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INVITED REVIEW

# How to estimate bleeding risk in mild bleeding disorders

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**Summary.** The concept of mild bleeding disorders (MBD) has evolved in contrast to severe hemophilia A and B to indicate less severe disorders, characterized by the presence of more frequent and/or more prominent bleeding symptoms than in the normal population. These symptoms occur mostly after a recognizable challenge and do not lead to major discomfort or organ damage, even in the absence of specific medical intervention. However, it has become clear that, from the most severe to the mildest hemostatic disorders, there is a continuous spectrum of bleeding manifestations, which overlap with the occasional bleeding occurring in people without any identifiable hemostatic abnormality. By reviewing the principal hemorrhagic disorders we have tried to identify those entities that could fit a diagnosis of MBD and result, at the same time, in a net benefit for treatment or prophylaxis of patients rather than being simply accurate. This goal can usually be achieved by comparing the patient's phenotype with known nosological entities. However, limitations of this approach are evident, considering the paucity of clinical data and the biases of most published reports on the different disorders. In addition, in a partial deficiency of a clotting factor, a reliable relationship between the residual activity and bleeding severity is not invariably found. Molecular characterization of the defects is also generally useless. Accordingly, an accurate bleeding history in the propositus and his/her family remains of major importance. For this purpose, new standardized and possibly quantitative tools are being developed in several institutions. Innovative approaches, combining into a single probability phenotypic and genetic data, could possibly estimate better the bleeding risk in specific disorders.

**Keywords**: bleeding questionnaire, bleeding risk, diagnosis, hemorrhagic disorders, inherited platelet disorders, von Willebrand disease.

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## Introduction

A brief historical account could be instructive to understand better how the definition of mild bleeding disorders (MBD) has evolved and to appreciate the relevance of these disorders in clinical practise [1,2]. We focus here on inherited bleeding disorders caused by coagulation or platelet defects, excluding bleeding due to vascular abnormalities.

Undoubtedly, the first familial bleeding disorder that attracted the attention of physicians was hemophilia, once known as 'bleeder's disease' before receiving its actual designation in a dissertation by Hopff in 1828. Its impressive severity, already manifest from the neonatal period, posed no doubt that it represented an ominous disease in which joint and visceral hemorrhages caused crippling organ failure and even precocious death. It was not until 1893 that Wright called specific attention to the prolonged coagulation time in these patients, paving the way for the discovery of factor (F) VIII. At that time, the only other recognized severe bleeding disorder was Werlhof's disease, first described in 1735 as a dermatologic disorder and only in 1895 related to thrombocytopenia by Hayem.

These two examples indicated that defects in the hemostatic system could cause hemorrhage severe enough to lead to death even in the absence of significant trauma. By the early 1960s, all coagulation factors had been identified and linked to severe hemorrhagic disorders when inherited in homozygous or hemizygous status without sufficient residual activity. The concept of severe hemorrhagic diathesis is still largely based on the clinical manifestations in these patients. Subsequently, some correlation between the circulating level of the implicated factor and bleeding symptoms was generally observed in patients with partial deficiencies. This finding raised interest in identifying such patients and the measurement of the residual level of the missing clotting factor was considered a reliable way to predict their bleeding risk, independently of bleeding symptoms (a 'laboratory marker of disease'). This approach led to an artifactual and simplistic separation of laboratory investigation from clinical presentation. Inherited MBD due to coagulation defects, with their phenotypic and genetic distinctive features, are summarized in Table 1.

Similarly to clotting disorders, inherited hemorrhagic manifestations due to platelet function defects were first identified in patients with the most severe diseases. Glanzmann

**Table 1** Partial coagulation defects causing MBED

| Disorder | Bleeding manifestations | Genetic background |
|---|---|---|
| Hypofibrinogenemia | Usually not evident with fibrinogen $> 50$ mg $dL^{-1}$; mainly post-traumatic or postsurgery | Typically null mutations, rarely missense mutations, with qualitative abnormalities |
| Dysfibrinogenemia | Rare and heterogeneous | Missense mutations; correlation with particular gene defects not always evident |
| Partial factor Deficiencies* | | |
| Prothrombin deficiency | Mild to moderate | Missense mutations? |
| FV deficiency | Mild to moderate | Missense mutations? |
| FVII deficiency | Mild to moderate | Missense mutations? |
| FX deficiency | Mild to moderate | Missense mutations? |
| FXI deficiency | Post-traumatic or post-surgery | Not linked to a definite genetic background in heterozygotes, more evident in dominant-negative mutations (e.g. Ser225Phe, Cys398Tyr, Gly400Val, Trp569Ser)? |
| FXIII | NO when level $\geq$ 2–3 U $dL^{-1}$ | |

*No bleeding in heterozygous subjects for null alleles.

thrombastenia, characterized by isolated defective clot retraction, was first described in 1918 and Bernard-Soulier syndrome, showing reduced consumption of prothrombin during clotting of whole blood, mild thrombocytopenia and giant platelets, in 1948. Both presented a very prolonged bleeding time. Up to the end of the 1960s, von Willebrand disease (VWD) was variably classified as a plasma or a platelet defect and its pleiothropic laboratory and clinical manifestations proved difficult to reconcile with a single locus disease. The introduction of platelet aggregometry in 1962 and other modern techniques in subsequent years led to the discovery of several distinctive platelet disorders in which bleeding time is not always prolonged and bleeding manifestations sometimes are very mild or ambiguous. A clinical classification of the main inherited platelet defects is shown in Table 2.

