Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study

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Summary

Rigorous evidence is lacking on long-term outcomes of factor VIII (FVIII) prophylaxis initiated in adolescent or adult patients with severe haemophilia A. The prospective, open-label Prophylaxis versus On-demand Therapy Through Economic Report (POTTER) study (ClinicalTrials.gov NCT01159587) compared long-term late secondary prophylaxis (recombinant FVIII-FS 20–30 IU/kg thrice weekly) with on-demand treatment in patients aged 12 to 55 years with severe haemophilia A. The annual number of joint bleeding episodes (primary endpoint), total bleeding episodes, orthopaedic and radiologic (Pettersson) scores, health-related quality of life (HRQoL), pharmacoeconomic impact, and safety were evaluated over a >5-year period (2004–2010). Fifty-eight patients were enrolled at 11 centres in Italy; 53 (27 prophylaxis, 26 on demand) were evaluated and stratified into 2 age subgroups (12–25 and 26–55 years). Patients receiving prophylaxis experienced a significantly lower number of joint bleeding episodes vs the on–demand group (annualised bleeding rate, 1.97 vs 16.80 and 2.46 vs 16.71 in younger and older patients, respectively; p=0.0043). Results were similar for total bleeding episodes. Prophylaxis was associated with significantly fewer target joints ($p<0.001$), better orthopaedic (p=0.0019) and Pettersson (p=0.0177) scores, better HRQoL, and fewer days of everyday activities lost ($p<0.0001$) but required significantly higher FVIII product consumption. The POTTER study is the first prospective, controlled trial documenting long-term benefits of late secondary prophylaxis in adolescents and adults with severe haemophilia A. The benefits of reduced bleeding frequency, improved joint status, and HRQoL may offset the higher FVIII consumption and costs.

Keywords

Bleeding, health-related quality of life, haemophilia, haemophilic arthropathy, prophylaxis

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Introduction

The introduction of prophylaxis (i.e. a long-term regular regimen of factor concentrate infusions aiming to prevent bleeding and its deleterious effects on joints) as a standard of care has revolutionised the natural history of severe haemophilia (1). Since the development of pioneer regimens in Sweden more than 50 years ago (2), clinical and social advantages of patients treated prophylactically compared with those treated on demand (i.e. when bleeding occurs) were clearly recognised, in terms of reduction in the number and severity of bleeding episodes, and impact of haemophilic arthropathy. This therapeutic approach, progressively and heterogeneously implemented in other European countries and in North America, led to the reversal of the hallmark of severe haemophilia as an unavoidably crippling disease (1). Prophylaxis has been recommended by the World Health Organisation (WHO) and the World Federation of Hemophilia (WFH) since 1994 (3). Two randomised trials (4, 5) have conclusively shown that preventing bleeding from an early age with primary prophylaxis (started before age three years or before two joint bleeds have occurred [6]) or early secondary prophylaxis (started later in childhood [6]) can preserve joint function, avoiding or greatly reducing

the clinical impact of arthropathy and its effects on health-related quality of life (HRQoL) (6).

Late secondary, or tertiary, prophylaxis is started in adolescent or adult patients with established haemophilic arthropathy, with the goal of stopping or slowing progression of musculoskeletal damage and preventing other bleeding-related morbidity (6). There is an open debate regarding prophylaxis in adolescent and adult patients due to the huge economic impact and the undefined cost-effectiveness of such treatment later in life. Data comparing late secondary prophylaxis with on-demand treatment are limited and most available studies have methodologic limitations, including retrospective or non-controlled design, heterogeneity of patients, varying regimens and data collection procedures, limited sample size and follow-up period (7–12). Two prospective studies have been published, both reporting 6- to 12-month follow-up (13, 14). In addition, results concerning bleeding episodes from the first year of the three-year SPINART trial, in which patients were randomised to prophylaxis or on-demand treatment, have been recently published (15). No long-term prospective study is presently available.

To further investigate the effects of long-term late secondary prophylaxis compared with on-demand treatment, we conducted a prospective five-year study in Italian patients with severe haemophilia A.

Methods

The Prophylaxis versus On-demand Therapy Through Economic Report (POTTER) study (ClinicalTrials.gov identifier NCT01159587) was an observational, prospective, open-label, two-arm, multicentre trial comparing long-term late secondary prophylaxis with on-demand treatment in adolescents and adults with severe haemophilia A (factor VIII (FVIII) activity < 1 IU/dl). The study was conducted from July 2004 to December 2010.

Patients were eligible if they were male, aged 12 to 55 years, had > 150 FVIII exposure days, had no measurable FVIII inhibitors (< 0.6 Bethesda units/ml), and had been treated with full-length sucrose-formulated recombinant FVIII (rFVIII-FS; Bayer HealthCare, Berkeley, CA, USA) for at least six months before study entry. Patients in the on-demand group were required to have had ≥ 6 joint bleeds requiring treatment with rFVIII-FS in the previous six months. Patients were enrolled 1:1 based on their current treatment regimen (prophylaxis or on demand) and stratified by age (12–25 or 26–55 years). Patients in the prophylaxis group had started such a regimen on the basis of clinical indications before study entry and, according to the Italian guidelines, received rFVIII-FS 20 to 30 IU/kg thrice weekly on nonconsecutive days (16). Patients treated on demand received rFVIII-FS when bleeding episodes occurred according to routine clinical practice (i.e. 25–40 IU/kg as soon as possible, repeated every 12–24 hours until resolution).

The study was conducted in compliance with international Good Clinical Practice and national and local regulatory requirements. The protocol was approved by the ethics committees of participating institutions, and written informed consent was obtained from patients or guardians in the case of minors.

Outcome measures

The primary efficacy endpoint was the number of joint bleeding episodes per year. Secondary efficacy endpoints included the number of total bleeding episodes per year, change in joint status, pharmacoeconomic assessment, and HRQoL.

Joint status was evaluated using the WFH Orthopaedic Joint Score (pain and physical examination) (17), assessed in six joints (knees, ankles, elbows), and the Pettersson radiologic score (18), obtained from plain film radiography of the same six joints.

