Von Willebrand disease type 1: a diagnosis in search of a disease

J. Evan Sadler

Von Willebrand disease (VWD) type 1 is reported to be common but frequently difficult to diagnose. Many people have nonspecific mild bleeding symptoms, Von Willebrand factor (VWF) levels display low heritability, and low VWF levels (15% to 50% of normal) are weak risk factors for bleeding. Therefore, bleeding and low VWF levels often associate by chance. Even with stringent diagnostic criteria based on a triad of bleeding symptoms, a low VWF level, and a positive family history, the prevalence of “false-positive” VWD type 1 is comparable to the published prevalence of the disease. Consequently, many patients diagnosed with VWD type 1 do not have a specific hemorrhagic disease at all, which limits the utility of the diagnosis. This unfortunate reality is a consequence of trying to force patients into binary categories of “diseased” or “healthy” that are incompatible with the continuous biologic context in which VWF functions. The problem may be avoided by substituting an empirical epidemiologic approach like that applied to other modest risk factors for disease such as elevated cholesterol and high blood pressure. Such a risk management strategy could be generalized to include other hemorrhagic and thrombotic risk factors. (Blood. 2003;101:2089-2093)

Introduction

Von Willebrand factor (VWF) is a multimeric plasma protein that mediates platelet adhesion at sites of injury, and normal platelet adhesion depends on the largest VWF multimers. Deficiency of VWF causes von Willebrand disease (VWD), a bleeding disorder of variable severity that is divided into several subtypes. The absence of VWF (VWD type 3) and many qualitative defects (VWD type 2) are straightforward to diagnose. Unfortunately, this is not true of VWD type 1, which refers to partial, quantitative VWF deficiency.1

VWD type 1 is reported to be the most common form of VWD, accounting for at least 75% of the total, but in practice the diagnosis can be difficult to make. Some cases are easy to diagnose because they suffer from repeated and serious bleeding, have exceptionally low VWF levels, and appear to have dominant negative mutations that may suppress the secretion2 3 or enhance the clearance4 of VWF. However, most persons alleged to have VWD type 1 have modestly decreased VWF levels that are associated with mild bleeding in some family members but not in others. These relatively numerous patients pose significant conceptual, diagnostic, and therapeutic problems, and they may be impossible to distinguish from healthy controls. In fact, this paradox is a necessary consequence of the broad distribution of normal VWF levels, the high prevalence of mild bleeding symptoms, and the weak relationship between VWF level and bleeding. The difficulty could be avoided by treating a low VWF factor as a continuously variable, modest risk factor for bleeding, just as we already treat other risk factors for disease such as blood pressure and cholesterol level.

VWF levels and bleeding symptoms

The normal range of VWF level is broad, with 95% of values falling between 50% and 200% of the mean,5 6 and most of this variation is unexplained. Genetic components account for about 30% to 60% of the variance in plasma VWF, and ABO blood type is one major genetic determinant of VWF level. The average VWF level for persons with blood type O is 25% to 35% below that of persons with blood type A, B, or AB,2 and ABO type accounts for approximately 30% of the genetic variance of VWF.9 Although null mutations in the VWF gene do have a significant effect on mean VWF level, the range in heterozygotes overlaps considerably with that of healthy persons. In a typical study, obligate carriers of VWD type 3 had a mean VWF level of 46% and a range of 11% to 116% of normal.6 Among 37 subjects heterozygous for the same frameshift mutation (2680delC), the mean VWF level was 46% with a range of 13% to 110% of normal.10 Furthermore, null VWF mutations are relatively rare, with a frequency of no more than 0.002 based on the prevalence of VWD type 3,11 and therefore cannot contribute significantly to observed variation in VWF level. Certain common polymorphisms in the VWF promoter correlate with changes in mean VWF level, but these effects are small. For example, among persons with blood type O, the single nucleotide polymorphism −1793G>C is associated with mean VWF levels of 77% for genotype C/C, 86% for genotype G/C, and 93% for genotype G/G. Because the −1793C allele has a frequency of approximately 0.65 among Canadian blood donors, it contributes significantly but modestly to the observed variation in plasma VWF levels.12 In summary, most of the variation in VWF level is not heritable, much of the heritable variation is not linked to the VWF locus, and VWF level does not reliably distinguish between healthy persons and carriers of VWF null mutations.

