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IN FOCUS

The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99

UK HAEMOPHILIA CENTRE DOCTORS' ORGANISATION

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Summary. *Background*: Previous studies of the development of inhibitors and their impact on mortality have been small. *Objectives*: To examine the development of inhibitors in people with hemophilia in the UK and their effect on subsequent mortality. *Patients*: 6078 males with hemophilia A and 1172 males with hemophilia B registered in the UK Haemophilia Centre Doctors' Organisation database, 1977–98. *Results*: In severe hemophilia A inhibitors developed at rates of 34.4, 5.2 and 3.8 per 1000 years at ages <5, 5–14 and $15+$ years; cumulative risks at ages 5 and 75 were 16% and 36%. In hemophilia A the rate of inhibitor development decreased during 1977–90, but increased during the 1990s. In severe hemophilia B inhibitors developed at rates of 13.3 and 0.2 per 1000 years at ages <5 and $5+$ and cumulative risks at ages 5 and 75 were 6% and 8%. With HIV, inhibitor development did not increase mortality. In severe hemophilia without HIV, inhibitor development doubled mortality during 1977–92, but during 1993–99 mortality was identical with and without inhibitors. In severe hemophilia without HIV but with inhibitors, mortality from causes involving bleeding decreased during 1977–99 ($P = 0.001$) as did mortality involving intracranial hemorrhage ($P = 0.007$). *Conclusions*: These data provide estimates of the rate of inhibitor development in hemophilia A and hemophilia B, and they show that the rate of inhibitor development has varied over time, although the reasons for this remain unclear. They also show that in severe hemophilia the substantial increase in mortality previously associated with inhibitors is no longer present.

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Introduction

In hemophilia the development of inhibitors [antibodies to infused factor VIII (FVIII) or factor IX (FIX)] is a serious problem. Studies of small numbers of previously untreated people with severe hemophilia A and followed prospectively have reported inhibitor development in 18–52% [1–6]. These numbers are higher than values from earlier reports, which were based on prevalence studies and so did not include individuals with transient inhibitors. Inhibitors develop less frequently in mild/moderate than in severe hemophilia A [1–8], while in hemophilia B inhibitors are known to develop only rarely.

Inhibitors reduce the efficacy of hemostatic treatment and clearly cause additional morbidity. Data on mortality are, however, conflicting. Some studies have reported increased mortality with inhibitors [9–13], whereas recent reports from Holland and Finland [14,15] showed no increase, suggesting that improved treatment of inhibitors may have improved outcome.

Studies to date of the development of inhibitors and of their effect on subsequent mortality have mostly been based on small numbers of individuals, and so their conclusions are subject to uncertainty. In addition, the incidence of inhibitors over time has not previously been examined. We have therefore investigated these issues in the Nationwide Database that has been maintained by the United Kingdom Haemophilia Doctors' Organisation (UKHCDO) for over 20 years.

Materials and methods

Since 1976 the UKHCDO Nationwide Haemophilia Database has included details of all males diagnosed with hemophilia A or B regardless of whether they were treated. The database is updated continuously, including notifications of patients in

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whom inhibitors have been detected for the first time. The present study includes all 7250 males with hemophilia A or B recorded as living in the UK during 1977–98. The vital status on 1/1/2000 for 96.3% of this group was ascertained using information from Haemophilia Centres and from the National Health Service (NHS) Central Registers, while 1% had emigrated and 2.7% were lost to follow-up. Death certificates were obtained from the Office for National Statistics and information on cause of death was also often available from hemophilia centers. All available information was examined to identify individuals for whom bleeding or intracranial hemorrhage was involved in causing death. Further information on data collection is given elsewhere [16].

Person-years at risk were calculated as the time from date of registration on the database to date last seen. This was usually 1/1/2000 or date of death, if earlier. For those who had emigrated prior to 1/1/2000 it was the date of emigration, and for those who were lost to follow-up it was the date last seen by a hemophilia center. Person-years at risk and numbers of deaths were subdivided by current age (5-year groups), calendar period (single years), whether or not inhibitors had developed, and type and severity of hemophilia. Testing for HIV-1 antibodies became available late in 1984 and, from 1/1/1985, person-years were also subdivided by HIV-status. Testing of stored blood samples has shown that most HIV infections took place before this, but there was no increase in mortality prior to 1985 [16,17]. Deaths and person-years at ages 85 + years were excluded from the analysis of mortality rates. The influence of inhibitor development and other factors on mortality was studied using Poisson regression. Significance tests were two-sided. Calculations were carried out using the computer package STATA [18].

