# Modern hemophilia treatment: medical improvements and the quality of life

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**Abstract.** Rosendaal FR, Smit C, Varekamp I, Bröcker-Vriends AHJT, van Dijck H, Suurmeijer TPBM, Vandenbroucke JP, Briët E (Department of Clinical Epidemiology and Department of Haematology, University Hospital, Leiden, the Netherlands Hemophilia Society, the Department of Health Sciences, State University, Groningen, and the Clinical Genetics Centre, Leiden, The Netherlands). Modern haemophilia treatment: medical improvements and quality of life. *Journal of Internal Medicine* 1990; **228**: 633–640.

Adequate replacement therapy in haemophilia has been available for two decades. This has led to considerable improvements in the life expectancy and physical status of haemophilia patients. A study was conducted to investigate whether this has also led to improvements in quality of life. With this aim, information was obtained from 935 Dutch haemophiliacs by mailed questionnaires on relationships, marriage, family life and employment. Haemophilia patients were less often married than men in the general population (13% fewer) and had a lower total number of children (30% lower, 17% for those who were married). Twenty-two per cent of the patients were not employed and received an income from the disability funds. While severity of haemophilia, joint damage and age increased the risk of disability, it was noted that home treatment was associated with a 50% reduction in this risk. Remarkably, haemophilia patients did not differ from the general population in their view of the quality of their own health. The results of this study show a positive influence of modern haemophilia treatment on quality of life. At present, AIDS overshadows all optimistic feelings one may have about this field. However, the results described here demonstrate the benefits that can be achieved with adequate replacement therapy, and justify the expectation of further improvements in the near future.

*Keywords:* employment, family life, haemophilia, home treatment, inhibitors, quality of life.

## Introduction

Clotting factor preparations for the treatment of haemophilia A and B have been used in the Netherlands since the late 1960s [1–4]. Since then, the use of coagulation products has steadily increased [5–7], enhanced by the introduction of prophylaxis [8, 9] and home treatment [10, 11]. The availability of effective treatment has led to substantial improvements in the health status of patients with haemophilia. Life expectancy, which was less than 30 years in 1960, is now almost normal [12–14]. The number and duration of hospital admissions have declined sharply, as has the extent of sick leave from school and work [12].

The purpose of the present study was to investigate whether these improvements have also led to an improved quality of life for haemophilia patients. Quality of life can be broadly defined as the degree of satisfaction with life in general [15, 16]. This may be reduced in haemophiliacs because of the acute symptoms of a bleeding, chronic arthropathy, or because

of prejudice towards patients with a genetic bleeding disorder [17].

Quality of life may be judged externally by objective parameters or subjectively by the individual himself [18]. We used both approaches. Since most people consider good health to be of paramount importance in securing a high quality of life [19], we investigated the patients' subjective interpretation of their own health and compared this with the view of the general population.

Objectively, the physical status of haemophilia patients has been greatly improved by replacement therapy. We studied the extent to which this improved physical status has affected other aspects of life that are generally perceived to be important, such as family life, relationships and employment.

Many haemophilia patients do not have regular employment because of their disability. The percentage of patients receiving a disability pension has increased slightly between 1972 and 1985 from 17% to 22%, although this reflects a decrease when related to the increased number of disabled persons in the general population, which more than doubled in the same period [12, 19, 20]. It is reasonable to assume that an impairment which removes the opportunities for certain types of employment may still allow other paid employment which, for instance, is less physically demanding. We therefore decided to investigate possible factors that could affect the risk of being unemployed due to disability.

## Methods

### *Patients and measurements*

The data were collected by standardized mailed questionnaires sent to all 1162 Dutch haemophiliacs who were registered at one of the treatment centres or at the Dutch Haemophilia Society [12]. The questionnaire covered a broad range of topics. The closing date for completion of questionnaires was 1st January 1986. The treatment centres presented us with supplementary information on the type and severity of haemophilia.

