied directly to a wound to stop bleeding. Their principle is based on promoting blood clotting or mechanically sealing the wound. Here are the main principles with examples [110- 112]:

1. Activation of blood clotting by chemical substances or promotion of platelet aggregation, e.g., thrombin-based agents (e.g., Thrombin-JMI®, a fibrin glue)
2. There are also bioactive agents that promote cell activation. E.g. Chitosan-based products (e.g. Celox®): Promote platelet activation and have an antibacterial effect.

3. Kaolin-containing products (e.g., QuikClot®): activate the intrinsic coagulation pathway
4. Mechanical sealing of the wound:
    - Gauze or cellulose sponges (e.g., Surgicel®): These are placed in the wound, absorb blood, and promote hemostasis through swelling.
    - Gelatin sponges (e.g., Gelfoam®): These act as a physical barrier and absorb blood. TABOTAMP-Nu-Knit (absorbable cellulose) [113] is also commercially available.

It is important to note that these products for local hemostasis are also prescription-only.

6.3.2 Tranexamic acid

Tranexamic acid (Cyklokapron®, a fibrinolysis inhibitor) can be used to support mucosal bleeding in all types of VWD. It is available as intravenous administration (not intramuscular), orals as well as a gel (nasal ointment) [114, 115].

The recommended dosage is:

- oral: 3 x 1-2 tablets of 500 mg per day.
- Ampoules of 500 or 1000 mg: 3 x 1 slow intravenous injection of one ampoule per day
  In other words, 3x25 mg/kg.

For tooth extractions, rinsing the mouth with tranexamic acid is recommended (1 ampoule in 1/2 glass of water, rinse mouth for 3 minutes and then spit out).

In children, tranexamic acid should only be used from the age of 1 year in a reduced dose of 20 mg/kg/day.

It should not be administered in cases of urogenital bleeding due to the possible formation of blood clots in the urinary tract [116, 117].

Furthermore, dose adjustments are advisable in cases of renal insufficiency.

6.3.3 Minirin (desmopressin, DDAVP)

Desmopressin (1-desamino-8-D-arginine vasopressin, or DDAVP for short) is a synthetically produced protein. It is very similar to the body's own hormone vasopressin (also known as antidiuretic hormone, or ADH for short). The administration of DDAVP releases VWF from the body's own endothelial stores.

In mild forms of VWE, especially VWE type 1, DDAVP can be used to increase the amount of von Willebrand factor (VWF) available in the blood. A 2–3-fold increase in VWF parameters is expected. This is mainly the case with VWE type 1 or some VWE type 2. A certain amount of residual activity must be present. However, since not all patients (e.g., VWE type 1C) respond to DDAVP, a DDAVP test should be performed once.

- The test must be performed in basic state of health.
- VWF antigen, VWF activity, and factor VIII levels are measured at baseline and 1 and 4 hours after administration.
- Response definition: At least a twofold increase in VWF antigen and activity levels and a VWF level (antigen or activity) and factor VIII level above 0.50 IU/mL.
- During this test, patients should also be informed about the restriction on fluid intake on that day to 1-1.5 liters.

It should be noted that desmopressin, due to its antidiuretic effect, can cause hyponatremia with all the associated complications such as flushing and seizures.

The contraindications and side effects result from the mode of action. It is particularly unsuitable for small children under 5 years of age and elderly people over 65. Other contraindications include coronary heart disease, arterial hypertension, kidney disease, known seizures, known allergy to ingredients, migraine, presence of TTP, and interactions with various medications.

Patients with VWE type 2B often have a contraindication to minirin administration due to the risk of thrombocytopenia.

Desmopressin (e.g., Minirin®, desmopressin acetate nasal spray, Octostim®) can be administered subcutaneously, intranasally, or intravenously, depending on availability and approval status. A common dosage is 0.3 µg/kg/bw in an infusion of 100 ml NaCl over 30 minutes. The maximum effect in terms of VWF increase occurs after 30 to 60 minutes and is detectable for approximately 6 hours. Octostim® is currently not commercially available, but desmopressin acetate nasal spray can be used instead. The dosage of the current nasal spray (desmopressin acetate spray) is 2x1 spray from 12 years of age = 300 µg, 1 x1 spray (ages 4-12) corresponds to 150 µg.

Subcutaneous administration is approved. The dose for subcutaneous administration is 0.3µg/kg/ body weight, and the maximum effect occurs after 60-90 minutes. It is reported to be better tolerated in terms of side effects such as facial flushing, increased heart rate, and decreased blood pressure.

The nasal spray can be confused with the spray for diabetes insipidus, which is approximately 10 times more concentrated.

Administration for a maximum of 3 days is recommended because tachyphylaxis may then occur. Sodium levels should be monitored during repetitive administration. For surgeries requiring prolonged bleeding control, factor concentrate administration should be planned. It should also be determined in advance whether fluid restriction and sodium control can be implemented.

There is little data on use during pregnancy. No randomized studies exist [118- 122].

6.3.4 von Willebrand factor concentrates

Table 4: Overview of von Willebrand factor concentrates

Trade name	Haemate/Voncento®	Wilate®	Willfact®	Veyvondi®
Manufacturer	CSL Behring	Octapharma	LFB Biomedicaments	Takeda
Active ingredient	Human VWF & FVIII (2.4:1)	Human VWF & FVIII (1:1)	Human VWF (FVIII ≤10%)	Recombinant VWF (Vonicog alfa)
FVIII content	250–1000 IU FVIII / 600–2400 IU VWF	500/1000 IU per 500/1000 VWF/FVIII	≤10 IU FVIII per 100 IU VWF	<0.01 IU FVIII per IU VWF
Multimer structure	Contains large multimers	Contains large multimers	Contains large multimers	Contains large multimers
Recommended dosage	20–40 IU/kg FVIII and 40–80 IU/kg VWF	20–50 IU/kg FVIII and 50–80 IU/kg VWF (for type 3	40–80 IU/kg VWF; additional FVIII if necessary	40–80 IU/kg VWF; additional FVIII if necessary
Half-life (FVIII)	12–14 hours	1. –11.8 hours	8–14 hours	18–23 hours
Virus inactivation	Pasteurization (60°C/ 10 h)/dry heat (V)	Solvent/detergent, dry heat (100°C/120 min)	Solvent/detergent, nanofiltration, dry heat (80°C/72 h)	Solvent/detergent, nanofiltration
Approval for VWE	Yes	Yes	Yes	Yes (from 18 years of age)
Special features	Higher VWF content	Equal ratio of VWF to FVIII	Pure VWF concentrate with traces of FVIII	Recombinant preparation without FVIII

