Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s

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Key points
Compared to intermediate-dose prophylaxis (3x 1000 IU/wk), high-dose prophylaxis (3x 2000 IU/wk) resulted in a 66% higher total cost.

At age 24 years, high-dose prophylaxis resulted in a small reduction in bleeding and hemophilic arthropathy but equal quality of life

Abstract
Prophylactic treatment in severe hemophilia is very effective but limited by cost-issues. The implementation of two different prophylactic regimens in the Netherlands and Sweden since the 1970s may be considered as a ‘natural experiment’. We compared costs and outcome of Dutch intermediate- and Swedish high-dose prophylactic regimens for patients with severe hemophilia (FVIII/IX <1 IU/dl) born 1970-1994 using prospective standardised outcome assessment and retrospective collection of cost data. 78 Dutch and 50 Swedish patients, median age 24 (range 14-37) were included. Intermediate-dose prophylaxis used less factor concentrates [median (IQR) Netherlands 2100 IU/kg/yr (1400-2900) vs Sweden 4000 IU/kg/yr (3000-4900); p<0.01]. Clinical outcome was slightly inferior for the intermediate-dose regimen (p<0.01): 5-year bleeding [median 1.3 (0.8-2.7) vs 0 (0.0-2.0) joint bleeds/yr] and joint health [HJHS score over 10/144 points in 46% vs 11%], while social participation and quality of life (EQ-5D) were similar. Annual total costs were 66% higher for high-dose prophylaxis: mean 180 (95%CI 163-196)X1000 USD for Dutch vs 298 (95%CI 271-325)X1000 USD for Swedish patients (p<0.01).
At group level, the incremental benefits of high dose prophylaxis appear limited. At patient level, prophylaxis should be tailored individually and many patients may do well on lower doses of concentrate without compromising safety.
Introduction

Patients with severe hemophilia have undetectable FVIII or FIX levels resulting in spontaneous and trauma related bleeding, especially in the joints. Repeat joint bleeding eventually leads to a crippling arthropathy. Severe hemophilia is rare, with a prevalence of about 40 per million inhabitants. Since its introduction in 1958 by Professor Nilsson in Sweden,1 many long-term observational studies2-5 and two pediatric randomized controlled trials (RCTs)6,7 have shown that prophylactic replacement therapy in severe hemophilia prevents bleeds and subsequent hemophilic arthropathy. This was confirmed by the latest version of the Cochrane review on prophylaxis.8 However, the increased use of factor concentrates in prophylaxis and associated costs (from €72 000 (USD 76 700) annually for small children9 to €146 000 (USD 155 600) for an adult10 on high-dose prophylaxis in the 1990s) have been a limiting factor of a more widespread introduction of prophylaxis.

The Swedish regimen originally aimed at maintaining minimum trough levels of clotting factor activity by using doses of 25-40 IU/kg three times a week for hemophilia A.11 In the Netherlands however, prophylaxis was introduced in 1968,12 using lower doses, tailoring dose based on clinical observation, aimed at preventing spontaneous joint bleeds. Although treatment was intensified over the years in both countries,3,13 the difference in dosing has remained considerable: today, a typical adult Dutch hemophilia A patient uses 3x1000 IU of FVIII/week, whereas a typical adult Swedish patient uses 3x2000 IU or 1500 IU every other day. Both groups reported favourable long-term results, but with increasing pressure on health care budgets and a formal cost-review by the Swedish authorities,14 it is important to assess the incremental gains of high-dose prophylaxis.

Assessment of long-term effects requires decades of follow-up and the number of patients with hemophilia is limited.15 Comparing birth cohorts from centres in two countries provides the best alternative to a randomized controlled trial to assess long-term outcomes of the Dutch intermediate and Swedish high-dose prophylactic regimens. Selection bias was avoided as the choice of prophylactic regimen depended on country of birth only. In addition, external factors such as social circumstances and level of general health care provision in Sweden and the Netherlands are quite similar.

The aim of the present study was to compare long-term outcomes and costs between the Dutch intermediate-dose and the Swedish high-dose prophylactic regimen for persons with severe hemophilia with a follow-up of up to three decades. As optimal dosing for
prophylaxis has never been established, this study provides a unique insight which could not have been reported previously.

