The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease

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**Key Points**

- The bleeding score helps to predict clinical outcomes in adult patients with von Willebrand disease.
- High bleeding scores correlate with intensive on-demand therapy and may identify cases requiring regular prophylaxis.

**Introduction**

von Willebrand disease (VWD) is considered the most common inherited bleeding disorder, even though its prevalence varies considerably according to the setting of diagnosis1-3: in population-based studies, prevalence was estimated to be as high as 0.6% to 1.3%,4,5 about 2 orders of magnitude higher than in specialized centers (0.005%-0.01%) to which symptomatic patients with VWD are usually referred.6-10 VWD is due to quantitative and/or qualitative defects of von Willebrand factor (VWF), a multimeric glycoprotein synthesized by endothelial cells and megakaryocytes that mediates platelet adhesion/aggregation and stabilizes factor VIII (FVIII) in the circulation.1,2 In VWD, bleeding events are caused not only by impaired platelet-VWF interactions, usually evaluated in plasma by ristocetin cofactor activity (VWF:RCo), but also by reduced FVIII levels that often accompany the VWF defect.

Whereas in classical hemophilia there is an excellent relationship between plasma levels of FVIII, frequency, and severity of clinical bleeding, in VWD such a relationship is less clear and straightforward. A plasma VWF level of 30 IU/dL has been suggested as a threshold to distinguish patients with a bleeding tendency from healthy subjects with low-borderline plasma levels of VWF.10-13 Usually, the bleeding history is an essential criterion for the diagnosis of inherited bleeding disorders, including VWD.14-17 A bleeding score (BS) based upon bleeding symptoms and calculated using the questionnaire proposed by Tosetto et al18 was used to confirm diagnosis in a large cohort of European families with type 1 VWD19 and was subsequently applied with some modifications to other clinical studies on VWD.20,21 More recently, in a limited number of patients with some VWD types (1, 2A, 2B, 2M), attempts were made to use the BS not only for diagnostic purposes but also to evaluate the patients’ tendency to bleed.22-24 With this background, we have prospectively analyzed number and types of spontaneous bleeding episodes and their treatments in a cohort of 796 Italian VWD patients with centrally obtained laboratory measurements to determine whether the BS calculated at the time of the baseline visit predicts the rates of bleeding events requiring treatment with DDAVP and/or VWF/FVIII concentrates.

**Patients and methods**

**Design and aims of the study**

Italian National Registry of von Willebrand Disease in its second part (RENAVI-2) is a prospective observational cohort study carried out in...
patients diagnosed and followed up at 6 comprehensive hemophilia centers, members of the Italian Association of Hemophilia Centers (AICE). This study is the continuation of the previously described Italian National Registry of von Willebrand Disease (RENAWI-1). The aim of RENAWI-2 is to evaluate the incidence, type, and severity of spontaneous bleeding episodes requiring treatment with DDAVP and/or VWF/FVIII concentrates in a large cohort of patients in whom phenotypic and genotypic diagnosis was centrally confirmed. Patients were informed about the anonymous use of their data and the purpose of this study and gave informed consent in accordance with the Declaration of Helsinki. This study was approved by the institutional review board of the participating hospitals after the endorsement by the AICE.

Inclusion and exclusion criteria

Patients were included in RENAWI-2 between June and December 2008 during a baseline visit, and prospectively followed from January 1, 2009 for 12 months onward. Moreover, those patients who bled during this period were further observed beyond the RENAWI-2 follow-up until 2013 to evaluate any shift from on-demand treatment to prophylaxis. The BS was calculated by the investigators on the basis of symptoms that had occurred before inclusion in RENAWI-2 using a standardized questionnaire administered to patients when blood samples were withdrawn. For the purpose of RENAWI-2, all cases were included without distinguishing between propositi and affected family members. Patients unable to participate in the follow-up visits or give informed consent were considered ineligible (n = 39) as well as those who did not meet criteria for VWD diagnosis after centralized laboratory reevaluation (n = 36). We also excluded individuals with concomitant hepatic or renal insufficiency (n = 43), those using antplatelet or anticoagulant drugs (n = 9), pregnant women (n = 5), or those with active malignancy (n = 6) at the time of the first study visit. Patients with incomplete follow-up (n = 10), and the only VWD2N case, were not included in the final analyses. At the end, 796 VWD patients were included in RENAWI-2.

