Sixth Åland Island Conference on von Willebrand disease

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ORIGINAL ARTICLE

Sixth Åland Island Conference on von Willebrand disease

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Abstract

Introduction: The sixth Åland Islands Conference on von Willebrand disease (VWD) on the Åland Islands, Finland, was held from 20 to 22 September 2018.

Aim: The meeting brought together experts in the field of VWD from around the world to share the latest advances and knowledge in VWD.

Results and discussion: The topics covered both clinical aspects of disease management, and biochemical and laboratory insights into the disease. The clinical topics discussed included epidemiology, diagnosis and treatment of VWD in different countries, management of children with VWD, bleeding control during surgery, specific considerations for the management of type 3 VWD and bleeding control in women with VWD. Current approaches to the management of acquired von Willebrand syndrome were also discussed. Despite significant advances in the understanding and therapeutic options for VWD, there remain many challenges to be overcome in order to optimise patient care. In comparison with haemophilia A, there are very few registries of

VWD patients, which would be a valuable source of data on the condition and its management. VWD is still underdiagnosed, and many patients suffer recurrent or severe bleeding that could be prevented. Awareness of VWD among healthcare practitioners, including non-haematologists, should be improved to allow timely diagnosis and intervention. Diagnosis remains challenging, and the development of fast, simple assays may help to facilitate accurate and rapid diagnosis of VWD.

KEYWORDS
diagnosis, pregnancy, surgery, von Willebrand disease, von Willebrand factor

1 | INTRODUCTION

In the 1920s, Erik von Willebrand studied the bleeding symptoms of a girl named Hjördis and her family on the Åland Islands, Finland. Hjördis had experienced several life-threatening bleeding episodes and bled to death during her fourth menstrual period at the age of 14 years. Erik von Willebrand discovered that 23 other family members experienced similar symptoms to Hjördis.[1] In his publication from 1926, he called this disease 'Hereditär pseudohemofili', which was later renamed von Willebrand disease (VWD).

The sixth Åland Island Symposium, held on 20–22 September 2018, was chaired by Prof Erik Berntorp and brought together experts from around the world with the objective to promote awareness of VWD and discuss the latest advances in the management of the condition. The symposium was the latest in a series of international meetings of experts in the field of VWD, dating back to 1998 and held on the beautiful Åland Islands in memory of Hjördis and her family. Hosting the symposium at this historic venue adds a sense of gravitas to the scientific discussions and contributes to the soul of the meeting.

2 | VWD EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT

2.1 | VWD from a World Federation of Hemophilia perspective, Glenn Pierce

The prevalence of VWD is estimated at 1% based on epidemiological studies.[2,3] However, up to nine out of 10 people with VWD are not diagnosed because symptoms are often mild and diagnosis of VWD is challenging.[4,5] Almost a century since the discovery of VWD, diagnosis remains difficult and there is a lack of awareness of the disease.[6,7] The World Federation of Hemophilia (WFH) has initiated several outreach projects, multidisciplinary training programmes, symposia and educational tools for VWD diagnosis (Figure 1).

2.2 | VWD in Lithuania, Sonata Šaulytė Trakymienė

The treatment of VWD patients in the small Baltic country of Lithuania is restricted to specialised centres in the five largest cities. VWD patients are treated with von Willebrand factor (VWF)/factor VIII (FVIII) concentrates, desmopressin (DDAVP), antifibrinolytic drugs and hormonal treatment. Generally, mild VWD cases are treated on-demand and only type 3 VWD patients are considered for prophylaxis. Since 2016, wilate is the only VWF/FVIII concentrate that is fully reimbursed by Lithuanian health insurances. Although DDAVP is generally available, it is not reimbursed. DDAVP nasal spray and tranexamic acid are not registered in Lithuania and special permission is required for their use.

Up to 2013, 127 patients were diagnosed with VWD in Lithuania: 121 adults and six children, comprising 126 type 1 VWD patients and one type 3 VWD patient (S. Trakymienė, unpublished data). However, at the time, no confirmatory tests were available to support the correct diagnosis of VWD. Based on a population of Lithuania of approximately 2.9 million, the prevalence of VWD would be .0044%.

In 2013, the VWF:glycoprotein Ib mutant (GPIbM) assay, which is based on the spontaneous binding of VWF to a gain-of-function mutant GPIbM fragment,[8] was introduced in Lithuania. In Lithuania, a VWF:GPIbM/VWF:Ag ratio of $< .6$ is used to define a qualitative type 2 VWD disorder; other assays to classify type 2 VWD subtypes are not available. Since the implementation of the VWF:GPIbM assay, 106 new cases (65 adults, 41 children) were identified between 2013 and 2017, which increased the VWD prevalence to .008% (S. Trakymienė, unpublished data). In the future, the wider availability of VWF activity tests and genetic testing might aid the diagnosis of VWD in Lithuania. Non-laboratory screening tests, such as bleeding assessment tools (BATs) might also improve the rate of diagnosis, and in 2017, the Lithuanian translation of the International Society on Thrombosis and Haemostasis (ISTH)-BAT became available.[9]

2.3 | VWD in Italy, Augusto Federici

In 1977, Mannucci et al.[10] were the first to describe the use of DDAVP in Italian VWD patients undergoing surgery. In 1987, Rodeghiero et al.[2] reported the prevalence of VWD in asymptomatic, healthy, Italian children and showed that the prevalence of VWD might be higher than previously assumed. The retrospective study by Tosetto et al.[11] correlated bleeding severity with clinical laboratory features in European patients with type 1 VWD using scores for bleeding assessment. These and other studies show the longstanding interest in VWD in Italy.

