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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. (Blood. 2004;104:3494-3500)

Introduction

Hemophilia is an 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 less 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 questions 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 has also 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 HIV.[2] Plasma-derived products have been safe for hepatitis B and HIV since 1985, and also for HCV patients since 1992.[14]

In 1995, recombinant factor VIII products were 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]

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 3 decades of hemophilia treatment.

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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 was given for all questionnaires that were returned, irrespective of diagnosis (ie, 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 (>0.05-0.4 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 5 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 (eg, home treatment in 1978 and AIDS in 1985). In the 2001 questionnaire, items on hepatitis C and type of product were added.

This 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 years, adolescents as patients between 16 and 25 years, 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 years 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 with national figures for the general male population that were provided by the Central Bureau of Statistics Netherlands StatLine databank.[20] Self-reported measures on joint impairment were obtained for a series of 16 joints: 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, elbows, and knees, these were analyzed separately.

Results

Response and patient characteristics

Response was 70% in 2001 compared with 84% in 1972,[19] 70% in 1978,[21] 81% in 1985,[22] and 78% in 1992.[18] One hundred 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. 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%) received 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.

The median age of starting prophylactic treatment was 2 years in 2001 (range, 0-11 years) compared with 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

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

	1972, N = 447	1978, N = 560	1985, N = 935	1992, N = 980	2001, N = 1066
Median age, y (range)	19 (0-74)	23 (0-70)	28 (0-85)	31 (0-84)	36 (0-90)
Severity of hemophilia, no. of patients (%)					
Severe, less than 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, greater than 0.05-0.4 IU mL	172 (38)	138 (25)	376 (40)	420 (43)	470 (44)
Type A hemophilia, no. of patients (%)†	377 (84)	481 (86)	801 (86)	853 (87)	925 (87)
Sporadic hemophilia, no. of patients (%)	112 (25)	128 (23)	237 (25)	195 (20)	246 (23)

N indicates the entire population under study.

*Severity data was missing for 33 patients in 1972, and for 71 patients in 1970.

†All other patients are patients with hemophilia B.

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

	1972	1978	1985	1992	2001
Severe hemophilia					
Prophylaxis, proportion of patients (%)					
Children, 0-16 y	22/65 (34)	41/91 (45)	69/111 (62)	64/92 (70)	112/130 (86)
Adolescents, 17-25 y	12/39 (31)	27/54 (50)	43/72 (60)	—	38/42 (90)
Adults, older than 25 y	8/57 (14)	28/99 (28)	71/201 (35)	119/232 (51)	134/248 (54)
Median age at first prophylaxis, y (range)	—	8 (0-15)	5 (1-15)	—	2 (0-11)
Home treatment, no. of patients (%)	7 (4)	72 (29)	259 (67)	286 (74)	346 (82)
Moderate hemophilia					
Prophylaxis, proportion of patients (%)					
Children, 0-16 y	6/41 (15)	9/41 (22)	7/59 (12)	7/41 (17)	7/46 (15)
Adolescents, 17-25 y	4/14 (29)	7/26 (27)	1/19 (5)	—	4/23 (17)
Adults, older than 25 y	1/27 (4)	4/39 (10)	10/97 (10)	11/98 (11)	10/107 (9)
Home treatment, no. of patients (%)	2 (2)	14 (13)	39 (22)	51 (30)	57 (32)

— indicates not available.

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 7 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).