Laboratory methods for VWD diagnosis

At each participating center, venous blood was withdrawn at the time of the baseline visit. Platelet-poor plasma was obtained and kept frozen at -40°C by each center. The following tests were performed at the central laboratory in Milan. FVIII was measured by a 1-stage coagulation assay. VWF:antigen (Ag) by commercial kits or homemade enzyme-linked immunosorbent assay (ELISA) using polyclonal antibodies against VWF. VWF:RCo was measured by aggegrometry using formalin-fixed platelets from normal donors; however, when plasma VWF:RCo was <15 U/dL, patients were reinvestigated using the more sensitive ELISA-VWF:RCo assay. According to predefined inclusion criteria, patients were included in this study if their plasma VWF:RCo was below the lower normal limit of 56 U/dL of the central laboratory, corresponding to 2 standard deviations (SDs) below the plasma levels of normal donors with non-O blood groups. The plasma VWF multimeric pattern was evaluated in patients’ plasma by low- and intermediate-resolution gel electrophoresis. For molecular diagnosis, genomic DNA was extracted from peripheral blood using standard methods. The oligonucleotides used and the detailed testing procedures are available on request. The final classification according to VWD types was confirmed by the coordinating center in Milan by also using multimeric analysis and mutations of the VWF gene. DNA was available in all affected patients with VWD2A, VWD2B, VWD2M, and in most VWD3 (82%) and VWD1 (63%). The majority of the identified mutations had been previously recorded in the International Society on Thrombosis and Haemostasis—Scientific Standardization Committee on VWF database (www.vwf.group.shef.ac.uk). To analyze the association of VWF:RCo and FVIII, the incidence rate of bleeding (any type, mucosal or nonmucosal) was calculated as the number of episodes during the follow-up period divided by the total number of patient-years for that period, and 95% confidence intervals (CIs) were calculated under the Poisson distribution assumption. For each patient, the follow-up started on January 1, 2009 and ended at the date of the first bleeding event or on January 1, 2010 (administrative censoring). An additional observation until 2013 in the group of bleeders treated on demand with VWF/FVIII concentrates was carried out, with the only purpose to describe their inclusion in a prophylaxis program.

Statistical analysis

Continuous variables were expressed as medians with minimum (min) and maximum (max) values, and categorical variables as counts and percentages. Comparison between groups was made by the Mann-Whitney U test for continuous variables and the x² test for categorical variables. The relationship between VWF:RCo plasma levels and BS (both taken as continuous) was assessed by means of linear regression analysis, using a restricted cubic spline function to check for possible deviations from linearity, and adjusting for age and sex. For different risk categories formed according to values and levels of BS, VWF:RCo, and FVIII, the incidence rate of bleeding (any type, mucosal and nonmucosal) was calculated as the number of episodes during the follow-up period divided by the total number of patient-years for that period, and 95% confidence intervals (CIs) were calculated under the Poisson distribution assumption. For each patient, the follow-up started on January 1, 2009 and ended at the date of the first bleeding event or on January 1, 2010 (administrative censoring). An additional observation until 2013 in the group of bleeders treated on demand with VWF/FVIII concentrates was carried out, with the only purpose to describe their inclusion in a prophylaxis program. At the beginning of follow-up, all VWD patients were free from bleeding for at least 1 month. A multivariable Cox proportional hazard model was used to calculate the risk of bleeding, expressed as hazard ratio (HR) with 95% CI, according to different predictors’ categories (BS <5, 5-10, >10, VWF:RCo <30, 30-100, <10 IU/dL, FVIII >40, 20-40, <10 IU/dL) and in which the effect of each predictor was adjusted for the confounding effect of the others and for those of age and sex. The reference group was the highest category for VWF:RCo and FVIII and the lowest for BS. Bleeding-free survival was computed with the Kaplan-Meier method, and the log-rank test was used for comparison between groups. P <.05 was taken as cutoff for statistical significance. All analyses were performed with the statistical software SPSS (release 19.0), except for the linear regression analysis using the spline function, for which the statistical software R was used (release 2.9.1; R Project for Statistical Computing).

