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How I treat Low von Willebrand Factor levels

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ABSTRACT

Partial quantitative deficiency of plasma von Willebrand factor (VWF) is responsible for the majority of cases of von Willebrand disease, the commonest inherited human bleeding disorder. International consensus guidelines recommend that patients with reduced plasma VWF:Ag levels and bleeding phenotypes should be considered in two distinct subsets. First, patients with marked reductions in plasma VWF levels (<30 IU/dL) usually have significant bleeding phenotypes and should be classified with 'Type 1 VWD.' In contrast, patients with intermediate reduced plasma VWF:Ag levels (in the range 30 – 50 IU/dL) should be considered in a separate category labeled 'Low VWF levels.' These patients with Low VWF commonly display variable bleeding phenotypes and often do not have *VWF* gene sequence variations. Since the pathophysiology underlying Low VWF levels remains largely undefined, diagnosis and management of these patients continues to pose significant difficulties. In this article, we present a number of clinical case studies to highlight these common clinical challenges. In addition, we detail our approach to establishing a diagnosis in Low VWF patients and discuss strategies for the management of these patients in the context of elective surgery and pregnancy.

KEYWORDS - von Willebrand factor; von Willebrand disease; Low VWF levels; Bleeding Assessment Tools

INTRODUCTION

Von Willebrand disease (VWD) is caused by either quantitative or qualitative deficiencies in plasma von Willebrand factor (VWF) and constitutes the commonest inherited bleeding disorder.[1] Reduced plasma VWF levels in combination with a family history of bleeding have a reported prevalence of 1%.[2] Furthermore, significant bleeding symptoms due to reduced VWF levels have been observed in approximately 1 in 1000 of the normal population.[3,4] Type 1 VWD is responsible for the majority of cases and is characterized by a partial quantitative VWF deficiency. In recent years, understanding of the pathobiology underlying quantitative VWF deficiency has progressed significantly following a number of type 1 VWD cohort studies.[5–8] Consequently, more recent clinical guidelines from the USA National Heart, Lung and Blood Institute (NHLBI), the European Group on von Willebrand disease (EUVWD) and the UK Haemophilia Doctors Organization (UKHCDO) recommend that patients with reduced plasma VWF:Ag levels and bleeding phenotypes should be considered in two distinct subsets.[9–11] Patients with marked reductions in plasma VWF levels (<30 IU/dL) usually have significant bleeding phenotypes and should be labeled 'Type 1 VWD'.[9–11] These patients are likely to have identifiable *VWF* gene mutations and exhibit autosomal dominant inheritance patterns.[7,12] In contrast, patients with intermediate reduced plasma VWF:Ag levels (in the range 30 – 50 IU/dL) should be considered in a separate category labeled 'Low VWF levels'.[9] These patients with Low VWF commonly display variable bleeding phenotypes and often do not have *VWF* gene sequence variations (Table 1).[7,13] Although the pathophysiology underlying Low VWF levels remains poorly defined, recent data suggest that reduced VWF synthesis and/or secretion from endothelial cells rather than enhanced VWF clearance.[13] Despite these advances, the diagnosis and management of these patients continues to pose significant difficulties. In this article, we present a number of clinical case studies to highlight these common clinical challenges. In addition, we detail our approach to establishing a diagnosis in Low VWF patients and discuss strategies for the management of these patients in the context of elective surgery and pregnancy.

DIAGNOSIS OF LOW VWF

Case 1:

A 26 year old female with a history of heavy menstrual bleeding (HMB) is referred from the gynecology service for assessment of a possible bleeding disorder. She describes spontaneous bruising since childhood with 5-10 bruises present on occasion. She required cauterization for epistaxis as a teenager and packing following a dental extraction (DE). Her periods have been heavy since menarche, lasting up to 8 days duration with pad changes every 1-2 hours on days of heaviest flow. She has used oral iron supplementation intermittently since the age of 14 due to recurrent iron deficiency. Her mother and older sister also have HMB, resulting in her mother undergoing a hysterectomy aged 42. Both her mother and sister have easy bruising and her sister required repeat presentation for suturing for bleeding post DE.

Discussion of Case 1

Previous studies have demonstrated that bleeding symptoms such as epistaxis, easy bruising and menorrhagia are all commonly reported in healthy controls.[14,15] Overall, these surveys suggest that the percentage of controls with at least one bleeding symptom could be conservatively estimated at approximately 25%.[16] Since the normal range for plasma VWF:Ag levels is 50-200 IU/dL, then by definition 2.5% of the normal population will also have VWF levels less than 50 IU/dL. These combined prevalence data mean that 0.6% of the general population coincidentally have both bleeding symptoms and reduced VWF levels and highlight the significant risk for false positive diagnosis of partial quantitative VWD in this context.[16] Consequently in patients referred for investigation of possible Low VWF, a systematic approach to (1) the clinical assessment of bleeding phenotype and (2) laboratory investigations (including VWF assays) is essential.

