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### **Citation**

Rosendaal, F. R. (1995). Mortality in patients with hemophilia: changes in a Dutch population from 1986 to 1992 and 1973 to 1986, 823-827. Retrieved from <https://hdl.handle.net/1887/1763>

Version: Not Applicable (or Unknown)

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# Mortality in Patients with Hemophilia

## Changes in a Dutch Population from 1986 to 1992 and 1973 to 1986

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■ **Objective:** To determine causes of death and mortality rates in patients with hemophilia over a period of 20 years, to assess changes in mortality, and to distinguish between hemophilia-related death and recent death induced by viral infections.

■ **Design:** Cohort study of 919 patients followed from January 1986 to June 1992. Results were compared with outcomes of previous follow-up from 1973 to 1986.

■ **Setting:** Consecutive national questionnaire surveys on hemophilia, using patient registries of the Netherlands Hemophilia Society and Dutch hemophilia centers.

■ **Patients:** 919 males with hemophilia A or B who participated in a national questionnaire survey on hemophilia in 1985. Median duration of follow-up was 6.4 years, which yielded 5753 person-years of follow-up. The mean age at study entry was 30 years (range, 1 to 85 years).

■ **Measurements:** Standardized mortality ratios, causes of death, median life expectancy, age-adjusted relative risks associated with the type or severity of hemophilia, presence of inhibitors, prophylaxis, and human immunodeficiency virus infection.

■ **Results:** 45 patients (5%) died between January 1986 and June 1992; 22.6 patients had been expected to die. Thus, the overall standardized mortality ratio was 2.0. The overall median life expectancy was 66 years for the cohort studied from 1973 to 1986 and 68 years for the cohort studied from 1986 to 1992. When deaths related to viral infection were excluded, the life expectancy almost equaled that of the general male population. Between 1986 and 1992, 1 patient died of ischemic heart disease compared with the 5.2 who were expected to die of this disease. Infection with HIV was the strongest independent predictor of death (relative risk, 27.5 [95% CI, 5.7 to 132.8]). After adjustment for HIV infection, no other hemophilia-related risk factors were associated with the risk for death.

■ **Conclusions:** The acquired immunodeficiency syndrome and hepatitis strongly influence mortality in patients with hemophilia. In the absence of viral infections, the life expectancy of patients with hemophilia would almost equal that of the general male population.

*Ann Intern Med.* 1995;123:823-827.

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Before 1960, hemophilia was characterized by excess mortality caused by hemorrhages, mainly intracranial (1, 2). Substitution therapy, introduced in the 1960s, has contributed to a decrease in hemophilia-related mortality (3–8). However, survival decreased sharply in the 1980s because of deaths from human immunodeficiency virus (HIV) infection or hepatitis, particularly in patients with severe hemophilia (5, 7). The acquired immunodeficiency syndrome (AIDS) caused an increase in mortality rates at relatively young ages. Chorba and colleagues (7) reported that for the years 1987 to 1989, AIDS had become the predominant cause of death (55.1%) among patients with hemophilia A in the United States; in addition, compared with the period from 1979 to 1981, the number of deaths from liver disease had increased more than threefold. Patients with hemophilia who died of HIV-related diseases between 1987 and 1989 had a median age of 34 years, whereas those who died of other causes had a median age of 56 years (7).

The effect of HIV infections on mortality in patients with hemophilia is obviously related to the percentage of infected patients. Among Dutch hemophiliacs, the overall percentage of those infected with HIV is approximately 13% (9), a relatively small percentage compared with that in other European countries or the United States (10).

We describe our experiences with a cohort of 919 patients with hemophilia who were followed from 1986 to 1992. This report, together with a previous report (11) on the results of a follow-up period from January 1973 to January 1986 ( $n = 717$ ), form a complete inventory of mortality among Dutch hemophiliacs over 20 years. We studied the manner in which virus-related deaths influence the survival of Dutch patients with hemophilia.

### Methods

We selected a cohort of 919 patients who had hemophilia A or B from 935 respondents to a questionnaire survey in 1985. The total number of respondents represented about 75% of all Dutch patients with hemophilia (12). The following respondents did not meet the inclusion criteria for follow-up: 5 female carriers, 3 respondents who had other bleeding disorders, 7 anonymous respondents to the 1985 survey, and 1 temporary foreign resident. The 919 remaining patients were followed from 1 January 1986 (closing date of the 1985 survey) to 1 June 1992. Five patients emigrated during follow-up, and the end dates of 33 patients were censored before the end-of-study date because the patients' addresses were no longer known. We used information from municipal registries, physicians, and the Hemophilia Society to assess the end dates of these patients.

