

## ORIGINAL ARTICLE

## Clinical haemophilia

# Long-term analysis of the benefit of prophylaxis for adult patients with severe or moderate haemophilia A

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## Abstract

**Introduction:** Prophylaxis with factor VIII (FVIII) concentrates in children with haemophilia A (HA) is current standard of care. The benefit of prophylactic treatment for adult HA patients is not commonly accepted.

**Aim:** To investigate the benefit of prophylaxis over on-demand treatment in adult and elderly patients with severe or non-severe HA in a real-life setting.

**Methods:** Data from 163 patients comprising 1202 patient-years were evaluated for 7.5 ( $\pm 5.3$ ) years. The effects on the annual bleeding rate (ABR, including spontaneous and traumatic bleeds) of treatment with a plasma-derived FVIII concentrate, the patient's age and disease severity were investigated. The effect of changing the treatment from on demand to continuous prophylaxis on the patients' ABRs was further analysed.

**Results:** Prophylaxis had the greatest effect on the ABRs of patients of any age with severe or non-severe HA. The difference in ABR of all patients treated on demand (median 31.4; interquartile range (IQR) 27.6; N = 83) compared with those treated prophylactically (median 1.3; IQR 3.6; N = 122) was statistically significant ( $P < .05$ ), even for patients with non-severe HA (median 8.4; IQR 15.5; N = 11) vs median 1.5; IQR 4.2 (N = 17),  $P < .05$ ). Patients, aged up to 88 years, switching from on demand to continuous prophylaxis showed the lowest median ABR (1.1; N = 51) after their regimen change.

**Conclusion:** Any (even low-frequency) prophylaxis results in lower ABR than on-demand treatment. Patients switching to prophylaxis benefitted the most, irrespective of age or HA severity. Prophylactic treatment—even tertiary—is the regimen of choice for patients of any age, including elderly patients, with severe or non-severe HA.

## KEYWORDS

adult and elderly patients, annual bleeding rate, effectiveness, haemophilia A, plasma-derived factor VIII concentrate, prophylaxis

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## 1 | INTRODUCTION

The frequency and severity of bleedings, as the main clinical feature in haemophilia A (HA), is generally correlated with the level of clotting factors.<sup>1</sup> In particular, patients with a residual factor VIII (FVIII) activity of 1%-5% may have frequent spontaneous bleeds that may also be clinically severe.<sup>2,3</sup>

The superiority of prophylactic FVIII replacement over on-demand treatment has been demonstrated for severe HA.<sup>1,4,5</sup> Starting a primary prophylaxis in children with severe HA can wholly or largely prevent life-threatening bleeds, chronic arthropathy and disability, thereby reducing the need for surgical interventions and contributing to improved health and social well-being for HA patients. Currently, primary individualized prophylactic regimens for children have become the standard of care to prevent joint bleeding and chronic arthropathy.<sup>1,6-12</sup>

In contrast, the superiority of regular and continuous prophylactic FVIII replacement over on-demand treatment in adult patients and in patients with non-severe HA is not generally accepted. Many middle-aged and elderly patients neither start with prophylaxis nor receive prophylactic FVIII substitutions, and they thus experience limitations in their activities of daily life.<sup>12</sup>

A Cochrane review from 2011 concluded that there was insufficient evidence from randomized controlled trials to confirm that prophylaxis decreased bleeding and related complications in patients with existing joint damage. Therefore, that review suggested that further studies were needed to establish the best preventative regimen, dose frequency and minimum effective dose.<sup>7</sup>

More recently, retrospective and prospective studies have established that even delayed prophylaxis decreases the number of bleeds, the severity of arthropathy and the patient's physical and psychological restrictions, while improving quality of life. These studies have revealed the benefit of (adherent) prophylaxis over on-demand treatment in adolescents and adults with HA.<sup>9,13-29</sup>

However, less information is available about the benefit of tertiary prophylaxis for reducing the annual bleeding rate (ABR) and annual joint bleeding rate. Furthermore, although follow-up documentation is limited, especially from real-life settings, opinion is shifting towards recommending lifelong prophylaxis.<sup>1,4,5,30,31</sup>

The present prospective long-term, non-interventional study (NIS) has been conducted under real-life conditions to investigate the influence of prophylactic FVIII treatment or the switch to this regimen on the ABR of HA patients of all age groups and HA severities, and the long-term effects of this regimen on the patients' ABRs. Final safety analyses have been published elsewhere.<sup>32</sup> The analyses presented in the following were performed with all 198 patients from one NIS (with an uniform data format).

## 2 | MATERIALS AND METHODS

### 2.1 | Study setting and design

The NIS was conducted as a prospective, non-interventional, multicentre, binational, long-term, safety and efficacy study with HA

patients (males of all ages) at 25 German and 8 Hungarian haemophilia centres during the observation period (May 1998 to December 2015). The study was approved by the relevant Ethics Committees, and informed consent was obtained from 2013 onwards according to the approved protocol.

### 2.2 | Study treatment

The plasma-derived (pd) FVIII concentrate administered in this study is marketed as Haemoctin® (pdFVIII) and is manufactured by Biotest Pharma GmbH. pdFVIII is produced from human plasma in a manner that complies with the relevant European Pharmacopoeia monograph. Its FVIII molecule is present in a physiological complex with von Willebrand factor without added artificial stabilizers.