Objective assessment of bleeding history in diagnosis of Low VWF

Initial assessment of this patient focuses on objective assessment of bleeding phenotype using a standardized bleeding assessment tool (BAT). While a number of different BAT iterations have been described, the two questionnaires most widely studied in VWD are the condensed MCMDM-1 VWD score and ISTH BAT scores respectively.[17–19] Previous studies have validated the use of both scores in the

diagnosis of type 1 VWD.[19,20] Both BATs assess bleeding over a number of specific domains, including menorrhagia, cutaneous bleeding and post-operative bleeding. The Condensed MCMDM-1 VWD score differs from the ISTH BAT in that negative scores are applied for two hemostatic challenges without bleeding in the post-operative, dental and postpartum domains.[19] As such, the threshold for positive scores differs between the BATs (≥4 for males and females for the Condensed MCMDM-1 VWD score; ≥4 for males or ≥6 for females using the ISTH BAT score).[19,20] Interestingly, recent studies have demonstrated that the ISTH BAT score may also be more sensitive than Condensed MCMDM-1 score in assessing heavy menstrual bleeding.[21] This difference relates to the fact that the ISTH BAT includes HMB since menarche and that no score is accrued for the menorrhagia domain of the Condensed MCMDM-1 VWD score unless medical intervention is sought, irrespective of the patient's HMB symptom severity.[21] Many patients with significant menorrhagia may not appreciate the severity of their symptoms and thus fail to seek medical attention. As such, the ISTH BAT score is more sensitive to detection of menorrhagia as it includes assessment of the presence of clots, flooding, frequency of pad change and the duration of symptoms.[18,21] Consequently, in our initial assessment of patients referred with possible Low VWF, we utilize the ISTH BAT score over the Condensed MCMDM-1 VWD score for the objective initial assessment of bleeding phenotype. Based upon her significant bleeding history, an ISTH BAT score of 10 was calculated for our index case.

Whilst utilization of BAT scores standardizes bleeding phenotype assessment in patients with Low VWF, a number of important caveats should be considered. First, BAT scores should be assigned at first diagnosis whenever possible. If scores are being calculated retrospectively, only symptoms experienced prior to initial diagnosis should be included as subsequent prophylactic treatments given for procedures may lead to falsely elevate scores.[17] Second, for younger patients or adults who have undergone a limited number of previous hemostatic challenges, the BAT score may be negative even in the presence of an underlying bleeding diathesis.[17] Third, although the MCMDM-1 VWD score has been shown to predict future bleeding risk, recent data suggest that the ISTH BAT may not predict risk of surgical bleeding.[22,23]

Laboratory investigations in the diagnosis of Low VWF

For patients with an abnormal BAT score, laboratory investigations should be performed to investigate for the presence of hemostatic defects. In addition, a complete blood count and ferritin levels should be assayed for all patients with a history of significant bleeding. For the bleeding state work up, in our institution, we first assess prothrombin time, activated partial thromboplastin time, fibrinogen level and VWF levels (VWF:Ag, VWF:RCo, VWF:CB). In patients with a marked bleeding phenotype, we proceed to assay clotting factor assays (Factors II, V, VII, VIII, IX, X, XI, and XIII), platelet aggregometry and platelet nucleotide testing. Importantly, in Low VWF patients with a marked bleeding phenotype, it is our practice to complete a full clotting factor screen and platelet aggregation studies to exclude the possibility that additional coagulation defects may be present. Whilst this is rare,[13] it clearly has direct relevance in determining optimal clinical management for these patients. The results for Case 1 are illustrated in Table 2. While factor assays, platelet aggregometry and nucleotides were all normal, plasma VWF levels were significantly reduced and consistent with Low VWF. As plasma VWF levels are known to vary significantly over time, recent guidelines have recommended repeat testing to ensure consistency in levels prior to assignation of a diagnosis. Importantly, there is limited evidence to guide when repeat testing should best be performed.[11] In our institution, in all patients with plasma VWF levels in the Low VWF range repeat VWF testing is performed a minimum of three months after initial sampling. Repeat testing in our index case confirmed that the Low VWF levels were a consistent finding (Table 2).

