Hemophilia on the threshold of the 21st century

Iris Plug

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The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!', but 'That's funny...'

Isaak Asimov

US science fiction novelist & scholar (1920 - 1992)

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Chapter 1

General introduction

General introduction

Hemophilia

Hemophilia is a hereditary clotting disorder which is caused by a deficiency of factor VIII (hemophilia A) or IX (hemophilia B). In the Netherlands the prevalence is around 10 per 100,000, resulting in about 1600 patients[1]. The severity of the disease is determined by the residual clotting factor activity. Patients with mild hemophilia (>0.05-0.40 IU/ml) show little spontaneous bleeding and bleed excessively only after major trauma; patients with moderate hemophilia (0.01-0.05 IU/ml) may show excessive hemorrhages after minor trauma, while severe hemophilia (<0.01 IU/ml) is characterized by major bleeding occurring spontaneously or after minor trauma. Frequent bleeding in joints results into damage of the synovial tissue and arthropathy. Hemophilia is a genetic recessive X-linked trait and therefore patients are mostly men. Female family members can be carriers of the disorder, which is characterized by a 25% chance of having a son with hemophilia, and a decreased clotting factor activity level.

History

Although effective treatment has only become available in the recent decades, hemophilia was known to the ancient world. The earliest written references to what appears to be hemophilia are encountered in Jewish texts of the second century AD. Rabbinical rulings exempted male boys from circumcision if two previous brothers had died of bleeding after the procedure[2]. The first modern description of hemophilia is attributed to Dr John Conrad, who clearly appreciated the three cardinal features of hemophilia: an *inherited* tendency of *males* to *bleed*[3]. However, the first use of the word "hemophilia" appears in an account of the condition written in 1828 by Hopff (Über die haemophilie oder die erbliche Anlage zu tödliche blutungen). Hemophilia is sometimes referred to as "the royal disease" because several

members of royal families in Europe were affected by it. Queen Victoria had no ancestors with the condition but soon after the birth of her eighth child, Leopold in 1853 it became evident that he had hemophilia. Two of Queen Victoria's daughters were also carriers of hemophilia. The condition was transmitted through them to several Royal families. Perhaps the most famous affected individual was the son of Tsar Nicolas II of Russia, Tsarevich Alexis, who was born in 1904[4].

Treatment and complications

Many reputable scientist claimed early success in treatment with unusual substances. As recently as 1964 a report in Lancet claimed that peanut flour was effective for the treatment of hemophilia[5]. The first hint of success came from Dr R.G. Macfarlane in 1934, who discovered that snake venom could accelerate the clotting of hemophilic blood[6]. Plasma derived factor VIII and IX preparations became available in the early 1960s[7]. Ever since the discovery by Dr Judith Pool of cryoprecipitate, replacement therapy with factor concentrates has been the most important component of hemophilia care. This treatment rapidly improved the medical and social situation of patients with hemophilia and considerably increased life expectancy[8,9]. In the early 1980s major side-effects became manifest when many patients became infected with the human immunodeficiency virus (HIV)[10]. Moreover, of all patients treated before 1992 with plasma-derived clotting factor preparations, 80 percent became infected with hepatitis viruses[11]. Today, clotting factor preparations are virtually safe regarding blood-borne viruses[12], and the risk of hepatitis and HIV transmission must be considered negligible, whereas the development of neutralizing antibodies (‘inhibitors’) against the infused factor VIII or IX is an important issue[13,14].

The characterisation and cloning of the factor VIII gene in 1984 led to the availability of recombinant factor VIII a decade later. The availability of products that are not made from

human blood and therefore even theoretically incapable of transmitting human blood-borne pathogens, has further stimulated the use of prophylactic treatment. In the Netherlands since the late 1970s treatment of hemophilia has consisted of the intravenous infusion of clotting factor concentrates performed either on demand (at the moment of bleeding) or prophylactically. Prophylactic treatment is primarily prescribed to patients with severe hemophilia. The rationale for prophylaxis in hemophilia is that patients with a factor level of 0.01-0.04 IU/ml rarely develop chronic joint changes. By maintaining the plasma concentration of clotting factors at a level above 0.01 IU/ml hemophilia can be converted from a severe to a milder form[15-17].

Outline of this thesis

The main aim of this thesis was to study the effects of hemophilia treatment on both the medical situation and social functioning of hemophilia patients. Effective treatment of hemophilia has been available since the late 1960s[7] and offered patients better prognosis but also had a large negative impact through blood-borne viruses. This has been described in Chapter 2. In Chapter 2.2 we studied mortality, causes of death and life expectancy in Dutch hemophilia patients between 1992 and 2001.With this study we complete the inventory of mortality in patients with hemophilia over thirty years, describing the period before[18], during[19] and after the use of potentially contaminated clotting products. In chapter 2.2 the results of the Hemophilia in the Netherlands-5 (HiN-5) project are described and data are compared to the previous surveys. This chapter focuses on both medical issues, such as haemorrhages and joint problems but also on social aspects such as absence from work and school. Social functioning and health related quality of life of hemophilia patients compared to the general population are described in Chapter 2.3. In Chapter 2.4 clinical characteristics of hepatitis C positive patients are evaluated. Recombinant clotting factor preparations were

introduced in the early 1990s. Despite the serious side effects of plasma-derived clotting products these new products were not accepted as quickly as expected. In Chapter 2.5 factors influencing the use of recombinant factor VIII were studied.

Female relatives of male patients can be carriers of hemophilia; besides its impact on family planning carriership of hemophilia may also lead to bleeding problems. Chapter 3 evaluates whether carriers of hemophilia have more bleeding problems than to non-carriers, with a focus on specific risk-enhancing factors.

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Chapter 2.1

Mortality and causes of death in patients with hemophilia, 1992-2001

A prospective cohort study

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Summary

We studied mortality, causes of death and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts, together spanning the periods before, during and after the use of potentially contaminated clotting products.

We performed a prospective cohort study among 967 patients with hemophilia A and B. Death rates, overall and cause-specific, were compared to national mortality figures for males adjusted for age and calendar period as Standardized Mortality Ratio (SMR's). Between 1992 and 2001, 94 (9.7%) patients had died and 2 patients were lost to follow-up (0.2%). Mortality was 2.3-times higher in hemophilia patients than in the general male population (SMR 2.3 95 % confidence interval 1.9-2.8). In patients with severe hemophilia life expectancy decreased from 61 to 59 years. Exclusion of virus-related deaths resulted in a life expectancy at birth of 72 years.

AIDS was the main cause of death (26%) and 22% of deaths were due to hepatitis C. In patients not affected by viral infections mortality was still slightly higher than in the Dutch male population. Thus mortality of patients with hemophilia is still increased; this is largely due to the consequences of viral infections.

Introduction

Hemophilia is an X-linked genetic bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Due to the hereditary pattern of hemophilia patients are almost invariably male, while women can be carriers of the disease. Severe forms are characterized by major bleeding occurring spontaneously or after minor trauma. These hemorrhages often occur into joints eventually causing disabling arthropathy[1].

Before the introduction of clotting factor preparations the mean life expectancy of patients with hemophilia was less than 30 years[2], and patients mostly died of intracranial[3-5] or other hemorrhages. Since the 1960s factor VIII and IX preparations have been available for the treatment of hemophilia. This rapidly led to medical and social improvements, with a decrease in the frequency of hemorrhages and considerably improved life expectancy of patients with hemophilia.

Despite these positive developments, mortality of patients with hemophilia again increased during the 1980s. In 1982, the first case of acquired immunodeficiency syndrome (AIDS) in a patient with hemophilia was reported[6,7]. Since then many more cases have been reported worldwide, of whom many have died. In addition, about 80 percent of the patients treated with clotting factor products before 1992 became infected with hepatitis C[8,9]. The full consequences of hepatitis C infections are only recently being recognized[10]

Since 1985, products have been safe for HIV and since 1992 also for the transmission of hepatitis C (HCV). Today, the most important complication of clotting factor treatment is the development of neutralizing antibodies (inhibitors) against factor VIII or IX[11].

Few studies have reported on mortality in the total population of hemophilia patients after the period of the risk of viral infection transmission. Several studies have aimed at describing mortality within a specific subpopulation, such as hemophilia patients infected with HIV[12-14]. This study completes the inventory of mortality in patients with hemophilia over the last 30 years in the Netherlands, which describes the period before[15], during[16] and after the use of potentially contaminated clotting products.

Objectives

We studied mortality, causes of death and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts from our national surveys on hemophilia, starting in 1972.

Material and methods

Study design

A prospective cohort study was performed as part of a survey among all known patients with hemophilia in the Netherlands. In June 1992, we sent questionnaires to all patients who were listed with the Netherlands Hemophilia Society, with the hemophilia treatment centers, or on updated mailing lists from previous surveys in 1972, 1978 and 1985[17]. For this national study, 1292 patients received a questionnaire of whom 967 (75%) responded. Vital status at the end-of study date was determined by the response to the survey of 2001, from the attending physician or from municipal population registries. Of patients who had died during follow-up dates of death were obtained from municipal registries and physicians. This study is part of the Hemophilia in the Netherlands-5 study, which has been approved by the Committee of Medical Ethics of the Leiden University Medical Center.

Cause of death

The causes of death were obtained from treating physicians or general practitioners and were categorized according to the tenth revision of the International Classification of Diseases, Injuries, and Causes of Death-10 (ICD-10)[18]. Overall and cause-specific mortality of the general Dutch male population was retrieved from the Central Bureau of Statistics[19]. Date of birth, severity of hemophilia, HIV status and information on inhibitory antibodies were derived from the self-reported answers to the questionnaire. Severity of disease and type of hemophilia were verified with the patients' physicians. Severity of hemophilia, depending on the residual clotting factor activity was categorized as severe (< 0.01 IU/ml factor VIII or IX), moderate (0.01-0.05 IU/ml) or mild (>0.05-0.40 IU/ml factor VIII or IX). The HIV status was based on self-reported answers of the patients. If patients were born after 1985 or if they reported no treatment with clotting factor between 1979 and 1985, HIV status was considered to be negative.

Statistical analysis

Standardized Mortality Ratios (SMR's) were calculated to estimate the rate of overall and cause specific death of patients with hemophilia relative to that of the general male population adjusted for age and calendar period. The SMR is the number of observed deaths divided by the number that was expected if the mortality rate in the cohort, with its specific age-distribution, was the same as that in the general population. Patients were followed from the 1st of June 1992 to the 1st of July 2001. We used mortality rates from the Dutch general male population between 1992 and 2001. Ninety-five percent confidence intervals (CI) were based on a Poisson distribution for the observed number of deaths. To put our findings into perspective they were compared to those of the previous cohort studies between 1972-1985[15] and 1985-1992[16]. For this comparison mortality ratios were calculated by direct

standardization using WHO standardization weight factors (http://www3.who.int/whosis/discussion_papers/pdf/paper31.pdf).

Two methods were used to exclude the effect of viral infections on mortality 1) exclusion of patients who reported to be HIV positive in 1992 and 2) censoring patients of whom death was a result of HIV (AIDS) or HCV (liver cirrhoses, hepatocellular carcinoma) at the date of death. Cause-specific SMRs were calculated by studying the specific cause of death as endpoint and censoring patients with other endpoints. Median life expectancy was calculated with left truncated survival analysis and was expressed as the median age at which cumulative survival was 50%.

Results

Table 1 shows the general characteristics of the patients with hemophilia in 1992. Between 1992 and 2001 the total number of patient-years of follow-up was 8868 (mean 8.6 (range 0-9) yrs), 94 patients died and two patients were lost to follow-up. Of all 967 patients in the cohort, 796 (87%) patients had hemophilia A and 125 (13%) patients had hemophilia B; 386 (39%) patients had severe hemophilia, 167 (17%) patients had moderate hemophilia and 414 (43%) had mild hemophilia; the mean age was 32 (range 0-82) years; 50 (5.2%) patients reported to have inhibitory antibodies against the deficient clotting factor; and 53 patients (5.5%) were HIV positive. The mean age at death was 52 years, with a range from 14 to 83 years. In 20% of deceased patients the presence of an inhibitor was reported at time of death.

The expected number of deaths during this same calendar period was 39. The standardized mortality ratio (SMR) was 2.3 (CI 1.9-2.8), indicating that the overall mortality rate of patients with hemophilia was two times higher than in the general male population. In patients with severe hemophilia mortality was five times higher than expected, SMR 5.1 (CI 3.8-6.8).

Table 1. General characteristics of participants at entry (1992)

	N=967
Age (yrs)	32 (0-82)
Severity of disease	
Severe (<0.01 IU/ml)	386 (40)
Moderate (0.01-0.05 IU/ml)	167 (17)
Mild (>0.05-0.40 IU/ml)	414 (43)
Type of hemophilia	
Hemophilia A	796 (87)
Hemophilia B	171 (13)
HIV infection	53 (6)
Inhibitor present*	50 (9)

Data presented are means(range) or numbers(percentages)
* Inhibitory antibodies against the deficient clotting factor

Standardized mortality ratios taking into account HIV infection and severity of disease are shown in Table 2. Restriction of the analysis to patients not infected with HIV revealed that mortality in patients with hemophilia was 70 percent higher than that in the general population (SMR 1.7, CI 1.3-2.7). After exclusion of deaths related to either HIV or HCV mortality rate among patients with hemophilia was 20 percent higher than among the general population (SMR 1.2, CI 0.9-1.6), in patients with severe hemophilia this was 40% (SMR 1.4,CI 0.8-2.4).

Table 2. Standardized Mortality Ratios (SMR) for severity and type of hemophilia taking into account the HIV status

	Observed deaths*	All patients SMR (95% CI)†	HIV negative patients‡ SMR (95% CI)
All	94	2.3 (1.9-2.8)	1.7 (1.3-2.1)
Severity			
Severe	47	5.1 (3.8-6.8)	2.8 (1.9-4.2)
Moderate	15	2.6 (1.5-4.3)	2.3 (1.3-3.9)
Mild	32	1.3 (0.9-1.9)	1.2 (0.8-1.6)
Type of hemophilia			
Hemophilia A	81	2.3 (1.9-2.9)	1.7 (1.4-2.2)
Hemophilia B	13	2.3 (1.3-4.0)	1.3 (0.6-2.7)

*Data presented are absolute numbers of observed deaths
† 95% Confidence Interval
‡ Only including patients who reported to be HIV negative or patients who were born after 1985

Direct standardization of mortality rates made comparisons between time periods possible. We found that mortality of the whole cohort of patients with hemophilia did not change over three time-periods. Relative rate, compared to subjects without hemophilia, i.e., the general population, was 1.6 between 1972 and 1985, 2.1 between 1985 and 1992 and it was 2.0 between 1992 and 2001. However, stratification for severity of hemophilia revealed that the rate of death of patients with severe hemophilia increased over the last three decades. It was three times higher than the rate in subjects without hemophilia during the period between 1985-1992 and it was 4.5 times higher during the last period of follow-up.

Cause specific mortality

Table 3 shows the primary causes of death between 1992 and 2001. Between 1992 and 2001 24 (26%) patients died of AIDS of whom 22 (87.5%) had severe hemophilia. In 21 patients (22%) death was due to a HCV infection; in two of these patients complications of a liver

transplantation were the cause of death, while in five patients a hepatocellular carcinoma or metastasis of a liver carcinoma was reported.

Table 3. Primary causes of death according to the ICD-10 classification

Cause of death (ICD-10* Code)	1973-1986 n=43 (%)	1986-1992 n=45 (%)	1992-2001 n=94 (%)
AIDS† (B20-34)	0 (0)	12 (27)	24 (26)
Hepatitis C	-	-	21 (22)‡
Hepatocellular carcinoma (C22)	-	-	5 (5)
Chronic liver disease (K70, K72.9, K73-K74, C78.7)	0 (0)	5 (11)	10 (11)§
Diseases of the circulatory system (I00-I99)	4 (9)	10 (24)	16 (17)
Ischemic heart disease (I20-I25)	1 (2)	0 (0)	6 (6)
Cerebrovascular disease (I60-I69)	3 (7)	9 (20)	4 (5)
Malignancies (C00-D48)	13 (30)	7 (15)	12 (15)
Hemorrhages	20 (47)	1(2)	5 (5)
Other (A40.3, A41.9, J18, R06.8, R54) or not natural cause of death (T14.9, V01-Y98)	3 (5)	6 (9)	13 (11)‖
Sudden death, cause unknown (R96, R99)	3 (7)	4(9)	3 (3)

*ICD-10=International Classification of Diseases, 10th revision,
†AIDS = Acquired ImmunoDeficiency Syndrome
‡2 patients due to complications of livertransplantation, 5 of hepatocellular carcinoma, 10 of chronic liver disease, in four patients only hepatitis C mentioned as cause of death
§ In four patients a hemorrhagic shock was reported
‖1 patient died due to 'natural causes',

A hemorrhagic shock resulting from end-stage liver disease (n=10) was reported in five patients. A co-infection with HIV and HCV was observed in five of the deaths resulting from hepatitis C. Mortality due to AIDS and chronic liver disease was highest in patients with severe hemophilia although these causes of deaths were also observed in patients with

moderate hemophilia (n=4, 27%). Among patients in whom death was not related to HCV or HIV (n=49) the main cause of death was hemorrhage (13/49), which also includes intracranial hemorrhages (n=4) and hemorrhages resulting from trauma (n=4). Compared to the Dutch male population the incidence of death from intracranial hemorrhages is higher in patients with hemophilia, 0.1 per 1000 person-years and 0.5 per 1000 person years respectively. Death from malignant neoplasm (including hepatocellular carcinoma) was reported in 22% of patients. Although the percentage of patients with mild hemophilia that died as a result of malignancies was higher than in the Dutch male population, at 41% vs. 31%, overall mortality of malignancies was lower, at 19% vs. 31%. Death due to disease of the circulatory system was lower in patients with hemophilia than in the Dutch male population 17% and 28% respectively. The cause of death remained unknown in three patients.

The proportion of patients that died of AIDS stayed constant during the last two periods of follow-up. Death due to hepatitis C increased compared to the period between 1985 and 1992, 11% vs. 22%. No deaths of AIDS or hepatitis C were reported in the first period of follow-up (1972-1985). The occurrence of cerebral vascular disease was lower than in 1986-1992, when it accounted for 20% of all deaths compared to 4% in the current period of follow-up.

In Table 4 cause-specific standardized mortality ratios are shown. Mortality due to viral infections was 117 times higher than in the general population, and mortality due to HCV was 16 times (SMR 16.1, CI. 7.7-33.8) higher in patients with hemophilia than in the general population.

Table 4. Primary cause of death specific Standardized Mortality Ratios

Cause of death (ICD-10 Code)	Observed*	SMR (95CI)†
AIDS (B20-B24)	24	117.2 (77-178)
Hepatitis C		
Hepatocellular carcinoma (C22)	4	17.2 (5.2-35.9)
Chronic liver disease (K70, K72.9, K73-K74)	10	16.1 (7.7-33.8)
Ischemic heart disease (I20-125)	6	0.5 (0.2-1.1)
Cerebrovascular disease (I60-I69)	4	1.0 (0.2-2.2)
Malignancies	18	1.5 (1.0-2.5)
Malignancies (no liver)	12	1.1 (0.6-1.9)

*Absolute numbers of death observed
† 95% Confidence Interval

Life expectancy

Life expectancy was calculated stratified for severity of hemophilia and based on extrapolation from the observed death rates (Table 5). In patients with severe hemophilia a life expectancy of 59 years at birth was observed, and censoring of patients that died due to virus infections resulted in a life expectancy of 71 years in patients with severe and moderate hemophilia. Life expectancy at birth of patients with mild hemophilia was lower than that of the male population, at 73 years compared to 76 years. After exclusion of viral infections the life expectancy of mild hemophilia patients was 75 years.

The overall life expectancy of the patients with hemophilia did not notably change between 1972 and 2001. The life expectancy of patients with severe hemophilia, however, decreased

from 63 to 59 years. For patients with moderate hemophilia life expectancy increased from 65 to 67 years.

Table 5. Life expectancy (years) according to severity in 30 years of follow-up

	1972-1985	1985-1992	1992-2001		
			All patients N=967	HIV negative* N=511	HIV and HCV† negative N=967
All patients (years)	66	68	67	70	74
Dutch males	71	74	76	76	76
Severity of hemophilia					
Severe (<0.01 IU/ml)	63	61	59	70	71
Moderate (0.01-0.05 IU/ml)	65	65	67	71	75
Mild (>0.05-0.40 IU/ml)	-	74	73	73	75
Type					
Hemophilia A	-	69	68	70	73
Hemophilia B	-	64	60	73	--‡

* Patients of whom HIV status was negative or who were born after 1985
† HIV and HCV related deaths are censored
‡ Not available due to limited numbers

Discussion

During the last decade hemophilia was characterized by an excess mortality as compared to the general population. Human Immunodeficiency Virus (HIV) infection was responsible for the largest number of deaths (n=24, 26% of deaths) and 16% of deaths were due to hepatocellular carcinoma or chronic liver disease resulting from a HCV infection. Overall, patients with severe hemophilia had a five-fold higher risk of death than men in the general population. Without the effects of HIV and HCV the rate of death among patients with severe hemophilia was 1.4-fold higher than expected. The remaining excess risk in all likelihood results from hemorrhages. Life expectancy of patients with severe hemophilia decreased compared to earlier studies, mostly influenced by HIV. Patients with severe hemophilia not affected by hepatitis C or HIV had a life expectancy of 71 years, which can be compared to a life expectancy of the Dutch male population of 76 years.

In the survey of 1992, 93% of all Dutch hemophilia patients were sent a questionnaire, of whom 75% participated in the survey, and were subsequently followed for this study on mortality. Only two patients were lost to follow-up and we were able to retrieve 96% of all causes of death. This resulted in a complete cohort comprising a large population of hemophilia patients. There was no difference in severity of hemophilia or mean age between the responding and non-responding population to the questionnaire of 1992, and therefore we consider our data to be generalizable to the Dutch hemophilia population. Theoretically, because the causes of death were reported by the treating hematologist or the general practitioner there may have been discrepancies with the general population data gathered through the Central Bureau of Statistics. We do not expect this to be of large influence. As always in research on life expectancy the findings may not hold for the present patients with hemophilia. Exclusion of effects of viral infections results in a reflection of the situation for patients not exposed to non-safe clotting products or not infected products. In our cohort no

deaths were reported in the youngest age-category between 0 and ten years. The youngest participant to this study was four months old, and therefore our study did not cover perinatal mortality. Due to limited information on the presence of inhibitory antibodies we have not been able to study the impact on mortality.

Our study shows a two-fold increased mortality for patients with hemophilia; in patients with severe hemophilia this was even a five-fold increase. We estimated the future perspective by excluding death due to HIV or hepatitis C. There still appeared to be a trend towards a moderately but enduring increased mortality for patients with hemophilia, especially in severe hemophilia. As nowadays products are safe from transmission of HIV and hepatitis C, preventive efforts should focus on factors causing this remaining excess mortality. The most important factor is an increased risk of death of hemorrhages, either intracranial or resulting from trauma. Although mortality of HCV and HIV is extensive and the numbers to compare with the general population are limited there seems to be a higher incidence of death from intracranial hemorrhages in patients with severe, moderate and mild hemophilia. This indicates the importance of adequate and specialized care for hemophilia patients. Although we also observed a high number of other hemorrhages, e.g., resulting from trauma we were not able to make a comparison with the general population. A second factor of impact could be deaths due to hepatitis C that had not been reported as such. However, as the hepatitis C status is well known and a good registration is used by treating physicians this is probably of limited influence

Over the last three decades causes of death of patients with hemophilia have changed; during the 1970s and early 1980s patients with hemophilia died mostly of intracranial hemorrhages, while during the late 1980s AIDS became the main cause of death. Although in the

Netherlands the impact of HIV was relatively low through the use of predominantly products from local voluntary unpaid donors, AIDS was responsible for a quarter of all deaths during the 1990s. In the present follow-up period about 80% of deaths from AIDS occurred before 1995, indicating that the impact of AIDS on mortality of patients with hemophilia is declining. This decreased influence is explained by a reduced number of survivors of an HIV infection, and by improved survival of patients infected with HIV through HAART therapy[20]. The effects of hepatitis C infections on mortality have increased considerably during the last ten years, and about 20% of deaths were due to the effects of hepatitis C, of which liver cirrhosis or liver failure were the most prevalent. Our study shows a highly increased risk of death of hepatocellular carcinoma, which is similar to a study by Darby et al in which a 20-fold increased risk was reported in non-HIV infected patients with severe hemophilia[21]. Although the introduction of new treatment methods combining pegylated interferon with ribavirin will positively influence mortality of HCV infected patients the effects of HCV will remain to be present in those patients in whom this therapy failed. For patients not affected by viral infections hemorrhage was still a relatively frequent cause of death. As this is similar to the period before the impact of viruses transmitted by clotting products we might conclude that the increased availability of clotting factor has not reduced the number of deaths due to hemorrhages. The number of deaths from malignant neoplasm was not higher than expected in this population. In concordance with earlier studies and findings by Rosendaal et al we observed a reduced rate of mortality of ischemic heart disease in patients with hemophilia[22].

