Physical activity in individuals with haemophilia and experience with recombinant factor VIII Fc fusion protein and recombinant factor IX Fc fusion protein for the treatment of active patients: a literature review and case reports

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The World Federation of Hemophilia and the National Hemophilia Foundation encourage people with haemophilia (PWH) to participate in routine physical activity. The benefits of physical activity for PWH include improvements in joint, bone, and muscle health. Accordingly, a number of studies suggest that levels of physical activity among PWH are similar to those of their healthy peers, especially among individuals who began prophylaxis at an early age (≤ 3 years). Importantly, several studies found either no increased risk or only a transient increase in risk of bleeding with more intensive physical activity compared with less intensive physical activity. Data on optimal prophylaxis regimens for PWH who participate in physical/sporting activities; however, remain sparse. Long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) and recombinant factor IX Fc fusion protein (rFIXFc) demonstrated efficacy for the prevention and treatment of bleeding episodes in Phase 3 clinical trials of participants with haemophilia A and B, respectively, with most individuals able to maintain or increase their physical activities. This manuscript reviews the current literature that describes physical activity in PWH. Additionally, case studies are presented to provide supplemental information to clinicians illustrating the use of rFVIIIFc and rFIXFc in physically active patients with haemophilia A and B, respectively. These case reports demonstrate that it is possible for patients to be physically active and maintain good control of their haemophilia with extended interval prophylactic dosing using rFVIIIFc or rFIXFc. *Blood Coagul Fibrinolysis* 27:737–744

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Introduction

Haemophilia is characterized by spontaneous, recurrent bleeding into joints and muscles that can lead to cartilage damage, joint disease, and haemophilic arthropathy [1,2]. Prior to the advent of factor replacement therapy in the late 1960s, people with haemophilia (PWH) were restricted from participating in most sports and rigorous physical activities to minimize the risk of bleeding [3]. However, physical activity is now considered to be generally beneficial for PWH [4,5]. Strengthening muscles can help improve joint health by reducing impact on joints, and participation in sporting activities may help individuals compensate for motor skill deficits that may arise because of complications of haemophilia, such as arthropathy [6]. Among adults with haemophilia, regular physical activity helps prevent obesity and other chronic conditions; in children and adolescents with haemophilia, exercise supports joint, bone, and muscle health, weight control, and anxiety reduction [7].

In this manuscript, we review the recommendations/guidance for PWH who participate in physical activity and the current literature that describes physical activity in PWH, including replacement factor treatment and the relationship between physical activity and bleeding risk. To illustrate the role of extended half-life replacement factor products for physically active PWH, we provide practical examples from case reports of the use of recombinant factor VIII Fc fusion protein (rFVIIIFc) and recombinant factor IX Fc fusion protein (rFIXFc) [8,9] in physically active patients with haemophilia A and B.

Physical fitness and activity guidelines for people with haemophilia

Although physical activity is encouraged for PWH to promote physical fitness and normal neuromuscular development [Oxford Centre for Evidence-Based Medicine (OCEBM) level 2 recommendation] [10], participation in these activities may be accompanied by the risk of traumatic bleeding. Because of this risk, the particular

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type of physical activity is an important consideration. Several organizations have established guidelines for PWH who participate in physical and sporting activities. The World Federation of Hemophilia (WFH) encourages participation in noncontact sports (e.g. swimming, golf) and suggests avoiding high contact and collision sports (e.g. soccer, hockey) [10]. The National Hemophilia Foundation groups physical activities into five total risk categories: safe (category 1; e.g. aquatics, hiking), safe-moderate (category 1.5; e.g. biking, spinning), moderate (category 2; e.g. bowling, tennis), moderate-dangerous (category 2.5; e.g. basketball, soccer), and dangerous (category 3; e.g. boxing, rugby); activities rated as being in category 3 are not recommended for PWH [11]. The risk category levels indicate whether or not the benefits of these exercises outweigh the risk involved. As risks vary amongst different activities, the specific risks were assessed individually for each activity and were not limited to risk of bleeding; however, because all bleeding episodes are not equivalent, the risk/benefit analysis for a particular activity may also depend on the type of bleeding episode that could occur. For example, the relative risk of bleeding for participation in figure skating was estimated to be similar to that of rugby; however, the potential for serious intra-cerebral bleeding is higher for rugby compared with figure skating, which may influence decision making [6,12]. The WFH recommends that individuals with target joints be encouraged to use braces or splints for protection during physical activities, particularly in the absence of clotting factor coverage (OCEBM level 4 recommendation) [10]. The American Academy of Pediatrics (AAP) has emphasized that participation in sports for children with medical conditions is a complex issue with many variables to consider (e.g. the sport in question, the position played, the level of competition, and the maturity of the child); the AAP recommends that children with bleeding disorders be evaluated by their healthcare professional to determine appropriate activities [13].

