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Developments in modern hemophilia care

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Chapter 2

Health and treatment outcomes of patients with hemophilia in the Netherlands, 1972-2019

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Summary

Introduction

We conducted six cross-sectional nationwide questionnaire studies among all patients with hemophilia in the Netherlands from 1972 until 2019 to assess how health outcomes have changed, with a special focus on patients > 50 years of age.

Methods

Data were collected on patient characteristics, treatment, (joint) bleeding, joint impairment, hospitalizations, human immunodeficiency virus and hepatitis C infections, and general health status (RAND-36).

Results

In 2019, 1009 patients participated of whom 48% had mild, 15% moderate and 37% severe hemophilia. From 1972 to 2019, the use of prophylaxis among patients with severe hemophilia increased from 30% to 89%. Their median annual bleeding rate decreased from 25 to 2 bleeds. Patients with severe hemophilia aged < 16 years reported joint impairment less often over time, but in those aged > 40 years joint status did not improve. In 2019, 5% of all 1009 patients were positive for the human immunodeficiency virus. The proportion of patients with an active hepatitis C infection drastically decreased from 45% in 2001 to 2% in 2019 due to new anti-hepatitis C treatment options. Twenty-five percent had significant liver fibrosis even after successful therapy. Compared with the general male population, patients aged > 50 years reported much lower scores on the RAND-36, especially on physical functioning.

Discussion & Conclusion

Our study shows that increased use of prophylactic treatment and effective hepatitis C treatment have improved joint health and nearly eradicated hepatitis C infection in patients with hemophilia in the Netherlands. However, patients still suffer from hemophilia-related complications, especially patients aged > 50 years.

Introduction

Hemophilia is a hereditary X-linked bleeding disorder, characterized by a lack of functional coagulation factor VIII (hemophilia A) or IX (hemophilia B). Patients with severe hemophilia suffer from spontaneous bleeds in joints/muscles, leading to disability. Patients with moderate/mild hemophilia mainly develop bleeds after trauma or surgery.¹

Effective treatment was lacking before the 1970s, and most patients with severe hemophilia lived with severe physical disabilities, and only survived until childhood or early adulthood due to bleeding in vital organs (with intracranial bleeds being especially common).^{2, 3} The introduction of cryoprecipitate and subsequently coagulation factor concentrates greatly improved survival.

Transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) through contaminated coagulation factor products during the 1980s led to many deaths.⁴ New viral inactivation techniques were introduced from 1985 onwards that eliminated the contamination risk after 1990. During this time, the first treatment for HIV and HCV became widely available³. Also, the first national consensus-based treatment guidelines were established.⁵

Around the 2000s, hemophilia treatment in the Netherlands was gradually centralized. From 2013 onwards, a standard set of quality criteria was introduced for comprehensive hemophilia treatment centers.⁶ Additionally, the national consensus-based treatment guidelines from 1987 were revised in 2009 to harmonize treatment practices.⁷ Lastly, treatment with direct-acting antivirals became available for all hepatitis C infected patients in 2014.⁸

Along with these developments, the life expectancy of patients with hemophilia is increasing.⁹ Elderly patients are now increasingly experiencing age-related diseases which require a more tailored approach. Additionally, as elderly patients age, the effect of bleeding-induced arthropathy on daily life may worsen despite adequate treatment.

From 1972 until 2019, six nation-wide surveys have been performed to assess the health status of the Dutch hemophilia population.¹⁰⁻¹² In this study we evaluated health outcomes of patients during the past five decades of hemophilia treatment,

with a special focus on the health status of aging patients with hemophilia > 50 years of age.

Methods

Study design

In 2019, a cross-sectional study was performed among all patients with congenital hemophilia in the Netherlands. The current study was preceded by 5 surveys in 1972, 1978, 1985, 1992 and 2001.¹⁰⁻¹² All patients registered at one of the six national hemophilia treatment centers were invited to participate. The first 5 surveys consisted of a questionnaire. The current study consisted of a questionnaire, as well as clinical data collection from medical records and sampling of blood and urine. For the current analysis, only data derived from the questionnaires and medical records were used. From June 2018 until July 2019, questionnaires were sent to patients by e-mail or regular mail, followed by 2 reminders. The study was approved in 2018 by the Medical Ethics committee at Leiden University Medical Center. Informed consent was obtained from all patients.

Measurements

Of the 2019 study participants, information on age, severity of hemophilia, HIV status, HCV status and inhibitor status was obtained from electronic health records. When electronic health record data were missing, answers from the questionnaire were used if available. In case of discrepancies between the electronic health records and questionnaire, data from the electronic health records were used. All other 2019 data were obtained from the questionnaire only.

The following patient characteristics were collected; age, type and severity of hemophilia, and family history of hemophilia. Hemophilia severity was categorized as severe (≤ 0.01 IU/mL), moderate (0.01-0.05 IU/mL) or mild (> 0.05 – 0.40 IU/mL). The following treatment characteristics were collected: treatment modality (prophylactic treatment or on-demand treatment), the annual coagulation factor consumption and the type of coagulation factor product.

The questionnaires contained the following self-reported outcomes: annual (joint) bleeding rate, level of joint impairment, orthopedic interventions, hospital admission rate and duration of stay, HIV status, HCV status, age-related co-morbidities and general health status.

Definition of outcome variables

Prophylaxis was defined as periodic infusion of coagulation factor products to prevent bleeding. Annual coagulation factor consumption was defined as the total number of units of coagulation factor used divided by bodyweight per year (IU/kg/year). The annual (joint) bleeding rate was defined as the number of self-reported (joint) bleeds in the preceding 12 months. In children, the annual (joint) bleeding rate was based on the results of the last 3 months, which was then multiplied by 4.

Joint impairment was calculated using a point system; no joint impairment (0 points), mild impairment (no daily problems, 1 point), moderate impairment (daily problems, 2 points) or severe impairment (no movement in joint, 3 points). This information was reported for the knee, elbow, ankle and wrist joints. Hospital admission was defined as having been admitted to the hospital in the preceding 12 months for at least 1 day (day admissions were included). Hospital duration was calculated as the number of nights spent in the hospital (day admissions were excluded). Age-related co-morbidities were defined as being treated by a medical specialist or a general practitioner for a set of age-related conditions (see Supplemental Table 1 for full list).

Inhibitor status was based on the Bethesda assay, using each center's own cut-off level, which varied from > 0.6 BU to > 1.0 BU. A current inhibitor was defined as being currently inhibitor-positive. A past inhibitor was defined as having been inhibitor-positive in the past but currently inhibitor-negative. HIV status was reported for patients treated with coagulation factor before 1985 and was defined as positive if the patient had a confirmed clinical diagnosis of HIV. HCV status was reported for patients treated with coagulation factor before 1992. Patients were classified as having a "past infection" when they had a confirmed clinical diagnosis of HCV infection in the past and "current infection" if they were currently HCV-RNA positive.

