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ORIGINAL ARTICLE

Significant reduction in hemarthrosis in boys with severe hemophilia A: The China hemophilia individualized low-dose secondary prophylaxis study

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Abstract

Introduction: In countries with restricted access to clotting factor concentrates, early implementation of low-dose prophylaxis is recommended over episodic treatment.

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Objective: The objective of this 1-year prospective secondary prophylaxis study was to evaluate the efficacy of a dose/frequency escalating protocol in young boys with hemophilia A in China.

Methods: Boys were started on a low-dose protocol (minimum 10–15 IU/kg of factor VIII [FVIII] twice weekly). Escalation was based on index joint bleeding, swelling/persistent joint swelling, and serial ultrasound (gray scale and color Doppler) examinations of index joints.

Results: Thirty-three boys, median age 4.8 years (interquartile range, 3.8-6.1) were enrolled in a 3-month observation period that preceded a 1-year prophylaxis phase. A significant reduction in total bleeding events (43.0%, $P = .001$), index joint bleeds (53.2%, $P = .002$), and target index joint bleeds (70.0%, $P = 0.02$) was observed during the prophylaxis phase. During the prophylaxis period, 40% of target joints resolved. The percentage of boys with zero index joint bleeds increased significantly ($P = .004$) from 51.5% during the observation phase to 81.8% in last quarter of the prophylaxis phase (months 10-12). There was no progression of arthropathy based on physical examination (Hemophilia Joint Health Score), X-ray, and ultrasound obtained at entry into the prophylaxis phase and at study exit. The median FVIII consumption over the prophylaxis phase was 1786 IU/kg/y.

Conclusion: A low-dose, individualized prophylaxis protocol, guided by individual bleeding profiles and serial assessment of joint status, enables escalation of treatment intensity in boys with severe hemophilia A, leading to a significant reduction in bleeding events and reduction in target joint bleeding.

KEYWORDS
China, health care, hemarthrosis, hemophilia A, outcome assessment, prophylaxis studies, ultrasonography

Essentials

- In resource-constrained countries, early low-dose prophylaxis is advised over episodic treatment.
- Significant reduction in total, index joint, and target joint bleeding was observed over 1 year.
- No progression of arthropathy based on physical examination, X-ray, and ultrasound was observed.
- Low-dose individualized secondary prophylaxis leads to reduced bleeding in boys with hemophilia A.

1 | INTRODUCTION

1.1 | Background

The hallmark of moderate/severe hemophilia is recurrent bleeding into joints leading to painful, disabling arthropathy over time. The joints (index joints) most frequently affected are the ankles, knees, and elbows. In pursuit of optimizing long-term joint health in persons with hemophilia, preventive prophylaxis regimens have shifted from fixed, weight-based regimens[1] to personalized regimens guided by individual clinical bleeding patterns[2,3] and/or pharmacokinetic profiles.[4-6] Of note, evidence from recent prospective prophylaxis trials demonstrates a discrepancy between objectively determined joint damage and clinically evident index joint bleeding, suggesting that subclinical bleeding into index joints may contribute to arthropathy in persons with hemophilia.[7,8]

Considering that the aim of long-term prophylaxis is to optimize joint health and quality of life (QoL) in persons with hemophilia, the use of outcome measures to assess the benefits of different prophylaxis regimens is becoming increasingly important. Included in the battery of available outcome measures are joint scores determined by physical examination using validated instruments such as the Hemophilia Health Joint Score (HJHS) and imaging studies that include some combination of plain radiographs (X-rays), magnetic resonance imaging, (MRI), and ultrasound.[9-11]

Until recently, care for boys with moderate/severe hemophilia in China was essentially episodic (on-demand) treatment leading to the development of clinically significant arthropathy in >90% of boys

by ages 6 to 9 years with an associated impairment in their QoL.[12] Following the introduction of weight-based, low-dose prophylaxis regimens demonstrating an impressive reduction in index joint bleeding rates, the need to introduce and evaluate personalized prophylaxis regimens for boys with moderate/severe hemophilia in China has become a high priority.[13-15] The objective of this 1-year prospective study (the China Hemophilia Individualized Prophylaxis Study [CHIPS]) was to evaluate and report the efficacy of a dose/frequency escalating dose secondary prophylaxis protocol in young boys with hemophilia A.

2 | MATERIALS AND METHODS

This was an investigator-initiated, industry-sponsored (Bayer) 1-year prospective single-arm, interventional (secondary prophylaxis), clinical trial (ClinicalTrials.gov, NCT02999308).

2.1 | Participating hemophilia treatment centers

The sponsor site for the CHIPS study was Beijing Children's Hospital (BCH), in collaboration with the Chengdu New Century Women and Children's Hospital (CNCWCH). Initiation and ongoing support and oversight were provided throughout the study by invited experts from Canada (VSB, ASD, PH, and KHL). Subjects were enrolled from May 2016 until June 2017.

2.2 | Research ethics approval

The study was approved by the Research Ethics Boards at BCH and CNCWCH. Informed consent was obtained from parents of all enrolled boys.

2.3 | Study design

There were two periods within the study, a preprophylaxis observation period of 3 months followed by a 1-year prophylaxis period using a dose/frequency escalation protocol (Table 1 and Figure 1). Subjects were evaluated at the hemophilia treatment centers (HTCs) at BCH or CNCWCH every 3 months. These visits included a detailed review of all recorded bleeding events and factor VIII (FVIII) infusions by the local clinical/research staff, a physical examination of the index joints by an experienced physical therapist familiar with the use of the HJHS, and imaging studies as specified in the study protocol (Table 1).

2.4 | Study monitoring

Teleconferences and in-person meetings between members of the local China study teams and the invited Canadian experts were held at regular intervals to review the progress of the study, bleeding events, and dose escalation of study participants (Table 2). Formal on-site study initiation and close-out visits by representatives of the expert team (ASD, PH, and KHL) occurred in 2017 and 2018. During these on-site visits, a comprehensive review of bleeding events and FVIII infusion logs, HJHS worksheets and scoresheets, imaging findings, and dose escalations were reviewed and cross-checked.

