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ARTICLE

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Mild or moderate hemophilia is not always a mild or moderate bleeding disorder: Back to the clinical phenotype

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Abstract

In a previous paper, a comprehensive clinicopathologic approach to mild and moderate bleeding disorders (MBD) was proposed by an international working group (IWG) as a part of a project promoted by the European Hematology Association (EHA) on the development of guidelines on the various MBDs. A single pre-diagnosis grade 4 bleeding event according to the ISTH-BAT scale or a comparable event after diagnosis was considered sufficient to classify a patient as affected by a severe bleeding disorder (SBD). In this article, the original IWG integrated by experts and patients' representatives proposed by the European Haemophilia Consortium (EHC) and European Association of Haemophilia and Allied Disorders (EAHAD) applied these criteria to mild and moderate hemophilia A and B to establish the proportion of cases that would be reclassified as SBD taking into account bleeding phenotype, thus improving over the current classification based exclusively on basal factor VIII or IX level. To this aim, publications of unselected cases with bleeding history available from birth to the time of publication were considered to estimate the incidence of a first severe bleeding event. More than 20% of cases with mild or moderate hemophilia met the criteria for SBD by experiencing joint or non-joint severe bleeding events. Furthermore, a significant proportion of patients developed an inhibitor against factor VIII or IX. These results, based on a rigorous methodologic approach, substantiate the criticism of the current classification of hemophilia and argue for the adoption of a new classification that takes into account bleeding phenotype in addition to basal clotting activity.

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INTRODUCTION

In the last years, increasing attention has been paid to inherited mild and moderate bleeding disorders (MBD) characterized by a milder bleeding phenotype when compared with the rarer severe bleeding disorders (SBD).[1] Patients with MBD are relatively common, with a wide variation in bleeding phenotype and overlap, in milder forms, with otherwise healthy people. In this regard, a clinicopathologic diagnostic approach should be designed to minimize the false positive classification while maintaining sufficient sensitivity for relevant disorders and minimizing the risk of improper resource utilization.[2]

With these premises in mind, under the auspices of the European Hematology Association (EHA), an international working group (IWG) of recognized experts proposed a conceptualization and a comprehensive clinicopathologic approach for the classification, diagnosis, and management of the various MBDs.[1] A provisional list of potential MBDs, including known defects with some residual functional activity of the relevant hemostatic component (≥1 IU/dL activity) was also proposed in agreement with the current prevalent classification, and based on the residual hemostatic activity more than on the actual bleeding phenotype.[1] At variance with these prevailing criteria, the IWG agreed that the occurrence of even a single severe bleeding episode was sufficient to qualify an individual as affected by a SBD, regardless of laboratory measurements.[1] On this ground, non-severe hemophilia A and B, still currently classified as moderate (1–5 IU/dL) or mild (>5–40 IU/dL) based on residual coagulation factor level activity[3] was chosen as the candidate for timely applying our new classification criteria, in the light of the current debate on the insufficiencies of its current classification. Experts have raised concerns that basing severity entirely on residual clotting activity could not provide the best guide for the management of individual patients and may have a negative impact on their quality of life (QoL).[4–6] This may prevent patients with a severe clinical phenotype associated with mild or moderate hemophilia from receiving benefits from novel treatment options such as emicizumab,[7] ultra-extended half-life clotting factor concentrates, and novel non-replacement therapies for which they cannot currently be reimbursed. In this article, we adopted a systematic unbiased approach based on predefined inclusion criteria to assess the proportion of patients with mild or moderate hemophilia, as currently classified,[3] who would need to be reclassified as affected by SBD according to our new proposed clinicopathologic definition. This reclassification will have obvious individual, clinical, and social impacts and could contribute to a more comprehensive management approach for these patients.

MATERIALS AND METHODS

Organization

The original IWG was enlarged with additional experts representing the EAHAD and patient representatives, indicated by the EHC, for a total of 24 members. EHA verified the absence of relevant competing conflicts of interest and supervised the project regarding compliance and consistency with the methodology adopted by its Committee on Guidelines. EHA and Hematology Project Foundation (HPF; Vicenza, Italy) provided funding for the project. None of the authors received any compensation apart from the professional personnel of HPF, which acted as the administrative and coordinating hub.