VWF deficiency can cause bleeding, but bleeding has many causes, is very common, and no symptom is specific. Surveys of healthy controls report excessive nosebleeds in 5% to 39%, gum bleeding in 7% to 51%, bruising in 12% to 24%, bleeding from...
trivial wounds in 0.2% to 2%, bleeding after tooth extraction in 1% to 13%, bleeding after tonsillectomy in 2.4% to 11%, postoperative bleeding in 1.4% to 6%, postpartum bleeding in 6% to 23%, and menorrhagia in 23% to 44%. Usually these very common symptoms are medically insignificant, but they frequently are the basis for diagnosing a bleeding diathesis consistent with VWD. Using the lowest value reported in any study for each symptom, and assuming the symptoms to be independent, 25% of males and 46% of females would have at least one bleeding symptom. (The probability, $P$, that a person will have no bleeding symptoms is the product of the probabilities that each symptom will be absent. The probability of having at least one symptom is then $1 - P$.) The assumption that bleeding symptoms are independent has not been validated directly. However, in one study multivariate analysis detected only a modest tendency for symptoms to cluster in patients with a diagnosed bleeding disorder, and no such tendency was reported for the controls. For this discussion, the percentage of controls with at least one of these many bleeding symptoms might conservatively be taken as 25%. I have used the lower value of 25% estimated for males, which is similar to the minimum reported prevalence for the single symptom of menorrhagia for females. Because this value is relatively large, bleeding and low VWF often will be associated by chance. In fact, the reported prevalence of VWD type 1 is comparable to the required prevalence of false-positive diagnoses.

Most diagnoses of VWD type 1 are false positives

The magnitude of the problem can be illustrated by imagining VWD to be removed from the earth, so that all “cases” would necessarily be false positives. For the purpose of diagnosing VWD type 1, most sources consider “low VWF” to be more than 2 SD below the mean, and 2.5% of the population qualifies. The use of ABO-adjusted reference ranges for VWF level has been recommended, but this modification does not change the proportion “at risk” by definition. If the prevalence of bleeding symptoms is 25% as discussed in the preceding paragraph, then about 0.6% of the population will coincidentally have both bleeding and low VWF. To be more stringent, one can add criteria for family history. The probability that a family member will have a bleeding symptom depends on the family size, and the chance is about 58% that at least 1 among any 3 relatives has bleeding. (If the probability that a person has a bleeding history is 0.25, then the probability that at least 1 among $n$ family members has a bleeding history is $(1 - 0.75^n)$; for $n = 3, P = .58$.) This estimate is comparable to the surprisingly high prevalence of a family bleeding history of 44% among healthy children undergoing tonsillectomy and 60% or 35% among patients referred for bleeding. Therefore, approximately 0.4% of the population will have bleeding and low VWF, plus a family history of bleeding, solely by chance.

The estimated 0.4% prevalence of false-positive VWD type 1 can be compared with the reported VWD type 1 prevalence of 1.3% among 600 healthy schoolchildren in the United States and 0.8% among 1218 schoolchildren in Italy who were screened using comparable criteria. In the United States study, no information was included about the prevalence of bleeding symptoms among the children with normal VWF levels or about the medical significance of bleeding among the cases. One of the Italian patients was known before screening to have severe VWD type 3, and none of the 9 new cases had medically significant bleeding during 13 years of follow-up. Importantly, the pedigrees showed a striking lack of concordance between low VWF levels and the occurrence of mild bleeding symptoms. These considerations suggest that a substantial fraction of VWD type 1 cases must represent the coincidental association of bleeding and low VWF. In practice, a family history of disease may not be required, further inflating the likelihood of false-positive diagnosis.

Population screening may overestimate the prevalence of medically significant disease by identifying cases with minimal symptoms. In contrast, referral to a specialized care center could select for patients with symptoms that merit treatment, and the prevalence of symptomatic VWD based on such referral ranges from 23 to 113 per million, of which most represents VWD type 1. The fraction of such cases due to coincidental association of low VWF and bleeding symptoms is unknown, but there is no reason to think it is lower than for cases identified by population screening because the standards used for diagnosis are similar.