HRQoL was evaluated using three self-administered questionnaires: two generic instruments [36-item Short Form (SF-36) and the five-dimension EuroQoL (EQ-5D)] and a validated disease-specific questionnaire, the Haemo-QoL for children up to age 16 years and the Haemo-QoL-A for adults (19). The latter covers six dimensions of health (physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns), with scores ranging from 0 to 100 (higher scores indicate better HRQoL) (20). Adherence to prophylaxis was evaluated and expressed as the percentage of rFVIII-FS infusions relative to the prescribed regimen.

The study included a pharmacoeconomic analysis, taking into account all direct and indirect healthcare costs. These data will be reported in detail elsewhere; however, annual rFVIII-FS consumption and the number of days of everyday activities lost by patients or their caregivers as a result of haemophilia are reported in this paper.

Safety was evaluated through reports of adverse events (AEs) and serious AEs (SAEs), including FVIII inhibitor development.

Data collection

Data were collected at each site at baseline and at visits scheduled every six months thereafter, according to the routine clinical practice in Italy. Data sources were patient files and patient-completed diaries, in which patients were instructed to report infusions with rFVIII-FS for prophylaxis or for on-demand treatment of bleeding (dose, time, and date of each infusion), type of bleeding episode, number of days of everyday activities lost, days in hospital, all medical visits, physiotherapy cycles, radiographic examinations, and concomitant drug intake.

At each follow-up visit, available clinical and diary data were collected, together with laboratory assessments including FVIII inhibitor titers, FVIII:C level, whole blood cell count, and liver function tests. Changes to the regimen (or dose) of treatment were recorded and patients continued with the study follow-up. Orthopaedic Joint Score and HRQoL questionnaires were obtained every 12 months. If available, Pettersson score and virologic status were evaluated at baseline and study end.

Sample size

Previous studies (21, 22) have shown that the mean (SD) number of joint bleeds per year in patients treated on demand is 15 (11.0). An expected clinical reduction in joint bleeds of ~60% was hypothesised in patients receiving prophylaxis, with lower variability (SD, 8.5) because of more stable clinical conditions. Assuming a two-tailed α-level of 5% with a power of 80%, the sample size needed to compare two group means with unequal variances (SD, 11.0 and 8.5) is 20 patients per group (nQuery Advisor 5.0; Statistical Solutions Inc., Cork, Ireland). Statistical power increases to 85% with enrollment of 50 patients.

Statistical analysis

All analyses were conducted using data from the intent-to-treat (ITT) population. Patients who switched from on demand to prophylaxis or vice versa during the study were considered for the total effective time spent in each regimen for annual bleeding rate calculations but were included in the initial treatment regimen group only for all other analyses. Stratification by age subgroup (12–25 vs 26–55 years) was adopted to account for a main confounding factor.

All recorded and derived variables were analysed using descriptive statistics. Comparisons between groups were made using analysis of variance (ANOVA) models or ANOVA models on ranks in cases of nonnormally distributed data (i.e. Shapiro-Wilk test, $p<0.05$) for continuous variables, and Chi-square tests or Fisher exact tests in case of small cell numerousness for categorical variables.

The number of bleeding episodes (total, joint, and other) during the calendar years of observation was computed using both prevalence and last observation carried forward (LOCF) approaches and annualised bleeding rates (ABR) were obtained. A repeated-measures ANOVA model was fitted to assess between-group differences, including treatment regimen, age stratum, and calendar year as effects and interactions. Incidence rates of bleeding episodes per year were computed for all patients as number of bleeding episodes on total patient-time at risk and analysed using a negative binomial regression model for count data able to manage the correlation among patients; the effects of the actual treatment cohort, age strata, and their interaction were included in the model.

Annual rFVIII-FS consumption (IU/kg per year) was summarised by treatment cohort and age stratum; an ANOVA model of average annual rFVIII-FS consumption during the five-year observation was performed with treatment cohort, age strata, and their interaction as independent variables. For Orthopaedic Joint Score and radiologic Pettersson score, change from baseline to last available evaluation was calculated; an analysis of covariance model on score changes was applied with baseline score, treatment cohort, age stratum, and regimen per age interaction as independent variables. In the Orthopaedic Joint Score model, the number of days elapsed in the treatment regimen cohort defined at the start of the study was also considered. Between-group comparisons for numbers of target joints and days lost were made using independent sample t-tests.

For yearly HRQoL assessments, patients who did not meet age criteria to answer a type of questionnaire (patients younger than 14 years for EQ-5D; patients younger than 16 years for SF-36; and patients younger than 17 years for Haemo-QoL-A) were excluded. On the basis of the different duration of patients' follow-up, a LOCF approach was used for assessments obtained after the 48-month-visits. An ANOVA model was performed for investigating relationships between quality of life and patients' clinical characteristics, including age, treatment regimen, bleeding frequency, and Orthopaedic Joint Score.

All statistical analyses were performed using SAS System for Windows version 9.2 (SAS Institute Inc., Cary, NC, USA). Data were reviewed in depth by two investigators (A.T. and A.C.) and analysed in consultation with Bayer statisticians. All authors were provided access to the clinical trial data.

Results

Patient enrollment and follow-up

Of 58 adolescents and adults enrolled in the study between July 2004 and September 2005 at 11 centres, one patient withdrew consent before receiving a rFVIII-FS dose and four had major protocol violations, leaving 57 patients evaluable for safety and 53 for efficacy (27 prophylaxis; 26 on demand) (►Figure 1). The proportion of patients enrolled in the two age subgroups (12–25 and 26–55 years) was similar. Baseline patient characteristics are shown in ►Table 1.

Consistent with the study inclusion criteria, the median number (range) of joint bleeding episodes in patients enrolled in the on-demand group in the six months before study entry was 7 (6–20) and 9 (6–46) for patients aged 12–25 and 26–55 years, respectively. Patients enrolled in the prophylaxis arm were switched from on-demand treatment prior to the study entry for reasons that were similar in both age subgroups: recurrent bleeding into target joints in 12 patients (44.4%), increased bleeding frequency and FVIII concentrate consumption in 13 (48.1%), and prophylaxis after successful immune tolerance induction in 2 (7.4%). Median number (range) of joint bleeding episodes in the year before the start of prophylaxis was 21 (5–92) and 30 (6–98) in the younger and older subgroups, respectively.

