

Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study

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Summary. *Background:* Prophylactic treatment for severe hemophilia A is likely to be more effective than treatment when bleeding occurs, however, prophylaxis is costly. We studied an inception cohort of 25 boys using a tailored prophylaxis approach to see if clotting factor use could be reduced with acceptable outcomes. *Methods:* Ten Canadian centers enrolled subjects in this 5-year study. Children were followed every 3 months at a comprehensive care hemophilia clinic. They were initially treated with once-weekly clotting factor; the frequency was escalated in a stepwise fashion if unacceptable bleeding occurred. Bleeding frequency, target joint development, physiotherapy and radiographic outcomes, as well as resource utilization, were determined prospectively. *Results:* The median follow-up time was 4.1 years (total 96.9 person-years). The median time to escalate to twice-weekly therapy was 3.42 years (lower 95% confidence limit 2.05 years).

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Nine subjects developed target joints at a rate of 0.09 per person-year. There was an average of 1.2 joint bleeds per person-year. The cohort consumed on average 3656 IU kg⁻¹ year⁻¹ of factor (F) VIII. Ten subjects required central venous catheters (three while on study); no complications of these devices were seen. One subject developed a transient FVIII inhibitor. End-of-study joint examination scores – both clinically and radiographically – were normal or near-normal. *Conclusions:* Most boys with severe hemophilia A will probably have little bleeding and good joint function with tailored prophylaxis, while infusing less FVIII than usually required for traditional prophylaxis.

Keywords: arthropathy, childhood, clinical trial, factor VIII, hemophilia, prophylaxis.

Introduction

Hemophilia is an important and costly disorder that may have serious consequences [1–5]. The greatest impact occurs from recurrent bleeding into joints and includes pain associated with acute bleeding and later chronic arthropathy [6]; 50% of children affected by severe hemophilia have joint damage and this damage is more frequent with increased bleeding [7]. The

prevention and treatment of bleeding is very expensive and finding a cost-effective treatment is of high priority.

The cost of caring for patients with hemophilia is high [8–10]. For example, in California the average treatment cost is about US\$140 000 annually. Costs are higher for patients with severe disease (usually defined as <1% or 2% of clotting factor activity, depending on the assay used), those with factor inhibitors and those with arthropathy [11].

There are two major treatment strategies to prevent arthropathy: on-demand therapy and factor prophylaxis. Prophylaxis is designed to convert the severe to the moderate phenotype (by providing circulating factor activity of >1%, with the goal of eliminating spontaneous hemarthroses). Primary prophylaxis was first proposed in 1958 in Malmö. In order to reach the target factor (F) VIII level, patients are treated with 20–40 IU kg⁻¹ of FVIII on alternating days (full-dose prophylaxis or Malmö protocol) [12,13].

Much work has been carried out that suggests the superior efficacy of prophylaxis [14,15]. The first comparative clinical trial supporting prophylaxis has only recently been reported in abstract form [16]. However, full-dose prophylaxis requires about three times as much clotting factor as treatment on demand [14,15].

The most efficacious and cost-effective regimens of prophylaxis have not yet been determined [8–10,17–20]. Prophylaxis is the emerging standard of care in many European countries [21]; in North America on-demand therapy remains a common choice, especially in adolescents and adults [22,23].

In order to further refine the therapy of severe hemophilia A, we studied a cohort of 25 young boys in a 5-year, multi-center single-arm trial. The subjects were all treated with a tailored prophylaxis protocol adjusted to the individual's bleeding pattern. Young boys with severe hemophilia A treated with tailored prophylaxis were asked: (i) what is the frequency of 'target joint' development?; (ii) what is the frequency of bleeding?; (iii) what is the annual consumption of clotting factor?; and (iv) what is the resultant joint health? We hypothesized, based on the clinical experience of one of our investigators [24] and of others [25], that tailored prophylaxis would lead to an acceptable frequency of bleeding, few target joints and good overall joint health.

