INTRODUCTION

Severe haemophilia A (HA) and haemophilia B (HB; factor levels <0.01 IU/mL) are characterised by spontaneous joint and muscle bleeding and represent approximately 30% of haemophilia cases in Europe. Patients with severe haemophilia experience acute pain and joint stiffness during bleeds, with recurrent bleed events leading to chronic synovitis and diminished range of movement (ROM) in the affected joint. Approximately 90% of patients will develop chronic haemophilic arthropathy, associated with chronic pain, disability and impaired health-related quality of life (HRQoL), by 30 years of age.

Introduction: Clinical severity and impact of haemophilia on quality of life have been generally considered to be lower for haemophilia B (HB) compared with haemophilia A (HA) patients.

Aims: To compare annual bleeding rate (ABR), target joint development and health-related quality of life (HRQoL) between adult (≥18 years) severe HA and HB patients using recent data from the Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS) study.

Methods: Multivariate generalized linear models (GLM) were constructed to assess the relationship between haemophilia type, ABR, HRQoL (derived from EQ-5D index scores) and the presence of target joints while controlling for covariates.

Results: Of the 1225 patients included, 77% (n = 949) had HA and 23% (n = 278) had HB. Of the 514 patients who completed the EQ-5D, 78% (n = 405) had HA, and 22% (n = 110) had HB. Unadjusted mean ABR was 3.79 in HA and 4.60 in HB. The presence of ≥1 target joint was reported in 59% and 54% of patients with HA and HB, respectively. Unadjusted mean EQ-5D index score was 0.78 in HA and 0.76 in HB. Haemophilia type was not a significant predictor of ABR, target joints or HRQoL when adjusted for confounding factors such as BMI, age and replacement therapy regimen.

Conclusion: Data suggest comparable ABR, incidence of target joints and HRQoL between patients with HB and HA indicating comparable clinical severity and disease impact on patient quality of life.

KEYWORDS

annual bleed rate, haemophilia type (A & B), target joints, health-related quality of life
There has been a perception that HB is associated with less severe clinical symptoms than HA, and that patients with HA have worse HRQoL when compared with HB.\textsuperscript{7,9} In 2009, Tagariello et al\textsuperscript{10} showed that patients with HA had a threefold greater risk of undergoing orthopaedic arthroplasty. Lower rates of prophylaxis use and overall factor concentrate consumption have been used to support the notion that HB is less severe than HA.\textsuperscript{11,12} Recently, it was reported in an Italian cohort of 105 patients that the proportion with a high incidence (>50) of haemarthroses across their lifetime was greater in HA compared with HB.\textsuperscript{13} A suggested explanation for the clinical symptoms in patients with HB being milder than HA may be genetic factors that are still poorly understood.\textsuperscript{4} However, this clinical perception of the differences between the severity of clinical findings and HRQoL in HA and HB remains to be supported or refuted within a single research cohort.

Recently, the findings from a cross-sectional, retrospective study, the Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS) was reported.\textsuperscript{14} The CHESS study evaluated the annual economic and psychosocial burden of severe haemophilia A and B, in patients sampled from five European countries. Using data from the CHESS study, this study aimed at comparing the annual bleeding rate (ABR), reporting of target joints and HRQoL between patients with HA and HB.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient data source: the CHESS study

The Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS) was a cross-sectional, retrospective study of patients ≥18 years with severe haemophilia (FVIII/FIX level <1 IU/dL) from five European countries: France, Germany, Italy, Spain and the UK.\textsuperscript{14,15} Participating clinicians (139 haematologists and, in France, also haemophilia care providers) selected consecutive patients consulting at their clinics or hospitals irrespective of the reason for consultation. Most clinicians recruited up to eight patients, with a small number recruiting up to 16. The main focus of the CHESS study was on direct and indirect costs of health care for patients with severe haemophilia, but the clinical data gathered from CHESS were available for this study.

Patient data were collected retrospectively between January and April 2015 and included 1285 patients referred from 139 haematologists and haemophilia care providers based on haemophilia treatment centres (HTCs), hospitals and clinics. Five hundred and fourteen patients provided an EQ-5D response. Inhibitor status was defined according to the CHESS study protocol: never (no recorded inhibitors at any time), previously (at least one recorded measurement at any time) or current. Patients who had inhibitors to replacement therapy at the time of the survey (n = 58) were excluded in this study sample.