The patients were divided into the following three groups depending on their treatment regimen(s) throughout the entire observational period: (a) patients with only on-demand treatment, (b) patients with only prophylactic treatment and (c) those whose treatment regimen changed during their observation time. Patients whose treatment regimen was changed continuously from on-demand treatment to continuous prophylaxis were further investigated, because these switches allowed intra-individual comparison regarding the development of ABRs. Regular, continuous prophylaxis was defined following the World Federation of Hemophilia guideline<sup>1</sup> as prophylactic administration for at least 45 consecutive weeks. From 2010 onwards, the patient's joint status and prophylaxis protocol (primary, secondary or tertiary), for which no (study-specific) definitions were provided in the study protocol, were documented in the case report form (CRF). In addition, tertiary prophylaxis was assumed if the patients suffered from affected joints and chronic haemarthrosis at start. Additionally, the frequency and dosing of patients treated prophylactically were assessed,<sup>33</sup> also considering different age groups ( $\leq 17$ , 18-39, 40-64, and  $\geq 65$  years) and their HA severity.<sup>3</sup>

### 2.3 | Variables and data sources

pdFVIII treatments and visits were at the discretion of the physician. Patients were expected to attend their haemophilia treatment centre at least once a year. Most of the patients had 3-4 routine visits per year.

The variables described below were documented in paper CRFs. In addition, doses of pdFVIII administered, bleedings and reasons for administration were recorded in patient diaries.

### 2.4 | Data sources and measurement

Data were entered from the CRFs and diaries into the clinical database at Metronomia Clinical Research GmbH. In addition, safety data for all patients were documented at the safety department of Biotest AG.

## 2.5 | Assessment of effectiveness

Effectiveness was analysed on the basis of the ABRs and documented bleedings in patient diaries taking into account the actual treatment regimen. 'Bleeding' was not predefined. The ABR calculations included both traumatic and spontaneous bleedings.

A mean ABR was first calculated for each patient and then summarized for all patients.

## 2.6 | Statistical analyses

Standard descriptive statistical methods were used. SAS system version 9.4 (SAS Institute Inc; Cary, NC, USA) was applied.

The effect of prophylaxis on ABR was analysed by Poisson regression with ABR as the dependent variable, and the influence of age and/or the HA severity was investigated.

Median differences of ABRs between treatment regimens were evaluated by using the non-parametric Wilcoxon signed-rank test with each test performed at a 5% alpha level and Bonferroni-adjusted for multiple testing, with a *P* value <.05 considered statistically significant.

The following comparisons between treatment regimens were made (Figure 1):

1. On demand (OD; *N* = 32) vs prophylaxis (PX; *N* = 71);
2. OD before switch (OD → PX; *N* = 51) vs PX (*N* = 71);
3. OD before switch (OD → PX; *N* = 51) vs PX after switch (OD → PX; *N* = 51);
4. OD before switch (OD → PX) + OD (*N* = 51 + 32 = 83; Table 5) vs PX + PX after switch (OD → PX; *N* = 51 + 71 = 122; Table 4);
5. PX (*N* = 71) vs PX after switch (OD → PX; *N* = 51).

This was done for all patients, followed by these with non-severe HA only.

Further methodological details are described elsewhere.<sup>32</sup>

## 3 | RESULTS

### 3.1 | Patients and treatment

Long-term data were collected from a total of 164 enrolled patients between May 1998 and December 2015. Three patients were excluded from efficacy analysis. Thus, 161 patients were included in the analyses of the effect of the treatment regimen on the ABR (Figure 1).

In this study, a total of 1202 patient-years were documented for all patients; of these, 1024 were documented for patients with severe HA.

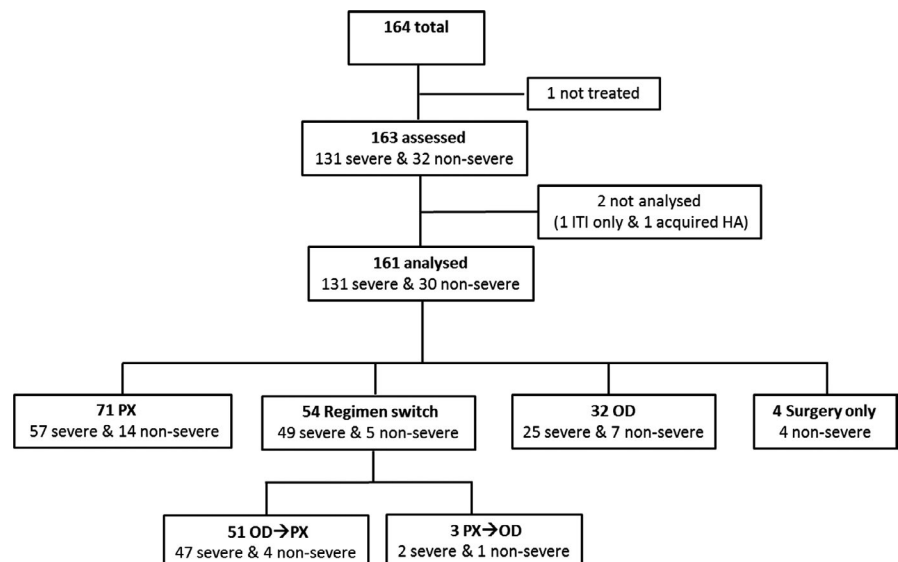
On average, all patients were documented for a period ( $\pm$ SD) of  $7.5 \pm 5.3$  years (median 6.0; 1 day to 16.5 years).

On average, the patients were followed up during one treatment regimen for approximately 5-6 years. The 51 Patients switching to prophylaxis were followed for an above-average period, with a documented duration of  $11.5 \pm 4.3$  years.