Median patient follow-up was 5.4 years (range, 0.5–6.0 years). All patients were followed for ≥4 years, with the exception of one patient in the on-demand older subgroup who dropped out of the study after six months because of unwillingness to complete the treatment diary.

Majority of patients (70%, 9/14 and 10/13 in the younger and older subgroup, respectively) maintained their prophylaxis regimen unchanged throughout the study. Only one younger patient increased prophylaxis dose following a severe knee haemarthrosis, whereas the remaining patients modified dose (3 increased, 1 reduced) or frequency (3 reduced) of infusions according to changes of lifestyle and physical activity.

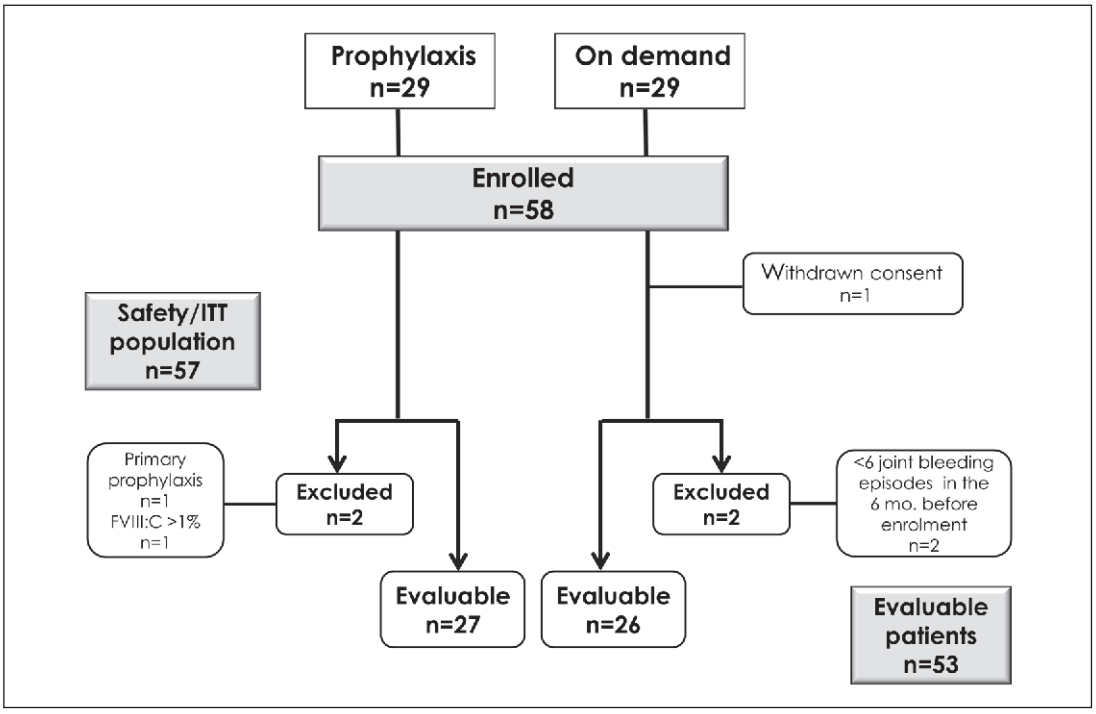

Figure 1: Patient disposition according to treatment regimen at study enrollment.
ITT=intent to treat.

Table 1: Baseline patient characteristics by treatment regimen* and age subgroup.

	Prophylaxis		On demand	
	Age 12–25 years (n=14)	Age 26–55 years (n=13)	Age 12–25 years (n=11)	Age 26–55 years (n=15)
Age, years Mean (SD) Median (range)	 17.0 (3.8) 17.5 (12–23)	 31.1 (3.9) 30.0 (27–39)	 18.1 (5.5) 17.0 (11–25)	 36.9 (7.5) 37.0 (26–49)
Age at diagnosis, years Mean (SD) Median (range)	 1.0 (1.4) 0.5 (0–4)	 2.0 (1.5) 2.0 (0–4)	 0.6 (1.2) 0.0 (0–4)	 3.9 (4.9) 2.0 (0–16)
Age at start of prophylaxis, years† Mean (SD) Median (range)	 11.5 (4.1) 12.2 (8–19)	 27.7 (5.5) 27.0 (20–38)	– –	– –
Duration of prophylaxis before study entry, years‡ Mean (SD) Median (range)	 4.8 (2.7) 4.0 (1–9)	 2.9 (2.7) 1.0 (0.5–7)	 – –	 – –
Prophylaxis dose, IU/kg Mean (SD) Median (range) Frequency (times/week), mean	 27.5 (3.6) 27.0 (20–35) 3	 25.0 (4.2) 26.0 (15–30) 3	 – – –	 – – –

*Forty-five patients maintained the same regimen of treatment throughout the study, whereas 8 patients shifted from one regimen to the other once (4 patients in the subgroup aged 26–55 years and 1 in the subgroup aged 12–25 years) or more than once (2 patients in the older and 1 in the younger subgroup). All five patients who changed regimen only once shifted from the on-demand to the prophylaxis regimen. The remaining three patients (1 on-demand patient and 2 prophylaxis patients) had 3 to 4 regimen changes, all concluding at the study follow-up on prophylaxis. †$P<0.0001$ between age groups (analysis of variance model). ‡$P=0.0354$ between age groups (analysis of variance model).

Table 2: Efficacy outcomes by treatment regimen and age subgroup.