Results

BS as predictor of bleeding in VWD

The main demographics and clinical-laboratory features of the whole cohort are shown in Table 1. This cohort was mainly composed of adult VWD: only 16 of 796 (2%) patients had <18 years at enrollment. Among the 796 cases, 75 (9.4%) had at least 1 spontaneous bleeding event requiring treatment during the 1-year follow-up: therefore, these patients can be defined as bleeders. Bleeders had median values of BS and baseline VWF:RCo/FVIII levels, respectively, higher and lower than nonbleeders (P <.001 for all comparisons). Considering

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Table 1. Demographic and clinical-laboratory features at baseline of the entire cohort (n = 796) vs bleeders (n = 75) of the VWD patients according to types

<table>
<thead>
<tr>
<th>VWD type</th>
<th>All cases, n = 796</th>
<th>Bleeders, n = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>183/274</td>
<td>10/13</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>39 (6-99)</td>
<td>39 (13-67)</td>
</tr>
<tr>
<td>BS, median (range)</td>
<td>4 (1.3-28)</td>
<td>6 (2-28)</td>
</tr>
<tr>
<td>VWF:RCo, median (range), IU/dL</td>
<td>31 (3-56)</td>
<td>25 (6-56)</td>
</tr>
<tr>
<td>FVIII:C, median (range), IU/dL</td>
<td>47 (2-187)</td>
<td>36 (13-129)</td>
</tr>
<tr>
<td>Previous DDAVP, case no. (%)</td>
<td>204 (45)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Previous conc., case no. (%)</td>
<td>146 (32)</td>
<td>11 (48)</td>
</tr>
</tbody>
</table>

Bleeders were defined as those VWD patients who had at least 1 spontaneous bleeding event requiring treatment during the 1-y follow-up.

Figure 1. Restricted cubic spline curve. Curve showing the age- and sex-adjusted relationship between VWF:RCo plasma levels and BS in all patients with VWD. Dotted lines represent 95% CIs. A plateau was found at a mean BS value of 3.5 (dashed horizontal line), that was reached for VWF:RCo levels above 30 IU/dL.
VWD2B, and VWD2M analyzed both separately and together, there was a nonstatistically significant difference in event bleeding-free survival according to BS and VWF:RCo levels (data not shown).

Primary outcome: annual bleeding events with replacement therapy

Among the 75 VWD bleeder, a total of 232 spontaneous bleeding events was recorded during the 1-year follow-up. The number of annual events per patient progressively increased according to VWD types (Table 3) but, when patients were analyzed according to BS, the proportion observed in all bleeders with BS < 5 was significantly lower (18 of 232 [8%]) than that observed in those with BS 5 to 10 (58 of 232 [25%]) and with BS > 10 (156 of 232 [67%]; P < .0001 for comparison between the 3 groups). The sites of mucosal (epistaxis, menorrhagia, gums, and gastrointestinal [GI] bleeds) and non-mucosal (hematoma and joint bleeding) bleeding events according to different VWD types are shown in Figure 4A. Overall, mucosal bleeds were more frequent than hematoma and joint bleeds: epistaxis and menorrhagia occurred in all VWD types, whereas GI bleeding occurred mainly in VWD3 and VWD2A, characterized by partial or complete loss of intermediate- and high-molecular-weight VWF multimers. On the other hand, hematomas and joint bleeds occurred mainly in VWD3 and in those patients with more severe VWD1 characterized by lower FVIII levels.