We compared the information from the patients with national data after adjustment for age differences. This comparison was possible for marital status [21], number of children [21], evaluation of one's own health [22], and employment [23]. No data were available on stable relationships in the general population.

We regarded as employed those individuals who held a paid job. Individuals who are not attending school may be either economically unemployed and receive an income from the unemployment funds, or be disabled and receive a disability pension. When we speak of disabled individuals we refer to this latter category, the term disability having a purely administrative and not a medical sense. The income from these funds may be supplementary for individuals who are still able to participate as members of the labour force to some extent: they are disabled and employed, or even disabled and economically unemployed. In the case of individuals who are not regarded as fit to work at all (administratively less than 20% working capacity), the disability funds may provide the only source of income. These individuals will here be described as completely disabled, again in a strictly administrative and not a medical sense.

With regard to educational level, we used a four-category classification as follows: 1, lower education (elementary school); 2, lower additional schooling (lower vocational training or lower levels of high school); 3, middle additional schooling (middle vocational training or high school) and; 4, higher additional schooling (vocational degrees or academic degrees). Occupational level was classified according to the Occupational Guide [24] in six categories (1, unskilled manual labour; 2, skilled manual labour; 3, lower employee; 4, small entrepreneur; 5, middle employee; 6, higher vocation).

Joint impairment for 16 joints was scored as follows: 0, no impairment; 1, some impairment without daily problems; 2, impairment with daily problems; 3, impairment with complete loss of function. The scores were added to form a scale ranging from 0 to 48 points. The number of bleedings was the total number over a 1-year period preceding the survey, which was used as an approximate estimate for lifetime bleedings.

### *Analysis*

We constructed a logistic regression model to investigate the independent contribution of several determinants of disability, i.e. complete disability in the administrative sense. For this analysis the patients were regrouped into two non-overlapping categories: employed (whether partially disabled or not), and unemployed because of complete disability. Putative determinants were age, severity of

haemophilia, inhibitor status, degree of arthropathy, number of bleedings, home treatment, educational level and occupational level.

For this analysis the factors under investigation were regrouped into a small number of categories as follows: five 10-year age classes; three categories of severity, according to the usual classification (severe, < 1% clotting factor activity; moderate, 1–5% clotting factor activity; mild, > 5% clotting factor activity); three groupings of joint score into tertiles (0 points, 1–5 points and > 5 points); three categories of bleeding frequency, also in tertiles (no bleedings in a year, 1–5 bleedings a year and > 5 bleedings a year); four categories of education as outlined above, and four categories of occupational level (unskilled manual labour, skilled manual labour/lower employee, small entrepreneur/middle employee and higher vocation).

First univariate odds and risk ratios on disability were calculated from simple cross-tabulation. Subsequently the variables were entered into the logistic model, which yielded multivariate odds ratios. Such a ratio gives a risk estimate which may be regarded as the independent contribution of a certain factor to the total risk, since the other variables have been held constant.

## Results

The response to our survey was 81% (947 forms returned, of which 935 could be analysed). The average age of the respondents was 33 years (general male population 36 years). Forty-one per cent had severe, 18% had moderately severe and 42% had mild haemophilia. Eighty-six per cent had haemophilia A and 14% had haemophilia B. Among those with haemophilia A, 40% had severe haemophilia; among those with haemophilia B, 49% had severe haemophilia. Comparisons of haemophilia A and B were therefore weighted for severity. Twenty-two patients had an inhibitor, in all cases but one to factor VIII.

Of the patients aged 15 years and older, 49% (363 of 742 patients) were married, while 3.5% (26 patients) were divorced. The proportion of married men in the general population, after adjustment for age differences, was 56%, while the number of divorced men was 3.4%. Therefore the observed/expected ratio for marriage was 87%, which implies that the chances of haemophilia patients being married were reduced by 13% (Table 1). Patients with haemophilia A and B did not differ significantly in this respect, and inhibitor patients did not differ from the other patients with severe haemophilia. By comparison with the general male population, the observed/expected ratio (O/E) was lowest for severe haemophilia (O/E, 76%).