Physical activity levels amongst people with haemophilia

Several published studies have assessed the level of physical activity among PWH compared with that of the general population. These studies varied in terms of the populations described (e.g. PWH of any severity vs. those with a specific severity, and PWH of all ages vs. those in a specific age group), and the methods by which the data were collected (e.g. self-reports, retrospective questionnaires, and the use of accelerometers to prospectively measure physical activity over time) [7,14–20].

Despite variations in methodology, many of these studies have found that PWH have similar or increased levels of physical activity relative to the general population [14–18] (Table 1). Additionally, in a study of US adults with haemophilia B, the majority met the physical activity level recommended in the 2008 Physical Activity Guidelines for Americans [7]; this level of activity was higher than that found in the Behavioral Risk Factor Surveillance System survey of healthy adults in the United States, which showed that a median of 51.6% of US adults met similar criteria in 2011 [21]. However, in a study of 61 Irish PWH, physical activity levels were found to be decreased relative to the general population, although the decreased activity levels in the haemophilia population may have been because of the inclusion of patients with functional limitations [19].

The age at which prophylaxis is initiated in childhood may also play a role in physical activity levels, as indicated in a study of Swedish adults with severe haemophilia A or B [20].

Factor replacement therapy for physically active people with haemophilia

Although many studies that assess physical activity in PWH have been published, details regarding treatment with replacement clotting factor are often not included. For example, a systematic review of 29 experimental and 27 observational studies found that nine original articles specified the type of treatment that patients followed during the study period (i.e., prophylaxis or episodic treatment), but 13 articles did not describe the treatment type; furthermore, a large proportion of the studies were published as abstracts and did not include treatment details [4]. However, two of the aforementioned studies that showed similar or increased levels of physical activity in PWH compared with the general population did provide some treatment information (Table 1). In a retrospective study of 120 individuals with moderate to severe haemophilia A or B in which data were reported by haemophilia severity (data for haemophilia A and B were pooled), all patients with severe haemophilia were on long-term prophylaxis with a higher median total weekly dose compared with that for patients with moderate haemophilia [17]. In a separate study of 13 boys with severe haemophilia A, all patients were on a prophylactic regimen [18]. In addition, in a case-crossover study, 75 participants with haemophilia A who were receiving factor VIII (FVIII) prophylaxis and 14 participants with haemophilia B who were receiving factor IX (FIX) prophylaxis had similar median total weekly prophylactic doses [12].

Optimal prophylaxis regimens for PWH who participate in sporting activities are still not well defined. Although many individuals schedule their prophylaxis to coincide with periods of high physical activity, this approach is not universal [6,22]. Guidelines from the WFH state that PWH should consult a healthcare professional before engaging in physical activities, in part to determine appropriate prophylactic treatment [10]. Recommendations proposed in a recent review article noted the importance of healthcare professionals in guiding

Table 1 Published studies that assessed physical activity in people with haemophilia

