Low von Willebrand Disease: A Bleeding Disorder of Unknown Cause?

James S. O'Donnell[1,2,3] Ross I. Baker[3,4,5]

[1] Irish Centre for Vascular Biology, School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin 2, Ireland
[2] National Coagulation Centre, St James's Hospital, Dublin, Ireland
[3] Irish-Australian Blood Collaborative (IABC) Network, Dublin, Ireland
[4] Western Australia Centre for Thrombosis and Haemostasis, Perth Blood Institute, Murdoch University, Perth, Australia
[5] Hollywood Haemophilia Treatment Centre, Hollywood Hospital, Perth, Australia

Address for correspondence James O'Donnell, MD, PhD, Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Ardilaun House, 111 St Stephen's Green, Dublin 2, Ireland (e-mail: jamesodonnell@rcsi.ie).

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Abstract

von Willebrand disease (VWD) represents the most common inherited bleeding disorder. The majority of VWD cases are characterized by partial quantitative reductions in plasma von Willebrand factor (VWF) levels. Management of patients with mild to moderate VWF reductions in the range of 30 to 50 IU/dL poses a common clinical challenge. Some of these low VWF patients present with significant bleeding problems. In particular, heavy menstrual bleeding and postpartum hemorrhage can cause significant morbidity. Conversely, however, many individuals with mild plasma VWF:Ag reductions do not have any bleeding sequelae. In contrast to type 1 VWD, most patients with low VWF do not have detectable pathogenic *VWF* sequence variants, and bleeding phenotype correlates poorly with residual VWF levels. These observations suggest that low VWF is a complex disorder caused by variants in other genes beyond *VWF*. With respect to low VWF pathobiology, recent studies have shown that reduced VWF biosynthesis within endothelial cells likely plays a key role. However, pathological enhanced VWF clearance from plasma has also been described in approximately 20% of low VWF cases. For low VWF patients who require hemostatic treatment prior to elective procedures, tranexamic acid and desmopressin have both been shown to be efficacious. In this article, we review the current state of the art regarding low VWF. In addition, we consider how low VWF represents an entity that appears to fall between type 1 VWD on the one hand and bleeding disorders of unknown cause on the other.

Keywords
- von Willebrand factor
- von Willebrand disease
- low VWF

Introduction

von Willebrand disease (VWD) is caused by quantitative or qualitative reductions in plasma von Willebrand factor (VWF) and represents the most common inherited bleeding disorder.[1] Approximately 1 in 1,000 individuals have bleeding symptoms associated with reduced VWF levels.[2] VWD is classified according to whether there is a quantitative and/or qualitative VWF defect.[3–6] Type 1 VWD accounts for 75% of cases and is characterized by partial quantitative deficiency of plasma VWF. This quantitative defect means that plasma VWF antigen (VWF:Ag) and VWF activity assays are similarly reduced in type 1 VWD patients.[6,7] Type 2 VWD constitutes approximately 25% cases and includes a variety of different VWF functional defects.[6] According to the nature of the

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qualitative VWF impairment, type 2 VWD is further subclassified into types 2A, 2B, 2M, or 2N, respectively. Finally, type 3 VWD is a rare autosomal recessive bleeding disorder that affects approximately 1 per million of the population.[1,6] Type 3 VWD is characterized by near-complete absence of plasma VWF (plasma VWF:Ag levels < 3 IU/dL), and is more prevalent in areas with higher consanguinity.[1]

With respect to bleeding phenotype, patients with VWD commonly experience mucocutaneous bleeding including epistaxis, oral bleeding, prolonged bleeding from minor wounds, and easy bruising.[1,8,9] Accumulating evidence has highlighted that heavy menstrual bleeding (HMB) is also common in women with VWD.[10,11] This HMB can significantly impair quality of life and has important socioeconomic consequences.[12] Patients with VWD also experience significant bleeding following trauma, surgery, dental extraction, or during the postpartum period.[1] Spontaneous gastrointestinal bleeding from angiodysplasia occurs in some VWD patients and appears to occur more frequently in type 2A VWD.[13] Since plasma FVIII levels are also reduced in type 3 VWD,[14] these patients also have the potential to develop spontaneous joint bleeding with subsequent arthropathy.[15]

