REGULAR ARTICLE

blood advances

The bleeding phenotype in people with nonsevere hemophilia

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Key Points

- Estimates for bleeding rates and the association between baseline FVIII/IX and joint bleeding rates in nonsevere hemophilia are reported.
- One-half of included persons with nonsevere hemophilia experienced a joint bleed in the past, despite low joint bleeding rates.

Detailed information on the onset, frequency, and severity of bleeding in nonsevere hemophilia is limited. We aimed to assess the bleeding phenotype of persons with nonsevere hemophilia and to analyze the association between baseline factor VIII/IX (FVIII/IX) levels and the joint bleeding rate. In the DYNAMO (Dynamic Interplay Between Bleeding Phenotype and Baseline Factor Level in Moderate and Mild Hemophilia A and B) study, an international multicenter cohort, we included males with nonsevere hemophilia (FVIII/IX, 0.02-0.35 IU/mL) aged 12 to 55 years. Information on age at first treated (joint) bleed, annual bleeding rates (ABRs), and annual joint bleeding rates (AJBRs) was collected from the medical files. The association between baseline FVIII/IX levels and the joint bleeding rate was assessed by using a frailty model for recurrent events. In total, 304 persons (70 with moderate hemophilia and 234 with mild hemophilia) were included. The median age was 38 years (interquartile range [IQR], 25-49 years), and the median baseline FVIII/IX level was 0.12 IU/mL (IQR, 0.05-0.21 IU/mL). In total, 245 (81%) persons had experienced at least 1 bleed, and 156 (51%) had experienced at least 1 joint bleed. The median age at first bleed and first joint bleed was 8 and 10 years, respectively. The median ABR and AJBR was 0.2 (IQR, 0.1-0.5) and 0.0 (IQR, 0.0-0.2). From baseline FVIII/IX levels 0.02 to 0.05 IU/mL to >0.25 IU/mL, the median ABR decreased from 0.6 (IQR, 0.2-1.4) to 0.1 (IQR, 0.0-0.2) and the AJBR from 0.2 (IQR, 0.0-0.4) to 0.0 (IQR, 0.0-0.0). Baseline FVIII/IX was inversely associated with the joint bleeding rate ($P < .001$). Low bleeding rates were observed in persons with nonsevere hemophilia. However, one-half of all adolescents and adults had experienced a joint bleed.

Submitted 17 March 2022; accepted 28 April 2022; prepublished online on *Blood Advances* First Edition 9 May 2022; final version published online 21 July 2022. DOI 10.1182/bloodadvances.2022007620.

Requests for original data may be submitted to the corresponding author (e-mail: s.c.gouw@amsterdamumc.nl).

The full-text version of this article contains a data supplement.

Introduction

Hemophilia A and B are inherited bleeding disorders characterized by a deficiency of coagulation factor VIII (FVIII) and factor IX (IX), respectively. Disease severity is based on the residual coagulation FVIII/IX level and is classified as severe (<0.01 IU/mL), moderate (0.01-0.05 IU/mL), or mild (>0.05-0.40 IU/mL).[1] Persons with hemophilia have an increased bleeding tendency in which those with mild hemophilia mainly experience bleeding events provoked by trauma or surgery. In contrast, persons with severe hemophilia, especially when not treated on prophylaxis, experience frequent spontaneous bleeding events.[2]

In persons with nonsevere hemophilia, there is a paucity of detailed information on the bleeding phenotype.[3] A limited number of studies reported heterogeneous results on the frequency and nature of bleeding episodes in nonsevere hemophilia.[3-12] A single-center cross-sectional study and a national surveillance registry reported on the association between baseline FVIII/IX levels and the joint bleeding rate. They found a decreasing annual joint bleeding rate with increasing baseline FVIII/IX levels.[4,8]

The heterogeneity between results may arise from differences in study designs, geographical locations, classification of bleeding episodes (self-reported vs physician-reported, treated vs untreated), and lengths of observation.[3,4,8,13,14] Comparing these results is therefore challenging. Studies in an international multicenter setting with detailed information and uniform definitions on the bleeding phenotype may provide more robust estimates. Moreover, research addressing the bleeding phenotype within different subgroups of FVIII/IX levels in mild hemophilia is scarce. Information on the onset of bleeding and bleeding rates increases our knowledge regarding the burden of disease in subjects with nonsevere hemophilia and may guide personalized care.

In severe hemophilia, the treatment landscape is changing. Presently, emicizumab is widely being adopted in the clinical care,[15] and other nonreplacement products and gene therapy are being developed. These products have the potential to convert the phenotype in persons with severe hemophilia to that of persons with nonsevere hemophilia, as individuals treated with these products achieve a steady-state hemostatic protection comparable to mild hemophilia.[16,17] Data on the bleeding phenotype in nonsevere hemophilia could provide information on what to expect in terms of the bleeding pattern and inform what factor levels should be aimed for to achieve bleed protection.

The aim of the current study therefore was to gain insight into the bleeding phenotype in persons with nonsevere hemophilia in an international multicenter setting. The secondary aim was to explore the association between baseline FVIII/IX levels and the joint bleeding rates.

Methods

Design and setting

The DYNAMO (Dynamic Interplay Between Bleeding Phenotype and Baseline Factor Level in Moderate and Mild Hemophilia A and B) study is an international multicenter cohort study that was performed in 15 hemophilia treatment centers (HTCs) from The Netherlands, United Kingdom, Italy, Austria, and Canada. Detailed information on the participating study sites are provided in Appendix. People were recruited between January 2018 and May 2021. Participation entailed retrospective clinical data collection, a questionnaire, and a blood draw. Before the blood draw, participants underwent a washout period of 3 days (hemophilia A) or 5 days (hemophilia B) for standard half-life products. For extended half-life products, this period was determined by the physician. Institutional review board approval was obtained in all participating centers according to the local and national requirements; written consent was also obtained. The DYNAMO study was registered in advance on ClinicalTrials.gov (#NCT03623295).

