Current challenges in the diagnosis and management of patients with inherited von Willebrand's disease in Italy: an Expert Meeting Report on the diagnosis and surgical and secondary long-term prophylaxis

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Abstract

Recent advances in the care of von Willebrand's disease (vWD) have allowed the majority of patients to be managed adequately. Even in the more severe forms, it is now possible to control recurrent bleeding through secondary long-term prophylaxis with von Willebrand factor-containing concentrates. Moreover, in the setting of surgical prophylaxis, the combination of interdisciplinary management and close patient monitoring yields a positive outcome in nearly all cases, although safety concerns remain. In clinical practice, the effectiveness of therapy is hindered by the difficulties in making a rapid, yet accurate diagnosis, in identifying the subgroup of bleeders who may benefit most from a specific strategy, and in selecting the optimal product and regimen.

Since specific guidelines for heavy bleeders requiring short- and long-term prophylaxis are still lacking, sharing the experience of experts dealing with vWD patients on a daily basis is crucial to fill gaps in information relating to patient management. To address this important issue, 13 Italian haematologists met in Milan on April, 2, 2016 and in Florence on July, 9, 2016. A 30-question survey constituted the input to discuss (i) optimisation of the diagnostic workflow for vWD, (ii) the characteristics of patients who may benefit from secondary long-term prophylaxis (in particular with the purified von Willebrand factor concentrate with a low content of factor VIII), (iii) the key elements to consider when selecting a concentrate and (iv) the pre-operative and post-operative management of vWD patients. A summary of the main points covered is provided in this report.

Keywords: von Willebrand's disease, secondary long-term and surgical prophylaxis, von Willebrand factor-containing concentrates, management.

Introduction

von Willebrand's disease (vWD) is a rare inherited bleeding disorder (Orphanet number: ORPHA903) caused by the quantitative or qualitative deficiency of von Willebrand factor (vWF)[1]. The clinical hallmark of vWD is mucocutaneous bleeding (e.g. epistaxis, menorrhagia and gastrointestinal bleeding), but in severe forms, in which factor VIII (FVIII) levels are also significantly reduced, spontaneous haemarthroses or haematomas may occur. The severity of bleeding phenotype is still not well defined within different types of vWD[2,3], and yet this is actually the key factor driving treatment decisions. As the bleeding pattern can affect quality of life and even survival[3-7], it is essential to optimise the diagnostic process in order to ensure the most adequate therapeutic strategy promptly in patients presenting with spontaneous bleeding. Unfortunately, in several Centres worldwide the correct clinical and laboratory diagnosis is still hampered by the marked heterogeneity of vWD phenotypes and the need for multiple, sometimes technically complex, tests[1,8-10].

In most patients with mild/moderate vWD, desmopressin (DDAVP) is an effective and affordable treatment option. For patients who do not respond,

or respond inadequately, or have contraindications to DDAVP, replacement therapy with purified vWF-containing concentrates is indicated. In the more severe forms, treatment aims at controlling recurrent bleeding and associated complications (e.g. arthropathy in the case of joint bleeding) and preventing life-threatening haemorrhages. This goal may be achieved through secondary long-term prophylaxis with concentrates, which, despite the lack of clear-cut evidence, seems to be an effective strategy for reducing the severity and frequency of bleeding episodes in vWD patients[11-16]. In Italy, as well as in other European countries, several plasma-derived vWF-containing concentrates have been licensed[17], including a high-purity vWF concentrate with a very low FVIII content (Wilfactin®; LFB, Les Ulis, France)[18], whose efficacy and safety in treating spontaneous bleeding episodes was demonstrated in a prospective study of 50 patients with severe vWD[13]. This concentrate also had the ability to reduce the number of bleeding episodes when administered as long-term prophylactic treatment[13,16] and to reduce the total FVIII consumption for break-through bleedings[13]. Interestingly, preliminary results from four patients on secondary long-term prophylaxis with Wilfactin confirm that such an approach is cost-effective, even in this setting[16]. In fact, despite a high cost *per se*, its use was associated with decreased consumption of hospital resources, fewer working days lost because of bleeds and a better quality of life[16].