General health status was assessed in adults using the RAND 36-Item Health Survey (RAND-36).¹³ The RAND-36 is a 36-item questionnaire that measures perceived health status across 8 different domains: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, energy/fatigue, bodily pain, and general health perceptions. Domain scores were calculated when a patient had completed at least half of the items of a domain according to RAND-36 scoring instructions.¹⁴ Domain scores were converted to a 100-point scale. Based on a review of the literature, a difference of 4 points on any RAND-36 domain between groups was regarded as clin-

ically significant.¹⁵ Scores were compared with RAND-36 scores of the Dutch general male population.¹⁶

Statistical analysis

Descriptive statistics were reported as mean/SD, median/IQR, or as proportions. Treatment characteristics and health outcomes were summarized and compared over all 6 surveys stratified by age or severity of hemophilia. Patients with missing data for a given analysis were excluded.

To measure the response rate, the total number of unique patients registered at each hemophilia treatment center was retrieved. This was done by anonymizing and then merging patient data of all registered patients. A trusted third party (ZorgTTP, Houten, the Netherlands) was responsible for the process of anonymization and merging of data.

Data sharing statement

For original data, please contact S.C.Gouw@lumc.nl.

Results

Response and patient characteristics

From 1972-2019 the number of participants in the questionnaire varied from 447 to 1009 patients. (Table 1) In the latest study 2192 patients were invited to participate of whom 33% had severe hemophilia, 13% had moderate hemophilia and 54% had mild hemophilia (Table 2). Of these, 1312 patients participated in at least one part of the study (by filling in the questionnaire, consenting to the use of their clinical data, or both). 1009 patients completed the questionnaire (a response rate of 46%). Of these 1009, 729 patients also consented to the use of their clinical data. Response rates of the previous questionnaires were 84% in 1972, 70% in 1978, 81% in 1985, 78% in 1992, 68% in 2001.¹⁰⁻¹²

Table 1 shows the patient characteristics of each survey. Of the 1009 patients, 378 (37%) had severe hemophilia, 149 (15%) moderate hemophilia and 482 (48%) mild hemophilia. The mean age of participants increased from 21 years in 1972 to 40 years in 2019. During this period the mean age of the Dutch male population increased from 32 years to a similar mean age of 41 years.¹⁷

Table 1. Characteristics of participants in the Hemophilia in the Netherlands studies obtained from questionnaire data.

	1972 (N = 447)	1978 (N = 560)	1985 (N = 935)	1992 (N = 980)	2001 (N = 1066)	2019 (N = 1009)
Age in years*						
Mean (range)	21 (0-47)	23 (0-70)	27 (0-85)	30 (0-84)	35 (0-90)	40 (0-88)
Severity of hemophilia (%)						
Severe	159 (36)	245 (44)	384 (41)	387 (39)	420 (39)	378 (37)
Moderate	83 (19)	106 (19)	175 (19)	173 (18)	176 (17)	149 (15)
Mild	172 (38)	138 (25)	376 (40)	420 (43)	470 (44)	482 (48)
Type of hemophilia (%)†						
Hemophilia A	377 (84)	481 (86)	801 (86)	853 (87)	925 (87)	867 (87)
Hemophilia B	70 (16)	79 (14)	134 (14)	127 (13)	141 (13)	129 (13)
Family history of hemophilia (%)‡						
Negative	112 (25)	128 (23)	237 (25)	195 (20)	246 (23)	168 (18)
Positive	335 (75)	432 (77)	698 (75)	785 (80)	820 (77)	753 (82)
HIV infection (%)§						
Current infection	-	-	36 (4)	55 (8)	29 (5)	22/412 (5)¶
Hepatitis C infection (%)**						
Current infection	-	-	-	-	344 (45)	8/412 (2)††
Past infection	-	-	-	-	97 (13)	226/412 (55)††
Inhibitory antibodies (%)‡‡						
Ever inhibitors	-	-	31/384 (8)	51/388 (13)	52/420 (13)	66/361 (19)§§
Current inhibitors	-	-	19 (5)	29 (7)	15 (4)	6/361 (2)§§
Past inhibitors	-	-	12 (3)	22 (6)	37 (9)	60/361 (17)§§

* Age was unknown for 8 patients.

† Type of hemophilia was unknown for 13 patients.

‡ Family history of hemophilia was unknown for 88 patients.

§ Reported for patients treated with coagulation factor before 1985.

¶ HIV status was unknown for 4 patients.

** Reported for patients treated with coagulation factor before 1992.

†† HCV status was unknown for 84 patients.

‡‡ Reported for patients with severe hemophilia.

§§ Inhibitor status was unknown for 17 patients.

Treatment characteristics

From 1972-2019, the proportion of patients with severe hemophilia receiving prophylactic treatment increased from 30% to 89%. In 2019, almost all (98%) patients aged 0-16 years were on prophylaxis. (Table 3, Fig 1a) Also, 25% of patients aged 0-16 years with moderate hemophilia were on prophylactic treatment. As expected only 3% of patients aged 0-16 years with mild hemophilia were treated with prophylaxis. The median age at initiation of prophylaxis in patients with severe hemophilia decreased from 8 years (range: 0-15) in 1978 to 3 years (range: 0-79) in 2019. (Table 3) Median annual coagulation factor consumption (in IU/kg) for patients with severe hemophilia on prophylaxis increased from 886 IU/kg (IQR: 632-1259) in the 1970s¹⁸ to 2535 IU/kg (IQR: 1885-3614) in 2019.

In 2019, only 5 out of 827 patients (1%) were treated with a plasma-derived coagulation factor product. In patients with hemophilia A, 48 out of 724 (7%) were treated with extended half-life FVIII products. Among patients with hemophilia B, 30 out of 103 (29%) used extended half-life FIX products. Six out of 724 patients with hemophilia A (1%) were treated with emicizumab, three of which were patients with an active inhibitor.

Treatment outcomes, 1972-2019

Annual bleeding rates

Since 1972, the median annual bleeding rate (ABR) of patients with severe hemophilia decreased from 25 to 2 bleeds. (Fig 1b) In 2019, the highest ABR (4 bleeds) was reported by patients in the youngest age group aged 0-16 years (Table 3 and Fig 1b). The same ABR was reported in 0-16 year-olds with moderate and mild hemophilia. The vast majority were nosebleeds (55%). For comparison, only 6% of bleeds were classified as nosebleeds in patients > 25 years.