Participants

Males with nonsevere hemophilia A and B (baseline FVIII/IX level, 0.02-0.35 IU/mL) aged 12 to 55 years were included. Upper age restrictions were set based on the historical availability of cryoprecipitate and clotting factor concentrates. The range of FVIII/IX levels was set to ensure only persons with true nonsevere hemophilia were investigated without one-off outliers in the FVIII/IX measurements. Exclusion criteria were factors that could potentially influence the bleeding phenotype: history or current presence of an inhibitor, hemophilia B Leyden, other bleeding disorders, participation in studies with an investigational product (eg, nonreplacement therapy, gene therapy), use of anticoagulants, and hemophilia-unrelated comorbidities affecting the musculoskeletal status.

Study outcomes

The study outcomes were parameters reflective of bleeding phenotype, which included age at diagnosis, age at first (joint) bleed and the annual (joint) bleeding rates.

Outcome definitions

The first (joint) bleed was defined as the first (joint) bleed requiring factor concentrates. Annual bleeding rates were defined as the number of all bleeding events treated with any type of treatment per year. The treatment options were factor concentrates, DDAVP, antifibrinolytic agents, red blood cell (RBC) transfusion, or unknown/other.

Annual joint bleeding rates were defined as number of joint bleeds per year treated with clotting factor concentrates, DDAVP, and/or a RBC transfusion.

Joint bleeds were defined according to the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis definition.[1]

Data collection

Retrospective clinical data. Retrospective data on the demographic characteristics, body mass index, laboratory parameters (historically measured baseline FVIII/IX levels, and von Willebrand factor [VWF] activity levels), age at diagnosis, family history of hemophilia (at moment of data collection), current and past treatment regimen, and detailed information on the bleeding phenotype was collected from the medical files through a standardized case report form. For the historical baseline FVIII/IX levels, only levels were collected with no preceding treatment affecting the endogenous baseline levels. Treatment regimen definitions were classified as prophylaxis, intermittent prophylaxis, and on-demand as defined by the Scientific and

Standardization Committee of the International Society of Thrombosis and Hemostasis.[1]

Bleeding data. Data on the age at first (joint) bleed requiring factor concentrates and history of an intracerebral hemorrhage were collected from the medical files over a lifetime. Data on the treated bleeding episodes used for calculation of the bleeding rates were collected from January 2009 onward, or from the moment of registration at the HTC, if registered after 2009 (due to migration or delay in diagnosis). Per bleeding episode, detailed information was collected, including the date, location, cause of bleed (spontaneous; activity-, trauma-, or surgery-related; or due to an underlying disease), and treatment of the bleed (treatment type and duration). Definitions of the cause of bleeds are presented in the supplemental Material. Bleed data were collected from the clinical notes in the medical files. In addition, for those who received home treatment, electronic and paper diaries were consulted. Data quality control was performed for all patient entries based on a predefined form to check for any inconsistencies. Inconsistencies were doubled-checked and adjusted according to the original data from the medical files.

Patient-reported data. All study participants received a questionnaire from which the age at diagnosis (if missing from the medical records) was collected.

Baseline FVIII and FIX levels. Measurement of the FVIII/IX activity levels was assessed centrally and in bulk to reduce inter-laboratory and intra-laboratory variability. FVIII/IX activity levels were measured by using one-stage clotting assays with corresponding FVIII/IX Actin FS reagent (Siemens, Sysmex CS-2500), and the FVIII/IX chromogenic assays were measured with reagents from Siemens and Rossix, respectively. Because an excellent correlation was observed ($r_s = 0.97$; $P < .001$) between the methods, the centrally measured one-stage assay FVIII/IX levels were used for the analysis. For subjects who did not provide a blood sample, baseline FVIII/IX levels were imputed from the most recent FVIII/IX level measured by using the one-stage assay.

Data analysis

Descriptive data are presented as medians and interquartile ranges (IQRs) or as frequencies and percentages for continuous and categorical data, respectively.

Age at first (joint) bleed was assessed by using Kaplan-Meier survival analyses with age (years) as the time scale with the occurrence of the first bleed and first joint bleed as events. Persons were left-censored if they had experienced the event but the age was unknown. Persons were right-censored if at the end of the follow-up period they had not experienced the event.

Bleeding rates were calculated from the number of bleeding episodes divided by the follow-up duration. Annual bleeding rates were calculated for treated bleeds (ABR), treated spontaneous bleeds, treated joint bleeds (AJBR), and treated spontaneous joint bleeds. The follow-up duration was calculated as the duration from January 2009 or moment of registration at the HTC until the moment of data collection minus the loss to follow-up years. Scatterplots of the ABR and AJBR for baseline FVIII/IX levels were presented with a smoothed local polynomial line of fit. Age at first (joint) bleed and ABRs were compared according to hemophilia severity (moderate and mild hemophilia) and vs the following mild hemophilia categories: 0.05 to 0.15 IU/mL, 0.15 to 0.25 IU/mL, and >0.25 IU/mL.

For analysis of the associations between the baseline FVIII/IX levels and the (spontaneous) joint bleeding rates, bleeding events from January 2009 until data collection were modeled as time to event data with age (years) as the time scale with the occurrence of joint bleeds or spontaneous joint bleeds as events during the follow-up duration. Any periods of loss to follow-up during the observation period were interval censored. The associations between baseline FVIII/IX levels and the (spontaneous) joint bleeding rate were assessed by use of a frailty model for recurrent events.[18] The model used was a Cox proportional hazards model with a patient-specific frailty term, which is a random effect that takes unobserved heterogeneity into account within the individual participant. The frailty term follows a log-normal distribution. From this model, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Potential confounding factors were selected based on clinical relevance and were adjusted for. Multiple imputation was used for missing values of VWF activity levels. The analyses were performed by using SPSS version 25 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and R Studio version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). The R packages used are provided in the supplemental Material.

