To prevent hemophilic arthropathy, prophylactic treatment of children with severe hemophilia should be started before joint damage has occurred. However, treatment is expensive, and the burden of regular venipunctures in young children is high. With the aim of providing information on starting prophylaxis on the basis of individual patient characteristics, the effect of postponing prophylaxis on long-term arthropathy was studied in a cohort of 76 patients with severe hemophilia born between 1965 and 1985. The median age at first joint bleed was 2.2 years (range, 0.2-5.8). Prophylaxis was started at a median age of 6 years (interquartile range [IQR], 4-9), and the median annual clotting factor use on prophylaxis was 1750 IU/kg/y (31 IU/kg/wk). Hemophilic arthropathy was measured by the Pettersson score (maximum, 78 points). At a median age of 19 years, the median Pettersson score was 7 points (IQR, 0-17). After 2 decades of follow-up, the Pettersson score was 8% higher (95% confidence interval, 1%-16%) for every year prophylaxis was postponed after the first joint bleed. This effect was independent of age at Pettersson score, age at first joint bleed, and prophylactic dose used.

In conclusion, most patients have their first joint bleed after the age of 2 years. Patients who start prophylaxis soon after the first joint bleed show little arthropathy in adulthood. The longer the start of prophylaxis is postponed after the first joint bleed, the higher the risk of developing arthropathy. (Blood. 2002;99:2337-2341)

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having started early. For age at start of prophylaxis, patients were categorized as first joint bleed and the start of prophylaxis, and number of joint bleeds 3 indicators of treatment delay: age at start of prophylaxis once a week as the start of prophylactic treatment. To make for 5 patients with hemophilia A who initially received prophylactic twice weekly for factor VIII or once weekly for factor IX. An exception was made for 5 patients with hemophilia A who initially received prophylactic infusions once a week for a short period and subsequently continued with prophylaxis 2 or 3 times weekly. Because the intention was to prevent bleeding episodes and these patients were switched to more frequent prophylaxis 2 or 3 times weekly. Data on the weekly dose of prophylaxis were collected from the medical files for each year the patient was treated at the center from 1972 onward. The means of the weekly dose of prophylaxis (IU/kg/wk) and annual clotting factor use (IU/kg/y) were calculated for all years on prophylactic treatment.

Prophylaxis was defined as regular clotting factor infusions, at least twice weekly for factor VIII or once weekly for factor IX. An exception was made for 5 patients with hemophilia A who initially received prophylactic infusions once a week for a short period and subsequently continued with prophylaxis 2 or 3 times weekly. Because the intention was to prevent bleeding episodes and these patients were switched to more frequent infusions in case of increasing bleeding frequency, we used the date of start of prophylaxis once a week as the start of prophylactic treatment. To quantify our determinant of interest (postponing prophylaxis), we assessed 3 indicators of treatment delay: age at start of prophylaxis, time between the first joint bleed and the start of prophylaxis, and number of joint bleeds before starting prophylaxis. The localization of the joint bleeds was not collected. For age at start of prophylaxis, patients were categorized as having started early (< 4 years of age), late (4-7 years), or very late (> 8 years). For the number of joint bleeds experienced before starting prophylaxis, patients were divided into 4 categories: fewer than 3 joint bleeds, 3 to 15 joint bleeds, 15 to 44 joint bleeds, or 45 or more joint bleeds. Cutoff points for categories were chosen so that patients were divided into 3 or 4 groups of approximately similar size and that cutoff points appeared clinically relevant.

Outcome assessment

For assessment of hemophilic arthropathy, the last x-rays of elbows, knees, and ankles were scored using the Pettersson score. All x-rays were scored by a single radiologist who had no knowledge of treatment characteristics. In addition, the clinical score according to the World Federation of Hemophilia was recorded. The clinical score was assessed by our physiotherapist (P.K.) at the time of or within 1 year of the last Pettersson score.

Data analysis

Because the distributions of the values of the Pettersson score, the clinical score, the annual number of joint bleeds, the weekly dose of prophylaxis, and annual clotting factor consumption were skewed, data are presented as medians and their 25th and 75th percentiles (ie, IQR). The statistical program Statistics/Data Analysis (STATA version 6.0, College Station, TX) was used for all statistical analyses.

