Treatment outcomes in persons with severe haemophilia B in the Nordic region

The B-NORD study

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Treatment outcomes in persons with severe haemophilia B in the Nordic region: The B-NORD study

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Abstract

Introduction: Data on outcome in persons with haemophilia B (PwHB) are limited and mainly extrapolated from studies of haemophilia A (HA).

Aim: To characterize treatment outcomes in persons with severe HB in the Nordic region, with a focus on joint health, compared with matched controls with HA.

Methods: PwHB attending haemophilia centres in Denmark, Finland, Norway and Sweden were enrolled and matched with controls with HA. Joint assessment using Haemophilia Joint Health Score (HJHS) and ultrasound according to Haemophilia Early Arthropathy Detection protocol (HEAD-US) was conducted. Adherence was evaluated using the Validated Haemophilia Regimen Treatment Adherence Scale (VERITAS).

Results: Seventy-nine males with HB, with median age of 30 years (range 1–75), were enrolled. Eleven patients (14%) had a history of or current inhibitor. Twenty-nine PwHB (37%) reported joint bleeds during the prior year, and 35% had previously undergone joint surgery. Ninety-five per cent were on prophylaxis, and 70% used recombinant concentrates, with a median factor consumption of 3,900 IU/kg/year for...
INTRODUCTION

Haemophilia B (HB) is a rare inherited X-linked bleeding disorder caused by the deficiency of coagulation factor IX (FIX). Patients with the severe form of the disease (FIX activity <0.01 IU/mL) suffer from the risk of traumatic and spontaneous bleeding, typically in the joints, causing arthropathy. To prevent bleeding, the use of prophylactic treatment with FIX replacement therapy was introduced in the 1960s and is still considered the gold standard of care.

There are few reports on treatment and outcome in HB, and when available, HB often constitutes a minor part of a larger cohort, mainly including patients with the more common haemophilia A (HA). Consequently, much of our knowledge and treatment regimens for HB have been extrapolated from studies based on persons with HA (PwHA). HA and HB have historically been considered identical disorders, but there are important differences between the diseases. These include the profile of causative mutations, inhibitor incidence, outcome of immune tolerance induction, treatment complications and differences in clearance and distribution volume of treatment products, with FIX entering the extravascular space. It is an ongoing debate whether the phenotypes of HA and HB differ. Reports claiming that the phenotype of HB is milder than that of HA have been published, as well as reports of prophylactic treatment being less frequently used in HB. However, the data are limited and the findings inconsistent. For example, Clausen et al. found no difference in phenotype in a prospective cohort of children and no difference in bleeding frequency, treatment intensity and/or number of arthroplasties was found at the Van Creveld Clinic.

To better understand HB and improve the care for our patients, studies focusing on persons with HB (PwHB) are of importance, and even more so today with new possibilities of individualized treatment. Extended half-life (EHL) products have recently been introduced, and non-factor products and gene therapy are emerging. Thus, due to the rarity of the disease, multicentre collaborations are needed. The Nordic countries have, through the Nordic Haemophilia Council, a collaborative network aiming to improve and standardize haemophilia care with guidelines and follow-up studies.

The aim of this study was to characterize persons with severe HB in the Nordic countries concerning treatment, bleedings and arthropathy, and to compare their joint health with matched PwHA.

MATERIALS AND METHODS

2.1 Study design

B-NORD is a multicentre, cross-sectional, observational study conducted in six haemophilia treatment centres (HTCs) in Denmark, Finland, Norway and Sweden. In Norway and Sweden, all haemophilia care is provided by the included centres. The HTC in Copenhagen, caring for approximately half of Denmark’s PwHB, was included, as well as the HTC in Helsinki, which covers approximately 60% of Finland’s haemophilia population. The data management system was operated at the Center for Thrombosis and Hemostasis Malmö, Sweden.

Ethical approval was obtained from the independent ethics committees in the different countries before enrolment started. The study subject or his legal representative signed an informed consent form before entering the study.

2.2 Study population

Individuals eligible for inclusion were all males or females, registered at one of the participating centres, with a confirmed diagnosis of congenital severe HB, defined as FIX activity <0.01 IU/mL in the one-stage or chromogenic assay. Exclusion criteria included concomitant bleeding disorders and the inability to provide informed consent.