### 2.2 | Annual bleeding rate (ABR)

Bleeding frequency was reported in this study as a combination of annual major and minor bleeding rates, derived from patient records, to generate the ABR. Bleeds were categorized as major or minor and defined by the bleeding component of the World Federation of Hemophilia (WFH) Physical Examination Score (Gilbert score).\textsuperscript{16} A minor joint bleed was defined as one with mild pain, minimal joint swelling, minimal restriction of movement (ROM) and resolution within 24 hours of treatment. A major joint bleed was defined as one with moderate-to-severe pain, effusion, limitation of ROM and failure to improve within 24 hours of bleeding episodes were pooled for analysis.

### 2.3 | Target joints

A “target joint” as defined in the CHESS study encompasses any joint with known chronic synovitis. To incorporate the nuanced definitions and diagnostic options that exist within registries, trials and guidelines,\textsuperscript{17} study investigators were given discretion as to any further criteria they might use to define target joints with respect to bleed frequency and period of observation.

### 2.4 | Health-related quality of life (HRQoL)

Health-related quality of life for patients in the CHESS study was assessed using the three-level version (no problems, some problems and extreme problems) of the EQ-5D patient questionnaire covering the following five dimensions: self-care, mobility, usual daily activities, pain/discomfort and anxiety/depression.\textsuperscript{18,19} A single weighted index score is derived through an amalgam of the five dimensions, with index scores anchored at 0 (dead) and 1 (perfect health), though scores of less than zero (“worse than dead”) can also be derived.\textsuperscript{20} The EQ-5D questionnaire was chosen for this study because it provided a validated method for measuring health status as shown in the recently reported findings of the CHESS study.\textsuperscript{14,18,19} Health status as described by the EQ-5D visual analogue scale (VAS), a 0-100 scale of the patient’s perception of their current health (0 = the worst health the respondent can imagine; 100 = the best health state), is also shown in the descriptive analysis.

### 2.5 | Statistical analysis

Descriptive analysis was used to summarize patient clinical characteristics. The mean and standard deviation (SD) were used for data and frequency analysis. Standard t tests and Pearson’s chi-squared test were used for between-group differences between data on HA and HB, including for ABRs, the presence of one or more target joints and EQ-5D index scores.

Multivariate models were constructed to determine whether haemophilia type (ie HA or HB) was a statistically significant predictor of ABR, target joints or HRQoL when controlling for additional covariates linked to these clinical outcomes. A generalized linear model (GLM) was used to specify the ABR and HRQoL (ie EQ-5D index scores) models,\textsuperscript{21} while multivariate logistic regression model was used to assess the relationship with the presence of target joints. Age and body mass index (BMI) were included as covariates in all three models; additional covariates in the ABR and target joint models
were current treatment strategy (primary/secondary prophylaxis/on demand) and history of inhibitor detection (never/once/more than once). Physician-reported therapy adherence as measured on a 1-3 scale (full, partial, none) was included as a further covariate in the ABR model. Additional covariates in the EQ-SD model were HCV/HIV seropositivity, physician-reported chronic pain using the pain component of the WFH Physical Examination Score (Gilbert score).16

To avoid censoring data, for prediction of EQ-SD index scores, the index score value \( Y \) was transformed using \( nY = 1 - Y \) and results reported as EQ-SD disutility. The final value output was the average marginal effect of HA and HB on ABRs, target joints and EQ-SD index score, expressed as additionally recorded bleeds and target joints per year, and disutility, respectively.

3 | RESULTS

3.1 | Population characteristics

Of the 1227 patients studied, 77% (n = 949) had HA (mean age, 35 years) and 23% (n = 278) had HB (mean age, 36 years; Table 1). The proportion of patients with inhibitors was similar for haemophilia A and haemophilia B; this may be a chance occurrence or possibly the result of clinical practice in the participating countries. There were slightly fewer HB patients receiving prophylaxis compared with HA (54% vs 58%), but this difference was not statistically significant (\( P = 0.194 \)). Two patients were excluded from the ABR analysis due to physician responses written as proportions (%) of minor vs major bleeds (sum of bleeds = 100). Patient record data were available for all patients on target joints. Of the 514 patients who completed the EQ-5D, 78% (n = 404) had HA, and 22% (n = 110) had HB.