A first draft was produced by a restricted group (including F.R., A.C., G.C., R.A.K., K.F., R.L., M.M., I.P., A.S., and J.W). After additional revisions by the whole panel, the final version was approved for publication.

Literature search, screening, and final inclusion

Literature search and inclusion/exclusion flow diagrams were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for reporting systematic reviews.[8] Literature search was primarily finalized for the production of future guidelines on mild to moderate hemophilia, a project already in progress. The search was carried out through MEDLINE using the Ovid system. The main search terms queried included: mild or moderate hemophilia A or hemophilia B, mild or moderate factor VIII disorder/deficiency, mild or moderate factor IX disorder/deficiency, hemophilia B Leyden, and carriers of these disorders (search strategies are reported in Supporting Information S1: Tables 1a and 1b). Only articles published in English after 1974 were searched, a time when the measurement of FVIII or FIX level was presumed to be reliable, considering that by 1971 a freeze-dried biological standard for FVIII measurement had been proposed.[9] A first search of papers based on abstract and title was carried out by ICON (a clinical for-profit research organization company, Dublin, Ireland) in collaboration with F.R. using largely inclusive search criteria. A second screening on abstract and title adopting more selective patient, intervention, comparison, and outcome (PICO) as a search strategy tool (Supporting Information S1: Table 2) was conducted by L.G. and L.P., with the supervision of F.R. Papers on general management, on biological or pharmacokinetic or genetic aspects, were excluded. PICO and outcome criteria were approved by the whole IWG. For our analysis, we adopted strict inclusion criteria. Only reports describing at least 10 patients were considered to avoid publication bias, and only papers including cohorts of unselected series of patients followed from birth to the time of reporting were included. Cross-sectional studies and registry studies were not included since they usually adopt pre-determined entry criteria, and thus are not representative of the whole patient population or limit the analysis to a specific period of time or to a pre-determined range of age. In addition, these studies often use standardized definitions for bleeding assessment which cannot fit into our strict definition of severe bleeding.

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Papers on hemophilia B Leyden, first described by Veltkamp et al. in 1970[10] and characterized by decreasing bleeding with increasing age due to the rise in FIX from <1 IU/dL toward near normalization were included due to their rarity, even on single cases or single families.

The final literature selection, based on full texts, was performed by a subgroup of members of the IWG (A.C., G.C., R.A.K., K.F., R.L., M.M., I.P., A.S., and J.W.) using a table template, previously validated using 30 random papers for feasibility, clarity, and accuracy. All doubtful papers and 15% of the overall articles were double-checked by F.R., L.P., and L.G., and discrepancies were resolved by discussion. All remaining panel members were updated on the progress of literature screening and final inclusion.

The literature search was updated in October 2023 with a total of 2882 papers retrieved on mild to moderate hemophilia A, B, and carriers and 44 papers on hemophilia B Leyden and carriers (Supporting Information S1: Figures 1 and 2 show flow diagrams based on PRISMA format for hemophilia A and B and hemophilia B Leyden, respectively). Carriers were not considered in this article in view of a future report specifically addressing their bleeding phenotype with particular attention to women's issues.

Finally, 46 papers were retained for final assessment: 26 papers on mild or moderate hemophilia A and B (Supporting Information S2) and 20 papers on hemophilia B Leyden (Supporting Information S3). From these papers, we extracted the number of patients (denominator) for calculating the incidence of patients with at least one severe outcome.

In addition, selected publications before the end of September 2024, although not fitting our selection criteria, but containing useful information for a contextual discussion, were considered.

Definition of severe outcomes in moderate and mild hemophilia A, B, and B Leyden

We assessed the severity of any single reported bleeding manifestation and the occurrence of any bleeding-related permanent organ damage. The classification of bleeding severity was carried out, first separately and then jointly by F.R., L.P., and L.G. In very few cases, further consultation with experts of the restricted group of experts was required to reach a consensus on final severity attribution.