Legend:
Key: *IU International units VWF von Willebrand factor*
VWE von Willebrand disease, FVIII Factor VIII
It is not necessary to convert the required package sizes according to content, because:
- The preparations are already available in standardized package sizes
- Dosage is based directly on the corresponding active ingredient content (FVIII or VWF)
- The product information provides clear dosage recommendations based on the respective content
Adapted from the prescribing information and approval status

6.3.5 Summary: Haemate®

Haemate® is approved for the treatment of von Willebrand disease and hemophilia A, both for the prophylaxis and treatment of bleeding or bleeding during surgery when treatment with desmopressin (DDAVP) alone is ineffective or contraindicated.It contains von Willebrand factor (VWF) and factor VIII (FVIII) from human plasma [123- 125]. It is approved for children and adults, although no data from clinical studies on the dosage of Haemate P® for prophylaxis in children are available.

It is administered intravenously at a recommended maximum rate of 4 mL/min.

In general, 1 IU/kg VWF:RCo raises the plasma level of VWF:RCo by 0.02 IU/mL (2%). VWF:RCo levels of >0.6 IU/mL (60%) and FVIII:C levels of >0.4 IU/mL (40%) should be targeted.

Usually, 40–80 IU/kg of von Willebrand factor (VWF:RCo) and 20–40 IU FVIII:C/kg body weight are recommended to achieve hemostasis. 100 IU/kg is also possible.

6.3.6 Summary of Voncento®

Voncento® is approved for the treatment of von Willebrand disease and hemophilia A, as well as for the prophylaxis and treatment of bleeding and bleeding during surgery in all age groups,

and contains von Willebrand factor (VWF) and factor VIII (FVIII) from human plasma. For further information, see approval status.

It is administered intravenously at a recommended maximum rate of 4 mL/min.

In general, 1 IU/kg VWF:RCo raises the plasma level of VWF:RCo by 0.02 IU/ml (2%). VWF:RCo levels of >0.6 IU/mL (60%) and FVIII:C levels of >0.4 IU/mL (40%) should be targeted.

Usually, 40–80 IU/kg of von Willebrand factor (VWF:RCo) and 20–40 IU FVIII:C/kg body weight are recommended to achieve hemostasis. 100 IU/kg is also possible.

6.3.7 Summary of Wilate®

Wilate® is a human combination preparation of von Willebrand factor (VWF) and coagulation factor VIII (FVIII). It is used to treat von Willebrand disease and hemophilia A. Indications include acute control of bleeding, perioperative bleeding control, and prophylactic reduction of bleeding episodes. Wilate® is approved for use in children and adults. Wilate is indicated for the prevention and treatment of bleeding or the treatment of bleeding during surgical procedures in patients with von Willebrand disease (VWD) when treatment with desmopressin (DDAVP) alone is ineffective or contraindicated. There are insufficient data on the use of Wilate in children under 6 years of age.

The drug consists of VWF and FVIII in a 1:1 ratio. It is derived from human plasma and is available as a lyophilized powder for the preparation of an intravenous solution. The dosage form facilitates precise dosing, especially in prophylactic treatment regimens [54].

The drug may cause hypersensitivity reactions, including allergic reactions.

To prevent bleeding during surgery, Wilate® should be administered 1–2 hours before the procedure. VWF:RCo plasma levels of ≥ 60 IU/dl (≥ 60%) and FVIII:C plasma levels of ≥ 40 IU/dl (≥ 40%) should be achieved. Repeated doses may be given after 12 hours. The dosage can be calculated using the following formula.

Required units = body weight (kg) × desired factor VIII increase (%) (IU/dl) × 0.5 IU/kg

In general, one unit of VWF:RCo and FVIII:C/kg BW increases the activity by 1.5–2 IU/dl of the respective protein. Normally, approximately 20–50 IU Wilate®/kg BW are administered to achieve adequate hemostasis. This increases VWF:RCo and FVIII:C in the patient by approximately 30–100%. An initial dose of 50–80 IU Wilate®/kg BW may be necessary [54, 126].

6.3.8 Summary of Willfact® (LFB)

Willfact® contains only human von Willebrand factor (pd-VWF). It is used for the treatment and prophylaxis of bleeding in patients with von Willebrand disease (vWD), including type 3, in which patients have a complete deficiency of VWF.

It is administered intravenously at a recommended maximum rate of 4 ml/min. It is approved for all age groups.

In general, 1 IU/kg of von Willebrand factor leads to an increase in the circulating level of VWF:RCo by 0.02 IU/ml (2%).

Levels of VWF:RCo > 0.6 IU/ml (60%) and FVIII:C > 0.4 IU/ml (40%) should be achieved. This means that, depending on the extent of the procedure and the individual's residual activity, a factor VIIIC preparation should be added. Alternatively, substitution can be started 12-24 hours before the procedure. The dosage here is 820 IU kg BW [127- 131].

6.3.9 Summary of Vonicog alfa (Veyvondi®)

This is a genetically engineered von Willebrand factor (rVWF) without FVIII [129].

It is used for the prophylaxis and treatment of bleeding, as well as bleeding during surgery in adults (aged 18 years and older) with von Willebrand disease (VWD) when treatment with desmopressin (DDAVP) alone is not effective or indicated. rVWF is a treatment option based on recombinant von Willebrand factor and was developed specifically for the treatment and prevention of VWD.

VEYVONDI must not be used to treat hemophilia A.

The on-demand dose, e.g., preoperatively, is 40 to 60 IU/kg VEYVONDI to ensure endogenous FVIII levels reach the target value of at least 0.4 IU/mL for minor procedures and 0.8 IU/mL for major procedures.

VEYVONDI should be administered together with recombinant factor VIII to control bleeding if FVIII:C levels are < 40% or unknown. The rFVIII dose should be calculated based on the difference between the patient's baseline FVIII:C level and the desired peak FVIII:C level in order to achieve an adequate plasma level of FVIII:C based on the approximate average recovery of 0.02 (IU/mL) /(IU/kg). The full dose of VEYVONDI should be administered, followed by rFVIII within 10 minutes.

6.3.10 General information on prophylaxis

The standard treatment for patients is with factor concentrates. When dosing these concentrates, the different content of VWF and FVIII should be taken into account..