The last decade has witnessed the birth of the genomic era that allowed an understanding of the molecular basis of inherited clotting and platelet defects. The Mendelian single locus model disease with clear-cut dominant or recessive inheritance pattern rarely applies to less severe bleeding disorders due to their more complex genetics, with increased variability in penetrance and expressivity. Two missense mutations or one missense mutation combined with a null allele in the same locus, leaving a variable residual synthesis of a functional factor, often occur. Dominant negative inheritance has also been demonstrated mainly in multisubunit factors such as von Willebrand factor (VWF) or FXI. Furthermore, coinheritance of additional hemostatic defects or superimposed genetic modifiers make the relationship between genotype and phenotype less stringent than previously appreciated. As a consequence, particularly in MBD, single laboratory measurement and even identification of a specific molecular defect is far from useful as a marker of individual bleeding risk. However, despite the continuing interest in a better understanding of the mechanisms that underlie normal or defective hemostasis and its modulation by a combined inheritance of polymorphic alleles, no one expects any longer that 'new' inherited defects associated with severe bleeding diathesis will be discovered.

The limitations of phenotypic or genotypic investigations in establishing the bleeding risk in MBD contrast with the increasing demand for complete information and for a higher standard of well-being and quality of life. The understandable desire of the patients to avoid even minor health risks may force physicians onto the defensive to protect themselves from a greater risk of liability. Increased attention to even mild bleeding symptoms is further justified by the wide availability of drugs (such as desmopressin, antifibrinolytics) that may safely ameliorate the bleeding diathesis of MBD. MBD (particularly type 1 VWD and platelet secretion disorders) are prevalent in the general population, at up to 1% of normal subjects, being an interesting potential target for specific interventions. Clearly, all these issues explain the increasing interest in MBD during the last decade. The alert that premenopausal bleeding is a 'public health crisis for hematology' recently raised by the Committee on Practice (COP) for the American Society of Hematology [3] further illustrates this public awareness.

Thus, developing tools to record bleeding symptoms in a systematic and standardized manner and to discriminate normal or acceptable bleeding manifestations from abnormal bleeding, demanding investigation and treatment, has become urgent.

## Bleeding risk in MBD and in normal subjects

Whereas the boundary between severe and mild bleeding disorders may be considered clinically well defined, the distinction between normal subjects and patients with MBD is often unclear. From a practical point of view, the evaluation of a possible MBD may start either from the clinical assessment of a subject referred for bleeding (i.e. a clinical-driven diagnosis) or from the investigation of an abnormal laboratory

**Table 2** Clinical features and severity of bleeding in main IPD

| Disorder | Platelet count | Associated co-morbidities | Clinical distinctive features | Molecular diagnosis | Inheritance |
|---|---|---|---|---|---|
| Severe bleeding | | | | | |
| Glanzmann thrombastenia | Normal | No | No | Feasible | Recessive |
| Bernard-Soulier syndrome | Reduced | No | No | Feasible | Recessive |
| Wiskott-Aldrich syndrome | Reduced, small size | Yes | Eczema, immunodeficiency | Feasible | X-linked recessive |
| Scott syndrome and related disorder * | Normal | No | No | NA | Recessive |
| Quebec platelet disorder * | Normal/reduced | No | No | NA | Dominant |
| Mild to moderate bleeding | | | | | |
| MYH9 disorders: May-Hegglin anomaly and related disorder | Reduced, large size | Yes | Döhle-like bodies in neutrophils, sensorineural, hearing loss, nephritis, cataracts | Feasible, required for confirmation | Dominant |
| Amegakaryocytic thrombocytopenias with or without radial abnormalities | Reduced | No / yes | Radial abnormalities ± other skeletal abnormalities in syndromic forms | NA | Recessive in most cases |
| Receptors: | | | | | |
| Collagen receptor defects ($\alpha_2\beta_1$ or Gp IV or VI); $TXA_2$ and ADP receptor (P2Y12) | Normal | No | No | NA | Variable |
| Signal transduction: | | | | | |
| Cyclo-oxygenase deficiency | Normal | No | No | NA | Variable |
| $TXA_2$ synthase deficiency | | | | | |
| Miscellaneous | | | | | |
| Secretion: | | | | | |
| Hermansky-Pudlak syndrome | Normal | Yes | Oculocutaneous albinism | NA | Variable |
| Chédiak-Higashi syndrome | Normal | Yes | Oculocutaneous albinism + infection | NA | |
| Grey platelet syndrome | Normal/reduced | No | Grey platelets | NA | |
| Idiopathic α- and δ- (dense) storage pool disease | Normal | No | No | NA | |
| Isolated prolonged BT † | Normal | No | No | NA | Variable |

NA, not available or not in general use.