Study	Population	n[a]	Treatment regimen	Type of physical activity	How activity was assessed	Key outcome(s)
Fromme *et al.* [3]; Germany; cross-sectional	Children/adolescents (aged 4–16 years) and adults (aged 18–72 years) with mild to severe haemophilia (type NR)	71	NR	88.6% (adolescents) and 66.7% (adults) performed at least one leisure sport	Self-administered questionnaire	17.6% of PWH reported bleeding episodes due to exercise Among children/adolescents, this proportion was significantly lower vs. adults (10.3 vs. 33.3%, respectively; $P < 0.05$) No statistically significant associations between bleeding rate and haemophilia severity
Niu *et al.* [7]; USA; prospective, cohort	Children, adolescents, and adults aged 5–64 years with mild to severe haemophilia B	135	NR	Vigorous and moderate intensity activities, and walking	IPAQ (aged 15–64 years). CPAQ (aged 5–14 years)	62% of patients aged 15–64 years reported high levels of physical activity 79% of children aged 5–14 reported participating in physical activities at least 4 days/week. 79% of adults achieved recommended physical activity levels
Groen *et al.* [14]; The Netherlands; cross-sectional	Children and adolescents aged 8–18 years with mild to severe haemophilia (type NR)	47	Prophylaxis (21/21 patients with severe and 4/7 with moderate haemophilia); episodic (all others)	Most common: football (36%), swimming (17%), tennis (11%), cycling (8%)	MAQ	Similar physical activity levels across haemophilia severities and compared with the general population (based on Dutch reference values)
Buxbaum *et al.* [15]; USA; prospective	Children/adolescents aged 11–18 years with mild to severe haemophilia A or B; controls: 44 healthy children/adolescents aged 10–16.5 years	17	Prophylaxis: all patients with moderate ($n = 1$) or severe ($n = 9$) haemophilia	Low, moderate, and high/vigorous physical activity	Biaxial accelerometer worn on waist for seven consecutive days while awake	PWH spent less time sedentary, more time in moderate activity vs. healthy controls PWH had similar self-esteem and anxiety level vs. healthy peers
González *et al.* [16]; Spain; cross-sectional	Children/adolescents aged 8–18 years with mild to severe haemophilia A; controls: 25 healthy adolescents	41	Prophylaxis (11/12 patients with severe and 4/7 with moderate haemophilia); episodic (all others)	Light, moderate, and vigorous physical activities (excluding swimming)	Triaxial Actigraph GT3X accelerometer worn on waist for 7 consecutive days while awake; ASAQ	PWH had a higher mean time engaged in light, moderate, and moderate-to-vigorous physical activity vs. healthy controls
den Uijl *et al.* [17]; The Netherlands; retrospective	Adults aged 18–32 years with moderate to severe haemophilia A or B; controls: 105 healthy, age-matched individuals	120	Prophylaxis: 80/80 patients with severe and 10/40 with moderate haemophilia; median (IQR) weekly dose: 47 (35–55) IU/kg (severe); 29 (17–84) IU/kg (moderate)	59% of patients with severe and 70% with moderate haemophilia participated in sports	HAL, IPAQ	QoL and physical activity were similar in those with moderate/severe haemophilia and healthy controls. 12 patients stopped prophylaxis completely, while maintaining low bleeding frequencies (median 1.0 joint bleed/year)
van der Net *et al.* [18]; The Netherlands; pilot/feasibility	Children/adolescents aged 8–15 years with severe haemophilia A	13	Primary prophylaxis (20–40 IU/kg^3 per week	NR	VO_{2peak}, self-reporting, ASK	PWH had comparable physical fitness (VO_{2peak}) and activity levels with those of healthy peers (based on Dutch reference values). Haemo-QoL scores in children ranged from 7.03 to 36.7% (100% reflects poor outcome)

Table 1 (*continued*)