3.2 | Unadjusted comparison of clinical outcomes and health status

The mean ABR was significantly greater in HB patients (4.6 ± 5.8) compared with HA (3.8 ± 4.4; \( P = 0.015 \); Table 2). However, the proportion of patients reporting 10 or more bleeds in the previous year (10% and 13% for HA and HB, respectively) was not significantly higher in HB. There were no significant differences between HA and HB with regard to the proportion of patients with ≥1 target joints (59% and 54% for HA and HB, respectively; \( P = 0.104 \)) nor the mean number of target joints affected (1.15 ± 1.37 vs 0.99 ± 1.33; \( P = 0.083 \)).

Of the 514 patients who completed the EQ-5D questionnaire, the mean EQ-5D index score for patients with HA (0.78 ± 0.26) and

| TABLE 1 | Characteristics of the 1227 patients with haemophilia A and B (HA and HB) |
|-----------------|-----------------|-----------------|
|                 | HA              | HB              | \( P \) value* |
| PRF, N          | 949             | 278             | -             |
| PSC (EQ-SD response), N (%) | 405 (43) | 118 (42) | -             |
| Age, mean ± SD  | 35.4 ± 14.4     | 36.3 ± 15.3     | 0.387         |
| BMI, mean ± SD  | 24.7 ± 3.4      | 24.8 ± 3.3      | 0.819         |
| Treatment History, N (%) | -           | -              | -             |
| On demand       | 255 (27)        | 82 (30)         | 0.594         |
| Secondary prophylaxis | 384 (40) | 107 (38) |                |
| Primary prophylaxis | 173 (18) | 44 (16) |                |
| Secondary on demand | 137 (14) | 45 (16) |                |
| History of inhibitor, N (%) | -           | -              | -             |
| Never           | 846 (89)        | 244 (89)        | 0.075         |
| Once            | 85 (9)          | 23 (8)          |                |
| More than once  | 16 (2)          | 11 (4)          |                |
| Physician-reported adherence, N (%) | -           | -              | -             |
| Low             | 65 (7)          | 24 (9)          | 0.594         |
| Moderate        | 304 (32)        | 86 (31)         |                |
| High            | 580 (61)        | 168 (60)        |                |
| Comorbidities, N (%) | -           | -              | -             |
| HCV             | 55 (6)          | 10 (4)          | 0.148         |
| HIV             | 31 (3)          | 4 (1)           | 0.106         |
| Chronic pain, N (%) | -           | -              | -             |
| None            | 333 (35)        | 120 (43)        | 0.111         |
| Mild            | 359 (38)        | 94 (34)         |                |
| Moderate        | 224 (24)        | 57 (21)         |                |
| Severe          | 31 (3)          | 7 (3)           |                |

ABR, annual bleeding rate; BMI, body mass index; PRF, patient record form; PSC, patient self-completion; SD, standard deviation.
*\( P \) value is calculated by independent t test or Pearson’s chi-squared test.

| TABLE 2 | ABR and target joint status of the 1225 patients with severe haemophilia A and B (HA and HB) |
|-----------------|-----------------|-----------------|
|                 | HA              | HB              | \( P \) value* |
| ABR             | - | - | - |
| Mean ± SD       | 3.8 ± 4.4       | 4.6 ± 5.8       | 0.015         |
| Reporting 10 or more bleeds, N (%) | 90 (10) | 35 (13) | 0.135 |
| Target joints   | - | - | - |
| No. of target joints, mean ± SD | 1.15 ± 1.37 | 0.99 ± 1.33 | 0.083 |
| Reporting ≥1 target joint, N (%) | 564 (59) | 150 (54) | 0.104 |

ABR, annual bleeding rate; SD, standard deviation.
*\( P \) value is calculated by independent t test or Pearson’s chi-squared test.
HB (0.76 ± 0.29) was similar (Table 3). A positive association between HB and the self-care domain of the EQ-5D was observed, with 77% and 82% of HA and HB patients reporting no problems, respectively (P = 0.048).