A number of different variables may impact significantly upon plasma VWF levels. In particular, it is well described that plasma VWF levels are 25% lower in blood group O compared to non-O individuals.[24,25] In addition, plasma VWF levels have been reported to vary according to the menstrual cycle and can be affected by use of the combined oral contraceptive pill (COCP).[26–28] Interestingly, plasma VWF levels also exhibit diurnal rhythm, with peak levels at midday and an amplitude of 22%.[29] Whilst these factors and others all have the potential to influence plasma VWF levels, expert consensus guidelines recommend against the need for timing of samples to menstrual cycle, or the use of blood group specific reference ranges.[9,11]

In terms of assigning a formal diagnosis of Low VWF, it is important to note that consensus guidelines differ in respect to their recommended laboratory criteria. Both

the NHLBI and UKHCDO recommend diagnosis for individuals with plasma VWF levels in the 30-50 IU/dL range.[9,11] In contrast however, the EUVWD propose a plasma VWF threshold level of 30-40 IU/dL.[10] Recent data from both the Low VWF Ireland Cohort (LoVIC) study and the Zimmerman program has shown that there is no significant difference in bleeding for Low VWF patients with lowest VWF levels in the 30 to 39 IU/dL range compared to those with lowest VWF levels in the 40 to 50 IU/dL range.[7,13] Based upon these cumulative findings, it is our practice to diagnose Low VWF for patients with a significant ISTH BAT score who also have at least two consistent plasma VWF levels in the 30-50 IU/dL range, taken three or more months apart. Our index case clearly satisfies these criteria. In our practice, all newly registered Low VWF patients are advised to minimize NSAID exposure where possible. In addition, patients are provided with a standardized letter for their dentist and given emergency contact information in the event of bleeding. Finally, they are informed to contact for a hemostatic management plan should any operations/procedures be required in the future or should they become pregnant.

MANAGEMENT OF LOW VWF FOR ELECTIVE MAJOR SURGERY

Case 2:

A 26 year old man with Low VWF is scheduled to undergo elective tonsillectomy for recurrent tonsillitis. The patient was diagnosed with Low VWF following investigation for recurrent epistaxis. This epistaxis has been problematic since childhood, with frequent nosebleeds lasting for 30 minutes that had responded poorly to previous cauterization. A previous dental extraction was complicated by persistent bleeding that necessitated dental review and suturing. The only abnormality identified on extensive laboratory investigations was persistently reduced plasma VWF levels, with baseline VWF:Ag and VWF:RCo levels consistently in the range 30-40 IU/dL. In view of his significant bleeding phenotype, the patient had previously undergone a DDAVP trial (0.3mg/kg intravenously, IV). A significant and sustained increase in plasma VWF levels was observed following DDAVP administration (one hour post DDAVP - plasma VWF:Ag 148 IU/dL and VWF:RCo 150 IU/dL; 4 hours post DDAVP - VWF:Ag 97 IU/dL and VWF:RCo 102 IU/dL).

Discussion of Case 2

On the basis of his bleeding history, this patient has an elevated ISTH BAT score of 6. This significant bleeding tendency appears discrepant to the moderate reduction in his plasma VWF levels. Given the prevalence of Low VWF levels in the general population, it is perhaps unsurprising that previous studies have described the coincidental occurrence of additional bleeding disorders in some patients with Low VWF resulting in a multifactorial bleeding defect. However, using the panel of investigations listed in Table 2, no additional abnormalities besides his Low VWF were identified. Interestingly, a number of recent independent studies have confirmed that some patients with Low VWF may have significant bleeding phenotypes even in the absence of any other detectable additional hemostatic abnormalities.[7,13] These observations are in keeping with the original concept proposed by Evan Sadler wherein the bleeding phenotype observed in patients with Low VWF levels was not likely to be attributable solely to the moderate reduction in plasma VWF levels alone. Rather, it seems likely that these patients may have other factors contributing to their bleeding, although definition of these additional

modulators using standard laboratory testing may be difficult. Hence Low VWF should be considered an epidemiologic risk factor for bleeding rather a disease.[16] For example, it should be noted that current routine hemostatic testing cannot exclude other disorders such as collagen vascular defects or certain platelet function defects (such as those identified on platelet electron microscopy). Critically therefore, when it comes to defining patient management plans, personal and family bleeding history are more important than absolute VWF levels. The objective BAT score is useful in this context and undoubtedly serves to facilitate communication between the multidisciplinary healthcare professionals involved in providing care for these patients. On the basis of his bleeding history and Low VWF levels, this patient will require hemostatic cover for his elective tonsillectomy.

