REVIEW ARTICLE

blood advances

Low VWF: insights into pathogenesis, diagnosis, and clinical management

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von Willebrand disease (VWD) constitutes the most common inherited human bleeding disorder. Partial quantitative von Willebrand factor (VWF) deficiency is responsible for the majority of VWD cases. International guidelines recommend that patients with mild to moderate reductions in plasma VWF antigen (VWF:Ag) levels (typically in the range of 30-50 IU/dL) should be diagnosed with low VWF. Over the past decade, a series of large cohort studies have provided significant insights into the biological mechanisms involved in type 1 VWD (plasma VWF:Ag levels <30 IU/dL). In striking contrast, however, the pathogenesis underpinning low VWF has remained poorly understood. Consequently, low VWF patients continue to present significant clinical challenges with respect to genetic counseling, diagnosis, and management. For example, there is limited information regarding the relationship between plasma VWF:Ag levels and bleeding phenotype in subjects with low VWF. In addition, it is not clear whether patients with low VWF need treatment. For those patients with low VWF in whom treatment is deemed necessary, the optimal choice of therapy remains unknown. However, a number of recent studies have provided important novel insights into these clinical conundrums and the molecular mechanisms responsible for the reduced levels observed in low VWF patients. These emerging clinical and scientific findings are considered in this review, with particular focus on pathogenesis, diagnosis, and clinical management of low VWF.

Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by quantitative or qualitative reductions in plasma von Willebrand factor (VWF).[1,2] Previous studies have reported that ~1% of the normal population has reduced plasma VWF levels[3] and estimated that 1 in 1000 people have significant bleeding symptoms associated with their reduced VWF levels.[4] Consensus guidelines recommend that VWD be classified according to whether it involves a quantitative or qualitative VWF defect.[5-8] Quantitative VWD accounts for 75% of all cases. In these patients, plasma VWF antigen (VWF:Ag) and VWF activity assays are reduced concordantly. Current National Heart, Lung, and Blood Institute and UK Haemophilia Doctors Organization guidelines recommend that patients with quantitative VWD be classified into 3 subgroups based upon residual VWF:Ag levels.[9] Rare patients (~1 per million population) with almost complete VWF deficiency (levels <3 IU/dL) should be diagnosed with type 3 VWD. Individuals with plasma VWF levels <30 IU/dL and bleeding should be assigned a diagnosis of type 1 VWD. Patients with mild to moderate reductions in plasma VWF in the range of 30 to 50 IU/dL should be labeled as having low VWF. Recent large cohort studies have provided significant insights into the biological mechanisms involved in type 1 VWD.[10-14] In striking contrast, however, the pathogenesis underpinning low VWF remains poorly defined, and a series of clinically important questions remain to be addressed.

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Table 1. Significant differences between low VWF and type 1 VWD

	Low VWF	Type 1 VWD
VWD type	Partial quantitative	Partial quantitative
Plasma VWF levels, IU/dL	30-50*	<30
Bleeding phenotype	Variable bleeding. Independent of plasma VWF levels. Significant HMB & PPH in some patients	Mucosal bleeding. Correlates inversely with residual plasma VWF levels.
Sex	Marked female predominance	Less female bias
ABO blood group	Group O+++	Group O+
VWF sequence variants	~40% patients. Pathological importance for many variants unclear.	Present in >80% cases
Pathophysiology	Multifactorial. Predominantly reduced biosynthesis. Subtle increased clearance in ~25% patients (VWFpp/VWF:Ag ~ 2).	Dependent upon *VWF* mutation. Reduced biosynthesis. Enhanced clearance in ~45% cases. Type 1C VWD (VWFpp/VWF:Ag >3).
VWF glycosylation abnormalities	Enhanced SNA binding, increased RCA-I binding, and reduced sialylation	Increased RCA-I binding, PNA binding, and T antigen expression and reduced sialylation
Platelet VWF levels	May be reduced or normal	May be reduced or normal
Abnormal angiogenesis	Unknown	Previously reported

+, mild increase in prevalence; +++, markedly more prevalent; PNA, peanut agglutinin; RCA-I, *Ricinus communis* agglutinin I; SNA, *Sambucus nigra* agglutinin; VWFpp, VWF propeptide.

*There are some differences between International Consensus guidelines for the optimal range.

