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Costs of on-demand and prophylactic treatment for severe haemophilia in Norway and Sweden

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Summary. The expected annual cost (in the year 2000 prices) for a 30-year-old patient with average individual and treatment characteristics for on-demand EUR 51 832 (95% CI: 44 324–59 341) and for prophylaxis EUR 146 118 (95% CI: 129 965–162 271), was obtained from panel-data analysis of an 11-year retrospective panel of 156 patients with severe haemophilia in Norway and Sweden. Costs included haemophilia-related treatment costs within the health-care sector (factor concentrate, doctors' visits, diagnostic procedures, hospitalisation, invasive procedures, etc.) and cost for haemophilia-related resource use in other sectors (lost production, use of special equipment, adaptation of workplace and domicile, etc). Although costs of lost production, reconstructive surgery and hospitalisation were higher for on-demand, they did not balance out the higher costs of factor-concentrate consumption in prophylaxis. The cut-off risk of premature death, where on-demand and prophylaxis would have been equally costly, was 3.7 percentage units higher for on-demand than for prophylaxis. Such a great risk difference has not been reported elsewhere to our knowledge. Estimated cost-elasticities indicated that annual costs of prophylaxis would increase by approximately the same proportion as a potential increase in the price of factor concentrate and decrease less than proportionately with a reduction in prescribed dose kg^{-1}. For on-demand, the annual costs would increase by approximately the same proportion as an increase in the prescribed dose kg^{-1}.

Keywords: cost, longitudinal data analysis, on-demand, prophylaxis, sensitivity analysis

Introduction

There are two main factor-replacement strategies for severe haemophilia: on-demand and prophylaxis [1]. Treatment practice varies between countries [2–4]. Prophylaxis has, for instance, been the standard treatment in Sweden since the 1970s, while on-demand has been standard in Norway up to the 1990s. It has long been recognized that prophylaxis is associated with better outcomes [5–13]. In our previous study [5], we certainly found that patients on prophylaxis lost fewer days from work or school, had less need of special equipment and adaptations of homes and workplaces, experienced fewer in-hospital episodes, and had less reconstructive surgery than patients treated on-demand. However, prophylaxis patients also consumed substantially more costly factor concentrate.

The question still remains, then, whether the lower use of other resources outweighs the higher use of factor concentrate (a contra-indication has recently been provided by Miners et al. [14]). In order to answer this question, resource use has to be translated into costs. Moreover, the cost of treatment can also be used on a full-scale economic evaluation where benefits of treatment would also be assessed [15]. Our project, 'Treatment strategies for severe haemophilia – on-demand vs. prophylaxis', has

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estimated the benefits of on-demand and prophylactic treatment using the contingent valuation method and those results are reported in this issue in the parallel paper [16].

Thus, the objective of the present study was to calculate the annual cost of long-term on-demand and prophylactic treatment, respectively, to analyse the variation of the cost and to conduct a sensitivity analysis of the results. Costs included both costs within the health-care sector (consultations, surgery, hospitalisation, factor concentrate, etc.) and costs in other sectors (lost production because of sick leave and early retirement, adaptations of domicile and workplace, etc.). We were interested in the extent to which individual characteristics, as well as past- and present-treatment characteristics, affected the annual cost, in particular, whether different modes of treatment during childhood and adolescence had any significant effect on costs later in life.

A comprehensive sensitivity analysis was performed in order to test the robustness of our results. It included both the effect on annual costs of increasing/decreasing prices of the different resource categories and the estimation of cost-elasticities, i.e. the percentage change in annual cost with respect to one percentage change in input factors (price of factor concentrate and prescribed dose kg^{-1}). Finally, we investigated how much larger the annual risk of premature death under on-demand treatment would have to be in order to make the costs equal to those incurred under prophylaxis.

A societal perspective was applied, i.e. resource use both within the health-care sector and in other sectors was costed.

Materials and methods

Study population

All patients with severe haemophilia (factor VIII/IX activity <1%) in Norway and Sweden meeting the inclusion and exclusion criteria (Table 1) were included in the study. On-demand treatment also included periods of prescribed secondary prophylaxis (for instance before surgery or together with physiotherapy) since excluding these observations would underestimate the cost of on-demand treatment.