For bleeds occurring from birth up to the time of diagnosis, we used the ISTH-SSC BAT scale, where any bleeding with a score of 4 is classified as severe (Supporting Information S1: Table 3).[11] New criteria were used for scoring bleedings occurring post-diagnosis since the ISTH-SSC BAT is inappropriate in this instance. In fact, knowledge of the specific diagnosis may induce a more liberal treatment for prophylaxis or facilitate the control of a bleeding episode using specific agents, such as desmopressin or clotting factor concentrates, thus artifactually upgrading bleeding severity. For this reason, in the ISTH-SSC BAT scale, administration of desmopressin or some forms of replacement therapy should be scored only if given before a definite diagnosis. Hence, for bleeding reported post-diagnosis, new criteria were agreed upon for scoring the severity of bleeding and related complications independently from the specific treatment requirement.

As shown in Table 1, two main categories of bleeding, including joint bleeding and all other types of non-joint bleeding, are proposed together with criteria for qualifying them as severe. A conservative criterion was adopted by excluding reported bleeds with dubious/unclear interpretation. Traumatic bleedings were also included crediting the "bona fide" assessment of the treating physician who reported these events as a true manifestation of the disease.

The development of an inhibitor against the deficient factor was also considered a serious unfavorable event and included among severe outcomes even if its presence does not invariably cause a severe bleeding phenotype, as developing an inhibitor can make episodic treatment and prophylaxis more difficult. However, due to its largely unpredictable impact on the individual patient bleeding phenotype, inhibitor occurrence is reported separately. Our analysis was not designed to search for additional individual risk factors that could aggravate the course of the disease.

As per our preliminary definition,[1] the occurrence of at least one of these manifestations, even as a single event, was sufficient to qualify a patient as having a severe phenotype. In addition, for the reasons already mentioned earlier, inhibitor development was also classified as a severe outcome.

To calculate the proportion of patients experiencing one or more of the predefined severe outcomes at any time during follow-up, we considered only papers reporting the number of patients for whom the occurrence/non-occurrence of bleeding-related outcomes or inhibitor development occurred from birth to the time of publication. Based on reported or estimated patient's age at the time of publication, patients could be grouped into different categories (infants, children-teenagers, adults, and elders). On this basis, it was possible to approximate the average person-years at risk (average duration of observation), but not the precise time to the first qualifying event, apart from a minority of cases. Accordingly, only a partial lifetime risk for a severe outcome can be estimated.

RESULTS

A total of 46 papers were included for analysis: 26 papers on mild or moderate hemophilia A and B (Supporting Information S2) and 20 papers on hemophilia B Leyden (Supporting Information S3).

TABLE 1 Definitions of severe outcome for the two main categories of bleeding for hemophilia, joint bleeding, and all other types of non-joint bleeding.

Type of bleeding	Criteria defining a severe outcome
Joint bleeding and/or arthropathy	Any joint bleeding, spontaneous or traumatic, if disproportionate to the trauma and requiring in-hospital observation or presumed to cause chronic functional disability/impairment. Considering that arthropathy almost invariably develops after a severe joint bleed and that arthropathy itself is a major complication, its occurrence was invariably graded as a severe outcome, and the two manifestations were grouped into a unique category of severe joint bleeding and/or arthropathy.
Non-joint bleeding	(1) Any fatal bleeding; (2) any life or organ-threatening bleeding, spontaneous, traumatic, or post-surgery requiring hospitalization or blood transfusion; (3) any bleeding not adequately controlled by standard therapy (e.g., plasma, platelet concentrate, coagulation factor, or desmopressin given as prophylaxis or treatment) and/or requiring hospital admission for additional hemostatic procedures (e.g., suturing or nasal packing for non-traumatic bleeding or surgical intervention or prolonged in-hospital observation beyond the time strictly required for replacement therapy or desmopressin administration); (4) any intracerebral bleeding, spontaneous or traumatic, if judged disproportionate to the trauma; (5) any permanent organ damage secondary to bleeding (e.g., iliopsoas bleeding with functional sequela).

Hemophilia A and B

For hemophilia A and B, data were extracted for 1197 patients evaluable for bleeding-related events and 7226 patients evaluable for inhibitor occurrence. In a few papers, patients were only classified indistinctly as mild or moderate hemophilia A or B. A total of 26 papers were retained for the assessment of severe outcomes and distributed into distinct categories. The total number of evaluable patients, distinct for type and severity of hemophilia, and category of outcome severity are shown in more detail in Supporting Information S1: Table 4 and Figure 3. Further details may be found in Supporting Information S2: Table 1, which includes a detailed summary of findings such as age and FVIII or FIX levels at reporting and at the event, when available, the list of included articles with notes on relevant information, the number of patients with a severe outcome versus all patients, data on inhibitor development, and the list of complete references to articles.