One might propose that more stringent diagnostic criteria would control the problem of false-positive diagnosis. For example, with some sacrifice in sensitivity the likelihood of misdiagnosis could be reduced by requiring the proband and at least one relative to have both bleeding and low VWF, strengthening the basis for diagnosing an inherited disease. However, using the probabilities of low VWF and bleeding estimated herein, the prevalence of “false-positive” VWD type 1 under this stricter definition is still about 90 per million, which is comparable to the reported prevalence of VWD in a referral setting. (The probability that a patient bleeds and has low VWF is $0.25 \times 0.025 = 0.0062$. The probability that a relative bleeds and has low VWF is $(1 - 0.75^n) \times 0.025$; for $n = 3, P = .0145$. The probability that a patient and relative both bleed and have low VWF is $0.0062 \times 0.0145 = 9.0 \times 10^{-5}$, or 90 per million.) Because the criteria for the diagnosis of VWD type 1 in specialized centers usually are not this strict, the association of bleeding with low VWF often must be a coincidence.

So, false-positive, symptomatic VWD type 1 can be defined into existence with a prevalence that is greater than the prevalence of all VWD estimated in a referral setting and comparable to the prevalence of VWD type 1 estimated by population screening. It follows that many persons diagnosed with VWD type 1, perhaps most of them, do not have a disease at all. This conclusion entails several consequences that are supported by the literature. For example, bleeding symptoms and VWF level often are inherited independently, and the diagnosis of VWD type 1 does not exhibit consistent linkage to the VWF locus.

Low VWF is a modest risk factor for bleeding

A low VWF level might yet be useful clinically if it conferred a sufficiently high risk of bleeding, but it does not appear to do so. Patients with undetectable VWF usually do have serious bleeding. More than two thirds of women with VWD type 3 have severe menorrhagia and iron deficiency anemia, and many require transfusions or hysterectomy. The problem is that the modest quantitative VWF deficiency typical of VWD type 1 confers at most a modest risk of bleeding. For example, in the course of investigating their severely affected relatives, at least 191 obligate heterozygous carriers of VWD type 3 alleles have had VWF levels measured and bleeding histories taken (Table 1). The mean VWF level was about 45%, with a range of less than 5% to 130% of normal. In this heterogeneous group, the risk of bleeding was not quite significantly different between 117 subjects with VWF less than
50% and 74 subjects with VWF more than 50% (relative risk 2.0 for low VWF, $\chi^2 = 3.81, P \leq .051$). In general, any bleeding was mild and consisted of bruising, epistaxis, subjectively excessive menstrual bleeding, or bleeding after tooth extraction; significant postoperative bleeding was reported in only one patient, whose VWF level was more than 50%.\(^{28}\)

An analysis of menorrhagia suggests that the correlation between bleeding and low VWF is more robust if we use an objective measure of bleeding and sample a wider range of VWF levels. Menorrhagia is defined as menstrual blood loss more than 80 mL per month, which often causes iron deficiency anemia.\(^{31}\) Three studies have defined low VWF as more than 2 SD below the mean and have used a quantitative measure of menorrhagia; 2 used an alkali hematin test,\(^{32,33}\) and 1 used a validated pictorial chart score.\(^{34}\) Although some patients were subsequently diagnosed with VWD type 1, in fact the only criterion for the diagnosis was a low VWF level. Among 218 women with objective menorrhagia, 19 (8.7%) had low VWF. Two of the studies included results for 32 historical\(^{32}\) or 38 contemporaneous\(^{33}\) controls with menstrual blood loss less than 80 mL per month, and only one of these controls (1.4%) had low VWF. Taking the prevalence of menorrhagia as approximately 12%\(^{31}\) and the prevalence of low VWF as 2.5% by definition, the increased prevalence of low VWF in women with menorrhagia is highly significant ($\chi^2 > 35, P \leq 10^{-7}$). Barring a hidden bias in the selection of the patients, the relative risk of menorrhagia, given a low VWF, is about 3.9 (Table 2).

These comparisons suggest that natural variations in VWF level cause moderate differences in the prevalence of some bleeding symptoms. For example, a low VWF level appears to be a modest risk factor for menorrhagia at the population level. However, a causal relationship between low VWF and menorrhagia usually cannot be established for a specific patient. About 25 000 million women have low VWF, among whom 11 000 may be predicted to have menorrhagia (Table 2). It does not seem useful to diagnose a specific hemorrhagic disease in so many women when most of those with low VWF do not bleed and a quarter of those who bleed have low VWF merely by chance.