Table 2. Risk of bleeding in the 796 VWD patients according to clinical and laboratory predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Crude HRs (95% CI)</th>
<th>Adjusted HRs (95% CI)*</th>
</tr>
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<tbody>
<tr>
<td>BS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>5-10</td>
<td>2.10 (1.10-3.90)</td>
<td>2.05 (1.07-3.91)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>6.80 (3.80-12.30)</td>
<td>7.27 (3.83-13.83)</td>
</tr>
<tr>
<td>VWF:RCo, IU/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>10-30</td>
<td>1.51 (0.72-3.14)</td>
<td>1.16 (0.54-2.47)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>3.27 (1.77-6.06)</td>
<td>1.12 (0.50-2.51)</td>
</tr>
<tr>
<td>FVIII:C, IU/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>20-40</td>
<td>2.07 (1.16-3.69)</td>
<td>1.52 (0.80-2.90)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>4.20 (2.43-7.26)</td>
<td>2.20 (1.05-4.62)</td>
</tr>
</tbody>
</table>

*The effect of each predictor on the bleeding risk was adjusted for that of the other ones, and for age and sex, in a multivariable Cox proportional hazard model.
†Reference group.

Other outcomes: intensity of replacement therapy and indications for prophylaxis

In general, a total of 292 (7.7 per patient per year) DDAVP injections and 795 (15 per patient per year) infusions of VWF/FVIII concentrates were used to treat spontaneous bleeds during the 1-year observation period. Pertaining to DDAVP, 38 of 75 patients (51%) with VWD1 (n = 18), VWD2A (n = 8), and VWD2M (n = 12) were treated with varying median annual doses per patient depending on types (Table 3). The most intensive on-demand therapy was used for VWD2A and VWD1. DDAVP was the only treatment of the majority of relatively mild bleeding events (epistaxis, menorrhagia, gum bleeds) although it was used together with VWF/FVIII concentrates in cases of more severe events such as GI bleeding, hematomas, or joint bleeds.

Pertaining to VWF/FVIII concentrates, 53 of 75 (71%) patients were treated on demand with varying annual doses per patient, not only in VWD3 (n = 25), VWD2A (n = 10), VWD2B (n = 5) but also in VWD2M (n = 7) and VWD1 (n = 6); median doses were particularly high in VWD3, VWD2A, and in a few patients with more severe forms of VWD1 (Table 3). GI or joint bleeds did usually require the most intensive treatment with VWF/FVIII concentrates. Treatment intensity was also analyzed according to the BS of bleeders (Table 3); for both DDAVP (Figure 4B) and VWF/FVIII concentrates (Figure 4C), cumulative dosages progressively increased with increasing BS values. Pertaining to VWF/FVIII concentrates, a few patients with severe forms of VWD1 were treated with median annual dosages similar to those used for VWD3 patients. Because of the intensive on-demand treatment needed for recurrent spontaneous bleeds, 12 of 53 patients (23%) were shifted by the investigators at the end of 12-month follow-up to long-term prophylaxis, owing to GI bleeds (5 of 12 cases) in VWD1 (n = 2) and VWD3 (n = 3), to hemarthroses (5 of 12 cases) in VWD3, and menorrhagia (2 of 12 cases) in VWD3 and VWD1. All 12 of these VWD patients had very high BS (median, 22; range, 11-33).

Discussion

The main goal of this prospective observational cohort study of 796 Italian patients with VWD was to use the BS not only for diagnostic purposes as hitherto but also to evaluate clinical outcomes by assessing the annual incidence rate of spontaneous bleeding and the
The diagnosis of VWD types was confirmed by central reevaluation of the laboratory measurements as reported previously\textsuperscript{25}; in RENAWI-2, patients were also evaluated using the BS calculated at baseline visit according to the questionnaire originally used by Tosetto and colleagues in the frame of the European study on VWD type 1.\textsuperscript{18} This BS was subsequently proposed together with VWF levels and family history to obtain evidence-based diagnosis of VWD type 1.\textsuperscript{33} More recently, BS was also considered as a determinant of clinical outcomes in a few VWD types.\textsuperscript{34} With this background, we thought that the prospective approach of RENAWI-2 was appropriate to assess whether there was a more extensive role for the use of BS in all VWD types.