Long-term prophylaxis, which has become standard for hemophilia, is not very common for VWE. However, recent data suggest that a significant number of VWE patients could benefit from prophylactic treatment with VWF-containing concentrates. For example, 35 Swedish VWE patients who required prophylaxis (mainly due to nose/mouth and joint bleeding) showed a significant overall reduction in bleeding episodes, and children who were treated with prophylaxis before the age of 5 did not develop arthropathies. Studies on VWE prophylaxis are urgently needed to develop evidence-based guidelines for this approach. The VWE Prophylaxis Network has therefore initiated the international VWS Prophylaxis Study [132].

All factor concentrates are subject to stringent documentation requirements ensuring traceability. Each batch must be documented in the patient's medical record. The Paul Ehrlich Institute, in collaboration with patient associations (Interessengemeinschaft Hämophiler e. V., or IGH for short, and the German Hemophilia Society, or DHG for short) and the medical association GTH (Gesellschaft für Thrombose- und Hämostaseforschung e. V.), has been maintaining the German Hemophilia Registry (DHR) since 2008. Patients who receive factor concentrates are to be recorded anonymously in an annual report, either individually or as a collective report, in accordance with § 21 (1a) TFG. It is advisable for patients to document their own substitutions and bleeding episodes. Both paper and electronic substitution calendars are available for this purpose.

Prophylaxis with von Willebrand factor (VWF) concentrates is indicated for patients with a history of severe and frequent bleeding. It is particularly suitable for patients with type 3 VWE or severe forms of type 1 and type 2A, who experience spontaneous bleeding or gastrointestinal bleeding. In addition to gastrointestinal bleeding, frequent reasons for prophylaxis include bleeding into the joints, severe epistaxis or heavy menstrual bleeding, and anticoagulation as concomitant medication. A distinction is made between long-term prophylaxis and short-term

(intermittent prophylaxis). Both forms can significantly reduce the risk of bleeding and improve quality of life [129].

All factor concentrates are approved for prophylaxis.

One standard dosage is 20–40 IU/kg body weight and is administered intravenously two to three times a week. The exact dose and frequency can be adjusted individually based on the patient's bleeding profile.

Patients should be monitored regularly, as is the case with patients with hemophilia. Continuous communication with the treatment team ensures that the therapy is optimally adapted to the patient's changing needs.

A therapy diary (paper, app) documenting infusions and possible bleeding episodes facilitates the adjustment of therapy.

It is also advisable to check VWF levels and the effectiveness of prophylaxis at regular intervals of between 3 and 6 months.

As a concomitant measure, patient and family education regarding infusion administration techniques, promotion of a salubrious lifestyle, and the importance of optimal oral hygiene to mitigate oral hemorrhaging have demonstrated efficacy.

After receiving appropriate training, patients can administer their own infusions at home, which increases adherence to the prophylaxis regimen.

It should be noted that prior to surgical procedures or traumatic events, the dose should be temporarily adjusted to minimize the risk of bleeding [10, 54, 133].

Table 5: Summary table of treatment options (adapted from [74])

Basic therapy: Topical treatment Tranexamic acid		
Subtype	**Diagnosis**	**Treatment**
1 (most common type)	Mild to moderate quantitative decrease in VWF. VWF level (quantitative antigen or activity) below 0.30 international units/mL regardless of bleeding history, or below 0.50 international units/mL with previous bleeding history. Functional defect is proportional to quantitative deficit.	VWF concentrates or desmopressin if previous desmopressin testing* outside of pregnancy showed efficacy. If desmopressin response history is unknown, treat with VWF concentrates (most patients with levels above 0.30 international units/ml respond to desmopressin). If the history of response to desmopressin is unknown, treat with VWF concentrates (most patients with values above 0.30 international units/ml respond to desmopressin).
2A	Mainly functional abnormality with a deficiency of high molecular weight multimers. Ratio of VWF activity/VWF antigen below 0.7 and low ratio of VWF-CBA/VWF antigen, which mainly indicates a functional defect.	VWF concentrates are usually required. Some patients may respond to desmopressin (requires prior positive desmopressin testing).
2B	VWF activity/VWF antigen ratio below 0.7 Multimer analysis (deficit of large multimers) Thrombocytopenia present. Confirm diagnosis with targeted genetic testing.	Desmopressin is contraindicated as it can exacerbate thrombocytopenia. Treat with VWF concentrates. If necessary, platelet concentrate.
2M	Ratio of VWF activity/VWF antigen below 0.7. Pathological interaction between VWF and platelet glycoprotein Ib-IX-V.	Most cases require VWF concentrates. Some patients may respond to desmopressin (requires prior positive desmopressin testing).
2N	Ratio of VWF activity/VWF antigen below 0.7. Limited VWF binding to factor VIII, resulting in low factor VIII levels.	Most cases require VWF concentrates. Some patients may respond to desmopressin (requires prior positive desmopressin testing).
3	Severe quantitative decrease in VWF.	VWF concentrates.

Legend:
Abbreviations: Ag: antigen; VWF: von Willebrand factor; VWF:CBA: von Willebrand factor collagen binding activity

6.3.11 Home care service

In recent years, home care service for patients has become increasingly established.

Various providers (e.g., pharmacies) offer support for people with von Willebrand disease and other bleeding disorders. Reasons for using a home care service include problematic vein conditions, fear of needles, emotional coping with the disease, and the organization of factor preparations. The support program is aimed at people of all ages. The services team consists mainly of health care professionals and nurses who also educate patients on prophylaxis and offer telephone support. This significantly increases patient adherence. In most cases, the services are supplemented by reminder management or assistance with documentation. Collaboration with the treating physicians is a matter of course.

We would like to emphasize once again that multidisciplinary care with close cooperation between hemostasiologists, gynecologists, and other specialists is crucial to ensure comprehensive care [10, 34][133- 135].

6.3.12 Treatment of emergencies

Patients with VWD should be trained for emergencies and carry an emergency card.

Patients should also know whether they can receive DDAVP and which factor preparation has already been used. Patients should also be familiar with self-help methods such as cold and pressure bandages. In individual cases, it is certainly difficult to assess the timing of a medical consultation. In our opinion, it is important that patients are offered the opportunity to consult a doctor and are aware that medical consultation is possible.

Due to the complexity of von Willebrand disease, not all therapies are suitable for all patients. This once again underlines the importance of an individual emergency card.