Each PwHB was matched by age, gender and treatment modality, to a control person with severe HA from one of the participating Nordic HTCs. The controls were identified in the KAPPA
register, a Web-based international register of PwHA developed by Haemophilia Systems (Munkeby Systems, Malmö, Sweden).

Enrolment of PwHB began in June 2017 and ended in April 2020. The controls were enrolled between October 2013 and December 2017.

2.3 Study procedures

The study procedure comprised one study visit at enrolment for the PwHB. Data on medical and inhibitor history, including inhibitor response (low-responding <5 BU, high-responding ≥5 BU) and treatment and bleeding episodes over the prior 12 months, were registered. Mainly paper diaries were used. Joint assessment using the Haemophilia Joint Health Score version 2.1 (HJHS) was completed, and ultrasound according to the Haemophilia Early Arthropathy Detection protocol (HEAD-US) was conducted by a physiotherapist or physician within the haemophilia team. The maximum total score for HJHS 2.1 is 124 (worst score possible) with a maximum score of four on global gait and 20 per assessed joint (elbows, knees and ankles). HEAD-US is a validated ultrasound scoring method for elbows, knees and ankles evaluating disease activity (hypertrophic synovium) and disease damage (articular surfaces including cartilage and bone). The maximum score is 8 per joint. Joints with arthropathies were recorded as missing data. In cases of severe arthropathy and reduced joint mobility preventing optimal ultrasound images, the maximum score was given. If not performed at the study visit, HJHS or HEAD-US results recorded within one year of enrolment the maximum score was given. If not performed at the study visit, and reduced joint mobility preventing optimal ultrasound images, the maximum score was given. If not performed at the study visit, absence from visits at the HTC due to illness, old age or poor compliance (n = 13), a wish not to participate (n = 7), language difficulties or cognitive disabilities (n = 3) or transfer to another HTC (n = 1). Due to local decisions, no ethical approval could be obtained for children in Denmark (n = 5).

3 RESULTS

3.1 Patient and treatment characteristics

Out of 108 registered persons with severe HB attending the study centres, 79 (73%) males were enrolled in the study. No females fulfilled the inclusion criteria. Reasons for non-participation were absence from visits at the HTC due to illness, old age or poor compliance (n = 13), a wish not to participate (n = 7), language difficulties or cognitive disabilities (n = 3) or transfer to another HTC (n = 1). Due to local decisions, no ethical approval could be obtained for children in Denmark (n = 5).

The clinical characteristics of the study subjects are provided in Table 1. The median age at enrolment for the PwHB was 30 years (Q1-Q3 19–53, range 1–75). Sixteen patients (20%) were under the age of 18 years. Eleven PwHB (14%) had a history of or current inhibitors, eight with high-responding and three with low-responding inhibitors. All had undergone at least one attempt of immune tolerance induction, and eight were considered tolerant at enrolment. Four patients (5.1%) had human immunodeficiency virus (HIV) infection, and 31 (39%) had a current or recovered hepatitis C infection. Seventy-five subjects (95%) were on prophylactic treatment, and the median age at start of prophylaxis was 3.0 years (Q1-Q3 1.0–16). Seventy per cent of the PwHB were on treatment with recombinant FIX, and 27% of these with EHL. In comparison, 89% of the PwHA were treated with recombinant FVIII. None of the controls were on EHL, explained by the earlier enrolment period. The annual median factor consumption for recombinant products was 3,900 IU/kg/year for both PwHA and PwHB on standard half-life products (SHL), and 2,000 IU/kg/year (Q1-Q3 1,500–2,400) for PwHB on EHL products. The corresponding figure for FIX plasma-derived (PD) products was 2,900 IU/kg/year (Q1-Q3 1,600–6,000) compared with 5,000 IU/kg/year (Q1-Q3 3,500–5,800) for FVIII PD products. Further descriptions of treatment characteristics are provided in Table 2.

