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ORIGINAL ARTICLE

Association of patient, treatment and disease characteristics with patient-reported outcomes: Results of the ECHO Registry

Charles R. M. Hay[1] | Michael Makris[2] | Midori Shima[3] | Azusa Nagao[4] | Víctor Jiménez-Yuste[5] | Mark Skinner[6,7] | Craig M. Kessler[8] | Sylvia von Mackensen[9]

[1]Manchester University Department of Haematology, Manchester, UK

[2]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

[3]Nara Medical University, Kashihara, Japan

[4]Department of Blood Coagulation, Ogikubo Hospital, Tokyo, Japan

[5]Autónoma University Madrid and La Paz University Hospital, Madrid, Spain

[6]Institute for Policy Advancement Ltd., Washington, DC, USA

[7]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

[8]Georgetown University Medical Center, Washington, DC, USA

[9]Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Charles R.M. Hay, Manchester University NHS Foundation Trust, Manchester Royal Infirmary, Oxford Rd, Manchester, M13 9WL, UK.
Email: Charles.Hay@mft.nhs.uk

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Abstract

Introduction: Patient-reported outcomes (PROs) in people living with haemophilia A (PLWHA) are often under-reported. Investigating PROs from a single study with a diverse population of PLWHA is valuable, irrespective of FVIII product or regimen.

Aim: To report available data from the Expanding Communications on Haemophilia A Outcomes (ECHO) registry investigating the associations of patient, treatment and disease characteristics with PROs and clinical outcomes in PLWHA.

Methods: ECHO (NCT02396862), a prospective, multinational, observational registry, enrolled participants aged ≥16 years with moderate or severe haemophilia A using any product or treatment regimen. Data collection, including a variety of PRO questionnaires, was planned at baseline and annually for ≥2 years. Associations between PRO scores and patient, treatment and disease characteristics were determined by statistical analyses.

Results: ECHO was terminated early owing to logistical constraints. Baseline data were available from 269 PLWHA from Europe, the United States and Japan. Most participants received prophylactic treatment (76.2%), with those using extended-half-life products (10.0%) reporting higher treatment satisfaction. Older age and body weight >30 kg/m^2 (>BMI) were associated with poorer joint health. Older age was associated with poorer physical functioning and work productivity. Health-related quality of life and pain interference also deteriorated with age and >BMI; >BMI also increased pain severity scores.

Conclusion: ECHO captured a variety of disease characteristics, treatment patterns, PROs and clinical outcomes obtained in real-world practice with ≤1 year's follow-up. Older age, poorer joint health and >BMI adversely affected multiple aspects of participant well-being.

KEYWORDS
body mass index, factor VIII, haemophilia A, patient reported outcome measures, quality of life, registries

1 | INTRODUCTION

Factor VIII (FVIII) prophylaxis may preserve musculoskeletal function and prevent chronic arthropathy in people living with haemophilia A (PLWHA) and remains the current recommended standard of care.[1] Although prophylaxis is recommended for those with severe haemophilia A, many are still treated on-demand, owing to barriers associated with routine FVIII infusions, including high treatment burden, high treatment costs and limited access to care.[2] Depending on the available resources, treatment patterns for haemophilia A may differ considerably between regions. This variation, combined with differences in demographics, geographical location and disease characteristics, has led to diverse treatment outcomes for PLWHA.[3]

Given the high cost of care and varied treatment options available, it is important to understand the impact of both treatment and disease from the PLWHA perspective. The treatment goals of a PLWHA may differ from those of their physician or caregiver and so, ideally, patient-reported outcomes (PROs) should also be used to inform decision-making and to evaluate new treatments.[4,5] Moreover, regulatory agencies recommend the inclusion of PRO endpoints in clinical trials to allow patient-focused drug development.[6,7] Health Technology Assessment agencies routinely seek PRO data for use in comparative effectiveness studies and value assessment.[8] As outcomes with new treatments improve, it becomes increasingly difficult to demonstrate differences in efficacy, and PROs become progressively more valuable as a measure of clinical outcome.

Nevertheless, it remains difficult to draw conclusions from PRO data currently available owing to the lack of standard PRO approaches.[9–11] Therefore, investigating PROs in a single study of a diverse population of PLWHA receiving a range of treatment options is valuable.

The Expanding Communications on Haemophilia A Outcomes (ECHO) registry was an international, longitudinal, observational study designed to address knowledge gaps in real-world PROs and clinical outcomes in PLWHA. Obstacles associated with the multinational design and breadth of PRO data collection led to early study termination and are discussed elsewhere.[12] Here, we present data from people enrolled in ECHO to provide insight into demographics, disease characteristics, treatment patterns and variables associated with better or worse PROs and clinical outcomes in PLWHA.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

ECHO was a prospective disease registry study (NCT02396862) initiated and funded by Bayer, Germany. ECHO aimed to explore the real-world associations of patient, treatment and disease characteristics with PROs (primary objective) and clinical outcomes (secondary objective) in PLWHA over 5 years. Other secondary objectives were to describe the impact of treatment patterns on patient-reported and clinical outcomes; to identify patient and disease characteristics associated with disease status, patient functioning and well-being; to identify drivers and predictors of successful transitioning from standard half-life (SHL) to extended half-life (EHL) FVIII treatments and vice versa; and to describe PLWHA perspectives on resource utilisation. There were no mandated tests or interventions.

