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Haemophilia early arthropathy detection with ultrasound and haemophilia joint health score in the moderate haemophilia (MoHem) study

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Abstract

Introduction: Detection of early arthropathy is crucial for the management of haemophilia, but data on moderate haemophilia are limited. Therefore, we evaluated joint health and treatment modalities in Nordic patients with moderate haemophilia A (MHA) and B (MHB).

Aim: To explore and compare the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and Haemophilia Joint Health Score (HJHS) to detect early arthropathy in moderate haemophilia.

Methods: A cross-sectional, multicentre study covering Nordic patients with MHA and MHB. Arthropathy was evaluated by HEAD-US and HJHS 2.1.

Results: We assessed 693 joints in 118 patients. HEAD-US scores (medians [interquartile ranges]) were as follows: elbows 0 points (0–0), knees 0 (0–0) and ankles 0 (0–1). Respectively, by HJHS: elbows 0 (0–1), knees 0 (0–1) and ankles 0 (0–1). Cartilage (14%) and bone (13%) were most commonly affected by HEAD-US. Frequent HJHS findings were crepitus on motion in knees (39%), and loss of flexion (23%) and extension (13%) in ankles. HEAD-US correlated strongly with HJHS (elbows $r = .70$, knees $r = .60$ and ankles $r = .65$), but 24% had discordant scores. Joints with HJHS zero points, 5% captured HEAD-US ≥ 1 point. Moreover, 26% had HJHS findings without HEAD-US pathology. Notably, 31% of knees had crepitus on motion and normal HEAD-US.

Conclusion: Overall, the joints attained low scores implying good joint health. HEAD-US correlated strongly with HJHS. In 5%, HEAD-US detected subclinical pathology. Crepitus on motion was frequently reported despite normal HEAD-US, thus not necessarily reflecting arthropathy. HEAD-US therefore improves the joint assessment in moderate haemophilia.

KEYWORDS
arthropathy, joint score, moderate haemophilia A, moderate haemophilia B, prophylaxis, ultrasound

1 | INTRODUCTION

Arthropathy is the main complication in haemophilia. Proper assessment of joint health is therefore crucial in the follow-up and evaluation of treatment modalities. Synovial and cartilage changes should be detected at an early stage to prevent further deterioration and irreversible joint damage with loss of function and impaired quality of life. In 2006, Hilliard et al developed Haemophilia Joint Health Score (HJHS) as a more sensitive tool for evaluation of haemophilic arthropathy than the World Federation of Haemophilia physical examination scale.[1] HJHS assesses arthropathy in elbows, knees and ankles and consists of structural and functional items. Reliability and validity are well established in children[1,2] and young adults.[3] In 2013, Martinoli et al developed Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) as a simplified evaluation of early arthropathy by non-radiologists.[4] HEAD-US assesses the synovium, cartilage and subchondral bone in elbows, knees and ankles. Data on reliability[5,6] and validity[7] have supported the use among clinicians with limited ultrasound skills. In previous publications, HEAD-US and HJHS have been considered as supplementary tools to evaluate joint health in haemophilia.[8-13]

Prophylactic replacement therapy has reduced the prevalence of arthropathy among patients with severe haemophilia.[14-16] In moderate haemophilia, treatment guidelines are less clear, and prophylaxis has been individualized, often with delayed onset. Previous publications have suggested that these patients are undertreated.[17-19] Detection of early-stage arthropathy may therefore be decisive for initiation of regular prophylaxis in patients with moderate haemophilia. In the MoHem study, we evaluated the current joint health in Nordic patients with moderate haemophilia A (MHA) and B (MHB) using HEAD-US and HJHS.[20] Overall, the joint health was close to normal with total HEAD-US 0/48 points (median; IQR 0–2) and HJHS 4/120 points (IQR 1–10). Moreover, correlation between the total scores was strong (r = .72). Baseline factor VIII/factor IX activity (FVIII/FIX:C) ≤ 3 IU/dl and MHA were associated with a more severe bleeding phenotype. The aim of this paper was to explore the HEAD-US and HJHS in detail on joint level and compare these assessment tools to detect early arthropathy in moderate haemophilia.

