Clinical practice of prophylaxis in severe haemophilia: navigating between the burden of treatment and risk of arthropathy

Annelies Nijdam

ISBN 978-94-6169-806-3

Cover illustration Stock image
Design & layout Tom Fincham
Print Optima Grafische Communicatie, Rotterdam

Clinical practice of prophylaxis in severe haemophilia: navigating between the burden of treatment and risk of arthropathy

Profylactische behandeling van ernstige hemofilie in de praktijk:
navigeren tussen de belasting van behandeling en het risico op artropathie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 26 januari 2016
des middags te 4.15 uur

door

Annelies Nijdam
geboren op 23 augustus 1971 te Groningen

Promotor:	Prof. dr. ir. Y.T. van der Schouw
Copromotor:	Dr. K. Fischer

CONTENTS

CHAPTER 1

Introduction

Haemophilia is a rare hereditary X-linked recessive genetic disorder that impairs blood coagulation due to lack of functional clotting factor. Patients with haemophilia A lack factor VIII (FVIII), while patients with haemophilia B lack factor IX (FIX). The prevalences of haemophilia A and B in the Netherlands are estimated at 17 and 2 patients in every 100,000 males, respectively [1; 2]. Patients with haemophilia suffer from spontaneous as well as trauma related bleeding. The severity of bleeding correlates with the residual clotting factor levels [3; 4] and as a result haemophilia is classified as severe (<0.01 IU/ml FVIII/IX), moderate (0.01–0.05 IU/ml) and mild (>0.05 IU/ml) [5]. Approximately 40% of the Dutch haemophilia population has severe haemophilia [6]. Patients with severe haemophilia suffer more excessive and more frequent bleeds, while most patients with moderate haemophilia seldomly experience spontaneous bleeding. Bleeds are most common in ankles, knees, elbows and muscles [7] and should be treated as quickly as possible by intravenous administration of clotting factor [8]. When not treated or not treated in time, (repeated) joint bleeding can lead to irreversible joint damage, known as haemophilic arthropathy [9; 10].

After the introduction of clotting factor products in 1965, patients were treated “on-demand”: at the time of clinically evident bleeding only [8; 11]. In the 1970s clotting factor products became available in the Netherlands on a scale that allowed prophylactic replacement treatment [12; 13]. Present-day prophylaxis is the regular infusion of clotting factor aimed at preventing bleeds. It is superior to on-demand treatment in maintaining joint health [11–18] and therefore the treatment of choice for patients with severe haemophilia in countries with available resources [8]. The current Dutch prophylactic regimen consists of infusing FVIII 3-3.5x/week or FIX 1-2x/week.

Prophylaxis does not reverse established haemophilic arthropathy, but does stabilise its progression [10; 15]. Early initiation of prophylaxis in children with severe hemophilia is therefore critical for effective prevention of arthropathy [15; 17]. As a result, prophylaxis was started at increasingly younger ages [6; 11; 15; 19]. In clinical practice, starting prophylaxis in young children is challenging. The need for frequent infusions and problems with venous access compete for dominance. On one hand, central venous access devices (CVAD) can be used as alternative route of infusion, but these require surgery and are associated with a considerable risk of infections and thrombotic complications.[20] On the other hand, step-up regimens starting at lower frequencies (1-2x/week) have been introduced to facilitate early prophylaxis and treatment acceptance by parents [21; 22]. As of yet the optimum regimen for starting prophylaxis in young

children with severe haemophilia has not been established. More information is needed on when and how to start prophylaxis, specifically on the effects of bleeding before prophylaxis, age at initiation of prophylaxis, and different regimens to start prophylaxis.

The importance of prophylaxis in severe haemophilia during the period of growth is well documented [14–18] and widely acknowledged [8; 22]. Whether prophylaxis should be continued in adulthood is still under debate [8; 23–26]. Keeping up this life-long treatment is a heavy burden for some patients and therefore adherence to treatment can include periods of reduced compliance. Especially teenagers and young adults are reported to discontinue prophylaxis and switch to on-demand treatment [27–29]. Two studies suggested that a proportion of young adults who started prophylaxis in early childhood, could possibly safely switch to on-demand treatment [28; 29]. However, the reported follow-up was only four years after discontinuing prophylaxis. As haemophilic arthropathy develops over time, this may have been too short to determine whether these patients jeopardised their joint health.

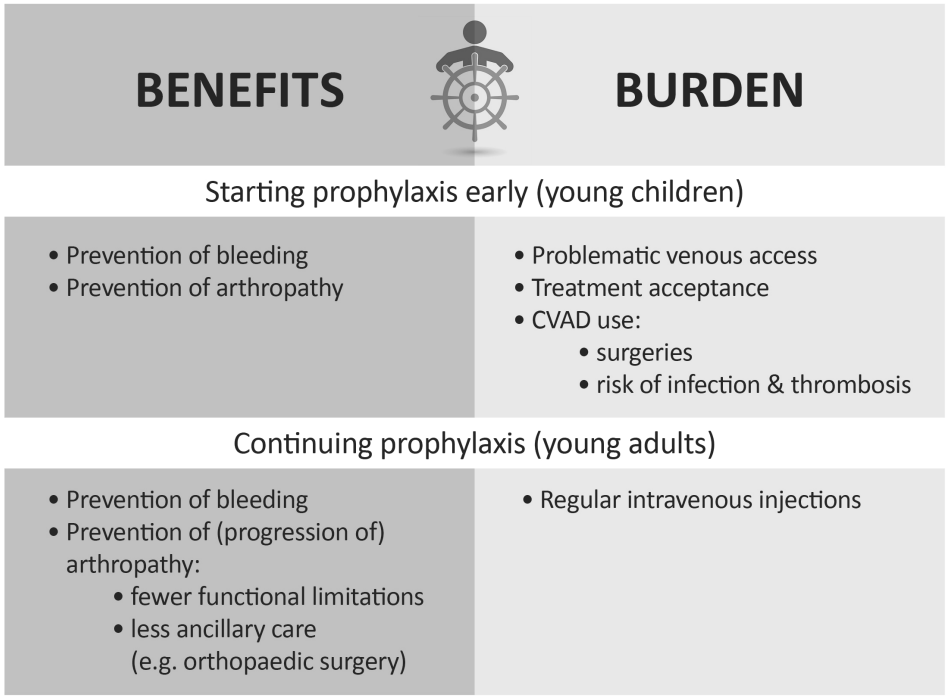

Figure 1. Navigating between the benefits and burden of prophylaxis: a parents'/patients' perspective.
CVAD = central venous access device

Aim and outline of this thesis

The aim of this thesis was to improve prophylactic treatment by assessing changes in clinical practice of prophylaxis and their consequences on long-term outcome. We focussed on starting and stopping prophylaxis in patients with severe haemophilia who started prophylaxis in early childhood. In this setting, treatment decisions are driven by navigating between the burden of treatment and risk of arthropathy, both for health care providers and patients (Figure 1).

Chapter 2 describes when prophylaxis was started over time and how this affected bleeding before prophylaxis, CVAD use, and initial prophylactic regimens. However, to determine the consequences of these (changing) strategies, treatment up to reaching 3-3.5 infusions per week must be included.

Chapter 3 identifies different prophylactic treatment strategies in European centres in the first four years of life. It compares their effect on bleeding, number of infusions, clotting factor consumption and CVAD use.

Chapter 4 explores whether routinely collected Haemophilia Joint Health Score (HJHS) can be used to compare prophylactic regimens in children in European centres.

Chapter 5 explores the long-term effects of postponing prophylactic treatment according to age and bleeding before starting prophylaxis.

Chapter 6 reports outcome after 10-year follow up of patient-initiated discontinuation of long-term prophylaxis.

Chapter 7 explores the correlation between objective and self-reported outcome assessment in adult patients on prophylaxis.

Chapter 8 discusses the findings presented in this thesis in a broad context, including suggestions for future research.

References

1. Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia B prevalence around the world. *Haemophilia* 2012; **18**: e91–4.
2. Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia* 2010; **16**: 20–32.
3. Biggs R, Macfarlane RG. Haemophilia and related conditions: a survey of 187 cases. *Br J Haematol* 1958; **4**: 1–27.
4. Den Uijl IEM, Mauser Bunschoten EP, Roosendaal G, Schutgens REG, Biesma DH, Grobbee DE et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia* 2011; **17**: 849–53.
5. White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; **85**: 560.

6. Plug I, Van der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L et al. Thirty years of hemophilia treatment in the Netherlands, 1972-2001. *Blood* 2004; **104**: 3494–3500.
7. Stephensen D, Tait RC, Brodie N, Collins P, Cheal R, Keeling D et al. Changing patterns of bleeding in patients with severe haemophilia A. *Haemophilia* 2009; **15**: 1210–1214.
8. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A et al. Guidelines for the management of hemophilia. *Haemophilia* 2013; **19**: e1–e47.
9. Fischer K, Van Hout BA, Van der Bom JG, Grobbee DE, Van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta Radiol* 2002; **43**: 528–32.
10. 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**: 113–7.
11. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: Effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446–452.
12. Van Creveld S. Prophylaxis in haemophilia. **Lancet** 1971; **1**: 450.
13. Van Creveld S. Prophylaxis of Joint Hemorrhages in Hemophilia. *Acta Haematol* 1971; **45**: 120–127.
14. Gringeri A, Lundin B, Von Mackensen S, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; **9**: 700–710.
15. Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med* 1997; **241**: 395–400.
16. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
17. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.
18. Van den Berg HM, Fischer K, Mauser-Bunschoten EP, Beek FJ, Roosendaal G, Van der Bom JG et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561–565.
19. Meunier S, Chambost H, Demiguel V, Doncarli A, Suzan F, Trossaert M. Use of clinical practice guidelines on long-term prophylaxis in severe hemophilia in France: A retrospective audit. *J Pediatr* 2013; **162**: 10–14.
20. Ljung R. The risk associated with indwelling catheters in children with haemophilia. *Br J Haematol* 2007; **138**: 580–586.
21. Meunier S, Trossaërt M, Berger C, Borel-Derlon A, Dirat G, Donadel-Claeyssens S et al. French guidelines. Long-term prophylaxis for severe haemophilia A and B children to prevent haemophiliac arthropathy. *Arch Pediatr* 2009; **16**: 1571–8.
22. Nederlandse Vereniging van Hemofiliebehandelaars. Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen. Alphen aan den Rijn: The Netherlands: Van Zuiden Communications, 68-69; 2009.
23. Hay CRM. Prophylaxis in adults with haemophilia. *Haemophilia* 2007; **13 Suppl 2**: 10–5.
24. Berntorp E, Astermark J, Björkman S, Blanchette VS, Fischer K, Giangrande PLF et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; **9 Suppl 1**: 1–4.
25. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V et al. A United Kingdom haemophilia centre doctors' organization guideline approved by the British committee for standards in haematology: Guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemo-

philia A. *Br J Haematol* 2010; **149**: 498–507.

26. Makris M. Prophylaxis in haemophilia should be life-long. *Blood Transfus* 2012; **10**: 165–168.
27. Richards M, Altisent C, Batorova a, Chambost H, Dolan G, De Moerloose P et al. Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. *Haemophilia* 2007; **13**: 473–479.
28. 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**: 107–112.
29. Fischer K, Van der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE et al. Discontinuation of prophylactic therapy in severe haemophilia: Incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–550.

CHAPTER 2

Bleeding before prophylaxis in severe haemophilia: paradigm shift over two decades

A. Nijdam, C. Altisent, G. Auerswald, M.D. Carcao, A.R. Cid, S. Claeyssens-Donadel, K. Kurnik, R. Ljung, B. Nolan, P. Petrini, H. Platokouki, A. Rafowicz, A.E. Thomas, and K. Fischer on behalf of the PedNet and CANAL study groups

Published as letter to the editor in Haematologica 2015; 100: e84-6

Abstract

Early initiation of prophylaxis is critical for prevention of arthropathy and can be initiated according to age or bleeding. This multicentre longitudinal observational cohort study assessed bleeding before prophylaxis and strategies for initiating prophylaxis. Data were collected on FVIII treatment in children with severe haemophilia A (FVIII<1IU/ml), born 1990-2009. Patients were followed until the 50th treatment day or inhibitor development. In 919 patients across 4 birth cohorts (1990-1994, 1995-1999, 2000-2004, 2005-2009), over time less bleeding was accepted before initiating prophylaxis: the proportion of patients starting before any joint bleeding increased from 29% to 43% (P=0.06) and the proportion starting before the third joint bleed increased from 65% to 85% (P<0.01). Concurrently the use of primary prophylaxis as defined by the WFH (starting before three years of age and the second joint bleed) increased from 35% to 70% (P<0.01). Prophylaxis was increasingly started with once weekly infusions (from 18% to 59%; P<0.01). The use of central venous access devices remained stable around 40%. In conclusion, since 1990 prophylaxis was started earlier and after fewer bleeds. This resulted in more patients starting primary prophylaxis. To determine which factors are crucial for optimal long-term outcome, outcome assessment, including subsequent treatment regimens, is needed.

Introduction

Prophylaxis for haemophilia is the scheduled infusion of the missing clotting factor with pre-specified dose, with the intention of preventing bleeds and the associated pathologic consequences of bleeding. It is the treatment of choice for patients with severe haemophilia A (clotting factor VIII [FVIII] <0.01 IU/mL) in countries with available resources [1-10].

Early initiation of prophylaxis proved to be critical for effective prevention of arthropathy [2,6]. Around 2000 several studies focused on specifying exact criteria for starting early prophylaxis. While some advocated starting prophylaxis before the age of three years or even earlier [1,11], others suggested waiting for the first or second joint bleed [10,12,13]. Concurrently, the first detailed definitions of primary and secondary prophylaxis were drafted [14]. The two most frequently used definitions of primary prophylaxis, both specify starting after a maximum of one joint bleed. The European Paediatric Network for Haemophilia Management (PedNet) specified primary prophylaxis as starting before two years of age *or* after the first joint bleed [14] and The World Federation of Haemophilia (WFH) as starting before the age of 3 years *and* before the second joint bleed, in the documented absence of osteochondral joint disease [7].

When starting prophylaxis early, central venous access devices (CVADs) may be needed to facilitate frequent venous access, but these devices carry a risk of infections and thrombotic complications [15]. Attempting to reduce the need for CVADs while initiating early prophylaxis, Petrini and colleagues started prophylaxis with once weekly infusions [11,16]. Many have subsequently published or recommended protocols starting with once weekly infusions [17-21].

The present study will assess how the increasing awareness of the importance of early prophylaxis affected bleeding before prophylaxis, CVAD use, initial prophylactic regimens, and achievement of primary prophylaxis.

Methods

Design and study population

The study population consisted of a cohort of patients with severe haemophilia A (FVIII<0.01 IU/mL), born from January 1990 until December 2009 from 31 Haemophilia Treatment Centres: one Israeli, two Canadian and 28 European. Data were collected for the CANAL study (Concerted Action on Neutralizing Antibodies in severe haemophilia A) and the PedNet registry (Paediatric Network for Haemophilia Management) [22,23].

Data

Anonymized data on patients' demographics, bleeding and treatment were collected by the participating centres. For the CANAL study, data were collected from the medical records using standardized case report forms (CRFs). For PedNet, data were collected using specially designed patient logbooks and submitted to the databases using web-based CRFs. The content of the CRFs and in-and exclusion criteria were the same for both datasets [22,23].

For the present analysis patients were followed from birth until the 50th exposure day or the development of a clinically relevant inhibitor. An exposure day (ED) was defined as a calendar day during which any FVIII was given. Clinically relevant inhibitor development was defined as the occurrence of at least two positive inhibitor titres according to the local laboratory, combined with a decreased in vivo Factor VIII recovery. For all factor administrations, dates, doses of infusion and reasons for treatment (prophylaxis, bleed, surgery, and follow-up of a bleed or surgery) were documented. A bleed was defined as any complaint, characterized by any pain, swelling and/or restriction of function, requiring treatment. Start of prophylaxis was defined as the regular infusion of FVIII, at least once weekly, continued for at least two months in the absence of an inhibitor. As start of prophylaxis was not explicitly specified in the CRF, two independent researchers assessed the start date, frequency and dose of prophylaxis for each patient. Discrepancies were resolved by discussion and/or checked with the patients' physician. PedNet data were repeatedly checked for completeness and inconsistencies using pre-specified protocols including monitor visits (www.Pednet.nl). For the current analysis, data collected until May 1st 2013 were used [22].

Data analysis

Data were analysed as a whole and in 5-year birth cohorts. Descriptive analyses were performed for patient characteristics, treatment characteristics and bleeding before prophylaxis. Trends over time were analysed using univariable linear or logistic regression. Kaplan-Meier survival analysis was used to assess the occurrence of the first joint bleed and cumulative incidences of start of prophylaxis and CVAD use, while accounting for differences in follow-up due to inhibitor development. Differences in survival curves across birth cohorts were assessed using the log-rank test. A P-value of <0.05 was considered to be statistically significant and all reported P-values are two-sided. All data were analysed using IBM® SPSS® Statistics version 20.

Results

The CANAL study and the PedNet registry provided 322 and 622 potentially eligible patients respectively. From CANAL and PedNet respectively 9 and 16 patients were excluded for not having any data on exposure days. Eventually, data on 919 patients with severe haemophilia A were analysed: 313 from CANAL and 606 from PedNet.

Initiation of treatment and prophylaxis

The initiation of prophylaxis according to birth cohort is shown in Table 1. The median age at initiation of prophylaxis decreased from 1.6 years in the first birth cohort, to 1.3 years in the last birth cohort (P<0.01). Concomitantly, the proportion of patients on prophylaxis before age three years increased from 45% to 84% (P<0.01). At the time of their 50th ED, 62%, 75%, 82%, and 93% of patients were on prophylaxis in the four respective birth cohorts (P<0.01). At the same time, the median age of receiving the 50th ED decreased from 3.1 years in the first birth cohort, to 2.1 years in the last birth cohort (P<0.01).

Table 1. Initiation of prophylaxis according to birth cohort.

Birth cohort	1990-94	1995-99	2000-04	2005-09	P trend
Patients (n)	138	172	302	307	-
Age at start of prophylaxis (years)	1.6 (1.1-3.1)	2.1 (1.1-2.9)	1.4 (1.1-2.1)	1.3 (0.9-1.9)	<0.01
On prophylaxis at 50ED† (%)	62%	75%	82%	93%	<0.01
On prophylaxis at age 3 years† (%)	45%	59%	75%	84%	<0.01

Values are numbers (n), medians (IQR) and percentages (%).
† Kaplan-Meier survival analysis censored at inhibitor development.

Bleeding before prophylaxis

The first joint bleed occurred at a median of 1.7 years (IQR 1.0-2.8; survival analysis censored at inhibitor development or start of prophylaxis). Bleeding before the initiation of prophylaxis according to birth cohort is shown in Table 2. The time from the first joint bleed until the initiation of prophylaxis decreased from a median of 0.5 years in the first birth cohort, to a median of 0.1 years in the last birth cohort (P<0.01). Over time, fewer bleeds were accepted before initiating prophylaxis. The median number of bleeds before initiation of prophylaxis progressively decreased over time from 6.5 bleeds, including 2 joint bleeds, in the first birth cohort, to 3 bleeds, including 1 joint bleed, in the last birth cohort (P<0.01). The proportion of patients starting prophylaxis before any joint bleed increased from 29% to 43% (P=0.06). Joint bleeding before prophylaxis is shown in Figure 1. It demonstrates that over the four birth cohorts,

especially the proportion of patients starting prophylaxis after no or only a single joint bleed increased, while the proportion starting after two or more joint bleeds decreased. As a result, the proportion of patients starting before the second joint bleed increased from 43% to 72% (P<0.01). Concomitantly, the proportion of patients starting prophylaxis before the third joint bleed increased from 65% to 85% (P<0.01).

The proportion of patients receiving primary prophylaxis according to the first PedNet definition [14] increased from 65% in the first, to 88% in the last birth cohort (P<0.01). The 1999 PedNet definition includes a maximum age *or* a maximum number of joint bleeds. As the WFH definition of primary prophylaxis restricts both age *and* number of joint bleeds, fewer patients started primary prophylaxis according to the WFH definition, yet the proportion still doubled from 35% to 70% (P<0.01). The WFH definition however, excludes the 21% of patients who were older than three years at the time of their first joint bleed and initiated prophylaxis afterwards.

Table 2. Bleeding before prophylaxis and primary prophylaxis according to birth cohort.

Birth cohort	1990-94	1995-99	2000-04	2005-09	P trend
Patients on prophylaxis (n)	74	101	202	238	-
Bleeding before prophylaxis					
Bleeds before prophylaxis (n)	6.5 (3.0-12.0)	4.0 (1.0-12.0)	4.0 (1.5-9.0)	3.0 (1.0-7.0)	<0.01
Joint bleeds before prophylaxis (n)	2.0 (0.0-4.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	<0.01
Time from 1st joint bleed to prophylaxis (years)	0.5 (0.3-1.4)	0.5 (0.1-1.3)	0.3 (0.0-0.7)	0.1 (0.0-0.5)	<0.01
Without joint bleeds before prophylaxis (%)	29%	40%	42%	43%	0.06
Primary prophylaxis					
PedNet definition (%)	65%	67%	86%	88%	<0.01
WFH definition (%)	35%	49%	67%	70%	<0.01

Values are numbers (n), medians (IQR) and percentages (%).

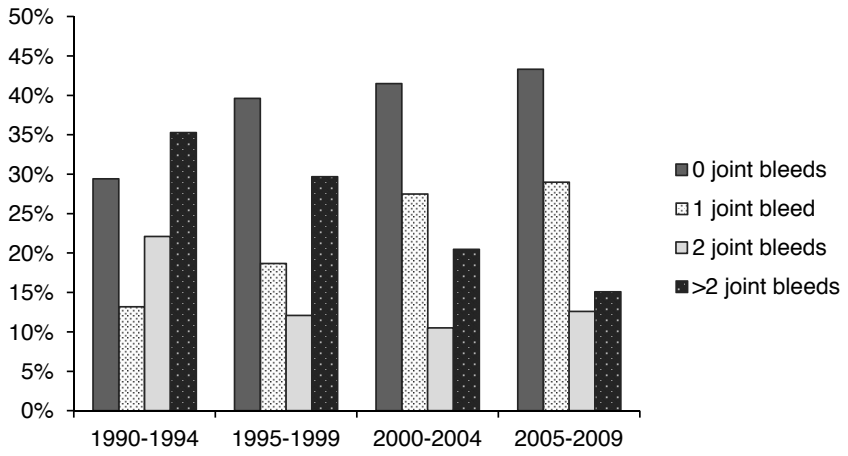

Figure 1. Joint bleeding before prophylaxis according to birth cohort.

Initiating prophylaxis: how

Despite the earlier start of prophylaxis, cumulative CVAD use in patients on prophylaxis was relatively stable of over time (P=0.85). At the age of four years, about 40% of patients who started prophylaxis had used a CVAD. Three out of 31 centres used CVADs in all patients.

Figure 2 demonstrates a large shift in initial prophylactic regimen. Around 2000, following the Swedish publication showing that early prophylaxis started with once weekly infusions resulted in good outcome [11], prophylaxis was increasingly started using once weekly regimens: from only 18% in the early 1990s to 59% in the last birth cohort (P<0.01). Concomitantly, starting prophylaxis ≥3x/week decreased from 41% to 18% (P<0.01). A few years later, following the first presentations on low dose prophylaxis [18,24], prophylaxis was increasingly started with a dose of 250 IU per infusion (median 25 IU/kg): from 12% in the 1990-1995 cohort to 27% in the 2005-2009 cohort (P<0.01). At the same time, the proportion of patients starting with infusions of 1000 IU or more decreased from 16% to 5% (P<0.01). However, the majority of the patients in all birth cohorts (around 62%), started prophylaxis with a dose of 500 IU per infusion and the median infused dose remained stable around 45 IU/kg/infusion.

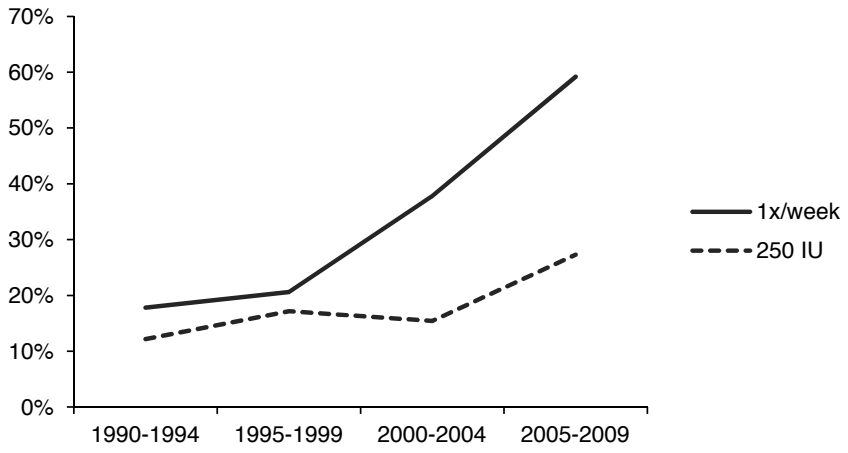

Figure 2. The use of low dose and low frequency in initial prophylaxis regimen according to birth cohort.

Discussion

This multicentre cohort study is the first to assess paradigm shifts in the initiation of prophylaxis for patients with severe haemophilia A. Over the last two decades prophylaxis was started at an increasingly younger age (reaching a median of 1.3 years in the last birth cohort) and after fewer bleeds (85% of patients starting prophylaxis before the third joint bleed in the last birth cohort), resulting in increased use of primary prophylaxis. In the last decade, the regimens used showed an increasing tendency to start prophylaxis with once weekly infusions and lower doses per infusion. The proportion of patients on prophylaxis who used a CVAD however remained stable at around 40%.

Study design

To appreciate these findings, some aspects of study design need to be discussed. Selection bias was avoided by including all patients from the specified birth years being diagnosed and treated in the participating centres only, while excluding children referred because of special problems or inhibitor development. As this study focused on prophylaxis initiated within the first 50 EDs, results should not be extrapolated to starting prophylaxis later in life. However, it is expected that the 38%-25% of patients without inhibitors in the first two birth cohorts and the 18%-7% of patients in the last two birth cohorts have started prophylaxis since. Therefore, limiting the window of observation to the first 50 EDs will have resulted in an underestimation

of the overall age at starting prophylaxis and the number of bleeds incurred before prophylaxis, especially in the earlier cohorts. Differences between the first and last two cohorts could therefore be larger than presented in this study.

Comparison with other studies- initiation of prophylaxis

The observed earlier start of prophylaxis is in line with reports in other studies [2,25-27]. Two different approaches to the timing of starting prophylaxis early have been described: according to age (e.g. before the age of three years [1,11]) and according to a patient's bleeding pattern (e.g. before the second [13] or third joint bleed [12]). Following these approaches, national guidelines and recommendations were issued in several European countries to start prophylaxis early [11,14,19-21,28-30], often combining criteria of both age and number of bleeds at the initiation of prophylaxis. The results of this study confirm that prophylaxis is not only increasingly started before the age of three years or before the third joint bleed, but also that more patients start on primary prophylaxis. Even though the term primary prophylaxis was already used in publications in the 1990s, PedNet was the first to formally publish a definition in 1999 [14]. The two circulating definitions have different benefits and drawbacks. The 1999 PedNet definition uses a maximum age of two years *or* a maximum of 1 joint bleed, and therefore potentially includes patients suffering many joint bleeds before the age of two years. The WFH definition, on the other hand, uses a maximum age of three years *and* a maximum of 1 joint bleed [7]. This makes it impossible to 'start primary prophylaxis' in the 21% of patients who had their first joint bleed after the age of three years, while still treated on-demand. The PedNet definitions were updated and refined in 2006 [31], specifying primary prophylaxis in two categories, and was therefore not used in the present analysis.

Comparison with other studies- prophylactic regimen & CVAD use

The idea to initiate prophylaxis with once weekly infusions, originated in Sweden where it was applied with the aim of reducing the need for CVADs [11,16]. This approach was subsequently adopted in several countries [17,19-21,29]. Our findings confirmed that once weekly infusions are increasingly used and that this strategy is now used in the majority of patients, even in countries without a formal protocol advising this strategy. The strategies used to subsequently increase prophylaxis extend beyond the first 50 EDs and have to be studied separately.

The reported CVAD use in this study was stable over time (40% up to the age of four years). The two trends, starting prophylaxis earlier and starting with once weekly infusions, likely balance out and cause the stable use of CVADs. Stable CVAD use over a period of 14 years was

also observed in a French audit on the use of early prophylaxis [27].

The observed trend towards starting prophylaxis with low dose infusions (250 IU), especially in children born after 2004, might be driven by the 2007 publication on the benefits of prophylaxis regarding inhibitor development and the risks of higher dosing [23], but also that 250 IU vials became more available on the market. An early low-frequency, low-dose prophylactic regimen (1x/week 250 IU) in Germany reported low incidences of inhibitors [18,24]. However, reduction of inhibitor incidence on this regimen was not confirmed in a prospective study [32]. Aside from attempting to prevent inhibitor development, this trend could also be driven by pharmaco-economic considerations. After all, a double dose only adds one half-life of protection to the patient, which is around 9 hours in young children [33].

Future research

These findings demonstrate that it is feasible to start prophylaxis early. The next step is to address the effects of the initial prophylactic regimens, while taking into account the subsequent strategies to intensify prophylaxis to reach the full protection of infusions 3x/week or every other day. This knowledge may be used to develop the optimum prophylactic strategy for preventing arthropathy. Concomitantly, this information can be used to develop a universal definition of primary, secondary and tertiary prophylaxis.

