

# Treatment of patients with von Willebrand disease

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**Abstract:** Von Willebrand disease (vWD) is the most common hereditary bleeding disorder. The aim of therapy is to correct the dual hemostatic defect, due to defective platelet adhesion-aggregation and abnormal coagulation due to Factor VIII (FVIII) deficiency. The choice of treatment depends on a number of factors, including the severity of the bleed, the procedure planned, the subtype and severity of the disease and the age and morbidity of the patient. Desmopressin (DDAVP) is the treatment of choice for type 1 vWD as it increases endogenous release of FVIII and von Willebrand factor (vWF) and is also used in some subtypes of type 2 vWD. In those patients in whom DDAVP is ineffective or contraindicated, levels can be restored by infusing vWF:FVIII concentrates. The role of antifibrinolytic treatment is an important adjunct to replacement therapy during minor or major surgery involving mucosal surfaces. The dosing and timing of vWF:FVIII concentrates is important depending on the nature of the surgical procedure. The role of secondary prophylaxis needs to be further defined.

**Keywords:** von Willebrand disease, treatment, DDAVP

## Introduction

Von Willebrand disease (vWD) is the commonest congenital bleeding disorder, with a prevalence estimated from population studies of about 1%.<sup>1</sup> It is caused by inherited defects in the concentration, structure or function of von Willebrand factor (vWF). vWF has two essential functions:

- Primary hemostasis – vWF enables platelets to adhere to injured vascular endothelium and then to form platelet aggregates.
- Secondary hemostasis – vWF binds to and stabilizes factor VIII (FVIII). In the presence of vWF the half-life of FVIII is 8–12 hours, in its absence it is <1 hour.

The vWF gene is located on the short arm of chromosome 12 (12p13.2).<sup>2</sup> Mutations in the vWD gene result in quantitative or qualitative defects of vWF. The current classification of vWD is as follows:<sup>3,4</sup>

Quantitative defects:

- Type 1 vWD – partial loss of vWF
- Type 3 vWD – total loss of vWF

Qualitative: type 2 vWD defects:

- Type 2A – absence of high molecular weight (HMW) multimers of vWF
- Type 2B – increased affinity of vWF for platelet glycoprotein Ib (GpIb), causing removal of HMW multimers from plasma and associated with thrombocytopenia

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- Type 2M – defective interaction between vWF and platelets and no loss of HMW multimers
- Type 2N – defect in the N-terminal region of vWF where the binding domain for FVIII is located resulting in reduced binding of vWF to FVIII. No loss of HMW multimers.

The aim of therapy in vWD is to correct the dual hemostatic defect, due to defective platelet adhesion-aggregation and abnormal coagulation due to FVIII deficiency. These deficiencies can be corrected by increasing endogenous production of FVIII and vWF function using desmopressin (DDAVP®) or by administration of vWF concentrates. The choice of treatment depends on a number of factors including the nature of the bleed or invasive procedure planned, the sub-type and severity of vWD, the duration of treatment, the age of the patient and the previous response to treatment. Other treatments, such as antifibrinolytic agents (eg, tranexamic acid), can be used alone or as an adjunctive treatment, in order to achieve a hemostatic effect, without affecting the vWF levels. This review summarizes our management of patients with vWD based on the literature and our experience.

## Desmopressin

Desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP), a synthetic vasopressin analog, increases endogenous vWF by secreting it from its natural site of synthesis and storage, the vascular endothelial cell.<sup>5</sup> It can be administered intravenously,<sup>6,7</sup> subcutaneously<sup>8</sup> or intranasally.<sup>7</sup> The intravenous dose is 0.3 mcg/kg (maximum dose 28 mcg), given diluted in normal saline over 30 minutes. Treatment can be repeated every 12–24 hours depending on the type or severity of the bleed. Plasma vWF:FVIII levels are increased to 2–4 times above the baseline within 30 minutes and in general high levels last in the plasma for 6–8 hours.<sup>11,12</sup>

DDAVP is a very valuable drug as it avoids exposure to blood products and is a cheaper alternative. The vWD subtype, however affects the decision on whether to use DDAVP or a vWF-containing concentrate. It has been used cautiously in children because of the risk of hyponatremic seizures, although this risk must be balanced against that of exposing a child to a pooled blood product.<sup>9</sup>