2.5 | Study participants

2.5.1 | Inclusion criteria

Eligible participants were boys aged 1 to 7 years with moderate or severe hemophilia A and a baseline circulating FVIII level of <2 IU/dL[16] who were receiving episodic (on-demand) treatment or low-dose prophylaxis (10–15 IU/ kg body weight twice per week) at the time of enrollment into the 3-month observation phase of the study (Table 1). A history of >50 exposure days to FVIII was an additional requirement to ensure that study participants were at low risk for developing neutralizing allo-antibodies (inhibitors) to FVIII during the period of the study.

2.5.2 | Exclusion criteria

Exclusion criteria included a current inhibitor to FVIII defined as an inhibitor level of >0.6 Bethesda Units (BU) using the Nijmegen

TABLE 1 Outline of CHIPS study protocol

Outcome measures	Prestudy observation period (3 months)	1-year prophylaxis period Q1	Q2	Q3	Q4
Review of bleeding events and FVIII infusions (IU/kg)	X	X	X	X	X
Physical examination of index joint scores (HJHS)		X	X	X	X
X-ray (Pettersson) scores		X			X
Ultrasound (gray-scale soft-tissue domain and color Doppler) scores		X	X	X	X

Abbreviations: FVIII, factor VIII; HJHS, Hemophilia Joint Health Score; IU, International Units; Q, Quarter.

TABLE 2 Dose escalation criteria

Index joint assessment	Frequency	Description	Score
Bleeding	Every 3 months	• ≥ 2 bleeds in any single index joint	2
		• 1 index joint bleed	1
Ultrasound (gray-scale soft-tissue domain and color Doppler)	Every 3 months	• Changes of gray-scale US score ≥3	2
		• Changes of gray-scale US score =1 AND changes of color Doppler perisynovial vascularity score ≥1; OR changes of gray-scale US score =2	1
Physical examination of index joints (HJHS)	Every 3 months	• Change of swelling score on HJHS from 0 to 2 or 1 to 3 (not considered to be related to an acute bleed)	2
		• Persistent swelling that is mild (score 1) or moderate (score 2)	1
Total score required for dose escalation			≥2

Note: Evaluation: <2 scores: "Sufficient", remain on current prophylaxis step (Figure 1). ≥2 scores: "Insufficient," escalate to the next prophylaxis step (Figure 1).

Abbreviations: HJHS, Hemophilia Joint Health Score; US, ultrasound.

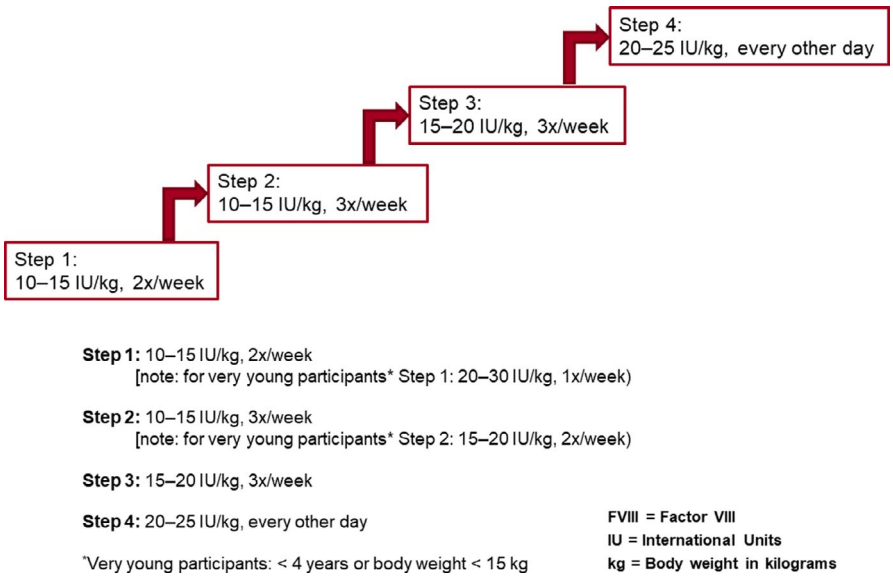


FIGURE 1 Dose and frequency escalation steps of the protocol

modification of the Bethesda assay confirmed by two separate tests[17] and presence of other bleeding or chronic disorders. Boys whose parents were deemed by the local study teams to be unable to comply with the study protocol were not eligible for study enrollment.

2.6 | Observation and prophylaxis phases

All participants started the 12-month prophylaxis phase of the study protocol (Table 1) on low-dose prophylaxis (Figure 1), including those boys who were on episodic treatment (n = 6) during the preprophylaxis observation phase. Intensification of prophylaxis (dose/frequency) occurred based on *a priori* escalation criteria that included frequency of index joint bleeding as recorded in participants' infusion logs; persistent or increased swelling (present from one 3-month assessment to the next) as assessed using the HJHS version 2.1[18]; and ultrasound findings using gray-scale soft-tissue domain (effusion or hemarthrosis, synovial hypertrophy, and hemosiderin) [11] and color Doppler (Table 2).[19] Treatment of breakthrough bleeding into index joints was at the discretion of the patients' local physicians. FVIII doses were rounded to the nearest vial to avoid waste.

2.7 | Outcome variables

2.7.1 | Target joints

In this study, a target joint was defined as an index joint in which three or more spontaneous bleeds occurred within a consecutive 6-month period.[16] Resolution of target joint bleeding was defined as ≤2 bleeds into an index joint within a consecutive 12-month period.[16]

2.8 | Outcome measures

Outcome measures included all bleeds, index joint bleeds, target index joint bleeds, index joint scores using the HJHS,[18] Pettersson X-ray scores,[10] gray-scale soft-tissue domain,[11] and color Doppler ultrasound scores.[19]

2.9 | FVIII consumption

The annual FVIII consumption (IU/kg/y) was calculated for each participant based on information retrieved from infusion diaries and FVIII dispensation records provided by the Pharmacy Departments in each of the two participating HTCs. Dispensation records also included FVIII used for breakthrough bleeding episodes.