Sensitivity analysis

Sensitivity analyses were performed for historically (most recent and lowest) measured FVIII/IX levels and for patients with measured FVIII/IX levels ≤0.35 IU/mL. The following outcomes were assessed: age at first (joint) bleed, bleeding rates, and the associations between FVIII/IX levels and the (spontaneous) joint bleeding rate.

STROBE checklist

A STROBE checklist is provided in supplemental Table 1.

Results

Patient characteristics

In total, 304 persons with nonsevere hemophilia A and B (70 with moderate hemophilia and 234 with mild hemophilia) were included in the DYNAMO study. Participants had a median age of 38 years (IQR, 25-49 years) and a median baseline FVIII/IX level of 0.12 IU/mL (IQR, 0.05-0.21 IU/mL). Centrally measured baseline FVIII/IX levels were known in 221 persons (73%). The historic most recently measured and centrally measured baseline FVIII/IX levels showed an excellent correlation ($r_s = 0.915$; $P < .001$). Nine included subjects met the initial inclusion criteria for a historic baseline FVIII/IX level ≤0.35 IU/mL but had centrally measured baseline FVIII/IX levels >0.35 IU/mL. People with moderate and mild hemophilia were of similar ages and had a similar distribution of hemophilia type; they differed in the use of prophylaxis with factor concentrates (ie, those with moderate hemophilia were on prophylaxis more often). In addition, none of the participants had received emicizumab treatment. Of the total cohort, 78% had a positive family history for hemophilia. Patient characteristics are presented in Table 1.

Table 1. Patient characteristics

Characteristic	Total cohort (N = 304)	Moderate hemophilia (n = 70)	Mild hemophilia (n = 234)
Age, y	38 (25-49)	39 (26-48)	37 (25-49)
Hemophilia type			
Hemophilia A	248 (82)	55 (79)	193 (82)
Hemophilia B	56 (18)	15 (21)	41 (18)
Baseline factor activity, IU/mL	0.12 (0.05-0.21)	0.03 (0.02-0.04)	0.15 (0.09-0.22)
Blood group			
O	92 (30)	29 (41)	63 (27)
Non-O	104 (34)	18 (26)	86 (37)
Unknown	108 (36)	23 (33)	85 (36)
Body mass index, kg/m^2*	25 (22-28)	26 (23-29)	24 (22-28)
VWF activity level, IU/mL†	0.92 (0.73-1.15)	1.06 (0.75-1.15)	0.90 (0.73-1.15)
Family history of hemophilia			
Positive	236 (78)	58 (83)	178 (76)
Negative	25 (8)	2 (3)	23 (10)
Unknown	43 (14)	10 (14)	33 (14)
Treatment regimen			
Prophylaxis	12 (4)	10 (14)	2 (1)
Intermittent prophylaxis	6 (2)	4 (6)	2 (1)
On-demand	286 (94)	56 (80)	230 (98)
History of prophylaxis			
Yes	28 (9)	23 (33)	5 (2)
No	260 (86)	44 (63)	216 (92)
Unknown	16 (5)	3 (4)	13 (6)

Data are presented as medians with corresponding IQR or as no. (%).
*Unknown in 54 of 304.
†Unknown in 149 of 304 participants.

Age at diagnosis

In 276 (91%) persons, the exact age at diagnosis was known. The median age at diagnosis was 3 years (IQR, 0-12 years). Diagnosis occurred at a younger age in persons with moderate hemophilia (median age, 1 years; IQR, 0-5 years) compared with persons with mild hemophilia (median age, 5 years; IQR, 0-15 years).

Age at first (joint) bleed

In total, 245 (81%) of the persons had experienced at least one bleed treated with clotting factor concentrates, and 156 (51%) had experienced at least one joint bleed treated with clotting factor concentrates. A higher proportion of persons with moderate hemophilia compared with persons with mild hemophilia had experienced a bleed (93% vs 75%) and a joint bleed (78% vs 40%) treated with clotting factor concentrates.

The age at first bleed and first joint bleed was known in 69% (169 of 245) and 69% (107 of 156), respectively, of the persons. In the total cohort, the median age at first bleed and first joint bleed was 8 years (IQR, 3-17 years; range, 0-55 years) and 10 years (IQR, 6-19 years; range, 1-51 years). The median age at first bleed was 3 years (IQR, 1-10 years) in moderate hemophilia and 11 years (IQR, 4-20 years) in mild hemophilia (Figure 1A). The median age at first joint bleed was 7 years (IQR, 4-15 years) in moderate hemophilia and 13 years (IQR, 7-20 years) in mild hemophilia (Figure 2A).

People with higher baseline FVIII/IX levels experienced their first bleeds at an older age (Figures 1B and 2B).

Bleeding rates

Data on bleeding episodes were collected over a median follow-up period of 11 years (IQR, 10-12 years). The median ABR was 0.2 (IQR, 0.1-0.5) for the total cohort and 0.6 (IQR, 0.2-1.4) and 0.2 (IQR, 0.0-0.4) for persons with moderate and mild hemophilia, respectively. In our cohort, the median AJBR was 0.0 (IQR, 0.0-0.2) for the total cohort, and 0.2 (IQR, 0.0-0.4) and 0.0 (IQR, 0.0-0.1) for persons with moderate and mild hemophilia (Table 2; Figure 3). The ABR and AJBR decreased with increasing baseline FVIII/IX levels to a median ABR and AJBR of 0.1 (IQR, 0.0-0.2) and 0.0 (IQR, 0.0-0.0) in persons with FVIII/IX levels >0.25 IU/mL.

In addition, the proportion of subjects with zero (joint) bleeds and zero spontaneous (joint) bleeds was higher in persons with higher baseline FVIII/IX levels (Table 2). Scatterplots for the spontaneous (joint) bleeding rates are presented in supplemental Figure 1. No differences were found between hemophilia A and B (supplemental Table 2).