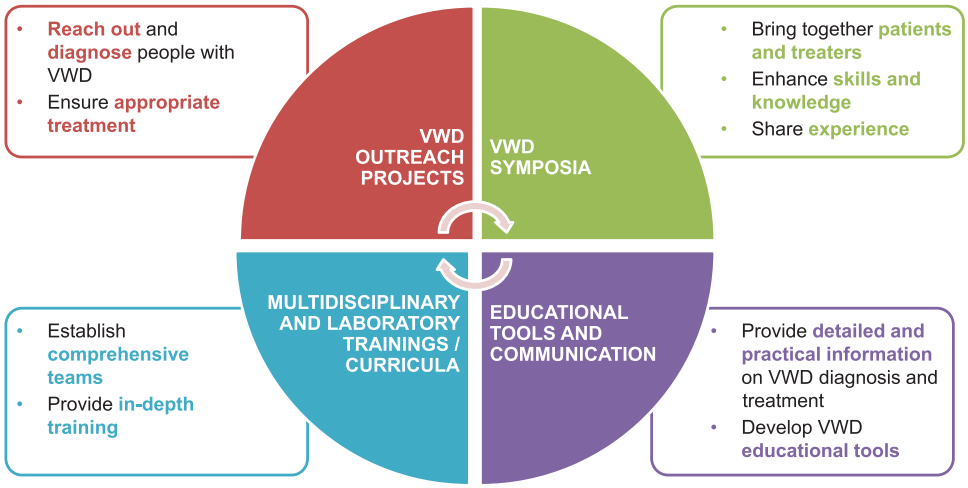

FIGURE 1 Overview of World Federation of Hemophilia initiatives

TABLE 1 Type of treatment of VWD patients in Italian Association of Haemophilia Centres (AICE) with at least one therapeutic plan released between October 2012 and October 2016[12]

Treatment	Type 1 VWD (*N* = 243)	Type 2A VWD (*N* = 45)	Type 2B VWD (*N* = 22)	Type 2M VWD (*N* = 17)	Type 2N VWD (*N* = 5)	Type 3 VWD (*N* = 37)
VWF/FVIII concentrate	60	31	21	4	2	37[a]
VWF/FVIII concentrate + DDAVP	57	10	–	10	–	–
DDAVP only	126	3	1	3	3	–
Therapeutic plan, *n* (%)	606 (100)	92 (100)	55 (100)	32 (100)	15 (100)	50 (100)
On-demand	582 (96)	81 (88)	48 (87)	29 (91)	15 (100)	30 (60)
Prophylaxis	24 (4)	11 (12)	7 (13)	3 (9)	–	20 (40)

[a]One patient with an inhibitor was treated with recombinant FVIII.

The registry of the Italian Association of Hemophilia Centres (AICE) comprises 3196 VWD patients (as of October 2017), of whom 2387 (74.7%) were diagnosed with type 1, 694 (21.7%) with type 2 and 115 (3.6%) with type 3 VWD.[12] Between 2012 and 2016, most Italian patients registered in AICE were treated on-demand (Table 1). However, 17 out of 37 patients with type 3 VWD were receiving secondary prophylaxis and all type 3 VWD patients were treated with VWF/FVIII concentrates. Type 1 VWD patients were treated with either VWF/FVIII concentrates or DDAVP or both while the majority of type 2 VWD patients received VWF/FVIII concentrates (Table 1).[12]

Despite the significant advances that have been made over the past 50 years, diagnosis and classification of VWD remain challenging in Italy, not only because awareness is low but also because VWD confirmatory laboratory testing is time consuming and not available at every centre. DDAVP challenge could be used for a quick assessment to distinguish between type 1 and type 2 VWD, because patients with type 2 VWD do not usually respond to DDAVP.[13] Better VWD confirmatory tests that can assess VWD quantity and activity within 1 day and tests that can correctly classify type 2 VWD based on high molecular weight multimers are needed.

2.4 | VWD in Germany, Katharina Holstein

The organisation of care in Germany is divided between the Ministry of Health, which provides the framework for reimbursement of patient care and treatment, the Paul Ehrlich Institute, which surveys safety and manages the German Haemophilia Registry [Deutsches Hämophilieregister (DHR)] and haemophilia treatment centres.[14] In addition to smaller local hospitals and medical practices treating patients with VWD, there are several comprehensive care centres across the country, which operate according to the European Haemophilia Safety Surveillance (EUHASS) definitions.[15] Data on the prevalence and epidemiology of VWD in Germany are limited. Based on the 2019 Annual Global Survey of the WFH, the prevalence of VWD in Germany is .005%, which likely underestimates the true prevalence.[4] All patients with VWD should be captured in the DHR.

VWD diagnosis in Germany is based on family and bleeding history, and laboratory testing [including assays of VWF:Ag, von Willebrand ristocetin cofactor (VWF:RCo) binding, VWF:GPIbM and von Willebrand collagen binding (VWF:CB), as well as analysis of VWF multimers and genetic testing]. Generally, all treatments for VWD,

including VWF/FVIII concentrates, are available and reimbursed in Germany.

There are no VWD-specific guidelines in Germany, and the general guidelines on therapy with blood components and plasma derivatives (*Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten*) do not provide specific recommendations on dosing or the use of prophylaxis in VWD.[16] Specific guidelines on VWD therapy would be useful to guide German healthcare practitioners.

In Hamburg, mild type 1 VWD patients are treated with DDAVP or with DDAVP and tranexamic acid. A DDAVP response test is recommended before treatment. If the response to DDAVP is insufficient, then VWF replacement therapy should be administered. The majority of type 2 and all type 3 VWD patients are treated with VWF/FVIII concentrates but few patients are on prophylaxis. However, our centre recommends prophylaxis in patients with severe type 1 VWD or with type 3 VWD, especially if there is spontaneous bleeding.

More research is needed to improve our knowledge on the pathophysiology of VWD. With that in mind, the shear flow regulation of haemostasis (SHENC) consortium includes 12 research groups from Germany and Austria who are collaborating to elucidate the structure and biophysical function of the VWF complex. Using a combination of atomic force microscopy and high-resolution light microscopy, Lippok et al.[17] have identified a new endoplasmic VWF binding partner, protein disulphide isomerase, that likely catalyses the dimerisation of VWF. Further results are expected from this collaboration that may shed light on the basic biology of VWF.

