Decreased mortality of ischaemic heart disease among carriers of haemophilia
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Summary

Background Coagulation plays an important part in ischaemic cardiovascular disease. Results of studies have shown that extremes in hypocoagulability protect against ischaemic cardiovascular disease. We have investigated overall mortality and death from cardiovascular causes in carriers of haemophilia, who in most cases have mildly decreased coagulability without clinical signs.

Methods We followed-up a cohort of 1012 mothers of all known people with haemophilia in the Netherlands from birth to death, or the end-of-study date (41 984 person years of follow-up). We obtained vital status and causes of death, if deceased, and compared overall and cause-specific mortality in our cohort with that in the general Dutch female population adjusted for age and calendar period by calculating the standardised mortality ratio (SMR).

Findings Overall mortality was reduced by 22% (261 observed deaths, 333-74 expected; SMR 0-78 [95% CI 0-69–0-88]). Deaths from ischaemic heart disease were reduced by 36% (39 observed deaths, 60-53 expected; SMR 0-64 [0-47–0-88]). We did not note decreased mortality for cerebral stroke (ischaemic and haemorrhagic combined) (28 observed deaths, 36-82 expected; SMR 0-76 [0-53–1-10]).

A separate analysis of these two types of stroke was not possible. Women in our cohort had an increased risk of death from extracranial haemorrhage (5 observed deaths, 36-82 expected; SMR 0-76 [0-53–1-10]).

Conclusion The results show that a mild decrease in coagulability has a protective effect against fatal ischaemic heart disease.

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Introduction

Severely impaired haemostasis protects against ischaemic heart disease. In a study with long follow-up, patients with haemophilia A or B (clotting factor VIII or IX deficiency, respectively) had an 80% reduction in the risk of fatal ischaemic heart disease. Oral anticoagulants and platelet inhibitors are used to induce coagulation defects and can successfully prevent ischaemic events. Increased coagulability, on the other hand, has been shown to be a risk factor for ischaemic cardiovascular disease, although results are not consistent.

Patients with haemophilia have concentrations of clotting factor at the extreme lower end of the range and they have spontaneous haemorrhages. Haemophilia is a genetic recessive X-linked trait. Therefore, although men are affected, women are heterozygous carriers and can transmit the disorder to their sons. Because they have one unaffected allele, carriers have concentrations of clotting factor VIII or IX of about 50% of normal and, hence, decreased coagulability. However, if carriers do have an increased bleeding tendency, it is mild.

To determine whether a mild, in most cases asymptomatic, decreased coagulability protects against ischaemic cardiovascular events, we compared overall and cause-specific mortality in carriers of the recessive gene for haemophilia with that in the general population. To make this comparison, we assessed death rates of mothers of haemophilia patients between 1861 and 2001.

Methods

Study population

We included mothers of people with haemophilia identified in nationwide surveys of haemophilia patients done in the Netherlands in 1985 and 1992. These surveys were sent to all registered patients in the Netherlands with haemophilia (1263 in 1992). Information on type and severity of haemophilia was ascertained through haemophilia treatment centres. Since Napoleonic times, all Dutch citizens are registered with municipal authorities in their town. We searched these registries using name and address information from the surveys to obtain information on vital status of mothers of patients with haemophilia. Follow-up lasted until death or the end of the study (Nov 1, 2000), whichever came first.

Causes of death

Causes of death were made available by the Netherlands Central Bureau of Statistics, which receives a copy of all death certificates and routinely codes them using the International Classification of Diseases (ICD). These causes of death were only available from 1950 onward. For analysis, we recoded codes used in ICD5–9 to match those used in ICD10. Causes of death were subsequently grouped into infections (ICD10: A00–B99), malignant disease (ICD10: C00–97), respiratory-tract diseases (ICD10: J00–99), cardiovascular diseases
(ICD10: I00–99), and external causes such as traffic accidents, suicide, homicide (ICD10: S00–Z99).