Types of bleeds

A total of 1523 bleeds were reported during the follow-up period. Joint and muscle bleeds occurred most frequently: 482 (32%) and 423 (28%), respectively (Table 3). The majority of bleeds (67%) were trauma related, activity related, surgery related, or due to an underlying disease. Of all spontaneous bleeds (N = 171), the majority (68%) were experienced by persons with moderate hemophilia. Since birth, intracerebral hemorrhage was reported in 4 persons (1 with moderate hemophilia and 3 with mild hemophilia [with FVIII/IX levels ranging from 0.02 to 0.49 IU/mL]), and all occurred after a provocative event (3 head trauma, 1 hypertensive crisis).

Baseline FVIII/IX levels and the (spontaneous) joint bleeding rate

In 286 persons (94%), the exact age at the experienced joint bleed(s) during the follow-up period was known. Baseline FVIII/IX levels were associated with the (spontaneous) joint bleeding rate (Table 4). The crude HR for the joint bleeding rate was 0.94 (95% CI, 0.93-0.96), and for the spontaneous joint bleeding rate HR was 0.88 (95%, CI 0.82-0.95). The HRs did not change after adjustment for VWF activity level and type of hemophilia. The HR may also be interpreted as a reduction of 6% in joint bleeding rate and 12% in spontaneous joint bleeding rate per 0.01 IU/mL increase in baseline FVIII/IX level. The frequency and nature of bleeds varied considerably within similar baseline FVIII/IX levels. Supplemental Figure 2 presents a box and whisker plot for all bleeding rates.

Sensitivity analyses

All results were similar in the sensitivity analyses (supplemental Tables 3-5).

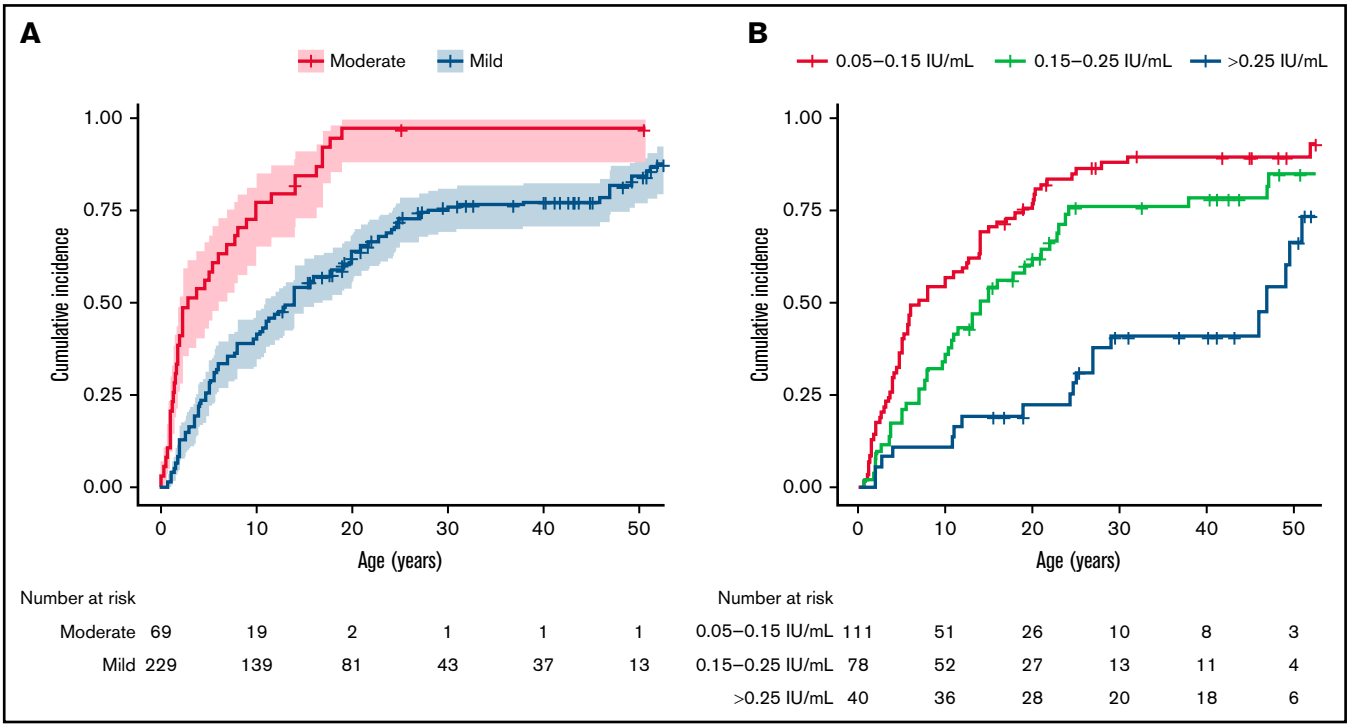

Figure 1. Kaplan-Meier analysis: age at first bleed. Analysis was conducted according to hemophilia severity (A) and categories within mild hemophilia (B). The line represents the cumulative incidence. The shaded area in panel A represents the 95% CI. Crosses represent right-censored patients.

Discussion

In this international multicenter study among persons with nonsevere hemophilia A and B, the age at diagnosis, the first bleed, and the first joint bleed occurred at a later age in those with mild hemophilia compared with those with moderate hemophilia. Overall low bleeding rates were observed. The bleeding rates decreased with increasing baseline FVIII/IX levels, although the bleeding rates varied considerably within similar baseline FVIII/IX levels.