2.10 | Data sources

2.10.1 | Bleeding/infusion records

Families were instructed to keep bleeding/infusion records in diaries that were reviewed at the 3-month study visits. As part of quality assurance for this study, parents of boys enrolled into this study received detailed training regarding the signs and symptoms of acute index joint bleeds based on the published ISTH definitions of an acute joint bleed.[16]

2.10.2 | HJHS version 2.1

Musculoskeletal evaluation of each participant's index joints was performed by experienced physiotherapists trained in the use of the HJHS at each of the participating HTCs as per the approved study protocol (Table 1). Since the HJHS is validated only for boys with hemophilia aged ≥4 years, younger participants were not evaluated with this tool until they reached the age of 4 years.

2.11 | Data acquisition of imaging studies

2.11.1 | Plain radiographs

Non–weight-bearing X-rays (anteroposterior and lateral) of the six index joints were obtained at entry into the prophylaxis phase and at study exit (month 12) as per the approved study protocol (Table 1).

2.11.2 | Ultrasound

Gray-scale and color Doppler ultrasound scans were performed at entry into the prophylaxis phase and at 3, 6, 9, and 12 months (study exit) by two experienced operators at BCH (NZ and AH) and one at CNCWCH (SY) using protocols for data acquisition of images as previously described.[20-22] Ultrasound images were acquired using a 12–5-MHz linear-array transducer on an iU22 scanner (Philips Medical Systems, Bothell, WA, USA). The focus and depth of the ultrasound beam was adjusted to the patient's biotype. For color Doppler low filter, flow rate at the range of ±2.3 cm/s and color gain settings of 79% and pulse-repetition frequency of 402 Hz were set up, and the imaging parameters were held constant throughout the examination. The gray-scale/color Doppler scan time for each joint was ≈10 minutes.

2.12 | Data interpretation of imaging studies

At BCH, X-ray and ultrasound studies were scored independently by two radiologists (NZ and AH) with 12 and 6 years of experience. Differences in scores were adjudicated by consensus.

At CNCWCH, X-ray studies were scored by YK, who at the time of evaluation had 3 years of experience. Ultrasound studies were scored by SY, who at the time of the evaluation had 10 years of experience. NZ, the senior study radiologist from BCH, acted as an independent reader for all X-ray and ultrasound studies from CNCWCH. Differences in scores were resolved by consensus.

Study readers were not blinded to the identity of patients when interpreting findings from different imaging modalities; however, they were blinded to clinical information, and they were not involved with decisions regarding escalation of individual subjects. These decisions were the responsibility of the clinical teams at the two HTCs.

2.12.1 | Plain radiographs

Both BCH and CNCWCH used the Pettersson scale [10] for scoring X-ray images.

2.12.2 | Ultrasound

Gray-scale soft-tissue domain ultrasound

Gray-scale ultrasound examinations were scored using a scale adjusted to the International Prophylaxis Study Group MRI scale.[11] The subscores of this ultrasound scale were based on the worst finding for the distal tibia and fibula and proximal talus for ankles; the distal femur, proximal tibia, and patella for knees; and distal humerus and proximal radius and ulna for elbows. Cutoffs for normal (score = 0), mild (score = 1), moderate (score = 2), and severe (score = 3) soft-tissue domain scores (range, 0–9) of ankles and knees were based on a priori described criteria.[11] Cutoffs for soft tissue scores of elbows were considered as similar to those of ankles given the similarity of size of the elbow and ankle joints.

Color Doppler ultrasound

The degree of synovial vascularity of study joints was measured on the plane that depicted the most marked vascularity

according to a scoring system modified from a publication by Backhaus et al (Appendix A1–Table A1).[19,23]

2.13 | Sample size

An a priori sample size calculation for this study was not possible given the lack of detailed bleed data in the medical records of potentially eligible subjects. An opportunity sample size of 46 subjects was used that yielded a total of 33 boys evaluable for analysis.

2.14 | Statistical methods

Descriptive statistics (median and interquartile range [IQR]) were used for data that was nonnormally distributed. McNemar's test was used for comparisons of all bleeds, index joint bleeds, target index joint bleeds, and subjects with zero bleeds. Wilcoxon signed-rank tests were used to compare the differences between HJHS, Pettersson, and ultrasound (gray-scale soft-tissue domain and color Doppler) scores obtained at entry into the prophylaxis phase and at study exit (month 12). Calculations and analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA). A two-tailed *P* value <0.05 was considered significant.

3 | RESULTS

3.1 | Characteristics of the study cohort

Between May 2016 and June 2017, 46 boys were assessed for eligibility; 9 boys were excluded from enrollment into the 3-month observation phase for the following reasons: baseline FVIII level >2 dL (n = 1); age >7 years (n = 2); FVIII infusion dose >30 IU/kg (n = 1); presence of an inhibitor >0.6 BU (n = 1); and parents unwilling for their sons to comply with the burden of the study protocol (n = 4). The median age of boys at the start of the 3-month observation phase was 4.8 years (IQR, 3.8-6.1 years); 78.8% (26/33) of the study cohort had baseline FVIII levels of <1 IU/dL, and 21.2% (7/33) had FVIII baseline levels of 1–1.8 IU/dL. Nineteen boys (57.6%) had a lifetime history of target joints (n=20) before study enrollment based on reviews of available medical records at the two participating HTCs. The joints affected were ankles (n=10), knees (n = 4), and elbows (n = 6). One boy had a history of two target joints: an elbow and an ankle. The characteristics of the study cohort are detailed in Table 3. Four boys were withdrawn before the start of the prophylaxis phase: two because of inadequate insurance reimbursement for FVIII, and two because of poor compliance.

Of the 33 boys who entered the 1-year prophylaxis phase, 72.7% (24/33) were on step 1, and 27.3% (9/33) were on step 2, as detailed in Figure 1; 84.8% (28/33) of boys were within window of the a priori defined steps. Slight discrepancies were a function of available FVIII vial sizes.

Throughout the secondary prophylaxis phase, boys received either a plasma-derived FVIII concentrate, Human Coagulation Factor FVIII, manufactured by Guangzhou Green Cross Pharmaceuticals Co Ltd (Guangdong, China; 21/33 boys) or a recombinant FVIII concentrate, Kogenate, manufactured by Bayer Health Care LLC (Whippany, NJ, USA; 12/33 boys). At entry into the prophylaxis phase, 42.4% (14/33) of boys were receiving clotting factor concentrates at home administered by one of their parents; this figure increased to 54.5% (18/33) of boys by the end of the prophylaxis phase.

