

How I treat type 2 variant forms of von Willebrand disease

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Type 2 von Willebrand disease (VWD) includes a wide range of qualitative abnormalities of von Willebrand factor structure and function resulting in a variable bleeding tendency. According to the current classification, 4 different subtypes can be identified, each with distinctive phenotypic and therapeutic characteristics. Current available laboratory methods allow a straightforward approach to VWD subtyping, and although the precise molecular characterization remains complex,

it is not required for appropriate treatment of the vast majority of cases. Desmopressin can be useful only in a few type 2 cases compared with patients with actual quantitative deficiency (type 1), most often in variants with a nearly normal multimeric pattern (type 2M). However, since no laboratory test accurately predicts response to desmopressin, a trial test should always be performed in all type 2 VWD patients, with the exception of type 2B ones. Replacement therapy with plasma-

derived von Willebrand factor-factor VIII concentrates represents the safe mainstay of treatment of all patients, particularly those not responding to desmopressin or requiring a sustained hemostatic correction because of major surgery or bleeding. A significant patient bleeding history correlates with increased bleeding risk and should be considered in tailoring the optimal antihemorrhagic prophylaxis in the individual patient. (Blood. 2015;125(6):907-914)

Introduction

von Willebrand factor (VWF) is a multimeric protein synthesized by endothelial cells and megakaryocytes, required for platelet adhesion to subendothelium, and platelet-to-platelet cohesion and aggregation, particularly under elevated shear stress conditions.^{1,2} VWF high molecular weight multimers (HMWM) are particularly efficient as bridging molecules through interaction with platelet GpIb and GpIIb-III, and subendothelial collagen.³ VWF binds to coagulation factor VIII (FVIII), protecting it from premature proteolysis in the circulation and increasing its availability at the site of the growing platelet thrombus.⁴

Quantitative (types 1 and 3) or qualitative defect of VWF (type 2) cause von Willebrand disease (VWD), the most frequent autosomal inherited bleeding disorder.⁵ Almost all cases identified by epidemiological investigations are type 1, and no data are available for type 2. Analysis of patient series registered at specialized centers shows that type 2 VWD patients are relatively rare compared with type 1 VWD patients (with a 1:3 ratio).⁶ However, because of their diagnostic and therapeutic challenges, they offer an extraordinary view of the clinical consequences of even tiny molecular perturbations.

Type 2 VWD: a heterogeneous disease subgroup

The gene coding for VWF (*VWF*) spans approximately 178 kb over 52 coding exons in the short arm of chromosome 12. After the initial identification of *VWF* missense mutations in exon 28 associated with type 2 VWD,⁷ causative mutations for most of the other types have been identified for each VWF domain⁸ (Figure 1). In general, mutations responsible for type 2 are highly penetrant, and the bleeding phenotype is highly reproducible within a given family; only in type 2N is a recessive inheritance evident.

The most common qualitative abnormality found in type 2 VWD affects epitopes involved in binding to platelet GPIIb/IIIa, an activity measurable in vitro after the addition of ristocetin and referred to as VWF ristocetin cofactor activity (VWF:RCO).⁹ A ratio between VWF:RCO

activity and VWF antigen (VWF:Ag) below 0.6 is paradigmatic of dysfunctional type 2A and 2M VWD. In type 2A VWD, there is a variable lack of HMWM, caused mainly by mutations in the A2 domain affecting the multimerization process or susceptibility to ADAMTS-13, but also in D1/D2 multimerization regions and the C-terminal CK region. In type 2M, point mutations in the A1, or rarely A3 domains, are usually found.¹⁰ Collagen-binding sites are mainly located in the A3 domain, and their activity is assessed by a collagen-binding assay (VWF:CBA) that is very sensitive to the loss of HMWM¹¹ occurring primarily in type 2A. Only a few mutations in the A3 domain leading to selective VWF:CBA defects without loss of HMWM have been reported.¹² Hence, a reduced VWF:CBA/VWF:Ag ratio (<0.6) helps discriminating between type 2A and type 2M VWD.¹³