Low VWF

The International Society of Thrombosis and Haemostasis (ISTH) classification criteria published in 2006 did not include a low VWF subgroup.[7] Rather, these guidelines recommended that all patients with partial quantitative VWF deficiency and bleeding phenotype should be diagnosed with type 1 VWD. Unsurprisingly, given that plasma VWF:Ag levels vary over a wide range (1-50 IU/dL), significant differences in bleeding are seen among this type 1 VWD cohort. Subsequent studies, as well as a number of insightful commentary articles, highlighted other important differences within this group.[15,16] In particular, genetic studies demonstrated that *VWF* coding mutations were significantly more common in patients with plasma VWF levels <30 IU/dL.[10,11,13,14] The VWD inheritance pattern in these families tends to be autosomal dominant in nature. Conversely, *VWF* mutations were significantly less common in patients with VWF:Ag levels in the 30 to 50 IU/dL range. Thus, the inheritance pattern underlying low VWF remains poorly understood. Moreover, the bleeding phenotype in subjects with mild to moderate reductions in the low VWF range is also difficult to predict. On the basis of these findings, more recent guidelines have recommended that patients with low VWF (30-50 IU/dL) should be recognized as a distinct group compared with those with type 1 VWD (<30 IU/dL) (Table 1).

Low VWF: clinical challenges

Diagnosis of low VWF in the clinic is a clinicopathological one. To be registered with low VWF, patients must have mild to moderate reductions in plasma VWF levels (30-50 IU/dL) and a bleeding phenotype. As highlighted previously by Sadler, the majority of individuals with VWF levels in the 30 to 50 IU/dL range will not exhibit a significant bleeding diathesis.[15] Consequently, reduced VWF levels should be regarded as a modest risk factor for bleeding, not a disease. Nonetheless, low VWF still constitutes the most common subtype of VWD. For example, the diagnosis is estimated to apply to >7.5 million individuals in the United States alone. Despite this population prevalence, low VWF patients continue to present significant clinical challenges with respect to genetic counseling, diagnosis, and management. Although recent studies have provided significant insights into type 1 VWD, it is important to note that the total number of patients with low VWF enrolled in these large cohort studies was limited. Indeed, some of these studies specifically excluded subjects with plasma VWF levels >30 IU/dL. Consequently, as highlighted in the National Heart, Lung, and Blood Institute guidelines,[5] important clinical questions pertaining to low VWF remain unanswered. In particular, there is limited information regarding the relationship between VWF:Ag levels and bleeding phenotype in subjects with low VWF. For example, it is not clear whether there is a critical VWF level with respect to bleeding risk.[17] This is obviously important in relation to defining useful diagnostic thresholds. In addition, it is not clear whether patients with low VWF need prophylactic treatment. This is particularly problematic in children or adult patients who may not have undergone previous hemostatic challenges. For those patients with low VWF in whom treatment is deemed necessary, the optimal choice of therapy remains unknown. Furthermore, it is not clear whether this need for therapy is influenced by the physiological increases in plasma VWF:Ag that are seen in association with normal aging or during pregnancy. Emerging recent data have provided some important insights into these clinical conundrums and the molecular mechanisms responsible for the reduced levels observed in patients with low VWF.[14,18-20]

Bleeding phenotype in low VWF

The Low VWF Ireland Cohort (LoVIC) study[19] and the US Zimmerman Program[14] have recently reported data regarding bleeding phenotype in patients with low VWF. Although there were differences in enrolment criteria between the studies, a number of consistent results were observed. Using previously validated bleeding assessment tools (BATs),[21,22] both studies clearly demonstrated that at least some patients with low VWF levels display significant bleeding phenotypes. For example, 77% of

female subjects in the LoVIC study (N = 126) had an ISTH BAT score ≥6 (normal range, 0-5 for adult females).[19] Furthermore, almost 40% of women had ISTH BAT scores ≥10, suggestive of significant bleeding. Significant bleeding was also confirmed using the alternate Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD (condensed MCMDM-1 VWD) BAT score.[19] Similarly, Flood et al reported significantly elevated ISTH BAT scores in a majority (62%) of low VWF patients in the Zimmerman Program (N = 170).[14] Importantly, the frequency of abnormal bleeding scores observed in these low VWF patients was similar to that seen in patients with plasma VWF levels <30 IU/dL.[14] Collectively, these data suggest that additional factors beyond the mild to moderate reduction in plasma VWF levels may be contributing to bleeding phenotype in patients with low VWF. Of note, increased BAT scores were observed in both studies, despite the fact that the mean age of patients enrolled was significantly different (19 years in the Zimmerman Program vs 39 years in LoVIC) study. Both studies also observed a marked predominance of female patients among the low VWF cohort.[14,19] Furthermore, 2 previous population-based studies also reported that mild to moderate reductions in plasma VWF levels were associated with bleeding in some patients.[23,24]