3.2 | Escalations

Thirty-four dose/frequency escalations were made in 69.7% (23/33) of boys during the 1-year study period. Escalations based on frequency of index joint bleeding exclusively accounted for the largest percentage, 47.1% (16/34) followed by combinations of index joint bleeding and swelling/persistent swelling by HJHS (23.5%; 8/34), and index joint bleeding and ultrasound (11.8%; 4/34). There was one escalation that had all three components representing just 2.9% (1/34) of all escalations. HJHS and gray-scale ultrasound alone accounted for 2.9% (1/34) and 5.9% (2/34) of escalations, and 5.9% (2/34) when combined (Table 4).

At the end of the 1-year prophylaxis period, participants were on the following steps: 12.1% (4/33) on step 1 (10-15 IU/kg, 2×/week); 24.2% (8/33) on step 2 (10-15 IU/kg, 3×/wk); 45.5% (15/33) on step 3 (15–20 IU/kg, 3×/wk); and 3.0% (1/33) on step 4 (20-25 IU/kg, every other day). For very young participants (aged <4 years or body weight <15 kg), 6.1% (2/33) were on step 1 (20-30 IU/kg 1×/wk) and 9.1% (3/33) on step 2 (15–20 IU/kg, 2×/wk) as detailed in Figure 1; 84.8% (28/33) of boys were within window of the a priori defined steps. Slight discrepancies were a function of available FVIII vial sizes.

3.3 | Safety

No subjects were documented to have neutralizing alloantibodies (inhibitors) to FVIII (>0.6 BU) during the study.

3.4 | Efficacy

3.4.1 | Bleeding events

The projected annualized median number of index joint bleeds for the study cohort (n = 31) during the observation phase was 4.0 (IQR, 0-8.0), compared to an observed annual bleeding rate of 3.0 (IQR, 1.0-4.5) during the prophylaxis phase on study. The median difference was 1.0 (95% confidence interval [CI,] −0.5 to 4.5. These values are not significantly different (*P* = .11). In comparison, the observed median number of index joint bleeds during the observation phase was 1.0 (IQR, 0.0-2.5), compared to 0.0 (IQR, 0.0-1.0) during the last quarter (months 10-12) on study. These values were significantly different (*P* = .02). During the first quarter (months 1-3) of the 1-year prophylaxis phase, the totals of all bleeds, index joint bleeds, and

target index joint bleeds for the study cohort (n = 33) were 179, 47, and 20. Corresponding values for the last quarter (months 10–12) were 102, 22, and 6, representing a significant decrease in bleeding events of 43.0% (all bleeds, $P = 0.001$), 53.2% (index joint bleeds, $P = 0.002$), and 70.0% (target index joint bleeds, $P = 0.02$). Bleeding events for the four quarters of the 1-year prophylaxis phase (months 1-3, 4-6, 7-9, and 10-12) are detailed in Figure 2. The median annual bleeding rates per subject, based on reported bleeding events over the 1-year prophylaxis phase, were 13 (all bleeds), 3 (index joint bleeds), and 6 (target index joint bleeds).

The percentage of boys with zero bleeds into their index joints during the three-month observation period was 51.5% (17/33); this figure increased significantly to 81.8% (27/33) based on reported bleeds into index joints in the last quarter (months 10-12) of the prophylaxis phase of the study ($P = 0.004$).

3.4.2 | Target joints

Ten boys (30.3%) entered the 1-year prophylaxis phase with target joints, based on reported bleeding into their index joints in the 3-month observation period, extrapolated to 6 months (to meet the ISTH definition of a target joint). The joints affected were ankles (n = 3), knees (n = 5), and elbows (n = 2). Resolution of target joint bleeding, defined as ≤2 bleeds during the one-year prophylaxis phase occurred in four boys.[16] One boy (age 2.2 years at entry into the prestudy observation period) had a new target index joint (left knee) develop during the first 6 months of the prophylaxis phase. He began the prophylaxis phase on step 1* and was escalated first to step 2* and then step 3, where he remained bleed free during the second 6 months of the prophylaxis phase.

TABLE 3 Characteristics of study cohort at enrollment into the observation and the 1-year prophylaxis phase

Characteristics	N	Median	Percentile	
			25th	75th
Age at enrollment, y	33	4.8	3.8	6.1
Weight at enrollment, kg	33	18.5	16.0	20.5
BMI at enrollment	33	14.8	14.1	16.0
Physical examination of index joint scores (HJHS)	18	8.0	3.0	11.0
X-ray (Pettersson) scores	32	0.0	0.0	3.0
Ultrasound (gray-scale soft-tissue domain) scores	33	4.0	1.0	6.0
Ultrasound (color Doppler) scores	33	0.0	0.0	1.0

Note: Reference ranges: The HJHS joint score ranges from 0 to 20 per index joint (total index joint score plus global gait, 0–124)[18]; the Pettersson joint score ranges from 0–13 per index joint (total index joint score, 0–78)[10]; the gray-scale ultrasound joint score ranges from 0 to 9 for soft tissues per index joint (total index joint score for soft tissues, 0–54)[11]; and the color Doppler ultrasound joint scores ranging from 0 to 2 per index joint (total index joint score, 0–12).[19] For imaging scores, the higher the score the more diseased the joint.

Abbreviations: BMI, body mass index; HJHS, Hemophilia Joint Health Score.

3.5 | Musculoskeletal status

3.5.1 | HJHS version 2.1

The median HJHS score at entry into the prophylaxis phase (n = 19) was 8.0 (IQR, 3.0-11.0). The corresponding value at the end of the 1-year prophylaxis phase (n = 18) was 5.0 (IQR, 2.2-9.8). The median difference was 1.5 (95% CI, −0.5 to 3.0. These values are not significantly different ($P = .2$) for the 18 boys with paired observations at the two time points (Table 5).

