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Physical activity and bleeding outcomes among people with severe hemophilia on extended half-life or conventional recombinant factors

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Abstract

Background: Few have assessed physical activity (PA) and annual bleed rates (ABRs) among people with hemophilia on extended half-life (EHL) factors (recombinant factor VIII Fc [rFVIIIFc]/recombinant factor IX Fc [rFIXFc]) and conventional factors (recombinant factor VIII [rFVIII]/recombinant factor IX [rFIX]).

Objective: To assess changes in PA and ABR at consecutive annual visits in individuals with severe hemophilia A and B (HA/HB) on prophylactic treatment with rFVIIIFc/rFIXFc versus rFVIII/rFIX.

Patients/Methods: We conducted a retrospective chart review of 344 people with severe HA/HB (ages 6-35) receiving prophylaxis with rFVIIIFc/rFIXFc (EHL factors) or rFVIII/rFIX (conventional factors) for ≥6 months in 2014-2015. Differences in changes in outcomes from 2014 to 2015 were compared across the treatment groups.

Results: Baseline characteristics and adherence to the prophylactic regimen were similar across the treatment groups. Greater increase in weekly PA frequency and duration were observed among all EHL groups, except for children treated with rFIXFc. The increase in PA frequency was greater among the children on rFVIIIFc group, adults on rFVIIIFc group, and adults on rFIXFc group by 1.2, 1.2, and 1.4 events/week, respectively, compared to their rFVIII/rFIX counterparts. The increases in PA duration were 44, 60, and 80 min/wk greater among the children on rFVIIIFc, adults on rFVIIIFc, and adults on rFIXFc groups, respectively. Larger reductions in total ABR were observed in children and adults treated with rFVIIIFc compared to rFVIII (0.4 and 0.7 fewer bleeds). Larger reductions were also observed in spontaneous ABR in adult rFVIIIFc and rFIXFc groups (0.8 and 0.3 fewer bleeds, respectively).

Conclusions: This study suggests that rFVIIIFc/FIXFc agents can positively impact PA while maintaining low ABRs.

Essentials

- Few studies assess physical activity and bleed rates across extended half-life (EHL) factors and conventional factors.
- This chart review assessed changes in outcomes among people with severe hemophilia A/B.
- Increases in physical activity were typically greater in EHL groups versus conventional groups.
- This study suggests that EHL recombinant factor VIII Fc /recombinant factor IX Fc may positively impact patients' physical activity.

1 | INTRODUCTION

An estimated 30 000 people live with hemophilia A or hemophilia B in the United States today.[1] Based on the World Federation for Hemophilia's (WFH's) annual survey, the global prevalence of hemophilia is approximately 400 000.[2] The disease is characterized by spontaneous and recurrent bleeds that lead to progressive, irreversible joint damage.[2] Prophylactic factor replacement therapy is recommended for the management of patients with severe hemophilia.[3] Prophylaxis is intended to decrease the frequency of bleeding, slow the progression of joint disease, and ultimately lead to better joint preservation and an improved quality of life.[2,4] However, prophylactic treatment with conventional factor therapy requires infusions several times weekly, with adherence to treatment critical to the success of therapy.

Several factors are associated with outcomes among people with hemophilia, including age of prophylaxis initiation, receipt of care in a hemophilia treatment center (HTC), and adherence to treatment and physician guidance.[5,6] Higher adherence to prophylaxis is associated with better outcomes among people with hemophilia, including in patients with severe disease, whereas poor adherence is associated with more bleeding events.[4,7] Extended half-life (EHL) recombinant factors VIII and IX Fc fusion protein (rFVIIIFc/rFIXFc; approved in the United States in June and March of 2014, respectively)[8,9] offer advantages over conventional recombinant factors VIII and IX (rFVIII and rFIX) through less frequent infusion, which can improve treatment adherence and lead to better patient outcomes.[10]

EHL recombinant factors can provide additional protection during physical activities or sporting events.[11] When infused at the same or similar dosing schedule as conventional recombinant factors, EHL recombinant factors increase factor trough levels, which may allow people with hemophilia to achieve a more active lifestyle while maintaining or decreasing the frequency of bleeds.[12,13]

Physical activity (PA) is necessary for people with hemophilia to maximize their health by strengthening muscles, maintaining joint mobility and bone health, and improving physical functioning.[2] However, guidelines for people with hemophilia have historically limited the activities that can be safely pursued because many activities, such as contact sports, may lead to severe bleeding events.[2] Thus, patients have historically been limited in their PA depending on the severity of their clinical disease, bleeding phenotype, and treatment regimen (eg, frequency and dosing).[2,14] It has been shown in phase 3 clinical trials as well as several case reports that people with severe hemophilia on prophylactic treatment with EHL rFVIIIFc and rFIXFc can maintain or increase their PA participation while still maintaining low bleeding rates.[15-17] To the authors' knowledge, no study has assessed whether these outcomes are observed beyond individual case reports. To investigate this, we conducted a retrospective medical chart review and assessed levels of participation in PAs and annual bleeding rates (ABRs) among people with severe hemophilia A (HA) and B (HB) treated with EHL rFVIIIFc/rFIXFc and conventional rFVIII/rFIX at a given prophylaxis treatment regimen.

