Optimization of Care Strategies in Hemophilia

Janske Lock

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Colofon

Printing of this thesis was kindly supported by: Bayer HealthCare, CSL Behring, Erasmus MC, Novo Nordisk, and Pfizer.

Cover lay-out: J.D. Lock.
Cover photo: stocksolutions / 123RF Stockfoto.
Lay-out and Printing: Optima Grafische Communicatie, Rotterdam, the Netherlands.

ISBN: 978-94-6169-918-3

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Optimization of Care Strategies in Hemophilia

Optimaliseren van behandelstrategieën bij hemofilie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 26 oktober 2016 om 13:30 uur

door

Jannetje Lock
geboren te Ede

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotoren:	Prof. dr. F.W.G. Leebeek
	Prof. dr. H.A. Moll
Overige leden:	Prof. dr. R.A.A. Mathôt
	Dr. M. Peters
	Prof. dr. H. Raat
Copromotor:	Dr. M.H. Cnossen

Old ways won't open new doors.

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CHAPTER 1

General introduction, aims and outline

GENERAL INTRODUCTION

Hemophilia

Hemophilia is a rare X-linked recessive bleeding disorder characterized by a lifelong bleeding tendency, specifically in muscles and joints. Hemophilia A and hemophilia B are caused by respectively a deficiency of coagulation factor VIII (FVIII) or factor IX (FIX) [1]. Hemophilia occurs in 1:5000 male individuals with a ratio of hemophilia A to hemophilia B of approximately 85:15 [2-4]. Severity is classified according to residual coagulation factor level in patient plasma. Severe hemophilia is defined as plasma levels < 0.01 IU ml^{-1}; moderate severe disease as plasma levels between 0.01-0.05 IU ml^{-1}; and mild disease as plasma levels > 0.05 to < 0.40 IU ml^{-1} [1]. Approximately 43% of patients are affected with severe disease, 26% with moderate severe, and 31% are mildly affected [5-7]. However, within each severity category of patients bleeding tendency is heterogeneous and not completely clarified [8-10].

In general, severely affected patients experience spontaneous bleeds from early infancy, moderately affected patients only sporadically experience spontaneous bleeds which usually develop after minor trauma or (dental) surgery, and patients with mild disease only experience bleeding after trauma or (dental) surgery. In the long run, when not treated adequately, muscle and joint bleeds lead to progressive joint destruction resulting in chronic pain and disability [2]. It has been reported that only a few hemarthroses may be sufficient to initiate progressive cartilage destruction and joint dysfunction [11, 12]. Other complications of hemophilia include life threatening intracranial or abdominal bleeds, and the development of alloantibodies (inhibitors) against FVIII or FIX concentrate. The latter greatly complicates treatment as these antibodies neutralize infused factor concentrate and necessitate treatment with bypassing products [13-15].

History of hemophilia treatment

Hemophilia treatment with factor concentrate is described as the intravenous replacement of deficient coagulation factor to achieve specified levels which vary according to severity or risk of the bleed. Major progress has been made with regard to hemophilia treatment and subsequent clinical outcome in patients over the last decades. Since the introduction of first plasma derived factor concentrates in the 1960s, hemophilia has evolved from a crippling disease with a life expectancy of about 20 years into a disease with an almost normal quality of life and life expectancy [16, 17]. This decrease in morbidity is illustrated by a decrease in bleeding frequency and an improvement of the medical and social circumstances of hemophilia patients. This is clearly demonstrated in the observational Hemophilia in the Netherlands (HIN) follow up studies [18-20]. This progress is even more impressive when it is taken into account that pathophysiological

mechanisms behind the disease were only recognised in the 1950's. At that moment in time, Dr. Rosemary Biggs described seven patients with deficiency of the Christmas factor, later named FIX. It was reported that this factor seemed to structurally differ from antihemophilic globulin, the later FVIII, that had been discovered to be deficient in men with a bleeding disorder [21]. Subsequently, important steps with regard to treatment were only made in the 1960's when cryoprecipitate became available for patients in cases of an acute bleed.

It was in the late 1960's, that prophylactic replacement therapy ("prophylaxis") was introduced by Ahlberg and implemented by von Creveld in the Netherlands [22, 23]. Prophylaxis with regular infusions of coagulation factor concentrate aims to convert the bleeding pattern of a severe patient into a moderate severely affected patient [24]. This not only prevents chronic arthropathy and long term disability but also reduces the risk of life threatening intracranial bleeding and directly increases quality of life [24-28]. Subsequently, prophylactic treatment in the home setting ("home treatment") by patients and by parents became regular practice around 1974 in the Netherlands [29-33]. All developments were facilitated by the introduction of refined plasma-derived and later recombinant factor concentrate that enabled more optimal self-administration in the home setting.

Historically, dramatic setbacks during this period were the transmission of life threatening viral diseases by plasma derived human blood products, including hepatitis B and C and HIV infections. This subsequently led to a temporary increase in morbidity and mortality of hemophilia patients in the 1980's, although not due to the bleeding disorder itself [19, 34]. The last two decades, product development has evolved ever further. The hemophilia community now awaits wide spread application of extended half-life products and institutionalization of gene therapy and other cellular techniques [35]. However, it is important to realize in the light of the progress made in resource rich countries, that prophylaxis and home-based therapy with factor concentrates is still not uniformly available to all patients worldwide [36-38].

Current treatment guidelines

Currently, most prophylactic regimens in hemophilia A patients are based on dosages of 25-40 IU kg^{-1} two to three times a week [1]. In the Netherlands, prophylaxis is generally initiated at a young age after the first joint bleed [39, 40]. Current dosing of FVIII concentrates is still mainly based on an estimated in vivo recovery (IVR) of 2.0 IU dL^{-1} per IU kg^{-1} body weight. This means that one unit of infused FVIII concentrate per kilogram body weight will lead to a transient increase in plasma FVIII levels of 0.02 IU mL^{-1} [40-42]. This however does not take clearance or volume of distribution, both important

pharmacokinetic parameters into account. Targeted plasma levels depend on indication for treatment and dosing on body weight. Although mainly based on body weight in kilograms, both prophylactic and on demand treatment in individual patients are also tailored according to bleeding tendency, the presence of target joints, daily activities and sports. Currently, only sporadically peak and trough coagulation factors levels are measured in plasma to monitor therapeutic interventions [43]. Overall according to guidelines in the Netherlands, perioperative treatment starts with a FVIII bolus infusion of 50 IU kg^{-1}, followed by either continuous infusion or intermittent once or twice daily bolus infusions based on crude estimations of clearance rate [40]. To maintain perioperative hemostasis, FVIII plasma levels are targeted according to guidelines for up to two weeks after surgery. In the perioperative setting plasma coagulation factors are monitored frequently [40].

Comprehensive care

Hemophilia is a lifelong, life-threatening disease with significant impact on many aspects of life. Therefore, optimal management of hemophilia care requires a holistic approach. Besides long term medical management of complications, attention should be given to education, employment and other psychosocial needs. In this light, multidisciplinary comprehensive care teams were established quite early in various resource rich countries. These teams consist of a medical director often a hematologist, a nurse coordinator, a physiotherapist, a social worker, and sometimes a psychologist [30, 44]. These world-wide established care programmes have led to an impressive overall improvement of care and are comparable to programmes installed for diabetes, cystic fibrosis and sickle cell disease [45-47]. Roles for nurses are important and diverse as they are often the first contact for patients with an acute problem or a symptom requiring follow-up. Furthermore, they provide educational services, and ensure a high quality of transitional care [48].

Patient outcome measures, adherence to treatment and personalized treatment

The World Health Organization has defined health as "a state of complete physical, mental and social well-being, and not merely as the absence of disease or infirmity". Therefore, when evaluating patient outcome measures in chronic diseases such as hemophilia, it is essential to incorporate all these specific aspects in the analyses [49]. An important patient outcome parameter which encompasses most, is health-related quality of life (HRQoL). HRQoL is defined as a multidimensional construct which describes the patient's (and his caregiver's) experiences with respect to the domains of functional status, psychological aspects and social well-being, health perceptions, and disease - and treatment-related symptoms [50]. Generic quality of life measures aims to compare quality of life in patients with different (chronic) diseases. For children, commonly used

instruments are the Child Health Questionnaire (CHQ), the Pediatric Quality of Life Inventory (PedsQoL), the TNO-AZL (Preschool) Children's Quality of Life questionnaire (TAPQoL/TACQoL) and the KIDSCREEN/DISABKIDS [51-55]. Disease-specific quality of life measures give insight into the extent to which hemophilia specifically affects the quality of life of hemophilia patients. In pediatric patients, this most often measured by the Haemo-QoI and the CHO-KLAT as constructed by Von Mackensen et al. and Young et al., respectively [56-58]. Other measures which are becoming increasingly important with regard to well-being in chronic diseases are self-management and self-efficacy. Furthermore, measures with regard to behavior, both in the home setting as well as in school are of importance with this regard.

Another important condition to achieve optimization of care is adherence to prescribed treatment in a broad sense. In reviews on adherence a number of terms are frequently utilized and defined as follows. The term compliance suggests that patients passively follow doctor's prescription and lifestyle advice. Therefore this term is not based on a therapeutic alliance between patient and doctor [59]. In contrast, the term adherence is now usually adopted. Adherence is defined by the WHO as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from the health care provider" [60]. Most recently, the alliance between physician and patient is underlined with shared decision making with regard to treatment options as an ultimate goal. This situation is named concordance, indicative of the mutual agreement between patient and doctor. It is believed that this may help to install a sense of control and self-efficacy in each patient. When regarded critically, concordance is an important aspect of individualization or personalization of treatment as this is defined as "care that is closely congruent with and in response to patients' wants, needs, and preferences" [61-63]. More specifically, personalized treatment it is used to describe individualization of treatment by increased knowledge of disease, genetic disposition of the individual, as well as pharmacokinetics and pharmacodynamics of the medication involved.

Areas of improvement

Although patient outcome has made great progress in last decades in the hemophilia population, there may still be room for improvement. Especially with regard to improvement of adherence to treatment, aspects of quality of life, and more personalized dosing of factor concentrates.

In patients on prophylactic treatment, non-adherence rates have been reported up to 50% in various studies [64-67]. Due to the lack of direct medical supervision, patients with home treatment report problems due to the increased responsibility associated

with home treatment [29, 32, 33]. During outpatient clinic visits there is often insufficient attention to therapeutic management, patient support and education. These aspects of care are essential to safeguard adherence, to increase self-efficacy and self-management abilities as is important in chronic diseases. Therefore, evaluation of mechanisms leading to non-adherence and development of related modalities such as self-efficacy are important in order to measure, monitor and improve adherence in hemophilia.

Currently, in resource rich countries, both prophylactic and perioperative hemophilia treatment are quite effective as morbidity due to joint and muscle bleeding and mortality are rare. However, with current dosing regimens, targeting of specific factor levels is challenging. This is due to significant inter-individual variation with regard to achieved factor levels due to inter-individual differences in various factors. One of these factors is pharmacokinetics (PK) of the specific factor concentrate in the individual [1, 42, 43, 68-74]. Momentarily, the impact of PK-guided dosing has not yet been studied widely and consensus is still to be reached how to further develop and implement this innovation. It is however most probably a more reliable dosing strategy as it takes important individual characteristics, such as clearance and volume of distribution into account. Furthermore, PK-guided dosing will make it possible to target specific factor concentrate plasma levels [26, 43, 72, 75-78] in the long run.

OPTIMIZATION OF CARE STRATEGIES IN HEMOPHILIA

AIMS OF THIS THESIS

The aims of this thesis are to study strategies that may further improve patient outcome in hemophilia, by optimization of both patient care by interventions in adherence as well as treatment innovations.

OUTLINE OF THE THESIS

This thesis consists of two parts. **Part I** will focus on strategies to further improve hemophilia patient care with regard to prophylactic home treatment and care in the outpatient clinic setting. In addition, two questionnaires to measure adherence and self-efficacy will be introduced that are of importance to quantify and monitor these aspects of treatment.

Firstly, we hypothesized that transmural support by a hemophilia nurse performing structured home visits may improve prophylactic treatment adherence, health-related quality of life, behavior, self-efficacy, and may lead to a reduced number of joint bleeds and less factor concentrate consumption in children with hemophilia on prophylactic home treatment. In **chapter 2,** a multicenter intervention study will be described that evaluates the effect of regular home visits by a hemophilia nurse. In order to be able to quantify and monitor treatment adherence, reliable and validated tools are necessary. Therefore, we will describe in **chapter 3,** the value of the VERITAS-Pro adherence questionnaire by Duncan et al. This questionnaire was translated in Dutch and validated in a pediatric patient population within our studies. Self-efficacy is a very important measure in patients with chronic diseases, as it is associated with higher development of self-management skills and increased quality-of-life. In **chapter 4,** we will describe the development and validation of a novel Hemophilia-specific Self-Efficacy Scale. During regular outpatient clinic visits, time limitations may lead to insufficient attention to therapeutic management and patient education. In addition, patient support and education by patients themselves may improve quality of care. The group medical appointment (GMA) therefore may be an effective and efficient option to improve the quality of the outpatient clinic visits. In **chapter 5** an observational study will be presented that compares participant's experiences with GMA to the usual standard of care.

Part II of this thesis will focus on strategies to improve current dosing of factor concentrates. To demonstrate the challenges involved with targeting of factor VIII values in the perioperative setting, we will present the results of the current dosing regimen in **chapter 6.** Subsequently, in **chapter 7**, a population PK model will be described that is applicable for various current FVIII concentrates in the perioperative setting. Although, the principle and benefits of PK-guided prophylactic dosing have been proven by others, it has still not been implemented in routine hemophilia care. To facilitate implementation, in **chapter 8** barriers and facilitators for PK-guided dosing of prophylaxis in will be reported as analyzed in patients, parents and professionals by Discrete Choice Experiment.

Finally, in **chapter 9** and **10** a summary of the thesis will be provided as well as an overview of the most important conclusions of our studies and methodological considerations. Moreover, we discuss the implications of our results with regard to current practice and future perspectives with regard to research.

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CHAPTER 2

Optimization of home treatment in hemophilia: effects of transmural support by a hemophilia nurse on adherence and quality of life

J Lock, H Raat, M Peters, M Scholten, M Beijlevelt,
R Oostenbrink, FWG Leebeek, HA Moll, MH Cnossen

Haemophilia. 2016; Accepted for publication.

ABSTRACT

Background Transmural support by a haemophilia nurse may improve treatment and may empower parents and patients.

Aim To measure the effect of structured home visits by a haemophilia nurse in (parents of) patient on aspects of prophylactic home treatment.

Methods A multicentre intervention study in two paediatric haemophilia treatment centres was performed. Primary outcome measures were: adherence to prescribed treatment, health-related quality of life, and behavioural scores. Secondary outcome measures were: total clotting factor consumption, self-efficacy, and number of joint bleeds.

Results Over a period of 22 months (median, IQR = 21-23) four to seven home visits in 46 patients (mean age 9.4 ± 4.2 years) were made. No difference in adherence to prescribed treatment was seen after the home visits when compared to baseline measurements. Both the Child Health Questionnaire (CHQ) scales on 'Role functioning - Emotional/ Behavioural' (P = 0.02, d = 0.53) and 'Parental Time Impact' (P = 0.04, d = 0.33) were reduced after intervention. The disease-specific Haemo-QoL questionnaire showed improvement in domains: 'Family' (P = 0.04, d = -0.14), 'Friends' (P = 0.03, d = -0.29), and 'Perceived support' (P = 0.03, d = -0.37). Significant improvement was observed with regard to domain 'Communication' of the VERITAS-Pro scale (P = 0.03, d = -0.28).

Conclusions After a period of transmural care by a haemophilia nurse, significant but small positive effects were demonstrated with regard to communication and increase of perceived support between parents and haemophilia treatment centre. No improvement was observed in other outcome measures.

INTRODUCTION

Haemophilia is an X-linked bleeding disorder which is characterized by a deficiency of coagulation factor VIII (FVIII; haemophilia A) or IX (FIX; haemophilia B) [1]. Depending on severity, haemophilia patients experience spontaneous and post-traumatic bleeding events, mainly in joints and muscles [2]. In the long run, these bleeds lead to progressive joint destruction with impairment of joint function and chronic pain, when not treated adequately. In most high resource countries, patients with severe and some with moderate severe disease are treated by intravenous prophylactic replacement therapy with clotting factor concentrate. Prophylactic therapy is initiated at a young age after the first joint bleed, to prevent the development of arthropathy and subsequent disability [1, 3].

Almost all patients on prophylaxis are treated in the home setting, where parents and/or the patient himself, regularly infuse clotting factor concentrate without direct medical supervision [4]. In the Netherlands, apart from an intensive training in the hospital and one home visit at the initiation of home treatment, no transmural care is offered. Home treatment has greatly improved quality of life and self-management abilities in haemophilia. Due to the fact that prophylactic treatment can be administered at home more rapid treatment of bleeding is possible, leading to less pain and disability, fewer hospitalizations, and less absence from school or employment [5-7]. However, home treatment also has disadvantages due to the lack of direct supervision, such as waning from prophylactic and on demand dosages and increased responsibility regarding self-management of patient's disease [5, 7, 8].

The full benefit of prophylactic treatment is only achieved by optimal adherence. Non-adherence to treatment in haemophilia has been reported to be associated with substantial increase in morbidity, mortality, and health care costs [9-11]. Besides social circumstances and developmental stages such as adolescence [12, 13], determinants of non-adherence include: lack of expertise or knowledge of disease, time investment involved to infuse prophylaxis, lack of balance between prophylactic treatment and social activities, anxiety towards needle insertion, lack of cooperation of the child, and a general feeling that treatment is not beneficial [5, 14]. Inversely, as described by Schrijvers et al. (2013) adherence and quality of life are positively influenced by adequate knowledge of the disease and belief in medical and psychological benefits of prophylaxis, mental health, disease symptoms, and an optimal relationship between patient and haemophilia team [12, 14-18].

We hypothesized that transmural support by a haemophilia nurse performing home visits may overcome the disadvantages mentioned above, attributed to home treatment

[19-23]. Therefore, we performed a multicentre intervention study with structured home visits by a haemophilia nurse in children on prophylactic home treatment. The aim of the study was to investigate the effect of home visits on adherence to treatment, health-related quality of life, behavioural scores, self-efficacy, total clotting factor consumption, and number of joint bleeds.

PATIENTS AND METHODS

Design

The study is a multicentre pre- and post-intervention study in a cohort of paediatric haemophilia patients aged 1-18 years on prophylactic home treatment for at least one year (Dutch Trial Register: 2543) [24].

Patients

Patients were recruited from two paediatric academic haemophilia treatment centres in the Netherlands, i.e. Erasmus University Medical Centre-Sophia Children's Hospital Rotterdam (Erasmus MC-Sophia, $n = 22$) and Academic Medical Centre-Emma Children's Hospital Amsterdam (Emma Children's Hospital AMC, $n = 31$). Exclusion criteria were inability to understand the Dutch language or home treatment with bypassing agents due to the presence of inhibiting antibodies. The study protocol was approved by a Medical Ethics Committee (MEC-2010-097) with written informed consent from parents of all children and from patients aged 12-18 years. The study was not subject to the Medical Research Involving Human Subjects Act.

Intervention

The intervention was defined as five to seven home visits by two experienced haemophilia nurses over a total period of two years. During each home visit with a duration of one to two hours, the nurse was instructed to inform parents and patient(s) on all aspects of treatment according to a standardized checklist focusing on logistical, technical, therapeutic, safety, educational and psychological aspects of haemophilia (see Appendix 1).

Data collection

Before and after the intervention period, the caregiver primarily involved in daily haemophilia treatment, as well as adolescents aged 10-18 years, were asked to complete a web-based questionnaire measuring health-related quality of life (HRQoL), behaviour, adherence, and self-efficacy (Figure 1). All endpoints were measured with validated questionnaires, which are described more explicitly in following sections. In the ques-

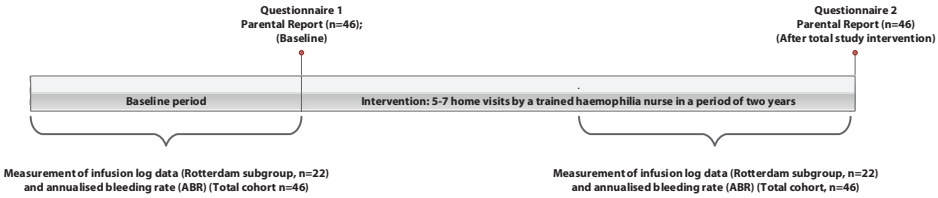

Figure 1. Study design.

tionnaire directly after the intervention, parents were also asked if they were satisfied with home visits and if these had improved home treatment in their opinion (visual analogue scale of 10 cm). Self-reported infusion log data were collected in patients from the Erasmus MC-Sophia Rotterdam treatment centre.

General patient characteristics were recorded: age, type and severity of haemophilia, body weight, prescribed treatment, number of bleedings, and pharmacy dispensations based on medical records. For level of education, the International Standard Classification of Education (ISCED) division into low, medium, and high educational level was applied [25].

Primary outcome measures

Adherence to prescribed prophylactic treatment according to infusion logs
Self-reported infusion logs were available in the Erasmus MC-Sophia cohort (n = 22), and were used to assess adherence to prescribed haemophilia treatment. Adherence to prophylactic treatment was quantified as the percentage of weeks per year (ratio n/n = 52) that the patient was adherent according to prescribed prophylactic regimen related to reported (i) frequency of infusions; (ii) interval between consecutive infusions; (iii) total consumption of clotting factor concentrate. Weeks with alterations in prophylactic treatment due to bleeding or dental care were excluded. Patients who underwent surgery or were involved in intensive sport activities were excluded from these analyses, as these circumstances may lead to long-term alterations in frequency, dose and interval of the treatment regimen, masking real adherence rates.

Generic and disease specific health-related quality of life (HRQoL)
The Child Health Questionnaire (CHQ) was used to assess the generic quality-of-life in children aged 4-18 years. For the parental report the CHQ-PF50 was used (reliability: α = 0.59-0.94), which consists of 50 items covering 13 physical and psychosocial scales, including Physical summary scale and Psychosocial summary scale [26, 27]. For adoles-

cents aged 10-18 years, the self-reported 87-item CHQ-CF87 was used (reliability α = 0.63-0.90), which encompasses 12 scales [27, 28]. In this questionnaire, higher scores indicate a higher generic quality of life (range = 0-100). The Haemo-QoL questionnaire was used to assess haemophilia-specific quality of life [29, 30]. This tool consists of 21-77 items which encompass 9-11 domains depending on age group of the patient (4-7 years, 8-12 years, 13-16 years; α = 0.85-0.91). The age-specific versions contain an identical core item set. Because of small number of patients per age group, results were merged for total scores and domain scores (when available) for all age groups. Higher scores indicate a lower disease-specific quality of life (range = 0-100).

Behavioural scores

The Strengths and Difficulties Questionnaire (SDQ) was used to assess behavioral problems in children aged 4-17 years [31-33]. The SDQ consists of 25 items encompassing 5 domains. Higher scores indicate increased severity of symptoms, and individual items are added to obtain a total scale score (range = 0-40).

Secondary outcome measures

Total clotting factor concentrate consumption and total number of joint bleeds

Total clotting factor consumption (kg^{-1} wk^{-1}) and total number of joint bleeds were recorded in self-reported infusion logs and medical records. Weeks with alterations in prophylactic treatment due to bleeding, surgery or dental procedures were excluded for this analysis. For number of bleeds only joint bleeds in larger joints were recorded. A new bleed was defined as a bleed occurring more than 72 hours after completing treatment for the original bleed for which treatment was initiated [34].

Adherence to treatment according to the VERITAS-Pro adherence scale

To quantify adherence to treatment in children on prophylactic home treatment, the Validated Haemophilia Regimen Treatment Adherence Scale (VERITAS-Pro) was used [35]. This instrument was translated in Dutch according to international guidelines and validated within this study [36]. The VERITAS-Pro consists of six subscales with four items, concerning a specific domain of haemophilia patient care: 'Time', 'Dose', 'Remember', 'Skip', 'Plan', 'Communicate'. Higher scores indicate worse adherence (subscale range = 4-20; total scale range = 24-120).

Self-efficacy

The Haemophilia-specific Self-Efficacy Scale (HSES) was used to quantify disease-specific capacities with regard to self-efficacy, and was validated within this study [37]. The HSES consists of 12 items focusing on an individual's perceptions of haemophilia disease symptoms and the ability to cope with or reduce these symptoms. An unweighted sum

score was calculated by adding the 12 items scores, with higher scores indicating greater self-efficacy (range = 12-60).

Sample size calculation

Sample size calculation determined that minimally 40 patients were needed to measure a significant difference ($S_d = 2\delta / S_d$) in the primary endpoint HRQoL, with a measurable Z score difference of 0.55, given a power of 80% (1-β) and an α of 0.05 (Dutch Trial Register: 2543). This number of patients also was sensitive enough to detect a minimal change of 1.4 bleeding episodes, 2.6 treatment days, or 4785 IU kg^{-1} clotting factor use per patient (secondary outcome).

Statistical analysis

Descriptive study statistics are presented as mean and standard deviation (SD) for continuous variables which are normally distributed, and otherwise as median and interquartile range [IQR]. For comparison of parametric outcome parameters before and after the intervention, the Student's t-test for paired data was used. Non-parametric data were compared using Wilcoxon signed rank test. Categorical data were compared using the Pearson Chi-Squared test. Effect size estimations (*d*) were calculated which relate the difference in mean scores to the dispersion of the scores. Given unequal score variance between groups, we used to following formula: d = [Mean(a)-Mean(b)]/√[((n(a)-1)*SDd(a)^2)+((n(b)-1)*SD(b)^2)/n(a)+n(b)-2]; $0.20 \leq d < 0.50$ was taken to indicate a small effect size, $0.50 \leq d < 0.80$ a moderate effect size, and $d \geq 0.80$ a large effect size [38]. To compare outcome measures of the infusion logs (i.e. total clotting factor use and annualised bleeding rate) baseline data (median = 45 weeks, IQR = 43-51) were compared to data collected at the second half of the intervention period (median = 49 weeks, IQR = 43-55). Data were analysed separately for parental reported and adolescent reported data. Data management and statistical analysis were performed using IBM Statistical Package for Social Sciences (SPSS) program, version 21.0 for Windows (IBM Corp, Armonk, NY, USA).

RESULTS

Patient characteristics

Between June 2010 and December 2011, 59 eligible haemophilia patients and their parents were invited to participate in the study (Figure 2). Of these boys, 53 patients (90%) and their parents agreed to participate. Seven patients were lost to follow-up (13%). Data of the remaining 46 patients (87%) were included in our study, and provided written informed consent (Table 1). Analysis of patient characteristics of the seven patients

not adherent with regard to the study protocol, showed that they were from one single centre (Emma Children's Hospital AMC), they were significantly older in comparison to the study group (mean age = 13.4 years, SD = 3.2 versus 9.4 years, SD = 4.2; $P = 0.02$), had a medium or high maternal educational level ($P = 0.02$). Other patient characteristics were not significantly different.

There were no major differences between parental and adolescent reports. The Adolescent reported data are depicted in Appendix 1.

Comparison of study groups from the Erasmus MC-Sophia and the Emma Children's Hospital AMC, overall showed no significant differences with regard to age, type and severity of haemophilia, duration of prophylaxis, parental age, marital status, or maternal

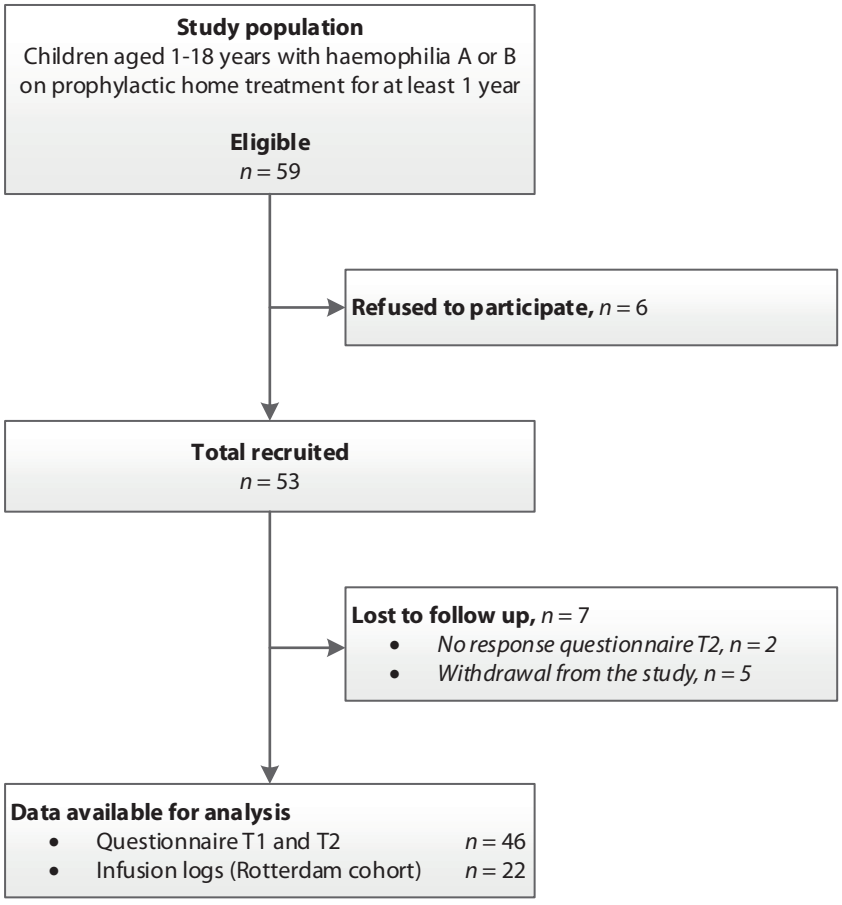

Figure 2. Study flow diagram.

paid employment. However, the maternal educational level was significantly higher in the study group from Emma Children's Hospital AMC when compared to Erasmus MC-Sophia (low = 24% vs 4%; medium = 67% vs 58%; high = 10% vs 38%; $P = 0.03$).

Intervention

During a median time period of 22 months (IQR = 21-23) two experienced haemophilia nurses performed four home visits in two patients (4%), five or more in 44 patients (96%). The median duration of the home visits was 71 minutes (IQR = 60-86).

Primary outcome measures

Log entries were available from all children in the Erasmus MC-Sophia ($n = 22$), of which six cases were excluded from analysis because of surgery and two cases were excluded because of intensive sport activities. Treatment adherence with regard to the frequency of infusions, interval between two consecutive infusions and dose did not change significantly after the intervention, as described in table 3.

After the intervention two domains on the generic quality of life questionnaire CHQ scored lower: 'Role functioning – Emotional/Behavioral' ($P = 0.02$; $d = 0.53$) and 'Parental Time Impact' ($P = 0.04$; $d = 0.33$), as depicted in Table 2. No significant differences in other CHQ domains were observed. Disease-specific quality of life improved in the following three domains after the intervention: 1) 'Family' ($P = 0.04$; $d = -0.14$), indicating less limitations experienced by families due to the child's general health and well-being; 2) 'Friends' ($P = 0.03$; $d = -0.29$), indicating an improved relationships and higher activity levels with friends; and 3) 'Perceived support' ($P = 0.03$; $d = -0.37$), indicating an increased feeling e.g. recipient's subjective judgment that providers will offer effective help when needed. No change was reported in other Haemo-QoL domains.

Behavioural scores on the SDQ questionnaire did not significantly change after the study intervention.

Secondary outcome measures

The total consumption of clotting factor did not change after study intervention in the Erasmus MC-Sophia population.

At baseline, median annualized bleeding rate was 1 (IQR = 0-3). The annualized bleeding rate did not change significantly after study intervention (Table 3).

The domain 'Communication' of the VERITAS-Pro scale changed positively after the intervention period, indicating communication between the patient and the Haemophilia Treatment Centre was reported to have improved significantly: $P = 0.03$; $d = -0.3$ (Table 2).

Table 1. Patient characteristics of total cohort (parental report) and subgroup (adolescent report) at study enrolment.

	Total cohort (*n* = 46)		**Subgroup (*n* = 22)**	
	Parental report		**Adolescent report**	
Characteristics	***N***	**(%)**	***N***	**(%)**
Patient characteristics				
Age patients (years), mean (SD)	9.4	(4.2)	12.9	(2.4)
Sex patients, male	46	(100)	22	(100)
Diagnosis				
Haemophilia A	36	(78)	19	(86)
Haemophilia B	10	(22)	3	(14)
Disease severity				
Severe (< 0.01 IU ml^{-1})	42	(91)	20	(90)
Moderate severe (0.01-0.05 IU ml^{-1})	3	(7)	1	(5)
Mild (0.06-0.40 IU ml^{-1})[#]	1	(2)	1	(5)
Duration of prophylactic treatment (years), mean (SD)	6.6	(3.7)	9.1	(2.5)
Parent characteristics				
Age parents (years), mean (SD)[$]	39.3	(6.3)	.	
Marital status[$]				
Married/living together	34	(76)	.	
Single / Widow(er) / Divorced	11	(24)	.	
Highest level of education of mother[$,&]				
Low	6	(13)	.	
Medium	28	(62)	.	
High	11	(25)	.	
Missing/ not specified				
Paid employment mother[$]	37	(82)	.	
Individual completing scale[$]				
Mother/female guardian	41	(91)	.	
Father/male guardian	4	(9)	.	
Adolescent	.		22	(100)

N = number (percentages); Median [IQR = Inter quartile range 25-75%]; SD = Standard deviation; [#] On prophylactic treatment due to bleeding tendency as a result of concomitant von Willebrand disease; [$] Of one participant, no information is available on marital status, highest level of education of mother, paid employment of mother, and individual completing scale. Of three participants, no information is available on age of parents. [&] The usual ISCED division into Low, Medium and High is adopted here, as in the Eurostat Labour Force Survey. Low is equivalent to ISCED 0-2, i.e. less than upper secondary level of education. Medium is given by ISCED 3-4, i.e. upper secondary level. High is ISCED 5-6, meaning tertiary level, or two more years of education after upper secondary level [25].

Table 2. Health care outcome questionnaire scores at baseline and after intervention, parental report.

Outcome measures; Parental report	Baseline			Post intervention			Effect				
	N	Median	[IQR]	*N*	Median	[IQR]	Median difference	[IQR]	*P*#		Effect size
Primary outcome											
CHQ; generic quality of life											
Physical Functioning (PF)	42	100	[89-100]	42	100	[88-100]	0	[-7-6]	0.82		-0.08
Role Functioning – Emotional/Behavioral (REB)	42	100	[100-100]	42	100	[89-100]	0	[-11-0]	0.02	*	-0.53
Role Functioning – Physical (RP)	42	100	[96-100]	42	100	[83-100]	0	[-4-0]	0.26		-0.34
Bodily Pain (BP)	42	20	[10-33]	42	20	[8-50]	0	[-10-23]	0.15		0.25
General Behavior (GB)	42	77	[68-84]	42	79	[68-86]	4	[-5-8]	0.27		0.11
Mental Health (MH)	42	80	[69-90]	42	80	[68-93]	5	[-10-10]	0.81		-0.05
Self Esteem (SE)	42	25	[13-29]	42	25	[13-29]	0	[-6-4]	0.76		0.08
General Health Perceptions (GH)	42	77	[60-83]	42	64	[52-82]	-4	[-13-4]	0.05		-0.32
Change in Health (CH)	42	50	[50-50]	42	50	[50-50]	0	[0-0]	0.69		0.10
Parental Emotional Impact (PE)	42	17	[8-33]	42	17	[8-33]	0	[-8-17]	0.45		0.19
Parental Time Impact (PT)	42	100	[78-100]	42	100	[67-100]	0	[-11-0]	0.04	*	-0.33
Family Activities (FA)	42	92	[79-100]	42	88	[71-100]	0	[-17-8]	0.18		-0.26
Family Cohesion (FC)	42	60	[30-85]	42	60	[15-85]	0	[-25-13]	0.67		-0.05
Physical summary (PhS)	42	46	[42-50]	42	46	[41-47]	-1	[-5-4]	0.38		-0.30
Psychosocial summary (PsS)	42	41	[39-42]	42	42	[38-43]	0	[-3-3]	0.73		-0.14
Haemo-QoL; disease-specific quality of life											
Total	46	18	[13-23]	45	17	[12-26]	-1	[-5-4]	0.62		0.02
Physical health	46	4	[0-13]	45	6	[0-21]	0	[-7-11]	0.41		0.25
Feeling	46	0	[0-13]	45	0	[0-18]	0	[-4-8]	0.55		0.16
View	46	3	[0-11]	45	3	[0-21]	0	[-3-11]	0.12		0.25
Family	46	13	[0-16]	45	3	[0-17]	0	[-13-0]	0.04	*	-0.14
Friend	46	50	[0-77]	45	38	[0-59]	0	[-25-0]	0.03	*	-0.29

Table 2. Health care outcome questionnaire scores at baseline and after intervention, parental report. (continued)

	Baseline			Post intervention			Effect				
Outcome measures; Parental report	***N***	**Median**	**[IQR]**	***N***	**Median**	**[IQR]**	**Median difference**	**[IQR]**	***P*#**		**Effect size**
Perceived support	34	72	[38-100]	33	63	[25-81]	-13	[-34-0]	0.03	*	-0.37
Others	46	0	[0-8]	45	0	[0-10]	0	[-4-2]	0.66		0.16
Sport	46	7	[0-31]	45	13	[3-33]	3	[-6-13]	0.10		0.23
Dealing	34	43	[35-54]	33	43	[29-54]	0	[-7-7]	0.78		-0.04
Treatment	46	19	[6-25]	45	15	[16-25]	0	[-11-6]	0.36		-0.13
Future	23	25	[19-38]	22	25	[13-38]	-3	[-13-9]	0.55		-0.16
Relationship	23	0	[0-0]	22	0	[0-0]	0	[0-0]	0.56		-0.24
SDQ; behavioral scores											
Total difficulties	46	6	[4-11]	45	5	[3-11]	-1	[-4-2]	0.33		-0.04
Emotional symptoms	46	1	[0-3]	45	1	[0-3]	0	[-1-1]	0.68		0.05
Conduct problems	46	1	[0-2]	45	1	[0-2]	0	[-1-1]	0.60		0.11
Hyperactivity-inattention	46	3	[1-5]	45	2	[0-5]	0	[-2-1]	0.23		-0.12
Peer problems	46	1	[0-3]	45	1	[0-2]	0	[-1-1]	0.50		-0.10
Prosocial behavior	46	9	[8-10]	45	9	[8-10]	0	[-1-1]	0.77		0.11
Secondary outcome											
VERITAS-Pro; adherence scale											
Total scale	46	36	[30-43]	44	35	[30-43]	0	[-5-7]	0.78		0.07
Time	46	5	[4-6]	44	6	[4-7]	0	[-1-2]	0.08		0.34
Dose	46	4	[4-5]	44	4	[4-6]	0	[0-1]	0.14		0.40
Plan	46	8	[5-10]	44	7	[4-10]	0	[-4-1]	0.10		-0.25
Remember	46	5	[4-8]	44	5	[4-7]	0	[-1-2]	0.63		0.18
Skip	46	4	[4-6]	44	5	[4-7]	0	[0-2]	0.08		0.32
Communicate	46	7	[5-10]	44	6	[5-8]	-1	[-2-0]	0.03	*	-0.28
Hemophilia Self-Efficacy Scale	39	57	[53-59]	45	57	[53-59]	-2	[-3-1]	0.10		0.27

N = number (percetages); Median [IQR = Inter quartile range 25-75%]; CHQ = Child health Questionnaire; Haemo-QoL = Haemophilia-specific Quality of Life; SDQ = Strenght and Difficulties Questionnaire; VERITAS-Pro = Validated Haemophilia Regimen Treatment Adherence Scale. # Wilcoxon signed rank test; *$P<0.05$.

Table 3. Infusion log variables in subgroup Erasmus MC-Sophia with detailed information (*n* = 22) and annualised bleeding rate in total cohort (*n* = 46).

	Baseline[#]			Intervention[$]			Effect		
Òutcome measures	***N***	**Median**	**[IQR]**	***N***	**Median**	**[IQR]**	**Median difference**	**[IQR]**	***P*[‡]**
Primary outcome									
Compliance[&]									
Frequency[i]	14	86	[75-91]	14	87	[78-95]	-3	[-5-11]	0.55
Interval[ii]	14	91	[85-96]	14	85	[78-93]	-6	[-13- -0]	0.07
Dose[iii]	14	100	[100-100]	14	100	[91-100]	0	[-7-0]	0.24
Secondary outcome									
Total clotting factor consumption (IU kg^{-1}wk^{-1})	22	27	[17-34]	22	26	[20-36]	-0	[-5-5]	0.99
ABR[†]	46	1	[0-3]	46	2	[0-6]	0	[-0-1]	0.87

N = number (percentages); Median [IQR = Inter quartile range 25-75%]; IU kg^{-1} wk^{-1} = International Units per kilogram per week; [&] Compliance to prescribed prophylactic treatment by comparison of prescribed prophylactic treatment dosages to actual infused units of clotting factor during prophylactic treatment as registered in infusion logs. Compliance is quantified as a percentage of weeks spent in compliance with prescribed therapy (%) to reported (i) frequency of infusions; (ii) interval between consecutive infusions; (iii) total consumption of clotting factor concentrate; [†] Annualised bleeding rate = number of bleedings/ number of weeks*52 weeks; [#] Baseline: Measurement before start of intervention (median 45 weeks, IQR = 43-51 weeks); [$] Intervention: Second half of intervention period (median 49 weeks, IQR 43-55 weeks); [‡] Wilcoxon signed rank test; *$P < 0.05$.

Self-efficacy measured at baseline was high in our population (median = 57, IQR = 53-59) and did not improve significantly after study intervention ($P = 0.10$; Table 2).

Other outcome measures

Parents of patients reported to be satisfied with home visits with a median of 8 (IQR = 7-10), found the visits useful (median = 8; IQR = 6-10) and that they improved the quality of haemophilia treatment (median = 8; IQR = 7-8). Concomitantly, haemophilia nurses agreed with respect to usefulness of home visits (median = 8; IQR = 6-9). At baseline patients were absent form school due to haemophilia for a median of 5 days per year (IQR = 2-10). Non-attendance did not change significantly after the intervention.

DISCUSSION

This study shows that transmural care by a haemophilia nurse, does not improve adherence to prescribed treatment in a population that at baseline demonstrates high levels of treatment adherence as well high quality of life, high capacity of self-

efficacy, and a low number of joint bleeds. In addition, no improvement was observed in Physical and Psychosocial summary measures of the generic HRQoL as measured by CHQ. Contrastingly however, a small decrease over time was seen in CHQ scales 'Role Functioning – Emotional/Behavioural' and 'Parental Time Impact'. Importantly, parents of patients did report a significant improvement of disease-specific HRQoL by means of the Haemo-QoL domains 'Family', 'Friends', and 'Perceived support' after home visits. Furthermore, communication between parents and the haemophilia treatment centre was reported to have improved significantly as reported by VERITAS-Pro adherence scale Although this effect was small, this is an important finding as communication with treating professionals is known to significantly influence adherence [14].Total clotting factor concentrate consumption, number of joint bleeds, and capacity to self-efficacy did not change significantly after study intervention. Overall, patients, parents and haemophilia nurses were satisfied with the concept of home visits as performed in the study.

These findings support a review of 182 randomized controlled trials (RCTs) on interventions to improve treatment adherence by Nieuwlaat et al [22]. Analysis of data from 17 RCTs (range n = 38-2097 patients, majority adults) of good quality studies, showed that interventions aiming to improve adherence have only modest overall effects. Furthermore, interventions varying from intense education to daily treatment support showed inconsistent effects on patient outcomes.

When interpreting effects of our intervention on HRQoL, a number of considerations are important. Firstly, the cohort reported a good HRQoL at baseline, which has been documented in several earlier studies [39-42]. This finding severely limits the ability of most instruments to detect improvement in endpoints after intervention [26, 29, 36, 37, 43]. In addition, such quality of life measurements are known to be influenced by age [44]. With regard to the generic HRQoL, no change was seen on the Physical and Psychosocial summary scales of the CHQ. However, two CHQ scales declined minimally after intervention ('Role Functioning – Emotional/Behavioural', and 'Parental Time Impact'), which is partially explainable. Smith et al. stated that adaptation to a chronic health condition requires a certain degree of disease acceptance and hope for improvement [45]. The home visits may have led to more intensive counseling of parents and patient, with more attention to actual problems and treatment of disease leading to an inverse effect on some quality of life scores [45-47]. The decrease reported in parental time, is most likely due to the time consuming nature of the intervention itself. However, it could be also a desired effect as parents are more aware of the importance of proper treatment for their child. With regard to the disease-specific HRQoL, Bullinger et al. reported satisfactory disease-specific HRQoL as measured by Haemo-QoL in a large cohort of 320 paediatric haemophilia patients from six European countries [48]. Although young children were

negatively affected in the areas 'Family' and 'Treatment', and older children showed impairments in social domains, such as 'Perceived support' and 'Friends' [48, 49]. In our study, except for the domain 'Treatment', an improvement was seen in these domains after intervention by haemophilia nurse.

