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ORIGINAL ARTICLE *Clinical haemophilia*

European retrospective study of real-life haemophilia treatment

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Introduction: Haemophilia treatment varies significantly between individuals, countries and regions and details of bleed rates, factor consumption and injection frequency are often not available. **Aim:** To provide an overview of the FVIII/FIX treatment practice and outcome for patients with haemophilia A (HA) or haemophilia B (HB) across Europe. **Methods:** Non-interventional, 12-month retrospective study where anonymized data were retrieved from haemophilia centres/registers in Belgium, France, Germany, Italy, Spain, Sweden and the United Kingdom. Male patients (all ages) receiving coagulation factor treatment 24 months prior to the study, with basal FVIII/FIX levels $\leq$5 IU dL^{-1}, without inhibitors, were included. Data were summarized descriptively. **Results:** In total, 1346 patients with HA and 312 with HB were included in the analysis; 75% and 57% had severe disease (FVIII/FIX < 1 IU dL^{-1}) respectively. Prophylaxis was most common for severe haemophilia, especially for children, whereas on-demand treatment was more common for moderate haemophilia in most countries. The mean (SD) prescribed prophylactic treatment ranged from 67.9 (30.4) to 108.4 (78.1) (HA) and 32.3 (10.2) to 97.7 (32.1) (HB) IU kg^{-1} per week, across countries. Most patients on prophylaxis were treated $\geq$3 times/week (HA) or two times/week (HB). The median annual bleeding rate (ABR) for patients on prophylaxis ranged from 1.0 to 4.0 for severe HA, and from 1.0 to 6.0 for severe HB, while those with moderate haemophilia generally had slightly higher ABRs. Median ABRs for on-demand-treated severe HA ranged from 4.5 to 18.0, and for HB, 1.5 to 14.0. **Conclusion:** Treatment practice varied greatly between centres and countries and patients treated on-demand and prophylactically both experienced bleeds, emphasizing the need for further optimization of care.

Keywords: factor VIII, factor IX, haemophilia A, haemophilia B, retrospective study, treatment

Introduction

Coagulation factor concentrates are effective in preventing and arresting haemorrhages in the majority of individuals with haemophilia. Although recommended best practise is the use of regular injections of coagulation factor concentrate to provide

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prophylaxis against bleeds in patients with severe haemophilia, there is no general agreement about how this should be provided [1]. Furthermore, there is no agreement about how patients with moderate severity haemophilia with frequent bleeding, should be managed [2].

The efficacy of prophylaxis depends, to a large extent, on the dose-interval and the dose administered, and the age at the start of treatment. The regimens commonly used can be characterized by high-, intermediate- and low-dose protocols as exemplified by the practice in Malmö, Utrecht and Beijing [3,4]. As there is accumulating evidence that early haemarthroses may initiate progressive haemophilic arthropathy, it is important to minimize bleeds during childhood to prevent disabling arthropathy later in life [5–7].

Health care budgets are frequently constrained and there is therefore a need to demonstrate the cost effectiveness and clinical effectiveness of different prophylactic regimens. The annual bleeding rate (ABR) is used as a surrogate marker for the effectiveness of therapy; bleeding into joints being a particularly pertinent measure.

Haemophilia management varies across Europe and the extent to which prophylaxis is available and effectively implemented is largely unknown [8]. Insight into the efficacy of different treatment regimens and their relationship with clinically important measurable outcomes may be obtained by reviewing current treatment practice.

This study was designed to see what insights into haemophilia care could be obtained by reviewing practice across different countries. The study reports retrospective data and provides a snap-shot overview on clotting factor use with on-demand and prophylactic therapy and ABRs in severe and moderate haemophilia A and B at 11 centres, one local register and one national register in seven European countries.

Subjects and methodology

Subjects

Male patients with moderate (basal FVIII/FIX level of 1 to $\leq$5 IU dL^{-1}) or severe (basal FVIII/FIX level of <1 IU dL^{-1}) haemophilia A or B without inhibitors in the previous 24 months were included. All patients were required to have been treated with FVIII/FIX for at least 24 months prior to the study. Patients participating in any interventional haemophilia clinical trial during this study were excluded. The study was approved by the regulatory authorities and independent ethics committees and informed consent was obtained from the patient or patient's legal representative, if applicable according to legal regulation.

Study design

This was a multinational, non-interventional, retrospective study where data were collected from haemophilia centres or registers covering a 12-month period specifically selected for each site between 2012 and 2014. Centres and registries were selected based on having a large number of eligible patients and representing recognized haemophilia treatment centres. Data were collected by direct transfer from databases or by manual transfer from patient charts to electronic case report forms.

Sample size and study populations

As the study was descriptive in nature, no formal sample size calculation was applicable. The total sample size reported from each site depended on data availability. The study population included all enrolled patients who met the inclusion/exclusion criteria and for whom key data could be verified. The investigator judged if the bleed information was complete and included only patients for whom reliable bleed data were available for the full 12-month study period in the bleed population. Collection of bleed data was an optional study variable.

At most centres, all eligible patients were included except for one centre (Bonn, Germany), with high access to patient data; 200 patients with haemophilia A were randomly selected for study inclusion to limit the data entry burden. At this centre, patients with moderate haemophilia A were not included in the study. Patients at two centres in France and Spain were also randomly selected since all could not be included due to local resource constraints. All haemophilia B patients satisfying the inclusion/exclusion criteria were included, except at one centre in France, where a limited number of patients were randomly selected due to resource constraints.

Databases

Data from two registers were included. The National Haemophilia Database (NHD) is a register of patients with bleeding disorders in the UK, maintained by the UK Haemophilia Centre Doctors' Organization (UKHCDO) [9]. Haemtrack is a national online patient-reporting treatment diary system developed by UKHCDO and endorsed by the UK Haemophilia Society. Patients report the amount of factor used and the reason for treatment (prophylaxis, on-demand, treatments for bleeds etc.) and the outcome of treatment. Thus, Haemtrack represents patients self-perceived bleeding data and actual factor administered. Data from April 2012 to March 2013 were censored to include only patients who appeared as compliant users of the Haemtrack mobile application.