As is true for many other conditions, the consequences of VWD misdiagnosis are not necessarily benign. Patients may be subjected to risky, expensive, and ineffective treatments, while a legitimate cause of symptoms is overlooked and untreated. Many of us have seen patients for whom the diagnosis of VWD type 1 has changed their self-image and caused them to limit activities for fear of bleeding or concern about transmitting a genetic disease. They may have received desmopressin (DDAVP) or blood products for dental and surgical procedures, and some have been denied insurance coverage. However, on repeated testing their VWF level and bleeding time may be normal.\(^{35}\) A detailed history may show they never had bleeding more serious than epistaxis or heavy menses, which are common in the absence of VWD. In short, the diagnosis of VWD type 1 cannot be confirmed and has been confusing rather than helpful. The customary criteria for diagnosing VWD type 1 exaggerate the significance of a low VWF level and trivialize the diagnosis.

### A proposal for an epidemiologic approach to VWF level and bleeding risk

These adverse effects could be avoided by abandoning the categorization of most patients as having VWD type 1 or not and instead using an approach like that applied to other modest risk factors for disease. For example, moderate increases in blood pressure or total cholesterol increase the risk of death from cardiovascular events by 2- to 4-fold. The increase in risk varies directly with the increase in either parameter, and the relative risk for patients with both increased blood pressure and cholesterol is roughly equal to the product of the relative risks for each factor alone.\(^{36,37}\) The decision to treat balances the risks and benefits of treatment, and the threshold for intervention is influenced by the presence of other risk factors such as diabetes or evidence of organ damage such as renal failure or proteinuria. Such an epidemiologic approach is appropriate for risk factors that are not, by themselves, managed as qualitative disease categories. Similarly, natural red hair color carries a relative risk of 2.4 to 9.7 for malignant melanoma and about 1.8 for squamous cell carcinoma of the skin.\(^{39}\) Red hair is a risk factor that is mitigated by the use of sunscreen; it is not a disease. A similar strategy is used already to make clinical decisions about thrombotic risk factors of similar magnitude, such as factor V Leiden, and it could be adapted easily to VWF level with minor changes in current practice.

### Reserve “VWD type 1” for dominant, symptomatic, and severe VWF deficiency

The term “VWD type 1” is reasonable for patients with exceptionally low VWF levels (eg, less than 15%) and frequent bleeding in whom the condition exhibits clearly dominant inheritance. Most such patients appear to have VWF mutations,\(^{2,41,42}\) and the diagnosis can be useful because some lifestyle changes, or prophylactic treatment, may be appropriate for affected children or adults. This narrow use of “VWD type 1” would avoid misdiagnosing an excessive number of healthy persons with an inherited hemorrhagic disease. Patients should not be forced to carry that psychologic burden in the absence of a clear indication.

### Manage “low VWF” as an epidemiologic risk factor for bleeding, not a disease

Unsurprisingly, screening of asymptomatic persons for low VWF does not have much value. A low VWF level did not predict surgical bleeding in 832 consecutive patients,\(^{43}\) and a prolonged bleeding time (a poor surrogate for low VWF) does not predict

### Table 2. Contingency table for VWF level and menorrhagia

<table>
<thead>
<tr>
<th>VWF Level</th>
<th>Menorrhagia</th>
<th>No menorrhagia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low VWF</td>
<td>11</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Normal VWF</td>
<td>109</td>
<td>866</td>
<td>975</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>880</td>
<td>1000</td>
</tr>
</tbody>
</table>

VWF levels were determined in women with menorrhagia\(^{32,33}\) and designated “low” if more than 2 SD below the mean. The table was completed based on a 2.5% prevalence of “low VWF” by definition and a 12% prevalence of menorrhagia.\(^{31}\) For a total of 218 subjects with menorrhagia, $\chi^2 > 35, P \leq 1 \times 10^{-7}$, Table entries are normalized for a cohort of 1000 women.

### Table 1. VWF level and bleeding symptoms in carriers of VWD type 3 alleles

<table>
<thead>
<tr>
<th>VWF Level</th>
<th>Blowing (%)</th>
<th>No bleeding (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF less than 50%</td>
<td>31 (76)</td>
<td>86 (57)</td>
<td>117 (61)</td>
</tr>
<tr>
<td>VWF more than 50%</td>
<td>10 (24)</td>
<td>64 (43)</td>
<td>74 (39)</td>
</tr>
<tr>
<td>Total</td>
<td>41 (100)</td>
<td>150 (100)</td>
<td>191 (100)</td>
</tr>
</tbody>
</table>

Obligate heterozygous carriers of VWD type 3 alleles with available bleeding histories and VWF levels were identified\(^{25,28}\) and analyzed for an association between bleeding symptoms and a VWF level less than 50% of normal. For each column, the values in parentheses represent the percentage with respect to the column total. $\chi^2 = 3.81, P \leq .051$. 