Annualised bleeding rate in our population was low (median = 1.0, IQR = 0-3) when compared to earlier research by Fisher et al. in 1998, in a Dutch paediatric population that reported 3.7 joint bleeds per year (IQR 1.7-5.0; *n* = 86) [50, 51]. In part, the difference in joint bleeds could be explained by current more intensive treatment, an overall younger age of our study population and differences in activity level and behaviour associated with age (17.9 vs 9.4 years). Moreover, annualised bleeding rate will only crudely measure effectiveness of prophylaxis and is therefore less useful in patients with infrequent or minor bleeds [52]. In patients with few joint and muscle bleeds, improvements in HRQoL and adherence can only be achieved by more optimal access to health care or improved factor concentrate administration. Inversely, aggravation of disease can only be measured by subtle soft tissue changes and assessment of participation in physical activities [52].

With regard to simple and effective measurement of adherence, patients' self-reports are of importance as Osterberg et al. have recently stated [9]. The self-reported VERITAS-Pro adherence scale as developed by Duncan et al., was translated and validated by Lock et al. in the Dutch population. Within this study, it was proven to be an easy to use instrument to measure adherence in the (moderate) severe haemophilia population on prophylactic treatment [35, 36] and showed slightly improved communication between (parents of) patient, and the haemophilia treatment centre. It is well known that bonding with treating professionals is important to optimize adherence to treatment [14]. In addition, long term investment in the relationship will uncover problems associated with non-adherence [53]. In literature, well-developed self-efficacy is related to better treatment adherence [54]. In our population, self-efficacy with regard to haemophilia treatment was high. This unfortunately also limited the possibility to detect an improvement in self-efficacy capacities after study intervention.

To appreciate study results, some methodological aspects should be considered. Firstly, this paper describes a pre- and post-intervention study designed to evaluate the effect of standardised transmural haemophilia care. Although a randomised controlled trial (RCT) is the gold standard to evaluate an intervention, this was not feasible due to the very low incidence of haemophilia. A strength of our study design is that it is not restricted to a highly selected cohort, which often leads to a lower external validity in RCTs [55]. Secondly, a limitation of the design is that time-varying confounders of both

medical and social nature could not be eliminated and may have influenced outcome parameters [56]. Life events experienced by patients and parents such as divorce, moving of house, passing away of relatives and comorbidity, have both a psychological impact as well as an effect on daily routines and therefore certainly affect quality of life. Perhaps, more than our intervention could ever have. As data on life events were not collected from the year before start of the intervention, it was not possible to correct for these events [56]. Thirdly, although response rate was high, reducing possible selection bias, the (seven) patients lost to follow-up were a substantial part (15%) of the study population. Analyses showed that these patients were significantly older than analysed study patients. Non-adherence to study participation may be suggestive of non-adherence to treatment in general. Therefore, the intervention may have had a larger effect in the lost to follow-up subgroup. Strikingly, mainly patients with a medium or high maternal educational level and maternal paid employment were lost to follow up. Although level of education is not consistently related with treatment adherence, selection bias cannot be ruled out completely with regard to the endpoints adherence to prescribed treatment and total clotting factor concentrate consumption. Fourthly, good quality of life, high adherence and high self-efficacy scores at baseline limited measurement of effects of the intervention due to a ceiling effect of applied instruments. These high baseline values are most probably the result of the intensive training before initiation of home treatment and the existing intense relationship between (parents of) patients and treating professionals as well as high accessibility of care in the Netherlands.

Importantly, a longitudinal study during a longer time span, in a high risk category for non-adherence (a.o. at initiation of home treatment, adolescence and older age, life events with a large social impact, socioeconomic level), may lead to more significant results. Lastly, only self-reported infusion logs from one single centre could be used for analyses.

Conclusions

Although effects are small, transmural care by a haemophilia nurse leads to improvement of perceived support by parents and of communication between parents and the haemophilia treatment centre. Taking the lifelong relationship between patients with the haemophilia treatment centre this is an important finding to increase and maintain quality of care.

ACKNOWLEGDEMENTS

The authors would like to thank A. de Goede-Bolder for initiating the study and M.A. Westenberg for help in data collection.

This study was financially supported by an investigator-initiated, unrestricted research grant from Bayer Schering Pharma and an unrestricted research grant from Pfizer.

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APPENDIX 1. Health care outcome questionnaire scores at baseline and after intervention, adolescent report.

Outcome measures; Adolescent report	Baseline			Post intervention			Effect			
	N	Median	[IQR]	*N*	Median	[IQR]	Median difference	[IQR]	*P*#	Effect size
Primary outcome										
CHQ; generic quality of life										
Physical Functioning (PF)	22	100	[99-100]	22	100	[99-100]	0	[0-0]	0.75	-0.13
Role Functioning – Emotional (RE)	22	100	[100-100]	22	100	[97-100]	0	[0-0]	0.23	-0.28
Role Functioning – Behavioral (RB)	22	100	[100-100]	22	100	[100-100]	0	[0-0]	0.68	-0.23
Role Functioning – Physical (RP)	22	100	[100-100]	22	100	[100-100]	0	[0-0]	0.28	-0.31
Bodily Pain (BP)	22	20	[0-30]	22	20	[0-33]	0	[0-23]	0.13	0.39
General Behavior (GB)	22	86	[80-93]	22	92	[79-98]	1	[-4-5]	0.38	0.25
Mental Health (MH)	22	88	[79-91]	22	88	[73-95]	1	[-4-7]	0.75	0.00
Self Esteem (SE)	22	21	[6-27]	22	20	[2-29]	-2	[-9-9]	0.77	-0.03
General Health Perceptions (GH)	22	79	[73-94]	22	80	[71-89]	2	[-10-7]	0.63	-0.12
Change in Health (CH)	22	38	[0-50]	22	50	[25-50]	13	[0-25]	0.07	0.63
Family Activities (FA)	22	100	[86-100]	22	100	[92-100]	0	[-1-8]	0.33	0.30
Family Cohesion (FC)	22	30	[23-60]	22	30	[0-60]	0	[-30-0]	0.07	-0.47
Total	22	19	[15-22]	22	14	[10-23]	-2	[-7--7]	0.12	-0.25
Haemo-QoL; disease-specific quality of life										
Physical health	22	2	[0-22]	22	9	[0-22]	2	[-5-11]	0.35	0.29
Feeling	22	3	[0-8]	22	0	[0-7]	0	[-3-0]	0.57	-0.02
View	22	6	[0-21]	22	9	[0-21]	0	[-6-13]	0.81	0.01
Family	22	6	[0-19]	22	2	[0-13]	0	[-7-1]	0.21	-0.17
Friend	22	44	[22-89]	22	25	[6-52]	-9	[-39-8]	0.06	-0.42
Perceived support	22	53	[19-89]	22	28	[17-64]	-6	[-44-6]	0.05	-0.53
Others	22	0	[0-9]	22	0	[0-6]	0	[-5-1]	0.53	-0.12

APPENDIX 1. Health care outcome questionnaire scores at baseline and after intervention, adolescent report. (continued)

	Baseline			Post intervention			Effect			
Outcome measures; Adolescent report	***N***	**Median**	**[IQR]**	***N***	**Median**	**[IQR]**	**Median difference**	**[IQR]**	***P*#**	**Effect size**
Sport	22	11	[0-26]	22	6	[2-19]	-3	[-19-3]	0.24	-0.10
Dealing	22	46	[27-61]	22	42	[29-46]	-13	[-22-11]	0.07	-0.30
Treatment	22	16	[9-24]	22	13	[2-30]	0	[-10-10]	0.89	-0.02
Future	22	19	[5-38]	22	25	[13-31]	0	[-8-13]	0.47	0.21
Relationship	22	0	[0-0]	22	0	[0-0]	0	[0-0]	0.41	-0.22
SDQ; behavioral scores										
Total difficulties	22	6	[5-13]	22	6	[2-10]	-1	[-4-1]	0.14	-0.24
Emotional symptoms	22	1	[0-3]	22	1	[0-3]	0	[-1-1]	0.60	-0.11
Conduct problems	22	1	[1-2]	22	1	[0-1]	0	[-1-0]	0.01 *	-0.64
Hyperactivity-inattention	22	4	[2-5]	22	3	[0-6]	-1	[-2-0]	0.18	-0.29
Peer problems	22	1	[1-2]	22	1	[0-2]	0	[0-1]	0.27	0.24
Prosocial behavior	22	9	[7-10]	22	9	[8-10]	0	[0-1]	0.50	0.14
Secondary outcome										
VERITAS-Pro; adherence scale										
Total scale	22	44	[39-54]	22	41	[36-46]	-2	[-10-2]	0.25	-0.25
Time	22	5	[4-7]	22	6	[6-7]	0	[-1-2]	0.33	0.40
Dose	22	5	[4-8]	22	4	[4-6]	0	[-2-1]	0.32	-0.24
Plan	22	10	[8-12]	22	8	[8-11]	-2	[-4-1]	0.07	-0.45
Remember	22	6	[4-8]	22	7	[7-8]	1	[-1-3]	0.14	0.38
Skip	22	5	[4-6]	22	5	[5-6]	0	[-1-0]	0.59	-0.09
Communicate	22	10	[7-16]	22	6	[6-13]	-1	[-4-0]	0.06	-0.46
Hemophilia Self-Efficacy Scale	20	58	[55-60]	22	57	[53-59]	1	[-2-2]	0.43	-0.26

N = number (percentages); Median [IQR = Inter quartile range 25-75%]; CHQ = Child health Questionnaire; Haemo-QoL = Haemophilia-specific Quality of Life; SDQ = Strength and Difficulties Questionnaire; VERITAS-Pro = Validated Haemophilia Regimen Treatment Adherence Scale; #Wilcoxon signed rank test; *$P<0.05$.

CHAPTER 3

Adherence to treatment in a Western European pediatric population with hemophilia: reliability and validity of the VERITAS-Pro scale

J Lock, H Raat, N Duncan, A Shapiro, M Beijlevelt, M Peters, RYJ Tamminga, FWG Leebeek, HA Moll, MH Cnossen

Haemophilia. 2014 Sep;20(5):616-23.

ABSTRACT

Background Treatment adherence in haemophilia is strongly associated with quality of life and the cost-benefit of treatment. Therefore, it is important to quantify and monitor it.

Aim This study aimed to validate a translation of the VERITAS-Pro cross-culturally and analyse treatment adherence in a Dutch population of paediatric haemophilia patients.

Patients and Methods Children aged 1-18 years with haemophilia were included from three Haemophilia Treatment Centres, on prophylactic clotting factor replacement therapy for more than 1 year. Parents and adolescents were analysed separately. The adherence scale for prophylactic therapy (VERITAS-Pro) was translated according to international guidelines. This instrument contains a total of six subscales ('Time', 'Dose', 'Plan', 'Remember', 'Skip', 'Communicate') each with four items. Lower scores reflect *higher* adherence.

Results Overall response rate was 85%, leading to a study population of 60 children. Mean age was 10 years (SD = 4.1). *Internal consistency reliability*: mean Cronbach's alphas were adequate (> 0.70) for total score and the subscales 'Skip' and 'Communicate'. Item-own subscale correlations were stronger than most item-other subscale correlations. *Convergent validity*: Total scores were higher for non-adherent participants compared with adherent participants according to patient infusion logs (n = 48; $P < 0.05$). *Test-retest correlations:* Significant for all scales except 'Dose' (n = 58; $P < 0.01$).

Conclusion This study demonstrates applicability of VERITAS-Pro outside the United States, as total score and most subscales effectively quantified treatment adherence in a Dutch paediatric population on prophylactic therapy. Non-adherent respondents' total scores were significantly higher, demonstrating the ability of VERITAS-Pro to identify non-adherent individuals.

INTRODUCTION

Patients' adherence to therapy and recommended lifestyle measures are strongly correlated with clinical outcome, quality of life and cost-benefit of treatment in chronic diseases such as haemophilia [1-3]. In Europe, when indicated, haemophilia patients are treated prophylactically with clotting factor replacement therapy in the home setting (prophylaxis), which significantly decreases spontaneous bleeding and joint damage [4-7]. In case of acute bleeding, haemophilia patients are also treated on demand with clotting factor concentrate. Both strategies require patient adherence and responsibility with regard to treatment.

In a meta-analysis assessing general adherence and clinical outcomes of medical treatment DiMatteo et al. found that 26% of patients experienced a better clinical outcome if adhering to treatment [2]. In haemophilia, non-adherence to prescribed clotting factor therapy is reported in up to 50% of patients on prophylaxis [8-11], clinically manifested by both under- and overtreatment. Expectedly, regular undertreatment leads to higher risk of repetitive joint bleeding, synovial hypertrophy, cartilage- and bone damage with arthropathy and disability as a result [1, 12]. On the other hand, overtreatment leads to unnecessary and avoidable costs, as well as a higher risk of complications such as development of inhibiting antibodies, adverse reactions, and infectious or thrombotic complications [13, 14].

The main reasons for non-adherence in haemophilia are the chronic and unpredictable course of disease, long-term dependency on treatment, obligatory lifestyle adjustments, and invasiveness of intravenous administration of clotting factor concentrate [15-19]. The importance of identifying treatment non-adherence was recently established in a review by Schrijvers et al. [11]. Primary determinants were infrequent or absence of symptoms and increasing age. Motivators of adherence were experience with the disease, positive ideas regarding necessity of treatment and an optimal relationship with the health care provider [9, 11, 20]. Recent developments with regard to pharmacokinetic-guided dosing of replacement therapy and the development of long-acting clotting factor products, underline the importance of adherence in the haemophilia population. This, as minimal and infrequent dosing schemes in combination with non-adherence, may lead to dangerously low clotting factor trough levels with increased risk of bleeding [21].

Although recognized as important, a recent study by Chan et al. indicated that up to 18% of haemophilia professionals do not assess adherence in the clinical setting at all [22]. This is most likely due to the lack of accurate and inexpensive instruments to quan-

tify adherence [23]. Healthcare professionals therefore rely on their personal judgment when evaluating treatment adherence; which has proven unreliable repetitively [24].

A valuable tool to quantify adherence in haemophilia is the Validated Haemophilia Regimen Treatment Adherence Scale - Prophylaxis (VERITAS-Pro), developed and validated by Duncan et al. (2010) in the United States [25]. This initiative combines qualitative research with quantitative survey techniques and has led to a time-efficient and feasible instrument to monitor adherence to prophylaxis, applicable in all age groups [26]. Until now, VERITAS-Pro has only been validated in the United States. However, to prove reproducibility and to promote broader application, it is necessary to validate it in other populations that differ with regard to language, culture and healthcare organization. In this study, we aimed to validate the Dutch-translated version of the VERITAS-Pro cross-culturally and analyse treatment adherence in a Dutch paediatric haemophilia population.

PATIENTS AND METHODS

Patients

In this cross-sectional, Dutch multicentre study data were collected as part of a larger prospective study on the efficacy of home-treatment intervention by a trained haemophilia nurse (Dutch Trial Register: 2543). Between June 2010 and December 2011, we enrolled children aged 1 to 18 years with haemophilia A or haemophilia B on prophylactic home treatment for at least 1 year, and their parents from three Dutch Haemophilia Treatment Centres (HTC). Patients and parents with language difficulties and patients with inhibitors were excluded. One caregiver, primarily involved in daily haemophilia treatment, and adolescents aged 10 to 18 years, were asked to complete the web-based questionnaire. To evaluate test-retest reliability of VERITAS-Pro, questionnaires were sent 2 weeks after the first administration to consenting participants. Participants not returning the questionnaire within 2 weeks received reminders and were considered lost to follow-up after two unreturned messages. The Medical Ethical Committee granted permission to perform the study and written informed consent was obtained [MEC-2010-097].

Data collection

Socio-demographic data were registered. For level of education the International Standard Classification of Education (ISCED) division into low (ISCED 0-2; less than upper secondary level), medium (ISCED 3-4; upper secondary level) and high educational level was applied (ISCED 5-6; tertiary level or the achievement of two more years after upper

secondary level) [27]. Haemophilia diagnosis, treatment and pharmacy dispensations were recorded. Infusion log data and bleedings were collected when available.

Adherence

VERITAS-Pro

To quantify treatment adherence in children utilizing prophylaxis, we used the VERITAS-Pro scale, which takes approximately 10 minutes to complete [25]. This instrument consists of six subscales, concerning a specific domain of haemophilia care. Each subscale is represented by four questions, leading to a total of 24 items (Table 2). VERITAS-Pro evaluates the necessity and dosing of clotting factor concentrate (subscales: 'Time', 'Dose') in relationship to prior prophylactic doses (subscales: 'Remember', 'Skip'), and if the patient's HTC was contacted (subscale: 'Communicate'). Also, management of clotting factor infusion and stock is monitored (subscale: 'Plan'). Each item is quantified on a five-point Likert scale ranging from 'Always' to 'Never'. Each rating on the five-point scale is given a numeric score, so that the response indicating the 'best' adherence scores one point and the response indicating the 'worst' adherence scores five points. Total cumulative score ranges from 24 to 120, with cumulative scores per subscale ranging from 4 to 20. Higher scores reflect *lower* adherence. We translated VERITAS-Pro into Dutch according to international guidelines with two forward (AdG and RvA) and two backward translations by native speakers (KS and MC) [28].

Self-reported infusion log

Adherence was also determined on the basis of prescribed prophylaxis and prophylactic infusions deduced from self-reported infusion logs, in relationship to recorded bleeds. Infusion log data were only included in statistical analyses if less than one-third of the data in the patient-reported infusion logs were missing [25]. We calculated the percentage of weeks per year that the patient was adherent according to prescribed therapeutic regimen related to reported (i) frequency of infusions; (ii) interval between two or three consecutive infusions; and (iii) total amount of clotting factor. Patients with an adherence score ≤ 75% were considered to have low adherence, those with scores > 75% were considered to display high adherence, based on earlier studies [9, 10, 15, 25, 29]. Bleeds were recorded in infusion logs and medical records.

Data analysis

Psychometric properties of VERITAS-Pro

VERITAS-Pro scores were described by conventional descriptive statistics.

Reliability

To evaluate consistency of results across items we determined *internal consistency reliability* using Cronbach's alpha. Assuming that test items measuring the same construct are correlated [30], we chose 0.70 to be an adequate alpha coefficient [31, 32]. Homogeneity of VERITAS-Pro was evaluated on the basis of inter-item correlations, which determines the correlation between each item and the subscale to which this item belongs. Inter-item correlations > 0.20 are generally acceptable [30, 33, 34]. Average inter-item, average item-own scale and average item-other scale correlations were assessed with standardized correlation coefficients.

To test reproducibility and consistency over time we determined *test-retest reliability* with Spearman effect size correlation coefficients (*r*) for non-parametric data; it assumes there will be no change in the construct measured. The *agreement* between the perceived adherence of parents and adolescents was also assessed by Spearman correlation [35]. According to established guidelines, concordance was determined as poor (< 0.30), moderate (0.30-0.50), or good (> 0.50) [36]. To test stability of scores, we used the rank-sum test to evaluate whether scores of aggregate test-retest reliability and inter-rater agreement groups systematically changed over time or between parents and adolescents.

Validity

Validity is the extent to which a test measures what it intends to measure. To determine the degree to which two constructs that are theoretically related practically relate within the test, we assessed the *convergent validity* [37]. It was hypothesized that patients with a high adherence according to infusion log documentation would report better adherence outcomes, thus lower VERITAS-Pro scores. In addition, that patients with the lowest quartile annual bleeding rate would report better adherence outcomes than patients with the highest quartile annual bleeding rate. Differences in median total scores were calculated and tested with Wilcoxon test, as a consequence of non-parametric data.

Data were analysed separately for parent-reported and adolescent-reported scales, except for the inter-rater agreement analysis which compared adolescent-reported with parent-reported scales. We considered *P*-values < 0.05 as statistically significant; all tests were two-sided. All analyses were performed using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Parent-reported questionnaires

Participants

Seventy-one children and their parents were eligible for the study; eleven refused participation or did not complete the questionnaire. The remaining 60 parent-reported questionnaires were analysed (response 85%). All sixty children were male with mean age of 10 years (SD = 4.1). The majority had severe haemophilia A with a mean annual bleeding rate of 4.9 (SD = 7.3). Mean duration of prophylactic treatment was 7 years (SD = 3.6) (Table 1).

Psychometric properties

Median scores on the different scales for the parent-report questionnaire were relatively low (4-7). Scores were the highest for subscales 'Plan' and 'Communicate'. Floor effects ranged from 20-57% and were observed most often in subscales 'Dose' and 'Skip'. No ceiling effects were observed (Table 3[A]).

The Cronbach's alpha mean over subscales was α = 0.71 (range = 0.01-0.79). The scales 'Time' and 'Dose' showed the lowest Cronbach's alpha scores (α = 0.38 and α = 0.01 respectively). The homogeneity of the VERITAS-Pro determined by average inter-item correlations was adequate for total score and subscales 'Plan', 'Remember', 'Skip' and 'Communicate' (range = 0.32-0.47, mean r = 0.30). Average inter-item correlation was lower for domains 'Time' (r = 0.18) and 'Dose' (r = 0.01). Scaling assumptions were met since all item-own scale correlations were considerably stronger than corresponding item-other scale correlations (Table 3[A]).

Test-retest Spearman's rho ranged from 0.45 to 0.85 and were significant for all scales (P < 0.01), except for 'Dose'. Scores did not significantly change over time (Table 4[A]).

In 32 patients, adequate infusion logs were available. Infusion log data in one HTC were not documented regularly and one participant was excluded due to underreporting of infusions. Median adherence with regard to reported (i) *frequency of infusions* per week was 90.7% [Interquartile range (IQR) = 73.3-94.1%]; (ii) *interval* between consecutive infusions was 91.1% (IQR = 79.7-95.9%); and (iii) *total amount of clotting factor* was 100% (IQR = 96.2-100%).

Patients with low adherence according to reported *frequency of infusions* showed significantly higher VERITAS-Pro scores for total score and subscales 'Time', 'Remember', 'Skip', and 'Communicate', but not for subscales 'Dose' and 'Plan'. Patients with low adherence

Table 1. Characteristics of the 60 participants at the time of study enrolment.

Characteristics	*N* (%)
Patient characteristics	
Age patients (years), mean (SD)	10.0 (4.1)
Sex patients, male	60 (100.0)
Diagnosis	
Haemophilia A	49 (81.7)
Haemophilia B	11 (18.3)
Disease severity	
Severe (<1%)	53 (88.3)
Moderate (1-5%)	6 (10.0)
Mild (6-40%)[#]	1 (1.7)
Duration of prophylactic treatment (years), mean (SD)	7.0 (3.6)
Annual bleeding rate, mean (SD)	4.9 (7.3)
Parent characteristics	
Age parents (years), mean (SD)	39.3 (7.6)
Level of education[$, &]	
Low	8 (14.0)
Medium	36 (63.2)
High	13 (22.8)
Marital status	
Married/ registered partnership	33 (56.9)
Unmarried	12 (20.7)
Widow/ widower	2 (3.4)
Divorced	11 (19.0)
Family composition[$]	
Living with partner and child(ren)	45 (77.6)
Single with child(ren)	12 (20.7)
Other	1 (1.7)
Individual completing scale[$]	
Mother/ female guardian	52 (89.7)
Father/ male guardian	6 (10.3)
Adolescent	30 (50.0)

[#] On prophylactic treatment due to bleeding tendency due to concomitant von Willebrand disease; [$] Of two participants no information is available on marital status, family composition and individual completing questionnaire. Of three participants no information is available on level of education; [&] The usual ISCED division into Low, Medium and High is adopted here, as in the Eurostat Labour Force Survey. Low is equivalent to ISCED 0-2, i.e. less than upper secondary level of education. Medium is given by ISCED 3-4, i.e. upper secondary level. High is ISCED 5-6, meaning tertiary level, or two more years of education after upper secondary level [27].

Table 2. Subscales and items evaluated by the VERITAS-Pro scale.[#,$]

'Time'	
1	I do prophylaxis infusions on the scheduled days.
2	I infuse the recommended number of times per week.
3	I do prophylaxis infusions in the morning as recommended.
4	I do infusions according to the schedule provided by the treatment center.
'**Dose**'	
5	I use the doctor-recommended dose for infusions.
6	I infuse at a lower dose than prescribed.
7	I increase or decrease the dose without calling the treatment center.
8	I use the correct number of factor boxes to total my recommended dose.
'**Plan**'	
9	I plan ahead so I have enough factor at home.
10	I keep close track of how much factor and how many supplies I have at home.
11	I run out of factor and supplies before I order more.
12	I have a system for keeping track of factor and supplies at home.
'**Remember**'	
13	I forget to do prophylaxis infusions.
14	Remembering to do prophylaxis is difficult.
15	I remember to infuse on the schedule prescribed by the treatment center.
16	I miss recommended infusions because I forget about them.
'**Skip**'	
17	I skip prophylaxis infusions.
18	I choose to infuse less often than prescribed.
19	If it is inconvenient to infuse, I skip the infusion that day.
20	I miss recommended infusions because I skip them.
'**Communicate**'	
21	I call the treatment center when I have questions about haemophilia or treatment.
22	I call the treatment center when I have haemophilia-related health concerns or when changes occur.
23	I make treatment decisions myself rather than calling the haemophilia center.
24	I call the treatment center before medical interventions, such as dental extractions, colonoscopies, visits to the emergency room, or hospital stays.

[#] Answer options (5): Always (all of the time, 100% of the time); Often (most of the time, at least 75% of the time); Sometimes (occasionally, at least 50% of the time); Rarely (not often, 25% of the time); Never (not at all, 0% of the time); [$] Reproduced with permission from Ref 25.

Table 3. Score distribution, internal consistency reliability and convergent validity of the VERITAS-Pro scale.
(a) Parent report

	Scale scores			Internal consistency reliability				Convergent validity		
(Sub)scales	Median [IQR]	Min (%)[#]	Max (%)[$]	Cronbach's alpha[&]	Average inter-item correlation[†]	Average item-own scale correlation	Average item-other scale correlation	Frequency (*P*-value)[‡]	Interval (*P*-value)[‡]	Dose (*P*-value)[‡]
Total scale	36 [29-41]	5	0	0.71	0.30	-	-	0.02	0.87	0.97
Time	5 [4-7]	30	0	0.38	0.18	0.59	0.16	0.04	0.87	0.97
Dose	4 [4-6]	57	0	0.01	0.01	0.43	0.16	0.56	0.91	0.23
Plan	7 [4-9]	35	0	0.58	0.35	0.69	0.17	0.38	0.21	0.79
Remember	5 [4-8]	47	0	0.52	0.32	0.68	0.18	0.02	0.24	0.63
Skip	4 [4-6]	53	0	0.71	0.45	0.76	0.17	0.01	0.87	0.36
Communicate	6 [5-11]	20	0	0.79	0.47	0.78	0.18	0.24	0.76	1.00

[#] Floor effect; percentage of respondents with best possible score (high adherence); [$] Ceiling effect; percentage of respondents with worst possible score (low adherence);
[&] Internal consistency reliability; [†] Each item was correlated with the applicable *ad hoc* scale without the item under consideration; [‡] Mann-Whitney *U* test.

(b) Adolescent report

	Scale scores			Internal consistency reliability				Convergent validity		
(Sub)scales	Median [IQR]	Min (%)[#]	Max (%)[$]	Cronbach's alpha[&]	Average inter-item correlation[†]	Average item-own scale correlation	Average item-other scale correlation	Frequency (*P*-value)[‡]	Interval (*P*-value)[‡]	Dose (*P*-value)[‡]
Total scale	44 [39-49]	3	0	0.70	0.27	.	.	0.95	0.82	0.50
Time	6 [4-7]	33	0	0.46	0.13	0.55	0.18	0.68	0.70	0.50
Dose	5 [4-6]	50	0	0.39	0.14	0.59	0.16	0.86	0.93	0.50
Plan	10 [7-12]	17	3	0.58	0.27	0.67	0.19	0.13	0.70	0.75
Remember	6 [4-8]	27	0	0.47	0.25	0.63	0.16	0.86	0.70	0.38
Skip	5 [4-6]	40	0	0.73	0.52	0.79	0.17	0.10	1.00	0.38
Communicate	10 [7-16]	13	0	0.71	0.35	0.71	0.18	0.86	0.60	0.88

[#] Floor effect; percentage of respondents with best possible score (high adherence); [$] Ceiling effect; percentage of respondents with worst possible score (low adherence);
[&] Internal consistency reliability; [†] Each item was correlated with the applicable *ad hoc* scale without the item under consideration; [‡] Mann-Whitney *U* test.

Table 4. Test-retest reliability of the VERITAS-Pro scale.

(a) Parent report

(Sub)scales	Test (*n* = 41) Median [IQR]	Retest (*n* = 41) Median [IQR]	*P*-Value (Wilcoxon)	Spearman's Correlation
Total scale	38.0 [30.5-43.5]	38.0 [30.5-41.5]	0.28	0.69**
Time	6.0 [4.0-7.0]	5.0 [4.0-7.0]	0.44	0.75**
Dose	5.0 [4.0-6.0]	5.0 [4.0-5.0]	0.63	0.10
Plan	8.0 [4.0-10.0]	8.0 [4.0-9.5]	0.28	0.85**
Remember	5.0 [4.0-8.0]	4.0 [4.0-6.0]	0.06	0.45**
Skip	4.0 [4.0-6.0]	4.0 [4.0-6.0]	0.55	0.72**
Communicate	6.0 [5.0-11.5]	7.0 [5.0-11.0]	0.89	0.57**

** Correlation is significant at the 0.01 level (2-tailed).

(b) Adolescent report

(Sub)scales	Test (*n* = 41), Median [IQR]	Retest (*n* = 41), Median [IQR]	*P*-Value (Wilcoxon)	Spearman's Correlation
Total scale	42.0 [39.5-50.5]	10.0 [35.0-47.0]	0.12	0.07
Time	6.0 [4.0-7.0]	5.0 [4.0-6.5]	0.84	0.62**
Dose	5.0 [4.0-7.0]	5.0 [4.0-6.0]	0.19	0.50*
Plan	10.0 [7.5-12.5]	10.0 [6.5-13.0]	0.51	0.54*
Remember	5.0 [4.0-6.5]	6.0 [4.0-7.0]	0.63	0.47
Skip	5.0 [4.0-5.5]	4.0 [4.0-6.0]	0.46	0.17
Communicate	5.0 [7.0-16.0]	8.0 [5.5-13.0]	0.13	0.26

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

according to reported *interval* between consecutive infusions showed significantly higher VERITAS-Pro scores on subscale 'Remember', but not on other scales. Patients with low adherence according to reported *total amount of clotting factor* showed significantly higher VERITAS-Pro scores on subscales 'Time', but not on other scales (Table 3[A]).

No significant differences on VERITAS-Pro scores, both parent-reported and adolescent-reported were seen between patients with lowest number of annual bleedings (lowest quartile) and patients with highest number of annual bleedings (highest quartile) (data not shown).

Adherence to prophylactic clotting factor replacement therapy according to VERITAS-Pro total score and subscale 'Time' was significantly lower in patients with higher age (respectively $r = 0.27$, $P = 0.04$; $r = 0.30$, $P = 0.02$) and in patients with longer duration of prophylactic treatment (respectively $r = 0.29$, $P = 0.03$; $r = 0.31$, $P = 0.02$), and not associated with level of education. Single parents reported significantly lower adherence on subscale 'Remember' (median = 7.5, IQR = 4.5-8.0) than those who living with a partner

(median = 4.0, IQR = 4.0-7.0; $P = 0.04$); no significant differences were reported on the other scales.

Adolescent-reported questionnaires

Participants

Forty adolescents, aged 10-18 years were eligible for the sub-study. Ten were unwilling to participate or did not complete the web-based questionnaire. The remaining 30 adolescent-reported questionnaires were analysed (response rate 75%).

The mean age of male adolescents was 13.5 years (SD = 2.5); the majority had severe haemophilia A; mean duration of prophylactic treatment was 9.8 years (SD = 3.0).

Psychometric properties

Median scores for the adolescent report were somewhat higher than the parent report (5-10). The highest scores were found for subscales 'Plan' and 'Communicate'. Floor effects ranged from 13% to 50% and were observed most often in subscales 'Dose' and 'Skip'. A ceiling effect of 3% was observed in subscale 'Plan' (Table 3[B]).

Internal consistency was generally adequate with mean Cronbach's alpha of 0.70 on the subscales (range = 0.39-0.73). Subscales 'Time' and 'Dose' had the lowest Cronbach's alpha scores ($\alpha = 0.46$ and $\alpha = 0.39$ respectively). Average inter-item correlations were adequate for total score and subscales 'Plan', 'Remember', 'Skip' and 'Communicate' (range = 0.25-0.52, mean $r = 0.27$), but were lower for subscales 'Time' ($r = 0.13$) and 'Dose' ($r = 0.14$). All item-own scale correlations were considerably higher than corresponding item-other scale correlations (Table 3[B]).

Adolescents' test-retest Spearman correlations were significant for subscales 'Time' ($r = 0.62$, $P < 0.05$), 'Dose' ($r = 0.50$, $P < 0.01$), and 'Plan' ($r = 0.54$, $P < 0.01$). No significant test-retest correlation was observed for the total scale and subscales 'Remember', 'Skip', and 'Communicate'. Scores did not change significantly over time (Table 4[B]).

Sixteen of the 30 adolescent patients had infusion logs available. Median adherence with regard to reported frequency of infusions per week was 88.6% (IQR = 73.2-96.9%); interval between consecutive infusions was 93.0% (IQR = 81.5-96.0%); total amount of clotting factor was 100% (IQR = 95.6-100%). In this subgroup, the sum scores per subscale did not correlate significantly with adherence scores recorded by infusion logs (Table 3[B]).

Adherence to prophylaxis according to the adolescent-report of VERITAS-Pro was not associated with age or education. Adherence on subscale 'Time' was significantly lower in adolescents on longer duration of prophylactic treatment ($r = 0.43$, $P = 0.02$). Adherence on subscale 'Skip' is significantly lower in adolescents with a single parent than in families with non-single parents (respectively median 6.0 and 4.0; $P < 0.01$); no significant differences were reported on the other scales.

Inter-rater agreement

Inter-rater agreement between parents and adolescents showed a significant correlation for subscales 'Time', 'Remember', 'Skip' and 'Communicate' (Spearman correlation range = 0.39-0.56, $P < 0.05$), but not for total scale ($r = 0.19$) and subscales 'Dose' ($r = 0.19$) and 'Plan' ($r = 0.26$).

DISCUSSION

Adherence is of utmost importance in haemophilia treatment to ensure quality of life by decrease of morbidity due to joint arthropathy. Therefore, a reliable tool to routinely measure adherence is urgently required. The adequate psychometric properties shown by our data confirm that the VERITAS-Pro by Duncan et al. [25] is a reliable and feasible tool to quantify adherence from a Dutch paediatric perspective. The internal consistency of the total scale and almost all subscales is adequate. Moreover, test-retest reliability and the ability of the instrument to discriminate between high and less optimal treatment adherence shows promising results.

Strengths and limitations

Feasibility is illustrated by the optimal acceptance of VERTIAS-Pro by the study population as judged by the high response rate [11]. However, although the VERITAS-Pro was adapted by an interdisciplinary panel of experts, critical appraisal by respondents was omitted. Possibly, readability and perceived relevance could have been even greater if applied. Although the population tested by Duncan et al. was older and more heterogeneous in terms of age (mean 10 ± 4.1 compared to mean 15.2 ± 12.7 years), our data still shows that VERITAS-Pro is valid and reliable and applicable in varying populations. VERITAS-Pro was validated using patient infusion log data, in line with previous studies [10, 25]. Although the representativeness of a home infusion log has been questioned, we still regard it as essential, as there is no alternative and ethical method [38]. In one participant, infusion log data were excluded due to underreporting; therefore, selection bias could have occurred in favour of more adhering patients. Unfortunately, analyses of subgroups were limited by low number of participants.

Psychometric properties and scores

VERITAS-Pro scores in the Dutch study population were somewhat higher than those from the United States, especially in subscales 'Plan' and 'Communicate', representative of less adherence. This may be explained by socio-demographic data and cultural differences between populations, such as age, duration of prophylactic treatment, family composition, and a tendency of Dutch haemophilia professionals to focus on self-management [14, 23, 39]. Although the HTCs in the United States and the Netherlands provide high quality of care, transcontinental differences in care are most probably due to shorter distances to the HTCs in the Netherlands. Hypothetically, the more frequent regular HTC visits may paradoxically lead to greater patient- and parent autonomy with more emphasis on self-management as there may be more trust and the HTC is always nearby in case of problems.

Pronounced skewing towards greater adherence with a floor effect of more than 50% was seen in subscales 'Dose' and 'Skip'. This phenomenon is unavoidable, but limits discrimination among participants with a high perceived adherence and restricts detection of change in follow-up assessments in this subgroup [40].

VERITAS-Pro's internal consistency was adequate and almost similar to the original survey, with exception of subscales 'Time' and 'Dose' [25]. Methodically, a lower Cronbach's alpha in these subscales may be due to high floor effects and a small amount of random variance caused by the more homogeneous Dutch population [41]. In addition, the higher percentage of adolescents in our sample may have influenced reliability as adolescents often share responsibility for treatment with parents [17].

VERITAS-Pro test-retest reliability was adequate for all subscales, except for subscale 'Dose'. The most probable explanation is the high floor effect with small amounts of random variation and lower internal consistency of this subscale. As our study did not assess the VERITAS-Pro's responsiveness to change, further studies with a repeated-measures design in more varied samples are required [42].

Total score and most subscales were supported by the validity analysis. Particular attention should be paid to 'Dose' and 'Plan' subscales and items considering these subscales in future analysis. Overall, only five scale items (2, 5, 6, 9, and 21) failed to show any correlation at a $P < 0.10$ level with any of the validity indices (data not shown). In these items, there were indications of their potential value from either restricted range or internal consistency analyses. Retention of all items on the VERITAS-Pro at this time is therefore supported by either the validity or reliability data. No significant difference was found in median VERITAS-Pro scores between patients with lowest and highest

bleeding rates. However, this analysis is most likely affected by low bleeding incidence in our population.

The lower adherence score in adolescents is most likely explained by shared responsibility with regard to haemophilia treatment [25, 43]. This may also explain lower reliability and validity scores for the adolescent report and the lower agreement between perceived adherence of parents and adolescents. The latter is not surprising, as quality of life studies with proxy observations regularly show divergent answers between parents and adolescents which is explained by a variety of different factors [44-46]. Therefore, both views are of importance for insights in actual adherence. Moreover, monitoring of adherence in adolescence may prove an important tool in the transitional process towards adult care, measuring the magnitude of adherent behaviour and pinpointing areas in need of improvement.

Conclusion

Our data support that the VERITAS-Pro is a valuable tool to quantify and specify adherence to haemophilia treatment also in the Netherlands and therefore in other Western European countries in which prophylactic treatment is common.

ACKNOWLEDGEMENTS

We thank R. van Aalsburg, K. Spong, A. de Goede-Bolder, and prof. dr. F.C. Verhulst for their help in the translation process of the VERITAS-Pro scale. J. Lock, M. Beijlevelt, M. Peters, R.Y.J. Tamminga and M.H. Cnossen performed the research; J. Lock, H. Raat, F.W.G. Leebeek, H.A. Moll, and M.H. Cnossen designed the research study; N. Duncan, A. Shapiro contributed essential tools; J. Lock, H. Raat and M.H. Cnossen analysed the data; J. Lock and M.H. Cnossen wrote the paper. All authors critically reviewed and approved the final version of the manuscript. The Dutch version of the VERITAS-Pro can be obtained from M.H. Cnossen; m.cnossen@erasmusmc.nl.

This study was financially supported by an investigator-initiated, unrestricted research grant from Bayer Schering Pharma and an unrestricted research grant from Pfizer.

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CHAPTER 4

Reliability and validity of a novel Hemophilia-specific Self-Efficacy Scale

J Lock, H Raat, M Peters, RYJ Tamminga, FWG Leebeek, HA Moll, MH Cnossen

Haemophilia. 2014 Jul;20(4):e267-74.

ABSTRACT

Background Higher self-efficacy in chronic disease patients is associated with higher development of self-management skills and increased quality of life. Quantification and monitoring of self-efficacy is therefore of importance. Self-efficacy in haemophilia patients has received little attention due to lack of standardized scales.

Aim To validate the novel Haemophilia-specific Self-Efficacy Scale (HSES) in haemophilia patients on prophylactic home treatment.

Patients and Methods Haemophilia patients aged 1-18 years on prophylactic treatment ≥1 year were included from three Dutch Haemophilia Treatment Centres. The HSES consists of 12 items, relating to perceptions of the ability to function on a day-to-day basis with regard to patient's disease. Retest was performed in a subsample. Validity was proven by the General Self-Efficacy Scale and by the health-related quality of life assessment tool Haemo-QoL.

Results Data were analysed from 53 children (response 75%), with a mean age of 9.8 years (SD = 4.0). Mean total scale score of HSES was 55.5 (SD = 4.7; range = 38–60), with a ceiling effect of 17%. The HSES showed adequate *internal consistency* (Cronbach's alpha 0.72) and good *test-retest reliability* (Intra-Class-Correlation coefficient 0.75; $P < 0.01$; $n = 37$). The c*onvergent validity* was adequate as haemophilia-specific self-efficacy correlated significantly with general self-efficacy ($r = 0.38$; $P < 0.01$). High HSES scores correlated significantly with quality of life as measured by the Haemo-QoL ($r = -0.42$; $P = < 0.01$).

Conclusion The novel HSES is a reliable and valid tool to assess self-efficacy in paediatric haemophilia patients on prophylactic home treatment. High self-efficacy correlated with higher quality of life, further underlining the importance to standardly assess, monitor and improve self-efficacy.

INTRODUCTION

In haemophilia, as in other chronic diseases, self-management skills of patients and caretakers are of relevance for treatment adherence, prognosis of disease, and quality of life [1]. Prophylactic replacement therapy with clotting factor concentrate in the home setting requires a high ability of self-management as organization of care is complex [2, 3]. It includes insight on the necessity and dosing of clotting factor concentrate, taking prior prophylactic doses into account. Also practical and logistic capacities are of significance with regard to clotting factor concentrate infusion, stock and timely communication with the Haemophilia Treatment Centre (HTC).

Bandura developed the concept of 'self-efficacy'. This term describes the actual confidence an individual possesses with regard to specific actions necessary to achieve certain results [4]. It summarizes the integration of a motivated attitude towards a disease and its treatment, a capacity towards adequate judgment with regard to therapeutic interventions and demonstration of adherence to prescribed therapy [5]. Patients with low self-efficacy are less likely to persevere in a specific task when impediments arise, obliterating usual proceedings. Those with high self-efficacy will deploy all abilities to master obstacles. In clinical practice, self-efficacy is considered an antecedent for modification of behavior [6, 7]. Furthermore, development of disease-specific self-efficacy questionnaires is required to take disease-specific aspects into account not dealt with by the current validated general questionnaire.

In various chronic diseases high levels of self-efficacy are associated with higher quality-of- life and less clinical and psychological symptoms [6, 8-10]. In addition, Richardson et al. reported that patients with a wide range of chronic diseases value self-efficacy highly, and are willing to trade reductions in health-related quality of life for improvements in their self-efficacy [11]. In haemophilia, a number of studies have evaluated general self-efficacy and possible training modules, but few have looked at disease-specific self-efficacy.