**Methods**

*Design and setting*

The study was designed as an observational study comparing two cohorts using retrospective assessment of treatment and prospective assessment of outcome. The study was performed at the hemophilia treatment centres of the University Medical Center Utrecht, the Netherlands (Van Creveldkliniek), the Karolinska University Hospital in Stockholm, Sweden, and the Skåne University Hospital in Malmö, Sweden. These clinics had routinely collected annual data on treatment and bleeding, hospital admissions and surgical procedures for decades. Data for this study were collected between January 2006 and July 2009. Ethical approval for this study was obtained from the IRBs of Utrecht (nr 06-002) and Malmö (nr 413/2006 and 493/2007).

*Patients*

All patients with severe hemophilia (FVIII/IX < 1% or <1 IU/dl), born between 1-1-1970 and 1-1-1994, treated at the participating centres, with life-long access to care and treatment data available were eligible for this study. Patients with a history of inhibitors (any inhibitor activity > 0.6 BU with decreased recovery) were excluded. Assessments were performed during regular outpatient visits. Patients aged 18 years and older were considered as adults. Informed consent was obtained from all patients prior to participation.

*Patient characteristics and treatment history*

Baseline patient characteristics registered included: date of birth, date of diagnosis, type of hemophilia, hepatitis C- and HIV status, and date of first joint bleed. To assess treatment history, date of first treatment, start of home treatment, onset of prophylaxis, as well as complete history of prophylactic regimens used were collected. In addition, orthopaedic surgical procedures (including arthroscopies and radioactive synovectomies) were extracted from patient files.

*Current treatment*

For the last 5 years before evaluation, annual clotting factor consumption was extracted from patient logs and hospital pharmacy records. In addition, number of visits to the center and details on hospital admissions were documented.
**Outcome**

The primary outcome parameter was clinical joint status, assessed by the center’s physiotherapist, using the Haemophilia Joint Health Score (HJHS version 1.0).\(^{16,17}\) The HJHS is based on physical examination of elbows, knees, and ankles (max 20-26 points per joint) and observation of gait for knees and ankles (0-4 points). The total score was calculated without adding overall global gait to the individual joint scores resulting in a total score ranging from 0, signifying perfect joint health, to 144. The HJHS score was originally developed to assess subtle joint damage in children with hemophilia. The score was used for this study because the items scored are not age-specific and differences in outcome were expected to be small. All HJHS scores were performed by one physiotherapist at each participating center. Standardisation and reliability was established during a training session (January 2006, 12 patients, intra-class correlation (ICC) 0.84) with all three designated physiotherapists.\(^{18}\)

Secondary outcome parameters were the annual number of joint bleeds, self reported activities, health-related quality of life and social participation. The annual number of joint – and soft tissue bleeds over the last five years was extracted from the patient logs, medical files, and hospital databases by research nurses at each center. Bleeds were defined as any complaint requiring treatment with clotting factor concentrate. Bleeds located in shoulders, elbows, wrists, hips, knees, or ankles were considered as joint bleeds. All data were entered in an electronic case report form (eCRF) using predefined definitions. To minimise bias, all definitions and how to complete the eCRF were documented and discussed prior to the study start.

Questionnaires were administered to adult patients only. Self-reported limitations in activities were assessed using the Haemophilia Activities List (HAL),\(^{20-21}\), while physical activity levels were assessed by the International Physical Activity Questionnaire (IPAQ).\(^{22}\) Health related quality of life expressed as utility was assessed using the EQ-5D.\(^{23}\) EQ-5D utility values were calculated using the Dutch tariff\(^{24}\) for both cohorts.

To compare social participation, data on achieved level of education and labour market participation were collected and compared to the age-matched general male population in the respective countries using the Labor Force Survey at Statistics Netherlands\(^{25}\) and Statistics Sweden,\(^{26}\) respectively; and the Swedish Registration of Education.\(^{27}\)
Cost and resource use
Dutch prices for the year 2010 were collected for evaluation of health care resource use and lost production in both cohorts. Prices were based on national price lists\textsuperscript{28,29} and academic hospital prices from 2011 for surgeries (Table 1). Days lost from work were valued according to the human capital approach.\textsuperscript{30} Costs were translated to USD using the European Central Bank 2010 bilateral average annual exchange rate: 1 Euro=1.3257 USD (http://sdw.ecb.europa.eu).
Direct medical costs (factor concentrate costs and other costs) and indirect costs (cost of days lost from work) for the five-year evaluation period were compared between cohorts. In addition, life-long use of factor concentrates according to age and treatment strategy was estimated from individual-level data on history of prescribed prophylactic regimens and body weight for Swedish patients and from an earlier study for Dutch patients.\textsuperscript{31} Factor consumption according to age and treatment strategy were also compared graphically.