Cardiovascular disease was further subdivided into ischaemic heart disease (ICD10: I20–25) and cerebrovascular diseases (ICD10: I60–69, haemorrhagic and ischaemic cerebrovascular diseases combined). We also analysed deaths attributable to coagulation disorders and extracranial haemorrhages (ICD10: D66–69) and death from thrombosis and pulmonary embolism (ICD10: I26, I80, and I82). We ascertained the cause of death of nearly all mothers who had died between 1950 and 2000 (243 of 247, 98%).

**Statistical analysis**

We compared overall and cause-specific mortality for our cohort with that in the general Dutch female population after adjustment for age and calendar period. Adjustment was done by calculating the standardised mortality ratio (SMR), which is the ratio of the observed number of (cause-specific) deaths and the expected number of deaths based on the mortality rates of the reference population. Expected mortality is established by multiplication of the total number of years lived by the study population per category of age and calendar period with the corresponding (cause-specific) mortality rates of the reference population. Mathematically, the SMR is the ratio of the standardised incidence rates. Mortality rates are published every year by the Netherlands Central Bureau of Statistics. We calculated 95% CI for the SMR presuming a Poisson distribution for the observed number of deaths. Since the carriers in our study were selected through their offspring, and therefore had to live at least until reproductive age, the first two decades of life were ignored to avoid underestimation of the SMR. To determine differences in mortality by type of haemophilia and severity, we used Cox regression analysis. For the SMR determination of the overall mortality we used exact age and date of death for the mothers.

For population calculations, we used 20-year (1840–1900) and 10-year (1900–2000) calendar time intervals, and for age we used 5-year intervals as supplied by the Netherlands Central Bureau of Statistics. For the cause-specific SMR, calendar periods were divided into 5-year intervals. For reasons of privacy, individual causes of death were not made available in The Netherlands. Because it was impossible to obtain informed consent for an individual’s cause of death to be released, they were made available in a grouped fashion with a minimum of three women per cell (eg, by type of haemophilia, by age, by severity).

**Role of the funding source**

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or in the writing of the report.

**Results**

1012 women born between 1861 and 1968 were included in this study. We could not ascertain vital status for 33 people (3-3%), in most cases because of emigration. For all other women, we did establish vital status at the end-of-study date. Of 979 mothers, 849 (87%) had one or more sons with haemophilia A, and 130 (13%) with haemophilia B. With respect to severity, 388 (40%) carried severe haemophilia (ie, clotting factor VIII or IX concentrations <1 IU/dL in the son), 170 (17%) carried moderate to severe haemophilia (concentrations of 1–5 IU/dL), 409 (42%) carried mild haemophilia (5–25 IU/dL). The severity of haemophilia was unknown for the sons of 12 (1%) women. 261 women (27%) had died before the end of study date (Nov 1, 2000), with age at death between 30 and 98 years. General characteristics are shown in table 1.

979 women were included in the analysis of overall mortality (41 984 person years of follow-up). During follow-up, 261 women had died, whereas 333-74 deaths were expected based on the population figures (table 2). The reduction in overall mortality was 22% (SMR 0·78 [95% CI 0·69–0·88]). The reduction in overall mortality remained unchanged when we ignored the first three or four decades of life in the analysis (0·81 [0·72–0·92]; and 0·83 [0·73–0·94], respectively). In fact, mortality was reduced most, in absolute numbers, in the oldest age groups: 217 of all 261 deaths occurred after age 60 years, whereas 252 of 65 deaths were expected (0·86 [0·75–0·98]). The reduction in overall mortality remained unchanged when subgroups of haemophilia were analysed (ie, by type and severity of haemophilia) and was noted in all calendar periods—1880–1940 (SMR 0·43 [95% CI 0·22–0·68]), 1940–70 (0·73 [0·54–1·07]), and 1970–2000 (0·83 [0·72 to 0·95]).