2 | MATERIALS AND METHODS

2.1 | Data source and data collection

This multisite retrospective medical chart review study was conducted at 13 HTCs and 3 hematology/oncology (non-HTC) clinics across the United States. Efforts were made to ensure that a geographically representative sample of hematologists treating hemophilia were recruited for the study to ensure that the study findings are generalizable. The study was submitted to the Institutional Review Board (IRB) and was deemed as exempt because it examined existing data in which patients could not be identified. Potential physician participants, identified from an HTC list (n = 147) provided by the Centers for Disease Control and Prevention and a national database of private/office-based practice physicians, acquired from Firstmark, Inc, a mailing list company (n = 17,659; September 2015), were contacted using a random sampling strategy.[1,18]

If eligible, the interested physicians were recruited for participation. Eligible physicians included hematologists/oncologists providing treatments to ≥15 individuals with HA or HB aged 6-35 years at their center, and who collected patient information on physical activity, bleeding frequency, and treatment at least annually. Each participating physician was provided study materials, including patient chart review forms (CRFs) and facility profile forms (FPFs). The CRF and FPF were developed using findings from a targeted literature review and from the results of a feasibility assessment conducted with 12 sites (8 HTC and 4 non-HTC clinics). The feasibility assessment determined how sites recorded key outcomes, including

TABLE 1 Distribution of hemophilia patient sample by hemophilia type, prophylaxis treatment type, and age

	Conventional factor (rFVIII/rFIX)	Extended half-life (EHL) factor (rFVIIIFc/rFIXFc)	Total
Hemophilia A	118	83	201
Children (ages 6-17)	67	38	105
Adults (ages 18-35)	51	45	96
Hemophilia B	78	65	143
Children (ages 6-17)	33	36	69
Adults (ages 18-35)	45	29	74
Total	196	148	344

Abbreviations: rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc; rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc.

PA frequency and duration, to ensure that the CRF and FPF asked for data in such a manner consistent with clinic reporting practices. The forms were pilot tested with 4 physicians representing 2 HTCs and 2 non-HTC clinics to confirm the availability of the data required for the study as well as to ensure the clarity, time to complete, and ease of use before data collection. A double-blinded approach was used; that is, the study sponsor was blinded to the identity of the participating physicians, affiliated HTCs/non-HTC clinics, and patients, and the study sponsor was not disclosed to the participating physicians and clinics.

Each participating site/physician was instructed to identify all eligible individuals with HA and/or HB and extract relevant information including demographic and clinical characteristics, bleeding patterns and history, treatment history, and types and duration of PA participation from their 2014 and 2015 annual comprehensive exam visits (baseline and follow-up visits). Participating sites/physicians then completed the CRF for each patient based on data captured during the annual visit. Medical charts were not directly accessed for the purposes of this study. Annual visits were selected for medical data review to ensure comprehensive data related to the patients' treatment details, relevant clinical characteristics (eg, joint health, comorbidities), and the key outcomes of interest including bleeding history and participation in PAs, were available. Completed forms were returned to Medical Data Analytics (MDA), a contracted agency overseeing recruitment, data collection efforts, and renumerations. MDA reviewed all forms for completeness and consistency. Any inconsistencies or outliers were identified and verified with the sites.

Since the annual exam visits ranged from January 1, 2014, to December 31, 2015, the study period ranged from January 1, 2013, to December 31, 2015; that is, each annual visit captured information such as treatment and bleeding frequency for the prior 12 months. The study period overlapped with the timing of the US Food and Drug Administration's approval of the EHL factors. This ensured that

baseline data included mostly patients naïve or newly introduced to rFVIIIFc/rFIXFc, and among patients receiving prophylaxis treatments with rFVIIIFc/rFIXFc, they had exposure to at least 6 months of treatment with rFVIIIFc/rFIXFc by the annual visit in 2015. Data were anonymous and nonidentifiable.

2.2 | Patient population

Medical charts were selected for data abstraction if the patients were males aged 6-35 years with a diagnosis of severe HA or HB (ie, initial clotting factor <1%), were on prophylaxis treatment continuously for ≥6 months on either rFVIII/rFIX or rFVIIIFc/rFIXFc, had no inhibitors during the study period, and did not participate in any hemophilia treatment-related clinical trial during the study period. Patients who received only conventional rFVIII/rFIX prophylaxis in both years were defined as the conventional rFVIII/rFIX group. Patients receiving rFVIIIFc/rFIXFc prophylaxis continuously for ≥6 months in 2014 or 2015 were defined as the EHL rFVIIIFc/rFIXFc group.