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

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

	1972	1978	1985	1992	2001
Severe hemophilia, N	159	245	384	387	420
Hemorrhages, median no. per year (range)*					
Children, 0-16 y	20 (0-98)	20 (0-70)	10 (0-65)	10 (0-98)	5 (0-51)
Adolescents, 17-25 y	20 (0-98)	17 (0-100)	10 (0-90)	10 (0-98)	6 (0-75)
Adult, older than 25 y	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, median no. of d/patient (range)	28 (2-252)	20 (1-180)	11 (1-100)	5 (0-330)	7 (0-89)
Absenteeism due to hemophilia, d (range)*					
School†	30 (0-80)	15 (0-80)	4 (0-80)	2,5 (0-80)	7 (0-90)
Work‡	15 (0-80)	20 (0-213)	7 (0-319)	8 (0-330)	5 (0-365)
Moderate hemophilia	23	106	175	173	176
Hemorrhages, median no. per year (range)*					
Children, 0-16 y	4 (0-40)	10 (0-104)	3 (0-66)	7 (33)	2 (0-57)
Adult, older than 25 y	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, median no. of d/patient (range)	17 (2-180)	10 (1-50)	7 (1-50)	5 (0-72)	6 (0-31)
Absenteeism due to hemophilia, d (range)*					
School†	30 (0-80)	5 (0-80)	3 (0-50)	0 (0-15)	5 (0-20)
Work‡	2 (0-80)	13 (0-130)	7 (0-319)	5 (0-365)	3 (0-120)

N indicates the entire population under study.
*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 years of age.

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

	1972, n = 113	1978, n = 168	1985, n = 330	1992, n = 352	2001, n = 341
No. of inactive patients, median (%)	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, (range)	32 (16-60)	36 (19-64)	41 (19-64)	42 (20-62)	49 (17-63)

N indicates the entire population under study.
*$\chi^2 = 3.44$; $P < .05$.
†The inactivity ratio was calculated as the ratio of inactivity in hemophilia patients and inactivity in Dutch males.

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 (eg, 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, 0-36 days). Restriction on the capacity to perform regular labor among patients between 15 and 64 years of age with severe and moderate hemophilia is shown in Table 4. Of the "inactive" patients, 69 patients (75%) were officially registered as fully or partially disabled. Although the percentage of "inactive" patients decreased compared with 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). 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). 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 to 16 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 6 joints. The mean number of reported joints with severe impairment did not change over the years (data not shown).

Of all patients with severe hemophilia, 22% did not report impairment of any of the main joints in 2001 compared with 19% in 1992 (Table 8). The absence of joint impairment was related to age, as it was reported by 59% of patients aged 0 to 16 years, 17% of those aged between 17 and 25 years, and 3% of patients with severe hemophilia older than 40 years of age. In 3 decades the percentage of patients that reported no joint damage in the age category 0 to 16

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

	Severity of hemophilia	
No. of impairments, (%)	Severe, less than 0.01 IU mL, N = 420	Moderate, 0.01-0.05 IU mL, N = 176
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)

N indicates the entire population under study.

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

	1972	1978	1985	1992	2001
Aged 0-16 y					
Median joint score (range)*	1 (0-19)	1 (0-25)	1 (0-10)	0 (0-7)	0 (0-33)
Severe joint impairment, proportion of patients (%)†	7/65 (11)	8/92 (9)	4/111 (4)	1/92 (1)	4/130 (3)
Aged 17-25 y					
Median joint score (range)*	5 (0-16)	4 (0-25)	3 (0-19)	3 (0-12)	3 (0-13)
Severe joint impairment, proportion of patients (%)†	9/39 (23)	12/54 (22)	11/84 (13)	12/64 (19)	8/42 (19)
Aged 25-40 y					
Median joint score (range)*	10 (2-13)	9 (0-22)	8 (0-31)	7 (0-28)	5 (0-24)
Severe joint impairment, proportion of patients (%)†	22/39 (56)	21/69 (30)	41/115 (36)	42/119 (35)	30/89 (34)
Older than 40 y of age					
Median joint score (range)*	12 (4-26)	11 (3-41)	12 (0-42)	12 (0-40)	15 (0-48)
Severe joint impairment, proportion of patients (%)†	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, proportion of patients (%)†	49/159 (31)	57/245 (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 as follows: 0 indicates no impairment; 1, some impairment; 2, some impairment with daily problems; and 3, severe impairment with total loss of function.