### 3.2 | Demographic data

Demographics per age group are summarized in Table 1. At inclusion, 143 comorbidities were documented for 73 patients (45%), including mainly (74%; 54/73) patients treated with continuous prophylaxis (34/73) or those who changed to continuous prophylaxis (20/73) (Table 2). Number and percentage of comorbidities increased with age. Most frequent comorbidities at inclusion were hepatitis virus infection (30%), hypertension (11%) and arthropathy (7%).<sup>12</sup>

Overall, patients with an on-demand regimen were included at greater ages than patients under continuous prophylaxis (median



**FIGURE 1** Patient distribution by treatment regimen

**TABLE 1** Demographics per age group, pretreatment and severity of haemophilia A

Age group Pretreatment	≤17 (N = 60)	18-39 (N = 59)	40-64 (N = 38)	≥65 (N = 4)	All (N = 161)
	n (%)	n (%)	n (%)	n (%)	n (%)
PUP	19 (32)	0 (0)	0 (0)	1 (25)	20 (12)
s/ns	15/4	0/0	0/0	0/1	15/5
PTP	41 (68)	59 (100)	38 (100)	3 (75)	141 (88)
s/ns	39/4	51/8	28/10	0/3	118/25

Abbreviations: Ns, non-severe; PTP, previously treated patient; PUP, previously untreated patient; s, severe.

42 vs 21 years), and patients with non-severe HA were older at inclusion than those with severe HA (median 40 vs 20 years; Table 3).

### 3.3 | Treatment data

A total of 185 694 262 international units (IU) were administered in 110 078 treatments. On average, considering all patients, prophylactic infusions were administered in 62.4% (median 80.2%; 0%-100%) of infusions and bleeding or follow-on in 36.9% (median 19.5%).

At patient level, the mean number of administrations was  $683.7 \pm 605.9$  (median 473.0; range 1.0-2528.0). At the beginning of the study period, the type of treatment had varied considerably between patients treated in Germany or Hungary. These initial country-specific differences in regimens and dosing decreased during the study period.<sup>32</sup>

The combined median prophylactic doses, their frequencies per week and the annual consumption of pdFVIII of patients with a continuous prophylactic regimen since inclusion (N = 71) and after a switch from an initial on-demand regimen (N = 51) are shown in Table 4. Respective data of patients with only on-demand regimen (N = 32) and those who later switched to prophylaxis (N = 51) are displayed in Table 5.

### 3.4 | Analyses of the effect of treatment regimen on ABR

Among the 161 patients analysed, a strong relationship was found between prophylactic treatment and mean ABR (Poisson regression,  $\beta = -0.02$ ,  $P < .001$ ). Thus, administering X additional prophylactic administrations per year (range 0-7 infusions per week) led to a reduction of ABR by 2\*X%. Thus, the more prophylactic administrations a patient received, the lower his ABR. No differences in this relationship were detected between patients with severe and non-severe HA or between age groups.

Remarkably, patients with non-severe HA who continuously received prophylactic pdFVIII doses had similar or even higher median ABRs than patients with severe HA treated continuously prophylactic with pdFVIII (Table 4, Figure 2).

Overall, the median ABR of patients receiving pdFVIII on demand was considerably higher than the median ABR of patients treated

prophylactically with pdFVIII (Tables 4 and 5; Figure 2). Considering all patients with severe and non-severe HA, the differences in ABR were statistically significant ( $P < .05$ ) for patients treated on demand compared with those treated continuously prophylactic with pdFVIII (comparisons 1-4, and comparison 4 for patients with non-severe HA, described in 'Statistical analyses'). Although this difference was higher in patients with severe HA than in those with non-severe HA, the difference was also statistically significant ( $P < .05$ ) considering all patients with non-severe HA. A remarkable drop, and an even greater and statistically significant ( $P < .05$ ) difference/benefit, was observed for patients, whose on-demand regimen was changed to continuous prophylaxis (Figure 2). The benefit of the change to continuous prophylaxis over on-demand treatment was demonstrated for all age groups, with high reductions in ABR in all HA patients irrespective of their HA severity (Figure 3). For adult and elderly patients, a reduction in median ABR of approximately 40 was observed for patients with severe HA and up to 29 in patients with non-severe HA.

### 3.5 | Haemophilic arthropathy

A pre-existing arthropathy was documented for 14 patients (7%). Thereof most (10/14) patients were treated continuously prophylactic. Joint status was documented more detailed for 55 patients, starting in 2010, including 3 of the 14 patients with an already documented arthropathy. More details per age group are presented in Table 2. Two of the 4 PTPs who developed an inhibitor suffered from an arthropathy (section safety and tolerability).

Of these 52 patients, most (30) switched their treatment regimen from on-demand to prophylaxis. Sixteen of these 52 received a tertiary prophylaxis; of these 16, only 3 received pdFVIII as regular prophylaxis in respect of dose (20-40 IU/kg) and frequency (2-3 per week).<sup>33</sup>

### 3.6 | Patients with no or 1 bleed per year

Overall, for the 51 patients switching to prophylactic therapy, reductions of their ABRs started directly. Twenty-five (49%) of the 51 patients switching to prophylaxis suffered on average from <1