Treatment options for patients with Low VWF

Treatment options for patients with Low VWF and significant bleeding phenotypes include anti-fibrinolytic agents such as tranexamic acid or aminocaproic acid), 1-desamino-8-D-arginine vasopressin (DDAVP) and VWF-containing concentrates. Tranexamic acid has been widely used in the management and prevention of bleeding in VWD.[9] Tranexamic acid can be administered orally (typical dose 15-25mg/kg TID), as a mouthwash (typical dose 10ml of 5% w/v solution QID) or intravenously (typical dose 15mg/kg TID).[30,31] Adverse effects associated with use of tranexamic acid include nausea, vomiting and abdominal pain.[30] In addition, tranexamic acid is generally avoided in patients with significant hematuria (to prevent ureteric clot colic and obstruction). [30] Although concerns regarding possible thromboembolic risk with tranexamic acid therapy have been expressed, recent systematic reviews have failed to demonstrate any significant increased risk.[32–34]

DDAVP is a synthetic analogue of vasopressin that stimulates EC secretion of stored VWF into the plasma.[35] Consequently, DDAVP can be utilized to transiently increase plasma VWF levels in some patients with VWD.[9] DDAVP is licensed for intravenous (IV), intranasal and (in some countries) subcutaneous (SC) administration.[36–38] Dosing is route dependent, with 0.3µg/kg given IV/SC and 300 µg to adults intra-nasally. Interestingly lower doses of DDAVP have also been reported to elicit significant plasma VWF responses.[39–41] For patients with type 1 VWD, significant inter-individual variability in VWF responses to DDAVP has been reported.[42] However, for a given individual patient, VWF responses to DDAVP

administration are typically reproducible over time.[41] These findings likely reflect the different pathogenic mechanisms that can underlie type 1 VWD.[43,44] For example, type 1 VWD patients with *VWF* mutations that interfere with VWF synthesis are unlikely to have significant EC stores of VWF and thus are less likely to respond to DDAVP.[44] In contrast, type 1 VWD can also result from enhanced VWF circulatory clearance (e.g. VWF Vicenza R1205H).[45] Plasma VWF levels typically increase significantly in type 1C VWD patients following DDAVP, but the half-life of the secreted VWF is markedly reduced.[45] Given this inter-individual variation, a DDAVP trial is usually recommended for patients with VWD.[9,11] In addition to measuring peak VWF responses at 30-60 min following DDAVP, assays are commonly repeated at later time points (4-6 hours) to confirm the duration of VWF response.[11] Recent data suggest that in contrast to type 1 VWD, the vast majority of patients with Low VWF demonstrate excellent and sustained responses to DDAVP.[13] In the LoVIC study, 100% of Low VWF patients studied had plasma VWF:Ag and VWF:RCo levels >50 IU/dL at both 1 and 4 hours post DDAVP. In addition, plasma VWF levels were >100 IU/dL in 88% patients at 1 hour and sustained in 72% patients at 4 hours.[13] On the basis of these findings, in our practice we no longer perform routine DDAVP trials in patients with Low VWF levels, but instead monitor plasma VWF levels over time to confirm adequacy of response at the time of first therapeutic use of DDAVP.

With respect to our index case, he has previously been shown to have an excellent initial and sustained VWF response to DDAVP. Consequently, for his elective tonsillectomy, we would treat with DDAVP and tranexamic acid. Tranexamic acid 1g TID would be commenced preoperatively and continued for 7-10 days.[46–48] DDAVP would be administered (0.3µg/kg in 100mls of normal saline infused over 20min) on the morning of his procedure with plasma VWF:Ag, VWF:RCo and FVIII:C levels checked 1 hour post DDAVP, prior to surgery. Post-operatively, VWF and FVIII levels would be repeated to determine optimal timing for subsequent DDAVP infusions. Although DDAVP treatment can be repeated at 12-24 hour intervals as required, tachyphylaxis with a progressive decrease in response has been reported and thus plasma VWF levels should be monitored.[49] In terms of adverse effects, DDAVP can cause fluid retention, secondary hyponatremia and seizures.[36] Fluid intake should be restricted to 1 litre for adults in the 24 hours post DDAVP administration to minimize risk of dilutional hyponatremia, the rate of which may be higher in adolescents.[11,50] Confirmation of normal serum sodium levels is essential

prior to any subsequent doses of DDAVP.[11] Plasma FVIII and VWF levels should be monitored daily and maintained >50 IU/dL for 5-7 days post tonsillectomy.[11] As the eschar post tonsillectomy may shed at days 7-10, there is an increased risk of bleeding at this time period and we advise continuing tranexamic acid to 7-10 days post operatively Further doses of DDAVP should be considered for any bleeding complications that may develop despite ongoing tranexamic acid therapy.

