Treatment of von Willebrand Disease in Spain Consensus Document
Introduction

Von Willebrand disease (vWD) is the most common congenital bleeding diathesis caused by a qualitative or quantitative abnormality of von Willebrand factor (vWF) of autosomal dominant or, less frequently, recessive inheritance. There is also an acquired form associated with multiple clinical situations (von Willebrand syndrome). Since vWF stabilises factor VIII (FVIII) in blood circulation, vWF abnormalities in vWD cause bleeding by preventing platelet adhesion and blood coagulation. The various types of vWD are a heterogeneous group with a diversity of phenotypes, which vary in severity —mild forms being the most common. The revised classification of vWD, which has been internationally accepted, aims to reflect the differences in the pathophysiology of the different phenotypes of vWD (Table 1). A correct diagnosis is important for optimal management, because treatment decisions often depend on the specific type of vWD.

In a recent epidemiological study conducted in Spain by surveying patients referred to different hospitals, it was estimated that the prevalence of patients with evident vWD is approximately 122 patients per million. Distribution by type is as follows: 74% of type 1, 21% of type 2 (11% of type 2A, 4% of type 2B, 4% of type 2M and 2% of type 2N) and 5% of type 3. Despite the existence of different treatment guidelines for vWD, controversial issues of concern for both patients and physicians remain. This being the principal reason for developing consensus recommendations on the treatment of vWD in Spain. We have analysed the data available, highlighting the most relevant data, and proposed criteria for dubious situations. Haematologists working at Spanish hospitals with vast experience in this field have participated in the drafting of this document. The final document has also been presented and endorsed by the Spanish Society of Thrombosis and Haemostasis (SETH).

Table 1. Revised updated classification of vWD

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of vWF</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative vWF defect</td>
</tr>
<tr>
<td>2A</td>
<td>Decreased vWF-dependent platelet adhesion with selective deficiency of HMWMs</td>
</tr>
<tr>
<td>2B</td>
<td>Increased affinity for platelet GPIb</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased vWF-dependent platelet adhesion without selective deficiency of HMWMs</td>
</tr>
<tr>
<td>2N</td>
<td>Markedly decreased binding affinity for FVIII</td>
</tr>
</tbody>
</table>

vWD: von Willebrand Disease; vWF: von Willebrand Factor; HMWMs: High Molecular Weight Multimers. From Sadler et al. [1].

Optimal treatment requires: a) correct diagnosis, including determining the type of vWD, b) knowledge of previous haemorrhagic history, c) assessment of values of vWF and FVIII, and d) assessment of the severity of the bleeding episode to estimate the type, dose and duration of the treatment to apply. These guidelines are also recommended for patients without a definitive diagnosis of vWF with slightly decreased (30-50 IU/dL) ristocetin cofactor (vWF:RCo), who may benefit from prophylaxis or treatment under certain clinical situations.

The goal of treatment is to correct the deficiencies of vWF and FVIII and is aimed at ceasing or preventing bleeding in surgical procedures.

The following must be taken into account: a) the decrease in FVIII is secondary to a defect of vWF; b) restoration of normal levels of FVIII is usually accompanied by the control of non-mucosal and soft tissue bleeding after surgery, even in the absence of primary haemostasis correction; c) the restoration of primary haemostasis to control severe mucosal
bleeding is necessary; and d) vWF replacement therapy restores plasma compartment, but not platelet compartment. Therapy should be primarily planned through drug administration and treatment of bleeding sites. When these are not effective or sufficient, concentrated haemostatic replacement therapy should be used instead.

Persistence of bleeding despite adequate correction of vWF and FVIII requires an assessment of the patient to rule out other causes of bleeding, including anatomical lesions or surgical problems.

In all patients with congenital bleeding diathesis, it is recommended: a) to maintain adequate dental hygiene; b) to facilitate local haemostasis (compression suture after tooth extraction, etc.) to prevent and restrain minor bleeding during surgical procedures; c) to prevent and warn of the risk posed by the use of drugs that affect platelet function, such as antiplatelet and antiinflammatory drugs (except COX-2), in case of fever or pain, paracetamol or metamizol can be used; d) to avoid strenuous exercise and intramuscular injections, and e) to administer vaccines subcutaneously. An immunisation programme against hepatitis viruses A and B must be administered, proving that adequate levels of immunity are attained. Although no consensus exists, it is necessary to periodically check the levels of antibodies to such viruses, except for patients subjected to treatments that induce a state of immunodeficiency (for example, anti-CD20).

**Pharmacological resources**

**Desmopressin acetate**

Desmopressin acetate (DDAVP) is a synthetic derivative of vasopressin. It releases FVIII and vWF from its storage place, raising circulating plasma levels, without significant modification of other clotting factors. In parallel, it induces releasing of tissue plasminogen and urokinase plasminogen activators. Typically, it induces elevated levels of FVIII and vWF 3-5 times above baseline levels. Its effectiveness varies depending on the subtype of vWD. Approximately 75-80% of patients respond to DDAVP. In Spain, it is marketed for intravenous use (Minurin®, Ferring) or high concentration –150 g– intranasal spray (Octostim® nasal spray, Ferring).

It is advisable to evaluate the response to DDAVP in baseline conditions, preferably in patients with activity levels above 10 IU/dL of vWF:RCo and above 20 IU/dL of FVIII:C. It is necessary to analyse the response by measuring levels of vWF preferably at baseline, at the time of administration, 2 hours later and, if possible, 4 hours after administration. In order to evaluate an exacerbated clearance of vWF, a further measuring can be performed 30 minutes after administration. Even though the response is predictably poor in patients with lower levels, it may be useful to conduct this assessment.

**Dosages and methods of administration**

The intravenous route is most often used at doses of 0.3 mg/kg in 50-100 cc of saline in 30 min. infusions. Maximum response of FVIII and vWF is reached one hour after infusion and levels of FVIII increase between 3 and 5 times, while vWF increase is lower. It is also effective intranasally; 150 μg of desmopressin acetate is delivered per actuation. 300 μg is administered (1 spray actuation in each nostril in patients weighing ≥ 10 kg) and 150 μg (1 spray actuation in one nostril) in children. For surgical procedures, desmopressin used intravenously (IV) is the recommended administration method. In the latter case, 15-30 min. slow administration by IV infusion of 0.3 μg/kg of body weight in adults and children over 10 kg diluted in 50-100 mL of physiological saline is recommended.

DDAVP response is transient, about 4-6 hours, with large individual variations. DDAVP administration may be repeated every 24 hours, but may initially be administered at 12 hours.

**Tachyphylaxis**

Tachyphylaxis is the progressive reduction of the response after repeated doses of DDAVP, which can be inconvenient in long-term use of the drug. This phenomenon is increased when administered every 12 hours.

**Adverse effects**

No relevant adverse effects have been described. It causes a transient facial and conjunctival flushing and mild haemodynamic changes (reduction in systolic/diastolic pressure and a slight pulse increase). Hyponatraemia, fluid retention, and even water intoxication, especially in children and postoperative patients receiving great amounts of hypotonic fluids, have been reported.

**Precautions**

When multiple doses are needed, it is advisable to restrict fluids, monitor urine output and monitor serum sodium levels in on-going treatment. Isolated cases of myocardial infarction, stroke and even coma have been reported in patients treated with DDAVP. Use of DDAVP in patients at high risk of cardiovascular or cerebrovascular disease, especially in the elderly, is not recommended. DDAVP should be administered with caution in patients with a history of epilepsy. Use of DDAVP in children under 2-3 years is not recommended.

- **Pregnancy:** Studies on reproduction in rats and rabbits at DDAVP doses higher than 100 times the human dose have shown no evidence of harm to the foetus. One researcher described 8 cases of malformations in children of mothers with diabetes insipidus that received
DDAVP during pregnancy. However, published reports of more than 120 similar cases showed that women treated with DDAVP during pregnancy gave birth to normal children. Moreover, a review of a large data set identified 29 children who were exposed to DDAVP throughout pregnancy. No increased rate of malformations in the children was observed. In fact, it has successfully and safely been used to prevent bleeding in early pregnancy\(^{(12)}\). However, this clinical experience is not sufficient to recommend its use in pregnancy. Doctors should assess the risk versus the benefit of treatment in each particular case.