Heavy menstrual bleeding in low VWF

Examination of the individual domains within the ISTH BAT score revealed that heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH) were particularly important contributors to the increased bleeding scores observed in the LoVIC cohort.[18,19] Almost 75% of female patients with low VWF reported a history that included ≥2 symptoms suggestive of menorrhagia (changing pads/tampons more frequently than every 2 hours, clots and flooding, or bleeding duration >7 days).[18] In the majority of women, HMB had been present since menarche, and 40% reported missing >2 days of work or school per year because of their menorrhagia. Overall, 67% had required hormonal treatment in the form of a combined oral contraceptive pill or a hormone-releasing intrauterine device.[18] Despite this treatment, one third of these women ultimately required surgical intervention (including dilation and curettage, endometrial ablation, or hysterectomy). The clinical burden associated with HMB in women with low VWF was also confirmed using an independent Philipps score assessment.[18] In addition to these objective data, there is subjective evidence of the clinical significance of HMB in this cohort. In women registered with a diagnosis of low VWF, prospective follow-up in a comprehensive care center identified reduced ferritin levels and overt iron deficiency in 46% and 22%, respectively.[18] Cumulatively, these findings suggest that menorrhagia is common in women with low VWF and that it is associated with significant morbidity. Of concern, only 60% of the women with HMB had presented for medical consultation prior to their diagnosis with low VWF.[18] Furthermore, even following the initial health care professional consultation, there was a significant delay before VWF testing was eventually performed.

PPH in low VWF

Seventy-four women in the LoVIC study had undergone ≥1 pregnancy, including a total of 181 successful pregnancies.[18] Sixty-four percent of these parous women with low VWF reported previous PPH. Interestingly, significant numbers of primary and secondary PPH were recorded. Overall, >20% of women had required transfusion, critical care, or radiological or surgical intervention because of PPH. Furthermore, PPH resulted in a delay in hospital discharge in 25% of women with low VWF.[18] Even following their formal diagnosis with low VWF, significant PPH continued to be observed. Critically, this bleeding was seen despite the fact that plasma VWF levels had been corrected to within or above the local normal range in all women by the time of delivery.[18] Collectively, these data emphasize that pregnancy-associated increases in VWF levels are not necessarily associated with correction of bleeding phenotype in women with low VWF.[25] Finally, it is important to note that bleeding scores in women with low VWF remained significantly elevated, even if gynecological bleeding domains (HMB and PPH combined) were removed, highlighting that other bleeding complications are also observed.[19]

Why are some low VWF patients presenting with bleeding?

On the basis of current data, it is clear that some low VWF patients have significant bleeding phenotypes that appear discrepant to the mild to moderate reductions observed in their plasma VWF levels.[14,18,19] In type 1 VWD, previous studies showed that bleeding correlated inversely with residual plasma VWF levels.[25] Conversely, however, no significant relationship between bleeding and VWF levels has been observed within the low VWF group. In particular, bleeding scores were similar for low VWF patients, with levels in the 30 to 40 IU/dL range compared with those with levels of 40 to 50 IU/dL.[19] For example, in the Zimmerman Program, abnormal BAT scores were observed in 66% of patients in the 30 to 40 IU/dL range as opposed to 63% of subjects in the 40 to 49 IU/dL range.[14] No correlation between plasma VWF:Ag levels and bleeding score was observed. Cumulatively, these findings are clearly important when it comes to assigning thresholds for low VWF diagnosis. Subsequent analyses have demonstrated that the increased bleeding in low VWF patients cannot be explained by abnormalities in VWF multimer distribution.[19] Although platelet VWF accounts for ~20% of total VWF in platelet-rich plasma,[26,27] bleeding in patients with low VWF did not correlate with reductions in platelet VWF levels.[19] In women with low VWF and HMB, underlying gynecological pathologies were rare and could not explain the increased observed bleeding.[18] Finally, although concomitant bleeding disorders have been described in a small number of patients with low VWF, these were usually mild in nature and did not significantly impact upon bleeding phenotype or BAT score.[19] In summary, it is clear that some patients with low VWF have a bleeding phenotype for which the etiology remains poorly understood. In this context, it is interesting that recent studies have described a series of additional nonhemostatic roles for VWF. For example, VWF has been reported to be important in innate immune response,[28-30] wound healing, and angiogenesis.[31] Additional studies will be necessary to determine whether any of these novel functions impact clinical bleeding in patients with low VWF.