Patients born before 1939 were excluded because replacement therapy was not available during a substantial part of their lives. Norwegian patients born after 1981 were excluded because prophylaxis was introduced for younger patients in the early 1990s. Prophylaxis patients born before 1949 were excluded, because the older patients would have had too long an initial period without prophylaxis to be representative of the long-term continuous form of treatment.

Table 1. Selection criteria for Norwegian and Swedish patients, respectively.

Patients treated with on-demand	
Inclusion criteria	Answer
Severe haemophilia A or B	Yes
Born between 1939 and 1981	Yes
Treated on demand 1989–1999*	Yes
Signed patient information	Yes
Exclusion criteria	
Ad mortem after 31 December 1988	Yes
Patient had developed inhibitors against factor VIII or IX	Yes
Patients treated with prophylaxis	
Inclusion criteria	
Severe haemophilia A or B	Yes
Born between 1949 and 1989	Yes
Regular prophylactic treatment 1989–1999 (twice weekly for haemophilia A and once weekly for haemophilia B)	Yes
Signed patient information	Yes
Exclusion criteria	
Ad mortem after 31 December 1988	Yes
Patient had developed inhibitors against factor VIII or IX	Yes

Patients were excluded if at least one inclusion criteria was *not* met or at least one exclusion criteria was met.
*Includes periods of secondary prophylaxis.

Patients who had ever developed inhibitors were excluded because this causes the content of treatment to diverge from that of the long-term form on-demand and prophylactic treatment [17]. Patients with hepatitis C and HIV/AIDS were included, as the treatment of haemophilia *per se* does not change according to our experience (however, the resource use incurred by the treatment of HIV/AIDS *per se* was not included in our cost analysis).

For further details on the study population and drop-outs, we refer to our previous publication in this journal from the same study [5].

Patient and treatment data

Prophylactic and on-demand treatment may differ in their short- and long-term effects. Hence, we used a long period of observation for the retrospective detailed resource use registration (1989–1999), and collected information on treatment characteristics from birth to the beginning of our observation period for each patient (Table 2).

Ethics committees at all participating centres approved the study.

Table 2. Standardized protocol for generation of data on resource use.

Part 1. Treatment history for the period prior to 1989
1 Type of treatment (on demand or prophylaxis)
2 Duration of type of treatment (from date, to date)
3 Prescribed dose of factor concentrate (IU per infusion when bleeding) during on-demand treatment
4 Prescribed dose of factor concentrate (IU per infusion) during prophylaxis
5 Frequency of prophylaxis (infusions per week)

Part 2. Annual use of resources within the health-care sector 1989–1999
6 Treatment strategy, standard dose, frequency of prophylaxis, body-weight, date when changes occurred
7 Amount of factor concentrate consumed
8 Number of visits to doctors, nurses and dentists (planned and emergency)
9 Use of invasive procedures (emergency or reconstructive surgery)
10 Use of auxiliary resources in connection with invasive procedures (artificial joints, other implants and factor concentrate)
11 Length of stay in hospital during invasive procedures including dates of admission and discharge
12 Length of stay in hospital during episodes not caused by invasive procedures, factor-concentrate consumption, and dates of admission and discharge

Part 3. Annual resource use outside the health-care sector 1989–1999 (telephone interviews with patients)
13 Marital status, household size, for children whether the father or mother answered the questions
14 Occupation (employed, unemployed, early retired, attending school or university, other) including start and stop date
15 Number of days lost from work or school (loss of production) because of haemophilia
16 Rehabilitation outside of hospital (number of episodes, duration of episode)
17 Use of home-care service (type of service, number of hours)
18 Use of special equipment (car, wheel chair, etc.) at home and/or at work
19 Adaptations at home and/or at work to compensate for disabilities caused by haemophilia

Part 4. Annual resource use outside the health-care sector 1989–1999 (telephone interviews with relatives)
20 Relationship to patient
21 Occupation (employed, unemployed, early retired, attending school or university, other)
22 Number of days lost from work because of the patient's haemorrhaging episodes

For further description of the patient and treatment data, as well as the data collection procedures, we refer to our previous publication [5].

Prices

We used Swedish prices from the year 2000 to convert physical quantities of resource use into monetary values. Table 3 shows the prices (in EUR) of the major cost-generators.