**Contraindications**

DDAVP should not be used in cases of psychogenic and common polydipsia, heart failure and other conditions requiring treatment with diuretics, unstable angina and decompensated heart failure, type 2B vWD and in type 1 vWD when FVIII:C is below 5% or in case of hypersensitivity to hemihydrate chlorobutanol (a preservative).

**Interaction with other medicinal products and other forms of interaction**

Concomitant administration of indomethacin can increase the magnitude but not the duration of response to DDAVP.

Some substances, including tricyclic antidepressants, chlorpromazine, carbamazepine and clofibrate, are known to cause endogenous release of antidiuretic hormone, which may potentiate the antidiuretic effect, increasing the risk of water retention. Glibenclamide, on the contrary, decreases the antidiuretic activity of DDAVP. Although the vasopressor activity of DDAVP is minimal compared to antidiuretic activity, it should be taken into account if other vasopressor drugs are administered at the same time.

**Indications**

DDAVP is the treatment of choice in most vWD type 1 patients, except in patients lacking platelet vWF or the Vicenza type, which has an initial response but also a marked clearance in plasma. In types 2A and 2M, the response is poor or absent, although it may be useful in some cases. In type 2B, although it may aggravate thrombocytopenia, some cases of successful treatment have been reported; in general, it is not recommended for this subtype. In type 2N, response depends on the type of mutation. In the homozygous form by R816W mutation, it is often ineffective. In some mutations, such as the R854Q mutation, whose affinity disorder to FVIII is milder, it may be clinically useful.

**Criteria of response to desmopressin acetate in von Willebrand disease**

- **Full response**: Increase of values of vWF:RCo and FVIII to a level of 50 IU/dL or higher.
- **Partial response**: Increase of vWF:RCo or FVIII lower than 50 IU/dL but at least 3 times above baseline values.
- **No response**: When the above criteria are not met. Patients with values of vWF:RCo and/or FVIII of about 50 IU/dL or higher at baseline are considered as full responders if they reach a level of 100 IU/dL or higher in both parameters\(^{(11)}\).

**Antifibrinolytic agents**

They are mainly useful as adjuvants\(^{(4-6)}\).

**Synthetic antifibrinolytic agents**

They are especially useful in bleeding from mucous membranes: epistaxis, gingival bleeding, menorrhagia and other. The most commonly used are tranexamic acid and epsilon-aminocaproic acid (EACA).

**Action mechanism**: They interfere with the binding of plasminogen to fibrin. Tranexamic acid is 10 times more potent and has a longer half life than EACA.

**Tranexamic acid and epsilon-aminocaproic acid**

In Spain, tranexamic acid and EACA are marketed under the names Amchafibrin® and Caproamin Fides® (Rotapharm S.L., España). They are often used in mucocutaneous bleeding before and after dental surgery and menorrhagia. Used in combination with DDAVP, they may be useful in mucosal bleeding.

**Dosages and methods of administration**: Orally or intravenously, tranexamic acid is used for 2 to 10 days, depending on haemorrhagic symptoms. Intravenously: 0.5-1 g (1-2 vials), 2-3 times daily\(^{(10)}\). Tranexamic acid (in injectable solution) must be administered directly into the vein slowly (at an infusion rate not exceeding 1 mL/minute). EACA dosage for adults is 4-5 g initially and then 1 g per hour intravenously or 4-6 g every 4-6 hours orally.

- **Children and adolescents**: The dosage of tranexamic acid for children is about 10 mg/kg/8 hours. Oral dosage of EACA is 50-60 mg/kg and should not exceed 24 g/day. The average recommended duration is 7 to 10 days during haemorrhagic symptoms\(^{(5)}\). In mucosal bleeding, it is very helpful to rinse with these agents.
**Contraindications:** In haematuria, as these agents facilitate the formation of fibrin clots in the lumen of the ureters and may cause urinary tract obstruction. They should be used cautiously in patients with thrombotic risk factors. They should not be used if there is significant renal impairment or the patient has a history of seizures. Antifibrinolytic agents can be found in maternal milk at a concentration 100 times lower than that found in blood. Caution in their use is therefore recommended during breastfeeding.

**Precautions:** Tranexamic acid should be used with caution in patients with renal insufficiency, as there is a risk of accumulation.

- **Pregnancy:** Data on the use of tranexamic acid in pregnant women are insufficient. As a result, although animal studies show no evidence of teratogenic effects, caution should be maintained regularly as with the use of other drugs during pregnancy.

**Adverse effects:** Antifibrinolytic agents are usually well tolerated, with the exception of some gastrointestinal toxicity at high doses and discomfort with hypotension, with or without loss of consciousness (usually after an IV injection at a fast rate and exceptionally after oral administration).

**Hormonal treatment**

Oral contraceptives are often used; a risk-benefit assessment should always be done. They reduce endometrial proliferation and that is why they may be useful in menorrhagia. Although they discreetly increase circulating levels of vWF, this might not be the only element responsible for its haemostatic function, although their mechanism is unknown so far. They are useful in the treatment of menorrhagia in mild to moderate vWD. Oral contraceptives should be prescribed under the supervision of a specialist in obstetrics/gynaecology.

**Haemostatic factor concentrates**

Treatment of bleeding through replacement of the deficient protein is a widely used therapeutic modality. Administration of fresh frozen plasma (FFP), except in some situations, has been abandoned because of its inability to achieve high and sustained plasma levels without causing volume overload. Plasma vWF concentrates are the treatment of choice when DDAVP is not effective or contraindicated and they are effective in all subtypes of vWD.

**Cryoprecipitate**

It was used when vWF concentrates were not available. Its use is not currently recommended in Spain.

**Von Willebrand factor and factor VIII concentrates available in Spain**

Plasma or recombinant purified FVIII concentrates do not contain vWF and are, therefore, not useful as the sole treatment of vWD. There are various concentrates used in the treatment of vWD in other countries. There are clear differences between the concentrates available, which are marked by the degree of product purity, methods of viral inactivation and the extent of functional preservation of vWF (assessed as the ratio vWF:RCo/vWF:Ag) and the relationship between the binding capacity of vWF to collagen (vWF:CB/vWF:Ag) and multimeric analysis of vWF content. The multimer pattern of vWF in these concentrates shows a significant variability of this protein in relation to the proportion of larger multimers and the degree of proteolysis, shown by the relative proportion of satellite bands of each multimer (Figure 1).

The functional state of preservation of vWF is considered to be related to the degree of its clinical efficacy. Their ratio of vWF to FVIII is also important; this is measured as the vWF/FVIII:C ratio. In 1993, Barrowcliffe introduced a classification of concentrates that were available at the time according to the specific activity of FVIII:C, which was clinically useful for clinical studies, especially in haemophilia.

Since the primary goal of treatment of vWD with these concentrates is to correct vWF deficiency, this classification is considered obsolete. Subsequently, in 2006, Budde proposed a new classification that takes into account vWF parameters.

Haemate-P® (CSL Behring, España) was the first virally inactivated (by pasteurisation) vWF and FVIII concentrate, in clinical use for over 25 years in the treatment of haemorrhagic diseases. Given its clinical efficacy, safety and functional preservation of vWF, it has been considered as the benchmark of these concentrates.

**Choosing the type of concentrate**

Choosing the best therapeutic option for an individual patient and the correct dosage requires: 1) knowing the characteristics, clinical efficacy, safety and concentration of each preparation, 2) establishing the minimum haemostatic level needed to treat each clinical situation, 3) evaluating the pharmacokinetics of the infused factor in an individual patient, and 4) choosing the most suitable mode of administration. A rational choice is based on the degree of safety and efficacy of each product, its availability and its cost-effectiveness in the short and long term.

Haemate-P® was the first concentrate registered in Spain for use in the treatment of vWD. In 2011, two more vWF and FVIII concentrates, Wilate® (Octapharma S.A.) and Fanhdi® (Instituto Grifols), were registered. Table 2 lists the characteristics of the three concentrates. FVIII and vWF content of the three concentrates is shown.
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in their vials. According to the data available about these two latter products and according to the new proposed reclassification, both fall into the high purity category. However, their vWF/FVIII ratios are different.

The measures taken to inactivate vWF and FVIII concentrates are effective for lipid-containing viruses such as human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses, and protein-enveloped viruses, such as hepatitis A virus.

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

**Therapeutic indications:** vWD. Treatment and prophylaxis of bleeding or bleeding in surgery in patients with vWD when treatment with DDAVP is ineffective or contraindicated. There is currently a single recombinant vWF product, which is being tested in clinical trials.