What mechanisms are responsible for the reduced plasma VWF levels in patients with low VWF?

A number of recent cohort studies have provided important insights into type 1 VWD pathogenesis. In essence, these studies have shown that reduced plasma VWF:Ag levels can result from a decrease in VWF biosynthesis and/or enhanced VWF clearance.

In contrast, the biological mechanisms responsible for the mild to moderate reductions in plasma VWF levels observed in low VWF patients remain poorly defined.

Decreased synthesis in the etiology of low VWF

A variety of methodologies have been used to study the contribution of reduced VWF biosynthesis to the etiology of quantitative VWD. These include assessment of the factor VIII/VWF ratio, platelet VWF levels, peak desmopressin acetate (DDAVP) responses, and VWF expression in patient-derived endothelial colony-forming cells. Recent studies have demonstrated that factor VIII/VWF ratios are significantly increased in patients with low VWF compared with normal controls (mean, 1.3 vs 1.07, respectively; $P < .0001$).[19] These data suggest that reduced VWF synthesis and/or secretion plays an important role in low VWF pathogenesis. In keeping with this hypothesis, 2 independent studies have shown that platelet VWF levels are also significantly reduced in low VWF patients.[19] For example, Lavin et al observed mean platelet VWF:Ag levels of 0.16 IU/10^9 in low VWF subjects compared with 0.21 IU/10^9 in controls ($P < .05$). Casonato et al also observed that platelet VWF levels were reduced in a proportion of patients with mild quantitative VWD.[32] Interestingly, in both studies, significant interindividual variation in platelet VWF levels was observed between low VWF patients, suggesting that the etiology underlying reduced VWF levels is likely multifactorial in nature. The concept that reduced endothelial cell (EC) synthesis and/or secretion of VWF may be important in low VWF pathogenesis is further supported by a number of ex vivo culture studies using patient-derived endothelial colony-forming cells. Furthermore, Franchini et al reported an association between subclinical hypothyroidism and concomitant low VWF levels.[33]

Enhanced clearance in the etiology of low VWF

A number of approaches can be used to investigate the role of enhanced VWF clearance in the etiology of quantitative VWD. These include measuring the VWF propeptide to antigen (VWFpp/VWF:Ag) ratio, as well as defining the duration of VWF responses following DDAVP administration.[34,35] In addition, in vitro binding studies and in vivo clearance studies in animal models have been used to study the effects of specific VWF mutations.[36] The Zimmerman Program and the Willebrand in The Netherlands study have reported that enhanced VWF clearance constitutes an important pathogenic mechanism in ~45% of patients with type 1 VWD.[14,37] Other studies, including the European Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD study, also confirmed that increased VWF clearance is common in type 1 VWD.[38] Cumulatively, these data have led to the proposal that affected patients should be diagnosed as a distinct type 1C (1-clearance) subgroup.[39] Recent data further suggest that enhanced VWF clearance can also contribute to the pathogenesis in patients with types 2 and 3 VWD.[37] These previous studies typically used a VWFpp/VWF:Ag ratio >3 to identify type 1C VWD patients. In the LoVIC study, <10% of patients had VWFpp/VWF:Ag ratios >3.[20] Nevertheless, the VWFpp/VWF:Ag ratio was significantly increased in the low VWF cohort compared with normal controls ($P < .01$). Calculations based on steady-state VWF:Ag and VWF propeptide levels estimated that 25% of patients with low VWF had plasma VWF half-lives <6 hours.[20] Together, these findings suggest that subtle enhanced clearance also likely contributes to the pathogenesis in at least some cases of low VWF (Figure 1).