	Prophylaxis		On Demand		P between treatment cohorts
	Age 12–25 years (n=14)	Age 26–55 years (n=13)	Age 12–25 years (n=11)	Age 26–55 years (n=15)	
Follow-up duration, years					
Median (range)	5.4 (4.0–6.0)	5.7 (4.0–6.0)	5.7 (5.0–6.0)	5.3 (0.5–6.0)	
Joint bleeding episodes					
Mean^ (SD)	2.0 (2.0)	3.4 (4.6)	16.6 (12.4)	13.7 (11.2)	
Median^ (range)	1.1 (0.2–5.6)	2.0 (0.0–17.6)	14.2 (2.4–48.6)	9.2 (1.6–40.6)	0.0043†
Annualised bleeding rate*					
Observed	1.97	2.46	16.80	16.71	
Estimated by model (95% CI)	1.92 (1.2–3.2)	2.46 (1.5–4.1)	16.05 (10.2–25.3)	18.04 (12.5–26.1)	
Total bleeding episodes					
Mean (SD)	2.6 (2.2)	4.5 (7.1)	19.5 (15.0)	17.7 (11.7)	
Median (range)	2.1 (0.2–6.8)	2.2 (0.0–27.4)	15.6 (6.0–60.8)	15.0 (2.2–47.6)	0.0048†
Annualised bleeding rate*					
Observed	2.54	2.95	19.77	21.49	
Estimated by model (95% CI)	2.47 (1.6–3.8)	2.95 (1.8–4.7)	19.14 (12.2–30.1)	22.40 (16.3–30.8)	
Target joints°					
Number of patients (%)	2 (14.3)	5 (38.5)	9 (81.8)	12 (80.0)	<0.001**
Mean number per patient (total number)	0.14 (2)	0.77 (10)	1.64 (18)	1.93 (29)	
Orthopaedic Joint Score (pain + physical examination), mean (SD)					
Baseline	3.2 (3.3)	13.3 (15.4)	5.4 (3.0)	17.1 (10.3)	0.0019§
Last evaluation‡	3.0 (2.4)	10.1 (12.5)	8. 8 (4.4)	21.5 (12.8)	
Change last evaluation vs baseline	–0.2 (3.4)	–3.2 (9.7)	+3.6 (4.8)	+4.4 (6.2)	
Pettersson score, mean (SD)‖					
Baseline	4.3 (4.5)	20.0 (18.9)	3.3 (4.9)	22.2 (15.1)	0.0177§
Last evaluation¶	5.5 (4.9)	22.2 (18.5)	5.7 (6.7)	35.0 (17.2)	
Change last evaluation vs baseline	+1.2 (1.6)	+2.2 (2.8)	+2.3 (2.1)	+12.8 (12.3)	
Total average consumption rFVIII, IU/kg/year					
Mean (SD)	3795.8 (1030.7)	3664.5 (763.8)	1367.7 (1330.1)	2004.2 (1321.1)	<0.0001#
Median	3998.0	3844.4	786.4	1651.3	
Range	887.8–4858.0	2259.3–5261.2	432.3–4305.1	211.8–4562.3	
Mean number of days of everyday activities lost/ patient-/caregiver-year	10.6	13.8	43.0	35.6	<0.001**

ANCOVA=analysis of covariance; ANOVA=analysis of variance; CI=confidence interval; rFVIII=recombinant factor VIII; SD=standard deviation. ^Number of events per patient per year. *Patients were counted in the effective following regimen. If patients switched treatment, they were considered in each regimen for the effective time spent in it. †Negative binomial regression model for bleeding episodes. ‡Mean elapsed time (±1 SD), years from baseline: prophylaxis 5.3 (0.6) and 5.6 (0.5), on demand 5.6 (0.5) and 5.0 (0.8) in the 12– to 25-year-old and 26– to 55-year-old subgroups, respectively. °Target joints (defined as a joint in which three or more bleeds occurred within a consecutive six-month period[6]) observed throughout the study period. §ANCOVA model adjusted for number of days elapsed in the regimen cohort defined at study start. ‖Pettersson score was available in 20 patients (11 receiving secondary prophylaxis, 9 treated on demand). ¶Mean elapsed time (±1 SD), years from baseline: prophylaxis 4.8 (1.3) and 4.9 (1.1), on demand 5.1 (1.8) and 4.7 (0.9), in the 12– to 25-year-old and 26– to 55-year-old subgroups, respectively. #ANOVA model. **Independent sample t-tests.

Efficacy outcomes: bleeding episodes

The annual number of bleeding episodes per patient was significantly lower with prophylaxis than on-demand treatment for all types of bleeding events in both age subgroups (▶Table 2). Observed ABR for joint bleeding episodes was 1.97 and 2.46 episodes per patient-year for prophylaxis for the younger and older age subgroups, respectively, vs 16.80 and 16.71 episodes per patient-year, respectively, for on-demand treatment (p=0.0043; ▶Table 2). Patients aged 12 to 25 years bled into joints 8.1 times less frequently (95% confidence interval [CI], 4.2–16.5) and those aged 26 to 55 years bled 7.3 times less frequently (95% CI, 4.5–11.9) when treated with prophylaxis vs on demand. Annual joint bleeding rates decreased 88.1% (95% CI, 76.4%–93.9%) and 86.4% (95% CI, 78.0%–91.6%) with prophylaxis versus on-demand treatment

in the younger and older age subgroups, respectively. Results for total bleeding episodes were similar (▶Table 2).

Of patients on prophylaxis, 50% of younger patients and 23% of older patients had an average of ≤1 joint bleeding episodes per year. No patient treated on demand had such a bleeding rate. Distribution of patients in the different treatment regimens according to mean annual joint bleeding rate is shown in ▶Figure 2. These reductions in bleeding rates with prophylaxis were associated with significantly lower development of target joints (6) throughout the study, particularly in younger patients (▶Table 2). Overall, 67% of patients on prophylaxis (12 in the younger group and 6 in the older group) were free of target joints throughout the study vs 19% of those treated on demand (n=5, 2 younger and 3 older, respectively; p<0.001).

Secondary outcomes

Orthopaedic Joint Scores were higher in older patients compared with younger ones, and in patients treated on demand compared with those on prophylaxis, both at baseline and last evaluation (p<0.05). However, changes in Orthopaedic Joint Scores were significantly different between the prophylaxis and on-demand groups (p=0.0019; ▶Table 2), being considerably worse with on-demand treatment after adjusting for age and baseline scores.