*Severe bleeding only in a minority of cases.

†Refers to cases with consistent prolongation of BT in the absence of any demonstrable coagulation defect, including VWD, and of any platelet function abnormality, as investigated by aggregometry, α- and δ-granules content and prothrombin consumption assay.

**Table 3** Frequency of hemorrhagic symptoms, as reported by Wahlberg (4) and Mauser-Bunschoten (6)

| Investigated symptom | Frequency |
|---|---|
| Profuse menstruation | 44% |
| Nosebleeds | 5–36% |
| Bleeding at delivery | 19.5–23% |
| Bleeding after tonsillectomy | 2–11% |
| Bleeding after surgery | 6% |
| Bleeding from small wounds | 2% |
| Various symptoms (1 or more) | 40–50% in men; 50–60% in women |

test (i.e. a laboratory-driven diagnosis, such as in a preoperative screening). Using the same diagnostic criteria for these two different populations may lead to uncontrolled biases.

In the clinical-driven diagnosis, one should remember that even normal subjects refer hemorrhagic symptoms quite frequently (Table 3) [4–6]. The number of symptoms reported by patients may be influenced by their education, family background (e.g. some symptoms may be under-reported by subjects belonging to a bleeding family) and personality, but also by the type of data ascertainment. For instance, using a self-reported questionnaire, Friberg *et al*. found that as many as 23% of Swedish girls reported three or more hemorrhagic symptoms [7], whereas using a questionnaire guided by a physician Rodeghiero *et al*. observed three or more hemorrhagic symptoms in less than 1% of normal controls [8]. Stringent criteria and clinical judgment are therefore always advisable in collecting a bleeding history, and the use of proper tools may ensure interobserver reproducibility of the process (see below) [9].

In the laboratory-driven diagnosis, specificity may be assumed to be constant, as the abnormality is usually defined as being below the 2.5 percentile of the normal distribution (hence specificity is fixed at a 97.5% level). The main disadvantage of a laboratory-driven diagnosis is that the correlation between the levels of a specific factor and the severity of bleeding symptoms is usually poor, and therefore the predictive value of laboratory tests (and hence, of the laboratory-driven diagnosis) is low. It is, therefore, not surprising that preoperative screening has been repeatedly reported to be of minimal value in predicting post-surgical bleeding [10]. In fact, screening for MBD before surgery may be considered similar to screening for thrombophilic abnormalities in asymptomatic women before contraceptive pill use [11].

Given these clinical and laboratory complexities, is it worthwhile to pursue the diagnosis of MBD at all? To fully answer this question, one should know whether the bleeding risk in those patients diagnosed as MBD is significantly higher than in the general population and, more importantly, if bleeding may be prevented or ameliorated by the diagnosis. In this statement, it is implicit that one should pursue a *clinically useful* diagnosis, which means that the diagnosis should be of some benefit for the patient and not simply be accurate (i.e. a diagnosis not biased by high false positive or negative rates) (Fig. 1). Unfortunately, for most MBD we do not have clinical data on the lifelong bleeding risk and consequently the cost-benefit ratio of such a diagnosis remains uncertain. In a recent analysis of a cohort of type 1 VWD patients (the European MCMDM-1 VWD Study), the risk of bleeding remained constant throughout the lifetime in patients with VWD, in contrast to occasional bleeding observed in normal controls or