In patients with severe hemophilia on prophylaxis, 125 out of 285 patients (44%, 95%CI: 38-50%) had at least one joint bleed in the past year. (Table 4) The median annual joint bleeding rate (AJBR) in 2019 for patients with severe hemophilia < 25 years was 0 (n 118, IQR 0-0), in both patients treated on-demand (n 4) or on prophylactic treatment (n 113) (Table 4). In patients with mild hemophilia (n 417) and moderate hemophilia (n 128), the AJBR in 2019 was 0 (IQR 0-0) for all age groups (Table 4). In patients with severe hemophilia with an active inhibitor the AJBR was 6 (n 5, IQR 0-12) vs. 0 (n 52, IQR 0-3) in patients with a previously cleared inhibitor and 0 (n 259, IQR 0-3) in non-inhibitor patients (Table 4). The median AJBR was the same

(zero) for both patients with severe hemophilia A and patients with severe hemophilia B. (Supplemental Table 6).

Table 2. Comparison of age distribution and severity hemophilia of the 2019 HiN-6 study with the Dutch hemophilia population.

	Dutch hemophilia population* (N = 2192)	2019 HiN-6 study (N = 1009)
Age category (%)		
0-17 years	446 (21)	196 (20)
18-25 years	254 (12)	108 (11)
26 years or older	1436 (67)	697 (70)
Missing	56 [†]	8
Severity of hemophilia (%)		
Severe	704 (33)	378 (37)
Moderate	282 (13)	149 (15)
Mild	1148 (54)	482 (48)
Missing	58 [†]	0

* All patients who were registered at a hemophilia treatment center in the Netherlands. [†]56 patients from one treatment center had missing data for age and severity of hemophilia. Furthermore, two patients from another treatment center had evaluable data for age but not for severity of hemophilia.

Joint impairment

Between 1972-2019, there was an increase in patients with severe hemophilia with no joint impairment in the ankles, elbows, and knees. (Fig 1c, Supplemental Table 2) The proportion of patients reporting no joint impairment changed between 1972-2019 from 40% to 95% in patients aged 0-16 years, from 5% to 70% in patients aged 17-25 years old and from 3% to 37% in patients 25-40 years old. In patients > 40 years, there were none without joint impairment in 1972, and this percentage did not improve much, only 5% in 2019. In patients with moderate hemophilia, a similar, but less pronounced trend was seen over time (Supplemental Table 2). In 2019, the proportion of patients with mild hemophilia with an absence of joint impairment ranged from 98% among the 0-16 year olds to 87% in the 40+ group (Supplemental Table 2). Patients with severe hemophilia B had similar joint impairment and instances of joint replacement surgery as patients with severe hemophilia A. (Supplemental Table 6).

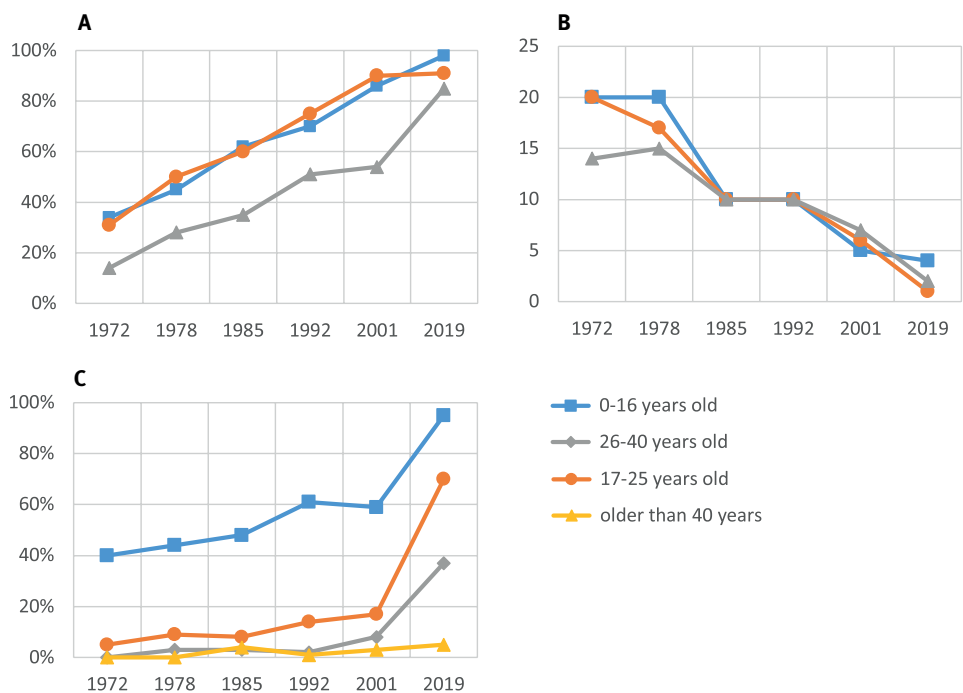
Figure 1. Health- and treatment outcomes over time.

Legend:

Graph **A** shows the proportion of patients with severe hemophilia on prophylactic treatment, from 1972 to 2019, stratified by age.

Graph **B** shows the median annual bleeding rate of patients with severe hemophilia, from 1972 to 2019, stratified by age.

Graph **C** shows the self-reported absence of joint impairment in ankles, knees and elbows in patients with severe hemophilia, from 1972 to 2019, stratified by age.



Hospital admissions

The proportion of patients with severe hemophilia requiring hospitalization in the previous year decreased from 51% in 1972 to 22% in 2019. (Table 3) The hospital admission rate in patients with mild hemophilia (25%) and severe hemophilia (22%) was similar. (Table 3) However, hospitalization for a non-hemophilia-related problem was more common in patients with mild hemophilia (29%) than in patients with severe hemophilia (17%).

Inhibitor development, HIV status and HCV status

The percentage of patients with severe hemophilia A or B with a past or current inhibitor increased from 8% in 1985 to 19% in 2019. (Table 1) In 2019, 21% and 7% of patients with severe and mild hemophilia A respectively reported having a past or current inhibitor.

Table 3. Prophylaxis usage, annual bleeding rates and hospital admission.