In conclusion

Publications in the late 1990s on the importance of early prophylaxis have led to a paradigm shift in clinical practice. Less bleeding is now accepted before the initiation of prophylaxis and consequently more patients are started before the third joint bleed and before three years of age. In addition, initial prophylactic regimens increasingly use once weekly infusions and smaller doses per infusion. To determine the consequences of the different regimens used to start prophylaxis, subsequent treatment and outcome need to be documented and analysed.

Acknowledgements

The data analysis was supported by an unrestricted grant from Novo Nordisk. The PedNet study group was supported by unrestricted research grants from Bayer Healthcare and Baxter Healthcare Cooperation.

References

1. Gringeri A, Lundin B, von MS, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with haemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; **9**: 700-710.
2. Lofqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med* 1997; **241**: 395-400.
3. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med* 2007; **357**: 535-544.
4. National Haemophilia Foundation. MASAC Recommendation Concerning Prophylaxis. MASAC Document #179. 2007; 1-2.
5. Nilsson IM, Blomback M, Ahlberg A. Our experience in Sweden with prophylaxis on haemophilia. *Bibl Haematol* 1970; **34**: 111-124.
6. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and *B. J Intern Med* 1992; **232**: 25-32.
7. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A et al. Guidelines for the management of haemophilia. *Haemophilia* 2013; **19**: e1-47.
8. Van Creveld S. Prophylaxis of joint hemorrhages in haemophilia. *Acta Haematol* 1971; **45**: 120-127.
9. Van Creveld S. Prophylaxis in haemophilia. *Lancet* 1971; **1**: 450.
10. Van den Berg HM, Fischer K, Mauser-Bunschoten EP, Beek FJ, Roosendaal G, Van der Bom JG et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561-565.
11. Astermark J, Petrini 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**: 1109-1113.
12. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, De Kleijn P et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe haemophilia. *Blood* 2002; **99**: 2337-2341.
13. Kreuz W, Escuriola-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**: 413-417.
14. Ljung R. Second Workshop of the European Paediatric Network for Haemophilia Management, 17-19 September 1998 in Vitznau/Switzerland. *Haemophilia* 1999; **5**: 286-291.
15. Ljung R. The risk associated with indwelling catheters in children with haemophilia. *Br J Haematol* 2007; **138**: 580-586.
16. Petrini P. What factors should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B? *Haemophilia* 2001; **7**: 99-102.
17. Feldman BM, Pai M, Rivard GE, Israels S, Poon MC, Demers C et al. Tailored prophylaxis in severe haemophilia A: interim results from the first 5 years of the Canadian Haemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006; **4**: 1228-1236.
18. Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. *Haemophilia* 2010; **16**: 256-262.
19. Meunier S, Trossaert M, Berger C, Borel-Derlon A, Dirat G, Donadel-Claeyssens S et al. French guidelines. Long-term prophylaxis for severe haemophilia A and B children to prevent haemophiliac arthropathy. *Arch Pediatr* 2009; **16**: 1571-1578.

20. Nederlandse Vereniging van Hemofiliebehandelaars (NVHB). Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen. 2009; 68-69.
21. Recommandations Thérapeutiques Françaises sous l'Egide de la COMETH. Prophylaxie primaire de longue durée débutée précocement et progressivement intensifiée pour les enfants hémophiles A sévères. 2002; 10-11.
22. Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. *Haemophilia* 2014; **20**: e280-e286.
23. Gouw SC, Van der Bom JG, Van den Berg HM. Treatment-related risk factors of inhibitor development in previously untreated patients with haemophilia A: the CANAL cohort study. *Blood* 2007; **109**: 4648-4654.
24. Auerswald G, Bidlingmaier C, Kurnik K. Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients--long-term follow-up and continuing experience. *Haemophilia* 2012; **18**: e18-e20.
25. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446-452.
26. Plug I, Van der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L et al. Thirty years of haemophilia treatment in the Netherlands, 1972-2001. *Blood* 2004; **104**: 3494-3500.
27. Meunier S, Chambost H, Demiguel V, Doncarli A, Suzan F, Trossaert M. Use of clinical practice guidelines on long-term prophylaxis in severe haemophilia in France: a retrospective audit. *J Pediatr* 2013; **162**: 1241-4, 1244.e1.
28. Berntorp E. Guidelines on treatment of haemophilia in Sweden. *Haemophilia* 1998; **4**: 425-426.
29. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V et al. A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol* 2010; **149**: 498-507.
30. Santagostino E, Mannucci PM, Bianchi BA. Guidelines on replacement therapy for haemophilia and inherited coagulation disorders in Italy. *Haemophilia* 2000; **6**: 1-10.
31. Donadel-Claeyssens S. Current co-ordinated activities of the PEDNET (European Paediatric Network for Haemophilia Management). *Haemophilia* 2006; **12**: 124-127.
32. Auerswald G, Kurnik K, Blatny J, Reininger AJ. The EPIC Study: A clinical trial to assess whether early low dose prophylaxis in the absence of immunological danger signals reduces inhibitor incidence in previously untreated patients (PUPS) with haemophilia A. *55th ASH Annual Meeting and Exposition, New Orleans* 2013; oral presentation-nr. 576.
33. Bjorkman S, Oh M, Spotts G, Schroth P, Fritsch S, Ewenstein BM et al. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood* 2012; **119**: 612-618.

CHAPTER 3

How to achieve full prophylaxis in young boys with severe haemophilia A: different regimens and their effect on early bleeding and venous access

A. Nijdam, K. Kurnik, R. Liesner, R. Ljung, B. Nolan, P. Petrini and K. Fischer
on behalf of the PedNet study group

Haemophilia 2015; 21: 444-50

Abstract

Introduction: To facilitate early prophylaxis, step-up regimens starting prophylaxis with infusions 1x/week were introduced. Choice of initial regimen may affect outcome. This study aims to classify initial prophylactic regimens and compare them on short-term outcome.

Methods: From the "European Paediatric Network for Haemophilia Management" (PedNet) registry, patients with severe haemophilia A without inhibitors, born 2000-2012, receiving prophylaxis were included. Treatment centres were classified according to the initial frequency of prophylactic infusions and the age at reaching infusions ≥3x/week. Bleeding, and Central Venous Access Device (CVAD) use were compared at age four years.

Results: In 21 centres with 363 patients, three regimens were identified: I) start prophylaxis with ≥3x/week infusions before age three (full: 19% of centres, 18% of patients); II) start 1-2x/week, increasing frequency as soon as possible (asap), reaching ≥3x/week before age three (43% of centres, 36% of patients); III) start 1-2x/week, increasing frequency according to bleeding (phenotype), reaching ≥3x/week after age three (38% of centres, 46% of patients). Prophylaxis was started at median 1.2 years on the full and asap regimen vs 1.8 years on the phenotype regimen. Complete prevention of joint bleeds was most effective on the full regimen (32% full vs. 27% asap and 8% phenotype), though at the cost of using most CVADs (88% full vs. 34% asap and 22% phenotype).

Conclusion: The three prophylaxis regimens identified had different effects on early bleeding and CVAD use. This classification provides the first step towards establishing the optimum prophylactic regimen.

Introduction

Long-term prophylaxis for severe haemophilia is used more and started at a progressively younger age since the 1970s [1-3]. Swedish data have shown that prophylaxis is most effective if started before reaching the age of three years [4] and suggested that starting at low frequencies facilitates early prophylaxis and reduces the need for central venous access devices (CVADs) [5]. Since then different step-up regimens starting at lower frequencies (1-2x/week) have been introduced to facilitate early prophylaxis [6-10] and/or reduce inhibitor development [11,12].

To evaluate effects of different strategies to start prophylaxis, subsequent treatment must be included. The common objective is progressing to 3-3.5 infusions per week to maintain minimum factor levels for optimum protection against bleeding. The Swedish reported good long-term outcome of starting prophylaxis once weekly and stepping up as soon as venous access allows [4]. French and Canadians subsequently introduced formal protocols stepping up according to bleeding [6,7,10]. Where the French step up after one spontaneous joint bleed [7,10], the Canadians step up only after a minimum of three joint bleeds within three months [6]. Systematic outcome assessment was reported for the Canadian regimen only: after seven years of follow-up, outcome at physical examination appeared favourable [13], but MRI showed structural joint changes in 50% of boys [14].

The optimum regimen for starting prophylaxis in young children with severe haemophilia has not yet been established. The aim of this study is to identify regimens used to start prophylaxis in European treatment centres and to compare their effect on bleeding, number of infusions, clotting factor consumption and CVAD use in the first four years of life.

Methods

Design and study population

The "European Paediatric Network for Haemophilia Management" (PedNet) registry provided data for this prospective observational cohort study. Only data from 21 centres providing follow-up after the first 75 EDs were included; resulting in a cohort of 468 patients with severe haemophilia A (FVIII<1IU/ml), born between 01.01.2000 and 01.12.2012. The PedNet registry includes full (birth) cohorts of patients, including all consecutive patients diagnosed and treated in each centre. Patients referred to a centre because of inhibitor development were excluded to avoid selection bias. All patients are treated according to their local centres' protocol. All centres obtained local ethical approval and written informed consent was obtained before inclusion. Data collection for the PedNet registry was retrospective up to 2004 and

prospective afterwards, including formal data monitoring. More details of the design of the PedNet Registry have been described elsewhere [15].

Data

Anonymised data on patients' demographics, bleeding and treatment were collected until May 1st 2013. For the present analysis, patients were followed from birth until age seven or the last evaluation recorded. Data were censored at the development of a clinically relevant inhibitor.

An exposure day (ED) was defined as a calendar day during which one or more infusions of FVIII were given. For all factor administrations up to the 75th ED, dates, doses of infusion and reasons of treatment (prophylaxis, bleed, surgery, and follow-up treatment) were documented. After the 75th ED, treatment and bleeding data were documented only at regular patient visits [15]. Dose per kg bodyweight was calculated using WHO Child Growth Standards for 0-5 years [16] and for 5-10 years [17]. Cumulative number of factor administrations was approximated by the cumulative number of EDs. Cumulative clotting factor consumption was derived from the treatment data.

Prophylaxis was defined as the use of clotting factor product in the absence of bleeding, with regular intervals, at least once weekly, for at least two consecutive months. As start of prophylaxis was not explicitly specified in the CRF, data were derived from individual ED records. By applying the definition of prophylaxis to this data, two researchers independently assessed the start date, frequency and dose of prophylaxis for each patient. Discrepancies were resolved by discussion.

Classification of treatment regimens

The aim of this study was to identify current strategies to start prophylaxis. At starting prophylaxis the paediatrician balances bleeding risk, venous access problems and treatment acceptance of patient and parents. The first decision is to start with once weekly infusions or more frequently; and if starting once weekly, when to increase the frequency of prophylactic infusions. In intensifying prophylaxis from 1 to 3-3.5x/week, two approaches are taken: escalation of frequency as soon as possible, or based on individual bleeding phenotype.

Each paediatrician has a preferred strategy, but in clinical practice starting prophylaxis is determined both by the preferred treatment strategy as well as patient characteristics: e.g. heavy bleeders generally step up to full prophylaxis earlier. Analysing regimens at patient level would therefore introduce selection bias (confounding by indication): heavy bleeders would be over-

represented in more stringent regimens. Instead, prophylactic strategies were classified at centre level, including full cohorts of patients with different bleeding phenotypes. For each centre the most prevalent regimen was determined by calculating the median initial frequency, and median age at reaching prophylaxis with 3-3.5 infusions per week. Based on these two values, each centre was categorised. The age of three years was used as a cut-off in reaching prophylaxis with 3-3.5 infusions/week, as it has been established that starting prophylaxis before the age of three years is most effective in preventing arthropathy [4].

Data analysis

Data were analysed only if prophylaxis was started before seven years of age. Simple descriptive analyses were performed for prophylactic regimen characteristics, including percentages, median values and interquartile ranges. Strategies were compared using the Kruskal-Wallis test for medians or Fischer's Exact test for proportions. Effects on cumulative numbers of bleeds were analysed using univariable regression analysis with a negative binomial distribution and a log-linear link function [18]. To account for differences in follow-up, Kaplan Meier survival analysis was used to calculate cumulative incidences of reaching ≥3 infusions per week and CVAD use. The survival curves were compared using the log-rank test. A P-value of <0.05 was considered statistically significant and all reported P-values are two-sided.

Results

Patients

The PedNet registry contained data on 468 patients with severe haemophilia A, born 01.01.2000 to 01.12.2012. Details on inclusion and exclusion are shown in Figure 1. Out of 468 patients, 20 patients were excluded for not having data on exposure days. Of the 448 remaining patients, 363 started prophylaxis before the age of seven years and in the absence of inhibitory antibodies. One patient started prophylaxis at 9.4 years only. The 26 patients who did not start prophylaxis, nor developed an inhibitor, were median 3.1 years at the end of follow-up (IQR 0.6-4.2).

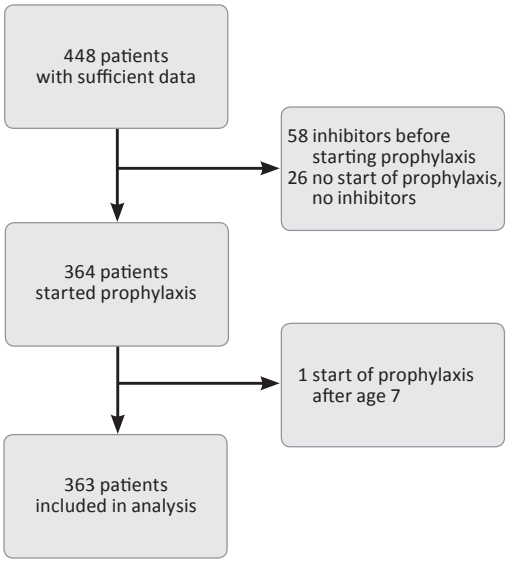

Figure 1. Inclusion flow chart.

Prophylactic regimens

At centre level, three regimens were identified based on the strategy used in the majority of patients (Figure 2):

I) starting prophylaxis with ≥3x/week infusions before three years of age (full);

II) starting prophylaxis 1-2x/week and stepping up as soon as possible, reaching ≥3x/week before three years of age (asap);

III) starting prophylaxis 1-2x/week and stepping up according to bleeding, reaching ≥3x/week usually after three years of age (phenotype).

No centres started prophylaxis with ≥3x/week infusions after three years of age.

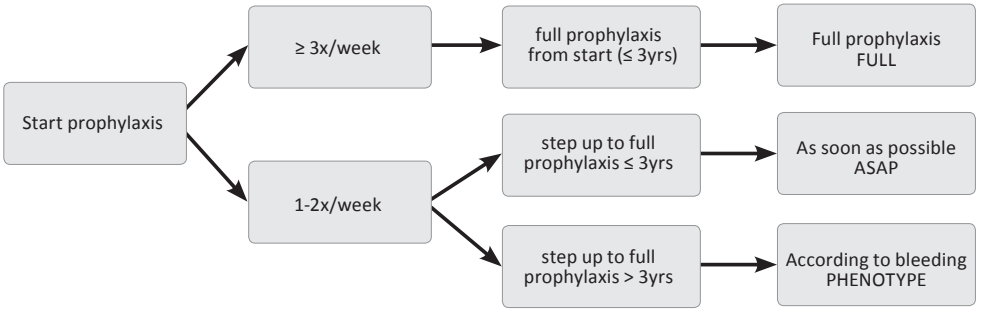

Figure 2. Prophylactic treatment decisions and corresponding strategies.

Out of the 21 centres, 4 centres (66 patients) applied the full regimen. The other 17 centres started prophylaxis at lower frequencies (1-2x/week): 9 centres (130 patients) applied the asap regimen and 8 centres (167 patients) applied the phenotype regimen. Patient and treatment characteristics according to regimens are presented in Table 1. Median age at first treatment was similar across all regimens (P=0.49).

Table 1. Patient and treatment characteristics according to prophylactic strategies.

Prophylactic strategy	**FULL** Full prophylaxis	**ASAP** As soon as possible	**PHENOTYPE** According to bleeding	**P-value** across strategies
Number of centres (%)	4 (19%)	9 (43%)	8 (38%)	-
Number of patients on prophylaxis (%)	66 (18%)	130 (36%)	167 (46%)	-
Age at 1st treatment (years)	0.8 (0.3-1.1)	0.9 (0.6-1.1)	0.8 (0.5-1.1)	0.49
At starting prophylaxis				
Age (years)	1.3 (0.9-1.8)	1.2 (0.9-1.5)	1.7 (1.2-2.6)	<0.01
Frequency 1x/week (%)	9%*	49%	55%	<0.01
Frequency 2x/week (%)	8%*	35%	31%	<0.01
Frequency ≥3x/week (%)	83%	16%*	14%*	<0.01
Infusion dose (IU/kg)	52 (40-87)	46 (28-51)	41 (32-48)	<0.01
At reaching ≥3x/week				
Age (years)	1.3 (0.9-1.8)	1.8 (1.2-3.1)	3.9 (2.3-6.0)	<0.01
Time to reach ≥3x/week since starting (years)	0.0 (0.0-0.0)	0.4 (0.1-1.9)	1.6 (0.2-3.8)	<0.01
Infusion dose (IU/kg)	51 (39-88)	34 (24-47)	29 (23-37)	<0.01

Values are numbers, proportions, medians (IQR) and P-values across strategies.
* Due to clinical circumstances not all patients in a centre started prophylaxis according to the local regimen.

Start of prophylaxis

At starting prophylaxis, the predominant frequency of the specified regimen was followed by 83-86% of patients only. These data reflect the clinical reality of starting prophylaxis. Even in a centre usually starting 1x/week, heavy bleeders would generally step up to full prophylaxis earlier, whereas in a centre usually starting 3x/week, some patients may refuse frequent infusions or venous access may be limiting.

While the full and asap regimens started prophylaxis at a similar age, patients on the phenotype regimen were the last to start prophylaxis at a median age of 1.7 years (P<0.01). The majority of patients first started prophylaxis before the age of 3 years: 92%, 96% and 84% in the

full, asap and phenotype regimen respectively (P<0.01). All regimens started prophylaxis with a median dose of 500 IU per infusion. Although statistically significant, differences in median infusion dose/kg were small and considered clinically insignificant (P<0.01).

Reaching ≥3x/week

The age at reaching ≥3x/week prophylaxis varied significantly across the three regimens (Figure 3a; P<0.01). At the age of four years, 87% of patients on the full regimen had reached prophylaxis ≥3x/week, compared to 65% and 38% on the asap and phenotype regimens. Compared to the full regimen, patients on the asap regimen reached ≥3x/week 0.5 years later and those on the phenotype regimen 2.6 years later (Table 1). Concurrently, patients on the asap regimen reached ≥3x/week within six months after starting prophylaxis, while patients on the phenotype regimen took more than 1.5 years (P<0.01). All regimens still used a median dose of 500 IU per infusion at reaching ≥3x/week. As patients on asap and phenotype regimens were older at the time, their dose/kg/infusion was significantly lower (P<0.01).

CVAD use

Figure 3b shows that the majority of patients (88%) on the full regimen were using CVADs to start prophylaxis ≥3x/week, versus 27% in regimens starting at lower frequencies (34% on asap and 22% on phenotype; P<0.01). Most CVADs were implanted before three years of age. On the asap and phenotype regimens, the proportions requiring CVAD implantation were similar when starting prophylaxis in the first 1.5 years of life (40%), versus 97% on the full regimen. After CVAD implantation, 54% of patients on asap and phenotype regimens did not directly step up to ≥3x/week.

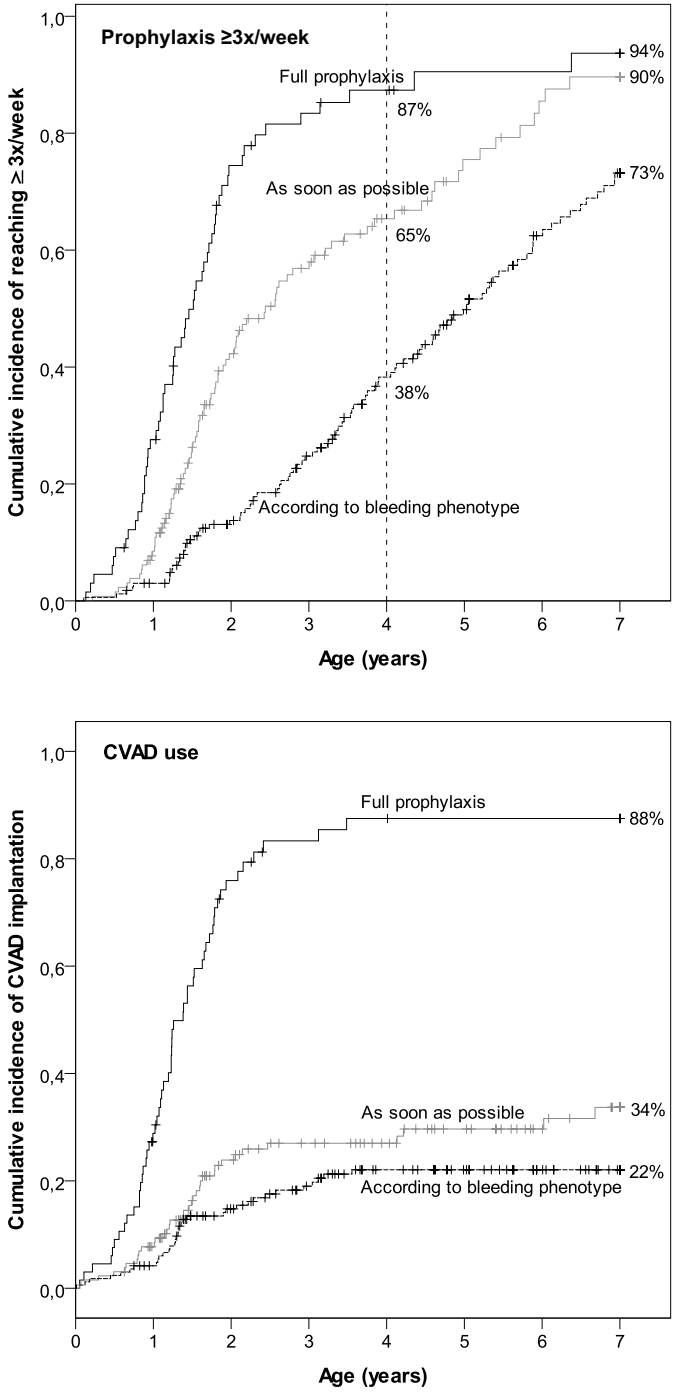

Figure 3. Cumulative incidence of (a) reaching ≥3x/week and (b) central venous access device (CVAD) use according to regimen. The Kaplan Meier one minus survival function estimates cumulative incidences, adjusted for inhibitor development and incomplete follow-up.

Bleeding

Bleeding and treatment up to age four years according to prophylactic strategy is shown in Table 2. Only on the asap regimen, the majority of patients started prophylaxis before the onset of joint bleeding, while patients on the full and phenotype regimens experienced a median of one joint bleed before starting prophylaxis (P<0.01). Starting prophylaxis before the third joint bleed was achieved in 89% of patients on the full regimen and 93% of patients on the asap regimen, but only in 68% of patients on the phenotype regimen (P<0.01).

By four years of age, life-time joint bleeding history was similar for the full and asap regimens: patients on both regimens had experienced median 1 joint bleed and around 30% still had suffered no joint bleeds. By then, patients on the phenotype regimen had experienced more joint bleeds: median 3 joint bleeds and only 14/167 (8%) patients had never suffered joint bleeds. Differences in bleeding in the period between starting prophylaxis and reaching ≥3x/week were pronounced: 64% of patients on the asap regimen had not experienced a joint bleed between starting prophylaxis and reaching ≥3x/week, compared to 31% on the phenotype regimen (P<0.01). On the full and asap regimens, no additional joint bleeds occurred in the median 2.5 years between reaching ≥3x/week and four years of age (median 0 joint bleeds, IQR 0-0.5), showing that ≥3x/week prophylaxis offers good protection against joint bleeds.

The majority (25 out of 26) of intracranial bleeds in the 363 study patients occurred before starting prophylaxis. Only one intracranial bleed occurred in a patient on once weekly prophylaxis at 3,8 years of age who did not follow the regular protocol in a centre using the asap regimen. This bleed prompted immediate stepping-up to infusions every other day. Overall, the proportion of intracranial bleeds and the age at which they occurred were similar across the three prophylactic regimens. No other potentially life-threatening bleeds were observed in the cohort.

Factor administrations and consumption

At the age of four years, the cumulative number of infusions received was close to 400 for both the full and asap regimens, while significantly lower on the phenotype regimen (223; P<0.01). Concurrently, the total clotting factor consumption at age four years was around 174000 IU on the full and asap regimens and about half of that on the phenotype regimen (P<0.01).

Table 2. Bleeding and treatment up to age 4 years according to prophylactic strategy.

Prophylactic strategy	**FULL** Full prophylaxis	**ASAP** As soon as possible	**PHENOTYPE** According to bleeding	**P-value** across strategies
Number of patients	66	130	167	
Before starting prophylaxis				
Cumulative number of joint bleeds	1 (0-1)	0 (0-1)	1 (1-3)	<0.01
Without joint bleeds (%)	42%	65%	20%	<0.01
Number of ICHs (% of all patients)	8 (10%)	7 (5%)	10 (5%)	0.22
At four years of age				
Cumulative number of joint bleeds	1 (0-2)	1 (1-3)	3 (1-5)	<0.01
Without joint bleeds (%)	32%	27%	8%	<0.01
Cumulative number of infusions	360 (186-500)	402 (275-496)	223 (119-343)	<0.01
Cumulative clotting factor consumption (in 1000IU)	177 (72-340)	172 (109-238)	90 (53-149)	<0.01

Values are numbers, proportions, medians (IQR) and P-values across strategies.
ICHs, intracranial haemorrhages.

Discussion

Principal findings

Three different regimens for starting prophylaxis were identified in European centres: starting with ≥3x/week before the age of three years (full), starting prophylaxis with lower frequencies (1-2x/week) and stepping up to ≥3x/week before the age of three years (as soon as possible: asap) or later (according to patient's bleeding phenotype).

Full and asap regimens showed similar bleeding and treatment intensity. However, patients on the asap regimen reached ≥3x/week six months later and used much less CVADs (88% vs. 34%). Patients on the phenotype regimen reached ≥3x/week last and experienced two additional joint bleeds at age four years, but needed fewer CVADs (22%) and infusions.

Internal and external validity

Analyses were based on the high-quality detailed database from the repeatedly checked and monitored PedNet registry; data on exposure days was missing in 4% only [15]. Start of prophylaxis was easy to assess, as it generally occurred within the first 75 EDs that were docu-

mented in detail. Follow-up of outcome data on bleeding, number of infusions and clotting factor consumption was limited to age four years, as it was available for the majority of patients and by then most patients had reached prophylaxis ≥3x/week.

The classification of regimens at centre level is an essential part of this study. Selection bias (confounding by indication) was avoided by analysing strategies at centre level, including full cohorts of patients with different phenotypes.

The classification of prophylactic regimens was based on published data showing the strong independent effect of age at starting prophylaxis on outcome [4,19]. Differences between centres, other than prophylaxis start regimen, may affect outcome, but are unlikely to be the main driver of differences between regimens.

The classification was verified with the treating physicians at the centres. Although few centres have formal protocols, all treating physicians agreed with the classification of their prophylactic strategy.

These data represent treatment in countries with good access to treatment and medical care and no restrictions in clotting factor consumption only. It is likely that prophylactic treatment strategies, including the introduction of prophylaxis, are different elsewhere.

Other studies

Most information on effective prophylaxis is available on starting prophylaxis before age three years or before the third joint bleed [4,19]. This is reflected in current clinical practice: all three regimens generally started prophylaxis before the age of three years and before the third joint bleed. However, to improve prophylactic treatment, it is important to study outcome of different regimens beyond the initiation phase of prophylaxis.

The full regimen can be compared to the randomized trials of the Joint Outcome Study (n=32) [20] and the ESPRIT study (n=21) [21] which started prophylaxis with 3-3.5x/week. However, as they started prophylaxis at older ages than those on the full regimen in this study, outcome cannot be compared.

The asap regimen originated in Sweden in the 1990s. Outcome of Swedish patients starting prophylaxis before the age of three years is good [4,22]. The UK guideline suggests the use of the asap regimen [23], unfortunately outcome data is unavailable.

The phenotype regimen may be compared to the Canadian tailored prophylaxis [6] and French national guidelines [7,10] which increase frequency of prophylactic infusions according to bleeding criteria. However, French outcome data is unavailable and evaluation of clinical practice in France suggested prophylaxis was actually escalated as soon as possible [24]. Outcome on the Canadian step-up protocol showed reason for concern: after seven years of follow-up

most boys had osteochondral and soft-tissue changes in joints on MRI evaluation [14]. However, the Canadian protocol is much less intensive than the phenotype regimen in PedNet: step up criteria are more lenient and prophylaxis ≥3x/week is reached a median age of 9.7 years only, compared to 3.9 years for the phenotype regimen.

To 'train the vein' and avoid CVAD use was the original aim of starting prophylaxis with once weekly infusions, but data on CVAD use in Sweden were not reported [4,5]. The current study effectively established that step-up regimens lowered CVAD use from 88% to 27%. As the majority of patients using CVADs on asap and phenotype regimens did not directly switch to ≥3x/week after implantation, avoiding CVAD use was not the only reason to start at lower frequencies. Introducing prophylaxis at lower frequencies is also thought to increase patients' and parents' acceptance of treatment [25].