2.3 | Outcomes

The key outcomes of interest included changes in frequency and duration of PA participation (eg, walking, running, swimming, bicycling, strength training, etc), as well as total and spontaneous bleeding frequencies from 2014 and 2015 assessed during annual examinations. Participating physicians collected these data via patient self-report during the 2014 and 2015 comprehensive examinations, and subsequently reported the outcomes of interest in the CRF for each patient based on the annual examination medical chart (see Appendix S1). Data were reported in the same manner for both the 2014 and 2015 annual examinations. Weekly frequency of PA participation (eg, weekly, 2-3 times/wk, daily) and

TABLE 2 Demographic and baseline characteristics of the study sample (patients with hemophilia A and B)

Baseline characteristics	Hemophilia A						Hemophilia B					
	Children (ages 6-17)			Adults (ages 18-35)			Children (Ages 6-17)			Adults (ages 18-35)		
	rFVIII	rFVIIIFc	P-value[a]	rFVIII	rFVIIIFc	P-value[a]	rFIX	rFIXFc	P-value[a]	rFIX	rFIXFc	P-value[a]
	(n = 67)	(n = 38)		(n=49-51)	(n = 43-45)		(n = 33)	(n = 36)		(n = 45)	(n = 29)	
Age, y, mean (SD)	13.3 (2.8)	12.9 (2.2)	.43	27.9 (3.6)	27.5 (4.0)	.56	12.5 (2.4)	13.1 (2.8)	.36	28.3 (4.2)	26.6 (3.6)	.09
Race/ethnicity, n (%)												
White	44 (65.7)	29 (76.3)	.26	44 (86.3)	26 (57.8)	.002	19 (57.6)	25 (69.4)	.31	28 (62.2)	21 (72.4)	.37
Other	23 (34.3)	9 (23.7)		7 (13.7)	19 (42.2)		14 (42.4)	11 (30.6)		17 (37.8)	8 (27.6)	
Patient/caregiver education, n (%)												
<4 y college degree	16 (23.9)	17 (44.7)	<.001	27 (52.9)	18 (40.0)	.25	9 (27.3)	14 (38.9)	.20	21 (46.7)	9 (31.0)	.26
4 y college degree or higher	9 (13.4)	14 (36.8)		23 (45.1)	27 (60.0)		9 (27.3)	13 (36.1)		23 (51.1)	20 (69.0)	
Unknown	42 (62.7)	7 (18.4)		1 (2.0)	0 (0.0)		15 (45.5)	9 (25.0)		1 (2.2)	0 (0.0)	
Patient/caregiver employment status, n (%)												
Employed (full, part-time, other)	28 (41.8)	22 (57.9)	.12	45 (88.2)	38 (84.4)	.22	14 (42.4)	19 (52.8)	.43	40 (88.9)	27 (93.1)	.68
Not employed[b]	14 (20.9)	9 (23.7)		4 (7.8)	7 (15.6)		7 (21.2)	9 (25.0)		4 (8.9)	2 (6.9)	
Unknown	25 (37.3)	7 (18.4)		2 (3.9)	0 (0.0)		12 (36.4)	8 (22.2)		1 (2.2)	0 (0.0)	
Body mass index, mean (SD)	20.9 (4.2)	20.3 (3.5)	.43	26.6 (4.0)	26 (4.2)	.49	20 (3.5)	20.1 (2.7)	.86	26.6 (3.4)	25.4 (2.5)	.13
Physical functioning/range of motion assessment, n (%)												
Improving/Stable	57 (85.1)	31 (81.6)	.47	44 (86.3)	42 (93.3)	.43	27 (81.8)	36 (100.0)	.03	38 (84.4)	29 (100.0)	.03
Worsening	7 (10.5)	3 (7.9)		6 (11.8)	2 (4.4)		5 (15.2)	0 (0.0)		7 (15.6)	0 (0.0)	
Unknown	3 (4.5)	4 (10.5)		1 (2.0)	1 (2.2)		1 (3.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Presence of any comorbidity[c], n (%)	10 (14.9)	2 (5.3)	.14	14 (27.5)	10 (22.2)	.56	1 (3.0)	2 (5.6)	.61	10 (22.2)	6 (20.7)	.88
Presence of any target joint, n (%)	24 (35.8)	12 (31.6)	.44	32 (62.8)	30 (66.7)	.69	12 (36.4)	14 (38.9)	.94	29 (64.4)	17 (58.6)	.61
Presence of any joint problem[d], n (%)	25 (37.3)	12 (31.6)	.55	34 (66.7)	31 (68.9)	.82	12 (36.4)	14 (38.9)	.83	29 (64.4)	17 (58.6)	.61
Number of days on prophylaxis treatment in 2014-2015, median (IQR)	724 (87.0)	707 (182.0)	.10	730 (57.0)	666 (365.0)	<.001	730 (74.0)	729 (152.5)	.96	729 (8.0)	707 (229.0)	.02
Average number of per month bleeds, mean (SD)	0.2 (0.3)	0.2 (0.4)	.98*	0.3 (0.4)	0.3 (0.3)	.75*	0.2 (0.2)	0.2 (0.1)	.76	0.3 (0.3)	0.2 (0.2)	.11*
Total number of major bleeds per year at baseline, mean (SD)	0.2 (0.6)	0.3 (0.6)	.45	0.4 (0.8)	0.1 (0.4)	.04§	0.3 (0.7)	0.3 (0.6)	1.00	0.2 (0.4)	0.2 (0.4)	.85
Total number of bleeds per year, mean (SD)	2.8 (3.3)	2.8 (4.6)	.99*	3.5 (4.4)	3.3 (3.0)	.75*	1.9 (2.3)	2.1 (1.7)	.76	3.1 (3.6)	1.9 (2.3)	.10*