	1972 (N = 447)	1978 (N = 560)	1985 (N = 935)	1992 (N = 980)	2001 (N = 1066)	2019 (N = 1009)
Severe hemophilia	159	245	384	387	420	378
Patients on prophylaxis (%)						
Children, 0-16y	22/65 (34)	41/91 (45)	69/111 (62)	64/92 (70)	112/130 (86)	93/95 (98)
Young adults, 17-25y	12/39 (31)	27/54 (50)	43/72 (60)	NR	38/42 (90)	42/46 (91)
Adults, older than 25y	8/57 (14)	28/99 (28)	71/201 (35)	119/232 (51)	134/248 (54)	193/228 (85)
Median age at first prophylaxis, years (range)	NR	8 (0-15)	5 (1-15)	NR	2 (0 -11)	3 (0-79)
Median ABR* by age (range, IQR [†])						
Children, 0-16y	20 (0-98)	20 (0-70)	10 (0-65)	10 (0-98)	5 (0-51)	4 (0-228, 0-12)
Young adults, 17-25y	20 (0-98)	17 (0-100)	10 (0-90)	10 (0-98)	6 (0-75)	1 (0-12, 0-2)
Adults, older than 25y	14 (0-97)	15 (0-100)	10 (0-90)	10 (0-82)	7 (0-75)	2 (0-100, 0-6)
Hospital admissions						
Hemophilia patients (%)	51	38	25	22	22	73/330 (22)
Median duration, (range)	28 (2-252)	20 (1-180)	11 (1-100)	5 (1-330)	7 (1-89)	7 (1-125)
Moderate hemophilia	23	106	175	173	176	149
Patients on prophylaxis (%)						
Children, 0-16y	6/41 (15)	9/41 (22)	7/59 (12)	7/41 (17)	7/46 (15)	6/24 (25)
Young adults, 17-25y	4/14 (29)	7/26 (27)	1/19 (5)	NR	4/23 (17)	4/19 (21)
Adults, older than 25y	1/27 (4)	4/39 (10)	10/97 (10)	11/98 (11)	10/107 (9)	14/104 (13)
Median ABR* by age (range, IQR [†])						
Children, 0-16y	4 (0-40)	10 (0-104)	3 (0-66)	7 (0-33)	2 (0-57)	4 (0-32, 0-8)
Adults, older than 17y	4 (0-50)	5 (0-100)	2 (0-40)	3 (0-52)	1 (0-71)	1 (0-100, 0-2)

Hospital admissions						
Hemophilia patients (%)	51	27	23	22	15	21/136 (15)
Median duration (range)	17 (2-180)	10 (1-50)	7 (1-50)	5 (1-72)	6 (1-31)	6 (1-120)
Mild hemophilia	NR	NR	NR	NR	NR	482
Patients on prophylaxis (%)						
Children, 0-16y	NR	NR	NR	NR	NR	2/68 (3)
Young adults, 17-25y	NR	NR	NR	NR	NR	1/43 (2)
Adults, older than 25y	NR	NR	NR	NR	NR	7/346 (2)
Median ABR* by age (range, IQR [†])						
Children, 0-16y	NR	NR	NR	NR	NR	4 (0-100, 0-14)
Young adults, 17-25y	NR	NR	NR	NR	NR	0 (0-88, 0-1)
Adults, older than 25y	NR	NR	NR	NR	NR	0 (0-40, 0-0.5)
Hospital admissions						
Hemophilia patients (%)	NR	NR	NR	NR	NR	103/415 (25)
Median duration (range)	NR	NR	NR	NR	NR	5 (1-175)

* Annual bleeding rate. [†]IQR: Interquartile range. NR: Not reported.

HIV was first reported in 1985 when 4% of patients were HIV infected. Among still-living patients treated with coagulation factor before 1985, the prevalence of HIV increased to 8% in 1992 and afterwards decreased to 5% in 2019. Currently, out of 412 patients that were treated with coagulation factor before 1985, 22 are HIV-positive. (Table 1) HCV infections among patients treated with coagulation factor before 1992 were common in the year 2001 with 45% of patients reporting to have an active HCV infection. In 2019, 8 (2%) patients had an active HCV infection. (Table 1)

Self-reported general health status

There were no clinically relevant differences in reported general health status measured using the RAND-36 between the 2001 cohort and the 2019 cohort. (Table 5) Compared with the Dutch general population, the 2019 cohort scored lower on all domains, except for emotional well-being (2019 cohort score: 77.1, general population score: 77.9) and role limitations due to personal or emotional problems (2019 cohort score: 85.0, general population score: 85.8). (Table 5) Patients under 50 years

of age had scores similar to the general population, except for the domain of energy/fatigue (2019 cohort < 50 score: 65.6, general population score: 71.6).

Current health status of patients older than 50 years

Bleeding rate and joint impairment

Only 4% of older patients with severe hemophilia had no joint impairment in the ankles, elbows and/or knees vs. 75% of patients with non-severe hemophilia. (Table 6) In addition, 75% of older patients with severe hemophilia had undergone orthopedic surgery and the mean number of life-time orthopedic interventions was 1.9. (Table 6) Twenty percent of older patients had joint impairment in their wrists, this number increased to 48% in patients with some knee impairment.

HCV status

Among older patients who were treated with coagulation factor products before 1992, 62% were currently or previously infected with HCV. Among patients with severe hemophilia, 97% were currently or previously infected (Table 6). Overall, only 2% of older patients were currently HCV-positive (Table 6).

Eighty-five percent of older patients had received antiviral treatment in the past. Half of these were treated with older treatment methods (interferon, peg-interferon and/or ribavirin), while the other half were treated with direct-acting antiviral drugs (Table 6). Among patients who were or had been HCV-positive, 25% had clinically significant liver fibrosis or cirrhosis. (Table 6)

Self-reported general health status

Patients > 50 years scored substantially lower on the RAND-36 than the Dutch general population and younger patients with hemophilia. (Table 5) Patients with severe hemophilia reported even more pronounced limitations, especially on the domains of physical functioning and role limitations due to physical health problems (Table 5). Emotional well-being scores of older patients were similar to those of the general population (Table 5).

Table 4. Self-reported annualized joint bleeding rates in 2019.

	N of patients	Median annual joint bleeding rate (range, IQR*)
Severe hemophilia	378 [†]	
Children, 0-16y	78	0 (0-12, 0-0)
Young adults, 17-25y	40	0 (0-6, 0-1)
Adults, older than 25y	204	2 (0-70, 0-4)
Patients on prophylactic treatment		
Children, 0-16y	77	0 (0-12, 0-0)
Young adults, 17-25y	36	0 (0-6, 0-1)
Adults, older than 25y	172	2 (0-70, 0-4)
Patients on prophylactic treatment with at least one joint bleed		
0 bleeds	160	NA
≥ 1 bleeds	125	NA
Patients treated on-demand		
Children, 0-16y	1	0 (0-0, 0-0)
Young adults, 17-25y	3	0 (0-0, 0-0)
Adults, older than 25y	32	1.5 (0-50, 0-6)
Inhibitory antibodies		
Never inhibitor-positive	259	0 (0-50, 0-3)
Currently inhibitor-positive	5	6 (0-15, 0-12)
Previously inhibitor-positive	52	0 (0-70, 0-3)
Moderate hemophilia	149 [‡]	
Children, 0-16y	23	0 (0-4, 0-0)
Adults, older than 17y	105	0 (0-20, 0-1)
Mild hemophilia	482 [§]	
Children, 0-16y	59	0 (0-0, 0-0)
Young adults, 17-25y	40	0 (0-4, 0-0)
Adults, older than 25y	313	0 (0-25, 0-0)

* IQR: Interquartile range.

