



# LUND UNIVERSITY

## Health-Related Quality of Life and Adherence in Haemophilia

Lindvall, Karin

2013

[Link to publication](#)

*Citation for published version (APA):*

Lindvall, K. (2013). *Health-Related Quality of Life and Adherence in Haemophilia*. [Doctoral Thesis (compilation), Clinical Coagulation, Malmö]. Clinical Coagulation Research Unit, Clinical Science, Malmö.

*Total number of authors:*

1

### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

# Health-Related Quality of Life and Adherence in Haemophilia

Karin Lindvall

Copyright © Karin Lindvall

Clinical Sciences, Malmö

Lund University, Faculty of Medicine, Doctoral Dissertation Series 2013:56

ISBN 978-91-87449-26-0

ISSN 1652-8220

Printed by Media-Tryck, Lund University

Lund 2013



*Illness invites a wake-up call about life.  
It arouses the need to be known,  
to be heard and to be validated. The need to know  
that one's life matters in the life of someone else  
and that the life one is living and has lived is worthwhile*

*Frank 1994*



# Contents

Contents	5
Abbreviations	9
Original Publications	11
Haemophilia	13
The coagulation process	13
The disease	14
Haemophilia: heredity and history	14
Bleedings in haemophilia	16
Treatment of haemophilia	18
Prophylactic treatment	19
On-demand treatment	24
Side-effects of treatment	24
Inhibitor	24
Hepatitis and HIV	25
Co-morbidities in haemophilia	26
Haemophilia care	27
Health-Related Quality of life	29
Generic instrument	29
Disease-specific instruments	30
HRQoL in the haemophilia population	30
Objective of thesis	33
Specific aims:	33

Material and Methods	35
Paper I.	35
Paper II.	35
Papers III and IV.	36
Paper V.	36
Instruments	37
Generic instruments	37
Disease-specific instruments	38
Statistics	41
Results and Discussions	43
Paper I.	43
Paper II-IV.	44
Socio-demographic data	45
SF-36	46
VAS interference of haemophilia in daily life	49
Caregiver Burden	49
Impact on Family Scale (IOF)	50
Result from questionnaire	51
Paper V.	51
EQ 5D	52
MedTap	52
VAS Interference of haemophilia in daily life	52
Discussion	53
Limitations	55
Conclusions	57

Future perspective	59
Important points to consider	60
Populärvetenskaplig sammanfattning	61
Acknowledgements	65
References	67





# Abbreviations

AD	Anno Domini
AIDS	Acquired Immunodeficiency Syndrome
aPCC	activated prothrombin complex concentrate
BU	Bethesda Units
CBS	Caregiver Burden Scale
CVAD	Central Venous Access Device
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ED	Exposure Days
EQ 5D	EuroQoL 5D
FVIII	Coagulation Factor VIII
FIX	Coagulation Factor IX
HAART	Highly Active Antiretroviral
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HJHS	Haemophilia Joint Health Scale
HRQoL	Health-Related Quality of Life
HTC	Haemophilia Treatment Centre
IOF	Impact on Family Scale
ITI	Immune Tolerance Induction
MCS	Mental Component Score
PAC	Port-A-Cath
PCS	Physical Component Score
PWH	Person With Haemophilia
QoL	Quality of Life
rFVIIa	Recombinant activated factor VII
SF 36	Short Form Health Survey
VAS	Visual Analogue Scale
WFH	World Federation of Hemophilia
WHO	World Health Organization



# Original Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals. The papers are included as appendices at the end of the thesis.

## I. Knowledge of disease and adherence in adult patients with haemophilia

Lindvall K, Colstrup L, Loogna K, Wollter I, Grönhaug S.

Haemophilia. 2010 Jul 1;16(4):592-6. doi: 10.1111/j.1365-2516.2009.02189.x.

Epub 2010 Feb 2. PMID:20136657

[PubMed - indexed for MEDLINE]

## II. Quality of life in adult patients with haemophilia - a single centre experience from Sweden

Lindvall K, Von Mackensen S, Berntorp E.

Haemophilia. 2012 Jul;18(4):527-31. doi: 10.1111/j.1365-2516.2012.02765.x.

Epub 2012 Mar 8.

PMID:22404485[PubMed - indexed for MEDLINE]

## III. Health-Related Quality of Life and Burden in Partners of Adult Patients with Haemophilia

Karin Lindvall, Sylvia von Mackensen, Sölve Elmståhl, Erik Berntorp

Submitted

## IV. Increased Burden on Caregivers of Having a Child with Haemophilia Complicated by Inhibitors

Karin Lindvall, Sylvia von Mackensen, Sölve Elmståhl, Kate Khair , Ann Marie Stain, Rolf Ljung, Erik Berntorp. Submitted

## V. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy.

Lindvall K, Astermark J, Björkman S, Ljung R, Carlsson KS, Persson S, Berntorp E.

Haemophilia. 2012 Nov;18(6):855-9. doi: 10.1111/j.1365-2516.2012.02879.x.

Epub 2012 Jun 11. PMID: 22681244 [PubMed - in process]

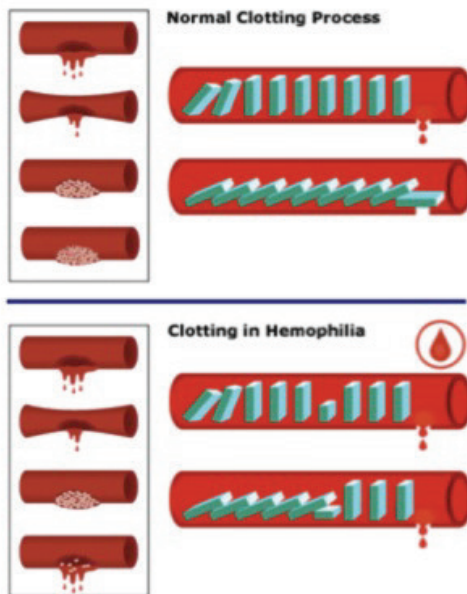


# Haemophilia

## The coagulation process

Clotting factors are proteins in blood that control bleeding. When a blood vessel is damaged, small blood cells called platelets stick to the site of the injury. The coagulation cascade is initiated and each coagulation factor is activated in a specific order, together with proteins, to plug the hole and stop the bleeding, and form a fibrin clot (Figure 1). In haemophilia, the deficient factor IX or cofactor VIII may be completely missing or partial but, in both cases, a normal clot cannot be formed. A person with haemophilia does not bleed more profusely than a normal person, but can bleed for a longer time.

Figure 1. The normal clotting process and clotting process in haemophilia – [www.wfh.org](http://www.wfh.org)  
04.01.12



## The disease

Haemophilia derives from the Greek word *haima* 'blood' and *philia* 'affection or love' – love of blood.

Haemophilia is a rare X-linked, recessively inherited, bleeding disorder, affecting males and caused by deficiency or absence of one of the clotting proteins in plasma, factor (F)VIII (haemophilia A) or FIX (haemophilia B or Christmas Disease). Carrier women may have FVIII/IX levels in the range of haemophilia, but this is rare. Depending on the residual plasma coagulation factor activity, i.e. FVIII or FIX, various levels of severity may be distinguished. Haemophilia A and B are defined as '*severe*' with the representative factor activity below  $< 1\%$ , '*moderate*' with a factor activity  $>1-5\%$ , and '*mild*' with a factor activity  $>5-40\%$  of normal [1]. Haemophilia A and B are comparable in heredity and are commonly considered to be clinically indistinguishable, although recent studies indicate a more benign course of haemophilia B [2]. Haemophilia A accounts for 80% of the haemophilia population and occurs in 11.2 per 100 000 males in all ethnic groups [3]. In both haemophilia A and B, about 35% of patients have severe, 15% moderate and 55% mild form of the disease. Figures may vary between countries, as mild haemophilia may be under-diagnosed.

At the beginning of the 1900s, patients with severe haemophilia faced a median life expectancy of about 11 years, with a corresponding figure of 58 years for the period 1969–1980 [4]. Today, patients with haemophilia in developed countries where treatment is available have almost the same life expectancy as the general population [5].

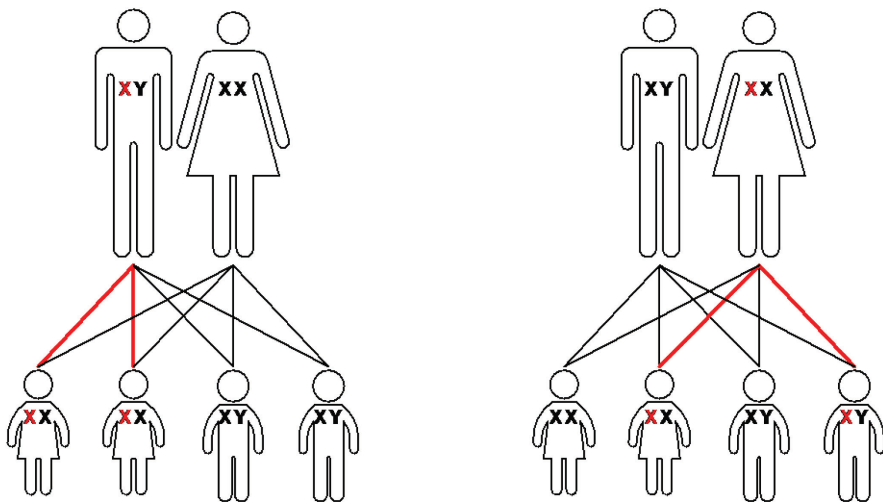
## Haemophilia: heredity and history

Jewish writings from the 2<sup>nd</sup> century AD describe a ruling from the patriarch Rabbi Judah, who exempted the third son of a woman from circumcision, since his two older brothers had died of bleeding after circumcision [6, 7]. In 1803, the American physician J.C Otto described families in which males suffered prolonged post-traumatic bleeding. He noted that, although only males showed symptoms, the disorder was passed on by unaffected females [6]. At the end of the 1940s, Pavlovsky in Argentina discovered that the coagulation defect in blood from one person with

haemophilia (PWH) could be normalized by blood from another PWH, i.e. two haemophilia persons with a deficiency in different proteins [6, 8]. In 1952 haemophilia A and haemophilia B were recognized as two distinct diseases.

A person with haemophilia has an abnormal FVIII or FIX gene on the **X** chromosome and a healthy Y chromosome. A son of a father with haemophilia (**XY**) and a healthy mother (**XX**) will inherit the Y chromosome from his father and the X chromosome from his mother. He will not have haemophilia and cannot pass on the disease, but the daughter of the same couple will be a 100 percent carrier (**XX**) of haemophilia. If a carrier of haemophilia (**XX**) and a healthy man (**XY**) have a son, their son will have a 50% risk of being affected by haemophilia and their daughter a 50% risk of being a carrier (Figure 2). Around 50% of newly diagnosed patients have no previous history of haemophilia in the family, i.e. sporadic cases [9, 10]. The type and severity of haemophilia will remain the same in the family.

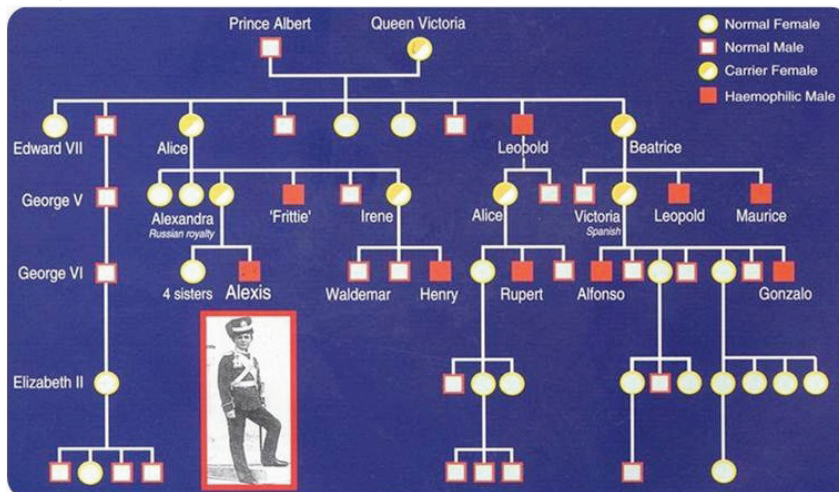
Figure 2. Heredity of haemophilia





Haemophilia has been called a royal disease because Queen Victoria of England was an obligate carrier [6, 11] of haemophilia B [12]. Two of her daughters proved to be carriers. Her youngest son had haemophilia and died of a cerebral haemorrhage after falling and hitting his head. One of Queen Victoria's granddaughters married Tsar Nicholas II of Russia, and their son Tsarevich Alexis was diagnosed with haemophilia and is probably the historically most famous haemophilia person [11] (Figure 3).

Figure 3. Queen Victoria and haemophilia heredity (Kabi/Octapharma Inga Marie Nilsson 1994)



## Bleedings in haemophilia

The occurrence of bleedings is related to the severity of haemophilia (Table 1). In severe haemophilia, bleedings can occur without any known trauma (spontaneous bleeding), they are more frequent, and are often more severe than in mild and moderate forms of the disease. The diagnosis of severe haemophilia is usually made within the first year [9, 13] of life due to abnormal bruising or bleeding, while in moderate and mild forms of the disease the diagnosis may be delayed and, especially in mild haemophilia, occur after investigation for prolonged bleeding or re-bleed after an invasive procedure.