DDAVP is usually effective in patients with type 1 vWD and baseline vWF and FVIII levels higher than 10 IU/dL.<sup>10</sup> In order to assess the response to DDAVP, a trial should be performed, measuring the FVIII and vWF ristocetin cofactor (vWF:RCo) pre-infusion and 1 hour post-infusion. An additional assay can be performed at 2–4 hours to evaluate for shortened survival of vWF, and should be considered in

patients with a poor response to treatment.<sup>11</sup> In a prospective trial conducted by Castaman et al, complete responses (post-infusion levels of FVIII:C and vWF:RCo of at least 50 IU/dL) or partial responses (post-infusion levels of FVIII:C and vWF:RCo less than 50 IU/dL, but at least 3-fold the basal levels) were observed in 84% and 13% of the cases, respectively. This was reduced in other sub-types of vWD.<sup>12</sup>

By performing half-life studies, patients with accelerated clearance of vWF and FVIII can be identified, such as those with Vicenza type vWD. This variant of vWD is due to a specific mutation, Arg1205His, which promotes increased clearance of vWF from the circulation (five times more rapidly than normal). This information could therefore influence treatment.<sup>13</sup>

The response to DDAVP is variable in types 2A and 2M and a therapeutic trial is indicated to assess the response of vWF:RCo and FVIII.<sup>14,15</sup> Its use in type 2B is controversial, as the release of abnormal vWF multimers with an increased affinity for glycoprotein Ib leads to the transient appearance of thrombocytopenia, but there are a few reports where it has been used safely.<sup>16,17</sup> DDAVP increases FVIII in Type 2N vWD in most patients but the half-life is significantly reduced,<sup>18</sup> therefore it is usually used in minor bleeding episodes, and vWF concentrate should be used to treat major bleeding or for invasive procedures.

DDAVP does not have any therapeutic use in type 3 vWD, and these patients must be treated with a vWF-containing concentrate.

The main limitation of using DDAVP is the development of tachyphylaxis, ie, the progressive reduction of responsiveness after repeated treatments.<sup>19</sup> Hyponatremia, volume overload and subsequent seizures can be associated with DDAVP, due to repeated dosing within short intervals, therefore fluid restriction and serum sodium monitoring are advisable.<sup>20</sup> As there have been reports of myocardial infarction and stroke in elderly patients with established atherosclerotic disease, DDAVP should be used cautiously in such patients.<sup>21,22</sup>

## von Willebrand factor-containing concentrate

For those patients in whom DDAVP is ineffective or contraindicated, vWF and FVIII levels can be restored by infusion of concentrates, which may contain both FVIII and vWF or very high-purity vWF with minimum or no FVIII.<sup>30</sup> When considering a vWF containing concentrate, there are minimal requirements: these products must have the same level of safety in eliminating the potential of blood-borne infections, and contain vWF that promotes adhesion and

aggregation of platelets as well as transport and stabilization of FVIII.<sup>23</sup> The pharmacokinetics and the efficacy of these products should be tested in patients with different types of vWD and be labeled with both vWF and FVIII potency.<sup>24</sup>

As vWF is a plasma-derived product, the risk of viral transmission has been minimized through the development of procedures for the viral inactivation of the plasma-derived concentrate. There is growing concern regarding the transmission of variant Creutzfeldt Jacob Disease (vCJD) through blood products. In the UK there have been 4 cases of infection transmitted by blood transfusions from individuals who later developed vCJD<sup>25</sup> and one case of a hemophilic who died of unrelated causes, but was found to have the vCJD prion protein in his spleen at post mortem.<sup>26</sup> These concerns are fuelling the demand for alternative treatment options such as recombinant vWF.