Recruitment of 2000 participants in nine countries was planned. Those eligible were aged ≥16 years with moderate (FVIII activity 1%–5%) or severe (FVIII activity <1%) haemophilia A. All had received treatment for haemophilia within the past 6 months and had life expectancies of ≥2 years. To enrol, participants also had to plan to receive ≥50% of their haemophilia treatment at their respective registry site and demonstrate the ability to comply with appropriate record keeping. All participants or their guardians provided written informed consent as required according to local regulations (all study sites obtained independent ethics committee/institutional review board approval prior to study start).

2.2 | Study assessments

Data were collected from participant records at baseline and 12-month intervals using electronic case report forms (CRFs). Data included demographic and disease characteristics, current treatment and comorbidities. Joint status was evaluated by the presence of target joints (≥3 spontaneous bleeds into a single joint within a 6-month period),[13] previous joint surgeries, range of motion, Hemophilia Joint Health Score (HJHS)[14] and modified Pettersson score.[15]

Participants were asked to complete a range of standardised PRO instruments and ad hoc questionnaires that were chosen based on previously identified key aspects by PLWHA in focus groups during the ECHO study planning phase.[12] PRO data collection was planned at baseline, 12 months and every 12–24 months thereafter depending on the PRO instrument. Data could be recorded either at the clinic, or at home in paper or electronic format. To evaluate health-related quality of life (HRQoL), participants were asked to complete the EuroQoL 5-Dimension questionnaire (EQ-5D-5L),[16] the EuroQoL visual analogue scale (EQ-VAS)[17] and the 12-item Short-Form Health Survey (SF-12),[18] which included a Mental Component Summary (MCS) and a Physical Component Summary (PCS); a randomly selected subset were also asked to complete the Haemophilia-Specific HRQoL Questionnaire for Adults (Haemo-QoL-A; data not shown).[19] Physical functioning (Haemophilia Activities List [HAL]),[20] treatment adherence (Validated Haemophilia Regimen Treatment Adherence Scale for prophylaxis [VERITAS-Pro])[21] and episodic treatment (Validated Haemophilia Regimen Treatment Adherence Scale [VERITAS-PRN]),[22] treatment satisfaction (Haemophilia Treatment Satisfaction Questionnaire for Adults [Hemo-Sat$_A$]),[23] pain (Brief Pain Inventory—Short Form [BPI-SF])[24] and productivity impairment (Work Productivity and Activity Impairment Scale [WPAI])[25] were also assessed in all participants. Ad hoc questionnaires were created to capture socio-demographic characteristics and well-being, physical functioning, resource utilisation/satisfaction and haemophilia treatment regimen and adherence. Participants were asked to complete a paper or electronic bleeding diary weekly for 1 year following study enrolment and for 6 months following major treatment change.

2.3 | Statistical methods

Categorical and continuous variables were described by frequency variables and sample statistics, respectively. Data were stratified according to severity of haemophilia, treatment regimen and participant age. Data from validated PRO instruments were also stratified according to HJHS category (mild [4–14], moderate [15–28] and severe [>28] joint disease), target joints, treatment product (EHL vs. SHL), prophylaxis frequency, body mass index (BMI), educational level and joint procedures.

Data analyses were exploratory. Associations between patient, clinical and disease variables and PRO scores (primary endpoint) were analysed by analysis of covariance (ANCOVA). Factors that showed an association in univariate models were included in a multivariate model in which a stepwise procedure was used (type 3, *p* value of .1 for inclusion). Treatment regimen, baseline age group, baseline BMI group, target joint, comorbidities, HJHS category, treatment product and disease severity were included as covariates in the multivariate model. Associations between patient characteristics and clinical outcomes were analysed by logistic regression (binary or ordinal outcomes) and ANCOVA (continuous outcomes).

3 | RESULTS

3.1 | Early termination of the study

ECHO was terminated early by the sponsor owing to challenges associated with the multinational design, extensive PRO data collection and competing studies.[26] Between 17 December 2015 and 2 November 2017, 271 of 280 participants screened were enrolled. The full analysis population comprised 269 participants (1 participant withdrew consent; 1 participant did not meet all inclusion criteria) from United Kingdom (n = 144), Japan (n = 76), Spain (n = 25) and United States (n = 24).

3.2 | Baseline demographic and disease characteristics

Median (range) time in study for all 269 participants was 7.5 (.2–24.8) months, 6.9 (.2–24.8) for participants with severe haemophilia (n = 229, 85.1%), and 10.2 [1.3–24.8] months for participants with moderate haemophilia (n = 40, 14.9%). Baseline characteristics by age group are reported in Table 1.

The numbers of participants and median BMI values were similar across age groups.[27] Median BMI was 24.8 and 26.7 for participants with severe and moderate haemophilia, respectively.