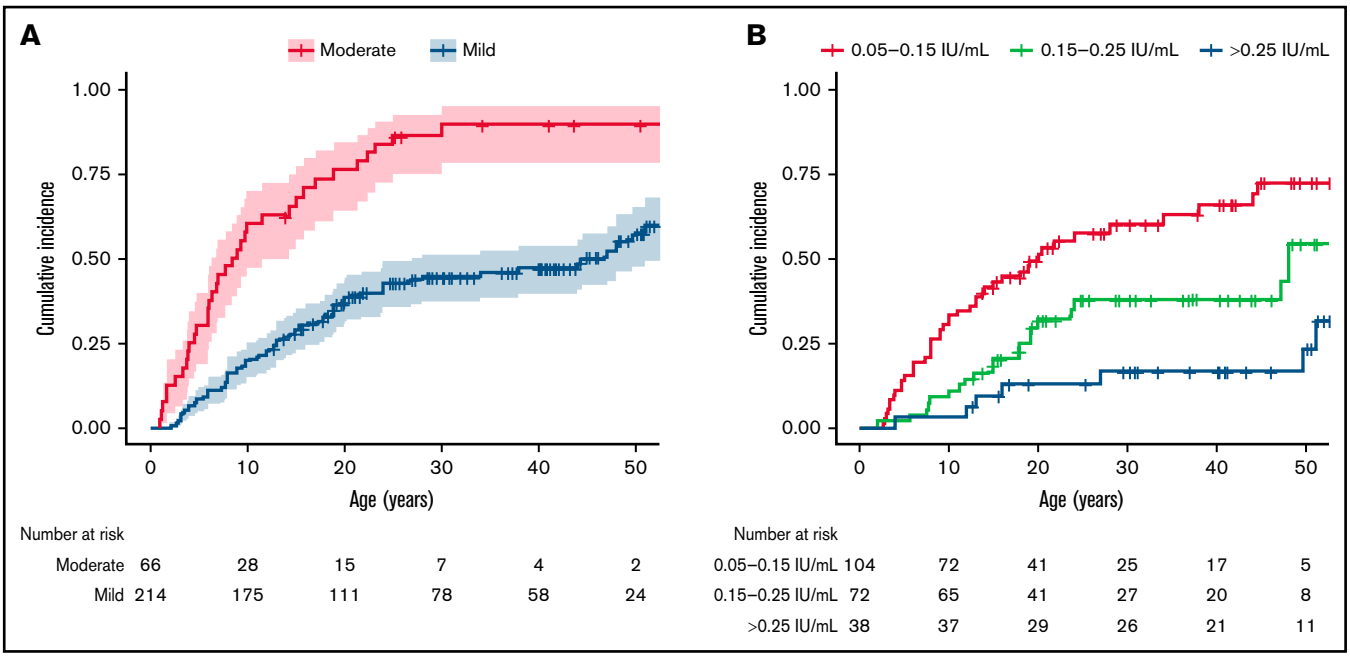

Figure 2. Kaplan-Meier analysis: age at first joint bleed. Analysis was conducted according to hemophilia severity (A) and categories within mild hemophilia (B). The line represents the cumulative incidence. The shaded area in panel A represents the 95% CI. Crosses represent right-censored patients.

Table 2. Bleeding rates and numbers of patients with zero bleeds during the study follow-up period

		Severity				
	Total cohort (N = 304)	Moderate hemophilia (n = 70)	Mild hemophilia (n = 234)	Mild 0.05-0.15 IU/mL (n = 114)	Mild 0.15-0.25 IU/mL (n = 80)	Mild >0.25 IU/mL (n = 40)
Bleeding rates						
ABR, median (IQR)	0.2 (0.1-0.5)	0.6 (0.2-1.4)	0.2 (0.0-0.4)	0.3 (0.1-0.5)	0.2 (0.1-0.4)	0.1 (0-0.2)
Range: minimum-maximum	0-10.9	0-10.9	0-3.1	0-3.1	0-1.8	0-1.9
sABR, median (IQR)	0 (0-0)	0.1 (0-0.2)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Range: minimum-maximum	0-2.4	0-2.4	0-0.5	0-0.5	0-0.5	0-0.2
AJBR, median (IQR)	0 (0-0.2)	0.2 (0-0.4)	0 (0-0.1)	0 (0-0.2)	0 (0-0.1)	0 (0-0)
Range: minimum-maximum	0-4.0	0-4.0	0-1.3	0-1.3	0-0.9	0-0.6
sAJBR, median (IQR)	0 (0-0)	0 (0-0.1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Range: minimum-maximum	0-1.2	0-1.2	0-0.5	0-0.3	0-0.5	0-0
Patients with zero bleeds, no. (%)						
Zero bleeds	68 (22)	7 (10)	61 (26)	26 (23)	18 (23)	17 (43)
Zero spontaneous bleeds	230 (76)	31 (44)	199 (85)	89 (78)	72 (90)	38 (95)
Zero joint bleeds	183 (60)	21 (30)	162 (69)	71 (62)	58 (73)	33 (83)
Zero spontaneous joint bleeds	267 (88)	48 (69)	219 (94)	102 (90)	77 (96)	40 (100)

Percentages have been rounded to whole numbers. sABR, spontaneous annual bleeding rate; sAJBR, spontaneous annual joint bleeding rate.

Age at diagnosis, first bleed, and first joint bleed

Our findings on the age at diagnosis and first (joint) bleeds are in line with previously reported studies.[5,8,10] Two studies reported median ages at first joint bleed of 6.7 years[8] and 5 years[5] in moderate hemophilia and one study a median age of 14.2 years[8] in mild hemophilia. These are comparable to our median ages of 7 and 13 years for persons with moderate and mild hemophilia, respectively. On further categorization of the mild severity in our cohort, an increase in age at first joint bleed was found across increasing baseline FVIII/IX levels.