Type 2B is characterized by mutations in the A2 domain causing an increased affinity of VWF for platelet GpIb, resulting in enhanced ristocetin-induced platelet agglutination (RIPA). A solid phase assay using a gain-of-function GPIIb construct has been suggested as a diagnostic test alternative to RIPA.¹⁴ Apart from a strikingly different RIPA pattern, type 2B VWD closely resembles type 2A in terms of VWF assays and multimeric structure.¹⁵ Mild-to-moderate thrombocytopenia is present in about 40% of patients because of in vivo platelet clumping.¹⁶ Thrombocytopenia may further aggravate the bleeding risk in these patients.¹⁶ Type 2B should also be differentiated from an even rarer disorder, platelet-type VWD, in which the responsible mutation directly affects the GpIb gene, inducing a gain-of-function with increased affinity for normal plasma VWF. Molecular analysis of the GpIb gene is required for correct diagnosis.¹⁷

Missense mutations in the FVIII-binding domain at N-termini of VWF are responsible for type 2N VWD, producing a reduced ability of mutant VWF to bind FVIII.¹⁸ Type 2N is typically characterized by a discrepant FVIII/VWF:Ag ratio (<0.5) with normal or nearly normal

| Exon | Domain | Function | Laboratory Phenotype | VWD subtype |
|----------------|-------------|--------------------------------|--|-------------|
| 3-10 11-17 | D1 D2 | Propeptide, Multimerization | ↓ VWF:RCo/VWF:Ag ratio and ↓ VWF:CBA/VWF:Ag ratio | 2A |
| 18-20 | D' | FVIII binding | ↓ FVIII/VWF:Ag ratio and ↓ binding activity | 2N |
| 20-28 | D3 | Multimerization | ↓ VWF:RCo/VWF:Ag ratio and ↓ VWF:CBA/VWF:Ag ratio | 2A |
| 28 | A1 | GpIb α binding | ↑ RIPA | 2B |
| 28 | A1, A2 | | ↓ VWF:RCo/VWF:Ag ratio with normal ↓ VWF:CBA/VWF:Ag ratio | 2A, 2M |
| 28-32 | A3 | Collagen binding | | |
| 35-39 40-42 | D4 B1-B3 | | | |
| 42-48 | C1-C2 | GpIb/IIIa binding | - | - |
| 49-52 | CK | Dimerization | ↓ VWF:RCo/VWF:Ag ratio and ↓ VWF:CBA/VWF:Ag ratio | 2A |

Figure 1. Correlates between VWF molecular abnormalities, protein domain localization, laboratory phenotype, and subtype classification in type 2 VWD.

VWF:RCo/VWF:Ag, mimicking mild hemophilia A.¹⁹ Table 1 shows the main laboratory and clinical features of type 2 VWD.

A practical approach to type 2 VWD diagnosis

VWD should always be suspected in patients with a history of mucocutaneous bleeding symptoms.^{5,20,21} Personal and family history of bleeding symptoms should be carefully collected in all suspected VWD patients, and the clinical relevance of each bleeding symptom should be carefully interpreted by an experienced clinician. Bleeding assessment tools have been proposed and validated in type 1 VWD patients to help with the collection and interpretation of such data.²²⁻²⁵ These tools usually comprise a bleeding questionnaire and a severity scale; each bleeding symptom is scored from 0 (absence or trivial symptom) to 3 or 4 for the most severe symptoms (eg, bleeding requiring transfusion of blood products). The overall patient bleeding score (BS) is determined by summing up the scores for all of the bleeding symptoms. An abnormal BS, usually >3 (or >5 in females), has been shown to be associated with types 1, 2, and 3 VWD and presence of platelet function disorders.²⁶⁻³⁰

We routinely screen all patients with a suggestive bleeding history with at least one VWF functional test. A reduction of at least one VWF functional test (below 30 IU/dL) discrepant from VWF:Ag is highly suggestive of type 2 VWD. At variance with type 1 VWD, the laboratory phenotype of type 2 VWD does not improve over age,³¹ and is therefore, consistent among family members. Since VWF:CBA has been shown to be reduced in all type 2 variants (with the exception of type 2N), it could be theoretically proposed as a sensitive screening tool for types 1 and 2 VWD.³² This is in accordance with recent data from the Zimmerman Program for the Molecular and Clinical Biology of VWD Study showing that a VWF:CB/VWF:Ag cutoff ratio of 0.6 has a 100% sensitivity to detect multimer abnormalities of types 2A and 2B VWD.¹¹

Unfortunately, VWF:CBA is only available on microtiter plates and is not standardized yet,³³ whereas sensitive GpIb fragment-based VWF:RCo are readily available for most clinical coagulometer as a substitute for the time-consuming, aggregometry-based VWF:RCo.^{14,34-36} A laboratory workflow based on the sequential

measurement of VWF:RCo, VWF:Ag, and VWF:CBA may be therefore more feasible for clinical laboratories (Figure 2). However, VWF:CBA would still be required to differentiate the reported rare mutations in the collagen-binding A3 domain from type 1 VWD.^{12,37}

Confirmatory multimeric and/or genetic analysis are useful complements to the definitive classification, but they are often of little clinical value, apart from differentiating type 2N from mild hemophilia A for genetic counseling, and not readily available to all laboratories.