At variance with other studies that limited the evaluation of VWD patients to those with plasma levels of VWF:RCo < 30 IU/dL, we chose to include in RENAWI-2 the largest possible number of VWD patients with mild (34%), moderate (28%), and severe (38%) laboratory phenotypes according to the European and Italian recommendations.\textsuperscript{3,6,35} Thus, a relatively large proportion (34%) of mildly affected VWD patients with low-borderline levels of VWF activity was also included, and only 5% of them had a spontaneous bleeding event. Pertaining to VWD types, the most frequent was VWD1 (58%), followed by VWD2M (21%), VWD2A (8%), and VWD2B (7%), whereas the rarest VWD3 patients accounted for 6% of the total cohort. These proportions of VWD types in RENAWI-2 are similar to those previously reported.\textsuperscript{1,3,6-10}

![Figure 3. Bleeding event-free survival (Kaplan-Meier method). According to: (A) VWD types; (B) BS and VWF:RCo levels in all VWD; (C) BS and VWF:RCo levels in VWD1; (D) BS and FVIII levels in VWD3.](image-url)
Because the patient population was mainly composed of adults, the use of a pediatric BS was not deemed necessary in the few included children. There were no significant differences in the BS pertaining to sex and age within VWD types. In RENAWI-2, the BS calculated at baseline was inversely and linearly correlated with plasma levels of VWF activity up to VWF:RCo levels of 30 IU/dL. Above this level, the relationship reached a plateau at a BS mean value of 3.5. These data are consistent with previous suggestions of Sadler and colleagues, who proposed a threshold level of VWF activity of 30 IU/dL to identify clinically relevant VWD patients.26 Over a 1-year observation, only 75 patients (9.4%) had at least 1 spontaneous bleeding. The clinical (BS) and laboratory (VWF:RCo and FVIII) parameters were all associated with a high risk of bleeding. However, only a BS >10, a measurement that can be obtained easily during medical visits, remained the most significant determinant of the risk of any bleeding at multivariable analysis. The cumulative probability of being free from bleeding events differed among the VWD types, confirming a progressively increased degree of severity from the milder VWD1, VWD2M, and VWD2B to more severe VWD2A and VWD3. To evaluate the role of the BS together with that of VWF:RCo, that is, the measurement of VWF activity chosen for this study, the bleeding-free survival was calculated in the whole cohort of patients and in different VWD types, comparing BS <5 or BS 5 to 10 and any level of VWF activity with BS >10 and VWF:RCo <10. In the whole patient cohort, 3 different curves did result, with the shortest bleeding-free survival in those with BS >10 plus VWF:RCo <10. Furthermore, considering that levels of VWF activity may affect the BS and the bleeding risk, patients with partial VWD1 (VWD1 = 457) or complete VWD3 (VWD3 = 49) VWF deficiency were analyzed separately. In both groups, the bleeding-free survival was heterogeneous and resulted in 3 different curves, being shorter in patients characterized by BS >10 plus VWF:RCo <10 (VWD1) or plus FVIII <5 (VWD3). The heterogeneous bleeding tendency in VWD3 patients, considered by definition homogeneous because of the complete absence of VWF in plasma and cellular compartments, is intriguing. Indeed, there were cases with severe (ie, bleeds every week), moderate (bleeds every month), or mild (1-2 events per year) phenotypes. The possible role played in this heterogeneity by tiny amounts of VWF present in patient plasma or platelets, as well as the role of varying plasma levels of FVIII, is currently under investigation in a large prospective study on VWD3 [see http://www.vwd-3winters-ips.com/]. Conversely, the probability of being free from bleeding was not significantly different according to BS and VWF levels in VWD2A, VWD2B, and VWD2M. Perhaps other hemostasis-related parameters play a role in these VWD types as additional determinants of clinical severity, such as thrombocytopoiesis in VWD2B, and the more marked defects of the high molecular weight multimers in VWD2A than in VWD2M.25