Clinical implications

To move towards more optimal treatment strategies, it is important to assess regimens used in clinical practice. The data presented provide extensive experience in starting early prophylaxis for severe haemophilia A. Comparing short-term benefits and burden across regimens, the asap regimen seems to provide the best of both worlds: low CVAD use, less stressful start of prophylaxis and no additional bleeding compared to the full regimen by the age of four years. At that age, patients on the phenotype regimen incurred less infusions, however at the cost of two additional joint bleeds. The key question is whether these additional bleeds result in differences in joint outcome and at what age such differences become apparent at physical examination (HJHS) or imaging (ultrasound, MRI, X-rays). The next important step is to systematically assess long-term outcome using tools that are sensitive to early joint changes.

Conclusion

Three prophylactic regimens were identified based on the frequency at start of prophylaxis (1-2x/week vs ≥3x/week) and age at reaching ≥3x/week (before vs after age three years). Regimens starting prophylaxis at lower frequencies were associated with reduced CVAD use (27% vs 88%). Starting at lower frequencies and subsequently stepping up to ≥3x/week according to bleeding, resulted in about 50% reduction of infusions and clotting factor consumption, but also two additional joint bleeds at the age of four years. To identify the optimum prophylactic regimen more information on the long-term outcome of different regimens, including the additional risk of early joint bleeding, is needed.

Acknowledgements

The PedNet Haemophilia Registry is a collaborative effort of the European PEDiatric NETwork for haemophilia management (www.pednet.nl). The PedNet study group was supported by unrestricted research grants from Bayer Healthcare and Baxter Healthcare Cooperation. The data analysis was supported by an unrestricted grant from Novo Nordisk.

References

1. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446-452.
2. Lofqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med* 1997; **241**: 395-400.
3. Plug I, Van der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L et al. Thirty years of hemophilia treatment in the Netherlands, 1972-2001. *Blood* 2004; **104**: 3494-3500.
4. Astermark J, Petrini 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**: 1109-1113.
5. Petrini P. What factors should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B? *Haemophilia* 2001; **7**: 99-102.
6. Feldman BM, Pai M, Rivard GE, Israels S, Poon MC, Demers C et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006; **4**: 1228-1236.
7. Meunier S, Trossaert M, Berger C, Borel-Derlon A, Dirat G, Donadel-Claeyssens S et al. French guidelines. Long-term prophylaxis for severe haemophilia A and B children to prevent haemophiliac arthropathy. *Arch Pediatr* 2009; **16**: 1571-1578.
8. Nederlandse Vereniging van Hemofiliebehandelaars (NVHB). Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen. 2009; 68-69.
9. Nijdam A, Petrini P, Carcao M, Kurnik K, Auerswald G, Nolan B et al. Trends in starting prophylaxis in the first 50 exposure days for severe haemophilia since 1990. *Haemophilia* 2013; **19**: 10-11.
10. Recommandations Thérapeutiques Françaises sous l'Egide de la COMETH. Prophylaxie primaire de longue durée débutée précocement et progressivement intensifiée pour les enfants hémophiles A sévères. 2002; 10-11.
11. Auerswald G, Bidlingmaier C, Kurnik K. Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients--long-term follow-up and continuing experience. *Haemophilia* 2012; **18**: e18-e20.
12. Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. *Haemophilia* 2010; **16**: 256-262.
13. Hilliard P, Zourikian N, Blanchette V, Chan A, Elliott B, Israels SJ et al. Musculoskeletal health of subjects with hemophilia A treated with tailored prophylaxis: Canadian Hemophilia Primary Prophylaxis (CHPS) Study. *J Thromb Haemost* 2013; **11**: 460-466.

14. Kraft J, Blanchette V, Babyn P, Feldman B, Cloutier S, Israels S et al. Magnetic resonance imaging and joint outcomes in boys with severe hemophilia A treated with tailored primary prophylaxis in Canada. *J Thromb Haemost* 2012; **10**: 2494-2502.
15. Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. *Haemophilia* 2014; **20**: e280-e286.
16. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006; **450**: 76-85.
17. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007; **85**: 660-667.
18. Den Uijl I, Fischer K, Van der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia* 2011; **17**: 41-44.
19. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, De Kleijn P et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood* 2002; **99**: 2337-2341.
20. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535-544.
21. Gringeri A, Lundin B, von MS, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; **9**: 700-710.
22. Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol* 2012; **88**: 329-335.
23. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V et al. A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol* 2010; **149**: 498-507.
24. Meunier S, Chambost H, Demiguel V, Doncarli A, Suzan F, Trossaert M. Use of clinical practice guidelines on long-term prophylaxis in severe hemophilia in France: a retrospective audit. *J Pediatr* 2013; **162**: 1241-4, 1244.e1.
25. Petrini P. How to start prophylaxis. *Haemophilia* 2003; **9 Suppl 1**: 83-85.

CHAPTER 4

Using routine HJHS for international comparisons of haemophilia outcome: standardisation is needed

A. Nijdam, M. Bladen, N. Hubert, M. Pettersson, B. Bartels, J. van der Net, R. Liesner, P. Petrini, K. Kurnik, and K. Fischer

Haemophilia 2015 Jul 14; doi: 10.1111/hae.12755 [Epub ahead of print]

Abstract

Introduction: Haemophilia Joint Health Score (HJHS) is the most sensitive validated score for physical examination of joint health in haemophilia. HJHS performed at regular intervals can be used for clinical monitoring as well as for comparative outcomes research.

Aim: to determine whether routinely collected HJHS could be used to compare outcome of three different prophylactic regimens in children with severe haemophilia A (primary) and which parameters caused variability in HJHS (secondary).

Methods: International retrospective observational multi-centre study comparing routine HJHS in 127 children with severe haemophilia A born 1995-2009, from London, Stockholm and Utrecht centres. Patient and treatment data were collected from the PedNet registry and patient files. The independent effects of regimens, physiotherapists, age, and inhibitor status on HJHS were explored using multivariable regression analysis.

Results: Prophylaxis varied across participating centres, with differences in initial frequency of infusions (1x/week vs. 3x/week), age at reaching infusions ≥3x/week, and dose/kg/week at HJHS assessment. Evaluation at median age of 11 years showed an illogical association of HJHS with treatment regimen: the least intensive regimen had the lowest HJHS. The HJHS increased with age and history of inhibitor, as expected (internal validity). But the comparison of prophylactic regimens was obscured by systematic differences in assessment, between physiotherapists, both within and between centres.

Conclusion: Inter-physiotherapist discrepancies in routine HJHS hamper comparison of scores between treatment regimens. For multi-centre research, additional inter-observer standardisation for HJHS scoring is needed.

Introduction

Several centres have adopted the Haemophilia Joint Health Score (HJHS) for routine monitoring of joint status in children with severe haemophilia. It is the most sensitive validated score for physical examination of joint health in haemophilia [1,2]. The HJHS increases with the cumulative number of bleeds and age [3-5].

Whereas the HJHS is increasingly used in single centre reports of outcome [3,6-11], it has only been used in two international comparative studies, in which HJHS physiotherapists joined a standardisation session before starting [12] or HJHS was scored by a single observer [5].

It has been established that the initiation of prophylaxis has a strong effect on the development of arthropathy [13,14]. Previously, in centres participating in the "European Paediatric Network for Haemophilia Management" (PedNet) registry, three different regimens for starting prophylaxis were identified by their median initial frequency, and median age at reaching prophylaxis with 3-3.5 infusions per week [15]: (I) 'full' regimen: start with ≥3x/week infusions; and two regimens starting with infusions 1-2x/week and stepping up to ≥3x/week as soon as possible (II: 'asap'), or according to bleeding (III: 'phenotype'). By 4 years of age, patients on the 'phenotype' regimen had suffered more joint bleeding compared to patients on the 'full' and 'asap' regimens: median 3 vs. 1 joint bleed and 8% vs. 30% without any joint bleeding [15]. Subsequent treatment was not reported. It is well known that joint damage due to (subclinical) bleeding into joints only manifests itself over time. The question is: do the differences in early bleeding and subsequent treatment result in differences in long-term joint health? To adequately compare the different prophylactic regimens, information on long-term outcome is needed. As certain PedNet centres routinely assess HJHS in all paediatric patients, this data provides a unique opportunity to study the effects of different regimens of prophylaxis.

The aim of this international pilot study was to determine whether routinely collected HJHS could be used to compare prophylactic regimens in children with severe haemophilia A and which parameters caused variability in HJHS.

Methods

Study population

The study population consisted of all children with severe haemophilia A, born 1995-2009 with HJHS available in three haemophilia treatment centres that routinely measure HJHS as part of their clinical practice: Great Ormond Street in London, Paediatric Department of Coagulation Disorders at Karolinska University Hospital in Stockholm and Van Creveldkliniek in Utrecht. Each centre started prophylaxis with a different regimen [15]: London applied the

'full' regimen, Stockholm the 'asap' regimen, and Utrecht the 'phenotype' regimen.

Patients with a history of inhibitors were included as an important subgroup, as they have likely had increased bleeding and therefore an increased risk of arthropathy. To avoid inclusion of patients with a transient increase in scores, data on patients with (suspected) clinical synovitis, a recent bleed or trauma (within two weeks prior to evaluation) were excluded. No patients had reported bleeding in the 2 weeks before assessment: one patient had a bleed one month prior to evaluation and another had twisted his ankle a few months before evaluation.

Data collection

Diagnosis, date of birth, prophylactic treatment data (excluding details of immune tolerance induction), inhibitor history, onset of joint bleeding, cumulative number of joint bleeds in the last five years, and circumstances causing a transient increase in HJHS were collected from patient files. Data on treatment and joint bleeds for patients born 2000-2009 were extracted from PedNet; for patients born 1995-2000 this data was collected from the patient files using standard case report forms. Joint bleeds were extracted from patient diaries, and defined as any complaint in a joint, characterized by any pain, swelling and/or restriction of function, requiring treatment [16]. Inhibitor development was defined as at least two consecutive positive inhibitor titres and a FVIII recovery <66% of expected. Long-standing inhibitors lasted ≥1 year, short-standing inhibitors lasted <12 months [16].

For each patient a single HJHS assessment (date, scores) was collected. The most recent routine assessment was selected. At each centre HJHS (version 2.1) was performed by one of two senior paediatric physiotherapists during scheduled visits to the clinic. Although all physiotherapists had full access to the HJHS instruction manual and DVD, pre-study training varied considerably. The UK physiotherapists (MB and NH) participated in a formal day-long HJHS training workshop conducted by P. Hilliard and N. Zourikian, co-developers of the HJHS [2]. They regularly assess patients together and/or discuss the assessments between each other. In contrast, the Dutch and Swedish senior physiotherapists (JN and B.M. Bergstrom) offered their respective colleagues (BB and MP) informal HJHS training on the job. The Swedish senior physiotherapist B.M. Bergstrom was one of the co-developers of the HJHS, but did not fully participate in the discussions, clarifications and update process of HJHS's current version 2.1. The Dutch physiotherapist JN is the co-chair of the IPSG physiotherapy group and participated in the HJHS validation study [1]. Both Dutch paediatric physiotherapists (JN, BB) only performed annual assessments but were not part of the regular haemophilia treatment team.

Data analysis

HJHS was evaluated at patient level (total score), and at the sub-score level of global gait. As many parameters had a skewed distribution, all parameters were presented as medians and interquartile ranges (IQR). Annual joint bleed rates were calculated from the cumulative number of bleeds five years preceding evaluation. When comparing scores on different patients at group level, only differences larger than the inter-observer variation, expressed as limits of agreement [17], represent clinically significant group differences. Inter-observer limits of agreement reported for the HJHS 2.1 were ± 6.4 points in haemophilia patients aged 14–30 years [18] and ±9.6 points in children aged 4-17 years [19,20]. To determine the proportion of clinically abnormal HJHS scores, the proportion of scores higher than the minimal inter-observer limits of agreement of 6 points was calculated. Differences in patient- and treatment characteristics between centres were compared using the non-parametric Kruskal-Wallis for continuous variables and Fisher's Exact Test for categorical variables. Differences in HJHS by centre, age, inhibitor status and physiotherapist were analysed both with univariable and multivariate regression using a Poisson distribution and log-linear link function. All data were analysed using IBM® SPSS® Statistics version 20.

Results

Patients

Out of 155 patients with HJHS measurements, scores of 12 patients were excluded due to synovitis (n=2), trauma (n=3) or a bleed (n=7) in the two weeks prior to evaluation. Data on 143 patients were analysed: 60 from London, 29 from Stockholm and 54 from Utrecht.

Regimens

Initial prophylactic regimens were significantly different between centres (Table 1) and consistent with regimens previously identified [15]: patients in London were on the most intensive prophylaxis regimen, starting prophylaxis at least three times weekly at young age (median 1.7 years). In Stockholm and Utrecht patients started prophylaxis with once weekly infusions; starting at a younger age in Stockholm than in Utrecht (median 1.3 vs. 2.1 years). While in Stockholm patients reached ≥3x/week before the age of three years, Utrecht patients reached ≥3x/week after three years of age. Differences in median weekly dose of prophylaxis at HJHS assessment were consistent with the intensity of the initial prophylactic regimens, with London using the highest and Utrecht the lowest weekly dose.

Patient characteristics

Patients were evaluated at approximately 11 years in all three centres (range 4-18 years). The proportion of patients with a history of inhibitors varied from 17% to 28%, but was not significantly different across centres/regimens (P=1.00). Median joint bleed frequencies in the last five years were low, but significantly higher in patients from Utrecht where the prophylactic regimen was least intensive (P<0.01).

Table 1. Regimen and patient characteristics, and HJHS per centre.

Centre	London	Stockholm	Utrecht	P-value
Patients (n, included + excluded)	62 (60 + 2)	34 (29 + 5)	59 (54 + 5)	NA
Regimen characteristics	full*	asap*	phenotype*	
Initial frequency of prophylactic infusions (/week)	3 (3-3)	1 (1-1)	1 (1-3)	<0.01
Age at start of prophylaxis (years)	1.7 (1.0-2.5)	1.3 (1.0-1.5)	2.1 (1.4-3.3)	<0.01
Age at reaching ≥3x/week (years)	1.7 (1.0-3.1)	2.6 (2.0-3.7)	3.3 (2.2-4.5)	<0.01
Weekly dose of prophylaxis at evaluation (IU/kg/week)	140 (110-166)	102 (77-119)	63 (54-78)	<0.01
Patient characteristics				
Age at evaluation (years)	10.8 (8.1-14.0)	10.9 (9.0-14.1)	11.7 (8.7-14.2)	0.65
History of inhibitors (%)	17%	28%	28%	1.00
Joint bleeds (/year)	0.4 (0.2-0.8)	0.6 (0.2-1.0)	1.0 (0.4-1.6)	<0.01
HJHS				
Physiotherapist (PT1 vs. PT 2 in %)	80% / 20%	59% / 41%	78% / 22%	0.09
HJHS total score (0-124)	1 (0-5)	3 (2-8)	0 (0-1)	<0.01†
With HJHS total score > 6 (%)	17%	35%	2%	<0.01
Global gait sub score (0-4)	1 (0-2)	0 (0-1)	0 (0-0)	<0.01
Global gait sub score > 0 (%)	53%	32%	6%	<0.01

Values are numbers, proportions or medians (IQR).
HJHS, Haemophilia Joint Health Score; NA, not applicable; IQR, interquartile range.
* 'full' regimen: start ≥3 infusions per week before 3 years of age; 'asap' regimen: start 1-2 infusions per week and stepping up to ≥3x per week as soon as possible, before median age 3 years; 'phenotype' regimen: start 1-2 infusions per week and stepping up to ≥3x per week according to bleeding, after median age 3 years.
† Log-linear regression with Poisson distribution, adjusted for age at HJHS measurement.

HJHS on detecting differences

In London and Utrecht one physiotherapist assessed the majority of children, while in Stockholm assessments were almost equally divided between two physiotherapists. HJHS scores did not show a consistent association with treatment strategy: patients on the least intensive 'phenotype' regimen in Utrecht had the lowest HJHS. At the same time, patients on the medium intensive 'asap' regimen in Stockholm started prophylaxis first, yet had the highest overall HJHS. This inconsistency remained when considering the proportion of clinically abnormal HJHS scores (i.e. total score >6 points): only 2% in Utrecht, versus 35% in Stockholm and 17% in London. When assessing the HJHS sub score on global gait (range 0-4), a different ranking appeared, yet still inconsistent with treatment strategy: Utrecht still scored lowest (6% with a global gait score>0), while London scored highest (53% with a global gait score>0).

Table 2 shows univariable (crude) and multivariable (adjusted) regression analysis for determinants of HJHS total scores. As joint damage is dependent on the cumulative number of joint bleeds [21], HJHS is expected to increase with age and long-standing inhibitor status. This was confirmed both in univariable and multivariable regression analysis, although statistical significance was not reached for inhibitor status in multivariable regression (P=0.43; most likely due to low patient numbers). In univariable regression analysis, Stockholm patients (on the 'asap' regimen) scored higher and Utrecht patients ('phenotype' regimen) scored lower than London patients ('full' regimen). In addition, significant differences were observed in HJHS total scores between physiotherapists from Utrecht and Stockholm. After adjustment for age, inhibitor status and physiotherapist, Utrecht patients still scored lowest, while London and Stockholm patients scored similarly. Multivariate regression showed that scoring differences between the Stockholm physiotherapists have, at least partially, attributed to the differences in HJHS total scores between the London and Stockholm centres. Only in London physiotherapists seemed to score patients similarly, independent of other factors affecting HJHS.

Table 2. Univariable and multivariate regression analysis for determinants of HJHS total scores.

	Patients (n)	**Crude exp(B)** (95% CI)	**P-value**	**Adjusted exp(B)*** (95% CI)	**P-value**
Age	143	1.1 (1.1-1.1)	<0.01	1.1 (1.1-1.2)	<0.01
Inhibitors					
Non-inhibitors, short inhibitors	129	1		1	
Long-standing inhibitors	14	1.4 (1.1-1.9)	0.02	1.1 (0.8-1.5)	0.43
Centre (regimen)					
London ('full')	60	1		1	
Stockholm ('asap')	29	1.6 (1.3-2.0)	<0.01	1.0 (0.7-1.3)	0.76
Utrecht ('phenotype')	54	0.3 (0.2-0.4)	<0.01	0.2 (0.1-0.3)	<0.01
Physiotherapists					
London 1	48	1		1	
London 2	12	1.0 (0.7-1.4)	0.91	1.3 (0.9-1.8) †	0.20
Stockholm 1	17	1.1 (0.8-1.5)	0.42	1	
Stockholm 2	12	2.2 (1.7-2.9)	<0.01	3.0 (2.1-4.2) †	<0.01
Utrecht 1	42	0.2 (0.1-0.3)	<0.01	1	
Utrecht 2	12	0.5 (0.3-0.8)	<0.01	2.3 (1.2-4.1) †	0.01

HJHS, Haemophilia Joint Health Score; CI, confidence interval.
* Adjusted for age, inhibitor status, centre, and physiotherapist.
† In multivariate regression physiotherapists were compared within centres only.

Discussion

Principal findings

Three different prophylactic regimens were compared using routinely administered HJHS. HJHS scores were low across regimens and did not show a consistent association with treatment strategy: the least intensive regimen had the lowest HJHS scores. The sensitivity of the HJHS for age and inhibitor status was confirmed. Systematic differences (independent of age, inhibitor status and treatment strategy) were found between physiotherapists within and between centres. This inter-observer variability obscured potential differences in HJHS between the three early prophylactic regimens.

Source of inconsistent findings

Why did we find an inconsistent association between HJHS and early prophylactic regimens? Most likely this was caused by observer bias: there were structural scoring differences between physiotherapists. Differences in HJHS training and experience of the physiotherapists

may have induced this bias. UK physiotherapists were trained by the Toronto team in a day-long workshop, while Dutch and Swedish senior physiotherapists trained their respective colleagues. As opposed to the UK physiotherapists, the Dutch and Swedish senior physiotherapists both participated in the development of the HJHS. Stockholm's senior physiotherapist however, did not fully participate in the development of the latest HJHS version 2.1. Even if the changes in the HJHS were limited, this may have contributed to the observed differences. Moreover, full access to the HJHS instruction manuals and DVD to all physiotherapists did not guarantee equal use of these materials, nor similar interpretation of its contents. It is possible that regularly assessing and discussing patients together helped keeping the scores of London physiotherapists consistent and calibrated. On the other hand, structural differences in prior knowledge of the patient (history) could have introduced additional bias as well: e.g. an observer involved in routine patient care would be more focussed on a joint with a recent problem. In contrast to the setting in Stockholm and London, the two physiotherapists from Utrecht were not involved in routine patient care and only saw patients during their annual check-up, perhaps contributing to lower scores in Utrecht patients.

In addition to the observer bias, the lack of a clear trend in HJHS across different regimens may be explained by the fact that the regimens were similar or that differences in outcome at age 11 were too small to be detected. However, our results clearly show that the regimens were different, at initiation as well as evaluation. Nevertheless, patients may have been too young to detect differences in outcome across/between regimens. In patients on the most intensive regimen ('full' regimen) joint changes measured by HJHS only appeared after the age of 13 years [3]. In patients treated on-demand, HJHS was already increased before the age of 10 years, and afterwards significant worsening of HJHS was observed [6]. It therefore seems likely that larger differences between treatment groups, such as when comparing prophylaxis and on-demand treatment [5,22], would have been picked up despite inter-observer variability.

Differences between physiotherapists within one centre may be caused by a different case mix, i.e. if one physiotherapist scored the more problematic patients, but would not introduce differences between centres. A case mix problem across centres seems unlikely, as all centres measure HJHS at least once a year as part of routine clinical practice. Nevertheless, it is suggested that Stockholm patients may be more motivated to see the physiotherapist in case of problems.

Differences in adherence could have attributed to differences in HJHS scores as well. Unfortunately this potential source of bias cannot be addressed, as we have no data on adherence to the regimes in the three centres. However, adherence is generally high in paediatric patients,

and we have no indication that there are differences in adherence between the centres.
Furthermore, a problem with the HJHS itself seems unlikely. The HJHS is a validated tool and showed a consistent association between joint damage due to age and a positive history of inhibitors against FVIII in this data set.

Inter-observer variation

How much difference is true difference? Only differences of more than 6 points between treatment groups are clinically significant, as inter-observer limits of agreement for the HJHS 2.1 were at least ± 6.4 points [18-20]. Differences in median HJHS scores between the three centres in this study were 3 points and did therefore not reflect significant differences between centres, even if results had been consistent with treatment strategies. When considering proportions of patients with HJHS scores above 6 points only, findings were still not consistent with treatment intensity. In addition, statistically significant differences between physiotherapists within centres interfered with the interpretation of the data. It is expected that assessment of all patients by a single physiotherapist or a joint standardisation session including all physiotherapists would reduce variation in assessment within the centres; this may change the results of the present comparison.
Unfortunately the source of differences between physiotherapists' HJHS assessments cannot be studied in this pilot study, as each patient was assessed by one physiotherapist only. The aim was not to study the reliability of the HJHS, but to assess if the HJHS, collected as part of routine clinical practice, could be used to compare treatment strategies between centres.

Clinical implications and conclusion

Large inter-centre and inter-physiotherapist discrepancies in routine HJHS assessment biased the comparison of scores between different treatment strategies. These data suggest that routinely collected HJHS data can only be used to monitor patients' joint status over time or to compare patients within centres and maybe even per physiotherapist. To be able to conduct research with HJHS in a multi-centre setting, prior standardisation and testing for inter-observer agreement of the HJHS assessment is warranted.

Acknowledgements

A. Nijdam has received funding for research carried out in this work by Novo Nordisk. K. Fischer has received unrestricted funding for this project from Novo Nordisk (as project leader). P. Petrini has received a fee for speaking from Pfizer, Baxter, Bayer and Sobi and attended medical advisory board for Pfizer and Baxter. The other authors have no competing interests.

References

1. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, Van der Net J et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res (Hoboken)* 2011; **63**: 223-230.
2. Hilliard P, Funk S, Zourikian N, Bergstrom BM, Bradley CS, McLimont M et al. Hemophilia joint health score reliability study. *Haemophilia* 2006; **12**: 518-525.
3. Bladen M, Main E, Hubert N, Koutoumanou E, Liesner R, Khair K. Factors affecting the Haemophilia Joint Health Score in children with severe haemophilia. *Haemophilia* 2013; **19**: 626-631.
4. Groen W, Van der Net J, Bos K, Abad A, Bergstrom BM, Blanchette VS et al. Joint health and functional ability in children with haemophilia who receive intensive replacement therapy. *Haemophilia* 2011; **17**: 783-790.
5. Saulyte Trakymiene S, Clausen N, Poulsen LH, Ingerslev J, Rageliene L. Progression of haemophilic arthropathy in children: a Lithuanian--Danish comparative study. *Haemophilia* 2013; **19**: 212-218.
6. Saulyte Trakymiene S, Ingerslev J, Rageliene L. Utility of the Haemophilia Joint Health Score in study of episodically treated boys with severe haemophilia A and B in Lithuania. *Haemophilia* 2010; **16**: 479-486.
7. Boadas A, Osorio M, Gibraltar A, Rosas MM, Berges A, Herrera E et al. Favourable impact of regular swimming in young people with haemophilia: experience derived from 'Desafio del Caribe' project. *Haemophilia* 2014; **21**: e12-8.
8. Den Uijl I, Biesma D, Grobbee D, Fischer K. Outcome in moderate haemophilia. *Blood Transfus* 2014; **12 Suppl 1**: s330-s336.
9. Groen WG, Takken T, Van der Net J, Helders PJ, Fischer K. Habitual physical activity in Dutch children and adolescents with haemophilia. *Haemophilia* 2011; **17**: e906-e912.
10. Khanum F, Bowen DJ, Kerr BC, Collins PW. Joint health scores in a haemophilia A cohort from Pakistan with minimal or no access to factor VIII concentrate: correlation with thrombin generation and underlying mutation. *Haemophilia* 2014; **20**: 426-434.
11. Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol* 2012; **88**: 329-335.
12. Fischer K, Steen Carlsson K, Petrini P, Holmstrom M, Ljung R, Van den Berg HM et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood* 2013; **122**: 1129-1136.
13. Astermark J, Petrini 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**: 1109-1113.
14. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, De Kleijn P et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood* 2002; **99**: 2337-2341.
15. Nijdam A, Kurnik K, Liesner R, Ljung R, Nolan B, Petrini P et al. How to achieve full prophylaxis in young boys with severe haemophilia A: different regimens and their effect on early bleeding and venous access. *Haemophilia* 2015; **21**: 444-50.
16. Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. *Haemophilia* 2014; **20**: e280-e286.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307-310.

18. Fischer K, De Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity. *Haemophilia* 2013; **19**: 944-950.
19. Feldman BM, Pullaneyagum E. Response to 'Limits of agreement between raters are required for use of HJHS 2.1 in clinical studies'. *Haemophilia* 2015; **21**: e71.
20. Sun J, Hilliard PE, Feldman BM, Zourikian N, Chen L, Blanchette VS et al. Chinese Hemophilia Joint Health Score 2.1 reliability study. *Haemophilia* 2014; **20**: 435-440.
21. 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**: 391-399.
22. Ingerslev J, Lethagen S, Hvitfeldt PL, Sorensen B, Lopatina E, Tentsova I et al. Long-standing prophylactic therapy vs. episodic treatment in young people with severe haemophilia: a comparison of age-matched Danish and Russian patients. *Haemophilia* 2014; **20**: 58-64.

CHAPTER 5

Long-term effects of joint bleeding before starting prophylaxis in severe haemophilia

A. Nijdam, W. Foppen, Y.T. van der Schouw, E.P. Mauser-Bunschoten,
R.E.G. Schutgens and K. Fischer

Submitted

Abstract

Introduction: Early initiation of prophylaxis in severe haemophilia is critical for effective prevention of arthropathy. However, the optimum time for starting prophylaxis has not been established yet.

Aim: This study assessed long-term effects of age at starting prophylaxis and joint bleeding before prophylaxis on haemophilic arthropathy.

Methods: In patients with severe haemophilia (FVIII/IX <0.01 IU/ml), born between 1965 and 2000, haemophilic arthropathy was evaluated on X-rays. Patient groups were compared by multivariable regression analysis, adjusted for bleeding phenotype and lifetime intensity of prophylaxis.

Results: 124 Patients were evaluated at a median age of 22 years. When comparing patients according to age at starting prophylaxis, starting before age 6 years was significantly better than starting later (P<0.01), but no additional benefit of starting before age 3 years was demonstrated. The number of joint bleeds before prophylaxis had a stronger association with arthropathy than age at starting prophylaxis. Starting prophylaxis before the onset of joint bleeding resulted in the best long-term outcome (P≤0.02); starting after one joint bleed appeared to have acceptable long-term outcome. The difference between starting after 0-1 and 2-5 joint bleeds was notable, but statistical significance was not reached (P=0.15).

Conclusion: Future research with more patients on early prophylaxis will have to clarify whether starting prophylaxis before joint bleeding is superior.

Introduction

The main objective of prophylaxis with clotting factor VIII/IX (FVIII/FIX) in children with severe haemophilia (FVIII/FIX<0.01 IU/ml) is the prevention of joint bleeds and subsequent haemophilic arthropathy [1–3]. Early initiation of prophylaxis proved to be critical for effective prevention of arthropathy [2, 4] and consequently prophylaxis has been started at an increasingly younger age and after fewer (joint) bleeds [5]. However, the optimum time for starting prophylaxis in young children with severe haemophilia has not yet been established. While some advocate starting prophylaxis before the age of three years [6, 7], others suggest starting before joint bleeding or after the first or second joint bleed [8–10].