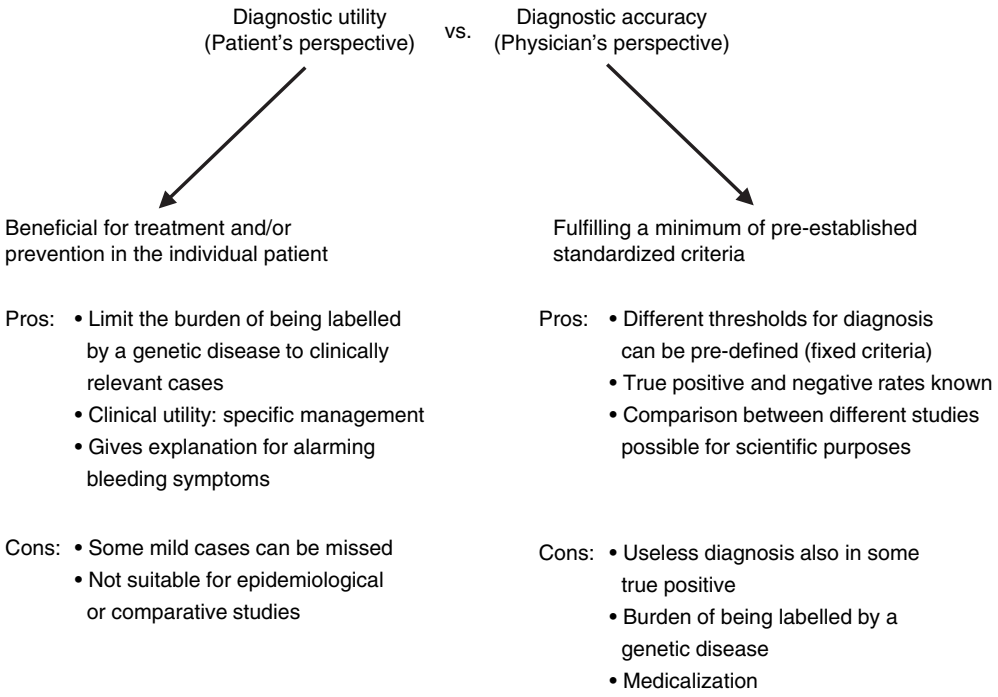


**Fig. 1.** Diagnostic utility versus diagnostic accuracy in mild bleeding disorders: characteristics, advantages and disadvantages.

unaffected family members [12]. Therefore, at least for bleeding disorders with bleeding manifestations comparable with those of symptomatic type 1 VWD, it seems likely that a clinically driven diagnosis could be of some benefit.

The use of standardized tools for a systematic collection of bleeding history and a more quantitative approach in its interpretation could allow some standardization of the diagnosis of MBD, with an improved distinction between patients with MBD and normal subjects.

## Tools for collecting bleeding history and quantitative assessment of bleeding severity

Several scales can be used to assess clinical hemorrhage for inherited and acquired conditions [13]. These tools, although useful to describe and to compare bleeding in different groups, have not been used for discrimination between bleeders and non-bleeders. More relevant to the present discussion are the several questionnaires [4,5,8,14,15] proposed with the aim of distinguishing patients with from those without inherited bleeding disorders and reviewed by Coller and Schneiderman [16]. Wahlberg *et al.* [4] were the first to use a self-administered questionnaire to discriminate frequency and types of bleeding between normals and those affected by a hemostatic disorder, such as VWD and qualitative platelet abnormalities, showing a great overlap between the two populations. Remarkably, 65% of healthy women and 35% of healthy men answered 'yes' to the question: Do you suffer from a bleeding disorder? Nosek-Cenkowska *et al.* [14] tried to differentiate children with significant bleeding disorders from non-bleeding children by a self-administered questionnaire. By using several combinations of different questions, no satisfactory sensitivity and specificity were obtained [14]. Šrámek *et al.* [5] used a self-administered questionnaire investigating type, frequency and intensity of symptoms to assess its usefulness in two different situations. First, in distinguishing among patients referred to a specialized center for bleeding symptoms between those with and those without a definite bleeding disorder, and secondly, between affected and normal individuals in the context of a primary setting (e.g. prior to surgery). This landmark study demonstrated that, while a simple interview is useful to screen patients affected by bleeding disorders, in a referred situation even a more detailed history is not able to discriminate between patients with or without a definite bleeding disorder [5].

Two experiences of a quantitative approach to MBD have been recently reported, one in a platelet function defect [15], the Quebec platelet disorder, and one in type 1 VWD [8]. It is important to remember that assessment of bleeding symptoms is a two-step process, comprising, first, collection of the bleeding history and, second, summation of the available data, possibly using pre-established criteria. This two-step approach was followed for both studies. Initially, a standardized bleeding questionnaire was administered by trained personnel or self-administered in the case of Quebec platelet disorder. Subsequently, a summative bleeding score was computed for both studies. While in the type 1 VWD study the score was pre-established for each symptom before analysis and was related to its severity (Table 4), in the Quebec platelet disorder study the score was either 0 or 1 only for those symptoms previously found to be related to the disorder. For type 1 VWD, bleeding symptoms were collected in 42 obligatory carriers and compared with 215 control subjects; for the Quebec platelet disorder, 23 affected were compared with 104 unaffected subjects within two large families. Both studies demonstrated that cutaneous bleeding, and bleeding after tooth extraction or surgery, were the symptoms most associated with VWD or Quebec platelet disorder. Furthermore, both studies demonstrated some overlap of bleeding score in normal vs. affected subjects. In the type 1 VWD study, a good specificity (greater than 99%) was obtained when considering for further investigations for a possible VWD those subjects with three or more symptoms or having a bleeding score greater than 3 in males or 5 in females. The sensitivity of this approach was suboptimal (between 50% and 64%), but satisfactory enough, as patients