Methods

This is a prospective, multi-center study. Ten Canadian pediatric comprehensive care hemophilia clinics chose to participate and had eligible subjects to enroll. Twenty-five subjects were enrolled in the first 5 years of study (Fig. 1).

Sample

Our sampling strategy was chosen to parallel the concurrent randomized trial of Manco-Johnson *et al.* (comparing Malmö, full-dose prophylaxis with on-demand therapy) [16,26] so that the results between the two studies could be compared. All

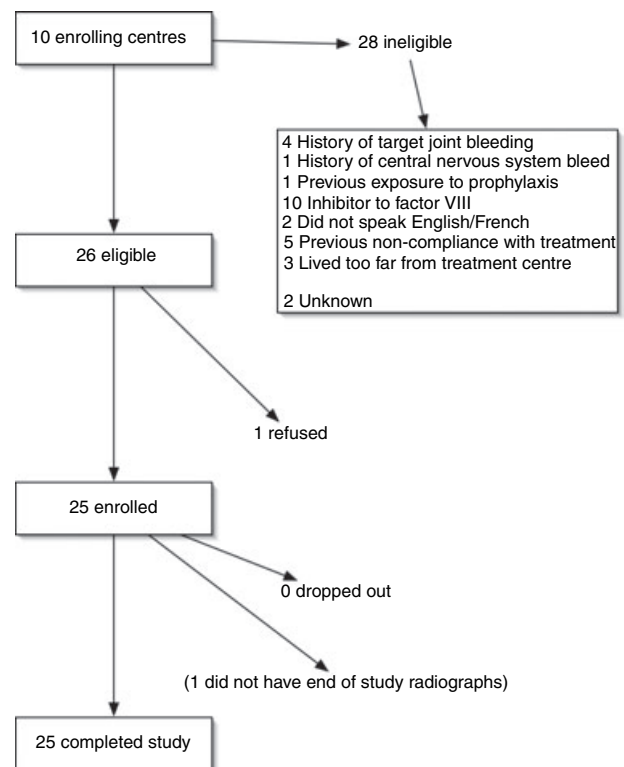


Fig. 1. Flow chart of patient disposition. Data regarding the number of potential subjects with severe hemophilia came from anonymous reports from the Canadian National Hemophilia Registry.

children with severe hemophilia, defined as a circulating FVIII activity of <2%, were consecutively approached for enrollment. Children were required to be between the ages of 1 and 2.5 years, and to have normal joints as defined by normal World Federation of Hemophilia physical examination and radiology scores. All parents provided written informed consent. The protocol was approved by the Research Ethics Board at The Hospital for Sick Children and at each of the participating centers.

The following exclusion criteria prevented enrollment.

- 1 History of ≥ 3 clinically determined bleeds into any one joint.
- 2 Presence or past history of a circulating inhibitor to FVIII [level ≥ 0.6 Bethesda Units (BU)].
- 3 Family lives too far from the regional comprehensive care clinic to participate or has demonstrated non-compliance with therapy.
- 4 Competing risk (symptomatic HIV infection, juvenile rheumatoid arthritis, metabolic bone disease, or other diseases known to cause or mimic arthritis).

Tailored (escalating dose) prophylaxis

Initial dose All subjects were prescribed full-length recombinant FVIII (rFVIII) at a dose of 50 U kg⁻¹ body weight, given once weekly (Table 1, step 1). The timing of infusion was negotiated with the family to take place when it would most benefit the child (i.e. on the day of maximal physical activity).

Table 1 The tailored (escalating dose) prophylaxis schedule

Dose and frequency of factor VIII infusions	
Step 1	50 units kg ⁻¹ , once weekly
Step 2	30 units kg ⁻¹ , twice weekly
Step 3	25 units kg ⁻¹ , alternate days (may go up in increments of 5 units kg ⁻¹ if bleeding persists)

The actual dose of rFVIII was rounded to the nearest vial to avoid waste. Only a full-length rFVIII product could be used in this study.