Results

Development of inhibitors

Among 6078 individuals with hemophilia A, 7.5% (457 individuals) had developed inhibitors before 1/1/2000. Among those infected with HIV 12.8% had developed inhibitors, while among others 19.0% of those with severe, 7.0% of those with moderate, and 0.9% of those with mild hemophilia A had developed inhibitors (Table 1). Among 1172 individuals with hemophilia B, 12 (1.0%) had developed inhibitors, including 11 with severe (one HIV + ve) and one with moderate hemophilia B.

For 282 individuals inhibitors were first detected during 1977–99. In severe hemophilia A inhibitors developed at a rate of 6.4 per 1000 years at risk for all ages combined. The rate varied with age, taking values 34.4, 5.2 and 3.8 per 1000 years at risk at ages < 5, 5–14 and 15 + years, respectively (Table 2), and the cumulative risks of inhibitor development at ages 5, 15, 50 and 75 years were 16%, 20%, 30% and 36%, respectively. For patients with moderate/mild hemophilia A the rate of inhibitor development was just over one quarter that for patients with severe hemophilia A of similar age, and cumulative risks of inhibitor development at ages 5, 15, 50 and 75 years were 5%, 6%, 10% and 12%, respectively. There was strong evidence that the rate of inhibitor development varied over time ($P = 0.001$ adjusted for age and severity). It

Table 1 Numbers of patients recorded as having developed inhibitors and numbers of deaths by 1 January 2000 in males with hemophilia A or B and registered in the UK Haemophilia Center Doctors' Organization national database, 1977–98

Developed inhibitors by 1 January 2000	HIV + ve, 1985–99[a]	Others			Total
		Severe[b]	Moderate[c]	Mild	
Hemophilia A		Numbers of individuals			
No	1050 (87.2)[d]	857 (81.0)	1032 (93.0)	2682 (99.1)	5621 (92.5)
Yes	154 (12.8)	201 (19.0)	78 (7.0)	24 (0.9)	457 (7.5)
Total	1204 (100.0)	1058 (100.0)	1110 (100.0)	2706 (100.0)	6078 (100.0)
Percentage treated[e]	100.0	97.4	94.5	73.0	86.5
		Numbers of deaths			
No	667 (86.4)	158 (73.2)	132 (90.4)	363 (98.9)	1320 (87.9)
Yes	105 (13.6)	58 (26.8)	14 (9.6)	4 (1.1)	181 (12.1)
Total	772 (100.0)	216 (100.0)	146 (100.0)	367 (100.0)	1501 (100.0)
Hemophilia B		Numbers of individuals			
No	27 (96.4)	252 (96.2)	365 (99.7)	516 (100.0)	1160 (99.0)
Yes	1 (3.6)	10 (3.8)	1 (0.3)	0 (0.0)	12 (1.0)
Total	28 (100.0)	262 (100.0)	366 (100.0)	516 (100.0)	1172 (100.0)
Percentage treated[e]	100.0	98.5	91.8	76.4	86.7
		Numbers of deaths			
No	16 (100.0)	31 (91.2)	31 (100.0)	68 (100.0)	146 (98.0)
Yes	0 (0.0)	3 (8.8)	0 (0.0)	0 (0.0)	3 (2.0)
Total	16 (100.0)	34 (100.0)	31 (100.0)	68 (100.0)	149 (100.0)

[a]Severe, moderate and mild hemophilia combined. [b]Clotting factor concentration < 1 international unit per dl. [c]Clotting factor concentration 1–5 international units per dl. [d]Column percentages in brackets. [e]These percentages reflect treatment recorded in the UKHCDO database. Some other patients may also have been treated but no record was made on the database.