TABLE 3 (Continued)

Baseline characteristics	Hemophilia A						Hemophilia B					
	Children (ages 6-17)			Adults (ages 18-35)			Children (Ages 6-17)			Adults (ages 18-35)		
	rFVIII	rFVIIIFc	P-value[a]	rFVIII	rFVIIIFc	P-value[a]	rFIX	rFIXFc	P-value[a]	rFIX	rFIXFc	P-value[a]
	(n = 67)	(n = 38)		(n = 49-51)	(n = 43-45)		(n = 33)	(n = 36)		(n = 45)	(n = 29)	
Total number of spontaneous bleeds per year, mean (SD)	0.9 (2.0)	1.1 (1.6)	.63	2.1 (3.0)	2.04 (1.9)	.86*	0.8 (1.1)	0.8 (1.0)	.86	1.7 (2.3)	1.1 (2.3)	.28

Abbreviations: rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc; rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc.

[a]Two sample t-test P-values reported for comparisons of mean values and chi-square P-values reported for binary and categorical variables.

[b]Not employed category included those reporting that they were unemployed, on disability, or retired.

[c]The following types of comorbidities were assessed: diabetes; hepatitis A, B, and C; HIV/AIDS; hypertension; other cardiovascular disease; stroke; and thrombosis.
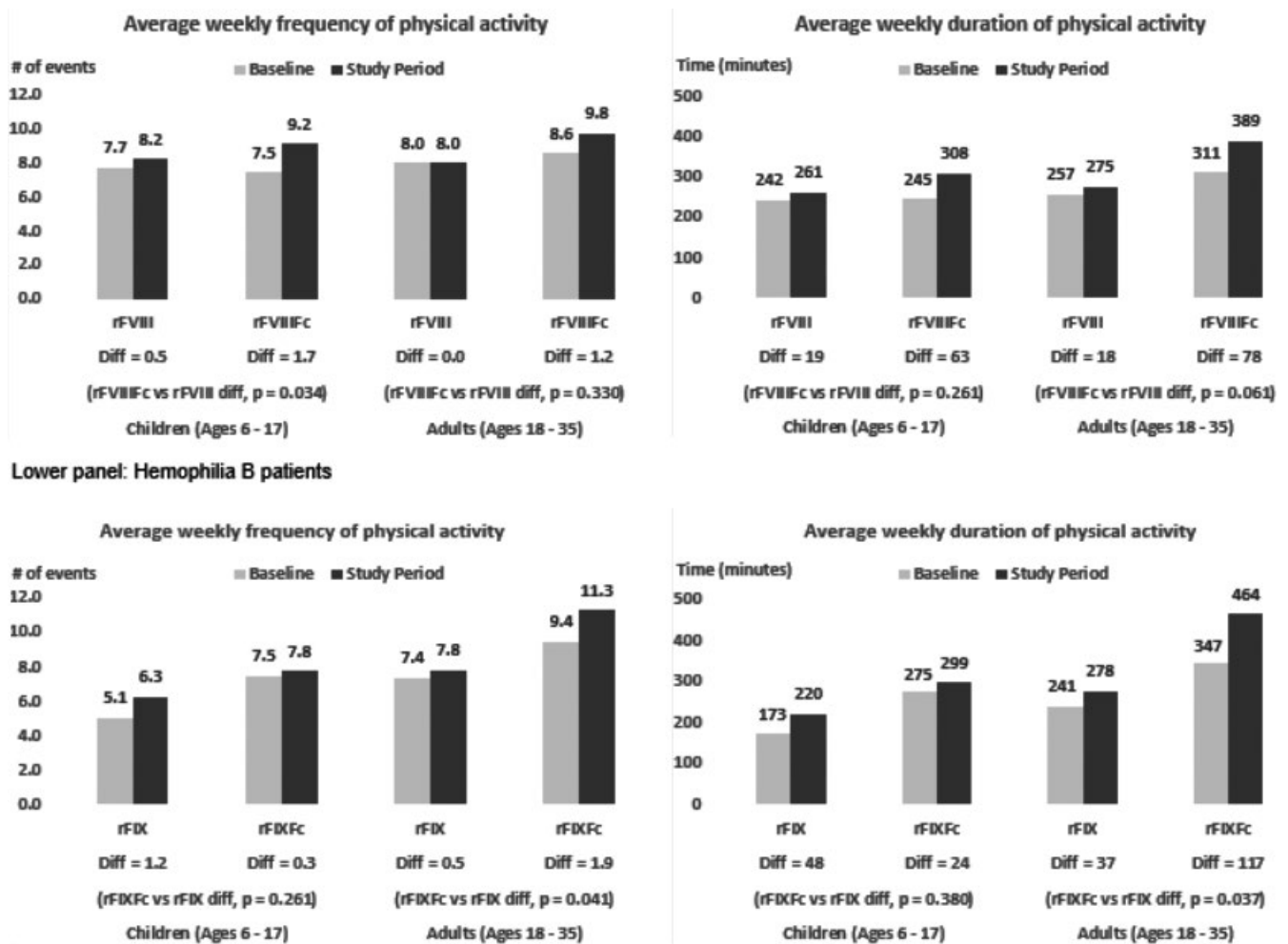
[d]Joint problem defined as having a joint surgery, target joint, or hemoarthropathy.