3.5.2 | Pettersson X-ray scores

The median Pettersson score at entry (n = 32) into the prophylaxis phase was 0.0 (IQR, 0.0-3.0). The corresponding value at the end of the 1-year prophylaxis period (n=32) was 0.0 (IQR, 0.0-3.3). The median difference was 0.0 (95% CI, −6.0 to 1.5). These values are not significantly different ($P = .53$) for the 32 boys with paired observations at the two time points (Table 5).

3.5.3 | Gray-scale soft-tissue domain ultrasound scores

The median gray-scale soft-tissue domain total ultrasound score at entry (n = 33) into the 1-year prophylaxis phase was 4.0 (IQR, 1.0-6.0). The corresponding value at the end of the 1-year prophylaxis phase (n = 33) was 3.0 (IQR, 1.0-4.0). The median difference was 0.5 (95% CI, −0.5 to 1.5). These values are not significantly different ($P = .19$) for the 33 boys with paired observations at the two time points (Table 5).

3.5.4 | Color Doppler ultrasound scores

The median color Doppler total ultrasound score at entry (n = 33) into the 1-year prophylaxis phase was 0.0 (IQR, 0.0-1.0). The corresponding value at the end of the 1-year prophylaxis phase (n = 33) was 0.0 (IQR, 0.0-0.3). The median difference was 0.0 (95% CI, 0.0-0.5). These values are not significantly different ($P = .31$) for the 33 boys with paired observations at the two time points (Table 5).

3.6 | Factor consumption

The median FVIII consumption (IU/kg/y) total during the observation period (n = 33) prophylaxis phase was 1118 (IQR, 519-1588). The corresponding value during the last quarter of the prophylaxis

phase (n = 33) was 2040 (IQR, 769-2711). The median difference was −779 (95% CI, −1158 to 398). This increase in consumption was significantly different (P = <.0001). The median annual FVIII consumption for the study cohort during the 12-month prophylaxis phase was 1786 IU/kg/y (IQR, 1635-2270).; 60.6% (20/33) of boys consumed <2000 IU/kg/year and 97.0% (32/33) <3000 IU/kg/y.

4 | DISCUSSION

The results reported in this communication provide new and important information in the rapidly evolving field of preventive treatment (prophylaxis) for boys with severe hemophilia A in countries with limited access to replacement hemostatic products. Key findings from this 1-year, prospective dose/frequency escalating secondary prophylaxis study in 33 boys with severe hemophilia, no inhibitors, and a median age of 4.8 years at study enrollment include a significant reduction in all bleeds (43.0%), index joint bleeds (53.2%), and target index joint bleeds (70.0%); a 40% resolution of target joints; and a significant increase in the percentage of boys with zero bleeds, from 52% to 82%, over the 1-year prophylaxis period. This impressive control of bleeding, achieved with a median FVIII consumption of only 1786 IU/kg/y, in a cohort of young boys with severe hemophilia, many of whom had target index joints at study entry and were therefore at high risk for spontaneous bleeding into index joints, is therefore of clinical significance.[24]

A novel and potentially very important aspect of the prophylaxis protocol used in this prospective study was the incorporation, in addition to reported index joint bleeds, of joint swelling/persistent joint swelling and color Doppler ultrasound evidence of increased perisynovial vascularity in the synovium of the six index joints into the a priori determined criteria for dose/frequency escalation. These objective measures of joint health influenced the decision to escalate the intensity of prophylaxis in 52.9% of escalations, suggesting that reported index joint bleeds alone may be insufficient to guide personalization of prophylaxis with the goal of optimizing joint health in persons with hemophilia.

The CHIPS study confirmed the significant heterogeneity in bleeding profiles that exists between boys with severe hemophilia A. A total of 18.2% (6/33) of boys remained on low-dose prophylaxis (step 1) at the end of the 1-year prophylaxis period and 3.0% of cases (1/33) required escalation to full-dose prophylaxis (step 4). These findings emphasize the need to identify, as soon as possible following the start of long-term prophylaxis, boys with a severe bleeding phenotype, thus allowing more rapid dose/frequency escalation in prophylaxis regimens with the goal of rapidly eliminating target joints and reducing to a minimum spontaneous bleeding into index joints.

The results of low-dose prophylaxis studies in countries with limited access to clotting factor concentrates have been reported by investigators from China,[13,14] India,[25] Indonesia,[26] Thailand,[27] Tunisia,[28] and the Ivory Coast.[29] Collectively, these eight studies enrolled a total of 251 boys with hemophilia (hemophilia A = 232 [92.4%], hemophilia B = 19 [7.6%])[29] over a 28-year period (1992-2020). The starting low-dose prophylaxis regimen most commonly used for boys with hemophilia A was 10 IU/kg given twice weekly.[13,14,25,26] Significant differences in study design, duration, and characteristics of enrolled participants preclude direct comparisons among these studies. All eight studies met the ISTH criteria for secondary or tertiary prophylaxis.[16] Details of these eight studies are provided in the supplement to this manuscript (Appendix A2). Key findings from these published studies of low-dose prophylaxis include the following: significant reductions in total bleeds and index joint bleeds in all studies[13,14,25-29] and increased activity[14] and significant reductions in time lost from school.[13,25-27]

To the best of our knowledge, the CHIPS study is the first prospective study of a low-dose individualized prophylaxis regimen to be conducted in a country with limited access to clotting factor concentrates at the time of the conduct of the study. The major strength