Important progress has been made in the standardization of vWF measurements in both plasma samples and concentrates which has been facilitated through the calibration of the WHO first International Standard for vWF:Ag and vWF:RCo.<sup>27</sup>

Studies demonstrate the hemostatic efficacy of a number of vWF-containing concentrates in the clinical settings of acute bleeds and surgical procedures, but there is no data to support the view that any concentrate has superior efficacy to any other. Commonly used products and their pharmacokinetic properties are shown in Table 1.<sup>28–36</sup>

The amount of vWF-containing concentrate required to correct the hemostatic defect in vWD is dependent on the nature of a bleed, a patient's baseline vWF:RCo and FVIII and their subtype of vWD. In addition different types of surgery require different target vWF:RCo and FVIII levels.<sup>36</sup>

Patients vary in their response to infusions of vWF-containing concentrate, therefore treatment regimens need to be individualized. Knowledge of an individual's pharmacokinetic response to infused vWF-containing concentrate is a therapeutic advantage, and the previous demonstration of hemostatic efficacy correlates well with prospective therapy for surgery or management of acute bleeding episodes.<sup>37</sup>

The vWF:RCo and FVIII levels required for hemostasis have not been established in clinical trials. The general consensus however, for major operative procedures or significant bleeding, is that the vWF:RCo and FVIII should be raised to above 80 IU/dL and maintained above 50 IU/dL until hemostasis is secured and the FVIII level should be maintained above 50 IU/dL until wound healing is complete. Minor surgery may be performed successfully with a vWF:RCo and FVIII of approximately 50 IU/dL.<sup>35,41–43</sup>

Sustained high levels of FVIII may increase the risk of venous thrombosis,<sup>38–40</sup> therefore when repeated infusions of vWF:FVIII concentrates are necessary (eg, surgical procedures), the FVIII:C plasma levels should be measured daily to avoid levels in excess of 150 IU/dL.<sup>40</sup> As vWF:RCo has a half life of 8–10 hours, and FVIII:C a half-life of 24–26 hours, both these levels should be monitored during prolonged treatment. Mannuci et al<sup>41</sup> recommend primary thromboprophylaxis in vWD patients undergoing replacement therapy for major surgery and procedures at high risk of venous thromboembolism, at the same dosing schedules as for non-vWD patients.

All patients with vWD produce FVIII. In order to avoid excessively high FVIII levels after infusing vWF concentrates, a highly purified vWF (HP-vWF) concentrate containing very little FVIII has been developed. This differs from other vWF concentrates as the post-infusion levels of FVIII rise slowly, reaching a peak 6–12 hours post-infusion. Combined data from a number of trials for a HP-vWF concentrate (Wilfactin) has shown that clinical outcomes were excellent or good in 89% of patients with spontaneous bleeds, although 38% of cases needed concomitant FVIII. Excellent or good efficacy was also observed in 95 elective surgical procedures without the need for prophylactic therapy with FVIII; however FVIII concentrate was required in 13 other patients needing surgery.<sup>42</sup>

A HP-vWF concentrate could potentially be utilized when prolonged infusion of product is needed, such as major elective surgery in those patients who are at a higher risk of developing thrombosis (old age, cancer, orthopedic surgery). Further studies are needed to identify the most appropriate patients and indications for use.

## Adjunctive treatments

Management of mucosal bleeding, menorrhagia or prolonged oral bleeding after dental extraction involves the administration of antifibrinolytic amino acids (eg, tranexamic acid, epsilon aminocaproic acid). These agents inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilize clots that have been formed. They can be administered either intravenously or orally, and can be used alone or as an adjunct to replacement therapy, to prevent or treat bleeding in mucosal tracts characterized by a rich fibrinolytic activity.<sup>44</sup>

These agents are also useful in administration along with replacement therapy during minor or major surgery involving mucosal surfaces.<sup>44</sup> Tranexamic acid should be administered at a dose of 15–25 mg/kg orally (or 0.5–1 g