**Table 4** Grades of bleeding severity used to compute the bleeding score

| | Score | | | |
|---|---|---|---|---|
| Symptom | 0 | 1 | 2 | 3 |
| Epistaxis | No or trivial | Present | Packing, cauterization | Blood transfusion or replacement therapy |
| Cutaneous | No or trivial | Petechiae or bruises | Hematomas | Consultation |
| Bleeding from minor wounds | No or trivial | Present (1–5 episodes/year) | Consultation | Surgical hemostasis |
| Oral cavity | No or trivial | Present | Consultation only | Surgical hemostasis/blood transfusion |
| GI bleeding | No or trivial | Present | Consultation only | Surgery/blood transfusion |
| Tooth extraction | No or trivial | Present | Suturing or packing | Blood transfusion |
| Surgery | No or trivial | Present | Suturing or resurgery | Blood transfusion |
| Menorrhagia | No or trivial | Present | Consultation, Contraceptive pill use, iron therapy | Blood transfusion, hysterectomy, dilatation and curretage, |
| Post-partum hemorrhage | No or trivial | Present, iron therapy | Blood transfusion, dilatatation and curretage, suturing | Hysterectomy |
| Muscle hematomas | No or trivial | Present | Consultation only | Blood transfusion, surgery |
| Hemarthrosis | No or trivial | Present | Consultation only | Blood transfusion, surgery |

with VWD that would have gone unrecognized by the proposed criteria actually did not show severe hemorrhagic symptoms at a limited follow-up evaluation. These data further strengthen the notion that a 'gray-zone' does indeed exist where subjects with MBD and subjects without any demonstrable hemoststic deficiency cannot be clearly separated.

## When should a patient be considered for the evaluation of a MBD?

A balanced approach between clinical and laboratory data appears necessary. Although the best approach to an individual case remains the choice of the physician, some scenarios could be considered.

### *The patient with bleeding symptoms*

The use of a standardized questionnaire such as that used in the studies by Rodeghiero *et al*. [8] and by Castaman *et al*. [17] in carriers of type 1 and type 3 VWD is recommended. The questionnaire can be freely downloaded at http://www.med.unc.edu/isth/SSC/collaboration/Bleeding_Type1_VWD.pdf and should be administered by personnel (physician or nurse) with some experience in history taking. Indeed, a common pitfall is to consider as a bleeding symptom any trivial hemorrhage that is of no discomfort for the patient or caregiver. While the use of a bleeding score in MBD different from VWD has not yet been validated, a bleeding score above 3 in males and 5 in females could be generally considered frankly abnormal, at least in adults [8]. Any abnormality identified in these subjects is likely to be linked to a significant bleeding tendency that may benefit from treatment (e.g. anti-hemorrhagic prophylaxis before surgery or tooth extraction).

### *The asymptomatic patient with a family history of bleeding*

Counseling an asymptomatic relative of a patient with known MBD (the proband) could be particularly difficult. Even if the same laboratory phenotype is identified, there are no clues that it may be used to predict bleeding. Selection bias, presence of circumstantial factors (e.g. aspirin use), and co-inheritance of other MBD, may have worsened the bleeding diathesis in the proband. Therefore, extreme caution should be used before labeling such an asymptomatic relative as 'affected' and reassurance is always advisable before any evaluation for a specific laboratory defect.

### *The pediatric patient*

The pediatric patient with bleeding symptoms should be carefully evaluated because he/she may be referred for only rare manifestations that would be otherwise dismissed as 'trivial' in an adult. Data from other family members should always be collected, as bleeding in other relatives may be frequently reported for autosomal dominant disorders [15]. However, the family history may be negative in recessive disorders and a complete evaluation should always be performed in all doubtful cases.

### *The patient with a single bleeding symptom: lessons from investigating menorrhagia*

In recent years, much attention has been paid to menorrhagia in otherwise healthy women and in women with inherited bleeding disorder. It is subjectively reported as excessive menstrual blood loss, but this perception needs to be objectively assessed due to different psychological and behavioral awareness of menstrual bleeding. The current definition of menorrhagia requires a menstrual blood loss $>80$ ml by objective measurement. To avoid these troublesome measurements, a pictorial chart for semi-quantitative assessment of blood losses has been recently adopted, with reasonable sensitivity and specificity [18]. Menorrhagia is the most frequent problem for a woman during reproductive life and occurs in about 10% of women [19]. On the other hand, menorrhagia may be the most prominent manifestation of a congenital bleeding disorder [19–21]. For example, a primary coagulation defect was found in 20% of adolescents admitted for menorrhagia [22]. In some studies, up to 20% of women with objectively documented menorrhagia turned out to have mild VWD [23]. In a recent study including 150 consecutive women with objectively confirmed menorrhagia without anatomical or hormonal causes, 14% had mild VWD and 3% mild FXI deficiency [21]. Accordingly, menorrhagia could be a valuable marker of a hidden bleeding disorder and considered as a sentinel symptom for inherited mild coagulopathies [21], and recently some experts claimed that investigating bleeding disorders in women of reproductive age represents a 'public health crisis' [3]. So, is screening for MBD advisable for all patients presenting with menorrhagia? The example of Fig. 2, which illustrates the ambivalent outcomes of a systematic screening for a definite hemostatic defect, like VWD, in women with menorrhagia, tempers any enthusiasm. It is evident that finding reduced VWF in women with menorrhagia may lead to labeling an alarming number of otherwise normal women as affected by VWD, possibly exposing them to the risk of inappropriate treatment. Thus, the best criteria to start investigations in women with isolated menorrhagia should perhaps involve a more conservative and thoughtful approach, requiring *ad hoc* prospective investigations.