[†] Annualized joint bleeding rate was unknown for 56 patients with severe hemophilia.

[‡] Annualized joint bleeding rate was unknown for 21 patients with moderate hemophilia.

[§] Annualized joint bleeding rate was unknown for 65 patients with mild hemophilia. NA: not applicable.

Age-related co-morbidities

Among 367 patients > 50 years, the most common age-related co-morbidities were hypertension (37%), hypercholesterolemia (17%), malignancies (13%) and type 2 diabetes (10%). (see Supplemental Table 1) The prevalence of hypertension was even higher in patients with severe hemophilia (47%).

Table 5. General health status of patients in HiN-5 cohort, overall HiN-6 cohort, HiN-6 cohort > 50 years and Dutch general male population.

Domains of the RAND 36-Item Health Survey	HiN-5 (2001)	HiN-6 (2019)	HiN-6 (≤ 50)	HiN-6 (> 50)	HiN-6 (> 50) severe hemophilia	HiN-6 (> 50) non-severe hemophilia	General Male Population (all ages) ¹⁶
N	623	706-757*	368-398*	339-358*	101-108*	236-250*	-
Physical functioning, mean (SD)	75.8 (29)	77.9 (27.5)	87.5 (20.1)	67.1 (30.5)	43.0 (27.3)	77.5 (25.6)	88.3 (21)
Social functioning, mean (SD)	82.0 (24)	83.3 (20.8)	86.1 (20.2)	80.3 (21.2)	77.0 (20.8)	81.7 (21.2)	87.5 (20)
Role limitations (physical health problems), mean (SD)	73.3 (40)	76.4 (37.5)	83.6 (32.6)	68.4 (40.9)	52.9 (43.7)	75.1 (37.9)	83.3 (32)
Role limitations (personal/emotional problems), mean (SD)	83.4 (34)	85.0 (31.4)	87.7 (28.3)	82.1 (34.3)	77.3 (36.5)	84.1 (33.2)	85.8 (30)
Emotional well-being, mean (SD)	76.9 (18)	77.1 (15.6)	77.7 (14.5)	76.4 (16.7)	75.5 (17.7)	76.8 (16.3)	77.9 (17)
Energy/fatigue, mean (SD)	67.1 (20)	64.7 (17.7)	65.6 (17.0)	63.7 (18.3)	60.0 (18.3)	65.3 (18.2)	71.6 (18)
Bodily pain, mean (SD)	78.8 (24)	77.4 (22.6)	82.0 (21.0)	72.3 (23.3)	64.9 (21.8)	75.5 (23.2)	83.5 (23)
General health perception, mean (SD)	67.0 (23)	64.5 (22.3)	69.1 (21.8)	59.6 (21.7)	54.7 (21.5)	61.7 (21.4)	72.9 (20)

* Scores for each domain were calculated if a participant had completed at least half of the items of that domain. Therefore, the total of number of participants for which a score was calculated differs per domain.

Discussion

We evaluated clinical outcomes in patients with hemophilia in the Netherlands from 1972-2019 using a series of 6 national questionnaires. The same outcome definitions were used for all questionnaires, enabling direct comparison of different cohorts over

time. Bleeding rate and joint impairment decreased dramatically. Furthermore, HCV has almost been eradicated.

The prevalence of hemophilia in the Netherlands was 25.5 cases per 100,000 males, which is higher than reported previously^{6,19} but similar to a recent estimate of the birth prevalence (29.6 cases per 100,000 live male births).²⁰ The higher prevalence is most likely due to the high level of care increasing survival⁹, as well as improved diagnosis and registration of patients with previously undetected mild hemophilia over time (Table 1). Although, our reported prevalence is high, it is still lower than the reported birth prevalence²⁰, indicating the presence of unregistered patients with mild hemophilia and/or excess mortality due to hemophilia.

Change in health outcomes, 1972 to 2019

The annual bleeding rate has decreased due to more prophylaxis usage and higher dosing schemes, enabling children with hemophilia to participate safely in sports. (which improves muscle function and quality of life²¹) Over time, factor consumption in patients on prophylaxis has increased, from 886 IU/kg/year in the 1970s¹⁸, 1514 IU/kg/year in the 1980s¹⁸, 1880 IU/kg/year in the 1990s¹⁸, and finally 2534 IU/kg in the 2010s. Despite coagulation factor accounting for > 90% of total treatment costs^{22,23}, direct comparisons of prophylactic dosing schemes are scarce. A previous study showed that a high-dose protocol (4000 IU/kg per year) only marginally improved outcomes compared with an intermediatedose protocol (2100 IU/kg per year), while being 66% more expensive.²⁴ Our results seem to confirm that intermediate-dose prophylaxis can lead to good joint outcomes.

The median ABR was highest in the 0-16 group (4 bleeds). However, joint bleeds were rare and most bleeds were nosebleeds, which were far less common in adults. Among non-hemophilic males, the prevalence of epistaxis is also highest in children²⁵, and is commonly caused by irritation due to digital trauma.²⁶

The median AJBR for patients with severe hemophilia on prophylaxis was zero. Still, 44% of patients (95%CI: 38%-50%) had at least one joint bleed, leaving room for improvement. This is similar to a report from the UK (another high-income country), which found that in 2018, between 32.5% to 59.9% of patients on prophylaxis still reported at least one joint bleed per year.²⁷ Details on the cause/severity of joint bleeds were not available.

The hospital admission rate in patients with severe hemophilia after 1985 was 22%, which is higher than for Dutch men (9.8% in 1986 to 8.6% in 2017).²⁸ The hospital

admission rate in patients with mild hemophilia was similarly high (25%). Interestingly, the proportion of hospitalizations for non-hemophilic problems was higher in mild hemophilia (29%) than in severe hemophilia (17%). The reason for hospitalization was not included in the questionnaire and similar studies to compare our results with were not available.

Table 6. Health outcomes in patients with hemophilia over 50 years old.