Unsurprisingly, screening of asymptomatic persons for low VWF does not have much value. A low VWF level did not predict surgical bleeding in 832 consecutive patients,\(^{43}\) and a prolonged bleeding time (a poor surrogate for low VWF) does not predict
surgical bleeding.44 However, it is reasonable to determine VWF levels in persons with symptomatic bleeding. The discovery of a low VWF level identifies a risk factor for bleeding but does not mandate a diagnosis of VWD type 1 any more than a myocardial infarction changes the interpretation of a modestly elevated cholesterol level, which remains a risk factor and does not indicate a diagnosis of familial hypercholesterolemia. Even for patients with a family history of bleeding, the high prevalence of both bleeding and low VWF requires the association to be coincidental in many cases. Most persons with bleeding and low VWF could be told they have “low VWF,” a neutral term that reflects what we know and does not imply more. VWF levels also vary significantly with stress, pregnancy, age, and other factors,31 so that patients with moderately low VWF levels may intermittently have test results within or outside the normal range.35 Such variation is difficult to incorporate into criteria for the diagnosis of a disease but relatively easy to handle in the context of risk management. Most patients readily accept the information that they fall at one end of a normal spectrum and have a slightly higher than average risk of bleeding.

In principle, multiple risk factors for bleeding and thrombosis could be incorporated into a comprehensive strategy for managing hemostatic risk.

**Treat or prevent bleeding empirically by raising the VWF level if it is low**

Just as measures to lower cholesterol or blood pressure can reduce the risk of cardiovascular disease, empiric treatment to raise the VWF level may control bleeding in patients with low VWF. Desmopressin, or DDAVP, acutely increases the plasma level of VWF and has been used in mild hemophilia and VWD for 25 years.45 Thus, the finding of a low VWF level adds another agent to the menu of interventions that may be considered to treat bleeding or, in some circumstances, to forestall bleeding by prophylactic treatment if the risk of reactive treatment is judged to be unacceptable.

The goal of the proposed epidemiologic approach is to deliver good care to bleeding patients, give advice on risk management to the many with low VWF, and offer genetic counseling to the few with a significant inherited hemorrhagic disease. To be most effective, however, we need more information about the likelihood of adverse events and the efficacy of treatment. Our continuously evolving approach to cardiovascular disease clearly illustrates the value of quantitative data for the management of disease risk factors. The choice to treat blood pressure or cholesterol level depends on an assessment of the risks and benefits of diagnostic procedures and of therapeutic alternatives. At present there are many gaps in our knowledge with respect to VWF and bleeding that prevent us from pursuing a similar approach. For example, the boundary between “VWD type 1” and “low VWF” needs better definition. Also, VWF levels just below the normal range confer a modest risk of bleeding, and the absence of VWF causes severe bleeding, but the landscape in between is poorly charted. Knowing the relative risk of bleeding is critical to guide clinical decisions.

These issues are being addressed by 2 studies of the molecular and clinical features of VWD type 1. Ian Peake and Anne Goodeve (University of Sheffield, United Kingdom) and Francesco Rodeghiero (S. Bortolo Hospital, Vicenza, Italy) are coordinating a study funded by the European Union (http://www.shef.ac.uk/euvwd), and David Lillicrap (Queen’s University, Kingston, Ontario, Canada) has organized a Canadian study. In total, these investigations will involve more than 350 patients with low VWF (all diagnosed with VWD type 1) and more than 1400 controls. In addition, Dr Rodeghiero is directing a study of carriers of VWD type 3 mutations. The protocols include extensive bleeding histories, comprehensive testing for VWF level and function, analysis for linkage to the VWF gene, and sequencing of the VWF coding region in affected patients. A particularly important feature is the inclusion of subjects with normal VWF levels. Many bleeding symptoms are difficult to evaluate and are susceptible to bias in their discovery by physicians and remembrance by patients. Therefore, the determination of relative risk for bleeding depends critically on unbiased comparisons with healthy controls. Such information should establish a solid foundation for the management of low VWF levels and the appropriate diagnosis of VWD type 1.

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**References**

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