Table 1. Degrees of severity in haemophilia and bleeding pattern (Inga Marie Nilsson 1973)

	<b>Severe</b>	<b>Moderate</b>	<b>Mild</b>
<b>Factor VIII or IX activity</b>	<1	1-5	<5-40
<b>Joint bleeds</b>	+++	+(+)	(+)
<b>Cause of bleeding episodes</b>	Spontaneous	Minor trauma	Major trauma Surgery

In the neonatal period, intracranial haemorrhage in children with haemophilia may be 40-80 times higher than that expected in the normal population and, in populations where circumcision is a common procedure, prolonged bleeding is likely to occur if the child has not yet been diagnosed [14-16]. Intracranial bleed is the most serious bleed in patients with haemophilia, with the highest risk in young children, but is also a risk in the ageing patient due to risk of falls [17, 18]. Even a minimal trauma can result in a severe intracranial haemorrhage. To decrease the risk of intracranial bleeds, small children with haemophilia in Sweden wear a protective helmet until they have learned to walk steadily. Subcutaneous bleeds like bruises on knees as children start to crawl and from falls as they learn to walk, and bleedings from the mouth – tongue bites and bleedings from torn frenulum – are common. In particular, cuts in the mouth may bleed for longer and re-bleed. Before treatment was introduced, many children died from bleedings from tongue or lip bites. Bleedings after injection or blood sampling can cause large soft-tissue bleeds.

Joint bleedings, or haemarthrosis, are common and important bleeding episodes, and these are the most characteristic symptoms of haemophilia. Approximately 60% of all bleeding episodes occur in the joints [19]. The most commonly affected joints are the knees, followed by elbows, ankles, shoulders and wrists, but bleedings can occur in any joint [19, 20]. According to a widely used definition, repeated bleeds into the same joint under a short period of time, i.e. three or more bleeds in a period of 3 months, is defined as a “target joint” [21]. Such a joint is not considered a target joint if there have been no more bleeds in the same joint during a period of 12 months [22]. Chronic haemarthrosis leads to inflammation of the synovium, synovitis, and subsequent haemophilia arthropathy and disability [23, 24]. Muscle bleed is the second most frequent bleed in haemophilia, comprising approximately 30% of all bleeding episodes. Bleeds into large muscles may resolve without any complication but can also result in dysfunction of the affected limb [19]. Bleeding episodes in mild

haemophilia are less frequent compared to severe and moderate haemophilia, and most commonly occur as a result of a serious injury [25].

## Treatment of haemophilia

Replacement of the deficient coagulation factor to normalize the bleeding defect is the treatment used in both types and all severities of haemophilia. Mild haemophilia A can sometimes be treated using desmopressin, which increases the endogenous FVIII level [26].

Before 1956, patients suffering from bleeds were given blood or plasma transfusions to resolve the bleed. In 1956 in Sweden, patients with haemophilia A had access to factor VIII concentrates (Cohn fraction I-O/AHF-Kabi) and, a few years later, concentrate for patients with haemophilia B became available [27]. Concentrates were manufactured from large plasma pools. These concentrates have been associated with transmission of hepatitis B, C and Human Immunodeficiency Virus (HIV). Several forms of virus inactivation have been used over the years, i.e. dry heat treatment, wet heat treatment, steam treatment and chemical inactivation [28]. In the late 1980s, more super-purified concentrates reached the market. Recombinant concentrates were introduced in the early 1990s. Since the early 2000s, concentrates with no albumin or other human proteins added in the manufacturing process have been used [29]. In the early stages, the volume for the administration of factor concentrate was 100 ml of sterile water mixed into 300 IU (one bottle) of lyophilized factor VIII. An adult patient needed 2-3 bottles per treatment to achieve sufficient haemostasis. Over the years, the volume has been reduced to between 2.5 and 5 ml diluents, depending on the factor concentrate that is used. For some factor concentrates, a pre-filled syringe is now available that makes the administration procedure easier for the patient and less time-consuming. The treatment is given as an intravenous injection, either as prophylaxis, or as on-demand treatment when a bleeding occurs.

Desmopressin (DDAVP) is a synthetic vasopressin analogue mainly used for its antidiuretic properties, but it can also be used in patients with mild haemophilia A [26, 30]. It increases the factor VIII level two-to-six-fold, with no risk of virus transmission. Not all patients respond to DDAVP – in particular, patients with mild haemophilia, with a lower level of FVIII, do not attain levels sufficient to secure haemostasis. Different modes of administration are recognized, i.e. intravenous, subcutaneous or intranasal administration.

Antifibrinolytic drugs (tranexamid acid, epsilon aminocaproic acid) are especially useful for mucocutaneous bleeds, such as bleedings from the mouth, nose bleeds, and in connection with surgery.

By-passing agents such as activated recombinant factor VII (rFVIIa) NovoSeven® [31] and activated prothrombin complex concentrate (aPCC), FVIII inhibitor by-passing agent Feiba®, constitute treatments for patients with high-responding inhibitors to achieve haemostatic effect. Both agents can by-pass factor VIII/IX in the coagulation cascade. Feiba® is a plasma concentrate and has been used for more than 30 years [32]. In the early 1990s, the first patient with haemophilia complicated with inhibitor was treated with NovoSeven® [33]. The half-life of infused Feiba® is approximately 7-11 hours while the half-life for NovoSeven® is shorter, 2-3 hours [34].

### **Prophylactic treatment**

Prophylactic treatment for boys with severe haemophilia A was started in Malmö, Sweden, by Inga Marie Nilsson in 1958 [35], and for severe haemophilia B in 1972 [23, 36]. The aim was to convert severe haemophilia to a milder form by regular treatment, so called prophylaxis [37]. When this prophylactic treatment started, many of the boys were quite old and had already developed haemophilic arthropathy [23]. Furthermore, the supply of factor concentrate was limited and the treatment interval could sometimes be up to 10 days. Despite these limitations, the benefit of prophylactic treatment in 60 patients with severe haemophilia was demonstrated in a study from 1992; an early start to treatment reduced the number of bleeds, thereby reducing the risk of haemophilic arthropathy, and lowering radiological and orthopaedic joint scores (Table 3, Figures 4 and 5) [23].

Table 3. Prophylactic treatment in severe haemophilia

Age	3-12	13-20	21-26	27-35
Age at start of treatment	1-2	2.5 (1-4.5)	4.9 (3-7)	7 (3-13)
Joint bleeds/y	0.2 (0-1.2)	2.6 (0.2-17)	5.6 (0.5-14)	5 (1.6-16)
Annual dose IUx10 <sup>3</sup> /kg	5.9 (4.1-9.8)	1.6-5.4 (0.8-7.2)	1.2-2.7 (0.5-6.5)	0.4-3.3 (0.2-5.9)
VIII:C/IX:C before infusion	2 (1-5)	<1-3	<1-2.5	<1-2.5
Orthopaedic score	0	1.2 (0-7)	2.9 (0-7)	6.6 (0-15)
Radiologic score	0	4.8 (0-22)	14.2 (0-22)	20.6 (0-41)

Figure 4

No prophylaxis and abnormal joints



Figure 5

Prophylaxis and normal joints



**Knee Joint of a Patient Receiving no Prophylactic Therapy**

Major joint damage visible in photo and X-ray of patient not receiving prophylaxis

**Patient information**

Age: 31	Radiological joint score: Left knee, 10
Dosage: Sporadic doses of 600 to 2000 IU FVIII as needed over a 23-year period	Orthopaedic joint score: Left knee, 10

**Knee Joint of a Patient Receiving a High Degree of Prophylactic Therapy**

Prevention of joint damage visible in photo and X-ray of patient receiving a high degree of prophylaxis

**Patient information**

Age: 19	Radiological joint score: Left knee, 0
Dosage: 1500 to 2500 IU FVIII 3 times weekly over an 18-year period	Orthopaedic joint score: Left knee, 0

Patients with severe haemophilia require life-long treatment with factor concentrate, starting at an early age in children with severe haemophilia (primary prophylaxis). This “primary prophylaxis” [38] is instituted as a long-term continuous treatment prior to any clinically evident joint bleeding and, ideally, continuous for 52 weeks a year or by definition at a minimum of 45 weeks/year. The aim of the treatment is to maintain a factor level in blood at a level that decreases the number of spontaneous bleeds to prevent the development of haemophilia arthropathy. [23, 36, 39, 40]. In 1994, this treatment was recommended in a joint meeting of the World Federation of Hemophilia (WFH) and the World Health Organization (WHO). Different standard definitions of prophylaxis have been developed both in Europe (Table 4) and North America [21, 41, 42].

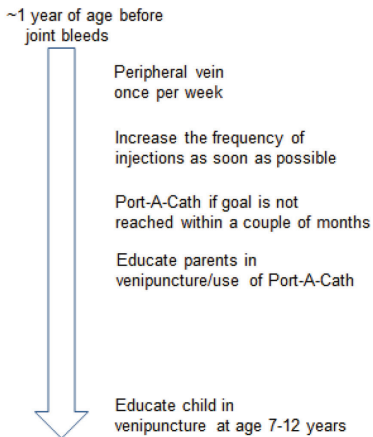
Table 4. Definition of prophylaxis according to European Paediatric Network for Haemophilia Management

<b>Definition</b>	
<b>Primary prophylaxis A</b>	Regular continuous treatment started after the first joint bleed and before the age of 2
<b>Primary prophylaxis B</b>	Regular continuous treatment started before the age of 2 without previous joint bleed
<b>Secondary prophylaxis A</b>	Regular continuous (long-term) treatment started after two or more joint bleeds or at an age older than 2
<b>Secondary prophylaxis B</b>	Intermittent regular (short-term) treatment, because of frequent bleeds

The mean half-life of factor concentrate is short: for factor VIII 11-16 hours and for factor IX about 18-20 hours [43]. The peak level (highest value) is often found 10-15 minutes after the end of infusion, but later peak values have been observed. More important than the peak value is the trough level (lowest value). To maintain a factor level of >1%, prophylactic treatment is most effective when it is administered at short and regular intervals – in haemophilia A usually every other day or 3 times/week, and in haemophilia B every third day [40]. However, daily administration of factor concentrate would be the most superior treatment for patients with severe haemophilia A. It would reduce the consumption of factor concentrate since lower

doses are needed and would also be more cost-effective [44]. In Malmö prophylactic treatment is nowadays started at the age of one before the joints become affected (Figure 6).

Figure 6. Start of prophylaxis



If the child is very active, an earlier start can be considered. However, many parents find this early start to prophylaxis stressful and demanding. Peripheral venous access is generally preferred but can be difficult to achieve in small children and, in some children, simply impossible (Figure 7).

Figure 7. Bleeding after venipuncture





In these cases, a Central Venous Access Device (CVAD) may be the only option to continue the prophylactic treatment, but the decision to insert a CVAD should be based on a combination of medical and social indications, the expected risk of complication and not only on psychological grounds [45]. Port-A-Cath (PAC), is the most commonly used system in the haemophilia population [46]. It is easy to access as the access area is larger than a peripheral vein and increases the possibility of a successful access at the first attempt. Irrespective of the kind of CVADs used, it facilitates an early start to home treatment, i.e. parents are able to administer the treatment themselves in a home setting. Both parents should be trained at the same time, i.e. treatment is not depending on only one parent. The PAC should be removed when it is not clinically required anymore, in general before school start. Before adolescence and around the age of 7-10, most children have learned how to administer the treatment themselves (Figure 8). In connection with a bleed, home treatment facilitates an early treatment, resulting in a reduced amount of factor concentrate and analgesics, and less pain. Less absence from work or school, a reduced number of days in hospital and independence are other advantages.

The most common complication associated with PAC is infection, but catheter-related thrombosis and technical problems like disconnection of the catheter from port and blockage of the catheter have been reported [47-49].

Figure 8. 10-year-old child administering self-treatment





The question of whether prophylactic treatment should continue through adulthood is intensively discussed. At the centre in Malmö, prophylactic treatment is given continuously through adulthood. Some patients lengthen the interval between treatments, but only a few switch to on-demand treatment. Studies have reported that prophylaxis can be reduced or discontinued in some patients during adolescence, but further studies are needed [50, 51]. An ethical dilemma is whether to lengthen the interval between treatments or even stop prophylactic treatment that has been going on from an early age, to eliminate the risk of bleedings and to increase Health-Related Quality of Life (HRQoL) when the severity of the patient's haemophilia is unchanged. On the other hand, as patients grow older, they are generally less physically active and therefore less likely to get traumatic bleeds, but will also have age-related co-morbidities such as balance dysfunction and a tendency to fall, thereby increasing the risk of intracranial haemorrhage [52]. Another aspect that must not be neglected is economics. Prophylactic treatment is more expensive than on-demand treatment, even though patients with prophylactic treatment have less bleeds, have fewer days of absence from school or work, and have a higher HRQoL [53].

### **On-demand treatment**

With on-demand treatment, patients do not receive regular treatment to reduce complications of haemophilia. Instead treatment is given when bleeds occur, and this may be the only option in many countries because of cost. Several studies have reported fewer joint bleeds, better joint outcome, and less orthopaedic surgery with prophylactic treatment compared to on-demand treatment [54, 55].