TABLE 4 Dose escalations throughout the 1-year prophylaxis period

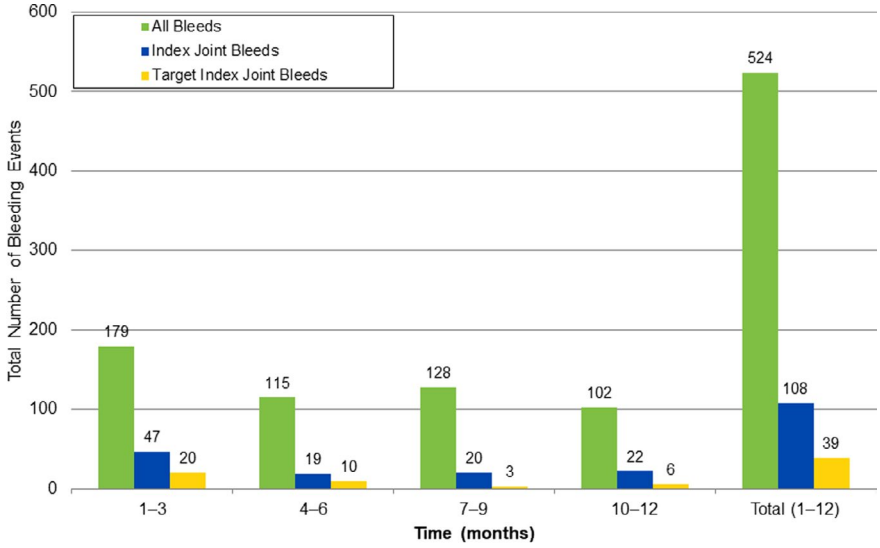
	First escalation		Second escalation		Total escalations	
Escalation criteria	No.	%	No.	%	No.	%
JB	12	52.2	4	36.4	16	47.1
JB +HJHS	4	17.4	4	36.4	8	23.5
JB +US[a,b]	2	8.7	2	18.2	4	11.8
JB +HJHS + US[b]	0	0.0	1	9.1	1	2.9
HJHS	1	4.3	0	0.0	1	2.9
US[b]	2	8.7	0	0.0	2	5.9
HJHS +US[b]	2	8.7	0	0.0	2	5.9
Totals	23	100.0	11	100.0	34	100.0

Abbreviations: HJHS, Hemophilia Joint Health Score; JB, Index Joint Bleed; US, ultrasound (gray-scale soft-tissue domain and color Doppler) scores.

[a]Gray-scale and color Doppler.

[b]Gray-scale.

FIGURE 2 Summary of bleeding events by quarter during the 12-month prophylaxis phase



Q1	2	0	2	1	0	1	1	0	0	1	0	0	8	1	5.5
Median	5	1	3	2	0	1	3	0	0	3	0	1	13	3	6
Q3	7	2	3.5	4	1	2	6	1	0.5	4	1	1.5	19	6	6

TABLE 5 Comparison of differences between outcome measures at entry and exit from the 1-year prophylaxis phase

	N	Observed median	Median[a] change	95% Confidence interval[a]		*P* value[a]
				Lower	Upper	
Physical examination of index joint total scores (HJHS)	18		1.50	−0.5	3.0	.21
Baseline		8.0				
End of study (12 mo)		5.0				
X-ray (Pettersson) total scores	32		0.0	−6.0	1.5	.53
Baseline		0.0				
End of study (12 mo)		0.0				
Ultrasound (gray-scale soft-tissue domain) Total score	33		0.5	−0.5	1.5	.19
Baseline		4.0				
End of study (12 mo)		3.0				
Ultrasound (color Doppler) total score	33		0.0	0.0	0.5	.31
Baseline		0.0				
End of study (12 mo)		0.0				
Index joint bleeds[b]	31		0.75	> 0.0	1.5	.02
Observation (pre−3 mo – baseline)		1.0				
Q4 on study (10 – 12 M)		0.0				
FVIII consumption (IU/kg)	33		−779	−1158	- 398	<.0001
Observation (−3 mo – 0 = baseline)		1118				
Q4 on study (10-12 mo)		2040				

Abbreviation: HJHS, Hemophilia Joint Health Score; Q, quarter.

[a]Wilcoxon signed-rank test.

[b]This analysis reflects comparison between the 3-month observation period and the last quarter (Q4) of the 12-month prophylaxis period.

of the study relates to the use of a priori ISTH definitions of bleeding events and target joint bleeding overseen by experienced pediatric comprehensive care hemophilia teams in collaboration with invited Canadian experts.

This study has limitations. Principal among them relate its short duration of 1 year. We now know that the development of clinically significant osteochondral changes in the index joints of boys with hemophilia receiving prophylaxis occurs over several years and the absence of serial changes in imaging findings of arthropathy assessed by ultrasound in short-term prospective studies of prophylaxis, as occurred in the CHIPS study and the study reported by Chozie and colleagues[26] from Indonesia, is not unexpected. Future prospective studies, conducted over a longer period of time, are needed to evaluate the long-term benefit of prophylaxis begun at an early age of life in countries with limited access to safe clotting factor concentrates.

The relevance of findings from the CHIPS study to the management of boys with moderate/severe hemophilia in countries with limited access to safe hemostatic agents should not be underestimated. There is now universal acceptance that standard of care for boys with severe hemophilia should include the introduction of programs of prophylaxis started at an early age of life before the onset of clinically overt arthropathy with the goal of ensuring long-term joint health and improved quality of life.[30] This goal is best achieved through the implementation of programs of personalized prophylaxis supervised by members of a comprehensive hemophilia care program.[30] A key for success is reliable access to safe and affordable hemostatic agents that now include not only plasma-based and recombinant clotting factor concentrates but also nonfactor therapies such as the bispecific antibody emicizumab (Hemlibra; Hoffmann-La Roche, Basel, Switzerland) that has been recently approved by the Food and Drug Administration for use in the United States in persons with hemophilia A with and without inhibitors to FVIII.[31] An advantage of nonfactor therapies is that they can be administered subcutaneously at a frequency of once weekly to once every 4 weeks with an impressive reduction in spontaneous index joint bleeding in both inhibitor negative and inhibitor positive persons with hemophilia.[32,33]

Finally, the potential economic impact and benefit of programs of individualized prophylaxis programs in countries with limited access to safe replacement clotting factor concentrates cannot be overemphasized. Such countries include China, India, Thailand, and Indonesia, among others[13,14,25-27]; it is important to stress that these four countries alone represent 37% of the world's current population of ≈7.9 billion.[33] The way forward in achieving improved care and long-term musculoskeletal outcomes for boys with moderate/severe hemophilia is clear, and the findings reported in this communication reinforce the now widely accepted recommendation that early introduction of low-dose prophylaxis regimens in countries with limited access to safe hemostatic factor therapies is superior to episodic (on-demand) therapy, and that, in the words of Dr. Kathelijn Fischer, "a little prophylaxis can go a long way."[34] The CHIPS study is a very important step forward, and the findings from this study provide a foundation for the design of future prophylaxis studies targeted at the preservation of long-term joint health of persons with hemophilia in resource-constrained settings.