Kang et al. proved that a self-help program for mothers of children with haemophilia significantly improved knowledge, self-efficacy, and quality of life [12, 13]. Mulders et al. reported that an educational e-learning program in patients on prophylactic home treatment significantly improved general knowledge of treatment [14]. However, in this cohort, self-efficacy scores were relatively high at initiation and did not increase after intervention. Conflicting results were found by Barlow et al. and Buxbaum et al., as the first documented high levels of self-efficacy in haemophilia patients, indicating a well-developed confidence with regard to disease management, whereas the latter

found lower self-efficacy scores in haemophilia patients than in healthy controls [15, 16]. All studies were performed using a general self-efficacy scale or a non-validated Haemophilia-specific Self-Efficacy Scale (HSES) as there is no validated HSES available. To adequately quantify and monitor self-efficacy and to identify subgroups at risk of higher morbidity and decreased quality of life, the HSES was recently developed and validated. This study aims to describe the psychometric properties of this novel instrument and the association between HSES and quality of life.

PATIENTS AND METHODS

Patients

Data for this cross-sectional, multicentre study were collected as part of a larger prospective study on the efficacy of home-treatment intervention by a trained haemophilia nurse (Netherlands Trial Register: 2543). Between June 2010 and December 2011, we enrolled children aged 1-18 years with haemophilia A or haemophilia B on prophylaxis and home treatment for at least 1 year, from three HTC's in the Netherlands (Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam; Academic Medical Centre - Emma Children's Hospital, Amsterdam; University Medical Centre Groningen). Patients and parents were required to speak and understand Dutch sufficiently. Patients with inhibitors against FVIII or FIX were excluded. One caregiver, primarily involved in the child's daily haemophilia treatment, and adolescents aged 10-18 years were asked to complete the questionnaire. To evaluate test-retest reliability of HSES, the questionnaire was sent two weeks after administration of the first questionnaire to consenting participants. Participants not returning the questionnaires within 2 weeks received reminders and were considered lost to follow-up after two unreturned messages. The Medical Ethical Committee granted permission to perform the study and written informed consent was obtained [MEC-2010-097].

Data collection

Socio-demographic data, including parental level of education, employment status, and family structure were provided. For level of education the International Standard Classification of Education (ISCED) division into low, medium and high educational levels was applied [17]. Low is equivalent to ISCED 0-2, i.e. 'less than upper secondary level'; medium to ISCED 3-4, i.e. 'upper secondary level'; and high to ISCED 5-6, meaning tertiary level, or minimally two years of education after upper secondary level. Haemophilia diagnosis, treatment and clotting factor consumption were extracted from medical files.

Self-Efficacy

Haemophilia-specific Self-Efficacy Scale

To specify disease-specific self-efficacy qualities, a novel scale was developed and validated, specifically for haemophilia patients. The HSES was composed by a team of haemophilia professionals and psychologists with items from the validated Sickle Cell Self-Efficacy Scale [8, 18], from the Pain Self-Efficacy Questionnaire [19], and from the validated General Self-Efficacy Scale [20, 21]. The first two questionnaires were used as they specifically encompass disease aspects such as periodic immobilization and pain. The novel HSES consists of 12 items focusing on an individual's perceptions of haemophilia disease symptoms and the patient's abilities to cope with or reduce these symptoms (see Appendix S1). In our view, all aspects of treatment are incorporated: treatment efficacy, quality of life, infusion technique, state of mind in case of a bleed, pain modification, confidence, modification of prophylactic regimen, continuation of daily activities, other therapeutic interventions besides clotting factor treatment, belief in leading of a normal life, communication, and attainment of personal goals. Items are scored ranging from 'I totally disagree' to 'I totally agree' (see figure). On a five-point Likert-scale, the lowest score was given one point and the highest score five points. An unweighted sum score was calculated by adding the 12 item scores, with higher scores indicating greater self-efficacy (range: 12-60).

General Self-Efficacy Scale

To assess the convergent validity of the HSES, we used the validated General Self-Efficacy Scale (GSES) [20, 21]. The GSES consists of 10 items on a four-point Likert-scale, ranging from 'I totally disagree' to 'I totally agree', with sum scores ranging from 10 to 40. Higher scores also indicate greater general self-efficacy. Although self-efficacy is considered to be task-specific, we assumed the concepts of general self-efficacy and haemophilia-specific self-efficacy to be related, which is supported by literature in other diseases, when assessing self-efficacy [22].

Haemo-QoL

The disease-specific quality of life instrument Haemo-QoL was used to assess the divergent construct validity. This is a self-report measure for children with haemophilia and their parents, consisting of 21-77 items which cover 9 to 11 domains depending on the age group of the patient. Higher scores indicate lower disease-specific quality of life [23].

VERITAS-Pro

To quantify treatment adherence in children on prophylaxis, we used the Validated Haemophilia Regimen Treatment Adherence Scale - Prophylaxis (VERITAS-Pro) [2, 3]. This instrument contains six subscales ('Time', 'Dose', 'Plan', 'Remember', 'Skip', 'Communi-

cate'), each represented by four questions concerning a specific domain of haemophilia patient care. Cumulative score of all subscales ranges from 24 to 120 and cumulative scores per subscale range from 4 to 20. Lower scores reflect *higher* adherence.

Data analysis

Psychometric properties of HSES

The following psychometric properties of the HSES were evaluated: feasibility, reliability and validity (convergent and divergent validity). Feasibility was expressed as response rate. Scale scores were described in terms of scale mean, SD, range, floor and ceiling effects, and percentiles.

The total scale internal consistency reliability was assessed using Cronbach's alpha. Amidst varying standards in the literature, we considered 0.70 to be an acceptable alpha coefficient [24].

The test-retest reliability was assessed by the Intra-Class-Correlation Coefficients (ICC). The agreement between the perceived haemophilia-specific self-efficacy of parents and adolescents was also assessed by the ICC.

Validity was assessed by comparing HSES outcomes with the validated GSES and the Haemo-QoL. It was hypothesized that a low HSES outcome should correlate with low self-efficacy outcomes on the GSES and a low quality of life (i.e. higher score) by Haemo-QoL. As data were not normally distributed correlations in overall median sum scores were calculated and tested with Spearman's correlation coefficient. Low haemophilia-specific self-efficacy was defined as the lowest quartile of HSES scores, while high haemophilia-specific self-efficacy was defined as the highest quartile of HSES scores as data were not distributed normally.

Subgroup analyses were assessed by comparing HSES outcomes with age, duration of prophylactic home treatment, number of siblings, level of education, marital status, and family composition. We compared the patient group with the lowest quartile of HSES scores with the patient group with the highest quartile of HSES scores. Due to non-parametrical data, the continuous outcomes were assessed using the Mann-Whitney *U*-test and categorical data were analysed by Chi-square test or the Fisher's exact test in case of low patient counts per subgroup.

Data were analysed separately for parent-reported and adolescent-reported scales, except for the inter-rater agreement analysis which compared adolescent-reported with parent-reported scales.

We considered *P*-values < 0.05 as statistically significant; all tests were two-sided. All analyses were performed using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Participants

A total of 71 patients of which 40 adolescents (10-18 years) were invited for study participation. Eighteen parents of children, including parents of 12 adolescents declined or did not fill out the questionnaire. Reasons for non-participation included time burden, and logistical reasons. Fifty-three parents of both young children and adolescents (parent-reported questionnaires; response 75%) and 28 adolescents (adolescent-reported questionnaires; response 70%) participated. Table 1 describes the baseline characteristics of all participants.

All 53 children were male with a mean age of 9.8 years (SD = 4.0), 81% were diagnosed with haemophilia A, 89% had severe haemophilia. Of the 53 children, 28 were adolescents. The mean age of this subgroup was 13.6 (SD = 2.5). Mean duration of prophylactic treatment was 7.1 years (SD = 3.6), with a median time span between prophylaxis initiation and start of the home treatment of 0.5 years. Of the 53 parents, the majority was female (88%), 8% were educated at a low level, 20% were single parents, and 30% had two children or more.

Psychometric properties of the HSES

Table 2 displays the total scale scores. Mean total scale scores were relatively high (55.5 for the parent report and 55.7 for the adolescent report) as were the median scores (57.0 for both the parent report and the adolescent report). Floor effects were absent. Ceiling effects were observed in 17% of the parents and in 29% of the adolescents.

The Cronbach's alpha of the total scale was $\alpha = 0.72$ for the parent report and $\alpha = 0.86$ for the adolescent report, indicating an adequate internal consistency (Table 2).

The test-retest reliability showed promising results, with a ICC of 0.75 (95%CI = 0.56:0.86; $P < 0.01$; $n = 37$) for the parent report and 0.67 (95%CI = 0.29:0.87; $P < 0.01$; $n = 17$) for the adolescent report. For the parent report there was no significant difference between the test (mean = 55.70; SD = 4.16) and the retest (mean = 55.88; SD = 4.87; $P = 0.34$); also the adolescent report showed identical results (test mean = 55.88; SD = 4.87; retest mean = 55.18; SD = 3.89; $P = 0.37$). The agreement between the perceived haemophilia-specific

self-efficacy of parents and adolescents was however not significant (ICC = -0.05; 95%CI = -0.43:-0.35; $P = 0.59$).

Table 1. Characteristics of the 53 participants at the time of study enrolment.

Characteristics	*N* (%)
Patient characteristics	
Age patients (years), mean (SD)	9.8 (4.0)
Sex patients, male	53 (100)
Diagnosis	
Haemophilia A	43 (81)
Haemophilia B	10 (19)
Severity of haemophilia	
Severe (<1%)	47 (89)
Moderate (1-5%)	5 (9)
Mild (6-40%)[#]	1 (2)
Duration of prophylactic treatment (years), mean (SD)	7.1 (3.6)
Parent characteristics	
Age parents (years), mean (SD)	39.8 (7.0)
Level of education[$,&]	
Low level of education	4 (8)
Medium level of education	33 (66)
High level of education	13 (26)
Marital status[$]	
Married/ registered partnership	11 (22)
Unmarried	30 (59)
Widow/ widower	2 (4)
Divorced	8 (16)
Family composition[$]	
Living with partner and child(ren)	40 (78)
Single with child(ren)	10 (20)
Other	1 (2)
Individual completing scale[$]	
Mother/female guardian	45 (88)
Father/male guardian	6 (12)
Adolescent	28 (53)

[#] On prophylactic treatment due to bleeding tendency due to concomitant von Willebrand disease; [$] Of two participants no information is available on marital status, family composition and whom filled out the questionnaire. Of three participants no information is available on level of education; [&] The usual ISCED division into Low, Medium and High is adopted here, as in the Eurostat Labour Force Survey. Low is equivalent to ISCED 0-2, i.e. 'less than upper secondary level of education'. Medium is given by ISCED 3-4, i.e. 'upper secondary level'. High is ISCED 5-6, meaning tertiary level, or two more years of education after upper secondary level [17].

Table 2. Score-distribution and internal consistency reliability of the Haemophilia-specific Self-Efficacy Scale (HSES).

	Scale scores					Internal consistency reliability Cronbach's alpha
	Mean (SD)	Range	Median [IQR]	Ceiling effect (%)[#]	Floor effect (%)[$]	
Parent-report (n = 53)	55.45 (4.27)	45-60	57 [54-59]	17	0	0.72
Adolescent-report (n = 28)	55.68 (5.41)	38-60	57 [54-59]	29	0	0.86

[#] Ceiling effect; percentage of respondents with best possible score; [$] Floor effect; percentage of respondents with worst possible score.

Significant Spearman's correlations were observed with the General Self-Efficacy Scale (parent report: r = 0.43; P < 0.05; adolescent report: r = 0.81; P < 0.01). For the quality of life determined by the Haemo-QoL, the correlation of the total score was only significant for the parent-report of the HSES (r = -0.45; P < 0.01) and not significant for the adolescent-report HSES (r = 0.02; P = 0.92). Parents with a higher perceived self-efficacy (HSES) reported significantly less adherence with regard to subscales 'Plan', 'Remember' and 'Communication' on the VERITAS-Pro scale when compared with parents with a lower perceived self-efficacy (respectively r = -0.28; r = -0.29; r = 0.37; P < 0.05). No other correlations were seen between the HSES (parent report), the HSES (adolescent report) and other VERITAS-Pro (sub)scales (Table 3).

Parents with HSES scores in the lowest quartile reported significantly lower median scores on the: GSES (P < 0.01); the Haemo-QoL (sub)scales 'Total score' (P < 0.01), 'Feeling' (P = 0.02), 'View' (P = 0.01), 'Others' (P = 0.03), and 'Sport' (P < 0.01); and on the VERITAS-Pro subscales 'Remember' (P = 0.05), 'Skip' (P < 0.01), and 'Communicate' (P = 0.01), compared to parents with HSES scores in the highest quartile (Table 4). Adolescents with HSES scores in the lowest quartile reported significantly lower median scores on the: GSES (P < 0.01); the Haemo-QoL subscales 'Others' (P = 0.04), and 'Treatment' (P = 0.02), compared to adolescents with HSES scores in the highest quartile (Table 4).

Perceived disease-specific self-efficacy was not associated with age, duration of prophylactic treatment, level of education, number of siblings, marital status, or with family composition. Neither in parents, nor in adolescents (data not shown).

DISCUSSION

The novel Haemophilia-specific Self-Efficacy Scale (HSES) is a feasible and reliable instrument to evaluate self-efficacy in Dutch paediatric patients with haemophilia on

Table 3. Convergent and divergent validity of the Haemophilia-specific Self-efficacy Scale (HSES) with validation measures.

	HSES total scale	
	Parent report	**Adolescent report**
GSES[#]	0.43 *	0.81 **
Haemo-QoI[$]		
Total score	-0.45 **	0.02
Physical	-0.11	-0.06
Feeling	-0.32 *	-0.36
View	-0.38 **	-0.13
Family	-0.27	-0.25
Friends	-0.09	0.34
Support	-0.04	0.14
Others	-0.30 *	-0.55 **
Sport	-0.30 *	0.02
Dealing	0.05	0.31
Treatment	-0.13	-0.48 **
Future	-0.36	-0.23
Relation	-0.11	-0.14
VERITAS-Pro[&]		
Total score	-0.12	0.08
Time	-0.10	-0.13
Dose	-0.11	0.16
Plan	-0.28 *	-0.03
Remember	-0.29 *	0.22
Skip	-0.26	-0.12
Communicate	0.37 **	0.14

[#] General self-efficacy scale; [$] Haemophilia-specific health-related quality-of-life questionnaire; [&] Validated haemophilia regimen treatment adherence scale – prophylaxis; * Spearman's correlation coefficient is significant at the 0.05 level (2-tailed); ** Spearman's correlation coefficient is significant at the 0.01 level (2-tailed).

prophylactic home treatment. As timely communication and intervention is obligatory to modify prognosis in a disease with periodic episodes of pain and immobilization, we believe regular evaluation of self-efficacy is essential. In our study, HSES showed satisfactory psychometric properties and was able to discriminate between high and low self-efficacy. High HSES scores correlated significantly with quality of life measured by the Haemo-QoL. Further evaluation in other populations with regard to age and cultural background is necessary to broaden application possibilities of this valuable tool. Differentiation of subgroups within the haemophilia patient population with regard to self-efficacy is of paramount importance in order to identify potential high risk patients with an increased risk of morbidity and decreased quality of life [25, 26]. Subsequently,

Table 4. Discrimination between validation measures between participants with low and high Haemophilia-specific Self-efficacy Scale (HSES) scores.

	HSES total scale					
	Parent report			Adolescent report		
Validity measures	Low HSES score[#] (*n* = 14); median [IQR]	High HSES score[$] (*n* = 9); median [IQR]	*P*-value[&]	Low HSES score[#] (*n* = 8); median [IQR]	High HSES score[$] (*n* = 8); median [IQR]	*P*-value[&]
GSES[†]	32.50 [30.00-36.00]	38.00 [35.50-39.00]	<0.01	30.00 [27.00-31.75]	39.50 [38.00-40.00]	<0.01
Haemo-QoI[‡]						
Total score	33.77 [25.97-42.59]	20.13 [6.25-24.91]	<0.01	21.59 [16.75-33.33]	23.21 [20.45-24.59]	1.00
Physical	3.57 [0.00-25.89]	0.00 [0.00-8.93]	0.31	3.57 [0.00-25.89]	0.00 [0.00-26.79]	0.80
Feeling	10.94 [0.00-33.59]	0.00 [0.00-1.56]	0.02	4.69 [0.00-39.06]	0.00 [0.00-2.34]	0.13
View	20.14 [0.00-45.00]	0.00 [0.00-1.39]	0.01	8.75 [0.00-28.75]	3.75 [0.63-11.88]	0.72
Family	17.19 [6.25-33.59]	0.00 [0.00-25.00]	0.12	15.63 [0.00-35.16]	1.56 [0.00-14.06]	0.23
Friends	50.00 [25.00-70.31]	0.00 [0.00-84.38]	0.52	37.50 [0.00-65.63]	62.50 [34.38-95.31]	0.20
Support	53.13 [48.44-81.25]	100.00 [37.50-100.00]	0.25	75.00 [37.50-90.63]	81.25 [32.81-92.19]	0.73
Others	6.25 [0.00-30.21]	0.00 [0.00-2.08]	0.03	10.42 [0.00-78.13]	0.00 [0.00-0.00]	0.04
Sport	36.98 [6.25-62.50]	0.00 [0.00-5.56]	<0.01	2.78 [0.00-20.83]	5.56 [0.00-11.11]	1.00
Dealing	41.07 [20.54-50.89]	42.86 [32.14-58.93]	0.37	42.86 [30.36-57.14]	51.79 [44.64-59.82]	0.28
Treatment	20.31 [9.38-32.81]	9.38 [0.00-34.38]	0.37	43.75 [22.66-75.00]	15.63 [7.03-33.59]	0.02
Future	34.38 [25.00-37.50]	21.88 [18.75-25.00]	0.07	37.50 [28.13-46.88]	21.88 [4.69-35.94]	0.13
Relation	0.00 [0.00-37.50]	0.00 [0.00-0.00]	0.57	0.00 [0.00-25.00]	0.00 [0.00-0.00]	0.83
VERITAS-Pro[¶]						
Total score	39.00 [29.75-43.00]	35.00 [29.00-38.50]	0.28	44.00 [40.50-54.75]	48.50 [39.25-55.25]	0.88
Time	5.50 [4.00-7.00]	5.00 [4.00-6.50]	0.48	6.50 [4.50-8.50]	6.00 [4.25-7.00]	0.72
Dose	4.50 [4.00-6.25]	4.00 [4.00-5.50]	0.48	4.50 [4.00-6.00]	5.00 [4.00-7.50]	0.72
Plan	8.00 [6.00-10.50]	4.00 [4.00-9.50]	0.10	10.50 [6.50-15.00]	9.00 [5.00-13.75]	0.80
Remember	8.00 [4.00-8.25]	4.00 [4.00-4.50]	0.05	5.00 [4.25-8.75]	7.00 [4.50-8.00]	0.72
Skip	5.00 [4.00-6.00]	4.00 [4.00-4.00]	<0.01	5.00 [4.25-5.75]	4.50 [4.00-5.75]	0.50
Communicate	5.00 [4.00-6.25]	10.00 [6.00-11.50]	0.01	11.00 [7.50-16.00]	14.50 [8.50-16.00]	0.44

[#] Lowest 25% of HSES scores; [$] Highest 25% of HSES scores; [&] Mann-Whitney *U* test; [†] General Self-Efficacy Scale; [‡] Haemophilia-Specific Quality of life questionnaire; [¶]Validated Haemophilia Regimen Treatment Adherence Scale – Prophylaxis.

patients may undergo interventions aiming to increase self-efficacy, ultimately leading to cost-reduction of treatment in this era of rising health care costs.

Strengths of the HSES are diverse. Firstly, the 12 items chosen cover all aspects of haemophilia care in which self-efficacy plays a role and follow the definition of self-efficacy as described by Bandura in 1977 [4]. Secondly, general self-efficacy and disease-specific self-efficacy correlated significantly as did a higher self-efficacy with a higher quality of life as evaluated by HaemoQoL, a validated and widely used tool to analyse quality of life in children and adolescents with haemophilia. Furthermore, a high response rate was reached among the study population, leading to reliability of conclusions. Fourthly, as the HSES is an easily applied tool, it will allow monitoring of interventions aimed to improve haemophilia-specific self-efficacy. Finally, HSES is another example of a combination of qualitative research and quantitative survey techniques, such as seen in the development of the VERITAS-Pro by Duncan et al. [3]. In our opinion, this approach leads to richer, more valid and more reliable findings, with clear clinical implications, than when adopting qualitative or quantitative methods alone [27].

The limitations of our study are discussed. Firstly, some may deliberate the capturing of self-efficacy by a limited number of questions with fixed answering categories. However, we have chosen to make HSES a feasible tool in daily clinical practice: quick, reliable and valid. Secondly, the lack of patient report in constructing of the questionnaire is an omission as solely expert opinion of haematologists, haemophilia nurses and clinical psychologists was employed. Therefore, patient interpretation of questions may differ. Thirdly, due to practical reasons we were forced to exclude patients with language difficulties due to the questionnaire-based nature of the study. We are thoroughly aware, that specifically this group is characterized by low self-efficacy and decreased adherence to medical treatment [28]. Just as patients with inhibiting antibodies against FVIII/FIX, may also be characterized by low self-efficacy. We excluded this group, due to the fact that their intensive treatment has such a severe impact on daily life that it is not comparable to standard prophylactic treatment. Exclusion of these groups may have biased results towards underreporting of low self-efficacy. However, despite exclusion of these groups, HSES still differentiates between high and low self-efficacy [29], proving the sensitivity of the tool and its applicability in daily clinical practice. Fourthly, we administered a parent report asking how parents perceive their own self-efficacy, but unfortunately omitted how they perceive the self-efficacy of their children, which would have been a valuable addition. Furthermore, statistical analysis of subgroups was of course limited by small sample size. We therefore recommend future studies to assess reliability and validity in other subgroups of patients, and in other settings and to utilize other qualitative research methods such as cognitive debriefing.

HSES scale properties were satisfactory. A floor effect was absent as is frequently the case in positively-skewed assessments of reported self-efficacy [22, 30, 31]. Skewing was observed towards the most positive category ('ceiling effect') as often reported in other surveys on self-efficacy in chronic diseases [22, 30, 31]. This limitation effects the discrimination between participants with a high self-efficacy and restricts participants with a high self-efficacy to acquire better scores in follow-up assessments. The ceiling effect can be explained by several factors such as the extensive education of patients with regard to disease. In addition, current treatment focuses intensively on self-management skills, patients and parents have been dealing with the disease for a longer period of time, and multiple family members may be affected, leading to more disease experience.

The HSES scale questionnaire's internal consistency was good. Cronbach's alpha coefficients in similar questionnaires were comparable [8, 18, 32]. The test-retest reliability was adequate both in parents and adolescents. The agreement between the perceived haemophilia-specific self-efficacy of parents and adolescents showed no correlation, as is often seen when comparing parent-reported and adolescent-reported outcomes on self-efficacy and quality of life questionnaires [33, 34]. This is most likely explained by the differences in treatment experience between parents and adolescents as well as diverging management responsibilities between parents and adolescents.

The convergent and divergent validity analyses of HSES showed promising test results, which is of paramount importance to discriminate between optimal and less optimal self-efficacy and to promote its future use. Both parents and adolescents clearly expressed similar opinions on their HSES report and their general self-efficacy report. In addition, parents also showed similar opinions on their disease-specific self-efficacy as expressed by the HSES and quality of life measurements by Haemo-QoL. However, the latter was only observed in some subscales of the Haemo-QoL in adolescents. Most probably, outcome is influenced by growing and not yet complete responsibility of adolescents for their disease, which directly correlates with self-efficacy outcome and not with quality of life outcome. Adequate transition towards disease responsibility is of course expected of the adult haemophilia patient. This development could be measured and monitored by HSES, making it an important tool in the challenging transitional period [8, 35, 36].

In line with our hypothesis, we found that adherence to administered clotting factor concentrate doses in relationship to prior prophylactic doses (subscales "Remember" and "Skip") was higher in parents with a higher perceived haemophilia-specific self-efficacy. In contrast, we found evidence that adherence to communication with the HTC determined by the VERITAS-Pro was significantly lower in parents with a high perceived disease-specific self-efficacy than in parents with a low perceived self-efficacy.

Our hypothesis is that the latter may be the consequence of the well-developed self-management strategies of these parents, decreasing communication moments. Further research is necessary to objectify patient outcome in these patients.

Conclusion

The HSES shows satisfactory psychometric properties to describe the self-efficacy in paediatric haemophilia patients on prophylactic home treatment. HSES parent report correlated with quality of life measures, further underlining the importance to standardly assess, monitor and improve self-efficacy. Validation in other cohorts is impending to augment the value of HSES.

ADDITIONAL SUPPORTING INFORMATION

Appendix S1. Hemophilia-specific Self-Efficacy Scale.

ACKNOWLEDGEMENTS

We thank A. de Goede-Bolder and C.T Hijmans for their valuable advice at the initiation of the project.

This study was financially supported by an investigator-initiated, unrestricted research grant from Bayer Schering Pharma and an unrestricted research grant from Pfizer.

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Appendix S1. Hemophilia-specific Self-Efficacy Scale.

Haemophilia Self-Efficacy Scale (HSES-parent)
- Parent Form -
English version

Options (5): Not at all - Hardly true - No opinion - Moderately true - Exactly true

1. In case my child has a bleed, I am confident I can treat him/her adequately with clotting factor concentrate.
2. I am confident I can manage my child's haemophilia in such a way that I can participate in activities I like to do.
3. I am confident I administer prophylaxis correctly.
4. I remain calm when my child has a bleed because I am confident about what to do.
5. I am confident I can adequately treat pain caused by a bleed.
6. I am confident I will manage, no matter what happens.
7. I know exactly how to adjust my prophylaxis in certain circumstances.
8. I am confident I can continue my daily routine in case my child has a bleed.
9. In case my child has a bleed, I know what to do besides infusion of clotting factor concentrate.
10. I am certain I can lead a normal life, despite my child's haemophilia.
11. I know exactly who to contact/warn in case I do not know how to handle a bleed.
12. I am certain I can achieve most of my goals in life, despite my child's haemophilia.

Haemophilia Self-Efficacy Scale (HSES-patient)
- Patient Form -
English version

Options (5): Not at all - Hardly true - No opinion - Moderately true - Exactly true

1. In case I have a bleed, I am confident I can treat myself adequately with clotting factor concentrate.
2. I am confident I can manage my haemophilia in such a way that I can participate in activities I like to do.
3. I am confident I administer prophylaxis correctly.
4. I remain calm when I have a bleed because I am confident about what to do.
5. I am confident I can adequately treat the pain caused by a bleed.
6. I am confident I will manage, no matter what happens.
7. I know exactly how to adjust my prophylaxis in certain circumstances.
8. I am confident I can continue my daily routine when I have a bleed.
9. In I have a bleed, I know what to do besides infusion of clotting factor concentrate.
10. I am certain I can lead a normal life, despite my haemophilia.
11. I know exactly who to contact/warn in case I do not know how to handle a bleed.
12. I am certain I can achieve most of my goals in life, despite my haemophilia.

CHAPTER 5

The group medical appointment (GMA) in hemophilia and von Willebrand's disease: a new development in outpatient pediatric care

J Lock, A de Bruin, M Scholten, M Joosten, FM Seesing, A Beishuizen, A de Goede-Bolder, MH Cnossen

Haemophilia. 2012 Sep;18(5):766-72.

ABSTRACT

Background The Group Medical Appointment (GMA) is a novel consultation form in which patients undergo individual consultations in each other's presence.

Aim To compare participants' experiences with GMA and Individual Medical Appointments (IMA), the usual standard of care.

Methods Our team recently implemented the GMA for children aged 0-18 years with haemophilia or von Willebrand's disease. Participants' experiences with GMA were measured using a standardized QUOTE-questionnaire. Of 100 addressed families, 53 participated in GMA. Of these 53 families, 38 parents (72%) and 14 adolescents (82%) filled in the questionnaire about the GMA. Patients not on prophylaxis were defined as less experienced and patients on prophylaxis, as experienced.

Results Although parents were satisfied with both GMA and IMA (median score 8.0 versus 9.0 out of 10), a significant difference was demonstrated between less experienced and experienced parents. After GMA, less experienced parents were significantly more satisfied (median score 8.0 vs 5.0; $P = 0.006$), felt more social support (82% vs 30%; $P = 0.005$) and reported additional learning effects with regard to disease and treatment (64% vs 0%; $P < 0.001$) than experienced parents. None of the less experienced parents reported privacy problems during GMA compared with 40% of experienced parents. In adolescents an identical trend was reported. Sixty-six percent of parents would join a GMA in the future and 87% would recommend a GMA to others.

Conclusion GMA is a valuable addition in haemophilia and von Willebrand care, especially for less experienced patients. It leads to improved satisfaction, social support and improved information.

INTRODUCTION

Patients with chronic haematological diseases, such as haemophilia or von Willebrand's disease, require intensive therapeutic management and patient education to acquire adequate self-management abilities [1-4], apply lifestyle modifications and to understand the inheritance of the disease. During an individual appointment, time limitations often lead to insufficient attention to these important, but time consuming aspects of disease care. A novel outpatient consultation form, leading to improvement of patient self-management may lead to benefits for patients and the health-care system as a whole [5, 6].

The Group Medical Appointment (GMA), which was introduced in Northern America by Noffsinger and Scott in 1996 [7-9] can be an effective and efficient option. In a GMA, a group of 8-12 patients spends 90 minutes with their treating physician and other health-care providers, rather than the usual 10 to 15 min during an individual appointment. In a GMA, all the components of an individual appointment are incorporated including patient interview and physical examination. However, it allows more time to discuss disease related topics by healthcare providers. In addition, information and social support from fellow-patients can greatly improve self-management and quality of life in participants [10, 11].

Various studies in adults with other diseases, such as diabetes, severe headaches, cardiovascular and urological problems have shown that participation in a GMA can enhance patient and physician satisfaction, patient self-management, quality of life, and may reduce hospital admissions and emergency visits [12-18]. To date, however, little has been reported on GMAs in chronically ill children. Two recent observational studies in paediatric diabetic care showed that GMAs had a positive effect [19, 20]; a randomized controlled trial of GMA effect in atopic dermatitis is ongoing (personal communication, study results available in 2012). To our knowledge, no studies on GMA in haemophilia care have been reported.

In 2008, our paediatric team successfully implemented the GMA. This report summarizes the characteristics of a GMA for patients with haemophilia and von Willebrand's disease and the experiences within our patient group with this innovative method of patient-doctor interaction.

The objective of this observational study was to compare participants' experiences with GMA to Individual Medical Appointments (IMA), our usual standard of care. Outcome measures were patient and parent satisfaction, the social support experienced by par-

ticipants, the team's attentiveness to the individual, informative value of a GMA, privacy aspects and the time investment. The hypothesis of this study was that less experienced patients, defined as patients not on prophylactic home treatment, would benefit more from a GMA than experienced patients, defined as patients on prophylactic home treatment. As this latter group has undergone an intensive on-site training programme and visits our Haemophilia Comprehensive Care Centre standardly every 3-4 months. Disease severity was taken into account, but not considered as most important to measure impact of GMA on measured endpoints.

MATERIALS AND METHODS

Patients

From October 2008 to December 2009, patients being treated for haemophilia and von Willebrand's disease at the Haemophilia Comprehensive Care Centre in the Erasmus Medical Centre-Sophia Children's Hospital were invited to participate in a GMA by letter and an informative brochure. Exclusion criteria to participate in a GMA were language problems, hearing loss or severe behavioural problems. Participants were subsequently asked to evaluate both the standard IMA and the GMA.

Less experienced patients were defined as patients with haemophilia or von Willebrand's disease not on prophylactic home treatment. These patients visit our Haemophilia Comprehensive Care Centre once to twice a year. Experienced patients were defined as patients on prophylactic home treatment, which implies they have undergone an intensive on-site training programme and standardly visit our Haemophilia Comprehensive Care Centre three to four times a year. Disease severity was taken into account, but not considered as most important to measure impact of GMA on measured endpoints.

Methods

Group Medical Appointment

The GMA was introduced to the Netherlands by the Dutch Institute for Healthcare Improvement (CBO) in collaboration with Noffsinger [20, 21]; it was implemented in our Haemophilia Comprehensive Care Centre in 2008 for all hemophilia and von Willebrand patients as a standard follow-up visit. We aimed to schedule six to eight patients for each 90 minute GMA in a conference room during regular working hours (Table 1). A GMA was planned approximately once a month. We aimed to invite each patient at least once every 2 years.

Table 1. Characteristics of Individual Medical Appointment (IMA) compared with Group Medical Appointment (GMA).

	IMA	GMA
Number of patients	1	6-8
Duration of appointment	20 minutes	90 minutes
Participation	Obligatory	Voluntary
Severity of disease	One severity of disease	Various severities of disease
Professionals	Treating physician, haemophilia nurse, physiotherapist, social worker.	Treating physician, haemophilia nurse, physiotherapist, social worker, clinical geneticist, guests depending on availability and topics. One medical caretaker functions as chairman.
Clinical examination	In doctor's office	Behind a screen in conference room
Privacy	Complete	Confidentiality protected by group

Table 2. Structure of (Paediatric) Haemophilia Group Medical Appointment (GMA).

1 Measurement of weight and height of all participants and copying of treatment log.

2 Introduction by GMA chairman (in our case: hemophilia nurse or social worker) with special attention to procedure, privacy, and allotted time.
Introduction of patients and severity of disease in each individual patient.

3 Individual interview by treating physician focusing on: acute bleeds and joint function, therapeutic interventions, administration of prophylactic treatment, future surgical or dental interventions, medication, physical activities and lifestyle.

4 Physical examination at the end of each patient interview by physician and physiotherapist.

5 During the GMA disease-related topics are discussed, in accordance to patient questions or introduced by the chairman:
Disease and therapy
- Pathophysiology of disease and mechanism of action of therapeutic interventions (a.o. clotting factor concentrate, anti-fibrinolytic agents, xylometazolin).
- Identification of bleeds, aspects of prophylactic home treatment and vena puncture techniques, importance of treatment log, timing of prophylactic medication with regard to physical activities, type and severity of bleeds with special attention to head trauma.
- In all bleeding disorders: Subcutaneous instead of intramuscular vaccinations. Avoidance of pain- and other medication influencing haemostasis (acetylsalicylic acid, non-steroidal anti-inflammatory drugs, heparin / low molecular weight heparin, coumarin derivatives).

Lifestyle
- Importance of physical activities for muscle tone and prevention of bleeds as well as psychosocial development.
- Safety measures such as SOS bracelets/ medallions.
- Education and informing of environment (day care/ school, family, friends, dentist, other medical specialists).
- Future job and career choice.
- How to cope with the disease during holidays.

Genetics and other family members
- Inheritance of the disease and importance of genetic counseling.
- Clinical consequences of carriership in X-linked diseases.

6 At the end of the GMA diagnostic vena punctures and more private individual consultations are performed, if necessary.

All haemophilia professionals were trained by the CBO in different aspects of GMA management, including GMA setting and practical aspects (Table 2). Within a GMA, the physician proceeds as in an individual appointment under supervision of a chairman, in the presence of other patients, parents and other haemophilia caretakers. The chairman hosts the session and facilitates the group process, while monitoring the allotted time. At the beginning of each GMA, the chairman emphasizes the confidentiality of the shared experiences and explicit oral informed consent of participants is obtained. General disease topics are discussed collectively under supervision of the chairman.

Questionnaires

The CBO provided a standardized and validated questionnaire (QUOTE-communication questionnaire) as used in similar surveys in different patient groups [21-23]. Before the GMA, all parents received a questionnaire concerning their expectations and experiences with an IMA and a similar questionnaire on their expectations of a GMA. After the GMA attendance they received a questionnaire concerning their experiences with a GMA. Children aged 12-18 years (adolescents) received only the latter questionnaire concerning their experiences with a GMA. Younger children did not receive a questionnaire. In the questionnaires, questions were asked regarding patient and parent satisfaction, the social support participants experienced, the team's attentiveness to the individual, informative value of a GMA, privacy aspects and the necessary time investment. All surveys were confidential and sent anonymously. Treating physicians and other haemophilia caretakers were interviewed separately.

Statistical analysis

Differences in patient characteristics between the IMA and GMA were tested with Chi-square analysis in the case of categorical data and with the Mann-Whitney *U*-test in the case of continuous non-parametric data. A Chi-square analysis was performed to analyze the differences between topics during the IMA and the GMA. Differences between expectations and experiences of the IMA and the GMA were analyzed using the Wilcoxon signed rank test for non-parametric paired data. Differences between less experienced and experienced patients were analyzed by the Chi-square analysis. Level of significance was set at $P \leq 0.05$. All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients, Group Medical Appointment and compliance

In 2008, 128 children from 103 families were treated in our hospital for haemophilia or von Willebrand's disease. Three of these 103 families (with a total of 6 children) were excluded from participation in GMA due to language problems. The other 100 families (with a total of 122 children between 0 and 18 years) were approached to join the study by a personal letter with accompanying questionnaire (Figure 1). Forty-seven families did not take part in a GMA, due to practical reasons or lack of interest. Patients not participating in a GMA did not differ significantly from the GMA participants with regard to baseline characteristics, and number of less experienced or experienced patients (Table 3). Parents not participating in a GMA reported no significant differences with regard to satisfaction of an IMA (only IMA median score 8.0 out of 10.0, IMA and GMA 9.0 out of 10.0; $P = 0.580$), although they reported less expectations from a GMA (data not shown).

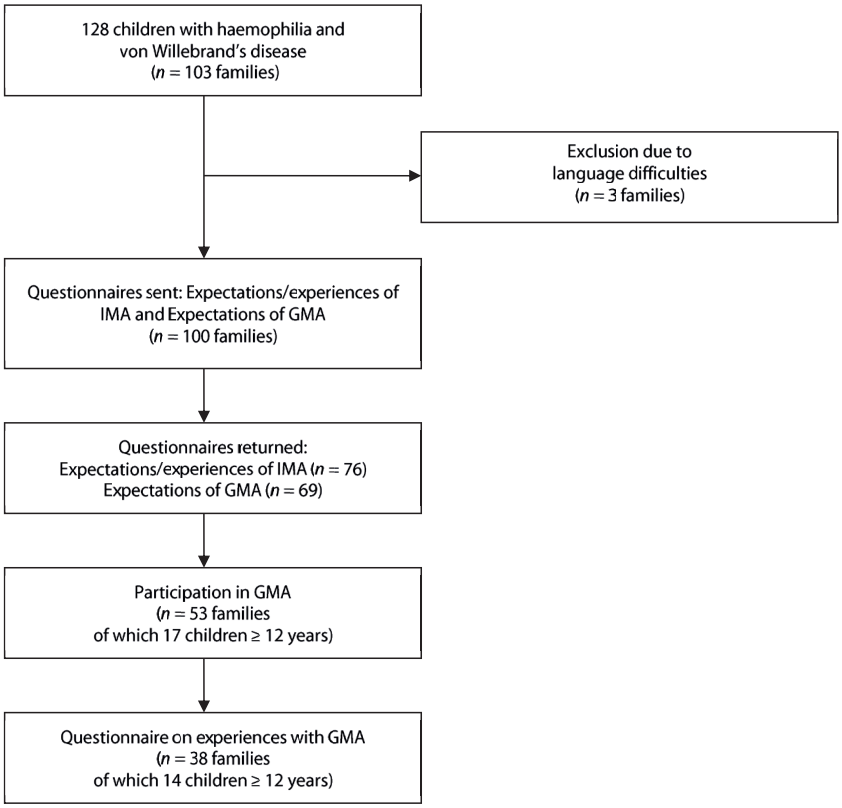

Figure 1. Flow diagram of patient inclusion.

Table 3. Patient characteristics in Individual Medical Appointment (IMA) questionnaire and Group Medical Appointment (GMA) questionnaire category.

	IMA	GMA	
	Parents (*n* = 76 families, 92 children)	**Parents (*n* = 38 families, 41 children)**	**Children ≥ 12 years (*n* = 14 children)**
Patient age, median (IQR)	8.0 (4.0-12.8)	9.0 (6-13.5)	14.0 (12.0-16.0)
Patient gender, *n* (% male)	78 (84.8)	37 (90.2)	14 (93.3)
Patient disease			
Haemophilia A, *n* (%)	61 (66.3)	27 (65.9)	11 (78.6)
Haemophilia B, *n* (%)	8 (8.7)	3 (7.3)	1 (7.1)
Von Willebrand's Disease, *n* (%)	19 (20.7)	11 (26.8)	2 (14.3)
Carrier Haemophilia A or B, *n* (%)	4 (4.3)	.	.
Experience (families)			
Experienced, *n* (%)	21 (27.6)	10 (26.3)	4 (28.6)
Less experienced, *n* (%)	55 (72.4)	28 (73.7)	10 (71.4)

No significant differences were found between parents who only participated in an IMA and parents who also participated in a GMA.

As a result of the unexpected non-attendance of patients, the average number of patients in a GMA was five (range 2-7), and the target of six to eight was not reached.

Seventy-six of the 100 families returned the questionnaire on expectations and experiences with an IMA and 69 parents returned the questionnaire on the expectations of a GMA. Thereafter, 53 of these families participated in a GMA of which 38 families returned the questionnaire on their experiences (compliance 72%). Out of 17 children ≥ 12 years that had participated in a GMA, 14 (82%) returned their questionnaire (Figure 1).

Of GMA participants the less experienced group consisted of 28 families with 30 children; 17 with haemophilia A [Factor VIII (FVIII) level range: 0.01-0.28 IU dL^{-1}], 2 with haemophilia B [both with Factor IX (FIX) level of 0.10 IU dL^{-1}], and 11 with von Willebrand's disease [von Willebrand Factor (vWF) antigen level range: < 0.10-0.28 IU dL^{-1}; vWF activity level range: < 0.10-0.27 IU dL^{-1}; FVIII level range: 0.03-0.59 IU dL^{-1}]. The experienced group consisted of 10 families with 11 children; 10 with haemophilia A (FVIII level range: 0.01-0.02 IU dL^{-1}), and 1 with haemophilia B (FIX level: 0.01 IU dL^{-1}).

Comparison of the Individual Medical Appointment and Group Medical Appointment

In this section, only results of patients ≥ 12 years (*n* = 14) and parents (*n* = 38) undergoing both IMA and GMA are presented. Sequentially, we present our results on (i) patient and parent satisfaction, (ii) social support and the team's attentiveness to the individual

during GMA, (iii) informative value of a GMA, (iv) privacy, (v) time investment, and (vi) preference for a future GMA. Table 4 shows the extent of agreement of patients/ parents with nine specified statements regarding a GMA.

Table 4. Characteristics of Group Medical Appointment (GMA) reported by parents and adolescents.

	GMA, parents			GMA, children ≥ 12 years		
	Less experienced (*n* = 28)	Experienced (*n* = 10)		Less experienced (*n* = 10)	Experienced (*n* = 4)	
	Agree (*n*, %)	Agree (*n*, %)	*P*	Agree (*n*, %)	Agree (*n*, %)	*P*
Social support and attention						
I felt supported by the other patients.	23 (82.1)	3 (30.0)	0.005*	5 (50.0)	3 (75.0)	0.580
I felt enough attention from the team members and the other parents for my situation.	27 (96.4)	10 (100.0)	1.000	.	.	.
Information						
I learned from other patients and their questions.	18 (64.3)	0 (0.0)	<0.001*	10 (100.0)	1 (25.0)	0.011*
Privacy						
I did not mind discussing my child in a group setting.	28 (100.0)	6 (60.0)	0.003*	.	.	.
I asked all relevant questions.	28 (100.0)	7 (70.0)	0.014*	.	.	.
I did not mind that the physical examination took place behind a screen.	23 (82.1)	6 (60.0)	0.205	6 (60.0)	2 (50.0)	1.000
Time investment						
The extra time investment in the GMA was worthwhile.	20 (74.1)†	3 (30.0)	0.023*	7 (70.0)	1 (25.0)	0.245
GMA in the future						
I would choose for a GMA again.	22 (84.6)‡	4 (40.0)	0.014*	5 (55.6)†	1 (25.0)	0.559
I would recommend participation in a GMA to others	25 (92.6)†	8 (88.9)†	1.000	.	.	.
Expectations fulfilled	27 (100.0)†	7 (70.0)	0.015*	.		.

* *P*-value < 0.05; † Missing = 1; ‡ Missing = 2.

Patient and parent satisfaction

All parents (*n* = 38) were satisfied with the IMA (median score 9.0 of a score from 1-10; IQR = 8.0-9.0) and 83% (*n* = 30) were satisfied with the GMA (median score = 8.0; IQR = 6.3-9.0). Less experienced parents were significantly more satisfied with the GMA than experienced parents (median score = 8.0; IQR = 7.0-10.0 versus median score = 5.0; IQR = 3.5-8.0; *P* = 0.006). The median satisfaction rate in children ≥12 years was 7.0 (IQR = 5.8-7.3). Less experienced adolescents tended to be more satisfied than experienced adolescents (*P* = 0.159).