**TABLE 2** Comorbidities and joint status per age group at inclusion

Age group	≤17 (N = 60)	18-39 (N = 59)	≥40 (N = 42) <sup>a</sup>	All (N = 161)
Comorbidities <sup>b,c</sup>	n (%)	n (%)	n (%)	n (%)
Total	15 (25)	27 (46)	31 (74)	73 (45)
Infections	8 (13) 7 HCV 6 HBV	18 (31) 19 hepatitis 15 HCV 3 HBV 1 HAV 3 HIV	21 (50) 20 hepatitis 19 HCV 1 HBV 3 HIV 1 bone tuberculosis 1 periodontitis	47 (29) 52 hepatitis 40 HCV 10 HBV 1 HAV 6 HIV 1 bone tuberculosis 1 periodontitis
Respiratory and thoracic disorders	—	1 (2) 1 vocal cord leukoplakia	4 (10) 1 asthma, 1 COPD 1 chronic bronchitis, 1 tonsillar hypertrophy	5 (3) 1 asthma 1 COPD 1 chronic bronchitis 1 tonsillar hypertrophy 1 vocal cord leukoplakia
Vascular disorders	—	4 (7) 4 hypertension	14 (38) 13 hypertension 1 peripheral arterial occlusive disease 2 peripheral venous disease	18 (11) 17 hypertension 1 peripheral arterial occlusive disease 2 peripheral venous disease
Cardiac disorders	—	—	2 (5) 1 ischaemic heart disease 1 coronary artery disease	2 (1) 1 ischaemic heart disease 1 coronary artery disease
Endocrine disorders	—	—	3 (7) 2 hypothyroidism 1 Struma nodosa	3 (2) 2 hypothyroidism 1 Struma nodosa
Renal and urinary disorders	—	1 (2) 1 nephrosis	3 (5) 2 nephrolithiasis 1 urinary tract obstruction	4 (2) 2 nephrolithiasis 1 nephrosis 1 urinary tract obstruction
Hepatobiliary disorders	—	3 (5) 1 alcoholic liver cirrhosis 2 liver cirrhosis	3 (7) 3 hepatic cirrhosis	6 (4) 1 alcoholic liver cirrhosis 3 hepatic cirrhosis 2 liver cirrhosis
Gastrointestinal disorders	—	2 (3) 1 gastric ulcer 1 rectal ulcer haemorrhage	2 (5) 1 Crohn's disease 1 irritable bowel syndrome	4 (2) 1 Crohn's disease 1 gastric ulcer 1 irritable bowel syndrome 1 rectal ulcer haemorrhage
Metabolism and nutrition disorders	1 (2) 1 obesity	3 (5) 1 hypercholesterolaemia 1 hypouricaemia 1 obesity	4 (10) 1 diabetes mellitus 1 hypercholesterolaemia 1 hyperuricaemia 1 lactose intolerance	8 (5) 1 diabetes mellitus 2 obesity 1 hypouricaemia 1 hyperuricaemia 2 hypercholesterolaemia 1 lactose intolerance
Skin and subcutaneous tissue disorders	—	—	2 (5) 1 psoriasis 1 chronic pigmented purpura	2 (1) 1 psoriasis 1 chronic pigmented purpura
Nervous system disorders	3 (5) 2 epilepsy 1 intracranial haematoma	1 (2) 1 epilepsy	3 (7) 2 cerebrovascular accident 1 migraine	7 (4) 2 cerebrovascular accident 3 epilepsy 1 intracranial haematoma 1 migraine

(Continues)



TABLE 2 (Continued)

Age group	≤17 (N = 60)	18-39 (N = 59)	≥40 (N = 42) <sup>a</sup>	All (N = 161)
Comorbidities <sup>b,c</sup>	n (%)	n (%)	n (%)	n (%)
Congenital and genetic disorders	3 (5) 1 alpha-1 antitrypsin deficiency 1 FII mutation 1 KISS syndrome	—	—	3 (2) 1 alpha-1 antitrypsin deficiency 1 FII mutation 1 KISS syndrome
Eye disorders	—	—	2 (5) 1 macular fibrosis 1 cataract	2 (1) 1 macular fibrosis 1 cataract
Malignancies	—	—	3 (7) 1 hepatic cancer 1 laryngeal cancer 1 malignant melanoma	3 (2) 1 hepatic cancer 1 laryngeal cancer 1 malignant melanoma
Musculoskeletal and connective tissue disorders	5 (8) 4 arthropathy 2 Perthes disease 1 Reiter's syndrome	5 (8) 5 arthropathy	8 (19) 5 arthropathy 1 haemarthrosis 1 osteoporosis 1 Rotator cuff syndrome	18 (11) 14 arthropathy 1 haemarthrosis 1 osteoporosis 2 Perthes disease 1 Reiter's syndrome 1 Rotator cuff syndrome
Joint status since 2010	11	31 <sup>e</sup>	14	55 (~50) <sup>d,e</sup>
Affected joints	9	30	13	52
No affected joints	2	1	1	3

Abbreviations: COPD, chronic obstructive pulmonary disease; FII, factor II; HAV, hepatitis A virus infection; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HIV, human immunodeficiency virus infection; KISS, kinematic imbalances due to suboccipital strain.

<sup>a</sup>Age group 40-64 y and age group ≥65 y were combined due to small numbers.

<sup>b</sup>All comorbidities at inclusion pertaining to the same System Organ Class (adapted), that were present in ≥5% of patients of at least one age group, are presented.

<sup>c</sup>Including acute, chronic or recovered comorbidities.

<sup>d</sup>In 2010, this was approximately the half of included patients (between 2008 and 2012 123 patients were included);

<sup>e</sup>Including 3 PTPs (18-39 y, and with only continuous prophylactic regimens) with arthropathy at inclusion.

bleed per year after the switch, and of these, 13 (25%) did not suffer from any bleed (ABR = 0.0), including, respectively, 2 and 1 patients with moderate HA (2%).