Pettersson scores were available for 20 patients. Younger patients had lower Pettersson scores than older ones. Pettersson scores increased from baseline to last evaluation in both the prophylaxis and on-demand cohorts (▶Table 2); the increase was greater in the on-demand cohort and in older patients (p=0.0177 and p=0.0413, respectively), irrespective of baseline scores. Radiologic signs of joint damage were lower with prophylaxis compared with on-demand treatment, with a greater effect of prophylaxis in

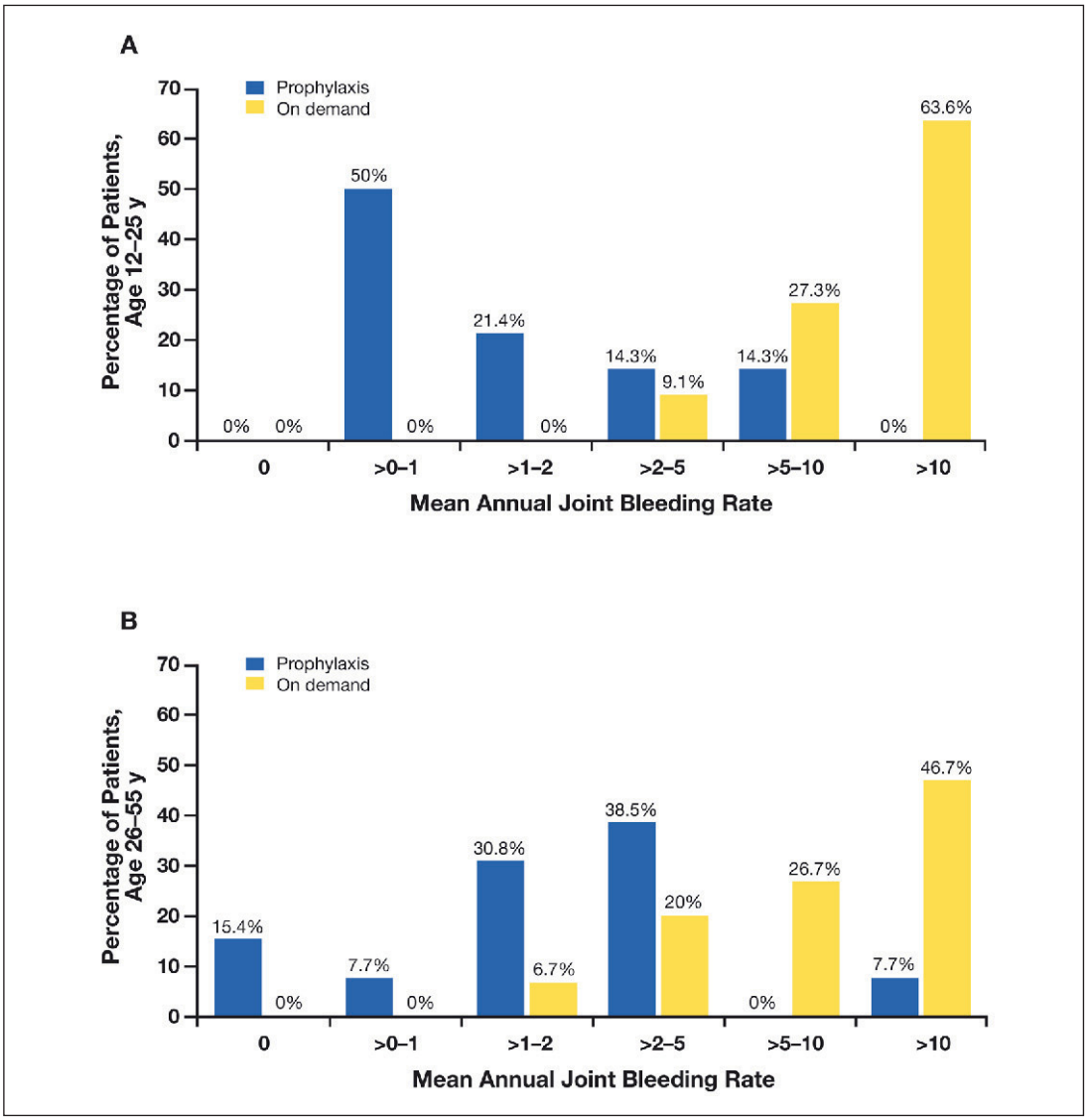

Figure 2: Distribution of patients according to mean annual number of joint bleeding episodes in the two treatment regimens (prophylaxis and on demand) in the (A) 12– to 25-year age group and (B) 26– to 55-year age group. Overall, among patients on prophylaxis, annual joint bleeding rates >5 were reported by 2 patients in the younger group (5.2 and 5.6, respectively) and by a single patient in the older group (17.6).

