Von Willebrand factor (vWF) is an adhesive and multimeric glycoprotein that is crucial for the initial adhesion and aggregation of platelets at sites of vascular injury, particularly through larger multimers, and it binds coagulation factor VIII (FVIII) in plasma, protecting it from inactivation and clearance\(^1\). vWF is synthesised in vascular endothelial cells and megakaryocytes and is stored, respectively, in Weibel-Palade bodies and alpha-granules and secreted in plasma and the subendothelial extracellular matrix\(^2,3\).

Von Willebrand's disease (vWD) is the most common inherited bleeding disorder and is characterised by great heterogeneity. The current classification of vWD identifies partial or complete quantitative vWF defects (types 1 and 3) or qualitative vWF defects (type 2)\(^4\).

The diagnosis of vWD is based on the bleeding history in combination with laboratory tests showing abnormalities in vWF, FVIII, or both. The assessment of the bleeding phenotype starts with the collection of a detailed history of all bleeding symptoms in the patient using a scoring system based on a structured questionnaire, usually referred to as the bleeding-assessment tool, which was recently developed and endorsed by the International Society on Thrombosis and Haemostasis (https://bh.rockefeller.edu/ISTH-BATR/)\(^5\).

The laboratory tests are based on measurement of vWF antigen and activity using mainly the von Willebrand factor-ristocetin cofactor activity assay (vWF:RCo). FVIII activity is also measured as a first line test because its level is frequently reduced. Additional tests, needed to distinguish and classify the types 2 vWD, include vWF multimer analysis, vWF collagen-binding activity (vWF:CB), vWF-FVIII binding and ristocetin-induced platelet aggregation (RIPA)\(^6\).

The severity of symptoms is usually proportional to the degree of the primary deficiency of vWF and the secondary deficiency of FVIII. The symptoms of vWD vary among patients, depending on the different type and subtype of disease, and also on age and sex. Clinically, patients with vWD exhibit a classic pattern of mucocutaneous bleeding, excessive haemorrhage after invasive procedures and, less commonly, soft tissue haematomas and joint bleeding, depending on the severity of disease\(^7\). In children with vWD, the most common symptoms are bruising and epistaxis, whereas in adults, the most frequent symptoms are haematomas and bleeding from minor wounds. In addition, the majority of patients (60-80\%) show bleeding after surgery or dental extractions. A well-known and serious bleeding complication is gastrointestinal bleeding in elderly patients with type 2 or 3 vWD\(^8\). In women with vWD, the primary symptoms is often heavy menstrual bleeding. The frequency of menorrhagia in women with type 3 vWD is 69\%\(^9\). The course of pregnancy is usually uneventful, but increased bleeding occurs at delivery (15\%), so pregnancies should be planned with input from a haematologist, obstetrician, and genetic counsellor to ensure the best outcomes\(^8,10\).

Non-replacement therapy with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is still the drug of choice during the bleeding episodes in milder cases of vWD (type 1 and some cases of type 2), since it can increase the endogenous vWF and FVIII in plasma\(^1,1-3\).

In addition, other biological therapies, such as oral contraceptives containing both progestin and oestrigen, are administered as adjuvant treatment in women with vWD who have gynaecological bleeding. Antifibrinolytic treatment with tranexamic acid may reduce menstrual blood loss\(^10\).

Patients who do not respond adequately to DDAVP or are to undergo major surgical procedures and patients with severe vWD (type 3, severe type 1, and many patients with type 2) may require vWF concentrates. The currently available plasma-derived concentrates contain vWF and FVIII in various ratios\(^11\). Both vWF and FVIII are raised by infusion of these plasma-derived concentrates containing a mix of vWF and FVIII, but after 6-8 hours endogenous production leads to a further increase in the level of FVIII. For this reason it is important to test FVIII and avoid very high levels that are associated with thrombotic risk, especially in elderly bed-ridden patients or during surgical procedures with higher baseline levels of FVIII\(^11,12,13\).

High-purity vWF concentrate with low amounts of FVIII (WilFactin) is also available and its use can be recommended in patients with normal FVIII or those with a high thrombotic risk. Infusion of only vWF with low amounts of FVIII will normalise levels of vWF instantaneously, without an immediate increase in FVIII.
levels. In the case of acute bleeding or urgent surgery, during which haemostatic levels of both factors need to be established immediately, infusion of high-purity vWF concentrate is problematic. Co-administration of a priming dose of FVIII is, therefore, needed to normalise both factors11,13,14.

An important alternative is represented by the development of a recombinant human vWF (rvWF, voncog alfa, Vonvendi) recently approved by the U.S. Food and Drug Administration. This is the first rvWF manufactured with a plasma-free method and the absence of animal proteins. This concentrate is characterised by the complete absence of FVIII and by the presence of ultra-large and high molecular weight vWF multimers. This product has significantly modified therapeutic strategies, particularly in patients with high baseline levels of FVIII and elderly subjects during surgery and prophylaxis15. Infusion of rvWF normalises levels of vWF instantaneously, whereas endogenous FVIII plasma levels reach haemostatic levels 6 hours after infusion. Therefore, in the case of acute bleeding, the first dose of rvWF must be associated with an additional dose of FVIII concentrate for those patients with low baseline FVIII levels. This can be avoided in patients with normal levels of FVIII at baseline, such as many type 1 and some type 2 vWD patients15.

More studies are needed on the indication for and dosage of the high-purity vWF concentrate and the novel rvWF, especially in different subgroups of patients, such as surgical patients, patients with major gastrointestinal bleeding from arteriovenous malformations and elderly patients.

On-demand treatment is the common strategy to manage patients with vWD. However, the prophylactic regimen successfully employed for patients with severe haemophilia has also been used for patients with severe vWD. Various studies have demonstrated the efficacy of a prophylactic regimen with reductions of bleeding rates, particularly for certain bleeding types (i.e. haemarthroses and haematomas)16,17. A recent prospective study in a small set of patients treated with a prophylactic regimen with dose escalation documented a significant reduction in the number of bleeding episodes, including gastrointestinal bleeding, joint bleeding and severe epistaxis18. Thus, a new perspective in the treatment of vWD is the use of prophylaxis even if there are no clear recommendations on the frequency and dosing.

In this issue of Blood Transfusion, Dr. Schinco with a group of Italian haematologists formulate the best diagnostic workflow for patients with vWD obtained by completing a 30-question survey and also based on their own clinical experience19. They report what could be the benefits of secondary long-term prophylaxis, how to select the product to use during the surgery and how to use the new high-purity vWF product with low content of FVIII.

Disclosure of conflicts of interest
FP received of honoraria or consultation fees by Freeline, Kedrion Biopharma, LFB, Octapharma. Honoraria for participating as a speaker at educational meetings organised by Ablynx, Bayer, Grifols, Novo Nordisk, and Sobi. She is a member of Ablynx and F. Hoffmann-La Roche Advisory Board.

Reference