**Pharmacovigilance:** Patients should keep a record of each dose of vWF/FVIII concentrate and the name and product lot number in order to keep track of the batches used for pharmacovigilance purposes and to relate them with any side effects related to their employment.

**Von Willebrand factor pharmacokinetics and dosage: new classification**

In vWD, low levels of FVIII are secondary to deficiency of vWF, as vWF stabilises FVIII and, in its absence, FVIII half-life is shorter. Therefore, this should be taken into account.

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**Table 2. Characteristics of vWF/FVIII concentrates that are available in Spain.**

Characteristics of high-purity concentrate of vWF (Wilfactin) are also included* for comparison**

<table>
<thead>
<tr>
<th>Product/Company</th>
<th>Fractionation</th>
<th>Viral inactivation</th>
<th>SA</th>
<th>vWF:RCo/vWF:Ag (ratio)</th>
<th>vWF:FVIII (ratio)</th>
<th>vWF:FVIII (ratio)</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemate-P/CSL-Behring</td>
<td>Multiple precipitation (glycine/NaCl)</td>
<td>Pasteurisation</td>
<td>75[a]</td>
<td>0.96</td>
<td>(2.5-2.9)</td>
<td>2.2-2.6</td>
<td>Y</td>
</tr>
<tr>
<td>Fanndi®/Grifols</td>
<td>Heparin affinity chromatography</td>
<td>SD + dry heat (72 h at 80°C)</td>
<td>40[b]</td>
<td>0.83</td>
<td>(1.29-1.6)</td>
<td>1.48</td>
<td>Y</td>
</tr>
<tr>
<td>Wilate/Octapharma</td>
<td>Precipitation, ion exchange chromatography and size exclusion</td>
<td>TNBP/Triton x 100 and dry heat 100°C, 120 min., with controlled residual moisture</td>
<td>&gt;100[a]</td>
<td>≥53[b]</td>
<td>≥60[b]</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Wilfactin® (LFB)</td>
<td>Ion exchange and affinity chromatography</td>
<td>SD + NF + dry heat</td>
<td>111 ± 11[c]</td>
<td>1.05</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>Y</td>
</tr>
</tbody>
</table>

[a] IU of vWF/mg; [b] IU of FVIII/mg of protein, prior to the addition of albumin; [c] IU vWF:RCo/mg protein. SA: Specific Activity; SD: Solvent/Detergent; NF: Nanofiltration.

* Wilfactin: High purity vWF included for comparison reasons (not registered in Spain). ** Adapted from Batlle et al. [9].
Table 3. Pharmacokinetics of Haemate-P and Wilate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All vWD types</th>
<th>vWD type 1</th>
<th>vWD type 2A</th>
<th>vWD type 2M</th>
<th>vWD type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery (%/UI/kg)</td>
<td>29</td>
<td>1.9</td>
<td>1.6</td>
<td>2.5</td>
<td>10</td>
</tr>
<tr>
<td>AUC (0-inf) (h+%): Wilate</td>
<td>23</td>
<td>2341</td>
<td>1695</td>
<td>3165</td>
<td>10</td>
</tr>
<tr>
<td>Half life (h): Wilate</td>
<td>29</td>
<td>15.6</td>
<td>9.0</td>
<td>28.4</td>
<td>10</td>
</tr>
<tr>
<td>MRT (h): Wilate</td>
<td>29</td>
<td>19.7</td>
<td>11.9</td>
<td>28.3</td>
<td>10</td>
</tr>
<tr>
<td>Clearance (ml/h/kg): Wilate</td>
<td>29</td>
<td>3.26</td>
<td>2.29</td>
<td>5.21</td>
<td>10</td>
</tr>
</tbody>
</table>

Also, the basal ratio between the levels of FVIII and vWF is variable and depends on the type of vWD. Thus, in vWD types where there is a quantitative deficiency, there is a correlation between the levels of both factors, while in vWD qualitative types, levels are more discrepant. In vWD type 2N, the vWF level is higher than that of FVIII whereas, in the other types, some parameters of vWF are generally lower than those of FVIII. After the infusion of vWF and FVIII concentrate, there is an immediate increase of vWF, with a half life of 8-12 hours, and of FVIII, which, after repeated administration, may be accompanied by a disproportionate elevation and may remain elevated for 48 hours after infusion, due to the release of endogenous FVIII. They induce a good postoperative haemostasis.

Pharmacokinetic studies are useful to properly administer replacement therapy as the optimal dose and duration, especially for surgical prophylaxis, have not fully been established in clinical trials. Most guidelines recommend replacement therapy of FVIII in IU or in vWF per kg of body weight; however, since concentrations of FVIII and vWF in available preparations are not equivalent, calculating the dose in relation to vWF units is advised. It is important to know their ratio in concentrates to optimise efficiency and reduce thrombotic risk.

Pharmacokinetic studies are difficult to evaluate because of the complexity of the vWF molecule and because vWF:RCo and vWF:Ag may not represent their biological effectiveness.

On the other hand, some authors note that in previous studies, clinical efficacy has been demonstrated even without obtaining complete multimeric normalisation of vWF or complete correction of bleeding time, so these latter parameters are of limited value. Two recently published articles argue that the determination of vWF:CB is very sensitive to the presence of high molecular weight multimers, so that measurement of this parameter—as well as the measurement of the vWF:RCo/vWF:Ag and vWF:CB/vWF:Ag ratios—might represent an advance in pharmacokinetic studies(19,20).

Recovery and half-life of vWF and FVIII are variable and depend on the type of disease and the concentrate used. The main pharmacokinetic data for vWF and FVIII concentrates are shown in Tables 3 and 4. No significant differences were observed regarding Haemate-P clinical response between the different types of disease, although it was observed to be less responsive to levels of vWF:RCo in type 3 vWD. This smaller increase might entail the risk of not reaching adequate haemostatic levels when using preparations with a similar ratio of vWF:FVIII and dosage is calculated in units of FVIII instead of units of vWF (Figure 2)(21). Regarding Fandhi, the double half-life of VIII:C compared to vWF:RCo is worth noting(22). Because of this longer half-life, when administered for a long time, levels of VIII:C should be monitored to prevent sustained and excessive VIII:C plasma levels, which can increase the risk of thrombotic events, especially in patients with known clinical or laboratory risk factors.

If excessive VIII:C plasma levels are observed, dose reduction, lengthening the dosage interval or using a vWF product with a low level of FVIII should be considered.

A recent article(23) has questioned the need for a pharmacokinetic study before surgery. A multicenter prospective study included 41 patients who underwent a pharmacokinetic study before surgery after administration of Haemate-P at doses of 60 IU/kg. Recoveries of 2.4...
IU/dL of vWF:RCo, 2.3 IU/dL of vWF:Ag and 2.7 IU/dL of FVIII:C per administered IU/kg were observed; these pharmacokinetic data are consistent with previous results from other studies with Haemate-P. 91.4% of patients achieved good haemostasis, but there was great variability in the individual analysis when comparing the results of the pharmacokinetic study with those from the postoperative period. Because of this large variability, the authors question the need for pharmacokinetic studies before surgery, recommending frequent monitoring of FVIII and vWF:RCo in the postoperative period.

Proposal for a new classification of von Willebrand factor and factor VIII concentrates

One of these concentrates, Wilfactin® (available in other countries, but not marketed in Spain) (Table 4) essentially consists of vWF with a minimum amount of FVIII. Wilfactin® has different pharmacokinetics, as it induces an immediate increase of vWF, while the increase in FVIII is slow and progressive, with a synthesis of $5.8 \pm 1.0$ IU x dL$^{-1} \times h^{-1}$ and a half life of $15.8 \pm 2.4$ hours$^{(24)}$.

This increase occurs at the expense of endogenous FVIII, with a peak at 12 hours, or even at 24. Therefore, normalising FVIII takes about 12 hours and, in cases of emergency, administering FVIII concentrates for immediate correction is also required.

This last differential fact is not reflected in the new classification proposed by Budde$^{(14)}$, which, therefore, seems incomplete since it does not make distinctions between concentrates with and without FVIII and their pharmacokinetics. Therefore, we believe that this new classification should be modified as proposed in Table 5.