**Table I** Pharmacokinetic properties of von Willebrand Factor-containing concentrates

| Product                                     | In vivo vWF:RCo recovery (IU/dL per IU/kg)                                 | In vivo FVIII recovery (IU/dL per IU/kg)                   | vWF:RCo/ FVIII ratio | Half life (hours)   | Source of plasma   | Viral inactivation   | Vial sizes (IU)            | Reference    |
|---|--|--|----------------------|---|--|--|----------------------------|--------------|
| <b>Alphanate</b>                            | 2.9 ± 1.3 (mean ± SD)  | 2.1 ± 0.4 (mean ± SD)                                      | 1.6:1                | vWF:RCo: 7.5 ± 3.2<br>FVIII:C: 21.5 ± 7.2<br>vWF:Ag: 13 ± 2.1 | USA  | SD<br>Dry heat (80°C for 72 hrs)                                     | 250<br>500<br>1000<br>1500 | (24)         |
| <b>Biostat</b>                              | 0.85 (0.77–0.92) mean (90% CI)   | 1.1 (0.88–1.32) mean (90% CI)                              | 2.1:1                | vWF:RCo: 11.6<br>vWF:CB: 12.2<br>FVIII: NA*                   | Australia  | SD<br>Dry heat (80°C for 72 hrs)                                     | 250<br>500                 | (21)         |
| <b>Factor 8Y</b>                            | Type 3: 1.4 ± 0.05<br>Type 2A: 2.0 ± 0.06<br>Type 1: 2.3 ± 0.5 (mean ± SD) | Type 3: 2.4 ± 1.1<br>Type 1: 5.0 ± 4.5 (mean ± SD)         | 2:1                  | 12–24   | USA  | Dry heat (80°C for 72 hrs)   | 250<br>500                 | (23)         |
| <b>Fanhdi</b>                               | No data  | No data  | 1.6:1                | 14.18 ± 2.55  | USA  | SD<br>Dry heat (80°C for 72 hrs)                                     | 250<br>500<br>1000<br>1500 | (25)         |
| <b>Haemate P/<br/>Humate P<br/>Immunate</b> | 2.1 (1.1–2.7) median (range)<br>1.8 (0.4–3.6) mean (range)                 | 2.7 (1.9–3.7) median (range)<br>1.9 (0.8–3.5) mean (range) | 2.5:1<br>No data     | 9.9 (range: 2.8 to 51.1)<br>No data                           | USA, Austria, Germany<br>USA, Austria, Germany, Sweden, Czech Rep. | Pasteurized (60°C for 10 hrs)<br>SD<br>Vapour heat (60°C for 10 hrs) | 500<br>1000<br>250         | (20)<br>(26) |
| <b>Wilate</b>                               | 1.5 (1.2–2.2) %IU/kg mean (range)  | No data in vWD   | 1:1                  | vWF:RCo: 17.5 (7.4–30.6) mean (range)                         | USA, Austria, Germany, Switzerland, Sweden                         | SD<br>Terminal dry heat (100°C for 120 mins)                         | 450<br>900                 |              |
| <b>Wilfactin</b>                            | 2.1 ± 0.3  | 5.8 ± 1 IU/dL (FVIII synthesis rate)                       | 10:1                 | vWF:RCo: 12.4 ± 1.8<br>vWF:Ag: 15.9 ± 1.5<br>FVIII: 5.8 ± 2.4 | Germany, France, Switzerland                                       | SD<br>Dry heat (80°C for 72 hrs)<br>Nanofiltration (35 nM)           | 1000                       | (22)         |

**Abbreviations:** SD, solvent detergent, in viral inactivation column; SD, standard deviation in columns 2 and 3; vWF, von Willebrand factor; vWD, von Willebrand disease; vWF:RCo, vWF ristocetin cofactor.

intravenously [IV]) every 8–12 hours and aminocaproic acid at a dose of 50–60 mg every 4–6 hours. These drugs are contraindicated in the management of urinary tract bleeding, due to the increased risk of intra-renal obstruction due to clot retention, in the renal pelvis or ureters.<sup>45</sup>

Topical Bovine thrombin or Fibrin sealant can be used as adjuncts to hemostasis in certain surgical situations especially in dental procedures.<sup>46</sup> They are not useful in massive hemorrhage. Topical collagen sponges are also of use for the control of bleeding wounds.<sup>47</sup>

Platelets contain 10%–15% of total blood vWF, and platelet transfusions have been used successfully to treat bleeding in patients with vWD.<sup>48</sup> Platelet transfusion should be considered in patients with type 3 or platelet-low vWD to control bleeding that is not responsive or poorly responsive to replacement therapy with vWF concentrate.