2.5 | VWD in India, Alok Srivastava

The prevalence of VWD in India is unknown because there is no national registry that systematically collects data on VWD prevalence, severity and treatment and VWD in India is likely to be highly underdiagnosed.[18] Although global epidemiological studies suggest that VWD is the most frequent bleeding disorder, in India there are five times more patients diagnosed with haemophilia than with VWD.[18] The WFH Annual Global Survey 2019 reported that there were 760 diagnosed VWD patients in India.[4] However, based on an approximate global prevalence of 1% and a population of approximately 1.2 billion people, there should be approximately 12 million people with VWD in India. If we assume that one in 10,000 show VWD symptoms, there should still be approximately 120,000 symptomatic VWD patients.[18]

Although VWD affects both sexes equally, women with VWD are more frequently diagnosed because they experience more frequent bleeding challenges. A prospective study evaluated 104 Indian women with unexplained menorrhagia and found that VWD was the cause of menorrhagia in 10 (9.6%) of the women.[19] Another retrospective study analysed data from 200 female Indian patients in whom a bleeding disorder was suspected.[20] Out of those 200 patients, 12 (6%) were diagnosed with VWD.[20] In both studies, VWD was the cause for bleeding and menorrhagia in more than one-third of cases in which a bleeding disorder was diagnosed.[19,20] This raises the questions of whether women with menorrhagia should be screened for VWD and if a self-BAT could help identify more VWD cases.

In India, VWD is diagnosed based on personal history, family history and abnormal laboratory tests. Only very few centres offer specific testing for VWD. In the whole of India, there are only 28 centres that offer VWF:Ag testing and nine providing VWF:RCo testing. At the Christian Medical College (CMC), Vellore, all VWD screening and confirmatory tests are available, except VWF multimer analysis because the results are not thought to affect the disease management. All VWD patients are treated on-demand with DDAVP, cryoprecipitate and VWF/FVIII concentrates, whichever is available at the time.

At CMC, Vellore, there is a preference not to use VWF:RCo to assess adequacy of haemostasis during the perioperative period. Instead of monitoring VWF activity, emphasis is placed on FVIII monitoring to avoid extremely high FVIII levels with the use of VWF/FVIII concentrates. More than 50 major surgeries in patients with VWD have been carried out at our centre using modest doses of VWF/FVIII concentrates with no cases of thrombosis in any patient (A. Srivastava, unpublished data).[21,22] Although rare, venous thromboembolic events have been reported in VWD patients treated with VWF/FVIII concentrates during surgery.[21] FVIII levels above 150% are a risk factor for venous thromboembolic events, and persistently high FVIII levels have been reported in some patients treated with repeated doses of VWF/FVIII concentrates for surgical coverage.[21] Notably, FVIII and VWF levels did not accumulate when wilate was used to manage bleeding during surgery in 28 patients with VWD in a multinational study including centres in India. Surgical prophylaxis with wilate was successful in 29 out of 30 surgeries and no thromboembolic events or sustained accumulation of FVIII over time was observed.[22]

Studies on VWD in India suggest that 30%–60% of identified cases are type 3 VWD, of which 60%–70% of cases are related to consanguineous marriages.[18] In comparison, less than 5% of VWD cases in western countries are type 3 VWD.[23] In 102 Indian type 3 VWD patients, 55 different disease-causing mutations were identified, of which 34 (61.8%) were novel mutations (Figure 2).[24] Only five mutations accounted for the defects in 40% (37 of 93) of patients.[24] These results suggest that there is a wide genotypic heterogeneity underlying type 3 VWD that needs to be investigated further to identify more disease-causing mutations on the VWF gene.

3 | CLINICAL ASPECTS

3.1 | Paediatric issues in VWD, Fernando F. Corrales-Medina

The clinical characteristics of VWD in children are very heterogenous.[25,26] For example, epistaxis, commonly present in children with VWD, occurs frequently in healthy children. Therefore its presence alone might not be necessarily indicative of a bleeding disorder.[25] At the same time, children with VWD might not be identified until late in childhood due to the lack of exposure to haemostatic challenges, such as surgery or menstruation. Although BATs were

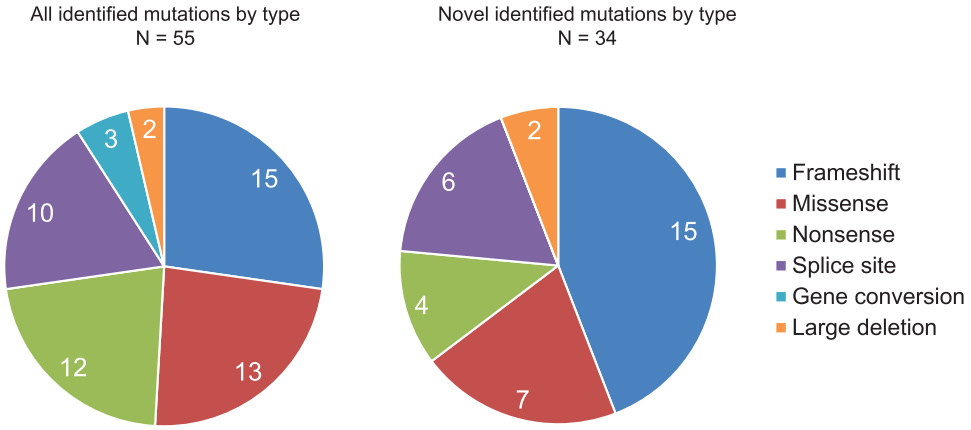

FIGURE 2 Distribution of the type of VWD gene mutations in 102 Indian type 3 VWD patients.[24] In nine patients, no mutation was identified

initially proven to be useful screening tools in adults with VWD, they had certain limitations in children.[27] The prevalence of VWD in adolescent females with menorrhagia is estimated to be between 3% and 36%,[26] raising the question of whether all adolescents with history of menorrhagia should be routinely screened for VWD. A study by Sidonio et al. concluded that screening for VWD in this population is more cost-effective than covering the costs that could result from a missed VWD diagnosis, such as postoperative bleeding or postpartum haemorrhage (PPH).[28]

BATs have proved useful in screening and identifying adults with VWD. In order to properly assess the bleeding tendencies in children that will help identifying those with VWD, a paediatric bleeding questionnaire (PBQ), adapted from the MCMDM-1VWD and including a 'children-specific' bleeding symptoms category, was developed in 2009.[29] Children-specific symptoms included umbilical stump bleeding, cephalohaematoma, post-circumcision bleeding, post-venepuncture bleeding and macroscopic haematuria.