Statistics
Students’ T-tests, non-parametrical Mann-Whitney U tests, and chi-squared tests were used to compare patient characteristics and outcomes according to treatment strategy. Panel data population-averaged generalised linear regression was used to predict the average annual cost of a mean-weight adult patient for each treatment regimen. Both logistic analysis (dependent HJHS $\geq 10$) and generealized linear models (GLM, dependent HJHS, gamma distribution, log link) were used to study the effects of age at start of prophylaxis, independent of country, age at evaluation, and 5-year factor consumption. Statistical analyses were performed using SPSS version 20 (Armonk, NY: IBM Corp.) and Stata version12 (College Station, TX: StataCorp LP).


Results

Patients
78 Dutch (intermediate-dose) and 50 Swedish (high-dose) patients were assessed during regular outpatient visits. The overall inclusion rate was 128/156 (78%); including 78/92 (85%) of Dutch patients (eight refusals, five unable to include due to irregular visits, and one patient not invited as he was currently taking interferon) and 50/71 (70%) of Swedish eligible patients (21 refusals).

To assess the impact of excluded patients on the overall study population we compared age, previous orthopedic surgeries and treatment with clotting factor concentrate during the last five years between excluded and included patients for both countries. Dutch excluded patients (n=14) were significantly older (mean age 32.3 vs 24.9 years, p<0.01), but had a similar history of previous orthopaedic surgery (21% vs 15%, p= 0.69); excluded patients showed a trend towards using full prophylaxis less often (64% vs 78%, p=0.31) and a 23% lower annual clotting factor consumption (mean 1680 IU/kg/yr, mean difference 500 IU/kg/yr, p=0.06). Swedish excluded patients (n=21) had a similar age (25.9 vs 23.8 years, p=0.24) and history of orthopaedic surgery (5 vs 8%, p=1.0), but also a trend towards using full prophylaxis less often (76% vs 86%, p=0.15) and a 21% lower annual clotting factor consumption (mean 3240 IU/kg/yr, mean difference 865 IU/kg/yr, p=0.03).

The majority of included patients were adults at the time of evaluation: (NL 62/78, 79%; SE 41/50, 82%). The number of patients with available data according to outcome parameter is shown in Figure 1.

Patient characteristics & treatment
The mean age of included patients was 24.5 years (range 14-37). The majority (115/128; 90%) of patients had hemophilia A. Overall, 34% of patients were hepatitis C positive and 5% were HIV positive. Although the prevalence of HIV was similar, Hepatitis C infection was more common in Dutch patients (42% vs 22%, p=0.04).

Patient characteristics and treatment according to prophylactic regimen are shown in Table 2. Patients were diagnosed with severe hemophilia early in life in both countries (median 0.7 years, IQR 0.2- 1.0 years). Dutch patients had entered the clinic about one year later than Swedish patients: at a median age of 1.8 years versus 0.6 years (p <0.01).

Treatment was started early in both countries. The first infusion was usually given around the age of one year, but still at a slightly older age in Dutch patients: median 1.1 years vs 0.9 years (p value <0.01). Patient characteristics and treatment in the two Swedish centers were comparable.
Both cohorts included one patient with a mild bleeding phenotype who never started prophylactic treatment: one Dutch patient born in 1972 and one Swedish patient born in 1979. Overall, the prophylactic treatment regimens were very different: patients treated with the Dutch intermediate-dose regimen started prophylaxis later, mostly after the onset of joint bleeding, and switched to home treatment at a later age. Since the start of prophylaxis, most patients continued this treatment although there was a trend towards more frequent discontinuation (p=0.19) and a significantly lower proportion of Dutch patients on full time prophylaxis over the last 5 years (78% vs 96%, p<0.01).