Social support and the team's attentiveness to the individual during a GMA

Eighty-two percent of less experienced parents felt supported by other patients, versus 30% of experienced parents ($P = 0.005$). Support was specified by participants as 'feeling less of an outsider' and as 'hearing valuable experiences' from fellow-sufferers. Contrastingly, only 50% of less experienced adolescents reported peer support, against 75% of experienced adolescents ($P = 0.580$). Especially, younger patients and parents of recently diagnosed children reported increased understanding of the disease and disease-related topics. Attentiveness received from the haemophilia professionals was not perceived as different between an IMA and a GMA (96% of less experienced and 100% of experienced parents; $P = 1.000$).

Informative value of a GMA

Sixty-four percent of less experienced patients acquired more knowledge in a GMA than in an IMA. They reported an increase in acquired knowledge with regard to disease-related topics (43%), health regimens (39%), side effects (32%), and therapeutic management (18%). None of the experienced patients reported an increase in acquired knowledge ($P < 0.001$). In children ≥12 years, all less experienced adolescents reported learning of new aspects of their disease, unlike the 75% of experienced adolescents who reported no learning effect ($P = 0.011$).

Privacy

After a GMA, none of the less experienced parents reported problems regarding privacy aspects, against 40% of the experienced parents ($P = 0.003$). However, whereas less experienced parents felt able to ask all questions, 30% of experienced parents reported avoidance of some questions due to privacy aspects ($P = 0.014$).

A physical examination behind a screen in the conference room was a problem in 18% of the less experienced parents and 40% of the experienced parents ($P = 0.205$). In children ≥12 years, 40% of less experienced adolescents and 50% of experienced adolescents reported problems with this GMA-adapted physical examination ($P = 1.000$).

Time investment

The majority of parents (62%) did not regard the additional time investment for GMA as inconvenient (74% less experienced, 30% experienced; $P = 0.023$). In adolescents, 57% did not find the time investment problematic. Exceptionally, one adolescent rated the GMA as too short.

GMA in the future

Sixty-six percent of parents returning the questionnaire would join a GMA in future (85% less experienced, 40% experienced; $P = 0.014$) and 87% would recommend a GMA to other patients (93% less experienced, 89% experienced; $P = 1.000$). Of the adolescents, 46% would join a future GMA (56% less experienced, 25% experienced; $P = 0.559$).

With regard to satisfaction and efficiency, all haemophilia professionals were positive about GMA experiences in individual interviews. They reported it to be: challenging and enjoyable. They also observed increased peer support within the group, significant learning effects and more effective counseling of patients. All underlined the importance of the chairman during a GMA.

DISCUSSION

In this observational study, whose objective was to compare experiences with GMAs and IMAs, we measured patient and parent satisfaction, the social support experienced by participants, the team's attentiveness to the individual, the informative value of a GMA, privacy aspects, and the time investment necessary.

Overall, parents and adolescents were very satisfied with both the GMA and with the IMA. In our opinion, the most important advantages of GMA in our study were the improvement in participants' knowledge of the disease and the social support they reported. Both were significantly higher in less experienced than in experienced parents and adolescents. A recent study on the value of GMA indicated that, due to the available time period and group interaction, disease-related topics are discussed more extensively during a GMA than an IMA [20]. Our results confirm prior studies on GMA that report high levels of participant satisfaction and advantages with regard to disease perspective, social support and therefore probably increased self-management abilities [19, 24-29].

An important characteristic of the GMAs are the group dynamics which acknowledge the individual patient and his family members as disease experts. Real-life experiences are strong advocates for behavioural changes and improved understanding of disease perspective and therapeutic interventions [30-32]. With regard to these aspects, a GMA could be superior to an IMA, especially in chronic patient care, which requires participants to deepen their knowledge of the disease and to improve adequate self-management [17, 24, 33, 34]. It has been suggested that GMAs may be especially effective in adolescents when they are offered according to their needs and requirements,

as adolescents may be more sensitive to peers and group dynamics. In our study it is difficult to be conclusive on this subject due to the small case series. Strikingly, less experienced adolescents received less peer support than experienced adolescents. This may be explained by feelings of solidarity within the latter group due to the intensity of the required treatment.

Most participants in our study did not report problems with time investment, privacy aspects, or less team's attentiveness to the individual. Less experienced participants reported fewer disadvantages of GMA than experienced patients. Notably, most of them felt free to discuss personal problems within the group. Almost half of the experienced parents and adolescents perceived the physical examination in the conference room as a problem. Therefore, it will be performed in a nearby consultation room in the near future. Despite their initial concerns, participants were positive about the introduction of the novel form of consultation. Most would join a GMA in the future and would recommend a GMA to other patients.

Possible reasons for the differences between less experienced and more experienced patients in our study include experienced patients' increased knowledge of the disease due to prior home treatment training. Also, the fact that more experienced patients are used to frequent, short outpatient clinic visits and often have a close personal relationship with the treating physician. This may lead to problems with the extra time investment involved in a GMA and with the need to adapt to a more distant setting.

A GMA should pursue a balance between individualized and witnessed interactions between patients and the treating physician, with focus on educational aspects. According to Thacker et al. there is no optimal standardized form for a GMA and healthcare providers should organize a GMA according to the needs of the patient population involved [28]. In our setting, we have now implemented the following adjustments. The heterogeneity of patients invited for GMA as recommended by Noffsinger was not feasible [35]. A complete lack of patient selection resulted in a lack of clarity between participants on patient diagnosis. Subsequently, we selected patients, differentiating between age, type and severity of disease. As participant involvement is essential for group dynamics, we were still careful to include both less experienced and experienced patients. Furthermore, results in our adolescent group led to a successful transitional GMA in which adolescents participated together with future adult haemophilia caretakers. Practical aspects such as unexpected unattendance must be anticipated, and it is essential that a sufficient number of healthcare providers attends [28, 36]. In addition, to safeguard quality of care, the physical examination during GMA is best performed by a physiotherapist, in another consultation room. The number of invited patients recom-

mended for GMA by Noffsinger (10-16) proved too large for our patient population [35]. As patients are accompanied by parents and siblings, we conclude that seven patients are optimal in our setting.

Limitations of our study were caused by the observational study design, patient numbers, and selection bias due to non-randomization. As the GMA was incorporated in standard haemophilia care, randomization was not feasible. Although, in the adolescent population, there were no significant differences between less experienced and experienced patients, most probably due to the small patient numbers. Also, it is difficult to assess whether respondent answers reflected their true opinion or were socially acceptable answers. Nevertheless, we regard our findings as valuable for chronic (paediatric) patient care, and more specifically for haemophilia and von Willebrand caretakers in general.

In conclusion, we have shown that the GMA is a valuable addition in paediatric haemophilia care, especially for less experienced patients, who compromise half of most Haemophilia Comprehensive Care Centres. In specific patient groups, it clearly improves satisfaction, peer support and informative value of a GMA of patients and parents. However, as not every patient may benefit from a GMA, a GMA will never be able to replace individual consultations. Ongoing research is required to further define the advantages of this new development in chronic patient care. Our team considers the GMA an important asset in chronic patient care and will implement it in other haematological patient groups, such as sickle cell disease, thalassemia and hereditary spherocytosis.

ACKNOWLEDGEMENTS

We acknowledge the Dutch Institute for Healthcare Improvement (CBO) for their support and for providing the study questionnaires.

Design of the GMA was financially supported by an unrestricted grant from Baxter.

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CHAPTER 6

Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications

HCAM Hazendonk, J Lock, RAA Mathôt, K Meijer, M Peters, BAP Laros-van Gorkom, FJM van der Meer, MHE Driessens, FWG Leebeek, K Fijnvandraat, MH Cnossen for the "OPTI-CLOT" study group

J Thromb Haemost. 2016 Mar;14(3):468-78.

ABSTRACT

Background Perioperative administration of factor VIII (FVIII) concentrate in hemophilia A may result in both underdosing and overdosing, leading to respectively a risk of bleeding complications or unnecessary costs.

Objectives This retrospective observational study aims to identify the extent and predictors of underdosing and overdosing in perioperative hemophilia A patients (FVIII levels < 0.05 IU mL^{-1}).

Patients and Methods One hundred-nineteen patients undergoing 198 elective, minor or major surgical procedures were included (median age 40 years, median body weight 75 kg). Perioperative management was evaluated by quantification of perioperative infusion of FVIII concentrate and achieved FVIII levels. Predictors of underdosing and (excessive) overdosing were analysed by logistic regression analysis. Excessive overdosing was defined as upper target level plus ≥ 0.20 IU mL^{-1}.

Results Depending on postoperative day, 7-45% of achieved FVIII levels were under and 33-75% were above predefined target ranges as stated by National guidelines. A potential reduction of FVIII consumption of 44% would have been attained if FVIII levels had been maintained within target ranges. Blood group O and major surgery were predictive of underdosing (odds ratio (OR) = 6.3, 95%CI = 2.7-14.9; OR = 3.3, 95%CI = 1.4-7.9). Blood group O patients had more bleeding complications in comparison to patients with blood group non-O (OR = 2.02, 95%CI = 1.00-4.09). Patients with blood group non-O were at higher risk of overdosing (OR = 1.5, 95%CI = 1.1-1.9). Additionally, patients treated with bolus infusions were at higher risk of excessive overdosing (OR = 1.8, 95%CI = 1.3-2.4).

Conclusion Quality of care and cost-effectiveness can be improved by refining of dosing strategies based on individual patient characteristics such as blood group and mode of infusion.

INTRODUCTION

Hemophilia A is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII). It is characterized by spontaneous bleeding or bleeding after minor trauma, typically in joints and muscles. In case of bleeding, patients are treated with intravenously administered factor replacement therapy. In severe (FVIII < 0.01 IU mL^{-1}) and some moderate severe (FVIII between 0.01 and 0.05 IU mL^{-1}) cases, prophylactic treatment is administered to prevent spontaneous and frequent bleeding [1, 2]. In order to safeguard hemostasis in the perioperative setting, FVIII plasma levels are targeted according to guidelines for up to 2 weeks after surgery and consist of a FVIII bolus infusion of 50 IU kg^{-1}, followed by either continuous infusion or intermittent daily infusions based on a clearance rate of 3-4 mL kg^{-1} h^{-1}, and under daily monitoring of FVIII plasma levels (Table 1) [3]. Perioperative factor concentrate consumption is substantial and amounts to 15% of annual use in the hemophilia population [4-6]. To illustrate this, in the Netherlands > €100 million (> $109 million) is spent annually on total factor concentrate for 1600 hemophilia patients per year, including €15 million ($16.4 million) alone for perioperative replacement therapy[3, 4, 6]. Fortunately, treatment is extremely effective as perioperative bleeding is rare, in those cases where replacement therapy is adequately available[7, 8].

Table 1. Target FVIII levels in the perioperative period*

Time		Target FVIII level (IU mL^{-1})
Day	**Hours**	
1	0 - 24	0.80 - 1.00
2-5	24 - 120	0.50 - 0.80
≥6	> 120	0.30 - 0.50

*The standard perioperative dosing regimen, as described by the consensus, consists of a factor VIII (FVIII) bolus dose directly before surgery of 50 IU kg^{-1}, followed by either continuous infusion or intermittent daily bolus infusions. The rate of infusion (IU h^{-1}) is obtained by multiplying the patient's bodyweight (kg) with clearance (3-4 mL kg^{-1} h^{-1}) and target FVIII level (IU mL^{-1}). Subsequent FVIII clotting factor concentrate dosing will be based on daily monitoring of FVIII levels and adjusted according to the physician's opinion, based on a standard clearance of 3-4 mL kg^{-1} h^{-1}. Data are according to the National Hemophilia Consensus of the Netherlands [3].

Previous studies evaluating perioperative dosing of FVIII concentrate in hemophilia A suggest that improvement is warranted as overdosing is widely reported [9-16]. This is attributed to current dosing strategies based on body weight and crude estimations of clearance, without taking into account other individual patient characteristics. Additionally, the complexity of achieving targeted factor levels and fear of bleeding play an important role in overdosing. Strikingly, in reported studies, extent and timing of under-

dosing and overdosing have not been specified. Moreover, risk factors for underdosing and overdosing have hardly been explored and are urgently required to individualize dosing in the near future.

We aim to quantify the extent and timing of underdosing and overdosing in the perioperative setting and to identify its predictors in severe and moderate severe hemophilia A patients. We believe that both underdosing and overdosing can be reduced by alternative dosing strategies that take into account individual patient characteristics, leading to optimization of care and a greater efficacy of consumption of costly factor concentrate.

MATERIALS AND METHODS

Patients

This is a retrospective multicenter observational cohort study. Eligible patients were male patients with severe or moderate-severe hemophilia A (FVIII levels < 0.05 IU mL^{-1}) of all ages undergoing elective, minor, or major surgery (Table S1) [17] between 2000 and 2013 under FVIII concentrate replacement therapy with monitoring of FVIII plasma levels. First surgical procedure was performed on January 7, 2000 and last surgical procedure on February 19, 2013. Patients were recruited from five Academic Hemophilia Treatment Centers in the Netherlands (Erasmus University Medical Center Rotterdam [*n* = 32]; Academic Medical Center Amsterdam [*n* = 32]; University Medical Center Groningen [*n* = 35]; Radboud university medical center [*n* = 12]; and Leiden University Medical Center [*n* = 8]). Exclusion criteria included: the perioperative presence of FVIII neutralizing antibodies, patients with severe infections during the perioperative period and patients lacking accurate perioperative documentation. The study was not subject to the Medical Research Involving Human Subjects Act, as patient data were analysed anonymously. Moreover, the study was approved by all local Medical Ethics Committees; one center requiring prior patient informed consent.

Objectives

The objectives of the study were to evaluate perioperative FVIII concentrate management in patients with hemophilia A with regard to defined FVIII target ranges as stated by the National Hemophilia Consensus of the Netherlands and to identify potential predictors of underdosing and overdosing.

Methods

Data were collected on patient characteristics, type of surgical procedure, timing, dosing of FVIII administration and timing of blood sampling of FVIII plasma levels (in IU mL^{-1})

during the hospitalization period. FVIII plasma levels were generally monitored daily and were measured by one-stage clotting assays in all participating centers. Perioperative blood loss and hemostasis were evaluated according to the definitions of the International Society of Thrombosis and Hemostasis [18] and quantified by severity of complications and/or necessity of second surgical intervention, hemoglobin decrease of ≥ 1.24 mmol L^{-1} and/or red blood cell transfusion necessity, or bleeding that prolonged hospitalization.

For our analysis, we defined severe bleeding complications as bleeding requiring a second surgical intervention and/or the necessity of a red blood cell transfusion. Duration of hospitalization was defined by day of discharge minus day of surgical procedure and initiation of FVIII concentrate infusion. To increase data reliability, data were collected and checked by two individual researchers.

To acquire accurate insight into achieved FVIII plasma levels with regard to the target ranges stated in guidelines, only steady state FVIII plasma levels were included when replacement therapy was administered by continuous infusion and only FVIII trough plasma levels in case of administration via bolus infusion. Steady state FVIII plasma levels were defined as perioperative FVIII measurements sampled when FVIII concentrate substitution is equal to clearance and FVIII trough plasma levels as FVIII measurements before FVIII concentrate bolus infusion. FVIII peak levels after FVIII bolus infusion were not included in this analysis.

Statistical analysis

For comparison of FVIII concentrate consumption between groups, the non-parametric Mann-Whitney *U* test was used. *P* for trend analysis using one-way ANOVA was performed to evaluate trends in FVIII consumption on consecutive days. Calculations were performed only on the first surgical procedure in each individual patient. Descriptive statistics are presented as median and interquartile range (IQR) for continuous variables and as number and percentages for categorical variables. Comparison between proportions was done by means of Pearson Chi-Square test.

A hypothetical reduction of FVIII concentrate consumption, if national guidelines for perioperatieve target ranges had been maintained, was calculated by comparing the difference of achieved FVIII plasma level in each individual at different time points to the prescribed lowest and highest target range level at that time point. First-order elimination curves were used to calculate the actual amount of FVIII concentrate underdosed or overdosed for the total population. The percentage of FVIII concentrate which could have been saved was calculated after subtraction of the amount of FVIII concentrate that was underdosed.

Prediction model for underdosing and overdosing

Underdosing was defined as all FVIII plasma levels below the lowest predefined target range level, and overdosing as all FVIII plasma levels above highest predefined target range level. Excessive overdosing was arbitrarily defined as the upper target range level with a deviation of ≥ 0.20 IU mL^{-1} to overcome the logistic delays caused by laboratory monitoring and adjustment of treatment. Potential predictors of underdosing in the first 24 hours after surgery, as well as overdosing and excessive overdosing, were analyzed by a backward stepwise logistic regression analysis with elimination of variables with $P > 0.10$. Potential predictors of underdosing or overdosing were defined before analysis on the basis of their potential effect on the pharmacokinetic (PK) parameters: clearance and/ or volume of distribution of infused FVIII concentrate. The following variables were collected: first: patient characteristics of age, body weight [19], blood group [20-22], historical values of von Willebrand Factor (VWF) antigen and VWF activity [23], history of FVIII neutralizing antibodies [8], type and brand of factor concentrate (recombinant or plasma-derived) [24] and mode of infusion (continuous or bolus infusion) [25]. Secondly, surgical characteristics were colected: type and severity of surgical procedure categorized according to Koshy et al. [17].

Data management and statistical analysis were performed with IBM SPSS statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA). A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Patient and surgical characteristics

Our study population consisted of 119 patients undergoing a total of 198 surgical procedures: 75 adults (140 surgical procedures, median age 48 years, median body weight 80 kg) and 44 children (58 surgical procedures, median age 4 years, median body weight 19 kg) (Table 2). The majority of patients were severe hemophilia A patients on prophylactic treatment (70%). Approximately half of all patients were known with blood group O (51%). In adults median VWF:antigen (Ag) level was 1.23 IU mL^{-1} and median VWF:activity (Act) level was 1.39 IU mL^{-1}. In children, median VWF:Ag was 0.92 IU mL^{-1} and VWF:Act was 0.88 IU mL^{-1}.

Forty-four patients underwent multiple surgical procedures; nine of these had more than four surgical procedures (Table 2). In adults, mainly major surgical procedures (n = 86; 61%) were performed, which were most often orthopedic procedures (n = 91; 65%). Children mainly underwent minor surgical procedures (n = 47; 81%), most frequently

Table 2. General characteristics

	Total cohort		Adults		Children	
Patient characteristics						
No. of patients	119		75		44	
Age (y)	40	[9-54]	48	[37-60]	4	[2-8]
Height (cm)	175	[162-182]	178	[173-182.0]	114	[89-136]
Body weight (kg)	75	[35-85]	80	[73-90]	19	[12-29]
Body mass index (kg m^{-2})	23	[17-26]	25	[23-28]	16	[14-18]
Severe hemophilia, FVIII levels <0.01 IU mL^{-1}	83	(70)	49	(65)	34	(77)
Prophylaxis	84	(71)	51	(68)	33	(75)
Blood group O*	51	(51)	34	(50)	17	(52)
Neutralizing antibody titer						
No.	131	(66)	82	(59)	49	(85)
Historically	67	(34)	58	(41)	9	(15)
Maximum titer (BU)	0.3	[0.2-0.7]	0.3	[0.2-0.5]	0.2	[0.2-2.4]
Historical VWF levels (IU mL^{-1})						
Antigen[#]	1.1	[0.9-1.4]	1.2	[1.0-1.4]	0.9	[0.7-1.2]
Activity[$]	1.1	[0.9-1.6]	1.4	[1.1-1.7]	0.9	[0.7-1.2]
Chronic hepatitis C	57	(48)	55	(73)	2	(5)
Surgical characteristics						
No. of surgical procedures	198		140		58	
Total No. of patients undergoing:						
1 procedure	75	(63.0)	43	(57.3)	32	(72.7)
2 procedures	26	(21.8)	15	(20.0)	11	(25.0)
3 procedures	9	(7.6)	9	(12.0)	0	(0.0)
> 4 procedures	9	(7.6)	8	(10.7)	1	(2.3)
Major surgical procedure	97	(49.0)	86	(61.4)	11	(19.0)
Type of surgical procedure						
General	6	(3.0)	6	(4.3)	NA	NA
Colorectal	5	(2.5)	4	(2.9)	1	(1.7)
Vascular	1	(0.5)	1	(0.7)	NA	NA
Cardiothoracic	1	(0.5)	1	(0.7)	NA	NA
Orthopedic	94	(47.5)	91	(65.0)	3	(5.2)
Urology	12	(6.1)	4	(2.9)	8	(13.8)
Maxillofacial	2	(1.0)	2	(1.4)	NA	NA
Ear-nose-throat	11	(5.6)	6	(4.3)	5	(8.6)
Eye	3	(1.5)	3	(2.1)	NA	NA
(Re)placement central intravenous catheters	32	(16.2)	1	(0.7)	31	(53.4)
Miscellaneous	31	(15.7)	21	(15.0)	10	(17.2)

Table 2. General characteristics (continued)

	Total cohort	Adults	Children
Replacement therapy with factor concentrate, hospitalization and blood loss			
Mode of infusion			
Continuous	115 (58)	88 (63)	27 (47)
Bolus	83 (42)	52 (37)	31 (53)
Product type			
Plasma derived	46 (23)	41 (29)	5 (9)
Recombinant	152 (77)	99 (71)	53 (91)
Duration of hospitalization (days)	9 [5-12]	9.0 [5-14]	7 [6-10]
Complications during the perioperative period			
No. of patients with a complication			
Bleeding	48 (24)	45 (32)	3 (5)
Re-operation	6 (3)	6 (4)	NA NA
Hemoglobin drop >1.24 mmol L^{-1} and/ or RBCTF	38 (19)	36 (26)	2 (3)
Bleeding with prolonged hospitalization	5 (3)	4 (3)	1 (2)
Thrombosis	NA NA	NA NA	NA NA

Values given in No. (%) or median [interquartile range 25-75%]. FVIII, clotting factor VIII; BU, Bethesda Units; VWF, von Willebrand factor; NA, not applicable; RBCTF, red blood cell transfusion. * Blood group available in 101 patients (172 surgical procedures). [#]VWF antigen available in 67 patients (118 surgical procedures). [$]VWF activity available in 57 patients (98 surgical procedures).

an insertion or removal of a central venous device (*n* = 31; 53%) (Table 2). In 115 (58%) surgical procedures, FVIII replacement therapy was given by continuous infusion; these patients were mainly adults (*n* = 88; 63%). In 83 (42%) surgical procedures, patients were treated via bolus infusion (Table 2). In 152 surgical procedures (77%) patients were treated with recombinant factor concentrates. Duration of hospitalization was similar in both adults and children treated via continuous infusion as compared with bolus infusion (adults: 9 [IQR 6-15] vs. 8 [IQR 4-13] days, *P* = 0.09; children: 7 [IQR 6-10] vs. 7 [IQR: 6-10] days, *P* = 0.99).

Achievement of FVIII target range levels

Most perioperative FVIII plasma concentrations were outside the predefined target range in both adults and children. Achieved FVIII plasma concentrations in relationship to defined target ranges on consecutive days are depicted in Figure 1. In summary, on consecutive days deviations of FVIII levels with regard to predefined target range levels were increasingly significant (*P* for trend < 0.01). The overall median deviation of FVIII plasma concentrations *below* the lowest required target range level varied from 0.17 to 0.11 IU mL^{-1} for consecutive postoperative days and *above* the highest required target

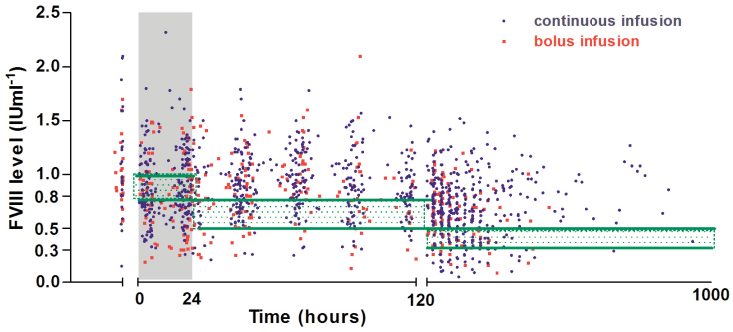

Figure 1. Achieved FVIII levels in adults and children receiving clotting factor replacement therapy.
Achieved factor VIII (FVIII) levels in adults and children receiving clotting factor replacement therapy. Achieved FVIII levels in hemophilia patients treated via continuous infusion (blue) and via bolus infusions (red). Predefined target levels as stated by the National Hemophilia Consensus are depicted as green boxes [3].

range level from 0.23 to 0.31 IU mL^{-1} for consecutive postoperative days (Table 3). In the first 24 h after surgery, 45% of measured FVIII levels were *below* lowest target range level with a median deviation *below* the lowest required target level of 0.17 IU mL^{-1}. After 6 days of postsurgical hospitalization, 75% of the FVIII levels were above highest target range level with a median deviation of 0.31 IU mL^{-1}. No evidence was found with regard to changes in dosing regimen over time during the overall study period as the proportion of underdosed and overdosed patients did not differ for surgical procedures

Table 3. Achieved FVIII levels after clotting factor replacement therapy

	Total cohort		Adults		Children	
	No. Samples (%)	Median deviation [IQR]	No. Samples (%)	Median deviation [IQR]	No. Samples (%)	Median deviation [IQR]
Preoperative: only peak levels	111	1.15 [0.9-1.41]	80	1.23 [0.94-1.50]	31	1.00 [0.82-1.18]
Day 1 (0-24 h)	308 (100.0)	0.83 [0.65-1.10]	237 (100.0)	0.87 [0.69-1.14]	71 (100.0)	0.76 [0.51-1.09]
FVIII levels outside target range	283 (77.3)	.	181 (76.4)	.	57 (80.2)	.
Above	101 (32.7)	0.23 [0.10-0.40]	81 (34.2)	0.24 [0.10-0.43]	20 (28.2)	0.20 [0.12-0.29]
Below	137 (44.5)	0.17 [0.08-0.33]	100 (42.2)	0.16 [0.08-0.29]	37 (53.6)	0.27 [0.08-0.46]
Day 2-5 (24-120 h)	510 (100.0)	0.88 [0.69-1.08]	389 (100.0)	0.92 [0.76-1.10]	121 (100.0)	0.66 [0.51-0.93]
FVIII levels outside target range	339 (66.5)	.	270 (69.4)	.	69 (57.0)	.
Above	303 (59.4)	0.23 [0.12-0.41]	262 (67.4)	0.24 [0.12-0.41]	41 (33.8)	0.19 [0.13-0.41]
Below	36 (7.1)	0.17 [0.07-0.24]	8 (2.1)	0.12 [0.03-0.23]	28 (23.1)	0.17 [0.08-0.24]
Day >6 (> 120 h)	471 (100.0)	0.68 [0.48-0.87]	422 (100.0)	0.70 [0.52-0.89]	49 (100.0)	0.44 [0.26-0.69]
FVIII levels outside target range	383 (81.3)	.	347 (82.2)	.	36 (73.5)	.
Above	343 (74.7)	0.31 [0.15-0.45]	321 (76.1)	0.30 [0.16-0.45]	22 (44.9)	0.19 [0.10-0.30]
Below	40 (8.7)	0.11 [0.05-0.16]	26 (6.2)	0.09 [0.05-0.14]	14 (28.6)	0.12 [0.09-0.20]

No., number; IQR, interquartile range.

performed before 2005 and after 2005 (Table S2). In addition, specific treatment center was not associated with proportion of underdosing or overdosing (data not shown).

Predictors of underdosing and (excessive) overdosing

In our logistic regression model, blood group O and major surgery were predictive of underdosing (respectively, odds ratio [OR] = 6.3, [95% confidence interval (95%CI) = 2.7-14.9] and OR = 3.3 [95%CI = 1.4-7.9]) (Table 4). Complementary, blood group non-O, increasing age (per year) and replacement therapy with a plasma derived product and via bolus infusion were predictive of overdosing (Table 4). Replacement therapy with a plasma derived product and via bolus infusion and increasing age (per year) were associated with excessive overdosing.

Table 4. Predictors of underdosing and (excessive) overdosing

	OR	95% Confidence interval		
Underdosing				
Age (per year)[#]	1.03	0.99	-	1.07
Blood group O[†]	6.30	2.65	-	14.93
Major surgical procedure[$]	3.30	1.38	-	7.90
Overdosing				
Age	1.02	1.02	-	1.03
Blood group O†	1.47	1.13	-	1.91
Product type (recombinant) [$$]	0.52	0.38	-	0.72
Mode of infusion (bolus)‡	1.78	1.34	-	2.37
Excessive overdosing				
Age	1.02	1.01	-	1.02
Product type (recombinant)[$$]	0.48	0.37	-	0.63
Mode of infusion (bolus)[‡]	1.92	1.45	-	2.54

Stepwise backward logistic regression analysis. OR, odds Ratio; CI, confidence Interval; [#] Increasing age (per year) [†] vs. blood group non-O; [‡] vs. continuous infusion; [$] vs. minor surgical procedure; [$$] vs. plasma derived clotting factor concentrate.

Clotting factor VIII concentrate consumption

For the first surgical procedure in each individual, the median total amount of infused FVIII concentrate per kilogram per day during hospitalization was significantly higher in children when compared with adults (children: 93 IU kg^{-1} day^{-1} [IQR 75-119 IU kg^{-1} day^{-1}] and adults: 57 IU kg^{-1} day^{-1} [IQR 41-77 IU kg^{-1} day^{-1}]; $P < 0.001$) (Table 5). Mode of infusion, type of concentrate (plasma derived or recombinant), and severity of surgical procedures were not associated with the amount of FVIII consumption for both children

Table 5. Treatment characteristics[#]

	Total cohort			Adults			Children		
	No.	**Median [IQR]**	***P*-value[#]**	**No.**	**Median [IQR]**	***P*-value[#]**	**No.**	**Median [IQR]**	***P* -value[#]**
FVIII consumption (IU kg^{-1} day^{-1})	119	69.0 [47.5-98.1]		75	57.1 [41.1-76.7]		44	92.7 [75.1-118.8]	
Mode of infusion									
Continuous	62	69.2 [51.9-94.6]	0.60	43	59.2 [46.9-77.2]	0.06	19	89.5 [77.7-117.1]	0.77
Bolus	57	65.8 [39.5-103.9]		32	52.3 [31.0-75.2]		25	97.9 [70.0-129.7]	
Product type									
Plasma derived[†]	32	58.6 [41.1-79.4]	0.02	28	53.3 [40.0-70.3]	0.32	4	89.2 [68.7-148.5]	0.95
Recombinant[‡]	87	76.7 [54.1-108.1]		47	59.1 [41.9-83.1]		40	92.7 [75.1-118.8]	
Severity risk of surgical procedure[17]									
Minor	66	79.4 [51.7-119.7]	0.05	29	58.0 [35.3-82.7]	0.76	37	91.3 [71.8-119.7]	0.49
Major	53	59.8 [47.3-87.3]		46	55.5 [46.3-74.0]		7	113.9 [85.1-117.5	

No., number; IQR, interquartile range; IU kg^{-1} day^{-1}, International Units per kilogram per day. [#] FVIII consumption analysis was performed for the first surgical procedure of each individual patient. [#] Non-parametric test, Mann-Whitney *U* test. [†] Including: Aafact (Blood Transfusion Council of the Netherlands Red Cross), Hemofil M (Baxter BioScience, Thousand Oaks, CA, USA). [‡] Including: Kogenate FS (Bayer, Berkely, Ca, USA), Helixate FS (CSL Behring, Marburg, Germany), and Advate, Recombinate (Baxter BioScience, Thousand Oaks, CA, USA), Refacto (Pfizer, New York, NY USA).

and adults. As expected, an overall decrease was observed in infused FVIII concentrates over consecutive postoperative days, both in adults and children, as set target range values also decrease accordingly (*P* for trend < 0.001) (Figure S1).

Total FVIII concentrate consumption of the whole study cohort during the entire perioperative period amounted to a total of 6,800,000 IU. If predefined FVIII target ranges had been maintained according to the national guidelines, this would have led to a reduction of consumption of FVIII concentrate of 44% (Figure 2). This percentage was calculated by subtracting the total amount of FVIII concentrate under lowest target range level (e.g. 491 000 IU) from FVIII concentrate consumed above highest target range level (e.g. 3 510 000 IU) and dividing it by total consumption as defined earlier.

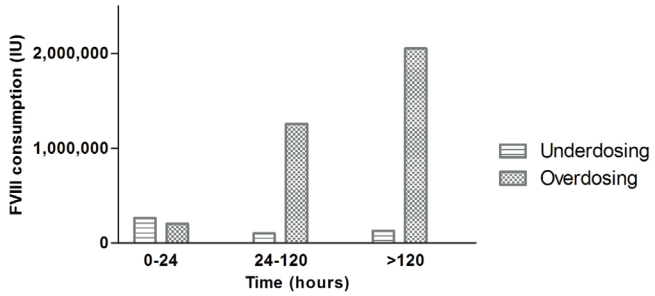

Figure 2. Total amount of FVIII consumption underdosed and overdosed in the perioperative setting.

Perioperative blood loss and haemostasis

Forty-five (32%) of the surgical procedures in adults and three (5%) surgical procedures in children were complicated by perioperative bleeding. In patients with blood group O, overall more bleeding complications were observed than in patients with blood group non-O (blood group O, *n* = 29 [64%]; blood group non-O, *n* = 16 [36%]; *P* = 0.047; OR 2.02, 95%CI 1.01-4.09) (Figure 3). These patients also experienced more severe bleeding; 15 (33%) severe bleeding complications were observed in patients with blood group O in comparison to 8 (18%) in blood group non-O patients. Overall, with regard to severity of bleeding, 6 of the 45 bleeding complications in adult patients and none of the bleeding complications in pediatric patients required a reoperation (Table S3 and S4). These six reoperations encompassed five for intra-articular bleeding in a total knee replacement and one for bleeding after drain removal. Bleeding complications were overall more common in patients undergoing an orthopedic surgical procedure.

Overall, we did not find an association between bleeding complications and actual FVIII plasma level at the time of the bleeding episode in adults (median FVIII level for patients

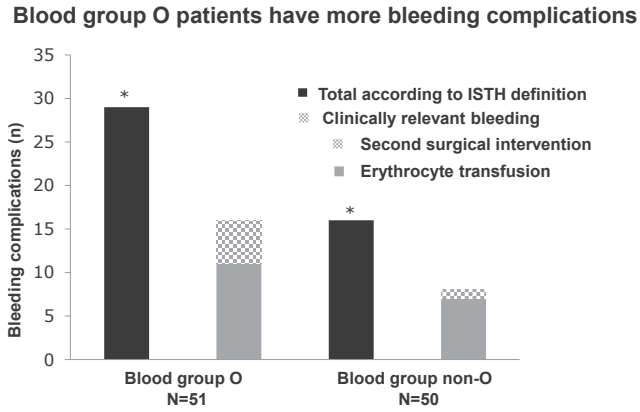

Figure 3. Blood group O patients have more bleeding complications.
*OR = 2.02 95CI [1.01-4.09]

with a bleeding complication or without a bleeding complication: 0.81 IU mL^{-1} [0.65-0.99 IU mL^{-1}] or 0.82 IU mL^{-1} [0.62-1.07 IU mL^{-1}]; $P = 0.92$) and children (median FVIII level for patients with a bleeding complication or without a bleeding complication: 0.66 IU mL^{-1} [0.43-0.92 IU mL^{-1}] vs 0.72 IU mL^{-1} [0.46-0.92 IU mL^{-1}]; $P = 0.66$). No thrombotic complications and no deaths were reported.

DISCUSSION

This is presently the largest study evaluating perioperative FVIII concentrate dosing in hemophilia A patients. Our data illustrate the challenges of maintaining FVIII target levels in current perioperative dosing and the magnitude of underdosing and overdosing when targeting prescribed FVIII ranges according to guidelines in a resource-rich country. In this study, depending on postoperative day, 7-45% of achieved FVIII plasma levels were under the lowest predefined target range level recommended by national guidelines and 33-75% above the highest predefined target range level [3]. If target ranges had been adequately maintained, an impressive overall reduction of FVIII consumption of 44% would have been possible. Patients with blood group O were at increased risk of underdosing and had a higher rate of both overall bleeding and severe bleeding complications. In this retrospective analysis, we were not able to demonstrate an association between an actual lower FVIII plasma level at the time of a bleeding episode, as FVIII levels were often not available directly during the event. The data do, however, suggest that patients with blood group O may have a higher perioperative bleeding risk due to overall lower FVIII levels. Most probably, this is explained by lower VWF levels in patients with blood group O. Unfortunately, VWF:Ag and VWF:Act levels were only sporadically

available in this study, as perioperative VWF testing is currently not common practice, making it difficult to analyze this association. Previous studies have reported that lower VWF levels lead to shorter FVIII half-life as VWF protects FVIII against proteolytic degradation in the circulation [20-23]. Inversely, in this study, overdosing was predicted by blood group non-O and older age. This also may be explained by VWF levels, which are generally higher in blood group non-O and higher with increasing age [26]. Further supportive of this hypothesis are data collected by Kahlon et al. in healthy individuals, describing a decrease of VWF levels 30 min after incision and higher VWF levels 1 day after surgery [27]. If patients with lower baseline VWF levels decrease according to this principle at initiation of surgery and are not able to subsequently increase VWF levels, this may coincide with a higher perioperative bleeding risk. Further predictors of overdosing, other than blood group non-O and older age, were replacement therapy with plasma derived clotting factor concentrates and treatment via bolus infusion.

Strengths and limitations

Strengths of the study are the large number of included patients and surgical procedures, not documented before, as well as the fact that patients were included from numerous treatment centers all work dedicatedly according to one national guideline [3]. The guideline was developed and approved by all hemophilia treatment centers collaborating within the Hemophilia Doctors Organization in the Netherlands. In the study, actual dosing regimens and subsequent FVIII plasma samples during the past 10 years were collected thoroughly, and complications were extensively documented. Data were collected and checked by two independent researchers. The cohort is therefore representative of severe and moderate hemophilia A patients undergoing surgery in a resource-rich country.

Study limitations include the retrospective nature of the data. Therefore, not all perioperative patients were monitored as intensively, and analyses of modifiers of consumption were difficult as data were not collected prospectively according to protocol. Major surgical procedures may be overrepresented in the study as these were, of course, monitored more intensely than minor surgical procedures. However, earlier reports show a similar prevalence of surgical procedures in other hemophilia populations [28, 29]. In addition, quantification and documentation of blood loss is notoriously difficult, especially in retrospective studies. Therefore, criteria were applied for blood loss as defined by the ISTH [18], leading to possible overreporting of blood loss as this definition is quite sensitive. We additionally reported clinically relevant, severe bleeding as defined simply and reliably by necessary red blood cell transfusion and/or reoperation.

Potentially, the use of one-stage laboratory assays to measure FVIII plasma levels may lead to biased results with regard to achieved FVIII plasma levels. This is especially a concern as these assays generally lead to higher FVIII levels in higher FVIII ranges than do two-stage (chromogenic) assays [30-32], with the exception of the measured FVIII levels after infusion of one specific B domain-deleted FVIII concentrate, which was also administered in this study. In this B domain-deleted FVIII concentrate, one-stage assays lead to measurement of lower FVIII plasma levels, potentially leading to overdosing specifically in these patients. Due to the latter, consumption was analyzed extensively according to product type in our study cohort. However, no association was found between consumption of FVIII concentrate and specific product type. Prospective studies in perioperative hemophilia A patients are required to verify the data with regard to FVIII levels and type of FVIII assay. Currently, the one-stage assay remains the most often applied assay, and study results depict daily practice in the majority of hemophilia treatment centres.

FVIII consumption and mode of infusion of replacement therapy

In our study, median total amount of infused FVIII concentrates per kilogram per day during hospitalization was comparable to that in previous reports, both in adults and children [13, 33-38]. As expected, the amount of infused FVIII concentrate per kilogram was higher in children compared with adults, which is explained by a higher clearance of FVIII in young children resulting in a shorter half-life [19] and due to a larger volume of distribution in children in comparion with adults [39]. Consequently, variables associated with FVIII consumption were analyzed separately for children and adults.

The extent and timing of FVIII underdosing and overdosing in the perioperative period have not been reported earlier. Both underdosing, most significant directly after surgery, and (excessive) overdosing, most significant > 6 days after surgery, can clearly be improved. During the entire study period, clinical practice in participating centers with regard to perioperative management of replacement therapy did not change as guidelines were not altered. Patients with preoperative or perioperative FVIII levels that were lower than expected, received additional bolus infusion(s) of FVIII concentrate to achieve target ranges as set by the consensus. Discrepancies between target ranges and actual FVIII plasma levels increased consecutively during the perioperative period, suggestive of a focus on prevention of bleeding and not on prevention of overdosing.

In two prospective studies by Batarova et al. and Bidlingmaier et al., savings of 30-36% of FVIII concentrate consumption were calculated for continuous versus intermittent bolus infusion [9, 16]. Our data, however, do not support continuous dosing as more cost reductive compared with intermittent bolus infusion. This may be due to the following

factors. In our study, the total amount of FVIII concentrate was corrected for duration of hospitalization, not only for body weight as in previous studies. Further, confounding by indication, for example, severity of surgical procedure, may have influenced outcome, as continuous infusion was more often used in more severe procedures. Moreover, when intermittent bolus infusion was applied in our study, it was often dosed more frequently per day in lower doses, thereby mimicking continuous dosing. All of these factors may have led to smaller differences in FVIII concentrate consumption between modes of administration of therapy. Last, type of concentrate and severity of surgical procedure were not associated with the overall amount of FVIII consumption in both children and adults, probably due to collinearity between these specific variables.

Complications

In this cohort, representative for surgical patients in hemophilia treatment centers in resource-rich countries [28, 29] bleeding complications were seen in 32% of adult patients and 5% of pediatric patients. This high percentage seems due to the broad ISTH definition applied in our study for bleeding, which was not used in comparable studies [29, 33, 35, 40]. Cases were mainly defined by the decrease of hemoglobin of ≥ 1.24 mmol L^{-1} included in the definition, which was not accompanied by hemodynamic problems or low FVIII plasma levels in study patients. Severity of bleeding was similar to earlier reports, as the percentage of study patients requiring a reoperation (3%) was comparable to a previous study, which reported a percentage of 2.7% [33]. We could not demonstrate that FVIII plasma levels were under lowest target range levels in patients with bleeding complications [33], although this may be due to a lack of FVIII testing at the bleeding occurrence and FVIII plasma levels measured after acute FVIII concentrate administration.

Theoretically, in our study, optimal maintenance of predefined target FVIII levels by refined dosing would have led to a reduction of FVIII consumption of maximally 44%, with a concomitant reduction of treatment costs. However, when using a strategy of optimal target value maintenance, it is, of course, not possible to completely eliminate underdosing and overdosing as the logistic delays caused by laboratory monitoring, and assessment of FVIII values and adjustment of treatment will persist. Although currently not yet available due to the lack of perioperative PK population models, we believe more optimal treatment will consist of individually dosed FVIII concentrate based on an individual FVIII PK profile with adaptive dosing according to a perioperative FVIII PK population model. Until recently, most studies on PK-guided dosing were performed in the prophylactic setting [41-43]. In the few studies in which perioperative PK profiling is mentioned it was solely used to establish a preoperative PK- guided loading dose [9, 11, 13].

Conclusion

Our findings demonstrate significant underdosing and (excessive) overdosing of FVIII concentrate and identify its predictors during the perioperative period with current dosing strategies based on body weight and crude estimations of clearance. Blood group O proved to be predictive of underdosing and was associated with a higher risk of bleeding complications; blood group non-O was demonstrated to be a predictor of overdosing. With regard to excessive overdosing, older age and replacement therapy via bolus infusion were shown to be predictive. Currently available PK population models for FVIII replacement therapy in the prophylactic setting support that age influence FVIII plasma concentrations significantly [20, 41]. These data underline that quality of care and cost-effectiveness can be improved by future refining of dosing strategies based on individual patient characteristics such as the predictors blood group and mode of infusion. However, we also believe that not all variables of influence on dosing and clearance of FVIII concentrate have yet been defined. Therefore, novel developments with regard to PK-guided dosing based on PK population models and Bayesian analysis, taking both known and unknown modifying factors into account as proposed by Bjorkman et al. [41], are more than promising.