For the cumulative distribution of the age at first joint bleed, data of 71 patients on whom data on the first joint bleed before starting prophylaxis were available were included, including 10 patients who later developed inhibitors and 6 patients who had significant interruptions of prophylactic treatment. The association between age at start of prophylaxis and outcome was analyzed for all 76 patients in the earlier-described cohort. The association of outcome with the number of years of prophylaxis was postponed after the first joint bleed was studied in 60 patients with available data on the date of the first joint bleed. The time between the first joint bleed and the start of prophylaxis was analyzed as a continuous parameter in the regression analysis. A subset of 43 patients with data available on the total number of joint bleeds experienced before prophylaxis was used to study the association between the number of joint bleeds before prophylactic treatment and outcome. The association between outcome parameters and the 3 indicators of treatment delay (age at start of prophylaxis, time between the first joint bleed and the start of prophylaxis, and number of joint bleeds before prophylaxis) was assessed using a generalized linear model with a gamma distribution (xtgee, family gamma, log link). The gamma distribution is a continuous distribution that is skewed toward the lower values. Using this distribution for the Pettersson score and clinical score in the analysis produced a symmetric distribution of residuals. Several important confounders were adjusted for in the statistical analyses: severity of bleeding pattern, the intensification of prophylactic treatment over the last decades, and differences in age at evaluation. To adjust for the severity of the patient’s bleeding pattern, we adjusted for the age at first joint bleed. Adjustment for the mean weekly dose of prophylaxis (calculated for the total period of prophylactic treatment for each patient) was used to adjust both for the intensification of treatment over time and bleeding pattern, because patients with more breakthrough bleeds were given higher dosages. Finally, all analyses were adjusted for age at Pettersson score, because the Pettersson score is a cumulative score and is likely to be higher in older patients.

Results

Patient characteristics and outcome

At the time of the last Pettersson score, the median age was 19.0 years (IQR 15.0-25.3) and median follow-up was 16.0 years (IQR 11.2-20.5). Patient and treatment characteristics are presented in Table 1. The cumulative distribution of the age at first joint bleed is depicted in Figure 1. The median age at the first joint bleed was 2.2 years (IQR 1.2-3.0; range 0.2-5.8). Ninety percent of patients had experienced at least one joint bleed at the age of 4.4 years. For all years on prophylactic treatment, the median annual number of joint bleeds was 3.7 (IQR 2.6-5.7). Overall outcome was favorable: The median last Pettersson score was 7 points (IQR 0-17), and 28% of patients had a score of zero. The median clinical score was 2 points (IQR 0-5.5).

Age at start of prophylaxis and delay of prophylaxis after the first joint bleed

Outcome and patient characteristics according to age at start of prophylactic treatment are shown in Table 2. Of all 76 patients, 16 patients started prophylaxis early (< 4 years), 34 patients started Table 1. Patient characteristics and treatment

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. (hemophilia A, B)</th>
<th>76 (66, 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last Pettersson evaluation, y</td>
<td>19.0 (14.7-25.0)</td>
<td></td>
</tr>
<tr>
<td>Age at first joint bleed, y</td>
<td>2.2 (1.2-3.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>1.2 (0.7-1.7)</td>
<td></td>
</tr>
<tr>
<td>Age at first treatment, y</td>
<td>6.3 (4.0-8.9)</td>
<td></td>
</tr>
<tr>
<td>Lag time (first joint bleed until start of prophylaxis), y</td>
<td>3.3 (1.4-6.1)</td>
<td></td>
</tr>
<tr>
<td>No. of joint bleeds before start of prophylaxis</td>
<td>16 (5-44)</td>
<td></td>
</tr>
<tr>
<td>Duration of prophylactic treatment, y</td>
<td>12.5 (8.0-18.2)</td>
<td></td>
</tr>
<tr>
<td>Weekly dose of prophylaxis, IU/kg/wk*</td>
<td>31 (25-39)</td>
<td></td>
</tr>
<tr>
<td>Annual clotting factor use, IU/kg/y*</td>
<td>1750 (1462-2191)</td>
<td></td>
</tr>
</tbody>
</table>

*For all years on prophylactic treatment.
between 4 and 7 years of age, and 26 patients started after reaching the age of 8 years. The trend of starting prophylaxis earlier in The Netherlands was represented in the age difference between groups: Patients who started prophylaxis earlier were younger. Despite the later occurrence of the first joint bleed, suggesting a milder bleeding pattern, patients who started prophylaxis later still had experienced more joint bleeds before the initiation of prophylaxis. The onset of joint damage was delayed by early prophylaxis: 50% experienced more joint bleeds before the initiation of prophylaxis. This is the first study to quantify long-term effect of postponing the start of prophylaxis on hemophilic arthropathy. In this cohort of patients with severe hemophilia, most patients first experienced a joint bleed after the age of 2 years. At the age of 19 years, arthropathy as measured by the Pettersson score was 8% higher for every year prophylaxis was postponed compared to those of patients who started prophylaxis after 15 to 44 joint bleeds. The median Pettersson score for all patients who had at least 15 joint bleeds before prophylaxis was 11 points (IQR 3-20). Analysis of the adjusted effect of the number of joint bleeds patients had at least 15 joint bleeds before prophylaxis was 11 points (IQR 3-20). Analysis of the adjusted effect of the number of joint bleeds before prophylaxis on Pettersson scores after 19 years of follow-up showed a similar increase in Pettersson score for each year that prophylaxis was delayed (RI, 1.08; CI, 1.01-1.16; P=.03).