Prophylaxis in very young children is often hampered by problematic venous access. Central venous access devices (CVADs) can provide an alternative route of infusion, but require costly surgery and are associated with a considerable risk of infections and thrombotic complications [11]. As bleeding patterns vary among patients with severe haemophilia, CVAD use can be minimized by initiating prophylaxis based on individual bleeding phenotype [12].

In clinical practice the need for frequent infusions and problems with venous access compete for dominance in starting prophylaxis. To choose the optimum time of starting prophylaxis more information is needed, specifically on the effects of bleeding before prophylaxis and/or the age at initiation of prophylaxis. Long-term follow-up in haemophilia patients on prophylaxis is needed, as joint damage takes time to develop and differences in outcome between prophylactic regimens are small. As a consequence, guidelines are based on limited evidence [3, 13]. This retrospective single centre cohort study assessed the long-term effects of age at starting prophylaxis and number of joint bleeds before starting prophylaxis on haemophilic arthropathy.

Methods

Study population

177 eligible patients had severe haemophilia A and B (FVIII/IX <0.01 IU/ml), were born between 1-1-1965 and 1-1-2000, and treated at the Van Creveldkliniek. In total, 53 patients were excluded because of long-term (>12 months) or high titre (≥5 BU/ml) inhibitor development (n=26), unavailable X-rays (n=21), significant other disorders (platelet function disorder (n=2), Von Willebrand disease(n=1), Ehlers-Danlos (n=1)), or not starting prophylaxis (n=2). The eventual population for analysis comprised 124 patients, including 76 patients born until 1985 studied previously for the effects of postponing prophylaxis [14]. The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

Treatment strategy

Prophylaxis was defined as the regular administration of FVIII/IX at least once a week [3, 15]. Over time prophylaxis was started earlier [5] and has intensified [14]. At the Van Creveldkliniek, generally one joint bleed is allowed for before starting prophylaxis. After starting, frequency and dose of prophylactic infusions are increased according to a patient's activity level and bleeding phenotype [3, 15], with an average of 10-20 IU/kg FVIIII 3x/week or 20-40 IU/kg FIX 2x/week, resulting in a median weekly dose of 46 IU/kg [16].

Data collection

All patients visited the clinic at least annually. At each visit infusion and bleeding logs were checked and number of bleeds, treatment type, dose and frequency of treatment documented. Data on clotting factor consumption, first treatment, first joint bleed, start of prophylaxis and number of joint bleeds before starting prophylaxis were extracted from the patients' medical files. Outcome was the degree of haemophilic arthropathy in knees, elbows and ankles on X-rays as measured by the Pettersson score; a validated radiological scoring system assessing osteochondral changes [17]. A patient's Pettersson score is the sum of the six joints (range 0–78; 13 per joint), with higher scores indicating more joint damage [17, 18]. X-rays were generally taken at 5-year intervals and scored by two assessors (good inter-observer agreement of 0.88, K. Fischer personal communication) blinded for patient and treatment characteristics. Patients were followed from diagnosis until the last Pettersson score, or until prophylaxis was stopped for a cumulative duration of at least six months. The most recent Pettersson score, or the last before stopping prophylaxis for a cumulative duration of >6 months, was analysed.

Data analysis

As the distribution of the values of most parameters was skewed, data are presented as medians with interquartile range (IQR: 25^{th} and 75^{th} percentiles). Weekly dose of prophylaxis and annual clotting factor use were calculated for all years on prophylaxis.

Two indicators of postponing prophylaxis were studied for their long-term effects on haemophilic arthropathy: age at starting prophylaxis and number of joint bleeds before starting prophylaxis. Cut-off points for categories of these indicators were chosen according to clinical relevance and categories published in the literature [6, 14]. For age at start of prophylaxis, patients were categorized as: started early (<3 years), late (3-5 years), or very late (≥6 years), according to the strata previously used by Astermark et al (1999). The number of joint bleeds before starting prophylaxis, available for 75 patients, was categorized into three categories:

few (0-1), some (2-5), and many (≥6) joint bleeds before prophylaxis. A second analysis consisted of four categories to gain more detailed information on the effect of bleeding before prophylaxis: the separate effects of no (0) or a single joint bleed (1) before prophylaxis, as well as some (2-5), and many (≥6) joint bleeds before prophylaxis.

The association between outcome (Pettersson score) and the two indicators for postponing prophylaxis (age at start of prophylaxis and number of joint bleeds before prophylaxis) was assessed using multivariable generalized linear regression modelling with a negative binomial distribution and a log link function to generate an optimal fit of the right skewed outcome data [19]. All regression models included age at Pettersson score, age at first joint bleed and weekly dose of prophylaxis (for the entire follow-up) to adjust for age at evaluation [18], bleeding phenotype and lifetime intensity of prophylaxis. In regression analysis, missing data on age at first joint bleed (n=24) and weekly doses of prophylaxis (n=2) were imputed with overall median values. To compare the performance of the regression models with age at starting prophylaxis and number of joint bleeds before starting prophylaxis, the Akaike information criterion (AIC) was used. The AIC is a measure of how good a model fits the data, compared to other models that are fitted; with the lowest AIC being the "better" model to explain the data [20]. To illustrate the effect of different categories of postponing prophylaxis on the development of arthropathy over time, regression curves were plotted. Predicted Pettersson scores according to age were calculated using the regression model parameter estimates and median values of the parameters that were adjusted for. All data were analysed using SPSS (IBM SPSS Statistics version 21.0, Armonk, NY: IBM Corp).

Results

Patient characteristics and outcome

Patient and treatment characteristics are presented in Table 1. Out of 124 patients with severe haemophilia, 111 (90%) had haemophilia A. In this cohort of patients born since 1965, the median age at the first joint bleed was 2.0 years (IQR 1.3-3.0; range 0.5-5.8). The median time between the first joint bleed and starting prophylaxis was 2.0 years (IQR 0.5-4.5). At a median age of 22 years (IQR 15.6-29.5; range 5.3-49.1 years), joint health was favourable with a median Pettersson score of 3 points (IQR 0-14), including 41% with a score of zero.

Table 1. Patient characteristics and treatment.

Patients (n=124)	**Median**	**IQR**
Age at last Pettersson evaluation (years)	22.0	15.6-29.5
Age at 1st joint bleed[1] (years)	2.0	1.3-3.0
Treatment		
Age at 1st treatment (years)	1.1	0.8-1.5
Age at start of prophylaxis (years)	4.7	3.0-7.4
Time between 1st joint bleed and start of prophylaxis (years)	2.0	0.5-4.5
Joint bleeds before start of prophylaxis (n)	6	1-21
Duration of prophylactic treatment (years)	18.2	10.2-22.5
Weekly dose of prophylaxis[2] (IU/kg/wk)	39	30-48

IQR: interquartile range.
[1] Estimated with Kaplan-Meier survival analysis independent of start of prophylaxis; based on 100 patients with date 1st joint bleed available.
[2] For all years on prophylactic treatment.

Age at start of prophylaxis

Table 2 shows patient characteristics and outcome according to age at start of prophylactic treatment. 24% of patients started prophylaxis early (<3 years), 40% started prophylaxis late (3-5 years), and 35% very late (≥6 years). Most patients who started prophylaxis early, started shortly after the first joint bleed. Patients who started prophylaxis later were older at evaluation and experienced their first joint bleed later, but also experienced more joint bleeds before starting prophylaxis. This was reflected in the Pettersson scores: scores increased when the start of prophylaxis was postponed.

Multivariable analysis of the effect of age at starting prophylaxis on outcome showed that with every year prophylaxis was postponed, the Pettersson score increased with 18% (relative increase 1.18; 95% confidence interval 1.07-1.29; P <0.01). The regression curves in Figure 1 show the effect of age at starting prophylaxis on outcome according to age at evaluation, independent of bleeding phenotype and lifetime intensity of prophylaxis. These curves showed that scores for those who started prophylaxis early (<3 years) and those who started late (3-5 years) were similar (P=0.63), but both groups had significantly better outcome than patients who started prophylaxis very late (≥6 years; P<0.01).

Table 2. Outcome and patient characteristics according to age at start of prophylactic treatment.

Age at start of prophylaxis (years)	Early: <3 (years)	Late: 3-5 (years)	Very late: ≥6 (years)
Patients			
Number	30	50	44
Age at last Pettersson score (years)	16.8 (14.1-21.0)	24.0 (14.8-36.6)	25.6 (17.0-32.8)
Age at 1st joint bleed[1] (years)	1.3 (0.9-1.5)	2.0 (1.3-3.0)	2.5 (1.6-3.7)
Treatment			
Age at start of prophylaxis (years)	1.5 (1.2-2.1)	4.3 (3.8-5.0)	8.8 (7.0-11.6)
Time between 1st joint bleed and start of prophylaxis (years)	0.1 (-0.3 - 0.5)	2.1 (1.3-3.3)	6.3 (4.5-8.3)
Started before the 1st joint bleed (%)	27	6	0
Joint bleeds before start of prophylaxis[2] (n)	1 (0-4)	9 (3-19)	58 (31-108)
Outcome			
Last Pettersson score (0-78)	0 (0-5)	1 (0-5)	16 (2-28)
Last Pettersson = 0 (%)	63	44	23

Values are numbers (n), percentages (%) or medians with IQR (interquartile range).
[1] Estimated with Kaplan-Meier survival analysis independent of start of prophylaxis; based on 100 patients with date 1st joint bleed available.
[2] Based on 75 patients with number of joint bleeds until prophylaxis available.

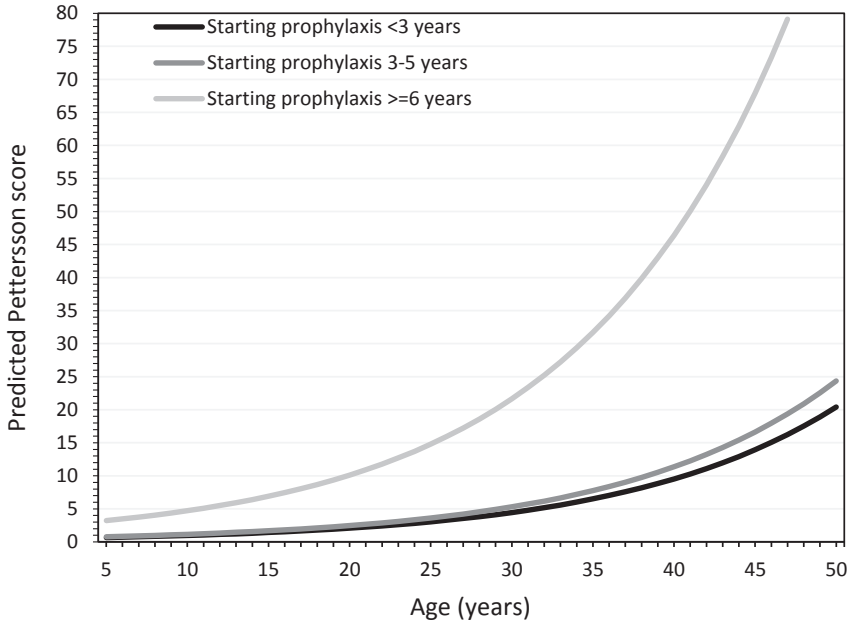

Figure 1. Predicted Pettersson scores by age, according to age at start of prophylaxis.
Lines represent predicted Pettersson scores for the different groups, independent of the effect of prophylactic dose and onset of joint bleeding (as a proxy for bleeding phenotype).
Statistical testing:
- starting prophylaxis before 3 years vs. starting after ≥6 years of age (P<0.01),
- starting prophylaxis between 3-5 years vs. starting after ≥6 years of age (P<0.01).

Number of joint bleeds before starting prophylaxis

Information on number of joint bleeds before the start of prophylaxis was available for 75 patients. Table 3 shows outcome and patient characteristics according to number of joint bleeds until start of prophylaxis. 16% of patients started prophylaxis before suffering any joint bleed, 13% started prophylaxis after a single joint bleed, 19% started prophylaxis after some/2-5 joint bleeds, and 52% after many/≥6 joint bleeds. There was no indication that the sub-group of patients who started before any joint bleeding were different from the other patients in this cohort: no intra-cranial haemorrhages were reported, nor had they received more intense treatment (initial prophylactic treatment ranged from 1x/week 250IU to 2x/week 500IU, and median weekly dose on prophylaxis ranged from 29 to 55 IU/kg per patient (group median 43 IU/kg/week)). There was some indication that patients starting prophylaxis after more joint bleeds may have included milder phenotypes, as they experienced their first joint bleed later (at 1.3, 2.0 and 2.5 years respectively; P<0.01). The trend of starting prophylaxis earlier over the last decades was reflected in the younger age of patients starting after less than six joint bleeds. Median Pettersson scores were highest (5 points) in patients starting after many joint bleeds

(≥6). When comparing the four subgroups of patients, there appeared to be a trend towards better outcome in those with less bleeding before prophylaxis, with increased joint damage in some older patients included in the group starting prophylaxis after a single joint bleed.

Table 3. Outcome and patient characteristics according to number of joint bleeds until start of prophylaxis.

Number of joint bleeds before start of prophylaxis	**0**	**1**	**2-5**	**≥6**
Patients				
Number	12	10	14	39
Age at last Pettersson score (years)	18.6 (13.6-23.6)	16.8 (11.3-33.6)	17.4 (13.9-21.2)	25.0 (20.8-30.6)
Age at 1st joint bleed[1] (years)	NA	1.3 (1.3-3.0)	1.6 (1.4-2.5)	2.3 (1.3-3.1)
Treatment				
Age at start of prophylaxis (years)	1.6 (1.0-3.0)	1.4 (1.2-3.3)	3.1 (1.6-4.3)	5.1 (4.1-6.9)
Time between 1st joint bleed and start of prophylaxis (years)	-1.6 (-2.8 - -0.5)	0.0 (0.0-0.4)	0.7 (0.3-1.8)	2.8 (1.7-4.5)
Joint bleeds before start of prophylaxis (n)	0 (0-0)	1 (1-1)	4 (3-5)	20 (11-43)
Outcome				
Last Pettersson score (0-78)	0 (0-1)	3 (0-10)	0 (0-4)	5 (0-14)
Last Pettersson = 0 (%)	75	40	57	36

Values are numbers (n), percentages (%) or medians with IQR (interquartile range).
[1] Estimated with Kaplan-Meier survival analysis independent of start of prophylaxis; based on 62 patients with date 1st joint bleed available.

The regression curves in Figure 2 show the effect of number of joint bleeds before starting prophylaxis on outcome according to age at evaluation, independent of bleeding phenotype and lifetime intensity of prophylaxis. Predicted Pettersson scores increased according to increasing number of joint bleeds before the start of prophylaxis and age at evaluation. Significant differences were found between patients who started prophylaxis before the onset of joint bleeding and all three categories with one or more joint bleed before starting prophylaxis (P≤0.02). Starting after 2-5 joint bleeds did not seem to provide any advantage over starting after six or more joint bleeds (P=0.76). When collapsing the lower two categories, significant differences in scores were found between patients who started after 0-1 joint bleeds and those who started prophylaxis after ≥6 joint bleeds (P=0.01; supplemental material). The difference between 0-1 and 2-5 joint bleeds was notable, but did not reach statistical significance (P=0.15).

The number of joint bleeds before starting prophylaxis had a stronger association with arthropathy than age at starting prophylaxis: with a much lower AIC of 374.526, the multivariable regression model using joint bleeding before starting prophylaxis fitted the data much better than the model using age at start of prophylaxis (AIC 674.186).

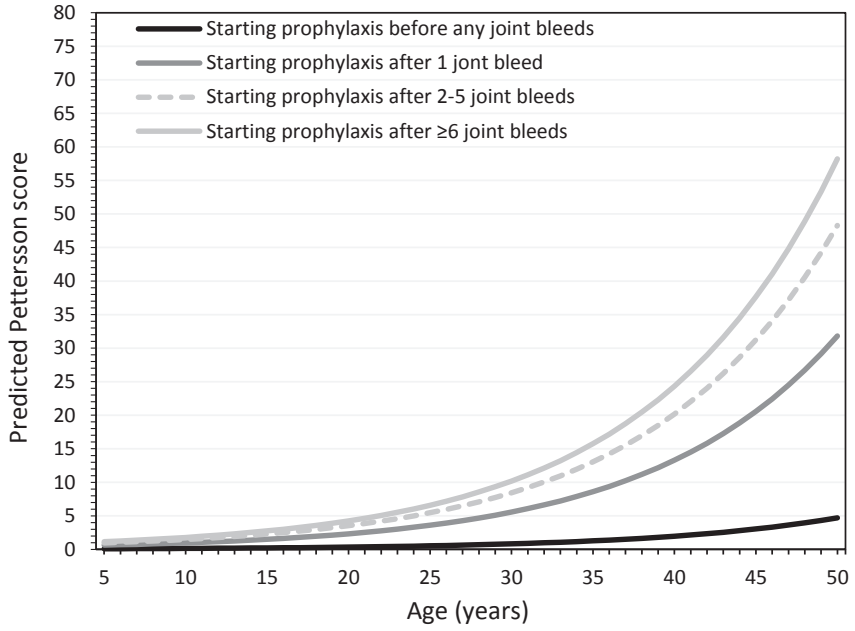

Figure 2. Predicted Pettersson scores by age, according to joint bleeding before start of prophylaxis.
Lines represent predicted Pettersson scores for the different groups, independent of the effect of prophylactic dose and onset of joint bleeding (as a proxy for bleeding phenotype).
Statistical testing:
- starting prophylaxis before any joint bleeds vs. starting after ≥1 joint bleed (P≤0.02),
- starting after 0-1 joint bleed vs. starting after ≥6 joint bleeds (P=0.01; supplemental material),
- the difference between starting after 0-1 and 2-5 joint bleeds was notable, but statistical significance was not reached (P=0.15; supplemental material).

Discussion

Principal findings

This single centre cohort study is the first to present long-term follow-up until a median age of 22 years on the effects of postponing prophylaxis. In multivariable analysis the number of joint bleeds experienced before starting prophylaxis had a stronger association with arthropathy than age at starting prophylaxis. Arthropathy increased according to increasing number of joint bleeds before starting prophylaxis. Starting before the onset of bleeding resulted in the best long-term outcome, however accepting one joint bleed before the start of prophylaxis may still yield acceptable long-term joint health. Patients starting prophylaxis before age six

years scored significantly better, but no additional benefit of starting before age three years could be demonstrated in this cohort.

Strengths and weaknesses

An important strength of the present study is the long follow-up, and the presentation of age-adjusted analyses of outcome based on X-rays, allowing a reliable evaluation of haemophilic arthropathy. Selection bias was avoided by including a cohort of all consecutive patients and outcome assessment was performed using routinely collected data. To study the independent effect of postponing prophylaxis, multivariable regression analysis was used to correct for other determinants for outcome, such as age at evaluation, changes in treatment intensity and a patient's bleeding tendency.

Cut-off points for categories of starting prophylaxis were chosen according to clinical relevance and a previous report suggesting that patients who started prophylaxis before three years of age had a better joint status on physical examination than patients who started later [6]. It is commonly known that allowing many (e.g. ≥6) joint bleeds is detrimental to (long-term) outcome. More information on lower numbers of joint bleeds before prophylaxis would be relevant for clinical practice. Unfortunately only small sub-groups of patients with ≤5 joint bleeds before prophylaxis could be studied. There were no indications of selection bias: bleeding pattern and prophylactic regimen in the patients who started before the onset of joint bleeding were similar to those in patients who started prophylaxis later.

Comparison with other studies

The results of the present study confirm the detrimental effects of postponing prophylaxis and the trend towards the earlier initiation of prophylaxis (both according to age and according to number of bleeds before initiation) [2, 5, 14]. Compared with the previous report, prevention of arthropathy improved, which may be attributed to a more intense prophylactic regimen. Moreover, the current study showed a higher increase in Pettersson with postponing prophylaxis: 18% increase/year vs. 8% in the previous study, with overlapping confidence intervals. This increase may be the result of the longer follow-up: differences between treatment groups are expected to become more prominent over time, as haemophilic arthropathy takes years to develop. These results corroborate the observation that haemophilic arthropathy increased with age at starting prophylaxis made in a recent cross-sectional study using magnetic resonance imaging (MRI) to assess haemophilic arthropathy [21].

The present study could not reproduce the results from the Swedish report that starting pro-

phylaxis before age three years resulted in better outcome [6] than starting between 3-5 years. While patient numbers were similar (121 vs. 124 in the current study), differences may be attributed to the use of different scoring systems (orthopaedic joint score vs. Pettersson score), different scoring frequency (annual joint scores vs. 5-year X-rays), and differences in follow-up (median 15 vs. 22 years). Although it was repeatedly shown that the Pettersson score is more sensitive to haemophilic arthropathy than the orthopaedic joint score [2, 22, 23], a direct comparison cannot be made. The comparison with the Swedish report [6] is further hampered by the lack of information on the number of assessors involved in the physical examination and the measures of agreement between assessors. The importance of standardization of clinical joint examination is emphasized by a recent report suggesting wide inter-rater variation in physical examination interfering with interpretation [24]. Moreover, in the present study, differences in outcome between starting prophylaxis before three years and between ages 3-5 years may have been underestimated due to confounding by indication: patients starting prophylaxis later, may have had a milder bleeding phenotype [25]. The effect of a potentially milder bleeding phenotype in patients who started prophylaxis later was not very prominent in our data; by adjusting for age at first joint bleed and weekly dose on prophylaxis in the multivariable analyses we have done everything possible to correct for bleeding phenotype.

Clinical interpretation

The present analyses showed that number of joint bleeds experienced before the start of prophylaxis was a stronger risk factor for arthropathy than age at starting prophylaxis. This is in accordance with the pathophysiology: arthropathy is caused by joint bleeding, with a cumulative effect. On the other hand, the association between age at starting prophylaxis and arthropathy is indirect and mediated by repeated bleeding due to postponing prophylaxis. Using a specific age at starting prophylaxis is therefore less suitable for clinical practice.

To study the effect of allowing one joint bleed before prophylaxis, starting prophylaxis before the onset of joint bleeding and starting after one joint bleed were presented separately. Multivariable comparisons of patient groups showed the best outcome in patients starting prophylaxis before the first joint bleed (n=12). The difference between starting prophylaxis after 0-1 (n=22) and 2-5 (n=14) joint bleeds was notable, but did not reach statistical significance (P=0.15). Caution is warranted in drawing strong conclusions based on such small groups of patients: starting prophylaxis before the onset of joint bleeding is not always possible in clinical practice and allowing one joint bleed may yield acceptable long-term outcome as well.

Future research

The present data still represent small patient groups, especially those who started prophylaxis before joint bleeding or after a single joint bleed. A definitive comparison of these two groups requires larger cohorts of patients with severe haemophilia, who would have to be followed into adulthood (Figures 1 and 2). In addition, this comparison would depend heavily on continued standardized outcome assessment. In this context, newly developed, more sensitive imaging modalities such as MRI or ultrasound may prove useful. Performing a randomized controlled trial would generate the highest level of evidence, but would take a long time and is ethically unacceptable. Using data from large cohort studies such as the PedNet registry may be more efficient, as it includes many patients with detailed information on bleeding and treatment [26]. However, PedNet patients are still too young (born since 2000), and confounding by indication may occur as data from the PedNet registry represent clinical practice and patients are not randomized.

Conclusion

At a median age of 22 years, the outcome of prophylaxis was highly dependent on its early initiation. The number of joint bleeds before prophylaxis showed the strongest association with outcome and therefore appears to provide best guidance in clinical decision making on starting prophylaxis. The results suggest that starting prophylaxis before the onset of joint bleeding is most effective in preventing arthropathy. Future research will have to elucidate whether starting before the onset of joint bleeding is indeed superior to starting after the first joint bleed.

References

1. Van Creveld S. Prophylaxis of Joint Hemorrhages in Hemophilia. *Acta Haematol* 1971; **45**: 120–127.
2. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A et al. Guidelines for the management of hemophilia. *Haemophilia* 2013; **19**: e1–e47.
4. Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients--a long-term follow-up. *J Intern Med* 1997; **241**: 395–400.
5. Nijdam A, Altisent C, Carcao MD, Cid AR, Claeyssens-Donadel S, Kurnik K et al. Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades. *Haematologica* 2015; **100**: e84–6.
6. Astermark J, Petrini 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**: 1109–1113.
7. Gringeri A, Lundin B, Von Mackensen S, Mantovani L, Mannucci PM. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost* 2011; **9**: 700–710.

8. Van den Berg HM, Fischer K, Mauser-Bunschoten EP, Beek FJ, Roosendaal G, Van der Bom JG et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561–565.
9. Kreuz W. When should prophylactic treatment in patients with haemophilia A and B start. *Haemophilia* 1998; **4**: 413–417.
10. Fischer K, Van der Bom JG, Molho P, Negrier C, Mauser-Bunschoten EP, Roosendaal G et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia* 2002; **8**: 745–752.
11. Ljung R. The risk associated with indwelling catheters in children with haemophilia. *Br J Haematol* 2007; **138**: 580–586.
12. Nijdam A, Kurnik K, Liesner R, Ljung R, Nolan B, Petrini P et al. How to achieve full prophylaxis in young boys with severe haemophilia A: different regimens and their effect on early bleeding and venous access. *Haemophilia* 2015; **21**: 444–50.
13. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V et al. A United Kingdom haemophilia centre doctors' organization guideline approved by the British committee for standards in haematology: Guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol* 2010; **149**: 498–507.
14. Fischer K, Van Der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, De Kleijn P et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood* 2002; **99**: 2337–2341.
15. Nederlandse Vereniging van Hemofiliebehandelaars. *Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen.* Alphen aan den Rijn: The Netherlands: Van Zuiden Communications, 68-69; 2009.
16. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, Van den Berg HM et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: Comparing outcome and costs since the 1970s. *Blood* 2013; **122**: 1129–1136.
17. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res* 1980; **149**: 153–9.
18. Pettersson H, Nilsson IM, Hedner U, Noréhn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatr Scand* 1981; **70**: 565–70.
19. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. *Haemophilia* 2011; **17**: 41–44.
20. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control* 1974; **19**: 716–723.
21. Oldenburg J, Zimmermann R, Katsarou O, Theodossiades G, Zanon E. Controlled , cross-sectional MRI evaluation of joint status in severe haemophilia A patients treated with prophylaxis vs . on demand. *Haemophilia* 2015; **21**: 171–179.
22. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Prejs R, Grobbee DE et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: Effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446–452.
23. Erlemann R, Pollmann H, Reiser M, Almeida P, Peters PE. [Staging of hemophilic osteoarthropathy using the Pettersson score. A study of 40 children and adolescents]. *Rofo* 1987; **147**: 521–6.

24. Nijdam A, Bladen M, Hubert N, Pettersson M, Bartels B, Van der Net J et al. Using routine Haemophilia Joint Health Score for international comparisons of haemophilia outcome: standardization is needed. *Haemophilia* 2015; doi: 10.1111/hae.12755. [Epub ahead of print]
25. Fischer K, Van der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE et al. Discontinuation of prophylactic therapy in severe haemophilia: Incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–550.
26. Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E et al. Prospective observational cohort studies for studying rare diseases: The European PedNet haemophilia registry. *Haemophilia* 2014; **20**: 280–286.

Supplemental material

Table 1s. Outcome and patient characteristics according to number of joint bleeds until start of prophylaxis.

Number of joint bleeds before start of prophylaxis	**0-1**	**2-5**	**≥6**
Patients			
Number	22	14	39
Age at last Pettersson score (years)	16.9 (13.4-25.1)	17.4 (13.9-21.2)	25.0 (20.8-30.6)
Age at 1st joint bleed[1] (years)	1.3 (1.3-3.0)[2]	1.6 (1.4-2.5)	2.3 (1.3-3.1)
Treatment			
Age at start of prophylaxis (years)	1.4 (1.0-3.0)	3.1 (1.6-4.3)	5.1 (4.1-6.9)
Time between 1st joint bleed and start of prophylaxis (years)	-0.2 (-1.7 - 0.0)	0.7 (0.3-1.8)	2.8 (1.7-4.5)
Joint bleeds before start of prophylaxis (n)	0 (0-1)	4 (3-5)	20 (11-43)
Outcome			
Last Pettersson score (0-78)	0 (0-5)	0 (0-4)	5 (0-14)
Last Pettersson = 0 (%)	59	57	36

Values are numbers (n), percentages (%) or medians with IQR (interquartile range).
[1] Estimated with Kaplan-Meier survival analysis independent of start of prophylaxis; based on 62 patients with date 1st joint bleed available.
[2] Based on 10 patients who started prophylaxis after 1 joint bleed; the 12 other patients started prophylaxis before the onset of joint bleeding.