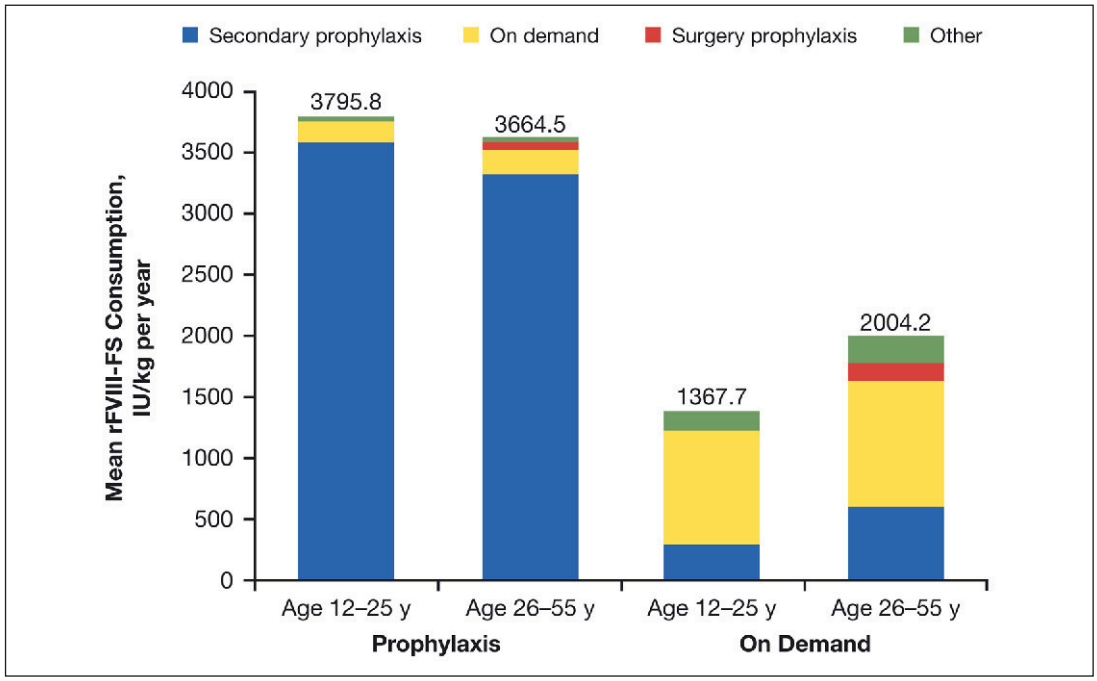

Figure 3: Annual rFVIII-FS consumption based on reason for treatment. Mean values of annual rFVIII-FS consumption (IU/kg per year) according to reason for treatment ($p<0.0001$, ANOVA model treatment regimen effect). ANOVA=analysis of variance; rFVIII-FS=recombinant full-length factor VIII product formulated in sucrose.

older than younger patients (87% and 48% reduction, respectively).

FVIII concentrate consumption was greater with prophylaxis than on-demand treatment, with the difference more pronounced in younger patients (2.8– vs 1.8-fold higher rFVIII-FS use for younger vs older patients, respectively; $p<0.0001$; ▶Table 2). However, FVIII consumption for treatment of bleeding episodes, surgical prophylaxis, and other events had a greater impact in patients treated on demand (▶Figure 3). Patients receiving prophylaxis lost significantly fewer days of participation in everyday activities than those treated on demand (4– and 2.6-fold fewer lost days in the 12– to 25-year-old and 26– to 55-year-old subgroups, respectively; $p<0.001$; ▶Table 2).

Among HRQoL assessments at study enrolment, six patients (3 on demand, 3 prophylaxis) were excluded for EQ-5D and SF-36 and 10 patients (5 on demand, 5 prophylaxis) for Haemo-QoL-A, because they did not meet age criteria. Few missing or invalid responses to questionnaires (range, 2–5) were found at yearly assessments. Consistent data were observed for any questionnaire between different assessments, with no relevant variation over the study follow-up. On average, patients receiving prophylaxis reported better HRQoL than those treated on demand, with similar trends across all questionnaires (▶Figure 4). Differences at baseline were significant in four SF-36 domains (physical functioning, $p=0.025$; role physical, $p=0.026$; social functioning, $p=0.025$; role emotional, $p=0.032$; data not shown), the EQ-5D visual analogue scale ($p=0.01$), 4 Haemo-QoL-A domains (physical functioning, $p=0.02$; role functioning, $p=0.026$; worry, $p=0.004$; consequence of bleeding, $p=0.017$), and the Haemo-QoL-A total score ($p=0.040$) and persisted throughout the study. Worse HRQoL was associated with a higher mean number of bleeds.

Mean adherence to the prescribed prophylaxis regimen was 97% (median (range), 96% (74%–108%)) for younger patients and 90% (91% (67%–101%)) for older patients. Overall, 60% of patients were ≥90% adherent to prophylaxis.

Safety

Twenty-four of the 57 patients (42%) evaluable for safety experienced ≥1 AE (overall 28 in 13 patients receiving prophylaxis and 14 in eight patients treated on demand, respectively (▶Table 3). Only one adult patient in the on-demand cohort experienced a suspected drug-related AE (mild cutaneous rash of lower extremities). Ten SAEs occurred in eight patients (5 treated on prophylaxis and 3 on demand). No drug-related SAEs, including FVIII inhibitor development, were reported. No patient withdrew from rFVIII-FS treatment or from the study because of AEs.

Discussion

The POTTER study is the first long-term prospective, controlled trial to document the clinical benefits of late secondary/tertiary prophylaxis (7, 8). Adolescents and adults on long-term prophylaxis, started before the study entry and here evaluated over a median follow-up of >5 years, showed significant decreases in total and joint bleeds, target joints, and improved joint status and HRQoL compared with those treated on demand.

A thrice weekly regimen of rFVIII-FS at a mean dose of 25 to 27 IU/kg decreased the total and joint ABRs seven- to eight-fold compared with on-demand treatment. Our five-year assessment in parallel treatment cohorts is consistent with recent short-term

