Effect of late prophylaxis in hemophilia on joint status: a randomized trial

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Essentials

• High-quality data are lacking on use of prophylaxis in adults with hemophilia and arthropathy.
• SPINART was a 3-year randomized clinical trial of late/tertiary prophylaxis vs on-demand therapy.
• Prophylaxis improved function, quality of life, activity and pain but not joint structure by MRI.
• Prophylaxis improves function but must start before joint bleeding onset to prevent arthropathy.

Summary. Background: Limited data exist on the impact of prophylaxis on adults with severe hemophilia A and pre-existing joint disease. Objectives: To describe 3-year bleeding, joint health and structure, health-related quality-of-life (HRQoL) and other outcomes from the open-label, randomized, multinational SPINART study. Patients/Methods: Males aged 12–50 years with severe hemophilia A, ≥150 factor VIII exposure days, no inhibitors and no prophylaxis for >12 consecutive months in the past 5 years were randomized to sucrose-formulated recombinant FVIII prophylaxis or on-demand therapy (OD). Data collected included total and joint bleeding events (BEs), joint structure (magnetic resonance imaging [MRI]), joint health (Colorado Adult Arthropathy; clinical trial; hemophilia A; magnetic resonance imaging; prophylaxis; quality of life.

Introduction

People with severe hemophilia A lack coagulation factor VIII and experience bleeding into joints, resulting in
pain and disability [1]. Primary prophylaxis (routine FVIII replacement started before age 3 years, two joint hemorrhages, and clinically determined arthropathy [2]) has established benefit in preventing arthropathy [3,4], and is recommended as the optimal therapy by the World Federation of Hemophilia (WFH) and the National Hemophilia Foundation [5,6]. Although high-quality evidence on the efficacy of prophylaxis is lacking, either secondary (started after two or more joint bleeds but without arthropathy [2]) or tertiary (started with arthropathy [2]), the Swedish and Dutch longitudinal studies highlight the benefits of early initiation of prophylaxis [7,8]. Limited data from cross-sectional studies have demonstrated benefits for prophylaxis in adolescents and adults regarding joint bleed rates, joint function, preservation of joint structure on magnetic resonance imaging (MRI), and health-related quality of life (HRQoL) [9–12]. Patient-centered outcomes, including improved functional capacity, HRQoL, and decreased pain, are essential in a lifelong condition such as hemophilia with no established cure [13].

The Study of Prophylaxis in Adults Randomized Trial (SPINART) was designed to determine the long-term benefits of secondary and tertiary prophylaxis versus on-demand treatment (OD) (given for bleeding) [14]. The primary endpoint of SPINART, i.e. bleeding frequency at 1 year, has been reported [14], and showed that the numbers of total, joint, spontaneous and trauma-related bleeding events (BEs) were markedly lower with prophylaxis than with OD [14]. This article presents all predefined secondary and tertiary outcomes from baseline to year 3, including bleeding, joint structure, joint health, safety, and healthcare resource utilization (HRU), which were chosen to align with the landmark pediatric primary prophylaxis study, the Joint Outcome Study (JOS) [3], in addition to key patient-reported outcomes (PROs), quality of life (QoL), pain, activity/participation, and treatment satisfaction.

Methods

Study design and participants

The inclusion criteria, study design, randomization methods and sample size determination for SPINART, a randomized, controlled, prospective, open-label, phase 3b/4 trial conducted from March 2008 to November 2013 (ClinicalTrials.gov identifier: NCT00623480), have been previously published [14]. Males aged 12–50 years with severe hemophilia A (<1% FVIII activity [FVIII:C]; up to 10% of participants could have 1–2% FVIII:C if they showed clinical severity, consistent with the JOS) and with ≥150 FVIII exposure days (EDs), no FVIII inhibitor or history of inhibitors, no regular prophylaxis for >12 consecutive months in the past 5 years and 6–24 documented BEs or treatments in the previous 6 months were eligible. All participants provided written informed consent and assent as appropriate before participating in any study procedure [14].

BEs in the previous 12 months were assessed at screening. Participants were stratified at screening on the basis of: (i) the presence or absence of target joints (defined as one or more joints, each of which had experienced four or more hemorrhages in the preceding 6 months, to align with the JOS); and (ii) bleeding frequency in the previous 6 months (<15 or ≥15 annual BEs).

All participants were randomized 1:1 to treatment with sucrose-formulated recombinant FVIII (Bayer, Berkeley, CA, USA) as OD or prophylaxis (25 IU kg\(^{-1}\) three times weekly; dose escalation of 5 IU kg\(^{-1}\) per dose permitted annually for ≥12 BEs per year). The ratio of total number of days on study to total number of EDs was used to assess prophylaxis adherence.

Radiologists scoring extended MRI (eMRI) and physiotherapists scoring the Colorado Adult Joint Assessment Scale (CAJAS) were blinded to treatment assignment and bleeding history. Physiotherapists determined whether a bleeding episode had occurred within 2 weeks, to ensure that the evaluation was performed when joints were stable.

