An Assessment of Annualized Bleeding Rates and Quality of Life Among Severe Haemophilia A and B Individuals in Europe

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INTRODUCTION

- Haemophilia is classified into two different types depending on the clotting factor deficiency of the patient. Both haemophilia A and B affect all races and ethnic groups equally. Haemophilia B (FIX deficiency) is less prevalent than haemophilia A (FVIII deficiency) occurring in approximately 1 in 25,000 male births compare to 1 in 5,000, respectively.
- The clinical severity of severe haemophilia B is perceived to be lower than severe haemophilia A, which may contribute to the thinking that haemophilia B has less negative impact on patients and better outcomes compared to haemophilia A (Manucci 2013).
- Patients with severe haemophilia, either A or B, with factor levels < 1% require either on-demand treatment of joint bleeds or prophylaxis for the prevention of such bleeding to preserve joint health (Srivastava 2013).
- A single joint bleed may cause a permanent joint damage (Gringeri 2014). Two or three bleeds into the same joint can result in increased bodily pain, reduced physical functioning or disability.
- Recurrent haemorrhage in the same joint may result in irreversible intra-articular damage, chronic pain, impaired mobility, inability to do certain jobs culminating in haemophilic arthropathy. This along with the psychological consequences for the patients and their social functioning can negatively impact their health-related quality of life (HRQoL).

OBJECTIVE

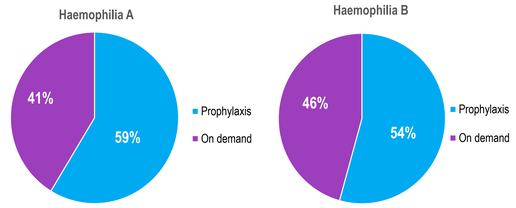
- The aim of this analysis is to compare the real-world annual bleeding rates (ABRs) and health-related quality of life (HRQoL) between severe haemophilia A and B patients.
- The incidence and clinical severity of severe haemophilia B compared to haemophilia A across the individual EU-5 countries (France, Germany, Italy, Spain, and the United Kingdom (UK) is presented in the analysis.
- The impact of the type of treatment regimen (on demand or prophylaxis) is explored in this research.

METHODS

- Data were taken from the "Cost of Haemophilia across Europe" – A cross-section of 139 haemophilia specialists (surveyed between January and April 2015) providing demographic and clinical information and 12-month ambulatory and secondary care activity for 1,285 patients via an online survey. In turn, 551 of those patients provided corresponding direct and indirect non-medical cost information, including work loss and out-of-pocket expenses. A cost database was developed for each country using publically-available information. Study ethics was governed and approved by the University of Chester Ethics Committee.
- Physician-recorded monthly bleeding rates were annualized to generate ABRs.
- Patient-reported HRQoL (n = 515) was assessed via the EQ-5D-3L. Predictions of EQ-5D values are confined to the range -0.594 to 1.0, where 1.0 represents 'perfect health', 0 represents 'death', and values less than zero are health states 'worse than death'.
- Standard t-tests were conducted in order to test for between-group statistically significant differences.
- Patients with inhibitors were excluded due to the differing pattern of HRQoL and ABR among these patients.
- Patients were separated depending on treatment regimens combining primary and secondary on demand and prophylaxis patients into either prophylaxis or on demand.
- ABR and HRQoL scores were also analysed across the different countries in the EU-5.

RESULTS

Figure 1: Treatment Regimen by Haemophilia Subtype



- 1,227 (excludes current inhibitor patients) patients provided information on number of bleeds in a year while 515 patients completed information for EQ-5D scores, these patients were the focus of this analysis.
- The average age of patients examined in this analysis was 36 years old (standard deviation (SD) 15yrs) with a mean age for start of treatment of 17 years old (SD 15.84).
- Patients examined in the analysis had a mean number of target joints of 1.12 (SD 1.37); haemophilia A 1.16 (SD 1.37, n = 949) and haemophilia B 1.00 (SD 1.34, n = 278).
- The proportion of haemophilia B and haemophilia A patients on prophylaxis therapy in this sample was 54% (n = 151) and 59% (n = 557), respectively.
- Mean ABR was significantly higher (p = 0.004) for haemophilia B patients (12.80, SD 13.11, n = 278) vs haemophilia A (10.70, SD 11.02, n = 949). It was also significantly higher (p = 0.008) for haemophilia B patients on prophylaxis (12.90, SD 13.79, n = 151) vs haemophilia A prophylaxis (10.00, SD 11.05, n = 557).
- Haemophilia B patients on-demand had higher mean ABR although not significant (p = 0.401, 12.7, SD 12.31, n = 127) vs on-demand haemophilia A (11.7, SD 10.92, n = 392) .
- The maximum number of bleeds experienced by a patient in a year was also higher for haemophilia B (84 vs 72 bleeds, respectively).