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RELATIONSHIP DISCLOSURE

RW reports she has received fees for participation in advisory boards/education events supported by Bayer and Shire/Takeda. She has received investigator-initiated and industry-supported research grants from Bayer and Shire/Takeda. XL reports she has received fees for participation in advisory boards/education events supported by Bayer and Shire/Takeda. She has received investigator-initiated and industry-supported research grants from Bayer and Shire/Takeda. ASD is a member of the International Prophylaxis Study Group (IPSG) and the Outcome Measures in Rheumatology special interest groups in MRI in juvenile idiopathic arthritis; she reports receiving speaker/consultant fees from Baxter Healthcare Inc./Takeda and Pfizer Healthcare Inc. and research support from Bayer Healthcare Inc., Novo Nordisk Healthcare Inc., Shire/Baxalta, Terry Fox Foundation, Physicians' Services Inc. Foundation, Society of Pediatric Radiology and the Garron Family Cancer Centre. PH reports she has a patent Hemophilia Joint Health Score 2.1 with royalties paid to the Hospital for Sick Children. PM reports that he was a former employee at Bayer Global (US) and has participated in advisory boards supported by Bayer Global. VB reports that he is chair of the IPSG, a cooperative study group that is funded by education grants from Bayer Healthcare, Bioverativ/Sanofi, Novo Nordisk, Pfizer, Shire/Takeda, and Spark Therapeutics to the Hospital for Sick Children ("SickKids") Foundation. He has received fees for participation in advisory boards/education events supported by Amgen, Bayer, Novo Nordisk, Pfizer, Roche, and Shire/Takeda and for participation in data safety monitoring boards for Octapharma and Shire/Takeda. He has received investigator-initiated, industry-supported research grants from Novo Nordisk, Bioverativ/Sanofi, and Shire/Takeda. K-HL has received fees for participation in educational events sponsored by Bayer, China and Takeda China. All other authors have no other relevant affiliations or financial involvement with any organization or entity with a financial

interest in, or financial conflict with, the subject matter or materials reported in the CHIPS manuscript.

AUTHOR CONTRIBUTIONS

RW led study concept, design, and operations; analysis and interpretation of data; revisions to the manuscript; and review of the final version of the manuscript. XL co-led study concept, design, and operations; analysis and interpretation of data; revisions to the manuscript; and review of the final version of the manuscript. WY contributed to study operations; clinical data collection; analysis and interpretation of data; and review of the final version of the manuscript. QZ contributed to study operations, clinical data collection, analysis and interpretation of data, and review of the final version of the manuscript. MZ contributed to study design and operations, clinical data collection, and review of the final version of the manuscript. NZ contributed to study concept, design, and operations; imaging data collection; analysis and interpretation of data; revising versions of the manuscript; and review of the final version of the manuscript. SY contributed to imaging data collection and review of the final version of the manuscript. ZC contributed to study operations, coagulation data collection, and review of the final version of the manuscript. YW contributed to musculoskeletal data collection and review of the final version of the manuscript. YK contributed to imaging data collection and review of the final version of the manuscript. LT contributed to study concept, design, and operations; clinical data collection; and review of the final version of the manuscript. YZ contributed to clinical data collection and review of the final version of the manuscript. AA contributed to study operations, analysis and interpretation of data, revisions to the manuscript, and review of the final version of the manuscript. ASD contributed to study design, analysis and interpretation of data, site training, revisions to the manuscript, and review of the final version of the manuscript. PH contributed to study design and operations, site training and oversight visits, analysis and interpretation of data, revisions to the manuscript, and review of the final version of the manuscript. DMI contributed to study operations, analysis and interpretation of data, revisions to the manuscript, and review of the final version of the manuscript. PM contributed revisions to the manuscript and review of the final version of the manuscript. DS contributed to statistical analysis and interpretation of data, revisions to the manuscript, and review of the final version of the manuscript. VSB contributed to study concept and design, analysis and interpretation of data, revisions to the manuscript, and review of the final version of the manuscript. KHL contributed to study concept, design, and operations; site training and oversight visits; analysis and interpretation of data; revisions to the manuscript; and review of the final version of the manuscript. This manuscript was prepared by the investigators without any assistance from Bayer, China or a professional writing agency. All named authors had full access to the CHIPS database and approved the final manuscript for submission to *Research and Practice in Thrombosis and Haemostasis*. Bayer, China was given the opportunity to review the final manuscript as a requirement of the investigator-initiated, industry-funded (Bayer, China) grant but had no input into the findings reported in the manuscript or discussed in the manuscript. The information reported in the CHIPS manuscript represents the opinions of the named authors only.

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APPENDIX A1

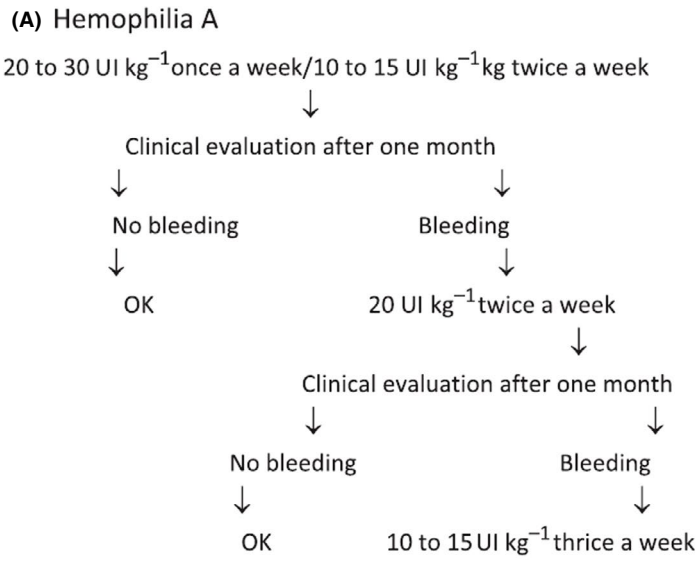
Grades	Criteria	Score
Normal (grade 0)	Normal: <4 dots within box	0
Mild to moderate (grade 1)	≥4 dots within box and <50% of ROI filled with color pixels representing hyperemia	1
Severe (grade 2)	≥50% of ROI filled with color pixels representing hyperemia	2