## **Side-effects of treatment**

### **Inhibitor**

Development of an inhibitor is a severe complication of haemophilia relating to replacement therapy, and is one of the biggest challenges in haemophilia care. Inhibitors are circulating antibodies that neutralize the infused factor that is deficient. Control of bleeding is difficult and severe trauma or need for surgery in these patients can be life-threatening. Approximately 30% of patients with severe haemophilia A develop inhibitors, compared with up to 5% of those with severe haemophilia B [56]. Most inhibitors occur in severe haemophilia but are also seen in patients with a moderate and mild form of the disease. In the latter patients, the clinical bleeding pattern is similar to that observed in patients with acquired haemophilia, where non-

articular bleeds such as subcutaneous and muscular bleeds dominate [57]. Most of the patients who develop inhibitors do within the first 50 exposure days (ED), with the greatest risk between 10 and 20 ED. Various genetic risk factors have been mentioned in the discussion on what could influence inhibitor development, i.e. family history of inhibitor and treatment-related factors etc. [58-60]. The presence of inhibitor is usually confirmed using a Bethesda Inhibitor assay. The amount of antibody is reported as number of Bethesda Units (BU), and is expressed as a Bethesda titre. Two categories are recognized, according to the highest peak activity level of inhibitor development: “low responding inhibitors” <5 BU and “high responding inhibitors” >5 BU [40, 61]. Patients with a low responding inhibitor may continue to respond to prophylactic treatment and to treatment for bleeds, but higher doses and/or shorter intervals between treatments may be needed to achieve haemostatic effect and to overcome the inhibitor. However, in patients with a high responding inhibitor, factor concentrate is not sufficient for treatment of bleeds, and by-passing agents such as NovoSeven® and Feiba® are required. The response of treatment with these products varies with type of bleeds and time between onset of bleed and treatment. The aims of the management of a patient with inhibitor are to treat acute bleeding episodes promptly, to prevent recurrent bleeds, to manage complications, and to preserve joint function [62] and, in a longer perspective, to eradicate the inhibitor by Immune Tolerance Induction (ITI) in order to continue prophylactic treatment. ITI is often a demanding treatment with daily injections, and in some cases, treatment twice a day. Since prophylactic treatment starts early, the children are very young at the time of inhibitor development. Good venous access is crucial when daily treatment is required and, for many children, a PAC must be considered. When ITI is successful, the inhibitors disappear, the response to factor concentrate returns to normal, and the patient can continue with ordinary prophylactic treatment.

### **Hepatitis and HIV**

In the past, when factor concentrates were manufactured from large donor pools with no screening of donors and no virus inactivation of factor concentrates, many patients with haemophilia were exposed to blood-borne diseases such as hepatitis and HIV. Since the start of screening of blood donors, viral inactivation of factor concentrates in the mid-1980s, and the development of recombinant factor concentrates, the risk of virus transmission has been virtually eliminated. Hepatitis A has not been a major problem in the haemophilia population although, in the early 1990s, several patients with haemophilia were infected through non-sufficient virus inactivating of factor concentrates [63]. Most patients with hepatitis B have cleared the virus spontaneously and, when vaccine became available, routine vaccination of patients against hepatitis

A and B was introduced at many HTC. Hepatitis C is a major cause of morbidity and mortality in the haemophilia population. Different genotypes can be recognized, and they may respond differently to treatment. Typing is necessary before starting the treatment, to determine the most appropriate approach for the patient. The objective of antiviral treatment is to eradicate hepatitis C virus (HCV) and stop progression of liver damage. A combination of antiviral therapy with interferon and ribavirin has been the mainstay of hepatitis C treatment [64]. Unfortunately, interferon is not always well tolerated: weight loss, fatigue and nausea are examples of side effects of the treatment and some virus genotypes respond better to interferon than others. For patients with severely affected liver, liver transplantation is the ultimate treatment; it also cures haemophilia, as both FVIII and FIX are synthesized by liver cells.

In Sweden, 96 patients with haemophilia, most of them with a severe and moderate form of the disease, were diagnosed with HIV during the 1980s, mainly from factor concentrates manufactured in the USA. In addition, four partners of haemophilia patients were infected. Approximately 50% of the patients died, either of AIDS or as a combination of HIV and hepatitis C. The introduction of Highly Active Antiretroviral Therapy (HAART), a combination of several antiretroviral medicines, has dramatically increased the survival among HIV positive patients [65].

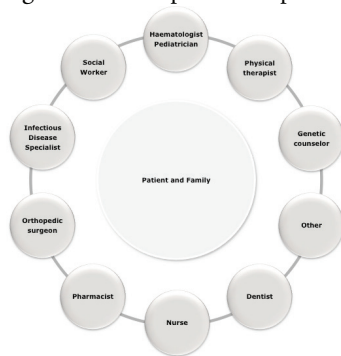
## Co-morbidities in haemophilia

In Sweden and in other countries with a long tradition of prophylaxis, patients with haemophilia have nearly reached the same life expectancy as the general population [66], and have to face the same problems relating to co-morbidities and cognitive impairments as the general population [67]. Hepatitis C and HIV will be a leading cause of mortality in the haemophilia population [68]. The prevalence of hypertension and renal diseases seems to be higher in haemophilia patients than in the general population [69]. Many patients with severe and moderate haemophilia who started prophylactic treatment late in life have developed haemophilia arthropathy, which may cause difficulty with mobility, risk of falls and chronic pain [52, 70] and increased orthopaedic interventions may be necessary for these patients, e.g. hip/knee replacement and ankle arthrodesis. Vision problems might cause difficulty for self-treatment, and the patient will become dependent on either health care providers or relatives to administer treatment.

## Haemophilia care

Sweden has three haemophilia treatment centres, in Malmö, Stockholm and Gothenburg. Malmö is an International Haemophilia Treatment and Training Centre appointed by the World Federation of Hemophilia (WFH) in 1976. All three centres have fully-developed haemophilia comprehensive care programs, defined as continuing supervision of all medical and psychosocial factors affecting the person with haemophilia and his family [71]. The haemophilia comprehensive care team in Malmö includes specialists in a variety of fields who are also specialized in haemophilia treatment (Figure 9).

Figure 9 Haemophilia comprehensive care team in Malmö



Patients with haemophilia are monitored regularly at the HTC and to evaluate the effects of treatment. Patients with severe and moderate haemophilia are called in for check-ups 1-2 times per year depending on age, while patients with a mild form of the disease are seen every 3-5 years due to fewer problems. These check-ups comprise medical examination, assessment of joint status by the physiotherapist and orthopaedic surgeon. The haemophilia nurse discusses and evaluates patients' adherence to treatment, patients' knowledge of the disease and HRQoL. The nurse provides experience and expertise, and is also a link between patient and family and the HTC.

At the time of the diagnosis, or shortly after, the family is given information about haemophilia by the paediatrician, nurse coordinator and social worker. If possible, arrangements are made to put the family in contact with another family who are experienced in haemophilia and have an older child with the same severity as the

newly diagnosed child. Meeting a family with a child with the same severity as their own child may help the family to deal with the new situation. A home visit to the family by the haemophilia nurse is made within a short period after the diagnosis when also grandparents are invited to join the meeting so that they can have the opportunity, together with the primary caregivers, to get information and ask questions.

There is no obstacle to a child attending day-care. Information about haemophilia is provided to the day-care centre staff by the nurse co-ordinator, together with the caregivers. This serves the dual purpose of avoiding over-protection, yet addressing the child's need. In some cases, supplementary resources at the centre may enable staff to be more vigilant about the child, providing reassurance for the caregiver that additional support is available for the child's need. The diagnosis of haemophilia inevitably leads to changes in the family and, to some extent, forces them to adapt to a new and permanent living condition. The caregivers should be encouraged to emphasize the normality of the child. It is important to explain to the family, at an early stage, that they will gradually take over responsibility for the treatment of the disease but with support from the HTC. In addition, increased knowledge of the disease presumably gives the patient/family a good HRQoL and also enables them to deal with problems that may arise, making them feel more secure in their daily life.

# Health-Related Quality of life

Health is defined by the World Health Organization (WHO) as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [72]. Quality of life is defined as an all-inclusive concept incorporating all factors that impact upon individuals’ lives, while HRQoL includes only those factors that are part of an individual’s health. Examples are well-being and functioning in life domains in terms of physical, social, emotional, mental and everyday-life role performance [73, 74]. Assessment of HRQoL is important for identifying needs in a patient population and factors affecting HRQoL, in order to maintain or if possible improve HRQoL in patients, and to deliver proper care among patients with a chronic disease and those who are disabled. The patient’s direct perception plays an important role. Data highlighting treatment results have contributed to a number of improvements in health care. For the health care provider, the results provide new information about the patient, and for the patient, it may make him more aware of the consequences of his disease and treatment. In general, instruments assessing HRQoL are either generic or disease-specific questionnaires, designed for adults or children.

## Generic instrument

Generic instruments evaluate overall HRQoL in the general population and allow comparison of HRQoL across diseases. Several generic instruments are available. The most frequently used instruments in haemophilia for comparing HRQoL of haemophilia patients with the general population, are the Short Form Health Survey (SF-36) and EuroQoL 5D (EQ 5D) [75, 76]. Both are instruments for adults, and are translated into several languages.

SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores, as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index [75].

EQ-5D is a standardised instrument used to measure health outcome. EQ-5D is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is applicable to a wide range of

health conditions and treatments, and provides a simple descriptive profile and a single index value for health status [76].

Visual Analogue Scales (VAS) have been used in psychological assessment since the early 1990s and are often used for measuring pain, but have also been incorporated into health-related quality of life instruments [77, 78].

Impact on Family Scale (IOF) assesses the consequences of chronic conditions and disability in childhood and adolescence for the family. The instrument covers aspects related to the chronic disease of the child, such as the general negative impact on parents, description of social relationships, concern for siblings, financial impact and problems in coping [79].

Caregiver Burden Scale (CBS) has been used among caregivers to patients with different diagnoses to assess the subjective burden of caregivers of chronically ill persons. The instrument has been used among caregivers for patients with various diagnoses such as dementia, stroke, Parkinson, fracture and multiple-disabled elderly, and also living in different care settings. CBS evaluates caregivers' health, feeling of psychological well-being, relations, social network, physical workload, and environmental aspects that might be important [80].

## Disease-specific instruments

Over the past 15-20 years, a number of disease-specific instruments have been developed for measuring health status for a specific disease or diagnosis, and with a focus on the most relevant health issues for that group [73, 81]. Several disease-specific instruments for haemophilia are available, both for children and for adults, measuring physical performance, disability, emotional impact, treatment concerns, consequences of bleeding, etc. HEP-Test-Q, CHO-KLAT, HAEMO-QoL-A), FISH [82-85].

## HRQoL in the haemophilia population

Health-related quality of life assessment has become increasingly important in haemophilia, allowing the assessment of patients' perception of the effect of haemophilia care. Haemophilia is a rare and lifelong condition. Improvement in

haemophilia care has increased life expectancy of patients to the same level as in the general population in countries where prophylactic treatment is available, and also influenced their HRQoL. In order to provide information for clinical decision-making, to evaluate health-economic outcomes and to verify the impact of haemophilia, the assessment of HRQoL is important. If new needs and demands, not only of patients but also their families, are to be met, the Haemophilia Comprehensive Care Team requires further information in order to improve caregiving of patients and family members. As demonstrated in several studies, haemophilia severity, mode of treatment and start of prophylactic treatment have an influence on patients' HRQoL [86-89]. Primary prophylaxis reduces the number of bleeds and consequently the development of haemophilic arthropathy with sometimes severe pain and disability as a result, and increases the patients' HRQoL. In a study from Italy among patients with severe haemophilia aged >65 years, the majority of patients with on-demand treatment, revealed more impairments in HRQoL. Psychological and social well-being was perceived worse by patients compared to healthy controls, and a poor orthopaedic status was negatively associated with HRQoL [90]. For patients with severe haemophilia arthropathy and pain, orthopaedic interventions may be the only solution in order to improve the patient's mobility and HRQoL. The majority of patients with moderate haemophilia generally have few complications of their disease, but in some patients with frequent bleeds prophylactic treatment should be considered in order to maintain a good HRQoL.

A major co-morbidity in the haemophilia population is hepatitis C, where decreased HRQoL has been reported [91, 92]. Some patients are reluctant to undergo treatment for hepatitis C due to side-effects, but new products have been introduced on the market with fewer side-effects, which will probably increase patients' motivation for treatment. Not only co-morbidities may have an influence on the HRQoL of haemophilia patients [93], but also age itself, lack of control and dependence; on the other hand, these problems are supposed to have a further impact on the burden of partners of haemophilia patients in terms of financial, physical and psychological aspects. In haemophilia, the presence of a medical condition and severe disability may lead to increased supervision and care, and may cause a reversal of roles where the partner becomes the caregiver of the haemophilia patient. It is natural for a partner to care for his/her loved one, and when it comes to health and social care, someone in the family is expected to assume this responsibility. The need for help and support for partners of haemophilia patients will change over time, as the chronically ill patient will need more help.