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Table 2 Numbers of patients developing inhibitors for the first time and rate of development of inhibitors by age, and severity and type of hemophilia, 1977–99

	Severe			Moderate/mild			All severities		
Age (years)	No. of individuals	Rate per 1000 years	95% CI	No. of individuals	Rate per 1000 years	95% CI	No. of individuals	Rate per 1000 years	95% CI
Hemophilia A									
< 5	72	34.4	(26.9, 43.3)	29	9.3	(6.2, 13.4)	101	19.4	(15.8, 23.6)
5–14	28[a]	5.2	(3.5, 7.6)	14	1.5	(0.8, 2.5)	42	2.9	(2.1, 3.9)
15 +	75[a]	3.8	(3.0, 4.8)	58[a]	1.2	(0.9, 1.6)	133	2.0	(1.7, 2.3)
All hemophilia A	175	6.4	(5.5, 7.5)	101	1.7	(1.4, 2.0)	276	3.2	(2.8, 3.6)
P for trend with age		< 0.001			< 0.001			< 0.001	
Hemophilia B									
< 5	4	13.3	(3.6, 33.9)	1	1.4	(0.0, 7.6)	5	4.8	(1.6, 11.3)
5 +	1	0.2	(0.0, 1.2)	0	0.0	(0.0, 0.3)	1	0.1	(0.0, 0.3)
All hemophilia B	5	1.0	(0.3, 2.4)	1	0.1	(0.0, 0.4)	6	0.3	(0.1, 0.7)
P for trend with age		< 0.001			< 0.002			< 0.001	

[a]13 individuals (2 severe aged 5–14, 8 severe aged 15+, 3 moderate/mild aged 15+) developed inhibitors after becoming infected with HIV.

decreased steadily from 5.4 (95% CI 3.5,7.4) per 1000 years in 1977–78 to 2.1 (95% CI 1.3,3.0) per 1000 years in 1988–90. After this it increased, reaching 4.1 per 1000 years (95% CI 2.9, 5.2) in 1997–99. Similar patterns were observed in severe and in moderate/mild hemophilia (see Table 3).

Five patients with severe hemophilia B developed inhibitors [in 1977, 1988, 1992 (2 patients) and 1994]. The rate of inhibitor development in severe hemophilia B was 13.3 per 1000 years at risk at ages < 5 years and 0.2 per 1000 years at risk at older ages, and cumulative risks of inhibitor development at ages 5, 25, and 75 years were 6%, 7% and 8% respectively. One patient with moderate/mild hemophilia B developed inhibitors in 1992. The rate of inhibitor development in moderate/mild hemophilia B was 1.4 per 1000 years at risk at ages < 5 years and 0.1 per 1000 years at risk at all ages.

Deaths in patients with inhibitors

Overall 184 patients who had previously developed inhibitors had died (hemophilia A: 181, hemophilia B: 3), including 79 who were not infected with HIV (Table 1). Among these 79, 5.1% died when aged < 15 years, and 19.0%, 22.8%, 39.2% and 13.9% died at ages 15–34, 35–54, 55–74 and 75+ years, respectively (Table 4). For 35 of the 79, inhibitors were first detected after 1/1/1977, so information was available on the interval between development of inhibitors and death. Eight died within a year of developing inhibitors, while for 8, 10, and 9 patients, respectively, the intervals between inhibitor development and death were 1–4, 5–9 and 10+ years, respectively. The5 patients with severe hemophilia who died when aged 75+ years had first developed inhibitors 11, 15, 24, 25, and 28 years previously.

Bleeding was involved in causing 59 of the 79 deaths in patients with inhibitors but without HIV infection and, of these, nine (8 severe, 1 moderate A) were due to intra-abdominal (retroperitoneal) bleeding and six (4 severe, 1 moderate, 1 mild A) to postoperative complications. Intracranial hemorrhage was involved in 27. Chronic liver disease was a cause of six deaths and hepatocellular carcinoma of one; bleeding was involved in all these seven deaths. The 105 deaths in HIV-infected patients with inhibitors were predominantly from HIV-related causes [16].

Table 3 Numbers of patients developing inhibitors for the first time and rate of development of inhibitors by calendar period and severity for patients with hemophilia A, 1977–99