## Obtaining a balanced diagnosis of an MBD: the case of type 1 VWD

Type 1 VWD, the most common inherited MBD, is defined by quantitative deficiency of VWF and bleeding symptoms in a proband who also has family members with the same features. Although simple, this definition can be difficult to translate into diagnostic operational steps for several factors. First, type 1 VWD, although generally transmitted in a dominant way, is variably penetrant in different families and may be variably expressed in the same family. The levels of VWF in affected

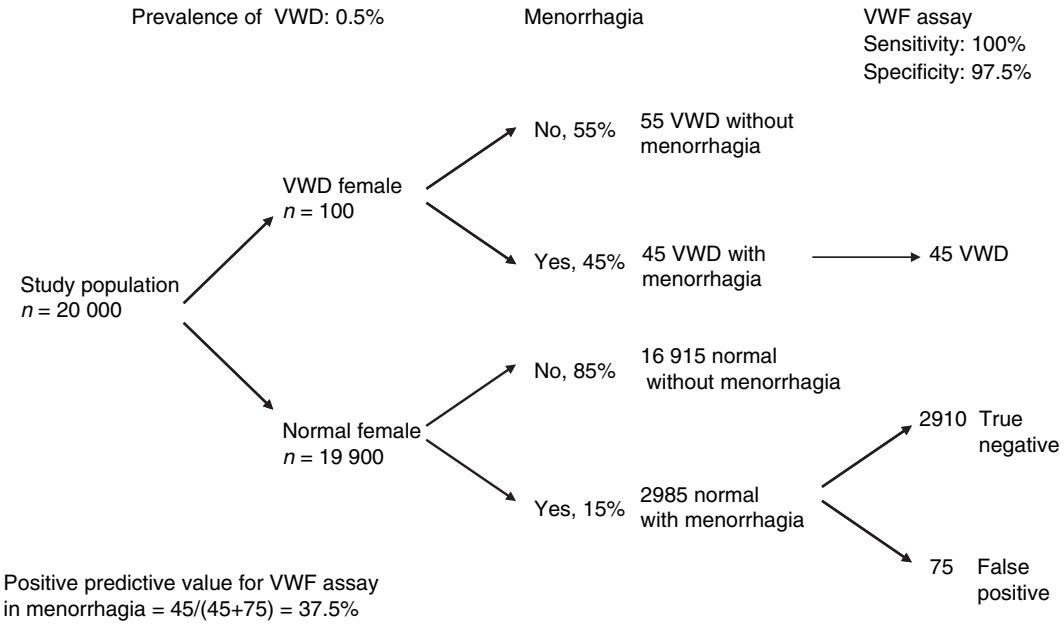


**Fig. 2.** Positive predictive value for VWF assay in women reporting menorrhagia. Based on a prevalence of VWD of 0.5% and on the frequency of menorrhagia in women with Type 1 VWD [12] and in otherwise normal women [8], the ratio of VWD/normal in women with menorrhagia is 45/2985 in a population of 20 000 fertile women. By using the same laboratory test, with a sensitivity of 100% and a specificity of 97.5% in all women complaining of menorrhagia, we should identify all the 45 women with VWD, but at the expenses of 75 false positive women. Thus, the positive predictive value of this approach will be only 37.5%.

patients and healthy controls overlap considerably and there is a weak relationship between VWF levels and bleeding manifestations, apart from the very severe cases. Furthermore, VWF levels are 25% to 30% lower in O blood group individuals, and blood type O is over-represented among VWD patients. Also, mucocutaneous bleeding symptoms are more common in the healthy population than is often recognized [24]. Despite these interfering factors, current criteria for the diagnosis of type 1 VWD in the individual patient rest on the concomitance of three main features: bleeding symptoms, reduced VWF and autosomal inheritance of the phenotype [25]. These criteria are, however, based on an experts' consensus and their specificity and sensitivity are not known.

Recently, the diagnostic value of bleeding symptoms in type 1 VWD has been estimated in a cohort of 42 obligatory carriers for type 1 VWD, to assess which symptoms could better identify type 1 VWD patients. The positive diagnostic likelihood ratio (LR) was 19.1 for surgery and cutaneous bleeding, 13.3 for postpartum bleeding, 13.2 for bleeding after tooth extraction and 10.2 for wound bleeding [8]. By using these symptoms in a classification and regression trees (CART) analysis, cutaneous bleeding was the best predictor of type 1 VWD among spontaneous symptoms, while in those who underwent tooth extraction or surgery, postextraction bleeding was the best predictor, followed again by cutaneous symptoms [8]. Quantification of bleeding symptoms has the potential for improving the diagnosis of VWD, by making feasible the incorporation of all these features into a single quantitative index. This could be achieved by estimating the final probability (odds) of having type 1 VWD by combining the LRs of having VWD as a function of each of the three diagnostic features in the investigated subject. According to the Bayes' theorem, the odds of being affected by a disease could be obtained by multiplying the incidence of the disease (pretest probability) by the LRs of having the disease given a specific test result. For this purpose, the incidence of VWD in the general population can be conservatively assumed as 1 in 1000 [26]. The LRs for individual VWF level and bleeding score have recently become available from multicenter large studies on different cohorts of type 1 VWD patients [8,12,27,28]. The LR linked to the number of family members with reduced VWF could be calculated by computer modeling of a theoretical nuclear family assuming dominant transmission and conservative allele frequency (0.005) and penetrance (50% in affected, 2.5% in non-affected). According to the different final odds, proposals for 'possible' or 'definite' VWD diagnosis can be made and compared with the proposed provisional criteria [25].