Notably, 9 patients switching to prophylaxis with affected joints documented zero bleeds after switching and 5 additional patients switching to prophylaxis suffered from less than 1 bleed per year.

Of the 71 patients treated by continuous prophylaxis, 25 patients (35%) on average suffered from less than 1.0 bleed per year, thereof 11 patients (15%) suffered from no bleed at all, including respectively 6 patients and 1 patient with moderate HA. Four additional of these 71 patients had a mean ABR of 1.0.

None of the patients treated under the on-demand regimen suffered on average from ≤1.0 bleeds per year (minimum = 2.9).

### 3.7 | Safety and tolerability

A detailed safety analysis is presented elsewhere.<sup>32</sup> Inhibitors were found in 13% (3/23) and high-titre inhibitors in 4% (1/23) of previously untreated patients with severe HA. Four previously treated

patients (PTP) with severe haemophilia A developed inhibitors, thereof 3 high-titre inhibitors (3.3 and 2.5 high-titre inhibitors in 1000 patient-years).

Severe bleedings, requiring treatment peaks of ≥3 and up to 15 consecutive days of on-demand treatment, were identified as potential risk factors for inhibitor formation. In addition, for previously treated patients an on-demand regimen was identified as a potential risk factor.<sup>32</sup>

## 4 | DISCUSSION

Prophylaxis is the gold standard for the treatment of severe HA during childhood and adolescence. Recent recommendations state that prophylaxis is the treatment of choice for all HA patients at any age on account of the improvements in their quality of life. Therefore, this treatment should be continued lifelong.<sup>1,4,9,13-25,34-36</sup> However, data on adult patients benefitting from prophylaxis are limited.

The results of the present analysis using real-life data collected prospectively over a nearly 18-year period support this

**TABLE 3** Treatment regimen sorted by FVIII-residual activity and age at inclusion

FVIII Activity [%] Median age (range) [years]	Prophylaxis N = 71 (44%)	On demand N = 32 (20%)	OD → PX N = 51 (32%)		PX → OD N = 3 (2%)	Surgery N = 4 (2%)	Total N = 161 (100%)
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)
≤1 (Severe)	57 (80)	25 (78)	47 (92)		2 (67)	0 (0)	131 (81)
Age [years]	15 (0-59)	32 (18-63)	22 (0-59)	30 (0-69) <sup>a</sup>	25 (9-48)	NA	20 (0-59)
≥2 (Non-severe)	14 (20)	7 (22)	4 (8)		1 (33)	4 (100)	30 (19)
2-5/6-40	13/1	3/4	4/0		1/0	1/3	22/8
Age [years]	21 (2-63)	42 (1-74)	49 (2-80)	59 (3-82) <sup>a</sup>	48	58 (47-65)	40 (0-80)
Total age [years]	16 (0-63)	41 (1-74)	22 (0-80)	30 (0-82) <sup>a</sup>	41 (9-48)	58 (47-65)	22 (0-80)

Abbreviations: NA, not applicable; OD, patients with only on-demand regimen; PX, patients with only prophylactic regimen.

<sup>a</sup>Age at switch to continuous prophylaxis

recommendation and strengthen comparable results of previous studies revealing the superior benefit of prophylaxis compared to on-demand treatment in adolescents and adults with HA.<sup>9,13-26,34</sup> This prospective study is the longest NIS of a single FVIII concentrate reported so far in which treatment data were collected from the routine treatment of HA patients.<sup>32</sup> In a broad range of patients with severe as well as non-severe HA, covering all age groups up to 88 years, long-term prophylaxis with a pdFVIII concentrate reduced the ABR remarkably, in some cases down to zero. Overall it was found, that the more prophylactic administrations a patient received, the lower his ABR was. ABRs of patients receiving continuous prophylaxis were statistically significantly different ( $P < .05$ ) from those of patients treated on demand, even for patients with non-severe HA. This beneficial effect of prophylaxis, including tertiary prophylaxis, on the ABR was further confirmed by assessing patients who changed treatment to continuous

prophylaxis and thus could be considered intra-individual controls. Irrespective of their ages and the severity of HA, these patients switching to prophylaxis experienced the highest median reduction in their ABR which were even lower than the median ABR of patients who received continuous prophylaxis from the start of documentation onwards. The reason for switching to prophylaxis was not documented in the study, but in most cases arthropathy and high ABR during on-demand therapy was obvious, including severe bleedings and related consequences, and also (in Hungary) the increasing availability of prophylaxis.

The median frequency of prophylactic doses in the patients with non-severe HA during continuous prophylaxis was slightly lower than that recommended for patients with severe HA.<sup>33</sup> This discrepancy might be the reason for their high ABRs compared to those of patients with severe HA. This finding is in line with data recently published by Scott et al,<sup>3</sup> which revealed that patients