The development of an inhibitor is a severe complication of haemophilia, resulting in increased risk of bleeds with haemophilia arthropathy. Reduced mobility, the need of wheelchair or walking aid, and joint pain are seen in these patients. Results from prophylaxis with rFVIIa or aPCC in patients with inhibitor are limited, but in a study comparing 3 months of prophylactic treatment with 3 months of on-demand treatment with rFVIIa, patients on prophylaxis had fewer bleeds and fewer days away from school/work, and HRQoL tended to increase during prophylactic treatment [94], which are positive results for the HRQoL in these patients. As inhibitors often occur in children, the development of inhibitors often has a psychosocial impact on their caregivers. Emotional stress, increased risk of complications, knowing treatment of bleeds may be less effective, fear of disability and death, and difficulties with other medical procedures may lead to increased concerns in their caregivers and interfere not only with caregivers' health status, but can also place a financial burden on the family in terms of an increased number of days lost from work. The care of a child with haemophilia is difficult enough without additional challenges. It may be suspected that children with inhibitors are more likely to be overprotected and so have fewer opportunities to meet and play with other children than healthy children of the same age. In turn, this could impact the social life and HRQoL of the family [87]. Results from a recent study in caregivers of children with inhibitor in the 4-7 age group showed the greatest impairment within the 'family' subscale [95].

# Objective of thesis

To study adherence and health-related quality of life in haemophilia in order to improve understanding of the needs and demands of patients with haemophilia, partners of haemophilia patients, and caregivers of haemophilia children.

## Specific aims:

Paper I: To investigate patients' knowledge of their disease and to evaluate whether adherence to haemophilia was comparable between different severities of haemophilia

Paper II: To assess patients' HRQoL and to compare it with the norm data of the general population of Swedish males in the corresponding age groups

Paper III: To investigate HRQoL and the burden in partners of adult patients with haemophilia in order to improve understanding of the needs and demands of haemophilia partners

Paper IV: To explore the burden and HRQoL of caregivers of children with haemophilia complicated by inhibitor

Paper V: To address whether daily dosing of FVIII or FIX is feasible and whether it has an impact on HRQoL



# Material and Methods

All studies were approved by the Regional Ethical Review Board in Lund, Sweden. In addition, Paper I was approved by the Ethics Committee (EC) in Norway and Denmark, and Paper IV by the EC in UK and Canada. Following EC approval, eligible subjects were approached by letter, telephone or during regularly scheduled haemophilia clinic visits. Informed consent was obtained prior to study entry from patients, partners and caregivers in each study and country. All studies comply with the Declaration of Helsinki.

Patients at the HTC in Malmö were identified from the UMAS Haemophilia Database, a centre-based registry for patients with congenital bleeding disorders (Papers I-V). The database, which has been in operation since 1986, contains information on clinical data, HRQoL issues (SF-36, VAS - Interference of Haemophilia with Daily Life), and socio-demographic information. Patients included in the studies and belonging to other participating HTC centres were identified according to local registries (Papers I and IV).

In all Papers subjects were adults > 18 years of age but in Paper V, both adults and children were included.

## Paper 1.

Patients with mild, moderate and severe haemophilia at HTC in Malmö, Stockholm, Gothenburg, Oslo and Copenhagen responded to a questionnaire regarding knowledge of disease, appropriate treatment, patients' perception of their disease, and their contacts with other healthcare facilities. This questionnaire was mailed to the patients, or completed during a regular check-up at the clinic.

## Paper II.

The study included patients at the HTC in Malmö, with all severities of haemophilia who had completed the SF-36 and the VAS during their annual check-ups between 2004 and 2008. Data was extracted from UMAS Haemophilia Database.

## Papers III and IV.

Partners either married to, cohabitating with, or living apart from haemophilia patients and belonging to the HTC in Malmö (Paper III) and caregivers of children with haemophilia complicated with inhibitor at HTC in Malmö, Stockholm, London and Toronto (Paper IV) independently completed HRQoL questionnaires. This was done either during an extra visit at the HTC, in conjunction with a regular check-up at the clinic, or in the family's home. On all occasions, the questionnaires were completed in the presence of the same investigator. Caregivers also responded to questions about age at start of day care, baby-sitting, socializing with friends, travelling, and number of contacts with healthcare providers per year, and thoughts at time of diagnosis of haemophilia and inhibitor development. In Paper IV, two matched control groups were included: caregivers of children with haemophilia receiving prophylactic treatment, and caregivers of healthy children. Children were matched by severity of haemophilia and age ( $\pm 2$  years). Each family with a child with haemophilia was requested to invite two families with a healthy child aged  $\pm 2$  years living in the neighbourhood to participate in the study. Caregivers of children receiving prophylactic treatment completed the same questionnaires as caregivers to index patient, while caregivers of healthy children completed only the SF-36 and a questionnaire concerning their socio-demographic characteristics, age at start of day care, and practices related to baby-sitting.

## Paper V.

This study, with a 12-month + 12-month crossover design, was to address the feasibility of daily dosing if it reduces concentrate consumption and if it is effective in preventing bleeding as the standard prophylactic dosing regimen. Patients at the HTC in Malmö were randomized to two groups, one starting with either 12 months at their own previously-prescribed standard dose and the other with daily dosing. The daily dose was calculated using computer simulation. In patients where this was not feasible, a daily dose was estimated, based on the average PK of the coagulation factor prophylactic dosing regimen. HRQoL was measured using EQ 5D, MedTap QoL (Haemo-QoL-A) and VAS at study onset, on completion of the first treatment segment (after 12 months), and at the end of the study (24 months). Of the 52 questions of MedTap QoL, 9 questions were selected for the study, as they were

considered most relevant for comparing the treatment arms. In addition, compliance was regularly evaluated comparing prescribed treatment with patient's reported treatment and IU of factor concentrate delivered to the patient.

## Instruments

### **Generic instruments**

Caregiver Burden Scale is a 22-item scale assessing subjectively experienced burden by a caregiver of a chronically disabled person. The instrument comprises five factors: 'general strain', 'isolation', 'disappointment', 'emotional involvement' and 'environment'. The caregiver is asked to tick one of four options (not at all, seldom, sometimes, or often) scored 1 to 4 for each question. Mean score of 1 to 1.99 implies low burden, 2 to 2.99 medium burden and 3 to 4 high burden [80] (Papers III and IV).

EQ 5D consists of five dimensions – mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For each, the respondent can select one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems). The respondent also records his/her self-rated health on a 20 cm vertical visual analogue scale with endpoints labelled 'the best health you can imagine' and the 'worst health you can imagine' [76] (Paper V).

IOF (Impact on Family Scale). The questionnaire contains 33 Likert-scaled items to assess five aspects related to the chronic disease of the child: 'general negative impact', 'social relationships', 'concern for siblings', 'financial impact' and 'coping' [79, 96]. Subscales and the total score are transformed into a value of 0-100, with low values implying a negative impact. The original questionnaire was translated and back-translated from English into Swedish by the investigator, and validated in a pilot-group of 20 caregivers [79] (Paper IV).

The Short Form Health Survey (SF-36) is a self-administered generic HRQoL questionnaire for adults [97], and enables comparison of a specific disease such as haemophilia with norm data for the general population. A manual with Swedish norm data for different age groups and gender is available [98, 99]. The study population was grouped into men in similar age groups to those used in the Swedish SF-36 manual (15-24, 25-34, 35-44, 45-54, 55-64, 65-74, and >75), to compare the results with the general population of Swedish males according to SF-36 norms. SF-

36 consists of 36 items pertaining to eight dimensions of HRQoL (PF=physical functioning, RF=role physical functioning, BP=bodily pain, GH=general health perception, VT=vitality, SF=social functioning, RE=role emotional functioning, and MH=mental health). Each of the eight domains can be transformed into scores ranging from 0 (worst quality of life) to 100 (best quality of life); two summary scores can be calculated for physical component score (PCS) and mental component score (MCS) respectively. The SF-36 has been translated, psychometrically tested, and normed in over 30 countries, and is available in most European countries [100] (Papers II-IV).

Visual Analogue Scale (VAS) is often used for measuring pain but has also been incorporated into HRQoL instruments. VAS is a line that represents the continuum of the symptom which has to be rated. The distance of the respondent's mark from the lower end of the scale, measured in millimetres, forms the basic score, ranging from 0-100 [101]. In this study, 0 was considered as meaning that haemophilia did not interfere at all with daily life (physically and mentally), and 100 was regarded as maximum interference (Papers II-V).

### **Disease-specific instruments**

The questionnaire about knowledge of haemophilia (Paper I) consists of 47 items regarding knowledge of disease (type and severity of haemophilia, factor level, etc), appropriate treatment, patients' perception of their disease and their contacts with other healthcare facilities. The respondent ticks the appropriate box. The question that involved self-rating of health was divided into excellent/very good, good, not so good, and poor. The questionnaire was developed for adult patients by haemophilia nurse coordinators at the HTC in Malmö and Oslo. The questionnaire was validated in a pilot-group of 10 patients in each participating country.

Questionnaire for caregivers of children with and without inhibitors (Paper IV), included socio-demographic data of caregivers, questions about age at start of day care, baby-sitting, socializing with friends, travelling, number of contacts with healthcare providers per year, and thoughts at time of diagnosis and at the time of inhibitor development. The questionnaire was validated in a pilot group of 10 patients and translated into English.

MedTap QoL (Haemo-QoL-A) was developed in USA, Canada, Spain and Germany. It consists of 41 items across six subscales ('physical functioning', 'role functioning', 'worry', 'consequences of bleeds', 'emotional impact' and 'treatment concerns') and four additional questions that are not included in scoring but offer clinical insight into the patients' well-being [84] (Paper V).





# Statistics

Data in all studies was entered in Excel for Windows (Microsoft 2010, Redmond, WA, USA). Statistical analyses were performed using the SPSS program (Inc, Chicago, IL, USA) version 17.0 (Papers II-V) but in Paper I, version 15.0 was used. Clinical and socio-demographic data for patients registered at the HTC in Malmö was obtained from UMAS Haemophilia Database. A p-value <0.05 was considered statistically significant in all studies.

Clinical and socio-demographic data were presented as frequency distribution in percentage or as mean (M)  $\pm$  standard deviation (SD) and range (min-max).

The study population was grouped according to the age groups in the Swedish SF-36 manual (Paper II, III and IV), i.e. 15-24, 25-34, 35-44, 45-54, 55-64, 65-74 and >75 years. This allowed comparison with the general population. In the comparison of HRQoL between patients with haemophilia (Paper II), partners of haemophilia patients (Paper III) and caregivers of children with haemophilia (Paper IV) with the Swedish general population, the Student's test was used. Paired Student's t-test for repeated measured was used for comparison of HRQoL before and after orthopaedic surgery (Paper II).

Student's t-test, univariate ANOVA and Chi-squared test were used to compare HRQoL across caregivers (Paper IV) of different groups (children with inhibitors, children on prophylaxis, healthy children) and for comparison between patients with haemophilia and partners of haemophilia patients (Papers III).

Fisher's exact test was used for tests of association (Paper I) and Pearson Product Moment Correlation for correlation of (Paper II and III).



# Results and Discussions

The results are summarized here, and more detailed results are available in the papers in the appendix.

## Paper I.

### *Knowledge of disease and adherence in adult patients with haemophilia*

A total of 413 (67% of total) subjects were included in the study, with a mean age of 49.7 years (Table 5).

Table 5. Study population

Centre	Severe haemophilia	Moderate haemophilia	Mild haemophilia	No. patients/centre
Malmö	51	28	55	134
Stockholm	21	11	11	45
Gothenburg	10	7	28	45
Oslo	60	29	41	130
Copenhagen	33	11	15	59
<b>Total</b>	<b>177</b>	<b>86</b>	<b>150</b>	<b>413</b>

The majority of patients were aware of their type and severity of haemophilia, but a greater knowledge regarding type of haemophilia ( $p = 0.025$ ) was found in patients with severe and moderate than in patients with a mild form of the disease. A significant association was found between different degrees of severity in terms of knowledge of severity ( $p < 0.001$ ). All patients with severe haemophilia knew their severity, while patients with moderate form had least knowledge. Better knowledge of effect of factor concentrate on coagulation activity was observed among patients with severe and moderate levels compared with patients with mild levels ( $p < 0.001$ ). The majority of patients were aware of the heredity of haemophilia. Fifty-nine percent of the patients were on prophylactic treatment and 76% of these patients were aware of the importance of administering treatment in the morning. The majority of patients treated a bleed but patients with mild haemophilia were least likely to treat a bleed ( $p < 0.001$ ). A higher number of patients with severe haemophilia were afraid of inhibitor development compared to the other severities, and the number of patients who feared virus transmission by factor concentrate was about the same in the three groups. The majority of patients with mild and moderate haemophilia contacted local health care

providers instead of HTC when problems occurred that were not haemophilia-related. Patients with severe haemophilia felt worse than patients with mild haemophilia, but no statistical difference was found between patients on prophylaxis and those with no prophylaxis (Table 6). Apart from severity of haemophilia, factors with negative influence on health were haemophilia arthropathy, HIV and hepatitis.

Table 6. Self-rating on health

<i>Severity/prophylaxis/ on-demand</i>	<b>Excellent/very good</b> n (%)	<b>Good</b> n (%)	<b>Not so good</b> n (%)	<b>Poor</b> n (%)
<b>Severe prophylaxis</b> n=104	39 (36)	47 (65)	14 (13)	4 (4)
<b>Severe on-demand</b> n=73	22 (30)	31 (42)	14 (19)	5 (7)
<b>Moderate prophylaxis</b> n=18	1 (6)	11 (61)	5 (28)	1 (6)
<b>Moderate on-demand</b> n=68	25 (37)	29 (43)	10 (15)	1 (1)
<b>Mild on demand</b> n=149	69 (46)	58 (39)	11 (7)	1 (1)
<b>Total</b>	<b>156 (38)</b>	<b>176 (44)</b>	<b>54 (13)</b>	<b>12 (3)</b>

## Paper II-IV.

The following results relate to Paper II (*Quality of life in adult patients with haemophilia-a single centre experience from Sweden*), Paper III (*Health-related quality of life and burden in partners of adult patients with haemophilia*) and Paper IV (*Increased burden on caregivers of having a child with haemophilia complicated by inhibitors*).