Efficacy assessments

Bleeding assessments A BE was defined as any episode of external bleeding (i.e. epistaxis), bruising, pain or limited function for which FVIII was infused. A joint BE (subset of total BEs) was defined as an event with pain, swelling, tingling, warmth or limited motion of an extremity for which FVIII was infused. Electronic diaries were used to record infusion and bleeding data. Cumulative and annualized numbers of total BEs and joint BEs at the end of 3 years were assessed.

MRI assessments Previously published MRI scales for hemophilic arthropathy emphasize early and moderate changes, but have no or low sensitivity for progression of arthropathy in severely damaged joints [15–18]. For this trial, the 45-item eMRI scale was validated and shown to provide greater discrimination over a broader spectrum of abnormalities and little to no ceiling effect [19]. The structures of six index joints (knees, ankles, and elbows) were evaluated. Each MRI was independently scored by three radiologists.

Each joint was evaluated for six items in two domains (soft tissue [effusion/hemarthrosis, synovial hypertrophy and hemosiderin items] and osteochondral [erosion, subchondral cysts and cartilage loss items]) [19]. Osteochondral findings were determined for each of the three bones that articulate the joint. Total eMRI scores range from 0 to 45 per joint (soft tissue scores, 0–9; osteochondral scores, 0–36). Higher scores indicate greater structural damage. The score for each joint was based on the median score
change for each of the 45 items from study entry to exit at 3 years. Total participant score (defined as the mean score change of the six joints) was subsequently derived to assess individual participant joint structures.

**Joint health assessment** The CAJAS, which was designed and validated [20] to measure the joint health of six index joints in adults (derived from the WFH scale [i.e. the Gilbert score] [21]) was used. The CAJAS provides an overall score derived from nine items for knees and ankles, and seven items for elbows. Each item is associated with one of two primary domains (structural functional impairment and activity functional impairment), with the exception of gait, which is included in both domains for ankles and knees. CAJAS assessments were completed at baseline and years 1, 2, and 3. The ranges of CAJAS scores for each joint are 0–25 for ankles and knees and 0–21 for elbows. The CAJAS total score (range, 0–23.67) for each participant (defined as the average of the mean score for each joint type) was subsequently derived. Higher CAJAS scores indicate worse joint health. The CAJAS score change was the change from study entry score to exit score; a positive score reflected disease progression, whereas a negative score change indicated improved joint health.

**HRQoL assessments** HAEMO-QoL-A, a disease-specific QoL questionnaire for adults that includes 41 items covering six domains (physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns), was completed at baseline, month 6, and years 1, 2, and 3 [22]. The HAEMO-QoL-A total score and the score for each of its domains range from 0–100 points, with higher scores indicating better HRQoL. In a previous validation of HAEMO-QoL-A, the mean distribution-based minimal important difference (MID) considered to be clinically meaningful ranged from 5.2 to 7.2 for the total score, and from 6.2 to 9.1 for the physical functioning domain [23].

Euro QoL-5D-3L (EQ-5D-3L), a standardized, generic QoL questionnaire assessing five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) ranked on three levels of severity (no problems, some or moderate problems, and severe problems), was completed with the HAEMO-QoL-A. EQ-5D utility index scores for each health state were determined by ranking the five domains (range, 1 [best possible health] to 0 [death]) to −0.59 [worse than death]); in previous validation studies, the EQ-5D demonstrated an MID of 0.074 [24]. The European quality of life (EQ) visual analog scale (VAS) measures health status ‘today’, which ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

**Pain assessment** The Short-Form McGill Pain Questionnaire total score, determined at baseline and years 1, 2 and 3, consists of the following components: last 4 weeks’ pain rating (0–100), current pain intensity (0–3), sensory pain score (0–33), and affective pain score (0–12). Higher scores indicate worse status.

**Change in activities** Participants responded to two questions at baseline and years 1, 2, and 3: (i) ‘In the past 4 weeks, did you change your physical activities or lifestyle?’ (responses: ‘more,’ ‘the same’ or ‘less’ physical activity); and (ii) ‘Check the statement that best describes your current activity level’ (responses: ‘unrestricted work/school and recreation,’ ‘full work/school with limited recreation,’ or ‘limited work/school and recreation’).

**Treatment satisfaction** Participants were asked about treatment satisfaction with three questions administered at baseline, month 3, 6, 12, 18, 24, 30, and 36: (i) ‘Has your treatment regimen met expectations?’; (ii) ‘How satisfied are you with your treatment regimen?’; and (iii) ‘Would you like to continue your treatment regimen?’

**HRU** Participants were asked weekly about HRU, including contacts with health professionals, procedures, and other events (including joint surgery or hospitalization).

**Safety assessments** Adverse events (AEs) and serious AEs (SAEs) were monitored throughout the study. The presence of inhibitors was considered to be an SAE, and was tested at screening and months 3, 12, 24, and 36, or when clinically suspected according to the results of the Nijmegen-modified Bethesda assay (≥ 0.6 Bethesda units was considered to be positive).