†Severe impairment with total loss of function reported in 1 or more of the 6 main joints.

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.

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

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

	1972	1978	1985	1992	2001
Aged 0-16 y					
Median joint score* (range)	0 (0-10)	0 (0-6)	0 (0-14)	0 (0-8)	0 (0-7)
Severe joint impairment, proportion of patients (%)†	5/42 (12)	2/41 (5)	1/59 (2)	—	1/46 (2)
Aged 17-25 y					
Median joint score* (range)	2 (0-9)	1 (0-7)	1 (0-8)	1 (1-5)	1 (0-10)
Severe joint impairment, proportion of patients (%)	1/14 (7)	—	1/22 (5)	—	1/23 (4)
Aged 25-40 y					
Median joint score* (range)	5 (0-27)	7 (0-17)	3 (0-20)	3 (0-12)	4 (0-16)
Severe joint impairment, proportion of patients (%)	2/18 (11)	6/24 (25)	10/58 (17)	8/45 (18)	6/35 (17)
Older than 40 y of age					
Median joint score* (range)	4 (0-10)	3 (0-15)	5 (0-24)	6 (0-24)	5 (0-44)
Severe joint impairment, proportion of patients (%)	3/9 (33)	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, proportion of patients (%)	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.

—indicates not present.

*The median joint score was calculated as the median over the sum of the scores of 16 joints, which have been scored as follows: 0 indicates no impairment; 1, some impairment; 2, some impairment with daily problems; and 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.

Table 8. Absence of joint impairment in patients with severe hemophilia in the left and right ankles, elbows, and knees

	1972	1978	1985	1992	2001
Severe hemophilia, no. of patients (%)					
Aged 0-16 y	26 (40)	40 (44)	53 (48)	56 (61)	76 (59)
Aged 17-25 y	2 (5)	5 (9)	7 (8)	9 (14)	7 (17)
Aged 25-40 y	—	2 (3)	3 (3)	2 (2)	7 (8)
Older than 40 y of age	—	—	3 (4)	1 (1)	4 (3)
Overall	28 (18)	47 (19)	66 (17)	74 (19)	94 (22)
Moderate hemophilia, no. of patients (%)					
Aged 0-16 y	23 (55)	28 (68)	42 (71)	29 (71)	37 (80)
Aged 17-25 y	5 (36)	13 (50)	9 (41)	17 (50)	11 (48)
Aged 25-40 y	2 (11)	3 (13)	14 (24)	14 (31)	13 (37)
Older than 40 y of age	3 (33)	5 (33)	11 (31)	15 (28)	17 (24)

—indicates not present.

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 nonresponders 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 3 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 with 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 with 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.

Table 9. Complications of hemophilia treatment

	1972	1978	1985	1992	2001
Inhibitory antibodies*					
Cumulative incidence, proportion of patients			31/384	51/388	52/420
Current inhibitors, no. of patients (%)	—	—	19 (5)	29 (7)	15 (4)
Past inhibitors, no. of patients (%)	—	—	12 (3)	22 (6)	37 (9)
HIV infection, no. of patients (%)†	—	—	36 (4)	55 (8)	29 (5)
Hepatitis C, no. of patients (%)‡					
Current infection	—	—	—	—	344 (45)
Past infection	—	—	—	—	97 (13)

—indicates no data available.
*Reported for patients with severe hemophilia.
†Reported for patients treated with clotting factor before 1985.
‡Reported for patients treated with clotting factor before 1992.

As we also observed in the 1991 survey, there was no further improvement in perceived joint impairment compared with the earlier surveys covering the period 1972 to 1985. A previous study presenting joint pathology by radiologic 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 younger than 25 years with severe hemophilia, 7% reported at least one joint with complete loss of function in the latest survey. The discrepancy between radiologic assessments and our findings will be the 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 HCV.

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[25] in 1998. 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 3 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 (eg, 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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