Life expectancy of patients with severe hemophilia was lower during the last decade as compared to earlier observations. An important part of this decline is explained by death due to viral infections. When AIDS and hepatitis C deaths were excluded, life expectancy, improved but although the general life expectancy in European countries is approached it

remains to be lower especially in patients with severe hemophilia [23]. Walker et al published the same observations in a Canadian population[24]. After exclusion of viral infections patients with mild and moderate hemophilia have a life expectancy that is about equal to the average Dutch male population.

Our data show that HIV and hepatitis C still largely influence mortality of hemophilia patients. The effects of hepatitis C will be present for many years to come. In patients with severe hemophilia not infected with viruses mortality is still 40 percent higher than in the general population. Although this suggests that the current patient with hemophilia benefits from safe clotting products life expectancy is still negatively influenced by this bleeding tendency.

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Chapter 2.2

Thirty years of hemophilia treatment in the Netherlands, 1972-2001

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Summary

Since the introduction of replacement therapy in the early 1960s by the infusion of plasma-derived factor VIII and IX preparations important changes have occurred for hemophilia patients. We studied the medical and social developments over 30 years of hemophilia treatment.

Since 1972 5 cross-sectional national postal surveys among all hemophilia patients in the Netherlands were performed, the latest in 2001. The prestructured questionnaires included items on treatment, the presence of inhibitory antibodies against factor VIII or IX, the annual number of bleeding episodes, use of inpatient hospital care and hepatitis C and HIV infections.

Response rate in 2001 was 70%. Young patients (<16 years) with severe hemophilia showed the largest increase in use of prophylaxis, from 34% in 1972 to 86% in 2001. The occurrence of hemorrhages has gradually decreased. Hospital admissions decreased from 47% of all patients in 1972 to 18% in 2001.

Our study shows that the treatment of patients with severe hemophilia in the Netherlands has focused on the use of prophylactic treatment, especially in children. This has resulted in a decrease in bleeding frequency and an improvement of the medical and social circumstances of patients.

Introduction

Hemophilia is a X-linked genetic bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Severe forms are characterized by major bleeding after minor trauma. These hemorrhages often occur into joints eventually causing arthropathy, which is associated with physical and psychosocial impairment[1].

Since the introduction of replacement therapy in the early 1960s, the infusion of plasma-derived factor VIII and IX preparations, important changes have occurred for hemophilia patients[2,3]. For patients with hemophilia mean life expectancy has increased over the years from lower than 30 years in 1960 to an almost normal life expectancy of 68 years in 1992[4,5]. Prophylaxis was introduced in the Netherlands in the late 1960s[6,7]. As from the 1970s it became possible for patients to treat themselves at home and the introduction of clotting factor concentrates in 1978 further facilitated developments. Although the general superiority of prophylactic treatment over on-demand treatment has been demonstrated[6,8,9], the question of when and in whom to start, and how to dose prophylactic therapy, remain a subject of discussion[10]. Some believe that intensified on-demand treatment may be as effective as prophylaxis. Arguments in favor of on-demand therapy include fewer exposures with a potential concomitant reduction in pathogen exposure, less financial burden for the family (depending on the health care system) and society and greater therapeutic maneuverability in times of reduced product availability[11]. Randomized clinical trials to compare cost-effectiveness of prophylaxis and on demand treatment are ongoing[12,13].

Although treatment with clotting factor concentrate has enabled patients to participate fully in normal life, the infusion of plasma products also has had important adverse effects, such as infections with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and

inhibitor development. Of the Dutch hemophilia patients who were treated with plasma-derived clotting factors before 1985 17% became infected with the human immunodeficiency virus (HIV)[2]. Plasma-derived products have been safe for hepatitis B and HIV since 1985 and also for HCV since 1992 [14].

In 1995 recombinant FVIII products have been introduced in the Netherlands and have become increasingly used[15], especially in previously untreated patients; along with the use of purified plasma-derived products, this minimizes the risk of transmission of HIV or HCV[16]. Today, the most important complication of clotting factor treatment is the development of neutralizing antibodies (inhibitors) against factor VIII or IX[17].

Objective

In the Netherlands a series of 5 national postal surveys[18,19] have been performed, from 1972 onward. In this study we evaluated the most important medical and social developments over the last three decades of hemophilia treatment.

Patients, materials, and methods

Patients

A nationwide postal survey was conducted in the Netherlands in 2001, following 4 previous surveys in 1972, 1978, 1985 and 1992[18,19]. We contacted patients who were listed with the Netherlands Hemophilia Society and the hemophilia treatment centers and we updated mailing lists from previous surveys. In April 2001, 1567 questionnaires were sent to all known Dutch hemophilia patients, followed by 2 reminders. Response is given for all questionnaires that were returned, irrespective of diagnosis (i.e. hemophilia or other bleeding disorders) Although some questionnaires were completed by patients with other bleeding

disorders or symptomatic carriers, this report is restricted to men with hemophilia A or B. The severity of hemophilia was classified according to residual percentage of factor VIII or IX clotting activity: severe (<0.01 IU mL), moderate (0.01-0.05 IU mL) or mild (>0.05-0.40 IU mL). The self reported type and severity of hemophilia were verified with data from the treatment centers. The parents or caretakers completed the questionnaire if the patient was younger than 12 years.

The five prestructured questionnaires that were used between 1972 and 2001 included many items that were identical: treatment modalities, the presence of inhibitors, the annual number of bleeding episodes, the use of inpatient hospital care, absence from school or work, degree of joint impairment, employment, and disability. The questionnaires differed on topical issues (e.g. home treatment in 1978 and AIDS in 1985). In the 2001 questionnaire items on hepatitis C and type of product were added.

The study was approved by the Medical Ethical Committee of the Leiden University Medical Center.

Data analyses

All analyses were stratified by the severity of hemophilia, and often by age category as well. As the clinical characteristics of hemophilia A and hemophilia B do not differ, we present combined results for hemophilia A and B. Data on the treatment modality, the number of bleeding episodes, the use of hospital facilities, and absence from school or work referred to the year that preceded the questionnaire surveys (2000). Children were defined as patients younger than 16, adolescents as patients between 16 and 25 and adults as patients older than 25 years. The use of prophylaxis refers to patients who received prophylaxis as their main treatment modality, excluding patients who received a combination of on demand treatment and prophylaxis during risk periods. Absence from school was calculated only for that part of

the population that followed a full-time education. Absence from work was calculated for patients aged 16 to 65 who had a paid job (full-time or part-time). The inactivity ratio was calculated as the ratio of inactivity in the study population and inactivity in Dutch men. Patients that did not have a full-time or part-time paid job were defined as inactive. Descriptive statistics for age, the use of hospital facilities, absence from work and employment were compared to national figures for the general male population that were provided by the Central Bureau of Statistics Netherlands Statline database[20]. Self reported measures on joint impairment were obtained for a series of 16 joints which are, the neck, the left and right shoulder, the back, the left and right elbow, the left and right wrist, the left and right hand and fingers, the left and right hip, the left and right knee and the left and right ankle. The possible scores were 0 (no impairment), 1 (some impairment without daily problems), 2 (some impairment with daily problems), and a maximum of 3 (severe impairment with complete loss of function).

From scores of the 16 separate joints a joint score was calculated with a minimum score of 0 and a maximum score of 48 points. As joint impairment was reported most frequently in the ankles, elbow and knees these were analyzed separately.

Results

Response and patient characteristics

Response was 70% in 2001, compared to 84% in 1972[19], 70% in 1978[21], 81% in 1985[22] and 78% in 1992[18]. One hundred and ninety eight patients participated in all 5 surveys. Table 1 shows the characteristics of participants in each of the 5 surveys. The mean age of participants increased from 21 years (median 19; range, 0-74 years) in 1972 to 35 years (median 36; range, 0-90 years) in 2001.

Table 1. Overview of characteristics of participants to the Hemophilia in the Netherlands studies obtained from self-reported data

	1972	1978	1985	1992	2001
N	447	560	935	980	1066
age (years)	19 (0-74)	23 (0-70)	28 (0-85)	31 (0-84)	36 (0-90)
Severity of hemophilia					
severe (<0.01 IU ml)	159 (36)*	245 (44)	384 (41)	387 (39)	420 (39)
moderate (0.01-0.05 IU ml)	83 (19)	106 (19)	175 (19)	173 (18)	176 (17)
mild (>0.05-0.40 IU ml)	172 (38)	138 (25)	376 (40)	420 (43)	470 (44)
Type of hemophilia					
type A†	377 (84)	481 (86)	801 (86)	853 (87)	925 (87)
Hereditary pattern					
sporadic hemophilia	112 (25)	128 (23)	237 (25)	195 (20)	246 (23)

Values presented are medians(range) or number(%)
*Of 33 patients severity was missing in 1972
†All other patients are patients with hemophilia B

This was still somewhat lower than the mean age of Dutch men, which increased from 32 to 37 years over the same period. Of all participants in 2001, 39% had severe hemophilia, 17% had moderate hemophilia, and 44% had mild hemophilia. In 23% of patients, the genetic inheritance pattern of the disease was that of isolated hemophilia: they had no other family members with hemophilia. This proportion had remained constant over the 30 years spanned by the surveys. Thirty-eight percent of patients with severe hemophilia were isolated patients, and 13% of patients with moderate hemophilia were isolated patients.

Treatment

In 2001, 580 patients (54%) received treatment on-demand, and 305 patients (29%) prophylaxis, whereas 127 patients (12%) were treated on-demand at times and prophylactically at other times. For 54 patients (5%), no data were available about treatment, and most of these patients (n=45) had mild hemophilia. Prophylactic treatment was used mostly in children and adolescents with severe hemophilia (Table 2). This group also showed the largest increase in use of prophylaxis, from 34% and 31% in 1972 to 86% and 90% in 2001; for adults with severe hemophilia this increased from 14% in 1972 to 54% in 2001. A substantial proportion of adult patients (15/39, 38%), who now were treated on-demand only, had been treated prophylactically in the past.

Table 2. Characteristics of treatment in patients with severe and moderate hemophilia given by age

	1972	1978	1985	1992	2001
Severe hemophilia					
prophylaxis					
children (0-16 yrs)	22/65 (34)	41/91 (45)	69/111 (62)	64/92 (70)	112/130 (86)
adolescents (17-25 yrs)	12/39 (31)	27/54 (50)	43/72 (60)	--	38/42 (90)
adults (above 25 yrs)	8/57 (14)	28/99 (28)	71/201 (35)	119/232 (51)	134/248(54)
age at first prophylaxis	--*	8 (0-15)	5 (1-15)	--	2 (0-11)
home treatment	7 (4)	72 (29)	259 (67)	286 (74)	346 (82)
Moderate hemophilia					
prophylaxis					
children (0-16 yrs)	6/41 (15)	9/41 (22)	7/59 (12)	7/41 (17)	7/46 (15)
adolescents (17-25 yrs)	4/14 (29)	7/26 (27)	1/19 (5)	--	4/23 (17)
adults (above 25 yrs)	1/27 (4)	4/39 (10)	10/97 (10)	11/98 (11)	10/107 (9)
home treatment	2 (2)	14 (13)	39 (22)	51 (30)	57 (32)

Values are medians (range), proportions (%) or number(%),
*Data are not available

The median age of starting prophylactic treatment was 2 years in 2001 (range, 0-11 years), compared to 8 years (range, 0-15 years) in 1978 and 5 years (range, 1-15 years) in 1985.

The majority of patients on prophylaxis (64%; n=195) infused clotting factor concentrate themselves. The percentage of patients on home treatment had increased from 4% in 1972 to 82% in 2001. In 2001, 88% (n=269) of patients on prophylaxis were on home treatment. Patients who had been treated in the year preceding the survey had used plasma-derived products (41%, n=300) and recombinant factor VIII or IX products (48%, n=349) equally as often. Among children younger than 16 years, a larger proportion solely used a recombinant product (78%, n=155).

Outcome of treatment

Table 3 shows effects of treatment over 30 years. Of all patients with severe hemophilia participating in 2001, 21 % (n=88) reported no hemorrhages in the previous year, compared with 36% (n=64) of patients with moderate hemophilia and 68% (n=319) of patients with mild hemophilia.

Since 1972 the annual median number of symptomatic hemorrhages has gradually decreased: from 20 (range, 0-98 symptomatic hemorrhages) in 1972 to 5 (range, 0-51 symptomatic hemorrhages) in 2001 in children with severe hemophilia, whereas a similar trend was seen for patients with moderate hemophilia. In patients with mild hemophilia the overall median number of hemorrhages was zero in all 5 surveys. Hemorrhages were most frequent into joints. In 2001 patients with severe hemophilia had on average 3 joint bleeds (range, 0-75 joint bleeds), compared with seven joint bleeds (range, 0-80 joint bleeds) in 1992. A substantial number of hemorrhages were traumatic, especially in children (46% versus 16% in adult patients).

Table 3. Outcome of treatment presented for patients with severe hemophilia and moderate hemophilia

	1972	1978	1985	1992	2001
Severe hemophilia	159	245	384	387	420
hemorrhages (nr.per year)*					
children (0-16 yrs)	20 (0-98)	20 (0-70)	10 (0-65)	10 (0-98)	5 (0-51)
adolescents (17-25 yrs)	20 (0-98)	17 (0-100)	10 (0-90)	10 (0-98)	6 (0-75)
adult (above 25 yrs)	14 (0-97)	15 (0-100)	10 (0-90)	10 (0-82)	7 (0-75)
hospital admissions*					
hemophilia (%)	51	38	25	22	22
Dutch males (%)	--	--	6	6	5
duration of stay (days/patient)	28 (2-252)	20 (1-180)	11 (1-100)	5 (0-330)	7 (0-89)
absenteeism due to hemophilia*					
school (days)†	30 (0-80)	15 (0-80)	4 (0-80)	2,5 (0-80)	7 (0-90)
work (days)‡	15 (0-80)	20 (0-213)	7 (0-319)	8 (0-330)	5 (0-365)
Moderate hemophilia					
hemorrhages (nr. per year)					
children (0-16 yrs)	4 (0-40)	10 (0-104)	3 (0-66)	7 (33)	2 (0-57)
adult (above 25 yrs)	4 (0-50)	5 (0-100)	2 (0-40)	3 (0-52)	1 (0-71)
hospital admissions					
admitted (%)	51	27	23	22	15
duration of stay (days/patient)	17 (2-180)	10 (1-50)	7 (1-50)	5 (0-72)	6 (0-31)
absenteeism due to hemophilia					
school (days)	30 (0-80)	5(0-80)	3 (0-50)	0 (0-15)	5 (0-20)
work (days)	2 (0-80)	13 (0-130)	7 (0-319)	5 (0-365)	3 (0-120)

Values presented are medians (range) or percentages
*Reported for the year previous to the questionnaire
†Due to hemophilia in patients following full time day education
‡Total absence in employed people between 15 and 64 yrs

One or more hospital admissions during the year preceding the survey decreased from 51% of patients with severe hemophilia in 1972 to 22% in 2001, which still clearly exceeded the rate of hospitalization in the general Dutch male population, which was 5% in 2000. The median

duration of stay in the hospital of patients with severe hemophilia decreased from 28 in 1972 to 7 days (range, 0-89 days) in 2001, which was similar to the figure for the general Dutch male population. Seventy percent of the admissions were directly related to hemophilia (e.g. hemorrhage or orthopedic surgery). Moderate and mild hemophilia also led to hospitalizations in excess of the rate in the population: in both patient populations 15% had to be admitted in 2001. Orthopedic surgery was a frequent indication for hospitalization, which occurred in 26% (n=107) of patients with severe hemophilia, in 17% of patients with moderate hemophilia and in 13% of patients with mild hemophilia in a 5-year period preceding the survey. In patients with mild hemophilia, 50% of orthopedic surgery was related to hemophilia, for patients with moderate and severe hemophilia this was 76% and 92%, respectively.

In 2001, absence from school was 7 days (range, 0-90 days) among the 121 patients (29%) with severe hemophilia who participated in full-time education, of which 4 days were due to hemophilia, in patients with moderate hemophilia this was 5 days, of which 2 days were due to hemophilia. The median number of days that patients with mild hemophilia were absent from school was 3 days (range, 0-40 days), of which 1 day was due to hemophilia. Absence from work for 157 patients with a paid job (full-time or part-time) in 2001 was on average 5 days, ranging from 0 days to a full year. Restricting to patients working full-time the median number of days absent from work was 3 (range, 0-242 days, mean,10.7 days). Considering a total work year of 260 days, absence from work was 4.1%. In the Dutch population this ranges from 5.5% (private companies) to 7.7% (civil service). In patients with moderate hemophilia this was 3 days (range, 0-365 days). Restriction on the capacity to perform regular labor among patients between 15 and 64 years with severe and moderate hemophilia is shown in Table 4.

Table 4. Inactivity of patients aged 15 to 64 with severe and moderate hemophilia who did not follow full daytime education, as compared to Dutch males

	1972 n=113	1978 n=168	1985 n=330	1992 n=352	2001 n=341
number of inactive patients (%)	24 (21)	52 (31)	115 (35)	125 (36)	92 (27)[†]
% inactive Dutch males	9	15	23	27	23
inactivity ratio[*]	2.3	2.1	1.5	1.3	1.2
median age of inactive patients	32 (16-60)	36 (19-64)	41 (19-64)	42 (20-62)	49 (17-63)

Data presented are numbers (%), percentages or median (range)
[*]The inactivity ratio was calculated as the ratio of inactivity in hemophilia patients and inactivity in Dutch males
[†] χ^2=3.44, p<0.05

Of the 'inactive' patients, 69 patients (75%) were officially registered as fully or partially disabled. Although the percentage of 'inactive' patients decreased compared to earlier surveys, the inactivity ratio remained constant over the last decade. In 2001 72% of patients with HIV infection performed a full-time or part-time paid job, compared with 51% in 1992. The median age of inactive patients had increased over the last 3 decades, from 32 years (range, 16-60 years) in 1972 to 49 years (range, 17-63 years) in 2001. Compared with the Dutch male population the unemployment rate was low, 2% in patients versus 2.5% in the Dutch male population.

Joints

Severe joint impairment was most frequently reported for the ankle, knee and elbow joints by patients with severe and moderate hemophilia (Table 5).

Table 5. Self-reported severe joint impairment in ankle, elbow and knee joints in patients with severe and moderate hemophilia

	Severity of hemophilia	
	severe (n=420) (<0.01 IU ml)	moderate (n=176) (>0.05-0.4 IU ml)
Ankle joints		
left	74 (18)	9 (5)
right	76 (18)	10 (6)
Knee joints		
left	67 (16)	13 (7)
right	69 (16)	17 (10)
Elbow joints		
left	34 (8)	5 (3)
right	45 (11)	5 (3)

None of the patients with mild hemophilia reported severe joint impairment in any of these 6 main joints. The overall proportion of patients with severe hemophilia reporting one or more severely impaired joints did not change much over the years: 31% in 1972 and 1992 and 34% in 2001 (Table 6).

Table 6. Self-reported impairment of the joints in patients with severe hemophilia

	1972	1978	1985	1992	2001
0-16 yrs					
median joint score (range)[#]	1 (0-19)	1 (0-25)	1 (0-10)	0 (0-7)	0 (0-33)
severe joint impairment[*]	7/65 (11)	8/92 (9)	4/111 (4)	1/92 (1)	4/130 (3)
17-25 yrs					
median joint score (range)	5 (0-16)	4 (0-25)	3 (0-19)	3 (0-12)	3 (0-13)
severe joint impairment	9/39 (23)	12/54 (22)	11/84 (13)	12/64 (19)	8/42 (19)
25-40 yrs					
median joint score (range)	10 (2-13)	9 (0-22)	8 (0-31)	7 (0-28)	5 (0-24)
severe joint impairment	22/39 (56)	21/69 (30)	41/115 (36)	42/119 (35)	30/89 (34)
above 40 yrs					
median joint score (range)	12 (4-26)	11 (3-41)	12 (0-42)	12 (0-40)	15 (0-48)
Severe joint impairment	11/16 (69)	16/30 (53)	44/74(60)	63/113 (56)	102/159 (64)
Overall					
median joint score (range)	5 (0-26)	5 (0-41)	5 (0-42)	6 (0-40)	5 (0-48)
severe joint impairment	49/159 (31)	57 (23)	100/384 (26)	118/388 (30)	144/420 (34)

Median joint score over 16 joints (min=0, max=48) and severe joint impairment in the left and right ankle, elbow and knee joints

[#] The median joint score was calculated as the median over the sum of the scores of 16 joints, which have been scored 0=no impairment, 1=some impairment 2=some impairment with daily problems, 3=severe impairment with total loss of function,

[*]Severe impairment with total loss of function reported in one or more of the six main joints

The same was observed for the median joint score, which was 5 in 1972 and in 2001. The percentage of patients reporting severe joint impairment in the age category 0 to16 years decreased since 1972. Although no change was observed in the percentage of patients with severe joint impairment in the age category 25 to 40 years, the median joint score showed a decrease. In patients older than 40 years, an increase was seen between 1992 and 2001 in the percentage of patients with severe joint impairment and the median joint score.

For patients with moderate hemophilia the median joint score remained low over 30 years: 1 point in 1972 to 2 points in 2001 (Table 7). The percentage of patients reporting severe joint impairment in at least one of the main joints slightly increased between 1992 to 2001 from 14% to 18%. In patients with moderate hemophilia older than 40 years, an increase in the percentage of patients reporting severe joint impairment was observed.

In the 2001 survey, 4 patients aged 0 to 16 years reported severe joint damage: all were treated with prophylaxis but still reported a high number of annual joint bleeds ranging from 3 to 10. No data were available on the severity of these bleedings. None of these patients reported the presence of inhibitory antibodies. In 2001, 43 % of the patients with severe hemophilia reporting severe joint impairment had one joint with total loss of function, 6% (n=8) reported a total loss of function in all six joints. The mean number of reported joints with severe impairment did not change over the years (data not shown).

Table 7. Self-reported impairment of the joints in patients with moderate hemophilia

	1972	1978	1985	1992	2001
0-16					
median joint score[#] (range)	0 (0-10)	0 (0-6)	0 (0-14)	0 (0-8)	0 (0-7)
severe joint impairment[*]	5/42 (12)	2/41 (5)	1/59 (2)	--	1/46 (2)
17-25					
median joint score (range)	2 (0-9)	1 (0-7)	1 (0-8)	1 (1-5)	1 (0-10)
severe joint impairment	1/14 (7.1)	--	1/22 (5)	--	1/23 (4)
25-40					
median joint score (range)	5 (0-27)	7 (0-17)	3 (0-20)	3 (0-12)	4 (0-16)
severe joint impairment	2/18 (11.1)	6/24 (25)	10/58 (17)	8/45 (18)	6/35 (17)
older than 40					
median joint score (range)	4 (0-10)	3 (0-15)	5 (0-24)	6 (0-24)	5 (0-44)
severe joint impairment	3/9 (33.3)	3/15 (20)	6/36 (17)	16/53 (30)	23/72 (32)
Overall					
median joint score (range)	1 (0-27)	1 (0-17)	1 (0-24)	2 (0-24)	2 (0-44)
severe joint impairment	11/83 (13)	11/95 (10)	18/157 (10)	24/173 (14)	31/176

Median joint score over 16 joints (min=0, max=48) and severe joint impairment in the left and right ankle, elbow and knee joints.
[#] The median joint score was calculated as the median over the sum of the scores of 16 joints, which have been scored 0=no impairment, 1=some impairment 2=some impairment with daily problems, 3=severe impairment with total loss of function,
[*]Severe impairment with total loss of function reported in one or more of the six main joints

Of all patients with severe hemophilia, 22 % did not report impairment of any of the main joints in 2001 compared to 19% in 1992 (Table 8).

Table 8. Absence of joint impairment in patients with severe hemophilia in the left and right ankle, elbow and knee.

	1972	1978	1985	1992	2001
Severe hemophilia					
0-16 yrs	26 (40)	40 (44)	53 (48)	56 (61)	76 (59)
17-25 yrs	2 (5)	5 (9)	7 (8)	9 (14)	7(17)
25-40 yrs	--	2 (3)	3 (3)	2 (2)	7(8)
above 40 yrs		--	3 (4)	1 (1)	4 (3)
Overall	28 (18)	47 (19)	66 (17)	74 (19)	94 (22)
Moderate hemophilia					
0-16	23 (55)	28 (68)	42 (71)	29 (71)	37 (80)
17-25	5 (36)	13 (50)	9 (41)	17 (50)	11 (48)
25-40	2 (11)	3 (13)	14 (24)	14 (31)	13 (37)
older than 40	3 (33)	5 (33)	11 (31)	15 (28)	17 (24)

The absence of joint impairment was related to age, it was reported by 59% of patients aged 0-16, 17% of those aged between 17 and 25 years, and 3% of patients with severe hemophilia older than years old. In 3 decades the percentage of patients that reported no joint damage in the age category 0 to16 years increased from 40% to 59%, and in the age category 17 to 25 years from 5% to 17%.