Of all 742 patients aged > 15 years, 211 (28%) subjects regarded haemophilia as an impediment to starting a relationship; 139 (19%) patients also thought it had a negative effect on the stability of an existing relationship. Such views were most often expressed by the patients with severe haemophilia: 44% thought haemophilia was an impediment to finding a partner, while 27% considered that it had a negative effect on an existing relationship. Eleven per cent (67 of 589) of the patients aged ⩾ 18 years who had ever had a relationship thought that haemophilia had once been the cause of such a relationship ending; again, this was highest in the case of patients with severe haemophilia (20%).

The 676 patients aged ⩾ 18 years had a total of 672 children. The expected number of children for men of the same age in the general population was 956, i.e. the haemophilia patients had 30% fewer children (O/E ratio, 0.70). The lower number of marriages could not entirely account for the low number of offspring of haemophilia patients: the 363 married patients had a total of 621 children, compared to an expected number of 749. Thus even the married patients had 17% fewer children than married men of the same age in the general population (Table 1). Fourteen per cent of the patients aged ⩾ 20 years without children stated that they had no children because of haemophilia, the most frequent reason being that they wished to avoid passing on the haemophilia gene to their daughters.

Eighty per cent of the patients considered their own health to be good or excellent (general male population, 83%). As is shown in Table 2, the patients with severe, moderate or mild haemophilia differed only slightly in their opinion of their health. No differences were observed between patients with haemophilia A and B. However, the inhibitor patients more frequently had a negative opinion of their own health, although 69% still considered their health to be good or excellent.

One hundred and fifty-five (22%) of the 716 patients aged 15–64 years received an income from one of the disability funds. In the general male population 8.3% were disabled (figure corrected for age differences; unadjusted figure, 11%). Seventy-

**Table 1.** Marriages and children of haemophilia patients

| | Married patients O/E | No. of children (all patients) O/E | No. of children (married patients) O/E |
|---|---|---|---|
| All | 0.87 | 0.70 | 0.83 |
| Severe | 0.76 | 0.54 | 0.74 |
| Moderate | 0.87 | 0.56 | 0.92 |
| Mild | 0.96 | 0.80 | 0.85 |

The ratio of the observed to expected number (O/E) is shown. The expected number is that which would be expected in a group of men of the same age from the general population, i.e. it is the population figure corrected for age differences. In haemophilia A the O/E ratio for marriage was 0.88, in haemophilia B it was 0.83. The number of marriages refers to 742 patients aged $\geq$ 15 years, and the number of children refers to 676 patients aged $\geq$ 18 years, of whom 363 were married.

**Table 2.** Responses to the question: 'How do you consider your own health?'

| | 'Good/excellent' | | 'Bad/moderate' | |
|---|---|---|---|---|
| | Patients (%) | Population (%) | Patients (%) | Population (%) |
| All | 80 | 83 | 20 | 17 |
| Severe | 77 | 86 | 23 | 14 |
| Moderate | 80 | 83 | 20 | 17 |
| Mild | 82 | 82 | 18 | 18 |

The figures apply to individuals aged $\geq$ 18 years. The population figures are adjusted for age by weighting to the age distribution of the patients. Since patients with severe haemophilia were on average younger than those with moderate and mild haemophilia, these figures vary for different groups. For patients with haemophilia A, 80% considered their own health to be good or excellent, the corresponding figure for patients with haemophilia B was 79%. The population figures refer to a sample of 1954 Dutch men [22].

five per cent (117 patients) of them were administratively completely disabled, and 25% were partially disabled, i.e. they were receiving an income from one of the disability funds, in addition to having paid employment. For most patients (86%) haemophilia was the cause of their administrative disability. Disability was most frequently observed in severe haemophilia (33% as compared to 7.5% in the general population, aged-adjusted figure).