**Statistical analysis** All statistical evaluations were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Comparisons of bleeding frequency between the two groups were made within a negative binomial regression model, as described previously [14]. The change in eMRI total score from baseline to year 3 was prespecified as the first in a hierarchy of two secondary endpoints, with change in the CAJAS total score as the second endpoint. Between-group comparisons were based on a constrained longitudinal data analysis (cLDA) model [25] adjusted for target joints and bleeding frequency at baseline. Time was treated as a categorical variable in the model. By use of the cLDA model, within-group least squares (LS) means (and 95% confidence intervals [CIs]) for change from baseline at year 3 for treatment and between-group differences were estimated. Tertiary variables of changes in eMRI and CAJAS domain scores and HAEMO-QoL-A total and domain scores were evaluated with similar methods. Tertiary variables of pain, activity, HRU and treatment satisfaction were analyzed descriptively.
The intent-to-treat population included all randomized participants. All reported results are for the full-analysis set, consisting of all randomized participants who had a measurement at baseline and/or at postbaseline visits, as appropriate, for the endpoint of interest.

Results

Participants and FVIII exposure

Demographics and baseline characteristics were similar between the two randomization groups (n = 42 per group) [14]. The median age at study entry was 29.0 years (range, 15–50 years) (mean, 30.6 years; standard deviation [SD], 9.2 years). Seventy participants (83.3%; 35 per group) completed the 3-year study (discontinuation details have been described previously [14]). All participants were included in the safety analysis. Baseline data and FVIII exposure are shown in Table 1. Prophylaxis infusions were given, on average, every 2.37 days (expected frequency, every 2.33 days); thus, very high prophylaxis adherence was recorded.

Efficacy

Bleeding events  At year 3, median (quartile [Q]1; Q3) and mean numbers of annualized total BEs per participant were lower in the prophylaxis group (0.7 [0; 1.6], 2.5 [SD 4.7]) than in the OD group (37.4 [24.1; 52.6], 37.2 [SD 19.9]). Figure 1 shows total and joint bleeding for study participants by treatment arm. Participants in the prophylaxis group had a 93.9% (95% CI 89.6%–96.4%, P < 0.0001) reduction in bleeding frequency. The annualized bleeding rate for joint BEs was also lower in the prophylaxis group (0.3 [0; 1.2], 1.9 [SD 4.1]) than in the OD group (27.3 [14.9; 41.1], 28.7 [SD 18.8]). Fifteen prophylaxis (35.7%) and no OD (0%) participants remained bleed-free during the entire study; 32 participants (76.2%) in the prophylaxis group had fewer than two BEs per year. Most BEs were into joints (77.4% [OD] and 75.8% [prophylaxis]). The ratio of mean joint bleed frequency for OD versus prophylaxis was 15.6 (95% CI 8.6–28.4, P < 0.0001).

Joint structural changes determined with eMRI Baseline mean eMRI total scores (prophylaxis, n = 41; OD, n = 38) were 19.14 (SD 9.81) (median, 20.9) in the prophylaxis group, and 14.56 (SD 10.82) (median, 13.0) in the OD group. No individual participant in either randomized arm had completely normal joints (MRI total score of 0) at study entry. In both the prophylaxis group and the OD group, deteriorations from baseline were detected on eMRI at year 3 (mean, 0.75 [SD 1.59] and 0.92 [SD 1.15], respectively). On the basis of LS mean changes (prophylaxis, 0.79; OD, 0.96), the estimated difference between the groups was –0.17 in favor of prophylaxis (P = 0.66).

Deteriorations in eMRI for both groups were mostly attributable to osteochondral changes (0.78 for prophylaxis versus 0.90 for OD; LS mean estimated difference, –0.12; P = 0.74); small LS mean deteriorations in eMRI soft tissue domain scores were found (0.01 for prophylaxis versus 0.06 for OD; LS mean estimated difference, –0.04; P = 0.53).

Mild deterioration in individual joints was detected for both the prophylaxis group and the OD group (LS mean changes in eMRI score, 0.30 and 0.89 [elbows], 0.59 and 0.56 [knees], and 1.61 and 1.05 [ankles]; there were no significant differences between treatment groups).

Categorical analysis based on eMRI participant total and separate joint scores showed consistent results. The percentage of participants with improvement was slightly higher with in the prophylaxis group than in the OD group (12.5% versus 6.7%), as was the percentage of improved joints (8.1% versus 3.7%). The percentages of participants and joints with a worse score at year 3 were similar between groups. Comparison of eMRI values for individual joints showed that a similar proportion of joints with a normal (0) score at baseline had a worse score at year 3 (4 of 50 joints [prophylaxis] and 3 of 59 joints [OD]).

Analysis of changes from baseline to year 3 in eMRI total scores stratified by participant age did not show marked differences between groups, although there was a suggestion of less eMRI progression in the youngest individuals receiving prophylaxis (Fig. 2).