At baseline, over half (55.4%) had target joints (Table 2), and 65 participants (24.2%) had undergone an invasive joint procedure, most commonly arthroplasty (11.9%) and ankle arthrodesis (6.7%). Target joints were more common in participants with severe haemophilia (57.2%) compared with those with moderate disease (45.0%), with 24.9% of participants with severe haemophilia and 20.0% with moderate haemophilia undergoing an invasive joint procedure. Severe joint disease (HJHS > 28) was more frequent in participants aged >47 years (53.7%) than in their younger counterparts (37–47 years [25.6%], 28–36 years [13.3%], 16–27 years [4.8%]). Similarly, the prevalence of chronic arthropathy also increased with age (Table 2), and with haemophilia severity (33.6% and 27.5% in severe and moderate haemophilia, respectively). Median (Q1; Q3) modified Pettersson scores were 1 (0; 5), but these data were only available for 135 evaluations in 93 participants.

Bleeding diaries were completed by 153 participants (56.9%) over a median (Q1; Q3) of 7.0 (5.0; 16.1) months. Median (Q1; Q3) annualised bleeding rates (ABRs) by age, haemophilia severity and treatment type are shown in Figure 1.

3.3 | Treatment patterns and adherence

Most participants were treated with FVIII concentrate (n = 248, 92.2%), with the majority receiving standard half-life recombinant FVIII products (n = 207, 77.0%), and 27 participants (10.0%) receiving extended half-life FVIII products. Of these 27 participants, 25 had severe haemophilia and 2 had moderate haemophilia. The remaining participants with moderate haemophilia were treated with recombinant FVIII (n = 34, 85.0%) or human FVIII containing von Willebrand factor (n = 1, 2.5%). Three (7.5%) participants with moderate haemophilia remained untreated. Prophylaxis was the most frequent treatment regimen for FVIII concentrate (76.2%), with the most common dosing frequency being three times per week (27.5%) (Table 1) and a tendency towards decreased use of prophylaxis with older age. Most participants (92.5%) were considered adherent to their treatment regimen according to physician CRFs. A small proportion of participants had been treated with products other than FVIII concentrates – 13 (4.8%) had received treatment for inhibitors; 2 (.7%) participants had treatment with non-plasma and topical products, and another participant (.4%) was treated with blood bank products.

Ad hoc questions related to haemophilia treatment were completed by 185 participants (68.8%). Nearly all these participants (n = 171, 92.4%) received their treatment infusion at home with 156 participants (84.3%) self-administering their treatment (Appendix Table S1a). Participants reported changing their treatment schedule owing to dental examinations (n = 38, 20.5%), immunizations (n = 8, 4.3%) and biopsies (n = 2, 1.1%), and 38 participants (20.5%) reported non-adherence to their haemophilia medicine (Appendix Table S1b).

3.4 | Patient-reported outcomes (PROs)

Validated PRO instruments were each completed by approximately three-quarters of participants at baseline.

TABLE 1 Baseline demographic, disease and treatment characteristics.

	Age group				
	Total (*N* = 269)	**16–27 years (*n* = 75)**	**28–36 years (*n* = 65)**	**37–47 years (*n* = 62)**	**>47 years (*n* = 67)**
Age, years, median (Q1; Q3)	36 (26; 47)	23 (21; 25)	32 (30; 34)	44 (40; 46)	56 (51; 62)
Race, *n* (%)					
White	166 (61.7)	51 (68.0)	34 (52.3)	37 (59.7)	44 (65.7)
Asian	88 (32.7)	21 (28.0)	24 (36.9)	25 (40.3)	18 (26.9)
Black or African American	6 (2.2)	0	3 (4.6)	0	3 (4.5)
Not reported	9 (3.4)	3 (4.0)	4 (6.2)	0	2 (3.0)
BMI, kg/m^2, median (Q1; Q3)	25.0 (22.2; 28.2)	24.7 (21.4; 27.8)	25.0 (23.0; 28.5)	24.7 (22.0; 27.1)	26.2 (23.2; 29.3)
History of PCCs/rVIIa, *n* (%)	23 (8.6)	3 (4.0)	5 (7.7)	7 (11.3)	8 (11.9)
Diagnosis of severity of haemophilia, *n* (%)					
0 to <1% (severe)	229 (85.1)	63 (84.0)	55 (84.6)	56 (90.3)	55 (82.1)
1 to <5% (moderate)	40 (14.9)	12 (16.0)	10 (15.4)	6 (9.7)	12 (17.9)
Measured FVIII level (IU/dL)					
Pre-dose, *n*	8	3	2	2	1
Mean (SD)	20.8 (37.8)	19.7 (28.9)	52.0 (72.1)	1.0 (.0)	1.0
Median (Q1; Q3)	2.0 (1.0; 28.0)	3.0 (3.0; 53.0)	52.0 (1.0; 103)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)
Post-dose, *n*	4	0	2	2	0
Mean (SD)	79.8 (33.3)	–	91.5 (13.4)	68.0 (50.9)	–
Median (Q1; Q3)	91.5 (57.0; 102.5)	–	91.5 (82.0; 101.0)	68.0 (32.0; 104.0)	–
Presence of past or current comorbidities, *n* (%)	149 (55.4)	22 (29.3)	28 (43.1)	46 (74.2)	53 (79.1)
Comorbidities listed in >5% of individuals					
Chronic arthropathy	88 (32.7)	11 (14.7)	15 (23.1)	28 (45.2)	34 (50.8)
Hepatitis C virus	73 (27.1)	1 (1.3)	9 (13.9)	25 (40.3)	38 (56.7)
HIV	42 (15.6)	0	2 (3.1)	23 (37.1)	17 (25.4)
Chronic liver diseases	35 (13.0)	0	4 (6.2)	12 (19.4)	119 (28.4)
Hypertension	29 (10.8)	1 (1.3)	1 (1.5)	6 (9.7)	21 (31.3)
Hepatitis B virus	16 (6.0)	1 (1.3)	3 (4.6)	6 (9.7)	6 (9.0)
Participants using FVIII product, *n* (%)	248 (92.2)	69 (92.0)	61 (93.9)	56 (90.3)	62 (92.5)
Prophylaxis	205 (76.2)	62 (82.7)	52 (80.0)	46 (74.2)	45 (67.2)
Daily	15 (5.6)	7 (9.3)	1 (1.5)	5 (8.1)	2 (3.0)
Every other day	48 (17.8)	15 (20.0)	15 (23.1)	11 (17.7)	7 (10.5)
Three times per week	74 (27.5)	26 (34.7)	20 (30.8)	14 (22.6)	14 (20.9)
Twice weekly	53 (19.7)	15 (20.0)	12 (18.5)	13 (21.0)	13 (19.4)
Once weekly	12 (4.5)	0	4 (6.2)	2 (3.2)	6 (9.0)
Other	4 (1.5)	0	0	1 (1.6)	3 (4.5)
Episodic	43 (16.0)	7 (9.3)	9 (13.9)	10 (16.1)	17 (25.4)
Participants with PCCs/rVIIa, *n* (%)	13 (4.8)	2 (2.7)	1 (1.5)	4 (6.5)	6 (9.0)