At evaluation, the overall annual consumption was 2150 IU/kg/yr (CI -2700 to -1600) lower for the intermediate-dose regimen: median 2100 IU/kg/yr vs 4000 IU/kg/yr (p<0.01). The frequency of infusions was similar around 3 infusions per week. Patient characteristics and treatment patterns were similar for hemophilia A and B (data on request).

Clinical outcome

Clinical outcome according to regimen is shown in Table 3. In total, 643 patient years were evaluated for bleeding and treatment. Overall, physical activity was high in both groups and bleeding frequencies were low. When comparing both regimens however, the intermediate-dose regimen resulted in a limited but statistically significant increase in the number of bleeds: just over one additional joint bleed per year (median 1.3 vs 0, p<0.01) and 7-8 additional bleeds (median 10 vs 2.5) over 5 years. During the 5-year observation period, one Dutch HIV positive patient experienced an intracranial bleed. No other life threatening bleeds were observed in either group.

In these young adults, only minor changes in joint status were observed and few limitations in activities were reported. However, again, in the direct comparison the patients treated with the intermediate-dose regimen had slightly, but significantly, higher HJHS scores (median 9.0 vs 7.0 points out of 144) and reported slightly, but significantly, more limitations in daily activities (median HAL scores of 93/100 vs 99/100). However, high-dose prophylaxis did not completely prevent joint damage in all patients: 5/44 (11%) of Swedish patients still had a HJHS of ≥ 10 points, compared to 31/68 (46%) of Dutch patients (p<0.01). A history of orthopaedic surgery was rare in both populations: 15% of Dutch patients, compared to 8% of Swedish patients (p=0.29). Regression analyses did not show an independent effect of age at start of prophylaxis on outcome (beta=0.098, p =0.21 for logistic regression, and beta=0.032, p=0.18 for GLM). Outcome parameters were similar for hemophilia A and B (data on request).
Quality of life
The quality of life measured by EQ-5D utility was high (Table 3), and was similar across both cohorts (p=0.93). At group level, values were close to those of the general male population aged 20-29: mean utility was 0.88 for Dutch patients vs 0.93 in the Dutch general population32, and 0.86 for Swedish patients vs 0.91 in the Swedish general population.33
The response rate was lower for Dutch patients (76% vs 83%, Fig 1) but this is not expected to have affected outcome, as non-responders and responders had similar age, education and employment, as well as joint status.

Social participation
The achieved level of education and labor force participation rates for adult patients are shown in Table 4. At evaluation, a higher percentage of Swedish participants reported having completed university education, but the differences in overall educational achievement were not significant. Compared to the general male population, fewer had achieved a university degree at evaluation, although this may result from some still being students and national statistics not including the youngest adults (the Netherlands age 25+ years, Sweden 20+ years).25,27
Among employed participants, full-time employment dominated: 38/43 (88%) of Dutch and 26/30 (87%) of Swedish patients were working full-time. Few patients were unemployed (the Netherlands 2, Sweden 4) and the unemployment rates among participants were similar (the Netherlands) or lower (Sweden) than those of their peers.
Overall, 86% of patients on either regimen did not report any days lost from work or school due to hemophilia during the five-year study period. Among patients who reported missing days from work or education on a short- or long-term basis, the median number of days lost during the five year period for Dutch patients (n=11) was 202 (IQR 39-536), compared to 28 (IQR 3-39) for Swedish patients (n=7). This large difference was driven by five Dutch patients: three undergoing interferon-based treatment for HCV infection and could not work for on average 7.7 months, and two who were disabled on a long-term basis, one after an intracranial bleed and another for severe arthropathy, HIV and HCV infection.
Costs
The mean and median 5-year treatment costs in 1000 USD per patient according to prophylactic regimen and Dutch prices are shown in Table 5. For the five-year period, median total costs per patient were 73% higher for high-dose prophylaxis: 0.85 million USD (0.66-1.09) for Dutch vs 1.48 million USD (1.15-1.79; p<0.01) for Swedish patients. Over this period, the clotting factor consumption dominated costs: 97.1% of costs for the intermediate-dose regimen and 99.6% for the high-dose regimen. On average, resource use and costs were 40-50% lower for the intermediate-dose regimen, except for a 700 USD higher ‘other health care’ (including surgery, hospitalizations, health care visits), which accounted for less than one per cent of total costs. Using five year data, the cost per bleed avoided would be USD 91 000.