### 3.3 Multivariate regression

The average mean effect (AME) of model covariates on ABR is shown in Table 4. Positive associations with ABR were BMI (AME = 0.07, 0.01–0.13) and history of an inhibitor (either once [AME = 1.40, 0.29–2.51] or more than once [AME = 3.48, 0.29–6.68]). Primary prophylaxis (AME = −2.24, −2.89 to −1.60) was negatively associated with ABR. Haemophilia type had no significant marginal effect on ABR (AME = 0.23, −0.38–0.84).

Adjusted odds ratios (aORs) of the model predictors on the presence of a target joint are shown in Table 5. Primary prophylaxis (aOR = 0.62, 0.43–0.90), age (aOR = 0.99, 0.98–1.00), BMI (aOR = 1.07, 1.02–1.11), secondary prophylaxis (aOR = 1.91, 1.42–2.55), secondary on demand (aOR = 1.69, 1.16–2.47) and inhibitor history (either once [aOR = 3.39, 2.02–5.72] or more than once [aOR = 3.24, 1.20–8.78]) were all positive predictors of the presence of one or more target joints. Haemophilia type was not found to be a significant predictor of the presence of one or more target joints (aOR = 0.77 [0.58, 1.02]).

The average mean effect of model covariates on EQ-5D index scores is shown in Table 6. Positive associations with EQ-5D were age (AME = 0.00, 0.00–0.01) and any nonzero level of chronic pain (mild: AME = 0.14, 0.06–0.22; moderate: AME = 0.25, 0.15–0.36; severe: AME = 0.71, 0.32–1.11). Haemophilia type had no significant marginal effect on EQ-5D index scores (AME = 0.04, −0.06–0.13).

### 4 Discussion and conclusion

This study compared the ABR and HRQoL between patients with HA and HB using recent data from the Cost of Haemophilia in Europe: a Socioeconomic Survey (CHESS) study. After controlling for potential confounding factors, study results showed that the diagnosis of HA compared with HB was not a significant predictor of ABR, target joint development or HRQoL in this patient cohort. Patients with HA and HB in the CHESS study experienced comparable haemophilia-related clinical and HRQoL impacts. These study findings support the recommendations of current clinical guidelines that efforts to

#### Table 3

|          | HA               | HB               | P value* |
|----------|------------------|------------------|----------|
| EQ-5D VAS, mean ± SD | 70.19 ± 15.68 | 68.09 ± 18.15 | 0.223    |
| EQ-5D index utility score, mean ± SD | 0.78 ± 0.26 | 0.76 ± 0.29 | 0.510    |
| Mobility, N (%) |                |                  |          |
| No problems | 246 (62) | 65 (57) | 0.431    |
| Some problem | 150 (38) | 48 (42) |          |
| Severe problems | 3 (1) | 2 (2) |          |
| Self-care, N (%) |                |                  |          |
| No problems | 307 (77) | 94 (82) | 0.048    |
| Some problem | 88 (22) | 17 (15) |          |
| Severe problems | 4 (1) | 4 (3) |          |
| Usual activities, N (%) |                |                  |          |
| No problems | 270 (68) | 72 (63) | 0.588    |
| Some problem | 121 (30) | 40 (35) |          |
| Severe problems | 8 (2) | 3 (3) |          |
| Pain, N (%) |                |                  |          |
| No problems | 152 (38) | 53 (46) | 0.274    |
| Some problem | 231 (58) | 59 (51) |          |
| Severe problems | 16 (4) | 3 (3) |          |
| Anxiety, N (%) |                |                  |          |
| No problems | 240 (60) | 68 (59) | 0.491    |
| Some problem | 142 (36) | 39 (34) |          |
| Severe problems | 17 (4) | 8 (7) |          |

SD, standard deviation; VAS, visual analogue scale.