Nevertheless, defining the potential candidates and the most suitable product and regimen for secondary long-term prophylaxis remains a challenge. Patients with severe disease who may benefit from prophylactic therapy are mostly affected by type 3 vWD, but cases of type 1, 2A, 2B and 2M have also been reported[3,11-13,16,19]. Notably, a recent 1-year prospective study of 796 Italian patients with different types of vWD showed that one of the bleeding scores (BSs) so far identified[20] may be a simple and inexpensive parameter to identify long-term prophylaxis requiring individuals regardless of disease type[3]. Currently available vWF-containing products differ mainly by the amount of FVIII, the activity of vWF, the presence of vWF high molecular weight multimers and the purification steps[17,18,21-24]. Furthermore, not all the concentrates are labelled for their vWF content, which should guide treatment according to recent international guidelines (American and European). Finally, there is no consensus on a standard regimen (dose and interval of concentrate administrations, duration of treatment) for any licensed product and so the regiments should be tailored on a case-by-case basis[3,15,25,26]. Some of these issues remain critical also in the management of vWD patients requiring surgery or invasive procedures. In order to prevent excessive bleeding, patients undergo short-term prophylaxis with DDAVP, continuous factor infusion and/or antifibrinolytics. According to the Italian recommendations for the management of vWD patients[27], a pharmacokinetic study is advised prior to the procedure, in order to tailor the loading and maintenance doses of concentrate. Moreover, the plasma levels of vWF and FVIII should be monitored before, during and after surgery, to prevent an excessive increase of FVIII[27]. The dose of concentrate, the administration schedule and the target levels of FVIII vary depending on the type of procedure. The combination of interdisciplinary management and close patient monitoring provides good to excellent haemostasis in most cases[28,29], but there is no consensus on the optimal product, regimen or factor levels to be achieved[27,30,31]. Furthermore, complications such as acute and delayed bleeding, transfusion, inhibitor development and thrombosis may occur in some patients[7,29].

To provide the optimal prophylactic strategy (in both surgical and secondary long-term regimens), it is of utmost importance to identify the vWD patients who may benefit the most from a specific vWF concentrate according to the content of FVIII and vWF, taking into account both the patients' clinical and laboratory characteristics and the features of each product.

With this background, 13 Italian experts in the field of vWD, from 11 Centres spread across the country, met in Milan on April 2, 2016 and in Florence on July, 9, 2016. Participants completed a 30-question survey covering some of the most critical aspects of vWD diagnosis and treatment encountered in clinical practice. Secondary long-term prophylaxis and surgical prophylaxis employing Wilfactin® were addressed in detail. Based on the results of the survey (the multiple-choice questions related to each topic are presented in Tables I-IV), a thorough discussion was triggered, which is summarised here.

How can the diagnostic workflow for von Willebrand's disease be optimised?

To ensure the best treatment to patients presenting with spontaneous bleeding, the diagnosis must be as accurate as possible, and employ tests feasible for virtually all Centres[10,32]. In the experts' opinion, this issue represents the most urgent, unmet need in the management of vWD patients in Italy, accounting for the open debate and the ongoing research efforts aimed at optimising the diagnostic procedure for the disease[1,9,10,32,33].

In line with these remarks, the first part of the survey focused on the importance of integrating information from the family bleeding history, the BSs[34] and specific laboratory tests[10]. A positive personal history of bleeding and reduced vWF activity levels were acknowledged

by the experts as the minimal criteria required to make the diagnosis of vWD (Table I, Question [Q]1). They also acknowledged the importance of questionnaires currently used to collect the bleeding history and calculate the BSs[3,20] (Table I, Q2), although considering such questionnaires time-consuming and cumbersome in a real-life clinical setting; even the standardised bleeding assessment tool (BAT), currently advised to calculate the BSs (Table I, Q3), raised some perplexity. In this context, the strong need for standardised criteria clearly defining the bleeding diathesis was underlined; notably, the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee Joint Working Group has recently agreed on the necessity to establish a single BAT to standardise the reporting of bleeding symptoms[34]. Experts in inherited bleeding disorders have, therefore, formulated a Consensus ISTH-BAT that comprises a questionnaire producing a BS[34] (https://c.ymcdn.com/sites/www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf). Unlike in previous tools, bleeding frequency is also considered and this BAT may be employed in both paediatric and adult populations. The ISTH Working Group has recommended its use to increase uniformity with the final aim of developing a large database of bleeding symptoms in well-defined cohorts of patients with bleeding disorders (BAT repository[35], https://bh.rockefeller.edu/ISTH-BATR/index.html). Treating physicians must be aware of the availability of these tools, in order to take advantage of them every time they have to describe bleeding symptoms or diagnose a bleeding disorder.

The discussion then moved to the relevance of the upfront evaluation of vWF activity over its expression. Although the board agreed on this point, some level of uncertainty emerged regarding the best test to use (Table I, Q4). Given that the impaired binding of vWF to its platelet glycoprotein Ib receptor accounts for the primary haemostatic defect of vWD (i.e. altered platelet adhesion), its assessment in the first line of investigations is the most appropriate strategy. Currently, there are several tests available, all included under the name of "platelet-dependent vWF activity", which may be performed using in-house methods or commercial kits[36]. Indeed, during the discussion, it was pointed out that the Platelet Function Analyzer-100®

Table I - Multiple-choice questions included in the survey and completed before the meeting, related to the topic "How can the diagnostic workflow for von Willebrand's disease be optimised?".