**TABLE 4** ABR and annual pdFVIII consumption of patients with continuous prophylaxis at inclusion and after switch

Age groups [years]	≤17	18-39	40-64	≥65	Total (N = 122 = 71 + 51)
Severity HA	Median ABR; IQR, range (n)				
Severe	2.2; 0.0-19.6 (43)	0.8; 0.0-17.6 (40)	0.4; 0.0-13.5 (19)	3.6; 1.2-6.0 (2)	1.2; IQR 3.5; 0.0-19.6 (104)
Non-severe	3.8; 1.4-9.8 (6)	0.3; 0.0-4.5 (7)	5.6; 0.5-5.8 (3)	0.2; 0.0-0.5 (2)	1.5; IQR 4.2; 0.0-9.8 (17)
Total	2.3; 0.0-19.6 (49)	0.7; 0.0-17.6 (47)	0.5; 0.0-13.5 (22)	0.8; 0.0-6.0 (4)	1.3; IQR 3.6; 0.0-19.6 (122)
Median prophylactic pdFVIII dose; range [IU/kg] (median prophylactic applications per week)					
Severe	31; 5-120 (3.1)	29; 12-48 (2.2)	29; 12-54 (2.1)	27; 25-28 (1.4)	30; 12-120 (2.5)
Non-severe	25; 20-45 (2.4)	34; 16-57 (1.2)	25; 12-35 (1.1)	43; 41-45 (4.0)	28; 12-57 (1.8)
Total	30; 15-120 (3.0)	29; 12-57 (1.9)	28; 12-54 (1.9)	35; 25-45 (2.4)	29; 12-120 (2.4)
Median pdFVIII consumption per year; range [IU/kg]					
Severe	4595; 485-25 357	3384; 516-229 000	3341; 468-7675	1991; 1822-2161	3683; 468-229 000
Non-severe	2939; 1732-7991	2023; 818-6705	1208; 841-2478	9587; 9099-10 074	2478; 818-10 074
Total	4419; 485-25 357	2930; 516-229 000	2368; 468-7675	5630; 1822-10 074	3547; 468-229 000

Abbreviations: HA, haemophilia A; IQR, interquartile range; OD, patients with only on-demand regimen; PX, patients with only prophylactic regimen.

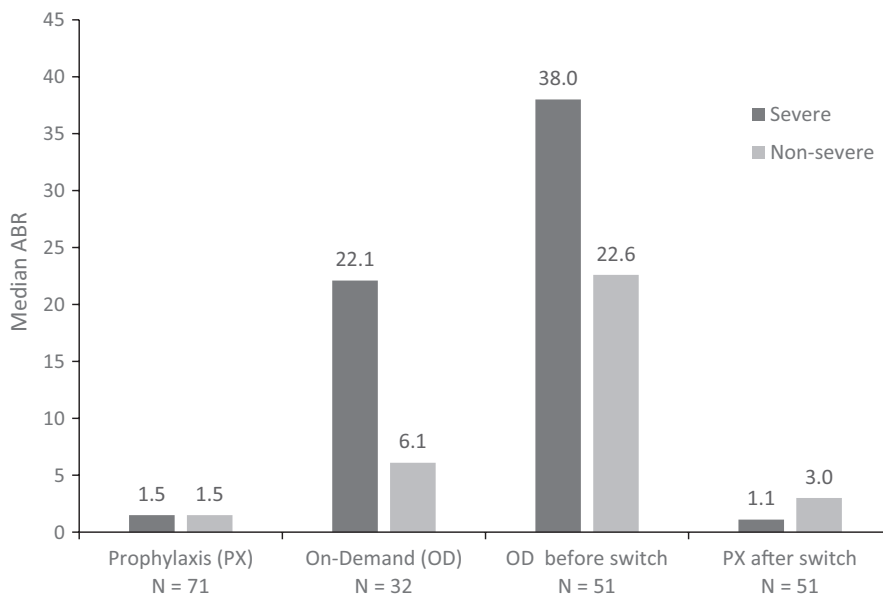
<sup>a</sup>Age at switch to continuous prophylaxis.



**TABLE 5** ABR and annual pdFVIII consumption of patients with on-demand regimen at inclusion

Age groups [years]	≤17	18-39	40-64	≥65	Total (N = 83 = 32 + 51)
Severity HA	Median ABR; IQR; range (n)				
Severe	30.4; 1.3-76.0 (18)	38.0; 6.2-64.6 (35)	29.2; 2.9-130.2 (19)	—	33.7; IQR 27.3; 1.3-130.2 (72)
Non-severe	25.4; 21.5-29.3 (3)	15.8 (1)	6.9; 5.3-9.1 (4)	6.0; 2.9-48.8 (3)	8.4; IQR 15.5; 2.9-48.8 (11)
Total	28.5; 1.3-76.0 (21)	37.5; 6.2-64.6 (36)	18.3; 2.9-130.2 (23)	6.0; 2.9-48.8 (3)	31.4; IQR 27.6; 1.3-130.2 (83)
	Median pdFVIII consumption per year (range) [IU/kg]				
Severe	895; 27-2121	1337 (182-3583)	1065 (173-5176)	—	1099 (27-5176)
Non-severe	3059 (2177-3941)	1313	545 (442-1031)	1817 (746-2327)	1172 (442-3941)
Total	924 (27-3941)	1326 (182-3583)	1020 (173-5176)	1817 (746-2327)	1099 (27-5176)

Abbreviations: HA, haemophilia A; IQR, interquartile range; OD, patients with only on-demand regimen; PX, patients with only prophylactic regimen.

**FIGURE 2** Median ABRs of patients by treatment regimen and severity of HA

with severe or moderate HA suffered from unexpectedly high ABRs. In contrast to those authors' results, an increase in ABR with age was not observed in the present study. However, overall ABRs as reported by Scott et al were comparable to those reported here.