## Management of specific bleeding problems

### Dental treatment

Treatment with DDAVP or concentrate is unnecessary for fillings performed under infiltration with local anesthetic; however treatment should be given if an inferior dental nerve block is used.<sup>35</sup> In patients unsuitable for DDAVP, vWF-containing concentrate should be used, aiming to increase the vWF:RCo and FVIII to >50 IU/dL.<sup>41</sup> Oral antifibrinolytic agents should be commenced before treatment (along with local measures such as antifibrinolytic mouthwash) and continued for 7–10 days following extraction.

### Bleeding in women

As mucocutaneous bleeding is the most common phenotype of bleeding in vWD, females with this disorder are frequently affected by reproductive tract bleeding and related complications.<sup>49</sup>

### Gynecological disorders

Menorrhagia is common in women with vWD, affecting an estimated 80%–90% of patients.<sup>50</sup> It may however, be a symptom of an underlying gynecological disorder,<sup>51</sup> therefore it should be fully investigated. A study on behalf of the International Society of Thrombosis and Hemostasis (ISTH), demonstrated that up to a quarter of women required a hysterectomy for menorrhagia.<sup>52</sup> Therefore, both medical and surgical treatments should be considered.

Both ovarian cysts and endometriosis occur more frequently in women with vWD compared with their normal counterparts.<sup>53</sup> It is hypothesized that endometriosis is caused

by retrograde menstruation and that vWD exacerbates and ‘unmasks’ this condition.

Medical therapies that have been used to control bleeding in vWD are the combined oral contraceptive pill (OCP), tranexamic acid, DDAVP and the levonorgestrel-releasing intrauterine system.<sup>54</sup> In females who don’t want to become pregnant, but who wish to have children in the future, the first choice of therapy should be the OCP (containing synthetic estrogen and a progestin).<sup>55</sup> The progestin prevents ovulation and the synthetic estrogen prevents breakthrough bleeding.<sup>56</sup> Studies have found that the OCP can increase levels of fibrinogen, FVIII and vWF.<sup>57–59</sup>

Intrauterine devices, such as the levonorgestrel-releasing intrauterine devices can be used as an alternative therapy in suitable candidates. This system is a progestin impregnated device, which is believed to reduce menstrual blood loss by opposing the estrogen induced growth of the endometrium.<sup>60</sup>

Alternative treatments in addition to medical therapy may have to be considered in difficult cases. This involves therapies such as endometrial ablation which has been proven to help control bleeding in women with vWD.<sup>61</sup>

### Pregnancy

In normal pregnancy there is a progressive increase in FVIII and vWF levels from the second trimester onwards.<sup>62</sup> This also occurs in women with vWD, which may explain the frequent improvement in minor bleeding manifestations during pregnancy.<sup>63–65</sup>

Most women with type 1 vWD have a progressive increase in vWF and FVIII, which may make the diagnosis difficult during pregnancy.<sup>66,67</sup>

In type 2 vWD, FVIII and vWF levels increase, but most studies show minimal or no increase in vWF activity levels and a persistently abnormal pattern of multimers reflecting the production of abnormal vWF.<sup>50,64,66,68</sup> Most patients with type 3 vWD have no improvement in FVIII or vWF levels during pregnancy.

Theoretical concerns have been raised regarding the use of DDAVP in pregnancy due to the potential risks of placental insufficiency (as a result of vasoconstriction), an oxytocic effect and maternal and/or neonatal hyponatremia.<sup>69</sup> No adverse effects were noted in association with DDAVP given in the second trimester in 32 women with vWD who underwent chorionic villous sampling or amniocentesis.<sup>70</sup> Similarly, a systemic review of DDAVP in pregnant women with diabetes insipidus found no evidence of uterine stimulation, prematurity or low birth weight associated with the use of DDAVP antepartum.<sup>71</sup>