*Due to presence of unequal variance, Satterthwaite P value reported. For all others, pooled P value reported.

duration of PA participation in increments of 15 minutes (eg, <15, 15-30, 31-45 min/wk) were captured for the 12 months preceding the annual examination date for each activity reported (eg, walking, running, swimming) in the patients' medical charts and transferred to the CRF. Weekly frequency of PA participation was defined as number of times per week that the patient reported engaging in the activity, regardless of the duration of each event. Frequency and duration of all types of PA were reported as categorical variables and transformed into count variables using the midpoint of the range (eg, 4-6 times per week became 5 times per week). The midpoints of these two outcomes from all reported activities were summed to capture total number of times per week a patient participated in any activity and total duration of participation per week. For patients who participated in multiple types of PA (eg, walking and bicycling), frequency and duration across all types of PA were summed to produce overall variables for frequency and duration of PA, respectively. The difference in total frequency and duration of participation between 2015 and 2014 data were calculated for each participant to capture changes in the two outcomes from 2014 to 2015. Both spontaneous bleeds and total bleeds were measured annually. Spontaneous bleeds were defined as bleeding episodes that occurred without apparent cause. Total bleeds included both spontaneous bleeds and traumatic bleeds, which were defined as bleeding episodes that occurred as a result of injury, a medical procedure, or other impact to the body. Changes in ABRs were calculated by subtracting the count of bleeds reported in 2014 from the bleeds reported for 2015. All patients in this study had data for both time periods for all key outcomes (ie, PA frequency, PA duration, annual spontaneous bleeds, and annual total bleeds).

2.4 | Statistical analysis

Descriptive analyses were performed stratified by hemophilia type, age groups, and prophylaxis treatment groups. Summary statistics for demographic and baseline clinical characteristics such as age, race/ethnicity, body mass index, comorbidity status, joint health, and baseline bleeding were compared across the two treatment groups, further stratified by hemophilia type and age group. Two sample t tests were performed to compare mean values, and chi-square tests were performed to compare proportional differences across the two treatment groups for continuous and categorical baseline variables, respectively. Average changes in the outcomes of interest were assessed across the two treatment groups, stratified by hemophilia type and age group. Using the mean differences in outcome changes obtained from paired t tests, a Wilcoxon rank-sum test was used to assess significance across the two treatment groups. Multivariable regression analyses were also conducted for HA (children and adults) and HB (children and adults) adjusted for other baseline characteristics. All analyses were conducted using SAS/STAT software, version 9.4 (SAS Institute Inc, Cary, NC, USA); alpha was set at .05, and all tests were two-tailed.[19]

Average weekly frequency of physical activity

Average weekly duration of physical activity

Lower panel: Hemophilia B patients

Average weekly frequency of physical activity

Average weekly duration of physical activity

FIGURE 1 Average weekly frequency and duration of physical activity involvement in baseline (2014) versus study period (2015) in rFVIIIFc/rFIXFc vs rFVIII/rFIX groups. rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc; rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc

3 | RESULTS

A total of 344 patients were included in this study, representing 16 sites (13 HTC, 3 non-HTC sites); 170 were adult patients, and 174 were pediatric patients. Among adult patients, 96 had hemophilia A (45 on rFVIIIFc, 51 on rFVIII) and 74 had hemophilia B (29 on rFIXFc, 45 on rFIX); among pediatric patients, 105 had hemophilia A (38 on rFVIIIFc, 67 on rFVIII) and 69 had hemophilia B (36 on rFIXFc, 33 on rFIX; Table 1). Baseline clinical characteristics were comparable across the two treatment groups in all subgroups assessed (ie, HA and HB, children and adults) for all relevant measures (eg, joint health, comorbidity status, annual bleeding rates; Table 2). Some demographic differences across the two treatment groups were observed for characteristics such as race/ethnicity among adults with HA and caregiver education level among children with HA.

During the study period, the median treatment persistence, or the duration of continuous treatment, reported across all study subgroups was 666-730 days (covering 91%-100% of the study period; Table 2), indicating high levels of adherence to prophylaxis treatment

regimen during the study period. However, all hemophilia subgroups on rFVIIIFc/rFIXFc, except for children with HB, had fewer days of continuous prophylaxis treatment compared to their rFVIII/rFIX counterparts during the study period (Table 2). Only the differences observed among adults with HA and HB were sufficiently large enough to reach statistical significance. Among children with HB, both rFIXFc and rFIX groups had similar periods with continuous prophylaxis treatment.

