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Prophylactic management of patients with von Willebrand disease

Massimo Franchini, Omid Seidizadeh and Pier Mannuccio Mannucci

***Abstract*:** Von Willebrand disease, the most common inherited bleeding disorder that affects both males and females, is due to quantitative or qualitative defects of the multimeric glycoprotein von Willebrand factor, which cause mucous membrane bleeding but also soft tissue bleeding owing to the secondary deficiency of factor VIII. The aim of treatment is to correct this dual defect of hemostasis. In addition to the episodic management of bleeding episodes, therapy includes their short- or long-term prevention. Short-term prophylaxis is mainly warranted in order to provide effective hemostatic coverage to patients undergoing surgery or invasive procedures and to affected women at the time of delivery or during menstruations associated with excessive bleeding. The aim of long-term prophylaxis is to prevent bleeding in particular categories of patients at increased risk of frequent and spontaneous bleeding in the joints, nose, and gastrointestinal tract.

Keywords: bleeding, long term, prophylaxis, short term, von Willebrand disease

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Introduction

Von Willebrand disease (VWD) is, together with hemophilia A, the most common inherited bleeding disorder.[1] It affects both males and females and results from quantitative or qualitative defects of von Willebrand factor (VWF), a plasma glycoprotein endowed with essential platelet-dependent functions in primary hemostasis but also a carrier and stabilizer for factor VIII (FVIII) in the circulation.[2] VWD is classified into different types. Types 1 and 3 reflect partial or complete quantitative deficiency of VWF, whereas type 2 (2A, 2B, 2M, and 2N) reflects qualitative defects. Type 1 is the most common form and is transmitted as an autosomal dominant trait with incomplete penetrance. It is characterized by a mild to moderately severe reduction of the plasma levels of VWF antigen (VWF:Ag) and platelet-dependent VWF activity (i.e. ristocetin cofactor activity, VWF:RCo). In type 1, VWF is functionally normal, as is the pattern of plasma multimers, but FVIII levels are usually reduced, roughly in proportion to those of VWF. Type 1 patients display a spectrum of bleeding symptoms, with the severity usually correlating with the degree of VWF and FVIII deficiencies. Type 2A is the most frequent qualitative defect of VWF, mainly inherited with an autosomal dominant pattern. The hallmarks of type 2A VWF are a low VWF:RCo to VWF:Ag ratio (<0.7), lack of larger and intermediate size multimers, and impaired ristocetin-induced platelet agglutination in platelet-rich plasma. As for type 2A, inheritance of type 2B is autosomal dominant and laboratory hallmarks are heightened ristocetin-induced platelet aggregation, mildly reduced to normal FVIII and VWF:Ag, low VWF:RCo and absence of large multimers in plasma, even though an intact multimeric pattern is seen in some patients. In type 2M, the multimeric pattern is normal, but platelet-dependent or collagen binding activities of VWF are reduced. Type 2N is characterized by normal to mildly reduced VWF levels and a normal multimeric pattern but plasma FVIII levels are low due to increased clearance of this moiety which binds poorly to a qualitatively abnormal VWF. Therefore, type 2N resembles mild hemophilia A, and a differential diagnosis is warranted. Type 3, inherited as an autosomal recessive trait, is characterized by undetectable VWF levels in

Correspondence to:
Massimo Franchini
Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, 46100 Mantova, Italy.
massimo.franchini@asst-mantova.it

Omid Seidizadeh
Pier Mannuccio Mannucci
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico and University of Milan, Milan, Italy

plasma and very low FVIII plasma levels (1–5 IU/dl) so that patients usually have a severe bleeding tendency manifested not only by mucocutaneous hemorrhages (epistaxis, menorrhagia, and gastrointestinal bleeding) but also by hemarthroses, as in moderately severe hemophilia A.[2–4]

In VWD, the general aim of therapy is to correct the dual defect of hemostasis, that is, abnormal platelet adhesion–aggregation and intrinsic coagulation due to low FVIII levels. Therapeutic mainstays are endogenous VWF/FVIII replacement with the synthetic drug desmopressin (DDAVP), exogenous replacement with plasma-derived VWF-/FVIII-containing products, or plasma-derived or recombinant VWF concentrates devoid of FVIII.[5–10] The main features of the products approved by regulatory agencies for the treatment of VWD are presented in Table 1. Therapeutic adjuvants are platelet concentrates, combined estrogen–progestogen drugs, and antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid.