Low VWF and Type 1 VWD

Plasma VWF:Ag levels vary over a wide range (50–200 IU/dL) in the general population.[1,3] Among the most important determinants of this interindividual variability is ABO(H) blood group.[16] Previous studies have consistently reported that plasma VWF:Ag levels are 20 to 30% lower in blood group O compared to non-O (A, B, or AB) individuals.[16,17] The reduced VWF levels in group O individuals likely result from enhanced VWF clearance.[18] Importantly, bleeding symptoms are also common in the general population.[19] This leads to significant clinical challenges with respect to the diagnosis and management of patients presenting with mild mucocutaneous bleeding and mild reductions in plasma VWF levels.[19–21] To address this issue, previous expert consensus guidelines recommended that patients with mild to moderate quantitative VWD be subclassified into two distinct groups.[3–5] These guidelines proposed that patients with plasma VWF levels < 30 IU/dL should be given a diagnosis of type 1 VWD. In contrast, the guidelines recommended that patients with a bleeding phenotype and mild to moderate reductions in plasma VWF in the range of 30 to 50 IU/dL be registered with a diagnosis of low VWF.[3,5] The rationale behind this classification stemmed from reported differences between patients with plasma VWF levels less than 30 IU/dL and those with VWF levels in the range of 30 to 50 IU/dL (►Table 1).[20–22] For example, in patients with plasma VWF levels less than 30 IU/dL, *VWF* coding mutations are commonly identified.[23–25] Furthermore, families with type 1 VWD typically demonstrate autosomal dominant inheritance, albeit with variable penetrance.[1] In addition, mucocutaneous bleeding is common in patients with plasma VWF levels less than 30 IU/dL, and severity correlates inversel with endogenous plasma VWF:Ag levels.[1] Conversely, for low VWF patients with mild to moderate reductions in plasma

Table 1 Low VWF is distinct from Type 1 VWD

	Low VWF	Type 1 VWD
Plasma VWF:Ag levels	30–50 IU/dL	< 30 IU/dL
VWF sequence variants	~ 40% of patients	Present in > 80% of cases
Rare non-synonymous *VWF* variants	48% of patients	74% of patients
Inheritance pattern	Unknown	Autosomal dominant with incomplete penetrance
Bleeding symptoms	Variable bleeding HMB and PPH prominent	Mucocutaneous bleeding including HMB and PPH
Bleeding and VWF levels	Independent of plasma VWF levels	Correlates inversely with residual plasma VWF levels
VWF biosynthesis in EC	Reduced in > 50% cases. Independent of *VWF* sequence variants	Reduced biosynthesis common. Associated with specific *VWF* sequence variants
Pathological enhanced VWF clearance	Subtle increased clearance in ~ 20% of patients VWF half-life ~ 6 h Independent of *VWF* variants	Markedly enhanced clearance in > 40% cases VWF half-life ~ 2–4 h Specific *VWF* sequence variants
Age-induced increase in VWF levels	Age-dependent increase in plasma VWF:Ag levels. Commonly rises > 50 IU/dL. Bleeding risk may remain	Plasma VWF:Ag levels may increase in some patients. Depends on underlying *VWF* sequence variants
Pregnancy-induced increase in VWF levels	Plasma VWF:Ag levels increase with pregnancy. Commonly rises > 50 IU/dL. Bleeding risk may remain	Plasma VWF:Ag levels may increase in some patients. Depends on underlying *VWF* sequence variants

Abbreviations: EC, endothelial cell; HMB, heavy menstrual bleeding; PPH, postpartum hemorrhage; VWF, von Willebrand disease.

VWF (30–50 IU/dL), bleeding phenotype is variable and difficult to predict.[26,27] Indeed, many people with VWF levels in the range of 30 to 50 IU/dL do not have any significant bleeding tendency.[20,28] Furthermore, bleeding risk in these individuals with mild VWF reductions does not correlate with residual VWF levels.[26,27] In addition, *VWF* mutations are less common in patients with VWF levels in the range of 30 to 50 IU/dL.[26] These data suggest that additional unknown modifier genes contribute to the etiology of mild to moderate reductions in plasma VWF. This hypothesis is supported by linkage analyses demonstrating that low VWF levels in many families are not linked to the *VWF* gene.[29,30] Consequently, again in contrast with type 1 VWD, the inheritance pattern and pathogenesis underlying low VWF in specific families remains poorly defined.