VWF gene sequence variants in patients with low VWF

To investigate the biological mechanisms responsible for low VWF, the Zimmerman Program performed full-length *VWF* gene sequencing studies.[14] *VWF* sequence variants were identified in only 44% of patients with low VWF. In contrast, *VWF* variants were much more commonly identified (82%) in patients with plasma VWF:Ag levels <30 IU/dL.[14] Similarly, using a custom genetic array methodology, the LoVIC study reported potentially damaging *VWF* sequence variations in only 40% of patients with low VWF.[19] Collectively, these genetic studies suggest that other unidentified modifier loci contribute to the pathogenesis of low VWF. This hypothesis is supported by previous linkage studies that demonstrated that, in many families with low VWF, inheritance is entirely independent of the *VWF* gene locus on chromosome 12.[40,41] In addition, genome-wide association studies have identified a series of other genetic modifiers that have subsequently been shown to play roles in regulating plasma VWF levels in normal individuals and in patients with quantitative VWD (recently comprehensively reviewed by Swystun and Lillicrap[42]).

ABO blood group and low VWF

Prior to its secretion from endothelial cells into plasma, VWF undergoes complex posttranslational modification that includes significant glycosylation.[2,43] Recent studies have highlighted that the *N*- and *O*-linked glycan structures expressed on VWF play critical roles in regulating in vivo clearance. Unlike most other plasma proteins, human plasma–derived VWF caries covalently linked ABO(H) blood group determinants on a proportion of its glycan structures.[43,44] Importantly, ABO blood group has a major effect on plasma VWF levels.[44,45] In particular, VWF:Ag levels are ~20% to 30% lower in normal blood group O individuals compared with non-O individuals.[45,46] The mechanisms through which this ABO blood group determines VWF levels are not fully understood. However, Gallinaro et al have demonstrated that VWF clearance after DDAVP infusion is significantly increased in group O individuals compared with non-O individuals (10.0 vs 25.5 hours).[47] In keeping with this effect, the Zimmerman Program and the LoVIC study observed that blood group O was significantly more prevalent in low VWF patients compared with the normal population.[14,19] For example, Flood et al reported that group O subjects accounted for 73% of patients with plasma VWF levels <50 IU/dL compared with a prevalence ~45% in the general population.[14] Group O phenotype was also significantly more common in the LoVIC cohort (89%) compared with the normal Irish population (55%).[19] Together, these data suggest that the enhanced VWF clearance observed in blood group O individuals is a significant contributing factor in the etiology of low VWF levels.

In addition to being expressed on red blood cells and VWF, ABO(H) carbohydrate structures are present on a number of platelet membrane receptors.[48,49] These include GPIb, GPIIa, GPIIIa, GPIV, and GPV.[50] Recent studies have reported that these ABO(H) glycans may have a role in regulating platelet function.[51,52] Dunne et al investigated platelet translocation dynamics on immobilized VWF under arterial shear conditions and demonstrated a significant reduction in the ability of group O platelets to interact with VWF in this assay compared with non-O platelets.[51] These findings raise the intriguing possibility