Side effects of treatment

The presence of neutralizing antibodies to factor VIII or IX (inhibitors), either in the present or in the past, was reported by 13% (52/420) of patients with severe hemophilia (14% or 51/388 in 1992), by 7% of patients with moderate hemophilia, and by 5% of patients with mild hemophilia (Table 9). Of these patients, 86 (96%) had hemophilia A.

Table 9. Complications of hemophilia treatment

	1972	1978	1985	1992	2001
inhibitory antibodies[*]					
cumulative incidence			31/384	51/388	52/420
current	--	--	19 (5)	29 (7)	15 (4)
past	--	--	12 (3)	22 (6)	37 (9)
HIV infection[†]	--	--	36 (4)	55 (8)	29 (5)
hepatitis C[‡]					
current infection	--	--	--	--	344 (45)
past infection	--	--	--	--	97 (13)

Values reported are number(%)
[*]Reported for patients with severe hemophilia
[†]Reported for patients treated with clotting factor before 1985
[‡]Reported for patients treated with clotting factor before 1992

In 2001, 29 patients (5%) treated before 1985 were HIV positive, of which 25 patients were also infected with HCV. In 1992, 55 (8%) patients were HIV positive. In 2001, 344 patients (44%) reported a current infection with HCV, whereas 97 patients (13%) had been infected in the past but have cleared the virus naturally or through treatment. As no specific items regarding this subject were included in the questionnaire we were not able to make a distinction between these 2 ways of clearance.

Discussion

In this repeated cross-sectional study, we studied the medical and social consequences of 3 decades of hemophilia treatment in the Netherlands. We observed a steady decrease in the annual number of hemorrhages, hospital admissions, duration of stay in hospital and days absent from school or work. Changes in treatment are reflected by an increase in the use of prophylaxis, especially in children. Despite intensified treatment, limited improvement was observed in self-reported impairment of joint function in patients older than 16 years. In the youngest patients a slight improvement was reported.

Our study offers a unique overview of the health status of hemophilia patients over a prolonged period of time. No other nationwide studies over such a long period of time are available. The estimated prevalence of hemophilia at birth is 20.3 per 100.000 male inhabitants[23]. With 7.91 million men in the Netherlands the estimated total number of hemophilia patients in the Netherlands is 1606. We reached 1567 patients with hemophilia and 70% participated in our study. As the non responders appeared not to differ from the responding patients in severity and type of hemophilia and were only slightly younger (33 vs. 36 years) we feel confident to generalize our findings to the total population of hemophilia patients in the Netherlands.

Self-reported data may be less objective compared with medical records or laboratory data but offer an important insight in the view of patients of their own situation. Because patients with hemophilia, especially patients with severe hemophilia, are confronted with their disease on a daily basis and are well informed about their disease, we assume data on treatment and side effects of treatment are trustworthy. To rule out error in information on type and severity of hemophilia, we contacted the treating physicians.

Between 1972 and 2001 the number of patients participating in the Hemophilia in the Netherlands project has doubled, which may be explained by the growth of the Dutch population and the registration of patients with hemophilia in treatment centers. Previously patients with severe hemophilia could be treated in hospitals all over the country. Since 2001 all patients with hemophilia need to be registered in one of the treatment centers.

Hemophilia treatment has intensified over the last three decades. We observed a marked increase in the use of prophylactic treatment in children, whereas in adults this was less pronounced. In 2001, 85% of all children with severe hemophilia and over half of the adult patients with severe hemophilia received prophylactic treatment. This increase is likely to have contributed to the decrease of the annual number of total hemorrhages. If only joint bleeds were taken into consideration, a lower number was observed in 2001 compared to 1992, which is in line with the findings of a single center study[8]. Although evolution to a more intense treatment regimen has resulted in a decrease of hospitalization, the percentage of patients with hemophilia annually admitted to hospital has still increased 3-fold compared to the Dutch male population. However, the number of days spent in hospital has decreased substantially from 28 to 7 days and is now equal to the mean duration of stay in hospital for all who are admitted. In our population, hospital admission occurred frequently in patients with mild and moderate hemophilia, which can be explained by the policy to admit patients with hemophilia for small operations or for observation after falls.

As we also observed in the 1991 survey, there was no further improvement in perceived joint impairment compared to the earlier surveys covering the period 1972 to 1985. A previous study presenting joint pathology by radiological assessments showed a clear improvement of the joint scores over the same period[8]. It may well be that perceived joint impairment did not

further improve due to different appreciations of signs and symptoms over time. Remarkably, even among patients under age 25 with severe hemophilia, 7% reported at least one joint with complete loss of function in the latest survey. The discrepancy between radiological assessments and our findings will be subject of future study. Some patients with moderate hemophilia reported severe joint impairment. Although our measure for joint impairment was self-reported and subjective, we may conclude from this that the goal of prophylactic therapy, which is aimed at a trough level of 1%, may not be ambitious enough.

We observed a cumulative incidence of inhibitors of 13% in patients with severe hemophilia, which is similar to other studies of previously treated patients[24] . Since 1985 this figure has stayed constant. The prevalence of HIV seropositivity has declined further, due to deaths and an increasing number of patients born after plasma products became safe. The positive effects of highly active antiretroviral therapy (HAART) in 1996 for HIV positive patients were observed through an improvement of participation in labor since 1992. About 40% of hemophilia patients treated with plasma-derived products before 1992 were infected with hepatitis C.

The number of days patients were absent from school or work due to hemophilia has decreased over the years. Similar figures for absence from work were shown by Szucs et al in 1998[25]. Remarkably, the percentage of absence from work in men with severe hemophilia working full-time was lower than in the Dutch male population in 2001. An improvement is also seen through a decrease in the percentage of inactive patients since 1992. This is in line with the Dutch male population. The inactivity ratio has become close to 1, from which we can conclude that patients with severe and moderate hemophilia participate as actively in the workforce as other men. These developments show that although a large number of adult

patients are limited in daily activities due to joint problems or viral infections, hemophilia has nowadays only a minimal influence on social participation.

It should be taken into consideration that the focus on the use of prophylactic treatment in the Netherlands has lead to a 260% increased annual clotting factor consumption over the last three decades. Mean clotting factor consumption for both patients on prophylaxis and on demand treatment increased from 610 IU kg^{-1} $year^{-1}$ in the 1970s to 1578 IU kg^{-1} $year^{-1}$ in the 1990s[8]. Clotting products have not become cheaper, which implies a larger increase in costs, which, however has been accompanied by direct and indirect gains (e.g., a decrease in absence from work and increased employment rates).

In conclusion our study shows that the treatment of patients with severe hemophilia in the Netherlands has focused on the use of prophylactic treatment, especially in children. This has resulted in an improvement of the medical and social situation of patients. Although the current situation of Dutch hemophilia patients proves to be good, more improvements are possible. A remarkable finding was that the prevalence of perceived joint impairments among young patients did not show the decrease we had expected.

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Chapter 2.3

Social functioning of patients with hemophilia

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Summary

Hemophilia is a hereditary clotting disorder characterized by bleeding occurring spontaneously (severe hemophilia) or after trauma and medical interventions (moderate and mild hemophilia). Since the introduction of replacement therapy in the 1960s medical and social circumstances have gradually improved. We compared social functioning and health related quality of life between hemophilia patients and the general male population.

All Dutch patients with hemophilia between 15 and 64 years were surveyed by a mail questionnaire. We gathered data on severity and type of hemophilia, viral infections, education, and employment. The Short Form 36 (SF-36) was used to assess Health Related Quality of life. Social functioning of patients born before (now 31-64 years of age) and after (now 15-30 years of age) the introduction of prophylactic treatment (around 1970) was compared to the general age-adjusted male population.

Of 1567 patients who were sent a questionnaire, 1066 returned it, of whom 733 were men between 15 and 64 years. Patients with severe hemophilia participated less in full time work compared to the general population; this difference with the general population was largest for the older patients. Occupational disability was reported by 35% of patients with severe hemophilia between 30 and 64 years, compared to 9% in the general population. Health-related quality of life of patients with severe hemophilia between 30 and 64 years was lower than of the general population on all domains. The differences with the general population in health related quality of life were least pronounced for patients between 15 and 30 years.

Despite major improvements in treatment during the last decades patients with hemophilia are still less involved in full time paid work and suffer more from occupational disability than men from the general population.

Introduction

Hemophilia is a X-linked hereditary bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Severe forms are characterized by major bleeding occurring spontaneously or after minor trauma. Repeated bleeding into joints may result in orthopedic problems due to hemophilic arthritis[1].

Since its introduction in the late 1960s replacement therapy with clotting factor VIII or IX has improved the medical and social situation of patients with hemophilia[2,3]. This is illustrated by considerable decreases in the annual number of hemorrhages, hospital stays and absence from work or school [4]. Furthermore, since the 1970s an increasing number of patients have successfully been treated prophylactically. In the 1980s many patients became infected with the Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV). Since 1985, products have been safe for HIV and since 1992 also for the transmission of HCV.

Our aim was to examine whether social functioning and quality of life of today's hemophilia patients differ from that of men without hemophilia.

Material and methods

Participants

A nationwide postal survey among all known patients with hemophilia, the Hemophilia in the Netherlands-5 study[4], was conducted in the Netherlands in 2001, following four previous surveys dating back to 1972. Details on this survey have been described previously[4]. Patients included were listed with the Netherlands Hemophilia Society, with the hemophilia treatment centers, or were known from updated mailing lists from previous surveys. The response to the

Hemophilia in the Netherlands-5 study was 70% (1066 out of 1519). For the present study we included all 733 participants who were between 15 and 64 years of age.

Assessments

A pre-structured questionnaire was part of a series of questionnaires that were used between 1972 and 2001 and included many items that were identical. We implemented the Short-Form-36 (SF-36) questionnaire that measures Health-related quality of life. The SF-36 is a 36-item questionnaire that measures eight parameters of perceived health status: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception. Viral status, treatment modalities, educational levels and annual numbers of hemorrhages were assessed through self-reported data. The self reported type and severity of hemophilia were verified with data from the treatment centers. Data on the absence from school or work referred to the year that preceded the survey (2000). Data on employment, occupational disability and employment levels were compared to national figures on the general male population that were provided by the Central Bureau of Statistics Netherlands (CBS)[5].

All occupations reported by participants were scored according to the Standard Occupational Classification (SBC) published by the CBS[6]. According to this classification, occupations are distinguished through the level of the needed abilities to perform the occupation. The classification differentiates between the following employment levels: elementary level, low level, moderate level, high level and academic level. The levels of employment are in line with educational level e.g. to perform a job at the elementary level primary education is needed and to perform a job at the high level secondary school at the highest level or college is needed. The jobs at the elementary level and the low level were considered to be blue-collar jobs in contrast to white-collar jobs defined as jobs at the high or academic level.

Occupational disability according to Dutch law

The Netherlands has an extensive social security system, which includes several social insurance schemes which offer protection against the risk of loss of income and exceptional expenditure due to old age, death, illness, disablement or unemployment.

The Occupational Disability Insurance Act (WAO) provides insurance against the financial consequences of long-term incapacity to work. Under the WAO people are entitled to benefits if they have been disabled for more than 52 weeks. According to the Dutch system occupational disability is defined as not being able to perform normal labour due to disease or a deficiency. In our study occupational disability status was self-reported.

Data analyses

We categorized the patients according to whether they were born before (now aged 30-64 years) or after (now aged 15 to 30 years) the introduction of prophylaxis in the Netherlands. As the clinical characteristics of hemophilia A and hemophilia B do not differ we present combined results for hemophilia A and B. The severity of hemophilia was classified according to residual percentage of factor VIII or IX clotting activity: severe (<0.01 IU/ml), moderate (0.01-0.05 IU/ml) or mild (>0.05-0.40 IU/ml). The inactivity ratio was calculated as the ratio of inactivity in the study population and inactivity in Dutch men. Patients that did not have a paid job were defined as inactive. The outcome values of the SF-36 were compared to age-specific reference data for the Netherlands[7]. In the analyses on health-related quality of life (HRQol) we only included patients without missing values on any of the domains. We calculated mean values and differences for all health-related quality of life scales; in addition we calculated differences adjusted for age.

Results

A total of 1066 patients with hemophilia A or B participated in our study (response 74%), and of all patients who responded 733 were aged between 16 and 64 years and therefore eligible for the current analyses. Of 6 patients information on employment was missing; they were excluded from the analysis.

Table 1. Personal characteristics of participants according to age and severity of hemophilia

	Severe hemophilia	Moderate/Mild hemophilia
Born before introduction prophylaxis (30-64 yrs)	N=200	N=337
Type of hemophilia		
Hemophilia A	170 (85)	297 (88)
Hemophilia B	30 (15)	40 (12)
Treatment modalities		
Prophylactic	105 (53)	8 (2)
On demand	28 (14)	271 (80)
Combination	60 (30)	22 (7)
Viral infections		
Hepatitis C positive	149 (75)	108 (32)
HIV positive	17 (9)	6 (2)
Born after introduction prophylaxis (15-30 yrs)	N=83	N=107
Type of hemophilia		
Hemophilia A	69 (83)	92 (86)
Hemophilia B	14 (17)	15 (14)
Treatment modalities		
Prophylactic	68 (82)	8 (8)
On demand	8 (10)	76 (71)
Combination	7 (8)	18 (17)
Viral infections		
Hepatitis C positive	41 (49)	18 (17)
HIV positive	6 (7)	0

Data presented are numbers (percentages)

Table 1 shows the characteristics of patients with severe hemophilia (n=283) and patients with moderate and mild hemophilia (n=444) according to the two age groups. Patients born after the introduction of prophylaxis more often used prophylactic treatment than patients before the introduction of prophylaxis (82 vs. 53%). The prevalence of HIV and hepatitis C positivity was higher in severe hemophilia than in moderate and mild hemophilia both in men born before the introduction of prophylaxis (difference =43%, 95% Confidence Interval (CI) 35-50) and born after the introduction of prophylaxis (difference= 33%, CI 20-46).

Employment status

Table 2 shows the employment status of hemophilia patients compared to the general population, according to whether patients were born before or after the introduction of prophylactic treatment.

The participation in full time paid work for patients with mild and moderate hemophilia was similar to the general population in both age groups (71% vs. 73% in those aged between 30 and 65 years, and 46% vs 52% in those aged between 15 and 30 years). Patients with severe hemophilia participated less in full-time paid work than the general male population, 50% vs. 73% (difference=23%, CI 17-31). In young patients (15-30 yrs) with severe hemophilia the difference with the general population was 19% (33% vs. 52%). One third of the younger patients participated in full time education (n=86, 30%).

Patients with severe hemophilia slightly more often were part-time employed than men of the general population, especially in the oldest age category. In both age groups unemployment occurred less often than in the general population: inactive patients were mainly legally disabled. Overall in 2001 27% of patients (severe and moderate hemophilia) were inactive compared to 23% in the Dutch male population, resulting in an inactivity ratio of 1.2.

Table 2. Professional characteristics of hemophilia patients born before or after the introduction of prophylaxis

	Severe hemophilia	Moderate/Mild hemophilia	General population
Born before introduction prophylaxis (30-64 years)	200	337	3.906.000
Full time education	0	0	?
Part time education	11 (60)[*]	15 (5)[†]	?
Full-time work	99 (50)	240 (71)	2860 (73)
Part-time work	35 (18)	26 (8)	378 (10)
Unemployed	2 (1)	6 (2)	(2.3)
Occupational disability	69 (35)[**]	52 (15)	282 (9)
Retired	7 (4)	12 (4)	
Born after introduction prophylaxis (15-30 yrs)	83	107	1.527.000
Full time education[‡]	37 (45)	49 (46)	?
Part time education[•]	6 (7)	14 (13)	?
Full-time work	27 (33)	47 (44)	792 (52)
Part-time work	21 (25)	17 (16)	371 (24)
Unemployed	1 (1)	3 (3)	(5.4)
Occupational disability	4 (5)	2 (2)	46.9 (2)

Data presented are numbers or number (percentage)
[*]8 patients were involved in either full-time or part-time work, [**]15 patients were both disabled and involved in either full-time or part-time work, [†] 13 patients were also involved in full-time or part-time work and 1 patients was disabled, [‡] 12 patients with severe hemophilia were also involved in part-time work and 13 patients with moderate or mild hemophilia, [•]5 patients with severe hemophilia and 12 with moderate/mild hemophilia hemophilia were involved in either full-time or part-time work

Table 3 shows the level of employment according to severity of hemophilia and among the general population. Fewer patients were employed in blue-collar work than in the general population (24%), both for patients with severe hemophilia (13%) and for patients with mild and moderate hemophilia (20%). The employment in managerial or academic positions especially in patients with severe hemophilia was higher, 29% vs. 21% and 12% vs. 9%.

Table 3.Employment level according to severity

Employment level*	Severe hemophilia N=181	Moderate/mild hemophilia N=331	General population
Elementary level	4	5	6
Lower level	13	20	24
Moderate level	36	39	38
High level	29	25	21
Academic level	12	7	9
Unknown	5	3	2

Data presented are percentages
Only patients included who have a full-time or part-time paid job
*All reported professions were scored according to a standard classification in which the employment levels resemble educational levels.

Limitations in work

Legal occupational disability was reported by 35% (69/200) of patients with severe hemophilia between 30 and 64 years, compared to 9% in the general population. In patients with mild and moderate hemophilia the difference in occupational disability with the general population was 6% for patients between 30 and 64 years. The proportion of young patients with moderate and mild hemophilia who were disabled was similar to that in the general population. A substantial number of the employed patients with severe hemophilia reported to experience restrictions in performing their job due to hemophilia (71 out of 181, 39%). In patients with mild or moderate hemophilia this was 19%. These restrictions consisted of pain and frequent absence from work.

Health-related quality of life

A total of 623 patients completed the SF-36 of whom 532 patients were eligible to work. Table 4 shows health-related quality of life of patients involved in a paid job, either full-time or part-time (n=422), and of patients who were not employed (n=110).

Table 4. Health-related Quality of life in relation to employment.

	Employment Full time or Part-time			
	Yes n=422 Mean (sd)	No n=110 Mean (sd)	Difference (95CI)	Adjusted for age (95CI)
Physical functioning	81.6 (24.0)	47.8 (31.9)	33.8 (28.3-39.2)	28.3 (22.9-33.6)
Social functioning	87.1 (20.2)	63.0 (26.9)	24.1 (19.5-28.7)	21.6 (16.9-26.3)
Role-Physical	79.6 (35.5)	39.8 (43.0)	39.8 (32.0-47.7)	37.3 (29.3-45.4)
Role-Emotional	88.2 (29.3)	59.4 (45.2)	28.8 (21.9-35.8)	26.5 (19.3-33.7)
Mental health	78.9 (15.9)	67.1 (20.9)	11.8 (8.2-15.4)	10.6 (6.9-14.3)
Vitality	69.1 (18.7)	54.7 (20.1)	14.4 (10.4-18.4)	13.2 (9.0-17.3)
Bodily pain	81.5 (21.3)	61.0 (29.0)	20.4 (15.6-25.3)	19.4 (14.4-24.4)
General health	70.3 (20.8)	50.7 (26.1)	19.6 (15.0-24.3)	18.0 (13.3-22.8)

Only patients included who were eligible to work (not involved in full-time education or retired).

Differences between the employed and unemployed patients were largest in the domain of physical functioning (28 points CI 23-34), role limitations due to physical problems (37 points CI 29-45) and role limitations due to emotional problems (27 points CI 19-34). Employed patients scored higher on all domains of health related quality of life than unemployed

patients. Patients with severe hemophilia aged between 30 and 64 years scored lower on all scales of the SF-36 except mental health than the general population (Table 5a).

Table 5. Quality of life of hemophilia patients born before the introduction of prophylaxis

	Severe N=144	Moderate/mild N=244	General population
Born before introduction of prophylaxis (30-64 years)	Mean (sd)	Mean (sd)	Mean (sd)
Physical functioning	45.9 (28.5)	83.1 (23.8)	84.0 (19.6)
Social functioning	72.5 (25.7)	83.5 (23.8)	83.5 (22.1)
Role-Physical	49.5 (43.8)	78.4 (37.5)	74.5 (36.8)
Role-Emotional	67.4 (42.9)	85.2 (33.0)	81.6 (33.2)
Mental health	73.4 (19.1)	76.6 (18.5)	75.6 (18.5)
Vitality	61.4 (20.7)	66.6 (21.1)	68.6 (20.2)
Bodily pain	64.5 (24.3)	82.5 (23.5)	71.8 (24.1)
General health perception	56.8 (23.5)	68.3 (23.3)	69.7 (20.6)

Table 6. Quality of life of hemophilia patients born after the introduction of prophylaxis

	Severe N=102	Moderate/mild N=133	General population
Born after introduction of prophylaxis (15-30 years)	Mean (sd)	Mean (sd)	Mean (sd)
Physical functioning	82.2 (21.4)	94.0 (12.9)	93.1 (11.8)
Social functioning	87.6 (20.2)	91.4 (17.5)	87.8 (19.1)
Role-Physical	73.0 (38.0)	90.4 (24.6)	86.4 (27.6)
Role-Emotional	86.6 (29.0)	94.9 (20.3)	85.4 (30.0)
Mental health	79.9 (14.0)	80.1 (14.5)	78.7 (15.2)
Vitality	71.9 (15.1)	72.2 (15.6)	70.7 (16.4)
Bodily pain	76.9 (22.9)	88.7 (18.9)	80.9 (19.4)
General health	69.9 (22.2)	76.2 (18.3)	78.4 (17.3)

Patients with severe hemophilia between 15 and 30 years scored lower on physical functioning, role limitations due to physical functioning, bodily pain and general health than the general population, but not on role limitations due to emotional functioning, mental health and vitality (table 6).

Patients with moderate and mild hemophilia between 30 and 64 years scored higher on role limitations due to physical limitations, role limitations due to physical problems, mental health and bodily pain than men from general population. Younger patients with moderate and mild hemophilia scored higher or had a similar score on all scales, but scored lower on general health. .

Discussion

When compared to the general population, patients with severe hemophilia participate less in full time work; they suffer more often from occupational disability, and mainly are employed at high job levels. Patients with moderate and mild hemophilia differ only slightly or not from their peers.

Our study offers an overview of the occupational status of Dutch hemophilia patients in 2001. The estimated prevalence of hemophilia is 20.3 per 100.000 inhabitants [8]. With 7.91 million men in the Netherlands the estimated total number of hemophilia patients in the Netherlands is 1606. We reached 1567 patients with hemophilia, and 70% participated in our study. As the non-responders appeared not to differ from the responding patients in severity and type of hemophilia and were only slightly younger (33 vs. 36 years) we feel confident to state that our findings validly describe the situation of hemophilia patients in the Netherlands. Our data were compared to information from the Central Bureau of Statistics (CBS) providing information on the social situation of Dutch males. Our data and most of the data by the CBS

were assessed using self-reported questionnaires. However misclassification may have influenced our findings on occupational disability; the CBS gathered these data through disability registries while we collected self-reported data.

In 1985, we performed a similar study examining prospects of hemophilia patients in the labour market, and found an overall percentage of employment (either full-time or part-time) of 58% in patients between 15 and 65 years[9]. In the present study, overall employment was 70%. Apparently since 1985 the social situation of hemophilia patients has improved. However, secular trends have also occurred in the general population, and therefore we calculated the inactivity ratio, which was 1.5 in 1985 compared to 1.2 in 2001 [4]. A study from Great-Britain reported that 65% of all patients with severe hemophilia were full-time employed[10].

Despite important improvements, employment figures among young patients were slightly lower than among the general population. One explanation may reside in the fact that hemophilia patients more often followed full time education. Additionally, hepatitis C infections may have affected employment status, especially among patients with severe hemophilia. Although the period between infection and clinical problems is long, some young patients may already be faced with physical problems such as liver cirrhosis. And, treatment of hepatitis C may cause serious side effects, which may also influence participation in "normal" social life.