ASH/ISTH/WFH/NHF Consensus Guidelines on VWD Diagnosis

Recently, the American Society of Hematology/International Society on Thrombosis and Haemostasis/World Federation of Hemophilia/National Hemophilia Foundation (ASH/ISTH/WFH/NHF) expert consensus guidelines reconsidered terminology for use in patients with partial quantitative reductions in plasma VWF levels.[6] These guidelines used the GRADEpro guideline-development tool and specifically addressed several questions that had been prioritized following an international survey (601 respondents from 71 countries).[31] One of the questions posed was "*For patients with an abnormal initial VWD screen suspected of type 1 VWD, should the diagnostic cut-off be at VWF:Ag and/or VWF platelet-dependent activity <0.30 IU/mL or <0.50 IU/mL*?" A subsequent systematic review found low certainty in the available evidence.[32] However, the panel recommended that a VWF level of <0.3 IU/mL should be enough to confirm a diagnosis of type 1 VWD, irrespective of whether the individual had any previous bleeding.[6] The panel further recommended that patients with abnormal bleeding and plasma levels in the range of 0.3 to 0.5 IU/mL should also be diagnosed with type 1 VWD (as opposed to "low VWF" in previous guidelines). The ASH/ISTH/WFH/NHF panel judged that patients with VWF levels in the range of 0.3 to 0.5 IU/mL and bleeding symptoms would be more likely to have access to clinical care, particularly in certain jurisdictions, if they had a clear type 1 VWD rather than low VWF diagnosis.[6] This decision has been the subject of subsequent discussion.[33,34] However, it is important to point out that the ASH/ISTH/WFH/NHF guidelines specifically highlighted that bleeding in patients with mild-to-moderate VWF reductions (0.3–0.5 IU/mL) is likely to be multifactorial in nature.[6] Furthermore, the guidelines also emphasized the need for additional research in this context. The lack of precision of VWF assays is estimated to be between 8 and 25% which makes comparison of mild-to-moderate VWF reductions (0.3–0.5 IU/mL) between laboratories less robust. Confirming the consistency of an abnormal test improves the certainty of VWF classification. The ASH/ISTH/WFH/NHF panel recommendation for the use of new assays that measure the binding of VWF to the recombinant platelet glycoprotein Ib (VWF:GPIbM and VWF:GPIbR) over the VWF Ristocetin Cofactor assay is likely to improve VWF precision at lower levels. In addition, important clinical issues still need to be elucidated.[22] For example, many individuals found to have mild to moderate reductions in plasma VWF levels may not have a definitive bleeding history. This is particularly true for children and for younger adults who have not been exposed to previous hemostatic challenges. These patients fall out with current guideline criteria and clinical management poses significant issues, particularly in the setting of elective surgical procedures.

Pathobiology of Low VWF versus Type 1 VWD

Previous studies have shown that pathogenic variants in the *VWF* gene cannot be identified in ~35% of type 1 VWD patients.[35] Moreover, pathogenic *VWF* variants are detected even less commonly in low VWF patients.[26] These findings suggest that type 1 VWD and low VWF are both complex disorders involving variants in other genes beyond *VWF*. In keeping with this concept, linkage studies found that only ~40% families with type 1 VWD demonstrated linkage to the *VWF* locus.[29,30] Interestingly, recent data from the Zimmerman Program has demonstrated that the number of rare nonsynonymous variants in the *VWF* gene is significantly increased in patients with type 1 VWD (1.26 per person) and low VWF (0.67 per person) compared to healthy controls (0.16 per person).[36] Overall, 88% of the healthy controls ($n = 210$) studied had no rare nonsynonymous *VWF* variants. In contrast, only 52% of low VWF patients ($n = 169$) and 26% of type 1 VWD subjects ($n = 153$) had no rare *VWF* variants. Finally, Sadler et al further showed that the number of rare nonsynonymous *VWF* variants inversely correlated with plasma VWF:Ag levels.[36] Interestingly, this association was also observed in type 2 VWD patients with known pathogenic *VWF* variants. Cumulatively, these data further support the hypothesis that low VWF and type 1 VWD are not monogenic traits. Further studies will be required to define the biological mechanisms through which rare *VWF* variants are associated with VWF levels.

