Received: 18 December 2020 | Revised: 12 May 2021 | Accepted: 31 May 2021

DOI: 10.1002/rth2.12565

ORIGINAL ARTICLE

Magnetic resonance imaging in boys with severe hemophilia A: Serial and end-of-study findings from the Canadian Hemophilia Primary Prophylaxis Study

Jennifer Stimec MD, FRCPC[1] | Saunya Dover MSc[2] | Eleanor Pullenayegum PhD[2,3] | Victor S. Blanchette MB, BChir(Cantab), FRCP(C)[2,4,5] | Andrea S. Doria MD, PhD, MSc, MBA[1] | Brian M. Feldman MD, MSc, FRCPC[2,3,4,6] | Manuel Carcao MD, MSc, FRCPC[2,4,5] | Georges E. Rivard MD[7] | Sara J. Israels MD[8] | Anthony K. Chan MD, FRCPC[9] | MacGregor Steele MD, FRCPC[10] | Stephanie Cloutier MD, FRCPC[11] | Robert J. Klaassen MD, FRCPC[12] | Victoria E. Price MB, ChB, MMed (Pediatrics), MSc, FRCPC[13] | Roona Sinha MD, FRCPC, MHPE[14] | Nicole Laferriere MD, PhD, FRCPC[15] | Elizabeth Paradis RegN[16] | John K. M. Wu MBBS, MSc, FRCPC[17] | Paul Babyn MDCM[18]

[1]Department of Medical Imaging, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

[2]Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, Toronto, ON, Canada

[3]Institute of Health Policy, Management & Evaluation, The Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[4]Department of Pediatrics, University of Toronto, Toronto, ON, Canada

[5]Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada

[6]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada

[7]Division of Hematology/Oncology, Department of Pediatrics, CHU Sainte-Justine, Montreal, QC, Canada

[8]Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB, Canada

[9]Department of Pediatrics, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada

[10]Section of Pediatric Hematology, Department of Pediatrics, University of Calgary and Alberta Children's Hospital, Calgary, AB, Canada

[11]Centre de l'hémophilie de l'est du Québec, Hôpital de l'Enfant-Jésus, Université Laval, Québec, QC, Canada

[12]Division of Hematology Oncology, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada

[13]Division of Pediatric Hematology/Oncology, IWK Health Centre, Halifax, NS, Canada

[14]Saskatchewan Bleeding Disorders Program, Royal University Hospital, Saskatoon, SK, Canada

[15]Division of Hematology/Oncology, Thunder Bay Regional Cancer Care, Thunder Bay, ON, Canada

[16]Health Sciences North, Sudbury, ON, Canada

[17]Division of Hematology/Oncology/BMT, Department of Pediatrics, UBC & BC Children's Hospital, Vancouver, BC, Canada

[18]Department of Medical Imaging, University of Saskatchewan, Saskatoon, SK, Canada

Correspondence
Paul Babyn, Department of Medical Imaging, University of Saskatchewan, Saskatoon, SK, Canada.
Email: paul.babyn@saskhealthauthority.ca

Funding information
Bayer HealthCare

Handling Editor: Pantep Angchaisuksiri

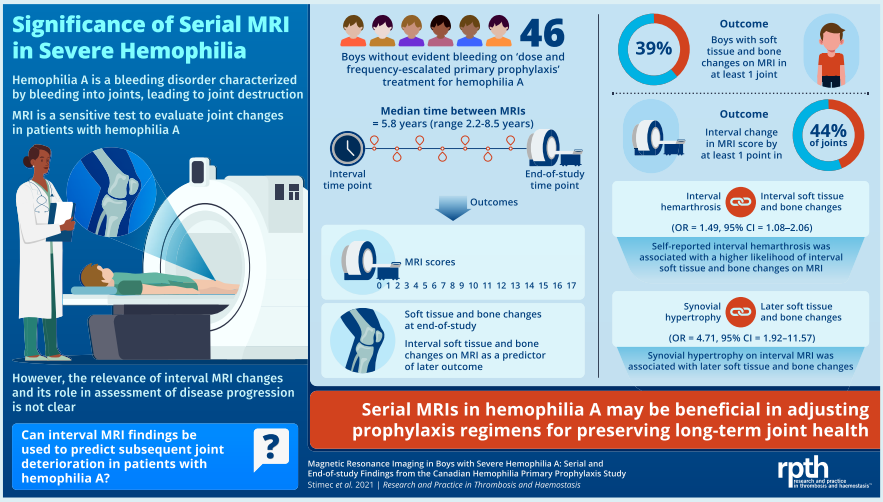
Abstract

Background: This study examined the structural outcomes for joints of boys with severe hemophilia A receiving frequency/dose-escalated primary prophylaxis using magnetic resonance imaging (MRI), and the importance of interval MRI changes.

Methods: Forty-six subjects (27 with interval studies) were evaluated by radiographs (X-rays) and mid- and end-of-study MRIs (using the International Prophylaxis Study Group scale), as part of the Canadian Hemophilia Prophylaxis Study. The primary outcome was the presence of MRI osteochondral findings.

Results: The median (range) time on study at the end-of-study MRI examination was 9.6 (4.8–16.0) years, during which 18 of 46 subjects (39%) had osteochondral changes in at least one joint. An interval change in MRI score of at least 1 point was observed in 44% of joints (43 ankles, 21 elbows, 4 knees); at least one joint showed this change in all 27 subjects. Self-reported interval hemarthrosis was associated with a higher likelihood of interval osteochondral change (odds ratio [OR], 1.49; 95% confidence interval [CI] = 1.08–2.06). Presence of synovial hypertrophy or hemosiderin on interval MRIs was associated with an OR of 4.71 (95% CI, 1.92–11.57) and 5.25 (95% CI, 2.05–13.40) of later osteochondral changes on MRI.

Discussion: MRI changes were seen in 39% of subjects. Interval index joint bleeding was associated with an increased risk of later MRI changes, and earlier soft-tissue changes were associated with subsequent osteochondral changes.



KEYWORDS
hemophilia, magnetic resonance imaging, musculoskeletal system, prophylaxis, X-rays

Essentials

- The relevance of changes on magnetic resonance imaging (MRI) in severe hemophilia A is unclear.
- Imaging studies from the Canadian Hemophilia Primary Prophylaxis Study were assessed.
- Joint bleeding was associated with an increased risk of changes in the end-of-study MRIs.
- Soft-tissue changes on MRI were associated with a higher risk of later osteochondral findings.