ACKNOWLEGDMENTS

This study is part of the "OPTI-CLOT" research programme (Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrate in clotting disorders)", an (inter) national multicentre study aiming to implement PK-guided dosing of clotting factor replacement therapy by initiating studies to prove the implications of PK-guided dosing, to construct perioperative and prophylactic PK population models and to evaluate the cost-effectiveness of a PK-guided approach. A complete list of the members of the OPTI-CLOT research programme appears in the online data supplement. The authors would like to thank H. Bouzariouh for aiding in data collection and J.G. van der Bom for statistical advice.

This study was financially supported by an investigator-initiated research grant from Baxter.

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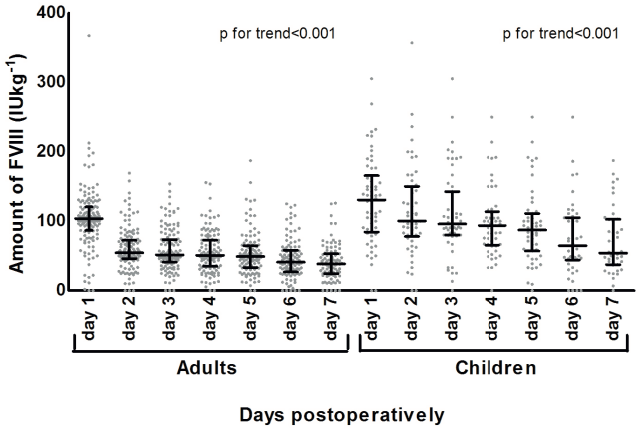

Figure S1. Amount of infused FVIII clotting factor concentrate.

Table S1. Classification of included surgical procedures*.

Surgical Type	High Risk**	Major	Minor
General			
Laparotomy		Major	
Liver Biopsy		Major	
Cholecystectomy and exploration of common duct		Major	
Colorectal Surgery			
Excision of anal fistula			Minor
Gastro duodenoscopy (biopt)		Major	
Diagnostic laparoscopy		Major	
Vascular			
Amputation of limb		Major	
Cardiothoracic Surgery			
Insertion of defibrillator		Major	
Coronary Angioplasty	High		
Coronary Artery Bypass Graft (CABG)	High		
Excision of mediastinal mass	High		
Neurosurgery			
Craniotomy	High		
Meningioma	High		
Shunt procedures	High		
Orthopedics			
Arthroscopy (shoulder/knee)		Major	
Foot or ankle surgery			Minor
Incision drainage			Minor
Internal fixation of tibia or fibula		Major	
Revision of total hip and knee replacement		Major	
Scoliosis surgery	High		
Total joint replacement (elbow, hip, shoulder, knee)		Major	
Hand or wrist surgery			Minor
Urology			
Circumcision			Minor
Vasectomy			Minor
Prostatectomy		Major	
Urethroplasty		Major	
Urerthrolithotomy		Major	
Maxillofacial			
Bimaxillary osteotomy		Major	
Craniofacial Surgery	High		
ENT (Ear-nose-throat)			
Adenoidectomy			Minor
Adenoido-tonsillectomy		Major	
ENT: insertion of stents			Minor

Table S1. Classification of included surgical procedures*. (continued)

Surgical Type	High Risk**	Major	Minor
Tonsillectomy		Major	
Eye Surgery			
Orbital surgery		Major	
Cataract/Virectomy/Retinal surgery			Minor
Miscellaneous			
Dental surgery			Minor
Drainage of abscess			Minor
Excision burns scars			Minor
Excision of lipoma			Minor
Hernia repair (inguinal/umbilical)			Minor
Central venous catheter removal/insertion			**Minor**

* Surgical risk score according to Koshy et al. 1995; ** Excluded

Table S2. Frequency of underdosing and overdosing in the perioperative period before 2005 and after 2005.

	2000 - 2013	< 2005	> 2005
Underdosing (%)			
0-24 hours	45	38	47
24-120 hours	7	10	4
>120 hours	8,5	12	8
Overdosing (%)			
0-24 hours	33	36	31
24-120 hours	59	58	58
>120 hours	73	64	73

Table S3. Characteristics of patients with a severe bleeding complication requiring a reoperation.

Patient	Surgical procedure	Day of occurrence of the bleeding complication	Description	FVIII level (IU mL^{-1})	Mode of infusion	Other medication	Blood group
1	Total knee replacement	Day 5	Intra-articular bleed	0.99	Bolus	Heparin	Non-O
2	Total knee replacement	Day 5	Intra-articular bleed	1.03	Continuous	Heparin	O
3	Total knee replacement	Day 4	Intra-articular bleed	0.68	Continuous	Tranexamic acid	O
4	Fixation of hip/ humerus	Day 2	Bleed after removal of a drain	0.99	Continuous	Tranexamic acid	O
5	Total knee replacement	Day 7	Intra-articular bleed	0.50	Continuous	Tranexamic acid, heparin	O
6	Total knee replacement	Day 9	Intra-articular bleed	0.64	Continuous	Tranexamic acid, heparin	O

Table S4. Surgical and patient characteristics of all bleeding complications and severe bleeding complications.

	Bleeding complication*		Severe bleeding complication	
	No	Yes	Reoperation	RBCTF
Type of surgical procedure				
General	4	2	0	0
Colo-rectal	4	1	0	1
Vascular	0	1	0	1
Cardio-thoracic	0	1	0	0
Orthopedic	64	30	6	12
Urology	10	2	0	1
Maxillofacial	1	1	0	1
Ear-Nose-Throat	7	4	0	1
Eye	3	0	0	0
(Re)placement central intravenous catheters	32	0	0	0
Miscellaneous	25	6	0	1
Mode of infusion				
Continuous	83	32	5	12
Bolus	67	16	1	6
Blood group				
O	60	29	5	10
Non-O	67	16	1	7

* According to the ISTH definition; RBCTF = red blood cell transfusion

CHAPTER 7

A population pharmacokinetic model for perioperative dosing of factor VIII in hemophilia A patients

HCAM Hazendonk, K Fijnvandraat, J Lock, MHE Driessens, FJM van der Meer, K Meijer, MJHA Kruip, BAP Laros-van Gorkom, M Peters, SN de Wildt, FWG Leebeek, MH Cnossen*, RAA Mathôt* for the "OPTI-CLOT" study group; *both are last authors

Haematologica. 2016 Jul; Epub.

ABSTRACT

Background The role of pharmacokinetic-guided dosing of factor concentrates in hemophilia is currently subject of debate and focuses on long-term prophylactic treatment. Few data are available on its impact in the perioperative period.

Objective In this study, a population pharmacokinetic model for currently registered factor VIII concentrates was developed for severe and moderate adult and pediatric hemophilia A patients (FVIII levels < 0.05 IU mL^{-1}) undergoing elective, minor or major surgery.

Methods Retrospective data was collected on FVIII treatment, including timing and dosing, time point FVIII sampling and all achieved FVIII plasma concentrations (trough, peak and steady state), brand of concentrate, as well as patient and surgical characteristics. Population pharmacokinetic modeling was performed using nonlinear mixed-effects modeling.

Results Population pharmacokinetic parameters were estimated in 75 adults undergoing 140 surgeries (median age: 48 years, median weight: 80 kg) and 44 children undergoing 58 surgeries (median age: 4.3 years, median weight: 18.5 kg). Pharmacokinetic profiles were best described by a two-compartment model. Typical values for clearance, inter-compartment clearance, central and peripheral volume were 0.15L/h/68 kg, 0.16L/h/68 kg, 2.81L/68 kg and 1.90L/68 kg. Inter-patient variability in clearance and central volume was 37% and 27%. Clearance decreased with increasing age ($P < 0.01$) and increased in case of blood group O (26%, $P < 0.01$). In addition, a minor decrease in clearance was observed when a major surgical procedure was performed (7%, $P < 0.01$).

Conclusion The developed population model describes the perioperative pharmacokinetic of various FVIII concentrates, allowing individualization of perioperative FVIII therapy for severe and moderate hemophilia A patients by Bayesian adaptive dosing.

INTRODUCTION

Hemophilia A is an X-linked hereditary bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII). Current management of hemophilia patients consists of replacement therapy with plasma derived or recombinant factor concentrates in case of acute bleeding ("on demand") or to prevent spontaneous or perioperative bleeding ("prophylaxis"). The aim of long-term prophylactic treatment is to prevent severe joint damage and subsequent long term invalidity by raising FVIII trough plasma concentrations to at least > 0.01 IU mL^{-1} [1, 2]. To acquire adequate hemostasis in the surgical setting, normalization of coagulation factor levels is advocated for 7-14 days after surgery in most perioperative protocols [3].

Treatment with factor concentrates is costly. In the Netherlands, total annual costs of replacement therapy are estimated at more than €130 million and include costs for prophylactic and on demand treatment [4-7]. In the Canadian Hemophilia registry, perioperative consumption amounts to 1-3% of the total annual amount administered [8].

As we have reported earlier, coagulation factor plasma concentrations as recommended by National and International Guidelines are often exceeded in the perioperative setting to avoid lower plasma concentrations and a possibly higher bleeding risk with additional costs [9, 10]. In a retrospective analysis of hemophilia A patients undergoing surgery, 45% of FVIII plasma concentrations were below the target range during the first 24 hours after surgery and 75% of the plasma concentration were above the target range after six days of hospitalization. In addition, a reduction of 44% in factor concentrates could have been reached if plasma concentrations had been maintained within target levels in the perioperative setting [9].

In the prophylactic setting, Carlsson et al. have shown that FVIII consumption can be significantly reduced by application of pharmacokinetic (PK) modeling to individualize dosing regimens [11-14]. In the perioperative setting, Longo et al. have reported excessive FVIII consumption and clearance in 50% of surgical hemophilia patients due to unidentified factors [15]. This suggests mechanisms of increased clearance due to hemostatic challenges during surgery. Although an initial preoperative factor concentrate bolus dose may be individualized by individual PK parameters obtained after an individual PK profile based on a prophylactic population PK model, this may not be applicable as soon as a surgical procedure is initiated. A perioperative population PK model, however would make PK-guided iterative adaptive Bayesian dosing with a potential concomitant decrease of factor concentrate consumption possible. During this procedure individual PK parameters are iteratively updated by combining PK in-

formation (e.g. dose, concentration, time) from the individual patient with a priori PK information (e.g. average clearance, variability) from the population. The latter does not currently exist and has therefore never been performed.

In order to construct such a perioperative population PK model facilitating Bayesian adaptive dosing in severe and moderate hemophilia A, we collected detailed retrospective FVIII infusion data in patients who had undergone surgery under replacement therapy with various similar FVIII concentrates, from five hemophilia treatment centers.

METHODS

Patients and data collection

Severe and moderate hemophilia A patients of all ages with FVIII plasma concentration < 0.05 IU mL^{-1} who had undergone elective, minor or major surgical procedures between 2000 and 2013 from five Academic Hemophilia Treatment Centers in the Netherlands were included [9]. Patients received replacement therapy consisting of various recombinant factor concentrates (Kogenate FS (Bayer, Berkely, Ca, USA], Helixate FS (CSL Behring, Marburg, Germany], Advate and Recombinate [Baxter Bioscience, Thousand Oaks, CA, USA], and Refacto AF [Pfizer, New York, NY USA]) or plasma derived factor concentrates (Aafact [Blood Transfusion council of the Netherlands Red Cross], Hemofil M [Baxter Bioscience, Thousand Oaks, CA, USA]) to achieve target FVIII plasma concentrations as set by the National Hemophilia Consensus. This guideline recommends peak and trough FVIII plasma concentrations on consecutive postoperative days (Table 1): 0-24 hours 0.80-1.00 IU mL^{-1}; 24-120 hours 0.50-0.80 IU mL^{-1} and >120 hours 0.30-0.50 IU mL^{-1} [3]. The following retrospective data were collected: FVIII dosages, detailed timing of administration and timing of FVIII blood sampling, mode of infusion (continuous or bolus infusion), all achieved FVIII plasma concentrations (both trough, peak and steady state plasma concentrations), patient and surgical characteristics, and concomitant medication with a possible effect on hemostasis (i.e. tranexamic acid, heparin, desmopressin and nonsteroidal anti-inflammatory drugs). Patient characteristics included: weight, length, lean body mass [16, 17], body mass index (BMI) [18], blood group,

Table 1. Prevalence of under- and overdosing in the perioperative period*

Time (hours)	**0-24**	**24-120**	**>120**
Consensus	**0.80-1.00 IU mL^{-1}**	**0.50-0.80 IU mL^{-1}**	**0.30-0.50 IU mL^{-1}**
% above	33% *(>1.00 IU mL^{-1})*	59% *(>0.80 IU mL^{-1})*	75% *(>0.50 IU mL^{-1})*
% below	45% *(<0.80 IU mL^{-1})*	7% *(<0.50 IU mL^{-1})*	9% *(<0.30 IU mL^{-1})*

* According to the National Hemophilia Consensus

von Willebrand Factor (VWF) antigen and VWF activity (historically measured), liver and renal function, clinical bleeding phenotype, history of FVIII inhibiting antibodies, intensity of prophylactic dosing regimen, brand of concentrate, and treatment center. Surgical characteristics included: type and severity of surgical procedure categorized into minor, major and high risk according to Koshy et al [19]. In all centers, FVIII plasma concentrations were measured by one-stage clotting assays. The study was not subject to the Medical Research Involving Human Subjects Act, as patient data were analysed anonymously. Moreover, the study was approved by all local Medical Ethics Committees; one center requiring prior patient informed consent.

Pharmacokinetic modeling

Population pharmacokinetics (PK) is defined as the study of sources of variability in drug concentrations after dosing that occurs within and between patients [20]. In the present population analysis, all plasma concentration time points were analyzed simultaneously using non-linear mixed-effects modelling software (NONMEM (version 7.2.0), Globomax LLC, Ellicott City, Maryland, USA) [21]. All PK related abbreviations and terminology are described in Table S1. More specifically, first-order conditional estimation (FOCE) method with interaction was applied, allowing interaction between structural and residual variance components. The statistical package R, version 2.14.2 (The R Foundation for Statistical Computing) and Xpose version 4 [22] were used for data set checkout, exploration and model diagnostics. Pirana software was used as an interface between NONMEM, R and Xpose [23].

Model diagnostics included the evaluation of the goodness of fit plots, the objective function value (OFV), the precision of the parameter estimates and the shrinkage of estimated random parameters. The OFV is a measurement of goodness of fit of the model and is proportional to minus two times the logarithm of the likelihood (-2log likelihood) of the data. Competing hierarchical models were compared by calculating the difference between their OFV. This ratio is assumed to be $\chi 2$ distributed. Therefore, if models differ by one parameter, a decrease in OFV of 3.84 corresponds to $P = 0.05$ (1 degree of freedom). And OFV decreases of 6.63 and 10.8 correspond to *P*-values of 0.01 and 0.001, respectively.

Structural model development

FVIII plasma concentrations were described by a two-compartment PK model. Estimated (fixed) parameters were clearance (CL), volume of distribution of the central compartment (V1), intercompartment clearance (Q) and volume of distribution of the peripheral compartment (V2). The structural model also accounted for the individual endogenous baseline FVIII plasma concentration. PK parameters were allometrically scaled to account

for the wide range of body weights of both adult and pediatric patients. An allometric power model was used with power exponents fixed at 0.75 for clearances and 1.0 for volumes of distribution [24], as described in the following equations:

$$CL_i = \theta_{CL} \times \left(\frac{BW_i}{68}\right)^{0.75}$$

$$V1_i = \theta_{V1} \times \left(\frac{BW_i}{68}\right)$$

In this expression, CL_i and V_i are the typical clearance and central volume of distribution for an individual i with body weight BW_i , θ_{CL} and θ_{V1} are the respective parameter values for a subject with a body weight of 68 kilogram.

The random parameters inter-individual variability (IIV) and inter-occasion variability (IOV) of the PK parameters were estimated using an exponential function according to:

$$CL_i = \theta_{CL} \times e^{(\eta_i + \kappa_i)}$$

where η_i and κ_i represent the IIV and IOV, respectively, and are assumed to be symmetrically distributed with a mean of 0 and an estimated variance of ω^2 and π^2. IIV and IOV were included in the model if shrinkage was less than 20% [25]. The structural model also accounted for under prediction of plasma concentrations of a B-domain deleted product (Refacto®) due to known discrepancies and influence of one-stage laboratory assays on plasma concentrations [26, 27], as described:

$$C_{pred,bdp} = C_{pred} \times (1 - \theta_{bdp})$$

Where $C_{pred,bdp}$ and C_{pred} are the predicted concentrations of the B-domain deleted product ($_{bdp}$) and other products, respectively, and θ is the fractional decrease in concentration.

Residual variability in FVIII concentration was described using a combined error model.

Covariate search

After obtaining the structural model individual empirical Bayesian estimates were obtained for all PK parameters. Correlations between these parameters and patient and surgical characteristics, and the use of concomitant medication were explored graphically. All covariates were tested in a univariate analysis. The most clinically relevant and statistically significant covariate was retained in the model: a stepwise forward approach was used to determine clinical and statistically significant covariates with *P*-values < 0.05. Backward elimination was performed to confirm that all included covariates in the final model were statistically significant with $P < 0.01$. As the occurrence of a bleeding complication could not be related to actual FVIII plasma concentrations [9], occurrence

of a bleeding complication was not included in the final model. Moreover, only a limited difference in clearance was observed between patients with and without a bleeding complication (7%). Also, time dependent changes in clearance were tested during the perioperative period.

Final model and model evaluation

The stability and performance of the final model was checked using an internal validation procedure via the bootstrap resampling technique in which 1000 bootstrap datasets were generated by random sampling with replacement [28]. Visual predictive check plots obtained after Monte Carlo simulations of the study population were used to evaluate if the final model adequately described observed data [29].

RESULTS

Patients and treatment in the perioperative setting

Our cohort consisted of 119 hemophilia A patients undergoing a total of 198 surgical procedures as described previously [9]. Patients were treated for up to two weeks after surgery according to the National Hemophilia Consensus (Table 1) [3]. Treatment consisted of a preoperative bolus infusion of approximately 50 IU kg^{-1} followed by a treatment scheme with either bolus infusions or continuous infusion therapy based on a clearance rate of 3-4 mL kg^{-1} $hour^{-1}$. General characteristics of these included patients are shown in Table 2. Seventy-five patients underwent only one surgical procedure. Half of all patients had blood group O (51%). In three percent of all surgical procedures a severe bleeding complication occurred, defined as necessity of a red blood cell transfusion (RBCT) and/or necessity of a second surgical intervention, which could not be related to FVIII plasma concentrations. In total 1389 FVIII measurements were obtained, equally distributed on consecutive days in the perioperative setting (Figure 1). Approximately 7 samples per patient were taken in the perioperative period. In summary, 45% of FVIII plasma concentrations were below the target range in the first 24 hours and 75% were above the tvarget range after six days of hospitalization (Table 1).

Pharmacokinetic modeling

Structural model development

Time profiles of FVIII plasma concentrations were best described by a two-compartment model with allometric scaling for body weight (Figure 2). By allometric scaling, all estimated PK parameters were normalized for a body weight of 68 kg. Model building steps that resulted in significant decrease of the OFV and consequently a better fit of the model are shown in Table 3. In the structural model, typical values for CL and V1 were

Table 2. Population characteristics

	Total cohort	Adults	Children
	No. (%); or Median [minimum; maximum]		
Patient characteristics			
No. of patients	119	75	44
Age (years)	40 [0.2-78]	48 [19-78]	4 [0.2-17.3]
Weight (kg)	75 [5-111]	80 [45-111]	19 [5-85]
Severe hemophilia (FVIII levels <0.01 IU mL^{-1})	83 (69.7)	49 (65.3)	34 (77.3)
On prophylaxis	84 (70.6)	51 (68.0)	33 (75.0)
Blood group O*	51 (50.5)	34 (50.0)	17 (51.5)
Historical VWF levels			
Antigen	1.1 [0.3-2.5]	1.2 [0.3-2.5]	0.9 [0.5-2.3]
Activity	1.1 [0.2-2.7]	1.4 [0.2-2.7]	0.9 [0.4-1.7]
Surgical characteristics			
Total no. of surgical procedures	198	140	58
No. of patients undergoing:			
1 procedure	75 (63.0)	43 (57.3)	32 (72.7)
2 procedures	26 (21.8)	15 (20.0)	11 (25.0)
3 procedures	9 (7.6)	9 (12.0)	0 (0.0)
> 4 procedures	9 (7.6)	8 (10.7)	1 (2.3)
Major surgical procedure	97 (49.0)	86 (61.4)	11 (19.0)
Type of surgical procedure			
General	6 (3.0)	6 (4.3)	0 0
Colorectal	5 (2.5)	4 (2.9)	1 (1.7)
Vascular	1 (0.5)	1 (0.7)	0 0
Cardio-thoracic	1 (0.5)	1 (0.7)	0 0
Orthopedic	94 (47.5)	91 (65.0)	3 (5.2)
Urology	12 (6.1)	4 (2.9)	8 (13.8)
Maxillofacial	2 (1.0)	2 (1.4)	0 0
Ear-nose-throat	11 (5.6)	6 (4.3)	5 (8.6)
Eye	3 (1.5)	3 (2.1)	0 0
(Re)placement of central intravenous catheters	32 (16.2)	1 (0.7)	31 (53.4)
Miscellaneous	31 (15.7)	21 (15.0)	10 (17.2)
Replacement therapy with factor concentrate, hospitalization and blood loss			
Mode of infusion			
Continuous	115 (58.1)	88 (62.9)	27 (46.6)
Bolus	83 (41.9)	52 (37.1)	31 (53.4)
Product type			
Recombinant	152 (76.8)	99 (70.7)	53 (91.4)

Table 2. Population characteristics (continued)

	Total cohort	Adults	Children
	No. (%); or Median [minimum; maximum]		
Plasma derived	46 (23.2)	41 (29.3)	5 (8.6)
Duration of hospitalization (days)	9 [1-50]	9 [1-50]	7 [1-16]
Complications during the perioperative period			
No. of patients with a complication			
Bleeding	48 (24.2)	45 (32.1)	3 (5.2)
Re-operation	6 (3.0)	6 (4.3)	0 0
Hemoglobin drop >20 gL^{-1} and/or erythrocyte transfusion	38 (19.2)	36 (25.7)	2 (3.4)
Bleeding with prolonged hospitalization	5 (2.5)	4 (2.9)	1 (1.7)
Thrombosis	0 0	0 0	0 0
FVIII data			
FVIII measurements (trough, peak and SS)	1389	1124	265
Prior to surgery	158 (11.4)	114 (10.1)	44 (16.6)
Day 1 (0 - 24 h)	323 (23.2)	246 (21.9)	76 (28.7)
Day 2 - 5 (24 - 120 h)	473 (34.0)	363 (32.3)	110 (41.5)
Day > 6 (>120 h)	436 (31.4)	401 (35.7)	35 (13.2)

No., number, %; percentages; kg, kilogram; FVIII, coagulation factor VIII; IU mL^{-1}, international units per milliliter; BU, Bethesda Units; VWF, von Willebrand factor; mmol L^{-1}, millimolar per liter; g L^{-1}, gram per liter; * Blood group known of 101 patients.

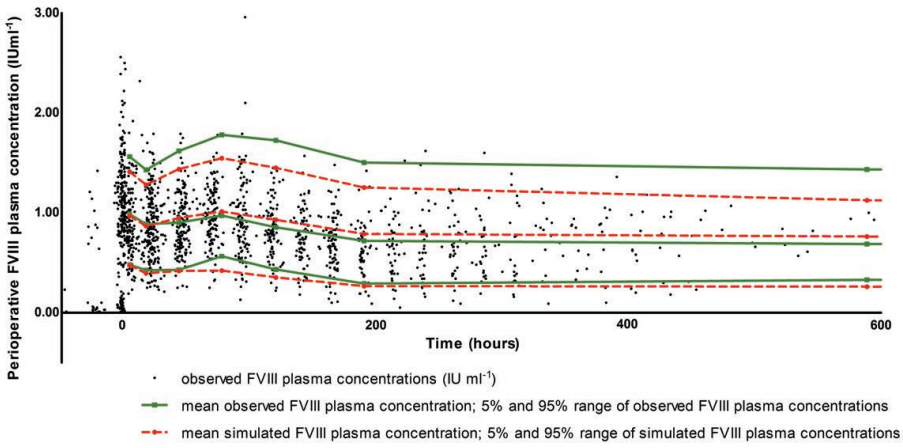

Figure 1. Perioperative FVIII plasma concentrations and visual predictive check for observed FVIII plasma concentrations.
Perioperative FVIII plasma concentrations consists of trough, peak and steady state concentrations for both modes of therapy (continuous infusion and bolus infusion therapy); Visual predictive check for the observed FVIII plasma concentrations, given the final model; observed FVIII plasma concentrations and mean, 5th percentile and 95th percentile observed and simulated FVIII plasma concentrations.

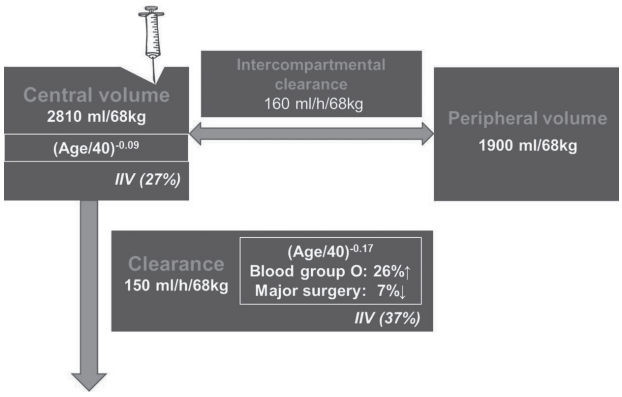

Figure 2. Visualization of NONMEM analysis and outcomes.
Allometric scaling based on body weight was applied with an allometric exponent of 0.75 for the clearance parameters and 1 for the volume terms; Age in years; IIV= inter-individual variability.

190 ml/hour/68 kg and 3030 ml/68 kg (Table 4). It was possible to estimate IIV for CL and V1 whereas estimates for IIV of Q and V2 were imprecise and accompanied by a large shrinkage of > 40% [25]. Although this may suggest that inter-patient variability in Q and V2 is absent, this is due to the fact that available data was not informative enough. The IIV for CL and V1 were respectively 45% and 29%, underlining the importance of individualization of therapy. Estimation of IOV on CL and V1 resulted in high shrinkage values for both parameters (respective value 34% and 46%); consequently IOV was not included in the model. Inclusion of individual endogenous baseline FVIII plasma concentrations and inclusion of a structural under prediction of plasma concentrations using a B-domain deleted product improved the model. A proportional under prediction of 0.34 (34%) in FVIII plasma concentration was estimated for this product. The residual error was described using a combined error model.

Covariate search

In the univariate analysis, significant covariates of clearance were age ($P < 0.001$), blood group ($P < 0.01$), severity of surgical procedure ($P < 0.01$), lean body mass ($P < 0.01$), use of tranexamic acid and heparin ($P < 0.05$), historically measured VWF antigen and activity levels ($P < 0.05$). Treatment center and type of product were not significant covariates. After the step forward analysis only age, blood group, and severity of surgical procedure were significantly associated with clearance. After the inclusion of age in the model, VWF antigen and activity levels were no longer statistically significant. Age was also associated with V1 (Table 3). Different models were used to test possible time dependent changes in clearance during the perioperative period; no differences were observed however. Differences in residual error were detected for the different centers.

Table 3. Model-building steps resulting in significant decreases in objective function value (OFV)

Model		NOP	OFV
Structural model[#]			
1	One compartment with IIV on V1 and CL	7	-2604.5
2	Two compartment with IIV on V1 and CL	9	-2799.3
3	Inclusion of individual endogenous baseline FVIII plasma concentrations	9	-2816.1
Covariates on CL (added to model 3)			
4	Age	10	-2851.8
5	Age, blood group	11	-2862.3
6	Age, blood group, bleeding complication	12	-2886.7
7	Age, blood group, bleeding complication, severity of surgical procedure	13	-2895.2
Covariates on V1 (added to model 7)			
8	Age	14	-2911.8
Error model (added to model 8)			
9	Center (two categories)	16	-2930.6

[#] Allometric scaling based on body weight was applied with an allometric exponent of 0.75 for the clearance parameters and 1 for the volume terms; under prediction of FVIII plasma concentrations of a B-domain deleted product was implemented NOP = number of estimated parameters, OFV = objective function value, IIV = inter-individual variability, V1 = volume of the central compartment, CL = clearance.

In the final model, IIV of CL decreased from 45% towards 37% after inclusion of these covariates. IIV of V1 decreased from 29% to 27%. The PK parameter estimates of the final model are presented in Table 4. Typical PK parameter estimates were described with the equations presented in Table 5.

According to the equation, clearance was 214, 169, 150 and 142 ml/h/68 kg for a typical patient (with blood group non-O undergoing a minor surgical procedure) with an age of 5, 20, 40 and 55 years, respectively. In case of a major surgical procedure, a small decrease in CL was observed of 7% (Table 4). Interestingly, individual post-hoc clearances were higher in patients with a major surgical procedure (Figure 3B). This was however explained by collinearity between covariates; older patients underwent more major surgical procedures (Figure 4). Clearance increased by 26% in patients with blood group O. CL and elimination half-life are depicted as functions of age and body weight in Figure 5.

The adequacy of the derived final model is shown in Figure 6. Population and individually predicted concentrations for all patients were plotted against the measured concentrations in Figure 6. A good agreement was observed between FVIII concentrations predicted by the model and those assessed by laboratory measurements. Overall,

Table 4. Parameter estimates for the final model and bootstrap analysis

	Structural model		Final model		Bootstrap analysis final model	
Parameter	**Mean**	**(%RSE)**	**Mean**	**(%RSE)**	**Mean**	**(%RSE)**
Structural model						
θ1 - Clearance (CL; ml/h/68 kg)	190	(5)	150	(8)	160	(5)
θ2 - Volume of central compartment (V1; ml/68 kg)	3030	(3)	2810	(4)	2810	(3)
θ3 - Inter-compartmental clearance (Q; ml/h/68kg)	170	(17)	160	(20)	170	(15)
θ4 - Volume of peripheral compartment (V2; ml/68 kg)	1930	(12)	1900	(11)	1890	(8)
B-domain deleted product	0.32	(11)	0.34	(13)	0.33	(10)
Covariate parameters						
θ5 - CL – Age (change with increasing age)			-0.17	(22)	-0.16	(13)
θ6 - CL – Blood group O (% difference)			26	(7)	27	(22)
Θ7 - CL – Major surgical procedure (% difference)			-7	(6)	-7	(34)
Θ8 - V1 – Age (change with increasing age)			-0.09	(28)	-0.09	(18)
Inter-individual variability						
Clearance (% CV)	45	(13)	37	(14)	36	(10)
Volume of central compartment (% CV)	29	(13)	27	(14)	26	(11)
Residual variability						
Additive residual error (SD; IU mL^{-1})						
Center 1,2,3			0.15	(12)	0.14	(9)
Center 4,5			0.05	(28)	0.05	(20)
Proportional residual error (% CV)						
Center 1,2,3			0.18	(15)	0.18	(9)
Center 4,5			0.23	(9)	0.23	(7)

RSE indicates relative standard error; and CV coefficient of variation.

Table 5. Model equations describing the perioperative population PK model

CL	CL (ml/h) = 150 x ((body weight / 68) ^ 0.75) x ((age / 40) ^ -0.17) x (1.26 ^ blood group) x (0.93 ^ severity of surgical procedure)
V1	V1 (ml) = 2810 x (body weight / 68) x ((age / 40) ^ -0.09)
Q	Q (ml/h) = 160 x ((body weight / 68) ^ 0.75)
V2	V2 (ml) = 1900 x (body weight / 68)

Body weight (kilograms); Age (years); Blood group equals one in case of blood group O and zero in case of blood group non O; Severity of surgical procedure equals one in case of a medium risk surgical procedure and zero in case of a low risk surgical procedure.

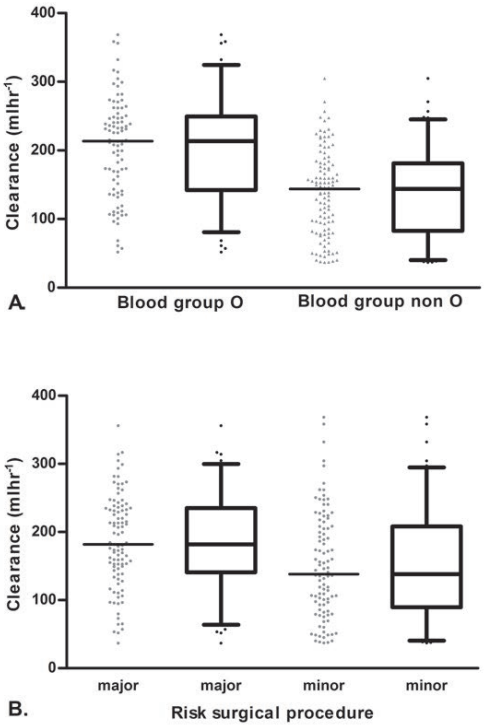

Figure 3. Graphical visualization of variability of the clearance and covariates.
Visualization of variability of the clearance; a. as a function of blood group O versus blood group non O; b. as a function of risk of surgical procedure.

standardized weighted residuals revealed a random distribution around zero, within -2 to +2 range indicative of an unbiased estimation (Figure 6C).

Model evaluation

A good agreement was found between parameter estimates of the final model and parameter estimates of the bootstrap analysis (Table 4). A visual predictive check was conducted by 1000 simulations based on the final model as shown in Figure 1. It confirmed, adequateness of the model, as seven percent of the measured concentrations were calculated above the 95th percentile of the simulated concentrations and nine percent of the measured concentrations were found to be below the 5th percentile of the simulated concentrations.

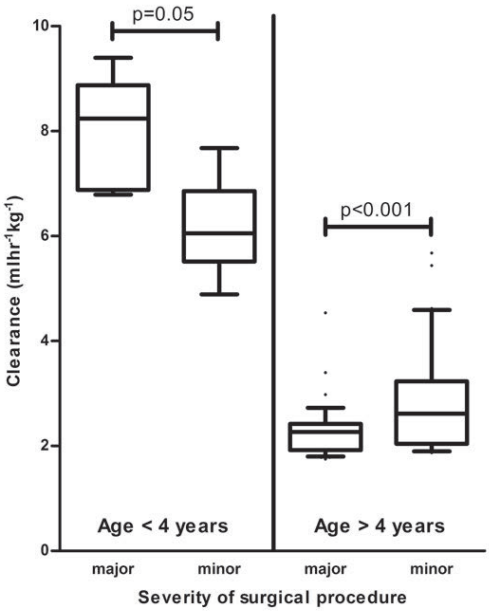

Figure 4. Clearance of FVIII in major and minor surgical procedures after stratification for age.
Post-hoc estimates of FVIII clearance, normalized for total body weight, and stratified for age (<4 years or >4 years) were categorized according to severity of surgical procedure. *A Spearman's correlation test was performed to test for clearance differences between major and minor surgical procedures. The median age of children included in the study was used as cut-off value for analysis. This was supported by results of figure 5A.

DISCUSSION

In this study, a population PK model was constructed describing the perioperative PK of several currently used FVIII concentrates. These factor VIII concentrates were in majority FVIII recombinant products (77% of surgical procedures), of which 14% were a B-domain deleted FVIII concentrate, as well as plasma-derived FVIII concentrates (23% of surgical procedures). In the population PK model, a difference in results due to the B-domain deleted FVIII concentrate (Refacto AF®) was accounted for. No other differences were observed between products. As this difference is incorporated into the population PK model, this perioperative FVIII population PK model can be used for all described FVIII concentrates. The developed model will facilitate Bayesian adaptive dosing, allowing individualization of FVIII dosing during the entire perioperative period. Earlier, only a few studies have reported application of PK-guided dosing during the perioperative period. Unfortunately, in all studies only the FVIII loading dose was based on an individual PK-profile derived several days before surgery [30-35]. Iterative perioperative FVIII dosing-adjustments after first loading dose could not be performed as a population PK

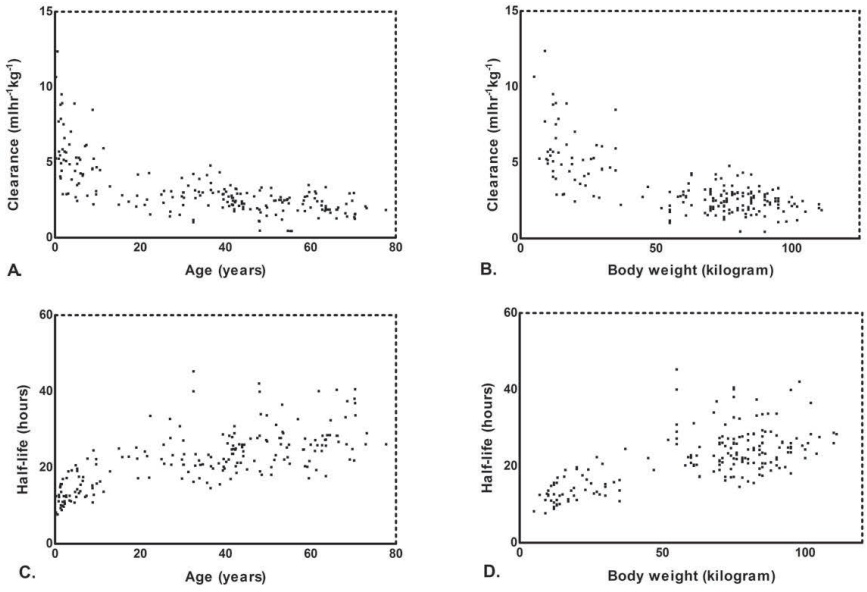

Figure 5. Clearance and elimination half-life as functions of age and body weight.
a. Clearance of FVIII, normalized for total body weight, as a function of age; b. Clearance of FVIII as a function of body weight; c. The elimination half-life of FVIII as a function of age; d. The elimination half-life of FVIII as a function of body weight. Eta shrinkage was 10% and 20% respectively for the estimates of inter-individual variability of clearance and volume of the central compartment.

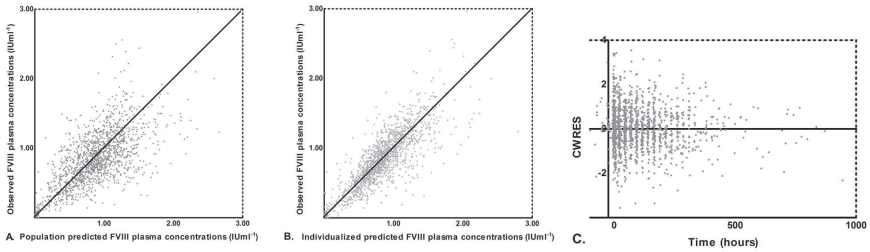

Figure 6. Observed and model-predicted FVIII plasma concentrations.
NONMEM model diagnostic plots, observed and model predicted FVIII plasma concentrations plotted against each other; a. population predicted FVIII plasma concentrations; b. individually predicted FVIII plasma concentrations; c. conditionally weighted residuals versus time

model was lacking . The perioperative population PK model presented, will now make Bayesian adaptive dosing in this setting possible. Moreover, it will take all important patient characteristics associated with clearance in the surgical setting into account.

The presented model consists of a two-compartment model with allometric scaling of the PK parameters for body weight. Both increasing age and increased severity of surgical procedure were overall significantly associated with a lower FVIII clearance, although individual clearance rates showed that patients with a major surgical procedure did demonstrate higher clearance rates. This contradiction may be due to the fact that included covariates in the PK model were confounders e.g. older patients with a decreased CL of FVIII concentrate underwent major risk surgical procedures more often than younger patients. Also, increased consumption of concentrates due to blood loss and activation of coagulation are other possible modifying factors. In addition, blood group O was associated with higher FVIII clearance, which will be discussed in following sections. Although it should be underlined that this population PK model is an important development, it is important to realize that it does not account for pharmacodynamic outcome measures, as the occurrence of a bleeding complication could not be related to actual FVIII plasma concentrations due to scarcity of FVIII plasma concentrations during an acute bleeding.

As in most resource rich countries, current perioperative replacement therapy in hemophilia A in the Netherlands, consists of a FVIII loading dose followed by either continuous FVIII infusion or treatment with FVIII bolus infusions, while targeting predefined peak and trough FVIII plasma concentrations as stated in the National Hemophilia Consensus [3]. The retrospective study performed to collect data for this PK model, has been described earlier [9]. Results show the challenges of current perioperative dosing of FVIII replacement therapy in daily clinical practice when targeting prescribed FVIII plasma concentrations as significant underdosing and overdosing were demonstrated. Moreover, it underlines the necessity of alternative, more individualized dosing strategies in the perioperative setting as is possible when PK-guided dosing based on a population PK model is applied.

PK-guided dosing based on population PK models has mainly been studied in the long-term prophylactic setting. However, to be able to apply Bayesian adaptive dosing, it is necessary to utilize a population PK model appropriate for the individual patient and the specific setting concerned. In analyses preceding the construction of this perioperative population PK model, it was confirmed that the mean estimated PK parameters for prophylactic dosing, as reported by Björkman et al. [12], did not reliably predict observed perioperative FVIII plasma concentrations. Using the prophylactic model, calculations showed an under prediction of perioperative FVIII concentrations < 1.00 IU mL^{-1} as well as an overprediction of FVIII concentrations > 1.00 IU mL^{-1}. In other words, actual FVIII plasma concentrations were higher and respectively lower than predicted by prophylactic population PK model (data not shown). Therefore, it was concluded that

prophylactic population PK models cannot be applied in the perioperative setting. Use of the prophylactic model in this setting would generate a bias of predicted perioperative FVIII plasma concentrations.

In the prophylactic setting, a similarly constructed population PK model has been applied earlier [12]. CL, V1 and Q were actually in accordance when a comparison was made between perioperative and prophylactic PK population model (CL: 150 versus 222 ml/hr/68 kg; V1: 2810 versus 3520 ml/68 kg; and Q: 160 versus 256 ml/h/68 kg, respectively). However, in the present perioperative model, a value of 1880 ml/68 kg was found for V2 in contrast to a value of 240 ml/68 kg found in the prophylactic situation, suggesting a rapid redistribution of FVIII concentrate following intravenous administration [12]. Due to increased V2, calculated distribution half-life and elimination half-life are significantly larger (as half-life is a derivative of the distribution volume) in the perioperative setting in comparison with the prophylactic state (respectively 4 hours and 25 hours versus 0.6 hours and 12 hours). These calculated half-lifes are in accordance with previously described half-life observed immediately after surgery and half-life observed at steady state of 10 surgical patients described with a surgical model (respectively 9.6 and 17.8 hours) in comparison to 10 surgical patients described with an estimated half-life of 10.1 hours described with a non-surgical model [15]. Unfortunately, the rapid redistribution was not quantifiable, due to minimal data of laboratory assessment after infusion. Previously, it has been suggested that V2 may reflect the FVIII distribution into extravascular spaces or within an intravascular compartment, more specifically as a reflection of adhesion to the vessel wall or that it may reflect the process of a rapid initial elimination [36,37]. We hypothesized that an extra intravascular component resulting in a large V2, may be the result of the high affinity and stoichiometry of FVIII to VWF [38], combined with the significant increase of VWF after surgery due to inflicted endothelial damage and its role in the acute phase reaction [39]. In addition, Deitcher et al. have shown that volume of distribution increases after desmopressin administration, which of course results in an overall increase in VWF levels [40].

Moreover, we believe that VWF may play a crucial role in the perioperative setting with regard to FVIII PK parameters, as previous studies have demonstrated a clear association between VWF plasma concentrations and FVIII half-life [41, 42]. This is not surprising, as VWF protects FVIII against proteolytic degradation by expression of ABH antigens on N-linked glycans and the uptake of the copper-binding protein ceruloplasmin [43, 44]. Additionally, it has been shown that in healthy individuals undergoing orthopedic surgery, VWF decreases significantly intraoperatively and rises immediately after surgery [39]. Therefore, we suspected a time-dependent FVIII clearance in the presented PK model, with an increased clearance during the surgical procedure itself and a decrease

in clearance directly after surgery. However, no time-dependent clearance could be established. Unfortunately, it was not possible to investigate the role of VWF plasma concentrations in our analyses in more detail, as VWF measurements are currently not routine practice in the perioperative setting and only historically measured VWF plasma concentrations were available in half of the study population. However, a 26% higher clearance rate was observed in blood group O patients in the perioperative setting, underlining the potential importance of measurement of VWF plasma concentrations in the perioperative setting if PK-guided dosing is implemented. This is supported by earlier reports that blood group O patients have around 25% lower VWF levels in comparison to patients with blood group non-O [43]. Strikingly, this effect of blood group on clearance was not significant in the prophylactic population PK model as shown by Bjorkman et al [12]. However, we are not informed if VWF levels were available for those analyses. Contrastingly, higher VWF levels may also help explain the unexpected overall lower clearance found in patients undergoing major surgical procedures. In the ongoing prospective randomized controlled "OPTI-CLOT" trial (RCT), which is described in more detail elsewhere [45], insight will be gained into the pathophysiology of VWF in hemophilia patients during the perioperative setting and the relationship between VWF levels and estimates of FVIII PK parameters, among others. These data will further validate the now presented perioperative PK population model, refining its applicability and further defining the influence of possible modifying factors of PK parameters. Moreover, extension of this population PK model, in combination with extended half-life (EHL) products in the near future, could be of great value. However, firstly, studies are needed to extensively document associations between clearance of current FVIII products and EHL products within individuals.