Our findings confirm those of earlier studies reporting a higher educational level of patients with hemophilia[11]. A survey performed in 1985 showed that 72% of patients with hemophilia were involved in white collar jobs compared to 57% of the general population[9]. This transition towards the "white collar" jobs can be explained by the fact that blue- collar jobs

may not be suitable for patients with hemophilia, in which case it is not so much that hemophilia patients are more often employed in high level jobs, but that they are less often employed in blue collar jobs. There are several aspects that hemophilia patients have to take into account of which the risk of bleeding due to daily activities in work is probably the most important. Another aspect influencing the choice of work may be the presence of hemophilic arthropathy resulting from repetitive bleeding into joints. Arthropathy has a negative effect on labor force participation [12]. Of course patients born before the introduction of prophylaxis may have developed joint damage earlier in their lives. It has been shown that prophylaxis started later in life does not halt the progression of arthropathy[13].

The association between employment and health related quality of life should be interpreted with caution. Many factors may influence health related quality of life, such as viral infections and the presence of arthropathy. Health-related quality of life of patients with severe hemophilia born before the introduction of prophylactic treatment in the Netherlands was lower than that of the general population. In young patients quality of life seems to be similar to the general population.

Despite major improvements in treatment during the last decades patients with hemophilia are still less involved in full time paid work and suffer more from occupational disability than men from the general population.

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Chapter 2.4

Hepatitis C infection among Dutch haemophilia patients: a nationwide cross-sectional study into prevalence and antiviral treatment

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Summary

Hepatitis C is a major co-morbidity among patients with haemophilia who received inadequately or non-virus inactivated clotting factor concentrates before 1992. The objectives of this study were to investigate the prevalence of hepatitis C and the use of antiviral therapies during the last decade among patients with haemophilia in the Netherlands.

We performed a cross-sectional study and a questionnaire was sent to all 1519 patients known with haemophilia in the Netherlands between 2001 and 2002. The study population for the present study consisted of 771 patients who had received clotting factor products before 1992 of whom 638 reported their hepatitis C status.

In total 441 of the 638 (68%) patients ever had a positive test for hepatitis C virus (HCV); 344 patients (54%) had a current infection, and 97 (15%) had cleared the virus. Among 344 patients currently HCV infected, 111 (32%) had received treatment for hepatitis C, while 34% (33/97) of patients with an infection in the past had been treated for hepatitis C.

In 2002 the prevalence of hepatitis C among patients with haemophilia who received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.

Introduction

Haemophilia is an X-linked bleeding disorder caused by a partial or complete lack of clotting factor activity: factor VIII in haemophilia A and factor IX in haemophilia B. Since the 1960s haemophilia patients have received intravenous factor VIII and IX replacement therapy[1]. In the following years it became apparent that viruses like Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV), formerly known as non-A non-B hepatitis, were transmitted due to transfusion of infected plasma products[2,3]. Patients treated with large pool products were infected with HCV in 98%, whereas patients treated with cryoprecipitate were infected in 66% of the cases[4]. In the early 1990s, methods were developed to adequately inactivate HCV and subsequently donor screening for HCV was introduced, resulting in HCV safe clotting products[4-6].

Once infected, about 10-20% of the patients are able to clear the virus spontaneously, while the others develop a chronic carrier state[7-9]. Untreated HCV infection may progress to liver fibrosis, cirrhosis or hepatocellular carcinoma[10,11]. Liver disease caused by HCV is now recognized as an important cause of morbidity in haemophilia patients[12]. Treatment for non-A non-B hepatitis became available in 1986[13,14]. Today pegylated interferon (Peg-IFN) in combination with ribavirin is the most effective therapy for hepatitis C[15].Success of therapy is mainly dependent on genotype and viral load[16]. Antiviral drugs cause side effects, like anaemia, neutropenia, depression and flu-like symptoms in the majority of the patients[17-19]. Little or no information is available on the current prevalence of hepatitis C and antiviral treatment history among patients who have received inadequately or non-virus inactivated clotting factor concentrates before 1992. We therefore investigated the prevalence of hepatitis C infection and assessed the use of antiviral therapy among patients with haemophilia in the Netherlands.

Materials and methods

Setting

Data for the present study were collected within the last survey of a series initiated by Veltkamp in 1972[20]. Since then nationwide surveys were repeated in 1978, 1985, 1992 and in 2001[21-24]. These studies aimed to assess the medical and social consequences of haemophilia in the Netherlands. In 2001, postal questionnaires were sent to all 1519 patients known with haemophilia in the Netherlands, who were either registered at the Netherlands Hemophilia Patients Society, at the haemophilia treatment centres or known from previous surveys. In this last survey items on hepatitis C were added for the first time.

Data

The study population consisted of patients who were treated with clotting factor products before 1992 and who reported their hepatitis C status. These patients were potentially at risk for HCV infection because they were treated with non-virus inactivated or inadequately inactivated clotting factor concentrates. Severity of haemophilia was defined by the percentage of factor VIII or factor IX clotting activity: severe haemophilia <1%, moderate haemophilia 1-5%, and mild haemophilia 5-40% clotting factor activity. Reported type and severity of haemophilia were verified with information from the treatment centres. In addition, data on haemophilia type and severity of non-responders were obtained from treatment centres or from the previous questionnaire performed in 1992. Haemophilia type and severity of 346 non-responders were similar to those in the study population. Items on hepatitis C and HIV were obtained from the questionnaire. Information on the hepatitis B status was not collected.

To assess the validity of the self-reported items on hepatitis C, a random sample of 92 patients (14%) was taken from the two largest participating centres verifying their reported hepatitis C status with information from their treating haematologist.

Statistics

Infection with HCV was defined as three possible status: never infected with HCV, HCV infection cleared and chronic hepatitis C. 'Never infected with HCV' was defined as negative for both HCV antibodies and HCV-RNA in serum. A 'cleared HCV infection' or ′infection in the past′ was defined as positive for HCV antibodies but negative for HCV-RNA. 'Chronic hepatitis C' was defined as positive for both HCV antibodies and HCV-RNA. In addition, 'ever infected with HCV' was defined as positive for HCV antibodies, regardless of the HCV RNA result.

To study risk of infection according to period of treatment, a sub-analysis was performed comparing infection rates between patients first treated before 1985 with patients first treated between 1985 and 1992. Patients with incomplete treatment history were excluded for this sub-analysis.

The HCV status according to type and severity of haemophilia was compared by using the Chi-Square test. Mean values with 95% confidence intervals of age according to severity of haemophilia and HCV infection status were calculated.

Results

A flow chart of the selection of patients for this study is shown in Fig. 1.

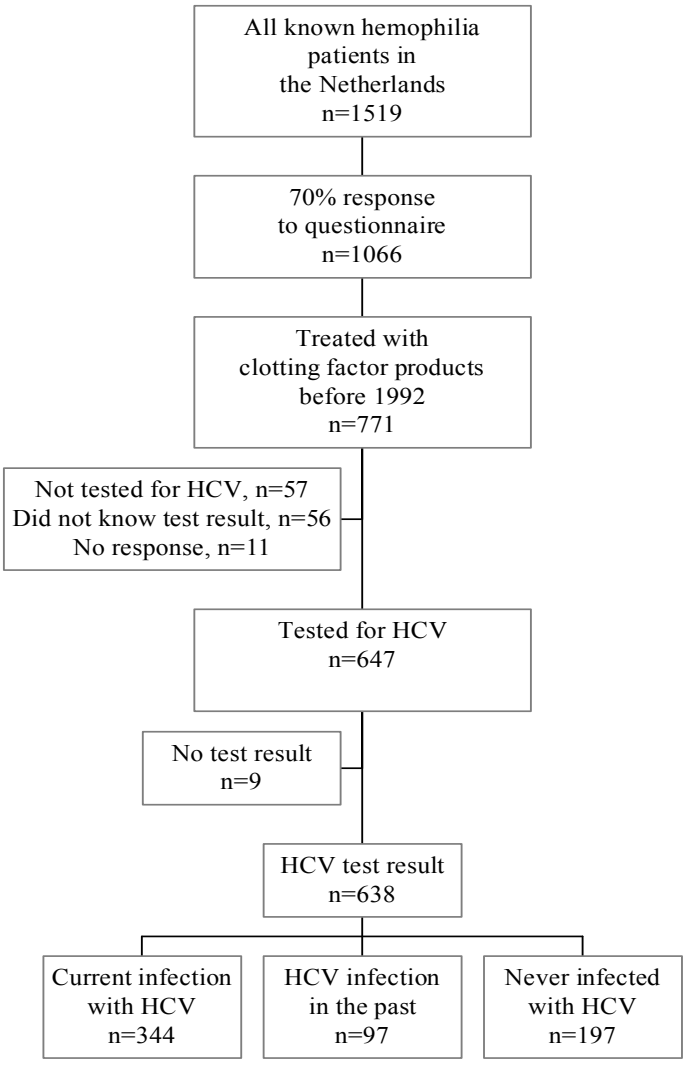

Fig. 1. Flowchart of selection of study population.

The response to the questionnaire was 1066 of 1519 (70%). General characteristics of the participants are shown in Table 1.

Table 1. Patient characteristics*

Total number of patients	638
Age in years	41 (10-87)
Haemophilia type	
A	557 (87%)
B	81 (13%)
Severity of Haemophilia	
Mild	211 (33%)
Moderate	112 (18%)
Severe	315 (49%)
Patients treated before 1985†	523 (82%)
HIV positive	28 (5%)
Patients treated before 1992‡	638
Anti HCV positive	441 (68% of tested patients)
HCV RNA positive	344 (54% of tested patients)

* Information of patients treated before 1992 with a reported HCV test result. Values are medians (range) or numbers (percentage)
† At risk for HIV infection due to not adequately or non-virus inactivated clotting factor products
‡ At risk for HCV infection due to not adequately or non-virus inactivated clotting factor products

Hepatitis C

Patients treated with clotting products before 1992

A total of 771 patients were at risk for HCV infection (i.e. treated before 1992); 599 were already treated with clotting products before 1985, 136 were treated exclusively between 1985 and 1992, whereas 36 patients reported to have been treated before 1992 but not whether they were also exposed to clotting products before 1985. 638 of these 771 patients reported their

HCV status. Among the 133 patients at risk without a HCV test result, 68% had mild haemophilia.

In the verification sample, 92% (85/92) reported their hepatitis C status correctly; 96% of patients with an HCV infection and 88% of patients with a cleared infection or those who where never infected.

Among 638 patients treated with clotting factor products before 1992 and tested for HCV, 441 (68%) ever had an anti-HCV positive test; 344 (54%) reported to be currently infected with HCV, 97 (15%) reported an infection in the past and 197 patients (31%) had never been infected. No infections with HCV occurred in patients who were treated after 1992 only.

HCV infection was related to type of haemophilia; patients with haemophilia B had been infected more often than those with type A (84% vs. 67%, $P < 0.01$). Among patients at risk for HCV transmission, patients with severe haemophilia had the highest prevalence of hepatitis C (severe 65%, moderate 53%, mild 37%, $P < 0.001$).

The mean age of patients differed according to severity of haemophilia and HCV status; patients with severe haemophilia, who were never infected, were younger (mean age 23 years, 95% confidence interval (CI) 19-28) than both patients with severe haemophilia who cleared HCV (37 years, CI 33-41), and those currently infected (43 years, CI 41-45).

Infection rate of HCV according to treatment period

Although HCV inactivating steps were applied since 1985, risk of HCV infection was not completely eliminated. 523 of 599 patients treated before 1985 and 95 of 136 patients treated 1985-1992 reported their HCV status. Among patients treated before 1985, 62% reported to be currently infected, while 17% cleared HCV. In contrast, the proportion of patients with chronic HCV infection was only 18%, with 7% clearing HCV and 75% never infected in those first treated between 1985 and 1992.

HIV infection

The prevalence of HIV infection among patients treated before 1985 and reporting their HIV status was 5% (28/523).

Treatment of hepatitis C

Among the 344 patients with a current HCV infection, 68% (233) had not been treated with antiviral drugs. The main reasons for refraining from therapy were shrinking from side effects (46%), normal liver function tests (45%) and expected low effectivity (35%). Other reported reasons were: doctor not convinced of benefit of treatment (19%), treatment not discussed by doctor (18%) and lack of time among patients (9%). Over the last decade, the proportion of patients having been treated is increasing (Fig. 2).

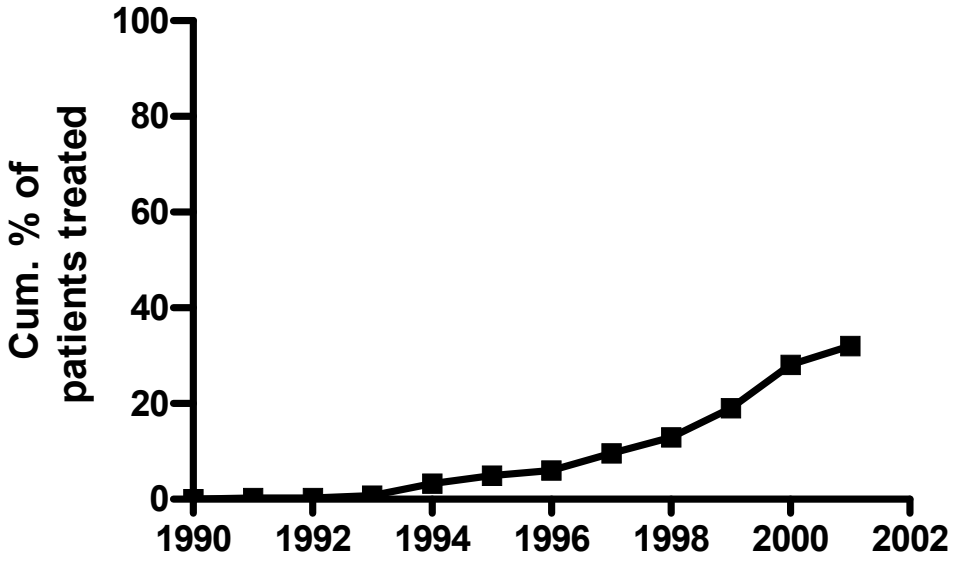

Fig 2. Cumulative percentage of all HCV infected patients with haemophilia treated with antiviral therapy during the last decade. Considering a spontaneous clearance of 15%, the maximum cumulative percentage would be 85%.

Treatment for HCV was completed among 128 patients and successful treatment was reported in 26% (33/128). Sixteen patients were currently on combination therapy of IFN and ribavirin. Among patients who finished therapy, 57 patients were treated with IFN monotherapy, 51 patients with the combination of IFN and ribavirin, while 13 patients were first treated with monotherapy and later retreated with combination therapy. Seven patients did not remember their treatment regimen.

Patients reported side effects of antiviral therapy in 84% (121/144). Fatigue (78%), flu-like symptoms (73%), and depressive symptoms (46%) were most frequently reported. In 15% of treated patients therapy was discontinued because of side effects.

Discussion

We report on a nationwide survey on the current prevalence of hepatitis C in haemophilia patients. Of 771 patients at risk for HCV infection, 638 reported their hepatitis C status. Fifty four per cent of tested patients reported to be currently infected with HCV, of whom 32% had been treated with antiviral therapy.

We performed a cross-sectional study to assess the prevalence of hepatitis C infection among patients with haemophilia in the Netherlands and to examine the use of antiviral treatment. To appreciate our findings some limitations need to be discussed. First, the response rate to the questionnaire was 70%, and selection bias cannot be ruled out. Non-responders to the questionnaire may have been less severely affected, therefore failing to see the need for a survey in this population. This may have led to an overestimation of the prevalence of hepatitis C. However, percentages of type and severity were similar in responders and non-responders, rendering bias less likely.

Secondly, self-reported data may be unreliable. We therefore performed a validation study, and found that these self-reported data were highly reliable, confirming previous observations

that, most patients with haemophilia are well informed about their disease and its complications[21].

In this study, 68% of all tested patients potentially exposed to insufficiently viral inactivated clotting factor products had ever been infected with HCV and 54% of them reported a current HCV infection. The prevalence of hepatitis C in this population is similar to that reported by others[4,9,25]. As expected, the prevalence was highest among patients with severe haemophilia due to a higher number of exposures to clotting products than patients with mild or moderate disease. Haemophilia B was associated with a higher HCV infection rate (84% vs. 67%) due to exclusive treatment with large pool plasma products, whereas patients with haemophilia A were in many cases exclusively treated with small pool cryoprecipitate[26]. Confirming data in a Dutch study on 316 patients, reported HCV infection rates of 66% and 98% in patients exclusively treated with small pool cryoprecipitate and patients treated with large pool products, respectively[4]. In addition, the proportion of patients with severe haemophilia was higher among patients with haemophilia B than in those with haemophilia A (58% vs. 48%), with concomitant higher exposure rates to potentially unsafe clotting factor products.

In our study, we found that the risk of HCV transmission was lower among younger patients. This may be explained by the lower number of exposures and the introduction of dry heat treatment (up to 68°C) in 1985. Although completely effective for HIV, this method of viral inactivation did not eliminate HCV infection risk, but resulted in a reduction of HCV load only[27]. This is also shown in our study, in which patients exclusively treated with clotting products between 1985 and 1992, had a lower risk of HCV infection than patients treated before 1985. Although this risk was decreased, HCV transmission was not eliminated. Finally, donor screening, pasteurisation, steam heat treatment and chemical viral inactivation through the combination of solvent and detergent methods were introduced on a large scale, eliminating transmission of HCV completely in 1992[6,28,29].

Although there has been a trend towards starting treatment of HCV infection, so far only 32% of the HCV infected patients reported use of antiviral therapy, with a success rate of 26%. The main reasons for refraining from antiviral therapy were expected low effectivity of therapy, normal liver function tests and expected side effects. The argument of low expected effectivity loses its strength as treatment with PegIFN and ribavirin results in a sustained response in 50- 90% in treatment naive patients dependent on viral genotype[18]. It has been suggested that refraining from therapy in case of normal liver function tests may be appropriate in patients with genotype 1 and 4 with normal histology at liver biopsy[30]. But this is inappropriate in patients with HCV genotype 2, 3 and 5, of whom 90% will achieve a sustained response.

Fatigue, flu-like symptoms and depression were the most frequently reported adverse events of antiviral therapy; this is in accordance with other reports[17]. Depression has been a common indication for dose reduction or even discontinuation of therapy[17,31]. Discontinuation of therapy due to adverse effects was reported in 15% in this study and was similar to that reported by others[18,19,32,33].

The reported reasons for refraining from antiviral therapy indicate that there are still uncertainties about long-term complications of hepatitis C and effectivity of antiviral therapy. Therefore, patients need to be fully informed about HCV infection, its consequences, possibilities of treatment, and its effectivity.

In summary, this study shows that hepatitis C is still a major comorbidity in the Dutch population of haemophilia patients and only a minority of patients with an HCV infection has been treated.

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Chapter 2.5

The uptake of recombinant Factor VIII in the Netherlands

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Summary

In comparison with other biotech substitutions, the adoption of recombinant Factor VIII (rFVIII) has been relatively slow. We sent a postal questionnaire to all Dutch haemophilia patients and haemophilia treating physicians, to determine which factors predict whether a patient uses plasma derived FVIII (pdFVIII) or rFVIII and to investigate patients' and doctors' opinions on both products.

Fifty-six per cent of patients received rFVIII. This percentage varied widely between centres. Only one doctor would choose to use pdFVIII if he would suffer from haemophilia A himself, and 74% would choose to use rFVIII. Younger patients, those not infected with HIV or hepatitis C, and those who did not have family members who used pdFVIII, switchted more often from pdFVIII to rFVIII. Patients who rated themselves as innovative, who had family members who used rFVIII, and those who were treated in a large haemophilia treatment centre, were also more likely to have switched. For physicians and patients alike, the respondents generally did not see large differences between rFVIII and pdFVIII, except for the risk of infections and the knowledge on long-term effects (both larger for pdFVIII). Although haemophilia patients represent one of the most empowered patient groups, physicians appear to have been influential in choosing between pdFVIII and rFVIII.

Introduction

In 1995, recombinant Factor VIII (rFVIII) was introduced in the Netherlands for the treatment of patients with haemophilia A, as a substitute for plasma derived Factor VIII (pdFVIII). Of the Dutch haemophilia patients who were treated with plasma derived clotting factors before 1985, 16-17% had become infected with the human immunodeficiency virus (HIV)[1,2]. In addition, the large majority (about 80%) of patients had been infected with hepatitis C[3,4]. Because of this history of infectivity with plasma derived clotting factors, one might have expected that rFVIII would have been quickly adopted by the market. This, however, has not been the case. In 2001, 6 years after its introduction, rFVIII was used by 50% of the Dutch haemophilia patients, while the other 50% continued to use pdFVIII[5]. Compared with other biotechnology substitutions, the uptake of rFVIII is slow. In the Netherlands, both recombinant human growth hormone and recombinant human insulin quickly completely replaced their organic counterparts, and the recombinant follitropins have captured an 80% market share within 4 years[6-8]. The uptake of rFVIII in the Netherlands has also been slower than in other countries. Ireland, Scotland and Denmark have completely switched from pdFVIII to rFVIII as a matter of health policy. In France rFVIII represents 80% of all FVIII used[9], and in Germany it represents 50% .

Apparently, doctors and/or patients have been hesitant to adopt rFVIII. Explanations may be that they fear some unforeseen long-term negative effect caused by the use of rFVIII, or that they are concerned about increased antigenicity of rFVIII, as this was debated in the early 1990s[10-12], even though the current scientific believe is that this is not the case[13-15]. The Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB) is the major provider of pdFVIII in the Netherlands. Loyalty towards this organisation might be another reason for the hesitation. As in the past the prevalence of HIV positivity was highest in countries that predominantly used FVIII preparations derived from plasma of paid donors

from the USA[2], there might be a preference for a Dutch not-for-profit organisation that relies on non-paid donors. Also, it has been argued that it is not possible to switch all patients to rFVIII, even if they wanted to, because the supply of rFVIII is not sufficient[5]. Indeed, at the time of our study there was a sudden shortage of rFVIII, as Bayer, one of the major producers of rFVIII, had suspended market release for its worldwide market[16]. In addition, there may have been doubts about the advertised increased safety of rFVIII with regard to transmission of infections. The first rFVIII preparations contained plasma-derived albumin as a stabilizer. In 1999 and 2000, three virtually albumin-free formulations (Refacto®, Kogenate Bayer® and Helixate NexGen®) were introduced. They contain 1000-times less plasma-derived albumin than the former formulations, and have an additional detergent based purification step, aimed at further reducing the potential for transmission of infectious agents[17].

As far as we know, the factors that underlie the choice for either plasma derived or rFVIII have never been systematically studied. Who is the most influential in choosing between pdFVIII and rFVIII: the doctor or the patient? Can the adoption of rFVIII be predicted from medical characteristics such as severity of the disease, treatment modality, or infections contracted through the use of clotting factors (HIV, hepatitis C)? What do patients actually think of the safety and antigenicity of rFVIII and pdFVIII? To address these questions we sent a postal questionnaire to all haemophilia patients and all haemophilia treaters in the Netherlands. The objective was to investigate the opinions of patients and doctors on the choice between pdFVIII and rFVIII, and to determine which factors predict whether a patient uses pdFVIII or rFVIII.

Methods

Mailing procedures

The study in patients was carried out as part of the Haemophilia in the Netherlands 5 (HiN-5) project. During the past 30 years, the effects of changes in haemophilia treatment have been monitored by four nation-wide postal surveys among Dutch haemophilia patients conducted in 1972, 1978, 1985 and 1992. In April 2001, patients received a letter about the forthcoming HiN-5 study on haemophilia. Where possible, this announcement was sent by their physician. Other patients were first informed by the Dutch Haemophilia Patients' Society or directly by the Study Group HiN-5. All haemophilia patients who were listed with the haemophilia treatment centres, with the Dutch Haemophilia Patients' Society, or on updated mailing lists from previous survey(s) were included in the mailing. After an extensive search for addresses the questionnaire was sent to 1567 patients in May 2001.The closing date for data collection for the current study was set at 12 September 2001.

In addition, in May 2001, we sent a postal questionnaire to the 26 directors of the licensed haemophilia care centres in the Netherlands. Supplementary questionnaires were included, which they were asked to distribute among the colleagues in their department who autonomously treated haemophilia patients as well. To enable us to measure the response, we requested the directors to report to how many of their colleagues had been given a questionnaire. Reminders were sent after two weeks.

Content

The prestructured patient questionnaire in 2001 was largely based on the four previous HiN-questionnaires. For this study, we added specific questions, which followed from a prior model that we developed and that incorporated all factors we assumed to be predictive of the choice between recombinant and plasma-derived clotting factors. To formulate this model and these questions, literature on clotting factors was consulted, and interviews were held with patients and representatives of the Dutch Haemophilia Patients Society, haemophilia-treating physicians, and clotting factor producers. Before the questionnaire was actually sent out, a small number of patients and a panel of experts was asked to complete the questionnaire and to give their comments. These 'pilots' were helpful in optimising the structure and content of the questionnaire.