Unlike patients with severe hemophilia, most patients with VWD generally have less frequent and clinically severe bleeding, so that they usually receive treatment episodically at the time of bleeding, in anticipation of invasive procedures, at menstruation, during and after labor, or after trauma. Exceptions are patients with more clinically severe forms, who may need long-term prophylactic therapy, particularly if they bleed repeatedly into the joints, nose, and gastrointestinal tract.[11,12] In patients with type 3 VWD, joint bleeds often start during childhood and may be associated with the development of arthropathy and a poor health-related quality of life.[13] Vascular malformations (angiodysplasia), more common in patients with type 2 and type 3, cause recurrent bleeding in the gastrointestinal tract (85%).[14,15] Epistaxis, particularly frequent in children, is usually not life-endangering but alarming for children and parents.

With this background, this narrative review focuses on the short-term and long-term prophylactic management of VWD patients. It critically reflects the available evidence stemming from the literature, but also the long-standing, real-life experience of the authors. This approach is not in contrast but complementary with recent guidelines for the management of VWD developed by four scientific societies or consumer organizations, which used the *G*rading of *R*ecommendation *A*ssessment *D*evelopment and *E*valuation (GRADE) for this purpose.[7]

Search strategy

The Medline and PubMed electronic database was searched with a nonsystematic approach for full-text publications on the short-term and long-term prophylactic management of VWD. The Medical Subject Heading and key words used for the search were as follows: 'VWD', 'von Willebrand disease', 'bleeding prevention', 'short-term prophylaxis', 'long-term prophylaxis', 'secondary prophylaxis', 'surgery', 'recurrent bleeding', 'von Willebrand factor concentrate', 'desmopressin', 'DDAVP', 'recombinant von Willebrand factor', 'menstruation', 'gastrointestinal bleeding', 'joint bleeding' 'pregnancy bleeding', and 'post-partum bleeding'. We also screened the reference lists of the identified publications and the most relevant review articles for additional items not captured in our initial literature search.

Short-term prophylaxis

The choice of the best treatment regimen for short-term prophylaxis lies among desmopressin (DDAVP), VWF-FVIII plasma-derived products, and products containing only VWF (plasma-derived or produced by recombinant DNA technology).

Desmopressin (DDAVP)

This synthetic drug is effective only when adequate and functionally normal endogenous VWF is present in cellular compartments, from which it is released into patients' plasma upon intravenous, subcutaneous, or nasal administration. An intravenous infusion of DDAVP (0.3 µg/kg) is recommended as a test to establish individual responses and accordingly plan the optimal clinical use of the drug. An adequate response is defined as an increase in baseline VWF activity by at least two times and a sustained increase in both VWF and factor VIII (FVIII):C levels to more than 50 IU/dl for at least 4 h.[3,7] DDAVP is the first choice for patients with type 1 VWD with baseline VWF and FVIII plasma levels higher than 10 IU/dl,[16,17] with the exception being the subset of patients characterized by a markedly

Table 1. Mean characteristic of concentrates of von Willebrand factor/factor VIII and von Willebrand factor alone approved for the treatment of von Willebrand disease.