2 | MATERIALS AND METHODS

The MoHem study is a cross-sectional, multicentre study that covers MHA and MHB (FVIII/FIX:C 1–5 IU/dl)[21] of all ages from Sweden, Finland and Norway. The recruitment to the study has been described previously.[20] Briefly, the enrolment took place at the Haemophilia Comprehensive Care Centres (HCCC) in Oslo, Malmö, Gothenburg, Stockholm and Helsinki between January 2017 and October 2019. Arthropathy in index joints (elbows, knees and ankles) was evaluated by HEAD-US and HJHS 2.1 for patients above 5 years of age. Trained physicians or physiotherapists affiliated to the HCCCs performed HEAD-US and HJHS. The order of the examinations in each patient was randomly assigned, and either one or two persons did the scores. Mainly, HEAD-US and HJHS were done

at enrolment; however, examinations performed within 1 year of enrolment were accepted. HEAD-US contains a score of 0–8 points per joint, including synovial hypertrophy (0–2 points), cartilage degeneration (0–4 points) and bone irregularities (0–2 points). HJHS 2.1 contains 0–20 points per joint, reaching a total score of 120 points, gait score excluded. The items assessed by HJHS are swelling, muscle atrophy, crepitus on motion, range of motion, joint pain and strength. Joints that had undergone arthroplasties or arthrodesis were excluded from HEAD-US. HJHS was scored in a regular way in all joints. However, for this HEAD-US and HJHS comparison, we only included joints that were assessed by both tools. In both HEAD-US and HJHS, score ≥1 point was defined as positive. The scores were categorized as discordant if only one of them was positive. Moreover, for each group of joints (elbows, knees and ankles), we report mean HEAD-US and HJHS values.

Statistical analyses used were mainly descriptive and performed on joint level. The parameters had a skewed distribution. Continuous data are summarized as medians and interquartile ranges (IQR), and categorical data are presented as numbers and percentages. We used Mann-Whitney U test and Spearman's correlation (r) for comparison between HEAD-US and HJHS (continuous variables). A p-value <.05 was considered statistically significant. The positive predictive value of HJHS with respect to HEAD-US was defined as the probability of positive HEAD-US score if HJHS captured ≥1 point. Correspondingly, the negative predictive value of HJHS with respect to HEAD-US was defined as the probability of normal HEAD-US if HJHS captured zero points. Statistical analyses were performed using SPSS Statistics 26.

3 | RESULTS

Patient characteristics and major outcomes of the MoHem study (Table 1) have been reported previously.[20] We assessed 693 joints in 118 patients by HEAD-US and HJHS. HEAD-US was low in all joint groups: elbows 0 points (median; IQR 0–0), knees 0 points (IQR 0–0) and ankles 0 points (IQR 0–1). HEAD-US had positive score (≥1 point) in 134 joints (19%): 36 elbows (15%), 45 knees (20%) and 53 ankles (23%; Figure 1). Respectively, HJHS was also low in all joint groups: elbows 0 points (median; IQR 0–1), knees 0 points (IQR 0–1) and ankles 0 points (IQR 0–1). HJHS had positive score in 257 joints (37%): 45 elbows (19%), 107 knees (47%) and 105 ankles (46%; Figure 1). Regarding the specific items, HEAD-US detected cartilage degeneration (14%) and bone irregularities (13%) twice as often as synovial hypertrophy (6%; Table 2). Recurrent HJHS findings included crepitus on motion in knees (39%), and loss of flexion (23%) and extension (13%) in ankles (Table 3).

3.1 | HEAD-US and HJHS comparison at joint level

Correlation between HEAD-US and HJHS was strong in all joints: elbows r = .70, p < .001, knees r = .60, p < .001 and ankles r = .65,

TABLE 1 Patient characteristics and major outcomes in the MoHem study (N = 145)

	All patients (N = 145)
Age (years)	28 (13–52)
Haemophilia A	89 (61%)
Baseline FVIII or FIX activity (IU/dl)	2 (2–4)
History of haemarthrosis	117 (81%)
Age at first joint bleed[a] (years)	5 (3–8)
Currently on prophylaxis	55 (38%)
Age at start of prophylaxis (years)	10 (4–24)
Joint bleeds during the last 12 months	0 (0–1)
HEAD-US total[b] (0–48 points)	0 (0–2)
HJHS total[c] (0–120 points)	4 (1–10)
Arthroplasties or arthrodesis	22 (15%)