3.1 | Physical activity participation

The weekly frequency of PA participation increased from 2014 to 2015 in all groups except for adults with HA in the rFVIII group, whose average frequency of participation remained similar to their baseline value (Figure 1). The magnitude of increase trended positively among all EHL groups compared to their rFVIII/rFIX counterparts, except for children with HB in the rFIXFc group. Among adults with HB, the increase in weekly PA frequency for the rFIXFc group was 1.9, whereas the increase in the rFIX group was 0.5,
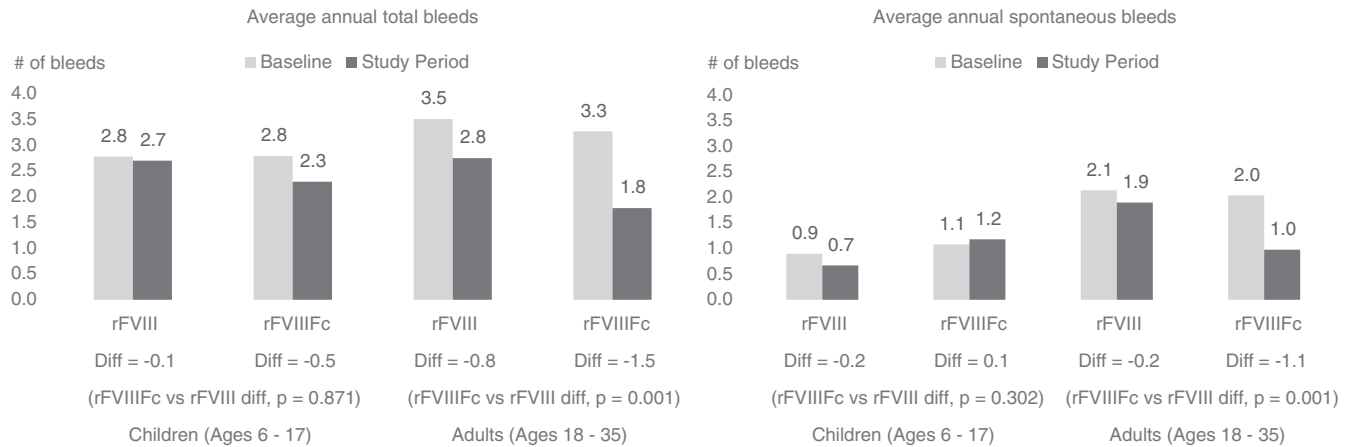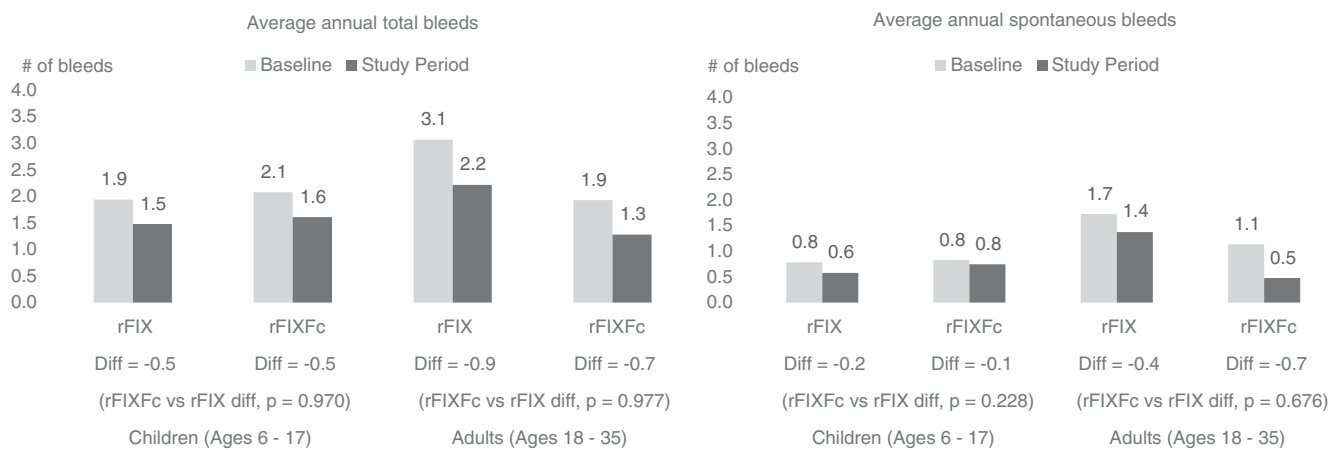
FIGURE 2 Average annual total and spontaneous bleeds in baseline (2014) versus study period (2015) in rFVIIIFc/rFIXFc vs rFVIII/rFIX groups. rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc; rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc

indicating a differential of 1.4 times per week ($P = .04$). Adults with HA also experienced a greater increase in weekly PA frequency in the rFVIIIFc group compared to the rFVIII group, though not statistically significant (1.9 versus 0.0; $P = .33$). Among children, the weekly PA frequency for the HA/rFVIIIFc group increased by 1.7, and for the HA/rFVIII group it increased by 0.5, indicating a differential of 1.2 times per week ($P = .03$). Conversely, the weekly PA frequency for the HB/rFIXFc pediatric group increased by 0.3 while the HB/rFIX pediatric group increased by 1.2 ($P = .26$). Despite the lower increase in the HB/rFIXFc pediatric group, the average weekly PA frequency was higher in this group compared to the HB/rFIX pediatric group both at baseline and during the study period (Figure 1).