Treatment of breakthrough bleeding episodes We used an 'enhanced episodic' schedule to parallel the one used in the concurrent randomized trial [16,26]. Treatment was with 40 U kg⁻¹ of rFVIII at the time of a bleeding episode, repeated at a dose of 20 U kg⁻¹ on the first and third days following the bleed.

Criteria for escalation of frequency per weekly dosage Subjects increased the frequency and weekly dosage of rFVIII replacement (Table 1, step 2) when one of the following three conditions applied.

- 1 The subject developed target joint bleeding (as defined by ≥ 3 clinically determined bleeds into any one joint over a consecutive 3-month period).
- 2 The subject developed four clinically determined bleeds – either significant soft tissue bleeds (i.e. leading to loss of function) or joint bleeds – into any number of joints over a consecutive 3-month period.
- 3 The subject developed ≥ 5 clinically determined bleeds into any one joint while on the same dosage (step) of factor therapy over any period of time.

If any of these conditions applied, the subject was prescribed rFVIII at a dose of 30 U kg⁻¹ given twice weekly (Table 1).

A second escalation (step 3) occurred if any of the escalation criteria recurred while on step 2. In these cases, the subject was prescribed rFVIII at a dose of 25 U kg⁻¹ given on alternate days (Table 1). Further incremental increases in dose (but not frequency) were allowed if bleeding continued.

Central venous catheters (CVCs) At any time during the escalation protocol, if venous access was difficult, a CVC (port-a-catheter) was offered.

Adherence Subjects documented all bleeding and treatments in treatment diaries, which were checked for adherence by site nurse coordinators. The nurse coordinators also telephoned the participating families on a monthly basis to reinforce the protocol and encourage adherence.

Length of follow-up Follow-up extended to 60 months.

Baseline assessment At the baseline assessment, families were given bleeding diaries and instructed on their use. Subjects were examined by the site physician and physiotherapist to ensure that enrollment criteria were met and to record baseline

data. Radiographs of the knees, elbows and ankles were performed where appropriate (see below). A blood sample was collected to confirm the FVIII level and to test for a circulating inhibitor.

Outcomes

Primary outcome The primary outcome was the time to development of target joint bleeding. Bleeding frequency was determined by monthly telephone interviews and daily diary records. The subjective report of joint bleeding is known to correlate with more objective measures and parallels physicians' global effectiveness in clinical trials [27]. If target joint bleeding occurred, the subject was asked to attend clinic for confirmation by the site physician and for escalation of the prophylaxis protocol.

Secondary outcomes Subjects were examined by the study physiotherapist every 3 months and by the physician every 6 months.

At these visits the following measures were assessed.

- 1 Number of rFVIII infusions and quantity of rFVIII infused.
- 2 History of any complications arising from CVC use since the last visit.
- 3 Protocol adherence. Adherence was determined by comparing the actual infusions received with those prescribed by the tailored prophylaxis regimen. In addition, at each visit, parents were asked about satisfaction with the program using a 7-point categorical scale with 7 representing 'most satisfied'.
- 4 Number of bleeding episodes.
- 5 Post-treatment levels of FVIII (48 h after treatment).
- 6 Circulating inhibitor.
- 7 Physical disability as measured by the Childhood Health Assessment Questionnaire (CHAQ) [28]. The CHAQ is a 30-item parent-report questionnaire that scores eight domains of activity. The resultant score ranges from 0 (no disability) to 3 (very severe disability). The version of the CHAQ that we used includes visual analog scales (VAS) measuring pain, overall illness impact and severity.
- 8 Joint damage as determined by the physiotherapy score [29], which is a modification of the World Federation of Hemophilia physical examination score [30]; the score has been modified to be more sensitive to early damage from hemarthrosis. Total scores can range from 0 (all joints completely normal) to 160 (most severe damage in all joints). In order to ensure reliability of the scores, the site physiotherapists were centrally trained and a detailed procedural manual was developed.