The relevance of bleeding history in guiding the optimal therapy

Variations in the biology of type 2 VWD results in different clinical patterns with highly variable hemorrhagic risk.³⁸ Prospective studies have demonstrated that the bleeding risk in type 2A patients is much higher than that observed in type 2M patients, with gastrointestinal hemorrhage being a very common symptom.³⁹ Mucocutaneous bleeding (epistaxis, ecchymosis, menorrhagia, and gastrointestinal bleeding) are the most prevalent manifestations in types 2A, 2B, and 2M variants. Type 2N VWD patients usually present with symptoms suggestive of mild-to-moderate hemophilia A, mainly related to trauma or surgery.^{40,41}

The personal bleeding history may be of some value in guiding the optimal therapy in VWD as suggested by several clinical observations. In the European MCMDM-VWD1 Study, the BS was superior to VWF measurement for the prediction of surgical bleeding.⁴² In a prospective cohort of 46 patients with type 2A and 61 with type 2M VWD, patients having a BS >9 had an almost sixfold higher risk of spontaneous bleeding during follow-up than those with a normal BS.³⁹ Finally, in a recent large prospective investigation performed in 796 patients with all types of VWD, a BS >10 at enrollment was the strongest predictor of bleeding with a 5.5-fold increased risk during 1-year follow-up.⁴³

These observations suggest that patients with a significant previous bleeding history may be at higher bleeding risk. These patients may require more stringent monitoring after surgery or a bleeding episode to assure that proper therapeutic goals are achieved.

Table 1. Overview of the main characteristics of type 2 VWD

| Type | Laboratory | Multimers | Mutations associated | Remarks |
|---------|--|---|--|---|
| Type 2A | Usually VWF:RCo/VWF:Ag and VWF:CBA/VWF:Ag <0.6 | Lack or relative decrease of the HMW and of intermediate multimers | Mutations in A2 domain; R1597W or Q or Y, S1506L and G1609R represent about 60% of cases. Mutations in D1/D2 multimerization regions and the C-terminal CK region are also described | Usually dominant. Group I: impaired secretion of HMWMs, due to defective intracellular transport. Group II: normal synthesis and secretion of a VWF with greater susceptibility to in vivo proteolysis by ADAMTS-13. Combined mechanisms may be present. Patients of Group II may respond to desmopressin |
| Type 2B | Usually VWF:RCo/VWF:Ag <0.6; RIPA occurs at low ristocetin concentration; thrombocytopenia present in 40% to 50% of cases; often abnormality of platelet morphology on blood smear | Lack of HMW multimers; a normal pattern is present in New York/Malmö variant | Mutations in A1 domain; 90% of cases are due to R1306W, R1308C, V1316M, and R1341Q. P1266L associated with gene conversion and New York/Malmö phenotype | Usually dominant. Enhanced affinity of abnormal VWF for platelet Gplb receptor. Thrombocytopenia after desmopressin, and sometimes during pregnancy or stress situations; thrombocytopenia may aggravate bleeding risk conferred by the abnormal VWF. Desmopressin usually contraindicated |
| Type 2M | Usually VWF:RCo/VWF:Ag <0.6, but normal VWF:CBA/VWF:Ag | All multimers present; inner abnormalities may be evident (eg, "smearly pattern") | A few heterogeneous, recurrent mutations in A1, or rarely, A3 domains (eg, V1279I, R1315C/L, G1342S/A, and I1425F) | Usually dominant. Some overlap with type 2A may occur. Desmopressin may be useful in selected cases |
| Type 2N | VWF may be normal or only slightly reduced; FVIII:C/VWF:Ag <0.5; defective FVIII-VWF binding | All multimers present | Mutations in NH ₂ -terminus; R854Q is by far the most frequent mutation | Differential diagnosis with mild hemophilia A. Usually recessive. Bleeding only for homozygosity or compound heterozygosity. Heterozygosity for R854Q in up to 2% of population in Northern Europe. Desmopressin may be useful for the majority of minor bleedings |

HMW, high molecular weight; RIPA, ristocetin-induced platelet agglutination.