VWF Biosynthesis in Low VWF

A variety of different *VWF* pathogenic variants have been shown to result in significantly reduced VWF biosynthesis and/or secretion in patients with type 1 VWD.[37] Even though *VWF* variants are significantly less common in low VWF patients, accumulating data suggest that reduced VWF synthesis also contributes to their reduced VWF levels.[26,27] For example, the ***Lo***w ***V***WF ***I***reland ***C***ohort (LoVIC) study reported that plasma factor VIII/VWF ratios were significantly elevated in low VWF patients compared to healthy controls.[26] Furthermore, significant reductions in platelet VWF:Ag levels have been observed in some patients with low VWF patients.[26,38] To identify novel modifiers that might be responsible for this impaired VWF biosynthesis within endothelial cell, Ng et al investigated endothelial colony-forming cells (ECFCs) derived from low VWF patients, compared to ECFC from healthy controls.[39] Overall, VWF levels in the cell supernatant were not significantly different between control ECFCs and low VWF ECFCs. In contrast, however, VWF secreted from low VWF

ECFCs following PMA activation was significantly attenuated compared to healthy control ECFCs.[39] Furthermore, immunofluorescent studies demonstrated a significant reduction in the number and size of Weibel Palade bodies in low VWF ECFCs. Subsequent single-cell RNA sequencing (scRNA-seq) showed reduced *VWF* mRNA transcription, together with evidence of mosaicism in *VWF* expression in low VWF ECFCs. Furthermore, 551 genes were differentially expressed in low VWF ECFC compared to control ECFCs.[39] Collectively, these findings suggest that, at least in some low VWF patients, reduced VWF synthesis and/or secretion in endothelial cells contributes to low VWF pathogenesis.

VWF Clearance in Low VWF

A variety of different receptors and cellular clearance pathways have been implicated in modulating physiological clearance of VWF and the VWF–FVIII complex from plasma.[40–44] In addition, a series of *VWF* mutations in patients with type 1 VWD have been shown to trigger pathological enhanced clearance in vivo, leading to reduced plasma VWF:Ag levels.[27,45–48] These include the archetypal VWD Vicenza (R1205H) variant.[49] Overall, reduced VWF half-life appears to be relatively common in type 1 VWD, where it is estimated to play a pathogenic role in more than 40% cases.[27,46] This has led to the suggestion that type 1 VWD patients with rapid clearance should be categorized as type IC (1—clearance).[47,48] Similarly, recent studies have shown that pathological enhanced VWF clearance also contributes to low VWF pathogenesis in some patients.[50,51] The ASH/ISTH/WFH/NHF guidelines recommend that enhanced VWF clearance in patients be assessed by measurement of sequential plasma VWF levels following desmopressin infusion.[6,12] The proposed threshold for defining pathological increased VWF clearance is a fall in plasma VWF:Ag levels >30% between +1 hour and +4 hours after desmopressin.[6] Recent data from the LoVIC study have demonstrated that ~20% of patients with low VWF demonstrate enhanced VWF clearance based on these criteria.[50,51] As an alternative approach, previous studies have successfully used a VWF propeptide (VWFpp)/VWF:Ag ratio > 3 to identify patients with type 1C VWD.[47,48] Interestingly, Doherty et al recently reported that the sensitivity of the steady-state VWFpp/VWF:Ag ratio for identifying increased VWF clearance in patients with low VWF was significantly reduced compared to gold-standard desmopressin fall-off rates.[50] This likely reflects the fact that the reduction in plasma VWF half-life in low VWF patients (~6 hours) is not as marked as that observed in type 1C patients (2~4 hours). Furthermore, VWFpp clearance kinetics may also vary between individual patients with low VWF and type 1 VWD.[50] Taken together, these data demonstrate that enhanced VWF clearance plays an important role in low VWF pathogenesis. Although the biological mechanisms responsible for pathological VWF clearance in patients without *VWF* sequence variants has not been defined, previous studies have reported altered VWF glycosylation in subsets of patients with both low VWF and type 1 VWD, respectively.[51–53]

Bleeding in Low VWF

Although BAT scores are associated with inherent limitations (e.g., the need to perform at the time of first diagnosis and lack of sensitivity in younger patients who have not undergone significant hemostatic challenges), the ISTH BAT score does offer an objective approach to assessing bleeding phenotype and is important in that it enables comparisons between different low VWF studies. Studies to date suggest that although patients with low VWF have only mild to moderate reductions in plasma VWF levels, at least some of these patients have a significant bleeding phenotype.[10,11,26,27,54] For example, almost 40% of females with low VWF patients in the LoVIC study had ISTH BAT scores ≥ 10 (normal range: 0–5).[26] In addition, 62% of patients with low VWF in the Zimmerman Program had significantly elevated ISTH BAT scores.[27] Flood et al further showed that abnormal BAT scores in low VWF patients were comparable to those seen in type 1 VWD patients.[27] Similarly, significant mucocutaneous bleeding has also recently been reported in a study of 111 adolescent females, 14% of who had BAT scores greater than 10.[11]