The predicted annual total costs for an average-weight patient (74 kg) were 66% higher for high-dose prophylaxis: mean 179 600 USD/yr (95% CI 163 000–196 200) for Dutch patients versus 297 900 USD/yr (95% CI 270 800–324 900) for Swedish patients (p<0.01).

A clinically and statistically significant difference in factor concentrate use between the two prophylactic regimens was also seen in a 30-years perspective (p<0.01 all ages ,Figure 2). Absolute differences in median annual factor use increased with age: ranging from around 50 000 IU/yr before school age, to 100 000 IU/yr at age 15, and 150 000 IU/yr at age 20-30 years. Extending the time horizon to a 70-year-perspective, life-time factor use per patient would amount to 8.2 versus 18 million IU assuming constant factor concentrate dosages at current median levels for adults on both regimens. At a price of 1.10 USD/IU, these differences are equivalent to a life-time cost of factor concentrate of 9.1 versus 20 million USD (undiscounted) or 3.3 versus 7.1 million USD (discounted by 3%).
Discussion

The present study is the first prospective study comparing outcome of two different prophylactic treatment regimens for patients with severe hemophilia with 20-30 years of follow-up.

Outcome was favorable in the majority of patients. At a median age of 24 years, 54% of those on intermediate-dose prophylaxis and 89% of those on high-dose prophylaxis had no significant arthropathy (HJHS score <10/144, p-value<0.01), while quality of life and employment status were similar. Due to differences in clotting factor consumption, costs were diverging widely over the last decades. Annual total costs for a 74 kg patient were 66% higher for high-dose prophylaxis: mean 179 600 USD/yr for Dutch patients versus 297 900 USD/yr for Swedish patients.

Over 5 years, the high-dose regimen was associated with a 73% higher total costs: median 0.85 Million for Dutch vs 1.48 Million USD for Swedish patients.

Study design

To analyse the long-term outcomes of prophylactic treatment regimens, we used a combination of state-of-the-art prospective outcome assessment and collection of retrospective data from patient files. Use of routinely documented data enabled extraction of bleeding and full treatment history; questionnaires were validated and every effort was undertaken to standardize joint assessment. Similar to a randomized controlled trial, the prophylactic regimen was allocated based on study group (i.e. country of birth) and not on clinical characteristics or ability to pay for treatment. The study aimed to compare ‘full’ birth cohorts to avoid selection bias. Key treatment characteristics of non-participants were analyzed. In both countries, non-participants showed a trend towards less intensive treatment with a lower annual consumption of factor concentrates (intermediate-dose regimen –23%; high-dose regimen –21%). This implies that results of this study slightly overestimated annual total costs but it is unlikely to have biased the results of the cost-comparison. The effects on outcome cannot be estimated: non-participants may have a milder bleeding pattern and/or a lower adherence to prophylaxis.

While it is common to report clinical results separately for hemophilia A and B, this distinction may be less important for the aim of this paper. As expected, the differences between prophylactic regimens was consistent when restricting the analysis to persons with haemophilia A only (see the Supplemental Data link at the top of the online article).
Comparison with other studies:
Earlier studies have covered long-term clinical outcomes of prophylactic treatment of Dutch and Swedish cohorts.\textsuperscript{3,5} A previous retrospective comparison of Dutch and Swedish adolescent patients, lacking formal outcome assessment and collection of cost data, observed statistically significant differences in joint outcome among patients younger than 15 years only.\textsuperscript{35} Other studies concern comparisons of high-dose prophylaxis to on-demand treatment in young patients aged up to 6\textsuperscript{4} and 11\textsuperscript{7} years, respectively. The lack of long-term controlled studies was recently considered as an important limitation of economic evaluations.\textsuperscript{36}