The weekly duration of PA participation increased from 2014 to 2015 in all groups (Figure 1). The magnitude of increase generally tended to be larger among EHL groups compared to their rFVIII/rFIX counterparts, again, except for the children with HB in the rFIXFc group. Among HA adults, the increase in weekly PA duration for the rFVIIIFc group was 78 minutes, whereas the increase in the rFVIII group was 18 minutes, indicating a differential of 60 minutes per week ($P = .06$). Similarly, the increase in weekly PA duration for the

adult HB/rFIXFc group was 117 minutes, whereas the increase in the rFIX group was 37 minutes, indicating a differential of 80 minutes per week ($P = .04$). Among children with HA, the weekly PA duration for the rFVIIIFc group increased by 63 minutes, and for the rFVIII group it increased by 19 minutes, indicating a differential of 44 minutes per week ($P = .26$). Children with HB in the rFIXFc group increased weekly PA duration by a mean of 24 minutes per week, while their rFIX counterparts increased weekly PA duration by a mean of 48 minutes per week ($P = .38$). The baseline and study period average weekly PA duration were both greater in the HB/rFIXFc pediatric group than in the HB/rFIX group, despite the lower increase from baseline to study period.

The results of multivariable analysis showed that the HA/rFVIIIFc group increased their weekly PA participation by 1.2 times ($P = .03$) and participated in PA for 47 minutes longer ($P = .09$) compared to the HA/rFVIII group, after adjusting for covariates. The HB/rFIXFc group increased their weekly PA participation by 0.24 times ($P = .68$) and lengthened their weekly duration of PA participation by 26 minutes ($P = .38$) compared to the HB/rFIX group, after adjusting for covariates (Appendix S1).

3.2 | Annual bleed rates

Decreases in total and spontaneous ABRs (Figure 2) from 2014 to 2015 were observed in all adult groups. The magnitude of decrease, however, was larger only among adults with HA in the rFVI-IIFc groups compared to their rFVIII counterparts. The decreases in total and spontaneous ABRs for the rFVIIIFc group were 1.5 and 1.1, respectively, whereas the decreases for the rFVIII group were 0.8 and 0.2, indicating differentials of 0.7 ($P = .001$) and 0.8 ($P = .001$) for total and spontaneous ABRs. A similar trend of larger decline in ABRs was not observed either among adults with HB in the rFIXFc group or among children with HA/HB in rFVIIIFc/ rFIXFc groups compared to their rFVIII/rFIX counterparts. Rather, differentials for total and spontaneous bleeds of −0.2 ($P = .98$) and 0.3 ($P = .68$) were observed for adults with HB in the rFIXFc group compared to their rFIX counterparts. Among children with HA, those receiving rFVIIIFc compared to rFVIII had a differential in decreased total bleeds of 0.4 ($P = .87$) and spontaneous bleeds of −0.1 ($P = .30$). Children with HB receiving rFIXFc versus rFIX therapies had a differential in decreased total bleeds of 0.0 ($P = .97$) and spontaneous bleeds of −0.1 ($P = .23$).

4 | DISCUSSION

To our knowledge, this is the first study beyond individual case reports to assess changes in PA and bleeding patterns among patients on prophylaxis with rFVIIIFc/rFIXFc, and to compare these outcomes against patients on rFVIII/rFIX. The findings from this study show an increase in PA for both conventional rFVIII/rFIX and EHL rFVIIIFc/ rFIXFc groups, though the magnitude of PA increase tended to be greater for patients that switched to EHL factors. Additionally, average annual total and spontaneous bleeds were stable or decreased from 2014 to 2015 across all groups. These results suggest that patients treated with EHL rFVIIIFc/rFIXFc increase their PA participation through an increase either in frequency or in duration of participation while still maintaining their ABRs, compared to conventional rFVIII/rFIX groups; only children with HB were an outlier.

In the pediatric HB group, we observed that, while patients in both rFIXFc and rFIX groups improved their PA participation during the study period compared to the baseline, the increase in PA participation among the rFIXFc group was smaller compared to the rFIX group, although not statistically significant. We hypothesize that the rFIX group, who had notably lower PA participation at baseline compared to all other groups including their rFIXFc counterpart (baseline PA frequency and duration: 5.1 vs 7.5 and 173 vs 275 minutes among rFIX and rFIXFc groups, respectively), may have been encouraged to increase their PA participation resulting in a larger improvement during the study period. Given that the pediatric patients with HB on rFIX at baseline more frequently reported worsening physical functioning compared to those on rFIXFc (see Table 2), despite having comparable treatment patterns, joint health, and bleeding rates, we suspect that this may have led to real-time efforts to engage in more

PA, resulting in better outcomes during the study period. To confirm this hypothesis, more nuanced data on physicians' recommendations for activity would have to be collected.