Radiological outcomes At baseline, any of the six index joints (those joints that bleed most frequently in hemophilia: ankles, elbows and knees) that had already bled were radiographed. At the end of the study all subjects had the six index joints radiographed, whether or not there had been clinical bleeding. The radiographs were scored by a single radiologist blind to all

clinical information, using the Pettersson method (maximum score of 78 for six joints) [31].

Measurement of FVIII and inhibitor levels To ensure standardization of FVIII and inhibitor levels, all samples were analyzed at a central laboratory. FVIII levels were measured with a one-stage assay using human pooled plasma as a standard (Precision Biologicals, Dartmouth, NS, Canada). This standard was referenced to the current World Health Organization standard for FVIII, 97/586. FVIII inhibitor studies were performed using the Nijmegen modification of the Bethesda assay [32].

Analysis

As hemophilia is a rare disorder and the subjects were enrolled throughout the study period, not all subjects were followed for the same length of time. Therefore, to account for right censoring, the median time and 95% confidence intervals (95% CI) until development of target joint bleeding was determined using the Kaplan–Meier method, as was the median time to escalation to each step of the protocol. When comparing the time-to-event for the bleeding outcomes between different patient groups, we used Cox proportional hazards regression models to determine the hazard ratio (risk ratio) and 95% CI. For the descriptive analyses we calculated means and standard deviations, or medians and minimum/maximum values as appropriate for numerical data, and proportions with 95% CI for categorical data. All analyses were carried out using DataDesk 6.1 (Data Description, Inc., Ithaca, NY, USA) and JMP 5.1 (SAS Institute, Cary, NC, USA) software.

Results

Sample

Twenty-five boys with severe hemophilia were enrolled at 10 centers; all were followed until the end of the study period. The numbers of eligible and excluded patients are shown in Fig. 1. Table 2 lists the demographic features of the 25 subjects studied. At baseline, all subjects had essentially undetectable FVIII activity (<0.015 U mL⁻¹, i.e. the lowest level of the assay available at the time).

Tailored (escalating) prophylaxis

Follow-up length The 25 subjects were followed for between 1.3 and 5 years (median 4.1 years). The total follow-up was 96.9 person-years.

Unacceptable bleeding Thirteen subjects met criteria for escalation to step 2. The median time to escalation was 1249 days (3.42 years, lower 95% confidence limit 2.05 years, Fig. 2). At 5 years, 40% of the subjects required only once-weekly prophylaxis (95% CI: 20–62%). Thirteen subjects had not had a joint bleed before enrollment. Those subjects were

Table 2 Demographic features of the study sample at enrollment

Characteristic	Result
Age (mean years) (SD)	1.6 (0.5)
Race (<i>n</i>) (%)	
African heritage	1 (4)
European Caucasian	19 (76)
South-east Asian	1 (4)
Mixed Latin–American	2 (8)
Mixed Aboriginal–Canadian	2 (8)
Male sex (<i>n</i>) (%)	25 (100)
Family history of hemophilia A (<i>n</i>) (%)	6 (24)
Weight (mean kg) (SD)	12.0 (1.4)
Central venous catheters placed prior to study (<i>n</i>) (%)	7 (28)
Treatment with factor VIII prophylaxis (any regimen) before study entry (<i>n</i>) (%)	3 (12)
History of joint bleeds before study entry (<i>n</i>) (%)	12 (48)
Number of joint bleeds before study entry (mean) (SD)	0.76 (1.1)

less likely to escalate, but this was not statistically significant (hazard ratio 0.86, 95% CI: 0.49–1.5). Four subjects met bleeding criteria for escalation to step 3. At 5 years the proportion requiring alternate-day prophylaxis was 28% (95% CI: 0–44%, Fig. 3).

Primary outcome

Occurrence of target joints Nine subjects developed target joints. The youngest was 23 months of age, the oldest 69 months. Two subjects had continued bleeding in the same joint despite escalation to step 2. No subject developed target joint bleeding in a second joint (Table 3). The rate of target joint bleeding was 0.09 per person-year; approximately 40% of subjects had developed a target joint by 3.5 years (Fig. 4).