Overall, and considering that 74% of patients with comorbidities received a continuous prophylaxis, the treatment regimen seems to require individualization with regard to frequency and dosage.<sup>33</sup> Concomitant diseases—including haemophilia-related and non-haemophilia-related comorbidities, such as age-related diseases—may be one important factor to be considered here, especially in older HA patients, who are at higher risk of bleeding owing to their comorbidities and ageing.<sup>5,30,37</sup>

Treatment peaks due to recurring joint bleeding and severe bleeding episodes were identified as risk factors for inhibitor development in both previously treated and untreated patients treated on demand with pdFVIII.<sup>32</sup>

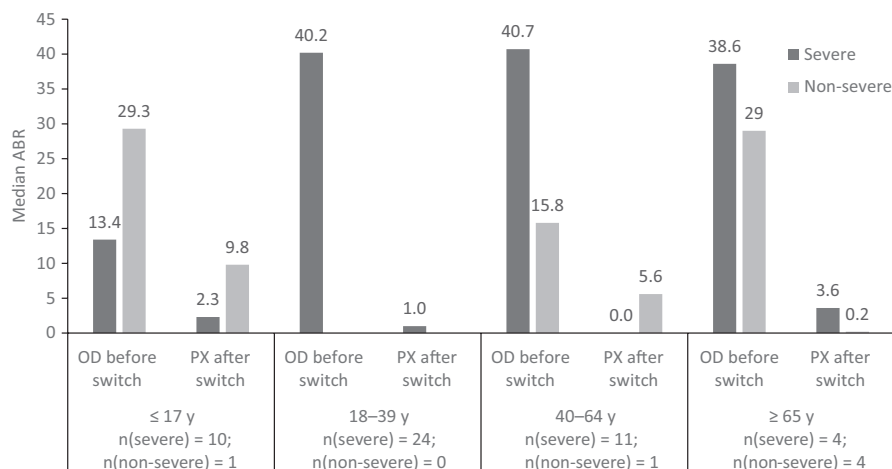
Therefore, more long-term data should be acquired under real-life conditions, to establish the best prophylactic regimen based on dose, frequency and the minimum effective dose.<sup>7,31,38</sup>

These data, which the present report may contribute to, will help to improve HA therapy and the quality of life of patients with HA.<sup>22</sup> Beside non-factor treatment options such as emicizumab,<sup>39</sup> prophylaxis with FVIII concentrates is still widely used to provide prophylaxis and treat HA patients to attain low ABRs or even a bleed-free life.

This study had limitations in data acquisition that were due mainly to the long observational period, especially at the beginning of the study, mostly on account of items documented at the start of the NIS two decades earlier. No special attention was given at the outset to the development of joint status over time; instead, the status of the type of prophylaxis, affected joints and their impact



**FIGURE 3** Median ABRs of patients switching from OD to prophylaxis (N = 51) by age group at onset of switch and severity of HA



on daily life was documented only from 2010 onwards. The ABRs were calculated on the basis of bleedings (for which no definition was prespecified), including spontaneous and traumatic as well as joint and non-joint bleeds, and were documented in patient diaries without the requirement that they be medically confirmed. This limitation is shared by most studies in the field. Although the overall group is relatively large, when broken down by severity and age, some of subgroups are very small. In addition, the initial country-specific differences in regimens and dosing have to be considered.

Individual prophylactic treatment and its frequency varied substantially within the study, reflecting real-life conditions during daily clinical practice. Notably, in this study 'real-life patients' instead of carefully selected study participants were observed. Therefore, these data cannot be compared directly with treatment data from (randomized) clinical trials.<sup>32</sup> However, median ABR under continuous prophylaxis in the present study (1.3) was comparable with that observed in clinical trials with other FVIII products (median 0.0–2.0) with observation periods of about 6 months.<sup>20,27–29,40</sup>

## 5 | CONCLUSION

This unique study of 'real-life' long-term follow-up documentation of HA therapies, including regimen switches, allows assessment of the benefit of prophylaxis over on-demand treatment including an intra-individual comparison regarding the development of ABRs. The analysis revealed a statistically significant benefit of prophylaxis compared to on-demand FVIII treatment in daily routine for patients of any age (postnatal to 88 years) with severe or non-severe HA. Long-term prophylaxis with FVIII in daily routine was shown to be highly effective, reducing ABR to ~1 including all bleeds and also in patients with haemophilic arthropathy. This benefit was greatest in patients (irrespective of age and severity of HA) who switched from on-demand treatment to continuous prophylaxis. Prophylaxis had the greatest effect on the ABR of all patients: In about 50% of patients switching to prophylaxis, their average ABR decreased to

less than 1, and 25% of these patients with pre-existing joint damage suffered from zero bleeds. Thus, prophylaxis with FVIII and the switch to it even at older age appears as an effective and safe option, resulting in very low or zero ABRs.

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## AUTHOR CONTRIBUTIONS

LN and CK contributed with a significant numbers of patients to this NIS. AB and TB designed the NIS. AB, JS, TB and SK performed the research. AS was responsible for data management and provided statistical support. SK, AB, TB and JS analysed the data. The main

writing was done by SK. Analyses were discussed with WM, CK and LN. All authors reviewed, commented and approved the final manuscript.