	Severe			Moderate/mild			All severities		
Calendar period	No. of individuals	Rate per 1000 years	95% CI	No. of individuals	Rate per 1000 years	95% CI	No. of individuals	Rate per 1000 years	95% CI
1977–78	22	9.0	(5.2,12.8)	9	2.8	(1.0, 4.7)	31	5.4	(3.5, 7.4)
1979–81	26	6.8	(4.2, 9.4)	13	2.2	(1.0, 3.5)	39	4.0	(2.8, 5.3)
1982–84	32	8.0	(5.2,10.8)	9	1.3	(0.4, 2.2)	41	3.8	(2.7, 5.0)
1985–87	22	5.2	(3.0, 7.4)	3	0.4	(0.0, 0.9)	25	2.2	(1.4, 3.1)
1988–90	14	3.2	(1.5, 4.8)	11	1.5	(0.6, 2.4)	25	2.1	(1.3, 3.0)
1991–93	12	2.9	(1.3, 4.6)	17	1.9	(1.0, 2.8)	29	2.3	(1.5, 3.1)
1994–96	22	5.7	(3.3, 8.1)	16	1.7	(0.9, 2.6)	38	2.9	(2.0, 3.9)
1997–99	25	8.1	(5.0,11.2)	23	2.6	(1.5, 3.6)	48	4.1	(2.9, 5.2)
P for heterogeneity with calendar period		0.007			*0.01*			*0.001*	

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Table 4 Numbers of patients who were not infected with HIV but who were recorded as having developed inhibitors and who died during 1977–99, by age at death and severity of hemophilia

Age at death (years)	Severe	Moderate	Mild	All severities
< 15	3 (4.9)[a]	1 (7.1)	0 (0.0)	4 (5.1)[b]
15–34	13 (21.3)[c]	2 (14.3)	0 (0.0)	15 (19.0)[c]
35–54	16 (26.3)	1 (7.1)	1 (25.0)	18 (22.8)
55–74	24 (39.3)	5 (35.7)	2 (50.0)	31 (39.2)
75+	5 (8.2)[d,e]	5 (35.7)[e]	1 (25.00)	11 (13.9)[d,e]
Total	61 (100.0)	14 (100.0)	4 (100.0)	79 (100.0)

[a]Column percentages in parentheses. [b]Ages at death 1 year 8 m (severe), 3 years 10 m (severe), 6 years 5 m (severe) and 14 years 2 m (moderate). [c]Includes 2 patients with hemophilia B. [d]Includes 1 patient with hemophilia B, who had developed inhibitors 25 years previously. [e]2 deaths occurred in patients aged 85+years, 1 involved bleeding.

Effect of inhibitor development on mortality rate from all causes

In HIV-infected patients the all-cause death-rate was similar in those who had and those who had not developed inhibitors (death rate ratio: 1.02, 95% confidence interval (CI): 0.83, 1.26; $P = 0.83$, adjusted for age, calendar period and type and severity of hemophilia) (Table 5). In contrast, among HIV-uninfected patients with severe hemophilia, the all-cause death-rate during the whole of 1977–99 in those with inhibitors was almost double that in those without inhibitors (death rate ratio: 1.79, 95%CI: 1.33, 2.42; $P < 0.001$), while for moderate/mild hemophilia the death rate in those with inhibitors was more than twice the rate in those without inhibitors (death rate ratio: 2.55, 95%CI: 1.56, 4.18; $P < 0.001$). The effect of inhibitor development on all cause mortality did not differ significantly between hemophilia A and hemophilia B ($P > 0.05$ for all three groups).

The annual all-cause death-rate among severely hemophilic patients without HIV infection and who had not developed inhibitors remained approximately constant throughout 1977–99 (Table 6). Among those with inhibitors the all-cause death-rate during 1977–84 and 1985–92 was more than double the corresponding death rate among those without (death rate ratio 2.17, 95%CI 1.55, 3.04, $P < 0.001$). In contrast, the death rates for those with and without inhibitors were identical during 1993–99.

For patients with moderate/mild hemophilia who were without HIV infection and who had not developed inhibitors, the all-cause death-rate was stable during 1977–99, and it was substantially lower than in patients with severe hemophilia who had not developed inhibitors (Table 6). Among patients with moderate/mild hemophilia with inhibitors the all-cause death-rate decreased significantly over time ($P = 0.03$), from 31.3 per 1000 years at risk (95%CI 10.7, 52.0) in 1977–84 to 12.8 (95%CI 1.5, 24.2) in 1993–99, similar to the death rate for patients with severe hemophilia in 1993–99. This substantial decrease cannot be explained by the inclusion of more asymptomatic mild patients during the later time periods (Table 6).