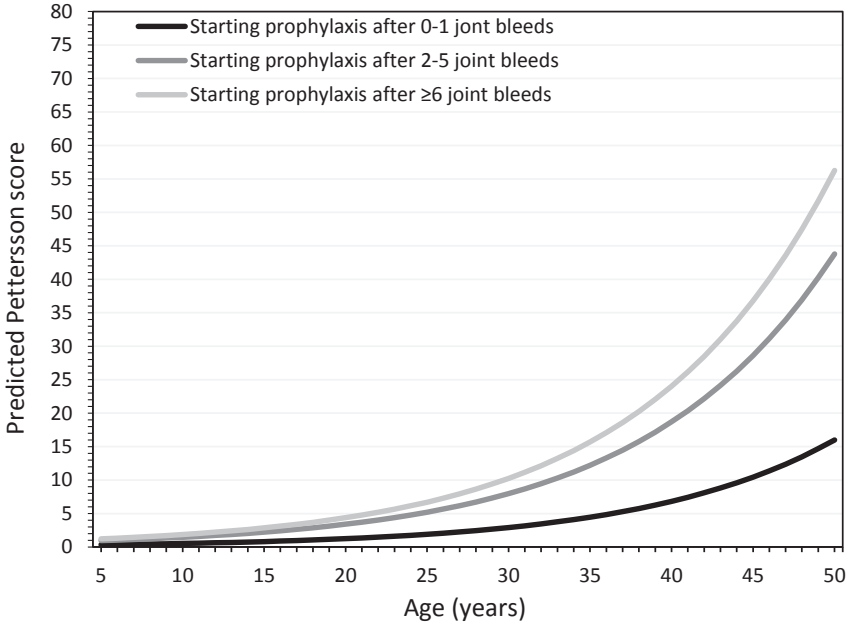

Figure 1s. Regression lines depicting predicted Pettersson scores by age according to three categories of joint bleeding before starting prophylaxis.
Lines represent predicted Pettersson scores for the different groups, independent of the effect of prophylactic dose and onset of joint bleeding (as a proxy for bleeding phenotype).
Statistical testing:
- starting after 0-1 joint bleed vs. starting after ≥6 joint bleeds (P=0.01),
- the difference between starting after 0-1 and 2-5 joint bleeds was notable, but statistical significance was not reached (P=0.15).

CHAPTER 6

Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates

A. Nijdam, W. Foppen, P. de Kleijn, E.P. Mauser-Bunschoten, G. Roosendaal,
K.P.M. van Galen, R.E.G. Schutgens, Y.T. van der Schouw, and K. Fischer

Submitted

Abstract

Prophylaxis is the recommended treatment for children with severe haemophilia A, but whether prophylaxis should be continued in adulthood is still under debate. In a setting of starting prophylaxis in early childhood, up to 35% of young adults have been reported to discontinue prophylaxis while maintaining low bleeding rates and good joint health after 4 years of on-demand treatment. This single-centre observational cohort study assessed the long-term consequences of discontinuing prophylaxis in patients with severe haemophilia A without inhibitors, born between 1970 and 1988. Patient-initiated changes in prophylaxis were recorded from time of starting self-infusion until last evaluation, including all switches to on-demand treatment for a minimum of two consecutive weeks. 66 Patients were evaluated at median 32.4 years: 26% of patients had stopped prophylaxis for a median of 10 years, 15% had interrupted prophylaxis and 59% had continued prophylaxis. Annual joint bleeding rate (AJBR), Haemophilia Joint Health Score (HJHS 2.1; 0-124 points), radiological Pettersson score (0-78 points) and Haemophilia Activities List (HAL; 100-0 points) were compared between patients who stopped and patients who continued prophylaxis. Although self-reported bleeding rates and functional limitations were similar in both groups (AJBR: 1.5 vs. 1.2; HAL: 84 vs. 84), arthropathy on objective outcome assessment was worse after 10 years of on-demand treatment in patients who stopped prophylaxis (HJHS: 23 vs. 14; Pettersson: 16 vs. 5; $P<0.01$). These results support continuation of long-term prophylaxis in adults and demonstrate the need for objective tools in monitoring joint status.

Introduction

To prevent joint bleeding and subsequent haemophilic arthropathy, prophylaxis with clotting factor VIII (FVIII) is the preferred treatment for children with severe haemophilia A (FVIII<0.01 IU/ml) [1–3]. Nevertheless, several studies have reported variable adherence rates to prophylaxis [4–10] especially in teenagers and young adults: in a setting of starting prophylaxis in early childhood (early prophylaxis), 22-35% of patients discontinued prophylaxis [7, 9, 10]. Whether prophylaxis should be continued in adulthood is still under debate [3, 11–13]. The TEEN/TWEN study showed a trend towards worse scores on outcome assessment in late teens and young adults who switched to on-demand treatment [14]. On the other hand, previous studies with 4-year follow-up after discontinuing long-term prophylaxis suggested that some patients with a milder bleeding phenotype could possibly switch to on-demand treatment safely [7, 10]. Patients who had stopped prophylaxis at around age 21 years were followed for four years. They showed low bleeding rates and similar degrees of arthropathy on X-rays compared with patients who had continued prophylaxis [7, 10]. However, low bleeding rates may not guarantee good joint health, as evidence of subclinical joint bleeding causing arthropathy in patients on on-demand treatment has been reported [15]. Prophylaxis could prevent or attenuate this process. Therefore, additional follow-up is needed to assess whether these patients may continue on-demand treatment without jeopardizing their joint health. This study presents a 10-year detailed follow-up of patient-initiated discontinuation of long-term prophylaxis in patients with severe haemophilia A.

Methods

Study population

Patients with severe haemophilia A (FVIII<0.01 IU/ml), born between 1-1-1970 and 1-1-1988, treated at the Van Creveldkliniek were eligible. Ethical approval was obtained (number 11-442); informed consent was waived.

Treatment strategy

Prophylaxis was defined as the regular administration of FVIII at least 1x/week [16]. Following the start of self-infusion, all patient-initiated switches to on-demand treatment for ≥2 weeks were analysed. At evaluation, patients were classified into three adherence groups: ‘stopped’, ’interrupted’ or ‘continued’ prophylaxis (Figure 1). At evaluation, only patients in the ‘stopped’ group were on on-demand treatment.

Data collection

All patients kept infusion logs and visited the clinic at least annually. At each visit, the number of joint bleeds, treatment type, dose and frequency of treatment were documented in the patient's medical file. Data on clotting factor consumption (CFC), first treatment, start of prophylaxis, start of self-infusion, and orthopaedic hospital admissions were extracted from patient's medical files until last visit up to April 2014. The most recent Haemophilia Joint Health Score (HJHS-2.1), Haemophilia Activities List (HAL) questionnaire, and radiological evaluation (Pettersson score, taken at 5-year intervals) were collected.

Patient-reported outcome assessments that were collected included the HAL questionnaire (normalized sum score, basic lower extremity, complex lower extremity, and upper extremity score, optimum 100 points) [17, 18], and annual number of joint bleeds (AJBR) [19].

Objective joint health of elbows, knees and ankles was assessed by the HJHS [20], Figure 8 walk test [21] and Pettersson score [22]. The HJHS-2.1 is a standardized physical examination, sensitive to early joint damage [20, 23, 24]. Scores range from 0 to 124, with higher scores indicating more joint damage. A single physiotherapist assessed all HJHS scores and Figure 8 walk tests on the same day; the latter measures the time taken to walk at normal pace around two pylons, placed 8 metres apart. The Pettersson score is a validated tool for assessment of osteochondral changes on plain X-rays (0-13 points/joint, maximum total score 78), with higher scores indicating more joint damage [22, 25]. X-rays were scored by two blinded assessors with a high agreement (intraclass correlation 0.88; 95% confidence interval: 0.32-0.97).

Data analysis

Adherence groups were compared for treatment and outcome parameters. Statistical comparison was restricted to the 'stopped' and the 'continued' groups, due to incomplete data and low numbers in the 'interrupted' group.

Missing data on the start of self-infusion (n=9) were imputed by the median group value of 15.3 years. Patients were followed until the HJHS assessment or last Pettersson score if no HJHS was available. Parameters were presented as medians with interquartile range (IQR). AJBR and CFC were calculated from data of the three years preceding evaluation. Groups were compared using non-parametric tests (Kruskal-Wallis and Mann-Whitney U tests), Fisher's Exact Test for categorical variables and log-rank test for survival analysis. Differences in HJHS, Figure 8 walk test, Pettersson and HAL scores were adjusted for age using generalized linear model regression analysis with Poisson distribution for HJHS and Pettersson score and Gamma distribution for HAL and Figure 8 walk test). A $P<0.05$ was considered statistically significant; analyses were performed in SPSS v21.

Results

Patients

Out of a total of 101 eligible patients, 35 were excluded from analysis because of a history of inhibitor development (≥5 BU at any time or 1-5 BU for more than one year; n=17), inadequate access to treatment during the first 4 years of life (mostly concerning immigrants; n=5), incomplete treatment history (recently joining the clinic; n=5, or visiting for surgical consultation only; n=4), never starting prophylaxis (n=2), starting self-infusion only after the last available outcome measurement (n=1), or other pathology influencing bleeding phenotype (Ehlers-Danlos; n=1). Overall, 66 haemophilia A patients were followed from start of self-infusion (median age 15.3 years) until last evaluation (HJHS/Pettersson at median age 32.4 years), resulting in a median follow-up of 16.6 years. Patients had started prophylaxis at a median age of 5.0 years (IQR: 3.4-6.9) and were treated according to the current Dutch intermediate dose treatment regimen [26]; in this cohort predominantly 1000IU FVIII 2-3x/week (median weekly dose 2400 IU/week; IQR: 1900-2900 IU/week). Only two patients were on once weekly prophylaxis at the time of evaluation: one patient from the 'continued', and the other from the 'interrupted' group.

All patients had either an HJHS or a Pettersson score, but not all outcome parameters were available for all patients (Figure 1). Nine patients had incomplete bleeding logs. Eleven patients did not have an HJHS and five patients did not have Pettersson scores, as they stopped visiting the clinic or it was impossible to combine visits with an appointment with the physiotherapist or radiology department. Two HJHS scores were excluded, as scoring was affected by fibromyalgia combined with neuropathy in one patient and severe back pain in another patient. Neither of these patients had previous HJHS scores available.

Adherence to prophylaxis

At the end of follow-up, 66 patients were categorized into three groups (Figure 1): 17 patients were on on-demand treatment (stopped, 26%), 10 had interrupted prophylaxis, but had reverted back to prophylaxis (interrupted, 15%) and 39 patients continued prophylaxis without interruption (59%). Outcome parameters were available for most patients who stopped or continued (range: 82%-95%, Figure 1).

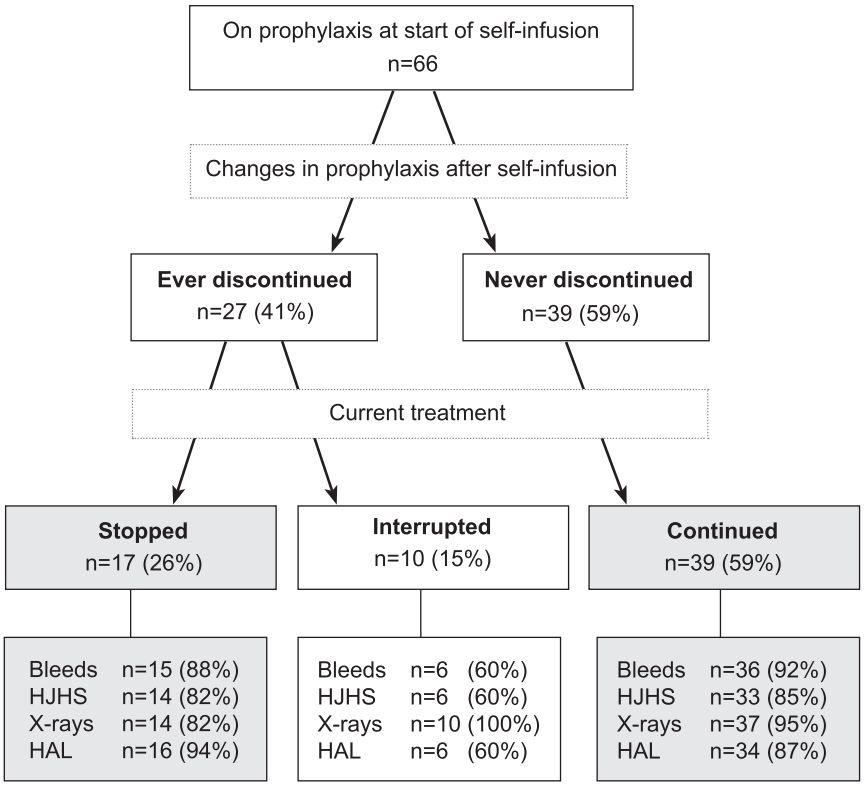

Figure 1. Patient-initiated discontinuation of prophylaxis and availability of outcome parameters.

Patient and treatment characteristics according to adherence group

Table 1 shows that patients across the different adherence groups had a similar age at first joint bleed, onset of treatment, start of self-infusion and follow-up. Overall, median age at first treatment was 1.1 years (IQR: 0.7-1.5 years) and median age at first joint bleed was 2.2 years (IQR: 1.2-3.5) in all groups. Patients in the 'continued' group had started prophylaxis earlier than patients who stopped or interrupted (age 4.2 vs. 6.5 years; P<0.01). The duration of prophylaxis since starting self-infusion depended heavily on adherence: patients who stopped received only a median of 3.4 years of prophylaxis after starting self-infusion, compared to 14.8 years in those who continued prophylaxis (P<0.01). These differences were also observed in lifetime prophylaxis. At evaluation, patients who continued and those who interrupted prophylaxis used similar prophylactic regimens: median 1000 IU FVIII per infusion, median 3x/week.

Table 1. Patient and treatment characteristics according to adherence group.

	Stopped median (IQR)	Interrupted median (IQR)	Continued median (IQR)	P-value§
Number of patients, n (%)	17 (26%)	10 (15%)	39 (59%)	NA
Follow-up since self-infusion	19.2 (11.0-24.1)	20.3 (12.8-25.5)	14.8 (12.2-18.2)	0.21
Treatment history				
Age at 1st treatment	1.1 (0.7-1.7)	1.1 (1.0-1.7)	1.0 (0.7-1.5)	0.80
Age at 1st joint bleed ‡	2.9 (1.8-3.8)	2.5 (2.1-3.7)	2.0 (0.8-2.7)	0.27
Age at start prophylaxis	7.1 (4.6-10.3)	6.3 (3.4-10.9)	4.2 (3.2-5.1)	0.01
Age at start self-infusion	15.8 (13.6-17.5)	14.9 (13.4-15.7)	15.3 (14.3-16.0)	0.43
Prophylaxis since self-infusion	3.4 (2.1-10.0)	17.4 (8.3-22.0)	14.8 (12.2-18.2)	<0.01
Lifetime prophylaxis	15.0 (6.4-18.0)	24.4 (14.4-30.5)	25.3 (22.1-30.5)	<0.01
Time on prophylaxis since start of prophylaxis (%)	59%	88%	100%	<0.01
Stopping/interrupting				
Age at start on-demand period	21.5 (18.6-26.8)	18.2 (14.4-22.2)†	NA	0.50
Number of on-demand periods, n/patient	1.0 (1.0-2.0)	2.0 (1.0-3.0)	NA	0.40
Follow-up after start last on-demand period	10.1 (5.9-13.8)	7.6 (3.6-15.5)	NA	0.63

Values are median years (IQR), unless otherwise stated.
§ Comparison across all three groups for follow-up since self-infusion and treatment history.
‡ Estimated with Kaplan-Meier survival analysis, censored for the start of prophylaxis.
† First discontinuation of prophylaxis.

Characteristics of stopping and interrupting prophylaxis

Patients in the 'stopped' group had stopped long-term prophylaxis at a median age of 21.5 years and were evaluated after median 10.1 years of on-demand treatment. Patients who interrupted prophylaxis, first switched to on-demand treatment at a median age of 18.2 years and reverted back to prophylaxis after a median of 1.2 years (IQR: 0.4-3.3). Most patients in the 'interrupted' group, interrupted prophylaxis more than once, resulting in a total of 4.0 years of on-demand treatment during a follow-up of 20.3 years.

Patient outcome assessment – comparing the 'stopped' with the 'continued' group

Outcome assessment according to adherence group is shown in Table 2. Age at evaluation was similar across adherence groups. FVIII consumption was lower in patients on on-demand treatment (P<0.01). The 'stopped' and 'continued' groups showed similar patient-reported outcome parameters: AJBR 1.5 vs. 1.2 (P=0.95), 40% vs. 44% of patients without joint bleeds in the year before evaluation (P=1.00), and few limitations in activity (HAL: 84 vs. 84 out of the

optimum score of 100; P=0.99). Most limitations were reported in subdomain scores on lower extremity functions: basic lower extremity 67 vs. 77, complex lower extremity 74 vs. 73, and upper extremity 92 vs. 96 points, for the 'stopped' and the 'continued' groups respectively. In contrast, the objectively measured outcome parameters HJHS and Pettersson were significantly worse for patients who had stopped prophylaxis (HJHS: 23 vs. 14 points; Pettersson: 16 vs. 5 points; P<0.01). Moreover, patients who stopped had more affected joints on the HJHS than patients who continued (median 2 vs. 1; P=0.04).

Table 2. Patient outcome assessment according to adherence group.

	Stopped median (IQR)	**Continued median (IQR)**	**P-value§**	**Interrupted median (IQR)**
Number of patients, n (%)	17 (26%)	39 (59%)	NA	10 (15%)
Age at evaluation, years	34.4 (29.4-39.0)	32.3 (26.9-34.9)	0.08	34.2 (27.8-41.4)
FVIII consumption, IU/kg/year‡	800 (600-1500)	2200 (1400-2600)	<0.01	1600 (1000-2000)
Patient-reported outcome				
Joint bleeding, n	15	36		6
AJBR, n/year	1.5 (0.0-5.8)	1.2 (0.3-2.5)	0.95	3.1 (2.2-11.6)
Last year without joint bleeds, %	40%	44%	1.00	50%
Limitations in activity, n	16	34		6
HAL score (100-0)	84 (67-98)	84 (78-97)	0.99†	67 (49-79)
Objective outcome				
Physical examination, n	14	33		6
HJHS score (0-124)	23 (11-36)	14 (6-20)	<0.01†	35 (26-40)
Number of joints with score >6, n	2 (1-3)	1 (0-2)	0.04†	3 (2-3)
Time Figure 8 walk test, seconds	13.9 (13.2-14.6)	13.8 (12.8-15.3)	0.42†	15.8 (14.0-17.5)
Radiological evaluation, n	14	37		10
Pettersson score (0-78)	16 (4-20)	5 (2-13)	<0.01†	25 (20-33)
Number of joints with score >4, n	1 (1-3)	0 (0-1)	0.35†	3 (2-3)
Hospitalization, n	17	39		10
for joint related problems, %	35%	10%	0.05	40%

Values are medians (IQR), unless otherwise stated.
§ P-value for the differences between patients who stopped and continued prophylaxis.
‡ Rounded to the nearest 100.
† Adjusted for age at evaluation using generalized linear model regression analysis.

The Figure 8 test results were similar in both groups: 13,8 seconds in the 'stopped' and 13,9 seconds in the 'continued' group (P=0,42). Patients who had stopped prophylaxis were more frequently admitted to the hospital for joint related problems: 35% vs. 10% in those who had

continued prophylaxis (P=0.05). Indications for hospital admission included: joint drainage, arthrodesis, arthroscopy, arthrotomy, debridement, Ilizarov joint distraction, intra-articular yttrium injection, surgical synovectomy, observation of joint bleed, and total knee replacement.

Trends in Pettersson scores over time were compared for the 'stopped' and the 'continued' groups (Figure 2). In total, 131 scores were analysed (median 2 scores per patient). These data showed a trend towards increasing Pettersson scores with age, with a sharper increase in those who stopped prophylaxis. Around the age of 15 years, the difference in median Pettersson scores between both groups was only small (5 vs. 3 points). At approximately 25 years of age, 4 years after stopping prophylaxis, Pettersson scores had increased, but with considerable overlap: median 11 points (IQR 4-15) for those who stopped, and 7 points (IQR 2-15) for those who continued (P=0.48 adjusted for age at evaluation). At approximately 35 years of age, Pettersson scores for those who stopped had further increased to median 17 points (IQR 5-20), while those who continued prophylaxis had remained stable at a median of 6 points (IQR 5-16; P<0.01 adjusted for age at evaluation).

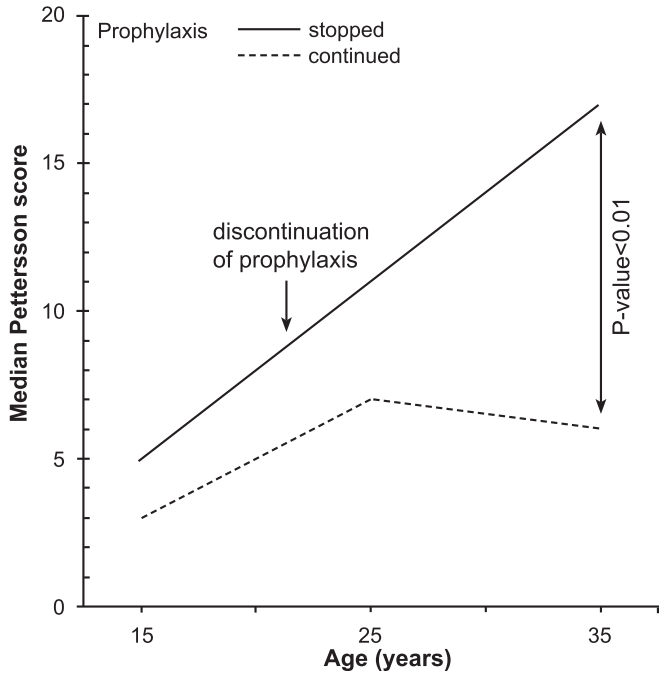

Figure 2. Pettersson scores across three age categories according to having stopped or continued prophylaxis. Age categories: 15: <20 years; 25: 20-30 years; 35: >30 years. P-value based on generalized linear model regression analysis within the age category, adjusted for age at evaluation.

Patient outcome assessment – the 'interrupted' group

At the age of 33 years, patients who had interrupted prophylaxis had a higher Pettersson score (25 points, n=10) than patients who stopped or continued prophylaxis. They scored worse on all other outcome parameters as well (n=6): they had higher AJBR, HJHS, and HAL scores, were slower on the Figure 8 test, and showed more affected joints on Pettersson and HJHS. Unfortunately, the small number of patients contributing to these numbers (n≤10; Figure 1), prohibited reliable statistical evaluation.

Mild bleeding phenotype

Previously, it has been suggested that patients with a milder bleeding phenotype could safely discontinue prophylaxis. These patients were identified by treatment characteristics only: a later start of prophylaxis, a lower weekly dose, and a lower joint bleed frequency on prophylaxis [7]. Based on treatment characteristics and objective joint assessment, we identified at least three patients (5%; 95% CI 1-13%) with a mild bleeding phenotype in this cohort: these patients had stopped prophylaxis, reported no joint bleeding and maintained low Pettersson scores (≤1 points) and low HJHS scores (≤3 points).

Discussion

Principal findings

Overall, 41% of young adults discontinued prophylaxis after starting self-infusion, while 26% stopped prophylaxis permanently at the age of 21.5 years. Patients who stopped prophylaxis reported only 1.2 joint bleeds/year and very few limitations in activity (HAL: 84 points). However, objective outcome assessment showed significantly worse arthropathy after 10 years of on-demand treatment, compared with those who continued prophylaxis (HJHS: 23 vs. 14 points; Pettersson score: 16 vs. 5 points).

Internal and external validity

Selection bias was avoided by including the entire birth cohort of patients seen at our haemophilia treatment centre. Outcome assessment was performed using routinely collected data and state-of-the-art outcome measures (HAL, HJHS, and Pettersson scores) [23]. The Figure 8 test did not seem sensitive enough to pick up significant differences between the adherence groups. Data on clotting factor use was objective and reliable, as FVIII is exclusively prescribed by the clinic. The availability of outcome measures in the 'stopped' and 'continued' groups was similar. Patient-reported outcome assessment could suffer from reporting bias if patients who

stop prophylaxis underreport bleeding and/or limitations on activity (HAL).

The observation that young adults on prophylaxis switch to on-demand treatment has been reported both in the Netherlands, and in other European countries [9]. The present study represents a single-centre experience with intermediate dose prophylaxis initiated at a median age of 5 years. As these patients had only minimal joint changes at the time of discontinuing prophylaxis, it is expected that these observations can be extrapolated to settings using high dose prophylaxis and/or starting prophylaxis earlier.

Other studies

This is the first study to report a 10-year objective assessment of outcome in patients who stopped long-term, early prophylaxis. A European survey of prophylactic practice reported similar proportions of patient initiated treatment changes: 30% of patients stopped, 12% interrupted and 58% continued prophylaxis during 3-72 months of follow-up [9], compared with respectively 26%, 15% and 59% in the present study. Discontinuing prophylaxis and its consequences were previously reported in a subset of patients from the current study, born 1970-1980. In this subset, up to 35% of patients stopped prophylaxis at the age of 21.5 years. Four years after stopping prophylaxis Pettersson scores were similar in the 'stopped' and the 'continued' groups [7, 10]. In the current study only 26% stopped prophylaxis. This difference may be explained by the extended follow-up, extension of the cohort with patients born 1980-1988, and/or exclusion of patients with haemophilia B, as well as a broader definition for prophylaxis used in the current study (i.e. considering infusions ≥1x/week as prophylaxis, in line with current definitions [19, 27], instead of ≥2x/week in previous studies). The current study corroborated the observation of similar Pettersson scores around age 25 years (Figure 2), but also demonstrated that differences in joint health between the 'stopped' and the 'continued' groups become apparent only after longer follow-up.

Joint bleeding rates were similar in the 'stopped' and 'continued' groups in this study, as opposed to the TEEN/TWEN study, where bleeding rates were lower in those who continued prophylaxis [14]. The difference may have been caused by a higher annual clotting factor use on prophylaxis in the TEEN/TWEN study (2100-5200 IU/kg/week vs. median 2200 IU/kg/week in the current study).

The current study reported less favourable HAL and HJHS scores than a recent report including the same birth cohort, reporting a median HJHS score of only 9 points, and a HAL of 93 points [26]. This may be explained by the fact that the previous study included younger patients (born 1988-1994) and assessed patients at a median age of 25 years as opposed to 32 years in the current study.

Annual FVIII use in the 'stopped' group seemed high for patients on-demand reporting few bleeds (800 IU/kg/year), but was in line with other studies reporting on severe patients on on-demand treatment: 700 IU/kg/year in a previous study from this centre [10], and 750 IU/kg/year in a large multicentre European study [28].

Possible mechanisms / Clinical interpretation

It was previously suggested that patients who stopped taking prophylaxis had a mild bleeding phenotype, characterized by a later onset of joint bleeding and less intensive prophylactic treatment [7, 29]. This was not confirmed in this cohort. The only indicator of a mild bleeding phenotype was a low bleeding rate on on-demand treatment, as the onset of joint bleeding was similar for the 'stopped' and 'continued' groups (P=0.27). In the current cohort, we identified only 5% of patients (95% CI: 1-13%) with a truly good joint status on on-demand treatment; this is in line with the 3-10% of patients with a mild bleeding phenotype reported elsewhere [30–32].

The difference in long-term joint status between the 'stopped' and 'continued' groups may in part be attributed to a three years' delay of prophylaxis in the 'stopped' group (P=0.01). It has been suggested that starting prophylaxis before the age of 3 years is an important determinant of long-term joint health [33]. However, more than 75% of patients in the 'continued' group started prophylaxis after the age of three years (lower quartile ≤3.2 years), suggesting that the age at onset of prophylaxis is not the main driver of the differences between the two groups. Moreover, the repeated finding of similar radiological joint health around the age of 25 years [10] corroborates this view and refutes that other systematic treatment differences before the start of self-infusion (e.g. interruptions of prophylaxis) attributed to the reported differences in long-term joint status. Other possible explanations of worse joint status are underreporting of bleeds and/or increased subclinical bleeding while on-demand treatment [15]. Assessment of underreporting is very difficult and may be a major limitation of this study. Subclinical bleeding is not formally demonstrated in this study, but may be detected on MRI [15] or ultrasound. Similar self-reported activity could be explained by the well-known phenomenon of response shift [34]: patients in the 'stopped' group adequately adapted to their functional limitations and therefore did not consider themselves as limited. Alternatively, it is possible that the increased joint damage did not (yet) translate to limitations in performing daily tasks. As joint damage in the 'stopped' group is expected to further increase with age, it is likely that this will eventually lead to reduced physical functioning [35].

Findings in patients who interrupted prophylaxis are more difficult to interpret due to the small

group size and incomplete outcome assessment. Even though no statistically reliable conclusions can be drawn, the 'interrupted' group seemed to score worst of all adherence groups. Why would patients in the 'stopped' group score better than those in the 'interrupted' group, without the benefit of prophylaxis? The data in this study is insufficient to answer this question. Our hypothesis is that the difference is explained by a more severe bleeding phenotype in those who interrupted prophylaxis compared with those who discontinued prophylaxis. This is supported by the higher bleeding frequencies reported in the interrupted group. Although the prescribed prophylactic regimen was similar across adherence groups, patients in the 'interrupted' group used less clotting factor and had higher bleeding rates on prophylaxis than patients who continued prophylaxis. While we have not formally studied this, our hypothesis is that this could reflect overall reduced treatment adherence in the 'interrupted' group and/or potentially a more severe bleeding tendency, which might explain their worse joint status.

Future research

As arthropathy is usually progressive, future research should focus on continued follow-up of patients on long-term prophylaxis who started immediately after the first joint bleed, with careful monitoring of joint status using objective tools. Especially in patients who discontinued prophylaxis, MRI or ultrasound may be able to monitor hemosiderin deposition(s) in clinically 'bleed free' joints or to detect early joint damage, which may be reason to continue prophylaxis. Orthopaedic surgery can be added to the set of outcome measurements in future assessments. With a median age of 32.4 years, the patients in this cohort were still too young to take orthopaedic surgical interventions into account.