We obtained information on date of birth, year of death, and vital status at the end-of-study date from the responses to the latest survey, the attending physicians, or municipal population registries. We obtained causes of death from physicians and categorized them according to the ninth revision of the Interna-

**Table 1. General Characteristics of 919 Patients Followed from 1986 to 1992**

Severity of Hemophilia	Patients with Hemophilia A	Patients with Hemophilia B	Mean Age at Study Entry y
	n(%)		
Severe*	315 (40)	66 (54)	27
Moderately severe†	152 (19)	20 (16)	29
Mild‡	329 (41)	37 (30)	33
Total	796	123	30

\* Clotting factor level, <0.01 IU/mL.

† Clotting factor level, 0.01 to 0.05 IU/mL.

‡ Clotting factor level, 0.05 to 0.40 IU/mL.

tional Classification of Diseases, Injuries, and Causes of Death (ICD-9) (13). This categorization permitted analyses of cause-specific mortality. Hemorrhages were defined as the cause of death only if no underlying fatal disorder was present. Data on the severity of hemophilia, the presence of neutralizing antibodies to factor VIII or IX (inhibitors), the use of prophylactic treatment, and the HIV test result were derived from the self-reported answers to the 1985 questionnaire. The severity of hemophilia, depending on the residual clotting factor activity, was categorized as severe (clotting factor level < 0.01 IU/mL or < 1% of the normal activity), moderately severe (clotting factor level, 0.01 to 0.05 IU/mL), or mild (clotting factor level, 0.05 to 0.40 IU/mL).

To estimate the relative risk for overall and cause-specific death, we used the patient-year method and calculated standardized mortality ratios (expressed as the ratio of the observed number of deaths to the number that would be expected if the mortality rates in the study cohort were the same as those in the general population, adjusted for sex and age). We used mortality rates for the general male population in 1990 to calculate standardized mortality ratios for the study population followed from 1986 to 1992. The 95% CIs were based on the Poisson distribution.

We extrapolated the median life expectancy at 1 year of age from life tables for the general male population in 1991. The population mortality rates in each age interval were multiplied by the overall relative mortality rate under the assumption that the relative mortality over age was equal for all ages. The median life expectancy is the age at which 50% of a hypothetical cohort of 1-year-old males will have died.

Finally, we simultaneously examined the contribution of several factors to the risk for death in a multivariate survival model (the Cox proportional hazards model) (14). The factors studied were the type and severity of hemophilia, HIV status, presence of an inhibitor, and prophylactic treatment; age was entered into the model as an adjustment variable (in 18 categories, with dummy variables). This model yielded the rate ratios (relative risk) for each factor compared with the reference category of that factor and adjusted for all other factors in the model.

## Results

The cohort followed from 1986 to 1992 consisted of 919 patients, 796 with hemophilia A and 123 with hemophilia B (Table 1). The mean age at study entry in 1986 was 29.6 years (range, 0.7 to 85.3 years). Patients with mild hemophilia were, on average, older when they entered the study than patients with moderately severe or severe hemophilia (33, 29, and 27 years, respectively).

With a median follow-up of 6.4 years, the 919 patients contributed 5753 person-years of follow-up. Forty-five patients died between 1986 and 1992; 22.6 deaths had been expected (that is, 22.6 deaths would have occurred in a hypothetical cohort of the general male population with an equal age distribution). The standardized mortality ratio was 2.0 (CI, 1.5 to 2.7), indicating that the overall mortality for patients with hemophilia was twice as high as that in the general male population. For patients with severe hemophilia, the mortality rate was four times higher than expected (standardized mortality ratio, 4.0 [CI, 2.4 to 6.3]), whereas almost no excess in mortality was seen for patients with mild hemophilia (standardized mortality ratio, 1.1 [CI, 0.6 to 1.8]).

The median life expectancy at 1 year of age for mildly affected patients with hemophilia was similar to that of the general Dutch male population in 1991 (74 years). Severely affected patients with hemophilia had the lowest median life expectancy (61 years) (Table 2).