We investigated the determinants of this disability for 534 patients who were either employed ($n = 425$) or disabled and unemployed ($n = 109$). First, we calculated univariate odds ratios and relative risks, which are shown in Table 3. Odds ratios are used as an approximation of the relative risk, and should be interpreted as the risk of being disabled relative to the lowest category for each factor. As shown in Table 3, the odds ratios vary in the same direction of magnitude as the relative risk, but remain a rather approximate estimation, due to the high proportion of disabled individuals. The relative risk of disability increased with severity of haemophilia, age, joint score and number of bleedings. The risk of being disabled was also higher for

**Table 3.** Determinants of disability: univariate analysis

| Factor | *n* | Disabled (%) | OR | RR |
|---|---|---|---|---|
| Severity | | | | |
| Mild | 230 | 9 | 1.0 | 1.0 |
| Moderate | 90 | 22 | 3.0 | 2.6 |
| Severe | 214 | 32 | 5.0 | 3.7 |
| Bleedings (per year) | | | | |
| 0 | 222 | 14 | 1.0 | 1.0 |
| 1-5 | 132 | 18 | 1.3 | 1.3 |
| > 5 | 180 | 28 | 2.5 | 2.0 |
| Joint score (points) | | | | |
| 0 | 148 | 7 | 1.0 | 1.0 |
| 1-5 | 190 | 12 | 1.6 | 1.6 |
| > 5 | 196 | 39 | 7.9 | 5.2 |
| Inhibitor | | | | |
| Absent | 521 | 19 | 1.0 | 1.0 |
| Present | 13 | 62 | 6.7 | 3.2 |
| Home treatment | | | | |
| No | 377 | 18 | 1.0 | 1.0 |
| Yes | 157 | 26 | 1.6 | 1.4 |
| Age (years) | | | | |
| 15–24 | 72 | 6 | 1.0 | 1.0 |
| 25–34 | 174 | 11 | 2.1 | 2.0 |
| 35–44 | 161 | 22 | 4.9 | 4.0 |
| 45–54 | 86 | 31 | 7.8 | 5.7 |
| 55–64 | 41 | 56 | 21.7 | 10.1 |
| Education level | | | | |
| Lower | 86 | 55 | 1.0 | 1.0 |
| Lower additional | 214 | 18 | 0.2 | 0.3 |
| Middle additional | 125 | 10 | 0.1 | 0.2 |
| Higher additional | 90 | 9 | 0.1 | 0.2 |
| Occupation | | | | |
| Unskilled worker | 34 | 29 | 1.0 | 1.0 |
| Skilled worker/lower employee | 272 | 22 | 0.7 | 0.8 |
| Small entrepreneur/ middle employee | 142 | 13 | 0.4 | 0.5 |
| Higher vocation | 64 | 6 | 0.2 | 0.2 |

The risks of being unemployed due to disability are shown. The odds ratios (OR) and the risk ratios (RR) are relative to the lowest category of each factor, which is set at 1.0, e.g. patients aged 25–34 years had a risk of disability twice that for those aged 15–24 years. These odds and risks ratios were calculated separately for each factor, without taking the other factors into account.