Total numbers of subjects and mean age per group for Papers II-IV are shown in Table 7.

Table 7 Total population and their mean age per group for Papers II-IV

	Mild haemophilia	Moderate haemophilia	Severe haemophilia	Inhibitor group	Prophylactic group	Healthy group
<i>Paper II</i> Patient (n)	28	21	56			
Age in years M± SD	48.8 ± 16.5	44.8 ± 16.3	39.0 ± 14.9	na	na	na
<i>Paper III</i> Partner (n)	40	21	47			
Age in years M ± SD	51.6 ± 15.5	45.2 ± 15.3	38.7 ± 14.2	na	na	na
<i>Paper IV</i> Caregiver (n)				39	37	67
Age in years M± SD	na	na	na	37.3 ± 6.1	39.4 ± 6.7	37.8 ± 5.0

### Socio-demographic data

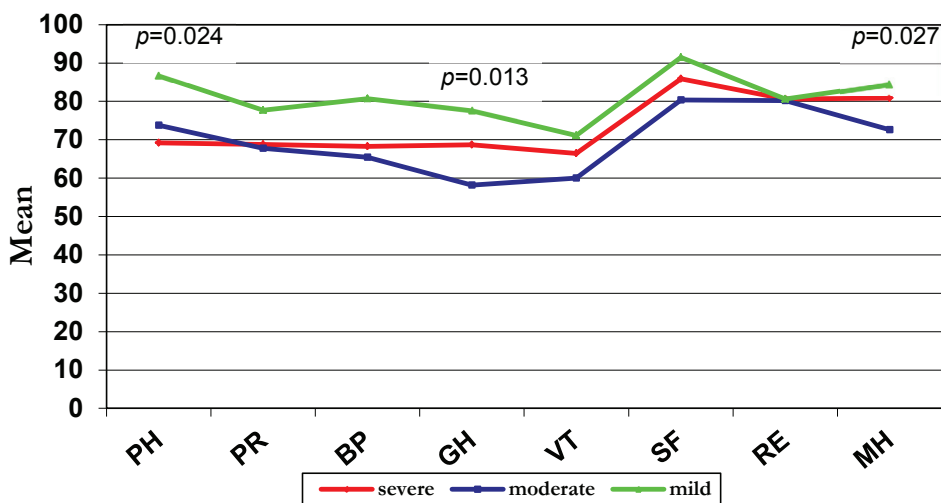
The majority of the patients were living with a partner (Paper II). The majority of the cohort was in full-time employment. Three per cent of the patients were unemployed and 8.3% had taken early retirement due to haemophilia. In Paper III, there was a significant difference in age across severity groups of haemophilia, both for patients ( $p<0.001$ ) and partners ( $p<0.001$ ). On average, couples with mild haemophilia were older than couples moderately or severely affected. A significant difference was seen between partners and haemophilia patients with highest levels of education and in terms of their working situation. No differences were seen in any of the groups compared to the general population except for employment, where a somewhat higher number of patients were unemployed. In Paper IV a significant difference was found for marital status ( $p=0.008$ ) and working situation ( $p <0.0001$ ) between caregivers in inhibitor and prophylactic groups, and caregivers of healthy children. Among caregivers of children with inhibitors, 17.9% were single compared to 5.4% of those with children on prophylaxis or 1.5% of caregivers of healthy children.

# SF-36

## Paper II

HRQoL, measured with SF-36, varied across severities of haemophilia. Severely affected patients were more impaired in their ‘physical functioning’ than mild and moderate patients. In contrast, moderate patients reported more impairment in ‘general health’ and ‘mental health’ than severe and mild patients (Figure 9).

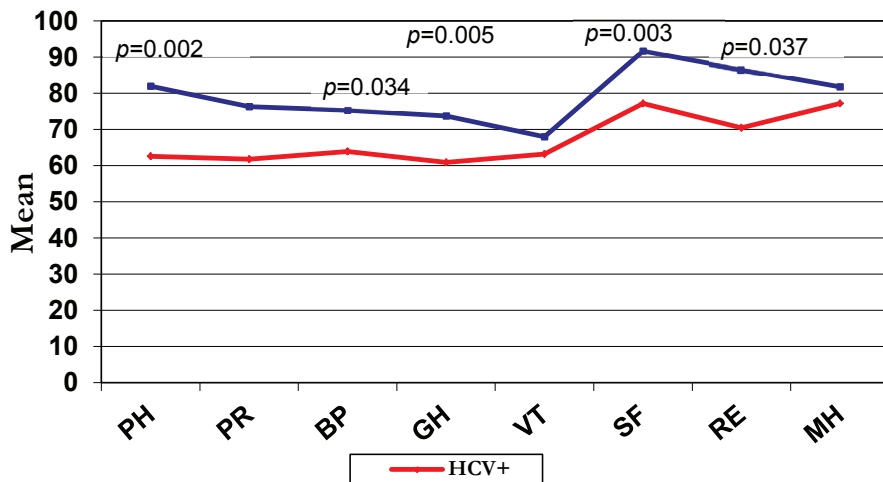
Figure 9. Comparison of HRQoL across patients with different severities



Comparison of HRQoL of patients with the Swedish general male population revealed no significant differences for the 15-24, 25-34 and 65-74 age groups. In the 35-44 age group, patients were significantly impaired in the domain ‘emotional role’ ( $p<0.025$ ), in the 45-54 age group in ‘physical functioning’ ( $p<0.001$ ) and ‘physical role’ ( $p<0.036$ ), and in the 55-64 age group in ‘physical functioning’ ( $p<0.023$ ).

In almost all the domains of SF-36, HCV-positive patients reported greater impairments than those without HCV infection (Figure 10). In contrast, no significant differences were found for HIV infection in the cohort, possibly because of the small number of patients.

Figure 10. Comparison of HRQoL between patients with and without HCV infection

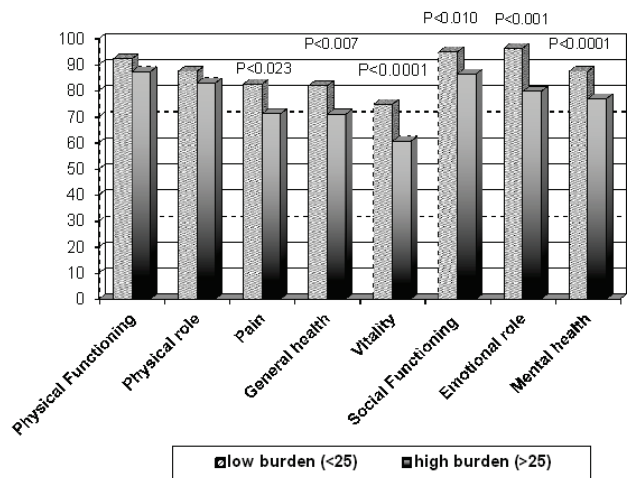


For the 9 patients who underwent orthopaedic surgery, HRQoL increased in most of the domains of SF-36, but decreased in the domain 'physical role', but these differences were not significant. For the 5 patients who underwent prosthesis surgery, 'physical functioning' increased significantly after surgery ( $p \leq 0.034$ ).

Patients and their partners (Paper III) reported, in general, quite similar HRQoL in SF-36; in contrast, partners reported significantly better HRQoL in the domains of 'physical functioning' ( $p < 0.001$ ) and 'general health' ( $p < 0.031$ ). No significant difference was found compared to the general Swedish population for the 45-54 age group. Partners of patients across severities reported lower HRQoL only in the domain 'emotional role' ( $p < 0.041$ ), with the highest impairment observed for partners of patients with moderate haemophilia. When partners were divided into two groups – low ( $< 25$ ) and high ( $> 25$ ) burden according to the median split of the summarized total score – partners who reported high burden had lower HRQoL in almost all domains of the SF-36 (Figure 11).

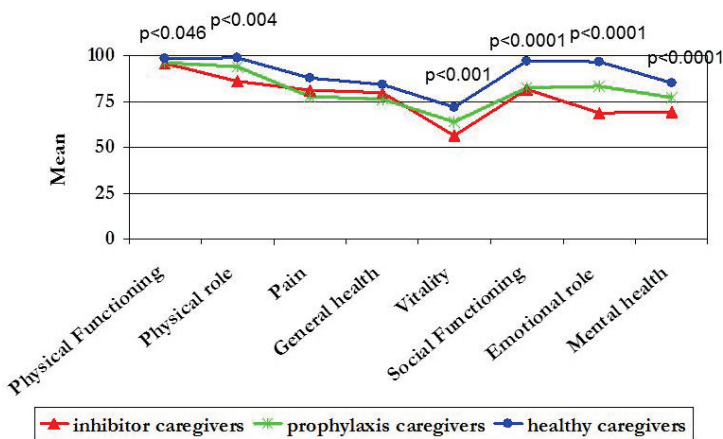


Figure 11. HRQoL (SF-36) in partners with low vs. high Caregiver Burden (summarized total score)



The comparison of SF-36 scores in Paper IV, between caregivers of children with inhibitors and children on prophylaxis, revealed no statistically significant differences. In contrast, when these two groups were compared with caregivers of healthy children, significant differences were found, indicating a lower HRQoL for all domains except ‘pain’ and ‘general health’ (Figure 12).

Figure 12. Comparison of SF-36 between caregivers in study groups



## VAS interference of haemophilia in daily life

Table 8

Patients with mild haemophilia reported less interference in their daily life due to haemophilia compared to the moderate and severe patients (Paper II). In Paper III, a significant difference between partners and patients was shown; partners reported less interference with their daily life compared to patients. Partners who reported a high degree of interference in daily life based on the median split ( $>6$ ) had lower HRQoL of the SF-36 in the domains of 'vitality' ( $p<0.013$ ), 'emotional role' ( $p<0.022$ ) and 'mental health' ( $p<0.003$ ) compared to those who reported low interference ( $<6$ ). A higher impact of haemophilia on life was seen in caregivers of children with inhibitors compared to caregivers of children on prophylaxis (Paper IV).

Table 8. VAS Interference of haemophilia in daily life per study group

	VAS Interference of haemophilia in daily life						
	Mild haemophilia M±SD	Moderate haemophilia M±SD	Severe haemophilia M±SD	<i>p</i> -value	Inhibitor group M±SD	Prophylaxis group M±SD	<i>p</i> -value
<i>Paper II</i> Patient Mean age	23.43 ±27.0 48.8	34.33 ± 23.5 44.8	32.48±26.7 39.0	n.s	na	na	na
<i>Paper III</i> Partner Mean age	8.95 ±13.1 51.6	17.86±27.2 45.2	12.72±16.1 38.7	n.s	na	na	na
Patient	11.10±18.5	37.10±34.1	27.15±28.7	0.001			
<i>Paper IV</i> Caregiver Mean age	na	na	na	na	52.51 ±22.8 37.3	29.14 ± 25.7 39.4	<0.0001

## Caregiver Burden

Table 9

Partners generally reported a low burden of haemophilia (Paper III). No significant differences were found across haemophilia severity groups. The total highest burden was reported in partners in the moderate group. Partners' burden was highly correlated with Physical Component Score (PCS) ( $p<0.0001$ ), and the orthopaedic status (HJHS) ( $p<0.0001$ ) of haemophilia patients. No correlation was found

between partners' burden and patients' MCS (SF-36). Caregivers of children with inhibitors reported a significantly higher total burden impact of haemophilia (mean 2.24) compared to the prophylactic group (mean 1.70), and four out of five domains of the scale were significantly higher in this group (Paper IV).

Table 9. Caregiver Burden in partners and caregivers

	Partners (Paper III)			Caregivers (Paper IV)		
	<i>Mild haemophilia</i> (n=40)	<i>Moderate haemophilia</i> (n=21)	<i>Severe haemophilia</i> (n=47)	<i>Inhibitor group</i> (n=39)	<i>Prophylaxis group</i> (n=37)	<i>p-value</i>
Mean age (range)	51.60 (20-79)	45.24 (22-73)	38.68 (20-73)	37.3 (25-50)	39.4 (26-52)	
General strain	1.28 (0.4)	1.39 (0.6)	1.36 (0.4)	2.50 (0.5)	1.88 (0.6)	0.0001
Isolation	1.13 (0.4)	1.40 (0.7)	1.21 (0.4)	2.12 (0.6)	1.56 (0.6)	0.0001
Disappointment	1.20 (0.3)	1.33 (0.5)	1.21 (0.4)	2.36 (0.6)	1.75 (0.6)	0.0001
Emotional Involvement	1.31 (0.4)	1.40 (0.5)	1.31 (0.5)	1.56 (0.6)	1.43 (0.5)	0.313
Environment	1.23 (0.3)	1.37 (0.5)	1.34 (0.5)	2.15 (0.7)	1.58 (0.6)	0.0001
<b>Total</b>	<b>1.24 (0.3)</b>	<b>1.37 (0.5)</b>	<b>1.29 (0.4)</b>	<b>2.24 (0.5)</b>	<b>1.70 (0.5)</b>	<b>0.0001</b>

### Impact on Family Scale (IOF)

Caregivers of children with inhibitors reported a significantly negative impact of the disease of their child on their lives, compared to caregivers of children with prophylaxis (Table 10).