The analysis of cause-specific mortality was restricted to the period 1950–2001, and included 965 women (34 548 person-years), of whom 247 (26%) died during follow-up (cause of death could not be obtained for four women). Table 3 shows cause-specific mortality for the major causes of death in our cohort compared with those in the general female population adjusted for age and calendar period. We did not note differences in causes of death between the two groups, except for ischaemic heart disease (SMR 0·64 [95% CI 0·47–0·88]). This reduction was present in both time periods (1950–79, 0·55 [0·27–0·93]; 1980–2000, 0·69 [0·45–0·98]). The risk reduction for ischaemic heart disease death was observed for the sons of 12 (1%) women. 261 women (27%) had died before the end of study date (Nov 1, 2000), with age at death between 30 and 98 years. General characteristics are shown in table 1.

**Table 1: General characteristics of mothers of haemophilia patients**

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Number of participants</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1881–1890</td>
<td>143</td>
<td>0</td>
</tr>
<tr>
<td>1891–1900</td>
<td>168</td>
<td>2</td>
</tr>
<tr>
<td>1901–1910</td>
<td>252</td>
<td>7</td>
</tr>
<tr>
<td>1911–1920</td>
<td>39</td>
<td>9</td>
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<tr>
<td>1921–1930</td>
<td>33</td>
<td>10</td>
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<td>1931–1940</td>
<td>39</td>
<td>12</td>
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<td>1941–1950</td>
<td>43</td>
<td>17</td>
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<tr>
<td>1951–1960</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>1961–1970</td>
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<td>0</td>
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<tr>
<td>1971–1980</td>
<td>87</td>
<td>3</td>
</tr>
<tr>
<td>1981–1990</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>1991–2000</td>
<td>101</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of child’s haemophilia</th>
<th>Number of participants</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>849 (87%)</td>
<td>228 (27%)</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>130 (13%)</td>
<td>33 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of child’s haemophilia</th>
<th>Type of child’s haemophilia</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>41 984</td>
<td>261</td>
<td>333–74</td>
<td>0·78 [0·69–0·88]</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>36 432</td>
<td>228</td>
<td>292–92</td>
<td>0·78 [0·68–0·89]</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>5552</td>
<td>33</td>
<td>40–82</td>
<td>0·81 [0·57–1·15]</td>
</tr>
<tr>
<td>Moderate</td>
<td>70 422</td>
<td>39</td>
<td>46–14</td>
<td>0·85 [0·62–1·16]</td>
</tr>
<tr>
<td>Mild</td>
<td>18 518</td>
<td>125</td>
<td>179–65</td>
<td>0·70 [0·58–0·83]</td>
</tr>
</tbody>
</table>

*Severities not known for 12 women.*
in all age groups, although precise age-specific estimates could only be obtained in elderly people, where most deaths occurred—for those aged over 60 years (0.66 [0.46–0.89]), for those over 70 years (0.56 [0.36–0.80]), and for those over 80 years (0.52 [0.27–0.84]). No evidently decreased mortality was noted for haemorrhagic and ischaemic stroke combined (0.76 [0.53–1.10]). ICD coding did not allow us to look at these two types of stroke separately. For coagulation disorders and extracranial haemorrhages, we noted a sharply increased mortality (27.8 [8.5–58]), although the absolute increase was small (five cases). For thrombosis and pulmonary embolism the study group was small, although the data were compatible with a reduced rate of death. We noted no differences in overall and cause-specific mortality by type or severity of haemophilia (data not shown).

### Discussion

Carriers of haemophilia have a 22% reduction in overall mortality, and a 36% reduction in death from ischaemic heart disease. There is an increased risk of death of haemorrhage, which, however, is much rarer than fatal ischaemic heart disease. We noted no clear effect of being a carrier of haemophilia on the incidence of stroke. Unfortunately, ICD codes do not allow a separate analysis of ischaemic and haemorrhagic stroke, where one would expect opposite effects.