Given the prevalence of Low VWF levels, patients may require management in settings outside Hemophilia Comprehensive Care Centers where laboratory testing may be delayed. In this setting, our practice is to base treatment on the patient's bleeding history, the bleeding risk associated with the surgical procedure and plasma VWF response to any previous DDAVP administration. Many patients with Low VWF can be managed using a single preoperative dose of DDAVP combined with tranexamic acid 1gm TID for 5-7 days post-op. If the patient has a very significant bleeding history or develops any post-operative bleeding despite on tranexamic acid therapy, we advise repeat DDAVP administration, provided no hyponatremia is present.

For patients with Low VWF and significant bleeding histories who are intolerant of DDAVP therapy (e.g. who develop significant hyponatremia despite fluid restriction) or for whom DDAVP is contra-indicated, a number of different commercial plasma-derived VWF containing concentrates are available. These VWF concentrates differ in several aspects, including source of plasma, purification methodology, viral inactivation steps, and FVIII content (recently reviewed in Lavin and O'Donnell).[51] In addition, a first recombinant VWF (rVWF) concentrate has recently been developed licensed for use in some countries.[36]

MANAGEMENT OF LOW VWF DURING PREGNANCY

Case 3:

A 30 year old woman with a diagnosis of Low VWF attends the combined hematology-obstetrics clinic at 20 weeks gestation in her second pregnancy. She was diagnosed with Low VWF 5 years ago, when her ISTH BAT was calculated at 6 (HMB since menarche, easy bruising and epistaxis lasting up to 20 minutes requiring consultation). Consistently reduced plasma VWF levels were observed on repeat testing (VWF:Ag 42 IU/dL, VWF:RCo 44 IU/dL, VWF:CB 45 IU/dL). A full bleeding state work up identified no other hemostatic defects. Subsequent to her diagnosis with Low VWF, the patient became pregnant in 2015. Laboratory testing performed during that first pregnancy confirmed that by the third trimester her plasma VWF levels had significantly increased (32 weeks gestation - VWF:Ag 167 IU/dL, VWF:RCo 142 IU/dL). Onset of labor was spontaneous and labor was not prolonged with normal vaginal delivery of a healthy female infant. No episiotomy was required and the placenta was delivered intact. Unfortunately however, she experienced a significant primary postpartum hemorrhage (PPH) with estimated blood loss of 1100ml and was treated with tranexamic acid and transfusion. In addition to this personal bleeding history, there is also a significant family history of bleeding. Two of her five siblings having also been registered with Low VWF, and her older sister has an ISTH BAT score of 10.

Discussion of Case 3

Normal pregnancy is associated with a progressive increase in VWF, such that plasma levels gradually increase from the first trimester through to term by which time there is usually a 2-3 fold increase.[52] This pregnancy-related increase means that by the third trimester, almost all female patients with Low VWF have plasma VWF:Ag levels >50 IU/dL. In fact, in our experience and as observed for our index case during her first pregnancy, most of these women actually achieve term VWF:Ag levels >100 IU/dL.[21]

Despite the fact that in most women with Low VWF plasma VWF levels increase into the normal range (50-200 IU/dL), it is important to note that VWF levels remain significantly lower than those observed in normal pregnant women of similar gestation.[21,52] Nevertheless, consensus guidelines recommend that neuraxial

anesthesia, vaginal delivery and Caesarean section can all proceed without the need for additional hemostatic treatment provided that plasma VWF levels are maintained >50 IU/dL.[53,54] Plasma VWF levels were repeated in our index case when she reached 34 weeks gestation in her current pregnancy. As these demonstrated VWF:Ag 169 IU/dL and VWF:RCo 158 IU/dL, no hemostatic therapy was recommended prior to her delivery.

Following delivery, plasma VWF levels gradually fall such that baseline levels are typically attained approximately 3 weeks postpartum.[52,55] Consequently, it is perhaps unsurprising that significantly increased rates of secondary PPH (defined as excessive bleeding between 24 hours and 12 weeks postpartum)[53] have been described in women with both Low VWF and type 1 VWD respectively (Table 3). For example, in women with VWD, secondary PPH has been reported in up to 33% of cases[21,56,57] (Table 3). Interestingly, despite the pregnancy-related increase in plasma VWF levels, recent studies have also observed a 1.5 fold increased risk of primary PPH (defined as blood loss ≥500ml within 24 hours postpartum) in women with type 1 VWD.[58,59] Significant primary PPH has also reported in women with Low VWF (in all of whom plasma VWF:Ag levels exceeded 50 IU/dL), with 22% requiring transfusion.[21] Together, these findings suggest that higher plasma VWF levels may be required to maintain optimal hemostasis in the peri-partum period. This hypothesis is supported by the observation that even in women with VWD treated with VWF concentrate peri-partum to maintain plasma VWF levels >50 IU/dL, up to 33% still experienced a primary PPH.[59] The important clinical question of whether higher VWF dosing regimens at delivery may be more efficacious in reducing PPH rates in women with reduced VWF levels is being addressed in ongoing studies.[60]