Table 1 Baseline characteristics, bleeding events during the study, and factor VIII exposure during the study

|                        | On demand (n = 42) | Prophylaxis (n = 42) |
|------------------------|-------------------|----------------------|
| Age (years)            |                   |                      |
| Median (range)         | 29 (17–48)        | 29 (15–50)           |
| Race, n (%)            |                   |                      |
| White                  | 38 (90.5)         | 38 (90.5)            |
| Asian                  | 1 (2.4)           | 1 (2.4)              |
| Hispanic               | 3 (7.1)           | 3 (7.1)              |
| Number of target joints/participant at baseline, n Median (range) | 1.5 (0–7) | 1.0 (0–5) |
| Participants with ≥ 1 target joint at baseline (%) | 73.8 | 66.7 |
| Follow-up days during the study | 1097 (1086; 1107) | 1104.5 (1092; 1114) |
| Exposure days during the study | 155 (92; 205) | 471 (433; 479) |
| Total bleeding events during the study (n) | 4338 | 264 |
| FVIII dose/infusion during the study (IU kg⁻¹) | 27.8 (25.3; 33.9) | 26.6 (26.0; 27.5) |
| FVIII consumption during the study (IU kg⁻¹ per year) | 1700 (1124; 2263) | 4102 (3904; 4312) |

Q1, quartile 1; Q3, quartile 3. All participants had <1.0% FVIII activity (FVIII:C), except for three participants (prophylaxis group) who had 1.1–1.3% FVIII:C.
Joint physical examination by use of the CAJAS Consistent with eMRI total scores, CAJAS data (n = 42 participants per group) showed that baseline joint health score per joint was somewhat better in the OD group (mean, 7.32 [SD 3.50]; median, 6.33) than in the prophylaxis group (mean, 8.24 [SD 3.60]; median, 8.25). No participant in either study arm had a normal total CAJAS score of 0 at study baseline. Functional joint examination with the CAJAS showed improvement by year 3 in 64.1% of prophylaxis participants and in 43.2% of OD participants; worsening occurred in 28.2% of prophylaxis participants and in 51.4% of OD participants. LS mean changes at year 3 showed that, whereas the prophylaxis group experienced a mild improvement in joint health (0.31; 95% CI −0.79 to 0.18), the OD group experienced a mild deterioration in joint health (0.63;
95% CI 0.08–1.18). The estimated change difference between treatment groups was −0.94 points, favoring prophylaxis (95% CI −1.61 to −0.26, \( P = 0.0072 \); Fig. 3).

**HAEMO-QoL-A** HAEMO-QoL-A data (prophylaxis, \( n = 41 \); OD, \( n = 42 \)) showed similar baseline total scores for the prophylaxis (mean, 72.16 [SD 11.59]; median, 73.09) and OD (mean, 68.90 [SD 20.50]; median, 71.37) groups.

LS mean changes in HAEMO-QoL-A total score from baseline to year 3 showed an improvement by 3.98 points in the prophylaxis group (95% CI −1.14 to 9.10; median, 4.40) and a deterioration by 6.00 points in the OD group (95% CI −11.62 to −0.38; median, 0.27). The estimated treatment difference was 9.98 points (95% CI 3.42–16.54, \( P = 0.0034 \)), favoring prophylaxis and exceeding the MID considered to be clinically meaningful.

The prophylaxis group had LS mean improvements in all HAEMO-QoL-A domains except for emotional impact, whereas the OD group experienced worsening in all domains (Table 2). Mean changes in physical functioning score over time (Fig. 4) showed improvements in the prophylaxis group versus the OD group that were apparent from 6 months to 3 years.

**EQ-5D self-report questionnaire** Baseline EQ VAS scores (\( n = 42 \) participants per group) were similar in the two randomization groups (mean [SD], median: prophylaxis, 72.69 [SD 15.43], 80.0; OD, 73.74 [SD 17.75], 79.0, as were EQ-5D utility index scores (means: prophylaxis, 0.81 [SD 0.10]; OD, 0.80 [SD 0.16]). Mean changes in EQ VAS and EQ-5D utility index scores from baseline to year 3 were 10.49 (SD 17.20) and 0.06 (SD 0.15), respectively, for the prophylaxis group, indicating improved HRQoL, whereas almost no change was seen for the OD group (−1.80 [SD 15.92] and −0.01 [SD 0.16] for EQ VAS and EQ-5D utility index scores, respectively).