Table 10. The impact of haemophilia on caregivers of children with haemophilia (IOF).

Scale	Caregivers of children with inhibitor (n=39) M ± SD	Caregivers of Children on prophylaxis (n=37) M ± SD	<i>p-value</i>
Financial	37.8 ± 14.8	51.4 ± 19.1	<0.001
Social	45.7 ± 11.1	57.6 ± 10.7	<0.0001
General negative	36.9 ± 13.0	48.2 ± 15.2	<0.001
Coping	56.2 ± 11.7	59.7 ± 10.5	0.177
Siblings	50.3 ± 12.7	58.8 ± 13.2	<0.026
<b>Total</b>	<b>49.3 ± 9.9</b>	<b>37.5 ± 11.6</b>	<b>&lt;0.0001</b>

Comparing mothers and fathers within couples, there were no differences between haemophilia groups for Caregiver Burden Scale, SF-36, VAS and IOF. The only significant difference ( $p < 0.033$ ) within couples was found in the prophylaxis group in the domain 'pain' of the SF-36, where mothers reported lower mean scores for 'impairments' compared to fathers.

### **Result from questionnaire**

In the group of children with inhibitors, more children did not attend day-care (due to haemophilia) compared to children with prophylactic treatment and healthy children. A significant difference was found for the babysitter of the child; none of the children with inhibitors were looked after by friends (as opposed to relatives) compared to 10% of children on prophylaxis and 22.9% of healthy children ( $p < 0.005$ ). Caregivers of children with inhibitors reported a higher number of check-ups per year compared to caregivers of children on prophylaxis ( $p < 0.002$ ).

## **Paper V.**

### *Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy*

Thirteen patients were included in the study, but 2 patients were excluded due to poor compliance during the study, and one patient decided to discontinue participation because of difficulties with venous access. Nine patients had severe haemophilia and one patient a moderate form of the disease. Eight patients were on every-other-day treatment and two patients 2 times / week. Standard dose varied from 20-50IU/kg/patient compared to 3.5-16IU/kg on daily dose. Compliance was observed in all patients except one, who only took 63% of the prescribed daily dose. Joint scores and the number of bleeds/treatment arms are shown in Table 14. For two patients, the dose had to be increased (Patients 8 and 10). There was considerable variation in costs between patients for both treatment arms. The mean annual cost per patient for standard prophylaxis was SEK 1.9 million and for daily prophylaxis SEK 1.3 million

Table 14. Joint scores and spontaneous and traumatic bleeds during standard and daily dosing

Patient	Joint score at baseline	Spontaneous bleeds (Standard/daily dosing)	Traumatic bleeds Standard/daily dosing
1	36	4 / 6	1 / 11
2	37	1 / 5	1 / 9
3	1	0 / 0	0 / 1
4	0	0 / 3	0 / 0
5	2	2 / 1	1 / 1
6	1	0 / 1	0 / 2
7	38	3 / 5	3 / 2
8	0	0 / 0	0 / 0
9	3	1 / 1	1 / 0
10	6	0 / 11	1 / 2

### EQ 5D

Patients reported decreased HRQoL during daily prophylaxis compared to standard dose. The greatest difference between the two treatment arms was observed in the pain/discomfort health dimension, where three of nine reported having some problems on standard prophylaxis, compared to five of nine on daily prophylaxis.

### MedTap

The largest difference between the two treatment arms was seen in difficulties performing physical activities. Patients on daily prophylaxis felt they had more problems than on standard prophylaxis. They reported a higher negative influence on daily activities and found the treatment more stressful.

### VAS Interference of haemophilia in daily life

Patients indicated that daily prophylaxis interfered slightly more with daily life compared to standard prophylaxis, daily prophylaxis was given a mean rank of 18 (range 3-51) and standard prophylaxis a mean rank of 13 (range 0-32).

## Discussion

Patients with mild haemophilia reported best HRQoL, which was also the case for their partners, and best health, but less knowledge of haemophilia compared to other levels of severity. They were also least likely to treat a bleed. For this cohort with mild haemophilia, the impact of haemophilia is quite low, i.e. in general they have few bleeds, no haemophilia arthropathy, retirement due to haemophilia is uncommon, and the majority of patients lead a normal life. Unfortunately, a substantial number of patients with mild haemophilia never come to their check-ups at the HTC, as this form of haemophilia has little impact on daily life. Poor knowledge of the disease in this cohort could also be explained by this less frequent contact with the HTC. In general, partners reported good HRQoL and low impact of the disease. However, partners of patients with moderate haemophilia seem to experience the highest negative impact. Although partners of patients with moderate haemophilia reported the highest total burden ( $M=1.37$ ), the impact of the disease is quite low. In addition to their older age, we noted a lower participation rate for couples in the moderate group (75%) compared to that of the severe group (92%). Also to be considered is the fact that some patients with moderate haemophilia did not start prophylaxis until later in life and had already developed haemophilic arthropathy. Most of the moderate haemophilia patients in this study had high HJHS, irrespective of having prophylaxis or treatment on demand. An advanced joint disease may be a possible reason for a feeling of greater interference and lower HRQoL in SF-36, which is also likely to have an influence on the partner. A lack of prophylactic treatment in patients in the moderate group may increase the anxiety for bleeds, with less physical activity as a result, which also could have an impact on both patients and partners in this group.

The earlier the patient started prophylaxis, the higher the HRQoL, which is reflected in SF-36 for the domain 'physical function' in the younger age groups, where no differences could be found compared to the general population. It could be expected that partners of patients with severe haemophilia who reported lower HRQoL in the SF-36 compared to the general population would report higher interference from haemophilia in daily life on the VAS scale, but this was not the case. Prophylactic treatment seems to have a positive impact on partners, i.e. reduced risk of bleeds and greater opportunity for physical activities. Many patients with severe and moderate form had hepatitis C and were HIV-positive, or had age-related diseases such as

diabetes, cancer and hypertension, which also have an impact on patients' health in addition to the haemophilia itself.

Having a child with a chronic disease often increases the burden in the family, with more hospital visits, treatment administration, and increased worries about the sick child. Caregivers in the inhibitor group reported higher impact of haemophilia compared to the prophylaxis group in all instruments except for SF-36, where no significant differences were found between the two groups. In contrast, significant differences were found when these two groups were compared with caregivers of healthy children in SF-36. Many caregivers try to adapt their lifestyles, and the attention of the caregivers is focused on the sick child, which might have an impact on the entire family and their HRQoL. No differences in HRQoL were observed between mothers and fathers within a couple, which might be a little surprising. In many families, the job of caring for children falls primarily on the mother. The mother of a child with haemophilia may feel guilty for bringing a child with a chronic disease into the world and, in order to compensate for this, assumes a disproportionate responsibility for the child's condition. In the long term, this may become a burden for her and lower her HRQoL. Children with inhibitors started day-care later than children without inhibitors and healthy children. Leaving a chronically ill child in the care of someone else, and not having control over what is happening, can be stressful, and sometimes extra arrangements are needed before the caregivers can feel secure.

In the study where daily prophylaxis was compared to standard prophylaxis HRQoL slightly decreased during daily prophylaxis. Although venous access was not a major problem in these patients, daily prophylaxis was found to be more stressful and had an impact on HRQoL, presumably in terms of time taken for mixing and administration of factor concentrate, and perhaps also by being constantly reminded of their disease. A cost reduction of 30% was seen for daily prophylaxis. Daily dosing has the potential to greatly reduce the cost of haemophilia treatment if a large proportion of persons with haemophilia are switched to a more frequent dosing regimen.

# Limitations

Haemophilia is a rare disease with a small population. Collecting data from the entire haemophilia population is difficult, which also reflects the sample sizes in this thesis. The relatively small number of participants with mild haemophilia indicates that this severity of the disease does not have a big impact on daily life.

In Papers I-III, participants included few patients with mild haemophilia; they either had no interest in participating or, as in Paper II, few patients had come for their check-ups during the period 2004-2008. In addition, in Paper III, patients with moderate haemophilia with no prophylactic treatment and less contact with the HTC were not willing to participate, which may introduce a bias.

In Paper I, it was not possible to collect information on patients' hepatitis C status in all HTC, as it was considered too time consuming. Furthermore, many patients with mild haemophilia have not been tested due to little contact with their HTC.

To increase the number of caregivers of children with inhibitors (Paper IV), the HTC in Toronto and London were approached. These centres were chosen because the structure of society and prophylactic regimen are similar to Sweden. However, caregivers of healthy controls could not be recruited from Toronto for regulatory reasons and, in London, parents of children with haemophilia were reluctant to recruit their neighbours with healthy children.

In Paper V, 53 patients showed interest in the study, but only 13 agreed to participate. The refusal of many patients to participate, however, may in part be attributable to the quite cumbersome protocol: the frequency of venipuncture, i.e. technical aspects, but also the time needed to prepare and administer the treatment. The convenience rating is consistent with this. Another possible reason for refusal was that daily treatment was a constant reminder of the disease and most patients are satisfied with their standard treatment. The small sample size limited the power of the statistical analysis and the general applicability of our conclusions and further studies are needed.





# Conclusions

Patients with mild haemophilia had less knowledge of their disease, but higher HRQoL, than those with moderate and severe haemophilia.

Comparison of HRQoL of patients with the Swedish general male population revealed no significant differences in the younger age groups, but in the older age groups, > 45 years, significant differences were found in 'physical functioning' and 'physical role'.

For patients undergoing orthopaedic surgery, HRQoL increased after surgery

Hepatitis C has a major impact on HRQoL of patients with haemophilia.

Partners of patients with severe haemophilia on prophylaxis reported, in general, good HRQoL and low burden of the disease. Partners of patients with moderate haemophilia reported decreased HRQoL and higher burden compared to those with mild and severe haemophilia.

Caregivers of children with haemophilia complicated by inhibitors reported an increased burden and higher impact of the disease on the family compared to caregivers of children with haemophilia who are on prophylaxis, and caregivers of healthy children.

Daily prophylaxis decreased HRQoL slightly among patients. Venous access and compliance was not a major problem. Daily dosing can be feasible in some patients but further studies are needed.



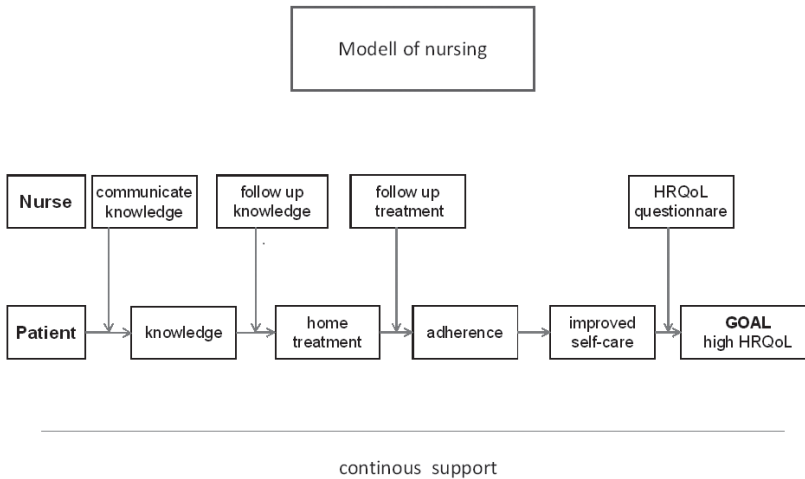
## Future perspective

If knowledge in the haemophilia population is to be increased, and HRQoL improved or maintained, these parameters must be evaluated regularly at the HTC more than is currently the case. Greater information about the disease is needed – for patients, various health care providers and also the patient's family. As patients with haemophilia become older, partners are likely to become more involved in their care, and responsibility for treatment may be transferred from the patient himself to his partner. Co-morbidities will add to haemophilic disease, and affect the well-being of partners of haemophilia patients. The HTC should not only focus on the patient with haemophilia, and must take a more holistic view of the patient and his family. Special attention should be paid to partners of patients with moderate haemophilia, as this group seems to under an extra burden because of the partners' disease.

Caregivers felt the time between diagnosis and first visit at the HTC was unnecessarily long, which meant increasing concern for the caregivers. In addition, on the occasions where the parents had received information at their local hospital, caregivers did not find this information sufficient. This shows that, as soon as possible after diagnosis, the family should visit the HTC and receive adequate information on haemophilia from specialists. Caregivers of children with haemophilia had decreased HRQoL compared to the general population, especially caregivers of children with inhibitors reported low HRQoL and an increased burden. These results carry an important message for members of the haemophilia team to emphasize the importance of being aware of potential problems and being alert to the need for support beyond what is standard.

## Important points to consider

- Regular follow-up of patient/partner/caregiver knowledge and awareness of haemophilia and evaluation of their HRQoL.



- Special attention should be paid to patients with moderate haemophilia and their partners as this group seems to have a decreased HRQoL and extra burden by the partners' disease.
- Identification of early symptoms of age-related diseases impacting HRQoL.
- Reduce the time interval from diagnosis to information about haemophilia to patient/caregivers.