**Number of joint bleeds before prophylaxis**

In a subgroup of patients in whom information on the number of joint bleeds before prophylaxis was available, a more detailed assessment was performed categorizing patients according to the number of joint bleeds before the start of prophylactic treatment. Outcome and patient characteristics according to these categories are shown in Table 3. Again, both the intensification of treatment with time and the consideration of bleeding pattern in starting prophylaxis are visible: patients who started prophylaxis earlier were younger and experienced their first joint bleed earlier than patients who started later. The early start of prophylaxis resulted in complete prevention of joint damage for 70% of patients, compared with 31% and less for patients who started after 3 or more joint bleeds. Although the median Pettersson score was 7 points for patients who started taking prophylaxis after 15 to 44 joint bleeds, they had a median clinical score of only 4 points, reflecting a good clinical condition. Although prophylaxis was postponed even longer for patients in the last category (≥ 45 joint bleeds before prophylaxis), both their Pettersson scores and clinical scores were comparable to those of patients who started prophylaxis after 15 to 44 joint bleeds. The median Pettersson score for all patients who had at least 15 joint bleeds before prophylaxis was 11 points (IQR 3-20). Analysis of the adjusted effect of the number of joint bleeds before starting prophylaxis on Pettersson scores after 19 years of follow-up showed a 7% higher Pettersson score per 10 extra joint bleeds before prophylaxis (RI 1.07, CI 1.00-1.15, P=.14).

**Discussion**

This is the first study to quantify long-term effect of postponing the start of prophylaxis after the first joint bleed on hemophilic arthropathy. In this cohort of patients with severe hemophilia, most patients first experienced a joint bleed after the age of 2 years. At the age of 19 years, arthropathy as measured by the Pettersson score was 8% higher for every year prophylaxis was postponed after the first joint bleed. This effect was independent of age at evaluation, age at first joint bleed, and prophylactic dosage.

To appreciate these findings, some aspects of the study design need to be discussed. First, the number of joint bleeds before prophylaxis is assessed within 1 year of the last Pettersson score.
prophylaxis is of course the most accurate and most important determinant of the effect of postponing prophylaxis, but it was not available for all patients. Therefore, we used (1) the age at start of prophylaxis and (2) the time between the first joint bleed and the start of prophylaxis as additional indicators of treatment delay. Both indicators are positively associated with the number of joint bleeds before the onset of prophylaxis. The age at start of prophylaxis was known in all patients, and delay between the first joint bleed and the start of prophylaxis was available for most patients. Secondly, it is important to note that in The Netherlands, prophylaxis is started on the basis of the patient's bleeding pattern. Although prophylaxis was started more promptly over the years, patients in whom prophylaxis was started early are likely to have had more severe and more frequent bleeding episodes than those in whom prophylaxis was started later. This is reflected in the fact that patients who started prophylaxis earlier had experienced their first joint bleed earlier (Tables 2 and 3). The effect of postponing prophylaxis on hemophilic arthropathy was adjusted for the age at first joint bleed but not for the severity and frequency of bleeding episodes prior to the initiation of prophylaxis. The latter 2 cannot be assessed accurately from the medical files. This, however, may have resulted in underestimation of the effect of postponing prophylaxis. Thirdly, we used the Pettersson score to measure long-term outcome. The Pettersson score has several advantages over clinical measurements: It is a validated scoring system,\(^{16}\) an x-ray is an objective image that can be reexamined at any time, and it is not obscured by acute joint problems. The disadvantages are the delay of several years up to the appearance of deformities on x-ray and, also, the poor correlation with clinical problems.\(^{17}\) Some of these problems might be solved by the ongoing development of a magnetic resonance imaging scoring system for hemophilic arthropathy.\(^{18}\) The clinical score according to the World Federation of Hemophilia is also presented in this paper; however, we consider it less appropriate for measuring long-term outcome in our population because it is not validated, it cannot be reexamined later, and it measures both short-term (eg, swelling due to bleeding episodes or synovitis) and long-term outcomes (eg, flexion contracture and pes equinus) at the same time. Finally, for 5 patients the date of starting prophylaxis once a week was used for the date of start of prophylactic treatment. This is justified by the fact that prophylaxis was intensified when bleeding frequency increased in all patients; thus, joint bleed frequency was appropriately regulated by prophylaxis. Furthermore, it has been shown that the effect of prophylaxis was not associated with the frequency of infusions at the start of this treatment.\(^6\)