**Short-form McGill pain questionnaire** Baseline scores for the last 4 weeks’ pain rating for participants at study entry (mean [SD], median [range]) were similar in both groups (prophylaxis, 33.1 [SD 23.0], 29.5 [0–83]; OD, 31.5 [SD 21.8], 29.5 [0–87]). At 3 years, prophylaxis participants reported a 50% decrease in pain for the previous 4 weeks (−17.2 [SD 22.9], −16.0 [–75 to 21]), whereas OD participants reported no change (0.0 [SD 25.1], −3.0 [−52 to 52]). Short-form McGill Pain Questionnaire total pain scores (sum of current pain intensity, sensory pain, and affective pain scores) range from 0 to 48; at study entry, pain scores were low and similar for both groups (mean [SD], median [range]: prophylaxis, 7.0 [SD 4.8], 6.0 [0–17]; OD, 7.5 [SD 8.1], 5.0 [0–35]). Although baseline scores were too low for MID changes to be recorded, prophylaxis participants reported a one-third decrease in total pain (−2.5 [SD 4.9], −2.0 [−17 to 11]), whereas OD participants reported a one-third increase (2.4 [SD 8.9], 1.0 [−21 to 24]).

**Change in activity level** At baseline, 7.1% of prophylaxis participants and 14.3% of OD participants reported increased 4-week activity. Maximal improvements were seen in both groups at 24 months (prophylaxis, 54.8%; OD, 64.9%)

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**Table 2** Change from baseline to year 3 in HAEMO-QoL-A scores: constrained longitudinal data analysis estimates

|                           | Change from baseline to year 3, LS mean (95% CI) | Difference*    | \( P \)-value |
|---------------------------|-----------------------------------------------|----------------|---------------|
|                           | On demand (\( n = 42 \))                       | Prophylaxis (\( n = 41 \)) |                |
| HAEMO-QoL-A total score   | − 6.00 (−11.62 to −0.38)                       | 3.98 (−1.14 to 9.10) | 9.98 (3.42–16.54) | 0.0034 |
| Domain subscales          |                                               |                 |               |
| Physical functioning      | − 5.30 (−11.97 to 1.37)                       | 7.86 (1.79–13.92) | 13.15 (5.23–21.08) | 0.0015 |
| Role functioning          | − 5.35 (−11.28 to 0.58)                       | 1.45 (−3.93 to 6.83) | 6.80 (−0.29 to 13.88) | 0.0597 |
| Worry                     | − 6.39 (−15.87 to 3.09)                       | 4.61 (−4.05 to 13.27) | 11.00 (0.43–21.56) | 0.0416 |
| Consequences of bleeding  | − 4.89 (−12.47 to 2.69)                       | 9.13 (2.16–16.09) | 14.02 (5.48–22.56) | 0.0016 |
| Emotional impact          | − 6.89 (−13.99 to 0.21)                       | − 0.17 (−6.76 to 6.41) | 6.72 (−0.83 to 14.26) | 0.0803 |
| Treatment concerns        | − 7.10 (−15.90 to 1.69)                       | 0.54 (−7.48 to 8.56) | 7.64 (−2.39 to 17.67) | 0.1331 |

CI, confidence interval; LS, least squares. *Prophylaxis versus on demand.

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OD, 23.8%). At 3 years, 40.5% of prophylaxis participants and 19.0% of OD participants reported increased activity. At baseline, the percentages of participants with unrestricted work/school and recreational activities were similar (prophylaxis, 33.3%; OD, 38.1%). By 3 years, unrestricted participation was increased in the prophylaxis group (47.6%) and decreased in the OD group (26.2%).

**HRU** Over a period of 3 years on study, OD participants reported more HRU than prophylaxis participants (Fig. 5), including: contacts with health professionals (hematologists [2.43-fold], primary-care physicians [3.17-fold], and nurses [2.2-fold]; laboratory utilization (1.79-fold); and joint surgeries (performed in 23.8% versus 9.5% of participants).

**Treatment satisfaction** At 3 years, 42.9% of prophylaxis participants and 26.2% of OD participants reported that treatment somewhat/greatly exceeded their expectations; 64.3% of prophylaxis participants and 42.9% of OD participants were very/extremely satisfied with treatment. At baseline, ~50% of participants in each group did not know whether they would like to continue with their former regimen. At the final visit, 66.7% of prophylaxis participants and 47.6% of OD participants reported that they probably/definitely would continue with their study treatment regimen.

**Safety**

Sixty-two of the 84 participants (73.8% [prophylaxis, \( n = 25; \) OD, \( n = 37 \)]) reported AEs and 21 participants (25.0% [prophylaxis, \( n = 9; \) OD, \( n = 12 \)]) reported SAEs during the study period; none was considered to be treatment-related. No inhibitors developed on study. As the study was not blinded regarding treatment regimen, it was possible that bias on the part of participants could alter subjective outcome reports. To control for this, the two most frequent non-bleeding-related AEs were compared between the treatment groups. The prophylaxis and OD groups did not differ in either the rate of reported infections or the rate of non-bleeding-related musculoskeletal conditions (\( P = 0.07 \) and \( P = 0.26 \), respectively).

**Discussion**

SPINART was undertaken in response to an unmet need for data to establish the benefits of secondary and tertiary prophylaxis in individuals with severe hemophilia A and established arthropathy in high-resource and low-resource countries. Substantial morbidity related to arthropathy was observed at baseline for all participants, as reflected in bleeding rates, joint MRI, joint health, QoL, pain, participation, and activity, which worsened following 3 years of continued OD. Progression of joint deterioration was similar in adolescents and adults.