Treatment of type 2 VWD: a case-based approach

The treatment goal in type 2 VWD is to achieve and maintain adequate hemostatic levels of VWF/FVIII for the time required for tissue healing while avoiding excessive peak concentrations. It should be remembered that although VWF activity is defective in type 2 VWD, FVIII biosynthesis is fully functional; the half-life of FVIII:C in VWD patients is usually approximately twice that of VWF:RCo (~20 to 24 hours vs ~10 to 14 hours) because of the endogenous production of FVIII.⁴⁴ Very high FVIII:C levels (>150 IU/dL) may be achieved in the patient because of the accumulation of the infused and endogenously synthesized FVIII after closely spaced infusions,⁴⁴ possibly increasing thromboembolic risk.^{36,37} A recent systematic review of prospective studies published after 1990 showed only two documented venous thromboembolic complications and five episodes of superficial thrombophlebitis in 361 VWD patients following over 8000 concentrate infusions.⁴⁵ We suggest monitoring trough VWF:RCo and FVIII:C plasma levels daily in these circumstances.

Desmopressin should always be considered in patients showing a good response to this agent and having minor hemorrhages or needing minor surgery. Table 2 shows the recommended interventions based on the patient's clinical setting, desired trough VWF levels, and treatment type.

Nontransfusal treatment of type 2 VWD

Case 1. A 27-year-old man is referred for evaluation of antihemorrhagic prophylaxis for dental extraction. He suffered from epistaxis and

gum bleeding, and was prescribed oral tranexamic acid to control nose bleeding in the past. His BS was 4, according to the International Society on Thrombosis and Hemostasis bleeding assessment tool,⁴⁶ therefore prompting an evaluation for VWD. Based on VWF assays (FVIII:C 33 IU/dL, VWF:Ag 26 IU/dL, VWF:RCo 12 IU/dL, VWF:CBA 24 IU/dL, and RIPA 1.5 mg/mL), a tentative diagnosis of type 2M was made (VWF:RCo/VWF:Ag ratio 0.46 and VWF:CBA/VWF:Ag ratio 0.92); no relatives were available for study. A test infusion with desmopressin was carried out to verify biological response. After 1 hour, FVIII:C rose to 135 IU/dL, VWF:Ag to 115 IU/dL, and VWF:RCo to 61 IU/dL with a slow decline after 4 hours (FVIII:C 125 IU/dL; VWF:Ag 92 IU/dL, and VWF:RCo 52 IU/dL). The compound was used prior to dental extraction along with oral tranexamic acid (around 25 mg/kg thrice daily for 5 days). No immediate or delayed bleeding was observed.

Desmopressin (1-deamino-8-*D*-arginine vasopressin, DDAVP) is cheap and carries no risk of transmitting blood-borne viruses.^{44,47-49} Desmopressin induces a significant increase of plasma FVIII and VWF levels after administration by triggering their release from endothelial cells and represents the first-choice option for patients with type 1 VWD, in whom cellular VWF is usually normal. Type 2 VWD patients have a highly variable pattern of response to DDAVP, although it is better in type 2M than in type 2A.⁵⁰ A test infusion of DDAVP (0.3 µg/kg) is always recommended to establish the individual response pattern and to plan its appropriate use. We routinely assess DDAVP response after 1 and 4 hours from the infusion to also evaluate the clearance pattern, as some patients may have a very short VWF/FVIII half-life