There are various types of emergencies that occur at home and are not caused by trauma. There is certainly room for improvement in patient awareness here, as emergencies are usually associated with accidents and not with bleeding that is difficult to stop. The following is a (probably incomplete) practical overview.

Epistaxis emergency: First, patients should sit upright and tilt their head slightly forward, not backward, while breathing calmly through their mouth. The soft wings of the nose should be pressed for 5-10 minutes. In addition, a cool compress on the neck or forehead is helpful [136].

It is important that patients know when to take further action: (1) if the bleeding does not stop after 15–20 minutes of pressure, (2) if the bleeding is very heavy, or (3) if symptoms such as dizziness, weakness, or palpitations occur.

In these cases, the priority is to stop the bleeding with factor concentrates. Desmopressin takes too long, as do tranexamic acid and nasal spray, and ointment is not effective enough.

Substitution with a VWF factor concentrate is a possible treatment: The dosage of the various factor preparations depends on the approval (see chapter 6 Treatment).

Emergency heavy menstrual bleeding: Despite taking basic medication such as tranexamic acid or having already taken hormones, uncontrollable, Hb-relevant bleeding occurs repeatedly [57].

Emergency upper gastrointestinal bleeding: Furthermore, upper gastrointestinal bleeding due to angiodysplasia (see chapter 4.1.3), which can also manifest itself in abdominal pain or

nonspecific symptoms, is an emergency, especially if the patient has not yet been diagnosed. Here, in addition, a switch to prophylaxis is advisable [137].

6.4 Special patient groups

6.4.1 Children and adolescents

The special feature in children and adolescents is that DDAVP etc. must be viewed critically and not all medications are approved. The information is included in the respective chapters.

6.4.2 Women

A survey of gynecologists showed that awareness of bleeding tendencies, including VWD, as a cause of heavy menstrual bleeding is low among gynecologists [138].

Where feasible, the utilization of multidisciplinary medical facilities that facilitate collaborative examinations by gynecologists and hematologists/hemostasiologists is recommended. These specialized settings are designed to optimize the treatment of heavy menstrual bleeding in patients with bleeding tendencies. [74].

Women with known bleeding disorders and heavy menstrual bleeding should undergo a standard gynecological examination, which is recommended for women with heavy menstrual bleeding in the general population, to rule out common pelvic disorders such as fibroids and polyps, especially those that do not respond to initial treatment [139].

Women with inherited bleeding tendencies such as VWD are still more likely to be referred for bleeding, have a longer diagnostic delay, and often require treatment for gender-specific bleeding [140].

It is important to mention that heavy menstrual bleeding in particular, with all its consequences (iron deficiency, dizziness, social withdrawal, etc.), is receiving greater awareness.

The basic treatment for heavy menstrual bleeding is tranexamic acid, which can be taken in doses of 3x500 mg to 3x1g for approximately 4-5 days.

6.4.2.1 Hormones

In 2021, international guidelines [74] issued recommendations for the treatment of heavy menstrual bleeding (hypermenorrhea) in VWD. First, tranexamic acid, if possible DDAVP or the administration of factor concentrates. Unfortunately, these recommendations are based on limited data and studies. Decisions on the use of a levonorgestrel-releasing intrauterine system should be made in accordance with the guideline as part of a multidisciplinary decision-making process (e.g., by gynecologists, hematologists, and patients).

It should be noted that most hormonal contraceptives are not officially approved for the treatment of bleeding tendencies, but primarily for contraception.

One exception is Qlaira®, a combination pill containing estradiol valerate and dienogest. This is approved in Germany for the treatment of non-organic menorrhagia [141].

Hormone therapy may offer benefits for some patients, such as the treatment of menstrual cramps and symptoms associated with endometriosis and polycystic ovary syndrome.

However, caution is advised with regard to the side effects of hormone therapy in patients at high risk for endometrial hyperplasia/malignancies, such as women over 35 and women with

polycystic ovaries, a high body mass index, and comorbidities such as diabetes and high blood pressure.

There is little data available on hormone treatment for VWE: there are two comparative studies: a randomized clinical trial comparing tranexamic acid with desmopressin [142] and an observational study comparing hormone therapy with desmopressin [143].

In addition, the colleagues found five case studies on a levonorgestrel-releasing intrauterine system [144- 148].

A general meta-analysis on hypermenorrhea from 2020 [149], which was not specific to VWE, demonstrated that the levonorgestrel-releasing hormone coil (LNG-IUS) can ameliorate heavy menstrual bleeding. However, the effect is analogous to that of endometrial ablation. In summary, the authors express uncertainty regarding the comparative efficacy of the results in relation to those of hysterectomy. They also note that the LNG-IUS is likely associated with adverse events of a similar severity to that observed with other medical therapies.

In summary, there is only one observational study that deals with hormone administration in patients with VWE, no prospective study, and no registry.

We therefore consider it sensible to reconsider the now "automated" recommendation of hormone administration to reduce or stop bleeding.

As a next step, the administration of DDAVP is recommended, if possible. This may also be useful in combination. However, it is important to note the restriction on fluid intake, which can be a challenge for affected women, especially in summer, and can then lead to hypotension itself.

The option of short-term (intermittent) prophylaxis during menstrual bleeding with a factor preparation should therefore be offered to all women who need it.

Another unmet need is older women with VWE. The treatment of hypermenorrhea is often associated with young women. However, women in early menopause (once again) experience heavy bleeding. However, there is little awareness of this issue.

We consider it essential to expand the data available on this topic.

Childbirth and the question of possible anesthesia, as well as bleeding during pregnancy, are also topics that are particularly important due to their complexity (see chapter 6.6).

Von Willebrand parameters usually increase during pregnancy (especially in mild forms) but may decrease again postpartum. This is difficult to communicate to both patients and the care team, such as obstetricians, midwives, etc. Unfortunately, in some clinics, patients are denied either the birth itself or epidural anesthesia, etc. [150]. Postnatal monitoring is also not always guaranteed, as the risk of postpartum hemorrhage is usually underestimated and, to make matters worse, varies in severity. The time it takes to return to pre-pregnancy levels is given as 3 weeks. Patients and postnatal midwives should be given this information [151].