The primary endpoint result of SPINART, i.e. low bleeding frequency with prophylaxis at 1 year, was maintained for 3 years [14]. The persistent and dramatic decrease in bleeding on prophylaxis, together with very high-level adherence, demonstrate that adolescents and adults are willing to continue three times weekly prophylaxis for an extended duration, with continued benefits in bleed reduction.

It is controversial whether articular damage can be reversed, be arrested, or have its progression attenuated; however, evidence from older uncontrolled studies in patients aged < 25 years suggested that a reduction in bleeding with prophylaxis was associated with decreased joint deterioration [9,26]. A cross-sectional study in adults and adolescents showed a reduction in joint bleeding, and suggested structural joint preservation with secondary and tertiary prophylaxis versus OD, although the benefits were greatest when prophylaxis had been initiated early in childhood [12]. The benefits of earlier initiation of prophylaxis have also been seen in other longitudinal and cohort studies [7,8,27,28], and early prophylaxis is recommended by the Scientific and Standardization Committee of the ISTH [29].

In SPINART, baseline eMRI scores suggested considerable joint damage in both groups. The prophylaxis group had evidence of worse arthropathy at the beginning of the study, but the 94% reduction in bleeding frequency on prophylaxis did not translate to improved eMRI results at 3 years, similarly to what was found in a previous study that used radiologic assessments [27]. Progressive deteriorations in eMRI total score, with most progression being seen in osteochondral defects, were detected in both groups after 3 years, with slightly less progression on prophylaxis. The reasons for a lack of improved MRI score following delayed prophylaxis are
unclear. In the JOS, in which MRI scores of all joints were 0 at baseline, the MRI score at 6 years was 0 in 93% of prophylaxis recipients and in 55% of OD recipients (P = 0.002). In SPINART, no participant had perfect scores for all six index joints (MRI score of 0). Prophylaxis is probably effective in preventing arthropathy, but is less or not effective in halting or reversing progression after the onset of damage. Alternatively, it is possible that the SPINART OD participants actually had greater progression in joint damage but eMRI was not sensitive in visualizing arthropathy progression. The observation period in SPINART was shorter than that in the JOS (mean, 33 months versus 49 months). Moreover, assuming auto-progression of arthropathy and considering that baseline eMRI scores were higher in the prophylaxis group, the short duration of the trial may have confounded the ability to detect slowing of arthropathy progression with prophylaxis. Four joints with normal eMRI at baseline developed abnormalities during SPINART, despite prophylaxis. It is possible that bleeding before and/or during prophylaxis caused eMRI changes following baseline imaging. Reduced progression of structural damage in participants aged ≤20 years receiving prophylaxis was seen in SPINART, suggesting that prophylaxis may halt osteochondral damage in young patients, similarly to previously reported results of secondary prophylaxis in children and adolescents [9].

In contrast to the eMRI results, there were clear advantages for prophylaxis regarding joint health on joint physical examination, which was mild but sustained over 3 years of prophylaxis. Although the joint score may be subject to performer bias, the physiotherapists determining joint score were blinded to the study arm of the participant and bleeding history; in addition, results were consistent across physiotherapists in four countries. Although bony joint deformities did not improve with prophylaxis, participants were able to be more active with bleeding cessation; other studies have found that joint functioning, pain and activity can improve in persons with hemophilic arthropathy using physiotherapy and exercise, despite fixed joint abnormalities [30,31].

Likewise, advantages for prophylaxis were found in PROs such as HRQoL, pain, and participation (activity level). The HAEMO-QoL-A total score difference of nearly 10 points clearly favored prophylaxis, exceeding the distribution-based MID considered to be clinically meaningful [23]. Most HAEMO-QoL-A domain scores improved with prophylaxis, with the largest improvements being seen in the physical functioning, consequences of bleeding and worry domains, consistent with previous research on HRQoL in hemophilia that showed deficits primarily in the physical functioning domain [10,11,22]. Furthermore, EQ-5D results were consistent with HAEMO-QoL-A results. Similar to bleeding cessation, improvements in joint health, HRQoL, pain, activity, HRU and treatment satisfaction are in support of adults receiving sustained benefit from prophylaxis.

Regarding limitations, the sensitivity of the rating scale or imaging technique as well as the sample size and follow-up duration may have been insufficient to detect major differences in joint MRI changes between prophylaxis and OD in this population. The open-label study design may potentially have affected participant-reported HRQoL, pain, and treatment satisfaction, as participants may have felt more optimistic by knowing that they were employing a preventive treatment strategy. However, expectation of a better outcome is recognized to promote

Fig. 5. Healthcare resource utilization during 3 years of prophylaxis versus on-demand treatment. (A) Contacts with any health professional. (B) Number of joint-related surgeries. (C) Number of laboratory tests.
improved outcomes in clinical practice as well as in clinical trials. Hope has been shown to mediate preventive practices and better health outcomes in other disorders, including childhood type 1 diabetes [32,33]. Participants using prophylaxis maintained positive PROs over a period of 3 years, and it is unlikely that positive PROs that were not in fact experienced would have been sustained over such a duration.

