Benchmarking prophylaxis with factor concentrates: reference data on annualized bleeding rates in children with severe hemophilia

Severe hemophilia A (SHA) and B (SHB) are rare inherited bleeding disorders characterized by recurrent bleeds. Regular infusions with factor VIII (FVIII) or factor IX (FIX) concentrates decreased bleeding rates significantly.[1-5] A randomized clinical trial confirmed that early FVIII prophylaxis significantly reduces bleeding rates and prevents joint damage in young boys with SHA compared to on-demand-treatment.[1] Fischer *et al*.[6] showed that delaying prophylaxis until after the first joint bleed increases bleeding rates and the risk of hemophilic arthropathy. These findings have driven earlier initiation of prophylaxis with coagulation factor concentrates (CFC) in developed countries.[7] Extended half-life (EHL) products were introduced to reduce the burden of frequent infusion and maintain higher through levels. More recently, new treatment options have emerged as alternatives to prophylaxis with traditional CFC, either by mimicking the effect of FVIII or by shifting the balance of hemostasis. Several non-replacement therapies are currently under development or have already received regulatory approval. However, clinical trials evaluating these new therapies often compare efficacy against only a limited period before switching, with patient selection potentially introducing bias, either due to prior suboptimal treatment or as enrollment criteria require prior bleeding events to demonstrate differences. Annualized bleeding rates (ABR) are the key short-term clinical outcome for the assessment of efficacy of any hemophilia therapy. Comparing the benefits of novel treatment options with those of classical prophylaxis requires valid data on bleeding rates in patients on full primary prophylaxis with FVIII or FIX CFC. Yet, real-world data on ABR on prophylaxis with CFC in western countries is lacking. Our goal was to establish reference data for ABR on optimal prophylaxis with CFC in severe hemophilia without inhibitors to serve as a comparator for new therapies.

The PedNet Registry collects data from 33 hemophilia treatment centers from diagnosis onwards in 19 countries.[8] The participating centers are listed in the *Online Supplementary Appendix*. Ethical approval is obtained from local or national ethical review boards, and written informed consent is obtained from the parents or guardians of all participants. The trial was registered at clinicaltrials.gov NCT02979119. All events treated with CFC outside prophylaxis or surgery are registered as bleeds. The present study, approved by the PedNet Scientific Board, includes bleeding rates in 876 patients with severe hemophilia (716 SHA, 160 SHB; 3 females) born after January 2000, without history of inhibitor development and on full prophylaxis until transition to non-factor therapy (emicizumab), end of follow-up at 18 years of age, or end of data extraction date (January 1, 2022). Start of prophylaxis is defined as use of CFC in the absence of bleeding, at least three times within 15 days for at least two consecutive months. For SHA, full prophylaxis is defined as the administration of standard half-life (SHL) CFC at least three times weekly or EHL CFC at least twice a week. For SHB, full prophylaxis was defined as administration of SHL CFC at least twice a week or EHL CFC at least once weekly. Only patients with at least three months of follow-up time on full prophylaxis were included. Mean (95% confidence interval [CI]) ABR and annualized joint bleeding rates (AJBR) for treated bleeds were calculated using a negative binominal model. Bleeds were categorized

Table 1. Patient characteristics.

	Hemophilia A N=716 Median (IQR)	Hemophilia B N=130 Median (IQR)
Age at start prophylaxis, years*	1.31 (0.94-2.09)	1.46 (0.92-2.30)
Age at start full prophylaxis, years**	2.44 (1.43-4.51)	2.03 (1.20-3.16)
Age at last evaluation, years	10.3 (6.6-15.1)	10.4 (6.5-14.2)
Total patient years on full prophylaxis	5,202	1,021
Median patient years per patient	6.55 (3.42-10.91)	7.59 (3.98-11.60)

*Start prophylaxis was defined as the use of coagulation factor concentrates (CFC) in the absence of bleeding, at regular intervals for at least two consecutive months. At least once weekly for standard half-life (SHL) CFC and at least once per two weeks for extended half-life (EHL) CFC. **Full prophylaxis for severe hemophilia A was defined as administration of SHL-CFC ≥3 times a week and EHL-CFC ≥2 times a week and for severe hemophilia B: SHL-CFC ≥2 times a week and EHL-CFC ≥ once a week. IQR: interquartile range (P25, P75); N: number.

as joint or non-joint bleeds. AJBR were analyzed by the following age periods: start of full prophylaxis-5 years, 6-11 years, and 12-18 years. For descriptive analyses, variables were summarized by number and percentage (%) for categorical variables and as median and interquartile range (P25, P75 [IQR]) for continuous variables. ABR and AJBR between patients treated with EHL and standard half-life FVIII/IX concentrates were compared using multivariate negative binomial regression analysis, adjusted for age at evaluation. Analyses were performed with Statistical Package for Social Science (SPSS) version 29.0.1.0 for Windows (IBM Corp, 2019) and Stata/SE 13.1 for Windows (StataCorp LP, 2014). $P<0.05$ was considered statistically significant.