Study	Population	n[a]	Treatment regimen	Type of physical activity	How activity was assessed	Key outcome(s)
Sherlock *et al.* [19]; Ireland; cross-sectional, observational	Adolescents/adults aged 16–63 years with mild to severe haemophilia (type NR)	61	NR	60% participated in sports	HAL, IPAQ	Although 46% of PWH achieved a high level of physical activity, overall activity level of PWH was only 66% of the general population average; 55% reported bleeds from sports
Khawaji *et al.* [20]; Sweden; prospective	Adults aged 19–56 years with severe haemophilia A or B; controls: 190 healthy adult men	38	Prophylaxis: regular infusions more than 2×/week depending on haemophilia type/severity	Most common: cycling, jogging, strength exercises, gardening	MAQ	PWH who began prophylaxis at 3 years of age or younger had similar physical activity levels vs. healthy peers; those who began prophylaxis after age 3 were less active than healthy peers PWH in the first group also had better joint scores than those in the second group
Broderick *et al.* [12]; Australia; case-crossover nested within a prospective cohort study	Children/adolescents aged 4–18 years with moderate to severe haemophilia A or B	104	Prophylaxis (85.6%); median (IQR) weekly doses: FVIII 107 IU/kg (84–151 IU/kg), FIX 99 IU/kg (63–150 IU/kg); episodic (14.4%)	Category 1 (e.g. swimming), category 2 (e.g. basketball), or category 3 (e.g. wrestling)	Telephone interviews	Median (IQR) bleeds/year: episodic, 4.3 (2.6–14.2); prophylaxis, 3.0 (1.1–7.4) Vigorous physical activities associated with a transient, moderate relative increase in risk for bleeding; bleeding incidence lowered by 2% for every 1% increase in factor activity level (95% CI, 1–3%; $P = 0.004$)
Koiter *et al.* [22]; Netherlands; observational	Children/adolescents aged 8–18 years with mild to severe haemophilia A or B	99	Prophylaxis (42%), episodic (58%); 72% tailored their prophylaxis to sports	Most common: soccer (42%), swimming (22%), and tennis (21%)	Movement and Sport Questionnaire	Most patients participated in sports 5×/week; 18 reported at least 1 painful joint
Tiktinsky *et al.* [23]; Israel; cross-sectional	Adolescents/young adults aged 12–25 years with severe haemophilia A or B	44	Episodic	Most common: ball games (36%), walking (34%), running (27%)	G&S	No significant differences in bleeding frequency between PWH participating in strenuous vs. nonstrenuous activities Higher proportion of bleeding episodes due to traumatic causes in strenuous vs. nonstrenuous group ($P < 0.01$)
Ross *et al.* [24]; USA; retrospective	Children, adolescents, and young adults aged 5–20 years with severe haemophilia A or B	37	Prophylaxis (all patients, with 92% infusing at least 2×/week)	73% participated in high-impact activities	Structured telephone interview	No difference in frequency of joint bleeding episodes for high-impact vs. only low-impact athletics Athletic participation level not significantly associated with joint bleeding
Pierstorff *et al.* [25]; Germany; prospective	Children/adolescents aged 4–16 years with mild to severe haemophilia A	8	Prophylaxis ($n = 6$); episodic ($n = 2$)	Individualized home exercise programme	Standardized questionnaire	Bleeding tendency significantly decreased over 18 months in seven of eight patients; no patients experienced a joint or muscle bleeding episode while exercising

ASAQ, Adolescent Sedentary Activity Questionnaire; ASK, Activities Scale for Kids; CI, confidence interval; CPAQ, Children's Physical Activity Questionnaire; G&S, Godin and Shephard questionnaire; Haemo-QoL, Haemophilia-specific Quality of Life questionnaire (children); HAL, Haemophilia Activities List; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; MAQ, Modifiable Activity Questionnaire; NR, not reported; PWH, people with haemophilia; QoL, quality of life; VO_{2peak}, absolute peak oxygen uptake. [a] n represents the number of patients with haemophilia in the study; control patients are excluded from this value.

treatment decisions for physically active individuals, and suggest coordinating the administration of replacement factor with planned physical activities (i.e., infuse in the morning on days of scheduled activities) [5]. Despite this guidance, the use of prophylaxis prior to physical activity among active PWH is variable and not universal. In a study of Swedish adults with severe haemophilia A or B, participants did not generally modify the timing of their prophylactic doses or take additional doses prior to physical activity, with a few exceptions (in these cases, the effect of infusion modification on bleeding rate was not assessed) [20]. In a study of PWH of all severities who were living in Ireland, 60% of patients reported participating in sports; of these, 3.2% reported infusing with replacement factor prior to training, 9.6% prior to a match, and 16% reported infusing with replacement factor prior to both training and matches [19]. Additionally, 68% of patients in the study (including six patients with severe haemophilia) reported never using replacement factor prior to sporting activities. In a study of 99 children and adolescents with mild to severe haemophilia A or B treated at Dutch haemophilia treatment centres, most patients tailored their prophylaxis infusion schedule to their sports activities [22].

Relationship between physical activity and bleeding profile

Three studies have evaluated the association between physical activity and bleeding outcomes in children with haemophilia; of these, two studies found no increased risk of bleeding with more intense versus less intense physical activity, and one study found only a transient increase in bleeding risk with vigorous physical activity [12,23,24] (Table 1). In a questionnaire-based study of PWH of all ages (42 severe, 16 moderate, and 12 mild), the frequency of bleeding episodes due to exercise was significantly lower among children and adolescents compared with adults [3]. Additionally, results from a prospective study suggest that implementing a regular, individualized home exercise programme could potentially reduce bleeding tendency in PWH [25].