The Malmö register is a local register in Sweden from which data from 2012 were retrieved for this study [10].

Definitions

Prescribed dose: the amount of FVIII/FIX prescribed as prophylaxis by the treating physician during the 12-month study period as indicated in the patient records. Total *issued* dose: the amount of factor dispensed, e.g. from pharmacy, home delivery or clinic, to the patient. The total *used* dose: the amount of factor administered as indicated in the patient records. Collection of either issued or used dose, or both, was a study requirement, while prescribed dose was a requirement for patients on prophylaxis only (except for UK where prescribed dose was not part of the available dataset).

Treatment regimens.

1. Regular prophylactic treatment: prescribed prophylactic treatment for at least 45 weeks (315 days) during the study period [11].
2. On-demand treatment: no prescribed prophylaxis.
3. Partly prophylactic treatment: prescribed prophylaxis but did not fulfil the criteria for regular prophylaxis, e.g. 'activity prophylaxis.'

For UK, the *treatment regimen* was estimated based on patients' reported injection frequency and treatment as 'for prophylaxis' (Haemtrack):

1. Regular prophylactic treatment: at least two injections/week (haemophilia A) or at least one injection/week (haemophilia B) for ≥45 weeks during the study period.
2. On-demand treatment: no reported regular prophylaxis.
3. Partly prophylactic treatment: reported prophylaxis but did not fulfil the criteria for regular prophylaxis.

Dosing frequency. The frequency of prescribed prophylactic dose was recorded in the eCRFs as daily, every other day, three times a week, twice a week or other (haemophilia A) and as once a week, twice a week or other (haemophilia B). For the UK, the injection frequency was estimated from the patient's individual recordings and the average number of injections/week was calculated for each patient.

Annual bleeding rate. Type of bleed was defined as joint, muscle/soft tissue, mouth, other or unknown location. ABRs were estimated based on the total number of bleeds perceived by each individual during 12 months. ABRs for all locations as well as joint bleeds are presented.

Results

Demographics

A total of 1346 haemophilia A and 312 haemophilia B patients were included in the full analysis. Children, adolescents and adults were all represented (Table 1). The highest average age for both haemophilia A and B was in Belgium (39.6 and 37.0 years respectively) and the lowest was in Spain (26.2 and 30.5 years respectively). The proportion of patients with severe haemophilia A ranged from 63% (UK) to 99% (Germany). The high proportion in Germany was due to an active selection of patients with severe haemophilia A for study inclusion at one of the two German centres. For haemophilia B, the proportion of patients with severe disease ranged from 14% (Belgium) to 74% (Germany). The use of recombinant, compared to plasma-derived, products varied considerably across countries. There was a higher proportionate use of recombinant products for haemophilia A (74–98%), than for haemophilia B (34–100%) between countries. While some countries issued almost exclusively recombinant products, others used a considerable proportion of plasma-derived concentrates for both haemophilia A and B. Children with haemophilia A from all countries were treated almost exclusively with recombinant products, whereas older individuals were more likely to be receiving plasma-derived products (Table S1).

Treatment regimen

Regular prophylaxis was overall the most common treatment regimen for severe haemophilia A (Fig. 1), with some variation both between and within countries (Figure S1). The proportion receiving prophylaxis was highest in children and decreased with increasing age. For patients with moderate haemophilia A, on-demand treatment was overall the most common treatment regimen with no observed trend across age groups (Fig. 1).

For patients with haemophilia B, regular prophylaxis was most common for severe haemophilia B in four out of seven countries, whereas on-demand treatment was the most common regimen for patients with moderate severity in four out of seven countries (Fig. 2). The limited number of patients did not permit analysis by age.

Prescribed and issued treatment

The mean (SD) weekly prescribed treatment for patients with haemophilia A on regular prophylaxis varied from 67.9 (30.4) IU kg^{-1} to 108.4 (78.1) IU kg^{-1} between countries (Table 2). Further breakdown by centre is available in Table S2. It should be noted that the prescribed dose only includes patients

Table 1. Demographics and characteristics of patients with haemophilia A and B in 11 Haemophilia Centres and two registers in seven European countries.