Bleeding rates in nonsevere hemophilia

In our study cohort, we report low (joint) bleeding rates that are in line with or lower compared with previous reported bleeding rates in

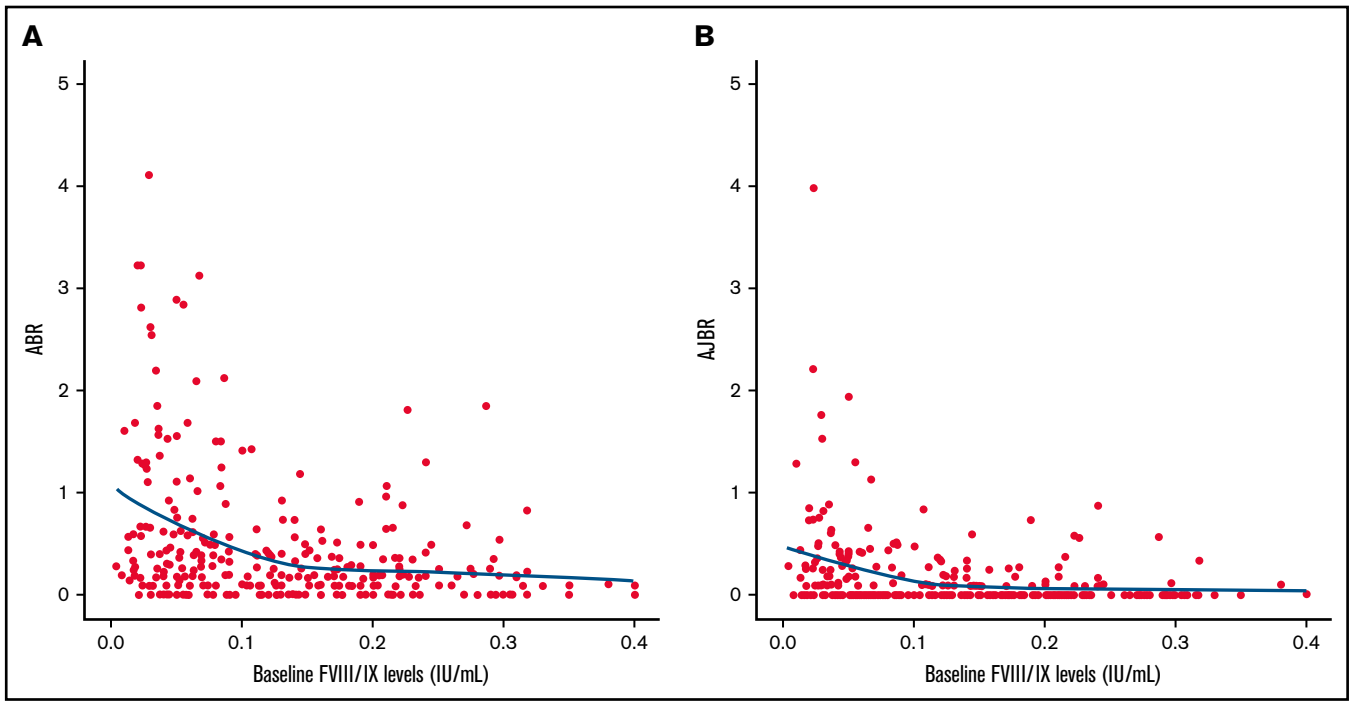

Figure 3. Scatterplots of the ABR and AJBR according to baseline FVIII/IX levels. Analysis was presented for ABR (A) and AJBR (B). A smoothed local polynomial line of fit is shown. Dots represent the individual participants. In the ABR graph, one outlier (ABR = 10.9) was omitted to allow detailed scaling.

Table 3. Location and cause of bleeds for the total population and per hemophilia severity during the follow-up duration

		Severity				
	Total cohort (N = 304)	Moderate hemophilia (n = 70)	Mild hemophilia (n = 234)	Mild 0.05-0.15 IU/mL (n = 114)	Mild 0.15-0.25 IU/mL (n = 80)	Mild >0.25 IU/mL (n = 40)
Total no. of bleeds (subjects with bleeds)	1523 (236)	762 (63)	761 (173)	477 (88)	214 (62)	70 (23)
Location of bleed						
Joint	482 (32)	274 (36)	208 (27)	139 (29)	53 (25)	16 (23)
Muscle	423 (28)	230 (30)	193 (25)	132 (28)	51 (24)	10 (14)
Subcutaneous	345 (23)	155 (20)	190 (25)	114 (24)	53 (25)	23 (33)
Mucosal	114 (7)	30 (4)	84 (11)	42 (9)	31 (14)	11 (16)
Intracranial hemorrhage	3 (0.2)	0 (0)	3 (0.4)	1 (0.2)	2 (0.5)	0 (0)
Other	138 (9)	64 (8)	74 (10)	42 (9)	23 (11)	9 (13)
Unknown	18 (1)	9 (1)	9 (1)	7 (1)	1 (0)	1 (1)
Cause of bleed						
Spontaneous	171 (11)	117 (15)	54 (7)	38 (8)	13 (6)	3 (4)
Nonspontaneous	1020 (67)	404 (53)	616 (81)	351 (79)	177 (83)	58 (83)
Trauma related	768 (50)	288 (38)	480 (63)	300 (63)	136 (64)	44 (63)
Activity related	138 (9)	78 (10)	60 (8)	42 (9)	15 (7)	3 (4)
Unknown	332 (22)	241 (32)	91 (12)	58 (12)	24 (11)	9 (13)

Data are presented as no. (%); percentages are rounded to whole numbers. Mucosal indicates epistaxis and oral cavity bleeds. Non-spontaneous indicates trauma-related, activity-related, surgery-related, tooth extraction, underlying disease, or other provoking factors.

nonsevere hemophilia. The median ABR in our study cohort was 0.6 and 0.2 for subjects with moderate and mild hemophilia, respectively. Previous studies reported median ABRs of 1.0 to 11.0 and median ABRs of 0 to 4 for moderate and mild hemophilia.[7,10,12] Joint bleeding rates were lower within our cohort as we found a median AJBR of 0.2 and 0.0 for moderate and mild hemophilia. In comparison, previous studies reported median AJBRs of 0[5,7,12] and median AJBRs of 0.0-1.0[7,12,13] for moderate and mild hemophilia. An overview of the rates reported in previous literature is found in supplemental Table 6. To our knowledge, only one previous study, performed by Soucie et al,[4] has presented data on the frequency of self-reported joint bleeds in categories of baseline FVIII/IX levels within the standard classification of mild hemophilia. They reported a mean number of 0.33 joint bleeds per 6 months for both categories 0.15 to 0.24 IU/mL and 0.25 to 0.40 IU/mL. For comparability, we calculated a mean number of joint bleeds per 6 months that resulted in 0.04 and 0.02 for these categories in our study, respectively. We present much lower joint bleeding rates, and these differences may be caused by the self-reported nature of joint bleeds.