Average factor VIII and IX concentrations of 50% of normal have been reported in carriers, irrespective of the severity of haemophilia they carry.\(^{19,20,21}\) Such concentrations usually do not lead to an increased bleeding tendency. However, because of unbalanced lyonisation, clotting factor concentrations can range from 22% to 116% of normal.\(^{22}\) An increased bleeding tendency has been established in people with low levels of clotting factor, especially after dental and surgical interventions or after childbirth.\(^{23}\) Coagulation factor concentrations less than 30% of normal, however, arise in only 2% of the carriers,\(^{24}\) and therefore our findings indicate a reduced risk of fatal ischaemic heart disease even for mildly reduced factor VIII.

The women in this study were selected through their offspring. Although haemophilia can arise in some patients from a new mutation either in women or in men, only about 40% of patients are isolated haemophilia patients (ie, patients without a family history of the disease) and about a fifth of the mothers of these isolated patients are expected not to be carriers.\(^{25}\) The presence of non-carriers in our study implies that the true reduction in mortality in carriers will only be more pronounced than that reported here, although the difference is likely to be negligible.

Results of our study show a substantial decrease in overall mortality in carriers of haemophilia. This decrease is largely accounted for by a decreased number of deaths from ischaemic heart disease; however, several other factors could explain the additional risk reduction. First, only women with offspring were selected in this study, and their risk of death was compared with that in the general female population, which includes women without children. Investigators in a Norwegian study noted a higher mortality in nulliparous women than in women who had had children.\(^{26}\) Because only a minority of the female general population remains childless, this explanation accounts for only a small part of the reduction in deaths. Moreover, in a methodological study aimed at assessing the magnitude of this effect, we compared mortality rates of pedigrees of probands randomly selected from the phonebook and mortality rates of spouses of various patients, with rates in the general population.\(^{27}\) We invariably noted SMRs of one for pedigrees and spouses of random probands, both of which were cohorts ascertained through living individuals.

Another explanation for the reduced mortality in our cohort is that the birth of a child with haemophilia might lead women to refrain from subsequent pregnancies, thus reducing the risk of death associated with childbirth.\(^{28}\) Reported maternal mortality by the Central Bureau of Statistics during pregnancy and delivery, however, is so low, at 3.6 per 1 million women in 1995, that a noticeable effect on our results is extremely unlikely. Finally, the presence of a severe hereditary disease in the family could promote health-conscious behaviour within the family. Again, although an effect cannot be ruled out, we believe it implausible, because we observed a risk reduction in people with sons with mild haemophilia, a mild disorder unlikely to affect lifestyle. Furthermore, in a previous study we noted that the risk profile for cardiovascular disease in patients with haemophilia does not differ greatly from that in the general male population.\(^{29}\)

Our results accord with those of other studies in which decreased coagulability has been associated with a protective effect against myocardial infarction. Such an effect has also been reported in patients with haemophilia,\(^{30,31}\) and in individuals with blood group O compared with non-O (group O is accompanied by lower concentrations of von Willebrand factor and factor VIII).\(^{32}\) A decreased tendency for occluding arterial thrombosis was also noted in pigs with a complete deficiency of von Willebrand factor.\(^{33}\) Furthermore, high concentrations of clotting factor VIII have been shown to be related to thrombotic risk, although this was less clear for arterial than for venous thrombosis.\(^{34,35}\) Results of our study underline the crucial role of haemostasis in the end stage of ischaemic heart disease, (ie, the formation of an occluding arterial thrombus).

We noted a reduced overall mortality in carriers of haemophilia, most probably resulting from a protective effect of low concentrations of clotting factor VIII and IX on ischaemic heart disease. Because concentrations of these factors vary between carriers, we cannot infer whether a gradually increasing protective effect occurs as concentrations decrease, or whether there is a threshold effect. Now, in many countries measurement of clotting factor concentrations in carriers of haemophilia is common practice. In the future, investigators will be able to assess the protective effect of various degrees of reduced concentrations of clotting factors.
Acknowledgments
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Conflict of interest statement
None declared.

References