1 | INTRODUCTION

Hemophilia A is characterized by a deficiency of clotting factor (F) VIII. The hallmark of this lifelong bleeding disorder, especially in people with moderate/severe hemophilia, is recurrent bleeding into index joints (ankles, knees and elbows) that may lead to progressive, irreversible joint destruction (arthropathy), impaired health-related quality of life, and the requirement of more intensive treatment.[1] This intra-articular bleeding can precipitate a biological cascade with adverse effects that may persist despite the clearance of blood from the joint.[2]

Primary prophylaxis is the preventive administration of clotting factor on a regular basis, before the onset of joint damage in people with hemophilia.[3] Primary prophylaxis is recommended as the standard of care for the treatment of boys with moderate/severe hemophilia and a severe bleeding phenotype by the World Federation of Hemophilia (WFH), with initiation ideally before age 3 years.[4]

Dose- and frequency-escalated primary prophylaxis is an escalation regimen in which young boys with moderate/severe hemophilia A initially receive weekly intravenous factor VIII (FVIII) infusions, with an increase in dose/infusion frequency based on clinically significant breakthrough bleeding into joints.[5-7] This management approach is less costly than standard full-dose primary prophylaxis which, for hemophilia A, involves intravenous infusion of a standard half-life FVIII concentrate, ideally on alternate days, a minimum of 3 times per week.[8] Dose/frequency-escalation programs, such as the Dutch intermediate prophylaxis regimen, aim to reduce the number of intravenous FVIII infusions at a young age, when vascular access can be very difficult.[7]

Evaluation of joint structure and function on any prophylaxis regimen is essential to determine its effectiveness. Magnetic resonance imaging (MRI) is the most sensitive imaging test because of its capacity to detect both early soft-tissue changes and osteochondral abnormalities.[9,10]

Most reports of long-term imaging studies compare cross-sectional joint outcomes, often comparing various joint measures, such as physical examination and/or measures of joint function, with MRI. As a result, the clinical relevance of joint changes on MRI is still not fully understood, but it is considered the gold standard, as it is the best tool available to assess early soft-tissue and osteochondral abnormalities.[11] Few studies have reported interval disease progression with serial MRI over a prolonged time interval or the potential of specific MRI findings to predict subsequent joint progression.

This study describes end-of-study and interval MRI changes in boys enrolled in the dose- and frequency-escalated Canadian Hemophilia Prophylaxis Study (CHPS), and assesses whether specific MRI findings and self-reported joint bleeding episodes may be predictive of subsequent joint deterioration.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

CHPS was a longitudinal, single-arm study with 11 participating hemophilia treatment centers (HTCs) located across Canada. Boys with severe hemophilia A, between the ages of 1 and 2.5 years, were consecutively enrolled over a 10-year period from 1997 to 2007. Data were collected until December 31, 2012, or the end-of-study MRI assessments, whichever was later.

Detailed descriptions of the study design have been previously published.[5,6] In brief, boys were eligible for enrollment in the study if they had normal index joints (ankles, knees, and elbows) as determined by plain radiography and joint assessment based on physical examination. Exclusion criteria included a history of three or more bleeds into any index joint, present or past history of a circulating inhibitor to FVIII (level ≥0.6 BU), and competing risk factors such as hepatitis C.

The study was approved by the research ethics boards at all participating sites. Parents or guardians gave written informed consent.

2.2 | Procedures

Participants attended study visits every 3 months for the first 5 years, and thereafter every 6 months. All boys were treated with dose- and frequency-escalated primary prophylaxis according to an a priori approved protocol based on bleeding criteria,[5,6] using standard half-life recombinant FVIII. The prophylaxis regimen started with once weekly infusions of 50 IU/kg of FVIII (step 1), and escalated to twice weekly infusions of 30 IU/kg of FVIII (step 2) and three times/week or alternate-day infusions of 25 IU/kg of FVIII (step 3).

Bleeding and treatments were recorded by parents, guardians, or the participants themselves, in diaries and confirmed by study personnel at each study visit.

2.3 | Imaging acquisition

Standard joint view radiographs (X-rays) and MRI studies of the six index joints were planned at two time points during the study: ages 6 and 12 years (±2 years), referred to as interval and end-of-study time points, respectively. Due to constraints on access to research MRI machines, several subjects were unable to have their imaging studies within this period; a number of images were acquired outside of the planned window. This also accounted for some missing data at both time points. To minimize this, some participants were flown to the central site (The Hospital for Sick Children, Toronto) for MRI studies when possible. Repeat X-rays were not required if participants had clinical X-rays within the previous 3 years.

MRI acquisition was performed on 1.5 T MRI scanners in all participating HTCs and included T2* gradient echo images (repetition time, 600 milliseconds; echo time, 20 ms; flip angle, 20°; bandwidth, 15.63; matrix, 256×192; number of excitations, 2; average field-of-view, 12 cm [to be adjusted according to the subject's joint size; slice thickness, 4 mm; gap, 0 mm]). The acquisition included coronal and sagittal planes for ankles and knees and axial, sagittal, and coronal planes for elbows. No contrast material was used, except for one subject who had intravenous administration of gadolinium for another clinical indication. Elbows were imaged separately with surface coils; both knees and both ankles were imaged simultaneously with extremity or head coils, respectively, according to joint size. The images from all participating HTCs were collected in a TeraRecon database at the coordinating center.

2.4 | Image interpretation

Plain X-rays were scored using the Pettersson score (range, 0-13 per index joint where 0 represents no evident joint damage and 13 the maximum possible score).[12] MRIs were scored using the International Prophylaxis Study Group (IPSG) MRI score, a scale that allocates 9 points for the soft-tissue domain (effusion/hemarthrosis, synovial hypertrophy, and hemosiderin) and 8 points for the osteochondral domain (surface erosions, subchondral cysts, and cartilage degradation). A score of 0 represents no joint changes and 17 the maximum possible score for an individual index joint.[13]

X-rays and MRIs were independently read by two experienced radiologists with >10 and 20 years of experience (JS and PB), blinded to subject identity and clinical data, and unblinded to the order of the MRI examinations—as previously recommended for paired readings in chronologic order.[14] A tutorial calibration session between the readers was conducted before the individual review of the MRI examinations.[14] Discrepant readings were discussed and both radiologists agreed upon a consensus score.

2.5 | Clinical information

Descriptive clinical information included the number and location of index joint hemorrhages, before study entry and up to the time of the MRI examination, age at study entry, the number of days on study, and age at time of the MRI studies.

2.6 | Outcome measures and statistical analysis

The primary outcome measure for this study was evidence of end-of-study osteochondral changes on MRI. Secondary outcomes for this analysis were evidence of index-joint bleeds on MRI, and the predictive ability of bleeding and interval MRI findings on subsequent joint deterioration.

The association between the number of prior lifetime index joint bleeds and clinical information (age at time of MRI, age at start of prophylaxis) was investigated with Spearman correlation coefficients (r_s), with random intercepts for subjects to account for within-subject clustering. Strength of the correlations were interpreted according to the following definitions: ≤0.40 indicated poor, >0.40 to ≤0.6 moderate, >0.60 to ≤0.80 strong, and >0.80 excellent agreement/correlation.[15]

Descriptive statistics were used (median, interquartile range, and range of values) to characterize the outcome measures at each time point.

The relationships between bleeding and change in MRI scores (i.e., the difference in score between the interval and end-of-study MRI), and interval MRI scores and end-of-study MRI and Pettersson scores were determined using a generalized linear mixed model with random intercepts for subjects to account for within-subject clustering. Results are expressed as odds ratios and 95% confidence intervals were estimated using standard errors.