Haemophilia A	Belgium *N* = 61	France *N* = 102	Germany *N* = 215	Italy *N* = 292	Spain *N* = 248	Sweden* *N* = 126	UK* *N* = 302
Age group, *n* (%)							
<12 years	4 (6.6)	19 (18.6)	19 (8.8)	24 (8.2)	55 (22.2)	28 (22.2)	41 (13.6)
≥12 to <20 years	6 (9.8)	19 (18.6)	29 (13.5)	43 (14.7)	40 (16.1)	21 (16.7)	37 (12.3)
≥20 to <40 years	18 (29.5)	32 (31.4)	70 (32.6)	98 (33.6)	100 (40.3)	38 (30.2)	110 (36.4)
≥40 to <60 years	23 (37.7)	25 (24.5)	79 (36.7)	95 (32.5)	48 (19.4)	25 (19.8)	98 (32.5)
≥60 years	10 (16.4)	7 (6.9)	18 (8.4)	32 (11.0)	5 (2.0)	14 (11.1)	16 (5.3)
Age							
Mean (SD)	39.6 (18.2)	29.9 (18.7)	35.5 (17.6)	35.6 (17.6)	26.2 (16.0)	29.8 (19.8)	32.7 (17.2)
Weight (kg)							
Mean (SD)	73.7 (22.2)	60.7 (21.7)	75.6 (21.9)	68.6 (16.8)	62.3 (23.0)	65.9 (25.9)	71.7 (25.3)†
Severity, *n* (%)							
Moderate	18 (29.5)	32 (31.4)	3 (1.4)	100 (34.2)	42 (16.9)	36 (28.6)	111 (36.8)
Severe	43 (70.5)	70 (68.6)	212 (98.6)	192 (65.8)	206 (83.1)	90 (71.4)	191 (63.2)
Type of product, *n* (%)							
Recombinant	60 (98.4)	95 (93.1)	161 (74.9)	217 (74.3)	200 (80.6)	123 (97.6)	289 (95.7)
Plasma-derived	1 (1.6)	7 (6.9)	54 (25.1)	75 (25.7)	48 (19.4)	3 (2.4)	13 (4.3)
Haemophilia B	**Belgium *N* = 14**	**France *N* = 29**	**Germany *N* = 50**	**Italy *N* = 51**	**Spain *N* = 45**	**Sweden *N* = 25**	**UK *N* = 98**
Age group, *n* (%)							
<12 years	1 (7.1)	2 (6.9)	7 (14.0)	6 (11.8)	8 (17.8)	3 (12.0)	13 (13.3)
≥12 to <20 years	0	5 (17.2)	5 (10.0)	7 (13.7)	7 (15.6)	3 (12.0)	20 (20.4)
≥20 to <40 years	8 (57.1)	14 (48.3)	25 (50.0)	21 (41.2)	15 (33.3)	7 (28.0)	35 (35.7)
≥40 to <60 years	2 (14.3)	6 (20.7)	9 (18.0)	9 (17.6)	13 (28.9)	9 (36.0)	24 (24.5)
≥60 years	3 (21.4)	2 (6.9)	4 (8.0)	8 (15.7)	2 (4.4)	3 (12.0)	6 (6.1)
Age							
Mean (SD)	37.0 (19.6)	33.0 (15.1)	30.8 (18.8)	36.1 (20.0)	30.5 (17.0)	36.1 (20.5)	30.6 (17.9)
Weight (kg)							
Mean (SD)	70.5 (17.5)	67.9 (18.1)	72.0 (24.6)	70.1 (18.3)	64.5 (20.3)	71.6 (23.6)	73.3 (26.5)†
Severity, *n* (%)							
Moderate	12 (85.7)	17 (58.6)	13 (26.0)	29 (56.9)	18 (40.0)	10 (40.0)	34 (34.7)
Severe	2 (14.3)	12 (41.4)	37 (74.0)	22 (43.1)	27 (60.0)	15 (60.0)	64 (65.3)
Type of product, *n* (%)							
Recombinant	14 (100.0)	20 (69.0)	17 (34.0)	39 (76.5)	31 (68.9)	19 (76.0)	91 (92.9)
Plasma-derived	0	9 (31.0)	33 (66.0)	12 (23.5)	14 (31.1)	6 (24.0)	7 (7.1)

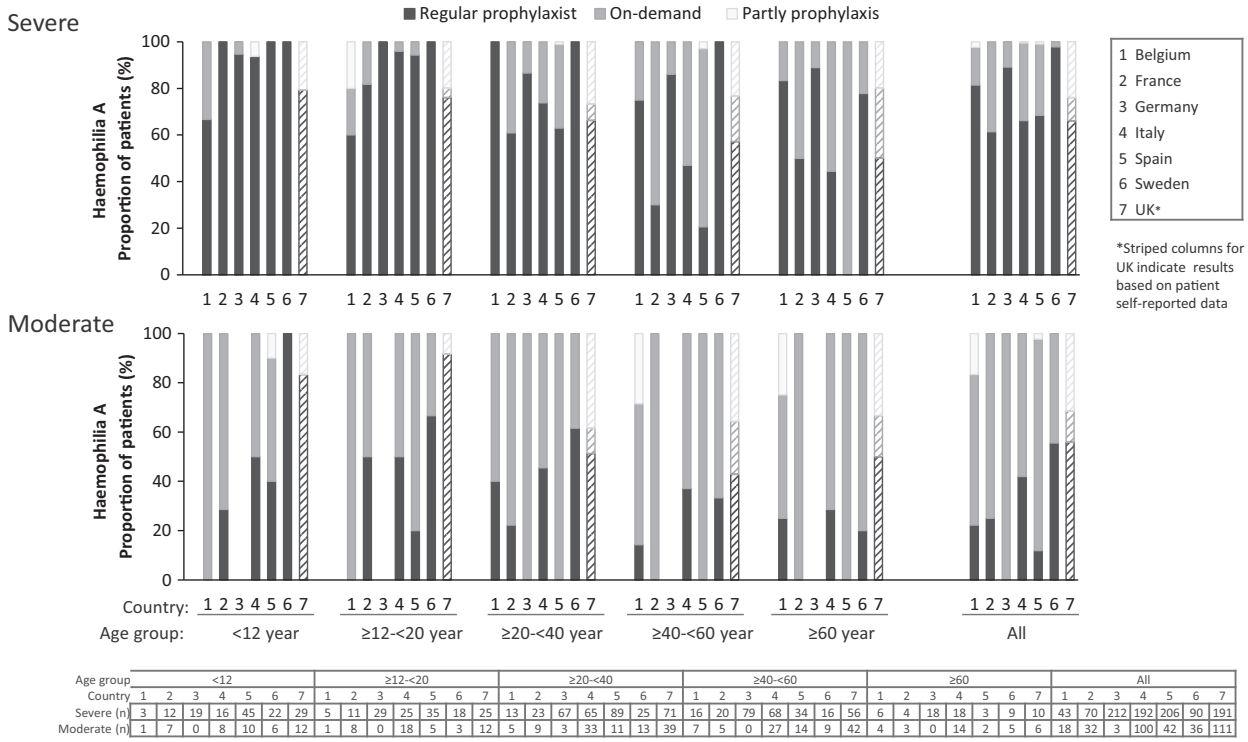
SD, standard deviation; y, years of age.
*Data from Sweden were retrieved from one registry and one Centre. Data from UK was retrieved from the national Haemtrack database.
†Weight was available for 276 patients with haemophilia A and 88 patients with haemophilia B.

on regular dose frequencies and not those on 'other' dose frequencies, which may influence the data from countries with a higher proportion of 'other' dose frequencies (Fig. 3). The consumption of clotting factor concentrate was slightly higher for patients with severe disease than for moderate disease in five out of the seven countries. For children with haemophilia A who were <12 years of age, the mean (SD) treatment varied from 75.7 (54.5) to 240.2 (122.5) IU kg^{-1} per week across countries. In four out of seven countries, these doses were higher compared to those for older patients (Table S3). Since information on prescribed treatment was not available from the UK, issued treatment is presented instead.