Secondary outcomes

Amount of rFVIII In total, the cohort infused 5 713 229 IU of rFVIII (both for prophylaxis and for bleeding-related infusions). This represents an average of 3656 IU kg⁻¹ year⁻¹. When only considering step 1, the total average consumption was 3325 IU kg⁻¹ year⁻¹.

CVCs Ten subjects had CVCs. Seven were inserted before study entry; in five, CVC placement may have been in anticipation of prophylaxis. Three subjects required CVC placement while on study. No CVC complications occurred.

Protocol adherence Adherence was excellent. Whilst on once-weekly therapy, subjects received 3546 of 3683 expected prophylaxis infusions (96%). A similar level of compliance was seen for twice-weekly and alternate-day therapy. The level of parental satisfaction was very high (Fig. 5).

Number of bleeding episodes There were 116 joint bleeds into the six index joints; an average of 1.2 per person-year. There

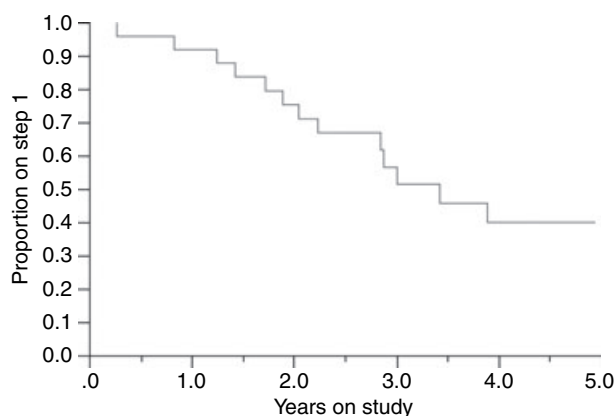


Fig. 2. Survival curve of time to escalation to step 2 of the protocol. The y-axis represents the proportion of subjects at any time who are still on step 1. The x-axis represents time in years.

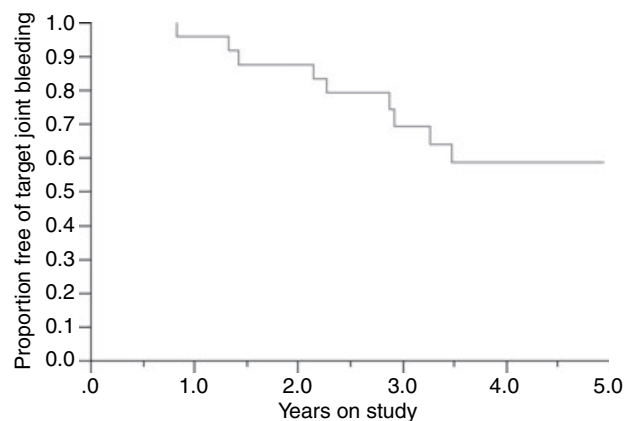


Fig. 4. Survival curve of time to development of a target joint. The y-axis represents the proportion of subjects at any time who are free of target joint bleeding. The x-axis represents time in years.

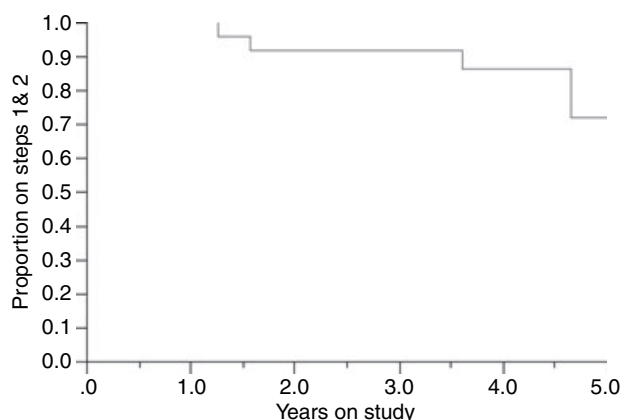


Fig. 3. Survival curve of time to escalation to step 3 of the protocol. The y-axis represents the proportion of subjects at any time who are still on step 1 or step 2. The x-axis represents time in years.