Questions	Answers	Responders (%)
1) What are the minimum criteria for diagnosing VWD in a female or male patient presenting with a history of significant mucosal haemorrhage?	a) Positive history of haemorrhage since birth and in parents	12.5
	b) Positive personal history of bleeding and decreased vWF activity levels	87.5
	c) Positive history of haemorrhage with autosomal dominant transmission	0
	d) Positive history of haemorrhage with prolonged bleeding time or PFA-100 closure time	0
2) What are the most important reasons for using specific and detailed questionnaires to define the severity of the bleeding history of an individual with suspected VWD?	a) It is useful to know the sites of mucosal and non-mucosal bleeding	0
	b) Questionnaires allow patients to report their personal history better	0
	c) Questionnaires used by physicians allow the sites and severity of bleeding to be assessed	100
	d) It is useful to know the yearly frequency of bleeding episodes	0
3) What is the standardised questionnaire currently advised in the diagnosis of male or female patients presenting with a history of significant mucosal haemorrhage to calculate the Bleeding Score?	a) The questionnaire used for quantitative platelet defects	0
	b) The questionnaire proposed by the European study on VWD type 1	25
	c) The ISTH-BAT questionnaire proposed for hereditary bleeding disorders	37.5
	d) Any questionnaire is fine provided it is well managed by the haematologist	37.5
4) Which vWF activity tests should be employed first-line to diagnose VWD?	a) PFA-100 with FVIII	50
	b) One of the available test assessing the in vitro interaction between vWF and its platelet receptor GPIb	37.5
	c) Ristocetin-induced platelet aggregation in platelet-enriched plasma	12.5
	d) vWF multimers or assessment of vWF collagen binding	0
5) What is the rationale behind re-assaying the vWF activity in cases of circulating vWF levels between 30 and 40 U/dL?	a) vWF level artificially increases in children if blood withdrawal is difficult	12.5
	b) vWF varies based on O and non-O blood groups	0
	c) In women, hormone (oestrogen and progesterone) levels affect the levels of vWF	0
	d) All three previous answers	87.5
6) Why is it advised to perform the infusion test with DDAVP at the time of diagnosis?	a) It allows a better evaluation of VWD type and determines response to the drug	87.5
	b) It distinguishes cases of mild haemophilia A	12.5
	c) It must always be performed in type 3 VWD patients	0
	d) It identifies patients with autosomal dominant-transmitted VWD	0

The percentage of responders for each answer is indicated. VWD: von Willebrand's disease; vWF: von Willebrand factor; PFA-100: platelet function analyzer-100; ISTH-BAT: International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool; FVIII: factor VIII; DDAVP: desmopressin. GP1b: glycoprotein 1b.

(Siemens AG, Munich, Germany) has a low specificity because several variables may influence its results and is sensitive to very low vWF levels, whereas the vWF collagen binding test (vWF:CB), considered a surrogate measure to screen for the presence of multimers, and the ristocetin-induced platelet agglutination (RIPA) test may be employed to identify specific vWD types. Agreement was then expressed on the reason for repeating the determination of the activity of circulating vWF, when it is between 30 and 40 U/dL (Table I, Q5). Indeed, it is well established that several factors such as storage and handling conditions of plasma samples, ABO blood group, stress, hormones and inflammatory states may contribute to intra- and inter-patient variability, possibly affecting test results[1]. When the reason to perform the infusion test with DDAVP at the time of diagnosis was addressed, the board consistently recognised its key role in indicating both the type of vWD and the potential therapeutic response to the drug (Table I, Q6). From the discussion it emerged that, despite DDAVP representing an optimal cost-effective option for most patients with mild/moderate vWD and even for some severe forms when used in combination with concentrates (except type 3 vWD), it is underutilised as front-line treatment in clinical practice. This is particularly true in cases of major surgery, pregnancy and delivery, and probably depends on physicians' excessive fear of adverse events, such as important water retention, hypertensive reactions and tachyphylaxis. The experts also underlined the importance of repeating the determination of vWF activity before and after the infusion test because the results, combined with the BSs, may indicate the appropriate therapy[3]. Moreover, the need for an appropriate assessment of the response to DDAVP was highlighted, in order to pick out patients with abnormal clearance resulting in a shortened vWF half-life[27].

Finally, costs were consistently recognised as a hurdle, especially with regards to the possibility of rendering vWD diagnostic tests accessible to virtually every laboratory, particularly in developing countries. Some of the experts pointed out the importance of convincing Institutions that implementation of less complex and expensive tests to diagnose vWD would reduce costs related to bleeding management and inappropriate therapies.

In conclusion, it is crucial to increase awareness on (i) which tests are strictly necessary in first-line to stratify patients according to the severity of bleeding, and, therefore, rapidly decide treatment, and (ii) which tests may be performed subsequently to refine the diagnosis of vWD type and identify subgroups of patients with specific features[10]. In this regard, taken as granted the usefulness of molecular diagnosis, the experts agreed that this is not an essential part of an upfront approach aimed at the quickest diagnosis. Molecular analysis is useful to confirm specific vWF defects in vWD families, but it does not help to classify the severity of bleeding[1]; moreover, it is complicated by several polymorphisms of the gene (>300 reported so far) and its length, the fact that mutations may be spread out over the gene itself (except for 2A, 2B, 2N and 2M), and the presence of a pseudogene on chromosome 22. Still, molecular analysis is important to assess the presence of homozygous large deletions in type 3 vWD patients, thus identifying individuals at risk of developing neutralising antibodies and anaphylactic reactions.