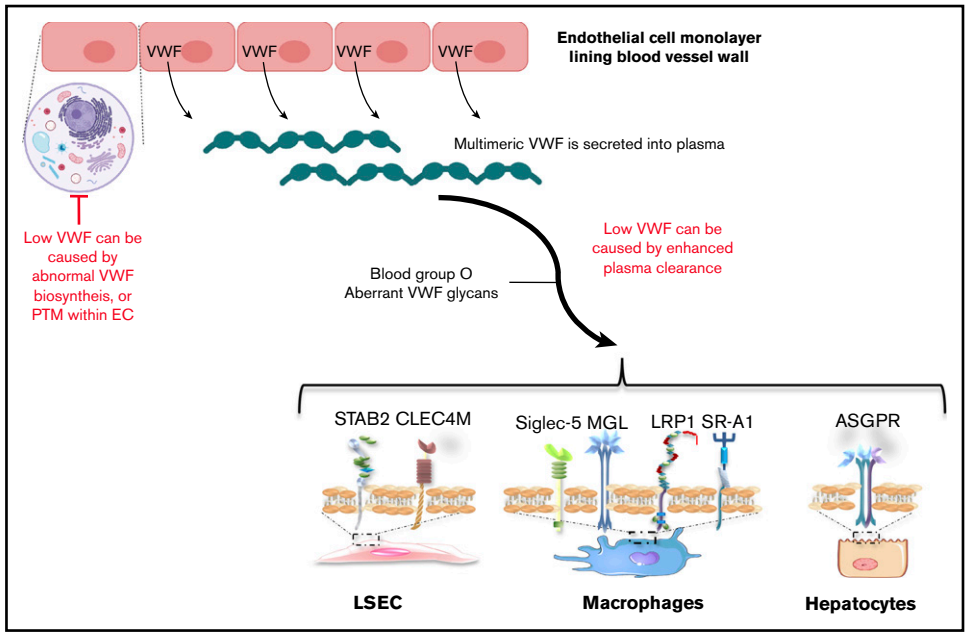

Figure 1. Pathophysiology underlying low VWF levels. Hepatic macrophages, liver sinusoidal ECs (LSECs), and hepatocytes contribute to regulating VWF clearance. A number of cell surface receptors have also been described. On LSECs these include stabilin-2 (STAB2) and C-type lectin domain family 4 member M (CLEC4M). Macrophage receptors include Siglec-5, the low-density lipoprotein receptor-related protein-1 (LRP1), the scavenger receptor class A member I (SR-A1), and macrophage galactose-type lectin (MGL). Finally, the asialoglycoprotein receptor (ASGPR) on hepatocytes has also been implicated. PTM, posttranslational modification.

that group O may impact upon plasma VWF levels in patients with low VWF, as well as contribute to the enhanced bleeding phenotype that is being observed.

In addition to the previously described effect of ABO(H) determinants, numerous studies have reported that other changes in VWF glycan structures can have major impacts on VWF clearance.[53-55] In particular, enzymatic removal of terminal sialic acid residues from the *N*- and/or *O*-linked glycans of VWF has been shown to result in a markedly reduced half-life in vivo.[56-58] Moreover, VWF clearance was also significantly enhanced in a transgenic ST3Gal-IV murine model.[54] Although the mechanisms through which VWF glycans regulate clearance remain poorly defined, a number of lectin receptors have been described to contribute to the rapid clearance of hyposialylated VWF.[34] These include the asialoglycoprotein receptor, which is predominantly expressed on hepatocytes,[55] as well as the macrophage galactose lectin.[59] In view of this critical role played by carbohydrate structures in modulating VWF clearance, studies have investigated whether abnormal glycosylation might have a role in the pathogenesis of quantitative VWD. Two studies reported aberrant increased binding of the lectin *Ricinus communis* agglutinin I to VWF in some VWD patients.[54,60] This lectin binds to subterminal galactose exposed following the loss of sialic acid residues. More recently, Aguila et al reported significantly enhanced *Ricinus communis* agglutinin I binding in a cohort of patients with low VWF.[20] Furthermore, a concurrent reduction in binding of the lectin *Sambucus nigra* agglutinin (affinity for terminal α2-6 linked sialic acid) was also seen. Together, these findings suggest that aberrant VWF glycosylation and, in particular, a reduction in terminal sialylation, is relatively common in patients with low VWF. Consistent with the concept that loss of terminal sialylation triggers enhanced VWF clearance, Aguila et al further demonstrated an inverse correlation between galactose exposure and estimated VWF half-life.[20]

Low VWF diagnosis: recent advances

Recent advances in our understanding of the pathobiology underpinning low VWF have important relevance for different aspects of clinical management. Collectively, these findings suggest that low VWF represents a discrete entity compared with type 1 VWD (Table 1). In terms of providing genetic counseling, it is clear that the genetic mechanisms involved in low VWF are often independent of the *VWF* gene. In addition, multiple genetic factors likely contribute to the etiology. Consequently, unlike type 1 VWD, in which inheritance is usually autosomal dominant, the inheritance pattern in low VWF families cannot be predicted. In addition, given the population prevalence of low VWF, it is not clear whether 2 parents with low VWF may be at risk of having children with markedly reduced plasma VWF levels.