### Cause-Specific Mortality

Causes of death are listed in Table 3. In the cohort followed from 1986 to 1992, 12 patients died of AIDS (10 with severe hemophilia, 1 with moderately severe hemophilia, and 1 with mild hemophilia), and 5 died of liver disease (3 with severe hemophilia, of whom 1 was HIV positive; 1 with moderately severe hemophilia; and 1 with mild hemophilia). The acquired immunodeficiency syndrome was the main cause of death between 1986 and 1992 (27%). Between 1973 and 1986, many deaths (35%) were caused by malignant neoplasms. Of the 88 patients who died in the 20 years spanned by both studies, 30 died of definite or probable bleeding (the latter including unspecified strokes and trauma).

In the cohort studied from 1986 to 1992, the mean age at death was 54 years (range, 16 to 91 years; median, 53 years). The average age of the patients who died of AIDS

**Table 2. Mortality Data (1986 to 1992) and Life Expectancies by Severity and Type of Hemophilia**

Variable	Patients	Patient-Years	Observed Deaths	Standardized Mortality Ratio (95% CI)*	Median Life Expectancy†
	n				
Severe hemophilia	381	2396	19	4.0 (2.4 to 6.3)	61
Moderate hemophilia	172	1070	11	2.6 (1.3 to 4.6)	65
Mild hemophilia	366	2287	15	1.1 (0.6 to 1.8)	74
Total	919	5753	45	2.0 (1.5 to 2.7)	68
Hemophilia A	796	4984	33	1.8 (1.3 to 2.5)	69
Hemophilia B	123	769	12	2.8 (1.4 to 4.8)	64

\* The standardized mortality ratio is the ratio of the observed number of deaths to the expected number, based on life-tables from 1990 for the general male population.

† Calculated with life-tables from 1991 (median life expectancy of Dutch males, 74 years).

**Table 3. Causes of Death for the Periods 1973 to 1986 and 1986 to 1992\***

Variable (ICD 9 Code)	1973 to 1986†		1986 to 1992‡	
	n(%)			
AIDS (042-044, 136 279, 798)	0 (0)		12 (27)	
Neoplasms				
Malignant neoplasms (140 208)	15 (35)		6 (13)	
Pseudotumor (229)	0 (0)		1 (2)	
Ischemic heart disease				
Myocardial infarction (410)	1 (2)		0 (0)	
Heart failure (411)	0 (0)		1 (2)	
Cerebrovascular disease and hemorrhages§				
Intracranial (431)	3 (7)		9 (20)	
Digestive tract (578)	1 (2)		1 (2)	
Other hemorrhages (459, 596, 599, 719)	5 (12)		0 (0)	
Chronic liver disease and cirrhosis (571)	0 (0)		5 (11)¶	
Injury and poisoning				
Trauma or violence (E800 999)	6 (14)		2 (4)	
Suicide (E950 959)	2 (5)		2 (4)	
Other	7 (16)**		2 (4)††	
Unknown	3 (7)		4 (9)	
Total number of deaths	43		45	

\* AIDS = acquired immunodeficiency syndrome ICD 9 = International Classification of Diseases 9th Revision

† 7788 person years of follow up

‡ 5753 person years of follow up

§ Hemorrhages counted only if no lethal underlying cause was present

|| One person had AIDS

¶ One person had alcoholic liver cirrhosis

\*\* Stroke (n = 3) renal failure (n = 3) and allergic reaction (n = 1)

†† Amyotrophic lateral sclerosis (n = 1) and old age (n = 1 aged 85 years)

was 46 years (range, 25 to 65 years, median, 47 years), which was 11 years less than the average of 57 years (range, 16 to 91 years, median, 62 years) for the 33 patients who died of other causes. The mean age at death of the 5 patients who died of liver disease was 50 years (range, 35 to 64 years, median, 49 years).

The overall mortality in both cohorts was approximately twice that in the general male population (Table 4), and the overall median life expectancy increased from 66 years during 1973 to 1986 to 68 years during 1986 to 1992. We recalculated the mortality ratios after first excluding all AIDS-related deaths and then all virus (HIV, hepatitis)-related deaths. This recalculation allowed us to obtain hypothetical mortality ratios in the absence of these infections. The exclusion of AIDS-related deaths

resulted in lower mortality ratios for 1986 to 1992, especially in patients with severe hemophilia. After we excluded deaths caused by liver disease, the mortality ratios of patients with severe hemophilia (standardized mortality ratio, 1.2) resembled those of patients with mild disease (standardized mortality ratio, 1.0). The exclusion of deaths related to AIDS and liver disease resulted in an extrapolated overall life expectancy of 73 years, a value equaling that of the general male population.