Summary of key points

1) Unmet need: accurate, rapid and feasible vWD diagnosis aimed to prompt selection of the most adequate treatment.
   Achievable by combining information from:
   - bleeding history, collected through the ISTH-BAT questionnaire;
   - BSs, calculated through the BSs of the ISTH-BAT;
   - few targeted tests: platelet-dependent vWF activity and DDAVP infusion test.
2) Challenges:
   - variables affecting test results;
   - costs.

How can the "ideal" patients needing secondary long-term prophylaxis be selected? Which subgroup may benefit from the use of the pure vWF concentrate with low FVIII (Wilfactin®)?

Secondary long-term prophylaxis with concentrates is an approach intended for a limited number of patients with severe, recurrent spontaneous bleeding, which overall represent a small group of vWD patients. However, the selection of eligible candidates and the specific regimen and product they may benefit from remains difficult. Care must be taken with regard to FVIII replacement, since the production of this clotting factor is actually intact in vWD patients and it is not, therefore, always necessary. Indeed, supplying FVIII is critical in cases of surgery, or to stop bleeding as soon as possible in the case of a haemorrhage, but sustained excessive FVIII levels might increase the risk of thrombotic events and should be avoided during surgery in patients at high risk of thrombosis (e.g. the elderly and those with cancer or prothrombotic comorbidities)[22]. Hence, when deciding the optimal therapeutic strategy, the treating physician must take into account the patient's characteristics as well as differences and related potential clinical implications of the various concentrates available. There was some hesitation regarding the features of patients presenting with severe disease (Table II, Q7) and also with a history of gastrointestinal bleeds (Table II, Q8). Indeed, the

most important parameter for defining clinical severity is a combination of vWF activity levels <10 IU/dL and FVIII <20 IU/dL, therefore applying not only to type 3 vWD patients but also to some type 1 and type 2 patients. Similarly, gastrointestinal bleeding may occur in vWD patients irrespective of the type of disease, although it is associated with a deficiency of high molecular weight multimers that characterises type 3 and some type 2 vWD[37]. Still, when the experts were asked which patients they would consider eligible for secondary long-term prophylaxis, they unanimously answered all the heavy bleeders, regardless of vWD type (Table II, Q9). The experts were then asked to rate specific clinical and laboratory characteristics of the patients (on a scale from 1 [low] to 10 [high]) by their weight in selecting patients requiring secondary long-term prophylaxis (Table II, Q10). Young age, recurrent episodes of gastrointestinal bleeding and a BS >10 (median score: 10) were acknowledged as key factors for initiating long-term prophylactic therapy, followed by angiodysplasia (median score of 8), menorrhagia (median score of 8) and recurrent haemarthrosis (median score: 7).

Advanced age was not considered a criterion as such (median score: 6) but it must be borne in mind that comorbidities in the elderly may worsen the haemorrhagic phenotype. Recurrent epistaxis and levels of FVIII <20 U/dL were judged less important (median score: 5), followed by a high risk of thrombosis (median score: 3.5) and FVIII levels <40 U/dL (median score: 2). The score attributed to high thrombotics risk is not surprising, due to the observation that it is an infrequent event, usually limited to the elderly or to patients suffering from severe inflammatory conditions or bearing thrombophilic traits.

When the same list of characteristics was evaluated in the context of prophylactic therapy with the purified vWF with low FVIII content (Wilfactin®; Table II, Q11), no important differences emerged.

In conclusion, to rapidly establish the most suitable strategy for secondary long-term prophylaxis for a patient presenting with recurrent severe bleeding, it is critical to consider the specific characteristics of both the individual and the vWF-containing concentrate (see the next paragraph).

Table II - Multiple-choice questions, included in the survey and completed before the meeting, related to the topic "How can 'ideal' patients needing secondary long-term prophylaxis-needing be selected? Which subgroup may benefit from the use of the pure vWF concentrate with low FVIII content (Wilfactin®)?".