Numbers (%) or medians (interquartile range). The number of the patients (n) is noted if it deviated from the total number: [a]n = 111/117; [b]n = 118/145; [c]n = 135/145.
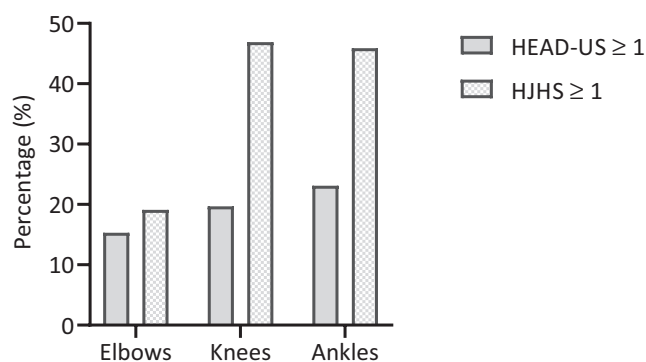
FIGURE 1 Percentage of joints with positive scores (≥1 point) by Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and Haemophilia Joint Health Score (HJHS; n = 693)

TABLE 2 Haemophilia Early Arthropathy Detection with Ultrasound; the number of joints (%) with positive score (≥1 point) according to each item

	Elbows (n = 236)	Knees (n = 228)	Ankles (n = 229)	Total (n = 693)
Synovium	11 (5%)	17 (7%)	15 (7%)	43 (6%)
Cartilage	34 (14%)	23 (10%)	39 (17%)	96 (14%)
Bone	24 (10%)	33 (14%)	35 (15%)	92 (13%)

Numbers (%).

p < .001 (Figure 2). However, 24% (167/693) of the joints had discrepancy between them (Figure 3A, Table 4). Out of joints with HJHS zero points, 5% (22/436) captured ≥1 point by HEAD-US, which indicate a HJHS negative predictive value of 95%. The HEAD-US items found

in these joints are illustrated in Figure 3B. In elbows, there were cartilage degeneration in 5% (10/191), bone irregularities in 3% (5/191) and synovial hypertrophy in 1% (2/191) of the joints. In knees, there were synovial hypertrophy (3/121) and bone irregularities (2/121) each in 2% of the joints. In ankles, there were cartilage degeneration in 4% (5/124) and synovial hypertrophy and bone findings in 1% (1/124) each. Severe synovitis, complete cartilage destruction or deranged subchondral bone were not seen among these joints which captured zero points by HJHS.

Five hundred and fifty-nine joints (81%) captured zero points by HEAD-US. Of these, 26% (145/559) had findings by HJHS (Figure 3C). In elbows, there was crepitus on motion in 4% (8/200) of the joints, while flexion loss (4/200), extension loss (3/200), muscle atrophy (3/200) and reduced strength (4/200) each was found in 2%. In knees, there was crepitus on motion in 31% (56/183), and extension loss and reduced strength in 4% (7/183) each. In ankles, 17% (30/176) of the joints had flexion loss, 11% (19/176) had crepitus on motion, 10% (17/176) had extension loss and 3% (6/176) had pain at physical examination. Thus, crepitus on motion, especially in knees, was reported frequently by physical examination without corresponding findings at HEAD-US. Of joints with positive score at HEAD-US, however, crepitus on motion had a weak/moderate correlation with cartilage degeneration (r = .32, p < .01) and bone irregularities (r = .45, p < .001), but not with hypertrophic synovium (p = .18). Crepitus on motion and synovial hypertrophy correlated weakly in elbows (r = .38, p < .001), but not in knees or ankles.

HJHS 1–3 points corresponded with HEAD-US zero points in 67% (137/206) of the joints (Table 4), thus these low HJHS scores had a positive predictive value of 33% with respect to positive HEAD-US score. Moreover, HJHS >3 points had a positive predictive value of 84%, which increased to 91% for HJHS >6 points. Notably, in 4% (10/230) of elbows, 6% (14/223) of knees, and 4% (8/215) of ankles, there was synovial hypertrophy at HEAD-US without signs of swelling at HJHS. Median HJHS of these joints was 3 points (IQR 1–7). Vice versa, 1% (3/223) of elbows, 1% (2/211) of knees, and 3% (7/214) of ankles had swelling at HJHS without synovial hypertrophy at HEAD-US. Median HEAD-US of these joints was 2 points (IQR 0–6).