**Dosage:** Should be calculated according to the following formula:

$$\text{Dosage} = \text{Calculation formula}$$

### Table 4. Pharmacokinetics of Fandhi and Wilfactin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All vWD Types</th>
<th>vWD Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life (h)</td>
<td>11.7 ± 7.1</td>
<td>12.4 ± 1.8</td>
</tr>
<tr>
<td>AUC (IU/mL)</td>
<td>1.636 ± 871</td>
<td>3.444 ± 654</td>
</tr>
<tr>
<td>Recovery (%)</td>
<td>78 ± 22</td>
<td>89 ± 13</td>
</tr>
<tr>
<td>Incremental recovery (IU/kg)</td>
<td>1.9 ± 0.5</td>
<td>2.1 ± 0.3</td>
</tr>
</tbody>
</table>

AUC: Area Under the Curve; vWF: von Willebrand Factor; MRT: Mean Residence Time.

Figure 2. Evolution and changes in the mean value (A) vWF:RCo, (B) vWF:Ag and (C) of FVIII:C up to 48 hours after the infusion of vWF and FVIII concentrates (Haemate-P). Error bars indicate standard deviation. The curves were constructed from the best fit of exponential decay of such activities weighted with the inverse of the variance. Adapted from Lethagen et al.$^{(21)}$. 

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Table 4. Pharmacokinetics of Fandhi and Wilfactin

<table>
<thead>
<tr>
<th>Recovery (IU/dL/IU/kg)</th>
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<th>Type 2</th>
<th>Type 3</th>
</tr>
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<tbody>
<tr>
<td>vWF:RCo</td>
<td>1.9 ± 0.6</td>
<td>2.5 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>FVIII:C</td>
<td>14.4 ± 10.5</td>
<td>29.5 ± 16</td>
<td></td>
</tr>
<tr>
<td>vWF:RCo</td>
<td>15.29 ± 10.03</td>
<td>36.60 ± 32.73</td>
<td></td>
</tr>
<tr>
<td>FVIII:C</td>
<td>5.6 ± 3.3</td>
<td>1.8 ± 1</td>
<td></td>
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AUC: Area Under the Curve; vWF: von Willebrand Factor; MRT: Mean Residence Time.
Required units = body weight (kg) x desired increase in vWF (% or IU/dL) x 0.5

In children, the dose should be considered 20% greater than that of an adult taking into account the increased plasma volume.

**Continuous infusion:** replacement therapy is usually administered by IV bolus injection.

Continuous infusion is a useful alternative for the treatment of severe bleeding or in case of surgical intervention. Knowing the product stability at room temperature, the plasma clearance and having an infusion pump available are requirements for continuous infusion.

The advantage of this mode of administration is that it prevents peaks and troughs and the control is stricter, since it allows an immediate adjustment of the rate of infusion, which is calculated with the following formula:

\[ \text{Infusion rate} \times \text{IU/kg/h} = \text{clearance} \times \text{mL/kg/h} \times \text{IU/mL target concentration} \]

In the case of using continuous infusion, an IV bolus dose directly (at a rate of 1-5 mL/min.) should first be administered, depending on the tolerance of the patient, followed by continuous infusion. To prevent the possibility of thrombophlebitis and maintain vein permeability, if the hourly infusion rate is very low, connecting the infusion in Y to a saline drip is recommended. Saline drip connection in Y should be in the nearest location to venous access, to prevent dilution of the concentrate before infusion. Alternatively, to prevent phlebitis, low molecular weight heparin may be added to the vWF and FVIII concentrates, to a final concentration of approximately 10 IU ani-Xa/mL, in the final solution to be infused. Since this latter strategy is not in technical file, it must be done through compassionate use. Finally, if a central venous access is available, this can be used for continuous infusion.

The first clinical trial involving a large number of patients treated with continuous infusion was a clinical trial for Haemate-P®. This study included the results of 8 cases treated for surgery and for bleeding. Previous pharmacokinetic studies for 5 patients were available, so the bolus dose and infusion rate was adapted to these previous results; for the other 3, the initial clearance of vWF:RCo was calculated at 3.0 mL/kg/h. The infusion bags were changed every 1-3 days and sodium heparin was added at a dose of 0.4 IU per mL of anti-FXa factor concentrate.

Good haemostatic control was achieved in all patients; vWF:RCo was used to control treatment. Figure 2 shows the values of VvWF:RCo, vWF:Ag and FVIII during the 8-day treatment. It shows that while FVIII levels remain elevated, vWF:RCo levels are kept within limits considered as therapeutic. Note also the decrease in clearance time of the three parameters, as observed in previous studies. The authors believe that levels of vWF:RCo are ideal to assess haemostasis. Thus, continuous infusion is effective and safe and reduces costs by more than 30%.

**Other haemostatic concentrates**

In addition to vWF/FVIII concentrates for the treatment of vWD, two other concentrates can be used in special situations: platelet concentrates and active recombinant FVII concentrate.

**Platelet concentrates**

Platelets contain 10-15% of total blood vWF. In some patients, even after correcting the levels of vWF and FVIII, bleeding does not stop and the closure time of the platelet function analyzer (PFA-100) is still very long. In these cases, usually of type 3 or low platelet vWF, and if the bleeding is severe, transfusion of platelet concentrates at doses of 1 IU/10 kg of body weight or 1 IU of apheresis may be indicated. Note that these concentrates are not inactivated and patients run a potential risk of alloimmunisation.

**Recombinant activated factor VII concentrate**

Recombinant activated factor VII (FVIIIr) concentrate has been used occasionally and effectively in special situations of type 3 vWD with alloantibodies.

**Topical haemostatic drugs**

There are various adjuvants for the treatment of bleeding episodes, mainly in surgical situations. They are effective in different clinical situations, including dentistry and surgery. Fibrin adhesives are haemostatic drugs derived from human plasma for topical application that increase concentrations of fibrinogen and thrombin at the bleeding site. Besides being useful for the control of localised or diffuse bleeding, they promote wound healing by fibroblast proliferation on fibrin plugs. In general, commercial products contain various amounts of

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**Table 5. Classification of vWF concentrates. Proposed modification**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active*</th>
<th>High activity*</th>
<th>vWF with low FVIII content</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF:RCo/vWF:Ag</td>
<td>&lt;70%**</td>
<td>&gt;70%**</td>
<td>&gt;70%**</td>
</tr>
<tr>
<td>HMWM of vWF (band 11 and higher)</td>
<td>&lt;70%**</td>
<td>&gt;70%**</td>
<td>&gt;70%**</td>
</tr>
<tr>
<td>vWF:RCo/vWF:Ag</td>
<td>≤1</td>
<td>&gt;1</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

* Proven consistency between batches guaranteed by the manufacturer; ** Percentage compared to normal human plasma; vWF: von Willebrand Factor; HMWM: High Molecular Weight Multimers.
fibrinogen, fibronectin, factor XIII, plasminogen, thrombin and calcium, and they are subjected to viral inactivation processes.

They have been used in a wide range of surgical procedures to promote haemostasis. Patients with coagulation disorders, with high risk of prolonged or excessive bleeding during or after invasive surgery, can also benefit from the use of fibrin adhesives. Martinowitz et al. reported their use in a total of 356 (orthopedic, dental and general) surgical procedures in 176 patients with some type of congenital or acquired coagulopathy, including patients with vWD. A reduction of blood loss, replacement therapy requirements and hospital stay was found (29,30). In the field of oral surgery for patients with haemorrhagic coagulopathy its use has been most successful. Suwan nuraks et al. published a series of studies on 19 patients with bleeding disorders, including 3 patients with vWD on whom 6 extractions were performed, and in which local haemostasis was obtained by applying fibrin adhesive and antifibrinolytic drugs (31).

Besides the risk of viral transmission, typical of any plasma-derived product, other adverse effects, such as hypotension and anaphylactic reactions to compounds with bovine thrombin and even secondary thromboembolic events after accidental IV injection, have been reported (31-34).

There are also topical collagen sponges used in the treatment of bleeding wounds and new products currently under investigation. Experience with these products for topical use is broad, but its therapeutic effectiveness has not been proven clearly and objectively (4,6,34) and the level of scientific evidence on their effectiveness is limited.