Clinically in the perioperative setting, adaptive Bayesian dosing can be used to optimize and individualize dosing in order to obtain desired target FVIII plasma concentrations with increased certainty. Bayesian analysis combines individual PK information with information from an available population PK model. Such a population PK model is constructed from PK data of many individuals, and not only embodies defined patient characteristics known to influence clearance and other PK parameters, but also currently unidentified patient characteristics which cannot be quantified. Individual patient information that is entered into the model must include dose and time point of factor concentrate administration as well as achieved FVIII plasma concentrations. Incorporation of the patient's weight, blood group, age and severity of surgical procedure will improve estimation of the individual clearance of factor concentrate. In clinical practice, individual clearance and other PK parameter estimates can be made by a clinical pharmacologist with experience with this methodology and iteratively updated, leading to calculated dose adjustments. Currently, we are planning to develop a PK tool to imple-

ment this perioperative population PK model in daily clinical practice. The first dose of FVIII concentrate, still in steady state, will be based on individual PK parameters deducted from an individual PK profile constructed according to the prophylactic population PK model. As we were not able to demonstrate time dependent changes in PK parameters during the perioperative setting, the perioperative population PK model described here can be applied to the complete perioperative period with varying target FVIII plasma concentrations as described by National guidelines.

In conclusion, we have constructed a perioperative population PK model facilitating iterative dose-adjustments by Bayesian analysis. We believe this model will prove its value as it will lead to optimization of current dosing strategies by a decrease of underdosing and overdosing, and therefore both a decrease of bleeding risk and an expected overall reduction of factor concentrate consumption with concomitant cost reduction.

ACKNOWLEGDMENTS

This study is part of the "OPTI-CLOT" research programme (Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrate in bleeding disorders)", an (inter) national multicenter study aiming to implement PK-guided dosing of clotting factor replacement therapy by initiating studies to prove the implications of PK-guided dosing, to construct perioperative and prophylactic PK population models and to evaluate the cost-effectiveness of a PK-guided approach. A complete list of the members of the OPTI-CLOT research programme appears in the online data supplement.

This study was financially supported by ZonMW, the Dutch Organization for Health Reserch and Development, and an investigator-initiated, unrestricted research grant from Baxter.

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Table S1. Terminology and definitions used to develop population PK models.

Terminology	Definitions
NONMEM®	Non-linear mixed-effects modelling software to construct a population analysis, where all plasma concentration time points are analyzed simultaneously
OFV	Objective function value; a measurement of goodness of fit of the model. OFV is proportional to minus two times the logarithm of the likelihood (-2log likelihood) of the data
PK parameters	Pharmacokinetic parameters (e.g. CL, V1, Q, V2)
CL	Clearance
V1	Volume of distribution of the central compartment
Q	Intercompartment clearance
V2	Volume of distribution of the peripheral compartment
Allometric scaling	PK parameters are allometrically scaled to account for the wide range of body weights of both adults and pediatric patients
IIV	Inter-individual variability; variability between patients
IOV	Inter-occasion variability; variability within patients

CHAPTER 8

Facilitating implementation of pharmacokinetic-guided dosing of prophylaxis in hemophilia care by Discrete Choice Experiment

J Lock, EW de Bekker-Grob, G Urhan, M Peters, K. Meijer, P Brons, FJM van der Meer, MHE Driessens, PW Collins, K Fijnvandraat, FWG Leebeek, MH Cnossen for the "OPTI-CLOT" study group

Haemophilia. 2016 Jan;22(1):e1-e10.

ABSTRACT

Introduction Patients', parents' and providers' preferences with regard to medical innovations may have a major impact on their implementation.

Aim To evaluate barriers and facilitators for individualised pharmacokinetic (PK)-guided dosing of prophylaxis in haemophilia patients, parents of young patients, and treating professionals by discrete choice experiment (DCE) questionnaire.

Patients and Methods The study population consisted of patients with haemophilia currently or previously on prophylactic treatment with factor concentrate (n = 114), parents of patients aged 12-18 years (n = 19), and haemophilia professionals (n = 91). DCE data analysis was performed, taking preference heterogeneity into account.

Results Overall, patients and parents, and especially professionals were inclined to opt for PK-guided dosing of prophylaxis. In addition, if bleeding was consequently reduced, more frequent infusions were acceptable. However, daily dosing remained an important barrier for all involved. 'Reduction of costs for society' was a facilitator for implementation in all groups.

Conclusions To achieve implementation of individualised PK-guided dosing of prophylaxis in haemophilia, reduction of bleeding risk and reduction of costs for society should be actively discussed as they are motivating for implementation; daily dosing is still reported to be a barrier for all groups. The knowledge of these preferences will enlarge support for this innovation, and aid in the drafting of implementable guidelines and information brochures for patients, parents and professionals.

INTRODUCTION

Patients', parents' and providers' preferences with regard to medical innovations may have a major impact on their implementation, often delaying initiation significantly [1]. Therefore, it is of importance to thoroughly investigate existing barriers and facilitators with regard to the targeted intervention in all involved.

In haemophilia, prophylactic treatment with regular infusion of factor concentrate aims to convert the bleeding pattern of severe haemophilia patients to a milder phenotype. Replacement therapy with factor concentrate thus prevents morbidity due to haemophilic arthropathy and mortality due to lethal bleeds [2]. As early as 1997, it was suggested by Carlsson et al. that a 30% reduction of factor concentrate consumption in prophylaxis could be attained by dosing based on an individual pharmacokinetic (PK) profile in relationship to a PK population model (PK-guided dosing) with adjustment of dose and frequency of dosing, with concomitant reduction of costs of this expensive treatment [3, 4]. Moreover, PK-guided dosing may also optimize care as inappropriately low or infrequent dosing is corrected before bleeding occurs [5].

To date, PK-guided dosing has still not been implemented in routine haemophilia care, due to different reasons such as: the long-time absence of PK population models; lack of knowledge of PK in haemophilia professionals; lack of belief in the cost-effectiveness of PK-guided dosing due to studies hampered by small sample size; and lack of financial motives in resource rich countries to improve cost-effectiveness of treatment [2, 6]. However, routine PK-guided dosing of prophylaxis may now become within reach, due to the PK population models developed by Björkman et al. [7, 8] and a recent global initiative for a web-based portal for PK consultation by Iorio and Hermans [9]. Therefore, practical insights into successful implementation of this most probably cost-effective approach are urgently required.

Barriers and facilitators with regard to certain interventions can be quantified by discrete choice experiment (DCE) [10]. A technique that is increasingly applied with regard to the implementation of healthcare innovations [11, 12]. Thus far, only a limited number of studies have investigated preferences with regard to haemophilia treatment [13-18]. No studies have focused on preferences with regard to PK-guided dosing of prophylaxis.

We performed a DCE to quantify preferences towards PK-guided dosing of prophylaxis in haemophilia patients, parents of young patients and professionals, using it as a diagnostic tool to rank barriers and facilitators. In our opinion, increased insight into these

mechanisms will generate wider support for this innovation and will help develop successful implementation strategies.

PATIENTS AND METHODS

Study population

Patients older than 12 years with severe and moderate severe haemophilia currently or previously on prophylactic treatment, parents of patients between 12 and 18 years, and haemophilia professionals from throughout the world, were invited to participate in the study. All subjects were required to speak either Dutch or English. Patients and parents were recruited from five Dutch Haemophilia Treatment Centres. Professionals were included during the World Federation of Haemophilia Congress, 2012. Patients and parents received a study information brochure and a questionnaire in the home setting. A reminder was sent in case of non-response. The study protocol was approved by a Medical Ethical Committee (MEC-2011-456) with written informed consent from patients and parents. Oral informed consent was obtained from haemophilia professionals.

Survey

A cross-sectional self-completion DCE questionnaire assessing a range of barriers and facilitators regarding PK-guided dosing was used [6]. Individuals were presented with a questionnaire that consisted of a sequence of choice sets with two (hypothetical) haemophilia treatment scenarios that varied along several characteristics (i.e. attributes). Attributes were further specified by varying choice levels of that attribute (i.e. attribute levels) (see Table 1 and Appendix S1). It was assumed that attribute levels determined the value for each healthcare intervention, and that individuals will select the preferred healthcare intervention with the highest benefit according to their opinion within each choice set [19]. Within a DCE, it is possible to consider both health and non-health outcomes simultaneously [20]. As the study population must choose between different options and make trade-offs between several attributes and their levels, DCE can be used as a diagnostic tool to prioritize potential barriers and facilitators and to specify implementation strategies [10, 21, 22]. To assess the internal consistency of responses, a rationality test was added consisting of a choice set where one of the two options was clearly superior at all levels.

The proposed attributes with regard to PK-guided dosing of prophylaxis were deduced from literature and from face to face interviews with professionals. They were asked to comment on proposed attributes and to rank them to make an *a priori* selection of the five most relevant attributes. These were: 'number of blood samples necessary to con-

Table 1. Attributes and attribute levels for pharmacokinetic (PK)-guided dosing of prophylaxis with factor concentrate compared to current treatment.

Attributes[#]	Levels
Current treatment[$]	
1. Number of blood samples necessary to construct PK-profile	No blood samples
2. Advised frequency of prophylactic infusions	Two to three times weekly
3. Frequency of repetitive PK-profiling	No PK-profile
4. Risk of bleeding	No reduction
5. Estimated cost reduction of treatment with benefit for society (%)	0
PK-guided dosing regimen	
1. Number of blood samples necessary to construct PK-profile	At 1 time point *(reference level)*
	At 3 time points
2. Advised frequency of prophylactic infusions[†]	Two to three times weekly *(reference level)*
	Every other day
	Daily
3. Frequency of repetitive PK-profiling	Every other year *(reference level)*
	Once
4. Risk of bleeding	No reduction *(reference level)*
	Decreased
5. Estimated cost reduction of treatment with benefit for society (%)	0, 15, 30

[#] Attributes 1,2, 3, and 4 entered the analyses as categorical variables. The attribute 'Estimated cost reduction of treatment with benefit for society' entered the analyses as a numerical variable; [$] Attribute levels for 'current treatment' entered the analyses as fixed variables; [†] For haemophilia B patients current treatment consisted of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrates.

struct an individual PK-profile', 'advised frequency of prophylactic infusions', 'frequency of repetitive PK-profiling' (especially applicable in the paediatric population), 'risk of bleeding', and estimated 'cost reduction of treatment with benefit for society' (Table 1). Attributes were evaluated in a pilot study (n = 10) to study the feasibility and acceptability, time investment, intelligibility, and validity of the questionnaire. Questionnaire answering took 15 min. The first 15 study patients were contacted by the treating team to assure understanding of study design and questionnaire. No changes were made as requirements were met in all respondents.

The attributes and levels chosen, resulted in 2628 potential choice sets (see Supporting Information). As it is not feasible to present this number of choice sets to a single respondent, a subset of scenarios was generated by maximizing D-efficiency using Ngene

software (version 1.1.1, http://www.choice-metrics.com/), leading to a DCE design containing 24 choice sets. To further reduce respondent burden, a blocked design was used, which resulted in two questionnaire versions [23, 24]. Study participants were randomly allocated to one questionnaire version.

Characteristics of patients, parents and professionals were collected. For level of education the International Standard Classification of Education division was used [25]. In addition, as an internal control, all respondents were asked to rank attributes of the DCE (Appendix S4), to rate their experience with the DCE questionnaire (five-point scale), satisfaction with current treatment (three-point scale), willingness to modify treatment (three-point scale), and willingness to increase frequency of infusions on a visual analogue scale of 10 centimetre (cm) with 0 cm: 'very willing' and 10 cm: 'not willing'. The questionnaire ended with an open question in which respondents were given the opportunity to record comments.

Sample size calculation

Sample size calculation of the study was impeded due to the small number of eligible haemophilia patients, and available health care professionals in this rare disease. The power of the study was explored *a priori* using a parametric sample size method approach as a well-considered survey instrument with an experimental design was present (see Supporting Information).

Statistical analyses

State-of-the-art analyses of the discrete choice data were performed by use of a panel latent class model, allowing identification of different utility functions (i.e. taking preference heterogeneity into account) across unobserved subgroups [26]. These unobserved subgroups are known as classes. Class membership of respondents is latent because it is based on a modelled probability and not assigned by the analyst *a priori*. To determine the number of classes, the model with the best fit based on the Akaike information criterion was selected. See Appendix S2 for detailed information on the utility functions that were used for estimation of the model. For the class coefficients, the sign (positive or negative) of a coefficient reflects whether the attribute has a positive or negative effect on the utility of the alternative to PK-guided dosing of prophylaxis. In other words, individuals feel positive or negative with regard to this aspect of treatment and its influence on implementation. The value of a coefficient indicates the relative importance of the corresponding attribute (level). The statistical significance of a coefficient ($P \leq 0.05$) indicates that the respondent underlines the importance of the attribute within the options in the DCE. Beforehand, it was expected that all attributes would be significant,

and that the attributes 'decrease risk of bleeding' and 'estimated cost reduction of treatment with benefit for society' would have a positive effect (i.e. a positive sign) [27, 28].

Importance scores and trade-offs

Preference coefficients of all attributes were translated to importance scores (IS) and to trade-offs that the respondents were willing to make between the attributes [29]. This method gives more insight into which attribute is most important (IS of 1) and quantifies the willingness to trade different attribute levels. In our DCE, we set out to quantify the willingness to trade between attributes when taking 'estimated cost reduction of treatment with benefit for the society' into account. This willingness was calculated by taking the ratio of a coefficient of a different attribute with 'estimated cost reduction of treatment with benefit for the society' as the dominator. This value represents how much 'cost reduction for society' is required, before respondents accept a unit change in the attribute of interest (e.g. higher 'advised frequency of prophylactic infusions'). Confidence intervals of this trade-off were estimated using the Krinsky and Robb procedure [30].

To compare mean age of non-respondents with mean age of respondents, an independent-samples *t*-test was used. Age of non-respondents was calculated with median date that questionnaires returned.

We used NLogit 4.0 Software (Econometric Software, Plainview, NY, USA) to estimate the latent class model. All other statistical analyses were performed with IBM SPSS statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Participants

Between December 2011 and January 2014, 176 haemophilia patients and 33 parents of young patients were invited to participate in the study. Of these, 114 patients and 19 parents filled out the questionnaire (response rate 64%). Table 2A and 2B summarize the characteristics of all participants. Patients had a mean age of 38.0 years (SD = 18.5), which was significantly older than non-respondents [mean age 30.8 years (SD = 19.1); $P < 0.01$]. In addition, 91 haemophilia professionals from both the Netherlands (37%) and other countries (63%) participated. Participants were equally distributed across each questionnaire version.

Table 2A. Characteristics of haemophilia patients and parents of young patients.[#,$]

Characteristics	Patients (*n* = 114)	Parents (*n* = 19)
Mean age (years) (SD)	38 (18.5)	44 (5.8)
Male gender	112 (100.0)	14 (73.7)
Type of haemophilia		
A (clotting factor VIII deficiency)	92 (82.1)	15 (78.9)
B (clotting factor IX deficiency)	20 (17.9)	4 (21.1)
Severity of haemophilia		
Severe (clotting factor VIII or IX <1 IU mL^{-1})	102 (91.1)	18 (94.7)
Moderate (clotting factor VIII or IX 1-5 IU mL^{-1})	8 (7.1)	1 (5.3)
Mild (clotting factor VIII or IX >5 IU mL^{-1})	2 (1.8)	.
Actual haemophilia treatment		
On demand, prophylactic treatment in the past	11 (9.8)	.
Prophylactic infusions: two to three times weekly	81 (72.3)	17 (89.5)
Combination of periods of prophylactic infusions alternating with on demand treatment	20 (17.9)	2 (10.5)
Educational level		
Lower	27 (24.8)	2 (11.8)
Intermediate	48 (44.0)	8 (47.1)
Higher	34 (31.2)	7 (41.2)

[#] Numbers are *n* and % unless stated otherwise; [$] Baseline characteristics of two patients were not available, and in three other patients educational level was not available.

Table 2B. Characteristics of haemophilia professionals.[#]

Characteristics	Professionals (*n* = 91)
Age (years)	
18-29	12 (13.2)
30-49	53 (58.2)
50-64	22 (24.2)
≥65 years	4 (4.4)
Country[$]	
High income countries with high standard haemophilia care	69 (75.8)
Low income countries lacking high standard haemophilia care	22 (24.2)
Profession	
Nurse	29 (31.9)
Haematologist	47 (51.6)
Other	15 (16.5)
Clinic employed	
Academic Hospital	74 (81.3)
Haemophilia Treatment Centre	15 (16.5)
Regional Hospital	1 (1.1)
Other	1 (1.1)
Ability to determine clotting factor plasma levels in laboratory	77 (95.1)

[#] Numbers are *n* and % unless stated otherwise; [$] Country and Lending Groups | Data. Data.worldbank.org. Retrieved on 2013-07-12.

Overall satisfaction with actual treatment and willingness to change

Of the patients and parents, 99% were satisfied or very satisfied with current treatment (see Appendix S4). When asked in general, 92% were willing to change the current treatment, of which 36% were willing to change under certain conditions such as no increase in frequency of infusions, improvement of clinical outcome and feasible and reliable PK-profiling. Of the professionals, 75% were satisfied or very satisfied with current treatment and 98% was willing to change the current treatment (of which 34% were only under certain conditions). These percentages correspond with the DCE choice sets in which a majority of 64% of patients and parents of young patients, and 80% of the professionals preferred a PK-guided dosing regimen over the current treatment regimen. On a visual analogue scale of 10 cm, patients and parents scored a mean of 6.3 cm (SD = 3.1) and professionals scored a mean of 6.1 cm (SD = 2.4), indicating they were not willing to increase frequency of prophylactic infusions if there were no additional facilitating factors ($P = 0.74$).

Results from DCE

Of the respondents, 98% passed the rationality test that was included in the questionnaire, and 83% of the respondents did not find the DCE questionnaire difficult.

Haemophilia patients and parents of young patients

Overall, patients and parents were willing to opt for PK-guided dosing of prophylaxis. However, preference heterogeneity was substantial. Two latent classes of preferences were identified (Appendix S3). Respondents belonging to latent class 1 were generally more willing to choose for PK-guided dosing of prophylaxis than those belonging to latent class 2, e.g. the value of the constant 'current treatment' vs. 'new treatment' was -0.99 for latent class 1 and 0.26 for latent class 2 (Appendix S3). The average probability that someone within the sample population belongs to latent class 1 was 41% and to latent class 2 was 59%. We found no evidence that the probability of belonging to a specific class depended on age, severity of haemophilia or educational level. This suggests the fact that it is important to actually discuss reasons to opt for PK-guided dosing as patients and parents are willing to change, but sometimes hesitate.

In the final model, all coefficient directions were as expected (Appendix S3). The importance scores (IS) based on the relative importance of the attributes (Figure 1A and Appendix S3) showed that respondents' choices were influenced most strongly by the attributes higher 'advised frequency of prophylactic infusions' (barrier; overall IS = 1) and reduction of 'risk of bleeding' (facilitator; overall IS = 2). Also, 'estimated cost reduction of treatment with benefit for society' was considered highly important (facilitator; overall IS = 3).

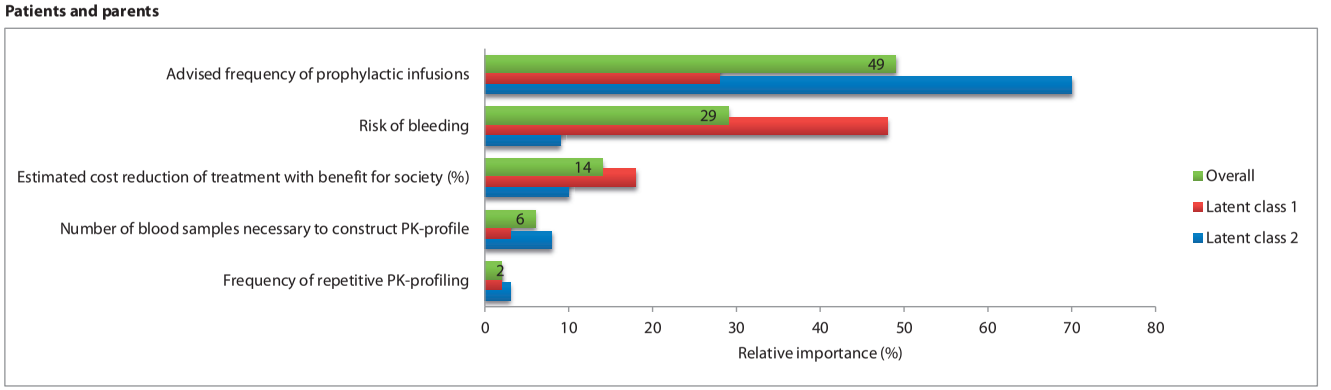

Figure 1A. Relative importance of attributes scored by haemophilia patients and parents of young patients.

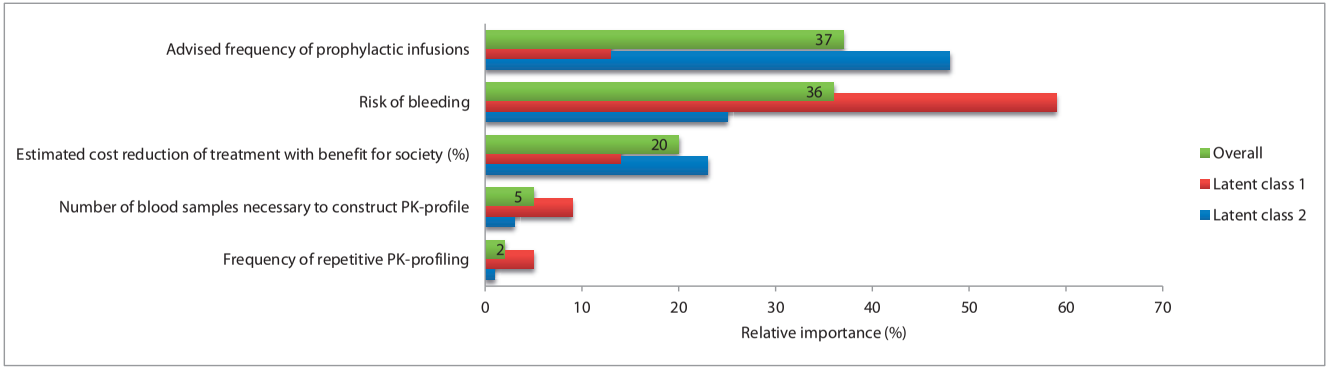

Figure 1B. Relative importance of attributes scored by haemophilia professionals.

In Figure 2, three alternatives of PK-guided dosing of prophylaxis are compared with current treatment that only differ with regard to 'advised frequency of weekly prophylactic infusions' and 'risk of bleeding'. As depicted, respondents belonging to latent class 1 preferred a PK-guided treatment programme as defined in column 1 above current treatment (choice probability = 0.61). When frequency of 'advised prophylactic infusions' was reduced to two to three times weekly, it only slightly influenced their choice probability (0.60). However, when a PK-guided treatment programme led to a reduction in 'risk of bleeding' their choice probability for PK-guided dosing increased to 0.84, with only 0.16 preferring current treatment. In contrast, respondents belonging to latent class 2 did not prefer a PK-guided treatment programme above current treatment (choice probability = 0.49). However, when a the 'advised frequency of prophylactic infusions' was lower or a reduction in 'risk of bleeding' was added the majority was also positive about a PK-guided treatment programme (choice probability, respectively, 0.64 and 0.55).

Trade offs

Patients and parents required an 'estimated cost reduction of treatment with benefit for society' of at least 12% (CI = 7 – 20) to consent to a PK-profile with blood samples at three time points instead of one time point (Table 3A). Willingness to increase prophylactic infusions to every other day instead of two to three times weekly was stated, if a cost reduction for society was reached of at least 25% (CI = 16 – 38). Patients and parents were only willing to consent to daily prophylactic infusions if a reduction in bleeding risk was achieved. Solely a cost reduction was not sufficient as more than 100% cost reduction was required (104%; CI: = 75 – 151). The wide range of CIs shows that the difference in willingness to trade different attribute levels for 'estimated cost reduction of treatment with benefit for the society' was considerable, supporting preference heterogeneity between groups.

Haemophilia professionals

Haemophilia professionals had an even more positive attitude towards implementing PK-guided dosing than patients and parents of young patients (see Figure 1B and Appendix S3). Within haemophilia professionals two latent classes were also identified (Appendix S3), with an average class probability of 26% for latent class 1 and 74% for latent class 2. Professionals belonging to latent class 1 were most positive towards PK-guided dosing of prophylaxis. Overall importance scores of the attributes were the same as in patients and parents of young patients. As depicted in Figure 2, professionals preferred a PK-guided approach over the current treatment (choice probabilities for latent class 1: 0.56 and for latent class 2: 0.73; see Appendix S2, equation (1) and Figure 2).

Attributes	Current treatment	PK-guided dosing of prophylaxis		
		1	2	3
1. Number of blood samples necessary to construct PK-profile 	*No PK-profile* 	*PK-profile* Determination Factor VIII/IX levels at 3 time points after single administration of Factor VIII/IX 	*PK-profile* Determination Factor VIII/IX levels at 3 time points after single administration of Factor VIII/IX 	*PK-profile* Determination Factor VIII/IX levels at 3 time points after single administration of Factor VIII/IX 
2. Advised frequency of prophylactic infusions 	*Dosage <u>not</u> adjusted to PK-profile,* with infusions two to three times a week Su Mo X Tu We Th X Fr Sa	*Dosage adjusted to PK-profile,* with infusions every other day Su X Mo Tu X We Th X Fr Sa X	*Dosage adjusted to PK-profile,* with infusions two to three times a week Su Mo X Tu We Th X Fr Sa	*Dosage adjusted to PK-profile,* with infusions every other day Su X Mo Tu X We Th X Fr Sa X
3. Frequency of repetitive PK-profiling	No construction of PK-profile	Every other year	Every other year	Every other year
4. Risk of bleeding	Current frequency of bleeding 	Current frequency of bleeding 	Current frequency of bleeding 	Reduced frequency of bleeding 
5. Estimated cost reduction of treatment with benefit for society 	Cost reduction of 0% 	Cost reduction of 25% 	Cost reduction of 25% 	Cost reduction of 25% 
Choice probability for PK-guided dosing of prophylaxis (compared with current treatment)				
Patients and parents; total		0.60 (0.40)	0.73 (0.27)	0.87 (0.13)
Latent class 1		0.61 (0.39)	0.60 (0.40)	0.84 (0.16)
Latent class 2		0.49 (0.51)	0.64 (0.36)	0.55 (0.45)
Professionals; total		0.78 (0.22)	0.84 (0.16)	0.94 (0.06)
Latent class 1		0.56 (0.44)	0.61 (0.39)	0.74 (0.26)
Latent class 2		0.73 (0.27)	0.78 (0.22)	0.85 (0.15)

Figure 2. Choice probability of current treatment versus PK-guided dosing of prophylaxis.

* For haemophilia B patients current treatment consists of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrates.

Trade offs

Based on the expressed preferences, professionals required an 'estimated cost reduction of treatment with benefit for society' of 1% (CI = -3 – 5) to perform a PK-profile with blood samples at three time points instead of at one time point (Table 3B). They were willing to prescribe infusions every other day instead of two to three times weekly

Table 3A. Willingness of haemophilia patients and parents of young patients to trade-off among attributes of PK-guided dosing of prophylaxis dosing to achieve cost reduction for society.

Trade-offs	Patients/parents of patients are willing to…..	If this will lead to a cost reduction for the society of …% (CI)
Number of blood samples necessary to construct PK-profile	…get a PK-profile with blood sample at three time points instead of one time point	12.2 (7.0 - 20.0)
Advised frequency of prophylactic infusions	…get infusions every other day instead of two to three times weekly	24.6 (15.9 - 38.1)
	…get infusions daily instead of two to three times weekly[#]	104.4 (75.3 - 151.4)
Frequency of repetitive PK-profiling	…get a PK-profile once instead of every other year	0.7 (-3.1 - 4.4)
Risk of bleeding	…get no additional reduction in risk of bleeding instead of additional reduction	62.2 (45.0 - 90.1)

CI = Confidence Interval. CI, 95% confidence interval based on the Krinsky Robb method adjusted for class probabilities. The average values of the interactions are taken into account; (i.e., costs = […]); [#] For haemophilia B patients current treatment consists of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrate.

Table 3B. Willingness of haemophilia professionals to trade-off among attributes of PK-guided dosing of prophylaxis to achieve cost reduction for society.

Trade-offs	Professionals are willing to…..	If this will lead to a cost reduction for the society of …% (CI)
Number of blood samples necessary to construct PK-profile	…get a PK-profile with blood sample at three time points instead of one time point	1.2 (-2.5 - 4.7)
Advised frequency of prophylactic infusions	…get infusions every other day instead of two to three times weekly	16.9 (8.7 - 27.0)
	…get infusions daily instead of two to three times weekly[#]	51.7 (37.0 - 75.7)
Frequency of repetitive PK-profiling	…get a PK-profile once instead of every other year	1.4 (-2.3 - 5.2)
Risk of bleeding	…get no additional reduction in risk of bleeding instead of additional reduction	55.3 (39.8 - 80.6)

CI = Confidence Interval; CI, 95% confidence interval based on the Krinsky and Robb method adjusted for class probabilities. The average values of the interactions are taken into account; (i.e., costs = […]); [#] For haemophilia B patients current treatment consists of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrate.

when a cost reduction was reached of at least 17% (CI = 9 – 27) and they required a cost reduction of 52% (CI = 37 – 76) to prescribe patients daily prophylactic infusions if no reduction of bleeding was achieved.

DISCUSSION

Our DCE study reveals that the majority of patients, parents of young patients and professionals have an overall positive attitude towards changing their current haemophilia treatment and towards implementation of PK-guided dosing of prophylaxis. However, the preference heterogeneity is substantial and there is a group of slower adapters, that may be willing to change treatment under certain conditions.

In general, more frequent infusions were acceptable if bleeding was consequently reduced. Prioritization of preferences, revealed that the most important barrier was daily 'advised frequency of prophylactic infusions'. Illustrated by a requirement of a cost reduction of more than 100% as a trade-off to consent to daily prophylactic infusions without reduction of bleeding. It is important to realize that daily prophylactic dosing is only considered by professionals in the presence of frequent bleeding or when resources for replacement therapy are minimal. On the other hand, it is also important to underline that PK-guided dosing does not always lead to more frequent dosing, as in some cases, especially in older patients, it may even lead to less frequent dosing due to lower clearance rates [31]. Overall, the most important facilitators for implementation of PK-guided dosing of prophylaxis in this study, were reduction of 'risk of bleeding' and 'estimated cost reduction of treatment with benefit for society'. The attributes 'number of blood samples necessary to construct PK-profile' and 'frequency of repetitive PK-profiling' did not influence patient's, parent's and professional's preferences and should not be regarded as important with regard to acceptance of this medical intervention.

Implications of results

Prevention of bleeding and subsequent complications is the ultimate goal in haemophilia treatment. Prophylaxis with intravenous infusions of factor concentrate on a regular basis, with dosage based on patient weight and clinical bleeding phenotype, is currently the best approach to prevent bleeds and subsequent arthropathy. The majority of patients and professionals seem satisfied with current prophylactic treatment. However, all involved are conscious of the fact that treatment is expensive and that breakthrough bleeds do still exist, leading to pain, (joint) damage, and life-threatening situations. Some may be caused by increased individual clearance rates of factor concentrate or trough levels not appropriate for the individual patient due to

bleeding phenotype, target joints or high activity level. Dosing of factor concentrate according to an individual PK profile in relationship to population PK data may lead to both optimisation of care in these cases as well as cost reduction of treatment in some patients. However, the true impact of large scale PK-guided dosing outside of a clinical trial setting is still to be demonstrated. It is important to keep in mind that Lindvall et al. [32] demonstrated increased bleeding in a small patient sample after PK-guided decrease of dosing. Although it may be discussed that PK-guided dosing may lead to increase of costs due to increased dosing in under dosed patients, we believe that even then, PK-guided dosing will lead to an overall cost reduction. This, as we hypothesize that the majority of overdosed patients will be adult, leading to a large reduction of factor concentrate consumption due to greater body weight, and those under dosed will be mainly children, with a small increase in consumption due smaller body weight.

Results of this study will increase the likelihood of effective implementation of PK-guided dosing of prophylaxis as a medical intervention that may optimize haemophilia patient care. They will provide professionals with motivational factors to persuade patients to opt for PK-guided dosing and additionally lead to feasible guidelines and appealing patient brochures. Its implications are also of importance in the light of the development of the longer acting factor VIII and IX concentrates [33]. This, as the cost per unit of these novel factor concentrates will be significantly higher, making overdosing unacceptable and individualized replacement therapy a necessity. In addition, infrequent dosing schemes will lead to increased inter-individual variation in clearance and therefore increased variation in dosing frequency. Naturally, calculated costs of an individual PK-profile to initiate PK-guided dosing of prophylaxis dosing are minimal when compared to possible long-term cost reduction of PK-guided dosing in both current products and longer acting products.

Although six prior DCE studies have been performed in haemophilia patients [13-18], none have been performed on preferences with regard to PK-guided dosing of prophylaxis. Literature in other diseases demonstrates that DCE is a valuable method to tailor implementation strategies to specify barriers and facilitators in an implementation process [21, 34, 35].

Although a DCE gives more insight in considerations of patients and professionals, a drawback of the DCE methodology is the modelling based exercise with hypothetical scenarios. It may therefore not depict what the individual will actually do when confronted with these choices in daily life, and may lack a link between the proposed choices and the individual's health status or current clinical practice [21]. It has also been suggested that subjects may employ simplification of decision making [36]. In our study,

it is conceivable that subjects have focused on the avoidance of frequent prophylactic infusions (19% of patients and parents and 1% of professionals) or on a decrease of bleeding risk (17% of patients and parents and 26% of professionals) and therefore may ignore other information. Gigerenzer et al. however conclude in a review that simplification of decision making does not necessarily lead to judgmental biases [36].

Strengths and limitations

As all involved with the implications of PK-guided dosing of prophylaxis, were included in our study, conclusions seem valid for all groups. This is of importance as groups may express different opinions and possibly conflicting interests, illustrated by different preferences. Secondly, Discrete Choice tasks and the concept of PK-guided dosing were introduced thoroughly as most respondents (> 80%) did not find the concept of the study and the questionnaire difficult to understand. Thirdly, our DCE model demonstrated good theoretical validity, as all coefficients had the expected positive or negative value sign. Fourthly, 98% of the respondents passed the rationality test, included in the questionnaire. We therefore believe that the inclusion of numbers and rates in our DCE, which may have caused interpretation problems with regard to the choice tasks, cannot have influenced results to a large extent.

This study also has some limitations. Firstly, the response rate for this clinical study was low in comparison with other questionnaire studies in a clinical setting e.g. 64% instead of an optimal 80% [36]. Secondly, although the attributes have been carefully selected and generated by face to face interviews with professionals with subsequent ranking of attributes, the DCE could have been even more valid if focus groups had been used. This, as recent literature recommends this methodology for formulating such questions. Thirdly, selection bias cannot be excluded as respondents and non-respondents (mean age = 38.8 vs 30.8 years) differed significantly with regard to age. However, no covariates, including age, significantly influenced the probability of belonging to one of the two specific latent classes. Fourthly, unfortunately no data was collected on actual bleeding phenotype, presence of arthropathy, availability of venous access, the individual responsible for administration of prophylaxis and detailed information of current prophylactic dosing regimen. These characteristics may have provided insight into the differences between groups more inclined to implement PK-guided dosing of prophylaxis and those less inclined to confer. Lastly, patients and parents of young patients were all inhabitants of the Netherlands, therefore data may reflect Dutch values and may not be extrapolated. However, professionals were from both developing and resource rich countries and analyses did not reveal any influence of country of origin on results.

Conclusions

Our study is an important documentation of heterogeneity of opinions around PK-guided dosing, recognizing decisions are complex and multifactorial. PK-guided dosing of prophylaxis may be successfully implemented in haemophilia care if all involved, weigh the pros and cons in each individual patient. And when PK-guided prophylaxis is thought to be beneficial realize the impact of daily dosing of factor concentrate and motivate patients and parents of young patients by underlining the potential reduced 'risk of bleeding' and the 'estimated cost reduction of treatment with benefit for society' as quantified in this DCE analysis. The knowledge acquired through this study may facilitate the long-awaited implementation of PK-guided dosing of prophylaxis as a potential strategy to individualize and optimize dosing in the haemophilia population.

ADDITIONAL SUPPORTING INFORMATION

Appendix S1. Example of a choice set.
Appendix S2. Utility functions.
Appendix S3. Latent class regression coefficients.
Appendix S4. Ranking of attributes and overall satisfaction with actual treatment and willingness to change.

ACKNOWLEGDMENTS

This study is part of the 'OPTI-CLOT' research program (Patient tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates in clotting disorders)', a national multicentre study aiming to implement PK-guided dosing of factor replacement therapy by initiating studies to prove the importance of PK-guided dosing, to construct perioperative, on demand and prophylactic PK-models and to evaluate cost-effectiveness of a PK-guided dosing approach. The investigators and institutions participating in the OPTI-CLOT research programme in the Netherlands are as follows. Steering committee - M.H. Cnossen (principal investigator and chair), Erasmus University Medical Centre - Sophia Children's Hospital, Rotterdam; F.W.G. Leebeek, Erasmus University Medical Centre, Rotterdam; K. Fijnvandraat, R.A.A. Mathôt, Academic Medical Centre, Amsterdam. Principal Investigators and Local Collaborators in the Netherlands -, M.H. Kruip, S.N. de Wildt, S. Polinder, E.W de Bekker-Grob, W.G. Ista, J. Lock, H.C.A.M. Hazendonk, I. van Moort, E.W. Steyerberg, G.J.J.M. Borsboom, Erasmus University Medical Centre, Rotterdam; R.A.A. Mathôt, K. Fijnvandraat, T. Preijers, E. Stokhuijzen, M. Coppens, M. Peters, S. Middeldorp, Academic Medical Centre, Amsterdam; K. Meijer, R.Y.J. Tamminga, University Medical

Centre Groningen; P. Brons, B.A.P. Laros-van Gorkom, Radboud university medical centre, Nijmegen; F.J.M. van der Meer, H.C.J. Eikenboom, Leids University Medical Centre, Leiden; R.E.G. Schutgens, University Medical Centre Utrecht; M.H.E. Driessens, J. de Meris, Dutch Haemophilia Patient Society; Website, trialbureau and databases - C.M. Zwaan, S. Ramnarain, R.M.M. Bosschaart-Castermans, Erasmus University Medical Centre, Rotterdam and; A.E. Rotte, A. Koolma, A.C.J. Ammerlaan, Academic Medical Centre, Amsterdam, The Netherlands. We gratefully thank Dr. Rienk Tamminga, Prof. Dr. Saskia Middeldorp and Dr. Britta Laros-van Gorkum for their valuable contributions to this particular study and Arienne van Heusden for data collection.

This study was financially supported by ZonMW, the Dutch Organization for Health Reserch and Development, and an investigator-initiated, unrestricted ASPIRE research grant, sponsored by Pfizer.

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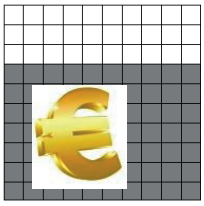
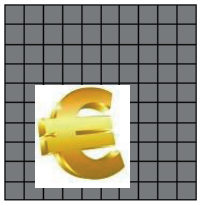
SUPPORTING INFORMATION

Appendix S1. Example of a choice set.

Attributes	New treatment 1	New treatment 2
1. Number of blood samples necessary to construct PK-profile 	*PK-profile* Determination Factor VIII/IX levels at 3 time points after single administration of Factor VIII/IX 	*PK-profile* Determination Factor VIII/IX levels at 1 time point after single administration of Factor VIII/IX 
2. Advised frequency of prophylactic infusions[a] 	*Dosage adjusted to PK-profile,* with infusions two to three times a week Su Mo X Tu We Th X Fr Sa	*Dosage adjusted to PK-profile,* with infusions every day Su X Mo X Tu X We X Th X Fr X Sa X
3. Frequency of repetitive PK-profiling	Once	Every other year
4. Risk of bleeding	Reduced frequency of bleeding 	Current frequency of bleeding 
5. Estimated cost reduction of treatment with benefit for society 	Cost reduction of 30% 	Cost reduction of 0% 
Which alternative would you choose?	☐	☐

Appendix S1. Example of a choice set.

[*] For haemophilia B patients current treatment consists of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrate.

Appendix S2. Utility functions and sample size calculation.

Utility functions

DCE is a methodology which aims to quantify individual's preferences, as choices are made within a sequence of choice sets with two or more hypothetical treatment scenarios. It is assumed that individuals act rationally and will choose the alternative with the highest level of benefit. DCE modelling is based on Lancaster's economic theory of value and on the random utility theory.

In our study each treatment scenario be made up of five attributes and their levels, which resulted in 72 (2^3 X 3^2) potential scenarios. Assuming two scenarios per choice set, 2,628 different choice sets could be created (i.e. 2,558 (72 X 71 / 2) choice sets containing two PK-profiling treatment scenarios, plus 72 choice sets containing a PK-guided treatment scenario and a non-PK-guided or current treatment scenario). As it is not feasible to present this number of choice sets to a single respondent, a subset of scenarios was generated using Ngene software by maximizing D-efficiency (version 1.1.1, http://www.choice-metrics.com/), leading to an efficient DCE design containing 24 choice sets.

The following utility functions were used to model DCE data:

The utility functions were:

$V_{PK\text{-}profiling\_nsj|c} = \beta_{0|c} + \beta_{1|c}\text{blood samples\_at three points}_{nsj|c} + \beta_{2|c}\text{ infusion\_daily}_{nsj|c} + \beta_{3|c}\text{ infusion\_every other day}_{nsj|c} + \beta_{4|c}\text{frequency PK-profiling\_once}_{nsj|c} + \beta_{5|c}\text{risk of bleeding\_decreased}_{nsj|c} + \beta_{6|c}\text{cost reduction}_{nsj|c}$

$V_{\text{current treatment }\_nsj|c} = 0$

Where:

$V_{nsj|c}$ represents the observable utility (i.e., preference score) that respondent 'n' belonging to class segment 'c' has for alternative 'j' in choice set 's';

$\beta_{0|c}$ represents an alternative-specific constant for a certain class;

$\beta_{1\text{-}6|c}$ are class-specific parameter weights (coefficients) linearly associated with each attribute (level) of the DCE

Hence, the cost attribute acted as a linear attribute, whereas all other attributes were categorical. The reference levels for 'blood sample', 'infusion', 'frequency PK-profiling', and 'risk of bleeding were respectively: 'at one time', 'two to three times weekly', 'every other year', and 'no reduction'.

In addition to the utility function, the final DCE model allowed for several covariates such as age, severity of disease, type of disease, level of education to enter into the class assignment model [37]. This gives insight into the composition of the different latent classes.

Sample size calculation

To explore the power of the study a priori a parametric sample size method approach as a well-considered survey instrument with an experimental design was present. The following method was applied [38]: assuming a sample size of 90-100 respondents, a significance level $\alpha = 0.05$, and using the outcome of the pilot study as initial estimates of the true parameter values, (except for the attribute 'frequency of PK-profiling' - the most critical parameter – for which we assumed a value of 0.2 as clinically relevant), a statistical power of at least 0.8 was estimated that all attribute (level) values were not equal to zero.

Appendix S3. Latent class regression coefficients.