Product, manufacturer	Purification method	Viral Inactivation method	VWF:RCo/Ag (ratio)*	VWF:RCo/FVIII (ratio)*
Alphanate, Grifols	Heparin ligand CT	S/D + dry heat (80°C, 72 h)	0.9	1.2
Factor 8Y, Bio Products Laboratory	Heparin/glycine precipitation	Dry heat (80°C, 72 h)	0.6	1.8
Fanhdi, Grifols	Heparin ligand CT	S/D + dry heat (80°C, 72 h)	0.8	1.2
Haemate P, CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 h)	0.8	2.4
Immunate, Baxalta	Ion exchange CT	S/D + vapor heat (60°C, 10 h)	0.6	0.8
Talate, Takeda	Ion exchange CT	S/D + vapor heat (60°C, 10 h)	0.5	1.1
Voncento/Biostate, CSL Behring	Multiple precipitation + albumin ligand CT	S/D + dry heat (80°C, 72 h)	0.8	2.4
Vonvendi, Takeda	Recombinant VWF, IA purification	NF	–	Negligible FVIII
Wilate, Octapharma	Ion exchange + size exclusion CT	S/D + dry heat (100°C, 72 h)	0.9–1.0	1.0
Wilfactin, LFB	Ion exchange + affinity CT	S/D + NF + dry heat (80°C, 72 h)	0.7	60

Ag, antigen; CT, chromatography; FVIII, factor VIII; IA, immune-affinity; NF, nanofiltration; RCo, ristocetin cofactor; S/D, solvent/detergent; VWF, von Willebrand factor.
*Data derived from the WFH Online Registry of Clotting Factor Concentrates, 2018.

shortened plasma survival of VWF, that is, type 1C. There are limitations to using DDAVP in VWD cases other than type 1. In type 2A, the drug is of little value because VWF levels are raised but remain dysfunctional. Type 2M patients have a variable pattern of response and in many cases the use of DDAVP is inappropriate. In type 2N, the drug usually corrects FVIII deficiency but with a short plasma half-life.[8] In type 2B, it is contraindicated because of the potentially transient appearance or aggravation of thrombocytopenia and related higher risk of bleeding. Patients with type 3 are unresponsive.[8] Moreover, DDAVP use is often inappropriate in patients undergoing major surgery or labor, because they may require repeated doses and are thus at risk of developing tachyphylaxis.

Plasma-derived VWF/FVIII concentrates

These products, with the characteristics summarized in Table 1, are recommended at the dosages shown in Table 2[6] in cases with no or inadequate response to DDAVP. Table 3 summarizes data on the efficacy of VWF/FVIII for short-term bleeding prophylaxis in patients undergoing surgery or invasive procedures according to our critical analysis and compilation of the main reports.[18–37]

Haemate P

The majority of data on the prophylactic use of VWF-/FVIII-containing products in surgical procedures, reported in Table 3, regard this product as the first to be largely employed in VWD.[18] A prospective multicenter trial reported in 2004 investigated its clinical use in surgery and documented both safety (no serious drug-related adverse events) and efficacy (100% of hemostatic efficacy).[19] In a subsequent study,[20] for the first time, it was decided to employ pharmacokinetic analysis to choose the optimal dosage for patients undergoing elective surgery. It was shown that Haemate P provided excellent or good surgical hemostasis in the great majority of cases. This study also demonstrated that *in vivo* recovery is constant over a wide range of dosages of the concentrate with a linear dose–response relationship and that the pre-treatment pharmacokinetic analysis provided a reliable basis for serial dosage

Table 2. Recommended dosage regimens of concentrates of von Willebrand factor/factor VIII or von Willebrand factor only in patients with von Willebrand disease undergoing surgical prophylaxis.

Indication	Dosage regimen	Target plasma VWF:RCo/FVIII:C level*
Major surgery	40–60 IU/kg once daily until wound healing is complete	50–100 IU/dl; maintain levels for 5–10 days
Minor surgery	30–50 IU/kg once daily (may require for only 1–3 days)	>30 IU/dl
Dental extraction or other invasive procedures	20–30 IU/kg (usually a single dose prior to procedure)	>30 IU/dl for >12 h

*These dosages are indicated for patients with von Willebrand disease with reduced factor VIII activity/von Willebrand factor risotecin cofactor levels (<10 IU/dl).