The median age at the start of prophylaxis was 1.31 (IQR: 0.94-2.09) years for SHA and 1.46 (0.92-2.30) for SHB. Full prophylaxis was reached at a median age of 2.44 years (IQR: 1.43-4.51) in SHA and 2.03 years (1.20-3.16) in SHB. The total follow-up time on full prophylaxis for the whole group was 6,223 patient-years and the median follow-up per patient was 6.67 years (IQR: 3.47-11.01). Clinical characteristics of the study population are shown in Table 1.

Table 2 presents overall bleeding rates for treated bleeds during the time on full prophylaxis for the whole group and separate for SHA and SHB by age groups. Mean overall ABR for the whole group was 1.33 (95% CI: 1.22-1.46). The AJBR was 0.40 (95% CI: 0.35-0.45) for SHA and 0.37 (95% CI: 0.29-0.49) for SHB. The ABR for non-joint bleeds was 1.35 (95% CI: 1.23-1.49) for SHA and 1.25 (95% CI: 1.00-1.56) for SHB. There were no significant differences in ABR or AJBR between SHA and SHB. Full prophylaxis did not prevent all life-threatening bleeds: 10 children (7 with SHA and 3 with SHB) had a life-threatening bleed on a full prophylaxis regimen; 4 had intracranial bleeds, 5 had iliopsoas bleeds, and one had a pharyngeal bleed (*Online Supplementary Table*

Table 2. Annualized bleeding rates in severe hemophilia A and B during full prophylaxis according to age group.

	SHA N=716	SHB N=130	TOTAL N=846	*P*
ABR joint bleeds, mean (CI)	0.40 (0.35-0.45)	0.37 (0.29-0.49)	0.40 (0.35-0.44)	0.649
ABR non-joint bleeds, mean (CI)	0.82 (0.74-0.92)	0.77 (0.60-0.98)	0.81 (0.74-0.90)	0.619
ABR all bleeds, mean (CI)	1.35 (1.23-1.49)	1.25 (1.00-1.56)	1.33 (1.22-1.46)	0.534
Age at start of full prophylaxis - 5 years				
N of patients	579	118	697	-
Total patient years	1,742	387	2,129	-
Years per patient, median (IQR)	3.10 (1.80-4.13)	3.41 (2.10-4.45)	3.18 (1.89-4.18)	0.046
ABR joint bleeds, mean (CI	0.38 (0.33-0.44)	0.30 (0.22-0.41)	0.37 (0.33-0.42)	0.163
ABR non-joint bleeds, mean (CI)	0.99 (0.87-1.11)	0.86 (0.66-1.13)	0.97 (0.86-1.08)	0.370
ABR all bleeds, mean (CI)	1.54 (1.38-1.72)	1.24 (0.97-1.59)	1.49 (1.35-1.64)	0.111
Age 6 - 11 years				
N of patients	529	99	628	-
Total patient years	2,264	435	2,699	-
Years per patient, median (IQR)	4.86 (2.60-5.78)	5.02 (3.03-5.81)	4.90 (2.63-5.78)	0.583
ABR joint bleeds, mean (CI)	0.47 (0.41-0.54)	0.42 (0.31-0.56)	0.46 (0.41-0.52)	0.446
ABR non-joint bleeds, median (CI)	0.84 (0.75-0.95)	0.79 (0.60-1.03)	0.83 (0.74-0.93)	0.666
ABR all bleeds, median (CI)	1.42 (1.28-1.58)	1.32 (1.03-1.69)	1.41 (1.28-1.55)	0.579
Age 12 - 18 years				
N of patients	293	53	346	-
Total patient years	1,196	199	1,395	-
Years per patient, median (IQR)	4.04 (2.35-5.69)	4.00 (1.65-5.57)	4.01 (2.14-5.69)	0.305
ABR joint bleeds, mean (CI)	0.27 (0.23-0.32)	0.45 (0.317-0.64)	0.30 (0.26-0.35)	0.009
ABR non-joint bleeds, mean (CI)	0.46 (0.39-0.53)	0.44 (0.31-0.63)	0.45 (0.39-0.52)	0.848
ABR all, mean (CI)	0.78 (0.69-0.89)	1.03 (0.77-1.39)	0.82 (0.73-0.92)	0.083

ABR: annualized bleeding rates; CI: 95% Confidence Intervals; IQR: quartiles P25, P75; N: number; SHA: severe hemophilia A; SHB: severe hemophilia B.