Treatment of physically active patients with recombinant factor VIII Fc fusion protein and recombinant factor IX Fc fusion protein

Prophylaxis with standard factor replacement products requires frequent infusions (typically 3–4 times per week for haemophilia A and 2–3 times per week for haemophilia B) because of their relatively short half-lives [26]. rFVIIIFc and rFIXFc were developed to prolong the half-lives of FVIII and FIX, respectively. Phase 3 clinical trials of previously treated adults, adolescents, and children with haemophilia A and B demonstrated the safety, efficacy, and prolonged half-life of rFVIIIFc (A-LONG/Kids A-LONG) and rFIXFc (B-LONG/Kids B-LONG), respectively [27–30]. Most participants in the Phase 3 studies of rFVIIIFc and rFIXFc reported that they were able to maintain or increase their level of physical activity during the study with extended interval prophylaxis compared with baseline, although specific details on types of physical activity were not captured [31,32]. The following case reports of physically active individuals provide examples of the types of physical activity that individuals have participated in while being treated with rFVIIIFc or rFIXFc. It is important to note that these patients may not be representative of all individuals treated with rFVIIIFc or rFIXFc, but were selected by the authors as examples of what they have observed in their own practices.

Patient 1

A young boy with severe haemophilia A received prophylaxis with recombinant factor VIII (rFVIII) 50 IU/kg three times per week at 3 years of age (total weekly prophylactic dose 150 IU/kg), which continued for a period of years, regardless of sporting activity. On this regimen, he never experienced any bleeding episodes related to sporting activities, which included swimming twice per week. He has no target joints. Upon beginning prophylactic treatment with rFVIIIFc (beginning with twice-weekly dosing; he is currently dosing 65 IU/kg every 5 days) at the age of 15, the patient maintained physical activities at school and began skating once per week for 1 h. There has been no breakthrough bleeding after playing sports since starting treatment with rFVIIIFc over 3.5 years ago.

Patient 2

A man in his late 20s with severe haemophilia A had target joints of the left elbow and left ankle, was treated episodically, and experienced 1–3 bleeding events per month depending on activity. He was active, working out in a gym four times per week and playing basketball with friends. He began treatment with twice-weekly rFVIIIFc (25 IU/kg on Day 1 and 50 IU/kg on Day 4) and continued with rFVIIIFc prophylaxis for 4 years. He reported no bleeding events and increased physical activity since starting prophylaxis with rFVIIIFc. He transitioned to once-weekly prophylaxis (65 IU/kg) and has reported only one possible bleeding episode, which he treated with one infusion of rFVIIIFc. He continues to exercise (lifting weights, cardio, running/jogging, and playing basketball). He also reported that his left ankle, which always had pain (but for which he does not take any pain medication), was doing much better and was no longer painful.

Patient 3

A 10-year-old boy with severe haemophilia A, no history of inhibitors, and no target joints was treated with prophylaxis with 43 IU/kg rFVIII twice per week and reported approximately four spontaneous bleeds in the past year. He began prophylaxis treatment with rFVIIIFc at 25 IU/kg on Wednesdays and 50 IU/kg on Saturdays

and continued on this dosing schedule for over 2 years with no reported bleeding episodes. He remains physically active, participating in martial arts once per week, and playing baseball, with practice twice per week and games once per week. He has not been administering additional factor doses before games or practices, and he tolerates these activities without any breakthrough bleeding.

Patient 4

A 34-year-old adult with severe haemophilia A was prescribed rFVIII prophylaxis at 33 IU/kg three times per week. He played golf once every couple of weeks along with occasional football (soccer), timing his prophylaxis before these activities. He began twice-weekly prophylactic treatment with rFVIIIFc and is receiving once-weekly prophylaxis (65 IU/kg/week), with no additional doses prior to physical activity, and has reported no bleeding episodes since beginning treatment approximately 3.5 years ago. His rFVIIIFc half-life is 18.8 h. Despite his right ankle being affected by haemophilic arthropathy [joint score of seven on the Hemophilia Joint Health Score (HJHS)], which was present prior to beginning rFVIIIFc prophylaxis, he is now an endurance runner and participates in marathons and Olympic distance triathlons. He continues to play football (soccer) and referees, as well as playing golf in his spare time. His HJHS joint score has not changed since beginning rFVIIIFc prophylaxis.