Management of specific bleeding problems

The amount of vWF concentrate required to correct the haemostatic deficiency in vWD depends on the nature of the bleeding or invasive procedure, the vWF:RCo ratio and FVIII baseline levels and the subtype of vWD. Different types of surgery require different target levels of both vWF and FVIII. Table 6 shows the recommended dose of vWF and FVIII concentrates depending on the type of surgery or bleeding complication.

### Odonto-stomatologic treatment

Interventions that include only local anaesthesia do not require treatment with DDAVP or vWF concentrates. However, if nerve block anaesthesia is used (8), DDAVP should be administered—or vWF concentrates if DDAVP is not sufficiently effective—to increase plasma vWF:RCo levels above 50 IU/dL. Oral antifibrinolytic therapy should be started 12 hours before surgery, as well as performing oral rinses with these drugs. In important interventions (e.g. tooth extraction), it may be necessary to maintain the antifibrinolytic treatment for 7-10 days after surgery.

### Bleeding in women

#### Gynaecological disorders

Perception of the magnitude of menstrual bleeding is often difficult (35). Specifically, women underestimate their bleeding coagulopathies when they compare their bleeding to that of other women of their own family who have menorrhagia (36). Menorrhagia is defined as the loss of over 80 mL of blood in each menstrual period (37). The use of pictograms to assess bleeding during menstruation is much more objective and easier for patients; it offers a sensitivity of 86% and a specificity of 89% (38) (Figure 3).

Pictograms of losses in menorrhagia can be delivered to patients for completion and then be assessed at the doctor’s office. Using pictograms for assessing menorrhagia and evaluating therapeutic measures is recommended (7,38).

In patients with menorrhagia, other causes of vaginal bleeding (including endometrial polyps, submucosal fibroids, cervicitis, vaginal or cervical lesions) should be ruled out by gynaecological examination (4,37).

Menorrhagia is an important negative factor in the quality of life of patients of childbearing age with vWD (39). Similarly, the negative effect of menorrhagia in young

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>Dose (IU/kg)** No. of Infusions</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery *</td>
<td>40-60</td>
<td>1 every 24-48 h</td>
</tr>
<tr>
<td>Minor surgery and caesarean</td>
<td>30-60</td>
<td>1 every 24-48 h</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>20-40</td>
<td>Single</td>
</tr>
<tr>
<td>Delivery and epidural anaesthesia</td>
<td>30-40</td>
<td>Single</td>
</tr>
<tr>
<td>Spontaneous or traumatic haemorrhage</td>
<td>20-40</td>
<td>Single</td>
</tr>
</tbody>
</table>

* It depends on the type of surgery. ** Indicative dose.

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Table 6. Recommended dosage of vWF and FVIII concentrates

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women has been observed to put significant restrictions on their activity, travel, work, education and sex\(^{(40)}\). Menorrhagia is, therefore, a manifestation of major bleeding in women with vWD that affects their quality of life. It occurs in up to 80-90% of women with vWD\(^{(4)}\). A study has found that 25% of women with vWD require hysterectomy to treat their menorrhagia. Hence, both medical and surgical resources should be weighed.

Ovarian cysts and endometriosis are also more frequent in women with vWD\(^{(41)}\).

**Management of menorrhagia**

Treatments of menorrhagia in patients with vWD can be classified broadly into medical or surgical treatments.

### Medical treatment

#### Tranexamic acid

An increased fibrinolytic activity in the uterus has been reported in patients with menorrhagia compared with patients with normal menstruations. This increase is probably due to increased levels of endometrium-derived plasminogen and plasmin activators. Several studies have reported that the use of oral tranexamic acid has been effective, reducing the incidence of bleeding up to 50%. The recommended dose is the standard one (see section on antifibrinolytic treatment)\(^{(42)}\).

#### Desmopressin

Several studies supported the use of intranasal DDAVP with subjective improvement of menorrhagia by between 86 and 92%\(^{(43,44)}\). However, in a randomised placebo-controlled study that analysed bleeding using pictograms, bleeding did not show significant differences in patients treated with DDAVP\(^{(45)}\). There is no consensus regarding the dose or the duration of treatment and these should be individualised for each patient.

#### Nonsteroidal antiinflammatory drugs

These drugs inhibit cyclooxygenase and reduce endometrial prostaglandins; using inhibitors of COX-2 may be useful in treating patients with menorrhagia and vWD\(^{(34)}\).

#### Combined oral contraceptives

Combined oral contraceptives (COC) are generally safe and effective in the treatment of menorrhagia in general and they have become first-line treatments in patients with vWD, except in cases of contraindication\(^{(34)}\). Their effectiveness in reducing menorrhagia is not entirely known. In patients with vWD type 2 and 3, a reduction of up to 88% has been reported\(^{(46)}\). The continuous use of these drugs compared to classical schemes of 21 days, which eliminate menstruation, should be considered in patients with anemia or those suffering from haemodynamic changes with menstruation\(^{(37)}\), without differences in terms of efficacy and safety between the two regimes; although with the long-term treatment (longer than 28 days) the results were better regarding headaches, genital irritation, tiredness, bloating and dysmenorrhea, which were lower than in the group that was given a conventional treatment (28 days)\(^{(47)}\).

#### Levonorgestrel-releasing intrauterine devices

These devices release daily amounts of levonorgestrel, which effectively suppress endometrial growth and reduce menstrual bleeding and dysmenorrhea. They have been proved to be effective in the general population, but there are few data on its use in patients with vWD\(^{(48)}\).

### Surgical treatment

#### Plasma-derived concentrates of von Willebrand factor and factor VIII

These are indicated in situations in which there is no response to previous medical treatments, especially in teenagers, in severe cases and in cases of acute bleeding. A multidisciplinary approach between haematologists and gynaecologists is crucial when treating these women\(^{(7)}\).

In general, desmopressin, antifibrinolytics or vWF and FVIII concentrates can be recommended in women who want to become pregnant to control menorrhagia.

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**Figure 3. Pictogram of menstrual bleeding evaluation.**

It gathers information on the number of pads and tampons used in each cycle, as well as their degree of saturation.

Adapted from Higham et al.\(^{(38)}\).
depending on its severity, being aware, however, that these drugs do not control bleeding due to follicular rupture. In adolescent or adult women who do not want to become pregnant, but may want to in the future, COCs should be the first-line treatment. If a woman with vWD would otherwise be a suitable candidate for an intrauterine device, the second choice of therapy should be the levonorgestrel-releasing intrauterine system.

**Surgical treatment**

**Conservative surgery: endometrial ablation**

In patients with vWD, this is an alternative to hysterectomy. Second-generation techniques through controlled application of heat, cold, microwaves or other forms of energy are safer than first generation techniques and equally effective. Experiences in vWD patients show divergent results and require prophylactic treatment.

**Hysterectomy**

It is an effective and definitive treatment for menorrhagia. However, hysterectomy is a major surgery operation with important physical and emotional implications. It also presents long-term complications such as premature failure of ovarian function, urinary complications and sexual problems. In an American study of 1,358,133 hysterectomies, 545 were performed in patients with vWD. An increase of intra- and postoperative bleeding and transfusion requirements than in the normal population was reported.

vWD patients undergoing surgical techniques to control bleeding should receive prior prophylactic treatment. Surgery should be performed by experienced professionals with special skills on haemostasis management.

**Pregnancy and delivery**

**General recommendations**

It is recommended that all women with vWD should plan pregnancy in advance and be evaluated both by a haematologist and an obstetrician prior to pregnancy in order to estimate bleeding risk and to design appropriate monitoring during pregnancy and delivery.

**Management of pregnancy**

In general, there is an increase in FVIII:C and vWF:RCo from the second quarter onwards in women with type 1 vWD; these tend to stabilise to normal levels in the third quarter. This may explain the frequently observed improvement in haemorrhagic manifestations that occur during pregnancy in patients with mild or moderate type 1 deficiency, but not in patients with serious deficiencies.

In type 2 vWD patients, levels of FVIII:C and vWF increase during pregnancy, but levels of vWF:RCo do not. In women with type 3 vWD, hardly any changes in these levels are observed during pregnancy.

**Monitoring during pregnancy**

Given the significant variability in the haemostatic response of patients with vWD during pregnancy, levels of FVIII:C and vWF:RCo should be monitored before any invasive procedure and in the third trimester of their pregnancy. Some researchers recommend monitoring vWF:RCo and FVIII:C at least once during the third trimester of pregnancy and within 10 days before the expected date of delivery. If the levels of both parameters are greater than 30 IU/dL, the risk of bleeding is minimal, but if vWF:RCo is below that level, prophylactic treatment should be considered before any invasive procedure and delivery.