In this case as well, further research and analysis of registry data would be beneficial

Providing detailed information to patients and their families, materials for midwives and obstetricians, and a letter explaining the birth are important measures to prevent this. The clinic should provide the factor preparation. An emergency card alone is not sufficient. A multidisciplinary team of experts in obstetrics, maternal-fetal medicine, hemostaseology, and anesthesiology should be available.

6.4.3 Patients with inhibitors against VWF

It is important to our committee that inhibitors can also occur in patients with VWE.

Type 3 von Willebrand disease (VWD) is characterized by the complete absence of von Willebrand factor (VWF) and leads to a severe bleeding phenotype. The standard treatment is replacement therapy with VWF-containing products. A key problem with this therapy is that the immune system can produce anti-VWF antibodies against the administered VWF. These antibodies can either have a neutralizing effect by blocking the function of VWF, or they can be non-neutralizing, which can nevertheless impair the effectiveness of the therapy or even lead to severe allergic reactions such as anaphylaxis.

- 18% of the 49 patients with type 3 VWE tested had anti-VWF antibodies (inhibitors).
- Of these antibodies, 67% were neutralizing and 33% were non-neutralizing.
- The antibodies targeted various VWF binding partners such as factor VIII, collagen III, collagen IV, and platelet glycoprotein Ibα (GPIbα).
- 89% of the identified antibodies belonged to the IgG class, specifically the IgG1 and IgG4 subclasses.

These important findings were obtained as part of the Zimmerman Program and should be noted by clinicians. It is possible to detect the antibodies using ELISA [152].

A recent study also investigated the occurrence of anti-VWF antibodies. These were found in 8.4% of subjects with type 3 VWE, while neutralizing VWF inhibitors were found in 6%, mainly in subjects who were homozygous for VWF null alleles [153, 154].

6.5 Special situations

6.5.1 Surgical procedures

A distinction is made between minor and major surgical procedures, i.e., those with a high and low risk of bleeding.

A review provides guidance on classification [155]:

Table 6: Surgical procedures

	General surgery	Orthopedics	Other
Major	• otomy	Osteotomy	Tooth (more than 2)
	• ectomy	Arthrodesis	
		Joint replacement	
		Osteosynthesis	
	Pseudotumor	Arthroscopy	
		Amputation	
Minor	Central venous catheter placement	RSO*	Cataract
	Gastrointestinal endoscopy, etc.		1-2 teeth

Legend:
Key: *CVC: central venous catheter RSO: radiosynoviorthesis*

While there is good data on the risk of bleeding in hemophilia, there is little data available for VWE. The table should therefore be used as a guide, based on the recommendations for patients with hemophilia.

For major surgery, both FVIII and VWF activity levels of ≥0.50 IU/ml should be targeted for at least 3 days postoperatively. The respective target values should be determined individually depending on the patient, the type of surgery, the bleeding history, and the availability of VWF and FVIII tests.

The duration of treatment may vary depending on the type of surgery. On the one hand, this gives practitioners freedom in their choice of therapy, but on the other hand, it underscores the significance of von Willebrand disease as a complex clinical picture.

There is an interesting meta-analysis on the question of optimal postoperative VWF:Ag/FVIIIc levels [156].

Here, too, given the limited evidence available as a basis for treatment decisions, a process of shared decision-making for individualized treatment plans is of great importance.

Another publication examined the target values for surgical procedures. It showed a mean FVIII activity of 1.344 IU/ml (134%) and a mean VWF activity of 0.924 IU/ml (92%). Below this, hemostatic efficacy was excellent in 92% of cases, good in 4% of cases, and poor in 4% of cases. There were no postoperative bleeding complications, therapy-related adverse events, or thrombotic events. Another study reported a mean FVIII level of 1.15 IU/mL (IQR, 0.97-1.34 IU/mL) and a mean VWF level of 0.85 IU/mL (IQR, 0.67-1.03 IU/ml) with 100% hemostatic efficacy and no thrombotic events. These case series probably reflect the practice of many clinicians to bring VWF:Ag and FVIIIC levels within the normal range [157, 158].

There is little data on the bleeding risks associated with vaccinations, especially in comparison to patients with hemophilia. In principle, all vaccinations can be administered, and standard vaccinations are highly recommended. The bleeding risk is not considered high, even with intramuscular administration. Prior to vaccination, prophylactic administration of von Willebrand factor/concentrate or desmopressin (for mild forms) or tranexamic acid can help reduce the risk of bleeding, especially in patients with a history of bleeding and/or residual activity below 10%.

It should also be noted that most vaccinations are also approved for subcutaneous administration (see German RKI website).

General measures such as a pressure bandage after the injection are advisable [159, 160].

6.6 Management during pregnancy and childbirth

6.6.1 Pregnancy

An individual risk assessment should be carried out, taking into account the patient's diagnosis and medical history. Regular monitoring of VWF and FVIII levels is advisable but is strongly recommended in the third trimester.

VWE type 1: In many women, VWF activity levels rise to normal levels in the third trimester. Nevertheless, the risk of bleeding remains, especially in cases with low baseline values (<30%).

VWE type 2: VWF levels may appear normal, but the factor is dysfunctional. Therefore, factor administration is often necessary.

VWE type 3: Women with this subtype do not show an increase in VWF during pregnancy and have a particularly high risk of bleeding complications.

The care of women with VWE during pregnancy and childbirth requires interdisciplinary collaboration between obstetricians and hematologists. The goal is to prevent bleeding complications without risking unnecessary interventions. Factor therapy should be planned early to ensure the safety of both the mother and the child. Both the risk of postpartum hemorrhage (PPH) in the mother and potential bleeding in the newborn must be taken into account. Therapeutic measures include factor administration, antifibrinolytics (e.g., tranexamic acid), and platelet transfusions. Recommended for platelet counts <50 × 10^9/L, especially in type 2B VWD [161].

6.6.2 Peri- and postpartum management

6.6.2.1 Introduction

Patients with von Willebrand disease are at risk of PPH (postpartum hemorrhage).

Primary PPH is defined as blood loss of more than 500 ml within the first 24 hours after delivery.

Secondary PPH is defined as bleeding occurring between 24 hours and 6 weeks after delivery [162- 164].

6.6.2.2 Peripartum recommendations/obstetric measures

There is initially no preference for a mode of delivery. A cesarean section is not considered a routine procedure but is performed when medically necessary. Adequate factor replacement therapy should be ensured.