When considering the incremental cost of providing life-long prophylaxis instead of on-demand treatment there are very few data available. So far, only two studies have presented cost data in unselected cohorts of severe hemophilia patients treated on demand. At price levels of year 2000, mean direct medical costs of 79 000 EUR/yr (73 000 USD) were reported in France\textsuperscript{37} and 52 000 EUR/yr (48 000 USD) in Norway.\textsuperscript{10} Quality of life was not measured in these studies. Currently, the Hemophilia Utilization Group Study (HUGS part Va) are collecting cost data in the USA.\textsuperscript{38} It is evident that on-demand treatment is much less costly than the prophylactic regimens presented in this study. However, the long-term outcome of on-demand treatment is worse in terms of joint status, serious haemorrhages, quality of life and labor force participation.\textsuperscript{4,37,39} Previous health-economic evaluations have addressed issues of cost-effectiveness in haemophilia care\textsuperscript{9,40} and one cost-benefit analysis in a Swedish setting reported that the average willingness to pay for prophylaxis in the general population exceeded the average cost of provision of prophylaxis per taxpayer.\textsuperscript{41} This study does not contain a formal economic evaluation as the cost differences were nearly USD 159 000 per year and the difference in utility was not statistically significant in these data. Using five year data the cost per bleed avoided would be USD 120 600. Therefore, any cost-utility analysis on these data will show that compared to intermediate dose prophylaxis, general provision of high-dose prophylaxis will not be cost-effective at current prices and cost-effectiveness thresholds (e.g. 80 000 EUR or 106 056 USD per QALY in the Netherlands).

Clinical implications
This study shows a statistically significant but small incremental benefit after nearly doubling the annual prophylactic dose. The benefit was observed in all outcome parameters, except quality of life. This may reflect the limited clinical effects of one additional joint bleed per year, or the inability of the generic EQ-5D questionnaire to pick up small differences. From a life-long perspective, it is expected that differences in
outcome between these two cohorts will have increased in another 20 years. However, we do not know the extent nor the clinical implications of such an increase. Is the difference attributable to dose difference only? One of the drivers of the slightly better outcome in the high-dose group may be the earlier start of prophylaxis. This is well established, and both countries have started prophylaxis earlier over the last decades. Regression analyses failed to identify a statistically significant and independent effect of age at start of prophylaxis in outcome. This unexpected finding may be due to two limitations in the present data: lack of variation and limited power. Lack of variation was present in the Swedish data: all patients started prophylaxis very early. Power was limited by small differences in outcome and limited patient numbers.

Currently, prophylactic dosing is mostly based on the Swedish regimen of 25-40 IU/kg per infusion and dosages used in pediatric trials have been consistently high: 25 IU/kg thrice weekly or every other day, i.e. 3900 and 4550 IU/kg/yr, respectively. For older patients, guidelines on dosing are unavailable, and the recommendation is to just keep this dose, in spite of the fact that adults have more regulated activity patterns, a longer FVIII half-life, and a weaker association between trough levels and bleeding. For clinical practice, it will always be important to prevent bleeding, especially in joints. Overall, these favorable results support the need for an early start of prophylaxis and continuing this treatment in adults with severe hemophilia. At patient level, the data on joint outcome suggest that a proportion of patients are equally well-off with intermediate-dose prophylaxis while others need a high-dose regimen to control their bleeding. In the absence of valid laboratory paramaters to assess a patients’ phenotype, clinical parameters of bleeding frequency and physical activities, combined with pharmacokinetic information are the only tools available to individualize prophylactic dosing. Eventually, some adult patients even discontinued prophylaxis without experiencing frequent bleeding, as was observed in these cohorts, but also in others.

In conclusion, this first direct comparison of two prophylactic regimens suggest that at group level, a more intensive and higher dosed regimen may provide slightly improved outcome at a significant cost increase. At patient level, the challenge is to identify patients who will be as well-off on lower doses without compromising patient safety. Even in small patient groups such as these, improving cost effectiveness of treatment should be considered.
Contributors: KF, KSC, PP, MH, RL, MB and EB conceived the study. KF, PP, KSC, MB and EB designed the study. KF and EB secured funding. KF, MH, and EB managed all study procedures (ethics and governance, recruitment, patient assessment, data management). KF and KSC planned and undertook the statistical analysis. KF and KSC drafted the manuscript with input from all authors. All the authors had access to the data and analysis and approved the final manuscript. KF is the guarantor.