Mortality rates from specific causes

The above analysis was repeated for deaths involving bleeding of any type and also specifically for deaths involving intracranial hemorrhage. Death rates for both endpoints were approximately constant over time in patients with severe hemophilia who had not developed inhibitors (Table 6). For patients with inhibitors, however, there were decreasing trends in the death rate both for bleeding and for intracranial hemorrhage ($P = 0.001$ and 0.007 respectively). During 1993–99 death rates in severe hemophilia both for bleeding and for intracranial hemorrhage in those with inhibitors were similar to death rates in those without inhibitors, whereas earlier they had both been substantially higher in those with inhibitors (Table 6).

For patients with moderate/mild hemophilia who had developed inhibitors, death rates for bleeding and for intracranial hemorrhage also tended to decrease over the period studied, but the trend reached statistical significance only for deaths involving intracranial hemorrhage. In 1993–99 the death rates for both endpoints in patients with moderate/mild hemophilia and inhibitors were not significantly different from those in severe hemophilia with inhibitors.

Table 5 Effect of inhibitor development on mortality from all causes in males in the UK with hemophilia, 1977–99

	HIV +ve, 1985–99			Others					
				Severe			Moderate/mild		
	No. of deaths	Death rate ratio[a]	95% CI[b]	No. of deaths	Death rate ratio[a]	95% CI	No. of deaths	Death rate ratio[a]	95% CI
Ever developed inhibitors									
No[c]	683	1.00	–	186	1.00	–	543	1.00	–
Yes	105	1.02	(0.83, 1.26)	60	1.79	(1.33, 2.42)	17	2.55	(1.56, 4.18)
P for difference		0.83			< 0.001			0.001	
Total deaths[d]	788	–	–	246	–	–	560	–	–
Person-years[d]	12 443	–	–	27 099	–	–	71 651	–	–

[a]Adjusted for age, calendar period, type of hemophilia and, for analyses of moderate/mild patients and HIV +ve patients, severity of hemophilia. [b]CI: confidence interval. [c]Baseline category. [d]Deaths and person-years at ages 85 +years excluded.

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1. **The above analysis was repeated for deaths involving bleeding of any type and also specifically for ...**
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Table 6 Age-standardized annual death rates by calendar period in males in the UK with hemophilia who were not infected with HIV, 1977–99[a]

	Severe				Moderate/mild[b]			
	No inhibitors		With inhibitors		No inhibitors		With inhibitors	
Calendar period	No. of deaths	Rate per 1000 years[c] (95% CI)	No. of deaths	Rate per 1000 years[c] (95% CI)	No. of deaths	Rate per 1000 years[c] (95% CI)	No. of deaths	Rate per 1000 years[c] (95% CI)
All causes of death								
1977–84	79	10.0 (7.7, 12.2)	29	20.3 (12.9, 27.8)	139	6.5 (5.4, 7.6)	7	31.3 (10.7, 52.0)
1985–92	48	9.8 (7.1, 12.5)	21	23.4 (13.7, 33.2)	187	5.8 (5.0, 6.7)	4	15.0 (0.3, 29.7)
1993–99	59	11.9 (8.9, 15.0)	10	11.9 (4.5, 19.3)	217	6.0 (5.2, 6.8)	6	12.8 (1.5, 24.2)
P for trend		*0.64*		*0.16*		*0.09*		*0.03*
Deaths involving bleeding								
1977–84	44	5.5 (3.8, 7.2)	28	19.9 (12.6, 27.3)	43	2.0 (1.4, 2.6)	3	13.8 (0.0, 28.6)
1985–92	24	4.9 (2.9, 6.8)	17	18.9 (10.1, 27.6)	52	1.6 (1.2, 2.1)	3	11.7 (0.0, 25.0)
1993–99	29	5.6 (3.5, 7.7)	3	3.0 (0.0, 6.4)	55	1.6 (1.1, 2.0)	4	9.9 (0.0, 20.5)
P for trend		0.90		0.001		0.16		0.51
Deaths involving intracranial hemorrhage								
1977–84	25	3.1 (1.8, 4.3)	14	10.5 (5.0, 16.0)	24	1.1 (0.7, 1.5)	2	9.2 (0.0, 21.5)
1985–92	17	3.5 (1.8, 5.1)	7	8.2 (2.1, 14.2)	33	1.1 (0.7, 1.4)	1	3.5 (0.0, 10.2)
1993–99	19	3.5 (1.9, 5.1)	2	2.1 (0.0, 5.0)	23	0.7 (0.4, 0.9)	1	1.5 (0.0, 4.4)
P for trend		0.58		0.007		0.07		0.02
Person-years	23 833		3 266		70 657		994	

[a]HIV +ves excluded from 1985 or date of HIV-seroconversion, if later. [b]In this group the percentages of newly registered patients with mild hemophilia were 61, 74, 71, 71 and 69 in calendar periods 1976 or earlier, 1977–84, 1985–92 and 1993–99, respectively. [c]Death rates directly standardized for age to the age distribution of all patients with inhibitors.