Abbreviations: BMI, body mass index; FVIII, factor VIII; HIV, human immunodeficiency virus; PCC, prothrombin complex concentrate; Q, quartile; rFVIIa, recombinant factor VIIa; SD, standard deviation.

Limited data indicated that participants with moderate haemophilia (*n* = 40) had better functional status (HAL), less activity impairment (WPAI), better health status (EQ-5D-5L; no difference in EQ-VAS), better health-related quality of life (SF-12: MCS and PCS), better treatment adherence (VERITAS-Pro) and lower pain interference and severity (BPI-SF) than participants with severe haemophilia (*n* = 229); no difference in treatment satisfaction was seen (Table 3). Worse HRQoL scores were reported by participants receiving prothrombin complex concentrates and rVIIa (*n* = 20) than those receiving prophylaxis or episodic care (Appendix Table S2).

TABLE 2 Joint health at baseline.

	Age group				
	Total (*N* = 269)	16–27 years (*n* = 75)	28–36 years (*n* = 65)	37–47 years (*n* = 62)	>47 years (*n* = 67)
Presence of target joints, *n* (%)	149 (55.4)	33 (44.0)	38 (58.5)	36 (58.1)	42 (62.7)
Presence of chronic arthropathy, *n* (%)	88 (32.7)	11 (14.7)	15 (23.1)	28 (45.2)	34 (50.8)
Invasive joint procedure, *n* (%)	65 (24.2)	9 (12.0)	8 (12.3)	19 (30.7)	29 (43.3)
HJHS, median (Q1; Q3)[a]	14 (3.5; 28.5) (*n* = 152)	4.5 (0; 16) (*n* = 42)	8 (3; 13) (*n* = 30)	21 (8; 30) (*n* = 39)	30 (14; 40) (*n* = 41)
Modified Pettersson score, median (Q1; Q3)[b]	1 (0; 5) (*n* = 135)	0 (0; 4) (*n* = 52)	1.5 (0; 5) (*n* = 18)	3 (0; 7) (*n* = 32)	1 (0; 5) (*n* = 33)

n refers to the number of evaluations (data were available from 135 participants in total).

Abbreviations: HJHS, Haemophilia Joint Health Score; Q, quartile.

[a]Possible range 0–124 (high values indicate poorer joint disease): 4–14, mild joint disease; 15–28, moderate joint disease; >28 severe joint disease.

[b]Modified Pettersson additive scale was used for imaging-based classification of arthropathy as the values for all index joints were not available in most cases. Possible range 0–13 (high values indicate poorer joint disease).