Reasons for stopping were not collected, as they are not a determinant for outcome parameters in this study. However, they are relevant to future intervention programs. Especially in patients who interrupt prophylaxis, non-adherence to the prophylactic regimen should be explored.

Conclusion

Stopping prophylaxis during early adulthood is a common phenomenon. In this study 26% of young adults receiving prophylaxis since childhood stopped prophylaxis, while reporting only few joint bleeds. After 10 years of on-demand treatment, patients who stopped prophylaxis had developed significantly more arthropathy than those who continued prophylaxis. These results support the need for continued long-term prophylaxis for the majority of adults with severe haemophilia.

Acknowledgements

The present study was funded by an unrestricted grant from Novo Nordisk. Dutch Trial Registry number 3098; UTN U1111-1121-7069.

References

1. Van Creveld S. Prophylaxis of Joint Hemorrhages in Hemophilia. *Acta Haematol* 1971; **45**: 120–127.
2. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A et al. Guidelines for the management of hemophilia. *Haemophilia* 2013; **19**: e1–e47.
4. Collins PW, Blanchette VS, Fischer K, Björkman S, Oh M, Fritsch S 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**: 413–420.
5. De Moerloose P, Urbancik W, Van den Berg HM, Richards M. A survey of adherence to haemophilia therapy in six European countries: Results and recommendations. *Haemophilia* 2008; **14**: 931–938.
6. Du Treil S, Rice J, Leissinger CA. Quantifying adherence to treatment and its relationship to quality of life in a well-characterized haemophilia population. *Haemophilia* 2007; **13**: 493–501.
7. Fischer K, Van der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE et al. Discontinuation of prophylactic therapy in severe haemophilia: Incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–550.
8. Lindvall K, Colstrup L, Wollter IM, Klemenz G, Loogna K, Grönhaug S et al. Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. *Haemophilia* 2006; **12**: 47–51.
9. Richards M, Altisent C, Batorova A, Chambost H, Dolan G, De Moerloose P et al. Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. *Haemophilia* 2007; **13**: 473–479.
10. 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**: 107–112.
11. Berntorp E, Astermark J, Björkman S, Blanchette VS, Fischer K, Giangrande PLF et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; **9 Suppl 1**: 1–4.
12. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V et al. A United Kingdom haemophilia centre doctors' organization guideline approved by the British committee for standards in haematology: Guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *Br J Haematol* 2010; **149**: 498–507.
13. Makris M. Prophylaxis in haemophilia should be life-long. *Blood Transfus* 2012; **10**: 165–168.
14. Manco-Johnson MJ, Sanders J, Ewing N, Rodriguez N, Tarantino M, Humphries T. Consequences of switching from prophylactic treatment to on-demand treatment in late teens and early adults with severe haemophilia A: The TEEN/TWEN study. *Haemophilia* 2013; **19**: 727–735.
15. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.

16. Nederlandse Vereniging van Hemofiliebehandelaars. Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen. Alphen aan den Rijn: The Netherlands: Van Zuiden Communications, 68-69; 2009.
17. Van Genderen FR, Van Meeteren NLU, Van der Bom JG, Heijnen L, De Kleijn P, Van den Berg HM et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia* 2004; **10**: 565–71.
18. Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. *Haemophilia* 2006; **12**: 36–46.
19. 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**: 1935–1939.
20. Hilliard P, Funk S, Zourikins N, Bergstorm BM, Bradley CS, Mclimont M et al. Hemophilia joint health score reliability study. *Haemophilia* 2006; **12**: 518–525.
21. Creel GL, Light KE, Thigpen MT. Concurrent and construct validity of scores on the Timed Movement Battery. *Phys Ther* 2001; **81**: 789–98.
22. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res* 1980; **149**: 153–9.
23. De Moerloose P, Fischer K, Lambert T, Windyga J, Batorova A, Lavigne-Lissalde G et al. Recommendations for assessment, monitoring and follow-up of patients with haemophilia. *Haemophilia* 2012; **18**: 319–25.
24. Fischer K, De Kleijn P. Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity. *Haemophilia* 2013; **19**: 944-50.
25. Pettersson H, Nilsson IM, Hedner U, Noréhn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatr Scand* 1981; **70**: 565–70.
26. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, Van den Berg HM et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: Comparing outcome and costs since the 1970s. *Blood* 2013; **122**: 1129–1136.
27. Fischer K, Ljung R, Platokouki H, Liesner R, Claeyssens S, Smink E et al. Prospective observational cohort studies for studying rare diseases: The European PedNet haemophilia registry. *Haemophilia* 2014; **20**: 280–286.
28. Schramm W, Royal S, Kroner B, Berntorp E, Giangrande P, Ludlam C et al. Clinical outcomes and resource utilization associated with haemophilia care in Europe. *Haemophilia* 2002; **8**: 33–43.
29. Van Dijk K, Fischer K, Van der Bom JG, Grobbee DE, Van den Berg HM. Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed. *Haemophilia* 2005; **11**: 438–43.
30. 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.
31. Molho P, Rolland N, Lebrun T. Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. *Haemophilia* 2000; **6**: 23–32.
32. Rainsford SG, Hall A. A three-year study of adolescent boys suffering from haemophilia and allied disorders. *Br J Haematol* 1973; **24**: 539–51.
33. Astermark J, Petrini 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**: 1109–1113.
34. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation

to changing health: A meta-analysis of response shift. *Qual Life Res* 2006; **15**: 1533–1550.

35. Fischer K, Van der Bom JG, Mauser-Bunschoten EP, Roosendaal G, Van den Berg HM. Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters. *Haemophilia* 2005; **11**: 43–48.

CHAPTER 7

Evaluating outcome of prophylaxis in haemophilia: objective and self-reported instruments should be combined

K. Fischer, A. Nijdam, M. Holmström, P. Petrini, R. Ljung, Y.T. van der Schouw, E. Berntorp

Submitted

Abstract

Introduction: Routine outcome assessment of prophylaxis should use validated tools, while balancing comprehensiveness and burden. Collecting overlapping information should be avoided.

Aim: To assess correlations between different outcome assessment tools in haemophilia.

Methods: From an international cross-sectional study, data on objective outcome (Haemophilia Joint Health Score (HJHS 2.1, range 0-124), radiological Pettersson score) and self-reported joint bleeding, Haemophilia Activities List (HAL, range 100-0), health related quality of life (SF-36, including 5 physical and 5 mental domain scores, range 100-0), and Utility (SF6D and EQ-5D, range 1.0-0) were extracted. Spearmans correlations were calculated: ≥0.8 very strong, 0.60-0.79 strong, 0.40-0.59 moderate.

Results: 90 Patients with severe haemophilia, on prophylaxis since median age 3.4 years, were evaluated at median 25.5 years (range 16.0-37.6). Objective outcome was favourable (median HJHS 2.1 6 points, Pettersson score 9 points). Self-reported outcome showed a median of 7 joint bleeds in 5 years, median HALsum 96 points, high scores for physical domains of SF-36 (median 80-95) and high Utility values (median SF6D 0.87; EQ-5D 0.84).

Physical examination (HJHS 2.1) showed strong correlation with radiological scores, moderate correlation with physical domains of the SF-36 and Utility, but no correlation with self-reported bleeding or limitations in activities (HAL). Bleeding was not associated with any other outcome parameter. The HAL was only correlated with the SF36 'Physical functioning' domain.

Conclusion: Outcome assessment in patients on prophylaxis should not depend on self-reported bleeding only, but should include objective outcome assessment as well as self-reported limitations in activities and quality of life.

Introduction

The natural history of haemophilia is characterised by repeated bleeding, especially in ankles, knees and elbows. Eventually, this leads to blood-induced joint destruction (haemophilic arthropathy), characterised by loss of function, severe pain and disability [1]. Early prophylactic replacement therapy with clotting factor concentrates can stop development of haemophilic arthropathy by preventing joint bleeding [2]. Yet this treatment is very costly and the burden of frequent and regular intravenous injections is considerable. Outcome assessment in patients receiving prophylaxis is very important to help identify the optimum treatment strategy and justify the cost of expensive replacement therapy.

Traditionally, outcome assessment in haemophilia consisted of joint evaluation using radiography [3,4] and physical examination [5]. Since then, many new objective and patient-reported tools for outcome assessment have been introduced and validated. To capture the full spectrum of consequences of a disease, the WHO has proposed the to use the model of International Classification of Functioning, Disability and Health (ICF)) [6]. This model identifies the four sequential stages of the main disease-disability pathway: Health condition → Body Functions and Structures → Activities → Participation. For each of these stages, outcome can be measured with specific tools. Health Related Quality of Life (HRQoL) is seen as an overall concept and is not disease specific.

Ideally, outcome assessment should be used for both evaluation of treatment at patient level and at group level for research. Published recommendations describe different tools, both objective- and self-reported, without providing evidence-based guidance on which ones to use [7,8]. Objective tools require imaging or evaluation by a professional and are usually time-consuming, costly, and require scheduled appointments. While objective tools measure the consequences of bleeding and may impact treatment decisions, they may not be considered very relevant by patients. In contrast, self-reported tools are cheap, easy to use and more relevant to patients, but lack a direct relation with bleeding or arthropathy.

When choosing tools for routine outcome assessment of prophylaxis, only high quality validated tools should be considered, while measurement comprehensiveness and burden should be balanced. To maximise efficiency, it is important to know which instruments provide overlapping information and which instruments provide new data. To determine overlap between different instruments for outcome assessement, the present study assesses the correlations between the instruments using data from an international multicentre study.

Methods

Patients and setting

A cross-sectional study was performed using data from an observational study with detailed outcome assessment in patients with severe haemophiia (FVIII/IX < 1% or <1 IU/dl), born between 1-Jan-1970 and 1-Jan-1994, treated at the University Medical Center Utrecht, the Netherlands (Van Creveldkliniek), the Karolinska University Hospital in Stockholm, Sweden, and the Skåne University Hospital in Malmö, Sweden [9]. Eligible patients had had life-long access to care without a history of inhibitors (any inhibitor activity > 0.6 BU with decreased recovery). Because the questionnaires in this study were validated from age 16 years onwards, only patients with a minimum age of 16 years at evaluation were included.

Information on patient characteristics and treatment history were extracted from the medical files., Annual clotting factor consumption was extracted from patient logs and hospital pharmacy records, for the last 5 years before evaluation.

Outcome

Objective outcome was focused on ICF domain 'Body functions and Structure' clinical and radiological joint status of elbows, knees and ankles. Clinical joint status was assessed by the centre's physiotherapist, and scored according the Haemophilia Joint Health Score (HJHS) version 1.0 [10,11]. The HJHS is a structured physical examination of elbows, knees, and ankles (max 20-26 points per joint) and observation of gait for knees and ankles (0-4 points). The total score ranges from 0 (perfect joint health) to 148 points. Standardisation and reliability was established during a training session (intra-class correlation (ICC) 0.84) with all three designated physiotherapists [12]. In addition, HJHS scores were calculated according to HJHS version 2.1; based on new values for normal range of motion [13], more detailed scoring of pain and without scoring axial alignment or gait scores for knees and ankles (range 0-124 points, manual available through the International Prophylaxis Study Group e-mail: www. Ipsg.ca Audrey.Abad@sickkids.ca). Radiological joint status on X-rays was scored according to the additive Pettersson score [14]. The Pettersson score ranges from 0-13 for each joint, resulting in a total score of 0 (perfect joint health) to 78 points. Only X-rays made within 2.5 years from physical examination were included in the analyses.

Self-reported outcome included bleeding data and questionnaires (HAL, SF36 and EQ5D). The annual number of joint – and soft tissue bleeds over the last five years were extracted from the patient logs, medical files, and hospital databases by research nurses at each center. Bleeds were defined as any complaint requiring treatment with clotting factor concentrate.

Joint bleeds were defined as bleeds located in shoulders, elbows, wrists, hips, knees, or ankles. Questionnaires were administered during clinic visits. Self-reported limitations in activities were assessed using the Haemophilia Activities List (HAL) [15–17]. The HAL measures the ICF domains of 'Activities' and 'Participation', and includes three sub-scores (upper extremities, lower extremities, and complex lower extremities) as well as a sumscore, each with a range of 100 (no limitations) to 0 points. In addition to the ICF domains, Health Related Quality of Life (HRQoL) was assessed using the SF36 [18] and the Euroqol (EQ-5D) questionnaires [19]. The SF36 assesses HRQoL in four physical domains ('Physical funtioning', 'Role limitations due to physical problems', 'Bodily pain', 'General health') and four mental domains ('Social functioning', 'Role limitations due to emotional problems', 'Mental health', 'Vitality') with points ranging from zero to an optimum score of 100 points; as well as a physical and mental component score (PCS and MCS) with a mean of 55 points in the normal population [20]. In addition, the SF36 derived Utility value (SF6D) was calculated according to Brazier [21]. The EQ-5D assesses problems in five domains (mobility, self-care, activities of daily living, pain, and anxiety/depression) to produce a Utility value ranging from zero (death) to one (perfect health). EQ-5D utility values were calculated using the Dutch tariff [22].

Statistical Analysis

For the descriptive analyses of patient characteristics and outcome, medians and interquartile ranges (IQR: P25-P75) were calculated to describe both skewed and normally distributed parameters. Patient characteristics between groups were compared using the Mann Whitney U test and Fischers' exact test.

Correlations between different outcome parameters and –tools at patient level were calculated using nonparametric Spearman's Rho correlations. Correlation coefficients of ≥0.8 were considered very strong, 0.60-0.79 strong, 0.40-0.59 moderate, 0.20-0.39 weak [23]. Only correlation coefficients

of >=0.40 were considered relevant and are presented here.

Results

Overall, 90 of 128 patients in the original study cohort were included; 38 patients were excluded because they did not complete questionnaires (n=27) or were younger than 16 years at evaluation (n=11). Patient and treatment characteristics are shown in Table 1. Fifty-two patients were Dutch and 38 patients were Swedish, the majority (88%) had severe haemophilia A. The median age at evaluation was 25.5 years, ranging from 16.0 to 37.6 years. About one

third of patients (34.8%) was HCV-positive, 15.6 % already had a history of orthopedic surgery and 5.6% were HIV positive. The majority of patients was treated with prophylaxis 3x/week. An overview of objective and self-reported outcome is shown in Table 2. Data on physical exam were available for 87 (97%) patiens and Pettersson scores within 2.5 years of physical examination were available for 40/52 (77%) of Dutch patients only. Data on bleeding and HAL questionnaires were available for all patients, while EQ5D were available for 88 and SF36 for 89 patients.

Table 1. Patient and treatment characteristics.

	Median (IQR) or %
No.	90 (52 NL, 38 SE)
Haemophilia A (%)	88%
Age at evaluation (years)	25.5 (20.9-30.4)
Weight (kg)	70 (62-80)
HCV positive (%)	34.8%
HIV positive (%)	5.6%
History of orthopedic surgery (%)	15.6%
Treatment history	
Age at start prophylaxis (years)	3.4 (1.5-5.3)
Treatment during the last 5 years	
On prophylaxis (%)	89%
Weekly prophylactic dose (IU/kg)	54 (39-80)
Prophylactic infusions/week (n)	3.0 (2.0-3.0)
Annual consumption† (IU/kg/years)	2600 (1800–4000)

Values are median (IQR) of unit of measurement unless otherwise stated.
† Annual clotting factor consumption was rounded to the nearest 100.

Objective outcome

Overall objective outcome showed favourable total HJHS scores of 6.0 points (range 0-39 for HJHS 1.0 and 0-33 for HJHS 2.1), and median Pettersson scores of 9.0 points, ranging from 0 to 37. Non-parametric correlations between objective outcome parameters are shown in Table 3. As expected, the correlation between HJHS 1.0 and HJHS 2.1 was almost perfect. The correlation of Pettersson scores with the HJHS scores was strong with correlation coefficients of 0.66 and 0.67, respectively (P-value <0.01).

Table 2. Objective and self-reported clinical outcome.

	Median (IQR) or %
Objective outcome-Joint outcome (elbows, knees, ankles)	
Loss of function (n=87)	
HJHS 1.0 (max 148 points)	6.0 (2.0-16.0)
HJHS 2.1 (max 124 points)	6.0 (2.0-12.0)
HJHS 2.1 ≥ 10 points	32%
Changes on X-ray, (n=40)	
Pettersson score (PS, max 78 points)	9.0 (3.0-15.0)
Time between PS and HJHS (years)	0 (-0.7-+1.0)
Age at Pettersson score (years)	26.5 (20.4-30.6)
Self-reported outcome	
Bleeding over the last 5 years (n=90)	
Joint bleeds/year, n	1.0 (0.0-2.1)
Joint bleeds in 5 years, n	7.0 (1-15)
Limitations in activities (n=90)	
HAL sum (max 100 points)	96 (84-100)
HAL upper extremities	100 (91-100)
HAL lower extremities basic	97 (79-100)
HAL lower extremities complex	95 (75-100)
Health-related quality of life	
SF36 (n=89; max 100 points)	
SF36-Physical functioning	95.0 (85.0-100)
SF36-Physical role limitations	100 (75.0-100)
SF36-Pain	79.6 (67.3-100)
SF36-General Health	80.0 (65.0-90.0)
SF36-Social functioning	100 (87.5-100)
SF36-Emotional role limitations	100 (100-100)
SF36-Mental Health	84.0 (76.0-92.0)
SF36-Vitality	75.0 (56.2-85.0)
SF36-Physical Component Score (PCS)	52.3 (45.6-56.0)
SF36-Mental Component Score (MCS)	56.6 (53.3-59.4)
SF6D-utility (max 1.0)	0.87 (0.76-0.94)
Euroqol (EQ-5D, n=88)	
EQ-5D utility (max 1.0)	0.84 (0.81–1.00)

Table 3. Non parametric correlations for objective outcome parameters.

Spearmans' correlations	HJHS 1.0	
HJHS 2.1	0.99	HJHS 2.1
Pettersson Score	0.66	0.67

Correlations presented are statistically significant (p-value<0.01)

Self-reported outcome

Self-reported outcome showed a low annual joint bleed rate and few limitations in activities in the HAL questionnaire. Most limitations (scores < 100 points) were reported for the HAL Sum score (72%) and the HAL Lower extremities complex score (59%). The eight domains of the SF36 showed median scores varying between 75 and 100 points. For the domain of 'Physical functioning' scores were high at a median of 95 points, with 54% reporting problems (score <100). The median score for the domain of 'Pain' was 79.6 points with 74% of patients reporting any pain in the last six weeks. Median scores for the domains of 'Mental health' and 'Vitality' were unexpectedly low at 84 and 75 points respectively. Both the Physical (PCS) and the Mental (MCS) SF 36 component scores were around the normal average of 55 points. The median SF6D Utility value was 0.87, with 92% scoring <1.0. The EQ-5D Utility value was similar at 0.84, with scores <1.0 in 53% of patients. When comparing these self-reported outcome parameters between Dutch and Swedish patients, bleeding parameters and all HAL subscores were significantly different (p-values all <0.02), but all SF36 domains and Utility values were similar between the two countries (data not shown) [9].

Self-reported outcome parameters showed a very strong correlation between both bleeding parameters (0.87), but no correlation between joint bleeding and any of the questionnaires (Table 4). For the HAL questionnaire, the HAL sum score was mostly dependent on the lower extremity scores (correlation coefficients 0.92 and 0.96, respectively) and showed moderate correlations with SF36 'Physical functioning' (0.43) and the SF6D Utility (0.41). Correlations between the SF36 domains and SF6D and EQ5D Utility, were moderate to strong for most domains, especially the physical domains.

Table 4. Non-parametric correlations for self-reported outcome parameters.

Spearmans' correlations	annual joint bleeds							
5-year joint bleeds	0.87	5-year joint bleeds						
HAL_sum	NR	NR	HAL_sum					
HAL_upper extremities	NR	NR	0.76	HAL_upper extr				
HAL_lower extremities basic	NR	NR	0.92	0.61	HAL_lower extr basic			
HAL_lower extremities complex	NR	NR	0.96	0.66	0.90	HAL_lower extr complex	SF6D Utility	EQ5D Utility
SF36 Physical functioning	NR	NR	0.43	NR	NR	NR	0.73	0.66
SF36 Physical role limitations	NR	NR	NR	NR	NR	NR	0.69	0.56
SF36 Pain	NR	NR	NR	NR	NR	NR	0.69	0.64
SF36 General Health	NR	NR	NR	NR	NR	NR	0.59	0.48
SF36 Social functioning	NR	NR	NR	NR	NR	NR	0.72	0.66
SF36 Emotional role limitations	NR	NR	NR	NR	NR	NR	0.50	0.42
SF36 Mental health	NR	NR	NR	NR	NR	NR	0.72	0.57
SF36 Vitality	NR	NR	NR	NR	NR	NR	0.58	NR
SF36 PCS	NR	NR	NR	NR	NR	NR	0.69	0.67
SF36 MCS	NR	NR	NR	NR	NR	NR	0.45	NR
SF6D Utility	NR	NR	0.41	NR	NR	NR	-	0.75
EQ-5D Utility	NR	NR	NR	NR	NR	NR	0.75	-

NR: Non Relevant (Spearmans' rho <0.40)
All correlations presented are statistically significant (p-value<0.01)

Correlations between objective and self-reported outcome parameters

A subset of representative outcome parameters was chosen for the analysis of correlations between objective and self-reported outcome. The HJHS 2.1 (current version) and Pettersson score represented the objective parameters. For self-reported outcome, 5 year bleeding (more variability), HAL sum score (most representative), the SF36 physical domains and SF36-'Social funtioning' (may represent participation), as well as SF6D- and EQ5D Utility values were selected.

Correlations between objective and self-reported outcome parameters were very limited (Table 5). The HJHS 2.1 showed moderate correlations with physical domains of the SF36 and Utility values. None of the objective parameters showed any correlation with bleeding, the HAL scores, or the mental domains of the SF36 (data not shown). The Pettersson scores did not show any correlation with self-reported outcome (strongest correlation with SF36 'Physical Functioning': correlation coefficient 0.36, p value <0.05). These data suggest that both objective and self-reported outcome should be assessed, as both are independently associated with Health Related Quality of Life and Utility.

Table 5. Non-parametric correlations between selected objective and self-reported outcome parameters.

	Objective outcome	
Self-reported outcome	HJHS 2.1	Pettersson Score
5-year joint bleeds	NR	NR
HAL_sum	NR	NR
SF36 Physical functioning	-0.59	NR
SF36 Pain	-0.41	NR
SF36 Social functioning	NR	NR
SF36 PCS	-0.45	NR
SF6D Utility	-0.41	NR
EQ-5D Utility	-0.43	NR

NR: Non Relevant (Spearmans' rho <0.40)
All correlations presented are statistically significant (p-value<0.01)

Discussion

Principal findings

In search for the optimum outcome assessment 'toolkit' for evaluation of prophylaxis in patients with haemophilia the present multicentre study assessed the correlations between different outcome parameters. Our data showed that structured physical examination using the HJHS 2.1 had strong correlation with radiological scores, moderate correlation with physical domains of the SF36 and Utility values, but no correlation with self-reported bleeding or limitations in activities measured by the HAL questionnaire. In this population treated with early prophylaxis, self-reported bleeding was not associated with any of the outcome parameters collected, and the HAL was only correlated with a single SF36 domain. These results suggest that outcome assessment in patients on prophylaxis should not depend on self-reported bleeding only, but should include objective outcome assessment as well as self-reported limitations in activities and HRQoL.

Validity of the study

The present study included prospective standardised outcome assessment using validated outcome tools. Prior to this study, a standardisation exercise and reliability assessment was performed among the participating physiotherapists [12]; this is very important, as scoring variation between individual physiotherapists can be considerable [24]. HJHS 2.1 scores were derived from the raw data generating HJHS 1.0 scores; this conversion was possible and reliable because there were no patients with abnormalities in axial alignment and only two who scored positive on pain. Unfortunately, routine X-rays within 2.5 years of physical examination were only available in 40 Dutch patients. The present study included assessment of all ICF domains except participation. Participation was covered only indirectly with some items of the HAL and the domain of 'Social functioning' of the SF36. However, not all currently available haemophilia specific tools were used in this study. Especially for the interpretation of the HJHS 2.1 results, it would be interesting to include more sensitive imaging techniques, such as MRI and ultrasound. Likewise, haemophilia specific HRQoL questionnaires were not included; it could be expected that disease specific HRQoL would show more correlation with the HAL. The FISH (Functional Independence Scale for Haemophilia) is a validated tool that observes performance in walking and activities of daily living such as dressing and grooming. This tool was not included in the present study, as it,is relatively insensitive to early joint changes.

External validity of this study was limited by the study population, as it included only adults with severe haemophilia treated with early prophylaxis. However, it is this group that needs

careful monitoring for treatment adjustment and justification of treatment costs. As correlation coefficients are always low in data that lack variation, it is expected that correlations will be stronger when including patients with more prominent arthropathy.

Comparison with others

The results of the present study were corroborated by a recent report on correlations of objective outcome with annual joint bleeding in 38 children with severe haemophilia [25]. At a median age of 9 years, the HJHS showed moderate correlation with MRI and weak correlation with Pettersson scores; similar to our study, bleeding rates showed no correlations with other outcome parameters. The lack of correlation between HJHS and Pettersson scores is in contrast with our findings and may be explained by the young age of these patients. So far, most other studies reporting correlations of HJHS with other outcome parameters were HJHS validation studies. The study by Feldman et al in 226 children with haemophilia showed moderate correlation with life-time bleeding and physicians' joint assessment, but no correlation with self-reported outcome assessed by the modified Child-Health Assessment Questionnaire (C-HAQ) [11]. The lack of correlation between HJHS and activities was corroborated by a more detailed analysis in the same patients [26]. The HAL however, did correlate with measures of joint function in patients with more advanced arthropathy; in Rumanian children pedHAL showed strong correlation with HJHS (-0.59) and moderate correlation with the domain of physical functioning of CHQ-50(0.40), but not with its mental domains [27]. The SF36 was used in a large European study reporting on 1033 patients with a mean age of 36 years. It showed that the physical domains of the SF36 can discriminate between haemophilia patients and healthy controls, as well as between adult patients on prophylaxis and patients treated on demand [28]. However, an earlier comparison [29] and the present study show that these domains can not discriminate between different prophylactic regimens. A similar correlation of SF36 'Physical functioning' with the HJHS (-0.66) was published for a subgroup (n=22) of the present population [12]. Data on Utility values in haemophilia are limited in number, with only one study reporting on SF6D Utilities in 71 Belgian patients, and the rest using the EQ-5D. Again, only large differences [30,31] between patient groups could be detected by this self-reported instrument [9].

Clinical relevance & future research

This study shows that bleeding rates in patients on prophylaxis do not correlate with any of the objective and other self-reported outcome parameters, and that a deterioration in objec-

tive outcome does not immediately translate into self-reported limitations in activities or loss of HRQoL. It also shows good construct validity of the, originally paediatric, HJHS score in young adults and further strengthens the assumption that this tool, can be used after childhood. When considering outcome tools, their ability to discriminate between different patient groups should be evaluated. The original study generating these data showed that HJHS, bleeding rates, and HAL could discriminate between two prophylactic regimens, but the SF36, SF6D and EQ-5D could not [9]. The lack of correlation of the HRQoL measures with objective outcome may be due to a non-linear association; it is expected that HRQoL will only deteriorate after reaching a certain threshold of joint damage and/or loss of function. As there is no golden standard available, this study cannot address the issue of sensitivity and specificity of the outcome tools used in this study, nor whether one can replace the other. Outcome assessment is also heavily dependent on the population studied: the presence of significant arthopathy and/or the use of prophylaxis should be considered when choosing outcome assessment tools [32]. However in the case of early prophylaxis, it is clear that all aspects of the ICF should be addressed, and that objective and self-reported outcome should always be combined. Presenting objective outcome only would result in underrepresentation of the patient perspective, but could detect small differences in joint health. Presenting self-reported outcome only could lead to misleading results, as only large differences in joint health can be detected [32,33].

How about adding new outcome tools? MRI is very sensitive and will be able to detect the earliest joint changes even before the onset of any clinical symptoms. However, this modality is expensive and time consuming, and will therefore not be available for all patients. In this context, ultrasound may be a more accessible alternative. When considering the ICF, formal assessment of participation is lacking in the present study. This was partly covered by the HAL, which includes many aspects of participation, and showed a strong relation with participation in a previous study [34].

In conclusion, this study showed that structured physical examination using HJHS had strong correlation with radiological joint changes and physical domains of HRQoL. Self-reported bleeding did not correlate with any other outcome parameter, and self-reported activities only correlated with HRQoL. Therefore, outcome assessment in patients on prophylaxis should not depend on self-reported bleeding only, but should include objective joint assessment as well as assessment of activities and health related quality of life.

Acknowledgements

The authors want to thank the physiotherapists of the treatment centres in Utrecht, Stockholm and Malmö for joint assessment, and Wouter Foppen for scoring of X-rays.

Data used for the present study were collected in a study funded by a Bayer Haemophilia Award (special project, 2005). The input of AN was sponsored by an unrestricted grant from NovoNordisk.