The vWF:RCo and FVIII levels for pregnant women with vWD should be measured at least once during the third trimester of pregnancy and within 10 days of the expected date of delivery.<sup>74</sup> The risk of bleeding is minimal if FVIII and vWF:RCo are greater than 30 IU/dL. These levels should also be measured for at least 2 weeks post-partum. The rapid fall-off in vWF and FVIII levels that occurs post-partum, means that women are at an increased risk of post-partum hemorrhage (PPH), which is higher in type 2 and 3 disease and can persist for 7–21 days after delivery.<sup>73</sup> A study from the Centers for Disease Control found that 59% of women with vWD experience a PPH compared with 21% of controls.<sup>60</sup>

Epidural anesthesia for pain relief may be considered with caution in patients with type I vWD, as the majority will have levels which have risen to within the normal range during pregnancy.<sup>42</sup> Each individual patient's risk of bleeding, however, should be considered, depending on the degree of correction of FVIII and vWF level, and the anesthetist and obstetrician should be consulted. Epidural anesthesia is not recommended in type 2 and 3 vWD.<sup>42</sup>

In type 1 vWD, if the levels are lower than 30 IU/dL it may be necessary to administer DDAVP, which may be necessary for procedures during pregnancy or at the time of delivery.

In Type 2 and Type 3 vWD observation alone without treatment is sufficient if the FVIII > 50 IU/dL. Dosing at delivery is usually 40–80 IU/kg vWF-concentrate and prophylaxis has usually been targeted to maintain vWF:RCO and FVIII > 50 IU/dL for at least 3–5 days postpartum.<sup>72</sup>

When the fetus is at risk of having type 2 or 3 vWD, invasive measures such as fetal scalp monitoring, rotational forceps, or ventouse delivery should be avoided.<sup>42</sup> Irrespective of the mode of delivery, newborns at risk of type 2 or 3 vWD need to be tested for vWD using cord blood sampling and assessed to rule out an intra-cranial hemorrhage; early replacement therapy may be required depending on the nature of the delivery. Cord blood screening for type 1 vWD will not give reliable results.<sup>42</sup>

In type 2B vWD, increased production of mutant vWF may result in spontaneous platelet aggregation and severe thrombocytopenia during the third trimester. Platelet transfusion may therefore be required at delivery.<sup>48</sup>

## Acute bleeding

For severe spontaneous or trauma-induced bleeding the vWF:RCo and FVIII levels should be increased to approximately 80 IU/dL, until bleeding has been controlled. Adjunctive treatment, such as antifibrinolytic drugs and other local measures to achieve hemostasis should be considered,

especially in mucosal bleeding. Lower levels of vWF:RCo and factor VIII are sufficient for minor bleeds.

## vWD and surgical procedures

Patients with vWD undergoing surgical procedures, need regular assessment and correction of hemostasis pre and post-operatively. It is important to recognize that abnormal bleeding can be as a result of surgical bleeding, rather than inadequate hemostasis. The different subtypes of vWD have different product requirements, which are shown in Table 2.

A vWF:RCo and FVIII of 50 IU/dL should be adequate for minor procedures, and often only one infusion is required. Antifibrinolytics can be administered both pre and post operatively to assist with hemostasis.

An infusion of a vWF-concentrate calculated to increase the vWF:RCo level to 80–100 IU/dL at the time of surgery is recommended and this level should be maintained above 50 IU/dL until hemostasis is secure.<sup>35,41</sup> The FVIII should be raised to approximately 100 IU/dL perioperatively and maintained above 50 IU/dL until wound healing is complete. This requires regular monitoring of both vWF:RCo and FVIII.

HP-vWF concentrates are infused at a dose of 50 IU/kg vWF:RCo, 12–24 hours before surgery if the FVIII is less than 60 IU/dL. A further dose is given 1 hour before surgery and subsequent infusions are given to maintain a vWF:RCo level > 60 IU/dL and a FVIII level > 40 IU/dL. Unscheduled surgery is treated with HP-vWF concentrate at 50 IU/kg and FVIII to the same target levels.<sup>72</sup>

The risk of VTE should be assessed in patients undergoing major surgery, who receive vWF-containing concentrates, and therefore high levels of FVIII should be avoided, and thromboprophylaxis considered.<sup>41</sup>

A summary of the initial dosing recommendations for vWF concentrate replacement for prevention or management of bleeding is shown in Table 3.<sup>49</sup>