The performance of the PBQ was evaluated in 100 children with definite or possible VWD and a control group of unaffected siblings (n = 21).[25] Children with definite VWD were shown to have significantly higher bleeding scores compared with their unaffected siblings with the most frequently reported symptoms being epistaxis (34%), prolonged bleeding from minor wounds (33%) and bruising (24%). Scores tended to increase with age, likely due to exposure to haemostatic challenges as children get older (Figure 3).[25] Interestingly, the PBQ total scores in those children with VWD were found to be very heterogenous, even within the same VWD subtypes.

Another study assessed the PBQ's ability to discriminate and identify otherwise healthy multi-ethnic children (43% female) likely to have VWD between the ages of 30 days and 18 years.[30] A PBQ score of ≥ 3 showed a high sensitivity and specificity (both > 97%) for VWD detection in children, whereas the positive and negative predictive values were 48.6% and 99.9%, respectively.[30]

These studies suggest that the PBQ may help to discriminate bleeding tendencies in children with VWD from those of healthy children. However, approximately 25% of children with type 1 VWD are still only diagnosed after experiencing postoperative bleeding.[27] It is also important to consider that the children-specific symptoms are not commonly observed in children with type 1 VWD, the most common VWD subtype.[27]

Another limitation of BATs, including the PBQ, is that they usually require medical personnel with access to additional resources and expert training. As a result, self-administered BATs that can be performed by the patient or the caregivers have been developed and shown to be effective and reliable.[30] However, more studies are necessary to confirm the accuracy of self-reported symptoms and to determine their reproducibility in children.

Laboratory test cut-offs and ratios are crucial in the VWD diagnostic workup. Adults with VWD are known to have a FVIII/VWF activity ratio > 1.[31] A study found that healthy children had higher FVIII activity (FVIII:C) levels than healthy adults and that a FVIII:C/VWF activity > 1, which would be indicative of VWD in adults, could also be observed in healthy children. These ratios should therefore be interpreted with caution when evaluating children with suspected VWD.[31]

Haemostatic evaluation also requires laboratory-specific and age-appropriate coagulation factor reference ranges considering external variables such as concomitant medical conditions, lipid levels, hormones, recent physical activity, tourniquet time, proper tube filling, specimen processing and transport conditions. VWF secretion is regulated in response to stress. In children, repeated blood draws might cause such an elevation as a result of physical or mental stress associated with the procedure.[31] For this reason, additional laboratory tests such as the VWF:CB assay, performed on at least two separate occasions, might be needed to accurately confirm or exclude the presence of VWD in younger populations.[32]

To address some of these clinical and laboratorial diagnostic problems, Malec et al. recently developed a four-variable composite score that combines a Tosetto bleeding score ≥ 1, family history of VWD or abnormal bleeding, personal history of iron deficiency anaemia and positive PBQ score.[27] This diagnostic tool yielded a sensitivity of 64%–76%, a specificity of 34%–35% and positive and negative predictive values ranging from 5.5% to 25% and from 77% to 94%, respectively.[27] Further studies in larger paediatric populations are needed to further assess the utility of this score.

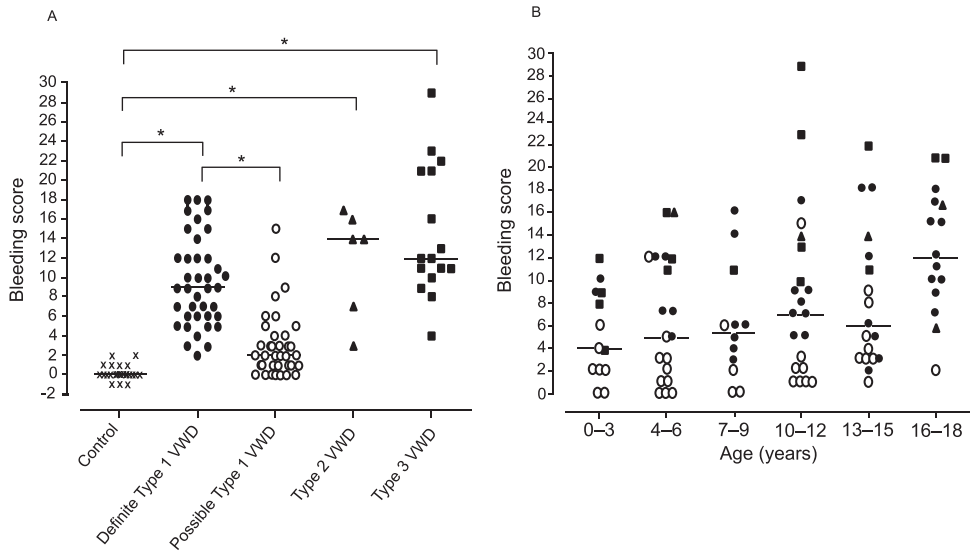

FIGURE 3 Bleeding scores in children with von Willebrand disease.[25] (A) Bleeding score in healthy controls (unaffected siblings) and patients with different types of VWD disease type ($n = 121$). (B) Bleeding score in children with VWD by age ($n = 100$). Horizontal lines represent median scores. *Significant between-group differences ($p < .001$)

In summary, VWD remains a diagnostic challenge in paediatric patients. An accurate clinical and laboratory assessment in children with VWD might sometimes be both challenging and complex.

3.2 | VWD and surgery, Mario von Depka Prondzinski

VWF/FVIII concentrates that provide haemostatic cover for patients with VWD undergoing surgery have been available for more than 40 years.[33] However, VWF/FVIII products have different ratios of VWF to FVIII and differ in their pharmacokinetic properties.[34] For surgery, it is therefore advisable to become familiar with the different products in order to avoid under- or overdosing.[33]

Hazendonk et al.[35] retrospectively evaluated 103 Dutch patients who underwent surgery between 2000 and 2015 with the aim of assessing perioperative management with the VWF/FVIII concentrate Haemate P/Humate P (VWF:FVIII ratio of 2.4:1). Out of 103 patients, 54 (52.4%) had type 1, 43 (41.7%) type 2 and six (5.8%) type 3 VWD. Of 148 surgeries, 110 were major and 38 minor. Bleeding was not associated with low VWF:Act and/or low FVIII:C trough levels. FVIII:C and VWF:Act greatly exceeded the target levels of >80% in the majority of patients. In 18 (8%) patients, FVIII:C trough levels exceeded 270%. Significantly higher FVIII:C levels compared with VWF:Act were observed postoperatively after the surgery, indicating an accumulation of FVIII, which could increase the risk for thromboembolic events (Figure 4).[35] Despite high FVIII levels, no thromboembolic events were documented in this study.