Clinical monitoring for at least 2 weeks after delivery for prevention of immediate and delayed bleeding is also recommended. The rapid decrease in vWF that occurs after childbirth is a risk of postpartum bleeding, which is higher in type 2 vWD patients and may persist for 7 to 21 days after delivery. A study by the US Centers for Disease Control and Prevention (CDC) noted that 59% of women with vWD experienced postpartum haemorrhage compared with 21% of control women.

In type 1 vWD patients, if the levels are less than 30 IU/dL, administration of DDAVP for procedures performed during pregnancy or at delivery may be required. In type 2 and 3 vWD patients, observation without treatment may be sufficient if the plasma level of FVIII:C is greater than 50 IU/dL. Dosage during labour is usually 40-80 IU/kg of concentrate and a prophylaxis after delivery with a dose of 20-40 IU/kg for at least 1 week should be followed. In type 2B vWD patients, a transfusion of platelet concentrates at the time of delivery in cases of severe thrombocytopenia can be used.

**Treatment**

**Desmopressin acetate and pregnancy**

Use of desmopressin acetate during pregnancy is controversial because of its potential oxytocic effect and the potential induction of placental insufficiency due to vasoconstriction. However, no adverse effects have been reported when it is administered in the second trimester of pregnancy. Nor is there evidence that it may stimulate prematurity or low birthweight when used before delivery.

The use of desmopressin during pregnancy is controversial with few data in medical literature. The use of low doses of desmopressin in pregnant women with diabetes insipidus has been reported to be safe for mothers.
and foetuses. In in vitro models, desmopressin does not cross the placenta in detectable amounts\textsuperscript{50}. Several studies suggest its effectiveness in preventing or controlling bleeding in cases of abortion or delivery complications\textsuperscript{50,52}. However, in a study in which several American haematologists were surveyed about practices during pregnancy in patients with vWD, 31\% of respondents considered that the use of desmopressin during pregnancy was a contraindication\textsuperscript{56}. Prolonged use should be avoided and exhaustively monitored, as well as observing fluid restriction in order to minimise hypovolaemia\textsuperscript{7,57}. Desmopressin can be used during pregnancy, but repeated administrations or its use in complicated pregnancies or situations of preeclampsia should be avoided. Its use should be under strict control and potential water retention should be monitored\textsuperscript{4,7}.

In type 1 vWD patients with levels below 30 IU/dL, administering DDAVP in preparation for delivery and as long as there is appropriate response to the drug is advisable. DDAVP can be used in patients with type 1 vWD and in some patients with type 2A vWD. It should be contraindicated in patients with type 2B vWD because it may trigger thrombocytopenia. Use of recombinant FVIII is recommended in patients with type 2N vWD\textsuperscript{50}.

Antifibrinolytics and pregnancy

Tranexamic acid crosses the placenta\textsuperscript{59}, but has been used during pregnancy in a limited number of cases with no adverse effects to the foetus\textsuperscript{4,60}. Regarding the use of EACA, the experience is much more limited, but studies in rabbits found it to be potentially teratogenic\textsuperscript{81}, and its use during pregnancy has not been associated with adverse effects on the foetus\textsuperscript{80}.

Plasma-derived vWF and FVIII concentrates are the treatment of choice for pregnant women who do not respond to DDAVP for the prevention or control of bleeding. Administration of the concentrate should begin before birth in order to increase FVIII:C and vWF:RCo to at least 50 IU/dL; these levels should be maintained at least for 3 days if the delivery is vaginal and at least for 5 days in case of caesarean section\textsuperscript{7,85}. In type 2B vWD patients with severe thrombocytopenia, platelet concentrates have been successfully employed.

Acute bleeding and pregnancy

Faced with a severe spontaneous or traumatic haemorrhage, levels of vWF:RCo and FVIII:C of about 80 IU/dL should be reached, and the same dosage should be maintained until bleeding is controlled. Using adjuvants, such as antifibrinolytics or local treatment, especially in mucosal bleeding, should be contemplated. In minor bleedings, administration of 40-50 IU/kg of vWF:RCo is usually sufficient, and at least 30-40 IU/kg of FVIII when levels of FVIII are under 20 IU/dL if the bleeding is severe\textsuperscript{80}.

Management of delivery

Women with severe vWD should give birth in maternity units with the necessary expertise, provided with appropriate laboratory resources and treatment for managing vWD patients\textsuperscript{47,57}. Vaginal delivery and caesarean section are considered to be safe for patients with vWD types 1 and 2 if vWF:RCo is greater than 50 IU/dL\textsuperscript{7}. Using suction, forceps and prolonged expulsive periods should be avoided, using early caesarean section if necessary, especially if the foetuses are at risk of having type 2 and 3 vWD.

Epidural anaesthesia (EA) is very rarely used in women with vWD due mainly to the potential risk of bleeding complications. There are currently no recommendations regarding the use of EA at the time of delivery in women with vWD. In a review on the use of EA in patients with vWD, 74 neuraxial techniques in 72 patients with mild to severe vWD were identified (type 1, n = 71, type 2A, n = 2, and type 3, n = 1)\textsuperscript{84}. No bleeding complications were reported in the 72 patients studied.

Of the 74 neuraxial techniques, epidural anaesthesia was used in 72 and combined spinal epidural anaesthesia was used in 2. In 64 of the 74 procedures, vWF levels were normal and did not require treatment. In 10 of the 74 procedures, prior treatment with desmopressin or vWF and FVIII concentrates was required. Several guidelines state that EA can be used in most patients with type 1 vWD with FVIII:C and vWF:RCo levels exceeding 50 IU/dL; they also recommend increasing these levels with prophylactic treatment when they are lower. EA is not generally recommended for patients with type 2 and 3 vWD\textsuperscript{7}.

Patients with type 1 vWD do not usually require prophylactic treatment for delivery. However, it is required for type 2 vWD patients undergoing caesarean section or suffering perineal trauma. It is always required for type 3 vWD patients regardless of the type of delivery\textsuperscript{7}.

As a general recommendation, all vWD patients whose FVIII: C and vWF:RCo levels are below 50% should receive prophylaxis before delivery, regardless of type\textsuperscript{6,7}.

Postpartum management

In the general population, the risk of bleeding in the immediate postpartum period (first 24 hours) varies from 4 to 5\%. This risk increases to 16-22\% in patients with vWD, making the bleeding between 15 and 20 times more frequent\textsuperscript{4,50}. Since levels of FVIII are the best predictor for risk of bleeding during and after childbirth, plasma levels of FVIII:C > 50 IU/dL should be maintained in the period immediately before delivery and for the following 3-4 days at least. Since vWF levels return to baseline 14-21 days after delivery, they should be monitored during this period.

The levels of FVIII:C and vWF:RCo should be monitored and maintained above 50% for at least 3 days if
the delivery is vaginal and for at least 5 days for caesarean section. Tranexamic acid or combined oral contraceptives should be considered to control prolonged or intermittent bleeding after delivery(4,7,37).

Management of the newborn

If the newborn is expected to have severe vWD, taking a sample of the umbilical cord to determine the level of vWF is recommended(37). In cases of infants with risk of type 2, type 3 or severe type 1 vWD, invasive fetal monitoring techniques and use of forceps or vacuum extraction should be contraindicated(4,7,37). In general, intramuscular injections, surgery and circumcision should be avoided until vWF levels are checked using laboratory techniques.

Vitamin K should be administered orally and vaccines subcutaneously until vWF levels are assessed using laboratory techniques(4,7).

Surgical prophylaxis in von Willebrand disease

Surgery in patients with vWD requires regular evaluation and correction of haemostasis pre-and postoperatively. Note that abnormal bleeding may have a surgical cause and not necessarily result from a bad control of haemostasis. Surgical prophylaxis depends on the type of vWD(4,48). For type 1 vWD patients with good response to DDAVP, this drug may be sufficient in minor surgery. Treatment with vWF concentrates is usually needed in major surgery, especially when aiming at a prolonged haemostatic deficiency correction.

For patients with type 2A and 2M vWD, DDAVP may be sufficient for minor procedures. However, in more important procedures or major surgery, using vWF concentrates is required. For type 2N vWD patients, vWF replacement therapy is required and levels of FVIII:C above 50 IU/dL are recommended perioperatively and until the wound is healed. DDAVP may be useful in surgery for patients with moderate phenotypes. Patients with type 2B and 3 vWD require replacement therapy for most invasive procedures.