decisions. Another prospective study on the management of elective surgery in adult and pediatric patients showed that long-lasting effective hemostasis was achieved in 94% of the cases.[21] Haemate P was also employed for bleeding episodes and surgical procedures: the rates of good-to-excellent responses were 97% overall and 99% for surgical procedures in the frame of a large retrospective study in Canada.[22] An experience in Italy with patients undergoing surgical or invasive procedures[23] showed that the concentrate was safe and effective in bleeding prevention. In a retrospective cohort of 100 patients, half of them undergoing surgical or invasive procedures, clinical responses were rated excellent/good in 97% of cases.[24] A more recent prospective study evaluating safety and efficacy of a new volume-reduced formulation showed good to excellent treatment response in 97% of patients undergoing surgery or invasive procedures.[25] Finally, a pooled and comparative analysis of data from clinical studies in the United States and European Union of this widely employed product showed once again its overall hemostatic efficacy and safety in surgical settings.[26]

Alphanate

A prospective evaluation of this concentrate, published in 2002, was based on data from patients who received short-term prophylaxis for surgical or invasive diagnostic procedures.[27] In type 3 VWD, the half-life of FVIII activity (FVIII:C) was approximately twice that of VWF:Ag due to the endogenous production of FVIII:C following VWF replacement. Of patients on short-term prophylaxis for surgery or invasive procedures, 96% had favorable clinical responses.[28] Similar efficacy rates were subsequently observed[29] in patients treated prophylactically at the time of surgical or invasive procedures with the VWF/FVIII concentrate Fanhdi, which is very similar in characteristics and manufacturing to Alphanate.[29] A high hemostatic efficacy was also observed with the VWF/FVIII Wilate in major and minor surgical procedures.[31] Other plasma-derived products, originally developed for the treatment of hemophilia A, were more recently approved by regulatory agencies also for the treatment of VWD cases with poor or inadequate response to DDAVP. Their characteristics are shown in Table 1 and the main clinical findings are shown in Table 3.

On the whole, short-term prophylaxis with all the approved plasma-derived VWF/FVIII products in patients undergoing surgical or invasive procedures showed excellent and efficacy profiles, with hemostasis being judged excellent or good in 93–100% of cases. The optimal management of patients undergoing surgery may involve a pharmacokinetic analysis in order to tailor loading and maintenance dosages of VWF/FVIII products, although the phenotypic complexity and variability of VWD make this approach much more problematic than in hemophilia A.[38] In addition, our analysis of the available studies suggests that along with VWF levels, FVIII plasma levels should be measured daily in the postoperative period, with the goal of not only monitoring hemostasis but also preventing the occurrence of very high plasma levels (more than 150 IU/dl) which may increase the risk of venous thromboembolism.[7,39] Indeed, rare thrombotic adverse events have been reported in VWD patients treated with VWF/FVIII concentrates, suggesting that both VWF and FVIII levels should be monitored.[40–42] Continuous concentrate infusion may be preferable to bolus infusion in order to avoid over-exposure to FVIII, but

Table 3. Main literature data on short-term surgical prophylaxis with concentrations of von Willebrand factor/factor VIII or von Willebrand factor only in von Willebrand disease.