Some papers report data on more than one severe bleeding outcome category (non-joint bleeding and joint bleeding and/or arthropathy), not allowing us to establish with certainty whether single or multiple events occurred in the same patient. Consequently, we could not calculate the proportion of patients fitting at least one of the two severe bleeding categories, since the same patient could have been included in more than one category. Hence, the proportion of patients with at least one qualifying outcome for severe phenotype could be lower than the sum of cases counted in the two categories but should be at least equal to that reported in the category with the more frequent outcome. In our analysis, the more frequent outcome invariably corresponds to joint bleeding and/or arthropathy, even in the extreme case that all patients had both outcomes. In short, our proportions for at least one severe outcome are strictly conservative. Overlapping due to the description of the same patient in different papers can be excluded since all papers were based on patients followed in different centers.

A summary of the overall proportion of patients, meeting a severe bleeding outcome, is reported in Table 2.

Due to our stringent inclusion criteria requiring a population denominator, reliable estimates of the proportion of cases meeting a severe bleeding outcome can be obtained only from a limited number of evaluable cases. Even with these limitations, the composite severe outcome of non-joint bleeding and joint bleeding and/or arthropathy was experienced by more than 20% of patients, with higher rates in moderate than mild cases. In general, joint hemorrhage or arthropathy are more frequently described than other types of severe bleeds and, when reported, the level of FVIII or FIX in most cases of joint bleeds is less than 25 IU/dL. A similar proportion and pattern of severe events are observed in hemophilia A and B. Importantly, most events are already reported at a relatively young age, since the exposure time at risk rarely extends beyond adulthood, and the exact age at the bleeding event was reported only in a few papers (see "Summary of relevant findings" in Supporting Information S2). The very low frequency of non-joint bleeding reported for indistinct hemophilia A and B should be interpreted with caution as it is based on two reports only. Very few traumatic bleedings fitting our pre-defined severity criteria for severity were included, indicating that the authors avoided reporting bleedings with a severity similar to that expected in healthy people if exposed to a similar trauma. Supporting Information S2: Table 1 offers a more detailed analysis by giving a more detailed description of the type of severe non-joint bleeding, including one fatal post-traumatic and eight non-fatal intracranial hemorrhages (five post-traumatic) for a total of

TABLE 2 Mild and moderate hemophilia A and B and indistinct hemophilia A or B: proportion of cases with at least one severe bleeding outcome.

Hemophilia type	Severity[a]	Cases with severe bleeding outcome (N)/evaluable cases (n) (%)[b]	
		Non-joint bleeding	Joint bleeding and/or arthropathy
Hemophilia A	Mild N/n (%)	15/205 (7.3%)	33/159 (20.8%)
	Moderate N/n (%)	9/27 (33.3%)	77/97 (79.4%)[c]
	Indistinct mild or moderate N/n (%)	NA	8/32 (25.0%)[d]
	All cases N/n (%)	*24/232 (10.3%)*	*118/288 (41.0%)*[c,d]
Hemophilia B	Mild N/n (%)	1/10 (10.0%)	2/7 (28.6%)[e]
	Moderate N/n (%)	2/10 (20.0%)	41/56 (73.2%)[f]
	All cases N/n (%)	*3/20 (15.0%)*	*43/63 (68.3%)*[e,f]
Indistinct hemophilia A or B[g]	Mild N/n (%)	3/226 (1.3%)[h]	85/257 (33.1%)
	Moderate N/n (%)	0/101 (0.0%)[i]	100/261 (38.3%)
	All cases N/n (%)	*3/327 (0.9%)*[h,i]	*185/518 (35.7%)*

Abbreviation: NA, data not available.

[a]Mild hemophilia: FVIII or FIX 6–40 IU/dL; moderate hemophilia: FVIII or FIX 1–5 IU/dL. One-stage classic method has been considered for the measurement of FVIII:C, when both one-stage and chromogenic measurements were available.