HMB and postpartum hemorrhage have been highlighted as significant clinical issues in low VWF.[10,11,26] Using the Pictorial Bleeding Assessment Chart (PBAC) score, Srivaths et al recently reported a median PBAC score of 630 in adolescent women with low VWF (normal < 100).[11] In the LoVIC study, 40% of patients reported missing more than 2 days off work or school per year due to HMB, and 67% had required treatment with either a combined oral contraceptive pill or hormone-releasing intrauterine device.[26] Importantly, however, Srivaths et al reported that hormonal therapy was not associated with significant clinical improvement in 29% of adolescents with low VWF.[11] Consistent with that concept, 30% of female patients with low VWF in the LoVIC study eventually required surgical intervention (including endometrial ablation and hysterectomy) to control their HMB.[26] Even though HMB is commonly associated with iron deficiency in women with low VWF, current evidence suggests that there are often significant delays before a diagnosis is reached.[10,26]

Importantly, in the LoVIC study, bleeding scores in female patients were still increased even after HMB and postpartum hemorrhage (PPH) were removed from the assessment.[10,26] Although further studies will be required to define the biological mechanism(s) that contribute to the increased bleeding phenotype in low VWF individuals, factors outside the hemostatic system are likely to contribute in at least some cases.

Treatment of Low VWF

Due to lack of evidence, management of patients with low VWF levels poses significant clinical challenges.[55] Treatment decisions are typically based on personal bleeding history, family bleeding history, and current plasma VWF levels.[55] Based on current literature, it seems reasonable to assume that many individuals with mild to moderate reduction in

plasma VWF:Ag levels will not need hemostatic treatment prior to procedures. Consistent with that hypothesis, Flood et al showed that bleeding complications were rare in pediatric low VWF patients who underwent tonsillectomy.[28] However, some low VWF patients will require hemostatic support for elective procedures, particularly those with significantly elevated personal ISTH BAT scores greater than 10.[55,56] Treatment options include antifibrinolytic agents such as tranexamic acid (TA) or aminocaproic acid, desmopressin, and VWF-containing concentrates.[55–57]

Doherty et al recently reported on the management of elective procedures in adult low VWF patients in the LoVIC study.[58] This retrospective review included 160 invasive procedures (40 dental, 109 minor, and 11 major procedures) performed in 60 patients. Notably, these low VWF patients all had abnormal ISTH BAT scores, with 21/60 (35%) patients having BAT scores greater than 10.[58] TA treatment alone, commencing on the evening prior to the elective procedure, was used for 25% of dental procedures and 23% of the minor elective procedures examined. Bleeding complications were seen in only three of these procedures managed with TA alone. All three bleeding episodes were associated with dental procedures, with no bleeding observed in any of the other elective minor surgeries.[58] Together, these findings suggest that TA alone is useful treatment for adult low VWF patients undergoing elective surgeries, particularly for non-dental minor procedures.

Even though reduced VWF biosynthesis and enhanced clearance are implicated in the etiology of low VWF, accumulating data have shown that adult low VWF patients typically demonstrate sustained desmopressin responses.[26,58] For example, in a cohort of 71 adult low VWF patients, Doherty et al showed that median plasma VWF:Ag levels were 167 (range: 139–196 IU/dL) at +1 hour and 130 IU/dL (range: 110–154 IU/dL) at 4 hours following desmopressin infusion.[50,58] All these low VWF patients therefore had a "*complete response*" to desmopressin as previously defined.[12,59] Consistent with these findings, Doherty et al went on to use desmopressin ± TA to manage 99 elective dental and minor surgical procedures.[58] Even though all these low VWF patients had significant bleeding histories, bleeding complications were observed in only one single dental extraction.[58] Cumulatively, these laboratory and clinical data therefore suggest that desmopressin has an important role to play in the management of low VWF.