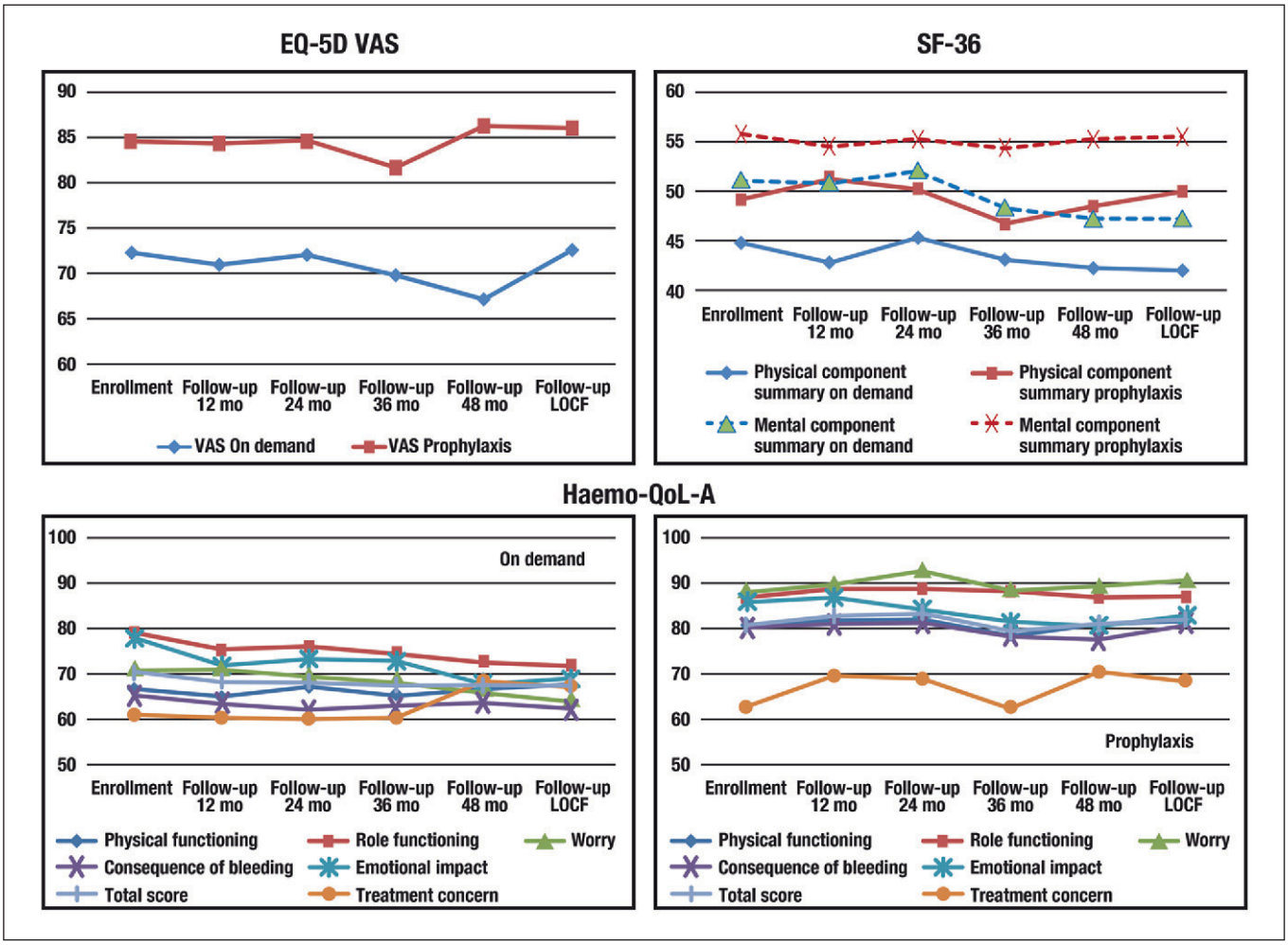

Figure 4: Assessment of health-related quality of life in the two treatment regimens (prophylaxis and on demand) according to EQ-5D (VAS), SF-36 (physical and mental component summaries), and Haemo-QoL-A questionnaires. EQ-5D=5-dimension EuroQoL; LOCF=last observation carried forward (data collected between 54 and 72 months); SF-36=36-item Short Form; VAS=visual analogue scale.

prospective studies confirming the efficacy of secondary prophylaxis in decreasing bleeding frequency, including first-year data from the randomised three-year SPINART study (13–15). Due to the short follow-up available, whether the significant decrease in joint bleeding episodes observed with prophylaxis will have long-term beneficial effects on joint outcomes of patients with established joint damage remains unanswered. In this respect, few retrospective and conflicting data are available (10, 11, 23).

The POTTER study documented significantly better joint outcomes, particularly in older patients, with prophylaxis compared with on-demand treatment, as revealed by orthopaedic scores. Additionally, changes in Pettersson scores (estimated as 0.3 and 0.4 points/year, in younger and older patients, respectively) indicated that prophylaxis may actually delay progression of arthropathy, even in patients with clinically relevant joint damage. These data reflect and extend to adolescent and adult patients previous findings in younger patients (24).

Our data on the beneficial effects of late secondary prophylaxis on HRQoL add strong support to the few data available in this setting (25), for the first time over a long-term assessment and through both generic and specific HRQoL questionnaires. Consistent with the improved physical status and social participation, in our study, prophylaxis resulted in a significantly lower number of days of everyday activities lost compared with on-demand treatment.

Mean adherence to prophylaxis in our long-term study was even higher than that reported in short-term trials (14, 15). These data seem to dispute the poor adherence to prophylaxis that is often reported in adolescents and adults (26–29), which is perceived as a major barrier for extending or starting prophylaxis later in life (27, 30). Patients with a significant bleeding tendency and long previous experience of on-demand treatment are well aware of clinical benefits of prophylaxis and are highly motivated to adhere to such regimens.

The clinical and HRQoL advantages of prophylaxis are unavoidably associated with significantly higher FVIII consumption compared with on-demand treatment. In our study with high adherence, this difference is similar (15) or even lower than in

previous prospective studies in adults (13) or children (5). The gap is smaller in older patients, consistent with the notion that FVIII use tends to increase with age in patients treated on demand owing to progression of joint disease and other age-related comorbidities, resulting in FVIII usage similar to that for prophylaxis over the long term (21, 31). In our five-year follow-up, FVIII use due to surgery or other reasons was higher in patients treated on demand than in those receiving prophylaxis, particularly in the older subgroup. Longer-term assessments are important to address the overall cost-effectiveness and cost-utility of late prophylaxis, in particular in light of the increased life expectancy of patients with haemophilia and the emerging bleeding risks due to age-related comorbidities (32). Indeed, while the increase in costs for FVIII concentrates remains the greatest barrier to prophylaxis in adult patients, even in developed countries, the potential decrease in other healthcare costs (e.g. less need for orthopaedic surgeries or rehabilitation treatment for haemophilic arthropathy) and indirect costs, together with improved HRQoL, should be considered. Long-term assessments have been conducted for primary prophylaxis (23, 33, 34) but are lacking for late secondary prophylaxis.