Discussion

This study has provided estimates of the rate of development of inhibitors in a large nationwide hemophilia population, subdivided by age and severity, for both hemophilia A and hemophilia B. In hemophilia A the rate is higher than previously reported for the UK [8,19]. This is partly due to corrections in the database, partly due to the use of more accurate methods for determining the number of years at risk in the analysis, and partly due to a change in the definition of severe hemophilia, from < 2 to < 1 international units per dl. The results demonstrate that inhibitor development is highest in children, with cumulative risk reaching 16% by age 5 years in severe hemophilia A. However, inhibitors continue to develop at older ages, albeit at a lower rate, and the cumulative risk rises to 36% by age 75 years. These data also confirm a lower rate of inhibitor development in hemophilia B than in hemophilia A, by a factor of 2.6 for children with a severe defect and by larger factors at older ages and in moderate/mild disease (Table 2). As hemophilia B is also less common than hemophilia A, this means that fewer than one inhibitor in 40 occurs in a patient with hemophilia B.

The reasons underlying the steady decrease in the rate of inhibitor development in hemophilia A until about 1990, followed by the steady increase during the 1990s are not yet clear. An earlier study of inhibitor incidence during 1990–93 noted that inhibitor incidence was increasing [19], but within the short period studied the trend was not significant statistically. In this longer study, the variation is highly significant statistically, and the changes cannot plausibly be explained by chance. Variations in the completeness with which transient inhibitors were detected also seem unlikely to explain such large changes. Similar patterns are seen in those with moderate/mild hemophilia, among whom 7% were infected with HIV, and in those with severe hemophilia, among whom 53% were infected with HIV [16], so that the increase in inhibitor incidence during the 1990s cannot be explained by HIV infection. Total consumption of FVIII increased steadily throughout the period studied, from 12 000 units/patient in 1977 to around 35 000 units/patient in the late 1990s [12,20,21], with increases in the consumption of both NHS and commercial concentrates. Cryoprecipitate was used in decreasing amounts up to the early 1990s, when it virtually ceased to be used, but its decline has not previously been associated with a decrease in inhibitor incidence. Recombinant (r)FVIII was first introduced in the UK in 1995, when it represented 5% of total FVIII. Since then its use has increased substantitally to about half in 1999.

Inevitably there are limitations to the data that it has been possible to collect for such a large population. Individuals are recorded in the UKHCDO database as having developed inhibitors if they were detected during routine clinical care or, in a few instances, during a clinical trial. Information is not available on inhibitor titers, transient inhibitors, the use of monoclonal or high purity products, or product usage by individuals. Genotype information is not available for this large population. However, a study of genotypes in moderate/mild hemophilia A which included some of the patients in this group [8] suggested that there may be a familial disposition to develop inhibitors.

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Inhibitors make it difficult to treat bleeding episodes, preclude prophylaxis and make surgery more hazardous. The present data confirm that in severe hemophilia inhibitor development was associated with a doubling of the all-cause death-rate during 1977–92. However, the mortality rates for deaths involving bleeding and for deaths involving intracranial hemorrhage have both decreased significantly and, during 1993–99, in severe hemophilia the all-cause death-rate was identical in individuals who had and individuals who had not developed inhibitors (Table 6). Apart from those born after 1985, almost all UK patients with severe hemophilia, and many of those with moderate/mild disease, were infected with hepatitis C virus. In patients with inhibitors but without HIV, liver disease or hepatocelluar carcinoma played a role in 9% [7/79] of deaths. This proportion is similar to that for all individuals with hemophilia and without HIV [16] and in neither group is it large enough to have affected substantially the overall trends in mortality.