Questions	Answers	Responders (%) or score (1-10)
7) Which VWD patients present with a severe bleeding phenotype?	a) Type 3 VWD	62.5
	b) Type 2A VWD	0
	c) Type 1 VWD with low vWF	0
	d) VWD patients with activity levels of vWF <10 U/dL and FVIII <20 U/dL	37.5
8) Which patients present with a severe bleeding history and GI bleeds?	a) VWD patients with BS >10, vWF activity <10 U/dL, and reduced or absent vWF multimers	37.5
	b) Type 3 VWD	12.5
	c) Type 2M and 2B VWD	0
	d) All the previous answers	50
9) Which patients would you consider eligible for secondary long-term prophylaxis?	a) Only subjects with type 3 VWD	0
	b) Also patients with type 1 and 2 VWD	0
	c) All "heavy bleeders", independently of VWD type	100
10) In your experience, what are the clinical characteristics identifying the "ideal" patient for secondary long-term prophylaxis? (ordered from the most to the least important, based on the median score on a 10-point scale)	a) Young age, recurrent GI bleeding and BS >10	10
	b) Angiodysplasia and recurrent menorrhagia	8
	c) Recurrent hemartrosis	7
	d) Advanced age	6
	e) Recurrent epistaxis and FVIII levels <20%	5
	f) High risk of thrombosis	3.5
	g) Basal levels of FVIII <40%	2
11) Which patients would you treat with secondary long-term prophylaxis with pure vWF concentrate? (ordered from the most to the least important, based on the median score on a 10-point scale)	a) BS >10	9
	b) Angiodysplasia	8
	c) Recurrent menorrhagia, recurrent haemarthrosis, recurrent GI bleeds and FVIII levels <20%	7
	d) Recurrent epistaxis and advanced age	6
	e) Young age	5
	f) High risk of thrombosis and basal levels of FVIII <40%	3

The percentage of responders for each answer (Q7-Q9) or the median score rated by the experts (Q10 and Q11) on a scale ranging between 1 (low importance) and 10 (high importance) are indicated. VWD: von Willebrand's disease; vWF: von Willebrand factor; FVIII: factor VIII; GI: gastrointestinal; BS: bleeding score.

What are the key factors to consider when selecting the product for secondary long-term prophylaxis?

Several products are currently registered for replacement therapy in vWD patients, including plasma-derived FVIII/vWF and vWF with a low FVIII content. Among the parameters proposed as important for choosing the most adequate product, the board unanimously acknowledged the role of phenotype, the possible co-existence of thrombotic risk factors (which should particularly influence the decision on whether to administer a vWF concentrate with high or low FVIII content), the clinical efficacy (if different among products), the price and cost/benefit ratio, and existing guidelines (Table III, Q12). It is worth noting that in Italy the latest guidelines date back to 2009[27] when Wilfactin® had not yet been licensed. However, several Italian haematologists were involved in the European Working Group of experts who published the European principles of care of vWD[38]. When evaluating the possibility of giving vWF with a low FVIII content, however, it is important to be aware that such products may not always ensure efficacy and better quality of life, since they depend strictly on the entity, the site and the frequency of bleeding episodes (Table III, Q13). So far, only one report demonstrated the greater efficacy

Table III - Multiple-choice questions, included in the survey and completed before the meeting, related to the topic "What are the key factors to consider when selecting the product for secondary long-term prophylaxis?".

Questions	Answers	Responders (%)
12) What are the most important factors to take into account when choosing the product for secondary long-term prophylaxis?	a) Entity of diathesis b) Possibly coexisting risk factor for thrombosis c) Clinical efficacy (if considered different among the available products) d) Cost and benefit/cost ratio e) Existing guidelines f) All the previous	0 0 0 0 0 100
13) In "heavy bleeders", do you think that prescribing the purified vWF concentrate for secondary long-term prophylaxis may guarantee a different clinical efficacy and QoL compared to the FVIII/vWF products?	a) Yes b) No c) Not always	60 20 20
14) What are the advantages associated with the use of the purified vWF over the FVIII/vWF concentrates in secondary long-term prophylaxis?	a) Higher efficacy b) Lower thrombogenicity c) Higher safety d) Better QoL e) Other (i.e. possible higher efficacy in bleeding due to angiodysplasia)	34 33 0 22 11
15) Based on your experience, do the dosages of the purified vWF concentrate considered effective allow a saving in terms of yearly estimated need for FVIII/vWF concentrates?	a) Yes b) No c) Unsure	60 20 20
16) In the setting of secondary long-term prophylaxis for VWD patients, how do you rate the importance of the following factors at the time of selecting one of the products currently available? (ordered from the most to the least important based on the median score on a 6-point scale)	a) Savings of costs for the management of prevented hospital admissions, improvement of patients' QoL, decrease in the number of lost working days b) Savings of costs for the management of prevented bleeding, savings of costs associated with caregiver and price of the concentrate	5 4
17) Do you think that the current price of the purified vWF concentrate discourages its use for secondary long-term prophylaxis?	a) Yes b) No, never, given its advantages c) No if the cost/benefit ratio favours the product	40 0 60
18) Do you think that, in the choice of the available products for treating VWD patients, the methods of viral inactivation/removal play an essential role?	a) Yes b) No c) Unsure	40 40 20

The percentage of responders for each answer (all except Q16) or the median the score rated by the experts (Q16) on a scale between 1 (low importance) and 6 (high importance) are indicated. vWF: von Willebrand factor; QoL: quality of life; FVIII: factor VIII; VWD: von Willebrand's disease.

of prophylactic vWF concentrates over other products, at least for preventing gastrointestinal bleeding[39] (Table III, Q14). It would, therefore, be important to undertake prospective studies directly comparing the efficacy of the vWF concentrate with a low FVIII content and vWF/FVIII concentrates.