The interreader reliability of interpretation of the IPSG MRI scale in this study was tested using intraclass correlation coefficients (ICCs).[16,17] ICC and $r \leq 0.40$ indicated poor, >0.40 and ≤0.60 moderate, >0.60 and ≤0.80 substantial, and >0.80 excellent agreement/correlation.[15,17]

Unlike in previous reports,[6] for those subjects who enrolled in the study toward the end of the recruitment period and thus had only one imaging study, we considered that their end-of-study imaging, regardless of their age. This resulted in some subjects being outside the a priori defined age range for their end-of-study imaging assessments.

We conducted intent-to-treat analyses, which included all available data, including participants who were lost to follow-up. We censored subjects at withdrawal and lost to follow-up. All analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).[18]

3 | RESULTS

3.1 | Subjects

Fifty-six boys with severe hemophilia A were followed in CHPS for a median of 10.2 (range, 0.2-16.1) years; 6 subjects were lost to follow-up (including the subject followed for 0.2 years). Forty-six of the 50 (92%) remaining subjects, followed for a median of 9.6 years (range, 4.8-16 years) had end-of-study MRI assessments. A few subjects had one or more missing joint examinations due to time constraints or personal preference, yielding a total of 89 ankles, 90 elbows, and 91 knees for analysis, representing 98% of potentially available joints. The median biologic age of the 46 boys at the time of the end-of-study imaging assessments was 11.4 years (range, 6.2-18.5 years). A timeline of study events is shown in Figure 1. Twenty-seven of the 46 subjects (59%) had interval and end-of-study MRIs. Clinical characteristics of the study cohort are presented in Table 1. Of the subjects who had at least one MRI, at the end of study, 2 of 46 (4%) remained on treatment step 1, 17 of 46 (37%) had escalated to step

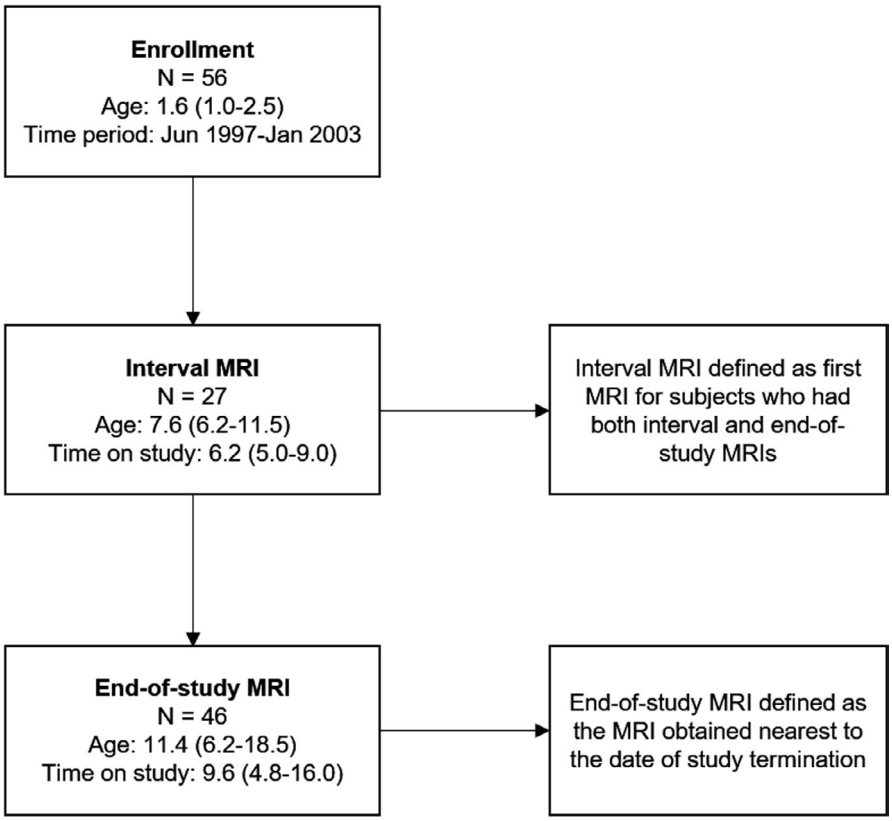


FIGURE 1 Flow diagram of key study events: enrollment, interval magnetic resonance imaging (MRI), and end-of-study MRI. Each milestone includes the number of patients (N), and their median (range) age and time on study in years. The time period over which enrollment occurred is also indicated

TABLE 1 Clinical characteristics of study subjects with end-of-study MRI examinations (n = 46) showing a breakdown of the number of joints evaluated that had either 0 or at least 1 reported joint bleed at the time of the MRI and a summary of the lifetime number of reported index joint bleeds

	Lifetime number of joints with bleeds at end-of-study MRI		
	0 bleeds	≥1 bleed(s)	
Joint	Per joint (%)*	Per joint (%)*	Lifetime number of joint bleeds at end-of-study MRI, median (range of values)
Ankles	28/89 (31)	61/89 (69)	2 (1–17)
Elbows	49/90 (54)	41/90 (46)	1 (1–46)
Knees	40/91 (44)	51/91 (56)	2 (1–12)
Total (all joints)	117/270 (43)	153/270 (57)	2 (1–46)

*Number of cases/total number of joints evaluated.

Abbreviation: MRI, magnetic resonance imaging.

2, and 27 of 46 (59%) had escalated to step 3. During the first 5 years of the study, there were 53 factor adjustments in 36 subjects, with 18 adjustments occurring in the last 5 years of the study. In the time between the interval and end-of-study MRI, 11 of 27 (41%) of subjects had dosing adjustments, including four from step 1 to step 2, one from step 1 to step 3, and six from step 2 to step 3.

3.2 | End-of-study findings

Of the 46 subjects who completed the end-of-study MRI, 25 (54%) had detectable soft-tissue changes in at least one index joint, indicated by a score on the IPSG 17-point MRI scale of >0 in at least one item in the soft-tissue domain (Table 2). Soft tissue changes were detected in the ankles of 18 (39%) subjects, in the elbows of 14 (30%) subjects, and in the knees of 4 (9%) subjects. Of the 25 subjects with soft-tissue findings, 17 (68%) had evidence of soft-tissue changes in more than one joint. Synovial hypertrophy and hemosiderin deposition were noted in 25 of 46 (54%) of subjects, with effusion or hemarthrosis seen in 6 of 46 (13%).

Of the 46 subjects who completed the end-of-study MRI, 18 (39%) had detectable osteochondral changes in at least one index joint, indicated by a score on the IPSG 17-point MRI scale of >0 in at least one item in the osteochondral domain (Table 3). Osteochondral changes were detected in the ankles of 10 (22%) subjects, in the elbows of 10 (22%) subjects, and in the knees of 2 (4%) subjects. Of the 18 subjects with osteochondral changes, 8 (44%) had evidence of changes in more than one joint, for a total of 26 joints

TABLE 2 End-of-study frequency of soft-tissue findings per subject detected by MRI assessed with the International Prophylaxis Study Group 17-point MRI scale

Types of MRI findings					
			Number of affected joints: n (%)		
			Ankles	Elbows	Knees
Soft-tissue domain item	Severity	Number of affected individuals (n = 46)* n (%)	(n = 89)+ n (%)	(n = 90)+ n (%)	(n = 91)+ n (%)
Effusion/hemarthrosis	Any effusion/hemarthrosis	6 (13)			
	Mild		3 (3)	3 (3)	3 (3)
	Moderate		0 (0)	0 (0)	0 (0)
	Severe		0 (0)	0 (0)	0 (0)
Synovial hypertrophy	Any synovial hypertrophy	25 (54)			
	Mild		18 (20)	12 (13)	1 (1)
	Moderate		6 (7)	5 (6)	2 (2)
	Severe		3 (3)	4 (4)	0 (0)
Hemosiderin	Any hemosiderin	25 (54)			
	Mild		17 (19)	12 (13)	1 (1)
	Moderate		7 (8)	5 (6)	2 (2)
	Severe		3 (3)	4 (4)	0 (0)

Abbreviation: MRI, magnetic resonance imaging.