Author	Product	Patients/surgical procedures	VWD types	Type of intervention	Median loading dose	Hemostatic efficacy (%)*
Thompson *et al.*[19]	Haemate P	39/42	16 type 1, 9 type 2, 8 type 3	25 major, 17 minor surgery	82.3 (range: 32.5–216.8) VWF:RCo IU/kg	100
Lethagen *et al.*[20]	Haemate P	29/29	10 type 1, 11 type 2, 8 type 3	16 major, 11 minor surgery	62.4 (range: 50.1–87.0) VWF:RCo IU/kg	96
Gill *et al.*[21]	Haemate P	35/35	12 type 1, 10 type 2, 13 type 3	25 major, 7 minor, 3 oral surgery	61.2 (range: 17.4–113.9) VWF:RCo IU/kg	94
Lillicrap *et al.*[22]	Haemate P	97/73	26 type 1, 20 type 2, 21 type 3	73 surgery	69.1 (range 11.9–222.8) VWF:RCo IU/kg	99
Franchini *et al.*[23]	Haemate P	26/43	19 type 1, 7 type 2	14 major, 11 minor, 11 oral surgery, 7 IP	48.8 (range: 27.3–81.1) VWF:RCo IU/kg	98
Federici *et al.*[24]	Haemate P	56/73	19 type 1, 27 type 2, 10 type 3	17 major, 28 minor, 19 oral surgery, 9 IP	80.0 (range: 27–146) VWF:RCo IU/kg	97
Castaman *et al.*[25]	Haemate P	55/126	26 type 1, 15 type 2, 12 type 3	126 surgery or IP	40.3 (range: 5–810.8) VWF:RCo IU/kg	97
Mannucci *et al.*[27]	Alphanate	39/71	6 type 1, 19 type 2, 14 type 3	71 surgery or IP	60 (range: 20–76) VWF:RCo IU/kg	96
Rivard *et al.*[28]	Alphanate	39/61	18 type 1, 12 type 2, 9 type 3	12 major, 28 minor surgery, 21 IP	NI	94
Federici *et al.*[29]	Fanhdi	14/14	5 type 1, 7 type 2, 2 type 3	7 major, 5 minor, 2 oral surgery	Range: 17–92 IU FVIII: C/kg/day	93
Federici *et al.*[30]	Fanhdi, Alphanate	120/131	56 type 1, 54 type 2, 10 type 3	45 major, 24 IP, 57 oral surgery, 5 delivery	48 (range: 11–137) VWF: RCo IU/kg	99
Windyga *et al.*[31]	Wilate	32/57	4 type 1, 9 type 2, 19 type 3	27 major, 30 minor surgery	41 VWF:RCo IU/kg	96
Srivastava *et al.*[32]	Wilate	28/30	7 type 1, 2 type 2, 21 type 3	21 major, 9 minor surgery	52.1 (range: 27–7) VWF:RCo IU/kg	97
Batty *et al.*[33]	Wilate	34/70	10 type 1, 19 type 2, 5 type 3	22 major, 29 major, 19 oral surgery	42.1 (range: 11.8–117.5) VWF:RCo IU/kg	94
Shortt *et al.*[34]	Biostate	43/58	26 type 1, 12 type 2, 5 type 3	24 major, 34 minor surgery	31 (range: 9–62) FVIII:C IU/kg	100
Dunkley *et al.*[35]	Biostate	19/29	5 type 1, 9 type 2, 6 type 3	10 major, 19 minor surgery	43.0 (range: 27.3–118.2) FVIII:C IU/kg	100
Borel-Derlon *et al.*[36]	Wilfactin	50/108	5 type 1, 27 type 2, 18 type 3	67 surgery, 43 IP	41.8 (range 14.2–74.5) VWF:RCo IU/kg	100
Peyvandi *et al.*[46]	Vonvendi	15/15	3 type 1, 4 type 2, 8 type 3	10 major, 4 minor, 1 oral surgery	55.1 (range: 36.1–59.9) rVWF IU/kg	100

FVIII:C, factor VIII coagulant activity; IP, invasive procedure; NI, not indicated; rVWF, recombinant von Willebrand factor; VWD, von Willebrand disease; VWF: RCo, von Willebrand factor ristocetin cofactor.
*Excellent or good.

this approach does not eliminate the need to monitor plasma levels.[43]

VWF products

Wilfactin

This high-purity VWF concentrate almost devoid of FVIII (Table 1) is produced from human plasma and its efficacy and safety were prospectively studied in patients with clinically severe forms of VWD.[36] Hemostatic outcome was judged excellent or good in all the patients undergoing surgical or invasive procedures and no adverse thrombotic complications were recorded. However, for emergency surgery, a priming dose of a FVIII-containing plasmatic product had to be co-administered with the first VWF infusion in order to increase FVIII:C when patients' baseline levels were considered inadequate for hemostasis (i.e. lower than 40–50 IU/dl).[36] This pioneering clinical study on the use of VWF-only replacement established the feasibility, efficacy, and safety of this novel therapeutic approach; these findings were recently confirmed by a large retrospective analysis of the data stemming from 5 years of use of Wilfactin in France.[37]