Haemostatic levels for minor procedures

Levels of vWF:RCo and FVIII:C of 50 IU/dL are usually sufficient and, in many cases, a single administration is sufficient. Concomitant use of antifibrinolytics is recommended.

Haemostatic levels for major procedures

Administration of a dose of vWF concentrate to reach a vWF:RCo level of 80-100 IU/dL at the time of surgery is recommended; levels above 50 IU/L to ensure good haemostasis should be maintained(43). The FVIII:C level should be increased to 100 IU/dL perioperatively and levels above 50 IU/L should be maintained until wound healing (3-5 days for minor surgery procedures and 7-11 days for major surgery procedures). This requires monitoring of both vWF:RCo and FVIII:C levels.

Prophylaxis in von Willebrand disease

The most important symptom in vWD is bleeding of the mucous membranes. Haemarthrosis and intramuscular haematomas are rare and usually occur in type 3 vWD patients (they occur at least once in 37-45% of these patients)(6).

Despite their frequency, only a small group of patients with vWD is treated with prophylactic schemes. This group is mainly made up of people with type 3 vWD who have frequent bleeding with significant impairment of their quality of life and chronic sequelae of bleeding episodes(80). The scientific evidence on the management of prophylaxis for patients with vWD is scarce.

The general indications for the use of secondary prophylactic schemes in the long run are the following:

a) Patients with severe forms of vWD presenting haemarthrosis of repetition and developing arthropathy with target joints similar to haemophilia, especially those with FVIII levels below 0.1 IU/mL.

b) Patients with recurrent gastrointestinal bleeding usually associated with lesions in the gastrointestinal tract.

c) Infants with frequent and severe epistaxis, as well as menorrhagia tending to anaemia that cannot be controlled by other pharmacological measures.

Prophylaxis rather than treatment on demand when developing bleeding episodes is recommended for this group of patients.

The most important experience for prophylaxis comes from Swedish and Italian research groups(2,3,37). Berntorp et al. report on a Swedish study with a cohort of 35 patients with a median of 11 years using continuous replacement therapy(66). It is important to note that those patients who started prophylaxis at an early age, children under 5 years, in order to reduce epistaxis, did not present haemarthrosis and showed no clinical signs of arthropathy in comparison with those who started when they were older than 15, who, despite the reduction in haemarthrosis, presented clinical and radiological signs of arthropathy. Efficiency in reducing bleeding episodes at different sites was demonstrated and the treatment was safe in terms of thrombotic episodes and viral safety(66).

The Italian study reported by Federici et al.(67) retrospectively analysed a cohort of 89 patients who required replacement therapy with factor concentrates to treat one or more bleeding episodes in the previous 2 years. Eleven patients from this group required the use of secondary
prophylaxis. Seven of them required secondary prophylaxis due to recurrent gastrointestinal bleeding and 4 due to hemorrhathosis of repetition. Prophylaxis was effective for the prevention of bleeding in 8 patients and it drastically reduced episodes in 3 patients. The analysis of consumption of factor concentrates, transfusions and hospital days showed a significant reduction in the 11 patients.

In a retrospective analysis of 100 patients with vWD treated in Italy, 12 of them received 17 schemes of long-term secondary prophylaxis for the same reasons described (47% due to bleeding in the gastrointestinal tract and 55% due to haemarthrosis).

**Prospective studies**

Following these studies, the availability of safe concentrates has encouraged different groups of researchers to conduct studies to establish the optimal scheme of prophylaxis for different types of bleeding. Thus, the von Willebrand Disease Prophylaxis Network (vWD PN) was formed in 2006. Of the 6,208 patients analysed in different treatment centres in Europe and the United States, 102 patients on prophylaxis were identified. This Group has started a prospective study, the vWD International Prophylaxis Study (VIP) aimed at: a) identifying patients with vWD who may benefit from prophylaxis schemes, b) studying the effect of prophylaxis on the frequency of bleeding episodes, c) establishing an optimal scheme of prophylaxis, d) analysing the impact on quality of life, e) studying the frequency of hospital care and treatment centres, and f) assessing adverse effects. It should be noted that this prospective study is not randomised and dose intervals vary depending on the response of bleeding episodes.

**Conclusion**

At present, there is little scientific evidence supporting the use of prophylaxis in vWD patients; however, the future results of the VIP study look promising in providing some guidelines based on prospective studies that may provide a level of greater evidence on the use of prophylaxis in patients with vWD.

**Treatment of von Willebrand disease complicated by alloantibodies**

10-15% of patients with type 3 vWD develop alloantibodies that inactivate exogenous vWF through the formation of circulating immune complexes; patients with genetic alterations consisting of large deletions are particularly prone to develop these alloantibodies. Administering concentrates with vWF would be ineffective, either because of direct interaction with the functional domains of vWF or because of the decrease in the half-life of the factor administered, and, moreover, it would be contraindicated in these patients due to the risk of anaphylactic reactions occurring because of the ability of these antibodies to activate the complement through the formation of immune complexes.

In mapping and functionality studies of such alloantibodies, inhibitors of all subclasses of immunoglobulin G (IgG) with an inhibitory action of the activity of vWF:RCo have been identified.

In the treatment of bleeding episodes in patients with type 3 vWD and alloantibodies, recombinant FVIII has been successfully used, in a very limited way; the absence of vWF in these concentrates prevents the formation of immune complexes and, thus, the risk of anaphylactic episodes. The short half-life of FVIII in the absence of its transporter in plasma requires administration by continuous infusion in high doses to achieve sustained haemostatic levels. Recently, an urticarial reaction in a patient with type 3 vWD and alloantibodies after a bolus infusion of first generation recombinant FVIII has been reported.

Studies on the use of recombinant activated factor VII (FVIIa) in patients with vWD and alloantibodies is very limited. Ciavarella et al. reported on two brothers who underwent oral surgery; Boyer-Neumann et al. reported on the complex management of a caesarean section and postpartum period which combined sequential administration of recombinant FVIII and FVIIa in continuous bolus infusion. Dietrich et al. reported on a bleeding episode, as a result of multiple facial lacerations, which required 3 doses of FVIIa. Sucker et al. recently described the case of a patient with type 3 vWD and gastrointestinal bleeding without an adequate response to vWF/FVIII concentrates who responded to the daily administration every 12 hours of FVIIa. Although the doses of FVIIa used and the intervals of administration were variable, repeated bolus of between 80 and 200 µg/kg every 2-3 hours have been the most widely used scheme with a greater than 95% efficacy. Continuous infusion following a bolus injection of FVIIa has also been used. Therefore, FVIIa has been suggested as treatment for bleeding episodes and prophylaxis before surgical procedures in patients with vWD type 3 and alloantibodies. Recommended doses range from 90 to 150 µg/kg by infusion at intervals of 2-3 hours.

**Treatment of von Willebrand disease and risk of thrombosis**

**Products to use**

As we have already mentioned, plasma-derived vWF and FVIII concentrates have different ratios of vWF:RCo/FVIII and this is related to the presence of high molecular
weight multimers (Table 2). Wilfactin is the product with the greatest ratio and its use is limited to emergency situations especially in type 3 vWD. Haemate-P is the concentrate with the highest vWF/FVIII ratio of the factor concentrates considered in this guide.

**Factor VIII levels and thrombosis**

Administration of plasma vWF concentrates entail increases of plasma FVIII, which are a result of the intrinsic factor formulation in product and the endogenous synthesis, as a result of the action of vWF in the prevention of the proteolysis and degradation of circulating isolated FVIII and the frequency of infusions. That is, the progressive increase during treatment with these concentrates is probably due to the stabilising effect of infused vWF not only on exogenous infused FVIII, but also on the endogenous pool. As a result, the half life of FVIII:C is about 3 times longer than that of vWF:RCo and about 2 times greater than that of FVIII:C in patients with haemophilia A.

The threshold for associated thrombotic risks has not been defined. The Leiden Thrombophilia Study (LETS) concluded that values of FVIII:C above 150 IU/dL are associated with a thrombotic risk that is 5 times higher than that of values below 100 IU/dL. Moreover, a recent study suggests that an activity of 279 IU/dL may be the upper accepted limit for patients without additional risk, according to Franchini (81). In a subsequent study, this author suggests that FVIII levels of 200 IU/dL–1 or higher are the highest rate of risk for the occurrence of thrombosis.