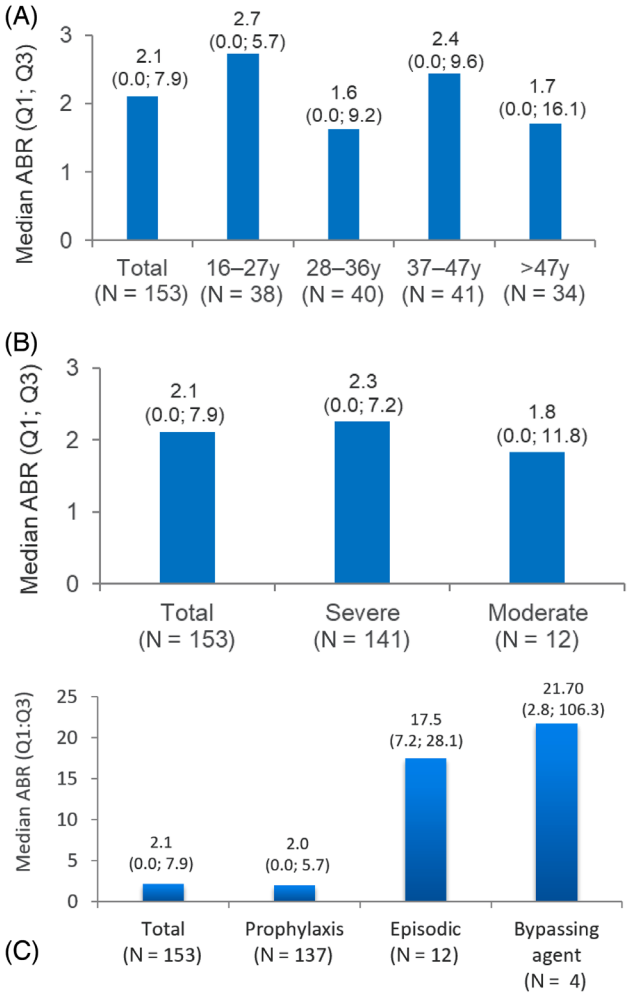

FIGURE 1 Annualised bleeding rate (bleeding diary data) by age (A), disease severity (B) and treatment regimen (C).

Ad hoc questions related to physical activity and exercise were completed at baseline by 190 participants (70.6%), of whom 128 (67.4%) had engaged in physical activities such as cycling, walking or golf during the prior 30 days. Ad hoc questions related to physical functioning, completed by 187 participants (69.5%), revealed that 84 participants (44.9%) and 32 participants (17.1%) used walking aids or a wheelchair, respectively (most occasionally). Joint replacement had been undergone by 39 participants (20.9%; 4 participants with moderate haemophilia). Overall joint-related activity was unrestricted (32.1%) or restricted regarding recreational activity (28.3%) for most participants (Appendix Table S1c).

Of the 183 participants (68.0%) who completed the ad hoc resource utilisation questions at baseline, 36 (19.7%) had visited hospital emergency departments (EDs) in the prior year. Participants with severe haemophilia (*n* = 159) had a mean of 1.43 ED visits per year, while participants with moderate haemophilia (*n* = 24) had a mean of 1.00 ED visit per year. Over half (54.2%) of all ED visits were related to haemophilia, and 32 participants (17.5%) required overnight stays. Seventy-two participants (39.3%) had outpatient hospital visits with the majority (81.6%) due to haemophilia. Most participants rated the quality of medical care and treatment options for haemophilia as 'good' or 'very good' (*n* = 153, 83.6%) (Appendix Table S1d).

3.5 | Associations between PROs and patient, clinical and disease characteristics

Multivariate analyses indicated that younger age was associated with better scores for most PROs (Table 4). EHL products were associated with greater treatment satisfaction than SHL products (Hemo-Sat$_A$). Presence of target joints was associated with reduced work productivity (WPAI), HRQoL (EQ-VAS) and physical functioning (SF-12 PCS). Severe joint disease (HJHS category) was associated with worse physical functioning/health outcomes (HAL, EQ-5D-5L, EQ-VAS, SF-12 MCS and SF-12 PCS) and pain interference (BPI-

TABLE 3 PROs according to severity of haemophilia.

PRO	Total ($N = 269$)	Severe ($n = 229$)	Moderate ($n = 40$)
HAL total score (+)	72.38 (52.2, 90)	69.29 (50, 87.8)	79.02 (60, 93.66)
WPAI Activity Impairment (−)	20 (10, 50)	30 (10, 50)	10 (0, 30)
WPAI Work Productivity Loss (−)	10 (0, 20.59)	20 (0, 21.5)	0 (0, 20)
EQ-5D-5L Index (+)	.74 (.61, .86)	.72 (.6, .84)	.77 (.68, 1.00)
EQ-VAS (+)	80 (60, 90)	80 (60, 90)	80 (60, 82)
Haemo-QoL-A total score (−)	74.61 (59.67, 82.42)	74.61 (59.67, 82.42)	–
SF-12: MCS (+)	48.62 (37.54, 56.69)	47.42 (37.44, 56.87)	52.05 (42.35, 56.52)
SF-12: PCS (+)	44.75 (34.77, 57.28)	44.41 (33.72, 55.19)	48.48 (36.75, 60.95)
Hemo-SATA total score (−)	22.43 (11.58, 30.88)	22.06 (11.96, 31.06)	22.79 (11.21, 29.41)
VERITAS-Pro total score (−)	44 (36, 52)	44 (36, 53)	40 (37, 49)
BPI-SF Pain interference (−)	1.86 (0, 4.57)	2.29 (.29, 4.86)	.29 (0, 2.86)
BPI-SF Pain severity (−)	2 (.5, 4.00)	2 (.75, 4.00)	1 (0, 2.63)

(+), higher scores indicate a better condition; (−), lower scores indicate a better condition; BPI-SF, Brief Pain Inventory—Short Form; EQ-5D-5L, EuroQoL 5-dimension questionnaire; EQ-VAS, EuroQoL visual analogue scale; Haemo-QoL-A, Haemophilia-Specific Health-Related Quality of Life Questionnaire for Adults; HAL, Haemophilia Activities List; Haemo-Sat$_A$, Haemophilia Treatment Satisfaction Questionnaire for Adults; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO, patient-reported outcome; SF-12, 12-item Short-Form Health Survey; VERITAS-Pro, Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis; WPAI, Work Productivity and Activity Impairment Scale.