Between 1986 and 1992, one patient died of heart failure and no patients died of myocardial infarction. On the basis of the incidence of fatal ischemic heart disease in Dutch men in 1989, 5.2 deaths from this cause were expected, resulting in a mortality ratio of 0.2 (CI, 0.0 to 1.1). The number of deaths from malignant neoplasms

**Table 4. Standardized Mortality Ratios and Median Life Expectancies according to Severity of Hemophilia for the Periods 1973 to 1986 and 1986 to 1992\***

Variable	Severe Hemophilia		Moderate Hemophilia		Mild Hemophilia		Total	
	Standardized Mortality Ratio	Median Life Expectancy	Standardized Mortality Ratio	Median Life Expectancy	Standardized Mortality Ratio	Median Life Expectancy	Standardized Mortality Ratio	Median Life Expectancy
	y		y		y		y	
1973 to 1986								
All (n = 717)†	2.9	63	2.3	65	1.6	69	2.1	66
1986 to 1992								
All (n = 919)‡	4.0	61	2.6	65	1.1	74	2.0	68
Without AIDS (n = 907)	1.9	69	2.3	66	1.0	74	1.5	70
Without AIDS or liver disease (n = 902)	1.2	73	2.1	67	1.0	74	1.2	73

\* AIDS = acquired immunodeficiency syndrome. Liver disease and AIDS were subsequently excluded from the analysis.

† 7788 person years of follow up

‡ 5753 person years of follow up

**Table 5. Multivariate Survival Analyses for 1986 to 1992, Adjusted for Age\***

Variable	All Patients (n = 919)		HIV-Tested Patients (n = 201)	
	Number of Patients	Relative Risk (95% CI)	Number of Patients	Relative Risk (95% CI)
Hemophilia A†	796	1.0	174	1.0
Hemophilia B	123	1.7 (0.9 to 3.4)	27	1.5 (0.3 to 7.6)
Severe hemophilia	381	2.2 (1.0 to 5.0)	126	1.3 (0.2 to 9.0)
Moderate hemophilia	172	2.2 (1.0 to 4.9)	38	1.5 (0.2 to 11.6)
Mild hemophilia†	366	1.0	37	1.0
Inhibitor present	22	1.0 (0.1 to 7.5)	10	2.9 (0.3 to 31.9)
No inhibitor present†	897	1.0	191	1.0
Receiving prophylaxis	200	1.4 (0.6 to 3.2)	68	0.5 (0.1 to 2.6)
Not receiving prophylaxis†	719	1.0	133	1.0
HIV-positive	—	—	36	27.5 (5.7 to 132.8)
HIV-negative†	—	—	165	1.0

\* HIV = human immunodeficiency virus. Age was divided into 5 year categories, in dummy variables. The model has separate results when HIV status is considered.

† Reference category.

(n = 7) was equal to the expected number (standardized mortality ratio, 1.0 [CI, 0.4 to 2.1]).

### Risk Factors

Multivariate analysis (Table 5) confirmed a higher mortality with more severe forms of hemophilia. The factor most strongly related to the risk for death was HIV infection. The multivariate model that accounted for HIV status, applied to a subgroup of 201 patients who were tested for and reported their HIV status in 1985, showed that seropositive patients (n = 36) had a 27.5-fold higher risk than seronegative patients (n = 165). No other factors included in this model were significantly associated with mortality. After adjustment for HIV infection, severity of hemophilia had little effect because HIV infection was most prevalent in patients with severe hemophilia. Of the 36 patients who were seropositive for HIV, 29 had severe hemophilia.

### Discussion

In the last decade, mortality rates for patients with hemophilia have dramatically worsened because of viral infections. Life expectancy would seem to have increased in the absence of viral infection. An increase in virus-related mortality was most apparent among the severely affected patients, who are the predominant users of clotting factor concentrates and are more likely to be infected with HIV or hepatitis than those with moderate or mild hemophilia. The observed mortality rate among patients with severe hemophilia between 1986 and 1992 was approximately four times higher than could be expected from mortality rates in the general male population.

Patients with severe hemophilia were, on average, younger than those with less severe forms. This finding implies that the mortality ratios, each standardized to the patients' age distribution, cannot be compared directly within severity categories (although each is in itself a fair comparison with the general male population). When these age differences between patient groups were considered and HIV status was not, as in the proportional hazards model (Table 5), the patients with severe hemophilia had a 2.2-fold increased risk compared with pa-

tients who had mild hemophilia. When HIV was considered, the patients with hemophilia had only a 1.3-fold increased risk. Whereas overall mortality remained about the same in 1986 to 1992 compared with 1973 to 1986, it worsened among patients with HIV infection, most of these patients had severe hemophilia.