Table 3. Prices (in EUR) of resource use. Market prices were obtained from Statistics Sweden (days of lost production), manufacturers (adaptations and orthopaedic prostheses) and the National Social Insurance Board in Sweden (factor concentrate). The accounting department at Malmö University Hospital (Malmö, Sweden) provided the administrative prices.

	Median	Range
Market prices		
Day of lost production*	115	91–237
Factor concentrate (per IU)†	59	49–81
Prosthesis, knee‡		1362–2358
Prosthesis, elbow‡		1368–2723
Adaptation of car‡	1 681	734–9590
Adaptation of domicile‡	2960	414–63 340
Administrative prices		
Hospital day§	405	327–757
Surgery, per anaesthesia min¶		13–15
Annual check-up visit	514	
Emergency outpatient visit (physician)	246	
Planned outpatient visit (physician)	282	
Emergency outpatient visit (nurse)	72	
Physiotherapist (per hour)	114	
Radiotherapy**	93	41–288
MR and CT scan**	429	173–643
Ultra sound**	84	74–130
Port-à-cath	237	

*Value of lost production = average salary in profession + payroll taxes + value added tax. Source: Statistics Sweden available at http://www.scb.se.
†Source: National Social Insurance Board in Sweden (http://www.rfv.se) and Pharmaceutical Benefits Board (http://www.lfn.se).
‡Price range of adaptation of car and domicile included different types of adaptations. Price range for prostheses included different brands for each category. Source: Communications with manufacturers.
§Price range included emergency, pediatrics, haematology, infections, cardiology, surgery, medicine, neonatal, neurological, orthopaedic and radiotherapy departments. Source: Accounting department at Malmö University Hospital, Malmö, Sweden.
¶Includes costs of operation team and equipment for orthopaedic and vascular surgery, respectively. Source: Accounting department at Malmö University Hospital, Malmö, Sweden.
**Price range of diagnostic procedures included different objects of investigation (knees, elbows, ankles, skull, etc.). Source: Accounting department at Malmö University Hospital, Malmö, Sweden.

Some prices were market prices (equipment to compensate for impaired function, adaptations of cars and domiciles, factor concentrate, orthopaedic prostheses, salaries), and others were administrative prices (doctors' and nurses' visits, surgical procedures, in-hospital care episodes).

Some of the factor-concentrate brands used in Norway were not marketed in Sweden and some of them used during the first years of the study period

were replaced by new brands. In these cases we used the price of an equivalent brand. Concerning orthopaedic prostheses, in some cases there was no information regarding the brand that had been used, and in some cases a brand used in Norway was not marketed in Sweden. In these cases, we used the price of the most common brand marketed in Sweden of that type of prosthesis.

The human-capital approach was used to translate absence from work into costs [18,19]. Thus, the costs of days absent from work were calculated using Swedish rates of pay for the jobs actually occurring in our material. That is, we assumed our sample to be representative concerning jobs for patients with severe haemophilia, and that if on-demand had been standard treatment in Sweden, Swedish patients would have had the same types of jobs as those found among the Norwegian patients. Days absent from school were assumed not to represent lost production if the absence did not imply a risk of delayed graduation. We had no evidence that that was the case for any of the individuals.

As most families in both Norway and Sweden own a car, the allowance granted for acquiring one was treated as a transfer payment and not as an extra cost to society [18]. Hence, we only considered measures taken to adapt a given car (installation of hand-operated speed and brake controls, extra-powered power steering, wheelchair lift, electrically-operated driver's seat, etc.) to the needs of the patient as costs of treatment.

We did not discount costs occurring at different ages for a given patient during our observation period. This was because our primary interest was to analyse differences between the strategies in the expected annual costs to society of treating the population of patients with severe haemophilia. Thus, although costs from the individual patient's perspective may arise at different ages depending on strategy (high costs when young under prophylaxis because of high annual factor-concentrate consumption vs. high costs when older under on-demand because of more invasive procedures), there is no such difference from society's perspective as there will always be patients of all ages.

Statistical methods

We used standard descriptive techniques to report on means, medians, standard deviations and quartiles. To further illustrate the importance of different sources of costs, we ranked patient-years according to the percentage of costs coming from factor-concentrate consumption.