The prescribed dose was not available for patients receiving on-demand treatment, therefore used dose is presented instead. The mean (SD) amount of on-demand treatment varied between countries from 6.7 (4.1) to 26.0 (29.9) IU kg^{-1} per week [equivalent to 348.4 (214.3) to 1351.7 (1557.2) IU kg^{-1} per year] for haemophilia A, and from 0 to 32.2 (18.6) IU kg^{-1} per week [equivalent to 0–1675.9 (968.1) IU kg^{-1} per year] for haemophilia B (Table S4).

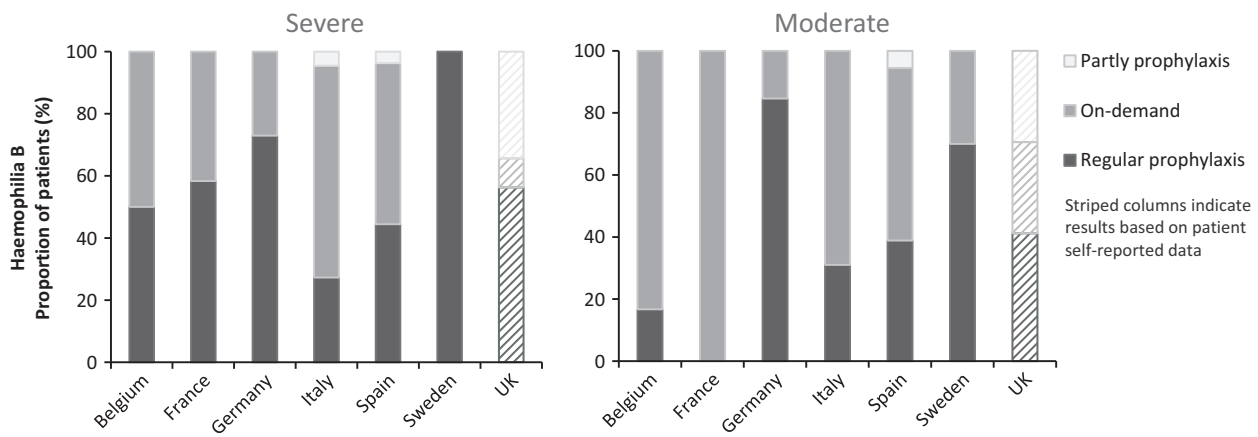
Dosing frequency

The most common dose frequencies for patients on regular prophylaxis, including both severe and moderate haemophilia A, were 'three times a week' followed by 'twice a week' (Fig. 3). For Sweden, a substantial proportion of patients with haemophilia A (23%) had 'other' as dose frequency, which represented patients with individualized treatment, most of which were irregular dose frequencies of ≥3 times a week. Similarly, the high proportion of 'other' dose frequency for haemophilia B in Germany (50%) also represented mostly individualized treatment. Daily prophylaxis was given to 14% and 16% of patients in Sweden and Germany respectively. In other countries, daily prophylaxis was less common. Dose frequencies for patients with haemophilia A on prophylaxis varies greatly within countries (Figure S2). There was no apparent relationship between dose frequencies and age groups, except in Germany where most patients who dosed daily were ≥40 years of age (Table S5).



Age group	<12							≥12-<20							≥20-<40							≥40-<60							≥60							All						
Country	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Severe (n)	3	12	19	16	45	22	29	5	11	29	25	35	18	25	13	23	67	65	89	25	71	16	20	79	68	34	16	56	6	4	18	18	3	9	10	43	70	212	192	206	90	191
Moderate (n)	1	7	0	8	10	6	12	1	8	0	18	5	3	12	5	9	3	33	11	13	39	7	5	0	27	14	9	42	4	3	0	14	2	5	6	18	32	3	100	42	36	111

Fig. 1. Treatment regimen for patients with haemophilia A by age group and by severity. The proportion in each treatment regimen was based on information from patients prescriptions, except for UK (striped columns), where it was estimated based on the patients self-reported treatments.



No. of pat. in each treatment regimen (severe/moderate)	Belgium	France	Germany	Italy	Spain	Sweden	UK
Regular prophylaxis	1/2	7/0	27/11	6/9	12/7	15/7	36/14
On-demand	1/10	5/17	10/2	15/20	14/10	0/3	6/10
Partly prophylaxis	0/0	0/0	0/0	1/0	1/1	0/0	22/10

Fig. 2. Treatment regimen for patients with haemophilia B. The proportion in each treatment regimen was based on information from patients prescriptions, except for UK (striped columns), where it was estimated based on the patients self-reported treatments. The number of patients with either severe or moderate disease in each country is indicated in the table below the graphs.

Annual bleeding rate

Information on bleeds was not mandatory in this study, but it was still collected for a substantial number of patients (Belgium A; 43/61, B; 12/14, France A; 81/102, B; 19/29, Germany A; 119/215, B; 23/50, Italy A; 206/292, B; 40/51, Spain A; 28/248, B; 7/45, Sweden A; 104/126, B; 21/25, UK A; 302/302, B; 98/98). The demography for these patients was similar to that of the complete study population (not shown). The proportion of patients with severe haemophilia A

Table 2. Prescribed or issued treatment (IU kg^{-1} per week) for patients with haemophilia A and haemophilia B on regular prophylaxis by severity.