For women with VWE who require neuraxial anesthesia, e.g., epidural anesthesia during labor, a VWF activity value above 0.50 (up to 1.50 IU/mL) was considered sufficient. Previous working groups recommended aiming for a target value of ≥ 0.50 IU/mL to enable neuraxial anesthesia, instead of the previously required activity level of > 1.50 IU/mL. This reduction was based on the assumption that even moderate activity values in this range ensure a sufficient level of hemostatic safety [74].

In a single-center study, higher target values for VWF and FVIII:C were aimed for at the time of delivery to reduce the risk of bleeding complications. The aim of this study was to investigate the obstetric outcomes of pregnant individuals with VWE under this treatment protocol. Between 2015 and 2023, 47 singleton births in 41 patients were included, resulting in 46 live births and one fetal death. Early PPH occurred in 12.8% (6/47) of deliveries. Two patients required blood transfusions. One patient experienced severe bleeding, requiring an unplanned hysterectomy and transfer to the intensive care unit.

No thrombotic events occurred. Targeting higher peak plasma levels of VWF and FVIII:C (≥100 U/dL) appears to be effective in reducing the risk of obstetric bleeding complications in patients with VWD. Nevertheless, the rate of early PPH remains unsatisfactorily high compared to the general population. This underscores the need for further optimization of care [165].

Another working group was able to show that despite the target values of ≥100 IU/dL for von Willebrand factor (VWF) and factor VIII:C (FVIII:C) at the time of delivery, the rate of PPH remains elevated in patients with von Willebrand disease (VWD), even with prophylactic factor replacement therapy [166].

The previous recommendation focused on the results of the anesthesia procedure itself and not on the effects of VWF levels on postpartum bleeding, where VWF activity levels of >1.50 U/dl may be recommended in some situations.

VWF activity levels should be maintained at >0.50 U/dl while epidural anesthesia is in place and for at least 6 hours after removal.

Patients should also be assessed for risk of thrombosis after delivery, and prophylaxis (e.g., compression stockings or low molecular weight heparin) should be instituted if indicated [167-170].

6.6.2.3 Postpartum management

Fortunately, some recommendations for action already exist.

If the von Willebrand parameters fall below the desired range of 50%, a 3- to 5-day substitution is recommended after a vaginal delivery, and an extension to 5 to 7 days after a cesarean section. Optimal control of von Willebrand parameters is recommended.

After delivery, VWF and FVIII levels drop rapidly, increasing the risk of secondary PPH. Colleagues, patients, and their families should be aware of this.

The use of low molecular weight heparin is recommended to prevent thrombotic complications.

Patients who intend to breastfeed should be informed about the safety of tranexamic acid during breastfeeding in conjunction with its benefits in reducing bleeding.

Tranexamic acid can be used to reduce postpartum bleeding in women with VWE. Secondary postpartum bleeding in particular can be effectively reduced. However, studies indicate uncertain effects in primary PPH and other types of severe bleeding. There was a tendency toward a reduction in the risk of PPH and severe bleeding (RR = 0.25; 95% CI: 0.04–1.75/RR = 0.36; 95% CI: 0.05–2.59). The risk of vaginal hematomas may have been reduced (RR = 0.34; 95% CI: 0.02–6.39) [171].

This applies to patients with type 1 VWE but may also potentially apply to type 2 (and 3) VWE. The oral dosage is 25 mg/kg (approx. 1000–1300 mg).

A recently published study presented impressive data on the efficacy of tranexamic acid in relation to secondary PPH, Hb decline, and the need for further medication. However, this study does not only apply to patients with VWE. The authors conclude that prophylactic administration of tranexamic acid at birth would be an option for all women [172].

Against this background, it seems sensible to collect further studies and registry data on this topic for patients [173].

There are no prospective or comparative studies, and the recommendations for patients with VWD are based on the recommendations for women with hemophilia.

6.7 Painkillers

The question of suitable painkillers for patients with VWE is a common issue in practice. In general, painkillers that impair platelet function or inhibit blood clotting should be avoided if possible. Patients with more severe forms (type 3 or severe type 2 forms) often require close monitoring and/or substitution.

Acetaminophen (paracetamol) is initially considered a suitable painkiller, as it does not interact with hemostasis and is particularly suitable for mild to moderate pain (e.g., headaches, toothaches). Another medication without anticoagulant properties is metamizole (Novaminsulfon). This can also be used for more severe pain. However, the potential risk of agranulocytosis must be taken into account.

Opioids (e.g., tramadol, morphine) are also available for severe pain (e.g., postoperative or chronic pain). Due to their side effects and the risk of dependence, these should not be taken without medical supervision.

Acetylsalicylic acid in particular is not recommended as a painkiller. If its use is necessary due to a concomitant disease: see chapter 6.8.4.

It should be noted that non-steroidal anti-inflammatory drugs (NSAIDs, e.g., **ibuprofen®**, **diclofenac®**) inhibit platelet function and can therefore increase the risk of bleeding. However, the risk of bleeding appears to be/is not as high with ibuprofen as with ASA, as it does not cause irreversible inhibition of platelet aggregation.

Evaluations have also shown that moderate use of ibuprofen does not lead to a clinically relevant risk of bleeding. It should be noted that these effects do not apply to patients with VWE. No data are available on this, although low-dose ibuprofen is used in practice without bleeding complications [174, 175].

For patients, selective COX-2 inhibitors (such as **Celecoxib®**) are available as alternatives, particularly in cases of irritation due to degenerative joint disease (activated arthrosis), rheumatoid arthritis, and ankylosing spondylitis (Bechterew's disease).

Overall, painkillers should be used in the lowest effective dose and for the shortest possible duration, and should be coordinated with the treating physicians whenever possible [176, 177].

6.8 Elderly patients, comorbidities, co-medication

6.8.1 Basics/Introduction

Patients with VWE have a life expectancy similar to that of the normal population and therefore may have comorbidities that influence treatment decisions and bleeding risk [178].

In particular, the question arises as to whether patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulants should receive such treatment (see chapter 6.8.4).

It should be noted that VWE does not protect against the occurrence of thrombosis and endothelial dysfunction as risk factors for cardiovascular disease [179]. Additionally, bleeding tendencies change with age (see chapter 5.2 Diagnosis).

6.8.2 Comorbidities

In principle, patients may have various comorbidities that affect therapy. The diseases listed below require evaluation to determine if prophylaxis is appropriate.

6.8.3 Joint damage (hemarthrosis and arthropathy)

The main reason why patients with VWD start prophylaxis is joint bleeding (40%) [180].