[b]Evaluable cases represent the denominators on which the proportion of cases with severe outcomes are calculated for non-joint bleeding or joint bleeding and/or arthropathy, respectively.

[c]Data were derived from only two papers (references 2 and 19 in Supporting Information S2), one of which with 76/89 with a history of hemarthrosis.

[d]Data are based on a single paper (reference 21 in Supporting Information S2) describing a mixed indistinct population of mild and moderate hemophilia A in which only joint bleeding and/or arthropathy is reported without specifically mentioning other outcomes.

[e]Data are based on a single paper (reference 13 in Supporting Information S2).

[f]Data are based on a single paper (reference 19 in Supporting Information S2).

[g]Collective data on hemophilia A and B from papers not distinguishing between the two types.

[h]Data are from only two papers (references 11 and 18 in Supporting Information S2).

[i]Data are based on a single paper (reference 11 in Supporting Information S2).

nine out of 30 non-joint bleeds (30%). Among other severe non-joint bleeding, some hemorrhages after circumcision and four life-threatening bleeds, not further specified, were reported.

Hemophilia B Leyden

For hemophilia B Leyden, the main outcomes are presented in Table 3. A total of 47 evaluable patients, including single non-overlapping case reports, were included for bleeding-related events, whereas inhibitor development was never reported (see Supporting Information S3: Table 1, which provides a detailed summary of findings, as well as the number of patients with a severe outcome versus all patients and the list of complete references).

Hemophilia B Leyden is characterized by a progressive increase of FIX level with age, particularly after puberty, hence the classification into moderate or mild is blurred and the actual FIX level at the time of bleeding occurrence is more relevant. Overall, the proportion of cases with a severe bleeding outcome is similar to that found in moderate hemophilia B, but most events are restricted to a younger age (<15 years) when FIX was lower than 5 IU/dL, often <1 IU/dL. As reported in more detail in Supporting Information S3, non-joint severe bleedings included hemorrhages following tonsillectomy or circumcision, or in the iliopsoas muscle, intracranial hematoma, subgaleal hematoma treated with exchange transfusion, and a suspected intracranial bleed. One death from hemorrhage after trauma was also reported.

As shown in the graph in Supporting Information S3, FIX level rises with age, beginning in puberty and stabilizing in adulthood as expected in this disease.

Inhibitor development

Table 4 summarizes the proportion of mild and moderate hemophilia cases with inhibitor development.

The overall risk of an inhibitor is quite high, particularly in moderate hemophilia A, while it is rather infrequent in hemophilia B. Its occurrence, although not necessarily translating into a more severe bleeding phenotype, represents an unfavorable event in case of treatment, thus contributing to the burden of the disease. However, since neither the number of patients exposed to replacement treatment nor the number of exposure days is available, no firm conclusion on the risk of inhibitor development in these patients can be inferred and probably a significantly higher incidence could be expected (see the last three columns in Supporting Information S2: Table 1 for more details).

None of the 47 cases with hemophilia B Leyden described in Table 3 developed an inhibitor. This might be due to the paucity of reported cases and/or to the increase of endogenous FIX levels with age making replacement therapy less frequent.

TABLE 3 Hemophilia B Leyden: proportion of cases with at least one severe bleeding outcome.

	Cases with severe bleeding outcome (N)/evaluable cases (n) (%)[a]	
	Non-joint bleeding	Joint bleeding and/or arthropathy
All cases N/n (%)[b]	9/47 (19.1%)	20/47 (42.6%)

[a]Evaluable cases represent the denominators on which the proportion of cases with severe outcome are calculated for non-joint bleeding or joint bleeding and/or arthropathy, respectively.

[b]Four patients had both joint bleeding and/or arthropathy, and non-joint bleeds.

DISCUSSION

The main finding of our systematic investigation shows that, based on the composite severe outcome of non-joint bleeding and joint bleeding and/or arthropathy, more than 20% of patients with mild or moderate hemophilia A and B, according to the 2001 SSC-ISTH criteria,[3] still in use, do not fit the definition of MBD previously proposed by this IWG, which requires the complete absence of any severe bleeding manifestation.[1] Inhibitor development occurred in a relatively lower percentage of mild or moderate hemophilia B than of hemophilia A, but with a relevant incidence if one considers that it is referred to the whole analyzed population and that it includes subjects not yet exposed to replacement therapy.