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## REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-47.
2. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.
3. Scott MJ, Xiang H, Hart DP, et al. Treatment regimens and outcomes in severe and moderate haemophilia A in the UK: the THUNDER study. *Haemophilia*. 2019;25(2):205-212.
4. Makris M. Prophylaxis in haemophilia should be life-long. *Blood Transfus*. 2012;10(2):165-168.
5. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125(13):2038-2044.
6. Colvin BT, Astermark J, Fischer K, et al. European principles of haemophilia care. *Haemophilia*. 2008;14(2):361-374.
7. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia. A or B. *Cochrane Database Syst Rev*. 2011;9:CD003429.
8. Fischer K, Konkle B, Broderick C, Kessler CM. Prophylaxis in real life scenarios. *Haemophilia*. 2014;20(Suppl 4):106-113.
9. Castaman G, Linari S. Prophylactic versus on-demand treatments for hemophilia: advantages and drawbacks. *Expert Rev Hematol*. 2018;11(7):567-576.
10. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.
11. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, Group ES. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost*. 2011;9(4):700-710.
12. Canaro M, Goranova-Marinova V, Berntorp E. The ageing patient with haemophilia. *Eur J Haematol*. 2015;94(Suppl 77):17-22.
13. Fischer K, van Dijk K, Van den Berg HM. Late prophylaxis for severe hemophilia: effects of prophylaxis started in adulthood. *J Thromb Haemost*. 2005;3(suppl 1):AbstrOR205.
14. van Dijk K, Fischer K, van der Bom JG, Scheibel E, Ingerslev J, van den Berg HM. Can long-term prophylaxis for severe haemophilia be stopped in adulthood? Results from Denmark and the Netherlands. *Br J Haematol*. 2005;130(1):107-112.
15. Hay CR. Prophylaxis in adults with haemophilia. *Haemophilia*. 2007;13(Suppl 2):10-15.
16. Tagliaferri A, Franchini M, Coppola A, et al. Effects of secondary prophylaxis started in adolescent and adult haemophiliacs. *Haemophilia*. 2008;14(5):945-951.
17. Collins PW, Blanchette VS, Fischer K, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. *J Thromb Haemost*. 2009;7(3):413-420.
18. Collins P, Faradji A, Morfini M, Enriquez MM, Schwartz L. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. *J Thromb Haemost*. 2010;8(1):83-89.
19. Coppola A, Franchini M, Tagliaferri A. Prophylaxis in people with haemophilia. *Thromb Haemost*. 2009;101(4):674-681.
20. Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost*. 2012;10(3):359-367.
21. Noone D, O'Mahony B, van Dijk JP, Prihodova L. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries. *Haemophilia*. 2013;19(1):44-50.
22. O'Hara J, Sima CS, Frimpter J, Paliargues F, Chu P, Presch I, Presch I. Long-term outcomes from prophylactic or episodic treatment of haemophilia A: a systematic review. *Haemophilia*. 2018;24(5):e301-e311.
23. Tagliaferri A, Feola G, Molinari AC, et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost*. 2015;114(1):35-45.
24. Oldenburg J, Zimmermann R, Katsarou O, et al. Controlled, cross-sectional MRI evaluation of joint status in severe haemophilia A patients treated with prophylaxis vs. on demand. *Haemophilia*. 2015;21(2):171-179.
25. Manco-Johnson MJ, Lundin B, Funk S, et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. *J Thromb Haemost*. 2017;15(11):2115-2124.
26. Zanon E, Tagliaferri A, Pasca S, et al. Physical activity improved by adherence to prophylaxis in an Italian population of children, adolescents and adults with severe haemophilia A: the SHAPE Study. *Blood Transfus*. 2019;1-6.
27. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood*. 2015;126(9):1078-1085.
28. Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). *J Thromb Haemost*. 2015;13(3):360-369.
29. Lissitchkov T, Klukowska A, Pasi J, et al. Efficacy and safety of simoctocog alfa (Nuwiq(R)) in patients with severe hemophilia A: a review of clinical trial data from the GENA program. *Ther Adv Hematol*. 2019;10:2040620719858471.
30. Gringeri A, Lambert T, Street A, Aledort L. Adolescent/Adult Prophylaxis Expert Working Group of the International Prophylaxis Study G. Tertiary prophylaxis in adults: is there a rationale? *Haemophilia*. 2012;18(5):722-728.
31. Sidharthan N, Sudevan R, Narayana Pillai V, et al. Low-dose prophylaxis for children with haemophilia in a resource-limited setting in south India-A clinical audit report. *Haemophilia*. 2017;23(4):e382-e384.
32. Kittler SFK, Miesbach W, Bauhofer A, et al. Long-term safety and efficacy data of a plasma-derived factor VIII concentrate with von Willebrand factor for treatment of patients with hemophilia A covering 18 years. *Hamostaseologie*. 2019;39(4):360-367.
33. EMA. Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products rev. 3. *EMA/CHMP/BPWP/1619/1999 rev 3*. 2018; [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-smpc-human-plasma-derived-recombinant-coagulation-factor-viii-products-revis-ion-3\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-smpc-human-plasma-derived-recombinant-coagulation-factor-viii-products-revis-ion-3_en.pdf). Accessed July 26, 2018.
34. Fischer K, Van Der Bom JG, Mauser-Bunschoten EP, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia*. 2001;7(5):446-452.

35. Coppola A, Di Capua M, Di Minno MN, et al. Treatment of hemophilia: a review of current advances and ongoing issues. *J Blood Med.* 2010;1:183-195.
36. Nijdam A, Foppen W, Kleijn PD, et al. Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. *Thromb Haemost.* 2016;115(5):931-938.
37. Boccalandro E, Mancuso ME, Riva S, et al. Ageing successfully with haemophilia: a multidisciplinary programme. *Haemophilia.* 2018;24(1):57-62.
38. EMA. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. *EMA/CHMP/BPWP/144533/2009 rev 2.* 2018; [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf). Accessed October 4, 2019.
39. Rodriguez-Merchan EC, Valentino LA. Emicizumab: review of the literature and critical appraisal. *Haemophilia.* 2019;25(1):11-20.
40. Mahlangu J, Kuliczowski K, Karim FA, et al. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. *Blood.* 2016;128(5):630-637.

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