In contrast, in another study, surgical prophylaxis with wilate in 28 patients with VWD did not lead to a sustained accumulation of FVIII (Figure 5). Surgical prophylaxis with wilate was effective and no thromboembolic events were observed.[22]

Peyvandi et al.[36] assessed the efficacy, safety and tolerability of rVWF in a phase 3 trial of severe VWD patients who underwent elective surgery. This prospective, open-label uncontrolled trial included 15 adult patients with severe VWD of whom three (20%) had type 1 VWD, four (26.7%) had type 2 and eight (53.3%) had type 3. The intraoperative efficacy was rated as 'excellent' or 'good' in 100% of patients. Mean FVIII:C levels gradually increased in response to administration of rVWF alone leading to a substantial increase of >60 IU/dl for all patients 6 h after infusion. A total of 80% of patients achieved the FVIII:C target levels (50–60 IU/dl for minor, 80–100 IU/dl for major surgery) 1–2 h before surgery and did not receive rFVIII co-administration. Haemostatically effective FVIII levels were maintained for 72–96 h after infusion of rVWF. During the study, two serious adverse events in two patients were documented including a deep vein thrombosis that was assessed as possibly treatment related.[36]

Although a lot of experience has been gained in the management of VWD patients undergoing surgery, there are still unanswered questions relating to specific differences and dosing of VWF/FVIII products, use of anticoagulation and how patients with concomitant thrombophilia should be treated.

3.3 | Type 3 VWD: from the history to 3WINTERS-IPS data, Augusto B. Federici

The prevalence of type 3 VWD is reported to be between .1 and 5.3 per million but varies between countries with and without frequent consanguineous marriages.[37] However, owing to the challenges of diagnosing VWD, the identified cases are likely to be just the tip of the iceberg.

In general, substantially more bleeding events in joints and the gastrointestinal tract can be expected in type 3 VWD patients compared

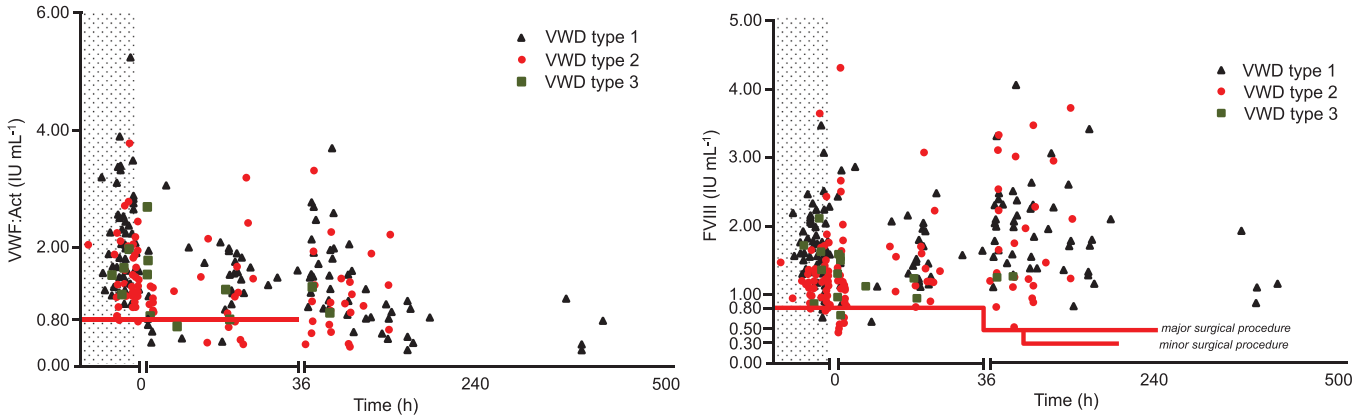

FIGURE 4 Achieved VWF:Act (A) and FVIII (B) levels in the perioperative period.[35] No differences were observed in achieved VWF:Act and FVIII levels between VWD types. Red lines indicate predefined target VWF:Act and FVIII levels (80% VWF:Act/FVIII levels). $T = 0$ is defined as the start of the surgical procedure

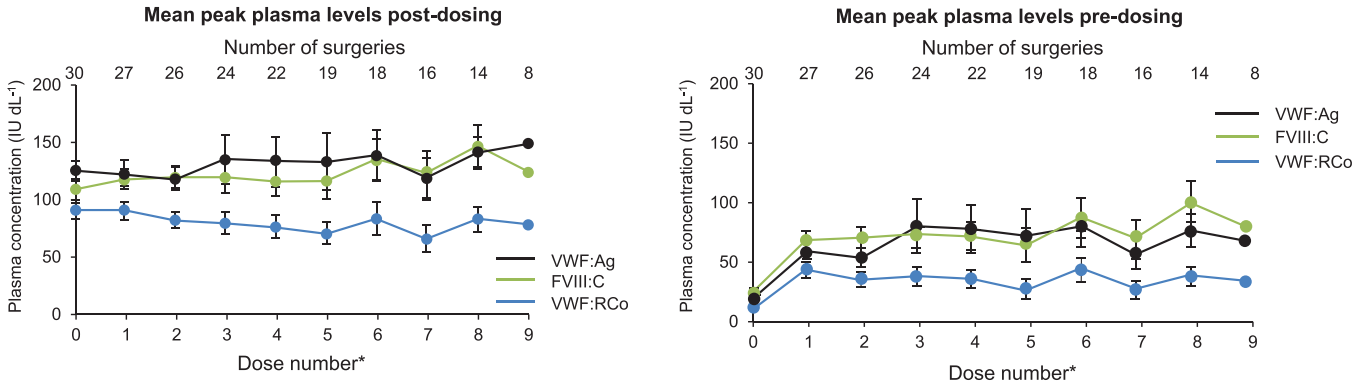

FIGURE 5 Mean peak plasma VWF/FVIII levels post-dosing and mean trough plasma VWF/FVIII levels pre-dosing in VWD patients undergoing surgery.[22] Only maintenance infusions with values available for more than one patient are shown. Numbers at the top of each figure represent the number of patients contributing to that particular time point. 0 = presurgery loading dose. Error bars represent the standard error of the mean

with type 1 VWD patients. However, even though type 3 VWD is clearly characterised by complete absence of VWF, there is a high heterogeneity in the clinical presentation.[38] In addition, the type 3 VWD phenotype is not as well characterised as type 1 VWD due to its much less frequent occurrence.[37]