Low VWF and Bleeding Disorders of Unknown Cause

In normal individuals and many patients with type 1 VWD, plasma VWF:Ag levels increase progressively with ageing.[60–62] These increases are likely due in large part to associated comorbidities including diabetes and hypertension.[63] Similar age-dependent increases in VWF levels have also been reported in low VWF patients. In the LoVIC study, plasma VWF:Ag levels increased by an average 1.9 IU/dL per annum.[26] Consequently, plasma VWF:Ag levels often increase into the normal range (>50 IU/dL) as low VWF patients become older. Importantly, however, reports suggest that this increase in plasma VWF:Ag levels is not necessarily associated with a complete correction in bleeding risk.[26,62] Pregnancy is also associated with a progressive increase in VWF levels in low VWF patients, so that plasma VWF:Ag levels typically rise to greater than 100 IU/dL by the third trimester.[10,26] Importantly, however, despite the

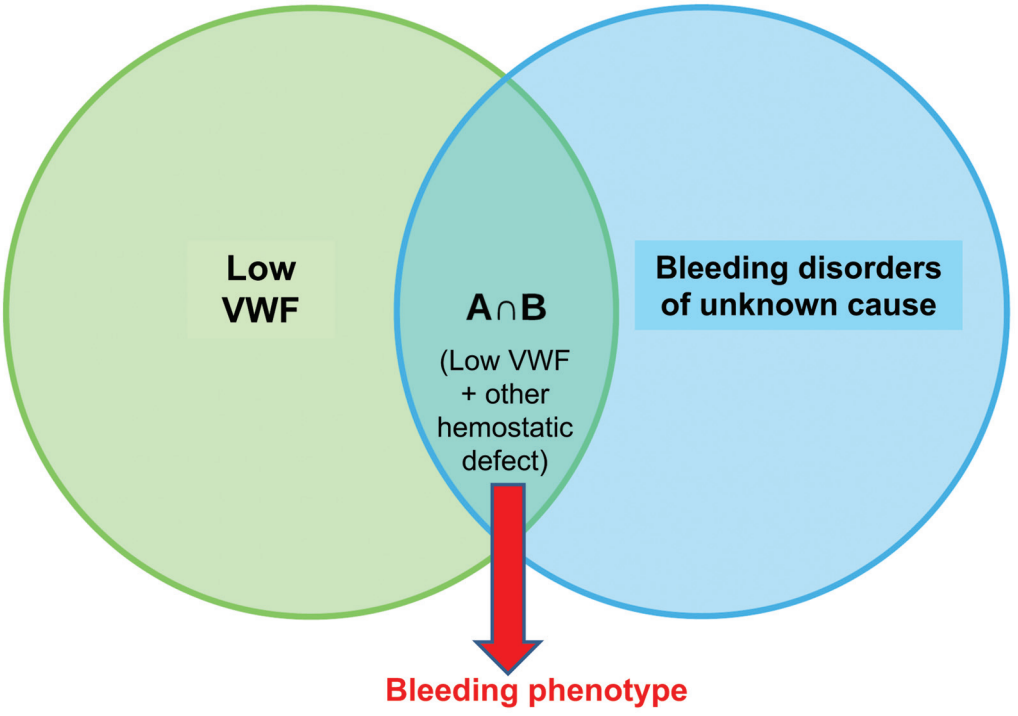

Fig. 1 **Low** von Willebrand disease (**VWF) and bleeding disorder of unknown etiology (BDUA).**

apparent correction in VWF levels, low VWF patients remain at significant increased risk for both primary and secondary PPH.[10,26]

These clinical observations suggest that mild reductions in plasma VWF levels do not explain all of the bleeding phenotype observed in patients with low VWF. Rather, it seems that other pathological mechanisms play important roles in bleeding.[64,65] In that context, the pathogenesis underlying bleeding in low VWF patients likely overlaps with those involved in patients with bleeding disorders of unknown cause (BDUC; ►**Fig. 1**).[66] This hypothesis is also consistent with the evidence that (1) only some patients with mild reductions in plasma VWF:Ag levels have any bleeding and (2) bleeding phenotype in these patients does not correlate with residual VWF levels. Head-to-head studies directly comparing bleeding phenotype in low VWF compared to BDUC cohorts will be of interest in addressing this hypothesis. In essence therefore, we propose that mild to moderate reductions in VWF levels represent a risk factor for bleeding, but of themselves are not sufficient to constitute a distinct disease.[19–21]

Authors' Contribution

R.I.B. and J.S.O'D. were involved in writing and reviewing the paper.

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Conflicts of Interest

J.S.O'D has served on the speaker's bureau for Baxter, Bayer, Novo Nordisk, Boehringer Ingelheim, Leo Pharma, and Octapharma. He has also served on the advisory boards of Baxter, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, and Pfizer. J.S.O'D has also received research grant funding awards from Baxter, Bayer, Pfizer, and Novo Nordisk.

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