The BS of the 75 bleeders (who had a total number of 232 annual events) was significantly higher than that of nonbleeders and the total annual rate of bleeds was significantly higher in patients with BS >10, irrespective of the VWD type. All of the other data on the type and frequency of bleeds were as expected from previous retrospective studies.1-10,25 DDAVP was used not only in VWD1 but also in more than half of the bleeders with VWD2A and VWD2M, the most intensive regimens being used in VWD2A and VWD1. DDAVP was the only treatment of the majority of minor bleeding events (epistaxis, menorrhagia, gum bleeds), although it had to often be used together with VWF/FVIII concentrates to handle GI bleeding or hematomas. More than two-thirds of the bleeders needed at least 1 infusion of VWF/FVIII concentrates, with varying annual doses not only in VWD3, VWD2A, VWD2B but also in VWD2M and VWD1: the doses were higher in VWD3, VWD2A, and in a few severe bleeders with VWD1. However, not all of these bleeders required the same treatment intensity with DDAVP and/or VWF/FVIII concentrates because dosages did progressively increase from patients with BS <5 to those with scores of 5 to 10 and >10. A few patients with clinically severe forms of VWD1 received median annual dosages of VWF/FVIII concentrates similar to those used in VWD3, suggesting that the intensity of replacement therapy does not depend on the VWD types but is mainly related to the BS, VWF, or FVIII levels.

Table 3. Amount of DDAVP and VWF/FVIII concentrates used to treat 232 spontaneous bleeding events in the 75 VWD patients who bled during the 1-y follow-up, according to VWD types and BS

<table>
<thead>
<tr>
<th>Bleeders at follow-up</th>
<th>VWD1, n = 23</th>
<th>VWD2A, n = 10</th>
<th>VWD2B, n = 5</th>
<th>VWD2M, n = 12</th>
<th>VWD3, n = 25</th>
<th>All VWD, n = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of bleeding events (events/pt)</td>
<td>49 (2.13)</td>
<td>35 (3.50)</td>
<td>13 (2.60)</td>
<td>36 (3.00)</td>
<td>99 (3.96)</td>
<td>232 (3.09)</td>
</tr>
<tr>
<td>No. of bleed/yr in VWD with BS &gt;10 (%) by VWD type</td>
<td>28 (57)</td>
<td>19 (54)</td>
<td>7 (58)</td>
<td>18 (50)</td>
<td>25 (75)</td>
<td>105 (67)</td>
</tr>
<tr>
<td>Cases treated with DDAVP, no. (%)</td>
<td>18 (78)</td>
<td>8 (80)</td>
<td>0 (0)</td>
<td>12 (100)</td>
<td>0 (0)</td>
<td>38 (51)</td>
</tr>
<tr>
<td>DDAVP dose, μg/pt/yr, median (range)</td>
<td>105 (42-252)</td>
<td>189 (63-305)</td>
<td>0 (0)</td>
<td>63 (21-345)</td>
<td>0 (0)</td>
<td>105 (21-345)</td>
</tr>
<tr>
<td>DDAVP dose in VWD with BS &gt;10, median (range)</td>
<td>210 (189-252)</td>
<td>235 (189-305)</td>
<td>0 (0)</td>
<td>302 (251-345)</td>
<td>0 (0)</td>
<td>241 (189-345)</td>
</tr>
<tr>
<td>Cases treated with VWF/FVIII concentrates, no. (%)</td>
<td>6 (26)</td>
<td>10 (100)</td>
<td>5 (100)</td>
<td>7 (58)</td>
<td>25 (100)</td>
<td>53 (71)</td>
</tr>
<tr>
<td>Concentrate dose of VWF/RCo 1000 U/pt/yr, median (range)</td>
<td>61 (16-256)</td>
<td>77 (5-126)</td>
<td>45 (7-93)</td>
<td>27 (5-75)</td>
<td>105 (18-235)</td>
<td>75 (5-256)</td>
</tr>
<tr>
<td>Concentrate dose in VWD with BS &gt;10, median (range)</td>
<td>157 (48-256)</td>
<td>82 (75-126)</td>
<td>93</td>
<td>44 (27-75)</td>
<td>156 (63-235)</td>
<td>138 (27-256)</td>
</tr>
</tbody>
</table>