	Patients and parents of young patients							Professionals						
	Latent class 1			Latent class 2				Latent class 1			Latent class 2			
Attributes	*Coefficient (P-value)*	*SE*	*IS*	*Coefficient (P-value)*	*SE*	*IS*	*Overall IS*	*Coefficient (P-value)*	*SE*	*IS*	*Coefficient (P-value)*	*SE*	*IS*	*Overall IS*
Constant 'Current treatment' vs 'New treatment'	-0.99 (***)	0.23		0.26 (NS)	0.25			-2.19 (***)	0.34		-0.74 (***)	0.25		
1. Number of blood samples necessary to construct PK-profile			4			4	4			4			4	4
At 3 time points	-0.09 (NS)	0.06		-0.18 (***)	0.06			0.22 (**)			-0.06 (NS)	0.06		
At 1 time point (reference level)	0.09			0.18				-0.22	0.10		0.06			
2. Advised frequency of prophylactic infusions			2			1	1			3			1	1
Daily	-1.24 (***)	0.12		-1.59 (***)	0.12			0.12	0.13		-1.12 (***)	0.12		
Every other day	0.68 (***)	0.11		0.26 (***)	0.08			-0.39 (***)	0.16		0.38 (***)	0.09		
Two to three times weekly (reference level)[#]	0.56			1.32				0.27			0.73			
3. Frequency of repetitive PK-profiling			5			5	5			5			5	5
Once	-0.07 (NS)	0.06		0.06 (NS)	0.06			0.12 (NS)	0.10		-0.02 (NS)	0.06		
Every other year (reference level)	0.07			-0.06				-0.12			0.02			
4. Risk of bleeding			1			3	2			1			2	2
Decreased	1.53 (***)	0.09		0.19 (***)	0.07			1.48 (***)	0.11		0.49 (***)	0.07		
No reduction (reference level)	-1.53			-0.19				-1.48			-0.49			
5. Estimated cost reduction of treatment with benefit for society			3			2	3			2			3	3
Cost reduction (per 10%)	0.39 (***)	0.06		0.14 (**)	0.06			0.23 (***)	0.09		0.30 (***)	0.07		
Class probability														
Average	0.41			0.59				0.26			0.74			
Model fits														
Log-likelihood	-589.17							-451.78						
AIC	0.78							0.86						

PK = pharmacokinetic; AIC = Akaike Information Criterion; IS = Importance Score; SE = Standard Error. ***, **, * Denotes significance at a 1%, 5%, and 10% level respectively. NS denotes non-significant coefficient. Effects coding used for categorical variables. The value for the reference levels of the categorical attributes equals the negative sum of the coefficients of the included attributes. Number of observations for patients and parents: 1,551 (133 patients/parents * 12 choice sets - 45 missing values). Number of observations for haemophilia professionals: 1,083 observations (91 professionals * 12 choice sets - 9 missing values). [#] For haemophilia B patients current treatment consist of prophylactic infusions one to two times weekly due to the longer half-life of factor IX concentrates.

Appendix S4. Ranking of attributes and overall satisfaction with actual treatment and willingness to change.

	Patients and parents of young patients			Professionals		
	n (%)	Mean (SD)	Rank	*n* (%)	Mean (SD)	Rank
Discrete Choice Experiment questionnaire						
Ranking of attributes						
Number of blood samples necessary to construct PK-profile	130	2.95	3	81	3.38	4
Advised frequency of prophylactic infusions	129	2.10	2	81	2.33	2
Frequency of repetitive PK-profiling	128	3.85	4	81	4.17	5
Risk of bleeding	128	1.73	1	81	1.79	1
Estimated cost reduction of treatment with benefit for society	127	3.88	5	81	3.16	3
General questions						
Satisfaction with current treatment	133	1.40 (0.51)		89	2.15 (0.56)	
Very satisfied	81 (60.9)			8 (9.0)		
Satisfied	51 (38.3)			59 (66.3)		
Unsatisfied	1 (0.8)			22 (24.7)		
Understanding of PK-guided dosing of prophylaxis	133	1.30 (0.52)		88	1.17 (0.38)	
Yes	97 (72.9)			73 (83.0)		
Yes, approximately	32 (24.1)			15 (17.0)		
No	4 (3.0)			0 (0.0)		
Willingness to change current treatment	131	1.51 (0.64)		88	1.39 (0.54)	
Yes, of course	74 (56.5)			56 (63.6)		
Yes, but under the following conditions	47 (35.9)			30 (34.1)		
No daily infusions	11 (26.8)			9 (33.3)		
Not more frequent infusions	12 (29.3)			3 (11.1)		
Better clinical outcome	6 (14.6)			3 (11.1)		
Health care available	1 (2.4)			. .		
Not too time consuming	2 (4.9)			1 (3.7)		

Appendix S4. Ranking of attributes and overall satisfaction with actual treatment and willingness to change.

Appendix S4. Ranking of attributes and overall satisfaction with actual treatment and willingness to change. (continued)

	Patients and parents of young patients					Professionals			
	n	(%)	Mean	(SD)	Rank	*n*	(%)	Mean (SD)	Rank
Want to discuss first with the doctor/patient	7	(17.1)				5	(18.5)		
PK-profiling reliable and feasible	2	(4.9)				4	(14.8)		
No worse adherence or quality of life						2	(7.4)		
No	10	(7.6)				2	(2.3)		
Willingness to increase frequency of prophylactic infusions (10-point scale)	132		6.25	(3.09)		80		6.13 (2.43)	
Experienced difficulty of the DCE questionnaire	132		2.55	(1.01)		80		2.59 (0.90)	
Very easy	17	(12.9)				6	(7.5)		
Easy	54	(40.9)				36	(45.0)		
Neutral	39	(29.5)				24	(30.0)		
Difficult	16	(12.1)				13	(16.3)		
Very difficult	6	(4.5)				1	(1.3)		

PK = pharmacokinetic; *n* = number; SD = standard deviation.

CHAPTER 9

General discussion and future perspectives

DISCUSSION

In the following chapter the main findings of this thesis are summarized and discussed. We will also elaborate on methodological issues and gaps in described studies. Subsequently, suggestions are given to further refine strategies to improve hemophilia patient outcome. Ultimately, future studies will be proposed in the respective areas of research.

The first part of this thesis focuses on improvement of adherence to treatment in order to enhance quality of hemophilia care and therefore patient outcome. Adherence to treatment was approached in different ways: by evaluation of the effects of transmural support of patients and their parents by specialized nurses, by implementation and validation of questionnaires to evaluate and monitor both adherence and self-efficacy and by analysis of alternative outpatient clinic approaches to increase the impact of contact moments with the hemophilia treatment center. The main finding of the first study was that transmural support has a positive effect on perceived support by hemophilia patients and/or parents and communication with the hemophilia treatment center. However, it did not improve other outcome measures, including adherence to prescribed treatment, overall quality of life, behavior, total clotting factor consumption, annualized bleeding rate and capacity towards self-efficacy. We did demonstrate that outpatient care for hemophilia and von Willebrand patients can be improved by implementation of Group Medical Appointments. We revealed that this setting leads to improvement in participant's knowledge of the disease and also to improved perceived support, especially for patients with less disease experience due to a milder bleeding phenotype. We translated and validated the VERITAS-pro adherence scale to measure and monitor adherence for application in the Netherlands and constructed and validated the Hemophilia-specific Self-Efficacy scale (HSES) to measure capacity towards self-efficacy. This is a capacity needed to develop adequate self-management abilities. Both scales proved to be reliable and valid tools to assess adherence and self-efficacy in pediatric hemophilia patients on prophylactic home treatment.

In the second part of this thesis, we verified that quality of care and cost-effectiveness can be improved by refining of FVIII dosing strategies perioperatively based on individual patient characteristics such as blood type and mode of infusion. Moreover, based on the retrospective data collected in order to evaluate current perioperative management in moderate and severe hemophilia A, we constructed a population pharmacokinetic (PK) model. This model describes the PK of various FVIII concentrates in the perioperative setting. Such a model, will make it possible to individualize perioperative replacement therapy with FVIII concentrate in moderate and severe hemophilia A patients by Bayesian adaptive dosing. To facilitate future implementation of these promising

treatment innovations, we performed a Discrete Choice Experiment to look at barriers and facilitators for PK-guided prophylactic dosing. An important conclusion was that to be able to achieve implementation of individualized PK-guided dosing of prophylaxis in hemophilia, reduction of bleeding risk and reduction of cost for society should be actively discussed with patients. Both were proven to be motivating for implementation. Importantly, daily dosing was reported to be a barrier for all groups. The latter was shown to only be acceptable when other aspects of care, such as risk of bleeding could be significantly influenced by daily dosing.

1. IMPROVEMENT OF ADHERENCE TO TREATMENT

Measurement of adherence and self-efficacy

The most important goal in hemophilia care is the prevention of bleeding in joints and muscles. This is of utmost importance as this ultimately leads to progressive degenerative arthropathy and chronic pain, with functional impairment [1]. To safeguard joint function, adherence to prophylactic treatment is essential in patients with hemophilia. When optimal joint function is maintained, hemophilia patients are able to pursue an active daily lifestyle with a high degree of quality of life and life fulfilment. To achieve optimal adherence, it is necessary to have tools to monitor adherence, as well as the possibility to optimize adherence and self-management skills by training and educational programs. In our opinion, the latter should include strategies to ensure active patient involvement, improve self-efficacy, train patient's problem-solving skills, and to enhance perceived interpersonal support, besides more traditional approaches such as patient education and lifestyle recommendations [2-4].

As no validated adherence scale was available in the Netherlands, we translated and validated the VERITAS-Pro scale (**chapter 3**). The adequate psychometric properties shown by our data confirm that this scale is a reliable and feasible tool to quantify adherence in a pediatric population in the Netherlands. The strength of this scale lies in the fact that it scores in different domains related to adherence e.g.: 'Time', 'Dose', 'Plan', 'Remember', 'Skip', and 'Communicate'. Therefore, it provides specific information to discuss issues related to non-adherence and causal mechanisms with patient and parents during outpatient clinic visits. The scale is valuable to quantify and monitor adherence and is currently the most reliable self-reported adherence measure in hemophilia. The VERITAS-Pro was developed by Duncan et al. in the United States [5] and is currently applied in 17 countries worldwide (personal communication). In our study population, the applicability was somewhat limited due to the high adherence at baseline described by pronounced floor effects (> 50%) of domains 'Dose' and 'Skip'. Moreover, our pediatric

population may not have been the most optimal to test the scale, as it is widely known that adult populations are much less adherent with regard to prophylactic treatment [6, 7]. We conclude that the scale may be more applicable in less adherent populations, such as adolescents or adults, and therefore promote a wider application in the Dutch hemophilia population.

We do have some suggestions to improve the scale. Firstly, it may be relevant to evaluate the contribution of domains 'Time' and 'Dose', as both showed low Cronbach's alpha scores (respectively 0.38 and 0.01) in our study compared with respectively 0.86 and 0.67 in the original study by Duncan et al. [5]. Specifically, in our study, this may have been due to high floor effects and small random variance caused by the homogenous Dutch pediatric population as well as the different cultural context of our study population. But this finding does imply that these domains may be less applicable in different populations. A shorter scale with revision of less valid domains, would improve overall validity and make it more efficacious. Naturally, a drawback of a novel version of the scale, is that it must be validated once again in all populations in which it has now been implemented. Another aspect which could be improved, is the fact that it remains difficult to associate a lower total scale score with higher adherence to treatment. Furthermore, the VERITAS-Pro scale does not take alterations of weekly prophylactic dosing into account. These are often applied to support intensive sporting activities or physiotherapy, and may be necessary after a large bleed, or postoperatively. And lastly, the VERITAS-Pro unfortunately evaluates adherence to prescribed prophylactic regimen retrospectively, which of course leads to less reliable patient reporting.

There is controversy in hemophilia research which level of non-adherence leads to reduced patient outcomes. This limits the establishment of normative values for example the VERITAS-Pro score and respective subscale scores [5, 6]. Recently, Schrijvers et al. conducted a Delphi procedure to define non-adherence according to a hemophilia professional's opinion [submitted, [8]]. Unfortunately, results of this Delphi procedure were based on expert opinion, and not on a large longitudinal study in which treatment adherence and patient outcome were objectively measured and compared by validated outcome measures. However, it is a first and important step in concordance of definitions of non-adherence. Conclusions were that patients should be considered adherent when < 15% of prescribed infusions is missed, when there are < 10% dosage (IU) changes, and when there is < 30% deviation in timing of infusions. Patient outcome and non-adherence were evaluated longitudinally in another single-center observational cohort (n = 66) study by Nijdam et al., which compared joint outcomes in patients with a median age of 34.4 years, who stopped prophylaxis at own initiative with patients on prophylaxis (median age: 32.3 years) [9]. Strikingly, self-reported bleeding rate and

functional limitations were similar in both groups. However, objective assessment of joint status after 10-year study follow up, revealed a decreased joint status in patients who discontinued prophylaxis compared to those still on prophylaxis. The authors concluded that these results support long-term continuation of prophylaxis in adults. In our opinion, it also underlines the necessity of a clear definition of non-adherence as well as long term follow up studies on the effects of different levels of non-adherence and its association with joint outcome.

Until now, most reports on adherence have been performed in patients with moderate or severe hemophilia, as we have also done. However, we also underline the importance of evaluation of non-adherence in more mildly affected hemophilia patients. We suspect that other mechanisms may play a role in these patient populations as several studies and reviews in other diseases have suggested [7, 10, 11]. Studies report a relationship between lesser disease symptoms and a decreased belief of necessity of treatment. The long awaited arrival of extended half-life (EHL) coagulation factor products and increased availability of gene therapy will lead to a hemophilia population that is overall, less severely affected. Potentially this may lead to non-adherence and loss of self-treatment abilities especially in severe hemophilia B. Contrastingly, the hemophilia community overall expects more optimal adherence to novel products as current pilotstudies show adherence levels of ≥ 76% and lower bleeding rates in the first studies performed [18]. It is of great importance to study the impact of these innovations on both patient outcome measures and adherence to treatment, to be able to analyze the long term impact at patient level.

General agreement between patients, parents and hemophilia professionals with regard to acceptable treatment goals and dosing regimens leads to the best long-term patient outcomes [12]. This concept of mutual agreement is named concordance and it is increasingly mentioned as the ultimate goal in the treatment of chronic diseases. We support this concept as it describes the ultimate setting of personalization of treatment. The term encompasses the feasibility of a specific treatment for the individual patient in his or her personal, ever changing life cycle. Concordance has not yet been applied in current studies in hemophilia but will be relevant for both somatic outcome measures as well as more subjective measures such as quality of life.

To understand non-adherence in the individual patient, it is crucial to uncover underlying problems and challenges in treatment adherence and self-management of the disease. Self-management refers to the ability of an individual to manage disease symptoms, treatment of symptoms, physical and psychosocial consequences of the disease as well as the implementation of lifestyle alterations necessary to cope with the specific chronic

disease involved [13]. One of the capabilities needed for adequate self-management is self-efficacy, which encompasses an individual's confidence in the ability to carry out necessary tasks or procedures to manage their or their child's personal health or health care [14, 15]. In order to quantify and monitor the capacity towards self-efficacy, we developed and validated the Hemophilia-specific Self-Efficacy Scale (HSES; **chapter 4**). The psychometric properties of the scale as illustrated by our data, confirm that it is a reliable and feasible method in a pediatric population in the Netherlands. Confirming earlier studies, we found high self-efficacy levels in our population [16]. This is most likely due to the intensive educational program given by hemophilia staff prior to initiation of home treatment. In addition, we showed that high self-efficacy was correlated with higher quality-of-life. This was supportive of our hypothesis that self-efficacy is an important condition to achieve higher quality of life. In contrast, we did not find a correlation between self-efficacy and higher levels of adherence. Unfortunately, high self-efficacy levels at baseline in our study limited the measurable positive effect of the intervention of a hemophilia nurse in the home setting. We believe that capacity towards self-efficacy may be an important measure, especially in patients with milder disease e.g. moderate severe and mild patients, who's ability to judge a possible bleed and to contact the hemophilia treatment center is of more importance than knowledge of appropriate dosing.

Home based intervention and Group Medical Appointment intervention

To improve hemophilia patient outcome by enhancement of patient empowerment, we conducted two interventions. The first study described effects of home visits by a hemophilia nurse on adherence to treatment, health-related quality of life, behavior, total clotting factor consumption, number of joint bleeds, and self-efficacy in children with hemophilia on prophylactic home treatment (**chapter 2**). Extra transmural care did not lead to improvement of adherence to treatment, but did lead to improved communication and an increase of perceived support by parents. This is important as communication with regard to (atypical) disease symptoms and barriers for adherence results in more effective treatment and therefore more optimal joint status. Outcome measures of generic quality of life scale CHQ, self-efficacy scores, total clotting factor consumption, and number of joint bleeds however did not change after intervention.

Critically, a number of factors should be taken into account. Firstly, overall scores on these outcome measures were already high at baseline in our cohort, making it difficult to achieve a visible effect. Secondly, a study period of two years may have been too short to establish an effect on joint bleeds. Study results of our small study however do confirm an extended recent Cochrane review by Nieuwlaat et al. [17] that reviewed 182 randomized controlled trials on interventions aiming to improve treatment adherence. Of these

182 trials, 17 studies (range n= 38-2097 patients) were selected with adequate study design. Interventions studied included tailored support from health care professionals by educational interventions, counseling by motivational interviewing or cognitive behavioral therapy or daily treatment support. General conclusions of the systematic review were that interventions to improve adherence are complex and laborious and not always associated with increased adherence and improvement of patient outcome. Therefore, it was stated that these interventions are often not cost-effective and should not be implemented without critical evaluation of effects.

The second intervention was the group medical appointment (GMA), which aimed to improve effectiveness of outpatient clinic visits (**chapter 5**). Aspects studied were: patient's and parent's satisfaction, social support experienced by participants, team's attentiveness to the individual, informative value of a GMA, privacy aspects and time investment. We established that GMA visits show high levels of participant satisfaction and advantages with regard to patient's disease perspective, social support, and enhanced information transfer. Therefore, a GMA probably leads to an increased patient and parent empowerment with increased self-management abilities and self-efficacy [18-25]. Strikingly, best results were documented in patients with less experience with their disease. Moreover, these results were achieved in a more cost-effective setting as 8-10 patients and parents were seen within a time span of 90 minutes. Although, an important conclusion, we must state that outcome was self-reported by patients and parents. Moreover, in the study design no direct measurements on quality of care outcomes, health care costs, and self-efficacy were actually measured. In future studies, addition of these outcome parameters would be valuable with regard to this intervention [25].

In both interventions studied, patient outcomes were measured. However, these were not fully discriminative. Overall in hemophilia research, there is a need for more sensitive patient outcome measures, e.g. early detection and quantification of joint disease, functional outcome measures, emotional problems related to self-esteem and body image and economic or cost-utility analyses evaluating the relationship between care investments and patient outcome [26, 27]. Moreover, these outcome measures should be developed in collaboration with hemophilia patients and representatives of patient societies as the opinion of health care professionals does not always reflect patient opinion [2, 27, 28]. Novel insights into value based care methodology as developed by Porter et al., may provide the measures valuable for hemophilia care [27, 29].

Other strategies to improve treatment adherence

In recent years, other strategies to improve self-care have been developed within the hemophilia community as in other chronic diseases. Often ICT-based methodology was applied to achieve this goal, e.g. short message services (SMS), mobile applications to document factor concentrate infusion and to provide immediate treatment advice, or e-learning modalities, such as the recently developed Cyberpoli in the Netherlands by the Stichting Artsen voor Kinderen (www.cyberpoli.nl) and the e-learning module developed by Mulders et al. [16, 30-36]. Next to more conservative approaches, such as informative patient meetings and hemophilia camps for younger patients [33]. A valuable addition to current care is the web-based health-related quality of life (HRQoL) application developed by Grootenhuis et al. for chronically ill children, which is able to systematically monitor HRQoL in the outpatient care clinic and makes it possible to discuss outcome measures directly during the visit to the outpatient clinic [37]. In children with juvenile idiopathic arthritis this systematic monitoring of HRQoL through electronic patient-reported outcome measures, resulted in increased attention for psychosocial topics during outpatient clinic visits [38].

2. TOWARDS MORE PERSONALIZED TREATMENT

Pharmacokinetic-guided dosing of factor concentrates and its implementation

In general, medical treatment is increasingly tailored according to individual needs and patient characteristics. In hemophilia, this is illustrated by adaptions of the frequency and timing of doses according to daily (sporting) activities, bleeding phenotype, and joint status [39]. Moreover, it is known that a large interpatient variability exists in clearance of factor concentrate between hemophilia patients [40]. This fact may be a patient characteristic and an aspect of treatment in which can be intervened. As other factors influencing phenotype and adequate treatment such as age, body weight, length, blood group, von Willebrand factor, presence of target joints, hyperlaxicity and activity level cannot or are difficult to be influenced.

Thanks to pioneering studies by Björkman and Collins, it is increasingly accepted that both prophylactic and on demand treatment with factor concentrates can be tailored according to individual patient pharmacokinetics (PK) [40-44]. This is possible, thanks to the development of population PK models for few FVIII and FIX concentrates [40, 41, 43, 45-47]. The theoretical background of this principle is that when population pharmacokinetic data from a large population are available, the amount of IU per kilogram necessary to achieve a certain plasma concentration of coagulation factor can be predicted based on the results of an individual PK profile with only a limited number

of sampling time points. To construct an individual PK profile, a standardized dose of factor concentrate is infused and achieved factor concentrations are measured at set time points to establish PK parameters in the individual patient [45]. PK modeling and simulation is based on Bayesian analysis and performed using non-linear mixed-effects modelling software (NONMEM® version 7.2.0, Globomax LLC, Ellicott City, Maryland, USA) [48].

In order to implement PK-guided dosing and to make it applicable in all individual patients, it is important to develop models that are representative for all patients, specific factor concentrates and under all different circumstances. In an optimal population PK model for dosing in a patient with a coagulation factor deficiency, these differences can be integrated into one single model with various covariates. Until recently, only population PK models were available for the prophylactic setting and only for recombinant FVIII concentrate developed by Baxter/ Baxalta (Advate®), for recombinant FIX developed by Pfizer (Benefix ®), and for plasma derived FIX [40, 41, 43, 45-47].

Although the concept and cost-effectiveness of PK-guided dosing according to population PK models for prophylactic treatment in hemophilia A was proven as early as 1993 by Carlsson et al. [41, 43], this has still not led to implementation in daily standard hemophilia care. This can be explained by various reasons. Firstly, an overall lack of population PK models for different concentrates, made it difficult to practice sparse sampling PK-guided dosing. Moreover, a wash out period for prophylaxis was necessary to perform an individual PK profile. Naturally, this principle put the patient at risk for bleeding, leading to reluctance of patients and hemophilia professions to perform such a profile and thus hampering implementation of PK-guided dosing. Secondly, early studies have been hampered by small sample size and selected patient populations using one single factor concentrate, leading to limiting generalization of results. Thirdly, lack of knowledge and practical insights into background of PK-guided dosing in hemophilia professionals may have played a role. As well as the lack of clinical pharmacologists practicing within a hospital setting. Lastly, lack of financial motives to improve cost-effectiveness of treatment most certainly has most probably also played a role in its delay in implementation.

Implementation of medical innovations is notably difficult as has been extensively studied by Grol et al. [49]. Therefore, it is of utmost importance to develop these strategies in an early stage of innovation. Part of our implementation strategy was to define possible barriers and facilitators in patients, parents of young patients and hemophilia professionals for implementation of PK-guided prophylactic by discrete choice experiment. Discrete choice experiment analysis is a quantitative method to gain insight into how patients value selected attributes of an intervention by asking them to state their choice

over different hypothetical scenarios [50-52]. It is used to determine the significance of attributes and the extent to which patients are willing to trade one attribute for another [52, 53]. Our study results showed that most patients, parents and hemophilia professionals were inclined to opt for PK-guided dosing of prophylaxis. Both, reduction of bleeding risk and reduction of costs for society were facilitating attributes to achieve implementation of individualized PK-guided dosing. Importantly, daily dosing remained an important barrier for all involved. However, if bleeding was consequently reduced, more frequent infusions were acceptable.

These results are relevant to successfully implement PK-guided prophylactic dosing in the near future. However it is important to realize that DCE is a modelling based exercise with hypothetical scenarios and may therefore lack a link with individual's current health status or current clinical practice [51]. Veldwijk et al. found the majority of participants are capable to adequately complete a DCE when provided information is understood and to employ the complex decision strategies associated with DCE choice tasks [54]. However, a smaller group of lower educated and less literate participants found it difficult to employ simplification of decision making. This group used less than three attributes to motivate decisions and did not apply trade-offs between attributes to make a choice [55]. Although, Gigerenzer et al. concludes that simplification of decision making does not necessarily lead to judgmental bias, Veldwijk et al. do recommend researchers to certify that participants understand choice tasks adequately [54, 55].

Critically, our DCE analysis would have been more valid when patient focus groups were organized to determine attributes, besides the face to face interviews with professionals that were performed. This was done subsequently by Reerds et al. (unpublished data) in a small study on implementation of a PK tool to support PK-guided dosing. Strikingly, results did not differ from our DCE analysis.

Collaborative interventions aimed to implement PK-guided dosing are currently embodied by the Dutch "OPTI-CLOT" research group (patient-tailOred PharmacokineTIc-guided dosing of CLOTting factor concentrates in bleeding disorders) initiated in the Erasmus MC, a multicenter international initiative aiming to implement PK-guided dosing of clotting factor replacement therapy by initiating studies to prove the implications of PK-guided dosing, to construct perioperative and prophylactic PK population models and to evaluate the cost-effectiveness of a PK-guided approach [56]. But other initiatives are also currently ongoing, such as the web-based portal initiated by Iorio and Hermans, which aims to make PK-guided dosing accessible for all hemophilia professionals worldwide [57]. In addition, development of easily applicable PK tools such as myPKFiT based

on Bjorkman's prophylactic population PK model are valuable contributions to install PK-guided dosing in the hemophilia community in the near future [58].

Perioperative management and PK-guided dosing based on a population PK model

Annual costs of factor concentrate in the Netherlands are estimated around €130 million, of which approximately 15% are consumed in the perioperative period [59-62]. In an era of increasing health care costs, it is clearly important to explore if PK-guided dosing may lead to both optimizations of treatment and cost-reduction by decrease of factor concentrate consumption.

To evaluate current perioperative management in (moderate) severe hemophilia A, retrospective data on FVIII concentrate infusions and achieved FVIII concentrations were collected (**chapter 5**). In this retrospective cohort study, aims were to identify the extent and predictors of underdosing and overdosing in this category of patients to quantify urgency of alternative dosing algorithms. The study population consisted of 119 patients of all ages, undergoing 198 elective, minor or major surgical procedures. Results confirmed that perioperative management is challenging as both under dosing (up to 45% in the first 24 hours) and over dosing (up to 75% after 120 hours) were considerable. Patients with blood type O were proven to be at increased risk of under dosing and had more bleeding complications in comparison to patients with a non-O blood type. Hypothetically, we concluded that this may have been caused by higher clearance rates in these patients due to lower VWF levels and concomitant lower FVIII levels due to decreased protection against proteolytic degradation in the circulation [63-68]. In addition, older patients and patients treated with bolus infusions, when compared to continuous infusion, were at higher risk of overdosing. Partly, this may be explained by confounding by indication. More specifically, as older patients underwent more severe surgical procedures, this may have led to maintenance of higher FVIII target levels by treating hemophilia professionals, due to a focus on prevention of bleeding by underdosing and less attention to avoidance of overdosing. In addition, as VWF levels increase with age, theoretically this may have also played a role in decrease of FVIII clearance due to higher VWF levels in these older patients [69]. Unfortunately, underlying mechanisms remain hypothetical as few VWF levels were measured in this retrospective study.

The retrospective data collected within this study, were used to construct a perioperative population PK model. With this population PK model, it is possible to iteratively perform dose adjustments of replacement therapy in the perioperative setting. Although a small number of studies has mentioned perioperative PK profiling, all studies only define a preoperative PK-guided loading dose [70-73].

The perioperative PK of various FVIII concentrates in the (moderate) severe hemophilia patients described in our study, were best described by a two-compartment model, with following values for clearance (CL): 0.15L/h/68 kg, intercompartment clearance: 0.16L/h/68 kg, central volume (V1): 2.81L/68 kg and peripheral volume (V2): 1.90L/68 kg. Compared to the prophylactic setting a larger V2 compartment was found, suggesting a more rapid redistribution of FVIII concentrates following intravenous administration in the perioperative setting [45]. We hypothesized that the significant increase of VWF after surgery due to the inflicted endothelial damage and its role in the acute phase reaction, combined with the high affinity and stoichiometry of FVIII to VWF may have resulted in a large V2 directly after surgery [78, 79]. Due to the retrospective nature of the data however, there were not sufficient samples of VWF plasma levels available to confirm this hypothesis. In addition, due to lack of FVIII samples at the acute occurrence of bleeding complications, it was not possible to reliably confirm FVIII plasma levels at time of bleeding. For that reason, this model cannot account for pharmacodynamical outcome measures.

Future prospective studies, such as the "OPTI-CLOT" trial mentioned, are necessary to uncover modifiers of FVIII clearance and to further refine this perioperative FVIII population PK model [56]. Subsequently, leading to more insight into the PK and pharmacodynamic (PD) parameters of FVIII, VWF pathophysiology during the perioperative period, and the complex relationship between VWF levels FVIII PK parameters.

Developments with regard to PK-guided dosing in the near future

In an era of new treatment modalities, such as EHL coagulation factor products, gene therapy and new hemostatic products such as ACE910 (a bispecific antibody designed to replace FVIII by mediating the juxtaposition of FIXa and FX), monoclonal antibody 2021 (an antibody against tissue factor pathway inhibitor), or ALN-AT3 (a RNA interference agent against antithrombin), international data collection on PK and PD of these hemostatic agents are of importance to further individualize treatment for these novel therapies [74]. Moreover, as it is probable that not all products will be optimal for all patients. Therefore, the principle of transparent and accessible population PK and PD models as a basis for therapeutic approaches as stated by the "OPTI-CLOT" initiative is of great value [56]. These population PK and PD models will be able to take both individual patient characteristics as well as probable modifying factors such as endothelial activation and acute phase reaction, and unknown factors into account with regard to optimal dosing [75-78]. In addition, this principle will safeguard implementation of these new products for all different individuals.

Conclusions

We have addressed a number of options to improve patient outcome in hemophilia care. Although transmural support seems promising, this intervention improved perceived support and communication with the hemophilia treatment center, but did not increase adherence or other quality of life measures. Valuable questionnaires, able to quantify and monitor adherence and self-efficacy were developed and validated within this study. Initiation of Group Medical Appointments did lead to improvement of care as experienced by patients and parents. These effects were most significant in less experienced patients as this group benefited from knowledge and advice given by experienced patients and parents.

We have proven that both quality of care and cost-effectiveness can be improved by refining of perioperative dosing strategies based on individual patient characteristics such as blood group and mode of infusion. Moreover, the data from this retrospective study were used to construct a perioperative population FVIII PK model that describes the perioperative PK of various FVIII concentrates. This model will individualize perioperative FVIII replacement therapy in (moderate) severe hemophilia A patients by iterative Bayesian adaptive dosing. To facilitate the implementation of PK-guided dosing, it is important to discuss possible positive effects on bleeding risk as well as a possible decrease of costs of treatment for society with patients and parents.

Overall, prospective systematic assessment of novel innovations such as studied within this thesis is important to establish which interventions are valuable and sustainable for patients, parents and professionals in the long run in hemophilia care.

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CHAPTER 10

Summary

The aims of this thesis were to study strategies that may further improve patient outcome in hemophilia, by optimization of both patient care by interventions in adherence as well as treatment innovations (**Chapter 1**). The first part of this thesis specifically described strategies to optimize patient care.

Part I: Improvement of patient outcome by optimization of hemophilia care

Patients with severe hemophilia and some patients with moderate severe hemophilia are treated prophylactically with factor concentrate to prevent (spontaneous) bleeding. Most patients administer factor concentrate intravenously at home (or by parents) without direct medical supervision. Although home treatment has many advantages with regard to joint status and quality of life, it also has disadvantages. Previous studies have reported that it may lead to waning from prophylactic and on demand dosages and to parents and patients" insecurity with regard to treatment decisions and when to contact the hemophilia treatment center due to the increased responsibility. In **chapter 2**, we conducted an intervention study in which the effects of transmural support by a hemophilia nurse on adherence to prophylactic treatment, health-related quality of life (HRQoL), prosocial behaviour and psychopathology, as well total factor concentrate consumption, capacity towards self-efficacy, and number of joint bleeds were evaluated. Hemophilia nurses conducted four to seven home visits in 46 patients (mean age 9.4 years) during a median time period of 22 months [Interquartile range (IQR = 21-23)]. Strikingly, before intervention (baseline), almost all parents of patients already reported a high level of adherence to treatment, high quality of life, and a high capacity for self-efficacy, as well as a low number of joint bleeds. No difference in adherence to prescribed treatment was seen after the home visits when compared with baseline measurements. A decrease was observed over time on Child Health Questionnaire (CHQ) domains "Role functioning – Emotional/Behavioural" and "Parental Time Impact". Improvement was observed with regard to disease-specific HRQoL on Haemo-QoL domains: "Family", "Friends", and "Perceived support". The domain "Communication" of the validated VERITAS-Pro scale also improved slightly.

No other outcome measures changed significantly after intervention. Parents, patients and nurses were satisfied with home visits and scored the intervention as valuable. Although effects are small, transmural care by a hemophilia nurse leads to improvement of perceived support by parents and of communication between parents and the hemophilia treatment centre. Taking the lifelong relationship between patients with the hemophilia treatment centre this is an important finding to increase and maintain quality of care.

Non-adherence in patients with a chronic disease is strongly associated with a decreased quality of life and reduction of cost-benefit of treatment. Therefore, it is crucial to be able to measure and monitor adherence with validated instruments. Duncan et al. (2010) developed and validated the VERITAS-Pro adherence scale for prophylactic treatment in a pediatric and adult hemophilia population in the United States. We translated this questionnaire in Dutch according to international guidelines and validated it in our pediatric population, which is described in **chapter 3**. The VERITAS-Pro consists of six subscales ("Time", "Dose", "Plan", "Remember", "Skip" and "Communicate") each including four items. Lower scores reflect higher adherence. In total, 60 children with a mean age of 10 years [Standard deviation (SD) = 4] with hemophilia on prophylactic clotting factor replacement therapy for more than 1 year were included from three hemophilia treatment centers (response rate 85%). With regard to the quality of the questionnaire, internal consistency reliability, was adequate as mean Cronbach's alphas were sufficient (> 0.70) for total score and the subscales "Skip" and "Communicate". In addition, item-own subscale correlations were stronger than most item-other subscale correlations and convergent validity analyses showed that total scores were higher for non-adherent participants compared with adherent participants according to patient infusion logs (n = 48; P < 0.05). Furthermore, test–retest correlations demonstrated significance for all scales except "Dose" (n = 58; P < 0.01). This study has demonstrated the applicability of VERITAS-Pro outside the United States, as total score and most subscales effectively quantified treatment adherence in a Dutch pediatric population on prophylactic therapy. Non-adherent respondents' total scores were significantly higher, demonstrating the ability of VERITAS-Pro to identify non-adherent individuals.

Self-efficacy describes the actual confidence an individual feels for specific actions necessary to achieve certain results. Higher self-efficacy in chronic disease patients is associated with a higher level of self-management skills and an increased quality-of-life. Therefore, quantification and monitoring of self-efficacy is important. In general, self-efficacy in hemophilia patients has received little attention due to lack of standardized scales. In **chapter 4**, we have described the development and validation of the novel Hemophilia-specific Self-Efficacy Scale (HSES) in patients on prophylactic home treatment. Hemophilia patients aged 1–18 years on prophylactic treatment ≥ 1 year were included from three Dutch hemophilia treatment centers. The HSES consists of 12 items, relating to parent and patient's perceptions of the ability to function on a day-to-day basis with hemophilia. Retest was performed in a subsample of the study population. Validity was proven by the General Self-Efficacy Scale and by the health-related quality of life assessment tool Haemo-QoL. Data were analysed in 53 children (response 75%), with a mean age of 9.8 years (SD = 4.0). Mean total scale score of HSES was 55.5 (SD = 4.7; range: 38–60), with a ceiling effect of 17%. The HSES showed adequate internal con-

sistency (Cronbach's alpha 0.72) and good test–retest reliability (Intra-Class-Correlation coefficient 0.75; $P < 0.01$; $n = 37$). The convergent validity was adequate as hemophilia-specific self-efficacy correlated significantly with general self-efficacy ($r = 0.38$; $P < 0.01$). High HSES scores correlated significantly with quality-of-life as measured by the Haemo-QoL ($r = -0.42$; $P < 0.01$). We therefore concluded that the novel HSES is a reliable and valid tool to assess self-efficacy in pediatric hemophilia patients on prophylactic home treatment.

In **chapter 5**, we describe the effects of Group Medical Appointments (GMA) as compared to Individual Medical Appointments (IMA), the usual standard of care in patients with hemophilia and von Willibrand disease. GMA is a consultation form in which patients undergo individual consultations in each other's presence. We measured effects of GMA with regard to participant's satisfaction, social support experienced, team's attentiveness to the individual, informative value of a GMA, privacy aspects, and time investment necessary. Overall, parents and adolescents were very satisfied with both GMA and IMA. In our study, most important advantages of GMA were the improvement in participant's knowledge of the disease and social support experienced by participants. Both were significantly higher in parents and adolescents with less experience with disease symptoms, thus those with a milder disease phenotype than in those with a significant experience with the disease symptoms. The results presented in this chapter therefore suggested that GMA is a valuable addition in hemophilia and von Willebrand care, especially for patients with less experience with disease symptoms, thus more mildly affected patients. It leads to improved patient and participant satisfaction, experienced social support and an improved transfer of information and therefore most probably leads to an increase in self-efficacy.

Part II: Improvement of patient outcome by optimization of hemophilia treatment

The second part of this thesis describes strategies to optimize hemophilia treatment itself. Several studies have reported on the challenges of targeting of clotting factor VIII (FVIII) levels during perioperative replacement therapy in hemophilia and mention both underdosing and overdosing with respectively a risk of bleeding complications or unnecessary costs. However, the extent of underdosing and overdosing is not specified in these studies. To identify the extent, timing and possible predictors of FVIII under and overdosing, we evaluated perioperative management in a large series of hemophilia A patients and discuss novel strategies towards more personalized treatment in hemophilia, in **chapter 6**. In this retrospective observational study, we included 119 moderate and severe hemophilia A patients (FVIII levels < 0.05 IU mL^{-1}; median age 40 years [IQR = 9-54]; median body weight 75 kilograms [IQR = 35-85]) undergoing 198 elective surgical

procedures. Perioperative management was evaluated by quantification of perioperative infusion of FVIII concentrate and achieved FVIII levels. Predictors of under dosing and (excessive) overdosing were analysed by logistic regression analysis. Excessive overdosing was defined as an upper target level plus ≥ 0.20 IU mL^{-1}. In summary, on consecutive days deviations of FVIII levels in relation to target range levels were increasingly significant (*P* for trend < 0.01). In the first 24 hours after surgery, 45% of measured FVIII levels were *below* lowest target range level with a median deviation of 0.17 IU mL^{-1}. Six days after surgery, 75% of the FVIII levels were *above* highest target range level with a median deviation of 0.31 IU mL^{-1}. A potential reduction of FVIII consumption of 44% would have been attained if FVIII levels had been maintained within target ranges. Blood group O and major surgery were predictive of under dosing [Odds ratio (OR) = 6.3, 95% Confidence interval (95%CI) = 2.7-14.9; OR = 3.3, 95%CI = 1.4-7.9]. Moreover, blood group O patients had more bleeding complications in comparison to patients with other blood groups (OR = 2.02, 95%CI = 1.0-4.1). Patients with blood group non-O were at higher risk of overdosing (OR = 1.5, 95%CI = 1.1-1.9). Additionally, patients treated with bolus infusions were at higher risk of excessive overdosing with upper target level plus ≥0.20 IU mL^{-1} (OR = 1.8, 95%CI = 1.3-2.4). These results suggest that quality of care and cost-effectiveness can certainly be improved by refining of dosing strategies that increasingly take individual patient characteristics into account, such as blood group and mode of infusion. The study also concluded, that pharmacokinetic (PK)-guided dosing may be an option to achieve this goal.

The role of PK guided dosing of factor concentrates in hemophilia is currently subject of debate and generally focuses on long-term prophylactic treatment. Few data are available on its impact in the perioperative period. In **chapter 7**, a population PK model was presented that describes the perioperative PK of various current FVIII concentrates for moderate and severe hemophilia A patients (FVIII levels < 0.05 IU mL^{-1}) undergoing elective, minor or major surgery. The developed model was constructed on the basis of the retrospective data collection described in chapter 6 which included data on FVIII treatment, time points of FVIII sampling and all achieved FVIII plasma concentrations. Population PK modeling was performed using nonlinear mixed-effects modeling (NONMEM). Population PK parameters were estimated in a total of 119 patients undergoing a total of 198 surgeries, of which 75 adults underwent 140 surgeries (median age 48 years [IQR = 37-60]; median weight 80 kg [IQR = 73-90]) and 44 children underwent 58 surgeries (median age 4 years [IQR = 2-8]; median weight 19 kg [IQR = 12-29]). Individual PK was best described by a two-compartment model. Values for clearance (CL), intercompartment clearance, central (V1) and peripheral volume were 0.15L/h/68 kg, 0.16L/h/68 kg, 2.81L/68 kg and 1.90L/68 kg. Inter-patient variability in CL and V1 were respectively 37% and 27%. CL decreased with increasing age (*P* < 0.01) and was increased in case of blood

group O (26%, $P < 0.01$). In addition, a minor decrease in CL was observed when the surgical procedure was considered major (7%, $P < 0.01$). We concluded, that in the near future perioperative population PK models will lead to individualization of perioperative FVIII dosing and make iterative PK-guided dose-adjustments possible with subsequent optimization of care.

In **chapter 8**, we described strategies to facilitate the implementation of PK-guided prophylactic dosing in hemophilia care by identification of barriers and facilitators for this novel dosing strategy. This is of importance as patients', parents' and providers' preferences may have a major impact on implementation. We conducted a discrete choice experiment (DCE) to evaluate barriers and facilitators for individualized PK-guided dosing of prophylaxis in hemophilia patients, parents of young patients, and treating professionals. The study population consisted of patients with hemophilia currently or previously on prophylactic treatment with factor concentrate ($n = 114$), parents of patients aged 12–18 years ($n = 19$) and hemophilia treating professionals ($n = 91$). DCE data analysis was performed, taking preference heterogeneity into account. Overall, patients and parents, and especially professionals were inclined to opt for PK-guided dosing of prophylaxis. In addition, if bleeding was consequently reduced, more frequent factor concentrate infusions were acceptable. However, daily dosing remained an important barrier for all involved. Strikingly, reduction of costs for society' was a facilitator for implementation in all groups. We concluded that to achieve implementation of individualized PK-guided dosing of prophylaxis in hemophilia, reduction of bleeding risk and reduction of costs for society should be actively discussed as they are motivating for implementation. The knowledge of these preferences will enlarge support for this innovation, and aid in the drafting of implementable guidelines and information brochures for patients, parents and professionals.

Finally, this thesis ends with a general discussion in **chapter 9.** Options to improve hemophilia patient outcome by optimization of patient care and hemophilia treatment are summarized and discussed. The importance of an increased insight into care and treatment innovations and the dynamics within these processes are underlined. Methodological issues and gaps in described studies are highlighted, resulting in recommendations and requirements to further refine these strategies. Ultimately, suggestions for future studies are proposed in the respective areas of research.

CHAPTER 10

Samenvatting

In dit proefschrift worden studies beschreven die het optimaliseren van patiëntenzorg door interventies die gericht zijn op verbetering van therapietrouw (deel I) en de hemofilie behandeling met stollingsfactor concentraten (deel II) als doel hebben. In **hoofdstuk 1** worden de achtergronden en doelstellingen van dit proefschrift beschreven.