Vonvendi

A recombinant VWF concentrate (vonicog alfa) has been more recently produced and approved based on its efficacy and safety profile established in phase I and III trials, in which it was used at a fixed dosage ratio together with a recombinant FVIII product.[44,45] When infused alone, vonicog alfa rapidly produced (within 6 h post-infusion) and sustained (for 72 h) hemostatically effective plasma FVIII:C levels.[44] Results of a phase III study assessing this product in elective surgery further supported its hemostatic efficacy, which was rated as excellent or good in all the surgical operations.[46]

On the whole, the aforementioned clinical studies of VWF products such as Wilfactin and Vonvendi summarized in Table 3 established that the historical therapeutic use of products such as desmopressin or VWF-FVIII targeted to correct the dual defect of FVIII and VWF at the same time should no longer be considered the only paradigm of management, because the sole replacement of the primarily deficient VWF manages to stabilize endogenous FVIII in plasma with patterns and timings compatible with an effective clinical use.

Another potential application of short-term prophylaxis in VWD is for the management of pregnant women at the time of labor with the goal of avoiding postpartum hemorrhage. The management of deliveries in VWD patients must be optimized, because of a high rate of postpartum hemorrhage[47] occurs if the post-treatment increase of VWF/FVIII fails to reach the levels of normal women or untreated women with milder forms of VWD.[48–50] Although plasma levels of VWF and FVIII increase during pregnancy, prophylactic treatment with VWF/FVIII products is warranted at the time of delivery when plasma levels are lower than 50 IU/dl.[7,47] Delayed postpartum hemorrhage may occur in some women, so that continued monitoring or treatment for at least 2 weeks after delivery is recommended.[48,49]

Long-term prophylaxis

The definition of long-term prophylaxis encompasses replacement therapy administered once weekly and for a period of at least 6 months.[7] VWD warrants long-term prophylaxis mainly in cases with a severe bleeding phenotype (i.e. hemarthroses with target joints and arthropathy). In such individuals, who generally have type 3 and more seldom severe type 1 VWD, long-term prophylaxis may be the optimal therapeutic approach instead of on-demand treatment when the occasion is a bleed.[51–53] A particularly challenging condition is angiodysplasia-related gastrointestinal bleeding, which occurs more frequently at older ages, mainly in type 2 and 3 patients, all lacking high-molecular-weight multimers. This manifestation is often poorly controlled by local hemostatic or surgical measures or by on-demand VWF/FVIII replacement, notwithstanding long periods of treatment.[51]

Data on secondary prophylaxis, generated over the last 15 years,[12,54–61] are summarized in Table 4. Pioneering experience was gained in Sweden in patients with severe disease,[53] mostly type 3. The main indications to initiate prophylaxis were recurrent nose, mouth, and joint bleeds.[53] The number of bleeds was lowered by prophylaxis and children starting this regimen before the age of 5 years had no joint bleeds and none developed