Conclusions

SPINART determined that, without prophylaxis initiated early in life, structural joint damage in patients with hemophilia A affects most index joints by early adulthood and progresses in spite of later prophylaxis, suggesting that pre-existing joint arthropathy may be irreversible. On the basis of the SPINART findings of sustained bleeding cessation, improved joint health, HRQoL, activity, participation, and treatment satisfaction, and reduced pain and HRU, prophylaxis should be standard-of-care therapy for all people with severe hemophilia and clinical bleeding, regardless of age and previous joint damage. Furthermore, these data strengthen the argument to continuously encourage the initiation and maintenance of prophylaxis before the onset of arthropathy.

Addendum

Each author contributed to the development of the manuscript, reviewed and commented on each draft, and approved the final draft. D. Walker contributed to the study protocol. S. Funk, B. Lundin, M. J. Manco-Johnson, and W. Hong contributed to the study design. B. Lundin, S. Funk, C. Peterfy, D. Raunig, M. Werk, C. L. Kempton, M. T. Reding, S. Goranov, L. Gercheva, M. Pierdominici, D. Walker, and W. Hong contributed to data acquisition. S. Engelen, D. Raunig, M. J. Manco-Johnson, J. Pocoski, and W. Hong contributed to data analysis. M. J. Manco-Johnson, S. Engelen, C. L. Kempton, M. T. Reding, S. Goranov, L. Gercheva, and W. Hong contributed to data interpretation. L. Rusen, V. Uscatescu, and M. Pierdominici participated in the conduct of the study.

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Disclosure of Conflict of Interests

M. J. Manco-Johnson has received honoraria for advisory board participation from Bayer, Baxter BioScience, Biogen Idec, CSL Behring, and Novo Nordisk, and has received research grant funding from and has participated in a steering committee for Bayer. S. Funk developed, and M. J. Manco-Johnson implemented, the use of the CAJAS PT scale, which will be copyrighted. B. Lundin is employed by the Center for Medical Imaging and Physiology at Skåne University Hospital, has been under contract to Bayer for work performed for the cross-sectional study 12948, and is under contract for work performed for SPINART. S. Funk is a paid consultant on the Bayer-sponsored SPINART study. C. Peterfy received a grant from Bayer and personal fees from Spire Sciences, Inc. D. Raunig is employed by ICON Medical Imaging, and is under contract to Bayer for work performed for SPINART on the validation of the eMRI scale and CAJAS. M. Werk is under contract to Bayer for work performed for SPINART. M. T. Reding has received honoraria for advisory board participation from Baxter, Bayer, Biogen Idec, Octapharma, and Novo Nordisk, and has received speaking fees from Baxter, Biogen Idec, Novo Nordisk, and Pfizer. L. Rusen has received personal fees from Bayer. J. Pocoski and D. Walker are employees of Bayer. S. Engelen and W. Hong were employees of Bayer at the time this work was performed. The other authors state that they have no conflict of interest.

Appendix

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References

1 Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. J Thromb Haemost 2010; 8: 1895–902.
2 Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A, Subcommittee on Factor VIII and Factor IX and Rare Coagulation Disorders. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2014; 12: 1935–9.
3 Manco-Johnson MJ, Ashbury TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357: 535–44.
4 Gringeri A, LUNDIN B, MACKENSEN SV, MANTOVANI L, MANNUCCI PM; ESPRIT Study Group. A randomized clinical trial of
prophylaxis in children with hemophilia A (the ESPRIT Study). J Thromb Haemost 2011; 9: 700–10.

5 National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC) recommendations concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding). Document #241. https://www.hemophilia.org/sites/default/files/document/files/241Prophylaxis.pdf. Accessed 25 May 2016.

6 Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on behalf of the World Federation of Hemophilia. Guidelines for the management of hemophilia. Haemophilia 2013; 19: e1–47.

7 Nilsson IM, Bertorpi E, Lofqvist T, Pettersson H. Twenty-five years’ experience of prophylactic treatment in severe hemophilic A and B. J Intern Med 1992; 232: 25–32.

8 Fischer K, van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, de Kleijn P, Grobbbee DE, van den Berg M. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood 2002; 99: 2337–41.

9 Manco-Johnson MJ, Nuss R, Geraghty S, Funk S, Kilcoyne R. Results of secondary prophylaxis in children with severe hemophilia. Am J Hematol 1994; 47: 113–17.

10 Fischer K, van der Bom JG, van den Berg HM. Health-related quality of life as outcome parameter in haemophilia treatment. Haemophilia 2003; 9(Suppl. 1): 75–82.

11 Royal S, Schramm W, Bertorpi E, Giarandrea P, Gringeri A, Ludlam C, Kroner B, Szucs T; European Haemophilia Economics Study Group. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. Haemophilia 2002; 8: 44–50.