Deel I: Verbetering van patiënten uitkomsten door het optimaliseren van de hemofilie zorg

Patiënten met ernstige hemofilie en sommige patiënten met matig-ernstige hemofilie worden profylactisch behandeld met stollingsfactorconcentraat om (spontane) bloedingen te voorkomen. De intraveneuze toediening hiervan wordt meestal door patienten zelf of door hun ouders gedaan. Dit gebeurt in de thuissituatie zonder directe medische supervisie. Hoewel deze thuisbehandeling veel voordelen heeft voor de toestand van gewrichten en de kwaliteit van leven, heeft het ook nadelen. Eerder onderzoek heeft aangetoond dat thuisbehandeling kan leiden tot een vermindering van therapietrouw voor zowel de profylactische als on demand toedieningen van stollingsfactorconcentraat. De grote verantwoordelijkheid die patiënten en hun ouders voor hun behandeling hebben, kan ook leiden tot onzekerheid over het eventuele toedienen van medicatie en inschakelen van het hemofiliebehandelcentrum. In **hoofdstuk 2** beschrijven we een interventiestudie met huisbezoeken door een hemofilie verpleegkundige. We evalueerden het effect hiervan op therapietrouw, gezondheids-gerelateerde kwaliteit van leven, pro-sociaal gedrag en psychopathologie, het verbruik van stollingsfactorconcentraat, de mate van zelf-effectiviteit en het aantal gewrichtsbloedingen. Hemofilie verpleegkundigen bezochten 46 patienten (gemiddelde leeftijd 9,4 jaar) 4-7 keer gedurende een periode van mediaan 22 maanden (IQR = 21-23). Deze huisbezieken werden uitermate gewaardeerd door ouders, patiënten en verpleegkundigen. Opvallend was dat bijna alle ouders van patiënten al voor start van de interventie een hoge mate van therapietrouw, kwaliteit van leven en zelfeffectiviteit rapporteerden alsook een gering aantal bloedingen. Na de periode met huisbezoeken werd geen verschil gezien in therapietrouw ten opzichte van de uitgangssituatie. Op de scores in de domeinen "Rol functioneren-Emotioneel/ Gedrag" en "U en uw gezin- Tijdsbesteding" van de generieke gezondheids-gerelateerde kwaliteit van leven vragenlijst CHQ werd een daling waargenomen. De ziekte-specifieke gezondheids-gerelateerde kwaliteit van leven die gemeten werd met de Haemo-Qol verbeterde op de domeinen "Familie", "Vrienden" en "Ervaren steun". Het domein "Overleg" van de gevalideerde VERITAS-Pro vragenlijst verbeterde ook enigszins. De andere uitkomst maten waren na de interventie periode niet significant verschillend. Alhoewel effecten klein zijn, werd geconcludeerd dat huisbezoeken door een hemofilie verpleegkundige leiden tot verbetering van de communicatie tussen patiënten en het hemofiliebehandelcentrum alsook tot een toename van de door ouders ervaren steun.

Dit is een belangrijke uitkomst gegeven de levenslange relatie tussen hemofiliepatiënt en het behandelcentrum.

Therapieontrouw bij patiënten met een chronische ziekte is sterk geassocieerd met een verminderde kwaliteit van leven en vermindering van de kosteneffectiviteit van de behandeling. Het is daarom cruciaal om therapietrouw te kunnen meten en vervolgen met gevalideerde instrumenten. Duncan et al. (2010) ontwikkelde en valideerde de VERITAS-Pro therapietrouw-schaal voor profylactische behandeling in een populatie van volwassenen en kinderen met hemofilie in de Verenigde Staten. Wij vertaalden deze vragenlijst volgens internationale richtlijnen in het Nederlands en valideerden deze in onze populatie kinderen (**hoofdstuk 3**). De VERITAS-Pro bestaat uit zes subschalen ("Tijd", "Dosering", "Planning", "Onthouden", "Overslaan" en "Overleg"), elk met vier items. Lagere scores komen overeen met een betere therapietrouw. We includeerden totaal 60 kinderen met hemofilie uit drie behandelcentra, met een gemiddelde leeftijd van 10 jaar (SD = 4) die al meer dan één jaar profylactisch behandeld werden met stollingsfactorconcentraat (respons 85%). De interne consistentie, als een maat voor de kwaliteit van de vragenlijst, was voldoende voor de totale score en de subschalen "Overslaan" en "Overleg" (gemiddelde Cronbach's alfa scores > 0,70). Bovendien waren de meeste inter-item subschaal correlaties sterker dan de correlaties met items uit andere schalen. Analyse van de convergente validiteit toonde aan dat patienten die volgens infusielogboekjes therapieontrouw zijn, hoger scoorden dan patienten die therapietrouw waren (n = 48; P < 0,05). Test-hertest correlaties toonden het belang aan van alle schalen met uitzondering van de subschaal "Dosering" (n = 58; P < 0,01). Deze studie heeft de toepasbaarheid van de VERITAS-Pro in hemofile patiënten met profylaxe buiten de Verenigde Staten aangetoond. De totale score en de meeste subschalen geven daadwerkelijk de mate van therapietrouw weer in een Nederlandse populatie kinderen die profylactisch worden behandeld met stollingsfactorconcentraat.

Zelf-effectiviteit beschrijft het vertrouwen van een individu in de eigen bekwaamheid voor specifieke acties die nodig zijn om bepaalde resultaten te bereiken. Hogere zelf-effectiviteit bij patienten met een chronische ziekte is geassocieerd met een hogere mate van zelfmanagement en een betere kwaliteit van leven. Het kwantificeren en vervolgen van zelf-effectiviteit is daarom belangrijk. Tot op heden is er weinig aandacht geweest voor zelf-effectiviteit bij hemofiliepatiënten vanwege het gebrek aan gestandaardiseerde meetinstrumenten. In **hoofdstuk 4** wordt de ontwikkeling en validatie van een nieuwe hemofilie-specifieke zelf-effectiviteitsschaal (HSES) bij patiënten die thuis profylactisch worden behandeld beschreven. We includeerden hemofiliepatiënten van 1-18 jaar uit drie Nederlandse hemofiliebehandelcentra die sinds minstens 1 jaar thuis profylactische behandeld werden. De HSES bestaat uit 12 items, die de perceptie weergeven van

ouders van hemofiliepatiënten en de patiënten zelf, hoe zij met hemofilie omgaan in het dagelijks leven. In een subgroep van de studie populatie werd een hertest gedaan. De validiteit werd bevestigd middels de generieke zelf-effectiviteitsschaal GSES en de ziekte-specifieke gezondheids-gerelateerde kwaliteit van leven vragenlijst Haemo-Qol. De gegevens van 53 kinderen (respons 75%) met een gemiddelde leeftijd van 9,8 jaar (SD = 4,0) werden geanalyseerd. De gemiddelde totale score van de HSES was 55,5 (SD = 4.7; range: 38-60), met een plafond effect van 17%. De HSES vertoonde adequate interne consistentie (Cronbach's alpha 0,72) en een goede test-hertest betrouwbaarheid (Intra-klasse-correlatie coëfficiënt 0,75; $P < 0,01$; $n = 37$). De convergente validiteit was voldoende gezien de hemofilie-specifieke zelf-effectiviteit significant gecorreleerd was met de generieke zelf-effectiviteit ($r = 0,38$; $P < 0,01$). Hoge HSES-scores waren significant gecorreleerd met de kwaliteit van leven gemeten met de Haemo-Qol ($r = -0,42$; $P < 0,01$). Wij concludeerden daarom dat deze nieuwe HSES een betrouwbaar en valide meetinstrument is om zelf-effectiviteit te meten bij kinderen met hemofilie die thuis profylactisch worden behandeld.

In **hoofdstuk 5** beschrijven we de resultaten van een studie waarin groepsconsulten (GMA) worden vergeleken met de gebruikelijke individuele poliklinische afspraak voor patiënten met hemofilie en de ziekte van von Willebrand. Een groepsconsult is een bijeenkomst waarbij iedere patiënt een individueel consult heeft, in aanwezigheid van andere patiënten en ouders. Na ieder groepsconsult werd de tevredenheid van de deelnemer met de ervaren sociale steun, aandacht van het team voor de individuele patiënt, de educatieve en informatieve inhoud, privacyaspecten en de benodigde tijdsinvestering gemeten. In het algemeen, waren zowel ouders als adolescenten zeer tevreden met zowel het groepsconsult als de individuele poliklinische afspraak. De belangrijkste meerwaarde van de groepsconsulten was de toename van kennis van de ziekte en de grote sociale steun die door deelnemers werd ervaren. Beide waren significant hoger bij ouders en adolescenten met minder ervaring met hun ziekte, dus met een milder fenotype. De in dit hoofdstuk gepresenteerde resultaten suggereren daarom dat groepsconsulten een waardevolle aanvulling zijn bij de zorgverlening aan patiënten met hemofilie en de ziekte van von Willebrand, vooral wanneer er minder ervaring is met ziektesymptomen, zoals bij milder aangedane patiënten. Het groepsconsult leidt daarom tot verbetering van de tevredenheid van patiënten en behandelteam, meer ervaren sociale ondersteuning en een verbeterde informatieoverdracht en waarschijnlijk ook tot een toename van zelf-effectiviteit.

Deel II: Verbetering van patiënten uitkomsten door optimalisering van behandeling met stollingsfactorconcentraat

Het tweede deel van dit proefschrift beschrijft strategieën om de behandeling van hemofilie te optimaliseren. We laten de complexiteit zien van het bereiken van streefwaarden van stollingsfactoren in de perioperatieve periode. Geconcludeerd wordt dat zowel onder- als overdosering van stollingsfactor VIII (FVIII) concentraat voorkomt, met respectievelijk een verhoogd risico op bloedingen en onnodige kosten. Om de mate, het tijdstip en mogelijke voorspellers van onder- en overdosering van FVIII te identificeren, evalueerden we de perioperatieve periode in een grote groep patiënten met ernstige en matig ernstige hemofilie A. De resultaten van deze studie hiervan beschrijven we in **hoofdstuk 6.** In deze retrospectieve observationele studie includeerden we 119 patiënten met matige en ernstige hemofilie A (FVIII-niveau < 0,05 IU mL^{-1}; mediane leeftijd 40 jaar [IQR = 9-54]; mediane lichaamsgewicht 75 kilogram [IQR = 35-85]) die 198 electieve chirurgische procedures ondergingen. De perioperatieve aanpak werd geëvalueerd door het kwantificeren van perioperatieve infusie van FVIII-concentraat en de bereikte FVIII-niveaus. De voorspellers van onder- en (extreme) overdosering werden geanalyseerd door een logistische regressieanalyse. Extreme overdosering werd gedefinieerd als een plasmaspiegel ≥ 0.20 IU mL^{-1} boven de bovengrens van de streefwaarde. Samenvattend blijkt dat in de dagen na de procedure de afwijking van FVIII ten opzichte van de streefwaarde steeds aanzienlijker wordt (*P* voor trend < 0,01). In de eerste 24 uur na de operatie is 45% van de gemeten FVIII-niveaus lager dan de ondergrens van de streefwaarde met een gemiddelde afwijking van 0,17 IU mL^{-1}. Zes dagen na operatie is 75% van de gemeten FVIII-niveaus hoger dan de bovengrens van de streefwaarde, met een gemiddelde afwijking van 0,31 IU mL^{-1}. In potentie zou 44% reductie van de FVIII-consumptie zijn bereikt als FVIII-niveaus binnen de streefwaarde waren gehandhaafd. Bloedgroep O en een grote operatie waren voorspellend voor onderdosering (OR = 6,3, 95%CI = 2,7-14,9; OR = 3,3, 95%CI = 1,4-7,9). Daarbij hadden patiënten met bloedgroep O meer bloedingscomplicaties vergeleken met patiënten met een andere bloedgroep (OR = 2,02, 95%CI = 1,00-4,09). Patiënten met een niet-O bloedgroep hadden een grotere kans op overdosering (OR = 1,5, 95%CI = 1,1-1,9). Bovendien hadden patiënten die behandeld werden middels bolus infusies een hoger risico op extreme overdosering (OR = 1,8, 95%CI = 1,3-2,4). Deze resultaten suggereren dat de kwaliteit van zorg en kosteneffectiviteit beslist kan worden verbeterd door een verfijnde aanpak van doseren die rekening houdt met individuele patiëntkarakteristieken zoals bloedgroep en wijze van infusie. Farmacokinetisch (PK) gestuurd doseren is een mogelijkheid om dit doel te bereiken.

De rol van het PK-gestuurd doseren van stollingsfactorconcentraten bij hemofilie is momenteel onderwerp van discussie en in het algemeen vooral gericht op de langdurige

profylactische behandeling. Er zijn maar weinig gegevens beschikbaar over de effecten in de perioperatieve periode. In **hoofdstuk 7** presenteren we een populatie PK-model voor patiënten met matige en ernstige hemofilie A (FVIII niveaus < 0,05 IU mL^{-1}) die een electieve, chirurgische ingreep ondergaan. Het model beschrijft de perioperatieve farmacokinetiek van de FVIII concentraten die op dit moment beschikbaar zijn. Het model werd ontwikkeld met de retrospectief verzamelde gegevens zoals beschreven in hoofdstuk 6: De dosering FVIII concentraat, bereikte FVIII plasma concentraties en exacte tijdstippen van toedieningen en metingen. Het populatie PK-model werd geconstrueerd met behulp van non-lineair mixed-effects modeling (NONMEM). De populatie PK-parameters werden vastgesteld op basis van gegevens van 119 patiënten die in totaal 198 operaties ondergingen. Hiervan ondergingen 75 volwassenen 140 operaties (gemiddelde leeftijd 48 jaar [IQR = 37-60]; mediaan gewicht 80 kg [IQR 73-90) en 44 kinderen ondergingen 58 operaties (gemiddelde leeftijd 4 jaar [IQR = 2-8]; mediaan gewicht 19 kg [IQR = 12-29]). De individuele farmacokinetiek werd het best beschreven door een twee-compartimenten model. De waarde van de klaring (CL), de intercompartimentele klaring en het centraal (V1) en perifeer volume was respectievelijk 0,15L/u/68kg, 0,16L/u/68kg, 2,81lL/68 kg en 1,90L/68kg. Verschillen tussen patiënten (inter-patiënt variabiliteit) in CL en V1 waren respectievelijk 37% en 27%. De klaring nam af met toename van de leeftijd (P < 0,01) en was verhoogd bij bloedgroep O (26%, P < 0,01). Daarnaast werd een wat verminderde klaring waargenomen bij grotere chirurgische ingrepen (7%, P < 0,01). We concludeerden dat populatie PK-modellen ook voor de perioperatieve setting zullen leiden tot individualisering van de perioperatieve FVIII concentraat doseringen en tot PK-gestuurde dosisaanpassingen met een significante optimalisering van de zorg.

In **hoofdstuk 8** beschrijven we strategieën om PK-gestuurd profylactisch doseren succesvol te implementeren. Dit werd gebaseerd op onderzoek waarbij de belemmerende en bevorderende factoren voor deze nieuwe doseringsmethode werden geïdentificeerd. Dit is van belang omdat de voorkeuren van patiënten, ouders en behandelaars grote invloed kunnen hebben op de uiteindelijke invoering van een medische innovatie. Om de voorkeuren te inventariseren werd een "discrete keuze-experiment" (DCE) analyse uitgevoerd naar mogelijke belemmerende en bevorderende factoren van geïndividualiseerde PK- gestuurde dosering van profylaxe. De onderzoekspopulatie bestond uit patiënten met hemofilie die nu of eerder profylactisch werden behandeld met factorconcentraat (n = 114), ouders van patiënten 12-18 jaar (n = 19) en hemofilie behandelaren (n = 91). In het algemeen waren patiënten en ouders, en vooral professionals geneigd te kiezen voor PK-gestuurde dosering van profylaxe. Bovendien was, als het risico op bloedingen werd gereduceerd, het frequenter toedienen van factorconcentraat aanvaardbaar. Dagelijkse doseren bleef echter een belangrijke barrière voor alle betrokkenen. Het

beperken van de kosten voor de maatschappij was opvallend genoeg in alle groepen een bevorderende factor voor implementatie. We concludeerden dat bij de invoering van geïndividualiseerd PK-gestuurd doseren van profylaxe bij hemofilie, het verlagen van het risico op bloedingen en de reductie van de kosten voor de samenleving actief besproken moet worden, omdat ze bevorderlijk zijn voor implementatie. De kennis van deze voorkeuren zal behulpzaam zijn bij het opstellen van richtlijnen en informatiefolders voor patiënten, ouders en professionals.

Dit proefschrift eindigt tenslotte met een algemene discussie in **hoofdstuk 9**. Hierin worden de mogelijkheden om de uitkomsten van de patiëntenzorg en de behandeling van hemofilie te verbeteren samengevat en besproken. Het belang van een beter inzicht in zorg en toekomstige innovaties van behandeling, en de dynamiek van deze processen wordt hierin onderstreept. Methodologische vraagstukken en lacunes in de beschreven studies worden ook belicht, resulterend in aanbevelingen en voorwaarden om besproken strategieën te optimaliseren. Tenslotte worden suggesties gedaan voor toekomstig onderzoek.

APPENDICES

I LIST OF ABBREVIATIONS

BMI	Body Mass Index
BU	Bethesda Units
BW	Body Weight
CBO	Dutch Institute for Healthcare Improvement
CHQ	Child Health Questionnaire
CI	Confidence Interval
CL	Clearance
CM	Centimeter
DCE	Discrete Choice Experiment
FIX	Coagulation factor IX
FOCE	First-order conditional estimation
FVIII	Coagulation factor VIII
GMA	Group Medical Appointment
GSES	General Self-Efficacy Scale
Haemo-QoL	Haemophilia-specific Quality of Life
HSES	Haemophilia-specific Self-Efficacy Scale
HTC	Haemophilia Treatment Center
ICC	Intra-Class-Correlation
IIV	Inter-individual variability; variability between patients
IMA	Individual Medical Appointment
IOV	Inter-occasion variability; variability within patients
IQR	Interquartile Range
IS	Importance score
ISCED	International Standard Classification of Education
ISTH	International Society of Thrombosis and Hemostasis
IU	International Units
IVR	In vivo recovery
KG	Kilogram
L	Liter
MEC	Medical Ethical Committee
ML	Milliliter
MMOL	Millimole
N	Number
NA	Not Applicable
NONMEM	Non-linear mixed-effects modelling software to construct a population analysis, in which all plasma concentration time points are analysed simultaneously

OFV	Objective Function Value, a measure of goodness of fit of the model. OFV is proportional to minus two times the logarithm of the likelihood (-2log likelihood) of the data
OR	Odds Ratio
PK	Pharmacokinetic
PK-parameters	Pharmacokinetic parameters (e.g. CL, V1, Q, V2)
Q	Intercompartment clearance
QUOTE-questionnaire	Questionnaire about quality of care
RBCT	Red Blood Cell Transfusion
SD	Standard Deviation
SDQ	Strength and Difficulties Questionnaire
SE	Standard Error
SPSS	Statistical Packages for Social Sciences
V1	Volume of distribution of the central compartment
V2	Volume of distribution of the peripheral compartment
VERITAS-Pro	Validated Haemophilia Regimen Treatment Adherence Scale - Prophylaxis
VWF	Von Willebrand Factor
VWF:Act	Von Willebrand Activity
VWF:Ag	Von Willebrand Antigen

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III AUTHORS AND AFFILIATIONS

Marlène Beijlevelt, RN
Department of Pediatric Hematology, Academic Medical Center - Emma Children's Hospital, Amsterdam, the Netherlands.

Auke Beishuizen, MD PhD
Department of Pediatric Oncology and Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Esther W. de Bekker-Grob, MD
Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands.

Paul Brons, MD PhD
Department of Pediatric Hematology, Radboud University Medical Center, Nijmegen, the Netherlands.

Annet De Bruin, RN
Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Pieter W. Collins, MD PhD
Arthur Bloom Hemophilia Center, School of Medicine, Cardiff University, Cardiff, UK.

Marjon H. Cnossen, MD PhD
Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Marriette H.E. Driessens, PhD
Netherlands Hemophilia Patient Society (NVHP), Nijkerk, the Netherlands.

Natalie Duncan, MD PhD
Department of Hematology, Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA.

Karin Fijnvandraat, MD PhD
Department of Pediatric Hematology, Academic Medical Center - Emma Children's Hospital, Amsterdam, the Netherlands.

Arja de Goede-Bolder, MD
Department of General Pediatrics, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Hendrika C.A.M. Hazendonk, MD
Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Marieke Joosten, MD PhD
Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, the Neterlands.

Britta A. Laros-van Gorkom, MD PhD
Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands.

Frank W.G. Leebeek, MD PhD
Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands.

Marieke J.H.A. Kruip, MD, PhD
Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands.

Ron A.A. Mathôt, PhD
Hospital Pharmacy – Clinical Parmacology, Academic Medical Center, Amsterdam, the Netherlands.

Felix J. van der Meer, MD PhD
Department of Hematology, Leiden University Medical Center, Leiden, the Netherlands.

Karina Meijer, MD PhD
Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands

Henriette A. Moll, MD PhD
Department of General Pediatrics, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Rianne Oostenbrink, MD PhD
Department of General Pediatrics, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Marjolein Peters, MD PhD
Department of Pediatric Hematology, Academic Medical Center - Emma Children's Hospital, Amsterdam, the Netherlands.

Hein Raat, MD PhD
Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands.

Mariejan Scholten, RN
Department of Pediatric Hematology, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands.

Femke M. Seesing, PhD
Department of Neurology, Radboud University Medical Center, Nijmegen, the Netherlands.

Amy Shapiro, MD PhD
Department of Pediatric Hematology, Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA.

Rienk Y.J. Tamminga, MD PhD
Department of Pediatric Hematology, University Medical Center Groningen, Groningen, the Netherlands

Gamze Urhan, MD
Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

Saskia N. de Wildt, MD PhD
Intensive care and Department of Pediatric Intensive Care, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands.

IV DANKWOORD

"Als het hoogste doel van de kapitein zou zijn om zijn schip te behouden, zou hij het voor altijd in de haven houden"

(Thomas van Aquino, 1225-1274)

Er zijn momenten die je niet vergeet. Zoals het moment waarop Marjon Cnossen mij zes jaar geleden op de Intensive Care kinderen van het Erasmus na een visite aansprak. Of ik ook zo'n ANIOS was die nog op zoek was naar een onderzoek. Met het ideaal voor ogen een goede arts te worden, sprak een promotieonderzoek mij zeker aan. Wel in het besef dat het een harde leerweg zou worden, maar Marjon wist mij met haar enthousiasme te overtuigen. Er lagen ambitieuze plannen, dat sprak mij aan! Maar, zoals Marjon mij later ook meegaf, "Onbereikbare doelen, die gaan zo lekker lang mee" (*Loesje*). Inmiddels is de derde promovenda bezig om de plannen van toen te realiseren en verder uit te bouwen. Deze dissertatie legt de basis voor die prachtige onderzoekslijnen. Velen hebben de afgelopen jaren deuren voor mij en voor het onderzoek geopend en direct of indirect meegeholpen aan dit resultaat. En daar wil ik in dit woord van dank bij stilstaan.

Allereerst wil ik alle patiënten en hun ouders/verzorgers bedanken die letterlijk hun deur hebben geopend of op een andere manier hun medewerking aan dit onderzoek hebben verleend. Medisch onderzoek gaat over mensen die patiënt zijn en dus in aanraking komen met de kwetsbare kant van het leven. Daarom vind ik het altijd bewonderenswaardig dat juist zij bereid zijn andere patiënten, die ze helemaal niet kennen en die misschien zelfs nog niet leven, te dienen door mee te werken. Daarbij is hemofilie een zeldzame ziekte. Dit betekent dat er weinig patiënten zijn die informatie kunnen aanleveren en dat ze regelmatig belast worden met de vraag (weer) aan een onderzoek te willen meedoen. Bedankt dat velen van jullie dit met veel geduld, passie en inzet hebben gedaan!

Geen promotie zonder promotoren. Prof. dr. F.W.G. Leebeek en prof. dr. H.A. Moll jullie steunden en stimuleerden mij en gaven mij keer op keer vertrouwen. Frank, als een leider heb je me door dit promotieonderzoek geloodst. Door je kritische vragen en jarenlange ervaring, wist je bij elke bespreking mijn geest te scherpen en het onderzoek weer een stap verder te brengen. Henriette, wat heb jij veel voor me betekend de afgelopen jaren. Je gaf me niet per se antwoorden, maar stelde met je voortreffelijke helikopterview altijd de goede vragen, zodat ik zelf de volgende stap kon zetten. Je bent er op cruciale momenten voor me geweest, waarbij je echt luisterde en me de ruimte gaf om mijn vleugels even op een andere manier uit te slaan. Frank en Henriette: bedankt!

Dr. M.H. Cnossen, lieve Marjon, samen zijn we ruim 6 jaar geleden van start gegaan. Jij als co-promotor en ik als jouw eerste promovendus. We hadden veel mooie momenten en hoogtepunten: de goedgekeurde METC-aanvragen, de prachtige beurzen en subsidies die we binnenhaalden om het onderzoek te kunnen financieren, de discussies, koffietjes, congressen, etentjes en wat al niet meer. Het was soms ook een zoektocht, want er is geen promotietraject zonder dat er ook deuren dichtgaan. Maar jouw enthousiasme, mensenkennis, en vooral jouw enórme doorzettingsvermogen zijn een inspiratiebron geweest om door te gaan. Met dit prachtige resultaat! En zelfs nog veel meer, want de zaadjes die we hebben geplant, zijn bijna allemaal tot ontwikkeling gekomen en een heel aantal staat volop in bloei!

Lieve Arja, ook jij hebt aan de wieg van deze dissertatie gestaan. Je hebt een enorm hart voor patiënten en jij bent de grondlegger geweest van het thuiszorgonderzoek. Met inzicht in de patiëntenzorg, gedegen kennis en eindeloze precisie, heb je mij de eerste anderhalf jaar van mijn promotie begeleid. Helaas, voor mij, ging je toen met pensioen. Het is prachtig te zien hoe jij in het leven staat. Arja, Henriette en Marjon, we delen onze roots in Indonesië en dat heeft toch wel iets speciaals!

Prof. dr. R.A.A. Mathôt, Dr. M. Peters en Prof. dr. H. Raat, dank voor het plaatsnemen in de leescommissie. Ron, ik ken weinig wetenschappers op jouw niveau die zoveel rust en aandacht hebben voor de mensen die zij begeleiden. Je brengt met passie en geduld je vak over aan jonge wetenschappers. Marjolein, met jouw leiderschapskwaliteiten, ideeën, enthousiasme, ondernemingszin en oog voor de patiënt en de organisatie daaromheen beteken je geweldig veel voor de hemofiliezorg en heb je ook veel betekend voor ons onderzoek. Hein, dank voor alle waardevolle discussies over het valideren van vragenlijsten en het thuiszorgonderzoek. Maar het meest heb ik genoten van het brainstormen over allerlei nieuwe onderzoeksvragen en -vormen.

Prof. dr. J.A. Hazelzet, beste Jan. Je hebt mij de beginselen van de bloedstolling en de magische verbinding met het immuunsysteem onderwezen tijdens mijn periode op de Intensive Care. Bijzonder dat je nu plaats neemt in de grote commissie. Prof. dr. V.W.V. Jadoe, beste Vincent. Je hebt me onderwezen tijdens de master Clinical Epidemiology en geïnspireerd door het onderzoek van Generation R. Prof. dr C.M. Zwaan, beste Michel. De laatste jaren heb je een stimulerende omgeving gecreëerd, waarin de Kinderhematologie en de onderzoekslijnen binnen de afdeling zich goed hebben kunnen ontwikkelen. Je maakt je onder andere sterk voor de beschikbaarheid van geneesmiddelen voor kinderen en daarmee ben je van grote waarde voor de kindergeneeskunde. Ik ervaar het als stimulerend dat jullie deel uitmaken van de promotiecommissie.

Wat is de zorg en het onderzoek zonder verpleegkundigen. Jullie zijn de spil van de zorg. Zowel qua organisatie als in het intermenselijke contact met patiënten én collega's. Fantastisch! Mariejan, je hebt een hart van goud. Wat zijn die jongens gek op je! Fijn dat je als ervaren hemofilieverpleegkundige het thuiszorgonderzoek wilde gaan doen. Je hebt mij wegwijs gemaakt in de hemofiliezorg én de leuke plekjes om iets te gaan eten. Annet, met passie voor het vak heb je ontzettend waardevol werk verricht voor het onderzoek naar de groepsconsulten. Het was fantastisch om dat onderzoek verder uit te mogen bouwen. Ook daarna stond je altijd klaar om te helpen of om een goed gesprek te voeren! Greta, Floor en Marlous, dank voor de waardevolle ondersteuning en betrokkenheid vanuit de volwassen hematologie! Ik heb warme herinneringen aan de congressen die we samen bezochten en jullie gezelligheid! Marlous, jij werkt inmiddels niet meer op de afdeling, maar jouw uitstraling, compassie, vrolijkheid en moed zijn een voorbeeld voor mij geweest en dat zal ik niet snel vergeten! Marlène, als researchverpleegkundige heb jij een belangrijke rol in het hemofilieonderzoek. Jij hebt onder andere het thuiszorgonderzoek in Amsterdam uitgevoerd. Geordend, rechtlijnig, gestructureerd én enthousiast en warm heb je het werk gedaan en kwaliteit aan het onderzoek toegevoegd. Dank! Marlies, wij zijn ongeveer tegelijkertijd met ons promotieonderzoek gestart. Jij bent al een tijdje gepromoveerd en bent inmiddels (inter)nationaal groots bezig met onderzoek naar adherence en personalized care. Dank voor de samenwerking en hopelijk komt er nog veel mooi onderzoek voort uit de samenwerking tussen de hemofiliecentra in Nederland!

Dank aan alle co-auteurs voor hun bijdrage aan het onderzoek. Auke, dank voor wat je voor me betekend hebt in het hemofilieteam. Als co-auteur met een scherp oog voor detail, en ook als hematoloog. Je bent daarin een voorbeeld voor me. Je staat naast mensen, zowel bij patiënten als bij collega's. Je straalt rust uit, bent doortastend, luistert en doorgrondt. Dear Natalie, thank you so much for being my co-author. It was so wonderful to work with you! Thank you! Esther, via je collega Suzanne kwam ik bij jou terecht. En het werd een succes! Dank voor de fijne en vruchtbare samenwerking en het vele werk dat je voor de "DCE-studie" hebt verricht.

Gamze en Hannan, ik heb jullie tijdens jullie keuze-onderzoek mogen begeleiden. En ondanks dat ik aan het einde van dit traject met zwangerschapsverlof ging, hebben jullie het onderzoek met succes afgerond! Inmiddels delen we de passie voor het huisartsenvak, wie had dat toen kunnen denken! Maurits en Arienne, dank voor jullie hulp bij het onderzoek. Heel veel succes met wat er nu op jullie pad komt.

Tijdens mijn onderzoeksjaren heb ik deel mogen nemen aan verschillende onderzoeksgroepen. Dank aan de collega's van de werkgroepen algemene kindergeneeskunde,

hematologie, farmacologie, en NONMEM. Het is bijzonder inspirerend om door de discussies over het onderzoek (van jezelf, maar ook van anderen!) nieuwe inzichten te verkrijgen, maar ook ontzettend verhelderend om de hiaten in je onderzoek te ontdekken. Deze werkbesprekingen hebben absoluut tot een betere kwaliteit van het onderzoek geleid.

Als promovendus heb je ook een werkplek nodig. De eerste jaren heb ik op de SP gezeten. Aangekondigd met een enorme bos bloemen, en ontvangen met verraste gezichten, heb ik geweldig warme herinneringen aan de SP-tijd. Inmiddels is bijna iedereen uitgevlogen, maar de warme band die we nu nog hebben, geeft blijk van een onderzoeksgroep die elkaar wist te respecteren, naast elkaar stond, elkaar verder hielp; als mens en als collega. Ik waardeer dat zeer. Lieve Janneke, Nienke, Evelien, Thijs, Yvette, Idse, Marieke, Ruud, Dorien, Eefje, Iris, Myrthe en Joany, dank voor al de keren dat de deur openstond, en we met koffie/thee en chocolade de beste gesprekken hadden!

Na de SP-tijd, kwam er de overgang van de kindergeneeskunde naar de afdeling hematologie. Yvonne, Carolien, Carina, Michelle, Shiraaz, Jossi, Johan, Iris, Eva, Shirley en Marc, jullie hebben deze tijd onvergetelijk gemaakt. Ik wil een aantal mensen nog in het bijzonder noemen. Eva, jij hebt me in het vak ingewerkt, en wat was het gezellig in Buenos Aires! Carolien en Iris, jullie zijn de nieuwe OPTI-CLOTTERS. Het was bijzonder om samen te werken. Carolien, heel veel succes met de laatste loodjes en Iris succes met het vervolg van de OPTI-CLOT! Yvonne, wat bijzonder dat we in dezelfde jaargroep, onderwijsgroep en ook nog in dezelfde subgroep werden geplaatst. Dank voor je collegialiteit als onderzoeker en ook de laatste maanden als huisarts in opleiding! Carina, je was multi-inzetbaar en stond altijd voor iedereen klaar! Michelle, met jouw gestructureerde manier van werken kon je bergen verzetten en dat was nog gezellig ook! Shirley, als post-doc vervul je een mooie rol op de afdeling. Zowel op onderzoeksvlak, waarbij je met passie de werkgroep stuurt, als ook persoonlijk vlak. Het was heerlijk dat je af en toe even om het hoekje kwam gluren tijdens de vele uurtjes in de 'vissenkom'. Moniek en Dick, dank voor jullie wetenschappelijke inzichten, waardevolle adviezen en persoonlijke aandacht in de afgelopen jaren.

Speciale dank aan het secretariaat van de afdelingen hematologie, oncologie en algemene kindergeneeskunde voor de waardevolle ondersteuning tijdens het promotie traject, maar vooral voor de samenbindende rol die jullie vervullen op de afdeling.

Natuurlijk wil ik ook de andere arts-onderzoekers in het Sophia en de Sophia Onderzoekers Vereniging bedanken. Door de jaren heen hebben jullie veel betekend voor de

promovendi in het Sophia. Het levert waardevolle informatie, collegialiteit, gezellige borrels en weekenden op, dank!

Sinds maart 2016 ben ik in opleiding tot huisarts aan het Erasmus MC te Rotterdam. Marleen, Carina en Irene, hartelijk dank voor het onderwijs, jullie steun, vertrouwen en begrip in mijn eerste maanden als huisarts in opleiding, waarbij ik ook de laatste hand heb gelegd aan deze dissertatie. Lieve collega HAIO's, dank voor de gezellige en leerzame momenten afgelopen maanden!

Vrienden maken het leven zoveel mooier! Babs, je staat al vanaf het eerste jaar van onze studie naast me. Het begon met samen blokken voor de tentamens, waarbij we enorm efficiënt waren en vervolgens dus heel veel tijd hadden om over de echte dingen van het leven te praten. Het is uitgegroeid tot een hechte vriendschap. De afgelopen jaren heb je me meer dan eens aangemoedigd om door te gaan. Wat bijzonder dat je als paranimf naast me staat, dank! Gerdien en Hanneke, elk jaar een week zeilen hebben we niet volgehouden, maar de vriendschap is er niet minder om geworden. Dank voor al die gezellige momenten! Marian, de klik en verbondenheid is er altijd weer! Sija, Willem, Veerle, Maaike en Renske. Heerlijk om jullie als vrienden te hebben en me daaraan op te mogen warmen! Dank ook voor alle praktische hulp en alle uurtjes dat Jesse bij 'de meiden' mocht spelen. Corina, Talitha, Tabitha, Madelinde, Christine, wat leuk dat we nog steeds zo'n mooie vriendenkring vormen! Cristel en Frank, wat geniet ik altijd van de speeluurtjes van Jesse en Eva en inmiddels ook van Pim, Ben, Luuk en Nora. Al die momenten zijn uitgegroeid tot een mooie vriendschap, bedankt!

Mijn levensreis is begonnen in Papua, een fantastische plek om op te groeien. Een plek die passie vormt en bagage meegeeft voor de reis die voor je ligt. Lieve papa en mama, dank voor jullie onvoorwaardelijke steun, de vele gesprekken over geloof, hoop en liefde en over het ontwikkelen van je talenten. Dank ook voor de ruimte die jullie geven om onszelf te zijn en onze eigen verantwoordelijkheid te nemen. Joris en Willem, het is bijzonder fijn om broers zoals jullie te hebben. Wat zijn we hecht met elkaar! Joris, jouw talent is enorm. Bedankt dat je de voorkant van mijn boekje hebt ontworpen! Willem, je hebt je eigen pad gekozen en bent ook geneeskunde gaan studeren! Allebei kiezen we nog steeds onze eigen wegen, maar ze kruisen elkaar steeds opnieuw. Dank dat je mijn paranimf wilt zijn! Joris, Arianne, Janiek, Jarik, Willem, Deborah en Loïs, wat vormen jullie een fijne familie! Lieve schoonfamilie, ik bof met jullie! We hebben heel wat doorstaan de afgelopen jaren, maar altijd is er die hechte familieband.

Jesse, Luuk en Nora, wat kan ik eindeloos van jullie genieten! Jesse, je levendige ogen verraden dat je een grenzeloze fantasie hebt en een prachtig karakter! Luuk, je obser-

veert, denkt erover na en doet het na als je denkt dat je het kunt. Je weet nu al zo goed wat je wilt! Nora, als je maar in beweging bent, dan is het goed! Wat geniet ik van je levendigheid en je karakter! Jullie hebben allemaal tijdens deze promotie het levenslicht gezien en kennen me dus niet zonder. In die zin breekt er voor mij én voor jullie een periode aan met een heel nieuwe dynamiek.

Rob, dit dankwoord had ik natuurlijk met jou moeten beginnen. Wat heb jij een enorme betekenis voor me! Je hebt me de afgelopen jaren alle ruimte gegeven om mijn onderzoek uit te voeren en veel meer dan dat! Ik ontdek steeds meer hoe mooi je bent en hoeveel ik van je hou! ~Soli Deo Gloria~

V PHD PORTFOLIO: SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student:	J. Lock
Erasmus MC Departments:	General Pediatrics – Pediatric Hematology
Research School:	NIHES
PhD period:	April 2010 – September 2016
Promotors:	Prof. dr. F.W.G. Leebeek and prof. dr. H.A. Moll
Supervisors:	Dr. M.H. Cnossen

1. PHD TRAINING	Year	Workload (ECTS)
General academic skills		
Biomedical English Writing and Communication	2011	4.0
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2012	1.0
Course Research Integrity	2012	2.0
Proefschrift schrijfdriedaagse	2014	0.7
Research skills		
Department Research Meetings, Department of General Pediatrics and Hematology, Erasmus MC, Rotterdam	2010-2015	3.0
Mini course Methodology of Patient-related Research Methodology, Rotterdam	2011	0.3
The National Institutes of Health Clinical Center, Principles of Clinical Pharmacology, e-course	2011-2012	2.0
Master of Science in Clinical Epidemiology, NIHES, Rotterdam		
Core curriculum		
Study Design	2011	4.3
Clinical Epidemiology	2011	5.7
Methodologic Topics in Epidemiologic Research	2011	1.4
Research proposal	2012	2.5
Advanced Short Courses		
Biostatistical Methods I: Basic Principles	2011	5.7
Epidemiology of Infectious Diseases	2013	1.4
Bayesian Statistics	2013	1.4
Biostatistical Methods II: Popular Regression Models	2011	4.3
Missing Values in Clinical Research	2013	0.7
Regression Analysis for Clinicians	2010	1.9
Principles of Epidemiologic Data-analysis	2013	0.7
Courses for the Quantitative Researcher	2012	1.4
Quality of Life Measurements	2011	0.9

Erasmus Summer Program Courses		
Principles of Research in Medicine	2011	0.7
Introduction to Data Analysis	2010	1.0
Clinical Decision Analysis	2011	0.7
Methods of Public Health Research	2011	0.7
Clinical Trials	2010	0.7
Topics in Meta-analysis	2011	0.7
Pharmaco-epidemiology	2011	0.7
Health Economics	2011	0.7
Markers and Prognostic Research	2011	0.7
The Practice of Epidemiologic Analysis	2011	0.7
Seminars and workshops		
Hematology Course "Hemophilia and von Willebrand's Disease", Netherlands Society of Hemophilia Patients (NVHP), Eerbeek	2010	0.7
PhD-day, Erasmus MC, Rotterdam	2010	0.3
2nd Hematology Symposium, Herfstpallet, Amsterdam	2010	0.3
Young Investigators Day, Congress of the Paediatric Association of the Netherlands, Veldhoven	2011	0.3
Expert meeting on Continues Infusion, Berg en Dal	2011	0.1
AMSTOL Symposium, State-of-the-art hemostasis, thrombosis, atherosclerosis and vascular medicine, Amsterdam	2012	0.3
COEUR Research Seminar on Hemostasis and Arterial Thrombosis, Rotterdam	2012	0.1
Symposium on "Kwaliteit en Implementatie: Durf de uitdaging aan!", Rotterdam	2013	0.3
NVTH annual AIO course on hemostasis and thrombosis, Koudekerke	2014	0.7
(Inter)national conferences		
XXIX World Federation of Haemophilia (WFH), Buenos Aires, Argentina	2010	1.0
Sophia Scientific Research Organization (SSWO), Erasmus MC – Sophia Children's Hospital, Rotterdam [2x oral presentation and 2x poster presentation]	2010, 2011	1.0
Dutch Society on Pediatrics (NVK) symposium, Veldhoven, [oral presentation and 2x poster presentation]	2010, 2011	0.8
Annual Meeting Belgian Society on Thrombosis and Haemostasis, Gent, Belgium	2010	0.6
4th Annual Congress of the European Association for Haemophilia and Allied Disorders, Geneva, Switzerland [poster presentation]	2011	0.3
Rodin Symposium, Amsterdam	2011	0.25
XXX World Federation of Haemophilia (WFH) Congress, Paris, France [poster presentation]	2012	1.5
6th Annual Congress of the European Association for Hemophilia and Allied Disorders (EAHAD), Warsaw, Poland	2013	0.7
XXIVth Congress of International Society on Thrombosis of Haemostasis, Amsterdam [5x poster presentation]	2013	1.6
Dutch Society on Thrombosis and Hemostasis (NVTH) Symposium, Koudekerke	2014	0.3

2. TEACHING

Supervising Master's theses		
G. Urhan, medical student, Erasmus MC	2012	3.0
H. Bouzariouh, medical student, Erasmus MC	2012	3.0
Supervising Scientific internship		
M. Westenberg, medical student, Erasmus MC	2014	0.3
A. van Heusden, medical student, Erasmus MC	2013	0.3

VI ABOUT THE AUTHOR

Janske Lock werd geboren op 30 augustus 1983 in Ede. Zij groeide op in Papua, Indonesië, waar zij met veel plezier haar jeugd heeft doorgebracht en waar haar passie voor ontwikkelingswerk is ontstaan. Na het behalen van haar VWO diploma in 2001 aan de Gomarus Scholengemeenschap in Gorinchem ging zij Geneeskunde studeren aan de Erasmus Universiteit te Rotterdam. In 2008 behaalde zij haar artsenbul. Om haar interesse in het ontwikkelingswerk vorm te geven volgde zij in 2007 een keuze-coschap in Nicaragua. Na haar coschappen werkte zij als arts-assistent op de afdeling Kindergeneeskunde in het Albert Schweitzer ziekenhuis te Dordrecht en op de Intensive Care Kinderen in het Erasmus MC - Sophia Kinderziekenhuis te Rotterdam.

In 2010 begon ze aan haar promotieonderzoek op de afdeling Hematologie en Algemene Pediatrie in het Erasmus MC te Rotterdam onder begeleiding van dr. M.H. Cnossen, prof. dr. F.W.G. Leebeek en prof. dr. H.A. Moll. De resultaten van dat promotieonderzoek zijn beschreven in dit proefschrift.

Ook tijdens deze periode zette zij zich in voor kansarmen. Zij ging in 2013 met een medische missie van Medical Checks for Children naar de Filipijnen. Tevens werkte zij op vrijwillige basis gedurende 6 weken in een vluchtelingenkamp op de grens van Thailand en Myanmar voor de Shoklo Malaria Research Unit. Hier ontdekte zij, naast een enorm grote passie voor de kindergeneeskunde, ook een passie te hebben voor patiënten die de kindertijd inmiddels ontstegen zijn. In 2015 werkte zij gedurende een aantal maanden in een verpleeghuis van stichting Humanitas te Rotterdam, waarbij dit bevestigd werd. Sinds maart 2016 volgt zij met veel voldoening de opleiding tot huisarts in het Erasmus MC te Rotterdam. Zij is getrouwd en moeder van 3 kinderen (2012, 2014 en 2014).


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