# Populärvetenskaplig sammanfattning

Hemofili, blödarsjuka, beskrevs som en ärftlig sjukdom redan i Talmud 400 e. Kr. Det är en recessivt könsbunden ärftlig sjukdom, som i regel endast uppträder hos män och kan överförs av kvinnliga bärare. Sjukdomsanlaget är bundet till könskromosomen X. Samtliga döttrar till en man med hemofili blir bärare av sjukdomen, medan sönerna inte får hemofili och inte bär på anlaget. I cirka hälften av alla nydiagnostiserade patienter, går det inte att identifiera någon i släkten med hemofili. Hemofili indelas i två typer: hemofili A (avsaknad av koagulationsfaktor VIII) och hemofili B (avsaknad av koagulationsfaktor IX). Sjukdomen indelas i svårighetsgraderna mild, moderat eller svår form, beroende på nivån av koagulationsfaktor i blodet. Inom en och samma familj har de sjuka alltid samma typ och svårighetsgrad av sjukdomen. Utan behandling får patienter med svår och moderat hemofili lätt blödningar i leder och muskler utan anledning. Upprepade blödningar i samma led kan ge svåra, smärtsamma ledförändringar ledande till invaliditet. Patienter med mild hemofili får som regel endast blödningar efter slag.

Behandlingen av hemofili beror på patientens svårighetsgrad av sjukdomen. Målet är att förebygga och förhindra blödningar, rörelseinskränkningar och andra komplikationer av sjukdomen. Detta gör man genom att tillföra den saknade koagulationsfaktorn som en intravenös injektion, det vill säga i ett blodkärl, flera gånger i veckan. Faktorkoncentrat framställdes i Sverige redan under 1950-talet för behandling av patienter med hemofili A och i slutet av 1960-talet för patienter med hemofili B. De första faktorkoncentraten framställdes ur blodplasma, för att under åren utvecklas, och framställs idag med hjälp av DNA- teknik. Faktorkoncentrat framställt ur blodplasma, har medfört att många patienter drabbats av hepatit C och HIV.

Sverige var det land som först initierade profylaxbehandling (förebyggande behandling), och som fortfarande kan betraktas som ett föregångsland när det gäller modern hemofilivård, där patienten tidigt får lära sig att hantera sin sjukdom. Avsikten med profylaxbehandling är att koagulationsfaktornivån ej ska sjunka under 1-2%, vilket innebär att patienten istället för svår hemofili har en mildare form av sjukdomen. Profylaxbehandling har inte bara minskat antalet spontana blödningar och därmed också ledförändringar, utan också minskat riskerna för allvarliga blödningar och dessutom minskat antalet vård dagar samt minskat frånvaron från skola respektive arbete. Tack vare profylaxbehandling uppnår idag patienter med

hemofili i stort normalbefolkningens medellivslängd jämfört med i början av 1900-talet då medellivslängden hos en patient med hemofili endast var 16 år. Annan komplikation till behandling för hemofili, förutom hepatit C och HIV, är bildandet av antikroppar, vilket innebär minskad eller ingen effekt alls av behandling med faktorkoncentrat. Vid låg nivå av antikroppar kan som regel profylaxbehandlingen fortsätta medan vid högre nivå måste profylaxbehandlingen avbrytas och annan behandling ges vid blödning. Patienter med hemofili lever idag ett ganska normalt liv tack vare profylaxbehandling vilken också ger patienten en ökad livskvalitet. Många patienter med hemofili uppnår sådan ålder att de förmodligen kommer att drabbas av åldersrelaterade sjukdomar, vilket kommer att påverka inte bara patientens livskvalitet utan även dennes partners livskvalitet.

Syftet med Paper I var att undersöka patients kunskap om sin sjukdom (hemofili) samt att skatta sin hälsa. Patienter med mild hemofili var den patientgrupp som hade sämst kunskap om sin sjukdom, oftast avstod från att behandla en blödning på grund av osäkerhet om det var en blödning och som skattade sin hälsa högst. Även hos patienter med moderat och svår hemofili fanns en viss brist på kunskap om sin sjukdom. Förutom hemofili hade inskränkningar i det dagliga livet till följd av ledproblem, hepatit C och HIV en negativ inverkan på hälsan.

I Paper II, III och IV var syftet att undersöka livskvalitet hos patient med hemofili, partners till patienter med hemofili och föräldrar till barn med antikroppar. I Paper II deltog patienter med olika svårighetsgrader av hemofili som besvarat livskvalitet-formulär och där på en skala skattat i viken omfattning hemofili påverkade deras vardag, både psykiskt och fysisk. I de yngre åldergrupperna var livskvaliteten i stort jämförbar med Sveriges motsvarande normalbefolkning. Störst problem i sin fysiska funktion hade patienter med svår hemofili. Patienter med hepatit C uppvisade betydligt sämre livskvalitet än de patienter som inte hade hepatit C. De patienter som rapporterade störst påverkan av sin hemofili i vardagen var patienter med moderat form av sjukdomen.

Patient med partner, som antingen var gifta, sambo eller särbo inkluderades i Paper III. Partner till patient rapporterade något högre livskvalitet än patient gällande fysisk funktion och allmän hälsa, men jämfört med normalbefolkningen i Sverige för åldersgruppen 45-54 år (åldersgruppen för patient och partners), hade hemofili-patienter och deras partner lika god livskvalitet som normalbefolkningen. Partners rapporterade generellt liten påverkan av sin egna livskvalitet på grund av sin partners hemofili. Vid jämförelse av livskvalitet mellan olika svårighetsgrader av hemofili

visade partners till patienter med moderat form av sjukdomen högre påverkan i det dagliga livet och större börda på grund av hemofili än partners i de andra svårighetsgraderna.

I Paper IV deltog föräldrar till barn med antikroppar, och som kontrollgrupper till dessa, föräldrar till barn utan antikroppar och med profylaxbehandling, samt föräldrar till friska barn. Totalt deltog 143 föräldrar i undersökningen, 39 föräldrar till barn med hemofili och antikroppar (antikropsgrupp), 37 till barn med hemofili utan antikroppar (profylaxgrupp) och 67 föräldrar till friska barn. Medelåldern för de tre grupperna var 38 år och skiljde sig inte nämnvärt åt mellan grupperna. De flesta barn i antikropsgruppen hade daglig behandling för att få bort antikroppar och i profylaxgruppen varierade behandlingen mellan varannan dag och 1-2 gånger per vecka. Oro, chock respektive lättnad över att barnet inte hade leukemi och över att en behandling finns tillgänglig var några av tankarna hos föräldrarna vid diagnostillfället. Om föräldrarna fick information om barnets hemofilidiagnos av läkare vid hemortssjukhuset var tiden mellan diagnostillfället och första besöket på hemofilimottagningen av stor betydelse – ju kortare tid desto bättre. Föräldrarna upplevde en trygghet av att få träffa sjukvårdspersonal väl förtrogen med hemofili och dess behandling. Hos föräldrar till barn som utvecklat antikroppar ökade oron. Sämre effekt av medicinering och svårare att behandla blödningar samt oro för barnets framtid rapporterades också från dessa föräldrar. Föräldrar till barn med hemofili, särskilt föräldrar till barn med antikroppar hade sämre livskvalitet än föräldrar till friska barn. En högre påverkan i det dagliga livet på grund av barnets sjukdom hos föräldrar sågs i antikropsgruppen, dels en allmän påverkan men också speciellt avseende ekonomi, socialt umgänge och syskonrelationer jämfört med profylaxgruppen. Föräldrar till barn med antikroppar rapporterade också en större börda än föräldrar i profylaxgruppen.

Syftet med Paper V var att utvärdera möjligheten av daglig behandling hos patienter med profylax. Totalt deltog 10 patienter i studien. Studien innebar 12 månader med gängse profylax och 12 månader med daglig profylax. Trots att patienten under 12 månader behövde injicera sig själv dagligen verkade detta inte vara något större problem. Ändå rapporterade patienterna i samband med daglig profylax något sämre livskvalitet och högre påverkan av hemofili i det dagliga livet jämfört med gängse profylax. Värt att notera är att en kostnadsreduktion för behandlingen med cirka 30 % noterades under daglig profylax. För att undersöka om daglig behandling är möjligt för patienter med hemofili utan alltför stor påverkan i det dagliga livet behövs ytterligare studier.



För att bibehålla en god livskvalitet hos patienter med hemofili och deras partner samt hos föräldrar till barn med hemofili är det viktigt att regelbundet utvärdera och följa upp deras livskvalitet och kunskapen om hemofili vid kontrollerna på hemofilimottagningen.

# Acknowledgements

I would like to express my deep gratitude to patients, partners and caregivers of children for participating in the studies and to all those who, in one way or another, have contributed to this thesis. Special thanks go to:

Erik Berntorp, my principal supervisor, for giving me the chance to write this thesis and for believing in me – for your enthusiastic encouragement, useful critiques and for giving your time so generously. Your characteristic sense of humour and unexpected twists in your contributions in various situations has added an extra dimension to many discussions. It is a pleasure to work with you.

Rolf Ljung, my co-supervisor, for your advice, professional guidance and valuable support.

Sylvia von Mackensen, the ‘Queen of HRQoL’. With your incisive comments, you have shared your experience with me, and analysed my data. Thank you for this generous help.

Camilla Månsson, for efficient help on any matter. This has been invaluable.

Eva Lindén, for validating entered data.

Erica Myrefelt, Jan and Lena Henrichsén, for criticism, encouragement and long-term friendship.

And last but not least:

To Richard and Johan, for endless patience, endurance and love.

This study was supported with funds from Bayer Health Care, Sweden, Baxter Nordic, Sweden, the Arosenius Fund and the Regional Fund (ALF).



# References

1. White GC, 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost.* 2001 Mar;85(3):560.
2. Mannucci PM. Is haemophilia B less severe than haemophilia A? *Haemophilia.* 2013;Mar 21. doi: 10.1111/hae.12133.:1-4.
3. Stonebraker JS, Bolton-Maggs PH, Michael Soucie J, Walker I, M. B. A study of variations in the reported haemophilia B prevalence around the world. *Haemophilia.* 2012;May;18(3):e91-4. doi: 10.1111/j.1365-2516.2011.02588.x. Epub 2011 Jun 7.
4. Larsson SA. Hemophilia in Sweden. Studies on demography of hemophilia and surgery in hemophilia and von Willebrand's disease. *Acta Med Scand Suppl.* 1984;684:1-72.
5. Lovdahl S, Henriksson KM, Baghaei F, Holmstrom M, Nilsson JA, Berntorp E, et al. Incidence, mortality rates and causes of deaths in haemophilia patients in Sweden. *Haemophilia.* 2013 Feb 4.
6. Ingram GI. The history of haemophilia. *J Clin Pathol.* 1976 Jun;29(6):469-79.
7. F R. Hemophilia in the Talmud and rabbinic writings. *Ann Intern Med.* 1969;Apr;70(4):833-7.
8. Pavlovsky A. Contribution to the pathogenesis of hemophilia. *Blood.* 1947;2 no 2:185-91.
9. Ljung R, Petrini P, Nilsson IM. Diagnostic symptoms of severe and moderate haemophilia A and B. A survey of 140 cases. *Acta Paediatr Scand.* 1990 Feb;79(2):196-200.
10. Baehner RL SH. Hemophilia in the first year of life. *The New England of Medicine.* 1966;275:524-8.
11. RF S. The history of haemophilia in the royal families of Europe. *Br J Haematol.* 1999;Apr;105(1):25-32.
12. Rogaev EI, Grigorenko AP, Faskhutdinova G, Kittler ELW, Moliaka YK. Genotype analysis identifies the cause of the Royal Disease. *Science.* 2009;326.
13. Kulkarni R, Soucie JM, Lusher J, Presley R, Shapiro A, Gill J, et al. Sites of initial bleeding episodes, mode of delivery and age of diagnosis in babies with haemophilia diagnosed before the age of 2 years: a report from The Centers for Disease Control and Prevention's (CDC) Universal Data Collection (UDC) project. *Haemophilia.* 2009 Nov;15(6):1281-90.
14. Ljung RC. Intracranial haemorrhage in haemophilia A and B. *Br J Haematol.* 2008 Feb;140(4):378-84.
15. Mansouritorghabeh H, Banihashem A, Modaresi A, Manavifar L. Circumcision in males with bleeding disorders. *Mediterr J Hematol Infect Dis.* 2013;5(1):e2013004.
16. Kulkarni R, Soucie JM. Pediatric hemophilia: a review. *Semin Thromb Hemost.* 2011 Oct;37(7):737-44.