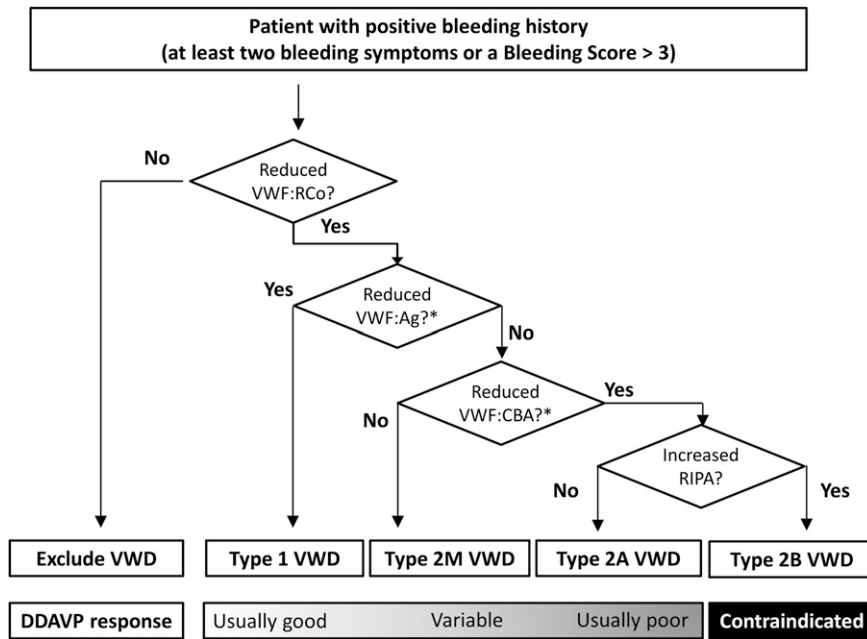


Figure 2. Diagnostic flow-chart for laboratory classification of type 2 VWD. Diagnosis should be considered in patients with a significant bleeding history and plasma VWF:RCo below 40 IU/dL. Asterisk denotes that VWF:Ag or VWF:CBA should be reduced proportionally to VWF:RCo. In addition to this flow-chart, type 2N should be considered in patients with a significant bleeding history and a FVIII/VWF:Ag ratio below 0.6; VWF:FVIII:B is used to differentiate from mild hemophilia A.

despite initially satisfactory peak values. We define as “DDAVP responders” those VWD patients with VWF:RCo and FVIII:C >50 IU/dL after 1 hour, but levels >30 IU/dL at 4 hours are also desirable for a sustained efficacy of the compound.⁴⁹

Desmopressin is recommended for prophylaxis of nonmajor surgery and treatment of not life-threatening hemorrhages in type 2 VWD variants responding to this agent (Table 2). We usually administer desmopressin at a 0.3 µg/kg dose for both test and therapeutic infusions, following originally proposed dosages.^{51,52} Some national guidelines recommend a capped dose of 20 µg,⁵³ and recent retrospective data suggest that even a capped dose of 15 µg may be useful.⁵⁴ Desmopressin is however, contraindicated in type 2B because the transient appearance or aggravation of thrombocytopenia may lead to an increased risk of bleeding. In type 2N associated with homozygous or heterozygous R854Q mutation (by far the most frequent mutation), desmopressin is usually able to correct FVIII

deficiency, although its half-life may be relatively short.^{41,49} In patients with isolated collagen-binding defects, desmopressin improves all VWF/FVIII measurements including VWF:CBA, albeit with a persistent discrepancy of VWF:CBA/VWF:Ag ratio.¹² Minor side-effects include tachycardia, headache, and flushing; hyponatremia and fluid overload with seizures may be a risk, particularly in small children receiving repeated infusions. In these situations, serum electrolytes should be monitored and fluid intake should be limited.⁵⁵

Replacement therapy for type 2 VWD

Case 2. A 4-year-old girl with VWD was referred for recurrent nosebleeds and easy bruising, with a BS of 2. In very young patients, the sensitivity of clinical assessment is suboptimal,³⁸ and even a slight increase of BS (such as in this case) should be carefully considered. The patient underwent a laboratory evaluation that disclosed a slightly

Table 2. Suggestions for therapy of bleeding and surgery prophylaxis in type 2 VWD

| Clinical situation | Target trough plasma VWF level (IU/dL) | Desmopressin responsive | Desmopressin unresponsive |
|---------------------------------------|--|--|---|
| Clinically relevant nonmajor bleeding | >30 | DDAVP 0.3 µg/kg body weight every 12-24 h until bleeding stops | 50 IU/kg of VWF/FVIII concentrate immediately, then 30 IU/kg every 24 h until bleeding stops |
| Major (life-threatening) bleeding | >50 | 50 IU/kg of VWF/FVIII concentrate immediately, then 30-50 IU/kg daily until bleeding stops | As per desmopressin responsive |
| Tooth extraction/endoscopy | >50 | Single dose DDAVP 0.3 µg/kg body weight preprocedure; oral tranexamic acid (15-25 mg/kg per day in 3 refracted doses) is also advised | Single dose 30 IU/kg of VWF/FVIII concentrate preprocedure |
| Minor surgery | >30 | DDAVP 0.3 µg/kg body weight every 12-24 h until healing is complete (usually 2-4 d) for nonmucosal tissue surgery | 40 IU/kg of VWF/FVIII concentrate preoperatively, then 30 IU/kg every 24 h until healing is complete (usually 5-10 d) |
| Major surgery | >50 | 50 IU/kg of VWF/FVIII concentrate preoperatively, then 30-50 IU/kg daily to maintain FVIII:C and VWF:RCo levels around 80-100 IU/dL until 36 h postoperatively; then 30 IU/kg daily until healing is complete (usually 5-10 d) | As per desmopressin responsive |
| Delivery and puerperium | >50 | Daily doses of 40 IU/kg for 3-4 d; oral tranexamic acid (15-25 mg/kg per day in 3 refracted doses) advised if heavy lochia are present | As per desmopressin responsive |