The duration of follow-up for which bleeds are reported varied widely between the studies (6 months to 14.8 years[4-7,9,12,13]) and may have contributed to this heterogeneity. Furthermore, some bleeding rates were based on self-reported data. Because bleeds occur infrequently, self-reported bleeding rates may come with a degree of recall bias and are open for subjectivity.

In the present DYNAMO study, predefined bleeding data from clinical files were obtained over a relatively long follow-up period and included only bleeds that required treatment. Therefore, the results from our study may provide a robust and conservative assessment, reflected by overall lower bleeding rates.

Baseline FVIII/IX level and the frequency of joint bleeds

The current study shows that baseline FVIII/IX levels are inversely associated with annual joint bleeding rate and that baseline FVIII/IX levels are more strongly associated with the occurrence of spontaneous joint bleeds compared with all joint bleeds. Two studies reported on the association between baseline FVIII/IX levels and the joint bleeding rate in nonsevere hemophilia and focused on self-reported joint bleeds. One study performed a multivariable linear regression, which showed a 0.09 decrease in the 6-month mean number of joint bleeds per baseline FVIII/IX increase of 0.01 IU/mL.[4]

Table 4. Crude and adjusted association between baseline factor levels and the (spontaneous) joint bleeding rate

	Crude estimate	Crude HR (95% CI)	*P*	Adjusted estimate*	Adjusted HR (95% CI)*	*P*
Joint bleeding rate						
Baseline FVIII/IX levels	−0.058	0.94 (0.93-0.96)	<.001	−0.056	0.94 (0.92-0.97)	<.001
Spontaneous joint bleeding rate						
Baseline FVIII/IX levels	−0.122	0.88 (0.83-0.94)	<.001	−0.126	0.88 (0.82-0.95)	<.001

*Adjusted for hemophilia type and VWF activity levels. VWF activity levels were imputed for 132 of 286 participants.

Another study performed a negative binomial model and reported an association between baseline FVIII levels and the self-reported joint bleeding frequency. They reported a rate ratio of 0.82 (95% CI, 0.77-0.86), translating into a reduction of 18% in the joint bleeding frequency per 0.01 IU/mL of the baseline FVIII level.[13] We used a frailty model due to its advantages of taking unobserved heterogeneity of the individual into account with a random effect term and not having to meet the assumption of a constant baseline risk for the occurrence in joint bleeding over time, thus providing a more realistic estimate. For comparability, we also analyzed our data using a negative binomial model and found similar results (supplemental Table 7). The relation between baseline FVIII/IX levels and joint bleeding rate is nonlinear, as reflected by Figure 3 and as described by the HR corresponding with a proportional 6% reduction of the joint bleeding rate per 0.01 IU/mL. Indeed, a study in nonsevere hemophilia B observed a nonlinear relationship between FIX levels and the ABR by different rates of reduction seen at the cutoffs 0.01, 0.05, and 0.10 IU/mL.[19] Unfortunately, explorations within specific FVIII/IX level ranges could not be performed in our study due to the sample size. However, it seems likely that the AJBR follows a similar nonlinear pattern with a steeper reduction in the lower FVIII/IX values.

Strengths and limitations

The study had a multicenter study design, and we collected detailed information on physician-reported bleeding episodes over a relatively long period of observation (±11 years), yielding robust estimates of the bleeding rates compared with shorter follow-up periods. However, these estimates reflected the last decade and may therefore not be representative of lifetime bleeding. Central FVIII/IX activity level measurements minimized intra-laboratory and inter-laboratory variability. Imputation from the historic measurements for missing central measurements was possible as the correlation between the historically and centrally measured levels was excellent. Another strength of our study is that we restricted several outcomes by the type of treatment used. For the age of first (joint) bleed, we only reported bleeds treated with factor concentrates; for the joint bleeding rate, only those joint bleeds treated with factor concentrate, DDAVP, or RBC transfusions were taken into account. We therefore ensured that true bleeds were captured. Potential limitations include underreporting or underdocumentation of bleeding episodes in the medical files. However, because we assessed treated bleeds only, and persons with nonsevere hemophilia need to visit the HTC for treatment, underreporting may be limited. Another potential limitation, which may lead to underestimation of bleeds, is missing data on bleeds treated with home treatment (factor concentrates or DDAVP). However, the number of persons who were able to self-infuse with factor concentrates was low, as only 6% received (intermittent) prophylaxis and in these persons bleed data were also collected from paper or electronic diaries. We included persons with (intermittent) prophylaxis use, as exclusion would introduce a selection bias toward a milder phenotype. This approach may lead to an underestimation of the bleeding rates and strength of the association between factor levels and joint bleeding rate. Lastly, because subjects with moderate hemophilia with the lowest FVIII/IX level of 0.01 to 0.02 IU/mL were not included, this might have led to lower bleeding rates in our nonsevere hemophilia population.