The type 3 von Willebrand International Registries Inhibitor Prospective Study (3WINTERS-IPS study) is a multicentre, investigator-initiated, observational and prospective study to assess the clinical phenotype, genetic background and the efficacy and safety of different treatment options in patients with type 3 VWD.[37] The study enrolled 223 European and Iranian type 3 patients (median age, 29 years, 58% female) with a history of bleeding and included a historical control arm of 417 patients with type 1 VWD for comparison. Bleeding scores were significantly higher in type 3 than in type 1 VWD. Epistaxis and menorrhagia were among the most frequently observed bleeding symptoms in type 3 VWD (Figure 6A). Deep haematomas, haemarthroses, oral cavity and CNS bleeding were more than five times more frequent in type 3 than in type 1 VWD (Figure 6B). In type 3 VWD, haemarthrosis was observed in clusters with gastrointestinal bleeding and epistaxis.[37] These results from the largest cohort of type 3 VWD evaluated to date show that type 3 VWD has a distinct clinical phenotype.[37] The prospective extension of 3WINTERS-IPS will assess the efficacy and safety of different VWF/FVIII concentrates in the treatment of patients with type 3 VWD. This additional observation time will be very useful to assess the annualised bleeding rate of patients exposed to secondary long-term prophylaxis versus those treated on demand.[37]

4 | ISSUES RELATING TO VWD IN WOMEN

4.1 | VWF and FVIII during pregnancy, Jill Johnsen

During healthy pregnancy, haemostatic equilibrium shifts towards a procoagulant state, which is believed to be adaptive in anticipation of bleeding during delivery and the immediate postpartum period.

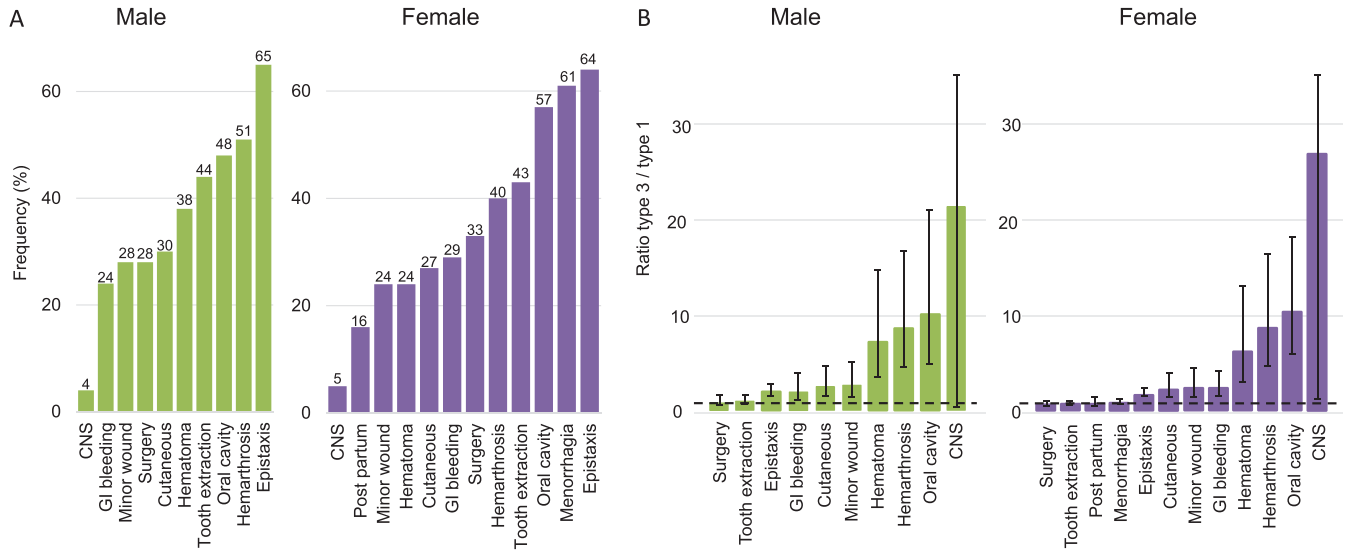

FIGURE 6 Frequency of bleeding symptoms (A) in male and female patients with type 3 VWD and frequency ratios of symptoms in type 3 versus type 1 VWD (B) for males and female patients.[37] Equivalence is marked with a horizontal dashed line (ratio = 1). 95% Confidence intervals around the ratio are shown. CNS, central nervous system; GI, gastrointestinal

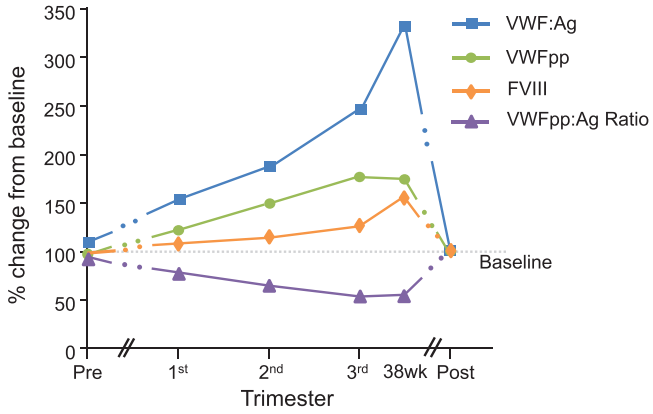

FIGURE 7 Changes from baseline to postpartum in VWF and FVIII parameters in normal pregnancies.[39] Pre-pregnancy $n = 14$, first trimester $n = 24$, second trimester $n = 38$, third trimester $n = 44$, 38 weeks $n = 12$ and postpartum $n = 41$

Drury-Stewart et al.[39] showed that in healthy pregnancies, VWF and FVIII levels rise dramatically, peaking in the third trimester and decreasing to baseline postpartum. The VWF:Ag levels rise dramatically to approximately 350% of the baseline levels by week 38 of pregnancy (Figure 7). In comparison, VWF propeptide (VWFpp) concentrations remain relatively constant, only changing significantly in the third trimester. The net result is a significant progressive decrease in the VWFpp/VWF:Ag ratio over the course of pregnancy. The authors conclude that the data support a scenario in which there is both increased VWF production and prolongation of VWF half-life during pregnancy. Most women also exhibit a loss of larger VWF multimers and altered VWF triplet structure. This observation supports that qualitative changes in VWF are acquired during pregnancy.[39] More research is needed to better understand the mechanisms and clinical implications of VWF changes during pregnancy.