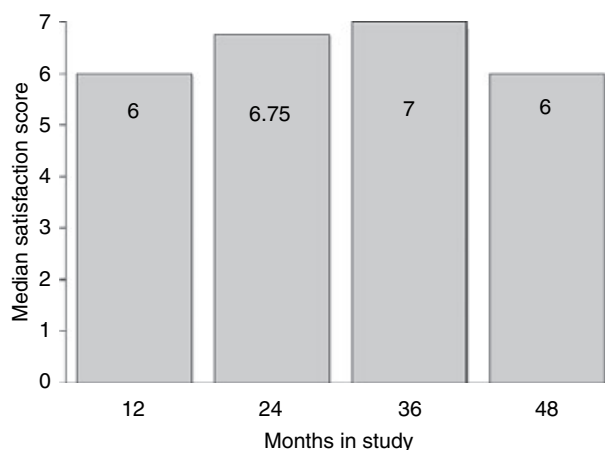


Fig. 5. Bar chart of parental satisfaction with the study protocol. The bars represent the median score (out of a maximum satisfaction score of 7) achieved by the study group at the study evaluations at 12, 24, 36 and 48 months on study.

Table 3 End-of-study results by index joint

Index joint	Target joint (n)	Median joint score	Range of joint scores
Left elbow	2	0	0–4
Right elbow	1	0	0–1
Left knee	0	0	0–3
Right knee	1	0	0–2
Left ankle	4	1	0–3
Right ankle	1	1	0–4

were 30 intramuscular bleeds (mean 0.31 per person-year) and 93 mucosal bleeds (mean 0.96 per person-year).

Post-treatment levels of FVIII Subjects who lived far from a study center were not always able to return for measurement of 48-h post-treatment levels. Accordingly, 249 of 407 (61%) of the scheduled levels were performed. The subjects' median post-treatment level ranged from undetectable to 6.9%. Eighty-three per cent of the levels was >1%. The median post-

treatment level did not influence the time to developing a target joint (hazard ratio 0.93, 95% CI: 0.72–1.2).

Circulating inhibitor to FVIII Only two tests in one patient showed inhibitor activity >0.6 BU. This inhibitor was transient; it occurred at 3 months following enrollment, reached a peak of 3.4 BU, and disappeared by 9 months.

Physical disability At the final visit the CHAQ was 0 for 24 subjects (indicating no disability) and 0.25 in one subject. The mean VAS (where 0 indicates best possible and 10 indicates worst possible) for pain was 1.8 (SD 2.1), for illness severity was 2.0 (SD 2.1) and for illness impact was 1.0 (SD 1.4).

Joint physical examination scores Overall, there was little evidence of arthropathy. The median total joint score (maximum value 160) was 3 (0–11). However, some of the scores reflected normal developmental changes in axial

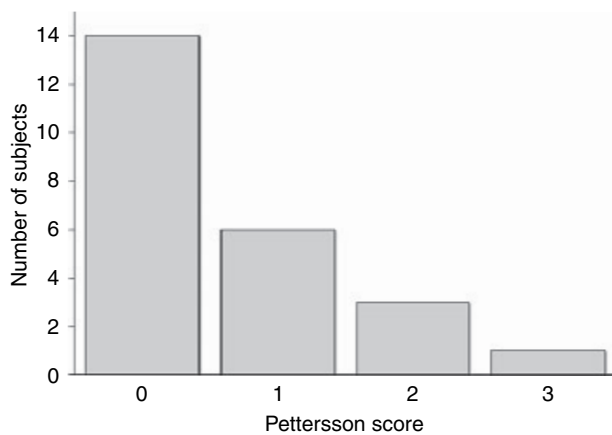


Fig. 6. Bar chart of the radiographic summary scores of the six index joints at the end of study. Each bar represents the number of subjects who achieved a given score on the Pettersson scale. The maximum Pettersson score that can be given is 78.

alignment, or were due to transient swelling from acute bleeding. With axial alignment and swelling removed, the median total score was 0 (0–4).