3.2 Bleeding Episodes

Bleeding characteristics are shown in Table 3. Twenty-nine PwHB (37%) reported one or more joint bleeds in the prior 12 months. Of these, five were younger than 18 years. The median number of joint bleeds for the HB cohort was zero (Q1-Q3 0–1.3) and ranged from zero to 18. The number of patients with reported bleeds in the knees, ankles and elbows was similar. Five PwHB (6.4%), one with
a current inhibitor, had a target joint, whereas five (all children between ages 1 and 9) reported no previous joint bleeds. Among those who had experienced a joint bleed, the median age at the first episode was 2.0 years (Q1-Q3 1.0–4.0).

To evaluate the association between bleeding rate and factor consumption, patients on SHL products were divided into three subgroups according to WFH’s definition of high-dose (>4,000 IU/kg/year), intermediate-dose (1,500–4,000 IU/kg/year) and low-dose (<1,500 IU/kg/year) prophylaxis. No significant differences in the number of bleeding events were found among these subgroups (Table 4). In addition, patients on PD FIX, recombinant SHL or EHL FIX products showed no significant differences in the occurrence of joint bleeds or other bleeds over the prior 12 months.

### 3.3 | Joint outcome

The HJHS and HEAD-US results are presented in Table 5 and Figure 1. The median total HJHS was significantly lower among PwHB compared with PwHA (*p* = 0.048), having median values of 4 (Q1-Q3 1.5–21) and 14 (Q1-Q3 2–35), respectively. The difference was significant in the age group 18–49 years, but not among those under 18 or above 49 years. Since HJHS 2.1 is not validated for children below four years of age, these patients (n = 3) were not examined. HJHS results were missing in an additional 11 PwHB. The HA controls for PwHB lacking HJHS assessment were excluded.
from the calculations, as were patients with a history of or current inhibitor.

The HEAD-US results showed overall low scores, with medians of 0 in both elbows (Q1-Q3 0–5) and knees (Q1-Q3 0–3) and 1 (Q1-Q3 0–6) for the ankles. The scores primarily reflected disease damage, equally divided by cartilage and bone, whereas only minor hypertrophic synovium was observed.

Twenty-seven PwHB (35%), with median age of 56 (Q1-Q3 40–66), had undergone joint surgery. Knee arthroplasty was the most common procedure followed by ankle arthrodesis. The detailed data on prior joint surgeries are presented in Appendix 1.

### 3.4 Treatment adherence

The median VERITAS-Pro score for PwHB was 38 (Q1-Q3 33–48). Only two patients had a total score of ≥57, the cut-off for ‘non-adherence’. As shown in Figure 2, the highest scores (least adherent) were reported in the subscale ‘communicate’ and the lowest scores (most adherent) in the subscales ‘dose’ and ‘skip’. The median total score was slightly higher, 43 (Q1-Q3 35–50), among the 18–49 years’ age group compared with younger and older age groups having scores of 37 (Q1-Q3 30–39) and 33 (Q1-Q3 27–39), respectively. The VERITAS-Pro score did not differ between patients on EHL and patients on SHL products, with median values of 36 (Q1-Q3 28–50) and 38 (Q1-Q3 34–46).

### 4 DISCUSSION

This is the first study in the Nordic region to describe treatment and outcome of patients with severe HB, including a comparison to matched controls with HA. The majority (95%) of the patients were on prophylaxis from a young age with no difference in age at start compared with PwHA. Despite the high prophylaxis frequency, 37% of the PwHB reported at least one joint bleed during the prior 12 months and 44% reported non-joint bleeding episode(s).

The median annual joint bleeding rate (AJBR) of zero in our material is at a similar level of reported AJBRs for patients on EHL products and lower than that of 3.8 in the cohort from the Van Creveld Clinic. In that cohort, however, only 73% of the patients were on prophylactic treatment. Our finding of 2.0 years as the median age at first joint bleed is similar to that of 1.2 reported by the PedNet group, as well as 2.4 years reported by Uijl et al.