Table 3. VWF/FVIII concentrates licensed for the treatment of VMD

| Product | Manufacturer | Purification | Viral inactivation | VWF:RCo/Ag # | VWF:RCo/FVIII # |
|-----------------------|------------------------|-------------------------------|--|--------------|-----------------|
| Factor 8Y | BioProducts Laboratory | Heparin/glycine precipitation | Dry heat (80°C, 72 h) | 0.29 | 0.81 |
| Fanhdi (Alphanate*) | Grifols | Heparin ligand chromatography | S/D + dry heat (80°C, 72 h) | 0.47 | 1.04 |
| Haemate P (Humate-P*) | CSL Behring | Multiple precipitation | Pasteurization (60°C, 10 h) | 0.59 ± 0.1 | 2.45 ± 0.3 |
| Immunate | Baxter | Ion exchange chromatography | S/D + vapor heat (60°C, 10 h) | 0.47 | 1.1 |
| Wilate* | Octapharma | Ion exchange + size exclusion | S/D + dry heat (100°C, 2 h) | — | 1.0 |
| Wilfactin | LFB | Ion exchange + affinity | S/D, 35 nm filtration, dry heat (80°C, 72 h) | ~ 0.95 | ~50 |

Adapted from Castaman et al⁴⁶ with permission.

Ag, antigen; FVIII, factor VIII; RCo, ristocetin cofactor; S/D, solvent/detergent.

*FDA approved for treatment of VWD in the United States under this brand name.

prolonged APTT ratio (1.20), associated with mildly reduced FVIII:C and VWF:Ag levels (FVIII:C 42 IU/dL, VWF:Ag 36 IU/dL). However, VWF:RCo and VWF:CBA were similarly severely reduced (5 IU/dL), with a clearly abnormal ratio to VWF:Ag (0.14). RIPA occurred at 2 mg/mL. A diagnosis of type 2A VWD was made. The same pattern was evident in the father, in whom a DDAVP trial showed normalization of FVIII:C and VWF:Ag, but persistent VWF:RCo reduction (11 IU/dL) at 1 hour. Two weeks later, the child was again seen because of epistaxis and her hemoglobin level being 7 g/dL; desmopressin was not considered as a therapeutic option because of the failure to normalize VWF:RCo in the father. The patient was infused with 50 IU/kg of a VWF-FVIII concentrate, with an immediate interruption of bleeding.

Case 3. A 70-year-old male with VWD type 2M VWD (FVIII:C 15 IU/dL, VWF:Ag 12 IU/dL, VWF:RCo 6 IU/dL, VWF:CBA 12 IU/dL, and RIPA 1.7 mg/mL) due to C1315L mutation requires major abdominal surgery because of an adenocarcinoma of the sigmoid colon. Despite a previous anamnestic satisfactory response to desmopressin, this agent was discarded because of the need to maintain sustained hemostatic levels (VWF:RCo >50 IU/dL at through) for at least 5 days to avoid bleeding. A dose of 60 IU/kg of VWF-FVIII concentrate was administered 30 minutes before surgery. Twelve hours later, his VWF:RCo and FVIII:C levels were 90 and 76 IU/dL, respectively; a further dose of 40 IU/kg was administered, followed by two 40 IU/kg further doses 24 hours and 48 hours later. He then received 25 IU/kg daily from day +3 to +7 postoperatively; FVIII:C and VWF:RCo levels were always between 50 to 150 IU/dL. Thromboprophylaxis with low-molecular weight heparin was started after the 2nd dose and continued for an additional 9 days. The clinical course was uneventful, and the patient was discharged on day 10.