We found a slightly higher risk for death in patients with hemophilia B than in those with hemophilia A, however, the CI was wide, and no significant difference was seen (Table 5). In the previous period (1973 to 1986), all 43 deaths had occurred in patients with hemophilia A. Therefore, over the total 20-year period (1973 to 1992), mortality in both types of hemophilia was similar, this finding is consistent with the clinical notion that both types run similar courses.

Because the use of prophylaxis, severity of hemophilia, inhibitor status, and HIV status are all related, relative risk can only be properly analyzed in a multivariate model. Such a model for 1986 to 1992 (Table 5) suggested that no hemophilia-related factors were independently associated with the risk for death. We could not establish the relative risk induced by co-infection with hepatitis C virus because we had no information on the hepatitis C virus status.

Patients who received prophylaxis appeared to have a risk for death that was only half that of patients who did not receive prophylaxis, although the CI was wide. Between 1973 and 1986 (11), mortality was lower in patients receiving prophylaxis, but the difference was less pronounced. Chance is unlikely to explain these repeated observations. The effect may have been caused, however, by other differences between patients who received and did not receive prophylaxis that may be related to the risk for death. Prophylactic treatment, that is, maintaining a greater clotting activity (clotting factor level, > 0.01 IU/mL), may indeed reduce mortality by diminishing the frequency or seriousness of bleeding.

Compared with 1973 to 1986, the effect of inhibitors on mortality decreased, this factor no longer contributed significantly to the risk for death. The crude mortality (that is, not adjusted for HIV status) for the patients followed from 1986 to 1992 who had an inhibitor was exactly the same as in the patients who did not have inhibitors (Table

5). After adjustment for HIV status, the relative risk was increased (relative risk, 2.9 [CI, 0.3 to 31.9]). The risk was more pronounced between 1973 and 1986 (relative risk, 5.3 [CI, 1.9 to 11.5]), when 7 of 30 patients with an inhibitor died (11), compared with 1 of 22 patients with an inhibitor between 1986 and 1992.

Although ischemic heart disease is a common cause of death in the general Dutch male population (causing approximately 19% of all deaths in 1991), it accounted for only 2% of all deaths among patients with hemophilia between 1986 and 1992. On the basis of the 1973 to 1986 follow-up, we concluded that hemophilia might offer protection against ischemic heart disease (11, 15), a conclusion that is substantiated by the results for the cohort followed from 1986 to 1992. Over the total 20-year period, 2 patients died of ischemic heart disease compared with the 10.2 who were expected to die of that condition; the resulting overall mortality ratio was 0.2 (CI, 0.0 to 0.7). Other researchers have suggested that a high level of factor VIII activity is associated with an increased incidence of ischemic heart disease because it predisposes patients to thrombosis (16); the opposite appears to be true with hemophilia.

Although the results of the previous follow-up study (11) showed an excess mortality from cancer (standardized mortality ratio, 2.5 [CI, 1.4 to 4.2]), we found no excess mortality from cancer in the cohort followed from 1986 to 1992 (standardized mortality ratio, 1.0).

Deaths from AIDS and liver disease markedly increased mortality rates, and, although this effect is expected to be temporary, the devastating consequences for survival will last as long as patients with hemophilia are infected with HIV or hepatitis virus. Although many patients survive for many years after being infected with HIV without developing AIDS (17), the prognosis for most patients with HIV infection remains bleak. Current estimates predict that at least 50% of patients infected with hepatitis C will develop chronic hepatitis and that many of them will progress to liver cirrhosis (18). In addition, the development of liver disease is accelerated by HIV infection (19, 20). Because most patients with hemophilia have become infected with hepatitis viruses or HIV, or both, we will see the consequences of this for many years to come unless effective therapies are developed. Although we can conclude from our studies that life expectancy in patients with hemophilia will be almost normal in the absence of viral infections, decades may pass before mortality is no longer excessive compared with that of the general male population.

**Acknowledgments** The authors thank the patients who participated in the ongoing national questionnaire survey on hemophilia, conducted for the fourth time in 1992, the Netherlands Hemophilia Society, the Dutch hemophilia treatment centers, and associated physicians for their help in compiling information on patients, Mrs A M T Borm and Mrs W Noteboom for clerical assistance in updating the patient registry and data entry, and Professor J P Vandenbroucke for his helpful comments on epidemiologic matters

**Grant Support** By grant 28-2139 from Het Praeventiefonds, the Netherlands

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