The decrease in mortality in those with inhibitors may, in part, be the effect of more complete identification of transient inhibitors, but it is likely to be chiefly a reflection of better treatment of bleeding episodes and more successful immune tolerance. Porcine FVIII has been used in the UK for the treatment of hemophilia A with inhibitors throughout the period studied, although its use declined from an average of 7000 units/patient during 1977–84, to 2000 units/patient during 1993–99 [12,20,21]. In contrast, use of the activated prothrombin-complex concentrate FEIBA increased from an average of 9000 units/patient during 1977–84, to 18 000 units during 1985–92, and further to 57 000 units during 1993–99. FEIBA was found to be more effective than nonactivated prothrombin-complex concentrate in a controlled comparison [22], and response rates with FEIBA have been reported to be as high as 80–90% [23]. In the late 1980s and early 1990s immune tolerance induction has also gained popularity in the UK [8] but information on its quantitative usage is not available for this population. A further therapeutic option became available in 1996 with the introduction of rFVIIa. It was evaluated in 518 serious bleeding episodes and found to be effective in 62% of muscle, 80% of ear, nose and throat, 88% of central nervous system, 76% of joint and 75% of retroperitoneal bleeds [24].

The present study also provides evidence that in moderate/mild hemophilia the development of inhibitors remains deleterious, with all cause mortality during 1993–99 similar to that in severe hemophilia. This is not surprising in view of the fact that in the majority of these patients the antibody cross-reacts with the patient's own FVIII, converting the patient from a mild/moderate to a severe phenotype often with bleeding manifestations similar to those observed in patients with acquired hemophilia [8].

HIV infection was associated with substantially increased mortality during the study period [16,17]. A further increase was not seen with inhibitors, and indeed some HIV positive patients who had inhibitors may lose them as their immune function deteriorates [25,26].

Previous studies of the effect of inhibitors on mortality usually involved small cohorts. Diamondstone [9] found that inhibitors increased mortality by a factor of 3.1 (95%CI 1.4, 6.9) amongst 751 American children and adults followed from 1986, and Larsson [11] reported that, during 1961–80, inhibitors were associated with increased mortality amongst 948 Swedish patients. When 717 Dutch patients were originally studied in 1989, inhibitors increased mortality by a factor of 5.3 (95%CI 1.9, 11.5) in severe hemophilia [13]. However, when the Dutch group was reviewed in 1995, mortality in those with and without inhibitors was identical during 1986–92 (relative risk = 1.0; 95%CI 0.1, 7.5) among 919 patients including 22 with inhibitors [14]. Similarly a 1982 Finnish study showed an increased risk of hemorrhagic death with inhibitors [10], but an updated analysis of 139 patients (25 with inhibitors) showed that the death rate with inhibitors had declined from 42 per 1000 in the 1970s to 6 per 1000 during the 1980s, similar to that in patients without inhibitors [15].

A recent study of the cost of treating bleeding episodes in patients with inhibitors considered quality of life [27]. Overall 0.6 bleeding episodes/patient/month were recorded in 52 patients followed up for 18 months. The patients' quality of life, measured through validated questionnaires, was similar to that of severe hemophiliacs without inhibitors: physical quality of life was similar to that in non-hemophilic diabetes patients and subjects with renal failure on dialysis, and psychological quality of life was comparable to that in the general population. The conclusion of this important study was that, although the treatment of hemophilia patients with inhibitors is expensive, the outcome is good in terms of a satisfactory quality of life.

In summary, this study has provided more precise estimates of the rate of development of inhibitors in hemophilia A than were available previously; it has provided them subdivided by age and severity of hemophilia and it has shown that the rate of inhibitor development has varied over time, with a steady decrease during 1977–90, followed by an increase during the 1990s. It has also provided estimates of the rate of development of inhibitors in people with hemophilia B. It has confirmed that during 1977–92 inhibitor development was associated with a doubling of the age-specific all-cause death-rate in severe hemophilia. Hemorrhagic death rates have, however, decreased in individuals with severe hemophilia and inhibitors and during 1993–99 the development of inhibitors was no longer associated with increased mortality. For individuals with moderate/mild hemophilia, death rates have also tended to decrease in individuals with inhibitors, but the development of inhibitors probably remains associated with increased mortality in moderate/mild hemophilia.

Analysis and Writing Committee

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Data collection was carried out by Rosemary Spooner, Sau Wan Kan, Paul Giangrande and Sarah Darby. The statistical analysis was designed by Sarah Darby and carried out by Sarah Darby and Sau Wan Kan. All members of the Analysis and Writing Committee participated in the preparation of the report.

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