arthropathy. Secondary long-term prophylaxis was also retrospectively evaluated in 11 patients (PRO.WILL study)[56] to whom it was given in order to prevent recurrent bleeding, mostly gastrointestinal and joint bleeding. Clinical responses were excellent or good in all cases, with a significant reduction in the annual historical consumption of VWF/FVIII concentrate, number of transfused blood units, and days spent in hospital. These early findings were confirmed by a small randomized study that demonstrated the superiority of secondary prophylaxis *versus* on-demand treatment.[57] More recently, the large, international, and multicenter VWD Prophylaxis Network (VWD PN) analyzed, retrospectively or prospectively, the efficacy of long-term prophylaxis with VWF/FVIII concentrates.[58] In the retrospective cohort, 59 patients, most of whom with type 3 VWD, were enrolled: the main indications for initiation of prophylaxis included epistaxis (23.6%), gastrointestinal bleeding (23.6%), and joint bleeding (21.8%). The effect of prophylaxis on the annualized bleeding rate was more pronounced for joint bleeding (median reduction 86%) and was attributed to the impact of higher FVIII:C levels obtained and sustained during treatment. The rate of favorable outcomes was lower for gastrointestinal bleeding (median reduction 49%), confirming the greater difficulty in managing this type of bleeding than other bleeds. No thrombotic complications were recorded.[62] In the VWD PN extension study, data from 105 patients were collected retrospectively or prospectively. There was a reduction in annualized bleeding rates, with the highest positive impact on epistaxis (−86.7%), joint bleeding (−86.9%), and menorrhagia (−100%), and again with the lowest impact on gastrointestinal bleeding (−44.3%). The most significant decrease in the overall bleeding rate was obtained in type 3 VWD.[62] A dose of 50 VWF:RCo IU/kg two or three times a week was employed in most cases with severe disease in the context of a prospective dose-escalating study, which showed a marked reduction of bleeding episodes.[59] Initiation of prophylaxis also had a positive impact on the number of hospitalizations. Similar findings of excellent efficacy were documented in a larger cohort that implemented long-term prophylaxis was implemented in adolescents and young adults.[63] Recurrent bleeding stopped in practically all cases and the monthly bleeding frequency as well as the bleeding score was significantly lowered in comparison with those prior to prophylaxis.[62] Moreover, following administration of a VWF/FVIII concentrate in pediatric patients, a lower rate of major bleeds was reported among those on prophylaxis (3.3%) than among those receiving on-demand therapy.[64]

Although inhibitor development in VWD is much less frequent (5–10%) than in hemophilia A (30%), management of this rare complication is challenging. Emicizumab, a humanized bispecific antibody approved for the treatment of hemophilia A, has been used off-label for prophylaxis in a small number of patients with type 3 VWD with inhibitory alloantibodies,[65,66] because this product mimics the deficient coagulant activity of FVIII, even though it is without effect on VWF deficiency or dysfunction.

In VWD, the pharmacoeconomic data and associated cost–benefit analysis of long-term prophylaxis *versus* on-demand treatment are not as well defined as in hemophilia. A report showed that in severe cases VWF replacement with low FVIII levels is a cost-effective treatment option.[67] Recently in the United States, long-term prophylaxis with the recombinant VWF concentrate was compared with on-demand treatment by using a Markov state transition model, which showed that prophylaxis is a cost-effective strategy in severe forms of VWD and avoids costly hospital admissions.[68]

Collectively, the results of these studies, reported in Table 4, document the feasibility and efficacy of secondary long-term prophylaxis in VWD. Nevertheless, uncertainties remain regarding the optimal dose and frequency of concentrates for prophylactic regimens as well as the duration of such regimens. VWF concentrates devoid of FVIII may be useful in patients who need prophylaxis, because such concentrates avoid the administration of exogenous FVIII present in plasma-derived VWF/FVIII products, thereby preventing or at least minimizing the development of very high plasma levels of FVIII:C and thus the need for laboratory monitoring. However, licensing authorizations of vonicog alfa do not currently include this indication, although phase III studies are ongoing to explore its use for secondary prophylaxis (NCT02973087) and in pediatric patients (NCT02932618).

Table 4. Main data on long-term prophylaxis with concentrates of von Willebrand factor/factor VIII or von Willebrand factor only products in von Willebrand disease.