SF Pain Interference), while lower treatment adherence (VERITAS-Pro) was associated with absence of joint disease. Individuals with BMI > 30 kg/m^2 had worse scores for physical and mental health (SF-12 PCS and SF-12 MCS) and pain interference (BPI-SF Pain Interference).

3.6 | Associations between patient characteristics and clinical outcomes

Associations between patient characteristics and clinical outcomes are shown in Table 5. Participants with a lower level of education (primary school grade or less) and participants who started prophylactic treatment during adulthood compared with childhood had poorer joint health (higher HJHS). Not unexpectedly, participants who received episodic treatment had a higher total bleeding rate. Target joints were less common in participants without comorbidities ($p = .0007$) and, as expected, in participants with no joint procedure ($p = .0005$) and no joint disease ($p < .0001$) (data not shown).

4 | DISCUSSION

ECHO provides real-world data, with a maximum of 1 year of follow-up, from 269 people with moderate or severe haemophilia A. This non-interventional study was designed to collect a wide range of clinical and PRO data in a standardised manner across a broad spectrum of people receiving a variety of haemophilia treatments. Consequently, baseline data from ECHO provides valuable insight into patient, treatment and disease characteristics associated with better or worse PROs and clinical outcomes.

A variety of patient, treatment and clinical characteristics were associated with PROs. Increased age was associated with worse PROs, including physical functioning (HAL, $p < .0001$), work productivity (WPAI, $p = .0009$), HRQoL (SF-12 PCS, $p < .0001$) and pain interference (BPI-SF, $p = .0163$). This association reflected other covariates that also worsened with age, including joint health (HJHS severity). HRQoL data were less favourable in PLWHA in ECHO compared with age-matched population scores for EQ-5D-5L[28] and SF-12.[29,30] These data suggest that the effect of increasing age on PROs can only be partially explained by anticipated age-related changes. The finding that lower treatment adherence (reported by VERITAS-Pro) was associated with absence of joint disease could be considered counterintuitive and could result from the lack of disease burden in these patients, causing them to see no necessity to be adherent to treatment.

An important observation is the association between obesity (BMI > 30 kg/m^2) and reduced well-being in PLWHA, including impairments in HRQoL (SF-12 PCS, $p = .0265$), increased pain severity (BPI-SF, $p = .0047$) and pain interference (BPI-SF, $p = .0392$). To our knowledge, this is the first study to demonstrate an association between being overweight and PROs capturing HRQoL and physical and emotional well-being in this setting.[31–33]

While physical activity is associated with better HRQoL in children and adults with haemophilia,[32,34] many refrain from sufficient physical exercise, in part owing to fear of bleeding.[35,36] However, FVIII prophylaxis can be individualised to accommodate a variety of their needs, including intensive sports activities, and has an important role in encouraging PLWHA to be physically active.[35]

Another strength of ECHO is that multiple, well-established PROs were assessed in a single study with a diverse population of PLWHA receiving a range of treatment options. Although associations between PROs have not been assessed, it is interesting to note that people

TABLE 4 Associations between PROs and patient, clinical and disease characteristics: Multivariate analysis.

PRO aspect	Dependent variable	Step: effect entered	*p* value	Interpretation
Physical functioning	HAL (*N* = 169)	Step 1: Age group	<.0001	Better in younger patients
		Step 2: HJHS category	.0186	Poorer for moderate/severe joint disease
Work productivity	WPAI (*N* = 165)	Step 1: Age group	.0009	Less impairment in younger patients
		Step 2: Target joint	.0131	Less impairment with no target joint
HRQoL	EQ-5D-5L Index	Step 1: HJHS category	<.0001	Poorer for severe joint disease
	(*N* = 164)	Step 2: Age group	.0626	Better in younger patients
	EQ-VAS (*N* = 164)	Step 1: Target joint	.0021	Better with no target joint
		Step 2: HJHS category	.012	Poorer for moderate/severe/no joint disease
	SF-12 MCS (*N* = 167)	Step 1: HJHS category	.0029	Poorer for severe joint disease
		Step 2: BMI group	.0611	Poorer for BMI > 30 kg/m^2
		Step 3: Age group	.0884	Poorer for age 37–47 years
	SF-12 PCS (*N* = 167)	Step 1: Age group	<.0001	Better in younger patients
		Step 2: Target joint	.0039	Better with no target joint
		Step 3: BMI group	.0265	Poorer for BMI > 30 kg/m^2
		Step 4: HJHS category	.0457	Poorer for moderate/severe joint disease
Treatment satisfaction	Hemo-Sat$_A$ (*N* = 166)	Step 1: Product type	.008	Better for EHL products
		Step 2: Age group	.0254	Poorer for age 37–47 years
Treatment adherence	VERITAS-Pro (*N* = 138)	Step 1: HJHS category	.0029	Lower adherence with no joint disease
		Step 2: Treatment regimen	.0918	Higher adherence with PCCs/rVIIa
Pain	BPI-SF pain interference (*N* = 156)	Step 1: HJHS category	.0022	Greater interference for moderate/severe joint disease
		Step 2: Age group	.0163	Greater interference for age 37–47 years
		Step 3: BMI group	.0392	Greater interference for BMI > 30 kg/m^2
		Step 4: Haemophilia severity	.0548	Greater interference for severe haemophilia
	BPI-SF pain severity	Step 1: BMI group	.0047	Greater pain severity with higher BMI
	(*N* = 156)	Step 2: Comorbidities	.0337	Lower pain severity for no comorbidities
		Step 3: Haemophilia severity	.0634	Greater pain severity with severe haemophilia