Clinical implications and future research

In the current cohort, persons with nonsevere hemophilia experienced a low bleeding frequency; the majority were joint and muscle bleeds. As we know from persons with severe hemophilia, persons with a limited number of joint bleeds may still develop joint abnormalities.[20] It is very important therefore to educate persons with nonsevere hemophilia on the prevention and early recognition of joint bleeds. In addition to baseline FVIII/IX levels, other determinants (eg, age, physical activity, prothrombotic mutations) could play a role on the bleeding phenotype, and research is needed to assess the associations with these determinants. Persons with moderate hemophilia have higher bleeding rates compared with those with mild hemophilia. For persons with moderate hemophilia with a more severe phenotype, prophylaxis should be considered as recommended.[21]

For persons with hemophilia treated with emicizumab, the phenotype is converted to a mild phenotype. Data from our study might provide insights regarding the expectations of bleeding outcomes in severe hemophilia or nonsevere hemophilia treated with emicizumab. The ABR reported in our cohort is comparable to the ABR of previous study populations on emicizumab.[22,23]

Persons with severe hemophilia who received gene therapy exhibit endogenous factor levels comparable with persons with nonsevere hemophilia. A previous study modeled data from persons with severe hemophilia treated with tertiary prophylaxis to predict the factor levels at which zero (joint) bleeds occur.[24] To achieve zero bleeds, zero joint bleeds, and zero spontaneous bleeds in all persons, it was predicted that the estimated trough FVIII levels would need to be 0.60 IU/mL, 0.60 IU/mL, and 0.40 IU/mL, respectively. Our results are in line with this prediction model, as only persons with FVIII/IX levels >0.25 IU/mL exhibited 100% zero spontaneous joint bleeds in our population. Even though we can appreciate low to zero (spontaneous) AJBRs, inter-individual variation in the bleeding frequency is still observed. This challenges the drawing of definite conclusions based on our results, in respect to what target level should be sought. In addition, preferable target levels will depend on the desired outcome in which several other factors (eg, quality of life, treatment costs, arthropathy) may be of influence other than bleed prevention.

In conclusion, our study showed that despite low bleeding frequencies, more than one-half of the persons with nonsevere hemophilia had experienced a joint bleed since birth. The joint bleeding rate was inversely associated with the baseline FVIII/IX level.

Acknowledgments

The authors thank all the participants of the DYNAMO study and thank the participating HTC research nurses. They especially thank Bianca Bakker and Caroline van der Tol-Klopper for their work on the execution of the central measurements of the baseline FVIII/IX activity levels.

This work was funded by a grant from Novo Nordisk and supported by the Parelsnoer clinical biobank Hemophilia at the Health-RI (funded by the Ministry of Health, Welfare and Sport). The funding sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

Authorship

Contribution: F.R.K. and A.-F.Z. collected, cleaned, analyzed and interpreted the data; F.R.K. wrote the manuscript; K.F. and S.C.G. designed the study; C.N.B., E.A.M.B., G.C., M.H.C., P.W.C., C.H., B.L.-v.G., F.W.G.L., C.M., K.M., I.P., S.S., M.C., K.F., and S.C.G. collected data or supervised data collection; M.H. provided statistical advice; and all authors reviewed and approved the final version of the manuscript.

A complete list of the members of the DYNAMO study group appears in the Appendix.

Conflict-of-interest disclosure: G.C. is a speaker at company symposia during scientific meetings for Bayer, Grifols, LFB, Roche, Sobi, Novo Nordisk, Werfen, and Kedrion; has received research funding directly to his institution from CSL Behring, Pfizer, and Sobi; and, during the last 2 years, has participated in advisory boards of Bayer, Takeda, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, SOBI, and UniQure. M.H.C. has received investigator-initiated research and travel grants as well as speaker fees over the years from the Netherlands Organisation for Scientific Research, the Netherlands Organization for Health Research and Development, the Dutch "Innovatiefonds Zorgverzekeraars," Baxter/Baxalta/Shire/Takeda, Pfizer, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis, and Nordic Pharma; and has served as a steering board member for Roche, Bayer and Novartis (all grants, awards, and fees go to the Erasmus MC). P.W.C. had received research support from CSL Behring; and consultancy fees from CSL Behring, Novo Nordisk, Sobi, and Roche. F.W.G.L. received unrestricted research grants from CSL Behring, Shire/Takeda, Sobi, and uniQure; is a consultant for CSL Behring, Shire/Takeda, BioMarin, and uniQure, of which the fees go to the University; and was a Data and Safety Monitoring Board member of a study sponsored by Roche. C.M. reports consultancy or speaker for Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Roche, and Takeda; has received travel support from Bayer, Biotest, CSL Behring, and Novo Nordisk; and his institution has received research support from Bayer, Baxalta/Shire/Takeda, Biotest, CSL Behring, Novo Nordisk, and Sobi. K.M. received speaker fees from Alexion, Bayer, and CSL Behring; fees for participation in trial steering committee for Bayer; consulting fees from UniQure; and fees for participation in data monitoring and end point adjudication committee for Octapharma (all fees paid to her institution). I.P. has received honoraria for lectures and/or advisory boards from Bayer, Biotest, CSL Behring, Sobi, Roche, Takeda, Pfizer, and Novo Nordisk; and her institution has received research grants from CSL Behring, Novo Nordisk, Sobi, and Takeda. M.C. has received financial support for research from Bayer, CSL Behring, Daiichi Sankyo, Portola/Alexion, Roche, Sanquin Blood Supply, and UniQure; and consultancy or lecturing fees from Bayer, CSL Behring, Medcon International, MEDtalks, Novo Nordisk, Pfizer, and Sobi. The institution of K.F. has received unrestricted research grants from Sobi, Pfizer, CSL Behring, and Novo Nordisk; and her institution received consultancy fees from Grifols, Takeda, Novo Nordisk, and Roche. S.C.G. has received an unrestricted research grant from Sobi. S.S. has received conference support, educational speaker fees, and/or advisory board fees from Pfizer, Bayer, Shire, Takeda, Sobi, Roche, and CSL Behring. The remaining authors declare no competing financial interests.

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