*Number of individuals studied.

+Number of joints studied.

with osteochondral changes. Surface erosions were seen in 14 of 46 (30%) subjects, subchondral cysts in 10 of 46 (22%) and cartilage loss in 18 of 46 (39%). Of the 26 joints with osteochondral changes, there was no reported prior hemarthrosis in 3 (12%).

At the end of study X-rays, osteochondral changes (Pettersson score >0) were present in 24/259 (9.3%) joints in 17/46 (37%) subjects. Twenty (83.3%) of the 24 joints also had corresponding osteochondral changes in MRI; the remaining 4 of 24 (16.7%) did not. Conversely, of the 26 joints with MRI osteochondral changes, 6 (23.1%) did not have damage on X-rays. The median (range) end-of-study Pettersson score for all index joints was 0 (0-10 for ankles, 0-9 for elbows, and 0-5 for knees). There was an excellent correlation between the Pettersson scores and the osteochondral subscores of the IPSG MRI scale ($r = 0.91$; $P < .0001$).

3.3 | MRI and bleeds

The MRI scores and Pettersson scores are compared with the total number of reported index joint bleeds in Figure 2A-C. Some joints had abnormal MRI/X-ray scores without reported bleeds, while other joints had normal MRI/X-ray scores despite many reported bleeds. Osteochondral MRI subscores, total MRI scores, and Pettersson scores had a moderate correlation with the number of reported index joint bleeds in the elbows ($r = 0.48$, $P < .0001$; $r = 0.49$, $P < .0001$; and $r = 0.53$, $P < .0001$, respectively). In ankles, weak correlations were noted between total number of study joint bleeding episodes and osteochondral MRI subscores, total MRI scores, and Pettersson scores ($r = 0.30$, $P = .003$; $r = 0.34$, $P = .001$; and $r = 0.25$, $P = .01$, respectively). The knees did not show a correlation between osteochondral changes, total MRI scores or Pettersson scores and bleeding episodes.

3.4 | Serial imaging findings

The median (range) time between the interval and end-of-study MRI for the 27 subjects with serial images was 5.8 (2.2-8.5) years.

A change in the MRI score between the two sets of imaging studies of at least 1 point was observed in 68 of 154 (44%) of index joints. Table 4 shows a breakdown of MRI items according to stability, improvement, or worsening over time. Of note, worsening of osteochondral subscores (cartilage thickness, surface erosions, and subchondral cysts) was detected in 16 index joints (7 elbows and 9 ankles in 13 subjects) with improvement in 4 index joints (4 ankles in 4 subjects); comparable figures for soft-tissue changes (effusion/hemarthrosis, synovial hypertrophy, and hemosiderin) were worsening in 25 joints (8 elbows and 17 ankles in 16 subjects) and improvement in 39 joints (13 elbows and 26 ankles in 21 subjects). Examples of subjects with serial deterioration and improvement on MRI are shown in Figures 3 and 4, respectively.

Twenty subjects had X-rays at both the interval and end-of-study time points. Compared to the interval X-ray, 8 of 40 (20%) of ankles and 7 of 39 (18%) of elbows in 10 of 20 (50%) subjects showed

TABLE 3 End-of-study frequency of osteochondral changes per subject detected by MRI assessed with the International Prophylaxis Study Group 17-point MRI scale

Types of MRI findings					
		Number of affected individuals (n = 46)* n (%)	Number of affected joints: n (%)		
			Ankles (n = 89)+ n (%)	Elbows (n = 90)+ n (%)	Knees (n = 91)+ n (%)
Osteochondral domain item	Sub-item				
Subchondral bone or joint margins, n (%)	Any surface erosion	14 (30)	8 (9)	9 (10)	1 (1)
	Half or more of the articular surface eroded in at least one bone	1 (2)	0 (0)	1 (1)	0 (0)
	At least one subchondral cyst	10 (22)	6 (7)	6 (7)	1 (1)
	Subchondral cysts in at least two bones, or cystic changes involving a third or more of the articular surface in at least one bone	5 (11)	2 (2)	4 (4)	0 (0)
Cartilage loss, n (%)	Any loss of joint cartilage height	18 (39)	11 (12)	12 (13)	2 (2)
	Loss of half or more of the total volume of joint cartilage in at least one bone	5 (11)	3 (3)	2 (2)	1 (1)
	Full-thickness loss of joint cartilage in at least some area of at least one bone	8 (17)	4 (4)	6 (7)	0 (0)
	Full-thickness loss of joint cartilage including at least one half of the joint surface in at least one bone	2 (4)	0 (0)	2 (2)	0 (0)

Abbreviation: MRI, magnetic resonance imaging.

*Number of individuals studied.

+Number of joints studied.

deterioration, indicated by an increase in Pettersson score of at least 1 point, while 2 of 40 (5%) of ankles and 3 of 39 (8%) of elbows in 5 of 20 (25%) subjects showed a decrease in score (i.e., improvement) of at least 1 point. There were no serial changes seen in the knees, where all scores remained at 0 at both the interval and end-of-study time points.

Self-reported joint bleeding between the MRI studies was associated with an almost 50% increase in the odds of a joint getting worse, after adjusting for time between the imaging studies (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.08-2.06).

Scores for synovial hypertrophy and hemosiderin present on the interval MRI were associated with an increase in the odds of a joint having osteochondral damage detected by X-ray (OR, 4.71; 95% CI, 1.92-11.57; and OR, 5.25; 95% CI, 2.05-13.40, respectively) and by MRI (OR, 4.87; 95% CI, 2.31-10.26; and OR, 6.31; 95% CI, 3.00-15.58). Having a total score >0 on the interval MRI was associated with about an 80% increase in the odds of having a Pettersson score >0 at the end-of-study X-ray (OR, 1.82; 95% CI, 1.36-2.45) and about a 90% increase in the odds of having an MRI osteochondral score of >0 on the end-of-study MRI (OR, 1.88; 95% CI, 1.40-2.56).

3.5 | Reliability of interpretation of MRI scores

The overall interreader reliability of the 17-point IPSG scale was excellent (ICC, 0.98; 95% CI, 0.97-0.98).

4 | DISCUSSION

This long-term primary prophylaxis study in boys with severe hemophilia A highlights the predictive value of soft-tissue changes in index joints (synovial hypertrophy and presence of hemosiderin) detected by MRI, and self-reported bleeding episodes for the development of subsequent osteochondral changes. Also of note was the variability in imaging findings in the ankles and elbows, with some showing disease progression and others improvement over a median interval period of 5.8 years.