S1). Overall ABR were highest in the youngest age group and decreased for the two older age groups. In the two younger age groups, non-joint bleeds dominated. Even in the oldest age group with SHA, non-joint bleeds were twice as common as joint bleeds. The oldest children with SHB had higher AJBR at similar frequency as non-joint bleeds. Overall, teenagers aged 12 years and older had lower ABR than younger children on full prophylaxis.

During the study period, 391 children with SHA and 88 with SHB received prophylaxis with EHL products. The median duration of EHL prophylaxis was 1.98 years per patient (IQR: 1.07-3.01, total follow-up of 840 patient years) for SHA, and 1.69 years (IQR: 0.97-2.50, total follow-up 165 patient years) for SHB. Bleeding rates for SHA observed during EHL-FVIII prophylaxis were significantly lower (incidence rate ratio 0.5, $P<0.001$) for both all treated bleeds and joint bleeds in all age groups compared to those treated with SHL-FVIII. Bleeding rates for SHL-FIX and EHL-FIX concentrates were comparable (Table 3).

Young children learning to walk frequently experience falls, and caregivers of children with severe hemophilia are often advised to administer extra CFC following any trauma, even in the absence of active bleeding symptoms. This practice likely contributed to the relatively high number of reported non-joint bleeds in our youngest cohort. The ABR of non-joint bleeds decreased with age and showed no significant difference between SHA and SHB. Children with SHB reached full prophylaxis earlier than those with SHA, likely due to the lower administration frequency required for FIX compared to FVIII concentrates.

Although our data on ABR and AJBR with EHL products is less extensive than for the entire cohort, the cohort on EHL product is still relatively large, with a median follow-up of nearly two years per patient. A recent meta-analysis[9] did not find any difference between bleeding rates between SHL and EHL products in hemophilia A while other studies[10-12] have suggested lower bleeding rates with EHL products compared to SHL products. In our study, patients with SHA appeared to benefit from EHL products. However, no benefit from EHL was seen for SHB, possibly due to the lower number of patients.

Previous studies comparing the phenotypes between severe hemophilia A and B have been controversial, with some studies suggesting that hemophilia A is more severe than

Table 3. Bleeding rates in severe hemophilia A and B during full prophylaxis on extended half-life products according to age group.

	SHA	SHB	Total	*P*
Age at start of full prophylaxis - 5 years				
N of patients	113	25	138	-
Total patient years	187	45	232	-
Patient years per patient, median (IQR)	1.33 (0.79-2.27)	1.66 (0.70-2.67)	1.42 (0.79-2.37)	-
ABR joint bleeds, mean (CI)	0.19 (0.12-0.29)	0.32 (0.15-0.65)	0.21 (0.14-0.31)	0.219
ABR non-joint bleeds, mean (CI)	0.60 (0.44-0.82)	0.97 (0.56-1.69)	0.66 (0.50-0.88)	0.125
ABR all bleeds, mean (CI)	0.83 (0.63-1.09)	1.35 (0.83-2.21)	0.92 (0.72-1.17)	0.086
Age 6 - 11 years				
N of patients	149	39	188	-
Total patient years	335	76	411	-
Patient years per patient, median (IQR)	2.06 (1.13-3.04)	1.63 (1.04-2.57)	1.96 (1.10-3.02)	-
ABR joint bleeds, mean (CI)	0.25 (0.18-0.35)	0.30 (0.17-0.54)	0.26 (0.19-0.35)	0.539
ABR non-joint bleeds, mean (CI)	0.56 (0.43-0.72)	0.92 (0.59-1.44)	0.62 (0.49-0.78)	0.054
ABR all bleeds, mean (CI)	0.85 (0.68-1.06)	1.35 (0.91-2.00)	0.93 (0.77-1.13)	0.044
Age 12 - 18 years				
N of patients	129	24	153	-
Total patient years	318	44	362	-
Patient years per patient, median (IQR)	2.26 (1.47-3.33)	1.84 (0.93-2.14)	2.10 (1.41-3.27)	-
ABR joint bleeds, mean (CI)	0.24 (0.17-0.33)	0.40 (0.20-0.81)	0.26 (0.18-0.35)	0.167
ABR non-joint bleeds, mean (CI)	0.35 (0.26-0.47)	0.29 (0.14-0.60)	0.34 (0.26-0.45)	0.628
ABR all bleeds, mean (CI)	0.61 (0.48-0.79)	0.85 (0.49-1.48)	0.64 (0.51-0.81)	0.277