Participation in PA is important to maintain overall health, quality of life (QoL), and physical function of people with hemophilia. As such, the WFH and the National Hemophilia Federation (NHF) recommend engagement in PA, either in primarily noncontact sports (WFH) or in activities graded as low-risk for traumatic bleeds (NHF).[2,14,20] However, there has been limited research assessing PA outcomes and ABR comparing patients on conventional and EHL factors.[15-17] In the A-LONG and B-LONG phase 3 multicenter clinical trials, the PA of patients with HA/HB (children and adults) on conventional FVIII/FIX was compared during the switch to EHL rFVIIIFc/rFIXFc, with the finding that those on EHL prophylaxis treatment maintained or increased their PA level while still maintaining low ABR.[16,17] Similarly, a case study report of 7 severe HA/HB patients who switched to EHL prophylaxis with either rFVIIIFc or rFIXFc, also reported similar or improved PA while maintaining low bleeding frequency.[15] Furthermore, people with hemophilia treated with rFVIIIFc and rFIXFc in two extension trials showed sustained improvement in "physical health" and "sports and leisure" scores on the Haem-A-QoL questionnaire, suggesting that improved PA is an important benefit for hemophilia patients' QoL.[21,22] The present study adds to this body of research suggesting that treatment regimens incorporating EHL prophylaxis may contribute to improvements in PA while maintaining ABR among people with hemophilia.

5 | STRENGTHS AND LIMITATIONS

Chart reviews provide valuable insight into the effects of therapies outside controlled clinical trial settings.[23,24] Nonetheless, we recognize several limitations with the current study. As a retrospective chart review, patients were not randomized to treatment groups as they would be in a clinical trial. Thus, the patients receiving one treatment may have differed importantly from their counterparts, making the comparisons across treatment groups more uncertain. Patients and their caregivers elected to receive EHL recombinant factors, and patients who chose to switch to these treatments may meaningfully differ from those who did not. For example, children on rFVIIIFc were more likely to have a caregiver with a 4-year college degree than children on rFVIII (36.8% and 13.4%, respectively; $P < .001$), while adults on rFVIII were more likely to be White than adults on rFVIIIFc (86.3% and 57.8%, respectively; $P = .002$). However, given the small sample size, it is difficult to ascertain meaningful patterns in the demographic data. Data were collected from patients or caregivers by physicians and thus is subject to potential biases. Patients/caregivers were asked to recall frequency and duration of PA as well as number of bleeds throughout the past year. Due to the extended recall period, responses may not accurately reflect the true values. Future research should incorporate prospective evaluation of PA with use of EHL and conventional factors. Future retrospective studies should include more frequent data collection to minimize risk of incorrect

recall. Additionally, future research should also explore how different types of PA with varying intensity (eg, running versus walking) may impact patients' overall health and bleeding occurrences. In cases where caregivers were reporting on PA (ie, for pediatric patients), observational measurements may not be reliable and may be subject to social desirability biases. Furthermore, some patients in the study had already begun using EHL recombinant factors at some point in 2014 (ie, at baseline)—particularly rFIXFc, which was available in the United States from April 2014—potentially attenuating the changes observed in this study. Multivariable regression analyses were conducted to test for covariates that may have impacted PA outcomes (Appendix S1). Covariates were selected based on comparisons made across treatment groups in descriptive tables, literature, and the availability of data with some variability across categories/groups. However, the study was not adequately powered to conduct subgroup analyses by age and hemophilia type and, as such, may have resulted in both less precise and accurate results. Even so, comparisons of baseline characteristics across the treatment groups did not show significant differences for relevant variables. Future studies should include subgroup analyses, particularly by age, due to different disease stages among children and adults that may have implications for treatment approaches.

6 | CONCLUSION

This study suggests that treating patients with EHL rFVIIIFc/rFIXFc can positively impact patient engagement in physical activity, while still maintaining good bleed control compared to patients on conventional rFVIII/rFIX. This study suggests that switching to EHL factor treatments, especially in certain patient subsets, may positively contribute to a patient's engagement in PA while maintaining or decreasing ABR. However, given the small nature of this study, larger, prospective studies that allow for appropriate adjustment for confounding variables are warranted to confirm these findings.

AUTHOR CONTRIBUTIONS
AS designed the study; analyzed data; and wrote, reviewed, and edited the manuscript. JS and NL provided input for analysis and reviewed and edited the manuscript. KE analyzed data and wrote, reviewed, and edited the manuscript. KB and ABJ provided input for the study design and wrote, reviewed, and edited the manuscript. CB and NJ reviewed and edited the manuscript. All authors had full editorial control of the paper and provided their final approval of all content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.