Ongoing research initiatives include the von Willebrand Factor in Pregnancy (VIP) study (NCT04146376), an investigator-initiated, prospective cohort study in the United States designed to document the rate of PPH in women with VWD and assess the effect of maintaining VWF levels between 100% and 150% on bleeding during and after childbirth. The VIP study should advance our understanding of managing bleeding complications during and after childbirth in women with VWD relative to VWF levels.

4.2 | Type 3 VWD: pregnancy and labour, Irena Zupan

Although VWF levels increase during pregnancy in women with VWD, PPH is still a major cause of death.[40,41] Many unanswered questions remain regarding the need for VWF/FVIII concentrates during delivery and postpartum, pregnancy outcomes and the mode of delivery for pregnant women with VWD.

Due to the rarity of type 3 VWD, clinical experience with type 3 VWD in pregnancy is limited. The case of a 40-year-old Slovenian women with type 3 VWD who delivered a healthy baby girl at our hospital serves to highlight the challenges of bleeding management during pregnancy and labour in women with type 3 VWD. During her pregnancy, she had no bleeding complications. FVIII:C, VWF:Ag and VWF:Act remained as low as before her pregnancy, as expected for

TABLE 2 Incidence of postpartum haemorrhage according to VWD subtype[41]

Event	Type 1 VWD (*N* = 39)	Type 2 VWD (*N* = 14)	Type 3 VWD (*N* = 4)	*p*-value
Median (range) blood loss, ml	450 (200–6000)	425 (200–1000)	1375 (400–3200)	.63
Primary postpartum haemorrhage, %	46.2	35.7	75.0	.37
Severe primary postpartum haemorrhage, %	20.5	7.1	75.0	.02
Vaginal haematoma, %	7.7	–	–	.65
Secondary postpartum haemorrhage, %	10.3	–	25.0	.27
Blood transfusion, %	7.7	–	–	.65

p-values calculated using Kruskal–Wallis test for median blood loss and Fisher's exact test for dichotomous variables.

type 3 VWD. To prevent excessive bleeding during delivery, she was given tranexamic acid at a loading dose of 2 g and 50 IU/kg wilate, which led to an increase of FVIII:C to more than 80% so that vaginal delivery was deemed safe. VWF:Act was between 30% and 50%. The woman had an episiotomy and in addition experienced a spontaneous vaginal laceration with consequent bleeding, for which she received a blood transfusion. Throughout her time in the hospital, she was treated with wilate to maintain FVIII activity > 80% and tranexamic acid (1 g/6 h). At 8 and 15 days postpartum, she experienced vaginal re-bleeding and needed surgical revision. Finally, she was discharged from hospital 17 days postpartum.

Data in the literature confirm that there is a high risk of severe primary PPH in women with type 3 VWD despite the use of prophylactic VWF/FVIII concentrates and tranexamic acid.[41,42] In addition, low levels of FVIII in the third trimester of pregnancy may predict PPH.[41]

Most guidelines recommend at least 50% FVIIII:C and VWF levels for delivery.[42] However, most of these recommendations are not based on clinical data but on experience and more data on type 3 VWD in pregnancy are needed to help guide treatment decisions.

4.3 | VWF: high-risk pregnancy and delivery, Susan Halimeh

Govorov et al.[41] assessed the incidence of PPH in women with VWD and the correlation of the occurrence of PPH with type of VWD, VWF levels, FVIII levels and haemostatic drug treatment in a retrospective analysis of 59 deliveries in 34 women with VWD. The incidence of primary PPH was 44% overall and 75% in type 3 VWD ($n = 4$). Type 3 VWD was associated with an increased risk for severe PPH compared with other subtypes (Table 2). The four patients with type 3 VWD, all received tranexamic acid and VWF/FVIII concentrate.[41]

James et al.[40] measured VWF and FVIII activity during pregnancy and postpartum in healthy women (40 pregnancies) and in women with VWD (35 pregnancies). Among the women with VWD, 15 women were treated during 17 pregnancies and 17 women were untreated.[40] In women with untreated type 1 VWD, VWF levels peaked (up to approximately 250% of pre-pregnancy values) 4 h postpartum, while in healthy women VWF peaked 12 h postpartum. Except immediately postpartum, VWF levels did not increase in treated women with VWD to the same levels as in healthy women, suggesting that women with VWD are at risk of PPH despite treatment.[40,43] Mittal et al.[44] analysed pregnancy-related outcomes of 15,258 pregnant women with VWD and confirmed that women with VWD were significantly more likely to experience antepartum haemorrhage and PPH. A study by Lavin et al.[45] indicated that women with 'low VWF' might be at a higher risk of bleeding in childbirth. Of 74 women who had at least one pregnancy prior to their diagnosis with low VWF, 63.5% self-reported excess bleeding at the time of delivery.[45]

Future studies should investigate the increase in FVIII and VWF levels during delivery and postpartum, what type of treatment is most suitable and how long treatment should be continued postpartum to effectively reduce the risk of bleeding during delivery and postpartum.

5 | BIOCHEMICAL AND LABORATORY INSIGHTS

5.1 | Platelet function and thrombin generation in type 3 VWD, Vuokko Nummi

The clinical phenotype of type 3 VWD can be variable.[46] Platelet function and thrombin generation, which are critical for haemostasis and coagulation, are only poorly studied in VWD.[46] Previously, a higher risk for bleeding has been observed in VWD patients with low peak thrombin.[47] However, this study did not specifically evaluate thrombin generation in a pure cohort of type 3 VWD patients.