In this study, we noted differences in the correlations of the different index joints to the total MRI scores, osteochondral subscores, and the plain X-ray Pettersson scores. Though it is unclear why, these differences may reflect variations in injury or cartilage maturation in a cohort of growing boys, since it is well known that cartilage thickness decreases as boys grow older, and interpretation of such physiologic changes is hampered by lack of normative data.[19] Differences in the way biomechanical forces are distributed within and between index joints could also play a contributory role. More research is needed to fully elucidate these and potentially other unknown factors.

Over the past two decades, many studies, summarized in Table 5, have been published using MRI for the assessment of joint structures in people with hemophilia with wide variations in arthropathy. The wide variability in findings likely reflects many factors, including the age at which prophylaxis is initiated, the intensity of prophylaxis, adherence to the prescribed prophylaxis regimen, and physical

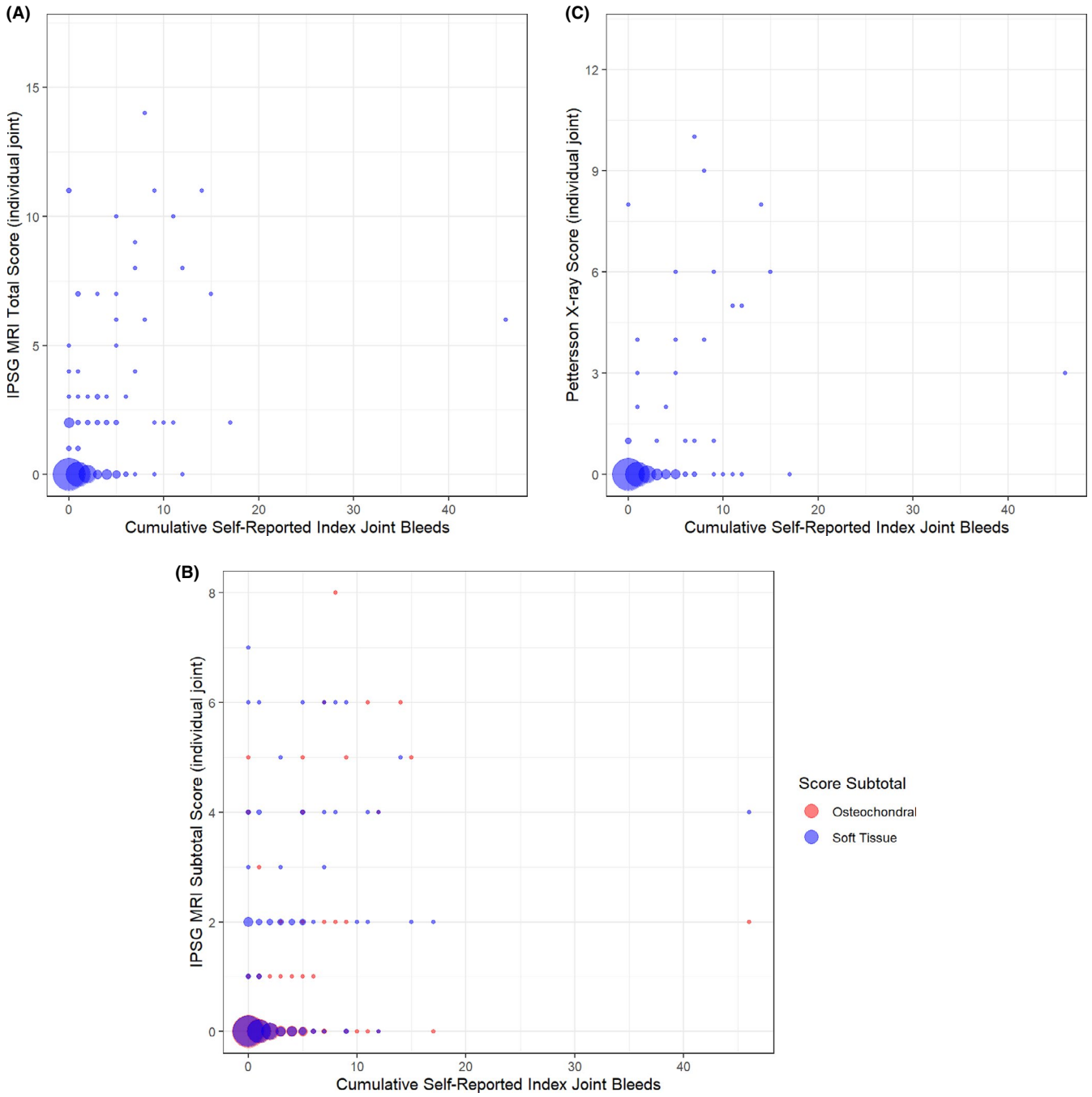


FIGURE 2 (A) Descriptive summary of the end-of-study International Prophylaxis Study Group (IPSG) 17-point magnetic resonance imaging (MRI) total score, out of a possible 17 points, for individual index joints according to the number of self-reported index joint bleeds. (B) Descriptive summary of the end-of-study IPSG 17-point MRI soft-tissue and osteochondral subtotal scores, out of a possible 9 and 8 points, respectively, for individual index joints according to the number of self-reported index joint bleeds. (C) Descriptive summary of the end-of-study X-ray Pettersson scores for individual index joints according to the number of self-reported joint bleeds. The size of each circle corresponds to the number of cases, with the larger circles representing more than one joint. The largest number of index joints had no self-reported joint bleeds and an MRI or X-ray score of 0

activity profiles. The imaging modalities and protocols used in the studies summarized in Table 5 also likely play a significant factor. For example, 3 T MRI units are able to achieve higher signal and shorter acquisition time periods, especially when performed with parallel imaging.[10]

The dose/frequency-escalated prophylaxis regimen reported in the CHPS cohort was initiated with the aim of achieving good joint outcomes while reducing the burden of frequent intravenous administration of clotting factor concentrates in young boys with severe hemophilia. Use of prophylaxis, regardless of whether dose/frequency-escalated (as in the current study),[6] or fixed weight-based full-dose regimens (eg, the "Malmo" regimen) reduces but does not fully eliminate joint bleeding, nor does it preclude the development of long-term joint damage in all individuals.[20,21] There were likely

TABLE 4 Summary of interval changes in the17-point MRI scores for the subset of subjects with serial MRIs between mid- and end-of-study images