References

1. Ahlberg A. Haemophilia in Sweden VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. *Acta Orthop Scand* 1965; **77** (suppl): 5–99.
2. 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.
3. Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. *J Bone Jt Surg* 1977; **59**: 287–305.
4. Pettersson H, Nilsson IM, Hedner U, Norehn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatr Scand* 1981; **70**: 565–70.
5. Gilbert MS. Prophylaxis: musculoskeletal evaluation. *Semin Hematol* 1993; **30**: 3–6.
6. WHO. The International Classification of Functioning, Disability and Health. *World Heal Organ* 2001; **18**: 237.
7. De Moerloose P, Fischer K, Lambert T, Windyga J, Batorova A, Lavigne-Lissalde G et al. Recommendations for assessment, monitoring and follow-up of patients with haemophilia. *Haemophilia* 2012 ; **18**: 319–25.
8. Nicholson A, Berger K, Bohn R, Carcao M, Fischer K, Gringeri A et al. Recommendations for reporting economic evaluations of haemophilia prophylaxis: a nominal groups consensus statement on behalf of the Economics Expert Working Group of The International Prophylaxis Study Group. *Haemophilia* 2008; **14**: 127–32.
9. Fischer K, Steen Carlsson K, Petrini P, Holmström M, Ljung R, Van den Berg HM et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood* 2013; **122**: 1129–36.
10. Hilliard P, Funk S, Zourikian N, Bergstrom BM, Bradley CS, McLimont M et al. Hemophilia joint health score reliability study. *Haemophilia* 2006; **12**: 518–25.
11. Feldman BM, Funk SM, Bergstrom B-M, Zourikian N, Hilliard P, Van der Net J et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res* 2011; **63**: 223–30.
12. Fischer K, De Kleijn P. Using the hemophilia joint health score (HJHS) in adult patients: Testing inter-rater reliability. *Haemophilia* 2012; **18**: 116.
13. Soucie JM, Wang C, Forsyth A, Funk S, Denny M, Roach KE et al. Range of motion measurements: reference values and a database for comparison studies. *Haemophilia* 2011; **17**: 500–7.
14. Pettersson H, Aledort LM, Bergman G, Gilbert MS, Savidge GF, Mannucci PM. Radiographic scores and implications. *Semin Hematol* 1993; **30**: 7–11.
15. Van Genderen FR, Van Meeteren NLU, Van der Bom JG, Heijnen L, De Kleijn P, Van den Berg HM et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia*

2004; **10**: 565–71.

16. Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van Den Berg HM, Helders PJM et al. Measuring patients' perceptions on their functional abilities: Validation of the Haemophilia Activities List. *Haemophilia* 2006; **12**: 36–46.
17. Brodin E, Baghaei F, Elfvinger P, Lindvall K, Sunnerhagen KS. The Swedish version of the Haemophilia Activity List. *Haemophilia* 2011; **17**: 662–8.
18. Ware JE, Sherbourne CD. The MOS 36-item short form health survey (SF36). Conceptual framework and item selection. *Med Care* 1992; **30**: 473–83.
19. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.
20. Ware JE, Kosinski M, Gandek B. SF-36 physical and mental summary scales; a user's manual. Boston: New England Medical Center; 1993.
21. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol* 1998; **51**: 1115–28.
22. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, Van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *NedTijdschrGeneeskd* 2005; **149**: 1574–8.
23. Swinscow TDV. Statistics at square one. 9th editio. Campbell MJ, editors. London: BMJ Publishing Group; 1997.
24. Nijdam A, Bladen M, Hubert N, Pettersson M, Bartels B, Van der Net J et al. Using routine Haemophilia Joint Health Score for international comparisons of haemophilia outcome: standardization is needed. *Haemophilia* 2015; doi: 10.1111/hae.12755. [Epub ahead of print]
25. Oymak Y, Yildirim AT, Yaman Y, Gurcinar M, Firat A, Cubuckcu D et al. The effectiveness of tools for monitoring hemophilic arthropathy. *J Pediatr Hematol Oncol* 2015; **37**: e80–5.
26. Groen W, Van der Net J, Bos K, Abad A, Bergstrom BM, Blanchette VS et al. Joint health and functional ability in children with haemophilia who receive intensive replacement therapy. *Haemophilia* 2011; **17**: 783–90.
27. Groen W, Van der Net J, Lacatusu AM, Serban M, Helders PJM, Fischer K. Functional limitations in Romanian children with haemophilia: further testing of psychometric properties of the Paediatric Haemophilia Activities List. *Haemophilia* 2013; **19**: e116–25.
28. Royal S, Schramm W, Berntorp E, Giangrande P, Gringeri A, Ludlam C et al. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia* 2002; **8**: 44–50.
29. Fischer K, Astermark J, Van der Bom JG, Ljung R, Berntorp E, Grobbee DE et al. Prophylactic treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia* 2002; **8**: 753–60.
30. Schramm W, Royal S, Kroner B, Berntorp E, Giangrande P, Ludlam C et al. Clinical outcomes and resource utilization associated with haemophilia care in Europe. *Haemophilia* 2002; **8**: 33–43.
31. O'Mahony B, Noone D, Giangrande PL, Prihodova L. Haemophilia care in Europe: a survey of 19 countries. *Haemophilia* 2011; **17**: 35–40.
32. Van den Berg HM, Feldman BM, Fischer K, Blanchette V, Poonnoose P, Srivastava A. Assessments of outcome in haemophilia - what is the added value of QoL tools? *Haemophilia* 2015 ; **21**: 430–5.
33. Buchbinder D, Ragni M V. What is the role of prophylaxis in the improvement of health-related quality of life of patients with hemophilia? *Hematology Am Soc Hematol Educ Program* 2013; **2013**: 52–5.

34. Van Genderen FR, Van Meeteren NLU, Fischer K, Helders PJM. Determinants of participation in patients with severe haemophilia. *Haemophilia* 2012; **18**: 860–7.

CHAPTER 8

General discussion

Clotting factor replacement therapy for patients with severe haemophilia has moved from on-demand treatment (at the time of clinically evident bleeding) to prophylaxis (regular and continuous treatment to prevent bleeding) in countries with the necessary resources [1]. One of the most clinically relevant outcomes is haemophilic arthropathy, caused by bleeding into joints. Prophylaxis prevents or postpones the development of arthropathy [2] and is therefore indicated in all patients with severe haemophilia. However, keeping up regular intravenous treatment is very costly and poses a heavy burden on some patients. Modern haemophilia care is trying to balance the burden of treatment and optimal joint health.

As haemophilia is a rare disease, research aimed at improving treatment is complicated by the small numbers of patients available. In patients on prophylaxis arthropathy takes years to develop, which further complicates research. Many studies use easy-to-collect, short-term outcome measures (e.g. patient-reported bleeding frequencies), therefore treatment guidelines in haemophilia are often based on limited evidence. The aim of this thesis was to improve prophylactic treatment by assessing changes in clinical practice of prophylaxis and their consequences on long-term outcome in patients who started prophylaxis in early childhood.

Regarding the question when to initiate prophylaxis, we demonstrated that the number of joint bleeds before starting prophylaxis provides best guidance in starting early prophylaxis. Starting after at most one joint bleed resulted in better long-term outcome compared to starting later, but we could not differentiate between starting before or after the first joint bleed.

Regarding the question which initial prophylactic regimen is best, we identified three different initial regimens, depending on frequency at start of prophylaxis (1-2 vs. ≥3x/week infusions) and age at reaching ≥3x/week (before vs. after age three years). Small differences were demonstrated in short-term outcome, but differences in long-term outcome could not yet be determined.

Regarding the question whether or not to discontinue prophylaxis in (young) adults, we showed that after switching to on-demand treatment patient-reported outcome remained favourable, while objectively assessed joint health worsened. These results support continuation of long-term prophylaxis in adults and demonstrate the need for objective tools in monitoring joint health.

Outcome assessment

Response shift

Living with chronic disease and subsequent disability is a process of change and adjustment. Patient-reported limitations in activities and health related quality of life (HRQoL) are likely to

be affected by the so called 'response shift' bias [3]: a process in which a patient adapts his (or her) internal assessment of quality of life and disability to his/her changing health [4]. Haemophilia patients might do the same and therefore report similar self-reported limitations in activities and HRQoL, despite worse objective joint outcomes. Studies on chronic diseases using patient-reported questionnaires, such as those used in this thesis (Haemophilia Activities List [5, 6], SF36 [7] and EuroQol (EQ-5D) [8]), should always take response-shift into account when interpretating results from different groups.

Response time

Outcome measures have different response times, i.e. time between an event and the measurable effect on outcome. In patients on prophylaxis, the effects of bleeding will result in detectable arthropathy only years later; joint damage takes time to develop and even more time to be picked up by the currently used tools (Haemophilia Joint Health Score (HJHS), radiological Pettersson score). Subsequent limitations in activities become apparent even later and might suffer from reporting bias and response shift. Other patient-reported measures (e.g. Quality of Life) are also influenced by social circumstances, a patient's ability to cope with the daily impact of haemophilia [9, 10] and co-morbidities [11, 12]. This, however, is outside the scope of this thesis.

The different response times may explain why this thesis (chapter 6 and 7) and other studies [13–15] show that bleeding is at most moderately correlated with other outcome measures. Other possible reasons include reporting bias, misclassification of joint bleeds, subclinical bleeding and/or lack of variation in bleeding rates in patients on early prophylaxis.

The response time of arthropathy depends on the setting. In a setting of (early) prophylaxis, arthropathy is postponed and as a consequence, differences in arthropathy will only surface years later. Figures 1 and 2 in chapter 5 (differences in age and number of joint bleeds at starting prophylaxis) and figure 2 in chapter 6 (stopping vs. continuing prophylaxis in young adults) illustrate that extended follow-up is needed to appreciate differences in arthropathy between treatment regimens. HJHS scores are still low in 11 years old patients treated with different early prophylactic regimens in chapter 4. Apart from the inter-observer bias, these patients may have been too young to detect possible differences in HJHS between the prophylactic regimens. In contrast, arthropathy is already prominent in young patients with severe haemophilia who have limited or no access to clotting factor products: ten year old Mexican children had already significantly decreased functional ability [16] and 19 year old Indian patients with severe haemophilia had a median Pettersson score of 18 [17].

Standardisation of measurement tools

In chapter 4, the comparison of the effects of different prophylactic regimens on joint status was hampered by large inter-observer bias on routinely collected HJHS. The HJHS is a validated tool that can very well be used to monitor patients' joint status over time and to compare patients within centres if scored by the same physiotherapist. However, the use of validated outcome measures alone is not enough to secure valid results. Studies that require more than one observer to measure objective outcome should ensure prior standardisation of outcome measurement, as well as report inter-observer agreement. Moreover, in treatment centres with more than one physiotherapist, HJHS assessments will have to be regularly calibrated to ensure reliable patient follow-up. This does not only apply to the use of the HJHS, but also to other objective outcome measures, such as the radiological Pettersson score [18, 19], MRI scores [20, 21], and the newly developed Haemophilia Early Arthropathy Detection with UltraSound (HEAD-US) [22]. Recently a consensus atlas was developed to facilitate uniform and reproducible scoring according to Pettersson [23]. The atlas contains reference X-rays of different stages of haemophilic arthropathy in elbows, knees, and ankles with descriptions of the corresponding Pettersson score items.

Future research & issues to be addressed in outcome assessment

If we want to optimise prophylaxis, we will have to detect small differences in arthropathy, ideally as soon as possible. Therefore future research on prophylactic treatment should focus on adequate outcome measurement. Conventional tools to assess haemophilic arthropathy (HJHS, Pettersson) are unable to detect early changes in joint health. In developed countries, more sensitive imaging techniques, such as MRI, can be used to detect early soft-tissue changes such as haemosiderin deposition and synovial hypertrophy. MRI detects more abnormalities than conventional X-rays [21, 24–26], but the clinical importance of these findings remains unclear. Recently, synovial changes on MRI were shown to be associated with a significantly higher rate of joint bleeds and changes on X-rays 5 years later [27]. Unfortunately, the costly and cumbersome nature of MRI assessment prevents large-scale application in clinical practice.

Ultrasound is less expensive and a viable alternative in the clinic, but still very much in development. In the hands of experienced radiologists using a standardized protocol, it was shown to be a reliable tool for assessing soft-tissue abnormalities in joints of haemophilia patients. On the other hand, it had variable diagnostic accuracy for assessment of osteochondral changes [28]. Designed for non-expert users, the relatively simple and fast ultrasound protocol HEAD-US [22] was capable of detecting early joint changes [29, 30]. Recently, validity

and inter-operator reliability of the HEAD-US score were shown to be good (intraclass correlation coefficient 0.72) [31]. This makes HEAD-US a promising tool for routine joint assessments in clinical practice.

Starting early prophylaxis

Chapter 5 shows that the number of joint bleeds before starting prophylaxis provides best guidance in starting early prophylaxis and suggests that starting before the onset of joint bleeding resulted in the best long-term outcome. However, in clinical practice starting before joint bleeding is not always possible, especially in patients with a negative family history of haemophilia who present with joint bleeding. Moreover, the time of the first joint bleed is quite variable: median age 1.7 years, IQR 1.0-2.8. This implies that 25% of patients with a less severe bleeding phenotype will have the first joint bleed only after age 2.8 years and suffer the unnecessary burden of difficult venous access in starting prophylaxis at a very young age. This makes allowing one joint bleed before starting prophylaxis an attractive alternative. Our results suggest that this may yield acceptable long-term outcome as well. However, these conclusions are based on a small number of patients only. As the trend to start prophylaxis earlier and after fewer joint bleeds continues, it may be feasible conduct a similar study in 5-10 years' time, when more children starting prophylaxis after no or a limited number of joint bleeds can be included.

When comparing regimens starting prophylaxis with 1-2 weekly infusions, the question whether differences in short-term outcome translate to long-term outcome differences remains unanswered (chapter 4). Such a comparison requires repeated and detailed outcome assessment, and HJHS assessments can only be used after standardisation. However, this standardisation is a distant prospect that requires regular training sessions to calibrate scoring between the different physiotherapists. Recently, a strong correlation (Spearman's correlation coefficient 0.70, $P < 0.01$) between HJHS scores and the ultrasound HEAD-US score was demonstrated [29]. If this is confirmed in other settings and/or patient groups, ultrasound examination could provide a viable alternative for routine assessment of arthropathy in future clinical practice. Until then, a standardised assessment of X-rays may be able fill this gap [23], even though these exams are usually taken at longer intervals.

Stopping early prophylaxis

In chapter 6, a comparison of patients who discontinued early prophylaxis in adulthood with those who continued, showed similar patient-reported joint bleeding but increased arthropa-

thy in patients who stopped prophylaxis. This difference in objective outcome is in contrast with earlier studies suggesting that those who discontinue early prophylaxis while maintaining a low bleeding rate represent patients with a milder bleeding phenotype [32]. Nor does it corroborate the higher bleeding frequency of patients who switched to on-demand treatment in the TEEN/TWEN study [33]. However, this study population is not comparable to ours, as patients on early prophylaxis were not included. In our study, the discrepancy between patient-reported and objectively measured outcome could be caused by reporting bias, if patients who stop prophylaxis (un)consciously underreport bleeding. Assessment of underreporting is very difficult and may be a major limitation of this study. Schrijvers et al. showed that motivators for a high adherence to prophylaxis in haemophilia patients are, among others, experiencing symptoms and a positive belief of necessity of treatment [10, 34]. If patients who switched to on-demand treatment really experience few bleeds and functional limitations, this might be part of the explanation why they are not motivated to continue prophylaxis.

Alternatively, the reported low joint bleeding frequencies might be due to misclassification of joint bleeds. Timmer et al. showed that it is difficult to differentiate between a joint bleed and (flare-ups of) haemophilic arthropathy in adult patients due to overlapping symptoms [35]. Another report showed that patient-perceived aetiology of joint pain was correct in only approximately one third of the episodes in adults with established arthropathy [36]. Even though misclassification may have occurred, we feel that our study population had less severe arthropathy and is therefore less likely to misclassify joint bleeds as arthropathy flare-ups.

The occurrence of subclinical bleeding in patients treated on-demand is a possible explanation of worse arthropathy in patients treated on-demand. There is increasing, yet inconclusive evidence for subclinical bleeding into joints from studies using very sensitive MRI joint scores [13]. Some studies showed joint damage in 19%-38% of clinically bleed-free joints [14, 15, 37], while another study did not corroborate occult bleeding into joints [26]. As of yet, subclinical joint bleeding warrants further research using MRI or ultrasound to monitor early joint damage in clinically bleed-free joints; especially in the light of low frequency early prophylactic regimens that are more and more used to initiate prophylaxis in young children.

Patients who had stopped prophylaxis are expected to use clotting factor only to treat bleeds. At the Van Creveldkliniek, joint bleeds are treated with one or more infusions of 25-40 IU/kg, until bleeding stops. Patients in our study used 800 IU/kg/year, which translates to treating about 7-12 bleeds in an 80 kg adult patient who needs 3 infusions to resolve bleeding. This is much more than the low number of patient-reported bleeds would suggest: overall median 3.2 bleeds/year (unreported data), of which 1.5 joint bleeds/year. The clotting factor

use of our patients on on-demand treatment was in line with those reported in other studies [38, 39]. Danish patients who had switched to on-demand treatment were reported to adopt some form of prophylactic administration of clotting factor before engaging in activities with a higher risk of injury, such as sports activities or maintenance chores around the house [39]. Unfortunately, these data were not collected in our study. To fully explain the clotting factor consumption in patients who switched to on-demand treatment, the reasons of factor consumption these patients should be assessed.

Prophylaxis in the context of new treatment modalities

New treatment modalities, such as long-acting factor and gene therapy, are expected to profoundly change treatment for haemophilia. In the last five years, new bio-engineered long-acting FVIII and IX products (using pegylation or fusion to Fc/albumin) have been developed [40, 41]. This resulted in a 1.5-1.7-fold prolongation of half-life in clotting factor VIII and 3- to 5-fold in factor IX. Half-life extension could greatly reduce the burden of treatment by reducing the frequency of intravenous infusions in patients on prophylaxis. It would thereby facilitate the use of, and adherence to prophylaxis in adults who would otherwise switch to on-demand treatment. Moreover, it could facilitate the initiation of early prophylaxis in young children. In particularly in those with problematic venous access, subcutaneous or oral delivery as alternative routes of administration are suggested as a future possibility [42]. However, the extended half-life products still require life-long (intravenous) treatment and the benefits for patients using factor FVIII are still modest. Gene therapy has the potential to cure patients with haemophilia by transferring a normal copy of the defective gene. Although haemophilia A is more common, most gene therapy studies have focused on haemophilia B, as the gene encoding for FIX is relatively small and its expression pathway less complex than that of the FVIII gene. Recently, long-term (1.5 to 4.3 years) therapeutic levels of biologically active FIX were demonstrated in 10 patients with severe haemophilia B after a single administration of the FIX gene [43]. It is expected that with the current rate of progress, gene therapy for haemophilia B will be commercially available over the next decade [44].

Concluding remarks

Treatment for severe haemophilia has come a long way from the introduction of clotting factor products to prophylaxis, improving the life expectancy to approach that of the general population and allowing patients to lead a near-to-normal life. Nevertheless, there are still issues that need to be tackled, as treatment is very costly and adherence sometimes difficult.

The research in this thesis presents small but necessary steps towards optimising treatment for severe haemophilia patients.

When to start prophylaxis: Starting prophylaxis in early childhood, after at most one joint bleed, seemed to result in good conservation of joint health. More research is needed to differentiate between starting prophylaxis before joint bleeding and after one joint bleed.

How to start prophylaxis: Prophylaxis was increasingly started with low frequency infusions. The regimens to subsequently step up to the 'full' protection of three prophylactic infusions per week had different short-term outcomes, but it is not yet clear how these differences translate to long-term joint health. In the Van Creveldkliniek the more lenient regimen seems to yield good outcome. However in the light of possible subclinical bleeding, we should be careful not to focus on clinically evident bleeds only.

Stopping prophylaxis in young adults: In adult patients who discontinue prophylaxis, we should not be fooled by first impressions: we have demonstrated that favourable patient-reported outcome does not imply good joint health. Regardless the treatment regimen, joint health should be closely monitored by objective outcome measures. With the results in this thesis, the clinician can strengthen a patient's belief of necessity of prophylaxis by demonstrating the risks of on-demand treatment.

Finally we have shown that different outcome measures each tell a different part of the story, and that only combined the whole picture emerges. Especially in studies assessing the optimum prophylactic regimen, both short-term and long-term outcome, as well as objective and patient-reported outcome should be included.

References

1. Van Creveld S. Prophylaxis in haemophilia. *Lancet* 1971; **1**: 450.
2. Fischer K, Van Hout BA, Van der Bom JG, Grobbee DE, Van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta Radiol* 2002; **43**: 528–32.
3. Schwartz CE, Andresen EM, Nosek MA, Krahn GL. Response shift theory: important implications for measuring quality of life in people with disability. *Arch Phys Med Rehabil* 2007; **88**: 529–36.
4. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers M a G, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. *Qual Life Res* 2006; **15**: 1533–1550.
5. Van Genderen FR, Van Meeteren NLU, Van der Bom JG, Heijnen L, De Kleijn P, Van den Berg HM et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia* 2004; **10**: 565–71.
6. Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. *Haemophilia* 2006; **12**: 36–46.
7. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and

item selection. *Med Care* 1992; **30**: 473–83.

8. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.
9. Binnema M, Schrijvers LH, Bos R, Schuurmans MJ, Fischer K. Coping in adult patients with severe haemophilia. *Haemophilia* 2014; **20**: 513–8.
10. Schrijvers LH, Kars MC, Beijlevelt-van der Zande M, Peters M, Schuurmans MJ, Fischer K. Unravelling adherence to prophylaxis in haemophilia: a patients' perspective. *Haemophilia* 2015; **21**: 612-21.
11. Fransen van de Putte DE, Fischer K, Posthouwer D, Mauser-Bunschoten EP. The burden of HCV treatment in patients with inherited bleeding disorders. *Haemophilia* 2011; **17**: 791–9.
12. Fransen van de Putte DE, Fischer K, Posthouwer D, Van Erpecum K, Mauser-Bunschoten EP. Occurrence, course and risk factors of depression during antiviral treatment for chronic hepatitis C in patients with inherited bleeding disorders: a prospective study. *Haemophilia* 2009; **15**: 544–51.
13. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
14. Lundin B, Ljung R, Pettersson H, Siimens M, Tervahartiala P, Tusell J et al. MRI scores of ankle joints in children with haemophilia - Comparison with clinical data. *Haemophilia* 2005; **11**: 116–122.
15. Kraft J, Blanchette V, Babyn P. Magnetic resonance imaging and joint outcomes in boys with severe hemophilia A treated with tailored primary prophylaxis in Canada. *J Thromb Haemost* 2012; **10**: 2494–2502.
16. Tlacuilo-Parra A, Villela-Rodriguez J, Garibaldi-Covarrubias R, Soto-Padilla J, Orozco-Alcala J. Functional independence score in hemophilia: A cross-sectional study assessment of Mexican children. *Pediatr Blood Cancer* 2010; **54**: 394–397.
17. Fischer K, Van den Berg HM, Thomas R, Kumar S, Poonnoose P, Viswabandya A et al. Dose and outcome of care in haemophilia--how do we define cost-effectiveness? *Haemophilia* 2004; **10 Suppl 4**: 216–20.
18. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res* 1980; **149**: 153–9.
19. Pettersson H, Nilsson IM, Hedner U, Noréhn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatr Scand* 1981; **70**: 565–70.
20. Lundin B, Manco-Johnson ML, Ignas DM, Moineddin R, Blanchette VS, Dunn a. L et al. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. *Haemophilia* 2012; **18**: 962–970.
21. Kilcoyne RF, Lundin B, Pettersson H. Evolution of the imaging tests in hemophilia with emphasis on radiography and magnetic resonance imaging. *Acta Radiol* 2006; **47**: 287–96.
22. Martinoli C, Della Casa Alberighi O, Di Minno G, Graziano E, Molinari AC, Pasta G et al. Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). *Thromb Haemost* 2013; **109**: 1170–9.
23. Foppen W, van der Schaaf IC, Beek FJA, Verkooijen HM, Fischer K. Scoring haemophilic arthropathy on X-rays: improving inter- and intra-observer reliability and agreement using a consensus atlas. *Eur Radiol* 2015; Sep 24. [Epub ahead of print]
24. Lundin B, Pettersson H, Ljung R. A new magnetic resonance imaging scoring method for assessment of haemophilic arthropathy. *Haemophilia* 2004; **10**: 383–9.
25. Funk MB, Schmidt H, Becker S, Escuriola C, Klarmann D, Klingebiel T et al. Modified magnetic resonance imaging score compared with orthopaedic and radiological scores for the evaluation of haemophilic ar-

thropathy. *Haemophilia* 2002; **8**: 98–103.

26. Den Uijl IEM, De Schepper AMA, Camerlinck M, Grobbee DE, Fischer K. Magnetic resonance imaging in teenagers and young adults with limited haemophilic arthropathy: baseline results from a prospective study. *Haemophilia* 2011; **17**: 926–30.
27. Foppen W, Fischer K. Prognostic value of MRI synovial changes in haemophilia patients: preliminary results. *Haemophilia*. 2015; **21 Suppl 2**: 41-2.
28. Doria AS, Keshava SN, Mohanta A, Jarrin J, Blanchette V, Srivastava A et al. Diagnostic Accuracy of Ultrasound for Assessment of Hemophilic Arthropathy: MRI Correlation. *Am J Roentgenol* 2015; **204**: W336–W347.
29. Foppen W, Van der Schaaf IC, Fischer K. Value of routine ultrasound in detecting early joint changes in children with haemophilia using the "Haemophilia Early Arthropathy Detection with UltraSound" protocol. *Haemophilia* 2015; doi: 10.1111/hae.12769. [Epub ahead of print]
30. Altisent C, Martorell M, Crespo A, Casas L, Torrents C, Parra R. Early prophylaxis in children with severe haemophilia A: clinical and ultrasound imaging outcomes. *Haemophilia* 2015; doi: 10.1111/hae.12792. [Epub ahead of print]
31. Fischer K, Oldenburg J, Astermark J, Dolan G, Morfini M, Marquardt N et al. Ultrasound evaluation of haemophilic joints by haemophilia physicians: a reliability study. *J Thromb Haemost* 2015; **13**: 601.
32. Fischer K, Van der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE et al. Discontinuation of prophylactic therapy in severe haemophilia: Incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–550.
33. Manco-Johnson MJ, Sanders J, Ewing N, Rodriguez N, Tarantino M, Humphries T. Consequences of switching from prophylactic treatment to on-demand treatment in late teens and early adults with severe haemophilia A: The TEEN/TWEN study. *Haemophilia* 2013; **19**: 727–735.
34. Schrijvers LH, Uitslager N, Schuurmans MJ, Fischer K. Barriers and motivators of adherence to prophylactic treatment in haemophilia: A systematic review. *Haemophilia* 2013; **19**: 355–361.
35. Timmer MA, Pisters MF, De Kleijn P, De Bie RA, Fischer K, Schutgens RE. Differentiating between signs of intra-articular joint bleeding and chronic arthropathy in haemophilia: a narrative review of the literature. *Haemophilia* 2015; **21**: 289–96.
36. Ceponis A, Wong-Sefidan I, Glass CS, Von Drygalski A. Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients. *Haemophilia* 2013; **19**: 790–8.
37. Olivieri M, Kurnik K, Pfluger T, Bidlingmaier C. Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis. *Haemophilia* 2012; **18**: 369–374.
38. Schramm W, Royal S, Kroner B, Berntorp E, Giangrande P, Ludlam C et al. Clinical outcomes and resource utilization associated with haemophilia care in Europe. *Haemophilia* 2002; **8**: 33–43.
39. 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**: 107–112.
40. Carcao M. Changing paradigm of prophylaxis with longer acting factor concentrates. *Haemophilia* 2014; **20 Suppl 4**: 99–105.
41. Pipe SW. The hope and reality of long-acting hemophilia products. *Am J Hematol* 2012; **87 Suppl 1**: S33–9.
42. Carr ME. Future directions in hemostasis: normalizing the lives of patients with hemophilia. *Thromb Res* 2010; **125 Suppl 1**: S78–81.

43. Nathwani AC, Reiss UM, Tuddenham EGD, Rosales C, Chowdary P, McIntosh J et al. Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B. *N Engl J Med* 2014; **371**: 1994–2004.
44. Lheriteau E, Davidoff AM, Nathwani AC. Haemophilia gene therapy: Progress and challenges. *Blood Rev* 2015; **29**: 321-8.

Summary

Clotting factor replacement therapy for patients with severe haemophilia has moved from on-demand treatment (at the time of clinically evident bleeding) to prophylaxis (regular and continuous treatment to prevent bleeding) in countries with the necessary resources [1]. Keeping up this regular treatment is very costly and poses a heavy burden on some patients, because the route of administration is intravenous. Treatment decisions are driven by navigating between the burden of treatment and risk of arthropathy, both for haemophilia health care providers as well as patients.

The aim of this thesis was to improve prophylactic treatment by assessing changes in clinical practice of prophylaxis and their consequences on long-term outcome in patients who started prophylaxis in early childhood. We focussed on two critical points in prophylactic treatment: starting prophylaxis in early childhood and stopping prophylaxis in young adults.

Early initiation of prophylaxis is critical for prevention of arthropathy and can be initiated according to age or bleeding. In clinical practice, venous access in young children is challenging. Initiating prophylaxis in young children can be facilitated using less frequent infusions and/or central venous access devices (CVADs). **Chapter 2** describes when prophylaxis was started over time and how this affected bleeding before prophylaxis and strategies for initiating prophylaxis. In this multicentre longitudinal observational cohort study, data were extracted from the "European Paediatric Network for Haemophilia Management" (PedNet) registry. 919 children with severe haemophilia A (FVIII<1IU/ml), born between 1990 and 2009, were followed until the 50th treatment day or inhibitor development. Trends were analysed across four birth cohorts: 1990-1994, 1995-1999, 2000-2004, 2005-2009. Over time, less bleeding was accepted before initiating prophylaxis: the proportion of patients starting before any joint bleeding increased from 29% to 43% (P=0.06) and the proportion starting before the third joint bleed increased from 65% to 85% (P<0.01). Moreover, the use of primary prophylaxis as defined by the WFH (starting before three years of age and the second joint bleed) increased from 35% to 70% (P<0.01). Concurrently, prophylaxis was increasingly started with once weekly infusions (from 18% to 59%; P<0.01), while the use of CVADs remained stable around 40%. The two trends, starting prophylaxis earlier and starting with once weekly infusions, likely balanced out and caused the stable use of CVADs. In conclusion, since 1990 prophylaxis was started earlier and after fewer bleeds, facilitated by using low frequency regimens and CVADs.