However, according to the experience of some participants, the following were indicated as possible advantages of the purified vWF concentrate with low FVIII content: (i) longer intervals between administrations and (ii) cost savings in terms of estimated consumption of FVIII/vWF concentrates on a yearly basis, at least for breakthrough bleedings (Table III, Q15). Accordingly, among the factors judged as relevant when selecting the concentrate to use in secondary long-term prophylaxis (Table III, Q16), the highest score (on a 1 [low] to 6 [high] scale) was attributed to savings in terms of avoided hospital admissions, improvement of patients' quality of life and reduction of working days lost (median: 5). The savings in the costs for the management of prevented bleedings, of caregivers and the price of the product were rated almost as important as the previous factors (median: 4). From the discussion it emerged that independence from caregivers strongly affects the quality of life patients, and stimulates them to comply with therapy. Poor compliance with secondary long-term prophylaxis was reported by some experts as being another critical issue. The price of the high purity vWF with a low FVIII content, which in Italy is greatly superior to that of vWF/FVIII concentrates, was reported not to represent a hindrance to its use, if clinically justified; however, a careful case-by-case evaluation of the cost/benefit ratio has been advised (Table III, Q17). In fact, patients requiring secondary long-term prophylaxis constitute only a small proportion of all vWD patients managed daily in Italian Centres. Thus, the use of the purified vWF concentrate may still represent a feasible option for selected cases, also in light of the fact that its price may be counterbalanced by savings of other resources[16].

Conflicting opinions emerged with regard to the impact of viral inactivation/removal techniques adopted in product manufacturing on the choice of the concentrate (Table III, Q18). The degree of purification of most of the formulations on the market is sufficient enough not to consider this a key factor in the choice of the concentrate and the effect on high molecular weight multimers of the nanofiltration step, introduced in the purification process of Wilfactin®, has been welcome since it has been shown that viral removal is more efficient but the content of high molecular weight multimers is comparable[24].

Summary of key points

1) Unmet need: tailoring the optimal secondary long-term prophylaxis strategy to a selected subset of patients with severe vWD suffering from recurrent spontaneous bleeding.
   Achievable by combining information from:
   - patients' characteristics: heavy bleeders (defined by vWF activity levels <10U/dL and FVIII <20 U/dL), BSs (possibly ISTH-BAT) >10, recurrent episodes of mucocutaneous bleeding, occurrence of angiodysplasia, age and associated factors that might worsen the haemorrhagic phenotype or increase the risk of thrombosis;
   - product characteristics: FVIII content, activity of vWF, high molecular weight multimers, associated resource savings.
2) Challenges:
   - adequate management of gastrointestinal bleeds;
   - patients' compliance with secondary long-term prophylaxis;
   - costs.

How can patients requiring surgical or invasive procedures be managed?

In the setting of surgical prophylaxis, the management of vWD patients may rely on the use of DDAVP and/or replacement therapy with vWF-containing concentrates, and antifibrinolytics, used alone or in combination. The choice of the optimal strategy depends on the type of invasive procedure or surgery required and on the severity of the vWD. As a general rule, the type of minor or major surgery also affects the optimal monitoring to assess the achieved levels of vWF:RCo and FVIII, which is a crucial factor. Indeed, in clinical practice, an interdisciplinary approach (involving surgeons, anaesthetists, haematologists and laboratory specialists) combined with careful monitoring of patients over time to tailor therapy provides a positive outcome in nearly all cases[28,29]. In Italy, DDAVP is recommended in the case of elective surgery only for responders[27], i.e. more likely patients with type 1, 2A, 2M or 2N vWD (Table IV, Q19). In DDAVP responders, 1 and 6 hours were indicated by the experts as the most significant time points for testing FVIII:C levels (Table IV, Q20). The usefulness of DDAVP in all types of surgical or invasive interventions, possibly in combination with antifibrinolytics, was acknowledged by most experts. They further agreed that vWF concentrates could also be added after surgery in the case of incomplete clinical efficacy of DDAVP (Table IV, Q21) or need for prolonged treatment. The experts agreed that the most important parameters to monitor during surgery are vWF:RCo and FVIII:C (Table IV, Q22). Nonetheless, the definition of the target levels of both, before and

Table IV - Multiple-choice questions, included in the survey and completed before the meeting, related to the topic "How can patients requiring surgical or invasive procedures be managed?".