## Bleeding risk in specific disorders

### *Partial coagulation defects (PCD)*

Few data assessing bleeding risk in subjects with partial coagulation defects are available. Some of these subjects are heterozygous for a defective allele that, in homozygosity, causes severe bleeding with almost no residual factor activity. These subjects are expected on average to have half of the normal value and are usually described as 'asymptomatic carriers'. However, this assumption is based on anecdotal reports rather

than on systematic evaluation. Anyway, in clinical practise, these subjects, usually encountered within family investigations, could be considered as 'normal subjects'. The case is different for the carriers of X-linked hemizygous defects (hemophilia A and B) where random chromosome X-inactivation causes a variable residual activity (between 0% and 50%) and a good relationship between bleeding risk and FVIII/FIX levels has been demonstrated [29]. Unfortunately, a clear-cut distinction between 'theoretical' heterozygotes, with average factor deficiency around 50%, and the larger group with more complex genetics causing a variably lower residual factor activity ranging, say, between 5% and 40%, is not always feasible. For example, in the North American registry the so-called heterozygous patients showed values of deficient factor ranging from 21 to 69% and had some evidences of bleeding tendencies, requiring treatment with plasma or plasma-derived clotting concentrates in a few of them (Table 5) [30]. The retrospective nature of the registry and the lack of genetic studies do not allow any further detailed evaluation of the factors influencing this purported increased risk of bleeding. Ideally, a prospective study with a standardized questionnaire administered to obligatory carriers or subjects with partial deficiency for coagulation defects would allow a clearer definition of the pattern, frequency and severity of bleeding episodes, if any. This standardized approach has been already used in obligatory carriers of type 3 VWD [17], demonstrating that some carriers may experience significant bleeding in the presence of significantly low VIII/VWF measurements.

Intuitively, and on the basis of limited experience, a relationship between circulating level of the factor and clinical severity of bleeding manifestations could be traced for each specific defect. In addition, usually a minimum threshold of circulating levels can also be identified above which bleeding risk becomes negligible. For example, in FXIII deficiency a level above 2–3% is almost sufficient for normal hemostasis, while these levels are not safe for patients with other deficiencies (e.g. FVII). For FVII deficiencies, large heterogeneity of molecular basis is evident, with several dysfunctional molecules being reported that do not cause bleeding even in the presence of markedly reduced circulating levels. Out of 123 patients with FVII $< 2\%$ reported in the IF7 database, 27 had mild disease, 34 moderate disease and only 56 severe disease, suggesting that extragenic components could also be important in modulating the clinical phenotype [31]. FXI deficiency requires particular attention. This disorder is associated with variable bleeding tendency in homozygotes, often due to trauma or surgery, especially in tissues rich in fibrinolytic activity [32]. However, a puzzling aspect is the purported increased risk of bleeding in patients with a partial deficiency. Homozygotes for E117stop mutation (so-called type II mutation) are at increased risk compared with homozygotes for P283 L missense mutation (so-called type III mutation, both mutations being particularly prevalent in Askhenazi Jews) due to a lower FXI levels [33]. Surprisingly, a clear-cut relationship between FXI levels and bleeding symptoms has not been found in the heterozygotes for the two mutations or in other heterozygous mutations. Possibly,

**Table 5** Bleeding in heterozygotes: the North American Registry [30]

| Disorder | Factor level, U $dL^{-1}$ (Median) | Clinical manifestations | Comments |
|---|---|---|---|
| Hypofibrinogenemia ($n = 11$) | 68 mg $dL^{-1}$ (51–117) | 73% symptomatic (80% of them trauma-related): 46% non-surgical bleeding, 18% postoperative bleeding, 45% mucocutaneous, 30% joint and muscle, gastrointestinal 10%, genitourinary tract 10% | 80% of episodes without treatment; cryoprecipitate (33%) and concentrate (17%); information not available for 42% |
| Dysfibrinogenemia ($n = 11$) | - | 73% symptomatic: 46% non-surgical bleeding, postoperative bleeding 18%. 71% of symptomatic, genitourinary 14%, musculoskeletal 7%, gastrointestinal 8% | 50% of episodes not treated. Cryoprecipitate used in 38%, no information on 12% |
| Prothrombin deficiency ($n = 6$) | 25 (21–35) | 83% with mucocutaneous bleeding (60% of them spontaneous) | 49% of episodes treated with PCCs or FFP |
| FV deficiency ($n = 19$) | 35 (21–55) | 17% bleeding, all spontaneous (in 50%, 62% with mucocutaneous bleeding, 19% musculoskeletal, 19% genitourinary | Treatment with FFP and EACA alone |
| FVII deficiency ($n = 88$) | 35 (21–69) | 25% bleeding (2% postoperative), 61% spontaneous. Among 36% of bleeders, mucocutaneous 76% | 44% of events required FFP (26%), cryoprecipitate, rFVIIa, EACA alone (5–8% each) |
| FX deficiency ($n = 15$) | 38 (23–47) | 33% symptomatic: 75% of them mucocutaneous, gastrointestinal 12%, postoperative 13% | 36% of bleeding episodes treated with FFP, PCCs, EACA (12% each) |