Szanto et al.[46] evaluated thrombin generation in nine adult type 3 VWD patients (five on long-term regular prophylaxis and four on on-demand treatment). Overall, thrombin generation variables, such as median peak thrombin, were abnormal in platelet-poor plasma from type 3 VWD compared with healthy controls. The median peak thrombin level was lower in patients who were treated on-demand compared with patients on prophylaxis. Low peak thrombin levels correlated with low FVIII levels. The results suggest that thrombin generation is reduced in platelet-poor plasma and could be regulated by FVIII in type 3 VWD.[46]

The thrombin generation test could be useful as an alternative test in combination with FVIII and VWF assays to assess the clinical phenotype and bleeding risk in VWD patients.[47]

TABLE 3 Differential diagnosis of AVWS and inherited VWD[52]

Aspect	In favour of AVWS	In favour of VWD	Limitations
Personal history	Late onset of bleeding	Early onset of bleeding No uneventful surgery or no previous high-risk situations	Variable penetrance of VWD
Family history	Negative	Positive	Variable penetrance of VWD
AVWS-associated disorder	Present	Absent	Coincidental presence of highly prevalent disorders (e.g., MGUS in the elderly)
Laboratory evaluation	Presence of inhibitor of VWF-binding antibodies	VWF gene mutation	Low frequency of detectable inhibitors in AVWS Alloantibodies in rare cases of VWD type 3
Treatment response	Remission after treatment of underlying disorder Response of IVIg (in IgG MGUS-associated AVWS) Short-lived response to VWF-containing concentrates or DDAVP	Normal recovery and half-life of VWF-containing concentrate Sustained response to DDAVP	Cannot be assessed before treatment

Abbreviations: IVIG, intravenous immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

5.2 | New VWF diagnostic assays, Jonathan Roberts

VWF:Ag, VWF:RCo, FVIII:C and VWF:CB are the standard assays for diagnosing VWD.[5] Additionally, the VWF:GPIbM has been developed and found superior to ristocetin-based VWF platelet activity assays.[48] However, these diagnostic tests can be costly and time consuming and are often only available at a small number of specialised centres. Therefore, new assays to support easy and accessible diagnosis are necessary.

We have validated an enzyme-linked immunosorbent assay-based screening assay that can analyse VWF physiological activity on a single testing platform, including VWF binding activity to GPIb, collagen III, FVIII:C, VWF:Ag and VWFpp, the VWF-multiplex activity assay (VWF-MAA).[49] Through linear discriminate analysis, the assay was able to correctly diagnose VWD, including classification of 1C, 2A, 2B, 2M and 2N subtypes, with an accuracy of 92.5% and a good correlation to conventional assays.[49]

This assay could deliver results within 1 day, including discrimination of variant or non-variant VWD, allowing a more diverse investigation of VWF and its physiological activities.[49] Potentially, this assay could be considered as a screening test for VWD with good accuracy.[49] Additional investigations are ongoing, and further analysis of the VWF-MAA was presented at the Hemostasis & Thrombosis Research Society 2021 Scientific Symposium and at the ISTH 2021 Virtual Congress.

5.3 | Current management of patients with acquired VWD, Augusto Federici

Acquired von Willebrand syndrome (AVWS) is a bleeding disorder with similar symptoms and laboratory findings to inherited VWD, such as prolonged bleeding time and reduced VWF:Act.[50] In comparison with VWD, AVWS typically occurs later in life without a personal and family history of bleeding.[50,51] Because the treatment approaches for AVWS and VWD may differ, a differential diagnosis is very important (Table 3).[52]

Various conditions are associated with AVWS, including myeloproliferative, lymphoproliferative, neoplastic, autoimmune and cardiovascular disorders.[51,52] AVWS has been frequently diagnosed in patients with aortic valve stenosis or continuous-flow left ventricular assist devices.[52] Gastrointestinal bleeding caused by Heyde's syndrome is thought to be common in patients with aortic valve stenosis. Heyde's syndrome is characterised by the loss of the largest VWF multimers, which is believed to result from shear-induced stress on VWF, which leads to structural alterations of VWF and its degradation.[53] Vincentelli et al.[54] prospectively evaluated 42 patients with severe aortic stenosis who underwent valve replacement. Nine (21%) of 42 patients had at least one bleeding episode in the 6 months prior to surgery. Loss of large VWF multimers and decreased collagen binding were observed in 79% and 67% of patients, respectively. The loss of high molecular weight VWF multimers correlated with the severity of the valve stenosis. Valve replacement completely normalised haemostasis in some patients.[54] Mechanical circulatory support devices, used in patients awaiting heart transplantation, can exert mechanical stress on the blood, and AVWS is common in patients with a mechanical circulatory support.[55]

As AVWS is a rare syndrome and underdiagnosed, evidenced-based treatment guidelines are limited.[52] Patients have been treated with DDAVP, VWF/FVIII concentrates and recombinant factor VIIa (rFVIIa).[52] However, the efficacy of these treatment options differed in patients with differing conditions underlying AVWS.[52] For example, the success rate with DDAVP was reported to be lower in patients with underlying cardiovascular diseases than in patients with

myeloproliferative syndromes.[52] In patients with alloantibodies to VWF, rFVIIa has been used successfully in 96% of patients.[52]

The Interactive Registry on Acquired Von Willebrand Syndrome (INTREAVWS, www.intreavws.com) aims to collect clinical evidence from around the world. Retrospective evidence will be collected in phase 1. In the second and third phases, patients will be followed prospectively with the aim of improving diagnosis and identifying the frequency and types of bleeding episodes in AVWS. This is an ongoing, 5-year study, expected to conclude in 2022.

6 | CONCLUSIONS

Despite significant advances, diagnosis and management of VWD remains challenging. Many translational topics, from management of VWD in different countries to clinical issues and biochemical advances, were discussed at the meeting by international leaders and young investigators in the field of VWD. It is hoped that meetings such as this one will continue in the future to further develop rich, international collaborations and advance progress in the diagnosis and management for individuals with VWD and other bleeding disorders. This has already begun in VWD with the publication of guidelines on diagnosis[6] and management[56] from a collaboration of the American Society of Hematology, the ISTH, the National Hemophilia Foundation and the WFH.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed.

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