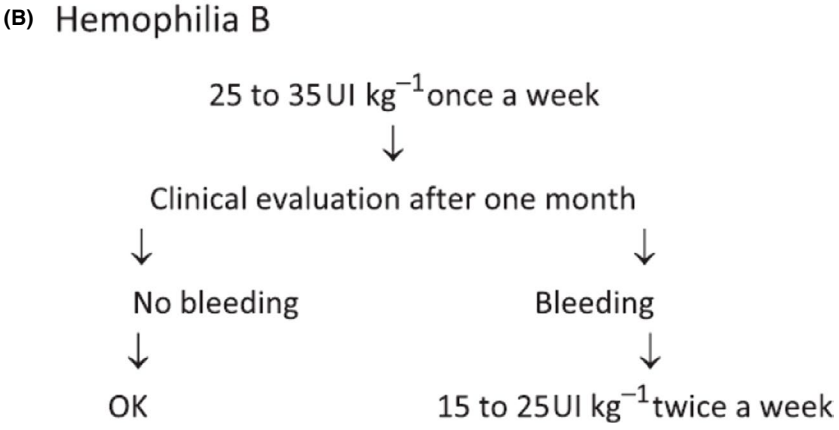
Note: Criteria: Based on the number of dots (color pixels) and extent of vascularity on the location with most severe findings and extent of vascularity within the color Doppler box.

Abbreviation: ROI, region of interest.

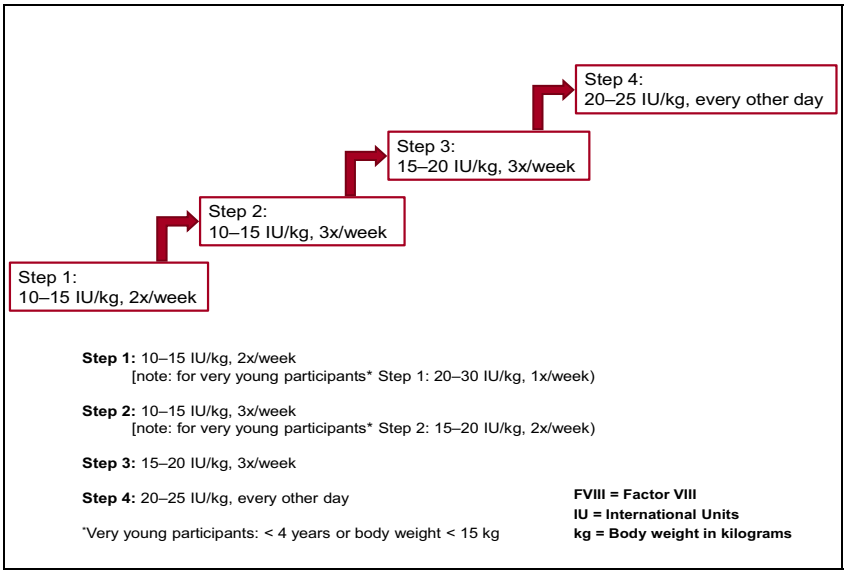
TABLE A1 Color Doppler scoring for assessment of ankles, elbows, and knees of patients with blood-induced arthropathies modified from Backhaus[19]

Imaging studies





(C)



APPENDIX A2

Low-dose prophylaxis studies in countries with limited access to clotting factor concentrates

Investigator (year of publication)	Chuansumrit A[27] (1995)	Wu R[13] (2011)	Tang L[14] (2013)	Verma SP[25] (2016)
Country	Thailand	China	China	India
Type of study	Observational	Observational	Observational	Randomized controlled trials
Period of study enrollment, y	1992	2007-2009	2008-2009	2013
Duration of prophylaxis	1 y-	12 wks	6-12 wks	11.5 mo
Type of prophylaxis	Tertiary	Secondary/ Tertiary	Secondary/ Tertiary	Secondary
Number of evaluable cases	6	34	66	11
Hemophilia A	6	28	66	11
Hemophilia B		6		
Regimen	FVIII: 8-10 IU/kg twice a week	FVIII: 10 IU/kg twice a week FIX: 20 IU/kg once weekly	FVIII: 10 IU/kg twice a week	FVIIII: 10 IU/kg twice a week
Factor consumption IU/kg/y	832-1040	FVIII =1040 FIX =1040	960	1050.1
Annualized index joint bleeds (AJBR) during the preprophylaxis period (eg, on demand)	ND			
Observed		9.9 (mean)		
Projected		39.6 (mean)	28.8 (mean)	
Age at start of prophylaxis, y	12 (median)	7.5 (median)	8.6 (mean)	4.3 (mean)
Annualized index joint bleeds (AJBR) in the period of low-dose prophylaxis	ND	1.7 (mean)		
Observed				0.96 (mean)
Projected		7.37 (mean)	6.0 (mean)	

Note: Data in this table are taken directly from the published manuscripts, with extrapolation where appropriate (ie, project annualized index joint bleeds).
Abbreviation: ND, No data provided.

Gouider E[28] (2017)	Chozie NA[26] (2019)	Lambert C[29] (2020)	Wu R (2021)
Tunisia	Indonesia	Ivory Coast	China
Observational	Randomized controlled trials	Prospective	Observational
ND	2016-2018	2018-2020	2016-2017
5 y	12.8 mo	17 mo	1 y
Secondary	Secondary/Tertiary	Primary/Secondary	Secondary
51	25	25	33
42	25	21	33
9		4	
FVIII: 20-30 IU/kg once weekly to 15 IU/kg twice a week with escalation based on bleeding FIX: 25–35 IU/kg once weekly with escalation based on bleeding	FVIII: 10 IU/kg twice a week	Fc-rVIII: 20 IU/kg once weekly; Fc-rIX: 20 IU/kg once every 10 days	FVIII: 10-15 IU/kg twice a week with escalation based on bleeding
1612	1010 (median)	ND	
		5.8 (mean)	
7.0 (median)	10.3		
			4.0 (median)
5.3 (median)	11.8 (mean)	5.6 (mean)	4.8 (median)
0.5 (median)	5.6	1.9 (mean)	3.0 (median)