	< 50 (N = 613)	50+, overall (N = 388)	50+, severe hemophilia (N = 115)	50+, non- severe hemophilia (N = 273)
Median annual bleeding rate	613	388	115	273
Rate (IQR)	1 (0-228)	0 (0-100)	3 (0-100)	0 (0-100)
Missing	109	45	14	31
Median annual joint bleeding rate	613	388	115	273
Rate (IQR)	0 (0-70)	0 (0-70)	2 (0-70)	0 (0-25)
Missing	95	44	14	30
Hospital admissions (%)	613	388	115	273
No	419 (82)	261 (72)	86 (77)	175 (69)
Yes	93 (18)	103 (28)	26 (23)	77 (31)
Missing	101	24	3	21
[†] Duration of hospital stay in days	66	83	25	58
Median (range)	5 (1-80)	6 (1-175)	7 (1-125)	5 (1-175)
Missing	5	2	0	2
Joint impairment (%)	613	388	115	273
Some impairment	123 (25)	153 (47)	96 (96)	57 (25)
No impairment	376 (75)	175 (53)	4 (4)	171 (75)
Missing	114	60	15	45
Orthopedic surgery in the past, any type (%)	613	388	115	273
No	280 (82)	219 (60)	28 (25)	191 (76)
Yes	63 (18)	145 (40)	84 (75)	61 (24)
Missing	270	24	3	21
Orthopedic surgery in the past, joint replacement surgery (%)	343	364	112	252
No	325 (95)	274 (75)	46 (41)	228 (90)
Yes	18 (5)	90 (25)	66 (59)	24 (10)

Orthopedic surgery in the past, arthrodesis (%)	343	364	112	252
No	327 (95)	311 (85)	72 (64)	239 (95)
Yes	16 (5)	53 (15)	40 (36)	13 (5)
Orthopedic surgery in the past, synovectomy (%)	343	364	112	252
No	334 (97)	346 (95)	100 (89)	246 (98)
Yes	9 (3)	18 (5)	12 (11)	6 (2)
Number of orthopedic interventions	343	364	112	252
Mean (SD)	0.4 (0.9)	0.9 (1.4)	1.9 (1.5)	0.5 (1.1)
Missing	2	4	1	3
§ HIV status (%)	136	280	108	172
Negative	126 (93%)	264 (95%)	95 (88%)	169 (100%)
Positive	9 (7%)	13 (5%)	13 (12%)	0 (0%)
Missing	1	3	0	3
* HCV status (%)	198	298	108	190
Always HCV-negative	85 (51)	93 (38)	3 (3)	90 (62)
Past infection	80 (48)	146 (60)	92 (93)	54 (37)
Current infection	2 (1)	6 (2)	4 (4)	2 (1)
Missing	31	53	9	44
HCV treatment among HCV-positive patients (%)	82	152	96	56
No	12 (15)	23 (15)	11 (12)	12 (22)
Yes	67 (85)	126 (85)	83 (88)	43 (78)
Missing	3	3	2	1
† Last treatment (%)	167	126	83	43
DAA	15 (28)	28 (25)	19 (26)	9 (24)
DAA + RBV	2 (4)	24 (21)	13 (18)	11 (29)
DAA + RBV + PEG-IFN	3 (6)	5 (4)	4 (5)	1 (3)
PEG-IFN + RBV	19 (35)	24 (21)	16 (22)	8 (21)
IFN + RBV	11 (20)	21 (19)	13 (18)	8 (21)
IFN	4 (7)	10 (9)	9 (12)	1 (3)
Missing	13	14	19	5

* Liver fibrosis/cirrhosis (%)	82	152	96	56
No significant fibrosis (< 9.5 kPa)	32 (91)	56 (75)	37 (76)	19 (73)
Significant fibrosis (9.5 -12.4 kPa)	1 (3)	7 (9)	4 (8)	3 (12)
Cirrhosis (> 12.4 kPa)	2 (6)	12 (16)	8 (16)	4 (15)
Missing	47	77	47	30

* Reported for 298 patients > 50 years treated with coagulation factor before 1992.

† DAA: direct acting antivirals, RBV: ribavirin, PEG-IFN: pegylated-interferon, IFN: interferon.

‡ Based on FibroScan measurements.

§ Reported for 280 patients > 50 years treated with coagulation factor before 1985

¶ Reported for patients that stayed at least one night in the hospital (day admissions were excluded).

Unlike patients < 40 years, patients > 40 years did not improve in joint function over time. This is due to accrued irreversible joint damage (in a period of time when there was no treatment or when it was still suboptimal). There is some evidence that hemophilia A and B differ in their clinical phenotype.²⁹ In the 2019 cohort, patients with severe hemophilia A and B reported roughly similar bleeding- and joint outcomes. However, given the small sample size, no conclusion can be drawn from these results.

The proportion of patients with severe hemophilia (A or B) with a past or current inhibitor increased from 8% in 1985 to 19% in 2019. Among patients with severe hemophilia A the percentage is 20%, which is low when compared to most clinical trials.¹ In contrast, a US study reported that between 1998-2011, 11.5%-17.0% of patients with severe hemophilia (A or B) had a past or current inhibitor.³⁰ The increasing prevalence over time may be due to more low-titer inhibitors being detected.³¹ Also, due to lower sensitivity tests and less testing in the past, some low-titer inhibitors in patients in the 1980s/1990s would have been missed. (this probably also explains the similarly low inhibitor prevalence in the US study)

General health status did not change meaningfully from 2001-2019. The probability of not detecting a meaningful improvement is unlikely as the RAND-36 questionnaire is reported to be sensitive to changes in health over time.³² Similar results have been reported by several European studies.³³⁻³⁵ A possible explanation for this may be response shift, which is defined as a change in the meaning of one's self-evaluation of quality of life as a result of changes in internal standards, values and the conceptualization of quality of life.³⁶ Persons with hemophilia may have changed their internal standards over time: while their health has deteriorated (e.g. as a result of recurrent bleeding), their previous idea of a bad health status may have been lower than what they currently experience.

Current health status of older patients

The prevalence of joint replacement surgery among patients with severe hemophilia of all ages was high (30%), which is in line with an earlier Dutch study (31%).³⁷ For comparison, a UK study reported a prevalence of 5% for joint replacement surgery among males > 60 years.³⁸ Eighty-four percent of patients with knee impairment also reported having wrist problems. This most likely due to the fact that these patients put more weight on their hands when standing up, in order to alleviate their knees.

Mental health status among 50+ patients appeared to be similar to that of the Dutch general male population, both in the 2001 survey³⁹, and in the 2019 survey, which is in agreement with several other studies.⁴⁰⁻⁴² The high level of mental health might be due to adequate hemophilia treatment in a multidisciplinary care setting.