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Competing interests: KF has acted as a consultant and participated in expert groups for Bayer, Baxter, Biogen and NovoNordisk, has received research grants from Baxter, NovoNordisk, Pfizer, and CSL Behring, and has given lectures for Bayer, Baxter, NovoNordisk, and Pfizer, and has received travel support from Baxter. KSC has acted as a consultant for Baxter, has received research grants from LIF(ass for the research-based pharmaceutical industry in Sweden), and has given lectures for Bayer. PP has participated in advisory board for Pfizer, has given lectures for Bayer, Baxter and Pfizer, and has received travel support from Bayer, Baxter and Pfizer. MH has received research grants from Octapharma and Baxter, has given lectures for Baxter, Bayer, CSL Behring, and Leo-Pharma. RL has acted as a consultant and participated in expert groups for Bayer and NovoNordisk, has received research grants from Baxter, and has given lectures for Bayer, Baxter, and NovoNordisk. HMB has received unrestricted funding from Baxter, Bayer and NovoNordisk, has acted as a consultant for Bayer, and has given lectures for Bayer and Baxter. EB has acted as a consultant and participated in expert groups for Bayer, Baxter, NovoNordisk, Sobi, Octapharma, and CSL-Behring, and has given lectures for Bayer, Baxter, NovoNordisk, Pfizer, Octapharma, Sobi, and CSL Behring.

Ethical approval: Ethical approval for this trial was granted by IRBs of Utrecht (nr 06-002) and Malmö (nr 413/2006 and 493/2007). This study was conducted in accordance with the Declaration of Helsinki.
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Table 1: Prices in USD.

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<th>Resource use</th>
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<td>Orthopaedic surgery †</td>
<td>12 643</td>
<td>Dutch Board of Insurance Companies, tariff- university hospital 2011²⁸</td>
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<tr>
<td>Other surgery †</td>
<td>8 429</td>
<td>Dutch Board of Insurance Companies ²⁸</td>
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<td>Hospital day †</td>
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<td>Dutch Board of Insurance Companies ²⁸</td>
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<td>Farmacotherapeutisch kompas 2010²⁹</td>
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<td>Cost per day of lost production by age group</td>
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* USD - US Dollar. Converted from Dutch prices in Euro using average exchange rate year 2010, 1 Euro = 1.3257 USD. † Use of factor concentrates was included separately. Orthopaedic surgery based on average of tariff for arthrodesis and arthroplasty. Price of hospital resources include staff, other material and overhead cost.
### Table 2. Treatment characteristics according to prophylactic regimen

<table>
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<th>Netherlands Intermediate-dose</th>
<th>Sweden High-dose</th>
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<td>Hemophilia A</td>
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</tr>
</tbody>
</table>

**Treatment history**

<table>
<thead>
<tr>
<th></th>
<th>Netherlands</th>
<th>Sweden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>0.7 (0.04-1.2)</td>
<td>0.6 (0.3-0.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>Age at 1st treatment, y</td>
<td>1.1 (0.9-1.7)</td>
<td>0.9 (0.5-1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at start prophylaxis, y</td>
<td>4.5 (3.2-6.0)</td>
<td>1.5 (1.1-2.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prophylaxis started before 1st joint bleed, n/N (%)</td>
<td>6/69 (9%)</td>
<td>19/45 (42%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at start of home treatment, y</td>
<td>5.7 (3.9-9.3)</td>
<td>3.3 (2.0-4.5)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Treatment during the last 5 years**

<table>
<thead>
<tr>
<th></th>
<th>Netherlands</th>
<th>Sweden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Full time prophylaxis, n (%)</td>
<td>61 (78)</td>
<td>48 (96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weekly dose, IU/kg</td>
<td>46 (34-55)</td>
<td>88 (61-113)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of infusions/week</td>
<td>3.0 (2.5-3.0)</td>
<td>3.3 (1.6-3.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Annual consumption, IU/kg/y†</td>
<td>2100 (1400–2900)</td>
<td>4000 (3000-4900)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

IU – international units. IQR – Interquartile range.
* Values are median (IQR) of unit of measurement unless otherwise stated.
†Annual clotting factor consumption were rounded to the nearest 100.
Table 3. Clinical outcome and social participation according to prophylactic regimen