	Improved		Worsened		No change	
(A)	Left (N = 26) n (%)	Right (N = 27) n (%)	Left (N = 26) n (%)	Right (N = 27) n (%)	Left (N = 26) n (%)	Right (N = 27) n (%)
Effusion hemarthrosis	4 (15.4)	7 (25.9)	1 (3.8)	1 (3.8)	21 (80.8)	19 (70.4)
Synovial hypertrophy	5 (19.2)	5 (18.5)	10 (38.5)	7 (25.9)	11 (42.3)	15 (55.6)
Hemosiderin	12 (46.2)	10 (37.0)	7 (26.9)	5 (19.2)	7 (26.9)	12 (44.4)
Soft-tissue subtotal	13 (50.0)	13 (48.1)	10 (38.5)	7 (25.9)	3 (11.5)	7 (25.9)
Surface erosions	0	2 (7.4)	3 (11.5)	1 (3.8)	23 (88.5)	24 (88.9)
Subchondral cysts	1 (3.8)	2 (7.4)	3 (11.5)	1 (3.8)	22 (84.6)	24 (88.9)
Cartilage degradation	1 (3.8)	3 (11.1)	5 (19.2)	3 (11.5)	20 (76.9)	21 (77.8)
Osteochondral subtotal	1 (3.8)	3 (11.1)	5 (19.2)	4 (15.4)	20 (76.9)	20 (74.1)
Total score	11 (42.3)	13 (48.1)	11 (42.3)	8 (29.6)	4 (15.4)	6 (22.2)
	Improved		**Worsened**		**No change**	
(B)	**Left (N = 25)**	**Right (N = 26)**	**Left (N = 25)**	**Right (N = 26)**	**Left (N = 25)**	**Right (N = 26)**
Effusion hemarthrosis	4 (16.0)	1 (3.8)	2 (8.0)	0	19 (76.0)	25 (96.2)
Synovial hypertrophy	1 (4.0)	1 (3.8)	3 (12.0)	5 (19.2)	21 (84.0)	20 (76.9)
Hemosiderin	6 (24.0)	3 (11.5)	3 (12.0)	4 (15.4)	16 (64.0)	19 (73.1)
Soft tissue subtotal	9 (36.0)	4 (15.4)	3 (12.0)	5 (19.2)	13 (52.0)	17 (65.4)
Surface erosions	0	0	4 (16.0)	3 (11.5)	21 (84.0)	23 (88.5)
Subchondral cysts	0	1 (3.8)	3 (12.0)	1 (3.8)	22 (88.0)	24 (92.3)
Cartilage degradation	0	0	4 (16.0)	2 (7.7)	21 (84.0)	24 (92.3)
Osteochondral subtotal	0	0	5 (20.0)	2 (7.7)	20 (80.0)	24 (92.3)
Total score	7 (28.0)	3 (11.5)	5 (20.0)	6 (23.1)	13 (52.0)	17 (65.4)

Note: Panel A shows ankles (left = 26, right = 27) and panel B shows elbows (left = 25, right = 26). Knees (left = 25, right = 25) showed no changes.
Abbreviation: MRI, magnetic resonance imaging.

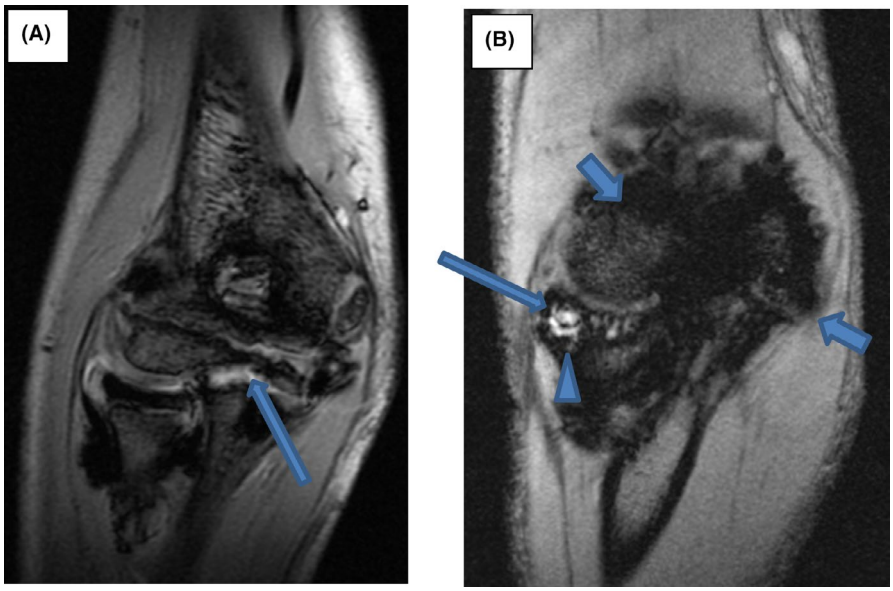


FIGURE 3 Serial deterioration of a right elbow over 7 years on study. (A) Coronal multiplanar gradient-recalled (MPGR) image through the right elbow at baseline demonstrating hyaline cartilage thinning and fissuring. Subject was 10 years of age with 7 reported right elbow bleeds at the time of the first magnetic resonance imaging (MRI). (B) Coronal MPGR image through right elbow at follow-up demonstrating progressive osteochondral changes including diffuse cartilage loss at the radiocapitellar joint (long arrow) and new surface erosions and subchondral cyst (arrowhead). Increased hemosiderin deposition is also present (short arrows). Subject was 17 years old with one additional reported bleed (eight total) into the right elbow at the time of the follow-up imaging