In patients in whom desmopressin could not provide a sufficient hemostatic effect, either because of low VWF-FVIII peak values or because of a shortened half-life such as in cases 2 and 3 above, the use of virally-inactivated plasma-derived concentrates is the mainstay of treatment. Several intermediate and high-purity products containing both VWF and FVIII are licensed in Europe and North America for the treatment of VWD (Table 3), with a VWF/FVIII ratio close to 1. A highly purified plasma VWF concentrate containing very little FVIII has also been developed for the exclusive use in VWD.⁵⁶ However, as postinfusion levels of FVIII:C rise slowly, reaching a peak between 6 and 8 hours, co-administration of a priming dose of FVIII may be required if prompt hemostasis is required in patients with baseline FVIII:C levels of 30 IU/dL or lower.⁵⁷

As reported in Table 2, the goal of treatment in patients undergoing major surgery (or having a major bleeding) is to maintain VWF/FVIII plasma levels around 80 to 100 IU/dL for at least a couple of days and trough level above 50 IU/dL for an additional 5 to 7 days thereafter. This is usually achieved with a loading dose of 50 to 60 U/kg of VWF:RCo, followed by similar daily doses for the next 2 days.⁵⁸ VWF/FVIII concentrates are usually also labeled to their VWF:RCo content. When not, the FVIII content must be used to guide replacement therapy.

Heparin thromboprophylaxis in VWD patients undergoing major surgery is safe and is advised at least during replacement therapy when FVIII:C levels are >50 IU/dL.

Secondary long-term prophylaxis in type 2 VWD

Case 4. A 65-year-old woman with type 2B VWD associated with C1308R mutation was referred for evaluation of fatigue and dyspnea, which were progressively increasing over the last few months. She was repeatedly treated in the past with fresh frozen plasma, cryoprecipitate, and then VWF-FVIII concentrates for epistaxis, menorrhagia, bleeding at delivery, and as prophylaxis prior to dental extraction and an appendectomy. At admission, her hemoglobin level was 6.5 gr/dL and mean corpuscular volume was 65 fL. Serum iron and ferritin were markedly decreased. The patient reported passing black stools on some occasions during the last 1 to 2 months. On endoscopic examination, several small angiodysplastic malformations were evident throughout the large bowel; surgery was deemed not possible. The patient was treated with packed red cells and infusion of 50 U/kg of VWF for 3 consecutive days with clinical improvement. During the year following discharge, she was transfused with 54 U of packed red cells, and treated with >250 000 U of VWF for the same reason. The patient started prophylaxis initially with 25 to 40 U/kg of VWF thrice weekly for 2 months, and then twice weekly. Over the next year, she received 6 U only of packed red cells with a consumption of 208 000 U of VWF concentrate.

Some patients with VWD, especially type 3 with FVIII:C levels <5 IU/dL, may have frequent hemarthroses or recurrent spontaneous bleeding (eg, epistaxis in infancy) that can benefit from secondary long-term prophylaxis. Life-threatening, recurrent gastrointestinal bleeding from angiodysplastic mucosal lesions may represent a therapeutic challenge in VWD because surgical treatment is seldom feasible in elderly patients. Angiodysplastic bleeding is a well-recognized complication of VWD, and it does often occur at a younger age and almost exclusively in patients lacking HMWM. There are several reports of bleeding from gastrointestinal angiodysplasia occurring mainly in type 2A and type 2B, both characterized by the lack of HMW VWF multimers in plasma.^{39,59-64} A few patients with type 2, especially with types 2A and 2B, may benefit from prophylaxis to manage this type of bleeding, as in the presented case. However, replacement therapy significantly reduces but does not completely abolish transfusion requirement. Prospective trials are needed to evaluate the cost-effectiveness and the improvement on a patient's quality of life of prophylaxis in comparison with on-demand treatment, although clinical experience has been rated as satisfactory.⁶⁵⁻⁶⁷ Antineoangiogenesis drugs (such as thalidomide), atorvastatin, and octreotide could have a role as occasionally reported.⁶⁰ Use of selective VWF concentrates (eg, Wilfactin) may be considered for secondary prophylaxis of patients with high basal levels of FVIII, to lower thrombotic risk.

Reproductive issues in women with type 2 VWD

Case 5. A 27-year-old woman with type 2A VWD and S1506L mutation was referred at week 8 of her first pregnancy. Her BS at diagnosis was 14, and she suffered in the past from recurrent nosebleeds, menorrhagia requiring levonorgestrel to control heavy menstrual losses, and easy bruising. She was unresponsive to desmopressin and required prophylaxis with VWF-FVIII concentrates to cover surgery and tooth extraction. At beginning of pregnancy, her FVIII was 51 IU/dL, VWF:Ag 36 IU/dL, which at 8 months were completely normalized (133 IU/dL and 140 IU/dL, respectively), but her VWF:RCo rose from 4 IU/dL to 10 IU/dL only.