Questions	Answers	Responders (%)
19) In the case of major surgery, which vWD patients may benefit from DDAVP ?	a) Type 3 vWD b) Type 2A, 2N and 2M vWD c) Type 1 vWD d) Type 2B vWD	0 27 73 0
20) In DDAVP responders requiring elective surgery, which are the most significant time-points for assessing FVIII?	a) 30 min b) 1 h c) 2 h d) 6 h e) 24 h	25 42 0 33 0
21) Which type of surgery can be treated with DDAVP?	a) Minor surgery only b) Minor and major surgery c) All types, possibly adding vWF-containing concentrates	22 11 67
22) Which parameters should be monitored before surgery?	a) FVIII:C b) vWF-FVIII binding c) vWF:RCo d) BT e) PFA-100	57 7 36 0 0
23) In the case of minor surgery, what are the recommended peri-operative target levels of FVIII:C and vWF:RCo?	a) 20-30% b) 30-40% c) ≥50%	37.5 25 37.5
24) In the case of major surgery, what are the recommended peri-operative target levels of FVIII:C and vWF:RCo?	a) ≥50% b) 70-80% c) ≥100%	11 67 22
25) What are the recommended post-operative target levels of FVIII:C and vWF:RCo?	a) 30% b) 50% c) 100%	12.5 75 12.5
26) What features make a vWF-containing concentrate suitable for surgical prophylaxis	a) A high vWF:RCo/FVIII:C Ag ratio b) A high vWF:Ag/FVIII:C ratio c) Pharmacokinetics d) Virus-inactivation step e) The profile of high molecular weight multimers	4 3 4 3 4
27) In your experience, is the concern regarding thrombotic risk due to an excessive post-operative level of FVIII:C (in the case of use of vWF-containing concentrate) real and practical?	a) It is a real problem, not to be underestimated b) It may be a real problem, but I have never observed any venous thromboembolic event after surgery c) It is just a theoretical issue	25 75 0
28) In the case of a type 3 vWD patient with high thromboembolic risk requiring elective major surgery, which product would you prefer?	a) Fanhdi®/Alphanate® b) Haemate P® c) Wilate® d) Wilfactin®	0 25 0 75
29) Would the in vivo recovery and pharmacokinetics of Wilfactin®, compared to the other concentrates, be a factor driving the therapeutic choice in a surgical setting?	a) Yes b) No c) Unsure	67 11 22
30) In your opinion, among all the products available, which features of a concentrate may justify its use despite a higher price?	a) vWF:RCo/FVIII:C b) Low content of FVIII c) High molecular weight multimer profile d) Pharmacokinetics e) Virus-inactivation step	20 6 27 27 20

The percentage of responders for each answer (except Q26) or the median score rated by the experts (Q26) on a scale between 1 (no importance) and 5 (very high importance) are indicated. vWD: von Willebrand's disease; DDAVP: desmopressin; FVIII: factor VIII; vWF: von Willebrand factor; FVIII:C: FVIII procoagulant activity; vWF:RCo: von Willebrand factor ristocetin cofactor activity; BT: bleeding time; PFA-100: platelet-function analyzer-100.

after surgery, remains one of the critical issues in this setting. Published recommendations on the target levels, dosing and duration of such prophylaxis before and after minor/major surgery vary[27,30,31]. For example, in the USA, the target levels recommended are >30% for both markers before and after minor surgery, whereas they are ≥100% for vWF:RCo and >50% for FVIII:C, in the case of major surgery[31]. From the results of the survey (Table IV, Q23-Q25), some degree of uncertainty emerged especially on the target levels to achieve before minor surgery (≥50% for 37.5% of participants, 20-30% for 37.5% and 30-40% for 25%) (Table IV, Q23). Of note, the experts pointed out that, in clinical practice, testing the levels of FVIII:C is preferred over testing vWF:RCo due to the less time required. Patients who do not respond adequately to, or are intolerant of, DDAVP and/or require major surgery undergo replacement therapy with vWF-containing concentrates. These include individuals with type 1 vWD and a severe phenotype, most type 2A and all type 3 vWD patients. As for the choice of the most suitable concentrate, the experts indicated a high vWF:RCo/FVIII:C ratio, pharmacokinetics and a high vWF:Ag/FVIII:C ratio followed by the high molecular weight multimer profile as the most important features (Table IV, Q26). However, the fact that the specific activity of concentrates is still expressed in units of FVIII rather than of vWF:RCo does not allow prompt evaluation of the dosage and timing of administration. After administration of a concentrate, both FVIII:C and vWF:RCo increase, but, over time and particularly for repeated administrations, the levels of FVIII:C exceed those of vWF:RCo mainly because of the stabilisation of endogenous FVIII in the presence of the increased vWF:Ag levels obtained after administration of the vWF concentrate with or without FVIII. In fact, the exogenous FVIII present in the vWF/FVIII products remains in the circulation only for the first 16 hours after the administration of the vWF/FVIII concentrate. Most of the measurable FVIII levels after replacement therapy are, therefore, from the endogenous FVIII bound to the exogenous circulating vWF:Ag that remains measurable for more than 48 hours. It is well established that high levels of FVIII are a risk factor for thrombosis, the effect being dose-dependent[40-43]. However, thrombotic complications were rarely reported in vWD patients undergoing surgery, and likely occurred in individuals with additional risk factors[44,45]. A systematic review of prospective studies evaluating the incidence of thrombotic events in patients receiving factor concentrates (N=5,579, of whom 361 with vWD) reported a low incidence of such events, which were mainly represented by superficial thrombophlebitis; few major venous thromboembolic events were recorded in patients with excessive FVIII levels, yet in the presence of additional thrombotic risk factors[45]. As available data, overall, are inconclusive in demonstrating a clear association between thrombotic events and high FVIII levels in vWD patients undergoing prophylactic therapy for surgery, a careful case-by-case assessment is needed. According to the participants' experience, the issue of thrombotic risk due to excessive post-operative levels of FVIII:C is a real concern, although none of them has ever observed any such case (Table IV, Q27). To prevent exposure to high levels of FVIII in vWD patients with an established high risk of thrombosis, Wilfactin® would be the product of choice (Table IV, Q28), due to its in vivo recovery and pharmacokinetics (Table IV, Q29). A feasible option for the prophylaxis of thrombosis in patients with known thrombotic risk factors requiring major surgery is low molecular weight heparin. However, the experts unanimously expressed the need to standardise the use of low molecular weight heparin, as the regimen and timing of administration for surgical prophylaxis remains highly variable and may affect the outcome of vWD patients undergoing treatment.