The trend to start prophylaxis 1x/week and step up to the 'full' protection of 3x/week infusions later, may affect outcome. In **chapter 3** early prophylactic regimens were studied in

21 centres from the PedNet registry. Data on 363 patients (severe haemophilia A, without inhibitors, born between 2000 and 2012, receiving prophylaxis) were studied. Treatment centres were classified according to the initial frequency of prophylactic infusions and the age at reaching three or more infusions per week. Outcome was compared at age four years. Three early prophylactic regimens were identified:

1. start prophylaxis with ≥3x/week infusions before age three (full: 19% of centres, 18% of patients);
2. start 1-2x/week, increasing frequency as soon as possible (asap), reaching ≥3x/week before age three (43% of centres, 36% of patients);
3. start 1-2x/week, increasing frequency according to bleeding (phenotype), reaching ≥3x/week after age three (38% of centres, 46% of patients).

Prophylaxis was started earlier on the full and asap regimens: at median age 1.2 years vs. 1.8 years on the phenotype regimen. Complete prevention of joint bleeds at four years of age was most effective on the full regimen (32% full vs. 27% asap and 8% phenotype), though at the cost of using most CVADs (88% full vs. 34% asap and 22% phenotype). The phenotype regimen resulted in about 50% reduction of infusions and clotting factor consumption, but also two additional joint bleeds by the age of four years. To identify the optimum prophylactic regimen more information on the long-term outcome of different regimens, including the risk of additional early joint bleeding, is needed.

The Haemophilia Joint Health Score (HJHS) is the most sensitive validated score for physical examination of joint health in haemophilia available today. Higher HJHS indicates more joint damage. HJHS performed at regular intervals can be used for clinical monitoring as well as for comparative outcomes research. **Chapter 4** assesses whether routinely collected HJHS can be used to compare outcome of different early prophylactic regimens and which parameters caused variability in HJHS. In this international observational multi-centre study, patient and treatment data were collected from the PedNet registry and patient files on 127 children with severe haemophilia A, born between 1995 and 2009, from London, Stockholm and Utrecht centres. The independent effects of regimen, physiotherapist, age and inhibitor status on HJHS were explored. Prophylactic regimens varied across the participating centres, with differences in initial frequency of infusions (1x/week vs. 3x/week), age at reaching infusions ≥3x/week, and weekly prophylactic dose at HJHS assessment. The HJHS increased with age and history of inhibitor, as expected. However, evaluation at a median age of 11 years showed an illogical association of HJHS with treatment regimen: the least intensive regimen had the lowest HJHS.

Multivariable regression analysis showed that the comparison of prophylactic regimens was obscured by systematic differences in assessment between physiotherapists, both within and between centres. We conclude that, for multi-centre research, additional inter-observer standardization for HJHS scoring is needed.

Chapter 5 assesses how age at starting prophylaxis and joint bleeding before prophylaxis affects long-term joint health. 124 patients with severe haemophilia (FVIII/IX <0.01 IU/ml), born between 1965 and 2000, were evaluated at median age 22 years for haemophilic arthropathy on X-rays using the Pettersson score. Outcome analyses were adjusted for age at evaluation The results showed that the number of joint bleeds before prophylaxis had the strongest association with radiologically evident arthropathy. Arthropathy increased according to increasing number of joint bleeds before starting prophylaxis. Starting before the onset of joint bleeding resulted in the best long-term outcome, while starting after one joint bleed still appeared to have acceptable long-term outcome. However, only 12 patients had started prophylaxis before any joint bleeding and 10 patients had started after one joint bleed; caution is warranted in drawing strong conclusions based on such small groups. Patients starting prophylaxis before age six years scored significantly better than patients who started later (P<0.01), but no additional benefit of starting before age three years was demonstrated. Future research with more patients on early prophylaxis will have to clarify whether starting prophylaxis before joint bleeding is superior to starting after one joint bleed.

Prophylaxis is the recommended treatment for children with severe haemophilia A, but whether prophylaxis should be continued in adulthood is still under debate. In a setting of starting prophylaxis in early childhood, up to 35% of young adults have been reported to discontinue prophylaxis while maintaining low bleeding rates and good joint health after four years of on demand treatment. **Chapter 6** assesses the long-term consequences of discontinuing prophylaxis in a single-centre cohort of patients with severe haemophilia A without inhibitors, born between 1970 and 1988. Patient-initiated changes in prophylaxis were recorded from the time of starting self-infusion until last evaluation, including all switches to on demand treatment for a minimum of two consecutive weeks. 66 Patients were evaluated at median 32.4 years: 26% of patients had stopped prophylaxis for a median of 10 years, 15% had interrupted prophylaxis and 59% had continued prophylaxis. Annual joint bleeding rate (AJBR), HJHS (0-124 points), radiological Pettersson score (0-78 points) and Haemophilia Activities List (HAL; 100-0 points) were compared for patients who stopped and patients who continued prophylaxis. Although

self-reported bleeding rates and functional limitations were similar in both groups (AJBR: 1.5 vs. 1.2; HAL: 84 vs. 84), arthropathy on objective outcome assessment was worse after 10 years of on demand treatment in patients who stopped prophylaxis (HJHS: 23 vs. 14; Pettersson: 16 vs. 5; P<0.01). These results support continuation of long-term prophylaxis in adults and demonstrate the need for objective tools in monitoring joint status.

Routine outcome assessment of prophylaxis should use validated tools, while balancing comprehensiveness and burden. To support choosing the best set of tools, in **chapter 7** correlations between different outcome assessment tools in haemophilia were assessed in data from an international cross-sectional study. Spearman's correlation coefficients were calculated between objective outcome (HJHS, radiological Pettersson score) and self-reported outcome (joint bleeding, HAL, health related quality of life (SF36), and Utility (SF6D and EQ-5D)): ≥0.8 very strong, 0.60-0.79 strong, 0.40-0.59 moderate, and 0.20-0.39 weak. In 90 patients with severe haemophilia, on prophylaxis since median age 3.4 years, objective outcome was favourable (median scores: HJHS 6, Pettersson 9) at median age of 25.5 years. Self-reported outcome showed a median of 7 joint bleeds in the last 5 years, few functional limitations (median HAL score 96), high scores on physical domains of SF36 (median 80-95), as well as Utility values (median 0.87 for SF6D and 0.84 for EQ-5D). HJHS scores showed a strong correlation with radiological Pettersson scores, moderate correlation with physical domains of the SF36 and Utility, but no correlation with self-reported bleeding or limitations in activities (HAL). Bleeding was not associated with any of the outcome parameters, and the HAL was only correlated with the SF36 'Physical functioning' domain. These results demonstrate that outcome assessment in patients on prophylaxis should not depend on self-reported bleeding only, but should include objective outcome assessment as well as self-reported limitations in activities and quality of life.

In **chapter 8** several aspects of outcome assessment, starting and stopping early prophylaxis and new treatment modalities are reviewed in a broad context. It provides a general discussion on the findings presented in this thesis, including suggestions for future research.

Samenvatting

Inleiding

Hemofilie is een zeldzame erfelijke bloedstollingsstoornis waarbij de aanmaak van functionerend stollingsfactor verminderd of afwezig is. Patiënten met hemofilie A hebben een gebrek aan factor VIII (FVIII), terwijl patiënten met hemofilie B een gebrek aan factor IX (FIX) hebben. Hierdoor kunnen spontane of trauma-gerelateerde bloedingen optreden. De ernst van de bloedingen hangt af van het percentage resterende stollingsfactor, ten opzichte van de normale hoeveelheid: hemofilie wordt daarom geclassificeerd als ernstig (minder dan 1%), matig (1-5%) en mild (meer dan 5%). Bij patiënten met ernstige hemofilie treden bloedingen vaker op en zijn ze ernstiger, terwijl de meeste patiënten met matige hemofilie zelden spontane bloedingen ondervinden. Bloedingen komen het meest voor in de enkels, knieën en ellebogen, en dienen zo snel mogelijk behandeld te worden met intraveneuze toediening van stollingsfactor. Wanneer (recidiverende) gewrichtsbloedingen niet of niet tijdig behandeld worden, kan onherstelbare gewrichtsschade, oftewel hemofilie-artropathie, ontstaan.

Toen in 1965 kwamen stollingsproducten beschikbaar kwamen, werden patiënten “on-demand” behandeld: dat wil zeggen alleen bij een bloeding. In de jaren 1970 kwamen stollingsproducten in Nederland op grotere schaal beschikbaar. Hierdoor konden hemofiliepatiënten profylactisch worden behandeld door regelmatige infusie van stollingsfactor ter voorkoming van bloedingen. Profylaxe gaat gepaard met een hoger verbruik van stollingsproducten en is daardoor duurder. Bovendien worden de frequente intraveneuze infusies door sommige patiënten als belastend ervaren. Echter, het gebruik van profylaxe resulteert in beter behoud van de gezondheid van gewrichten dan on-demand behandeling; profylaxe wordt daarom aanbevolen bij patiënten met ernstige hemofilie. De huidige Nederlandse profylactische behandeling bestaat uit het 3-3,5 infusies FVIII per week bij ernstige hemofilie A en 1-2 infusies FIX per week bij ernstige hemofilie B. De ontwikkeling van zogenaamde remmers (antistoffen tegen FVIII/FIX die de functionele activiteit van het stollingsproduct verminderen) is een belangrijke complicatie van behandeling met stollingsproducten. Hierdoor is profylaxe minder of niet effectief. Patiënten die (in het verleden) een remmer hebben ontwikkeld worden daarom van onderzoek naar de effectiviteit van profylaxe uitgesloten.

In de praktijk navigeren zowel hemofiliebehandelaars als hemofiliepatiënten tussen de belasting van behandeling en het risico op artropathie. In dit proefschrift wordt onderzocht hoe profylactische behandeling in de loop van de tijd is veranderd en hoe dit de gezondheid van patiënten op lange-termijn heeft beïnvloed. Hierbij richtten we ons op twee cruciale punten in de profylactische behandeling: de start van profylaxe in de vroege kinderjaren en het stoppen van profylaxe bij jongvolwassenen.

Profylaxe kan eenmaal ontwikkelde gewrichtsschade niet herstellen, maar het stabiliseert wel de progressie ervan. Het vroeg starten van profylaxe is daarom van cruciaal belang voor effectieve preventie van artropathie bij kinderen met ernstige hemofilie. Echter, in de praktijk kunnen frequente intraveneuze infusies in de kleine en fragiele aderen van jonge kinderen problematisch zijn. Het starten van profylaxe bij jonge kinderen kan worden vergemakkelijkt door minder frequente infusies (1-2 keer per week) en/of het gebruik van een centraalveneuze lijn (CVL) als alternatieve route van infusie. Helaas gaat de implantatie van een CVL gepaard met een operatie en het gebruik ervan met een aanzienlijk risico op infectieuze en trombotische complicaties. Vooralsnog is er nog geen overeenstemming over het optimale regime voor het van starten profylaxe bij jonge kinderen met ernstige hemofilie.

Hoofdstuk 2 beschrijft wanneer profylaxe in de loop van de tijd werd gestart en hoe dit het aantal doorgemaakte bloedingen voor het starten en de manier van starten heeft beïnvloed. In 919 kinderen met ernstige hemofilie A, geboren tussen 1990 en 2009, zonder remmerontwikkeling werden trends over vier geboortecohorten geanalyseerd: 1990-1994, 1995-1999, 2000-2004, 2005-2009. In de loop van de tijd werden steeds minder bloedingen voor de start van profylaxe geaccepteerd: het percentage patiënten dat profylaxe startte voor de eerste gewrichtsbloeding steeg van 29% naar 43% (P=0,06) en het percentage dat startte voor de derde gewrichtsbloeding steeg van 65% naar 85% (P<0,01). Bovendien is het starten voor de leeftijd van drie jaar en voor de tweede gewrichtsbloeding (primaire profylaxe zoals gedefinieerd door de World Federation of Hemophilia) gestegen van 35% naar 70% (P<0,01). Tegelijkertijd werd profylaxe steeds vaker gestart met één infusie per week (stijging van 18% naar 59%; P<0,01), terwijl het gebruik van CVL's stabiel bleef rond 40%. Het stabiele gebruik van CVL's is waarschijnlijk veroorzaakt doordat het eerder starten van profylaxe vergemakkelijkt werd door het starten met één infusie per week.

Het is nog onduidelijk hoe de trend om profylaxe met één infusie per week te starten en pas later te verhogen naar de 'volledige' bescherming van drie infusies per week, de gezondheid van de gewrichten beïnvloedt. In **hoofdstuk 3** werd de manier van starten van profylaxe onderzocht in 21 internationale hemofiliebehandelcentra, met 363 patiënten (ernstige hemofilie A, zonder remmerontwikkeling, geboren tussen 2000 en 2012, behandeld met profylaxe). Behandelingscentra werden geclassificeerd naar gelang de meest gebruikte infusiefrequentie bij het starten van profylaxe en de leeftijd waarop werd overgestapt naar drie of meer profylactische infusies per week. Drie verschillende regimes werden geïdentificeerd:

1. starten met ten minste drie infusies per week vóór de leeftijd van drie jaar (volledig: 19% van de centra, 18% van de patiënten);
2. starten met één tot twee infusies per week, en zo spoedig mogelijk verhogen van infusiefrequentie (z.s.m.), tot minimaal drie infusies per week vóór de leeftijd van drie jaar (43% van de centra, 36% van de patiënten);
3. starten met één tot twee infusies per week, en verhogen van infusiefrequentie op geleide van bloedingen (fenotype), tot minimaal drie infusies per week na de leeftijd van drie jaar (38% van de centra, 46% van de patiënten).

Profylaxe werd eerder gestart in de 'volledig' en 'z.s.m.' regimes: op een mediane leeftijd van 1,2 jaar, vs. 1,8 jaar op het 'fenotype' regime. Het 'volledig' regime was het meest effectief in de preventie van gewrichtsbloedingen op de leeftijd van vier jaar (32% zonder gewrichtsbloedingen bij 'volledig' vs. 27% 'z.s.m.' en 8% 'fenotype'), maar ten koste van CVL-gebruik (88% 'volledig' vs. 34% 'z.s.m.' en 22% fenotype). Daarnaast werden op het 'fenotype' regime ongeveer 50% minder infusies en stollingsfactor consumptie gebruikt, maar ten koste van twee extra gewrichtsbloedingen op de leeftijd van vier jaar. Om te bepalen of deze gewrichtsbloedingen zich vertalen naar meer gewrichtsschade op latere leeftijd, is onderzoek nodig naar de lange-termijn gevolgen van de verschillende regimes.

De Haemophilia Joint Health Score (HJHS) is op dit moment de meest gevoelige gevalideerde score voor de evaluatie van gewrichtsgezondheid bij patiënten met hemofilie, op basis van lichamelijk onderzoek door een fysiotherapeut. Een hogere score is een aanwijzing voor meer gewrichtsschade. Wanneer de HJHS met regelmatige tussenpozen wordt afgenomen, kan de score worden gebruikt voor het monitoren van gewrichtsgezondheid in de kliniek en voor vergelijkend onderzoek. **Hoofdstuk 4** onderzoekt of in de kliniek routinematig verzamelde HJHS kan worden gebruikt voor vergelijkend onderzoek naar gewrichtsschade op latere leeftijd bij verschillende profylactische regimes. In deze pilotstudie werden drie verschillende behandelcentra (Londen, Stockholm en Utrecht) met in totaal 127 patiënten (ernstige hemofilie A, geboren tussen 1995 en 2009, mediane leeftijd van 11 jaar) vergeleken. De profylactische regimes in de deelnemende centra verschilden in initiële infusiefrequentie (één vs. drie keer per week), leeftijd bij het bereiken van minimaal drie infusies per week, en profylactische weekdosis ten tijde van HJHS evaluatie. Londen hanteerde het meest intensieve en Utrecht het minst intensieve regime. De HJHS nam, zoals verwacht, toe met de evaluatieleeftijd en positieve remmer-geschiedenis. Echter, de HJHS vertoonde een onlogisch resultaat ten opzichte van regime: het minst intensieve regime had de laagste HJHS (indicatief voor gezondere gewrichten).

Multivariabele regressieanalyse liet zien dat de vergelijking van profylactische regimes werd vertekend door systematische verschillen in de scores van de afzonderlijke fysiotherapeuten, zowel binnen als tussen de centers. We concluderen dat voorafgaand aan vergelijkend onderzoek met meerdere fysiotherapeuten, altijd standaardisatie van HJHS evaluatie nodig is middels bijvoorbeeld een gezamenlijke trainingssessie.

Profylaxe kan op basis van leeftijd of op geleide van bloedingen worden gestart. In **hoofdstuk 5** wordt de effecten van de leeftijd van starten en het aantal gewrichtsbloedingen voor de start van profylaxe op de lange-termijn gewrichtsgezondheid onderzocht. In 124 patiënten (ernstige hemofilie, geboren tussen 1965 en 2000) werden gewrichten beoordeeld op de aanwezigheid van hemofilie-artropathie aan de hand van de radiologische Pettersson score. Analyses werden gecorrigeerd voor leeftijd van evaluatie. Op de mediane leeftijd van 22 jaar had het aantal gewrichtsbloedingen voor de start van profylaxe de sterkste associatie met hemofilie-artropathie op röntgenfoto's. Hoe meer gewrichtsbloedingen voor de start van profylaxe waren opgetreden, des te meer gewrichtsschade werd gezien. Starten vóór de eerste gewrichtsbloeding (12 patiënten), resulteerde in het beste lange-termijn resultaat, terwijl starten na één gewrichtsbloeding (10 patiënten) ook aanvaardbare resultaten op lange termijn leek te hebben. Echter, voorzichtigheid is geboden bij het trekken van conclusies op basis van dergelijke kleine groepen. Patiënten die profylaxe voor de leeftijd van zes jaar waren gestart, scoorden significant beter dan patiënten die later waren gestart ($P < 0,01$). Het starten voor de leeftijd van drie jaar leek geen extra voordeel op te leveren. Toekomstig onderzoek met meer patiënten die op jonge leeftijd met profylaxe zijn gestart, zal moeten uitwijzen of het starten vóór de eerste gewrichtsbloeding daadwerkelijk beter is dan het starten na één gewrichtsbloeding.

Het belang van profylaxe tijdens de groei is algemeen erkend, maar of profylaxe bij volwassenen moet worden voortgezet, wordt door sommigen in twijfel getrokken. Levenslange profylaxe is een zware belasting voor sommige patiënten, waardoor therapietrouw kan variëren. Vooral tieners en jongvolwassenen gaan stoppen met profylactische behandeling. Eerdere studies suggereerden dat een deel van de jongvolwassenen, die sinds hun vroege jeugd met profylaxe zijn behandeld, wellicht veilig zouden kunnen overstappen naar on-demand behandeling. Echter, aangezien hemofilie-artropathie pas in de loop van de tijd zichtbaar wordt, was de follow-up van 4 jaar in deze studies wellicht te kort om de gevolgen van het stoppen van profylaxe in kaart te brengen. In **hoofdstuk 6** worden daarom de gevolgen van het stoppen van

profylaxe met een follow-up van 10 jaar geïnventariseerd. In 66 patiënten (ernstige hemofilie A, zonder remmerontwikkeling, geboren tussen 1970 en 1988) werden patiënt-geïnitieerde veranderingen van profylactische behandeling gedocumenteerd, inclusief onderbrekingen van minimaal twee opeenvolgende weken (on-demand behandeling). Op een mediane leeftijd van 32,4 jaar was 26% van de patiënten met profylaxe gestopt gedurende mediaan 10 jaar, had 15% van de patiënten profylaxe tijdelijk onderbroken en was 59% van de patiënten ononderbroken met profylaxe doorgegaan. Patiënten die waren gestopt en patiënten die profylaxe ononderbroken hadden voortgezet werden vergeleken op het jaarlijkse aantal gewrichtsbloedingen, HJHS (0-124 punten), radiologische Pettersson score (0-78 punten) en Hemofilie Activiteiten Lijst (HAL; 100-0 punten). Hoewel het aantal patiënt-gerapporteerde bloedingen en functionele beperkingen in beide groepen vergelijkbaar waren (1,5 vs. 1,2 gewrichtsbloedingen per jaar; HAL: 84 vs. 84), was op objectieve maten meer artropathie te zien bij patiënten die met profylaxe gestopt waren (HJHS: 23 vs. 14; Pettersson: 16 vs. 5; P <0,01). Deze resultaten onderschrijven het nut van continuering van profylaxe bij volwassen hemofiliepatiënten en laten zien dat objectieve maten noodzakelijk zijn om hemofilie-artropathie te monitoren.

Voor het routinematig monitoren van hemofiliepatiënten in de kliniek moet men gevalideerde meetinstrumenten gebruiken. Bij de keuze van meetinstrumenten moet men een afweging maken tussen het gebruiken van alle beschikbare meetinstrumenten en belasting van patiënt en middelen. Om een gefundeerde keuze te faciliteren, worden in **hoofdstuk 7** correlaties tussen verschillende instrumenten en uitkomstmaten in hemofilie gepresenteerd. Hierbij definiëren wij Spearman's correlatiecoëfficiënten van ≥0.8 als zeer sterk, 0,60-0,79 als sterk, 0,40-0,59 als matig, en 0,20-0,39 als zwak. Objectieve uitkomstmaten (HJHS, radiologische Pettersson score) werden vergeleken met patiënt-gerapporteerde uitkomstmaten (aantal gewrichtsbloedingen, HAL, gezondheidsgerelateerde kwaliteit van leven: SF36, en utiliteit (SF6D en EQ-5D)). Bij 90 patiënten met ernstige hemofilie, op profylaxe sinds de mediane leeftijd van 3,4 jaar, waren de objectieve uitkomstmaten gunstig (mediane scores: HJHS 6, Pettersson 9) op een mediane leeftijd van 25,5 jaar. Patiënt-gerapporteerde uitkomsten: mediaan 7 gewrichtsbloedingen in de afgelopen 5 jaar, weinig functionele beperkingen (mediaan HAL score 96), en hoge scores op kwaliteit van leven (mediaan 80-95 op fysieke domeinen van SF36; mediane utiliteit 0,87 voor SF6D en 0,84 voor EQ-5D). HJHS scores vertoonden een sterke correlatie met radiologische Pettersson scores, matige correlatie met de fysieke domeinen van de SF36 en utiliteit, maar geen correlatie met patiënt-gerapporteerde bloedingen of functionele beperkingen (HAL). Het aantal gewrichtsbloedingen was niet gecorreleerd aan één van

de andere uitkomstmaten, en de HAL was alleen gecorreleerd met het 'Lichamelijk functioneren' domein van de SF36. Deze resultaten tonen aan dat routinematige evaluatie bij hemofiliepatiënten op profylaxe niet enkel uit patiënt-gerapporteerde bloedingen mogen bestaan, maar dat ook objectieve uitkomstmaten, patiënt-gerapporteerde functionele beperkingen en kwaliteit van leven meegenomen moeten worden.

Tenslotte bevat **hoofdstuk 8** een algemene discussie van de bevindingen in dit proefschrift, met inbegrip van suggesties voor toekomstig onderzoek. Het zet verschillende aspecten van uitkomstevaluatie, starten en stoppen van profylaxe en nieuwe behandelingsmogelijkheden in een bredere context.

Dankwoord

Onderzoek doe je nooit alleen. Het begint bij patiënten die hun medewerking verlenen. Ik ben de hemofiliepatiënten en hun ouders dan ook heel dankbaar voor hun medewerking aan het onderzoek in dit proefschrift.

Daarnaast had ik deze prestatie niet kunnen neerzetten zonder de toewijding van mijn co-promotor dr. Kathelijn Fischer en promotor Prof. dr. ir. Yvonne van der Schouw. Kathelijn, je was een onuitputtelijke bron van ideeën en oplossingen. Je niet aflatende energie en enthousiasme hebben mij geïnspireerd en door moeilijke punten heen geholpen. In je drukke schema wist je echt tijd voor me te maken; dat heb ik enorm gewaardeerd. Yvonne, je frisse blik en brede visie heeft dit proefschrift naar een hoger niveau getild en het toegankelijker gemaakt voor niet-hemofiliebehandelaars. Waar ik op het eind vastliep, wist jij me los te trekken en richting te geven. Kathelijn en Yvonne, bedankt voor de goede samenwerking.

De leden van de leescommissie Prof. dr. Rick Grobbee, Prof. dr. Flip de Groot, Prof. dr. Frank Leebeek, Prof. dr. Tim Leiner, en Prof. dr. Cindy Veenhof, bedankt voor het kritisch tegen het licht houden van dit proefschrift naast jullie andere werkzaamheden.

Mijn tijd op de Van Creveldkliniek was nooit zo fijn geweest zonder de goede onderlinge sfeer en behulpzaamheid. Er werd hard gewerkt, maar er was ook tijd en interesse voor elkaar op professioneel en persoonlijk vlak. De niet te stillen gezamenlijke honger voor lekkers zal ik niet vergeten: we wisten elkaar altijd te vinden voor een stukje taart of een greep in de snoeppot. Bedankt voor de medewerking, collegialiteit en de mooie jaren. In het bijzonder, Piet, Eveline, Goris, Wouter, Monique en de dames van het secretariaat, bedankt dat ik kon rekenen op jullie hulp bij de dataverzameling voor mijn onderzoek.
Mijn kamergenoten op de puppy-kamer van de Van Creveldkliniek Marlies, Mojtaba, Dietje, Merel, Federica, Lize, en alle andere ‘puppies’ die zijn gekomen en gegaan: bedankt voor alle steun, werkplezier en gezelligheid, zowel op als buiten het werk. Piet, met je wijze woorden wist je me altijd weer moed in te spreken: je bent een collega uit duizenden.

I am much obliged to the members of the PedNet group, as well as dr. Marijke van den Berg and Ella Smink. You allowed me to work with the data that you meticulously collected on young haemophilia patients. Your constructive feedback was much appreciated and it was a privilege to work with you.

Not in the least, I am grateful for the loving guidance of Sri Sri Ravi Shankar and the volunteers of the Art of Living Foundation. Their techniques to establish a clear and peaceful mind have greatly contributed to this thesis and my sanity.

Onmogelijk te vergeten, omdat ze zo belangrijk voor mij zijn: mijn vrienden en familie! Ik ben heel dankbaar dat jullie me tijdens deze klus zo trouw hebben bijgestaan, en ontspanning en een luisterend oor hebben geboden. Heleen en Romy, ik ben blij en vereerd dat jullie mijn paranimfen zijn.
Veel dank ook aan mijn ouders die mijn nieuwsgierigheid en doorzettingsvermogen hebben aangewakkerd en me altijd met raad en daad bijstaan. Jullie hebben de basis gelegd voor deze prestatie. Fijn dat jullie zo trots op me zijn.

Tom, ik leerde je kennen toen ik aan dit avontuur begon. In die tijd zijn we samen gegroeid en heb je je ontpopt tot een trouwe metgezel. Bedankt liefje, zonder jouw morele steun en liefde was de weg naar dit mooie eindresultaat een stuk zwaarder en minder leuk geweest. Je hebt ook nog eens dit boekje prachtig vormgegeven. We zijn een goed team!

Curriculum Vitae

Annelies Nijdam was born in Groningen, the Netherlands, on August 23rd 1971. In 1989 she graduated cum laude from the Rijksscholengemeenschap Kamerlingh Onnes in Groningen. From 1989 to 1995 she studied Computing Science at the University of Groningen with minors in Psychology and French. As a part of this degree she participated in a postdoctoral specialisation programme on Artificial Intelligence & Databases at the University of Bourgogne in Dijon (France) from October 1994 until March 1995. After graduating, she joined the Cognition & Neurosciences research programme at The School of Human Development & Communication Sciences, University of Texas at Dallas, United States, for one year. Returning to the Netherlands, she took up a career in Information Technology at Cap Gemini Ernst & Young. In this capacity she was deployed in various (international) projects as software designer, developer, technical contact and reviewer across several business sectors. She also contributed to the success of a pioneering business unit, focused on the application of innovative information technology. In 2002 she embarked on a new adventure, studying Veterinary Medicine of companion animals at Utrecht University in the Netherlands. To satisfy her interest in research, she participated in the faculty Honours Programme at the Ethology and Welfare group in the department of Animals in Science and Society. Here she explored the possibilities of more efficient data collection and analysis in animal experiments through automated behaviour observation. In 2008 she was invited to take part in the Leadership Program for Veterinary Students at Cornell University, United States. This programme, aimed at veterinary students who seek a science-based career, allowed her to gain more research experience and strengthen critical thinking, responsible leadership and teamwork skills. After graduating from Veterinary Medicine in 2010, she took up a temporary position as an anaesthetist at the University Clinic for Companion Animal Health in Utrecht. In 2011 she started working on several research projects at the Van Creveldkliniek which resulted in this thesis under the supervision of Prof. dr. ir. Y.T. van der Schouw and dr. K. Fischer. As part of this PhD project, she obtained a post academic master's degree in Clinical Epidemiology at Utrecht University in 2014.