Somewhat unexpected, the median factor consumption among the Nordic PwHB on SHL products was just below 4,000 IU/kg/year, indicating that less than 50% of the population received high-dose prophylaxis as defined by the WFH. However, no difference in bleeding rate was observed in a subgroup analysis of high and low factor consumption and the overall preserved joints indicate successful use of individualized treatment. It is also worth pointing out that PwHB on

### TABLE 3 Bleeding characteristics of the haemophilia B population in B-NORD

| Age at first joint bleed, years, median† (Q1-Q3)| 2.0 (1.0–4.0) |
| Target joint at visit (%)‡ | 5 (6.4)¶ |
| Annual joint bleeding rate last 12 months, median‡ | 0 (Q1-Q3 0.0–1.3, range 0–18) |
| On-demand treatment | 5 (range 0–10) |
| Prophylactic treatment | 0 (Q1-Q3 0–1, range 0–18) |
| ITI/bypass therapy§ | 4 |
| Number of patients with at least one joint bleed last 12 months (%)‡ | 29 (37) |
| Location of joint bleed, number of patients (%) |  
| Knee | 12 (15) |
| Ankle | 10 (13) |
| Elbow | 10 (13) |
| Shoulder | 6 (7.7) |
| Hip | 4 (5.1) |
| Wrist | 2 (2.6) |
| Number of patients with at least one non-joint bleed last 12 months (%) | 35 (44) |

Numbers (%) or median (Q1, first quartile—Q3, third quartile). †n = 57. ¶n = 78. ‡n = 1; missing data=1. ¶including one patient with a current inhibitor.

### TABLE 4 Bleeds and treatment intensity in haemophilia B patients on prophylactic treatment with standard half-life products

| High dose n = 26 | Intermediate dose n = 28 | Low dose n = 4 | p |
| Number of patients with at least one joint bleed last 12 months (%) | 11 (42) | 10 (35.7) | 1 (25) | 0.84 |
| Number of joint bleeds last 12 months, median [Q1-Q3] | 0 (0–2.3) | 0 (0–1) | 0 (0–0.75) | 0.61 |
| Number of patients with at least one non-joint bleed last 12 months (%) | 11 (42) | 12 (43) | 1 (25) | 0.85 |
| Number of non-joint bleeds last 12 months, median [Q1-Q3] | 0 (0–2) | 0 (0–2) | 0 (0–1.5) | 0.80 |

Numbers (%) or median (Q1, first quartile—Q3, third quartile). High dose: >4,000 IU/kg/year. Intermediate dose: 1,500–4,000 IU/kg/year. Low dose: <1,500 IU/kg/dose.
PD products had a 26% lower median factor consumption compared with recombinant SHL FIX, consistent with the differences in pharmacokinetics between these types of concentrates. Moreover, the PwHB on EHL products consumed about half of the amount of factor compared with those receiving SHL products with a preserved bleed protection, emphasizing the value of EHL agents in clinical practice.

Fourteen per cent of the PwHB had a history of or current inhibitor. This is a relatively high number compared with previously published data, and further characterization of these patients will be reported separately.

### Joint outcome

We found a significantly lower HJHS, indicating better joint health, among PwHB compared with PwHA. This was explained by findings among persons between 18 and 49 years of age, whereas the outcomes for the younger and the older subgroups showed no difference. The reason for this is not clear, and treatment provided over the years needs to be taken into account, but this may indicate that arthropathy develops earlier in PwHA than in PwHB. Arthropathy is a progressive disorder, and the HJHS are, as expected, higher in the

![Figure 1: HJHS in haemophilia patients divided by type of haemophilia and age group. Patients with a current or previous inhibitor are excluded from the calculations. HJHS, Haemophilia Joint Health Score 2.1 (Colour figure can be viewed at wileyonlinelibrary.com)](image-url)
older age groups of both HA and HB, but without significant difference between the groups. This could indicate that the difference may even out at older age or represents a more successful prophylactic treatment in PwHB compared with PwHA. The difference in median scores between the age groups 18–49 years and ≥50 years may be larger than expected. This might partly be explained by the fact that prophylaxis was introduced later in life in the older age group compared with the younger group. However, the number of study subjects in the older group is relatively small and firm conclusions cannot be drawn. In agreement with our findings for children, the PedNet group reported no difference in bleeding phenotype among young children with severe HA and HB, whereas Melchiorre et al. compared arthropathy in patients with severe HA and HB and concluded that the degree of arthropathy was more severe in PwHA. This conclusion is supported by Nagel et al., who reported more bleeding episodes and surgical procedures in PwHA than in PwHB despite similar factor consumption. Consistent with this, Tagariello et al. found a threefold higher risk for undergoing joint arthroplasty among PwHA compared with PwHB. These studies suggest, in agreement with our findings in persons 18–49 years, a lower risk of developing arthropathy for PwHB than PwHA. We believe it unlikely that the difference in HJHS in our study is an effect of lesser treatment intensity for PwHA, since the factor consumption was similar between the groups, although lifelong consumption has not been taken into account. The potential anti-inflammatory role of FVIII described by Mignot et al., as well as the role of extravascular FIX in coagulation, has been debated, but whether this has an impact on joint outcome and can explain differences between HA and HB is not clear. The same applies for the suggestion that the higher prevalence of missense mutations over null mutations in PwHB compared with PwHA could contribute to a milder clinical phenotype.