12 Oldenburg J, Zimmermann R, Katsarou O, Theodossiades G, Zanon E, Niemann B, Kellermann E, Lundin B; Cross-sectional MRI study investigators. Controlled, cross-sectional MRI evaluation of joint status in severe hemophilia A patients treated with prophylaxis vs. on demand. Haemophilia 2015; 21: 171–9.

13 Aledort L, Bullinger M, von Macensen S, Wasserman J, Young NL, Globe D, Health Related Quality of Life Expert Working Group of the International Prophylaxis Study Group. Why should we care about quality of life in persons with haemophilia? Haemophilia 2012; 18: e154–7.

14 Manco-Johnson MJ, Kempston CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L, Rusen L, Ghina M, Uscatescu V, Rescia V, Hong W. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINAT) [published correction appears in J Thromb Haemost 2014;12:119-122]. J Thromb Haemost 2013; 11: 1119–27.

15 Nuss R, Kilcoyne RF, Geraghty S, Shroyer AL, Rosky JW, Mawhinney S, Wiedel J, Manco-Johnson M. MRI findings in haemophilic joints treated with radiosynoviorthesis with development of an MRI scale of joint damage. Haemophilia 2000; 6: 162–9.

16 Lundin B, Pettersson H, Ljung R. A new magnetic resonance imaging scoring method for assessment of haemophilic arthropathy. Haemophilia 2004; 10: 383–9.

17 Lundin B, Manco-Johnson ML, Ignas DM, Moineddin R, Blanchette VS, Dunn AL, Gibikotie SV, Keshava SN, Ljung R, Manco-Johnson MJ, Miller SF, Rivard GE, Doria AS; International Prophylaxis Study Group. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. Haemophilia 2012; 18: 962–70.

18 Lundin B, Babyn P, Doria AS, Kilcoyne R, Ljung R, Miller S, Nuss R, Rivard GE, Pettersson H; International Prophylaxis Study Group. Compatible scales for progressive and additive MRI assessments of haemophilic arthropathy. Haemophilia 2005; 11: 109–15.

19 Hong W, Raunig D, Lundin B. SPINART study: validation of the extended magnetic resonance imaging scale for evaluation of joint status in adult patients with severe haemophilia A using baseline data. Haemophilia 2016; 22: e519–26.

20 Funk S, Walker D, Engelen S, Benjamin K, Moskovich O, Gentile B, Church N, Manco-Johnson M. Validation of the Colorado Adult Joint Assessment Scale in adult patients with severe hemophilia A. Haemophilia 2016; 22: 42.

21 Gilbert MS. Prophylaxis: musculoskeletal evaluation. Semin Hematol 1993; 30: 3–6.

22 Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, Garrido RP, Scharrer I, Schramm W, Gorina E, Members of the HAEMO-Qol-A Steering Committee. Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. Haemophilia 2008; 14: 1023–34.

23 Flood E, Valluri S, Mink D, Bell JA, Pocoski J, Sasane R. Minimal important difference (MID) of the Haemophilia-Specific Quality-of-Life Questionnaire (HAEMO-QOL-A) for adults with severe hemophilia A. Presented at: World Federation of Hemophilia, 5–12 July 2012; Paris, France.

24 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005; 14: 1523–32.

25 Liang K, Zeger S. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankhya: Indian J Stat 2000; 62: 134–48.

26 Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. J Intern Med 1994; 236: 391–9.

27 Kreuz W, Escriuila-Ettingshausen C, Funk M, Schmidt H, Kornhuber B. When should prophylactic treatment in patients with haemophilia A and B start? – The German experience. Haemophilia 1998; 4: 413–17.

28 Astermark J, Petrin P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. Br J Haematol 1999; 105: 1109–13.

29 Fischer K, Collins PW, Ozelo MC, Srivastava A, Young G, Blanchette VS. When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH. J Thromb Haemost 2016; 14: 1105–19.

30 Cuesta-Barriuso R, Torres-Ortuno A, Nieto-Munuera J, Lopez-Pina JA. Effectiveness of an educational physiotherapy and therapeutic exercise program in adult patients with hemophilia: a randomized controlled trial. Arch Phys Med Rehabil 2017; 98: 841–8.

31 Gurcan Y, Eksioglu E, Ezer U, Cakir B, Cakci A. A prospective series of musculoskeletal system rehabilitation of arthropathic joints in young male hemophilic patients. Rheumatol Int 2008; 28: 541–5.

32 Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, Sigmund ST, Yoshinobu L, Gibb J, Langlee C, Harney P. The will and the ways: development and validation of an individual-difference measure of hope. J Pers Soc Psychol 1991; 60: 570–85.

33 Van Allen J, Steele RG, Nelson MB, Peugh J, Egan A, Clements M, Patton SR. A longitudinal examination of hope and optimism and their role in type 1 diabetes in youths. J Pediatr Psychol 2016; 41: 741–9.