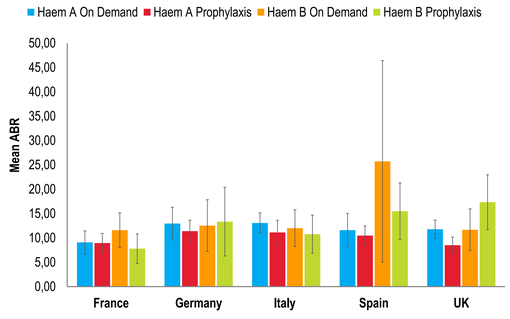
Table 1: Breakdown of Haemophilia A and B Treatment Regimens

Total Sample	Haemophilia A	Haemophilia B
Treatment type	N (%)	N (%)
Prophylaxis	557 (58.69%)	151 (54.32%)
On demand	392 (41.31%)	127 (45.68%)
Total	949 (100%)	278 (100%)

Table 2: Haemophilia A and B Treatment Regimens by Country

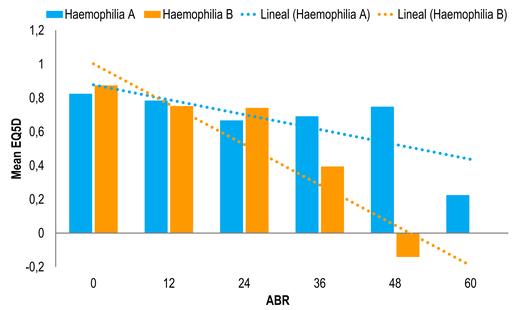
By Country	Haemophilia A		Haemophilia B	
	Prophylaxis	On Demand	Prophylaxis	On Demand
France	110 (19.75%)	78 (19.88%)	37 (24.50%)	29 (22.83%)
Germany	98 (17.59%)	51 (13.01%)	18 (11.92%)	23 (18.11%)
Italy	109 (19.57%)	102 (26.02%)	29 (19.21%)	31 (24.41%)
Spain	110 (19.75%)	58 (14.80%)	31 (20.53%)	7 (5.51%)
UK	130 (23.34%)	103 (26.28%)	36 (23.84%)	37 (29.13%)

Figure 2: ABR by Country and Treatment Regimen



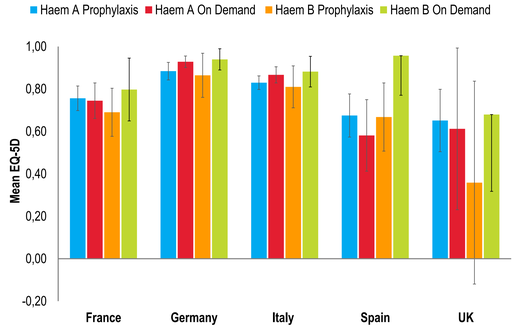
- The greatest number of bleeds reported in the previous 12 months was reported in Spain for patients with haemophilia B receiving an on demand treatment regimen with a mean ABR of 25.71 (SD 22.37, n = 7).

Figure 3: EQ-5D Scores by ABR and Haemophilia Subtype



- Overall the mean EQ-5D score was similar but not significantly different for haemophilia B patients of 0.78 (SD 0.26, n = 115) vs 0.76 (SD 0.29, n = 400) for haemophilia A.
- For both haemophilia A and B, HRQoL scores declined inversely with ABR, with patients with zero recorded bleeds (n = 172) reporting the highest mean EQ-5D-3L score with a mean of 0.82 (SD 0.22, n = 135) for haemophilia A patients and a mean of 0.87 (SD 0.19, n = 37) for haemophilia B patients.
- The greatest impact on HRQoL was reported in haemophilia B patients with 36 bleeds per year and 48 bleeds per year, with a mean EQ-5D-3L score of 0.39 (SD 0.17, n = 2) and -0.14 (SD 0.31, n = 3), respectively. Greatest impact for haemophilia A patients was observed in patients with > 24 bleeds per year with mean EQ-5D-3L scores up to 0.75 (SD 0.16, n = 4) at 48 months and down to 0.225 (SD undefined, n = 1) at 60 months.
- Mean ABR across the remaining groups were similar with means ranging from 7.78 to 17.33.
- The percentage of patients with zero bleed was not statistically different between haemophilia A and haemophilia B patients (36.9% vs. 31.7%, Chi-square test p = 0.11).
- ABR categories were not statistically different between haemophilia A and haemophilia B patients (Fisher's Exact test p = 0.05).

Figure 4: EQ-5D by Country and Treatment Regimen



- Patients from Germany experienced the highest HRQoL in the study sample with mean EQ-5D-3L scores of 0.88 (SD 0.14, n = 49), 0.93 (SD 0.07, n = 29), 0.86 (SD 0.11, n = 7) and 0.94 (SD 0.75, n = 11) for haemophilia A prophylaxis, haemophilia A on demand, haemophilia B prophylaxis and haemophilia B on demand, respectively.
- In contrast the United Kingdom reported the lowest HRQoL scores in the study sample with mean EQ-5D-3L scores of 0.65 (SD 0.32, n = 21), 0.61 (SD 0.36, n = 6), 0.36 (SD 0.52, n = 7) and 0.68 (SD 0.15, n = 3) for haemophilia A prophylaxis, haemophilia A on demand, haemophilia B prophylaxis and haemophilia B on demand, respectively.

DISCUSSION

- The analysis indicates that patients with haemophilia B experienced significantly higher (p = 0.004) mean ABR when compared to haemophilia A patients.
- Although severe haemophilia B patients had higher ABR they had similar HRQoL compared to severe haemophilia A patients in Europe. This indicates that haemophilia A and haemophilia B patients have similar clinical severity.

CONCLUSION

- This research supports the assertion that burden and unmet need within the haemophilia B population is at least comparable to haemophilia A and should not be underestimated.
- Further analysis is required to control for heterogeneity within the haemophilia population and confirm these results.
- These results provide preliminary evidence that efforts to promote the same standard of prophylaxis treatment for haemophilia A and haemophilia B patients are warranted.

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DISCLOSURES

*Author an employee of Baxalta ([1]Baxalta US, Inc., Cambridge, MA USA), now part of Shire. The studies were sponsored by Baxalta US, Inc., now part of Shire. The original CHESS study was supported by unrestricted research grants from Swedish Orphan Biovitrum AB (Sobi) and Novo Nordisk. The study was approved by the University of Chester Ethics Committee.