**Table 2** Product types required, depending on sub-type of vWD, in minor and major surgical procedures

| vWD subtype | Minor surgical procedures treatment | Major surgical procedure treatment |
|-------------|-------------------------------------|------------------------------------|
| Type 1      | DDAVP                               | vWF concentrate                    |
| Type 2A/2M  | DDAVP                               | vWF concentrate                    |
| Type 2B     | vWF concentrate                     | vWF concentrate                    |
| Type 2N     | DDAVP                               | vWF concentrate                    |
| Type 3      | vWF concentrate                     | vWF concentrate                    |

**Note:** Antifibrinolytic therapy, both pre and post-operatively (until wound healing achieved) should be used as an adjunct in both minor and major surgical procedures.  
**Abbreviations:** DDAVP, desmopressin (1-desamino-8-D-arginine vasopressin); vWF, von Willebrand Factor; vWD, von Willebrand Disease.

**Table 3** A summary of the initial dosing recommendations for vWF concentrate replacement for prevention or management of bleeding

|                  | Major surgery  | Minor surgery  |
|------------------|--|--|
| Loading dose     | 40–60 IU/kg  | 30–60 IU/kg  |
| Maintenance dose | 20–40 IU/kg<br>every 8–24 hours                        | 20–40 IU/kg<br>every 12–48 hours                       |
| Monitoring       | Daily trough and peak<br>vWF:RCo and FVIII             | Trough and peak<br>vWF:RCo and<br>FVIII at least once  |
| Therapeutic goal | vWF:RCo and FVIII<br>trough >50 IU/dL<br>for 7–14 days | Trough vWF:RCo and<br>FVIII > 50 IU/dL<br>for 3–5 days |

**Abbreviations:** FVIII, Factor VIII; vWF:RCo, von Willebrand Factor ristocetin cofactor.

## Prophylaxis

The most prominent symptom in vWD is that of mucosal bleeding (eg, epistaxis, gastrointestinal bleeding and menorrhagia). Hemarthrosis (joint bleeding), and spontaneous muscular bleeding, resembling those of hemophilia, may occur rarely, particularly in patients with a secondary deficiency of FVIII. It has been reported, in some series that 37%–45% of subjects with type 3 vWD had experienced at least one episode of hemarthrosis.<sup>73,74</sup>

The first data on the usefulness of prophylaxis was obtained from Sweden, where retrospective data from 35 patients demonstrated that vWF/FVIII infusions administered at least once weekly were found to substantially reduce mucosal bleeding and hemarthrosis and there was no evidence of progression to arthropathy.<sup>75</sup> There is a potential role for prophylaxis in vWD.

According to a survey of 74 centers in Europe and North America approximately three-quarters of patients receiving prophylaxis have type 3 vWD. Indications for prophylaxis include recurrent hemarthrosis (14%), epistaxis (23%), gastrointestinal bleeding (14%), and menorrhagia (5%).<sup>76</sup>

The optimum prophylactic regimen for vWD has not yet been established, and it is likely that it may not need to be administered as regularly as prophylaxis for patients with severe hemophilia A. Retrospective data from 120 patients enrolled on an Italian national registry has suggested that long-term secondary prophylaxis with vWF/FVIII (40 IU/kg) prevents or reduces bleeding in vWD patients with a history of recurrent hemorrhage.<sup>77</sup> There is now a prospective randomized study comparing on-demand and prophylactic treatment, and the results of these studies will help better define the role of prophylaxis in patients with von Willebrand disease, and also provide more data on the optimum treatment regimes.

## The future

The management of vWD has changed over the past 15 years, and treatments such as DDAVP, vWF containing concentrate are well established. The role of secondary prophylaxis needs to be further defined. The development of recombinant vWF currently undergoing phase 1 studies in type 3 vWD is likely to offer further treatment options in the future.<sup>78</sup> Alternative therapy such as gene therapy, which is attempting to partially correct vWF defects, may change management in the future in patients with type 3 vWD.<sup>49</sup>

## Disclosure

The authors declare that there are no potential conflicts of interest in this work.

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