These findings, based on very strict and conservative inclusion criteria, strengthen the need for a new classification incorporating bleeding phenotype as a critical aspect.

As shown in Tables 2 and 4, a significant proportion of patients with moderate or mild hemophilia A and B experienced a severe outcome in terms of bleeding, including ICH, arthropathy, or inhibitor development. These data should be considered as very conservative, being based on a limited individual time-exposure risk, since our estimates cover only the period between birth and age at reporting, approximately on average less than 40–50 years. Moreover, FVIII or FIX levels at diagnosis and at the time of an event are rarely reported, so the relationship between endogenous FVIII or FIX activities and severe bleeding outcome or the age at the first severe event could not be reliably assessed (see "Summary of relevant findings" of Supporting Information S2).

Fewer outcomes in hemophilia B compared to hemophilia A, as suggested by some authors,[12] are not as evident from our data which are limited to non-severe hemophilia.

In hemophilia B Leyden (Table 3), most events are restricted to a younger age (<15 years) when FIX was lower than 5 IU/dL, often <1 IU/dL, and no inhibitors were reported.

The current classification is rooted back in 1958 when Biggs and McFarlane in Oxford observed that patients with more than 5 IU/dL of FVIII or FIX had hemarthroses very seldomly and only after trauma. Moreover, patients with 1 or 2 IU/dL of FVIII or FIX seemed to be much less prone to serious bleeding after minor trauma than the group with no detectable FVIII, whereas patients undergoing surgery had excessive bleeding episodes with FVIII level <25 IU/dL or FIX < 15–20 IU/dL.[13]

TABLE 4 Mild and moderate hemophilia A and B: proportion of cases with inhibitor development.

	Cases with inhibitor development (N)/evaluable cases (n) (%)[c]		
Severity[a]	Hemophilia A	Hemophilia B	Indistinct hemophilia A or B[b]
Mild N/n (%)	86/2779 (3.1%)	1/1243 (0.1%)	5/85 (5.9%)
Moderate N/n (%)	126/1388 (9.1%)	7/1586 (0.4%)	3/145 (2.1%)
All cases N/n (%)	*212/4167 (5.1%)*	*8/2829 (0.3%)*	*8/230 (3.5%)*

[a]Mild hemophilia: FVIII or FIX 6–40 IU/dL; moderate hemophilia: FVIII or FIX 1–5 IU/dL.

[b]Collective data on hemophilia A and B from papers not distinguishing between the two types.

[c]Evaluable cases represent the denominators on which the proportion of cases with inhibitor development (Bethesda units (BU) > 0.5) are calculated. Previous exposure to replacement therapy was not generally indicated so that it is not possible to estimate the post-exposure risk.

Based on these early observations, factor levels of <1 IU/dL were agreed upon for severe, 1–5 IU/dL for moderate, and >5–40 IU/dL for mild hemophilia A and B, and these boundaries were formally endorsed by the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) in 2001[3] and confirmed in 2014 despite its insufficiency in describing the heterogeneity of bleeding phenotype.[14] The classification of individuals with FVIII levels between 40 and 50 IU/dL was also left unresolved, despite patients with FVIII levels exceeding 40 and up to 50 IU/dL may require support after significant trauma or invasive procedures.[15] To fill this gap, a new definition for mild hemophilia has been endorsed by SSC/ISTH which specifically considers individuals with FVIII or FIX higher than 40 IU/dL.[16] Similarly, carriers of hemophilia with ≥40 IU/dL levels of FVIII or FIX are also potentially considered at risk of bleeding.[17]

Furthermore, the current classification of hemophilia is also increasingly criticized for not being able to capture the variable and overlapping clinical phenotype of the different forms and for the lack of standardized and harmonized definitions of clinical outcomes and practices adequate to describe the clinical phenotype of patients, modifiable by the modern management.[4–6,18,19]