Pharmacokinetics, together with the high molecular weight multimer profile, the step of virus inactivation and the vWF/FVIII ratio were almost equally acknowledged by the board as the features that may justify the use of a concentrate despite a higher price (Table IV, Q30). Thus far, available data indicate a similar clinical effectiveness of the different products in the surgical setting, which ranges between 80 and 100%[13,27,28,46-51]. However, the possible explanation for this similarity remains overtreatment.

In any case, in clinical practice, safety and efficacy being substantially comparable, the choice of therapy may still be driven by costs.

Summary of key points

1) Unmet need: tailoring the optimal prophylactic strategy to a selected subset of vWD cases requiring surgery or invasive procedures, in the absence of guidelines.
   Achievable by combining information from:
   - patients' characteristics: vWD type, DDAVP responsiveness, levels of vWF:RCo and FVIII:C pre- and post-intervention and presence of risk factors for thrombosis;
   - product characteristics: vWF:RCo/FVIII:C, pharmacokinetics, high molecular weight multimer profile, cost and associated resource savings.
2) Challenges:
   - adequate monitoring of patients' parameters before and after surgery;
   - costs.

Conclusions

This meeting on selected topics regarding vWD diagnosis and treatment documented the degree of awareness, as well as the concerns of experienced Italian haematologists in managing vWD patients. In the absence of more detailed specific guidelines, sharing the experience of such professionals may help to fill the gaps encountered in daily practice.

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Authorship contributions

ABF and PS designed the survey and moderated the discussion on vWD diagnosis and treatment, respectively. Each co-Author has read the manuscript and approved its submission.

Disclousure of conflict of interest

PS has received grants from Kedrion for her Institutional research activity. All participating experts in vWD, except for ACG, received the honorarium for both meetings of the working group. Moreover, PS has been involved in advisory boards and has received honoraria as a speaker at educational meetings organised by Bayer, Baxter/Shire, CSL Behring, Grifols, Kedrion Biopharma, NovoNordisk, Pfizer, and Sobi; GC has received fees for advisory board participation and as speaker for Bayer, Baxalta, NovoNordisk, CSL Behring, and SOBI; AC has received fees as an invited speaker or consultant from Bayer, CSL Behring, NovoNordisk, and Octapharma; DC has received fees as an invited speaker from Kedrion; CE has received fees as an invited speaker or consultant from Bayer, CSL Behring, NovoNordisk, Octapharma, and Baxalta; EM has received fees as a consultant or invited speaker from Bayer, Pfizer, and Kedrion; RM has received fees as a consultant or invited speaker from Bayer, NovoNordisk, and Shire; MM has received fees as a speaker or consultant from Sobi, Kedrion and Abbvie, and a research fellowship from Bayer; CM has received fees as a consultant or invited speaker from Bayer, CSL Behring, Kedrion, NovoNordisk, Pfizer, Shire, and Sobi; EZ has received fees as an invited speaker or consultant from Bayer, CSL Behring, NovoNordisk, Baxalta, and Kedrion; ABF has been involved in advisory boards and has received honoraria as a speaker at educational meetings organised by Baxter/Shire, CSL Behring, Grifols, Kedrion Biopharma, LFB, Octapharma, and Werfen-Instrumentation laboratories. SMS declares no additional conflicts of interest.

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