Patients with phenotypically severe VWD have an increased risk of developing arthropathy, especially after joint bleeding. Joint bleeding is observed in approximately 50% of patients with VWD type 3 and in 5-10% of patients with moderate to severe forms of VWD type 1 and type 2. However, comprehensive data on the prevalence and severity of arthropathy are limited [181, 182].

Retrospective analyses suggest that joint bleeding has a negative impact on joint health and health-related quality of life [183]. A Dutch case-control study investigated the incidence and severity of arthropathy in VWD patients and social participation in VWD patients with and without clinically manifest joint bleeding.

The Hemophilia Joint Health Score (HJHS) was developed and validated to assess arthropathy in children [184].

It is also used in everyday clinical practice to assess joints in patients with von Willebrand disease.

It was found that 40% of VWE patients with a documented history of treated joint bleeding showed arthropathy (HJHS ≥10) on physical examination, while 25% exhibited radiological signs of arthropathy in the ankles, knees, or elbows (PS >3). In contrast, the prevalence of arthropathy in VWD patients without a history of joint bleeding was significantly lower—10% with HJHS ≥10 and 4% with PS >3.

Arthropathy was strongly associated with clinically significant joint pain, reduced social participation, and greater functional limitations. Predictors for the development of arthropathy ly in VWD patients were a factor VIII (FVIII) level of <10 IU/dl and the cumulative number of joint bleeds. Arthropathy in these patients correlates with significant functional limitations, reduced social participation, and frequent joint pain, underscoring the long-term effects of joint bleeding in VWD [185].

We therefore recommend routine screening (HJHS, ultrasound, or radiological) in patients with residual activity below 30 IU/dl regardless of severity, as well as in all patients with known joint pain of any kind [186, 187].

Prophylaxis should be considered in patients who have experienced joint bleeding (see chapter 4.1.1 and chapter 6.3.10).

Further studies are warranted.

6.8.4 Cardiovascular and thrombotic disease and atrial fibrillation

No comparative studies have been conducted on the circumstances under which anticoagulants can be administered without significantly increasing the risk of bleeding. A review of the literature revealed two case series reported in three sources [188- 190].

Patients should be informed about the risks and benefits of antiplatelet agents or anticoagulants to enable shared decision-making.

In patients with a severe bleeding phenotype (e.g., severe VWD type 1, type 2, or type 3), prophylaxis with VWF concentrate may be necessary to prevent bleeding during antiplatelet or anticoagulant therapy.

DDAVP therapy is generally contraindicated in individuals with cardiovascular disease (e.g., coronary artery disease, cerebrovascular disease, and peripheral vascular disease) and/or an increased risk of thrombosis.

Among the 26 patients with VWE in the series (see above literature), there was 1 serious bleeding event. Serious adverse events, hospitalizations, transfusions, health-related quality of life, or heavy menstrual bleeding were not reported.

The ISTH/WFH guidelines committee reported on their experience with 65 patients with VWD who were recommended antiplatelet or anticoagulant therapy for cardiovascular disease. In the 56 patients who received this therapy and in the 9 patients who did not receive therapy despite it being recommended, the mean mortality, thrombotic events, serious adverse events, hospitalizations, and bleeding were low in both groups, and most patients had an acceptable health-related quality of life according to their physicians.

In summary, based on the evidence, both antiplatelet agents and anticoagulants reduce the risk of thromboembolic complications.

Due to the significant potential benefits of these therapies, which have been demonstrated in large cardiovascular disease studies involving patients without VTE, these therapies should not be withheld from patients with VTE.

In line with the WFH/ISTH guidelines, measures should be considered that limit the duration of the required antiplatelet or anticoagulant therapy (e.g., non-drug-coated stents). In patients with a severe bleeding phenotype, prophylaxis with VWF concentrate or the administration of tranexamic acid may be necessary to minimize bleeding. An individual treatment plan (e.g., administration of VWF concentrate for prophylaxis) should be developed.

However, second-generation drug-eluting stents are now available that are compatible with patients at risk of bleeding due to the short one-month dual antiplatelet therapy; they have therefore recently been proposed as the first choice for hemophilia patients. This approach also appears to be appropriate for patients with VWD [191].

An interdisciplinary discussion with cardiologists is important [192].

In addition to questions about long-term anticoagulation due to atrial fibrillation or similar conditions, treatment recommendations exist for coronary angiography and catheter ablation. These treatments appear safe and feasible after substitution with VW factor in patients with VWE and HA. The recommended dosage is similar to that used for minor surgical procedures. These recommendations are similar to those for patients with hemophilia [193, 194].

6.9 Quality of life and fatigue/depression

Several studies have shown that depression and anxiety do occur in patients with VWD. It has also been shown that a lack of social support and the frequency of bleeding are important factors associated with depression and anxiety in these cohorts [195- 197].

For a long time, the mental health of von Willebrand disease (VWD) patients was overlooked. Screening for mental health is also useful in patients with VWD for a comprehensive clinical assessment [198].

There are no data on fatigue.

6.10 Sports

Currently, there are no prospective studies. A questionnaire evaluation and registry data generally showed that patients with von Willebrand disease participate in sports and sometimes have bleeding problems. No recommendations for action can be derived from this data [199].

The recommendations, which can be found online, are primariy based on those for hemophilia. In summary, sports with a high risk of injury and therefore an increased risk of bleeding should be avoided. However, this does not do justice to the complexity of VWD and patients with reduced von Willebrand factor in the gray area, but also with existing bleeding. A universal recommendation cannot be made for all types of VWE.

6.11 Alternative and complementary treatment methods

To our knowledge, there are no studies and no sufficient data that explicitly examine complementary medicine drugs in patients with VWE.

Agnus castus is a complementary medicine preparation that is frequently used in everyday practice. t is valued for its use in treating premenstrual syndrome. In various studies, it appears to have a positive effect and no side effects [200, 201].

The genus Arnica L. (Asteraceae) comprises perennial herbs that are native to the northern hemisphere. It has various biological activities such as antioxidant, anti-inflammatory, antibacterial, antifungal, and antitumor effects. Arnica formulations are mainly used for pain management. A systematic review summarized studies that looked at the use of arnica products for pain and inflammation symptoms caused by sports injuries and surgical procedures [202]. It appears to have positive effects on wound healing and pain.