*P value is calculated by independent t test or Pearson's chi-squared test.
TABLE 4  Regression analysis for annual bleeding rate (ABR) using a generalized linear model (GLM)

|                      | AME (95% CI)         | P value |
|----------------------|----------------------|---------|
| Haemophilia B (vs HA)| 0.23 (0.38, 0.84)    | 0.459   |
| Age                  | −0.01 (−0.03, 0.01)  | 0.176   |
| BMI                  | 0.07 (0.01, 0.13)    | 0.024   |
| Current treatment strategy (vs primary on demand) | | |
| Secondary prophylaxis | −0.32 (−1.00, 0.35)  | 0.344   |
| Primary prophylaxis  | −2.24 (−2.89, −1.60) | <0.001  |
| Secondary on demand  | 0.11 (−0.79, 1.01)   | 0.807   |
| History of inhibitor detection (vs never) | | |
| Once                 | 1.40 (0.29, 2.51)    | 0.013   |
| More than once       | 3.48 (0.29, 6.68)    | 0.033   |
| Adherence (vs low)   |                      |         |
| Moderate             | −0.14 (−1.33, 1.06)  | 0.824   |
| High                 | −0.65 (−1.80, 0.50)  | 0.268   |

AME (95% CI): average marginal effect and 95% confidence interval.

TABLE 5  Regression analysis for the presence of one or more target joints using logistic regression

|                      | aOR (95% CI)   | P value |
|----------------------|----------------|---------|
| Haemophilia B (vs HA)| 0.77 (0.58, 1.02) | 0.066   |
| Age                  | 0.99 (0.98, 1.00) | 0.005   |
| BMI                  | 1.07 (1.02, 1.11) | 0.001   |
| Current treatment strategy (vs primary on demand) | | |
| Secondary prophylaxis | 1.91 (1.42, 2.55) | <0.001  |
| Primary prophylaxis  | 0.62 (0.43, 0.90) | 0.012   |
| Secondary on demand  | 1.69 (1.16, 2.47) | 0.007   |
| History of inhibitor detection (vs never) | | |
| Once                 | 3.39 (2.02, 5.72) | <0.001  |
| More than once       | 3.24 (1.20, 8.78) | 0.021   |

aOR (95% CI), adjusted odds ratio and 95% confidence interval.

TABLE 6  Regression analysis for EQ-5D disutility using a generalized linear model (GLM)

|                      | AME (95% CI)   | P value |
|----------------------|----------------|---------|
| Haemophilia B (vs HA)| 0.04 (−0.06, 0.13) | 0.484   |
| Age                  | 0.00 (0.00, 0.01) | 0.013   |
| BMI                  | 0.00 (−0.01, 0.02) | 0.801   |
| HCV seropositive     | 0.03 (−0.14, 0.20) | 0.741   |
| HIV seropositive     | −0.05 (−0.30, 0.21) | 0.715   |
| Chronic pain (vs none) |               |         |
| Mild                 | 0.14 (0.06, 0.22) | <0.001  |
| Moderate             | 0.25 (0.15, 0.36) | <0.001  |
| Severe               | 0.71 (0.32, 1.11) | <0.001  |

AME (95% CI), average marginal effect and 95% confidence interval.
ACKNOWLEDGEMENTS

Editorial support for writing this manuscript was provided by Dinah Parums. Review and feedback on the manuscript were provided by Shire.

DISCLOSURES

This study was funded by Shire Pharmaceuticals. JB and AO are full-time employees of Shire. JOH has been an invited speaker at meetings organized by Bayer, Biogen, Pfizer and Roche, served on advisory boards for Bayer, Roche, Shire and Sobi, and has acted as an occasional paid consultant for Roche and Shire. SW, LC, DGD, TS and BOM declared no interests which might be perceived as posing conflict or bias.

AUTHORS’ CONTRIBUTIONS

JB, AO and JOH were involved in the conception and design of the study, verification of the results and interpretation of data. SW and CC were involved in the analysis of results, verification of results and interpretation of data. All authors were involved in drafting and revising the manuscript and reviewed and approved the final version of the manuscript.

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How to cite this article: Booth J, Oladapo A, Walsh S, et al. Real-world comparative analysis of bleeding complications and health-related quality of life in patients with haemophilia A and haemophilia B. Haemophilia. 2018;24:e322–e327. https://doi.org/10.1111/hae.13596