pt patient. *Some patients were treated with both DDAVP and VWF/FVIII concentrates. †Each patient was treated with the same dosage of DDAVP equal to 0.3 μg/kg. The median doses of DDAVP calculated in microgram per patient per year are shown also according to BS <5, 5 to 10, >10 by 3 VWD types (see also Figure 4A-C). ‡Patients have been treated with different dosages (30-80 VWF:RCo U/kg) according to the different sites and severity of bleedings based on the judgment of the investigators. The median doses of VWF/FVIII concentrates expressed in total VWF:RCo IU × 1000/patient per year are shown also according to BS >10 by the 5 VWD types (see also Figure 4A-C).
indications and benefits of prophylaxis vs on-demand therapy in VWD is scanty and based mainly on retrospective analyses. Our cohort was mainly composed of adult VWD patients, with a relatively small number of pediatric VWD; hence, the potency of BS might have been different in children. An additional limitation is the absence of patients with VWD2N, who might represent a peculiar bleeding phenotype. Furthermore, because this project started before 2009, we could not adopt the bleeding assessment tool (International Society on Thrombosis and Haemostasis, Bleeding Assessment Tool [ISTH-BAT]) recommended by the International Society on Thrombosis and Hemostasis. However, both ISTH-BAT and the BS used in the RENAWI-2 were derived from the first proposed BS. On the other hand, strengths of this study are the prospective follow-up of a large cohort representative of the general distribution of VWD types and the centralized performance of the main laboratory assays.

Based upon these findings, we conclude that, at variance with hemophilia A, spontaneous bleedings occur in a relatively small proportion of patients with VWD from a cohort representative of the 5 different VWD types. Patients characterized by high BS and low VWF activity are more likely than others to have a high bleeding tendency and to use more therapeutic products for replacement therapy. Therefore, a simple and inexpensive parameter such as BS is proposed as a useful predictor of clinical outcomes of inherited VWD, and may also help to identify those cases at higher risk of frequent and severe bleeds requiring more intensive regimens, such as long-term prophylactic replacement therapy.

Acknowledgments

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Authorship

Contribution: A.B.F. designed the study, enrolled the patients, supervised the centralized confirmation of VWD phenotypic and molecular diagnoses, analyzed the data results, and wrote the manuscript; P.B. performed statistical analysis, analyzed the data results, and reviewed the manuscript; G.C. designed the study, enrolled patients, supervised the molecular diagnosis, analyzed the data results, and reviewed the manuscript; M.G.M., M.M., A.R., and M.S. enrolled the patients, analyzed the data results, and reviewed the manuscript; F.P. supervised the molecular diagnosis, analyzed the data results, and reviewed the manuscript; F.R. analyzed the data results and reviewed the manuscript; and P.M.M. discussed the original study, analyzed the data results, and extensively reviewed the final draft of the manuscript.

Conflict-of-interest disclosure: A.B.F. has been involved in advisory boards and had received honoraria as a speaker at educational meetings organized by Baxter, CSL-Behring, Grifols, Kedrion Biopharma, LFB, and Octapharma. P.M.M. had received honoraria as...
References


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