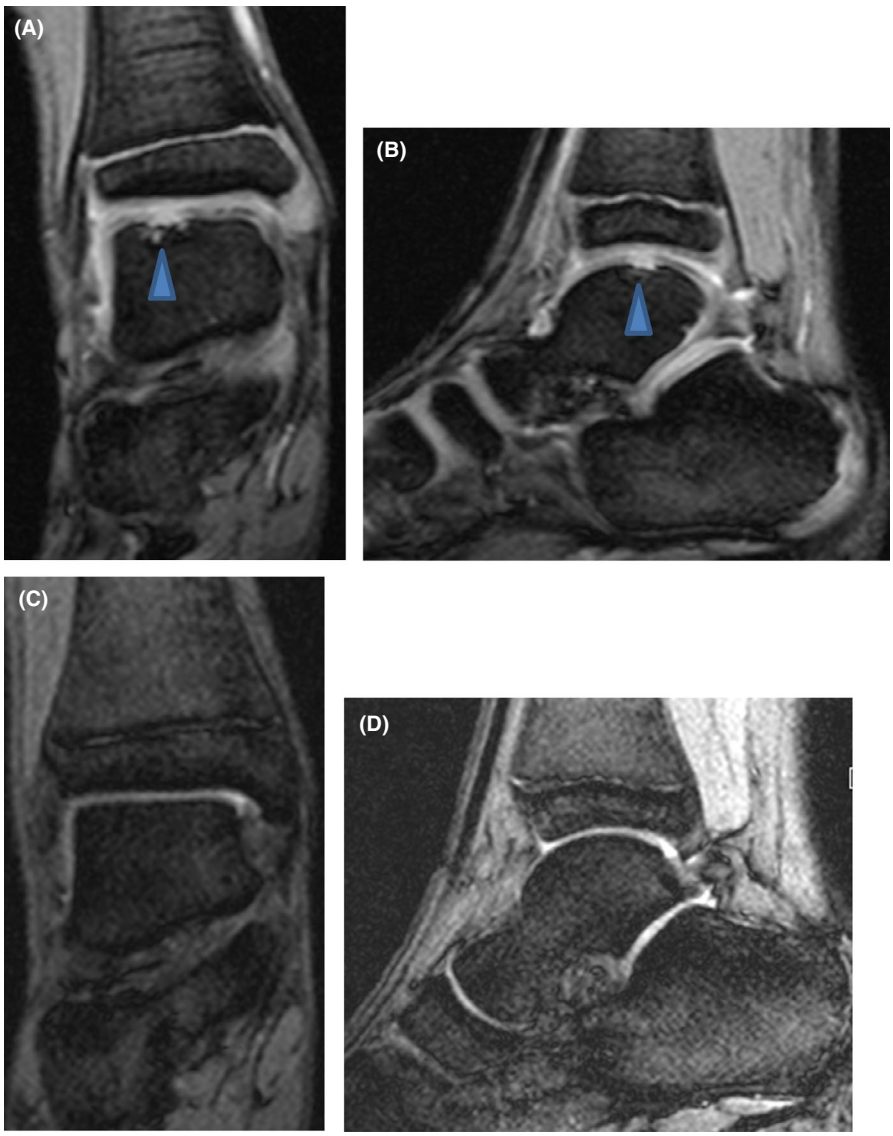


FIGURE 4 Serial improvement of a right ankle over 8 years on study. Coronal (A) and sagittal (B) multiplanar gradient-recalled (MPGR) images through the right ankle at baseline demonstrating focal osteochondral damage with subchondral cyst formation. Subject was 8.5 years old with two reported joint bleeds at the time of imaging. Coronal (C) and sagittal (D) MPGR images through the right ankle at follow-up with complete resolution of previous osteochondral changes. Subject was 16.5 years old with two additional reported bleeds (four total) at the time of follow-up imaging

multiple reasons for failure in the present study, including, in some subjects, nonadherence to the prescribed prophylaxis regimen,[22] unfavorable pharmacokinetics of FVIII clearance, and differing levels of physical activity. Of note, two subjects, on study for 14.1 and 10 years respectively, remained on once-weekly prophylaxis. However, several subjects had adjustments to their prophylactic factor dosages occurring in the period between the mid- and end-of-study MRI, meaning that a significant number of clinically overt bleeds were still occurring. These finding support the need for individualized prophylaxis regimens guided by serial physical examination and imaging findings, rather than sole reliance on reported bleeding episodes for guidance regarding modifications to preventive prophylaxis regimens in boys with moderate/severe hemophilia and a severe bleeding phenotype, as is currently recommended by the WFH.[4]

The interpretation of radiological findings is not always straightforward in people with hemophilia, as findings may potentially represent anatomic variants or nonhemophilic joint disease or result from traumatic injuries.[23,24] However, as observed in this study, even in the absence of reported bleeding events, many boys with hemophilia on prophylaxis have clinically significant findings on MRI.[21,25-27] Conversely, the opposite is also possible, given that a number of MRIs in our study and previous studies[21,26] showed no evident articular changes despite a significant number of self-reported joint bleeds.

It is still unclear whether normal joint morphology on conventional MRI is indicative of no joint damage. Zhang and colleagues used quantitative evaluation of articular cartilage with T2 mapping and demonstrated in preliminary work in 15 subjects that T2 mapping can reveal focally increased T2 values despite normal appearance on conventional MRI.[28] While T2 mapping may be a tool to further understand the functional status of cartilage in children/adolescents with hemophilic arthropathy, longer-term assessment of the clinical significance of these findings is needed.

Osteochondral changes in hemophilia are generally thought of as progressive; however, our results show that there is a small proportion of subjects who do show improvement in osteochondral scores over time, visible on both MRI and X-ray, supportive of previous findings.[29] More in-depth assessment of the significance of these results

TABLE 5 Comparative prophylaxis studies that included serial MRIs in people with hemophilia

Author (Ref)	Cohort description	Subject age at baseline, y	Treatment offered	Bleeding rate	Time between serial MRIs	Joint health measurements and MRI scale used
Manco-Johnson 2007[21] (Joint Outcomes Study [JOS])	32 boys with severe hemophilia A <2.5 years	Mean 1.6	Full-dose primary prophylaxis	Median AJBR 0.2 (mean 0.63 ± 1.35)	Approximately 4.5 years (MRI at enrollment and age 6)	7% with joint changes detected by MRI (Denver scale) and 4% by radiography
Pergantou 2010[31]	24 boys with severe (n = 18) and moderate (n = 6) hemophilia (A:22, B:2)	10.5 ± 3.6	16 boys on secondary prophylaxis; after first assessment, prophylaxis intensified in 11 boys and initiated in 4	Mean AJBR at time 0: 2.0 ± 1.8 and time 1: 0.7 ± 1.8 ($P < .01$)	3.8 ± 1.4 years	MRI assessed using modified Denver scale; 34% of joints showed deterioration on serial MRI while 16.5% showed improvement
Gringeri 2011 (ESPRIT study)[32]	21 boys with severe hemophilia A	Mean ± SD 4.1 ± 2.2	Primary prophylaxis	11/21 (52%) subjects with mean AJBR < 1	Unclear, radiographs planned at enrollment, every 2.5 years and at end of follow-up	Radiographic evidence for arthropathy in 29% of boys (median Pettersson score, 5; range, 3–14)
Olivieri 2012[26]	38 MRIs in 26 subjects with hemophilia A or B; prophylaxis started at mean age of 4 y in 23 subjects	Evaluated between 27–35	Prophylactic treatment initiated at mean age of 4 y (range, 1-15 y)	Median AJBR, 0.4 (0–1.4)	Median follow-up, 9 y	4 point MRI scale (0 = normal), 5 asymptomatic ankles at baseline got worse on MRI with no clinical impairment
Manco-Johnson 2013[33] (SPINART)	42 men with severe hemophilia A	Median (range) 29 (15-50)	Prophylaxis	Median (IQR) AJBR, 0.3 (0-1.2) Mean, 1.9; SD, 4.1	3 y	45-point extended MRI scale; baseline mean (SD) score of 19.14 (9.81) with mean (SD) deterioration at 3 y of 0.75 (1.59)
Oldenburg 2015[34]	25 subjects who started primary prophylaxis at age <2 y	MRI completed at age 12-35 y	Full-dose primary prophylaxis	Median (range) AJBR in previous 5 y by current age: – 12–16: 0.3 (0–1.4) – 17–21: 0.1 (0-0.6) – 22-26: 0.4 (0-1.4) – 27–35: 0.2 (0-0.4)	Between 12 and 35 y (based on age of subject at time of MRI)	Compatible additive MRI scale; in primary prophylaxis group, median maximal ankle score was 0 (range, 0–9) in subjects between ages of 12 and 35; 76% of subjects in this group had no pathologic findings on MRI; ankles had more progressive disease than other joints (i.e., elbows and knees)
Warren 2018[27] (Joint Outcomes Study Continuation, JOS-C)	37 young adults with severe hemophilia A from the JOS (18 from prophylaxis group and 19 from on demand group)	Follow-up at age 18	Early prophylaxis (started prophylaxis before 30 mo); late prophylaxis (started prophylaxis at mean age of 7.5 y)	Not reported	≈12 y (age 6 in JOS and age 18 in JOS-C)	Scored using extended MRI scale (eMRI). Relative risk of osteochondral changes in those on delayed prophylaxis vs. early prophylaxis was 6.5 (95% CI, 1.3-33.6; $P = .03$)