**Table 4.** Determinants of disability logistic regression

| Factor | OR | CI95 |
|---|---|---|
| Severity | | |
| Mild | 1 0 | |
| Moderate | 4 2 | 1 5 to 11 4 |
| Severe | 8 0 | 2 8 to 23 0 |
| Bleedings (per year) | | |
| 0 | 1 0 | |
| 1-5 | 1 1 | 0 4 to 2 6 |
| > 5 | 1 1 | 0 4 to 2 7 |
| Joint score (points) | | |
| 0 | 1 0 | |
| 1-5 | 1 4 | 0 5 to 4 0 |
| > 5 | 3 6 | 1 2 to 10 7 |
| Inhibitor | | |
| Absent | 1 0 | |
| Present | 2 9 | 0 6 to 14 3 |
| Home treatment | | |
| No | 1 0 | |
| Yes | 0 5 | 0 2 to 1 1 |
| Age (years) | | |
| 15–24 | 1 0 | |
| 25–34 | 3 6 | 0 4 to 30 2 |
| 35–44 | 11 0 | 1 3 to 92 0 |
| 45–54 | 19 7 | 2 2 to 172 8 |
| 55–64 | 110 0 | 11 2 to 1107 7 |
| Education | | |
| Lower | 1 0 | |
| Lower additional | 0 4 | 0 2 to 0 8 |
| Middle additional | 0 2 | 0 1 to 0 6 |
| Higher additional | 0 2 | 0 1 to 0 6 |
| Occupation | | |
| Unskilled worker | 1 0 | |
| Skilled worker/lower employee | 0 9 | 0 3 to 2 9 |
| Small entrepreneur/ middle employee | 0 4 | 0 1 to 1 4 |
| Higher vocation | 0 2 | 0 0 to 0 9 |

These odds ratios (OR) indicate the independent effect of a factor The odds ratio estimates the multivariate relative risk, e g. when all other factors such as severity and joint score were controlled for those on home treatment had a risk of disability 50% of that for patients not on home treatment For educational and occupational level information for 37 patients was missing the odds ratios refer to 497 patients CI95 is the 95% confidence interval of the odds ratio The odds ratio for type of haemophilia (A vs B) was exactly 1 00

patients on home treatment. However, this risk ratio is not controlled for severity of haemophilia, while severe haemophilia is overrepresented among patients on home treatment.

Subsequently, we calculated multivariate odds ratios by logistic regression (Table 4). These should be interpreted as the risk (approximated by the odds) relative to the patients within the lowest category for that variable, while all other factors in the model are kept constant. For example, severity had an independent effect on the risk of being disabled: compared to patients with mild haemophilia, patients with moderate haemophilia had a 4.2-fold higher risk of being disabled, while in those with severe haemophilia it was 8.7-fold higher. The type of haemophilia was not related to the risk of disability. When controlled for severity, the presence of an inhibitor still increased the risk almost threefold.

Home treatment, which in the univariate analysis had been confounded by severity, reduced the odds ratio for disability considerably: those patients on home treatment had a risk of disability only 50% of that for individuals not on home treatment. A higher educational level and higher occupational level were accompanied by a lower risk of disability.

The fit of the model was tested by calculating the probability of disability for each individual from the logistic risk function:

$$P = 1/(1+e^{-z})$$

in which $z = \alpha + \Sigma\beta_i x_i$ ($x_i$ is each factor, 1 when present and 0 when absent), and $P$ is the probability of being disabled. For different cut-off points of $P$ we compared the number of employed and disabled patients above and below the cut-off points. In this way the information about the determinants is used as a 'diagnostic test' for disability, and sensitivity and specificity can be calculated. At a cut-off point of $P = 0.13$, sensitivity was 0.95 and specificity was 0 74 (predictive value 45%). Given these figures, we conclude that the model is a fairly reliable predictor of disability, despite the approximate nature of some of the estimates, such as the bleeding frequency and arthropathy.

## Discussion

The availability of coagulation products for the treatment of haemophilia has greatly improved the quality of daily life of haemophilia patients in the Netherlands. Further improvement may be expected, as an increasingly large number of patients will have received adequate treatment from childhood onward. It has been suggested that, even though haemophilia A and B have identical natural histories [25, 26], differences in treatment might eventually result in a different clinical presentation of both states [25]. In this study, however, we found no difference between haemophilia A and B. Inhibitor patients have bene-

fited least from substitution therapy. Therefore, the management of these patients will remain one of the major challenges of haemophilia treatment.