The postpartum period is associated with increased fibrinolysis and recent data from the WOMAN study have highlighted the efficacy of early tranexamic acid administration in the management of primary PPH.[61] Importantly, this therapeutic effect use was achieved without any significant increase in thromboembolic events.[61] Similarly, use of prophylactic tranexamic acid in women with VWD has also been associated with a significant reduction in secondary PPH.[62] On this basis, recent consensus guidelines have suggested that tranexamic acid be considered for use in women with VWD in the postpartum period.[53] With respect to our index case, it is notable that she developed a significant primary PPH following her first delivery

despite having plasma VWF:Ag levels >100 IU/dL. Consequently, we would recommend prophylaxis with 1g tranexamic acid IV to commence at time of delivery and thereafter to continue 1g TID for 7 days postpartum. Current evidence suggests that although limited amounts of tranexamic acid are secreted into breast milk, these are too low to impact the infant.[63] Should the patient develop significant bleeding complications despite tranexamic acid prophylaxis, we would consider second line therapy with DDAVP. DDAVP is minimally excreted in breast milk and previous experience suggests that it is safe for use during pregnancy and the postpartum period.[36]

In most families with type 1 VWD, the condition is inherited in an autosomal dominant manner albeit with variable penetrance.[5,43,64] In contrast however, the genetic and molecular basis underlying the pathogenesis of Low VWF levels remains poorly understood. This provides significant issues in relation to counseling of parents prior to delivery. Critically, several previous studies have demonstrated that in more than 50% families, Low VWF do not display linkage to the *VWF* gene on chromosome 12.[12] Nevertheless, as illustrated in this case, Low VWF levels can be inherited in some families. Further studies are investigating the genetic basis underpinning Low VWF. Regarding management of the fetus in this case, the bleeding risk is considered low and consensus guidelines suggest that no specific precautions are required.[53]

Conclusion

In spite of the population prevalence of Low VWF levels, the diagnosis and management of these patients continues to pose significant clinical challenges (Table 4). The diagnosis of Low VWF levels should be a clinic-pathological one, reliant on both the presence of Low VWF levels and a personal history of bleeding. The subsequent clinical management of patients with Low VWF should be based primarily upon their personal and family bleeding histories. The challenges in the management of patients with Low VWF levels are predominantly attributable to the fact that we have limited understanding of the molecular mechanisms involved in the pathogenesis of Low VWF levels. Clinical management of Low VWF is further complicated by the fact that these patients commonly display variable bleeding phenotypes. In addition, few previous clinical trials have focused primarily on subjects with Low VWF. Further adequately powered studies are urgently required to address a series of critical basic scientific and clinical questions (Table 5) so that treatment for patients with Low VWF can be optimized and in order to enable the development of evidence-based treatment guidelines.

AUTHORSHIP

Contribution: M. L., and J. S. O'D. were involved in writing and reviewing the paper.

CONFLICT OF INTEREST DISCLOSURE:

M.L. has received has served on advisory boards for Baxalta and on a speakers bureau for Shire. 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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TABLES:

TABLE 1: Differences between Low VWF and type 1 VWD.

	Low VWF	Type 1 VWD
Diagnosis	Plasma VWF levels consistently 30-50 IU/dL.	Plasma VWF levels consistently <30 IU/dL.
***VWF* gene sequence variations**	Detected in 40% - 64% of patients.	Detected in majority of patients (up to 91.8%).
Pathogenic mechanism	Predominantly due to reduced VWF synthesis/secretion within EC. Subtle enhanced clearance in some cases.	Depending upon *VWF* gene mutation – can be attributable to either a major impairment in VWF synthesis and / or markedly enhanced VWF clearance (Type 1C VWD).
Response to DDAVP	Consistent and reproducible plasma VWF responses with levels sustained >50 IU/dL at 4 hours.	Variable responses, related to the nature of the underlying *VWF* mutation. Complete, partial or failure to respond may be seen. In patients with type 1C VWD, VWF half-life may be less than 4 hours.
Need for DDAVP trial	No need for routine DDAVP trial but confirm plasma VWF:Ag levels and duration of response at time of first therapeutic use.	DDAVP trial should be performed and should to include plasma samples at 4 hours post-DDAVP to ensure no rapid fall off in plasma VWF levels.
Plasma VWF half life	Some Low VWF patients have elevated VWF:pp/VWF:Ag ratios consistent with subtly increased VWF clearance.	Related to underlying *VWF* mutation but patients with type 1C VWD may have markedly enhanced VWF clearance with half-lives less than <4 hours.
ABO effect	Blood group O is strongly over-represented.	The effect of ABO blood group is less significant.
Impact of ageing	Plasma VWF levels increase with age and often correct into the normal range (>50 IU/dL). Not clear whether age-related VWF correction necessarily equates to resolution of bleeding phenotype.	Depending on underlying VWF gene mutation, plasma VWF levels may increase with age, but often remain <50 IU/dL. Unknown whether age-related increase in plasma VWF levels attenuates bleeding risk.