Age group (16–27 years, 28–36 years and 37–47 years vs. >47 years); BMI group (>20 to ≤25, >25 to ≤30 and >30 vs. ≤20 kg/m^2); haemophilia severity (FVIII severe vs. moderate); HJHS category (mild [4–14], moderate [15–28] and severe [>28] joint disease vs. unknown); product type (EHL vs. SHL); target joint (yes vs. no); treatment regimen (PCCs/rVIIa and episodic vs. prophylaxis).

Abbreviations: BMI, body mass index; BPI-SF, Brief Pain Inventory—Short Form; EHL, extended half-life; EQ-5D-5L, EuroQoL 5-Dimension Questionnaire; EQ-VAS, EuroQoL visual analogue scale; HAL, Haemophilia Activities List; Haemo-SatA, Haemophilia Treatment Satisfaction Questionnaire for Adults; HJHS, Haemophilia Joint Health Score; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCC, prothrombin complex concentrate; PCS, Physical Component Summary; PRO, patient-reported outcome; rFVIIa, recombinant factor VIIa; SHL, standard half-life; SF-12, 12-item Short-Form Health Survey; VERITAS-Pro, Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis; WPAI, work productivity and activity impairment scale.

with moderate disease have similar treatment satisfaction scores (Hemo-Sat$_A$) to people with severe haemophilia, despite having better functional status, activity impairment, health status and pain. This suggests that comprehensive psychosocial review may be helpful to identify current issues that PLWHA may be facing.

Baseline data from ECHO reveal that prophylactic treatment was the most used FVIII regimen (76.2%) and, while only a small proportion (10.0%) received EHL FVIII products, these were associated with greater treatment satisfaction than SHL formulations. This may partly be attributable to improved efficacy of EHL versus SHL products, or reduced treatment burden as FVIII products with extended half-lives allow for less frequent dosing intervals of up to 7 days,[37] although reasons for treatment satisfaction and bleeding data by dosing interval were not captured by the registry.

ECHO had several limitations. Only 2.2% of recruited participants described their race as 'Black or African American' which is likely a gross under-representation of the diversity of PLWHA. The broad nature of the data planned for collection from people across multiple countries with differing regulatory environments presented obstacles that resulted in early termination of the study (key challenges encountered and insights for researchers undertaking similar studies are discussed separately).[12] Consequently, fewer PLWHA were

TABLE 5 Associations between patient characteristics and clinical outcomes.

Outcome	Variable	Parameter	ANCOVA estimate (95% CI)	*p* value	Interpretation[a]
HJHS score	Age group	16–27 years vs. > 47 years	−17.7 (−23.1, −12.2)	<.0001	Lower
		28–36 years vs. > 47 years	−17.2 (−23.4, −11.0)	<.0001	Lower
	Target joint	No vs. yes	−7.7 (−12.4, −2.9)	.0016	Lower
	Joint procedure	No vs. yes	−16.1 (−20.9, −11.4)	<.0001	Lower
		Unknown vs. yes	−12.7 (−18.6, −6.9)	<.0001	Lower
	Education level	Grade (primary) school or less vs. professional/technical training	34.9 (21.9, 47.9)	<.0001	Higher
	Comorbidities	No vs. yes	−9.8 (−14.4, −5.2)	<.0001	Lower
	Prophylaxis frequency	3 × week vs. 1 × week	−17.4 (−33.0, −1.9)	.0283	Lower
		Daily vs. 1 × week	−19.2 (−35.7, −2.7)	.0232	Lower
		Alternate days vs. 1 × week	−19.0 (−34.6, −3.4)	.0171	Lower
		Other vs. 1 × week	−22.0 (−43.0, −1.0)	.0404	Lower
	Age at start of prophylaxis	Adult vs. childhood	6.7 (.1, 13.4)	.0465	Higher
Modified Pettersson score	Target joint	No vs. yes	−2.1 (−3.5, −.8)	.0017	Lower
	Joint procedure	Unknown vs. yes	−2.5 (−4.3, −.8)	.0044	Lower
	Comorbidities	No vs. yes	−2.1 (−3.5, −.7)	.0029	Lower
	HJHS category	No vs. unknown joint disease	−3.4 (−5.5, −1.3)	.0019	Lower
Joint bleed rate	Treatment regimen	PCCs/rVIIa vs. prophylaxis	13.6 (5.6, 21.6)	.001	Higher
Total bleed rate	Treatment regimen	Episodic vs. prophylaxis	13.5 (5.1, 22.0)	.0017	Higher
		PCCs/rVIIa vs. prophylaxis	18.7 (9.5, 27.9)	<.0001	Higher

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HJHS, Haemophilia Joint Health Score; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

[a]'Lower' and 'higher' refers to whether the specific outcome score for the first mentioned answer category was lower or higher than the latter one.

included in this study than planned, resulting in too few participants to provide insight into treatment differences between countries, and data were insufficient to permit analysis of all planned endpoints. Furthermore, the reported findings on real-world associations between patient, treatment and disease characteristics and PROs and clinical outcomes would be more robust in a larger dataset. Nevertheless, baseline data from ECHO provide useful insight into factors influencing the well-being of PLWHA, which could provide guidance for disease management, future studies and comparisons of treatment and treatment regimens.