(Continues)

TABLE 5 (Continued)

Author (Ref)	Cohort description	Subject age at baseline, y	Treatment offered	Bleeding rate	Time between serial MRIs	Joint health measurements and MRI scale used
Foppen 2020[11]	26 young adults with hemophilia (16 severe, 8 moderate)	Median (range) 21 (12-29) y	Prophylaxis in 15/16 subjects with severe hemophilia (median weekly dose 38 IU/kg)	Baseline median AJBR 0.5 (IQR 0.2–1.2)	MRI at baseline, follow up X-ray at median 5.1 (IQR, 4.6-5.6) y	MRI scored using IPSG 17-point scale, X-ray scored using Pettersson scale; synovial hypertrophy (OR, 24.7; 95% CI, 3.7-163.3) and osteochondral changes (OR, 78.0; 95% CI, 8.6-705.7) on MRI were associated with radiographic progression
CHPS Imaging Analysis (current study)	56 boys with severe hemophilia A <2.5 y; 27 with serial MRI	Median (range) age at enrollment 1.6 (1.0-2.5)	Tailored, frequency-escalated prophylaxis	Median AJBR 0.95 (0-13.3)	Initial MRI at 5 y, median (range) time between MRIs 5.8 (2.2-8.5) y	Worsening of 17-point IPSG MRI scale in 38% of ankles and 22% of elbows with serial MRI

Note: In studies with multiple treatment arms, only the results from the prophylaxis group(s) are presented.

Abbreviations: AJBR, annualized joint bleeding rate; CI, confidence interval; IPSG, International Prophylaxis Study Group; IQR, interquartile range; MRI, magnetic resonance imaging; OR, odds ratio; SD, standard deviation.

is required, as it remains unclear if these findings represent true reversal of bleed-related osteochondral changes or reflect physiologic changes associated with growth, or even potential variations in the joint structures unrelated to hemophilia.

Our study has the following strengths: its prospective nature, early start of primary prophylaxis, number of subjects and participating pediatric hemophilia treatment centers, length of continuous follow-up, and centralized reading by two experienced musculoskeletal radiologists.

Our results have some potential limitations. In general, there is a lack of a reference standard (eg, arthroscopy, which would not be ethical to perform in this population) to confirm the presence of MRI findings. However, our results corroborate previous findings and provide further support for the importance of early findings on MRI for individual management of boys with severe hemophilia.[11]

The CHPS study population had very good joint outcomes over the course of the study period; therefore, there were a limited number of joints with abnormal findings. Further, the use of binomial modeling necessitated several variables being classified as absent or present, which reduced the available information on the strength of the associations.

Finally, our selected MRI protocol was limited. Significant progress in MRI scanners and acquisition techniques has occurred over the long period of this study; newer technologies now allow for increased spatial detail and reduced overall acquisition times. However, the information presented in this study is robust and provides strong evidence for the predictive importance of early MRI findings regarding the progression of joint disease in our cohort of boys with severe hemophilia A. Further, the agreement between the readings from our radiologists was excellent, suggesting that our results are reliable.

How the findings reported in this long-term study might be used in clinical practice in the fast-evolving era of factor and nonfactor replacement therapies should be the subject of future research.[30] The findings from this long-term primary prophylaxis study lend support for a personalized prophylaxis strategy that allows intensification of the regimen based on physical examination and image findings with the goal of optimizing long-term joint health, and suggests that ankles and elbows in boys with hemophilia on programs of long-term prophylaxis, initiated from an early age in life, should be closely monitored.

5 | CONCLUSIONS

Dose- and frequency-adjusted prophylaxis did not completely prevent the progression of MRI-detected joint changes in boys with hemophilia, with 39% of subjects developing objectively determined joint changes, most notably in ankles and elbows. Joint bleeding was associated with an increased risk of arthropathy on end-of-study MRI. Soft-tissue changes in interval MRIs were associated with an increased risk of osteochondral findings in end-of-study MRIs and X-rays, suggesting that serial MRIs (or other imaging techniques such as ultrasound) in populations of boys with hemophilia could be beneficial in guiding choice of

individualized prophylaxis regimens aimed at minimizing subclinical and clinically overt joint bleeding and thus preserving long-term joint health.

ACKNOWLEDGMENTS

The Canadian Hemophilia Primary Prophylaxis Study was initially funded by grants from the Medical Research Council of Canada/Pharmaceutical Manufacturers Association of Canada Partnership Fund and the Bayer/Canadian Blood Services/Hema-Quebec Partnership Fund. Subsequent renewals were funded by Bayer Inc.

AUTHOR CONTRIBUTIONS

PB, VB, and BF contributed to the contents and design. PB, AD, SD, EP, BF, and MC contributed to the analysis and/or interpretation of data. PB, JS, and SD drafted the manuscript. All authors contributed to the critical writing or revising of the intellectual content, and approved the final version submitted for publication.

RELATIONSHIP DISCLOSURES

VB reports that he is chair of the International Prophylaxis Study Group (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. AD reports research grants from Baxalta-Shire, Novo Nordisk, Terry Fox Foundation, PSI Foundation, Society of Pediatric Radiology, and Garron Family Cancer Centre; and education grants from the Radiological Society of North America. She is a member of the International Prophylaxis Study Group and OMERACT Special Interest Group in MRI in Juvenile Idiopathic Arthritis (JIA). BF reports grants from Bayer and the Canadian Institutes of Health Research (CIHR). MC reports grants from Bayer, grants and personal fees from Bioverativ/Sonofi, Novo Nordisk; and Takeda; and personal fees from CSL-Behring, Pfizer, Roche, LFB, and Grifols. RK reports personal fees from Agios Pharmaceuticals Inc, Amgen Inc, Hoffman-LaRoche LTD, Shire Pharma Canada ULC, Novo Nordisk Canada Inc, Octapharma AG, Takeda, and Sanofi. MS reports personal fees from Octapharma, Takeda, and Meducom. JKMW reports grants and nonfinancial support from Bayer. The remaining authors have nothing to disclose.

ORCID

Saunya Dover https://orcid.org/0000-0001-5935-8101
Victor S. Blanchette https://orcid.org/0000-0003-3341-5010
Andrea S. Doria https://orcid.org/0000-0003-3202-0447
Brian M. Feldman https://orcid.org/0000-0002-7813-9665
Georges E. Rivard https://orcid.org/0000-0002-2861-9441
Sara J. Israels https://orcid.org/0000-0002-1849-4825
Anthony K. Chan https://orcid.org/0000-0003-1551-3995
MacGregor Steele https://orcid.org/0000-0001-6864-0598
Robert J. Klaassen https://orcid.org/0000-0002-6913-2808

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How to cite this article: Stimec J, Dover S, Pullenayegum E, et al. Magnetic resonance imaging in boys with severe hemophilia A: Serial and end-of-study findings from the Canadian Hemophilia Primary Prophylaxis Study. *Res Pract Thromb Haemost*. 2021;5:e12565. https://doi.org/10.1002/rth2.12565