With respect to low VWF diagnosis in the clinic, as previously noted, it should be a clinicopathological one based upon a combination of a personal bleeding history coupled with mild to moderate reductions in plasma VWF levels (Figure 2).[15] Studies have demonstrated that many patients with reduced VWF levels in the 30 to 50 IU/dL range do not have a significant bleeding phenotype.[61] Consequently, a critical first step in diagnosis is to objectively assess bleeding using a validated BAT. The 2 scores most widely used in this context are the ISTH and condensed MCMDM-1 VWD BATs.[21,22] Interestingly, recent evidence suggests that the ISTH BAT may be more sensitive than the condensed MCMDM-1 VWD score in assessing menorrhagia in women with low VWF.[18] Patients with abnormal BAT scores should proceed to laboratory hemostatic work-ups that include VWF antigenic and activity assays. In terms of diagnostic VWF thresholds, it is important to note that the bleeding phenotype is identical for patients with plasma VWF levels in the 30 to 40 IU/dL range compared with those in the 40 to 50 IU/dL range.[14,19] In addition, the frequency of *VWF* gene sequence variations is similar in both groups.[14] Consequently, the recommended 30 to 50 IU/dL range

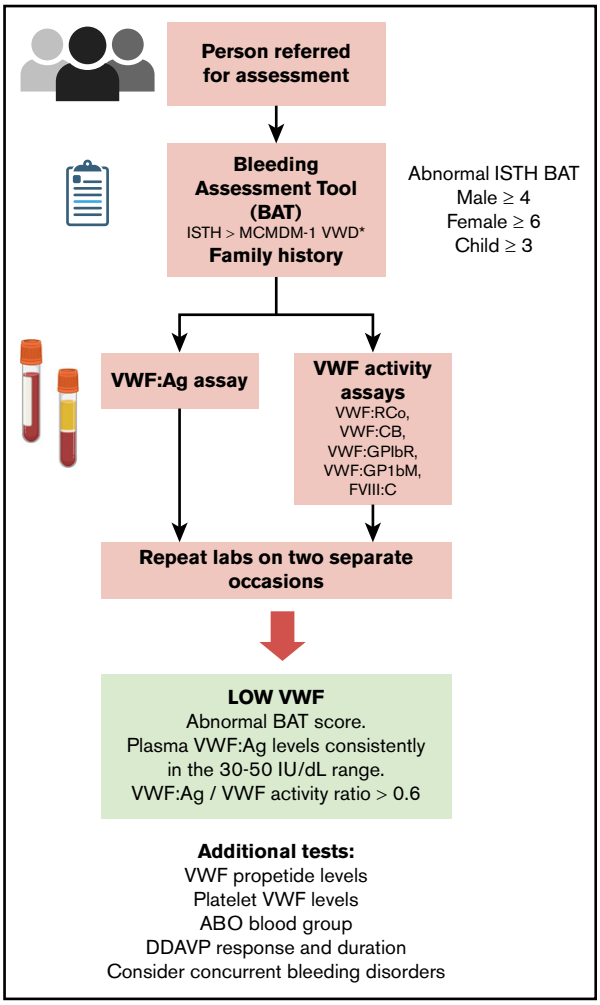

Figure 2. Proposed low VWF diagnostic algorithm. FVIII:C, FVIII clotting activity; VWF:CB, VWF collagen binding activity; VWF:GPIbR, Ristocetin-induced binding of VWF to a recombinant wild-type GPIb fragment; VWF:GP1bM, spontaneous binding of VWF to a gain-of-function mutant GPIbM fragment; VWF:RCo, VWF ristocetin cofactor activity.

for low VWF diagnosis seems rational; however, this does not exclude the possibility that borderline VWF:Ag levels in the 50 to 60 IU/dL range may contribute to bleeding risk in some patients.[14,15]

On the basis of current data, it seems highly likely that many patients with mild to moderate reduced plasma VWF levels and significant bleeding remain undiagnosed in the general population. By definition, 2.5% of the normal population would be expected to have plasma VWF:Ag levels <50 IU/dL. Based on these numbers, we would expect 120 000 people in Ireland alone to potentially fall into the low VWF category. However, <500 Irish patients are registered with a low VWF diagnosis. This discrepancy is likely attributable to the fact that many patients with mild to moderate reductions in plasma VWF levels do not experience any bleeding issues. Thus, although reduced VWF levels in the 30 to 50 IU/dL range may constitute a risk factor for bleeding, they may not be sufficient to cause a bleeding phenotype in the absence of other hemostatic factors.[14,61,62] However, it also seems likely that a significant cohort of patients with low VWF and bleeding complications (particularly women with HMB) is not being diagnosed.[18] Given the significant associated morbidity, it is imperative that awareness among the general population and health care professionals is actively promoted.