Although HCV has almost been eradicated, 25% of cured patients still have moderate-severe liver fibrosis. Follow-up of these patients is warranted as they remain at increased risk for complications.⁴³

Limitations

Reported study response rates have decreased over time (from 84% in 1972, to 46% in 2019). The burden of participating in multiple studies (which is becoming more common), as well as the requirement of a hospital visit may have dissuaded some. However, participation rates in previous studies may have been overestimated, as evidenced by the high prevalence of hemophilia in 2019 (25.5 cases per 100,000 males). Despite lower participation, the 2019 cohort was similar to the Dutch hemophilia population with regards to age distribution and severity of hemophilia. (Table 2) Therefore, the results are likely to be highly generalizable. Nevertheless, non-response bias cannot be ruled out. Patients who participated in the questionnaire might have been more adherent to treatment, which would have skewed results towards a more positive direction.

Differentiating between joint bleeds and flare-ups of chronic arthropathy is difficult.⁴⁴ Therefore, the bleeding rate in patients with significant hemophilic arthropathy is probably slightly overestimated. The annual bleeding rate in children was based on the results of the last 3 months, multiplied by 4. This may have artificially increased bleeding rates due to recall bias.

The RAND-36 reference values were obtained from a validation study from 1992-1996¹⁶ and may not be representative of the current Dutch population. Yet, RAND-36

domain scores were shown to remain relatively stable over a time-period of almost 20 years.⁴⁵ In addition, age-specific domain scores were not available, so domain scores of the overall population (mean age: 43.1) were used for comparisons with the hemophilia cohort.

Lastly, patients tend to underreport co-morbidities.⁴⁶ This might explain the higher prevalence of hypertension reported by other studies.^{47,48}

Conclusion

Even though the increase in prophylactic treatment, coagulation factor dosage and centralization of care has improved outcomes, many patients with severe hemophilia still experience joint bleeds and report decreased physical health. Many older patients with severe hemophilia suffer from severe painful joint impairment, which greatly decreases quality of life. This emphasizes the need for personalized treatment focusing on bleed control, adequate pain management and timely reference to an orthopedic surgeon or physiatrist.⁴⁹ With the increased use of novel treatment options and expected further health gains, regular measurements of patient-relevant outcomes may identify areas for improvement and directions for further research.

In conclusion, our study shows that bleeding rates, joint health and HCV cure rates have strongly improved over the past five decades. However, there are still opportunities for improvement.

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Supplemental Table 1. Age-related co-morbidities in patients > 50 years old (self-reported information from questionnaire).

* Disorder (%)	Overall (N = 367)	Severe hemophilia (N = 109)	Non-severe hemophilia (N = 258)
Hypertension	135 (37)	51 (47)	84 (33)
Hypercholesterolemia	62 (17)	20 (18)	42 (16)
Ischemic heart disease	7 (2)	1 (1)	6 (2)
Ischemic stroke	5 (1)	1 (1)	4 (2)
Hemorrhagic stroke	3 (1)	2 (2)	1 (0)
Diabetes type 2	35 (10)	13 (12)	22 (9)
Osteoporosis	5 (1)	0 (0)	5 (2)
Chronic kidney disease	6 (2)	2 (2)	4 (2)
Malignancy [†]	42/322 (13)	13/98 (13)	29/224 (13)

* Self-reported treatment by a medical specialist or physician for a disorder. [†]Information on malignancies is missing in 45 patients.

Supplemental Table 2. Self-reported absence of impairment in ankles, knees, and elbows in patients with mild, severe or moderate hemophilia.

	1972	1978	1985	1992	2001	2019
Severe hemophilia						
No joint impairment (%)						
0-16 years old	26 (40)	40 (44)	53 (48)	56 (61)	76 (59)	76/80 (95)
Aged 17-25 years old	2 (5)	5 (9)	7 (8)	9 (14)	7 (17)	23/33 (70)
Aged 25-40 years old	0 (0)	2 (3)	3 (3)	2 (2)	7 (8)	18/49 (37)
Older than 40 years of age	0(0)	0(0)	3 (4)	1 (1)	4 (3)	7/147 (5)
Moderate hemophilia						
No joint impairment (%)						
0-16 years old	23 (55)	28 (68)	42 (71)	29 (71)	37 (80)	22/22 (100)
Aged 17-25 years old	5 (36)	13 (50)	9 (41)	17 (50)	11 (48)	15/18 (83)
Aged 25-40 years old	2 (11)	3 (13)	14 (24)	14 (31)	13 (37)	20/29 (69)
Older than 40 years of age	3 (33)	5 (33)	11 (31)	15 (28)	17 (24)	21/60 (35)
Mild hemophilia						
No joint impairment (%)						
0-16 years old	NR	NR	NR	NR	NR	58/59 (98)
Aged 17-25 years old	NR	NR	NR	NR	NR	36/37 (97)
Aged 25-40 years old	NR	NR	NR	NR	NR	46/52 (88)
Older than 40 years of age	NR	NR	NR	NR	NR	209/241 (87)

NR: Not reported in previous publications.

Supplemental Table 3. HCV status and treatment in all patients who were treated with clotting factor before 1992.

	N = 496
HCV status (%)	
Always HCV-negative	178 (43)
Past infection	226 (55)
Current infection	8 (2)
Missing	84
HCV genotype (%)	234
genotype 1, subtype unknown	19 (12%)
genotype 1a	39 (25%)
genotype 1b	59 (37%)
genotype 2, subtype unknown	8 (5%)
genotype 2a	9 (6%)
genotype 2b	5 (3%)
genotype 3	16 (10%)
genotype 4	3 (2%)
missing	76
Hepatitis C treatment (%)	234
No	35 (15)
Yes	193 (85)
Missing	6
* Last treatment (%)	193
DAA	43 (26)
DAA + RBV	26 (16)
DAA + RBV + PEG-IFN	8 (5)
PEG-IFN + RBV	43 (26)
IFN + RBV	32 (19)
IFN	14 (8)
Missing	27
† Liver fibrosis/cirrhosis (%)	234
no significant fibrosis (< 9.5 kPa)	88 (80)
significant fibrosis (9.5 -12.4 kPa)	8 (7)
cirrhosis (> 12.4 kPa)	14 (13)

* DAA: direct acting antivirals, RBV: ribavirin, PEG-IFN: pegylated-interferon, IFN: interferon.

† Based on FibroScan measurements.

Supplemental Table 4. Characteristics of participants in the Hemophilia in the Netherlands studies obtained from questionnaire data, according to type of hemophilia (A or B).