ECHO has provided greater insight into disease burden, treatment patterns and associated clinical outcomes and a range of PROs that were reported from other haemophilia disease registries. For example, PRO data from the Advate/Adynovi HaEmophilia A outcome Database (AHEAD) registry were limited to people who received a single haemophilia product,[38] while the multinational, cross-sectional Haemophilia Experiences, Results and Opportunities survey focused on psychosocial issues that people with haemophilia A and B faced.[39] The Patient Reported Outcomes Burdens and Experiences (PROBE) study, a patient-led research network, is currently underway to collect data on PROs in individuals with haemophilia A, haemophilia B and controls without bleeding disorders.[40]

5 | CONCLUSION

This analysis of non-interventional, real-world data from PLWHA across a range of geographical locations captured a wide variety of disease characteristics, treatment patterns, PROs and clinical outcomes in routine clinical practice. These findings demonstrate that older age and poorer joint health are among the factors associated with greater disease burden, reflected by PROs. Importantly, BMI > 30 kg/m^2 was found to be associated with worse well-being. Taking steps to address this modifiable factor could improve the HRQoL of PLWHA.

AUTHOR CONTRIBUTIONS

Charles Hay was a member of the Steering Committee, wrote and designed the protocol, interpreted and analysed the data and edited the manuscript. Michael Makris was a member of the Steering Committee, wrote and designed the protocol, interpreted and analysed the data and edited the manuscript. Midori Shima was a member of the Steering Committee, wrote and designed the protocol, interpreted and analysed the data and edited the manuscript. Azusa Nagao contributed to the study, analysed data and revised the manuscript. Victor Jiménez-Yuste was a member of the Steering Committee, contributed to the study design and protocol, analysed data and edited manuscript

revisions. Mark W. Skinner was a member of the Steering Committee, reviewed the study protocol and participated in the evaluation of the study protocol, data analysis and manuscript revisions. Craig M. Kessler was a member of the Steering Committee, enrolled participants, wrote and designed the protocol, analysed the data and wrote and edited the manuscript. Sylvia von Mackensen consulted regarding PRO measures, constructed and analysed the feasibility questionnaire, and contributed to the design of the study, the writing of the manuscript and critical manuscript revisions.

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CONFLICT OF INTEREST STATEMENT

Charles RM Hay is Director of the UK Haemophilia Database, which has received funding from Bayer, CSL, Novo, Pfizer, Roche and Takeda. He has also received speaker's honoraria and sponsorship to attend scientific meetings from BioMarin, CSL, Roche, LFB, Pfizer and Takeda. Michael Makris is project lead of the European Haemophilia Safety Surveillance (EUHASS) project, which receives partial funding from Bayer. Midori Shima has received grants from Chugai, CSL Behring and Takeda, and personal fees from Chugai, CSL Behring, Novo Nordisk, Pfizer and Sanofi. Azusa Nagao has received investigator-initiated research grants from Bayer, Chugai and Takeda, and has received honoraria from Bayer, Chugai, Takeda, Sanofi, CSL and Novo Nordisk. Victor Jiménez-Yuste has received reimbursement for attending symposia/congresses and/or honoraria for speaking/consulting and/or funds for research from Takeda, Bayer, CSL Behring, Grifols, Novo Nordisk, Sobi, Roche, Octapharma and Pfizer. Mark Skinner has received honoraria for educational presentations and advisory roles from Bayer, BioMarin, Roche, Pfizer, Novo Nordisk and Spark Therapeutics and received research support as the PROBE study Principal Investigator from Bayer, BioMarin, CSL Behring, Freeline, Novo Nordisk, Roche, Sanofi, Sobi, Takeda and uniQure. Craig M. Kessler is a consultant and advisory board participant for Bioverativ, Bayer, Freeline, Novo Nordisk, Octapharma, Pfizer, Roche and Shire and has received research funding from Bioverativ, Bayer, Novo Nordisk, Octapharma and Roche. He is a chair of Data and Safety Monitoring Committees for Octapharma and Bayer. Sylvia von Mackensen is a consultant for Bayer.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 01 January, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ETHICS STATEMENT

Prior to study start, all investigators were sufficiently trained on their ethical and regulatory obligations, all study sites obtained independent ethics committee/institutional review board approval and all participants or their guardians provided written informed consent as required according to local regulations.

ORCID

Charles R. M. Hay https://orcid.org/0000-0002-0162-6828
Michael Makris https://orcid.org/0000-0001-7622-7939
Midori Shima https://orcid.org/0000-0002-5922-7061
Mark Skinner https://orcid.org/0000-0002-0934-0680
Craig M. Kessler https://orcid.org/0000-0003-0599-5724

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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