	Prescribed treatment						Issued treatment
Haemophilia A	Belgium *N* = 39	France *N* = 51	Germany *N* = 189	Italy *N* = 169	Spain *N* = 146	Sweden *N* = 108	UK* *N* = 188
Severe							
n	33	40	143	113	137	69	108
Mean (SD)	69.0 (31.5)	91.4 (28.9)	108.4 (78.1)	101.4 (39.7)	93.8 (51.0)	91.4 (41.7)	88.5 (35.7)
Median (Q1, Q3)	56.4 (46.6, 85.3)	85.4 (74.3, 111.4)	85.6 (54.9, 125.3)	94.0 (72.8, 120.3)	83.6 (56.5, 115.7)	85.4 (68.2, 100.5)	82.9 (64.7, 106.8)
Moderate							
n	4	6	0	36	5	15	61
Mean (SD)	58.8 (19.5)	95.8 (11.5)		95.1 (34.5)	75.3 (22.9)	89.2 (35.6)	87.6 (36.6)
Median (Q1, Q3)	51.7 (46.1, 71.5)	89.4 (88.5, 103.7)		84.2 (69.2, 125.3)	74.8 (57.9, 75.2)	88.5 (62.7, 98.4)	79.7 (62.0, 106.2)
All							
n	37	46	143	149	142	84	169
Mean (SD)	67.9 (30.4)	91.9 (27.2)	108.4 (78.1)	99.9 (38.5)	93.2 (50.4)	91.0 (40.5)	88.2 (35.9)
Median (Q1, Q3)	55.7 (46.6, 85.3)	88.2 (75.2, 111.4)	85.6 (54.9, 125.3)	92.6 (72.4, 121.5)	80.3 (56.5, 114.6)	85.5 (67.7, 100.4)	81.6 (63.7, 106.4)
Haemophilia B	Belgium *N* = 3	France *N* = 7	Germany *N* = 38	Italy *N* = 15	Spain *N* = 19	Sweden *N* = 22	UK* *N* = 50
Severe							
n	0	6	13	6	12	14	34
Mean (SD)		97.7 (32.1)	41.4 (29.1)	83.5 (17.1)	63.6 (25.7)	88.4 (36.4)	82.8 (32.7)
Median (Q1, Q3)		84.1 (77.1, 115.7)	35.8 (23.6, 43.0)	85.4 (64.7, 100.3)	67.5 (39.4, 83.1)	84.4 (58.0, 95.9)	81.5 (61.4, 102.4)
Moderate							
n	2	0	5	8	7	4	12
Mean (SD)	32.3 (10.2)		53.5 (21.6)	54.6 (20.9)	67.3 (17.4)	69.7 (26.1)	67.0 (47.1)
Median (Q1, Q3)	32.3 (25.1, 39.5)		55.7 (53.5, 56.8)	54.6 (33.7, 75.2)	62.7 (50.1, 85.9)	65.4 (48.7, 90.7)	51.3 (38.7, 72.6)
All							
n	2	6	18	14	19	18	46
Mean (SD)	32.3 (10.2)	97.7 (32.1)	44.7 (27.2)	67.0 (23.9)	64.9 (22.5)	84.2 (34.6)	78.7 (37.1)
Median (Q1, Q3)	32.3 (25.1, 39.5)	84.1 (77.1, 115.7)	39.5 (23.6, 55.7)	69.9 (51.4, 83.6)	62.7 (50.1, 85.3)	79.7 (55.6, 95.9)	76.4 (51.0, 97.0)

IU, international units; Q1, first quartile; Q3, third quartile; SD, standard deviation.
*Due to lack of available data on prescribed dose, issued dose is presented for the UK.

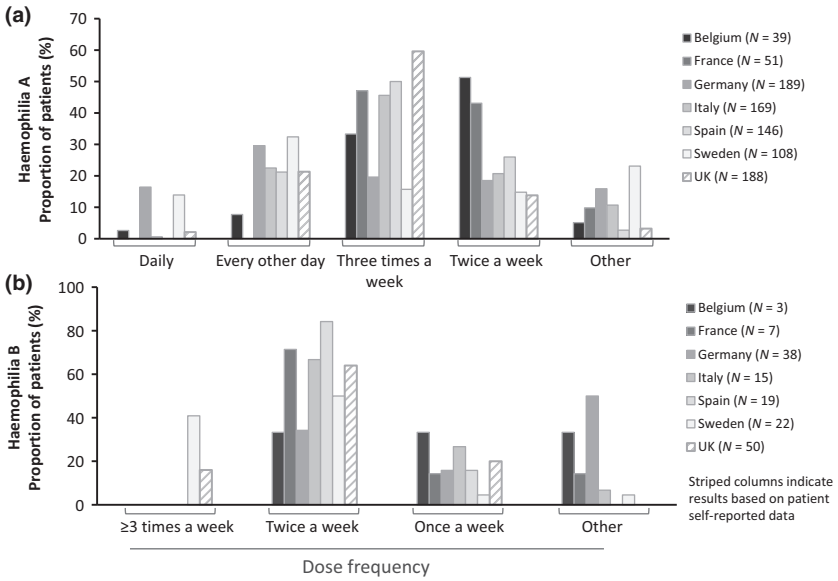


Fig. 3. Dose frequencies for patients with haemophilia on prophylaxis by country. (a) Prescribed dose frequencies for patients with haemophilia A for all countries except for UK, for which the dose frequency was estimated based on the patients' self-reported treatments in the Haemtrack database (striped columns). (b) Dose frequencies for patients with haemophilia B presented as in A. Dose frequencies ≥3 times a week for haemophilia B was only an option for registers (UK and Malmö, Sweden).

on prophylaxis experiencing ≥1 bleed during the study period ranged from 59% (Sweden) to 100% (Spain) (Table 3) and the median ABR varied from 1.0 (Belgium, Italy and Sweden) to 4.0 (France and UK). Of note is the higher ABRs, from 2.0 to 8.0, for patients with moderate haemophilia A on prophylaxis, although the low patient number should be considered when interpreting these data. Overall, most common were joint bleeds experienced by 43% (Sweden) to 77% (France) of the patients with haemophilia A. In addition, 25% of the patients had substantially higher ABRs, ranging from 2 to 12 (severe haemophilia A) between countries as indicated by the interquartile ranges. There were no apparent trends in the total number of bleeds (all types of bleeds) vs. patient age for haemophilia A (Figure S3), however, there was a slight tendency of lower number of joint bleeds among children in some countries (Fig. 4).