	2019 (N = 1009)	2019, HA (N = 867)	2019, HB (N = 129)
Mean age in years (range) *	40 (0-88)	41 (0-88)	36 (1-77)
Severity of hemophilia (%)			
Severe	378 (37)	325 (38)	53 (41)
Moderate	149 (15)	124 (14)	23 (18)
Mild	482 (48)	418 (48)	53 (41)
Type of hemophilia (%) [†]			
Hemophilia A	867 (87)	867 (100)	0 (0)
Hemophilia B	129 (13)	0 (0)	129 (100)
Family history of hemophilia (%) [‡]			
Negative	168 (18)	145 (18)	22 (20)
Positive	753 (82)	654 (82)	89 (80)
HIV infection (%) [§]			
Current infection	22/412 (5)	20/362 (6)	2/47 (4)
Hepatitis C infection (%) [¶]			
Current infection	8/412 (2) [#]	7/365 (2)	1/45 (2)
Past infection	226/412 (55) [#]	187/365 (51)	37/45 (82)
Inhibitory antibodies (%) ^{**}			
Ever inhibitors	66/361 (19) ^{††}	64/312	2/49 (4)
Current inhibitors	6/361 (2) ^{††}	6/312	0/49 (0)
Past inhibitors	60/361 (17) ^{††}	58/312	2/49 (4)

* Age was unknown for 8 patients.

† Type of hemophilia was unknown for 13 patients.

‡ Family history of hemophilia was unknown for 88 patients.

§ Reported for patients treated with coagulation factor before 1985.

|| HIV status was unknown for 4 patients.

¶ Reported for patients treated with coagulation factor before 1992.

HCV status was unknown for 84 patients.

** Reported for patients with severe hemophilia.

†† Inhibitor status was unknown for 17 patients.

Supplemental Table 5. Prophylaxis usage, annual bleeding rates and hospital admission, according to type of hemophilia (A or B).

	2019 (N = 1009)	2019, HA (N = 867)	2019, HB (N = 129)
Severe hemophilia	378	325	53
Patients on prophylaxis (%)			
Children, 0-16y	93/95 (98)	74/76 (97)	19/19 (100)
Young adults, 17-25y	42/46 (91)	38/42 (90)	4/4 (100)
Adults, older than 25y	193/228 (85)	171/199 (86)	22/29 (76)
Median age at first prophylaxis, years (range)	3 (0-79)	4 (0-79)	2 (0-58)
Median ABR* by age (range, IQR [†])			
Children, 0-16y	4 (0-228, 0-12)	4 (0-228, 0-12)	4 (0-64, 0-22)
Young adults, 17-25y	1 (0-12, 0-2)	1 (0-12, 0-2)	1 (0-4, 0.5-2.5)
Adults, older than 25y	2 (0-100, 0-6)	2 (0-100, 0-6)	1 (0-9, 0-3)
Hospital admissions			
Hemophilia patients (%)	73/330 (22)	65/285 (23)	8/45 (18)
Median duration, (range)	7 (1-125)	7 (1-125)	4 (1-15)
Moderate hemophilia	149	124	23
Patients on prophylaxis (%)			
Children, 0-16y	6/24 (25)	6/21 (29%)	3/3 (100)
Young adults, 17-25y	4/19 (21)	2/14 (14)	2/5 (40)
Adults, older than 25y	14/104 (13)	12/89 (13)	2/13 (15)
Median ABR* by age (range, IQR [†])			
Children, 0-16y	4 (0-32, 0-8)	4 (0-20, 0-8)	16 (0-32, 0-32)
Adults, older than 17y	1 (0-100, 0-2)	1 (0-100, 0-2)	0 (0-6, 0-1)
Hospital admissions			
Hemophilia patients (%)	21/136 (15)	20/115 (17)	1/19 (5)
Median duration (range)	6 (1-120)	6 (1-120)	21 (21-21)
Mild hemophilia	482	418	53
Patients on prophylaxis (%)			
Children, 0-16y	2/68 (3)	1/60 (2)	1/5 (20)
Young adults, 17-25y	1/43 (2)	1/36 (3)	0/7 (0)
Adults, older than 25y	7/346 (2)	6/306 (2)	1/35 (3)
Median ABR* by age (range, IQR [†])			
Children, 0-16y	4 (0-100, 0-14)	6 (0-100, 0-14)	0 (0-36, 0-36)
Young adults, 17-25y	0 (0-88, 0-1)	0 (0-88, 0-1)	1 (0-1, 0-1)
Adults, older than 25y	0 (0-40, 0-0.5)	0 (0-40, 0-1)	0 (0-2, 0-0)

Hospital admissions			
Hemophilia patients (%)	103/415 (25)	92/368 (25)	10/43 (23)
Median duration (range)	5 (1-175)	5 (1-175)	4.5 (1-7)

* Annual bleeding rate. †IQR: Interquartile range. NR: Not reported.

Supplemental Table 6. Bleed rates and joint outcomes of the 2019 cohort, according to type of hemophilia (A or B).

	HA (N = 867)	HB (N = 129)	severe HA (N = 325)	Severe HB (N = 53)
Mean age in years (range)	41 (0-88)	36 (1-77)	36 (1-82)	32 (1-75)
Severity of hemophilia (%)				
Severe	325 (38)	53 (41)	NA	NA
Moderate	124 (14)	23 (18)	NA	NA
Mild	418 (48)	53 (41)	NA	NA
Prophylaxis (%)				
No	536 (63)	71 (58)	34 (11)	7 (13)
Yes	311 (37)	51 (42)	283 (89)	45 (87)
Missing	20	7	8	1
Median age at first prophylaxis, years (range)	4 (0-79)	2 (0-58)	4 (0.79)	2 (0-58)
Missing	605	89	98	20
Annual clotting factor consumption for patients on prophylaxis (IQR)	2482 (1862-3564)	2777 (1962-3583)	2491 (1862-3614)	2819 (1968-3659)
Missing (no info on prophylaxis)	621	89	97	16
Median annual bleeding rate				
Rate (IQR)	1 (0-4)	0 (0-2)	2 (0-7)	2 (0-5)
Missing	122	29	53	12
Median annual joint bleeding rate				
Rate (IQR)	0 (0-1)	0 (0-0)	0 (0-4)	0 (0-0)
Missing	112	24	47	9
Joint impairment (%)				
Some impairment	237 (33)	37 (35)	160 (61)	25 (54)
No impairment	484 (67)	69 (65)	203 (39)	21 (46)
Missing	146	23	62	7
Orthopedic surgery in the past, joint replacement surgery (%)				
No	530 (85)	69 (85)	146 (67)	21 (70)
Yes	95 (15)	12 (15)	73 (33)	9 (30)
Missing	242	48	106	23