4 | DISCUSSION

We assessed arthropathy using HEAD-US and HJHS in Nordic patients with MHA and MHB. Overall, the joints attained low scores. Knees and ankles were most frequently affected. Correlation between HEAD-US and HJHS was strong in all joints, but nevertheless 24% had discordant scores. Crepitus on motion, especially in knees, was frequently reported without corresponding findings by HEAD-US. Moreover, in 5% of the joints, HEAD-US detected subclinical pathology.

Correlation between HEAD-US and HJHS was slightly stronger in elbows than in ankles and knees. In both assessment tools, however, ankle scores have been considered less reliable.[1,4,6] HJHS had

	Elbows (n = 236)	Knees (n = 228)	Ankles (n = 229)	Total (n = 693)
Swelling[a]	4 (2%)	5 (2%)	14 (6%)	23 (3%)
Duration of swelling[a] (>6 months)	1 (0.4%)	5 (2%)	7 (3%)	13 (2%)
Muscle atrophy	13 (6%)	13 (6%)	9 (4%)	35 (5%)
Crepitus on motion[b]	16 (7%)	88 (39%)	36 (16%)	140 (20%)
Flexion loss[c]	19 (8%)	18 (8%)	52 (23%)	89 (13%)
Extension loss[d]	24 (10%)	16 (7%)	29 (13%)	69 (10%)
Joint pain	8 (3%)	12 (5%)	16 (7%)	36 (5%)
Strength[e]	7 (3%)	19 (8%)	15 (7%)	41 (6%)

TABLE 3 Haemophilia Joint Health Score; the number of joints (%) with positive score (≥1 point) according to each item

Numbers (%). The number of joints (n) is noted if it deviated from the total number: [a]n = 234 elbows and 691 total; [b]n = 227 knees, 228 ankles and 691 total; [c]n = 234 elbows, 227 knees, 228 ankles and 689 total; [d]n = 234 elbows, 228 ankles and 690 total; [e]n = 230 elbows, 225 knees, 221 ankles and 676 total.


Elbows: $r = .70$, $P < .001$
Knees: $r = .60$, $P < .001$
Ankles: $r = .65$, $P < .001$
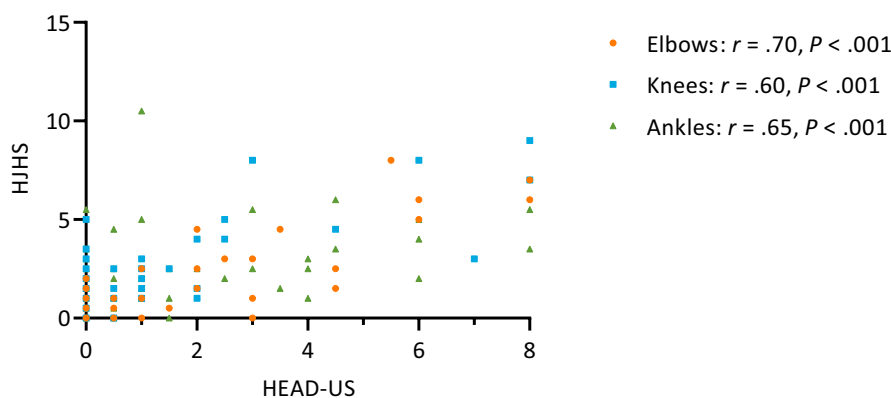
FIGURE 2 Scatter plot demonstrating Spearman's correlation (r) between mean Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and Haemophilia Joint Health Score (HJHS) for elbows (n = 118), knees (n = 117) and ankles (n = 117)