The ABRs for patients receiving on-demand treatment were in general higher for patients with severe than moderate haemophilia (Table S6).

Discussion

This large retrospective study on haemophilia treatment including 1346 haemophilia A and 312 haemophilia B patients from 12 haemophilia centres in six EU countries and one national register (UK), compiled data on the treatment and treatment outcome during 12 months and showed that treatment practice varies greatly throughout Europe and that many patients still bleed despite living in a relatively affluent part of the world. This is in line with recent data from the US, showing unacceptably high bleeding rates in a large proportion of severe haemophilia [12].

The use of plasma-derived products for both haemophilia A and B varied greatly between countries and age groups, and was more common among older patients. The proportional use of plasma-derived FIX was higher than that of plasma-derived FVIII, possibly due to the higher recovery of plasma-derived FIX *in vivo* than that obtained with recombinant FIX products. Moreover, only one recombinant FIX product was available on the market until recently, and the cost of plasma-derived FIX has generally been lower than that of recombinant FIX.

The mean prescribed treatment for patients receiving regular prophylaxis for severe haemophilia A ranged from 90 to 110 IU kg^{-1} per week in most countries; it is interesting to note that Sweden, known for its high-dose prophylaxis regimen [13], was in the same range or even lower than other countries in the study. For moderate haemophilia A, the mean prescribed treatment was lower than for severe haemophilia A, ranging from 75 to 95 IU kg^{-1} per week, presumably reflecting the higher basal FVIII level in moderate patients. The large standard deviations and dose ranges for both severe and moderate patients reflect a wide variety of individual patient consumption. In both severe and moderate haemophilia B, the range of therapy was even greater, and the average annual use considerably less, compared to haemophilia A, possibly reflecting the former being perceived as a milder bleeding disorder and FIX products having a longer half-life than FVIII products [14].

The median ABR for patients with severe haemophilia A on prophylaxis was as high as four in some countries and some patients experienced more than 12 bleeds per year, likely reflecting insufficient therapy, inappropriate dose-interval, presence of target joints, poor adherence or difficulty of correctly assessing bleeds by some patients. The most common FVIII prophylactic regimen was three times weekly, which is probably suboptimal in some cases due to a relatively

Table 3. Annual bleeding rates for patients with haemophilia A and B on regular prophylactic treatment (bleed population*).

Haemophilia A	Belgium *N* = 28	France *N* = 35	Germany *N* = 106	Italy *N* = 111	Spain *N* = 20	Sweden *N* = 94	UK† *N* = 188
Severe: all locations							
n (number of pat.)	24	34	106	93	19	75	126
Pat. with ≥1 bleed, *n* (%)	15 (62.5)	33 (97.1)	102 (96.2)	64 (68.8)	19 (100.0)	44 (58.7)	98 (77.8)
Mean ABR (SD)	4.1 (6.9)	8.0 (9.4)	4.5 (5.3)	2.8 (4.7)	2.7 (2.5)	1.9 (2.9)	5.8 (7.0)
Median ABR (Q1, Q3)	1.0 (0, 6)	4.0 (1, 12)	2.0 (1, 6)	1.0 (0, 4)	2.0 (1, 3)	1.0 (0, 2)	4.0 (1, 7)
Severe: joints							
Pat. with ≥1 bleed, *n* (%)	14 (58.3)	26 (76.5)	66 (62.3)	41 (44.1)	10 (52.6)	32 (42.7)	90 (71.4)
Mean ABR (SD)	3.4 (5.7)	5.5 (7.5)	1.7 (2.4)	1.8 (4.3)	1.4 (2.1)	1.2 (2.5)	4.0 (5.4)
Median ABR (Q1, Q3)	1.0 (0, 5)	2.5 (1, 6)	1.0 (0, 2)	0.0 (0, 1)	1.0 (0, 2)	0.0 (0, 1)	2.0 (0, 6)
Moderate: all locations							
n (number of pat.)	4	1	0	18	1	19	62
Pat. with ≥1 bleed, *n* (%)	3 (75.0)	1 (100.0)		17 (94.4)	1 (100.0)	13 (68.4)	52 (83.9)
Mean ABR (SD)	9.0 (8.9)	5.0		4.6 (5.0)	3.0	1.9 (2.2)	7.1 (14.3)
Median ABR (Q1, Q3)	8.0 (2, 16)	5.0 (5, 5)		2.5 (1, 8)	3.0 (3, 3)	2.0 (0, 2)	4.0 (1, 7)
Moderate: joints							
Pat. with ≥1 bleed, *n* (%)	3 (75.0)	1 (100.0)	0	12 (66.7)	1 (100.0)	9 (47.4)	46 (74.2)
Mean ABR (SD)	9.0 (8.9)	2.0		2.8 (3.4)	1.0	1.1 (1.6)	5.3 (11.4)
Median ABR (Q1, Q3)	8.0 (2, 16)	2.0 (2, 2)		2.0 (0, 4)	1.0 (1, 1)	0.0 (0, 2)	2.0 (0, 6)
Haemophilia B	**Belgium *N* = 3**	**France *N* = 7**	**Germany *N* = 18**	**Italy *N* = 8**	**Spain *N* = 5**	**Sweden *N* = 18**	**UK† *N* = 50**
Severe: all locations							
n (number of pat.)	1	7	12	3	2	12	36
Pat. with ≥1 bleed, *n* (%)	1 (100.0)	6 (85.7)	11 (91.7)	2 (66.7)	2 (100.0)	8 (66.7)	27 (75.0)
Mean ABR (SD)	6.0	3.7 (2.8)	3.4 (5.1)	1.7 (1.5)	2.0 (0.0)	3.2 (6.8)	6.5 (7.9)
Median ABR (Q1, Q3)	6.0 (6, 6)	4.0 (1, 6)	1.0 (1, 5)	2.0 (0, 3)	2.0 (2, 2)	1.0 (0, 2)	4.0 (1, 11)
Severe: joints							
Pat. with ≥1 bleed, *n* (%)	1 (100.0)	4 (57.1)	3 (25.0)	0	2 (100.0)	6 (50.0)	24 (66.7)
Mean ABR (SD)	6.0	2.3 (2.8)	1.7 (5.2)		2.0 (0.0)	2.3 (5.1)	4.1 (5.0)
Median ABR (Q1, Q3)	6.0 (6, 6)	1.0 (0, 4)	0.0 (0, 1)		2.0 (2, 2)	0.5 (0, 2)	2.5 (0, 6)
Moderate: all locations							
n (number of pat.)	2	0	6	5	3	6	14
Pat. with ≥1 bleed, *n* (%)	2 (100.0)		6 (100.0)	5 (100.0)	2 (66.7)	6 (100.0)	11 (78.6)
Mean ABR (SD)	8.0 (7.1)		3.3 (2.5)	2.4 (1.7)	4.0 (5.3)	4.0 (4.4)	8.5 (9.2)
Median ABR (Q1, Q3)	8.0 (3, 13)		2.0 (2, 6)	2.0 (1, 3)	2.0 (0, 10)	1.5 (1, 8)	6.0 (1, 14)
Moderate: joints							
Pat. with ≥1 bleed, *n* (%)	0	0	4 (66.7)	2 (40.0)	1 (33.3)	3 (50.0)	7 (50.0)
Mean ABR (SD)			2.2 (2.6)	1.2 (2.2)	0.7 (1.2)	1.3 (2.3)	5.1 (8.0)
Median ABR (Q1, Q3)			1.0 (0, 5)	0.0 (0, 1)	0.0 (0, 2)	0.5 (0, 1)	2.0 (0, 7)