A recent study emphasises that high levels (above 200%) of vWF:RCo and/or FVIII were observed in 22 patients treated with Haemate-P. The duration of these elevated levels was similar for vWF:Co (a range of 1–3 days) and FVIII (a range of 2–7 days). No thromboembolic events were reported in any of these patients in the perioperative period.

**Extent of the problem**

Half life of vWF:RCo is 3 times shorter than that of FVIII:C. Therefore, when levels of vWF:RCo are above 50%, FVIII:C may reach higher values. In 2002, supported by the Subcommitte on von Willebrand Factor Standardisation Committee of the International Society of Thrombosis and Haemostasis, Mannucci (81) sent a questionnaire to 520 centres that treated this disease with plasma derivatives to assess the number of patients that had developed a thrombosis in the previous 10 years. If they had, the centre was asked to provide additional information such as demographics, baseline percentage, vWF and FVIII values, concentrate brand, method of diagnosis and associated treatments, especially antithrombotic therapy. 160 centres responded. Overall, 1,268 patients for vWD and 14,125 for haemophilia A, regardless of severity, had been treated annually. Until 2002, only 3 cases of thrombosis in haemophilia A had been described. Of the 7 patients with vWD assessed for thrombosis (Table 7), 5 were 58 years old or older, 3 had been treated for long periods due to uncontrolled gastrointestinal bleeding and 2 of them had long been bedridden at the time of the thrombosis. Finally, 1 was continuing treatment for a target joint.

Thrombotic complications were serious; thrombotic risk factors such as obesity, estrogen administration or surgery were present in several cases. Of the 4 cases in which levels of FVIII:C were measured, 3 were above 200 IU/dL–1.

**Table 7. Thrombotic complications and treatment with vWF/FVIII concentrates**

<table>
<thead>
<tr>
<th>Country/City</th>
<th>Age/Sex/Type</th>
<th>Reason</th>
<th>Brand</th>
<th>Type of VTD</th>
<th>FVIII (%)</th>
<th>Associated risk</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>40/M/3</td>
<td>Art. diana profilaxis</td>
<td>Haemate-P</td>
<td>TCRV</td>
<td>ND</td>
<td>OC</td>
<td>No</td>
</tr>
<tr>
<td>France</td>
<td>33/F/1</td>
<td>THP</td>
<td>Conc.</td>
<td>TVP/PE</td>
<td>291</td>
<td>Orthopedic s./Ob</td>
<td>LMWH</td>
</tr>
<tr>
<td>Netherlands</td>
<td>75/F/3</td>
<td>KP</td>
<td>Haemate-P</td>
<td>PE</td>
<td>60</td>
<td>Orthopedic s./Ob</td>
<td>LMWH</td>
</tr>
<tr>
<td>France</td>
<td>65/F/3</td>
<td>KP</td>
<td>Innobrand</td>
<td>TVP/EP</td>
<td>238</td>
<td>Orthopedic s./Ob</td>
<td>No</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>61/M/1</td>
<td>GI haemorrhage</td>
<td>Haemate-P</td>
<td>SMVT</td>
<td>87</td>
<td>IID</td>
<td>No</td>
</tr>
<tr>
<td>United States</td>
<td>58/F/3</td>
<td>GI haemorrhage</td>
<td>Alphanate</td>
<td>PE</td>
<td>ND</td>
<td>Cancer</td>
<td>No</td>
</tr>
<tr>
<td>Australia</td>
<td>75/M/3</td>
<td>GI haemorrhage</td>
<td>CSL AHF</td>
<td>DVT</td>
<td>201</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

OC: Oral Contraceptives; IID: Intestinal Inflammatory Disease; PE: Pulmonary Embolism; VTD: Venous Thromboembolic Disease; GI: Gastrointestinal; LMWH: Low Molecular Weight Heparin; ND: Not Determined; Ob: Obesity; KP: Knee Prosthesis; THP: Total Hip Prosthesis; TCRV: Thrombosis of the Central Retinal Vein; SMVT: Splenic Mesenteric Venous Thrombosis; DVT: Deep Venous Thrombosis.
Mannucci recognises that the questionnaire has limitations regarding the causes of thrombosis, but its incidence (7 cases per 12,640 treatments in 10 years), although higher than that of haemophilia (3 in 141,250 treatments in 10 years), is not alarming. There is no reason to recommend limiting treatment in patients treated repeatedly. However, plasma levels of FVIII:C should not exceed 100% and antithrombotic therapy with low molecular weight heparins, especially when they are used to cover major surgical procedures, is recommended.

In 2009, Franchini reviewed and summarised the published data on thrombotic complications in patients with vWD after treatment with vWF/FVIII concentrates for different types of surgery (Table 8). Only 11 cases have been reported, confirming the rarity of this complication. It should be noted that many of these patients had significant risk of thrombosis, such as advanced age, surgery, immobility, obesity, history of previous thrombosis, hormone treatments and high FVIII.

According to a review of the literature by Girolami, the incidence of thrombosis and arterial thrombosis in vWD in nonsurgical situations is very rare. The number of arterial occlusions in patients with vWD is lower than that observed in patients with haemophilia A and B. Up to 2006, 55 cases had been reported, including myocardial infarction and cerebral vascular accidents in patients with haemophilia A and B, compared to 11 cases in patients affected by vWD. As the prevalence between the two disorders is very similar, between 1/5,000 and 1/10,000 people, it can be concluded that vWD has a degree of protection against atherothrombosis.

There is no difference between haemophilia A and B and vWD with regard to thromboembolic disease. The cases are rare and almost equal in number. This could suggest that coagulation deficiencies may be a protection against thromboembolism, but not against atherosclerosis, which depends on many other factors.

Most cases of vWD with venous thrombosis have received treatment with concentrates of vWF/FVIII:C before the thrombotic process was triggered and the same has happened in cases of haemophilia A and B. None of the cases of vWD had received FEIBA or FVIIa, suggesting that elevated levels of FVIII:C are sufficient cause (Table 7). It should be noted that the concomitant presence of other risk factors also plays a role. Thromboses occurred in both type 1 and 3 vWD, i.e., thromboses are independent of the severity of the deficiency.

### Recommendations

1. A diagnosis of vWD type as accurate as possible for each patient is recommended in order to make an adequate treatment.
2. A first-line drug therapy of vWD is recommended, as long as the patient responds to it. In case of insufficient response to drug therapy or if the bleeding episode is severe, replacement therapy with vWF and FVIII concentrates should be used.
3. We recommend a change in the classification of the vWF/FVIII concentrates, since the pharmacokinetics of those containing a small amount of FVIII is different from those that do not contain it.
4. Monitoring of replacement therapy should be done by measuring FVIII:C and, if possible, vWF:RCo. The post-event determination of this parameter is helpful to assess the patient’s biological response to the concentrate used in comparison with the observed clinical response.
5. Platelet concentrates should be used only in case of lack of clinical response to replacement therapy with vWF/FVIII concentrates, after ruling out local causes of bleeding (unhealed surgical wound or others).
6. Carrying out a pharmacokinetic study of vWF/FVIII concentrates before its therapeutic use has been con-
considered as useful. However, there is some recent controversy about its usefulness in surgery. Further studies will be needed to confirm or exclude this.

7. The treatment of vWD in women should be multidisciplinary, actively involving both obstetricians and gynaecologists.

8. When development of an antibody is suspected, it is necessary to prove its existence and prevent possible severe anaphylactic reactions after administration of vWF concentrates.

9. Unlike haemophilia, prolonged secondary prophylaxis in vWD has little scientific evidence, but can be seen as an option in patients with frequent and significant bleeding despite the use of conventional therapeutic measures.

10. There is considerable controversy regarding thrombotic risk and its prophylaxis in treating vWD. It seems reasonable to monitor the levels of FVIII:C in order to avoid its progressive increase by accumulation in situations that require repeated administrations. There is no clear consensus on the establishment of antithrombotic prophylaxis in surgery unless the patient has a previous personal history of thrombosis or other thrombotic risk factors. Randomised studies are needed to confirm clinical impressions and practices and assess the risks and benefits of thromboprophylaxis in patients undergoing surgery.

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References