TABLE 2: Hemostatic investigations performed in the investigation of bleeding phenotype for Case 1

Test:	Results:	Repeat testing:	Normal reference range:
Hemoglobin (g/dL). MCV (fl) MCH (pg) Platelets (x10^9/L) Ferritin (µg/L) TSH (mU/L). T3 (nmol/L). Free T4 (pmol/L)	13.7 95.3 30.9 250 8.0 1.79 1.4 11.3		11.5 – 16.4 83 – 98 26.7 – 32.5 140 - 400 20 – 300 0.45 – 3.5 1.2 –2.5 9 – 21
Routine coagulation			
APTT (seconds) PT (seconds) Fibrinogen (g/L)	34 11.8 3.0		24 – 36 9.7 – 12.8 2.2 –4.3
Von Willebrand Factor assays (IU/dL)			
VWF:Ag VWF:RCo VWF:CB	**38** **36** **40**	**40** **37** **39**	50 – 173 50 – 156 50 – 150
Coagulation Factors (IU/dL)			
Factor II Factor V Factor VII Factor X Factor VIII Factor IX Factor XI Factor XIII	122 131 107 105 69 119 87 80		72 – 131 63 – 133 51 – 154 64 – 150 60 – 136 57 – 189 72 – 152 73 - 160
Platelet aggregometry			
Adrenaline 10µM ADP 2µM Ristocetin 1.25mg Ristocetin 0.5mg Arachdonic Acid 1µM	Normal response Normal response Normal response No response Normal response		
Platelet nucleotides (nmol/10^8 platelets)			
Platelet ATP Platelet ADP Total Nucleotides Ratio	6.1 3.3 9.4 1.8		3.5 – 6.8 2.1 – 4.5 5.6 – 11.3 1.1 – 2.1

TABLE 3: Pregnancy outcomes in patients with partial quantitative VWD (Low VWF and type 1 VWD)

Study	Total number women with VWD, n (deliveries)	Number with type 1 VWD or Low VWF	PPH rates in women with quantitative VWD (unless specified)	Baseline pre-pregnant plasma VWF levels, median (range)
Ramsahoye *et al,* 1995[56]	13 (24)	n=7, type 1, 13 deliveries	Primary 0% Secondary 23.1%	VWF:Ag 8 IU/dL (5-40) VWF:Act 7 IU/dL (3.1-26)
Kadir *et al*, 1998[57]	31	n=27 type 1 54 deliveries	Primary 18.5% Secondary 20%	VWF:Ag 43 IU/dL (0.5-72) VWF:Act 40 IU/dL (0.5-70)
Ragni *et al*, 1999[65]	38	Type 1, n=38	Overall PPH 13.1%	Mean VWF:Ag 62 IU/dL
Kouides *et al*, 2000[66]	48	Type 1 VWD, n=25	Primary 42% in all VWD	No baseline levels provided
Kirtava *et al,* 2003[67]	102	All VWD, subtype unspecified	Overall PPH 59%	No baseline levels provided
James *et al*, 2007[58]	4067	All VWD, subtype unspecified	Overall PPH 6%	No baseline levels provided
De Wee *et al*, 2011[68]	314 (691)	Type 1, n=242	Overall PPH 37%	Not provided; all patients <30 IU/dL
Chee et al, 2012[69]	33 (62)	Type 1, n=24	Primary 19.4% in all VWD	Not provided; included those <50 IU/dL
Stoof *et al,* 2015[59]	154 (185)	Type 1, n=49 56 deliveries	Primary 37%	Median VWF:Act 50 IU/dL
James et al, 2015	32 (35)	Type 1 no treatment required, n=17	No PPH reported	Mean VWF:Ag 57 IU/dL Mean VWF:RCo 42 IU/dL
Hawke *et al,* 2016[62]	33 (62)	Type 1, 39 deliveries	Primary PPH 18% Secondary PPH 29% in all VWD	No baseline levels provided
Govorov *et al*, 2016[70]	34 (59)	Type 1, n=21 39 deliveries	Primary 46.2% Secondary 10.3%	No baseline levels provided
Sood et al, 2016[55]	11 (11)	Type 1, n=11	Primary 9% (1/11) Secondary 9% (1/11)	Mean VWF:Ag 41.1 IU/dL Mean VWF:Act 34.4 IU/dL
Lavin *et al,* 2018[21]	74 (181)	Low VWF, n=74 181 deliveries	Primary 48.6% Secondary 33.7%	VWF:Ag 49 IU/dL (33-72) VWF:RCo 39 IU/dL (30-54)