The POTTER study evaluated a standard prophylactic regimen, with dose and frequency of infusions similar to those used in children. Collins et al. (13) showed that median trough levels at 48 and 72 hours after infusion in patients on a similar prophylaxis regimen using the same recombinant FVIII product were consistently well above 1 IU/dl. Given that pharmacokinetic response to infused FVIII is largely heterogeneous, with longer half-lives in adults than in children (35), prophylactic regimens in adults likely could be individualised according to the specific pharmacokinetics or bleeding phenotype. This approach might be more cost-effective than standard regimens (36), although no significant difference in FVIII consumption was recently documented (14).

Study limitations include the nonrandomised multicentre design; the use of prophylaxis before the study entry, which could be a potential bias; and lack of radiologic data for some patients. However, patients were enrolled using rigorous criteria, avoiding the selection bias of patients with mild bleeding frequency. The observational nature of the study limited the availability of Pettersson scores, but evaluable patients were representative of the entire cohort.

Haemophilia studies are mainly based on home treatment and patient-reported bleeding. Therefore, FVIII infusions for signs or symptoms of chronic arthropathy mimicking a joint bleed cannot be ruled out. However, this bias may occur in both patients treated on demand or with prophylaxis, and the positive impact of prophylaxis in reducing arthropathy symptoms should be considered an additional benefit of such a regimen in patients with established joint damage.

Results from the POTTER study support the long-term safety and effectiveness of prophylaxis in adolescent and adult patients with severe haemophilia A. Late secondary/tertiary prophylaxis significantly decreased the frequency of all bleeding episodes, including joint bleeds, thereby improving joint status and substantially delaying the progression of haemophilic arthropathy. Patients on long-term prophylaxis also reported improved HRQoL

Table 3: Adverse events in the safety population by treatment regimen.

	Total	Prophylaxis	On demand
All AEs	42 (24)*	28 (13)*	14 (8)*
Severe AEs	10 (8)*	7 (5)*	3 (3)*
Type of AE†			
Musculoskeletal pain	4	3	1
Erythema, rash	3	1	2‡
Renal colic	3	2	1
Road traffic accident	3	2	1
Intestinal symptoms	3	2	1
Liver disorder	3	0	3
Nausea, dyspepsia	2	1	1
Gastrointestinal bleeding	2	2	0
Knee arthroplasty	2	1	1

*Number of patients reporting adverse events in parenthesis. †AEs occurring in >1 patient are listed. Drug hypersensitivity (amoxicillin/clavulanic acid), syncope, headache, upper abdominal pain, anaemia, hyperthyroidism, osteoarthritis, haemorrhoids, genitourinary tract infection, influenza, hip arthroplasty, carpal tunnel syndrome, facial bone fracture, and molluscus contagiosum were reported by a single patient on prophylaxis; pyrexia, suicide attempt, and cerebrovascular accident (ischaemic stroke) were reported by a single patient treated on demand. ‡1 mild cutaneous rash of lower extremities was the only reported AE suspected as drug related.

The POTTER Study Group

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What is known about this topic?

- Studies addressing the effects of prophylaxis started in adolescents and adults with severe haemophilia A vs on-demand treatment are limited. In particular, currently available prospective findings come from trials with short follow-up (6–12 months).
- These short-term studies reported significant reductions of joint and total bleeding rates in patients on prophylaxis; however, information on clinical outcomes requiring long-term assessment, like the progression of haemophilic arthropathy and health-related quality of life (HRQoL), is lacking.

What does this paper add?

- The POTTER study is the first long-term prospective controlled study (median follow-up 5.4 years) documenting clinical effects of prophylaxis in patients with severe haemophilia A aged 12–55 years.
- In adolescent and adult patients on prophylaxis with recombinant FVIII (20–30 IU/Kg thrice weekly), the expected highly significant lower annual rates of joint and total bleeding episodes are associated with better joint outcomes (as revealed by changes in orthopaedic and radiologic scores), higher HRQoL and fewer days of everyday activities lost, as compared with patients treated on demand.
- These physical and psycho-social benefits may offset the higher FVIII concentrate consumption and costs of prophylaxis in this setting, in particular when even longer-term assessments are taken into account.

and social participation. These benefits involved higher FVIII concentrate consumption and treatment costs. Studies with even longer follow-up are needed to assess the full impact of this investment on the overall comprehensive care of adult and ageing patients with severe haemophilia A.

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Author contributions

A.T. conceived the study and all the authors gave contributions in the finalisation of study design and protocol. A.T., G.F., A.C.M., C.S., G.F.R., D.B.C., F.G., E.Z., M.E.M., L.V., L.M., A.C., and the members of the POTTER Study Group enrolled patients and collected data over the study follow-up. A.T., A.C., S.A., and P.M. analysed the study data. A.C. wrote the first draft of the manuscript, and A.T., P.M., and A.C. revised the final version. All the authors approved the final version and gave contributions in the revision of the manuscript.

Conflicts of interest

A.T. acted as a member of an advisory board for Bayer Healthcare and Novo Nordisk, and as an occasional paid consultant for Bayer Healthcare, Kedrion, Novo Nordisk, and Pfizer; G.F. declares no conflict of interest; A.C.M. acted as a member of an advisory board for Bayer Healthcare and as an occasional paid consultant or speaker for Bayer Healthcare and Pfizer; C.S. received fees as a consultant for Bayer, Baxter, Novo Nordisk, and Pfizer; G.F.R. acted as an occasional paid consultant for Pfizer; D.B.C. received fees as a speaker in meetings organised by Bayer; F.G. declares no conflict of interest; E.Z. received fees as a consultant for Bayer, Baxter, CSL Behring, Grifols, and Novo Nordisk; M.E.M. received fees as a speaker in meetings organised by Bayer, Baxter, CSL Behring, Grifols, Kedrion, Novo Nordisk, and Pfizer and acted as a paid consultant for Bayer, Baxter, CSL Behring, Grifols, Kedrion, Novo Nordisk, and Pfizer; L.V. declares no conflict of interest; L.M. declares no conflict of interest; A.C. received fees as a speaker in meetings organised by Biotest and Novo Nordisk and acted as a member of an advisory board for Bayer Healthcare; S.A. and P.M. are employees of Bayer Healthcare.

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