The results of our investigation, including cases reported after 1974, might raise doubts about their generalization at a time when impressive progress has been made in hemophilia management. However, still at present several cohort studies have identified joint bleeding in a quite high proportion in patients with mild or moderate hemophilia. For example, Soucie et al., analyzing 3315 patients with non-severe hemophilia A and 1456 patients with non-severe hemophilia B, showed that a target FVIII or FIX levels of 15 IU/dL was unlikely to prevent all joint bleeding.[20] Similarly, the PedNet study, including 825 children with non-severe hemophilia A or B (FVIII or FIX activity 1%–25%), found that endogenous factor activity at least >5 IU/dL was required to significantly lower joint bleeding rate, while FVIII > 15 IU/dL and FIX > 10 IU/dL were required to achieve the goal of no bleeds.[21] Back in 2011, Den Uijl et al. already found flaws in the current classification noting a wide variation in clinical phenotype within the group of moderate hemophilia, leading to the conclusion that treatment decisions, such as starting prophylaxis, should be tailored according to the bleeding pattern rather than to the residual clotting factor activity levels.[22] These conclusions are in keeping with Mancuso et al.,[18] who showed, using a Delphi approach among experts in hemophilia treatment, that the residual FVIII/FIX activity level accounts for around 70% of the bleeding phenotype and the remaining 30% are potentially related to other unexplained individual variables.

The results of a recent large retrospective single-center analysis also seem of particular importance. In this study, 270 persons with mild hemophilia A aging ≥16 years, with a median age at the last follow-up of 45 years and a median lifelong FVIII level of 21 IU/dL (interquartile range 14–32) were included. At least one joint bleed occurred in 37%, which was spontaneous in 4% (minimum FVIII levels needed to prevent any lifelong bleeds and any spontaneous joint bleeds were 19.2 IU/dL and 17.7 IU/dL, respectively).[23] These data are similar to those of a Dutch study of 433 persons with hemophilia A including 73% with mild disease, wherein the FVIII target level necessary to prevent joint bleeds was slightly lower, 15%.[24] In keeping with these findings, in an international multicenter study, including 70 moderate (FVIII ≥ 2 IU/dL) and 234 mild hemophilia patients with a baseline clotting FVIII/IX level of 2–35 IU/dL, aged 12–55 years, 156 (51%) patients, mainly with moderate hemophilia, experienced at least one joint bleed requiring treatment with factor concentrate and the median age at the first joint bleed was 10 years. Four patients experienced intracerebral hemorrhage after trauma or a hypertensive crisis.[25]

Several cross-sectional studies also report a high rate of severe bleeding including joint damage in mild hemophilia. In a multicenter study including 111 adult patients (86 with mild and 25 with moderate hemophilia), 23.1% of the evaluable patients reported any joint bleeding in the past 5 years.[26] Another study on 51 patients with non-severe hemophilia A aged 24–55 years (19 moderate and 32 mild) demonstrated that a substantial proportion of adults have joint changes on MRI despite low joint bleeding rates.[27] The last update of the US Registry Bleeding Disorders Surveillance included data from 146 federally funded Hemophilia Treatment Centers and reported on bleeding events in infants and toddlers (males and females of ≤2 years) born during or after 2011.[28] The study enrolled between 2013 and 2021 patients with hemophilia A or B and a clotting factor <50 IU/dL. In 322 patients with mild or moderate hemophilia (FVIII or FIX ranging from 6 to 50 IU/dL), strikingly 22% experienced an ICH, the same rate observed in infants and toddlers born between 1998 and 2011. These data confirm our findings of a relevant risk of ICH even in mild or moderate hemophilia and the need for the identification of individual risk factors and improved prophylaxis strategies in these patients.[28] Unfortunately, so far, the current use of prophylaxis seems ineffective in reducing ICH as the main cause of death in these patients, as recently reported by Hassan et al, with a similar proportion of ICH in severe (2.4%) and mild (2.0%) hemophilia.[29]

We found relatively low rates of inhibitor development, especially for hemophilia B (Table 4). However, these figures particularly for hemophilia A should be considered very conservative, since they are calculated independently from previous exposure to substitution therapy, due to the lack of this information in many papers and considering that time exposure risk is limited from birth to age at reporting, thus not accounting for the increasing risk with age due to higher exposure to treatments. Also, any correlation with specific on *F8* gene mutation was not explored, which appears an important co-factor for inhibitor onset together with increasing FVIII exposure.[30] Under these considerations, the relatively low risk of developing inhibitor found in this review is not reassuring: indeed, one would expect a higher incidence when the analysis is targeted for a longer period resulting in a higher number of cumulative exposure days, as shown by several papers.[31–36] No inhibitor development has been reported in hemophilia B Leyden, but the available data are insufficient in this regard to draw a definite conclusion.