EACA, epsilon amino caproic acid; FFP, fresh frozen plasma; PCCs, prothrombin complex concentrates.

patients with some dominant-negative mutations inducing lower FXI levels than expected in heterozygotes could have a significant bleeding tendency [34,35], but this aspect has never been investigated in detail. In conclusion, it seems sensible to establish the bleeding risk in these disorders by considering personal and/or family history together with the actual circulating level of the factor measured by a functional assay. As a general rule, substitutive treatment seems advisable for values $< 20$–$30\%$, depending on the severity of trauma or surgery.

### *Inherited platelet disorders (IPD)*

The different IPD can be grouped according to the average severity of their bleeding manifestations on the basis of simple clinical and laboratory criteria (Table 2) [36]. Cases associated with a reduced platelet count may present variable platelet size and occur in isolated form or in association with other co-existing clinical abnormalities (syndromic forms). In all these forms, a mild to moderate bleeding diathesis is present and its severity can be usually anticipated on the basis of the circulating platelet mass. Notably, exceptions are Bernard-Soulier and Wiskott-Aldrich syndromes, in which bleeding is usually severe and life-threatening hemorrhages may occur regardless of the actual platelet count. Severe bleeding diathesis is also manifest in patients with Glanzmann thromboasthenia, Scott syndrome and related disorders, and Quebec platelet disorder, although to a lesser extent, could also present severe bleeding. A mild to moderate bleeding diathesis is usually found in all other platelet function disorders (Table 2).

The larger group of primary or idiopathic IPD described under the various types of predominant defects, including all cases with isolated α- and δ- (dense) storage pool deficiency or receptor and signal transduction disorders, remains clinically ill defined.

These disorders have generally been described in subjects with mild bleeding and prolonged bleeding time after the exclusion of coagulation defects. While most reports provided a better understanding of platelet physiology, they proved to be of little help for a systematic approach to the bleeding manifestations. Most disorders listed in Table 2 present a mild bleeding diathesis, and respond to Desmopressin and/or antifibrinolytics regardless of their specific defect, making characterization of these defects not always clinically useful. Platelet transfusions are very rarely required. Thus, after screening for the few most severe forms, a generic diagnosis of functional platelet defect based on simple aggregometric studies and nucleotide dense granule content may suffice to explain the associated mild bleeding symptoms or when the phenotype of another established bleeding disorder, like VWD, seems aggravated by an additional defect. Our consolidated practise is to look for a platelet disorder in all cases with at least three bleeding symptoms (or a single important symptom, requiring medical attention) in the presence of a prolonged bleeding time (BT) after exclusion of a coagulation defect and of VWD, with the caveat that a prolonged BT is not invariably present in subjects with Scott syndrome [37] or Quebec platelet disorder [15] and may not be sensitive to the mildest forms of storage pool deficiency [38]. Furthermore, prolonged BT is neither associated with the severity of the individual bleeding tendency nor is predictive of the risk of bleeding after trauma or surgery [39,40]. The non-invasive platelet function analyzer PFA-100® (Dade Behring, Marburg, Germany) could be an attractive substitute for BT but the test is burdened with a huge rate of false positive and false negative results and is not predictive of bleeding risk, and thus can not be recommended at present [36]. So, it remains completely unknown what the best criteria are for a suspected platelet disorder in an isolated subject. Accordingly, the incidence of these defects remains unknown strictly depending on minimal clinical and laboratory criteria but could be fairly high [38].

## Conclusions

An objective threshold, above which bleeding manifestations suggesting a MBD should demand laboratory investigation, to make a specific and clinically useful diagnosis, remains a formidable goal. Pros and cons of the different approaches have never been formally investigated. Despite a new interest in this issue and some recent studies, a reliable assessment of the bleeding risk in the individual patient can be obtained only in the context of a few specific MBD, whereas, for most of the remaining cases, estimating the bleeding risk remains more an art than a science. However, in the absence of an important bleeding history, our approach to patients with MBD should be guided by the reassuring awareness that simple screening laboratory tests such as platelet count, APTT and PT, supplemented by a few additional tests in specific circumstances, is all that is required to identify subjects at risk of major bleeding.

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## Disclosure of conflict of interests

The authors state that they have no conflict of interests.

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