Patient 5

A young adult man with severe haemophilia B was active in childhood, adolescence, and college playing competitive baseball. As an adult, he began mountaineering. He used recombinant factor IX (rFIX) since childhood for prophylaxis and before activity. In his mid-twenties, he began training to climb the highest peaks on all seven continents. During his training, he began using once-weekly rFIXFc prophylaxis at a dose (30 IU/kg) tailored by individual pharmacokinetics to target a FIX trough level of 1–3 IU/dl above baseline. Without additional prophylaxis before activity, he was able to train and then summit many of the highest peaks in the world. To date, he has climbed approximately 50 400 vertical feet to reach five of the seven summits, with greater than 100 000 additional vertical feet climbed during training.

Patient 6

For the past 15 years, a patient with severe haemophilia B participated twice weekly in Taekwondo. He administered prophylaxis with plasma-derived FIX twice weekly (165 IU/kg total weekly dose) during this time, timing his infusions to offer him the best protection from bleeding. He recalls minimal bleeding, and currently he only complains of an ankle with chronic mild soreness and swelling and decreased range of motion, none of which impedes his participation in martial arts. Three years ago, he began Kendo, which he also practices twice weekly. Shortly after starting Kendo, he began rFIXFc for once-weekly prophylaxis at a dose of 30 IU/kg per week, as determined by his individual recovery and half-life. Since starting rFIXFc, he practices martial arts four times per week and competes in tournaments without bleeding, including in his previously injured ankle, without additional on-demand doses of rFIXFc.

Patient 7

An older teenager with severe haemophilia B played competitive soccer for numerous years using rFIX prophylaxis. Prior to starting rFIXFc, he suffered a medial collateral ligament strain and patellar dislocation. This knee continued to have recurrent bleeding up until he started once-weekly rFIXFc prophylaxis at 30 IU/kg per week. This dose was tailored by a pharmacokinetic study. He had one recurrent bleed into the same knee shortly after starting rFIXFc. Because of slow improvement, physical therapy demands, and concern for re-bleeding, his prophylaxis dose was increased to 50 IU/kg/week. After 6 months of swimming and physical therapy (roughly 1 year after his initial injury), he regained most of the strength and range of motion in his knee, and he began to resume previous athletic activity. After 2 years of rFIXFc prophylaxis, he reported that he was pain free, participating in sports without limitation, and only using a knee brace intermittently to help with patellar tracking. The HJHS of his knee improved two points during his 2 years of rFIXFc prophylaxis, and he only reported one bleed in his knee while on rFIXFc prophylaxis.

Conclusion

PWH have been encouraged to participate in physical activities for multiple health-related reasons, and most studies have shown that PWH are similarly active or more active than the general population [7,14–18]. Although PWH should take precautions for certain types of activities, physical exercise has generally not been associated with an increased risk of bleeding [23,24]. Furthermore, physical activity can improve coordination and physical fitness, while potentially decreasing bleeding tendency in this population [6,25].

In general, studies that evaluate physical activity in PWH lack specific information on how participants were treated with replacement clotting factor. WFH and expert recommendations indicate that PWH should seek guidance from healthcare professionals to determine the appropriate treatment regimen when engaging in physical activities [10]. Although many PWH schedule prophylactic treatment regimens to coincide with physical activities, this approach is not universal, as illustrated by the case studies presented herein [19].

rFVIIIFc and rFIXFc are clotting factors with prolonged half-lives that have been approved for the prevention and

treatment of bleeding episodes in individuals with haemophilia A and B. Clinical studies of rFVIIIFc and rFIXFc in previously treated adults/adolescents and children with severe haemophilia demonstrated that these therapies led to low bleeding rates when dosed for prophylaxis one to two times per week (rFVIIIFc) or every 1–2 weeks (rFIXFc) [27,28]. In A-LONG (rFVIIIFc) and B-LONG (rFIXFc), patients were excluded from participating in the trials if they were unable or unwilling to refrain from taking additional prophylactic doses prior to sports activities or an increase in physical activity. The practical experiences with rFVIIIFc and rFIXFc presented here provide examples of the use of extended interval dosing with these long-acting factor replacement therapies in physically active PWH, and suggest that prevention doses may not be needed prior to physical activity. Alternatively, healthcare providers may choose to prescribe rFVIIIFc or rFIXFc dosing regimens that are similar to those for conventional products, which would have the potential to provide increased protection from bleeding during physical activity [33,34]. Such increased protection may be beneficial when a patient temporarily engages in physically challenging situations (e.g. skiing). Further research is needed to better characterize the type, duration, and intensity of physical activity in which individuals treated with rFVIIIFc or rFIXFc participate and the relationship between extended interval dosing and outcomes in physically active patients.

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