ABR, annual bleeding rate; Pat., patients; Q1, first quartile; Q3, third quartile.

Bleeding locations were reported as: joint, muscle/soft tissue, mouth, other or unknown bleed location, of which only all locations and joints are presented here. The number of bleeds can be more than one per patient.

*The bleed population consisted of those patients in the full analysis population for whom reliable bleeding data were available for the complete 12-month study period. For registers, all bleed data were included.

†For UK, the ABR is calculated based on patients self-reported bleedings in the Haemtrack database, while for other countries, data are retrieved from patient charts.

short half-life of conventional FVIII products [15]. The true level of joint bleeds is currently difficult to ascertain since patients report symptomatic bleeds and there is also evidence that asymptomatic joint bleeds may lead to both over- and under-reporting. In general, the more joint bleeds a patient experiences the greater the risk is of developing structural joint damage, however it has also become apparent that even patients without a history of perceived bleeds may have MRI detectable abnormalities [6,16]. Although zero bleeds may be difficult to achieve for those who already have target joints, appropriate prophylaxis, optimized by dose and dose-interval for each individual, should provide full protection against bleeds.

Although it was heartening to note that many children with severe haemophilia received prophylaxis, which increases their likelihood of entering adulthood with minimal joint damage, children on prophylaxis experienced occasional bleeds to an extent close to that of older patients in some countries. Bleeds in small children indicate that prophylaxis is driven to the minimal acceptable level, or even lower. This not only increases the risk of joint injury but probably also prevents patients from being fully physically active [2].

In individuals with moderate haemophilia A on prophylaxis improvement is needed since bleeds were as frequent or more frequent than for those with severe disease on prophylaxis. Patients with haemophilia B on prophylaxis experienced bleeds with a frequency similar to those with haemophilia A confirming a need for improved treatment also for these patients. Finally, the ABRs for patients treated on-demand were higher than for those receiving prophylaxis and a substantial number of these patients had relatively high ABRs as revealed by the interquartile ranges. Prophylaxis should be considered for on-demand-treated patients