findings in 26% of joints with normal HEAD-US. This occurred more often than previously reported by others, irrespective of the age of the patients.[6,8-10] Moreover, 67% of joints that captured 1–3 points by HJHS were normal by HEAD-US, which was twofold as many as found by Timmer et al (33%).[10] According to our results, HJHS must exceed 6 points to achieve a positive predictive value >90% with respect to HEAD-US score. HEAD-US may therefore clarify whether subtle findings on HJHS represent arthropathy, or may be of extra-articular origin. In our study, crepitus on motion (20%), especially in knees (39%), frequently captured positive scores by HJHS. Loss of flexion (23%) and extension (13%) in ankles were also common findings. Moreover, in joints with HEAD-US zero points, crepitus on motion was found in 31% of knees, and 17% of ankles had loss of flexion. Such HJHS findings have to a lesser extent (13% and 12%, respectively) been reported in healthy and physically active young adults without corresponding pathology on magnetic resonance imaging.[22] Thus, total HJHS up to three points does not necessarily represent arthropathy. This depends, however, on which HJHS items that are involved, and if the total score is based on findings in one or several joints. A direct comparison between patients with moderate haemophilia and matched healthy controls would have been of interest to explore the clinical significance of these findings. According to Hilliard et al, reliability of the separate HJHS items varied, and the intraclass correlation (ICC) was much lower for joint pain (0.06) and crepitus on motion (0.03) than for swelling (0.64), muscle atrophy (0.78) and gait (0.73).[1] The total score had ICC 0.83. Hence, crepitus on motion as the only finding may be considered less reliable with respect to arthropathy. Recently, a multidisciplinary expert group identified crepitus on motion as clinically less informative and a candidate for reduction in HJHS.[23] Our results from the MoHem study support this notion. Among the patients with positive score by HEAD-US, crepitus on motion had weak/moderate correlation with cartilage and bone destructions, but not with synovitis. The same pattern has been reported by others.[13]

We report HEAD-US abnormalities in 5% of joints with normal HJHS. This is in accordance with previous publications by Foppen et al (2%)[8] and Timmer et al (2%),[10] but lower than reported by others.[6,9,12] Moreover, we detected synovial hypertrophy on HEAD-US in 4% of elbows, 6% of knees and 4% of ankles without signs of swelling at HJHS. HEAD-US may therefore be more sensitive than
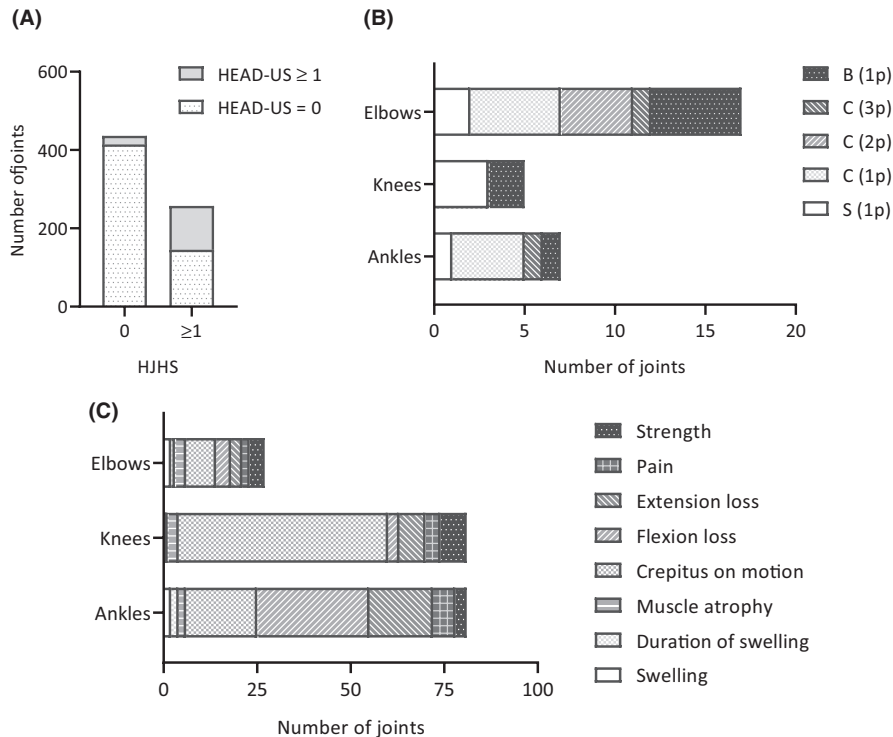
FIGURE 3 (A) Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) vs. Haemophilia Joint Health Score (HJHS); concordant (either 0, or ≥1 point at both) and discordant scores (only one of them ≥1 point; n = 693). (B) Number of joints with HJHS zero points and positive (≥1 point) HEAD-US (n = 22). Seven joints had positive scores at more than one HEAD-US item. S, synovial hypertrophy (0–2 points [p]); C, cartilage degeneration (0–4 p); B, bone irregularities (0–2 p). (C) Number of joints with HEAD-US zero points and positive (≥1 point) HJHS, irrespective of score value (n = 145). Forty-four joints had positive scores at more than one HJHS item