TABLE 4

	Alternate Clinical Scenarios	Clinical assessment	Suggested management strategy
Case 1	**22 year old male with Low VWF** **Baseline plasma VWF:Ag 35 IU/dL, VWF:RCo 32 IU/dL** **Requires a surgical molar dental extraction**	Assess personal and family bleeding history Calculate ISTH BAT score Determine whether the patient has previously been treated for any procedures with tranexamic acid and/or DDAVP	Single dose of DDAVP pre dental extraction If no previous record of DDAVP response, assess plasma VWF levels at baseline and 1, 2 and 4h post DDAVP Tranexamic acid 1g TID for 3-5 days post procedure Contact details in case of bleeding
Case 2	**65 year old with history of Low VWF levels** **Baseline plasma VWF:Ag 32 IU/dL, VWF:RCo 30 IU/dL** **More recent plasma VWF:Ag and VWF:RCo levels now consistently >50 IU/dL** **Has developed persistent atrial fibrillation**	Assess personal and family bleeding history Calculate ISTH BAT score Consider any co-morbidities / medications that may contribute to current bleeding risk Determine CHA2DS2-VASc score to assess risk of CVA	Treatment plan will be based upon global risk assessment for bleeding and thrombotic potential respectively If risk of stroke outweighs bleeding risk, consider introduction of anticoagulation with regular ongoing follow up at 3 monthly intervals to reassess Provide contact details in case of bleeding
Case 3	**70 year old woman with Low VWF levels** **Baseline plasma VWF:Ag 40 IU/dL, VWF:RCO 44 IU/dL** **More recent plasma VWF levels consistently >70 IU/dL** **Requires elective total knee replacement**	Assess personal and family bleeding history Calculate ISTH BAT score Consider any co-morbidities / medications that may contribute to current bleeding or thrombotic risks	If elevated bleeding history, treat with tranexamic acid cover (1g preoperatively and 1g TID postoperatively for 48-72 hours. Daily review by Coagulation Service to determine when tranexamic acid can be discontinued and LMWH introduced. Thromboembolic Deterrent Stockings (TEDS) Early mobilization as surgically appropriate

TABLE 5

Key outstanding questions for future study in Low VWF
1. What is the genetic basis underlying the reduction in plasma VWF levels in families with Low VWF levels in whom no *VWF* gene sequence variants have been identified?
2. In families with Low VWF due to other genetic loci, what is the inheritance pattern and how does bleeding phenotype relate to Low VWF levels?
3. What are the molecular mechanisms underpinning Low VWF levels? In particular, what is the relative importance of reduced endothelial cell synthesis /secretion versus enhanced circulatory clearance?
4. In establishing the diagnosis of Low VWF, should a specific BAT score be preferred?
5. For patients with Low plasma VWF on initial testing, what is the optimal time frame for performing repeat VWF testing in order to confirm an accurate diagnosis of Low VWF? Conversely, is there a threshold plasma VWF level (even allowing for acute phase-induced transient increases in plasma VWF) above which retesting is not in order?
6. Why is heavy menstrual bleeding such a common clinical presentation in women with Low VWF levels? Does this simply relate to the hemostatic function of VWF, or might other emerging biological functions of VWF (e.g. regulation of angiogenesis) also be of importance?
7. Are DDAVP trials necessary for patients with Low VWF?
8. In managing women with Low VWF peri-partum, what target plasma VWF levels should be utilized to reduce the high reported rates of both primary and secondary PPH?
9. How should minor and major surgery be managed in patients with Low VWF who have a very significant bleeding history? Is correction of the mild reduction in plasma VWF levels adequate to completely revert the bleeding phenotype?
10. Recent data have shown that plasma VWF levels often correct to within the 'normal' (50-150 IU/dL) in patients with Low VWF with ageing. Does this mean that the bleeding phenotype has been ameliorated, especially in patients with a previously severe bleeding phenotype?

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How I treat low von Willebrand factor levels

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