Case 6. A 32-year-old woman with type 2N VWD and homozygous R854Q mutation was referred at week 6 of her first pregnancy. Her BS at diagnosis was 8, and she suffered in the past from recurrent nosebleeds and post-tonsillectomy bleeding. At beginning of pregnancy, her FVIII was 21 IU/dL, VWF:Ag 48 IU/dL, and VWF:RCo 44 IU/dL. At the week 36, her VWF:Ag was 188 IU/dL and VWF:RCo 177 IU/dL, while her FVIII:C rose to 89 IU/dL. It was decided not to give any antihemorrhagic prophylaxis for a spontaneous vaginal delivery. No undue bleeding was seen, and the woman was discharged at day 5 without mishap.

Primary postpartum bleeding is observed in up to 37.5% of type 2 women not receiving FVIII prophylaxis,⁶⁸ and special care should be taken to avoid bleeding. This is particularly relevant in the 2 presented patients because of their lifelong history of mucous bleeding, suggesting greater bleeding risk (see “The relevance of bleeding history in guiding the optimal therapy” in this study). Pregnant VWD patients should be monitored for VWF:RCo and FVIII:C at least once during the third trimester of pregnancy. No intervention is recommended when FVIII:C and VWF:RCo levels are both around or higher than 50 IU/dL, which is always the case in type 1 VWD.⁶⁹ However, if responsive to DDAVP, women with levels only slightly above or around 50 IU/dL may receive a single dose of desmopressin at the beginning of labor, especially if epidural anesthesia is required.^{69,70} DDAVP can also be safely used in the first trimester of pregnancy to cover invasive procedures, such as villocentesis and amniocentesis.⁶⁹ Additional measures include managing the delivery without using ventouse or forceps and administering antifibrinolytic agents orally in the first week of puerperium to prevent delayed postpartum bleeding. There is no indication for cesarean section unless usual obstetrical indications exist.

In type 2A women, VWF:RCo almost invariably remains reduced and substitutive treatment is required to avoid bleeding at parturition. Usually, during labor and before epidural anesthesia (if needed), 40 IU/kg of VWF are administered, followed by the same dose daily for 3 to 4 days, as was done in case 5 (Table 2). Daily monitoring of the VWF:RCo level is recommended during the same period after parturition. In VWD type 2B, the increase of the abnormal VWF can cause or worsen thrombocytopenia⁷¹ and platelet concentrates have been sometimes transfused. The same therapeutic schedule proposed in Table 2 is recommended. In type 2M, the abnormal VWF:RCo/VWF:Ag ratio persists throughout pregnancy, but usually VWF:RCo reaches levels >50 IU/dL. Desmopressin

infusion may be however considered in women with significant bleeding history, especially for previous primary or secondary postpartum bleeding. In VWD type 2N, as shown for case 6, FVIII:C completely normalizes by the end of pregnancy, and antihemorrhagic treatment is seldom required.

Other than parturition, type 2 VWD women may present with several other gynecologic bleeding problems. Heavy menstrual losses, particularly at menarche, may be the first relevant bleeding symptom reported and leading to VWD diagnosis.^{72,73} Midcycle pain due to bleeding into the corpus luteum after ovulation has been described in up to 49% of women with type 1 VWD.⁷⁴ Corpus luteum bleeding may extend into the broad ligament, and even cause massive hemoperitoneum requiring blood transfusion and surgical drainage.⁷⁵ In type 2 VWD women with mild gynecologic bleeding, we recommend the use of tranexamic acid to control menstrual losses. However, in women with more severe bleeding, the use of oral contraceptives combined with pre-emptive use of desmopressin (if DDAVP responder) or VWF concentrate may be required. A levonorgestrel-releasing intrauterine device (Mirena) may also be useful to control menorrhagia.⁷⁶

In conclusion, an array of tests, easily available even in nonspecialized laboratories, allows an accurate diagnosis and typing of the different forms of type 2 VWD. In variant forms of VWD, testing for desmopressin response is of greatest importance in either the proband or related family members having the same VWF profile, as this compound may be conveniently used to treat common minor bleeding or procedures. The bleeding history should be carefully assessed at diagnosis by using a standardized approach, which may help identify those patients at greater risk of bleeding thereafter. A high index of suspicion is however required in young patients, who may present with a silent bleeding history and minor abnormalities of the screening tests. The therapeutic armamentarium is well standardized, readily accessible (at least in Western countries), and has a high safety profile, so that the risk of intractable bleeding because of VWF deficiency alone is exceptional.

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Authorship

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