Author	Patients (n)	Median age at start of prophylaxis (range)	VWD types	Median FVIII doses (range)	Indication (*n*)	Main results
Castaman *et al.*[25]	31	NI	9 type 1, 6 type 2, 16 type 3	30 IU/kg (1–169) 2–3 times weekly	GI and joint bleeding, menorrhagia	Excellent/good responses in 93% of cases
Berntorp and Petrini[53]	35	13 years (1–61)	1 type 1, 6 type 2, 28 type 3	24 IU/kg (12–50) 1–3 times weekly	Mucocutaneous and joint bleeding	Number of bleeds reduced after prophylaxis. No arthropathy in children starting prophylaxis before 5 years of age
Federici[56]	11	NI	1 type 1, 5 type 2, 5 type 3	NI	GI (7) and joint (4) bleeding	Excellent/good responses in 100% of cases. Reduction of annual consumption of VWF/FVIII concentrates, number of transfused blood units and days spent in hospital
Holm *et al.*[59]	105	26 years (1–81)	13 type 1, 38 type 2, 54 type 3	NI	Epistaxis (33%), GI (23%) and joint (23) bleeding	Reduction of ABR was statistically significant for all bleeding indications
Abshire *et al.*[60]	11	34.6 years (3–80.6)	6 type 2, 5 type 3	50 IU/kg 2–3 times weekly*	Epistaxis (6), GI (3) and joint bleeding (3)	Median ABR score decreased from 25.0 (IQR: 12.0–51.2) to 6.1 (IQR: 3.1–29.0)
Abshire *et al.*[62]	59	22.4 years (2.3–77.2)	5 type 1, 20 type 2, 34 type 3	40–60 IU/kg (30–6)* 2–3 times weekly	Epistaxis (13), GI (13) and joint bleeding (12)	Prophylaxis was effective in reducing the association bleeding rate, particularly joint bleeding
Halimeh *et al.*[63]	32	Children: 13 years, adolescent: 7 years, adults: 12 years	4 type 1, 15 type 2, 13 type 3	40 IU/kg (20–47) 2–3 times weekly*	GI and joint bleeding	Recurrent bleeding stopped in 31 patients. Monthly bleeding frequency significant reduced ($p < 0.001$)

ABR, annualized bleeding rate; FVIII, factor VIII; GI, gastrointestinal; IQR, interquartile range; NI, not indicated; VWD, von Willebrand disease.
*VWF:RCo IU/kg.

Final remarks

A wide array of efficacious therapeutic options is currently available for the management of VWD patients,[69,70] who have thus obtained a life-expectancy not different from that of their age peers without the disease, at least in high-income countries. However, women with the disease have a number of limitations to their daily life activities due to menstruation,[71] as well as low scores of health-related quality of life.[72] The healthcare burden of VWD is generally lower than that of hemophilia, as documented by a study which estimated that the number of VWD patients who need replacement therapy is about one-tenth of

those with hemophilia who need such therapy.[73] Nevertheless, there is growing interest in the long-term prophylactic management of selected VWD patients characterized by a prominent bleeding phenotype even though, in contrast to hemophilia A, the superiority of prophylaxis over on-demand treatment remains to be proven by a randomized clinical trial.

A particularly challenging condition to manage by means of long-term prophylaxis is bleeding in the gastrointestinal tract due to angiodysplasia, that is, the first and main cause of hospital admissions in patients with VWD. Perhaps the newly available recombinant VWF may help to tackle this problem, because, in contrast to other products, it has an intact multimeric structure, but at the moment this approach remains hypothetical. A personalized pharmacokinetic-guided dosing of replacement therapy is difficult to perform in VWD, owing to the complexity of the different types of VWD and the dual factor deficiency. Although the available data support the efficacy and safety of long-term prophylaxis in VWD, a number of issues remain to be addressed by prospective trials, such as dosing, frequency cost-effectiveness of this regimen *versus* an on-demand regimen, and impact on quality of life. Moreover, the choice of this regimen should be periodically re-evaluated.[7] In conclusion, we hope that the narrative suggestions for clinical management provided here on the basis of our experience will complement existing guidelines for the optimal management of VWD. We also hope that more robust evidence will be generated in the areas that we have highlighted above as requiring further studies.

Author contributions

M.F. and P.M.M. reviewed the literature and wrote the article. P.M.M. and O.S. revised the manuscript.

Conflict of interest statement

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ORCID iD

Pier Mannuccio Mannucci https://orcid.org/0000-0002-1915-3897

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