Questions on age, type of haemophilia, severity of disease, treatment modality, inhibitor formation, infectious diseases (HIV, hepatitis C), treatment centre, membership of the Dutch Haemophilia Patients' Society, education level and net income were included in the HiN-questionnaires. For this study, items were added: attitude towards innovations (innovativeness), aversion against switching, empowerment, first clotting factor used, current product used, consideration of future product switch, clotting factor used by family members, number of family members with HIV or hepatitis C through the use of clotting factors, most important influence in clotting factor choice (respondent himself, physician, or both equally influential), physician's advice (recombinant, plasma derived or neutral), preference for a specific producer (Dutch over foreign, not-for-profit over profit making), and opinion on albumin-free formulations of rFVIII (5-points scale: large deterioration, deterioration, no difference, improvement, large improvement). The first three items are described in Table 1 and were included at the beginning of the questionnaire, before the issue of recombinant versus plasma derived clotting factors was introduced.

Table 1. Selection of items included in the questionnaire for patients and physicians

Innovativeness

If a new treatment for haemophilia would become available, e.g. gene therapy, how would you react to that?

1 very negative
2 negative
3 neutral
4 positive
5 very positive

- In general, if a new treatment for haemophilia would become available, when would you adopt it?
  1 never
  2 when the treatment can hardly be escaped anymore
  3 when the treatment is proven superior in a large number of patients,
  4 when the treatment succesful in some other patients
  5 immediately
- With regard to the adoption of the latest insights and treatments in health care, patients can be categorised into five groups. In which group would you place yourself?
  1 laggards (10%)
  2 late majority (35%)
  3 early majority (35%)
  4 early adopters (15%)
  5 innovators (5%)

Empowerment[‡]

- I always make clear to my physician which treatment I prefer myself.
- I am well informed about the different treatment possibilities for haemophilia.
- I follow my physician's advice without questioning.[*]
- Besides the information my physician gives me, I look for information about clotting factors myself, as well.
- When my physician proposes a certain treatment, I ask if there are other treatment options as well.
  1 not at all
  2 a little bit
  3 quite a lot
  4 very much

Aversion against switching

- Switching from one clotting factor product to another may cause problems (e.g. inhibitor formation).
- If you are doing well with your current treatment, you should never change to another clotting factor product.
  1 totally disagree
  2 disagree
  3 neither agree nor disagree
  4 agree
  5 totally agree

[‡] *the items on empowerment were included in the patient questionnaire only*

[*] *reverse coding*

From a list of eight characteristics, which may be important to patients in choosing between different clotting factor products (price, effectiveness, user friendliness, producer's image, knowledge on long-term effects, risk of infections, risk of product shortages and risk of inhibitor formation), respondents were asked to rank the five most important characteristics (between 1 and 5 points). The average rating for a product characteristic could be a maximum of 5 (if all respondents ranked the characteristic as the most important one), and a minimum of 0 (if none of the respondents selected the characteristic in the top-five most important). In addition, their opinion on the eight characteristics was asked on a five-points scale (-2 very favourable for plasma, -1 favourable for plasma, 0 the same for plasma and recombinant, 1 favourable for recombinant, 2 very favourable for recombinant).

The questionnaire for doctors mainly contained the same items as the patients questionnaire. Items were added on the personal characteristics of the responding doctor, such as age, sex, year of graduation from medical school, medical specialism, and whether they treated mainly adults, children, or both. In addition, the respondents were asked which type of clotting factor they would choose for themselves if they had severe haemophilia (plasma derived, recombinant or no preference).

Only the directors, and not their colleagues were asked to fill the characteristics of their department's patient population: number of patients with haemophilia A and B, severity, number of patients on plasma-derived and recombinant clotting factors, number of patients with inhibitors and number of infections with HIV and hepatitis C. Before the questionnaire was actually sent out, two doctors were asked to complete the questionnaire and to give their comments. This 'pilot' was helpful in optimising the structure and the content of the questionnaire.

Analysis

As we were interested in the choice between, and the opinions about rFVIII and pdFVIII, we included in the analysis only patients with haemophilia A who had used FVIII during the 18 months preceding our questionnaire, and for whom we knew whether the first clotting factor product used had been recombinant or plasma derived. The type of first clotting factor used (recombinant or plasma derived) was investigated in relation to year of birth. In this analysis year of birth was used as a proxy for the year of first treatment.

Subsequently, to study switching behaviour, we included only those respondents who had started on plasma derived clotting factor, and excluded the respondents who had started on rFVIII, as switching from rFVIII to pdFVIII is very rare. Odds ratios (OR) for the association with switching from pdFVIII to rFVIII were calculated by logistic regression for all factors in our prior model. The factors that were statistically significantly associated with switching in these univariate analyses were subsequently included in a multivariate logistic regression model to calculate the adjusted ORs. The severity of haemophilia was classified according to the residual percentage of FVIII clotting activity: severe (<1%, i.e. <1 IU/dl), moderate (1-5%), or mild (>5-40%). Haemophilia treatment centres were categorised into 'small' and 'large' centres according to the number of patients ($n \leq 10$, $n > 10$ respectively). Different items that were designed to measure one common factor, such as e.g. the three items on innovativeness, were clustered together (as the average over the items), if Crohnbach's alpha for correlation was ≥0.70.

To calculate the response in the physicians' questionnaire, we assumed that directors who, after the reminder, did not respond to our questionnaire, had not distributed it among colleagues either. The departments were categorised into three groups: departments treating mainly adults, departments treating mainly children, and those treating both. Personal

characteristics of the respondents were described, as were the influences of patient characteristics on the doctor's advice about rFVIII versus pdFVIII. The personal opinions of doctors on matters related to the choice between pdFVIII and rFVIII were noted and were compared with the opinions of patients. For each respondent (both patients and doctors) the opinion on each of the eight product characteristic was multiplied by the importance attached to that characteristic. The sum of these eight multiplications was used as a summarising measure of the respondent's opinion on recombinant versus plasma derived clotting factor (range -30 to 30).

Results

Response, participants and first use

The total response to the patient questionnaire was 69% (*n*=1,084). Respondents who were excluded from the analysis were patients who did not have haemophilia A (*n* =188), patients who had not used FVIII in the past 18 months (*n*=337, mainly mild haemophilia A), and patients for whom the type of first clotting factor used was not known (*n*=22). In total, 537 respondents were eligible for analysis. Characteristics of the responding patients are presented in Table 2.

Table 2. Characteristics of the participating patients

	First use was rFVIII (*n*=84)	First use was plasma derived clotting factor (*n*=453)
Mean age in years (95% CI)	9 (6-11)	37 (35-38)
Male	84 (100)	444 (99)
Severity of disease		
mild	25 (31)	85 (19)
moderate	16 (20)	81 (18)
severe	41 (50)	277 (63)
Treatment modality		
Home treatment	27 (33)	318 (72)
Profylactic treatment	37 (45)	234 (53)
Infectious diseases		
HIV positive	0 (0)	26 (6)
Hepatitis C	4 (5)	284 (67)
(Past) development of inhibitor	5 (7)	51 (13)
Member of Haemophilia Society	72 (86)	344 (77)
High income	39 (62)	215 (52)
High education	30 (37)	167 (39)

All values are No. (%) except where otherwise indicated.
95% CI=95% confidence interval

First treatment had been with rFVIII for 16% (*n*=84) of the participants, and with plasma derived clotting factor for 84% (*n*=453). Because of the consensus among the Dutch haemophilia treaters to treat previously untreated patients (PUPs) with rFVIII, we expected that the large majority of respondents who started using clotting factor treatment after 1994 would start on rFVIII.

As we did not have data on the year of first treatment, we used year of birth as a proxy. Of all 537 respondents, 12% (*n*=67) was born after 1994. Figure 1 shows that these young patients had generally started on rFVIII.

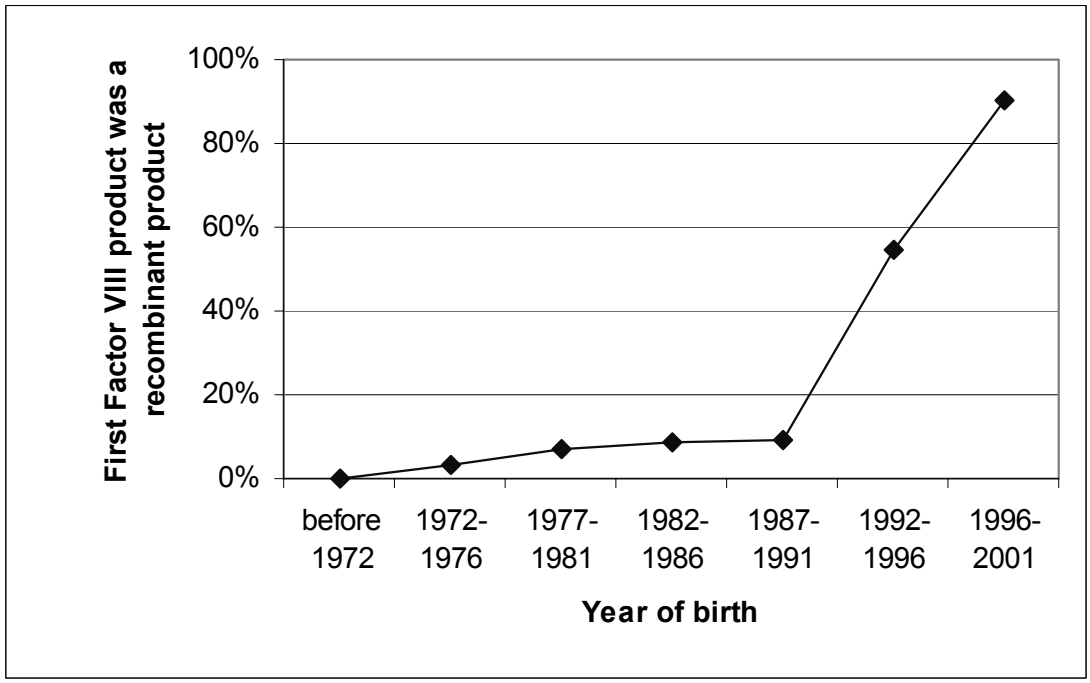


Figure 1
Percentage of patients who started on rFVIII versus year of birth

Eighteen directors returned the questionnaire (response 69%). They reported that they had forwarded the questionnaire to 18 colleagues. Overall, including colleagues, we received 30 completed questionnaires (response 30/44=68%). Together, the directors reported 1316 patients with haemophilia A and 169 patients with haemophilia B in their care. As such, our sample represents the treating physicians of >95% of all Dutch haemophilia patients. One director was excluded who no longer treated haemophilia patients. A total of 29 participating physicians, from 17 departments, remained for analysis.

Mean age of the physicians was 47 years (ranging 35-61 years). Fifty-nine per cent were men, and the average year of graduation from medical school was 1980. Seven per cent (*n*=2) were

general practitioners, 11% (*n*=3) internists, 46% (*n*=13) haematologists, 21% (*n*=6) paediatricians, and 14% (*n*=4) paediatric haematologists.

Switching behaviour

For the analysis of switching behaviour, we included the 453 responding patients whose first treatment had been with plasma-derived clotting factors. Of these 45% (*n*=206, switchers) had switched from pdFVIII to rFVIII and 55% (*n*=247, non-switchers) continued to use pdFVIII at the time of our questionnaire.

Influence of treating physician

The 453 responding switchers and non-switchers were treated in 30 different treatment centres. Eighty-eight per cent of these patients were treated in seven large centres (median number of respondents per centre was 31). In these large centres, the percentage of respondents who had switched from pdFVIII derived to rFVIII varied from 26% to 71% (median 40%). In the small centres (*n*=23, median number of respondents per centre was one), the percentage of switchers varied from 0% to 100% (median 0%). As such, treatment in a large haemophilia treatment centre was positively associated with switching from pdFVIII to rFVIII ($OR_{adj.}$ 3.2, 95% CI 1.1-9.8).

In the responding departments that treated mainly adults (*n*=8; 501 patients), the proportion of patients using rFVIII ranged from 0 to 75% (median 12%), and in the departments that treated mainly children (*n*=6; 167 patients), it varied between 0% and 100% (median 84%). On average the proportion of patients using rFVIII was three times higher in departments treating children than in departments treating adults (p=0.02).

To the question 'Who was the most influential in the choice of the type of FVIII product?', 54% of the patients answered ‘my treating physician’, 25% ‘both myself and my physician’,

and 21% ‘ myself’. There was no difference between switchers and non-switchers in this respect. Quite similarly, only one doctor indicated the patient to be the most influential in choosing a FVIII product. Forty-four per cent of the non-switchers had spoken with their physician about the choice between rFVIII and pdFVIII. Only 21% of all patients who did discussed the topic with their physician (switchers and non-switchers) initiated the conversation themselves. Eight per cent of the non-switchers and 52% of the switchers had been advised by their physician to use rFVIII.

Five of the 29 physicians (17%) gave the same advice to all patients (either pro-pdFVIII, pro-rFVIII or neutral), while the other 22 doctors gave different advice to different patients. The reasons for these differential advices were the limited availability of rFVIII (23%), differences between patients (32%), or both (46%). Young patients were preferentially advised to use rFVIII by 81% of these physician, and PUPs by 95% (Table 3). Thirty per cent preferred to give rFVIII to HIV negative patients. Twenty-nine per cent of the doctors were more inclined to advise rFVIII to patients who were afraid of bovine spongiform encephalopathy (BSE) than to patients who were not afraid of BSE. Twenty-four per cent took in consideration whether family members of the patient were already using rFVIII.

Table 3 To which patients do you tend to advise rFVIII instead of pdFVIII? Results are given in percentages (*n*=22 physicians)			
Patient characteristic	**Doctor's preference to advise rFVIII instead of pdFVIII**		
Severity of the disease	severe haemophiliacs 14	no preference 76	mild haemophiliacs 10
Previously untreated patients (PUPs)	PUPs 95	no preference 5	previously treated patients 0
Age	young patients 81	no preference 19	old patients 0
HIV	HIV positives 15	no preference 55	HIV negatives 30
Prophylaxis	patients on prophylaxis 5	no preference 91	patients not on prophylaxis 5
Home treatment	patients on home treatment 0	no preference 100	patients not on home treatment 0
Family members using rFVIII	patients with family members using rFVIII 24	no preference 76	patients without family members using rFVIII 0
Compliance	compliant patients 5	no preference 95	non-compliant patients 0
Inquirement	patients who do inquire about rFVIII 10	no preference 90	patients who do not inquire about rFVIII 0
Fear for BSE	patients afraid of BSE 29	no preference 71	patients not afraid of BSE 0

HIV=Human Immunodeficiency Virus; BSE=Bovine Spongiform Encephalopathy

Patient characteristics

The average age of the switchers (31 years, range 2-78) was lower than of the non-switchers (41 years, 5-83). Switching was not associated with severity of disease, history of inhibitor formation or home treatment (see Table 4).

Table 4 Univariate and multivariate logistic regression model of switching *vs.* nonswitching in patients

	OR_{crude} (95% CI)		$OR_{adj.}$* (95% CI)	
Parameters included in the multivariate model				
Patient characteristics				
Age	0.97	(0.96-0.98)	0.98	(0.96-1.0)
HIV positivity	0.4	(0.2-1.0)	0.3	(0.1-0.9)
Hepatitis C infection	0.4	(0.3-0.6)	0.4	(0.2-1.0)
No. of family members on plasma	0.7	(0.6-0.9)	0.6	(0.5-0.9)
No. of family members on recombinant	2.0	(1.4-2.6)	2.7	(1.6-4.4)
Innovativeness (1-5)	1.3	(1.0-1.8)	1.8	(1.1-3.1)
Profylactic treatment	1.5	(1.0-2.2)	1.4	(0.7-2.8)
Membership of Haemophilia Patients Society	1.6	(1.0-2.6)	1.4	(0.6-3.4)
Empowerment (1-4)	1.3	(1.0-1.8)	1.2	(0.7-2.1)
High income	1.4	(1.0-2.1)	1.4	(0.8-2.7)
Treatment centre				
Size of treatment centre (small/large)	5.6	(2.6-12.2)	3.2	(1.1-9.8)
Opinions				
Pro-recombinant opinion (-30 through 30)	1.1	(1.1-1.2)	1.1	(1.1-1.2)
'Never change a winning team' (1-5)	0.7	(0.6-0.9)	0.8	(0.6-1.1)
Preference for Dutch over foreign producer (1-5)	0.6	(0.5-0.7)	0.8	(0.5-1.1)
Preference for not-for-profit producer (1-5)	0.7	(0.6-0.8)	0.8	(0.6-1.1)
Other parameters from our prior model				
Severity of disease	1.1	(0.9-1.4)		
(Past) development of inhibitor	1.5	(0.8-2.7)		
Home treatment	1.4	(0.9-2.2)		
No. of HIV positive family members	0.7	(0.3-1.3)		
No. of family members with hepatitis C	1.2	(0.8-1.8)		
High education	1.0	(0.7-1.5)		
Agreement with 'Switching might cause problems, e.g. inhibitors' (1–5)	0.9	(0.8-1.2)		

95% CI=95% confidence interval
* *Adjusted for all other parameters in the model*

Patients who had been infected with HIV or hepatitis C switched less to rFVIII than patients who had not been infected ($OR_{adj.}$ 0.3, 95% CI 0.1-1.0). The fact whether patients did or did not have family members who had been infected with HIV or hepatitis C through the use of clotting factors was not associated with switching behaviour. The more family members were using pdFVIII, the less the patients themselves had switched from pdFVIII to rFVIII ($OR_{adj.}$ 0.7, 95% CI 0.5-0.9). On the other hand, the more family members who used rFVIII, the more the patients had switched to rFVIII ($OR_{adj.}$ 2.7, 95% CI 1.6-4.3).

The three items on innovativeness (Crohnbach's alpha 0.70), as well as the five items on empowerment (Crohnbach's alpha 0.75) were clustered together in the analysis. In univariate analyses both were positively associated with switching from pdFVIII to rFVIII.

Membership of the Dutch Haemophilia Patients' Society was also higher in the switchers than in the non-switchers (81% versus 73%). Net income and education correlated only weakly (Crohnbach's alpha 0.49), and therefore they were not clustered together as one measure of socio economic status. In univariate analysis high income was positively associated with switching, while high education was not. After adjustment for the other parameters in the model (see Table 4), the point estimates for the influence on switching of empowerment, income and membership of the Dutch Haemophilia Patients' Society stayed very much the same, only the confidence intervals were broader. The influence of innovativeness increased after adjustment.

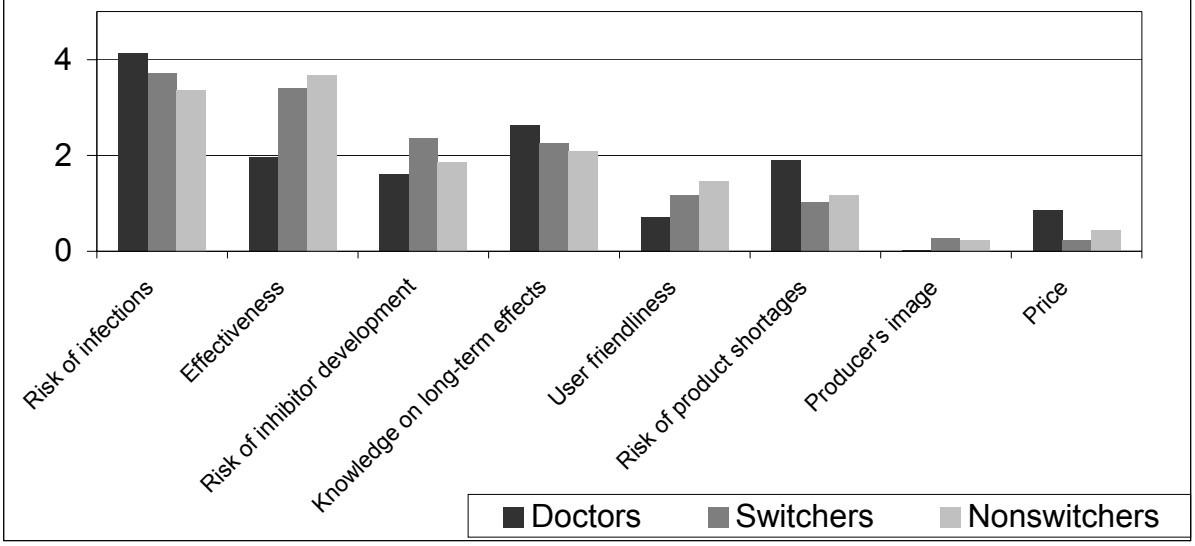
Opinions

Of the non-switchers, 21% (*n*=45) was thinking about switching to rFVIII in the future and 79% (*n*=167) wanted to continue using pdFVIII. In 2000, two virtually albumin-free formulations of rFVIII were introduced. Forty per cent of the switchers, 23% of the non-switchers and 90% of the physicians knew about the introduction of these albumin-free

formulations of rFVIII. Only 35% of the patients gave an opinion on this development, the large majority of whom (89%) thought that it was an improvement. Of the 45 non-switchers who indicated they were thinking about switching to rFVIII, 21 (47%) had done so since the introduction of the albumin-free formulations, and 25 (53%) already before this introduction. The large majority of physicians reported that the introduction of albumin-free products had not influenced their prescribing behaviour. Eleven percent had started to prescribe rFVIII more often.

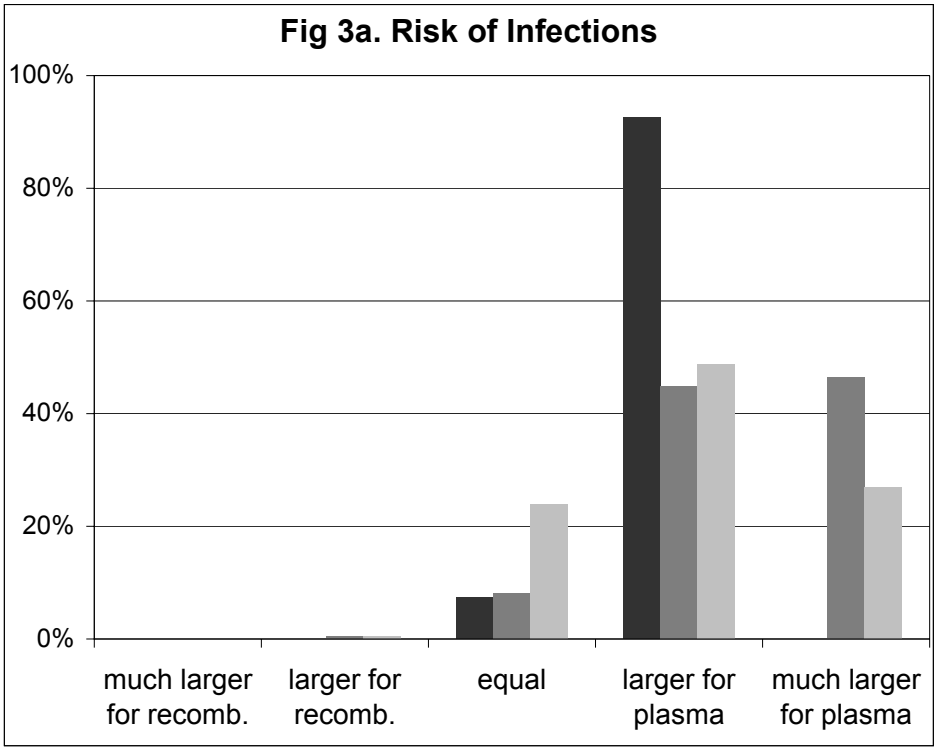
Fig 2 shows how doctors and patients respectively, rated the importance of the eight predefined product characteristics in choosing between rFVIII and pdFVIII. Risk of infections was a very important characteristic to both patients and physicians. Doctors attached a lot of importance to the knowledge of long-term effects, while patients, and especially the non-switchers were very much concerned with the effectiveness.