Radiological outcomes There was little change in end-of-study radiographs in the 24 subjects who had films that could be evaluated (Fig. 6). One subject moved from the country after the end-of-study visit but before radiographs were obtained; this subject had no joint bleeds during the study. None of the radiographic changes were seen in joints that had bled prior to study entry.

Discussion

Our results suggest that most boys with severe hemophilia A will have little bleeding for at least several years if treated with once-weekly FVIII prophylaxis. Moreover, with tailored prophylaxis we expect to see few adverse effects on the joint in the preschool years. Finally, tailored prophylaxis is expected to require considerably less FVIII than full-dose prophylaxis for young children.

Our subjects fared better than we would have expected had they been treated with on-demand therapy. For example, in Toronto, eight of 16 boys treated on demand developed a target joint by the age of 44 months [33]. In contrast, only four of our subjects (16%, 95% CI: 11–21%) developed a target joint by that age. It should be noted that our definition of ‘target joint’ is arbitrary; given the aggressive treatment of intercurrent bleeding in the protocol it remains to be seen whether these target joints will become damaged in the future. The only randomized trial comparing full-dose prophylaxis to on-demand therapy (using enhanced episodic therapy as above) has now been reported in abstract form. The average annual number of joint bleeds seen in our study (1.2) was lower than the reported number in patients from the randomized study who were not on prophylaxis (4.9) [16]. We expect better results from tailored prophylaxis than from on-demand therapy.

Any regimen of prophylaxis will not stop bleeding altogether. Our patients appeared to bleed no more often than patients treated with some other prophylaxis strategies that are more aggressive [17,18,25,34–37]. For example, in one study of 70 children with severe hemophilia, the most recent group (treated most aggressively with 20–40 IU kg⁻¹ rFVIII two or three times weekly) bled at a rate of 2.6 bleeds per patient-year [18]. Those protocols that use the highest doses (Malmö protocol) appear, however, to result in fewer annual bleeds [38,39]. For example, in the randomized trial reported by Manco-Johnson *et al.* [16], subjects on prophylaxis suffered from 0.47 joint bleeds per year. However, these protocols use more FVIII; patients treated with the full-dose Malmö prophylaxis protocol use about 6000 IU kg⁻¹ annually [12,21,38,39]. Our subjects used considerably less rFVIII. Recombinant FVIII is an expensive treatment; precise costing is difficult to determine but each unit costs more than \$1.00 in most countries [8,11,33,40,41] and more than 90% of the cost of hemophilia treatment is due to FVIII [8–10,20]. Therefore, reducing the amount of rFVIII will reduce the economic burden of those responsible for paying for hemophilia care.

Reducing the amount of required rFVIII, while still providing good prophylactic coverage, is likely to be especially beneficial in parts of the world where the supply of FVIII is limited. In many developing countries full-dose Malmö protocol prophylaxis is not possible. For example, in Turkey only 18% of boys with severe hemophilia had access to prophylaxis [42]. In several other developing countries, for example, India and Malaysia, prophylaxis is not currently feasible [43]. It is possible that, by reducing the amount of FVIII required, tailored prophylaxis will make early preventative therapy possible in some countries with developing economies.

An additional benefit of tailored prophylaxis appears to be a decreased need for CVC placement. In order to facilitate alternate-day infusions, a CVC is often needed. For example, in a survey of North American centers 82% of the preschool children on full-dose prophylaxis required a CVC [22]. CVC placement is often complicated by deep vein thrombosis (DVT) or line-related sepsis: in Toronto, 69% of boys with a CVC for hemophilia had a DVT when screened, and 81% had evidence at a second evaluation 2 years later [44]. In our study, the CVC complication rate was much lower; this may be due to very strict access procedures mandated in the protocol and to the fact that the CVC was accessed less often than in alternate-day prophylaxis. Moreover, only three subjects required CVC placement while on study. It seems that tailored prophylaxis may be delivered successfully using peripheral venous access even in very young children. Avoiding CVC insertion was one of our goals in setting up tailored prophylaxis.