Finally, some individuals will be found to have reduced plasma VWF levels in the 30 to 50 IU/dL range as a result of family testing. Because reduced VWF levels in this range are only a modest risk factor for bleeding, many of these individuals will not have a significant bleeding diathesis. Consequently, our practice is to follow-up these patients and consider their VWF levels as a risk factor for bleeding. They are not formally registered with a diagnosis of low VWF unless they also have evidence of a bleeding phenotype.

Low VWF treatment: recent advances

In addition to providing novel insights into low VWF pathobiology, recent studies have provided important information regarding treatment options for these patients. Importantly, the clinical management of patients with low VWF levels should be based primarily on their personal and/or family bleeding histories rather than just on plasma VWF levels.[15,16] Many individuals with low VWF may not require therapy. For example, Flood et al recently reported that bleeding complications were rare in pediatric patients with low VWF undergoing tonsillectomy.[61] Treatment options for patients with low VWF include antifibrinolytic agents (tranexamic acid or aminocaproic acid), DDAVP, and VWF-containing concentrates.[63,64] Although reduced VWF biosynthesis and subtle enhanced clearance have been implicated in the pathogenesis of low VWF, recent studies have reported that the vast majority of patients with low VWF demonstrate excellent and sustained increases in plasma VWF levels following DDAVP administration.[19] In the LoVIC study, almost 90% of patients had plasma VWF >100 IU/dL at 1 hour post-DDAVP.[19] Similarly, Sánchez-Luceros et al demonstrated the efficacy and safety of DDAVP therapy in children with low VWF levels.[65] On the basis of these data, it is clear that DDAVP has a key role to play in the management of low VWF. However, following the duration of VWF responses after the first administration of DDAVP in low VWF patients may still be useful, because recent studies have reported subtle enhanced VWF clearance in a subset of low VWF patients.[20]

In normal individuals, plasma VWF:Ag levels increase significantly with aging.[66] VWF levels have also been shown to increase with age in patients with type 1 VWD.[67,68] More recent studies have reported that a significant and progressive age-associated increase in VWF levels also occurs in patients with low VWF.[19,61,67] Overall, mean plasma VWF:Ag levels were estimated to increase by 1.9 IU/dL per year for low VWF patients in the LoVIC study. The biological mechanisms responsible for this age-related increase in VWF levels remain incompletely understood, but they may be attributable, in part, to associated comorbidities, including hypertension and diabetes.[69] Nevertheless, plasma VWF levels often correct into the normal range (>50 IU/dL), particularly for low VWF patients in whom plasma levels are only mildly reduced. Critically, however, current data suggest that this increase in VWF levels may not necessarily be associated with a correction in bleeding phenotype.[19,68] Therefore, the treatment of reduced VWF levels in elderly patients remains an important unresolved issue. Aged patients will likely not be suitable for DDAVP therapy, and after VWF containing factor concentrates may be at risk because elevated

VWF levels may be associated with thrombotic risk. Similarly, increased PPH was observed in a significant number of women with low VWF levels, despite the fact that plasma VWF levels in the third trimester were consistently >100 IU/dL. Altogether, these findings are consistent with the idea that mild reductions in plasma VWF levels may not necessarily explain all of the bleeding phenotypes observed in patients with low VWF. Further studies will be necessary to elucidate the additional mechanisms that contribute to the bleeding risk and to define how treatment of these patients may be optimized in the future. For women with low VWF levels and strong bleeding histories, my practice is to use antifibrinolytic therapy peripartum. Important ongoing clinical trials are also investigating whether higher VWF threshold levels are necessary to maintain physiological hemostasis during this period.

In summary, recent studies have provided novel insights into the pathobiological mechanisms involved in patients with low VWF levels. In addition, these studies have provided important data regarding the bleeding phenotype in this cohort of patients, as well as the utility of specific treatment options. Given the prevalence of this condition, these collective recent findings are not only of scientific interest but also direct clinical importance.

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Authorship

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