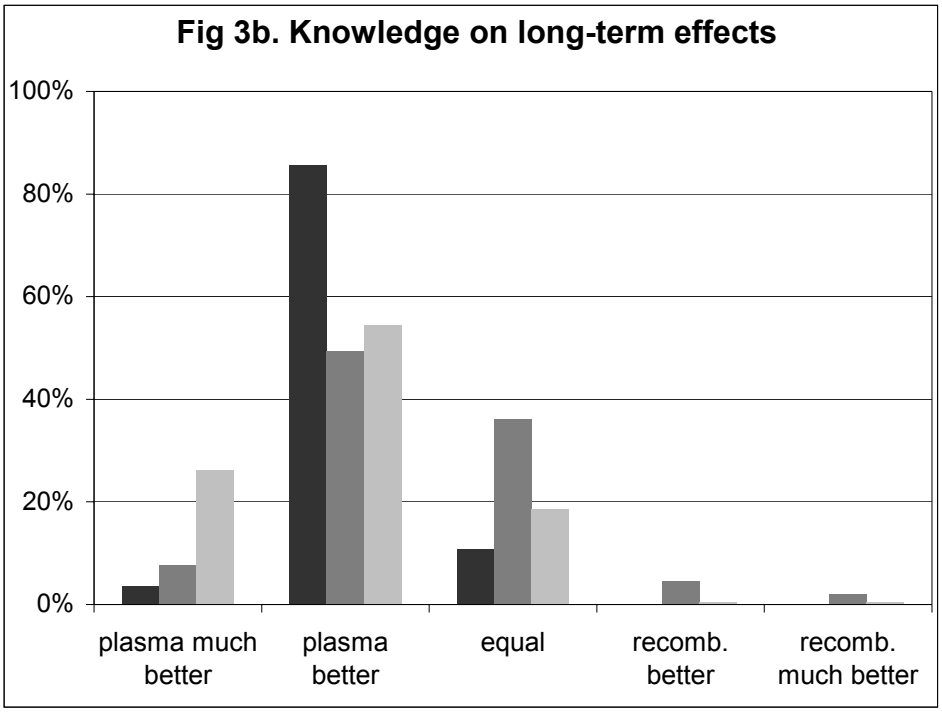
Fig 2. Importance of product characteristics in choosing between pdFVIII and rFVIII: average rating



If the physicians hypothetically suffered from severe haemophilia A themselves, 74% would choose to use rFVIII, 4% pdFVIII, and 22% had no preference.

The majority of both doctors and patients thought that the risk of infection was larger with pdFVIII than with rFVIII (Fig 3a).





On the other hand, they were also of the opinion that for rFVIII, less is known about the long-term effects (Fig 3b).

Switchers answered these questions more favourable for rFVIII than non-switchers did. All doctors and the large majority of the patients (73%) considered rFVIII and pdFVIII equally effective. The remaining minority of patients was divided: switchers believed rFVIII to be more effective, while non-switchers believed the opposite. Also on the topic of inhibitor formation, the majority of the patients (57%) and doctors (82%) did not percieve a difference between rFVIII and pdFVIII (Fig 3c). With respect to the risk of product shortages, the respondents were divided (Fig 3d).

To the question 'Have you been troubled by shortages of FVIII product during this year or last year (2000+2001)?', 27% (*n*=56) of switchers and 7% (*n*=16) of non-switchers answered in the affirmative. The large majority of the participants (67% and 75% of patients and doctors respectively) rated the image of the producers of rFVIII and of pdFVIII as equally good. To the remaining switchers the image of rFVIII producers was better, while the opposite was true for the remaining non-switchers.

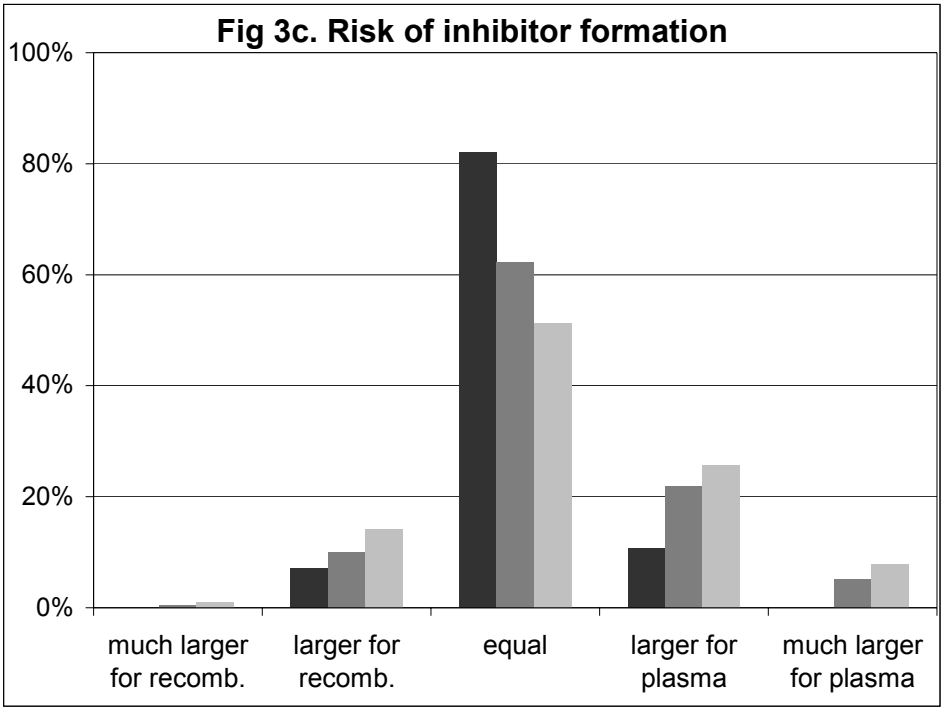


Fig 3c. Risk of inhibitor formation
100%
80%
60%
40%
20%
0%
much larger for recomb.
larger for recomb.
equal
larger for plasma
much larger for plasma

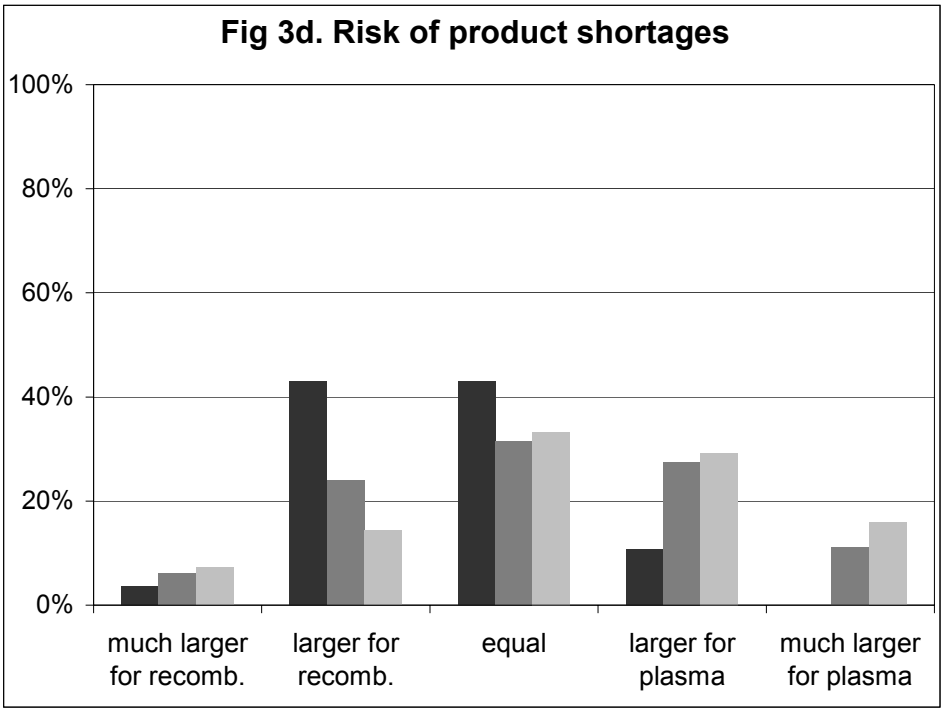
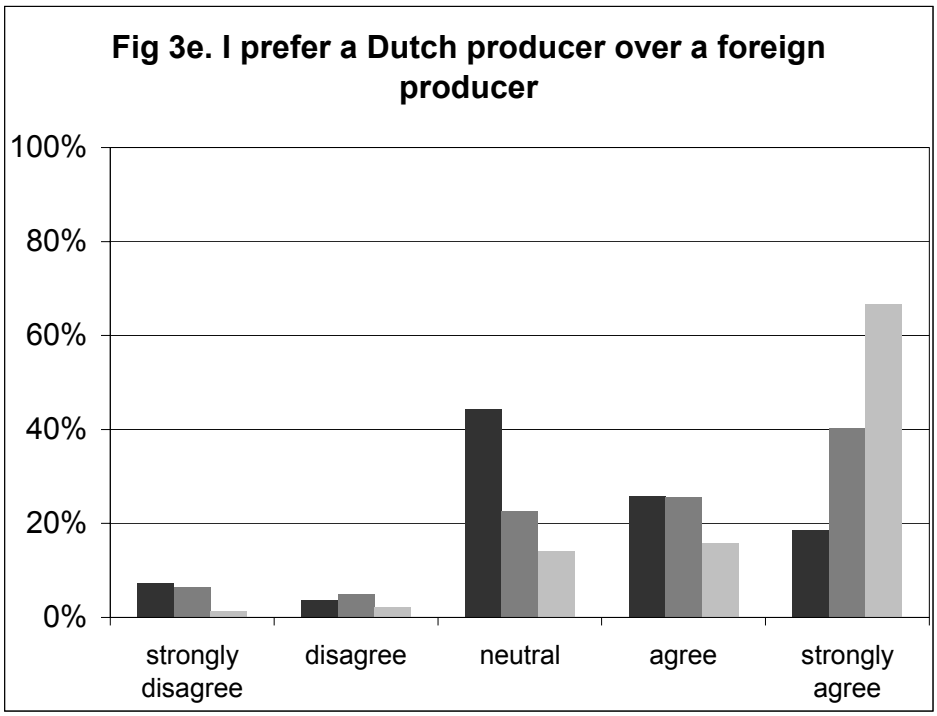
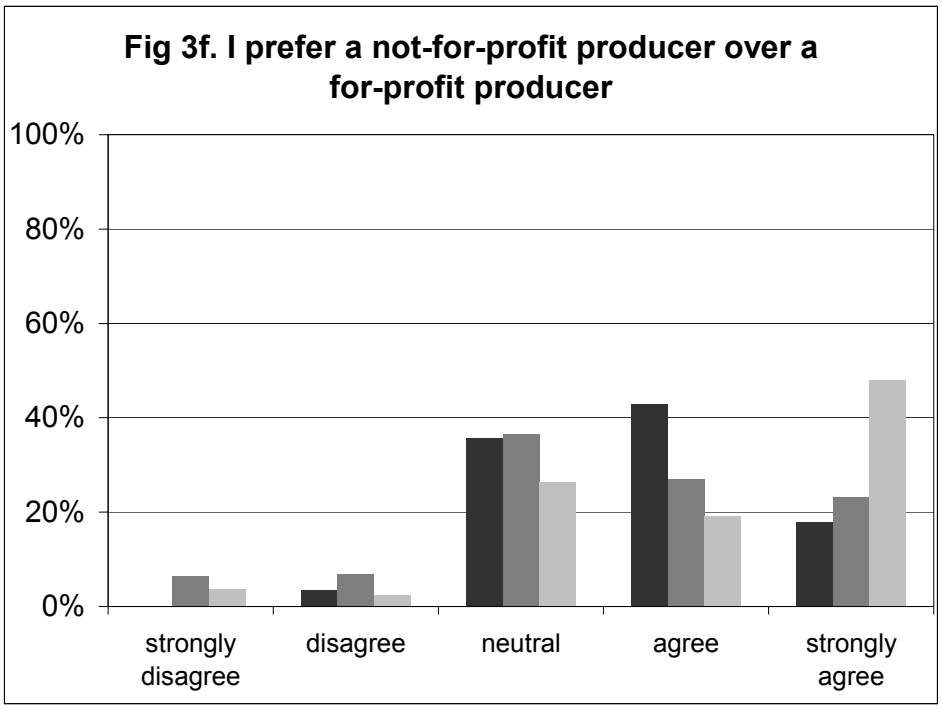
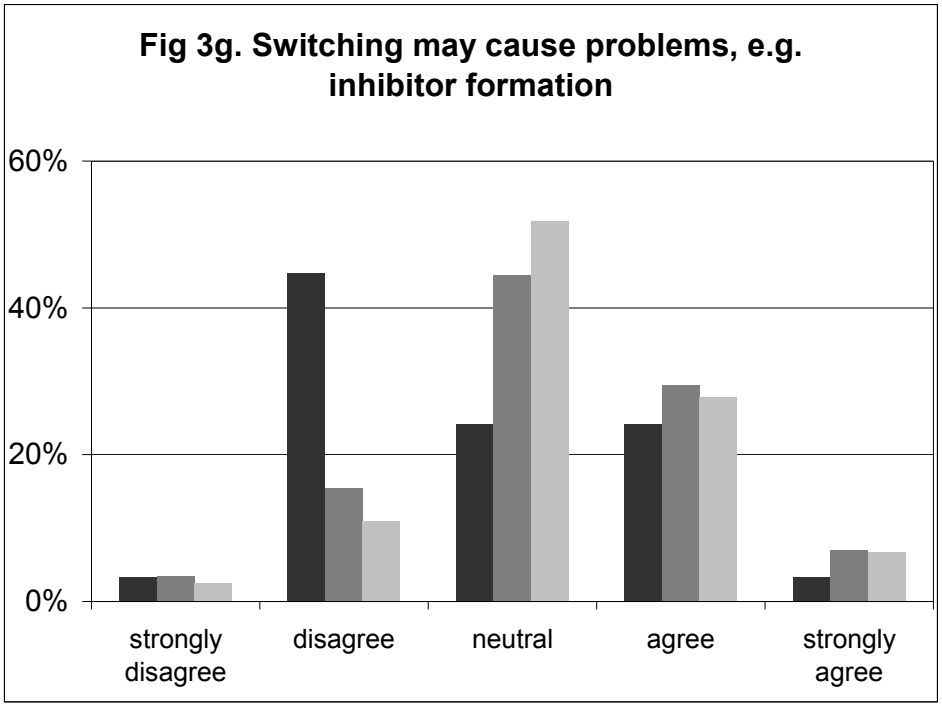


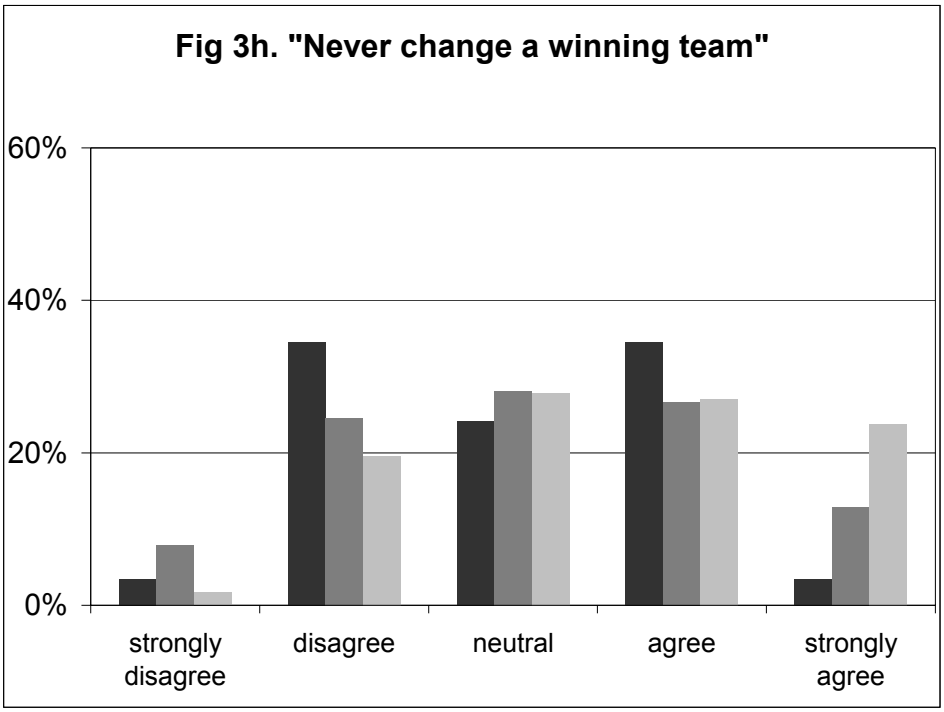
Fig 3d. Risk of product shortages
100%
80%
60%
40%
20%
0%
much larger for recomb.
larger for recomb.
equal
larger for plasma
much larger for plasma





Non-switchers expressed the strongest preference for a Dutch, not--profit-making producer (Fig 3e and 3f). On average, switchers were more positive about rFVIII (summarised score 6 (5-7)) than non-switchers (-0.3 (-1-1)).





The correlation between the two items measuring aversion against switching of clotting factor in general was too low (Crohnbach's alpha 0.42) to cluster them together in the regression analysis for patients (Table 4).

With the statement "Switching from one clotting factor product to another may cause problems", most patients neither agreed nor disagreed while most doctors (48%) disagreed (Fig 3g). Thirty-nine per cent of the switchers and 51% of the non-switchers agreed with the notion to "never change a winning team" (Fig 3h).

Discussion

From 1995 onwards, nearly all children who received FVIII for the first time (PUPs), were prescribed rFVIII. From all responding patients who had started using pdFVIII in the past, 45% had switched to rFVIII and 55% continued to use pdFVIII until the time of our questionnaire.

The percentage of patients who had switched from pdFVIII to rFVIII varied from 0% to 100% in small centres and from 26% to 71% in large centres. The proportion of patients using rFVIII was on average 2.9 times higher in departments treating mainly children than in children treating mainly adults. Even within the groups of child departments and adult departments, the proportion of patients using rFVIII varied tremendously. From this large variability, one may conclude that the treating physician strongly influences product choice. This conclusion is further strengthened by 41% of the doctors and 54% of the patients, regarding the treating physician as the most influential person in choosing a clotting product. Unfortunately, the number of departments was too small to investigate whether the opinions or the innovativeness of the physicians within a department were predictive of the proportion of patients on rFVIII.

Notwithstanding the physicians' strong influence, our results do show a small influence of the patients as well in the choice between pdFVIII and rFVIII. The majority of physicians reported that their advice to a specific patient was not influenced by HIV status or product

choice of family members. Therefore, the association of these factors must go largely through patient preferences and not through physicians' policies. The same holds true for innovativeness of patients and opinion on rFVIII. Also, there seems to be a weak association in patients between preferring a Dutch, or a not- profit-making producer, and continued use of pdFVIII. The interpretation of these results is, of course, complicated by the cross sectional characteristic of our data. We cannot determine, for example, whether a favourable opinion on rFVIII caused people to switch, or whether the switch caused the favourable opinion.
As there are no clear guidelines on which patients to switch from pdFVIII to rFVIII, we hypothesised that physicians mainly switched those patients who especially asked to be treated with rVIII, which we expected to be the most empowered patients, members of the Dutch Haemophilia Patients' Society or patients with a higher social economic status. Except for the absence of an effect of high education, our hypothesis was confirmed by the data.
After the many years of discussion about the perceived increased antigenicity of rFVIII, it is remarkable that only 13% of the patients thought rFVIII to be more antigenic than pdFVIII.

In the preparatory interviews, which we conducted to construct the questionnaire for patients, we learned that the haemophilia treating physicians, jointly with the Dutch Haemophilia Treatment Society, had agreed at the launch of rFVIII to introduce this new product very gradually to build up experience and to minimise the risk of shortages. They reasoned that a sudden and complete switch to rFVIII, would mean the end of the production of pdFVIII by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), the major provider of plasma derived FVIII (pdFVIII) in the Netherlands. They preferred to keep both the CLB and the producers of rFVIII in business, as history had showed that dependence on a single producer makes one vulnerable. The physicians have indeed adhered to this

agreement. Still, if they had suffered from haemophilia A themselves, only one doctor would choose to use pdFVIII, and 74% would choose to use rFVIII.

Acknowledgements

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Chapter 3.1

Bleeding in carriers of hemophilia

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Submitted

Summary

A wide range of factor VIII and IX levels is observed in heterozygous carriers of hemophilia, as well as in non-carriers. In female carriers extreme lyonisation may lead to low clotting factor levels. We studied the effect of heterozygous hemophilia carriership on the occurrence of bleeding symptoms.

A postal survey was performed among the majority of all women who were tested for carriership of hemophilia in the Netherlands between 1985 and 2001. The questionnaire included items on personal characteristics, characteristics of hemophilia in the affected family members, carrier testing and history of bleeding problems such as bleeding after tooth extraction, bleeding after tonsillectomy and operations. Information on clotting factor levels was obtained from the hospital charts. Logistic regression was used to assess the relation of carrier status and clotting factor levels with the occurrence of hemorrhagic events.

In 2004, 766 questionnaires were sent, 546 women responded (80%). Of these 274 were carriers of hemophilia A or B. The median clotting factor level of carriers was 0.60 IU/ml (range 0.05-2.20 IU/ml) compared to 1.02 IU/ml (range 0.45-3.28 IU/ ml) in non-carriers. Clotting factor levels between 0.60 and 0.05 IU/ml were increasingly associated with prolonged bleeding from small wounds, prolonged bleeding after tooth extraction, tonsillectomy and operations.

Carriers of hemophilia bleed more than other women, especially after medical interventions. Our findings suggest that not only clotting factor levels at the extreme of the distribution, resembling mild hemophilia but also mildly reduced clotting factor levels between 0.41 and 0.60 IU/ml are associated with bleeding.

Introduction

Hemophilia is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Resulting from the recessive X-chromosomal inheritance pattern mostly men are affected and their female relatives can be heterozygous for the mutation, often referred to as carriers of hemophilia. Previously, pedigree analysis and clotting factor VIII or IX levels were used to diagnose carriership hemophilia[1]. In the early nineteen eighties it became possible to ascertain the carrier status by means of DNA analysis, which has evolved from haplotyping, to mutation analysis offering certainty about the carrierstatus[2]. During the last three decades genetic counseling, carrier testing and prenatal diagnosis of hemophilia have become an integrated part of the comprehensive care for hemophilia[3].

Female carriers are expected to have a plasma concentration of FVIII or IX corresponding to half the concentration found in healthy individuals, which is generally sufficient for normal hemostasis. However, in carriers a wide range in clotting factor levels is seen, from very low, resembling affected males, to the upper limit of normal [4]. This range has been attributed to X-chromosome inactivation, which takes place in the early embryonic life[5]. Other genetic factors, such as ABO blood group, may also affect factor VIII and FIX plasma concentrations in carriers, as they do in non-carriers, where a wide distribution is observed, too[6].

Although Merskey et al[7] already reported excessive bleeding after tooth extraction in 47% of known carriers (n=19) in 1952, this first publication was not followed by larger studies. Some case series showed joint bleeds, prolonged bleeding after tonsillectomy or tooth extractions or post-partum bleeding[8-13]. It is important to assess the risk of bleeding in carriers of hemophilia, to assist help physicians in improving care for hemophilia carriers, for instance by the implementation of prophylactic intervention in carriers at risk for bleeding.

While extensive information on bleeding in men with hemophilia is available, only a few studies have focused on bleeding in carriers. We present a large national cross-sectional study examining bleeding in women in whom genetic testing for hemophilia was performed within the last decade. We focused on spontaneous bleeding and bleeding following surgical interventions.

Objectives:

The aim of this study was to examine the risk of bleeding among carriers of hemophilia A or B compared to non-carriers.

Methods

Subjects

We contacted all women who had been tested for carriership of hemophilia A or B before 2001 in the Netherlands. All women had to be 18 years or over to participate. Diagnosis of carriership of hemophilia consisted of DNA diagnostics, pedigree analysis or the assessment of clotting factor levels. Carriers of hemophilia were women in whom the genetical defect related to hemophilia was established through DNA analysis (haplotype or mutation analysis) or, before 1985, through the determination of clotting factor levels in combination with pedigree analysis. Non- carriers were women in whom testing showed that they were not carrying the mutation that caused hemophilia A or B in their family. By comparing carriers and non-carriers both from hemophilic families we excluded the possible bias introduced by knowledge on hemophilia.

Assessments

Questionnaires were sent by postal mail, followed by two reminding letters. The questionnaire included items on personal characteristics, type and severity of hemophilia in affected relatives, carrier testing and several bleeding problems. We assessed if patients ever reported spontaneous bleeding and bleeding after trauma: bruising, nose bleeds, gum bleedings and joint bleeds. Questions on bleeding after medical interventions included bleeding after tooth extractions, (adeno) tonsillectomy and operations. Prolonged bleeding after medical interventions was defined as bleeding for over three hours after tooth extractions, (adeno) tonsillectomy or operations. The topics on bleeding were based on a validated questionnaire developed by Šrámek et al, validated by means of sensitivity analysis[14]. Restrictions in daily life due to excessive blood loss during the menstrual period were measured on a seven-point scale in which the score one represented no restrictions and seven points severe restrictions. To evaluate the questionnaire a pilot study was performed in 12 carriers. Informed consent was obtained to allow us to verify the diagnosis and to obtain information on factor VIII and IX activity from the hemophilia treatment centres. In most women clotting factor activity had been determined at several time points, in which case the lowest value was used for evaluation in this study. Severity of hemophilia in the male family members was classified according to residual percentage of factor VIII or IX clotting activity: severe (<0.01 IU/ml), moderate (0.01-0.05 IU/ml) or mild (>0.05-0.40 IU/ml). The Committee of Medical Ethics of the Leiden University Medical Center approved this study.