Cold compresses also have a positive effect through vasoconstriction. However, they are not effective enough in cases of severe bleeding or for deeper-lying vesselsThe application of cold is supportive [203].

6.12 Innovative forms of therapy that are not approved

Newer therapeutic approaches for the treatment of von Willebrand disease (VWD) are producing some innovative drugs and treatment options [55].

6.12.1 Emicizumab

Emicizumab is a bispecific antibody developed for the treatment of hemophilia A with and without inhibitors. Emicizumab forms a bridge between activated factors IX and X, thereby replacing the function of FVIII. Emicizumab is not approved for VWE.

Off-label use of emicizumab has been successfully used in patients with VWD, particularly type 3 [204]. The drug is therefore a good alternative, especially for patients with inhibitors. Case reports show a significant improvement in hemostasis in patients who did not respond to other treatments. Subcutaneous administration also makes emicizumab more attractive for patients who prefer a less complex treatment for prophylaxis [205].

In contrast to intravenous prophylaxis, which involves several infusions of clotting factor concentrate per week, emicizumab is administered subcutaneously (SC) weekly, biweekly, or monthly, which significantly reduces the effort required [204][206- 208].

These case reports include the successful treatment of hemarthrosis in men and women and a significant improvement in hemoglobin monovolume concentration in an 11-year-old girl with VWE type 3, anemia, and hypovolemic shock. She had not responded to hormone therapy, cryoprecipitate, or tranexamic acid. After the addition of low-dose emicizumab (3 mg/kg sc, once a month), no further menorrhagia or bleeding occurred [208]. In addition, recent in vitro studies show an improvement in thrombus formation under shear stress in all types of VWD, which may extend its clinical use beyond VWD type 3 [209].

6.12.2 Gene therapy

Preclinical gene transfer studies for von Willebrand factor (VWF) already exist. However, there are no ongoing clinical studies specifically focused on VWD [210- 215].

6.12.3 Other drugs VGA039 and BT200 (rondoraptivon pegol)

Studies are currently being conducted in various phases on VGA039 (a monoclonal antibody that targets human protein S and inhibits its cofactor activity for tissue factor inhibitor α and activated protein C) and BT200 (rondoraptivon pegol). BT200 is a pegylated aptamer that binds specifically to the A1 domain of VWF and slows down the clearance of VWF and FVIII, thereby increasing their concentrations in the blood [216- 220].

For further information, see chapter 10 Clinical Studies and Approval Status (German Version).

7 Rehabilitation

7.1 Social law (applies only to the Federal Republic of Germany)

The assessment of the degree of disability (GdB) in accordance with Social Code Nine (SGB IX – Rehabilitation and Participation of Disabled Persons) is based on the Medical Care Principles (VMG) Part B. There are no specific guidelines for patients with von Willebrand disease. This falls under category 16.10, which is as follows: "Hemophilia; hemophilia and corresponding plasma bleeding disorders (depending on bleeding tendency)."

According to No. 16.10 of the VMG, the following degrees of disability are provided for, see Table 7.

Table 7: Degrees of disability

Bleeding tendency	GdB
No significant effects	10
Moderate effects	20
Severe effects (severe bleeding even with minor trauma)	50
Constant clinically manifest bleeding tendency (spontaneous bleeding, risk of life-threatening bleeding)	80

According to case law, only the actual tendency to bleed is decisive for the assessment, not the abstract possibility that severe bleeding could occur in the future.

7.2 Financial limits

The so-called cost limit sets a maximum annual value for co-payments. Above this value, co-payments are waived. For chronically ill patients, there is a low cost limit of 1% of family income.

7.3 Special considerations for children who need factor administration

Educators are not obliged to administer coagulation factors intravenously. There is no specific law governing the refusal of intravenous medication administration by educators, but the general legal structure (labor law, professional law, duty of supervision) clearly defines that educators are not obliged to do so. If the child is too young to administer the medication themselves,

it is advisable to store an emergency dose at the kindergarten/school so that relatives or the emergency doctor can administer the factor in an emergency.

In childcare facilities and schools, all children are subject to the duty of supervision by staff due to their minority (§ 832 BGB). Children with VWE are neither an exception nor are special requirements important here.

8 Follow-up

According to expert opinion, patients are advised to visit the treating center regularly. During the visit, open questions such as pain medication, severity of heavy menstrual bleeding, epistaxis, treatment satisfaction, trough levels, etc. can be clarified. In addition, the indication for prophylaxis should always be evaluated. Due to the known fluctuations in Von Willebrand parameters, it is important that a check-up takes place before a planned surgical procedure, if possible. For elective procedures, this should ideally take place 2-3 weeks in advance.

However, women in the postpartum period should also be examined, especially in cases of heavy bleeding. The common practice in Germany, Austria, and Switzerland is for patients with mild cases to be examined once a year, and those with severe cases every 3-6 months.

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10 Active clinical trials

- Efficacy, PK, Immunogenicity and Safety of Wilate in Severe Von Willebrand Disease (VWE) Patients <6 Years of Age ClinicalTrials.gov ID NCT04953884, EudraCT Number: 2020-004344-28
- A Study of Recombinant Von Willebrand Factor (rVWF) With or Without ADVATE in Children With Severe Von Willebrand Disease (VWE), NCT02932618, EudraCT Number: 2016-001477-33
- A Phase 2a Multiple Dose “Basket Design” Study Of The Safety, Tolerability, And Pharmacologic Activity Of BT200 In Patients With Hereditary Bleeding Disorders, EudraCT Number: 2020-003807-32
- Efficacy and Safety of BT200 (rondoraptivon pegol) in Patients with Type 2B von Willebrand disease, EudraCT Number: 2023-000044-34
- An Open-label, Multi-center Post-marketing Study to Assess the Efficacy and Safety of Voncento® in Subjects with Von Willebrand Disease, EudraCT Number: 2013-003305-25
- VIP Study (Phase 4, wilate®, national USA, NCT04146376)
  Title: Von Willebrand Factor in Pregnancy (VIP) Study

14 Links

- **Professional Association of German Hemostasiologists**
  https://bddh.org/
  Contact info@bddh.org
- **The von Willebrand Network**
  https://www.netzwerk-von-willebrand.de
- **German Blood Aid**
  https://deutschebluthilfe.com/
  Contact: mail@deutschebluthilfe.com

- **German Hemophilia Society DHG**
  www.dhg.de
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- **Interest Group for Hemophiliacs IGH**
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16 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.