<table>
<thead>
<tr>
<th></th>
<th>Netherlands Intermediate-dose</th>
<th>Sweden High-dose</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity METs</td>
<td>4294 (1037-13740)</td>
<td>3200 (1152-9292)</td>
<td>0.50</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint bleeds/y, n</td>
<td>1.3 (0.8-2.7)</td>
<td>0 (0.0-2.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Joint bleeds in 5 years n</td>
<td>10 (4-18)</td>
<td>2.5 (0-9.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Joint outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of function, HJHS, max 144 points</td>
<td>9.0 (2.0-18.0)</td>
<td>4.0 (2.0-6.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>HJHS≥ 10 points</td>
<td>31/68 (46%)</td>
<td>5/44 (11%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nr of joints affected</td>
<td>2 (1-4)</td>
<td>3 (2-3)</td>
<td>0.47</td>
</tr>
<tr>
<td>Limitations in activities</td>
<td>93 (81-98)</td>
<td>99 (93-100)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D utility</td>
<td>0.84 (0.81–1.00)</td>
<td>1.00 (0.81–1.00)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

IU – international units. METs – Metabolic Equivalent of Task. HJHS – Haemophilia Joint Health Score. HAL – Haemophilia Activities List. EQ-5D – Utility values by Dutch utility values.
Table 4. Level of education and labor force participation in adult patients according to prophylactic regimen and compared with the general population.

<table>
<thead>
<tr>
<th>Achieved level of education</th>
<th>Netherlands Intermediate-dose‡ % of n=62</th>
<th>General population‡ %</th>
<th>Sweden High-dose‡ % of n=41</th>
<th>General population‡‡ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compulsory/secondary</td>
<td>29</td>
<td>20</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Upper secondary/professional</td>
<td>68</td>
<td>43</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>University</td>
<td>3</td>
<td>36</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2‡</td>
<td>3‡</td>
<td>3</td>
</tr>
</tbody>
</table>

**Labor force participation**

<table>
<thead>
<tr>
<th>Active</th>
<th>Employed</th>
<th>Unemployed</th>
<th>Not active</th>
<th>Student</th>
<th>Disability allowance</th>
<th>Housekeeping</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td>69</td>
<td>6</td>
<td>24</td>
<td>21</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>85</td>
<td>82</td>
<td>3</td>
<td>15</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>3‡</td>
</tr>
</tbody>
</table>

78 87 73 81 5 7 20 13 17 0 2

‡Total 99% or 101% due to rounding error.
Table 5. Five year costs per patient according to prophylactic regimen.

<table>
<thead>
<tr>
<th></th>
<th>Netherlands Intermediate-dose</th>
<th>Sweden High-dose</th>
<th>p</th>
<th>Netherlands Intermediate-dose</th>
<th>Sweden High-dose</th>
<th>Median (IQR), 1000 USD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor use</td>
<td>867 (380)</td>
<td>1452 (483)</td>
<td>&lt;0.01</td>
<td>851 (647–1046)</td>
<td>1474 (1154–1776)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Other health care</td>
<td>5 (9)</td>
<td>4 (6)</td>
<td>0.28</td>
<td>2 (2–3)</td>
<td>1 (1–3)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Indirect costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost production</td>
<td>14 (50)</td>
<td>1 (3)</td>
<td>0.08</td>
<td>0 (0–0)*</td>
<td>0 (0–0)*</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>886 (382)</td>
<td>1457 (484)</td>
<td>&lt;0.01</td>
<td>852 (659–1094)</td>
<td>1475 (1155–1787)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>


*90th percentile values were USD 30 vs 2 for Netherlands and Sweden, respectively, in 1000 USD.

Interpretation: mean costs are influenced by outliers but reflect the total budget at group level, median costs reflect the cost of the middle person in a skewed distribution.
Figure 1: Overview of available data
Figure 2  Observed annual factor use for persons with severe hemophilia on high-dose and intermediate-dose prophylaxis (Mann-Whitney all ages p<0.001).
Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s

Kathelijn Fischer, Katarina Steen Carlsson, Pia Petrini, Margareta Holmström, Rolf Ljung, H. Marijke van den Berg and Erik Berntorp

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