HJHS in detection of early arthropathy. However, as reference values among healthy persons are lacking, it is difficult to know if these are disease-specific findings or present also among peers in the general population. According to Martinoli et al,[4] the inter-observer agreement in HEAD-US was highest for the synovium, and in elbows and knees. Moreover, Stephensen et al,[6] who studied HEAD-US reliability among physiotherapists, found less inter-observer agreement in ankles with respect to all HEAD-US items. In all joints, the agreement was best for bone (0.74) and least for articular cartilage (0.60). Foppen et al[7] reported high accuracy (>90%) for all HEAD-US items as compared with MRI, especially for synovial hypertrophy with positive and negative predictive values of 94% and 97%, respectively.

4.1 | Strengths and limitations

The MoHem study addresses joint health in a high number of patients with MHA and MHB of all ages. Arthropathy was broadly evaluated using validated assessment tools. With respect to HEAD-US, reliability has been classified as good.[5] However, inter-observer differences according to a multicentre design have been reported in HJHS.[24] Moreover, validity of HJHS among adults above 30 years of age has not been studied. Thus among the elderly, there might be confounding comorbidities and false-positive scores. In addition, there might be intra-observer bias among those patients in whom one person performed both joint assessments.

TABLE 4 Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US; 0–8 points (p)) and Haemophilia Joint Health Score (HJHS; 0–20 p); comparison of scores in examined joints (n = 693)

HJHS	n (%) per category	HEAD-US median (IQR)	0 p	1–2 p	3–4 p	5–6 p	7–8 p
0 p	436 (63%)	0 (0–0)	414 (95%)	16 (4%)	6 (1%)	0 (0%)	0 (0%)
1–3 p	206 (30%)	0 (0–1)	137 (67%)	49 (24%)	12 (6%)	6 (3%)	2 (1%)
4–6 p	28 (4%)	2 (1–6)	6 (21%)	9 (32%)	1 (4%)	8 (29%)	4 (14%)
7–9 p	21 (3%)	7 (4–8)	2 (10%)	3 (14%)	2 (10%)	3 (14%)	11 (52%)
>9 p	2 (0.3%)	6	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)

Numbers (%) or medians (interquartile range).

While HJHS assesses both structural and functional items, HEAD-US only evaluates the joint structure. Some HJHS items like pain, range of motion and loss of strength are therefore not covered by HEAD-US. Moreover, swelling due to effusions without synovitis does not give positive score at HEAD-US. Hence, a broad comparison between the two scores is beyond measure.

5 | CONCLUSION

Overall, the index joints in Nordic patients with MHA and MHB captured low scores by HEAD-US and HJHS implying good joint health. HEAD-US correlated strongly with HJHS in all joints; however, 24% had discordant scores. Crepitus on motion, especially in knees, was reported frequently without corresponding findings by HEAD-US and does not necessarily reflect arthropathy. Moreover, in 5% of the joints, HEAD-US detected subclinical pathology. HEAD-US may clarify whether low scores at HJHS represent intra-articular pathology or have extra-articular origin, and therefore improves the joint assessment in haemophilia. For patients with moderate haemophilia, a proper assessment of joint health may be decisive for the initiation of prophylactic replacement therapy.

DISCLOSURES
EB has acted as a paid consultant to Bayer. JA has received research grant from SOBI, Shire/Takeda, Bayer, Octapharma and CSL Behring, and acted as consultant/speaker for SOBI, Shire/Takeda, Bayer, Octapharma, Pfizer and Novo Nordisk. MA has acted as consultant for SOBI, Pfizer, Roche and Bayer, speakers fee by Sobi, Pfizer and Bayer, reimbursement for attending symposium by Bayer and Sobi, and research grant by Swedish Haemophilia Society, FBIS. PAH has acted as a paid consultant to Bayer, Shire, Novo Nordisk, Octapharma, CSL Behring, Pfizer and Sobi including lectures. RJM, JH, AO, MB, TF, VN and GET stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS
EB, PAH and RJM designed the study. RJM, JA, JH, AO, MB, TF, MA and VN collected the clinical data. RJM analysed the data and drafted the manuscript. RJM, PAH, EB and GET interpreted the data. All authors contributed to critically revision of the manuscript and gave approval of the final version.

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