ABR: annualized bleeding rates; CI: 95% confidence interval; IQR: quartiles P25, P75; N: number; SHA: severe hemophilia A; SHB: severe hemophilia B.

hemophilia B.[13-15] In our cohort of unselected patients, our data on ABR and AJBR were very low for both SHA and SHB. Bleeding rates were comparable, except for a clinically non-significant increased AJBR in adolescents with SHB compared to adolescents with SHA.

A key strength of our study is the extensive follow-up period, up to a median of more than 11 years for the oldest age group, thus providing more comprehensive prospective data on long-term bleeding rates. However, most bleeding events were self-reported. Extra administration of CFC during prophylaxis was reported as a bleed by definition. Parents are often instructed to administer additional CFC doses at home to prevent potential bleeds following trauma. This practice may have led to inflated bleeding rates. Several factors likely contribute to the low bleeding rates observed in our cohort. Firstly, our study included only children without a history of inhibitors. Second, primary prophylaxis was initiated at an early age for the children in our cohort, which has likely played a role in achieving these lower bleeding rates.

Our large cohort, characterized by early initiation of primary prophylaxis (median age at start of prophylaxis 1.31 years for SHA and 1.46 for SHB) and long-term follow-up (total follow-up time 6,223 years) is unique and provides valuable reference values for ABR achievable with primary prophylaxis using CFC. We report low bleeding rates on full prophylaxis with CFC in children with severe hemophilia, with mean ABR for treated bleeds at 1.3 in the entire cohort. Our findings establish critical data for evaluating the efficacy of emerging novel therapies in pediatric severe hemophilia, filling a gap in the literature where comparative data have not previously been available.

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Contributions

HMvdB designed the study. MdK and KF performed the primary analyses of the data. SR wrote the first draft of the manuscript. All authors contributed to collecting and the final analysis of the data, as well as writing the final manuscript, and have approved the final version for publication.

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Data-sharing statement

The data that support the findings of this study are recruited from the registry of the PedNet Haemophilia Research Foundation. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the PedNet Haemophilia Research Foundation (www.pednet.eu).

References

1. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535-544.
2. Franchini M, Mannucci PM. The history of hemophilia. Semin Thromb Hemost. 2014;40(5):571-576.
3. Fischer K, Steen Carlsson K, Petrini P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. Blood. 2013;122(7):1129-1136.
4. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. Haemophilia. 2001;7(5):446-452.
5. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992;232(1):25-32.
6. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood. 2002;99(7):2337-2341.
7. Ljung R, de Kovel M, van den Berg HM; PedNet study group. Primary prophylaxis in children with severe haemophilia A and B-Implementation over the last 20 years as illustrated in real-world data in the PedNet cohorts. Haemophilia. 2023;29(2):498-504.
8. Fischer K, Ljung R, Platokouki H, et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. Haemophilia. 2014;20(4):e280-286.
9. Mannucci PM, Kessler CM, Germini F, et al. Bleeding events in people with congenital haemophilia A without factor VIII inhibitors receiving prophylactic factor VIII treatment: a systematic literature review. Haemophilia. 2023;29(4):954-962.
10. Dettoraki A, Michalopoulou A, Mazarakis M, et al. Clinical application of extended half-life factor VIII in children with severe haemophilia A. Haemophilia. 2022;28(4):619-624.
11. Malec LM, Cheng D, Witmer CM, et al. The impact of extended half-life factor concentrates on prophylaxis for severe hemophilia in the United States. Am J Hematol. 2020;95(8):960-965.
12. Sun HL, Yang M, Poon MC, et al. Factor product utilization and health outcomes in patients with haemophilia A and B on extended half-life concentrates: a Canadian observational study of real-world outcomes. Haemophilia. 2021;27(5):751-759.
13. Franchini M, Mannucci PM. Haemophilia B is clinically less severe than haemophilia A: further evidence. Blood Transfus. 2018;16(2):121-122.
14. Melchiorre D, Linari S, Manetti M, et al. Clinical, instrumental, serological and histological findings suggest that hemophilia B may be less severe than hemophilia A. Haematologica. 2016;101(2):219-225.
15. Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. Haematologica. 2019;104(9):1702-1709.