In summary, our findings suggest that the current classification of severe, moderate, and mild hemophilia should be re-considered. From the individual patient perspective, the specification of an individual level of clinical severity, in addition to the canonical biological classification, will have obvious consequences for optimal management and an adequate lifestyle, including social and job activities, especially if one considers the impact of recent progress, given the availability of more efficacious, less invasive therapeutics that increase the feasibility of adequate short- or long-term prophylaxis, and the availability of innovative novel treatments and promise of gene therapy. As recently claimed by Dolan et al.,[37] innovative replacement therapies are being used in patients with severe hemophilia to maintain FVIII or FIX levels above those present in a large proportion of patients with mild or moderate hemophilia. As a result, we are approaching a point where patients with mild or moderate hemophilia may, at least in high-income countries, have a higher risk of bleeding and life-style restrictions than those with severe disease. This situation poses a serious problem of equity.[38] In this context, individualization of bleeding risk becomes even more important for low- and middle-income countries, which require a strict prioritization of health assistance costs.

As shown by our literature analysis, the bleeding phenotype may not be already apparent at birth or at the time of diagnosis. Hence,

the IWG proposes a dynamic classification to include a reference to the actual patient clinical phenotype, which becomes effective only after a severe outcome. For example, a patient with a basal FVIII level of 10 IU/dL (mild hemophilia) would be reclassified as having mild hemophilia A with a severe bleeding phenotype. However, for many mild or moderate patients before such an outcome the bleeding history, including also minor events and the endogenous factor level, must continue to guide the best prophylaxis and treatment. Moreover, caution should be used in adopting this dynamic classification in particular settings, such as surgery in patients with a mild or moderate form according to plasma levels that have not previously presented with a severe bleeding manifestation. In fact, without adequate treatment, they might heavily bleed during and after surgery and the decision on preventive treatment cannot only rely on their previous bleeding history.

The contrasting terminology "mild/moderate" with "severe", where the first terms refer to the basal factor VIII or IX activity and the second to the actual clinical phenotype, might be confusing and a more appropriate terminology could be proposed. Nevertheless, the European Medicines Agency has adopted this terminology to extend the indication of emicizumab (Hemlibra) for patients with moderate hemophilia with a severe bleeding phenotype,[39] whereas the US Food and Drug Administration made no distinction between the different hemophilia severity.[40]

We hope that the World Federation of Hemophilia and the International Society on Thrombosis and Haemostasis, the major international organizations in this field, will take the appropriate actions to formalize a more adequate definition for hemophilia for the sake of the benefit of people with this disease and to assure that future guidelines or recommendations take into due consideration not only the basal FVIII or FIX level but also the bleeding phenotype.

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AUTHOR CONTRIBUTIONS

Francesco Rodeghiero coordinated the project, analyzed literature, and wrote a preliminary version of the manuscript. Lisanna Ghiotto and Luca Pontalto analyzed literature and contributed to writing the manuscript. Francesco Rodeghiero, Lisanna Ghiotto, Luca Pontalto, Alessandro Casini, Giancarlo Castaman, Rezan Abdul-Kadir, Karin Fijnvandraat, Riitta Lassila, Mike Makris, Ingrid Pabinger, Alok Srivastava, and Jerzy Windyga produced the first draft. Francesco Rodeghiero, Lisanna Ghiotto, Luca Pontalto, Rezan Abdul-Kadir, Alessandro Casini, Giancarlo Castaman, Erik Berntorp, Imre Bodó, Manon Degenaar-Dujardin, Karin Fijnvandraat, Paolo Gresele, Nigel S. Key, Riitta Lassila, Frank W. G. Leebeek, David Lillicrap, Mike Makris, Stephan Meijer, Diego Mezzano, Patrizia Noris, Ingrid Pabinger, Margaret V. Ragni, David Silva, Alok Srivastava, Alberto Tosetto, Jerzy Windyga, and Barbara Zieger contributed to writing the manuscript, reviewed the progressive drafts of the manuscript, and approved its final version.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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