Although our findings are gratifying, it is not clear why more severe bleeding did not occur. Our findings contradict conventional understanding of the mechanism of prophylaxis; we would expect our subjects, when on once-weekly prophylaxis, to be without FVIII protection for much of the week. Once-

weekly prophylaxis might prevent bleeding in several ways. Our tailored approach provides factor coverage for at least part of the week; perhaps by preventing some of the potential hemarthroses we delay or prevent the development of target joints. Also, in some patients with severe hemophilia it seems, even in a joint that has no clinical bleeds, that there is constant low-grade bleeding as demonstrated by increased joint fluid on screening magnetic resonance imaging (MRI). Low-grade bleeding might be a source for toxic iron (which can lead to synovial hypertrophy and fragility, which in turn may lead to spontaneous clinical hemarthrosis). It is possible that by limiting subclinical constant bleeding, tailored prophylaxis can prevent some overt clinical bleeds. Finally, although the conventionally accepted half-life for FVIII would indicate that no procoagulant protein remains 1 week after treatment, there may still be sufficient amounts of thrombin generation to provide some hemostatic benefit, or there may be mechanisms that sequester the procoagulant protein at sites where hemostasis is required (e.g. synovium). In addition, our patients who did bleed were treated with an aggressive 'salvage therapy' (a minimum of three rFVIII treatments). This more aggressive approach to treating bleeds may account for why our patients fared better than historically treated 'on-demand' patients, who generally receive only one or two treatments for a joint bleed.

Our study results must be considered in the light of several potential limitations. Our study is not a comparative study; it is possible that the results in our population may have been similar if other treatment strategies were used. However, considering that historical data from Canadian patients treated on demand suggests a much worse outcome [33], it is highly likely that our subjects benefited from tailored prophylaxis. We designed our study so that our subjects would be comparable to a concurrent randomized trial [26] and it would seem that our tailored prophylaxis results in bleeding rates that are between those seen with Malmö-style full-dose prophylaxis and on-demand therapy. It should be possible to determine whether tailored prophylaxis has a favorable incremental cost-effectiveness ratio (compared with full-dose prophylaxis) when the Manco-Johnson study is fully reported. Finally, it may be that our subjects' outcomes will be worse when they are older. Significant joint damage from bleeding may not occur until children are, on average, about 10 years old [34]. Long-term follow-up is essential before we can know the utility of tailored prophylaxis and for this reason we have secured funding to continue studying this unique cohort of boys with severe hemophilia A.

Conclusions

Most boys with severe hemophilia A appear to have little bleeding if treated with once-weekly FVIII prophylaxis, at least for several years. Tailored prophylaxis is associated with good joint function and normal or near-normal radiographs in the preschool and early school-age years. Finally, tailored prophylaxis would appear to require considerably less FVIII than some other reported prophylaxis strategies, which may make it an

attractive option in terms of cost and clotting factor availability.

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Authorship addendum

This study was a cooperative venture undertaken by the Association of Hemophilia Clinic Directors of Canada.

B.M. Feldman assisted in conception and design of the study, was co-principal investigator, obtained funding, assisted in the analysis of the data and wrote the first draft of the manuscript.

V.S. Blanchette assisted in conception and design of the study, was co-principal investigator, obtained funding, assisted in the analysis of the data and critically revised the manuscript.

P. Babyn assisted in conception and design of the study, reviewed all of the study radiographs, assisted in interpretation of the data and critically revised the manuscript.

C. Demers assisted in conception and design of the study, participated in data collection, assisted in interpretation of the data and critically revised the manuscript.

K. Gill assisted in conception and design of the study, participated in data collection, assisted in interpretation of the data and critically revised the manuscript.

S. Israels assisted in conception and design of the study, participated in data collection, assisted in interpretation of the data and critically revised the manuscript.

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