Data analysis

Women with clotting disorders due to other causes than hemophilia or who used antithrombotic medication were excluded from the analysis. The prevalence of bleeding symptoms in women who were carriers of hemophilia A or B was compared to that of women

not carrying a hemophilia mutation. Due to the limited number of women reporting hemophilia B in the family we could not distinguish between the two types of hemophilia in the analysis. The risk of bleeding related to the carrier status and clotting factor levels was determined, and we tested for a graded response using a Wald test. If in the comparison between carriers and non-carriers a specific bleeding event showed a relative risk (RR) above 1 and a 95% confidence interval (CI) not including one, its association with clotting factor levels is also presented. In the analysis of bleeding risk caused by specific interventions only women who ever underwent this intervention were included in the analysis. Women who were treated with cyclokapron (tranexamic acid), desmopressin or clotting factor preparations before the medical intervention were excluded from the analysis. Clotting factor levels were analyzed as a categorical variable, the studied categories were <=0.40 IU/ml, 0.40-0.60 IU/ml and >0.60 IU/ml. In the analysis of excessive blood loss during the menstrual period only women were included who were pre-menopausal. To exclude the effect of referral for carrier testing because of bleeding problems we repeated the determination of the risk of bleeding after (adeno) tonsillectomy or operations among women who were not tested because of an increased bleeding tendency.

Results

Response and patient characteristics

A total of 766 questionnaires were sent, and 546 questionnaires were completed and returned (response of 80%). Excluded from analyses were women who reported other clotting disorders than hemophilia (19 women of whom 13 had Von Willebrands disease) and 10 women in whom the carrier status was not conclusive or unknown. This resulted in 274 carriers and 245 non-carriers for the current analyses. Of these, 73% (n=384) reported hemophilia A, 9% (n=48) hemophilia B, whereas of the of the other 95 (18%) women the type

of hemophilia in the family was unknown. Table 1 shows the general characteristics according to hemophilia carrier status. The median age of the carriers and non-carriers was similar, 39 years (yrs) (range 18-77 yrs) and 40 years (range 20-90 yrs), respectively.

Table 1. General characteristics of study population

	Carrier of hemophilia	
	Yes (n=274)	No (n=245)
Mean age at questionnaire (range)	39 (18-77)	40 (20-90)
Use of oral contraceptives*	79 (29)	65 (27)
Family		
Severe hemophilia in family	140 (51)	113 (46)
Hemophilia A in family	230 (84)	151 (62)
Clotting factor		
Clotting factor levels available	225 (82)	143 (58)
Median FVIII activity (IU/ml)	0.60 (0.05-2.19)	1.02 (0.45-3.28)

Data presented are numbers (percentages) of median (range)
*Current use of oral contraceptives
** hemophilia in family, not including own children

Current use of oral contraceptives in carriers and non-carriers was similar, 29 % and 27% respectively. Past use of oral contraceptives was reported by 159 carriers (51%) and by 119 non-carriers (56%). Severe hemophilia in the family was reported by 140 (51%) of carriers and 113 (46%) non-carriers. Thirty-one carriers (11%) and 42 non-carriers (21%) were not aware of the severity of hemophilia within their family. Carrier testing by means of DNA diagnostics, available in the Netherlands since 1985, was performed in 177 carriers (57%) and in 122 non-carriers (58%).

Factor VIII and IX characteristics

Clotting factor levels were missing for 18 % (49/274) of carriers and 43% (103/245) of non-carriers. The median clotting factor level in carriers was 0.60 (range 0.05-2.19) IU/ml compared to 1.02 (range 0.45-3.28 IU/ml) in non-carriers. Sixty-two women had a clotting factor levels lower than 0.40 IU/ml, all carriers. Figure 1 shows the distribution of clotting factor levels in carriers and non-carriers.

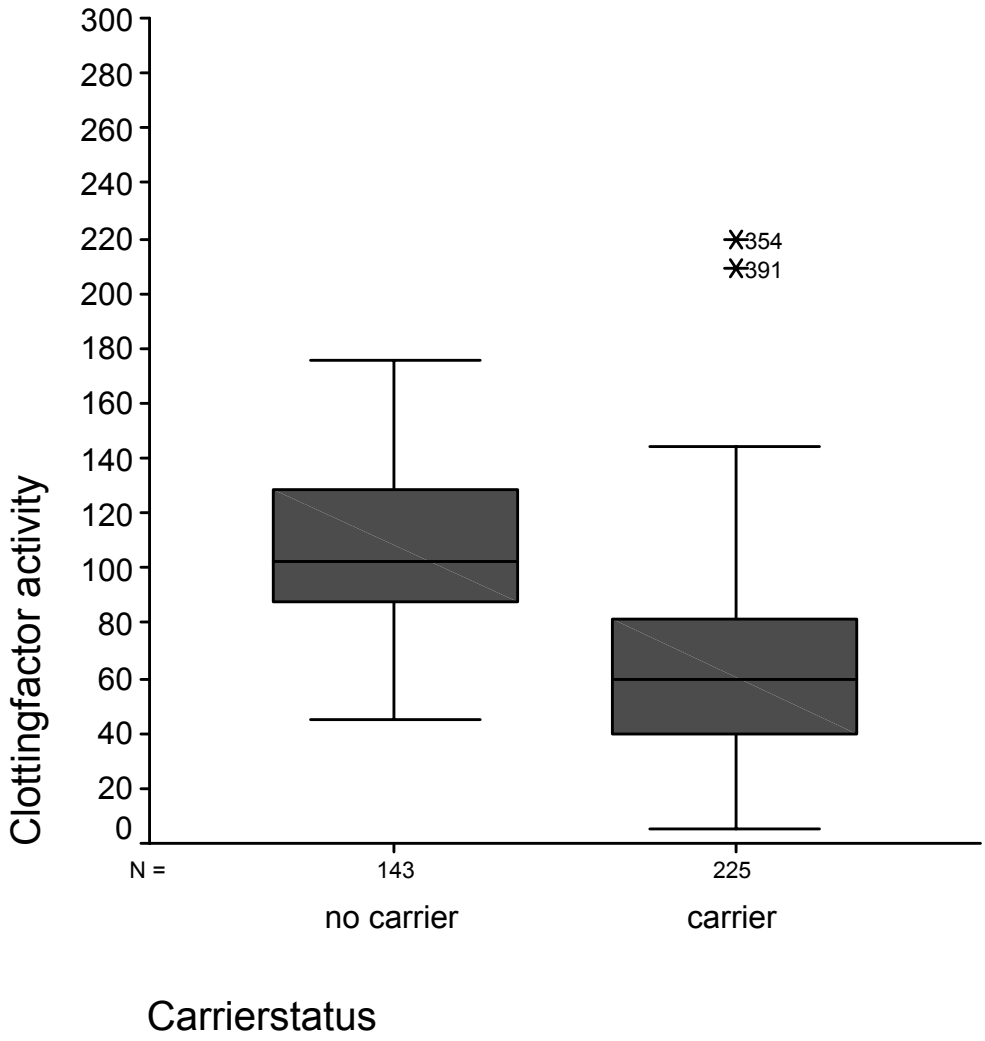

Figure 1. Clotting factor level in relation to carrier status shown for participants of whom clotting factor level is known.
This box-whisker plot shows the median and the interquartile range of clotting factor activity levels in carriers and non-carriers. The box is marked by the first and the third quartile, the whiskers extend to the range

Bleeding symptoms

Spontaneous bleeding and bleeding after trauma

Table 2a presents the risk of (ever having experienced) bleeding of carriers compared to non-carriers. The risk of prolonged bleeding (>5 minutes) from small wounds was two times higher (relative risk (RR) 2.2, 95% confidence interval (CI) 1.4-3.5) in carriers compared to non-carriers.

Table 2a. Spontaneous bleeding or bleeding after trauma in carriers and non-carriers of hemophilia

Risk moments	Carriers	Non-carriers	Relative Risk (CI)*
Nose bleeds			
Ever reported	115/270 (43)	105/237 (44)	1.0 (0.8-1.2)
Bruising	50/269 (19)	42/243 (17)	1.1 (0.7-1.6)
Small wounds	56/262 (21)	23/237 (9)	2.2 (1.4-3.5)
Gum bleeding			
Present (yes/no)	164/271 (60)	148/243 (61)	1.0 (0.9-1.1)
Joint bleeds	23/271 (8)	11/240 (5)	1.9 (0.9-3.7)

Data presented are numbers(percentage)
*CI= 95% Confidence Interval

Table 2b. Risk of bleeding after medical interventions

	Carriers	Non-carriers	RR (CI)*
Tooth extraction†			
Prolonged bleeding (> 3 hours)	61/228 (27)	26/219 (12)	2.3 (1.5-3.4)
Treatment after intervention	24/228 (11)	1/219 (0.5)	23.1 (3.1-169)
Tonsillectomy or adenotomy†			
Prolonged bleeding (>3 hours)	29/123 (24)	16/122 (13)	1.8 (1.0-3.1)
Treatment after intervention	10/123 (8)	1/122 (0.8)	9.9 (1.3-76.3)
Operations†			
Prolonged bleeding (> 3 hours)	52/170 (31)	19/146 (13)	2.9 (1.6-5.3)
Treatment (ever)	16/174 (9)	6/149 (4)	2.3 (0.9-5.7)
Blood transfusion	29/174 (17)	18/149 (12)	1.4 (0.8-2.4)

Data presented are frequencies (percentage)
*RR (CI)= Relative Risk (95% Confidence Interval)
†Participants who had been treated prior to the clinical intervention with clotting factor preparations, cyclokapron or desmopressin were excluded from the analysis.

Low clotting factor levels were associated with an increased occurrence of prolonged bleeding from small wounds and joint bleeding (Table 3). Joint bleeds were reported by 8% of carriers and by 5% of women not carrying hemophilia, which was a two times increased risk (RR1.9 CI 0.9-3.7). Although no higher risk of nose bleeds was observed in carriers compared to non-carriers, prolonged nose bleeding occurred more often in carriers: 9% of carriers had nose bleeds that lasted longer than 10 minutes compared to in 2% of non-carriers. Seventeen percent of carriers had received treatment for nosebleeds, compared to 10% of non-carriers. Carriers of hemophilia did not have a higher risk for large bruising and gum bleeding.

Table 3. Bleeding tendency according to decreasing clotting factor level

	> 0.60 IU/ml	0.40-0.60 IU/ml	<0.40 IU/ml	p for trend
Small wounds				
Frequency (%)	28/233 (12)	25/64 (39)	11/60 (18)	
RR (CI)*	1	3.3 (2.0-5.2)	1.5 (0.8-2.9)	0.009
Joint bleeds				
Frequency	12/241 (5)	9/65 (14)	6/62 (10)	
RR (CI)	1	2.8 (1.2-6.3)	1.9 (0.8-4.9)	0.06
Tonsillectomy				
Frequency (%)	21/124 (17)	6/26 (23)	11/31 (35)	
RR (CI)	1	1.4 (0.6-3.0)	2.1 (1.1-3.9)	0.06
Tooth extraction				
Frequency (%)	18/139 (13)	14/51 (27)	15/36 (42)	0.00
RR (CI)	1	1.8 (1.0-3.0)	2.5 (1.5-4.2)	
Operations				
Frequency (%)	18/139 (13)	14/49 (29)	15/36 (42)	0.00
RR (CI)	1	2.2 (1.2-4.1)	3.2 (1.8-5.7)	
Bleedingscore>=2	1	3.0 (1.5-5.8)	4.0 (2.1-7.7)	0.00

Women who ever received treatment with clotting factor concentration, cyclokapron or desmopressin before tooth extraction, tonsillectomy of operations were excluded from the analysis.
*RR (CI)= Relative Risk (95% Confidence Interval)

Bleeding after medical interventions

Tooth extractions had been performed in 228 carriers and 219 non-carriers, and the risk of bleeding for more than three hours after tooth extraction was two times higher in carriers compared to non-carriers (RR 2.3 CI 1.5-3.4) (Table 2b). In 24 of 228 carriers additional treatment due to bleeding after tooth extractions had been required, compared to one of 219 non-carriers. Treatment included intervention by a dentist or the use of cyclokapron, desmopressin, or administration of clotting factor concentrate. Clotting factor levels below 0.60 IU/ml were associated with prolonged bleeding after tooth extraction. A total of 123 carriers and 122 non-carriers underwent tonsillectomy and or adenotomy, 24% of carriers and 13% of non-carriers reported bleeding for more than three hours following tonsillectomy (RR=1.8, CI 1.0-3.1). Six carriers and one non-carrier (1%) were treated prophylactically with either cyclokapron or desmopressin before the intervention. In eight carriers (3%) a blood transfusion was required after (adeno) tonsillectomy compared to none of the non-carriers. Eleven per cent of women carrying hemophilia needed treatment for bleeding following surgery. In the majority of cases a second intervention to treat bleeding had to be performed. Decreasing clotting factor level were also associated with prolonged bleeding after (adeno) tonsillectomy. Women with a clotting factor level of 0.4 IU/ml or below had a 2.1 times (RR=2.1, CI 1.1-3.9) increased risk compared to women with a clotting factor level above 0.6 IU/ml. Prolonged bleeding for more than three hours after one or more operations was reported by 52 of 170 carriers and by 19 of 146 non carriers, RR=2.9 (CI 1.6-5.3). Women with a clotting factor level of 0.4 IU/ml or below had a three times (RR=3.2, CI 1.8-5.7) increased risk of prolonged bleeding after operations compared to women with a clotting factor level of 0.6 IU/ml and above.

Additional treatment during or after surgery due to bleeding problems was necessary in 12%(51/421) of the carriers and in 5% (13/270) non-carriers. One or more blood transfusions

were required in 11% of operations in participants carrying hemophilia compared to 7% in non-carriers. Other additional treatment consisted of infusion of clotting factor concentrate or a second operation.

After the exclusion of women in whom bleeding problems were not the indication for carrier testing the risks of prolonged bleeding after operations (RR=2.8 CI 1.6-5.0) or tonsillectomy (RR=1.8 CI 0.9-3.4) was similar to the finding in the whole study population.

Excessive bleeding during the menstrual period

Women with lower clotting factor levels reported more often excessive blood loss during the menstrual period (menorrhagia) (Table 4).

Table 4. Characteristics of the menstrual period in relation to clotting factor level

	>0.60 IU/ml	0.4-0.60 IU/ml	0-0.40 IU/ml	p for trend
Excessive blood loss				
Frequency	93/195 (48)	31/54 (57)	31/51 (61)	
Risk	1	1.2 (0.9-1.6)	1.3 (1.0-1.7)	0.07
Anemia				
Frequency	16/195 (8)	9/54 (17)	8/51 (16)	
Risk	1	2.0 (1.0-4.3)	1.9 (0.9-4.2)	0.07
Iron suppletion				
Frequency	15/195 (8)	11/54 (20)	7/51 (14)	
Risk	1	2.6 (1.3-5.4)	1.8 (0.8-4.1)	0.07
Hysterectomy[*]				
Frequency	7/44 (16)	2/10 (20)	2/11 (18)	
Risk	1	1.3 (0.3-5.2)	1.1 (0.3-4.8)	0.9
Restrictions in daily life[†]	17/189 (9.0)	9/53 (17)	9/49 (18)	
	1	2.0 (0.8-4.9)	2.3 (1.0-5.6)	0.04

[*]Reported by postmenopausal women due to excessive blood loss.
[†] Moderate to severe restrictions in daily life due to excessive blood loss during the menstrual period

Similarly, the risk for requiring iron suppletion was 80% increased (RR 1.8 CI 0.7-5.0) in women with a clotting factor level of 0.40 IU/ml or below compared to women with a clotting factor level of 0.6 IU/ml and above. Sixty-two (23%) women carrying hemophilia visited the general practitioner for excessive bleeding during the menstrual period, compared to 20% (n=47) of non-carriers. Fifty-eight women (31 carriers (11%) and 21 non-carriers (9%)) consulted a gynecologist and in 18 women a hysterectomy was performed for this reason. Mild to severe restrictions in daily life due to excessive blood loss during the menstrual period was reported by 18% of women with a low clotting factor level compared to 9% of the women with a clotting factor level above 0.60 IU/ml (RR=2.3 CI 1.0-5.6).

Discussion

Although hemophilia is a well-known bleeding disorder in men, it is seldom recognized that female carriers of hemophilia might not only have an increased bleeding tendency, but that the symptoms may be frequent and severe. We studied the risk of bleeding among carriers of hemophilia A or B compared to that of non-carriers. Although usually a level of 0.40 IU/ml is used as the upper limit defining hemophilia, we found an increased risk of bleeding in women with clotting factor levels between 0.40 and 0.60IU/ml. Carriers of hemophilia experience more spontaneous and provoked hemorrhages than non-carriers, with a higher risk of prolonged bleeding after operations, tooth extractions, tonsillectomy. The risk is highest in those with the lowest clotting factor levels.

Strengths and limitations

In this study we approached all women who had been counseled and tested for carriership of hemophilia A or B in the Netherlands. Eighty per cent of women responded to the questionnaire. We included 519 women, which makes this currently the largest survey into

the hemorrhagic risk in female relatives of men with hemophilia. Non-responders were somewhat older than the responders. Yet, age did not modify the association between the clotting factor levels and the risk of bleeding. We therefore assume our results to be generalizable to carriers of hemophilia in general. Recall bias may have influenced the reporting of bleeding symptoms as questions were asked after carrier testing. Yet, Mauser-Bunschoten et al showed by comparing bleeding tendency in obligatory carriers with normal factor VIII levels to non-carriers that the awareness of carrier status has little influence on the reported frequency of bleeding[10]. A more serious problem is that women, who grew up in families with hemophilia patients, may judge bleeding symptoms differently from women in the general population. Selection bias may have been introduced if carrier testing was done because of bleeding problems. To counter this problem, as well as the possible incomparability of carriers from hemophilia families to women from the general population, we only included women from families known with hemophilia. The carriers and non-carriers in our study had grown up in the same environment and had not been aware of their carrier status until testing. Therefore, even if carrier testing was done because of bleeding symptoms, which was the case in 7% of participants, this would not have affected the comparison. Clotting factor levels were missing for 18% of carriers and 43% of non-carriers. Although the group of women in whom clotting factor levels had been measured is most likely to be different from the group in whom these are missing this will not affect the observed relation between clotting factor levels and bleeding.

In the literature mild hemophilia is defined as a clotting factor level of below 0.40 IU/ml. This cut-off point is also described in the guidelines set by the subcommittee of the ISTH[15] and is used in clinical practice. Our study shows that the risk of bleeding is increased in women who would be defined as mild hemophilia, but also in women with clotting factor levels

between 0.40 and 0.60 IU/ml. These findings could have implications for the currently used definition of clotting factor levels considered to be "reliable" to perform medical interventions.

We found a moderately increased risk of joint bleedings in carriers. As joint bleedings are relatively rare the reported joint bleeds may be overestimated and they may have been confused with superficial bleeding of tissue in the joint region.

Our study mainly shows an increased risk of bleeding after trauma and medical interventions, which is similar to the clinical profile of mild hemophilia, and in line with a previous study in carriers[10]. Our findings underline the importance for clinicians and carriers to be aware of the complications that may occur after operations in carriers of hemophilia. Both the clinician and the carrier should be informed on the clotting factor level, which is strongly related to the hemorrhagic risk.

However in many carriers the clotting factor levels were either not measured or not known to the woman. It is clear that not only in obligatory carriers, like daughters of hemophilia patients, but also in potential carriers clotting factor levels should be measured preceding a medical intervention, also at a young age. The clotting factor levels in carriers are independent of severity of hemophilia within the family and vary from person to person[16] . This indicates the importance of clotting factor measurement during carrier testing in all women related to men with hemophilia, independent of the severity of hemophilia and family history.

In conclusion our study suggests a higher risk of bleeding in carriers of hemophilia related to clotting factor levels especially after medical interventions. This implicates the importance of the measurement of clotting factor levels before interventions in all carriers and potential carriers of hemophilia.

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General discussion

General discussion

Hemophilia is a hereditary bleeding disorder affecting both mortality and morbidity. Since the discovery by Judith Poole of cryoprecipitate and the introduction of clotting factor preparations in the 1970s the prospects for patients with hemophilia have improved considerably[1]. This was offset by disease due to blood borne viruses, such as the human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Since 1985 clotting factor preparations have been safe for HIV and since 1992 also for transmission of hepatitis C.

The aim of this thesis was to describe temporal changes in the medical and social situation of patients with hemophilia. In addition we examined the hemorrhagic tendency of female relatives of hemophilia patients. In the present chapter we discuss our considerations regarding the methods we used and the validity of our findings. In addition we discuss potential implications for the care of patients with hemophilia and we make suggestions for future research.

Study design

We performed two cross-sectional surveys. The first survey was the fifth of a national cross-sectional study that periodically collected information on the medical and social situation of patients with hemophilia in the Netherlands, the Hemophilia in the Netherlands (HiN) study. Patients' ascertainment was through the membership of the Netherlands Hemophilia Society, the hemophilia centers and by updated mailing lists from previous surveys.
Comparison over time was made possible by the repeated use of similar pre- structured questionnaires that included items on treatment, the annual number of bleeding episodes, the use of inpatient hospital care and hepatitis C and HIV infections. The number of participating patients increased over the years from 540 in 1972 to 1066 in the latest survey; the introduction

of specialized hemophilia treatment centers and an increasing interest for treatment of all patients with hemophilia, including patients with mild hemophilia, contributed to this growth. The cooperation in this project between the Netherlands Hemophilia Society, hemophilia treatment centers and the Netherlands Society of hemophilia treating physicians added to the national character of the HiN study. It is likely that we have been able to address all Dutch patients with hemophilia. The extensive time period of 30-years covered by the project and its national character make the Hemophilia in the Netherlands an unique project. Because of the HiN surveys hemophilia has become one of the best-described rare diseases in the Netherlands. The second survey was performed among all women who underwent carrier testing of hemophilia between 1985 and 2003.

Validity

Selection

The biggest threat to the validity of studies of a descriptive nature is non-participation. Subjects who participate differ, by definition, from those who do not respond, although not necessarily on aspects relevant to the research question of the study. In virtually every survey, only a proportion of those who are eligible to participate do so. The result of the difference between these groups affects the generalizability of the study results. In the HiN-5 study response was 70%. Non-responders to the questionnaire may have been less severely affected, failing to see the need for a survey in this population. However in the non-responders the distribution of severity was similar to the participants. As age and type of hemophilia were also comparable therefore we consider the results of the HiN-5 study to be generalizable to all Dutch hemophilia patients. Mortality of patients with hemophilia was studied among those who had participated in the Hemophilia in the Netherlands-4 survey in 1992. In the HiN-4, it was estimated that 93% of all Dutch hemophilia patients had been sent a questionnaire, of whom 74% were willing to

participate. As again no differences in the distribution of severity and age were observed between the responding and the non-responding individuals we considered our data to be generalizable to the Dutch hemophilia population.

Response in the cross-sectional study among women who had been tested for carriership of hemophilia A or B between before 1985 and 2001 in the Leiden University Medical Center and the University Medical Center Utrecht was 80%. In this period, these were the two centres where carrier testing was offered, and therefore they performed virtually all carrier tests for hemophilia in the country. We included 519 women, which made our study currently the largest survey into the hemorrhagic risk in female relatives of men with hemophilia. In the non-response group the average age was slightly higher than in the response group. Since clotting factor levels increase with age we may have somewhat overestimated the bleeding frequency in our study population. This however has no effect on the comparison between bleeding frequency in carriers and non-carriers. Selection bias might have been introduced when carrier testing was done because of bleeding problems. As this was reported by a limited number of women we do not think this will affect the comparison between women included in our study and women from the general population eligible for carrier testing for hemophilia. To counter the problem of the possible incomparability of carriers from hemophilia families to women with the general population, we only included women from families with hemophilia. The carriers and non-carriers in our study had grown up in the same environment and had not been aware of their carrier status until testing. As these women are confronted with hemophilia and the related bleeding problems during life they may report bleeding more often or may find this less important and report it less often.

Misclassification

As in every study using questionnaires the value of self-reported data may not be as precise as information from the laboratory or a medical chart. Although this may be a disadvantage, self-reported data offer the opportunity to get an insight into the patient's own perception of his situation. Moreover, many relevant data are not reported in medical charts, or not even known to the physician. To avoid errors in the severity and type of hemophilia these data were verified with the treating physicians. In the study regarding hepatitis C (chapter 2.4) a validation study was performed for a group of patients from two large treatment centers showing a high correspondence between self-reported hepatitis C status and the hepatitis C status reported by the treating physician. As patients with hemophilia, especially those with severe forms, are confronted with their disease every day, they are well informed of their treatment and medical situation. They are undoubtedly better able to respond to questions on social participation, education, and absence from work and school, bleeding frequency and quality of life than their physicians. We therefore consider our data to be a reliable overview of the situation of hemophilia patients in the Netherlands.