The favorable effects of starting prophylaxis at an early age\(^6\) or after a limited number of joint bleeds\(^8\) have been described earlier. The present study, however, is the first to quantify the effect of age while adjusting for other factors. Other studies have reported a similar variation in the onset of joint bleeds in patients with severe hemophilia. One prospective study in 27 patients reported a median age at first joint bleed of 1.63 years (range, 0.73-4.28).\(^{19}\) Another, retrospective, study found joint bleeds in only 33% of 49 patients until the age of 2.5 years.\(^{20}\) Ideally, prophylactic treatment is started from birth onward, maintains clotting factor levels at normal levels, and is continued for life. In practice, however, the burden of intravenous injections together with the costs of clotting factor concentrates need to be balanced against the level of arthropathy and quality of life of the patient. When to start prophylaxis is an important issue, because it has been shown that early prophylaxis can prevent joint damage\(^7\) and late prophylaxis may decrease but does not stop further deterioration of damaged joints over a period of several years.\(^{3,21}\) In the present study, prophylaxis only seemed to prevent arthropathy in most patients when started before the third joint bleed. The first question remains: Should we start prophylaxis before the first joint bleed? It has been shown that patients on prophylaxis still experience joint bleeds\(^2,3,9,22,23\) Thus, starting prophylaxis before the occurrence of the first joint bleed postpones its occurrence but does not entirely prevent joint bleeds. Animal studies have suggested that young cartilage is more susceptible to damage by hemarthroses than older cartilage.\(^{24}\) However, we do not know how much could be gained by postponing the first joint bleed. According to our data, starting prophylaxis after the first joint bleed (instead of starting between 1 and 2 years\(^8\) would mean postponing the start of prophylaxis for several months in most patients or even more than a year for some. This would mean postponing the burden of intravenous injections, reducing costs, and perhaps even avoiding the use of a central venous catheter in very young children. The second question is how many joint bleeds can be tolerated before starting prophylaxis without inducing too much joint damage. The results of our study suggest that postponing prophylactic treatment has a negative effect on outcome and that prophylaxis started before the third joint bleed may prevent joint damage. The increase in long-term arthropathy as a result of postponing prophylaxis is quantified in this study: an 8% increase in Pettersson score after 2 decades per year of postponing prophylaxis or 0.7% per extra joint bleed experienced before the start of prophylaxis. Due to the low number of patients, statistical significance was not reached in this last analysis.

### Table 3. Outcome and patient characteristics according to number of joint bleeds until start of prophylaxis

<table>
<thead>
<tr>
<th>No. of joint bleeds until start of prophylaxis</th>
<th>Less than 3</th>
<th>3-14</th>
<th>15-44</th>
<th>45 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients No.</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Age at last Pettersson score, y</td>
<td>15.8 (14.1-17.0)</td>
<td>17.5 (13.9-20.8)</td>
<td>17.2 (14.3-22.9)</td>
<td>22.3 (16.2-26.6)</td>
</tr>
<tr>
<td>Age at first joint bleed, y</td>
<td>1.0 (1.0-1.3)</td>
<td>1.4 (0.8-3.5)</td>
<td>2.4 (1.8-2.7)</td>
<td>3.0 (2.3-3.7)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of prophylaxis, y</td>
<td>1.4 (1.1-2.6)</td>
<td>4.1 (2.4-5.0)</td>
<td>5.6 (5.1-6.9)</td>
<td>8.7 (8.3-16.7)</td>
</tr>
<tr>
<td>Lag time, y</td>
<td>–0.2 (–1.8 + 0.3)</td>
<td>1.6 (1.4-2.6)</td>
<td>3.5 (2.6-4.6)</td>
<td>7.1 (4.8-13.7)</td>
</tr>
<tr>
<td>No. of joint bleeds until prophylaxis</td>
<td>0.5 (0-1)</td>
<td>11 (7-13)</td>
<td>32 (24-42)</td>
<td>100 (81-132)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last Pettersson score (maximum 78)</td>
<td>0 (0-2)</td>
<td>5 (3-13)</td>
<td>7 (0-17)</td>
<td>8 (4-14)</td>
</tr>
<tr>
<td>Pts with last Pettersson above 0, %</td>
<td>30</td>
<td>82</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>Clinical score (maximum 90)*</td>
<td>0 (0-1)</td>
<td>2 (0-5)</td>
<td>4 (1-6)</td>
<td>4 (0-5)</td>
</tr>
<tr>
<td>Pts with clinical score above 0, %</td>
<td>30</td>
<td>73</td>
<td>77</td>
<td>67</td>
</tr>
</tbody>
</table>

\*The clinical score was assessed within 1 year of the last Pettersson score.

Values are numbers or medians (IQR: 25th and 75th percentiles).
In conclusion, most patients have their first joint bleed after the age of 2 years. Patients who start prophylaxis soon after the first joint bleed show little arthropathy in adulthood. The longer the start of prophylaxis is postponed, the higher the risk of developing arthropathy.

Acknowledgment

The authors thank Professor Michael Hills, statistician, for his advice on statistical analysis.

References

The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia

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