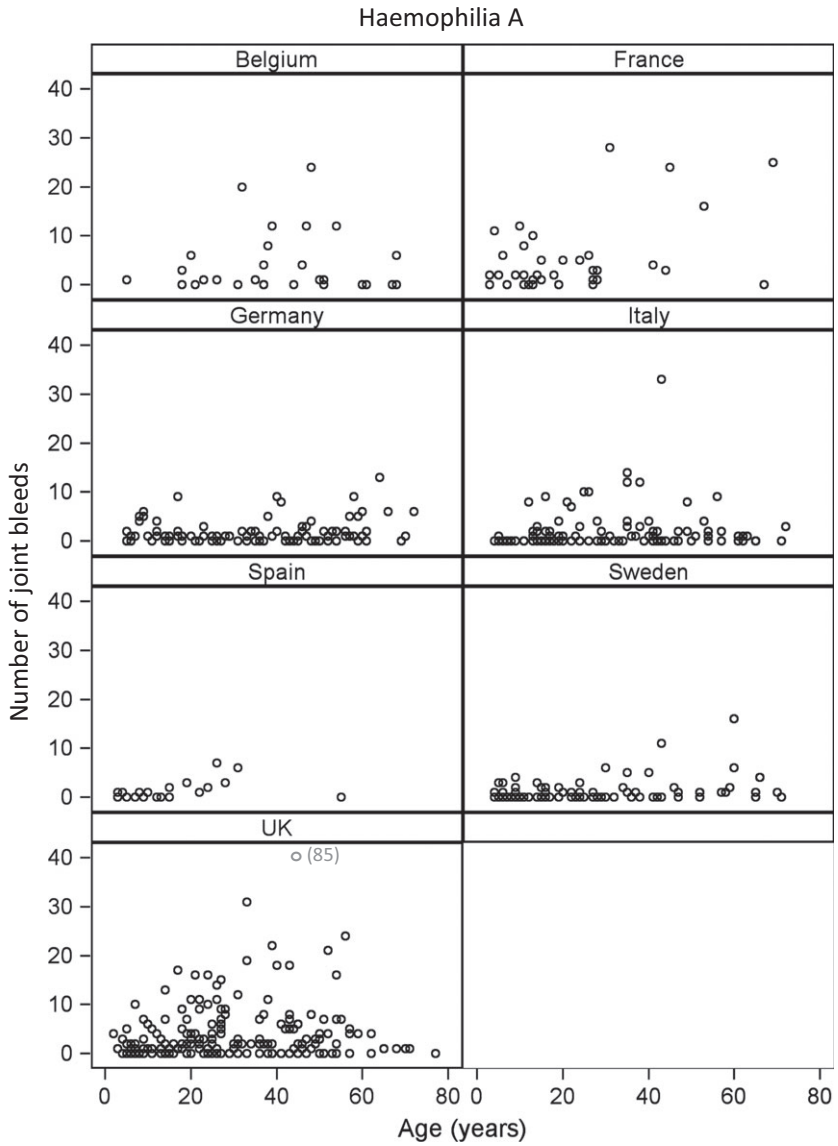


Fig. 4. Total number of joint bleeds by age for patients with haemophilia A on regular prophylaxis during the 12-month study period. Each dot represents one patient. One patient in the UK, 46 years of age, with an outlier bleed value of 85 is indicated in grey.

with frequent bleeds to avoid pain and deterioration of joint function [2].

A limitation of this study was that the local variation in patient care at the haemophilia centres may not truly reflect the country as a whole, apart from the UK (national register). Another limitation was the differing arrangements for recording patient information. The study attempted to obtain data on the amount of factor that was issued and/or used by each patient as well as the prescribed dose for all patients on prophylaxis. Unfortunately, only partial data were retrievable for both issued and used doses, while data on prescribed dose were complete for all countries, except for UK where prescribed dose was not part of the available dataset. Prescribed dose in some countries included treatment for bleeds, while in others, it was not included. For the purposes of this study, issued and prescribed dose were assumed to offer equivalent insight into therapeutic practice, although possibly the issued dose reflects usage more accurately due to a degree of patient non-adherence. Finally, another limitation was the low number of patients with haemophilia B reflecting its low incidence, preventing subgroup analysis such that the results might be generalizable to the whole patient population.

This study was an ambitious project to assess the efficacy of haemophilia care in real life. Future studies may be easier to undertake if a more uniform set of data can be collected, e.g. using smart phone technology, and the establishment of national registers as supported by the World Federation of Haemophilia and the European Medicines Agency. This will allow increased monitoring of haemostasis and product use, which will benefit patients and be of value to funders. Many patients on prophylactic and on-demand treatment still experience an appreciable number of bleeds, which should strongly encourage the use of more efficient treatment. Higher FVIII/FIX trough levels and

increased patient adherence will undoubtedly reduce bleeding and these pose significant challenges for all haemophilia services.

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Author contributions

Stefan Lethagen, Christopher Ludlam and Erik Berntorp contributed to the conceptualization and design of the study. Erik Berntorp was coordinating investigator for the study and Stefan Lethagen coordinated and supervised the overall study performance. Erik Berntorp, Gerry Dolan, Charles Hay, Silvia Linari, Elena Santagostino, Alberto Tosetto, Giancarlo Castaman, Teresa Álvarez-Román, Rafael Parra Lopez, Johannes Oldenburg, Albert Thilo, Ute Scholz, Margareta Holmström, Jean-François Schved, Marc Trossaërt, Cedric Hermans and Ana Boban recruited patients to the study. Stefan Lethagen, Christopher Ludlam drafted the manuscript and all authors contributed to the analysis and interpretation of data and revised the manuscript and approved of the final manuscript as submitted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Treatment regimen for patients with haemophilia A by age group, by severity and by centre. The proportion in each treatment regimen was based on information from patients prescriptions, except for UK (striped columns) where it was estimated based on the patients self-reported treatments.

Figure S2. Dose frequencies for patients with haemophilia on prophylaxis by centre. Prescribed dose frequencies for patients with haemophilia A for all countries except for UK, for which the dose frequency was estimated based on the patients' self-reported treatments in the Haemtrack database (striped columns).

Figure S3. Total number of bleeds (all types of bleeds) by age for patients with haemophilia A on regular prophylaxis during the 12-month study period. Each dot represents one patient. One patient in the UK, 46 years of age, with an outlier bleed value of 107 is indicated in grey.

Table S1. Number of patients with haemophilia A and haemophilia B treated with recombinant or plasma-derived products, by age group.

Table S2. Prescribed or issued treatment (IU kg^{-1} per week) for patients with haemophilia A or haemophilia B on regular prophylaxis by severity and by centre.

Table S3. Prescribed or issued treatment (IU kg^{-1} per week) for patients with haemophilia A or B on regular prophylaxis, by age group.

Table S4. Used treatment (IU kg^{-1} per week) for patients with haemophilia A or B with on-demand treatment.

Table S5. Dose frequency for patients with haemophilia A on regular prophylaxis by age group [*n* (%)].

Table S6. Annual bleeding rates for patients with haemophilia A and B on on-demand treatment (bleed population[a]).