Since the early days of substitution treatment, the aim in haemophilia care has shifted from the treatment of severe bleedings alone to the prevention of the sequelae of bleedings, notably arthropathy. This implies prompt treatment of bleedings with adequate dosage [27–30]. In a recent consensus meeting on haemophilia treatment, the Dutch haematologists emphasized that treatment of joint bleedings at the first sign, and within at least 2 h after onset, may be of paramount importance in the prevention of joint damage [31, 32]. In patients with a high bleeding frequency, i.e. more than one bleed per week, prophylactic treatment should be considered. Home treatment should be encouraged because it ensures early treatment, increases independence and maximizes opportunities for schooling and employment. Haemophilia care should preferably be performed or supervised by specialized centres with comprehensive care teams, which implies involvement of professionals from different fields.

At present, the physical well-being of many haemophilia patients is threatened by AIDS. In this respect, our study demonstrates the benefits of modern haemophilia care, but predominantly for those patients who escaped HIV infection. In the Netherlands, about 17% of haemophilia patients are HIV positive [33]. This implies that here and in other countries with a low prevalence of seropositivity, such as Belgium [34, 35], Norway [36] and Finland (Ikkala, personal communication), many patients will already be receiving the full benefit of the improvements reported here. However, even in the countries with the highest HIV seroprevalence, AIDS among haemophilia patients will be a temporary tragedy. For those countries our study is of both historical and future relevance, for it demonstrates the benefits that may be expected after this tragedy of AIDS has passed.

Family life and employment are the most prominent features of daily life. It is obvious that before clotting products became available, when patients usually did not survive beyond early adulthood [13], few had the opportunity for stable relationships or employment. At present, the difference between haemophilia patients and the general population is small. Haemophilia still poses some barriers to the initiation of relationships, but most patients are able to overcome these problems.

Haemophilia patients had fewer children than men of the same age in the general population, and this was the case even for those who were married. Of necessity, however, these data refer to older patients, many of whom have not benefited from adequate replacement therapy from childhood onward.

As we have reported previously, haemophilia patients were less frequently unemployed for economical reasons alone than the average Dutch male [37]. Furthermore, the patients who were employed had obtained positions in employment that were appropriate to the education they had received, and they did not have to perform jobs below their level of ability. Equally encouraging was the observation that the educational level of haemophilia patients in The Netherlands was the same as that of the general population [12, 38]. In the present study we found that severity of haemophilia and joint damage were factors that increased the probability of being disabled in an administrative sense, while home treatment reduced this probability. We have the firm impression that modern replacement therapy prevents or at least slows the rate of progression of arthropathy, and that if effectively prevents many other problems related to the severity of haemophilia. This justifies the expectation that increasing numbers of haemophilia patients will succeed in obtaining employment. It is readily understood that home treatment—which might in this case perhaps be more accurately termed 'factory or office treatment', since patients also administer transfusions at their place of work—is of practical importance in facilitating employment. Although these figures should be regarded with a certain degree of caution, since the analysis was performed on patients who were 'administratively disabled', a prevalent status which may already have existed for years, the determinants in our model proved to be remarkably discriminatory. If modern haemophilia treatment leads to the expected prevention of progression of joint damage, we will in the future see a decrease in unemployment because of disability.

Quality of life remains an ill-defined subject. In a similar study, patients with end-stage renal disease were asked to assess their own quality of life by means of several questionnaires that had also been used in the general population. However, these subjective quality assessments correlated poorly with objective measurements, as functional impairment and ability to work. Moreover, the results showed

that these chronically ill patients were almost as satisfied with the quality of their lives as healthy people. This led to the conclusion that, despite a serious illness, satisfaction can be reached through a normal process of adaptation [39, 40]. It appeared that the patients rated their own quality of life higher than it would be assessed by others, which raises the following question: 'quality according to whom?'

To paraphrase a commercial slogan, 'a man is as healthy as he feels'. In this respect, haemophilia patients differ very little from the general population, and most patients consider themselves to be in good or excellent health. This may be the most promising observation of all, for if patients with haemophilia are able to maintain the view that they are as fit as any other individual, and are no different from them, they will succeed in founding families, finding employment and overcoming the remaining problems that face them.

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