In the study on mortality the vital status of patients was determined either by the response to the questionnaire in 2001, or from the treating physicians, or from the municipal registries. It is unlikely that any distortion could have occurred with regard to overall mortality data. Theoretically, because the treating hematologist or the general practitioner reported the causes of death there may have been discrepancies on causes of death with the general population data gathered through the Central Bureau of Statistics. We do not expect this to be of large influence. In the study examining bleeding in female relatives of hemophilia patients in a cross sectional design the bleeding symptoms were ascertained in women who were aware of their carrierstatus. This may have implications for the interpretation of the results. One could argue that the reporting on bleeding could have been influenced by the knowledge about the carrier

status, and that ideally women should have been questioned prior to carrier testing. Carriers may have overreported bleeding symptoms because they are more aware of their status. Yet, a previous study suggested little influence of awareness of carriership of hemophilia on responses to questions on bleeding [2]. Yet, our findings may in part reflect the association between awareness of carrier status and an expected tendency to bleed. However, many women and physicians are unaware of the relationship between bleeding and carriers status of hemophilia.

Implications for care of patients with hemophilia

Our data give insight in the current situation of patients with hemophilia, which is important for both clinicians and patients. We showed that many improvements have been achieved, a reduction in the annual number of hemorrhages, in the percentage of admitted patients and in absence from both school and work. Besides these improvements we emphasize that the prevalence of perceived joint impairment among young patients did not show the decrease we expected. This group of patients merits extra attention during follow-up of patients in a clinical setting.

In chapter 2.1 we emphasize the persisting influence of viral infections on mortality of hemophilia patients. Treatment of the effects of viral infections, particularly HIV and hepatitis C virus, will result in an improved survival of patients with hemophilia.

In the Netherlands guidelines for the treatment of hemophilia were drawn up during a consensus meeting in 1996. According to these guidelines in patients with severe hemophilia prophylactic treatment is preferable to on demand treatment[3]. An international consensus meeting also stated that despite the lack of controlled studies, long-term prophylaxis should be the standard for treating children with severe hemophilia in developed countries. No data are available for forming a consensus on stopping prophylaxis in adult patients. Our findings show that current guidelines are not strictly followed by all patients with severe hemophilia[3,4]. This

raises the question whether the guidelines should be reconsidered or adjustments should be made in treatment strategies prescribed by treating physicians. Various aspects should be taken into consideration in answering this question, for instance, the burden of treatment for the patient and his relatives associated with frequent venapunctures and financial constraints. Our data may be a starting point for revision of the guidelines.

Treatment of patients with hemophilia should become more individualized. From a previous study it has become clear that some patients, especially adolescents, tend to interrupt their prophylactic treatment schedule for a short or longer period[5]. Overall these were patients with a milder phenotype. In determining the right treatment schedule the treating physician should consider the personal aspects of the patient; age, daily activities (work, school, sports), existing joint impairments and the patients opinion on treatment. This may for some patients result in a reduced use of clotting factor preparations while in others there may be a need for a more intense treatment schedule. In chapter 3.1 the association between carriership of hemophilia, clotting factor levels and bleeding after interventions was investigated. An awareness of this risk of bleeding in carriers by physicians may result in a reduction of the frequency of bleeding. Assessment of the clotting factor level of carriers of hemophilia should become a part of the standard measurements performed before a medical intervention in these women. Our study shows that the risk of bleeding is not only increased in women who would be defined as having mild hemophilia, but also in women with clotting factor levels between 0.40 and 0.60 IU/ml. These findings could have implications for the currently used definition of "safe" clotting factor levels.

Future research

We have shown that although well treatable, hemophilia is still a disease affecting life and death. We found an excess number of fatal intracranial hemorrhages in patients with hemophilia, which has also been reported in a study performed in the UK[6]. Future studies should address whether these deaths can be prevented. Other studies might focus on the risk of death related to different treatment strategies (prophylaxis vs. on demand).

We may also discuss our own raison-d'être: is there a rationale for a sixth Hemophilia in the Netherlands survey? Over the years we have gathered a large amount of data and have shown the improvements related to the changes in treatment. The introduction of the electronic patient file will provide us with the data previously gathered through HiN questionnaires. This will enable us to study more precise aspects of treatment. Another future research project may involve expansion of the study into hemorrhagic risk of carriers of hemophilia. To avoid misclassification of clotting factor levels we should measure these levels in a standardized way and determine factor VIII or IX levels in certified laboratories. By performing a survey prior to the carrier testing we might reduce the effect of recall bias.

Although the medical situation of hemophilia has considerably improved over the last three decades, through an intensive treatment regimen, there are still many aspects that require attention: biological, in medical care and social. The need for continued study of the problems of hemophilia is witnessed by the excess risk of mortality in patients, even those without viral infections. In this thesis, we intended to give an overview of the current medical and social situation of patients with hemophilia. In addition, the results of our study among female carriers of the hemophilia gene may lead to an increased awareness by treating physicians about the problems they face and the importance of the determination of clotting factor levels in these carriers.

What was already known on this topic?

- Since the introduction of replacement therapy in the early 1960s important changes have occurred for hemophilia patients.

- Since 1985 clotting factor products have been safe for HIV and since 1992 also for the transmission of hepatitis C. Few studies have reported on mortality in the total population of hemophilia patients after the period of risk of viral infections transmission.

- The uptake of recombinant factor VIII products has been slower in the Netherlands compared to other countries.

- Hepatitis C is a major co-morbidity among patients with hemophilia who received inadequately or non-virus inactivated clotting factor concentrates before 1992.

- Extensive knowledge is available on bleeding in men with hemophilia; the risk of bleeding in carriers of hemophilia has not often been studied.

What does this thesis add?

- National and international guidelines describing the use of prophylactic treatment were not strictly followed.
- A steady decrease was observed in the annual number of hemorrhages, of hospital admissions, of duration of stay in hospital and of days absent from school or work.
- Despite intensified treatment limited improvement was observed in self-reported impairment of joint function in patients older than 16 years.
- Hepatitis C and AIDS had a large impact on mortality of hemophilia patients.
- Even without virus infections hemophilia patients live a few years less than the average Dutch male.
- Although hemophilia patients represent one of the most empowered patient groups, physicians' opinions appeared to have been dominant in choosing between pdFVIII and rFVIII.
- In the Netherlands 65% of patients received rVIII, this percentage varied widely among centres.
- In 2002 the prevalence of hepatitis C among patients with hemophilia who received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.
- Social functioning was worse in patients with hemophilia than the general male population, especially among elder patients.
- Carriers of hemophilia experience more bleeding than non-carriers, especially after medical interventions.
- Although in the literature the level of 0.40 IU/ml is used to define mild hemophilia and is related to bleeding, we also found increased risk of bleeding in women with levels between 0.4 and 0.60 IU/ml.

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Summary

Summary

Hemophilia is hereditary clotting disorder which is caused by a deficiency of factor VIII (hemophilia A) or IX (hemophilia B). Due to the X-chromosomal inheritance pattern patients are primarily male, while women can be carriers of the disease.

This thesis aimed to describe changes in both the medical situation and social functioning of hemophilia patients. The first part focuses on medical and social functioning of hemophilia patients taking into account changes in treatment and the effect of viral infections. In the second part the hemorrhagic risk of carriers of hemophilia is evaluated.

In the Netherlands a series of five postal surveys have been performed from 1972 onwards. In **chapter 2.1** we studied mortality, causes of death and life expectancy of hemophilia patients between 1992 and 2001. We performed a prospective cohort study among 967 patients with hemophilia. The findings were compared with those of previous cohorts, together spanning 30-years of observation from 1972 onwards, which shows the period before, during and after the use of potentially contaminated clotting products. We observed an excess mortality of hemophilia during the last decade. Although currently clotting factor products are safe from the Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV), viral infections had a large influence on mortality. AIDS was responsible for the largest number of deaths (24% of deaths) and 15% of deaths were due to hepatocellular carcinoma or chronic liver disease. Without the effects of HIV and HCV the rate of death among patients with severe hemophilia was 1.4-fold higher than expected. The remaining excess risk in all likelihood resulted from hemorrhages. Life expectancy of patients with severe hemophilia decreased compared to earlier studies, mostly due to AIDS. Patients with

severe hemophilia not affected by hepatitis C or HIV had a life expectancy of 71 years, which was still slightly lower than the life expectancy of the Dutch male population of 76 years.

In **chapter 2.2** we investigated the most important medical and social developments over the last three decades of hemophilia treatment. In April 2001, we sent questionnaires to all known Dutch hemophilia patients, with a response of 70%. We compared different age categories, and children were defined as patients younger than 16, adolescents as patients between 16 and 25 and adults as patients aged above 25 years. Changes in treatment were reflected by an increase in the use of prophylaxis; especially in children. The occurrence of hemorrhages has gradually decreased. Hospital admissions decreased from 47% of all patients in 1972 to 18% in 2001. Despite intensified treatment limited improvement was observed in self-reported impairment of joint function in patients older than 16 years.

In **chapter 2.3** we compared social functioning and health-related quality of life between hemophilia patients and the general male population. We assessed data on full-time or part-time participation in work, disability and health related quality of life in hemophilia patients between 15 and 64 years old. In the analysis we compared our findings with the general population, separately for patients born before the introduction of prophylaxis (30-64 years of age) and patients born after the introduction of prophylaxis (15-30 years old). Our study showed that although important physical improvements had been achieved, hemophilia patients were less involved in full time labour and were more often occupationally disabled. The involvement in labour seems to be important for quality of life as employed patients had a higher quality of life than patients without employment.

Chapter 2.4 reports on the prevalence of hepatitis C and the use of antiviral therapies during the last decade among patients with hemophilia. Hepatitis C is a major co-morbidity among patients with hemophilia who received inadequately or non-virus inactivated clotting factor concentrates before 1992. Analyses were performed in the HiN-5 population. The study

population for the present study consisted of 771 patients who had received clotting factor products before 1992 of whom 638 reported their hepatitis C status. A total of 441 of the 638 (68%) patients ever had a positive test for hepatitis C virus (HCV); 344 patients (54%) had a current infection, and 97 (15%) had cleared the virus. Among 344 patients currently HCV infected, 111 (32%) had received treatment for hepatitis C, while 34% (33/97) of patients with an infection in the past had been treated for hepatitis C.

In 2002 the prevalence of hepatitis C among patients with hemophilia who had received clotting factor products before 1992 was 54%. The majority of patients with a current HCV infection had not been treated with antiviral therapy.

In **chapter 2.5** the uptake of recombinant factor VIII in the Netherlands was assessed. In comparison with other biotech substitutions, the adoption of recombinant Factor VIII (rFVIII) has been relatively slow. We sent a postal questionnaire to all Dutch haemophilia patients and haemophilia treating physicians, to determine which factors predicted whether a patient used plasma derived FVIII (pdFVIII) or rFVIII and to investigate patients' and doctors' opinions on both products. The use of recombinant FVIII varied widely between centers. Younger patients, those not infected with HIV or hepatitis C virus, and those who did not have family members who used pdFVIII, switched more often from pdFVIII to rFVIII. Patients who rated themselves as innovative, who had family members who used rFVIII, and those who were treated in a large hemophilia treatment center, also more often had switched. For physicians and patients alike, the respondents generally did not see large differences between rFVIII and pdFVIII, except for the risk of infections and the knowledge on long-term effects (both larger for pdFVIII). Although hemophilia patients represent one of the most empowered patient groups, physicians appear to have been influential in choosing between pdFVIII and rFVIII.

In **chapter 3.1** bleeding in carriers of hemophilia were investigated. A wide range of factor VIII and IX levels was observed both in carriers and non-carriers. In carriers extreme

lyonisation may lead to low clotting factor levels. A postal survey was performed in all women tested for carriership of hemophilia between 1985 and 2001.We compared bleeding after trauma and medical interventions in carriers and non-carriers. Clotting factor levels lower than 0.60 IU/ ml were increasingly associated with prolonged bleeding from small wounds, prolonged bleeding after tooth extraction, tonsillectomy and operations. We showed that carriers of hemophilia have a higher risk of bleeding compared to non-carriers especially after medical interventions.

Samenvatting

Samenvatting

Hemofilie is een zeldzame aandoening. In Nederland bedraagt de prevalentie 8 á 9 per 100, 000 inwoners. Dit komt in Nederland neer op ongeveer 1600 patiënten. Van deze patiënten heeft het merendeel (85%) hemofilie A (een tekort aan stollingsfactor VIII) en het overige deel hemofilie B (een tekort aan stollingsfactor IX).

Hemofilie is een recessief geslachtsgebonden erfelijke aandoening en komt vrijwel uitsluitend bij mannen voor. De ernst van de aandoening wordt bepaald door de residuele activiteit van de stollingsfactor. Ongeveer de helft van de patiënten heeft een ernstige vorm van hemofilie, dat wil zeggen dat minder dan 1% van de normale concentratie van de stollingsfactor in het bloed aanwezig is. Deze vorm wordt gekenmerkt door het optreden van spontane of door geringe traumata geïnduceerde, grote bloedingen. De lichte vorm van hemofilie wordt gekenmerkt door aanwezigheid van enige stollingsfactor in het bloed. Bloedingen treden in dit geval meestal op bij kiesextracties, operaties, ongevallen of na grote sportieve prestaties of krachtsinspanningen.

Hemofilie wordt behandeld door toediening van stollingsfactorconcentraat, de zgn. substitutie therapie. Wanneer de therapie erop gericht is het aantal bloedingen sterk terug te brengen of zelfs geheel te voorkomen, spreekt men van profylactische therapie. De profylactische toediening van stollingsfactorconcentraat gebeurt veelal thuis. Tegenover profylactische behandeling staat de zgn. ‘on demand’ therapie, waarbij alleen stollingsfactorconcentraat wordt toegediend in geval van een bloeding. Elke bloeding dient dan zo snel mogelijk te worden behandeld met een voldoende hoge dosering van de ontbrekende stollingsfactor.

Hemofilie is in Nederland een van de best beschreven zeldzame aandoeningen. Het Hemofilie in Nederland onderzoek (HiN) heeft hier een belangrijke bijdrage aan geleverd. Het HiN onderzoek is een landelijk onderzoek onder mensen met hemofilie dat voor het eerst werd

uitgevoerd in 1972 onder leiding van professor dr J. Veltkamp. Sinds dit eerste onderzoek is de HiN studie vier keer herhaald, in 1978, 1985, 1992 en in 2001.
Dit proefschrift beschrijft de resultaten van het Hemofilie in Nederland-5 onderzoek. Daarnaast werd het bloedingsrisico bij vrouwelijke familieleden van hemofiliepatiënten onderzocht.

Hoofdstuk 2.1 beschrijft de resultaten van een prospectief vervolgonderzoek onder patiënten met hemofilie A en B naar sterfte, levensverwachting en doodsoorzaken tussen 1992 en 2001. onze resultaten hebben wij vergeleken met eerder perioden van follow-up om een beeld te geven van de periode voor, tijdens en na het gebruik van mogelijk met virusinfecties besmette stollingsproducten. De sterftecijfers zijn vergeleken met de algemene Nederlandse mannelijke bevolking. Hierbij kwam naar voren dat hemofilie nog steeds gepaard gaat met oversterfte. De belangrijkst doodsoorzaken waren AIDS en levercarcinoom en levercirrhose als gevolg van hepatitis C. Opvallend was dat in patiënten met ernstige hemofilie zonder besmetting met HIV(humaan immunodeficiëntie virus) of het hepatitis C virus de kans op sterfte nog steeds hoger was dan de algemene populatie. De levensverwachting van deze patiënten was 71 jaar, in vergelijking met 76 jaar in de algemene bevolking. Dit betekent dat de huidige patiënt wel profiteert van een behandeling met veilige stollingsproducten, maar de levensverwachting nog steeds negatief beïnvloed wordt door de stollingsafwijking.
Hoofdstuk 2.2 beschrijft de medische en sociale ontwikkelingen gedurende 30 jaar hemofiliebehandeling. Wij hebben alle in 2001 in Nederland bekende hemofiliepatiënten een vragenlijst gestuurd, waarbij ongeveer 70% van hen bereid was deel te nemen. De vragenlijst bestond uit twee delen; een algemeen deel en een specifiek deel. Het algemene deel bestond uit vragen die gelijk waren aan die uit eerdere vragenlijsten, o.a. over bloedingfrequentie, ziekenhuisopnames en behandeling. In het specifieke deel werd hepatitis, de invoering van de

hemofiliebehandelcentra en de keuze tussen recombinant en plasma stollingsproducten behandeld. Uit ons onderzoek is gebleken dat het gebruik van profylactische therapie vooral bij kinderen en adolescenten is toegenomen. Oudere patiënten combineren veelal 'on demand' behandeling met profylaxe op risicovolle dagen. De verbeterde therapeutische mogelijkheden hebben geleid tot een afname in het jaarlijks aantal bloedingen, het percentage patiënten dat opgenomen moest worden in een ziekenhuis en het aantal dagen dat patiënten afwezig waren van school of werk. Een opvallende bevinding in dit onderzoek was dat ondanks een intensieve behandeling patiënten van 16 jaar en ouder beperkingen in gewrichten die rapporteren.

Het sociaal functioneren en de kwaliteit van leven van patiënten met hemofilie wordt beschreven in **hoofdstuk 2.3**. Sinds de introductie van stollingsfactorconcentraat is er veel verbeterd voor mensen met hemofilie. Behalve 'on demand' kan behandeling ook profylactisch worden gegeven. De verwachting bestaat dat wanneer alle bloedingen voorkomen kunnen worden met profylaxe, patiënten met hemofilie een volledig normaal bestaan kunnen leven. Ons onderzoek studie toont aan dat de deelname aan het arbeidsproces vooral voor patiënten met ernstige hemofilie lager is dan in de algemene mannelijke populatie. Dit was zowel het geval voor jonge mannen die hun leven lang met profylaxe zijn behandeld als voor oudere mannen bij wie deze behandeling pas later is begonnen. Hierbij leek er een verband te zijn tussen deelname aan het arbeidsproces en kwaliteit van leven: patiënten die geen werk hadden, rapporteerden een lagere kwaliteit van leven. Het verschil in kwaliteit van leven tussen hemofiliepatiënten en de Nederlandse bevolking was groter in oudere patiënten. Ondanks een verbeterde behandeling is de deelname aan het arbeidsproces van hemofiliepatiënten nog niet op het niveau van de Nederlandse man.

In hoofdstuk 2.4 werd in de HiN-5 studie de prevalentie van hepatitis C en het gebruik van antivirale medicatie bestudeerd. Hepatitis C is een voor patiënten die voor 1992 zijn

behandeld met onveilige stollingsproducten belangrijke co-morbiditeit. De studiepopulatie bestond uit deelnemers aan de HiN-5 studie die voor 1992 behandeling hebben ontvangen. Van deze patiënten was 54% op dit moment hepatitis C positief, van wie 32% werd behandeld met antivirale therapie. Om de betrouwbaarheid van de gerapporteerde data te controleren is een validiteitsanalyse uitgevoerd. Deze analyse bevestigde onze aanname dat patiënten met hemofilie goed geïnformeerd zijn over hun aandoening en de verwante complicaties. Met ons onderzoek hebben wij aangetoond dat hepatitis C nog steeds een belangrijke co-morbiditeit is en dat slechts een minderheid van de patiënten zich laat behandelen. Belangrijke redenen voor afzien van behandeling waren de onzekerheid over de lange termijn effecten en de effectiviteit van de behandeling.

Hoofdstuk 2.5 behandelt de introductie van recombinant Factor VIII (rFVIII) als een alternatief voor uit plasma gewonnen Factor VIII (pFVIII) voor de behandeling van hemofilie A. We vonden dat het verspreidingspatroon voor een groot deel werd bepaald door de Nederlandse Vereniging van Hemofilie Behandelaren, die had besloten tot een geleidelijke introductie van rFVIII. De hemofiliebehandelaren kwamen tevens overeen dat voorheen onbehandelde patiënten bij voorkeur zouden worden behandeld met rVIII. De enquête wees uit dat beide afspraken grotendeels zijn nageleefd. Zowel artsen als patiënten gaven aan dat de arts en niet de patiënt de meeste invloed heeft op de keuze voor een bepaald type FVIII product. In totaal schreven de artsen pFVIII voor aan 56% van hun patiënten, en de variatie in dit percentage per arts was groot. De artsen gaven aan dat leeftijd de enige factor was die een rol speelde bij de productkeuze voor een bepaalde patiënt. Een infectie met HIV, infectie met het hepatitis C virus, en het gegeven dat iemand familieleden had die pVIII gebruikten waren negatief geassocieerd met het overstappen van pFVIII naar rFVIII.

Hoewel een uitgebreide kennis bestaat over bloedingen bij mannen met hemofilie heeft niet veel onderzoek zich gericht op bloedingen bij draagsters van hemofilie. Dit onderwerp wordt

behandeld in **hoofdstuk 3**. In dit hoofdstuk bestuderen we de kans op bloeden onder draagsters van hemofilie A of B in vergelijking met niet-draagsters. Voor dit onderzoek hebben alle vrouwen die getest zijn op draagsterschap in het Leids Universitair Medisch Centrum of het Universitair Medisch Centrum Utrecht een vragenlijst ontvangen. Draagsterschaponderzoek voor hemofilie beperkt zich in Nederland voornamelijk tot deze centra. Tevens zijn gegevens verzameld met betrekking tot factor VIII en IX levels. We hebben zowel draagsterschap als stollingsfactorniveaus geassocieerd met het risico van bloeden. Onze studie toont aan dat draagsters van hemofilie een grotere kans hebben op bloedingen, vooral na medische interventies zoals operaties en tandextracties. Daarnaast is gebleken dat niet alleen stollingsfactorniveaus die vergelijkbaar zijn met de niveaus bij lichte hemofilie geassocieerd zijn met bloeden, maar ook hogere niveaus tussen 0.4 en 0.6 IU ml. Dit suggereert dat de als "veilig" aangenomen stollingsniveaus wellicht herzien moeten worden.

Deze studie laat zien dat hoewel de situatie van hemofiliepatiënten op medisch gebied verbeterd is door een intensievere behandeling, er nog veel aspecten zijn waar aandacht aan besteed dient te worden. De oversterfte in patiënten zonder virale infecties is hier een voorbeeld van. Wij hopen met deze studie een beeld te hebben gegeven van de medische en sociale omstandigheden van mensen met hemofilie. Belangrijk zijn ook de resultaten uit het onderzoek onder vrouwelijke familieleden van mannen met hemofilie. Wij hopen dat de resultaten van deze studie zullen leiden tot een verbeterd inzicht onder artsen van het belang van de bepaling van stollingsfactorniveaus bij vrouwen die draagster zijn van hemofilie.

Nawoord

Tijdens je promotieperiode leer je heel wat mensen kennen. Ondanks dat een nawoord te kort is om iedereen de credits te geven die ze verdienen, wil ik toch van deze gelegenheid gebruik maken om een aantal mensen in het bijzonder noemen. In oktober 2000 ben ik als promovendus onder leiding van prof. dr Frits Rosendaal gestart op het Hemofilie in Nederland-5 onderzoek. Op dat moment was het van groot belang om het onderzoek zo snel mogelijk op de rails te krijgen. Doeltreffende hulp is dan onmisbaar. Inge, je hebt mij in korte tijd de fijne kneepjes van datamanagement bijgebracht. Vooral in het begin was jij een steun met alle kennis over Access, scannen en de logistiek rond vragenlijsten.
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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 11 juni 1976 te Geervliet. Na het doorlopen van de middelbare school (Blaise Pascal Spijkenisse, VWO diploma 1995), begon zij aan de studie Biomedische Wetenschappen aan de Universiteit Leiden. Tijdens deze studie heeft zij onder andere stage gelopen bij de afdeling Klinische Genetica (Erasmus MC) in samenwerking met de afdeling algemene kindergeneeskunde (Erasmus MC/Sophia Kinderziekenhuis) en de afdeling Klinische Epidemiologie (Leids Universitair Medisch Centrum). In 2000 is zij gestart als promovendus op de afdeling Klinische Epidemiologie onder leiding van Prof.dr F.R. Rosendaal op het Hemofilie in Nederland-5 project. Gedurende haar promotieperiode heeft zij tevens twee evaluaties uitgevoerd naar aanleiding van de invoering van gecentreerde zorg voor hemofiliepatiënten in hemofiliebehandelcentra in opdracht van het College voor Zorgverzekeringen (CVZ). In het kader van de opleiding tot epidemioloog B heeft zij onder andere deelgenomen aan de Boerhaave cursus Klinische Epidemiologie op Schiermonnikoog, Regression Analysis (Stanley Lemeshow) en Principles and Methods of Epidemiologic Research van Kenneth J. Rothman. Sinds maart 2005 werkt zij als post-doc op de afdeling Klinische Epidemiologie onder leiding van prof. dr F.R.Rosendaal.