4.2 | Treatment adherence

Adherence to treatment is crucial for the risk of developing arthropathy. In our cohort, evaluation by VERITAS indicated overall good adherence. However, it remains to be settled whether these scores reflect the benefits of the structure of haemophilia care in the Nordic region, with centralized care and extensive patient education. Or is it perhaps, the result of bias, as the patients answering the questionnaire (70%) may be the ones with the highest adherence? We found the least adherent scores in the category ‘communicate’ with 36% of the patients having a score consistent with ‘non-adherence’. This category evaluates how often the patients call the HTC for advice and treatment decisions. The use of modern technology for communication might be a way to improve this adherence. The highest adherence was seen in the subgroup of patients ≥50 years and the lowest among patients 18–49 years, potentially indicating the impact of work and family life. It is a limitation of our study that no
VERITAS data were available for the PwHA. However, in support of our findings, Miesbach et al. observed a similar VERITAS-pro median total score of 34 and a significantly higher score among patients aged 20–59 in a cohort of 397 PwHA or PwHB.

4.3 | Strengths and limitations

Despite its international multicentre design, our study has the limitations of a retrospective observational investigation with a limited number of subjects. Furthermore, information on bleedings and joint surgery was incomplete in the KAPPA register; hence, these parameters could not be compared. In addition, the enrolment period for PwHB and PwHA was slightly different. However, our study, in contrast to the majority of previous studies of haemophilia, is focusing on PwHB and includes closely matched controls with HA from the same HTCs. The patients are also from a homogenous geographic area, and the number of included patients is, compared with previously published reports on persons with severe HB, relatively high.

5 | CONCLUSION

Our study indicates that the Nordic cohort of patients with severe HB is well treated and adherent to individualized treatment regimens. Despite this, the goal of zero bleeds for all has not been reached. Hence, in an era of new treatment options, more attention should be given to improve the care for PwHB. Our findings also suggest and support previous findings that patients with severe HB suffer from milder arthropathy than patients with severe HA.

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DISCLOSURES

KK has received research grants from CSL Behring, Stockholm, Sweden. FB has received honoraria as member of advisory board and/or speaker from Sobi, Shire/Takeda, Novo Nordisk, Bayer, Roche, UniQure, Octapharma, BioMarin and Pfizer. MB was supported by funds from Stockholm County Council. EF has received honorarium as speaker for Shire, Roche, Sobi and Takeda. PAH has acted as a paid consultant to Bayer, Shire, Novo Nordisk, Octapharma, CSL Behring, Pfizer and Sobi including lectures. RL has been a member of advisory boards for Sobi, CSL Behring, Takeda, BioMarin, Novo Nordisk, Pfizer, ROCHE and Bayer. MO has received speaker/consultant fees from Novo Nordisk, Shire and Bayer. EB has received research grants and paid consultancy from CSL Behring, Stockholm, Sweden. JA has received research grants from Sobi, CSL Behring, Takeda/Shire and Bayer and speakers’ fee and consultant for Octapharma, Novo Nordisk, Pfizer, Bayer, Sobi, CSL Behring, Takeda/Shire, BioMarin, UniQure and Spark Therapeutics. VN and SR stated that they had no interests, which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

JA, EB and KK designed the research study. KK analysed the data. KK and JA interpreted the data and drafted the paper. KK, JA, MB, EF, PAH, RL, VN and SR enrolled patients and collected the clinical data. MO and EB designed the KAPPA study and developed the KAPPA registry. All authors critically reviewed the manuscript and have read and approved the final version of the manuscript.

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APPENDIX 1

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