17. Zanon E, Iorio A, Rocino A, Artoni A, Santoro R, Tagliaferri A, et al. Intracranial haemorrhage in the Italian population of haemophilia patients with and without inhibitors. *Haemophilia*. 2012;Jan;18(1):39-45.
18. Nuss R, Soucie JM, Evatt B. Changes in the occurrence of and risk factors for hemophilia-associated intracranial hemorrhage. *Am J Hematol*. 2001 Sep;68(1):37-42.
19. Arun B, Kessler C, RW C. Basic Principles and Clinical Practice. Hemostasis and Thrombosis. 2000;4th ed(Philadelphia, Pa: Lippincott, William & Wilkins):815-24.
20. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSS J*. 2010 Feb;6(1):37-42.
21. Ota S, McLimont M, Carcao MD, Blanchette VS, Graham N, Paradis E, et al. Definitions for haemophilia prophylaxis and its outcomes: the Canadian consensus study. *Haemophilia*. 2007 Jan;13(1):12-20.
22. Berntorp E, Astermark J, Bjorkman S, Blanchette VS, Fischer K, Giangrande PL, et al. Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia*. 2003 May;9 Suppl 1:1-4.
23. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med*. 1992 Jul;232(1):25-32.
24. Jansen NW, Roosendaal G, Lafeber FP. Understanding haemophilic arthropathy: an exploration of current open issues. *Br J Haematol*. 2008 Dec;143(5):632-40.
25. Franchini M, Favaloro EJ, Lippi G. Mild hemophilia A. *J Thromb Haemost*. 2010 Mar;8(3):421-32.
26. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost*. 2003 Feb;29(1):101-6.
27. Nilsson IM, ed. Blödnings- och trombosjukdomar. Uddevalla: KABI, Almqvist&Wiksell, 1973.
28. Horowitz B, AM P. Laboratory and preclinical evaluation of the virus safety of coagulation factor concentrates. *Dev Biol Stand*. 1987;67:291-302.
29. Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. *N Engl J Med*. 2001 Jun 7;344(23):1773-9.
30. Mannucci PM. Desmopressin: an historical introduction. *Haemophilia*. 2008 Jan;14 Suppl 1:1-4.
31. Hedner U. Recombinant coagulation factor VIIa: from the concept to clinical application in hemophilia treatment in 2000. *Semin Thromb Hemost*. 2000;26(4):363-6.
32. Turecek PL, Varadi K, Gritsch H, Schwarz HP. FEIBA: mode of action. *Haemophilia*. 2004 Sep;10 Suppl 2:3-9.
33. Hedner U. Activated factor VII: my story. *Haemophilia*. 2012 Mar;18(2):147-51.
34. Berntorp E. Differential response to bypassing agents complicates treatment in patients with haemophilia and inhibitors. *Haemophilia*. 2009 Jan;15(1):3-10.
35. Nilsson IM, Blombäck M, Ahlberg A. Our experience in Sweden with prophylaxis on haemophilia. *Bibl Haematol*. 1970;34:111-24.

36. Nilsson IM. Experience with prophylaxis in Sweden. *Semin Hematol.* 1993 Jul;30(3 Suppl 2):16-9.
37. Ahlberg A. Haemophilia in Sweden. VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. *Acta Orthop Scand Suppl.* 1965;Suppl 77:3-132.
38. Ljung R. Prophylactic therapy in haemophilia. *Blood Rev.* 2009 Nov;23(6):267-74.
39. Petrini P, Lindvall N, Egberg N, Blomback M. Prophylaxis with factor concentrates in preventing hemophilic arthropathy. *Am J Pediatr Hematol Oncol.* 1991 Fall;13(3):280-7.
40. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet.* 2012 Apr 14;379(9824):1447-56.
41. Donadel-Claeyssens S. Current co-ordinated activities of the PEDNET (European Paediatric Network for Haemophilia Management). *Haemophilia.* 2006 Mar;12(2):124-7.
42. Feldman BM, Pai M, Rivard GE, Israels S, Poon MC, Demers C, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost.* 2006 Jun;4(6):1228-36.
43. Bjorkman S, Berntorp E. Pharmacokinetics of coagulation factors: clinical relevance for patients with haemophilia. *Clin Pharmacokinet.* 2001;40(11):815-32.
44. Carlsson M, Berntorp E, Bjorkman S, Lindvall K. Pharmacokinetic dosing in prophylactic treatment of hemophilia A. *Eur J Haematol.* 1993 Oct;51(4):247-52.
45. Ljung R. Central venous catheters in children with haemophilia. *Blood Rev.* 2004 Jun;18(2):93-100.
46. Komvilaisak P, Connolly B, Naqvi A, Blanchette V. Overview of the use of implantable venous access devices in the management of children with inherited bleeding disorders. *Haemophilia.* 2006 Dec;12 Suppl 6:87-93.
47. Ljung R. The risk associated with indwelling catheters in children with haemophilia. *Br J Haematol.* 2007;Sep;138(5):580-6.
48. Tarantino MD, Lail A, Donfield SM, Lynn H, Peddle L, Hunsberger S, et al. Surveillance of infectious complications associated with central venous access devices in children with haemophilia. *Haemophilia.* 2003 Sep;9(5):588-92.
49. Bollard CM, Teague LR, Berry EW, Ockelford PA. The use of central venous catheters (portacaths) in children with haemophilia. *Haemophilia.* 2000 Mar;6(2):66-70.
50. Richards M, Altisent C, Batorova A, Chambost H, Dolan G, de Moerloose P, et al. Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. *Haemophilia.* 2007;Sep;13(5):473-9.
51. Fischer K, Van Der Bom JG, Prejs R, Mauser-Bunschoten EP, Roosendaal G, Grobbee DE, et al. Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome. *Haemophilia.* 2001 Nov;7(6):544-50.
52. Siboni SM, Mannucci PM, Gringeri A, Franchini M, Tagliaferri A, Ferretti M, et al. Health status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. *J Thromb Haemost.* 2009 May;7(5):780-6.

53. Steen Carlsson K, Hojgard S, Lethagen S, Berntorp E, Lindgren B. Economic evaluation: what are we looking for and how do we get there? *Haemophilia*. 2004 Mar;10 Suppl 1:44-9.
54. Steen Carlsson K, Astermark J, Donfield S, Berntorp E. Cost and outcome: comparisons of two alternative bypassing agents for persons with haemophilia A complicated by an inhibitor. *Thromb Haemost*. 2008 Jun;99(6):1060-7.
55. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007 Aug 9;357(6):535-44.
56. Lusher JM. Inhibitor antibodies to factor VIII and factor IX: management. *Semin Thromb Hemost*. 2000;26(2):179-88.
57. Hay CR. Factor VIII inhibitors in mild and moderate-severity haemophilia A. *Haemophilia*. 1998 Jul;4(4):558-63.
58. Astermark J, Altisent C, Batorova A, Diniz MJ, Gringeri A, Holme PA, et al. Non-genetic risk factors and the development of inhibitors in haemophilia: a comprehensive review and consensus report. *Haemophilia*. Apr 14.
59. Wight J, S P. The epidemiology of inhibitors in haemophilia A: a systematic review *Haemophilia*. 2003;9:418-35.
60. Gouw SC, van der Bom JG, Marijke van den Berg H. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood*. 2007 Jun 1;109(11):4648-54.
61. Haya S, Moret A, Cid AR, Cortina V, Casana P, Cabrera N, et al. Inhibitors in haemophilia A: current management and open issues. *Haemophilia*. 2007 Dec;13 Suppl 5:52-60.
62. Santagostino E, Morfini M, Auerswald GK, Benson GM, Salek SZ, Lambert T, et al. Paediatric haemophilia with inhibitors: existing management options, treatment gaps and unmet needs. *Haemophilia*. 2009 Sep;15(5):983-9.
63. Mannucci PM. Outbreak of hepatitis A among Italian patients with haemophilia. *Lancet*. 1992 Mar 28;339(8796):819.
64. Posthouwer D, Yee TT, Makris M, Fischer K, Griffioen A, Van Veen JJ, et al. Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: an international, multicenter cohort study. *J Thromb Haemost*. 2007;Aug;5(8):1624-9.
65. van de Putte DE, Fischer K, Roosendaal G, Hoepelman AI, EP M-B. Morbidity and mortality in ageing HIV-infected haemophilia patients. *Haemophilia*. 2013;2013 Jan;19(1):141-9.
66. Larsson SA. Life expectancy of Swedish haemophiliacs, 1831-1980. *Br J Haematol*. 1985 Apr;59(4):593-602.
67. Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE. Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy. *Haemophilia*. 2009 Jul;15(4):853-63.
68. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Hill FG, Hay CR, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007 Aug 1;110(3):815-25.

69. Fransen van de Putte DE, Fischer K, Makris M, Tait RC, Collins PW, Meijer K, et al. Increased prevalence of hypertension in haemophilia patients. *Thromb Haemost.* 2012 Oct;108(4):750-5.
70. Street A, Hill K, Sussex B, Warner M, Scully MF. Haemophilia and ageing. *Haemophilia.* 2006 Jul;12 Suppl 3:8-12.
71. Evatt B, Back C, Batarova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia.* 2004;Oct;10 Suppl 4:9-13.
72. WHO WHO. Definition of health. [cited; Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 8.]. Available from:
73. Globe D, Young NL, Von Mackensen S, Bullinger M, Wasserman J. Measuring patient-reported outcomes in haemophilia clinical research. *Haemophilia.* 2009 Jul;15(4):843-52.
74. Torrance G. Utility approach to measuring health-related quality of life. *J Chronic Dis.* 1987;40(6):593-603.
75. Ware JE, Snow KK, Kosinski MA, MS G. SF-36 Health Survey: Manual and Interpretation Guide. 1993(Health Institute, New England Medical Center).
76. EuroQoL. [cited; Available from:
77. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. *The Journal of rheumatology.* 1990 Aug;17(8):1022-4.
78. McDowell I, Newell C. Measuring health. A guide to rating scales and questionnaires. Oxford University Press 1996
79. Ravens-Sieberer U, Morfeld M, Stein RE, Jessop DJ, Bullinger M, Thyen U. [The testing and validation of the German version of the impact on family scale in families with children with disabilities]. *Psychother Psychosom Med Psychol.* 2001 Sep-Oct;51(9-10):384-93.
80. Elmstahl S, Malmberg B, Annerstedt L. Caregiver's burden of patients 3 years after stroke assessed by a novel caregiver burden scale. *Arch Phys Med Rehabil.* 1996 Feb;77(2):177-82.
81. Aledort L, Bullinger M, von Mackensen S, Wasserman J, Young NL, Globe D. Why should we care about quality of life in persons with haemophilia? *Haemophilia.* 2012 May;18(3):e154-7.
82. von Mackensen S, Czepa D, Herbsleb M, Hilberg T. Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with haemophilia--the HEP-Test-Q. *Haemophilia.* 2010 Jan;16(1):170-8.
83. Young N, Bradley C, Wakefield C, Barnard D, Blanchette V, McCusker P. How well does the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) measure the quality of life of boys with haemophilia? *Pediatr Blood Cancer.* 2006;Sep;47(3):305-11.



84. Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, Garrido RP, et al. Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. *Haemophilia*. 2008 Sep;14(5):1023-34.
85. Poonnoose PM, Manigandan C, Thomas R, Shyamkumar NK, Kavitha ML, Bhattacharji S, et al. Functional Independence Score in Haemophilia: a new performance-based instrument to measure disability. *Haemophilia*. 2005 Nov;11(6):598-602.
86. Solovieva S. Clinical severity of disease, functional disability and health-related quality of life. Three-year follow-up study of 150 Finnish patients with coagulation disorders. *Haemophilia*. 2001 Jan;7(1):53-63.
87. Miners AH, Sabin CA, Tolley KH, Jenkinson C, Kind P, Lee CA. Assessing health-related quality-of-life in individuals with haemophilia. *Haemophilia*. 1999 Nov;5(6):378-85.
88. Hartl HK, Reitter S, Eidher U, Ramschak H, Ay C, Pabinger I. The impact of severe haemophilia on the social status and quality of life among Austrian haemophiliacs. *Haemophilia*. 2008 Jul;14(4):703-8.
89. Den Uijl I, Biesma D, Grobbee D, Fischer K. Outcome in moderate haemophilia. *Blood Transfus*. 2012 Nov 20:1-7.
90. von Mackensen S, Gringeri A, Siboni SM, Mannucci PM. Health-related quality of life and psychological well-being in elderly patients with haemophilia. *Haemophilia*. 2012 May;18(3):345-52.
91. Lindvall K, Von Mackensen S, Berntorp E. Quality of life in adult patients with haemophilia--a single centre experience from Sweden. *Haemophilia*. 2012 Jul;18(4):527-31.
92. Posthouwer D, Plug I, van der Bom JG, Fischer K, Rosendaal FR, Mauser-Bunschoten EP. Hepatitis C and health-related quality of life among patients with hemophilia. *Haematologica*. 2005 Jun;90(6):846-50.
93. Franchini M, Mannucci PM. Co-morbidities and quality of life in elderly persons with haemophilia. *Br J Haematol*. Feb;148(4):522-33.
94. Hoots WK, Ebbesen LS, Konkle BA, Auerswald GK, Roberts HR, Weatherall J, et al. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. *Haemophilia*. 2008 May;14(3):466-75.
95. Dekoven M, Wisniewski T, Petrilla A, Holot N, Lee WC, Cooper DL, et al. Health-related quality of life in haemophilia patients with inhibitors and their caregivers. *Haemophilia*. 2013;Mar;19(2):287-93.
96. Stein RE, Riessman CK. The development of an impact-on-family scale: preliminary findings. *Med Care*. 1980 Apr;18(4):465-72.
97. Barr RD, Sek J, Horsman J, Furlong W, Saleh M, Pai M, et al. Health status and health-related quality of life associated with von Willebrand disease. *Am J Hematol*. 2003 Jun;73(2):108-14.

98. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Social science & medicine*. 1995 Nov;41(10):1349-58.
99. Sullivan J, Karlsson J, Taft C, Ware J. SF-36 Hälsoenkät: Svensk manual och Tolkningsguide, 2:a upplagan (Swedish Manual and Interpretation Guide, 2nd edition). Gothenburg: Sahlgrenska Universitetssjukhuset, 2002.
100. Sullivan M, Karlsson J, Ware JE J. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Social science & medicine*. 1995;Nov;41(10):1349-58.
101. Huskisson EC. Measurement of pain. *Lancet*. 1974 Nov 9;2(7889):1127-31.