Panel-data regression methods [20] were suitable for analysing the determinants of annual costs as they do not require all observations to be independent. The regression takes into account the fact that characteristics may vary both between patients and, for a given patient, over the study period. Formally, we estimated the random-effects model

$$c_{it} = \beta x_{it} + \theta u_i + e_{it} \qquad (1)$$

where c_{it} is the total cost for an individual i in year t, $\boldsymbol{x}_{it}$ denotes the vector of individual and treatment characteristics, $\boldsymbol{\beta}$ is the vector of coefficients to be estimated, and u_i and e_{it} denote the individual and observation specific residuals. A particular individual's annual costs are interdependent with a correlation term, θ, that is assumed to be constant, regardless of distance in time.

Initial analysis of the variable annual costs showed that the variation was greater for adults than for children and there were differences in the variation for the two strategies. Hence, in order to obtain the best fit for the regression model, four separate regressions were estimated: for each treatment strategy, we estimated one regression for children (0–11 years old) and one for adults (18+).

In particular, we were interested in the estimated vector of coefficients, $\hat{\beta}$; i.e. the marginal effect on the annual costs of a change in a particular variable, holding all other factors constant. Variables age and bodyweight were highly correlated and could not both be included in Eq. (1) without causing multicollinearity. Instead, we used age and the residual bodyweight, i.e. the individual's deviation from the average weight for a patient of that age, calculated from a regression of bodyweight on age.

We used an explorative design, meaning that all panel-data estimations started with a very general model, where we allowed all collected patient- and treatment-characteristics, past and present, to influence the annual cost (Table 2). The least significant variable was then rejected and the model re-runs. The procedure was repeated until all remaining variables were significant at conventional levels ($P < 0.05$).

Treatment history

The treatment regime during childhood and adolescence (age: 2–18 years) was hypothesized to influence costs of treatment also later in life. Four regimens were explored: no form of replacement therapy at all, on-demand treatment, old prophylaxis, and modern prophylaxis. The cut-off point between old and modern prophylaxis was here set

to infusions at least twice weekly for haemophilia A and at least once weekly for haemophilia B patients. In addition, we explored specifications of the time period both in terms of number of exposure months, and as percentages of the 2–18-year-old period.

Sensitivity analysis

The sensitivity of results to the fact that patients on on-demand and on prophylaxis had different age distributions was investigated by re-running regressions with the age-matched sample with patients born between 1949 and 1981. Since some of the prices used for the analysis were not competitive market prices, but rather negotiated prices (for instance wages and factor concentrate), they may not fully capture the societal costs of the resource use [18,21]. Thus, to investigate how sensitive the results were to the choice of price vector, we: (a) doubled the prices of all resources used within the health-care sector, except those of factor concentrate; (b) doubled the prices of all resources used outside the health-care sector; (c) assumed that all patients used the most expensive brand of factor concentrate; and (d) assumed that all patients used the least expensive brand of factor concentrate.

Severe haemophilia may also cause premature death, which is viewed as a cost to society in an economic evaluation. However, there is, to our knowledge, no epidemiological evidence in the literature that the mortality would differ between the two treatments strategies on which we could base our calculation. Instead, we have, hypothetically, calculated how much larger the annual risk of premature death would have to be under on-demand to make the annual costs equal to those incurred under prophylaxis. We have used the concept *value of a statistical life* (VOSL), i.e. the value society would attach to a reduction in the mortality risk by an amount large enough to save one expected life [22]. Given the average costs, C_{od} (on demand) and C_p (prophylaxis), the total number of patients, n, and an estimate of VOSL; the annual critical risk r ($0 < r < 1$) can be expressed as

$$n(C_{\mathrm{od}}) - rn(C_{\mathrm{od}}) + rn(\mathrm{VOSL}) = n(C_{\mathrm{p}})$$
$$\Rightarrow r = \frac{C_{\mathrm{p}} - C_{\mathrm{od}}}{\mathrm{VOSL} - C_{\mathrm{od}}} \qquad (2)$$

We used a recent Swedish estimate of VOSL (EUR 2.61 million) [23].

Finally, we investigated how sensitive our cost estimates would be to changes in prices and doses by calculating *cost-elasticities*. For example, the cost-elasticity, ε, with respect to the price, p, may be calculated using

$$\varepsilon = \frac{\partial C}{\partial p}\frac{p}{C} = \frac{\partial \ln C}{\partial \ln p} \qquad (3)$$

where C is the annual cost. Cost-elasticities were obtained from panel-data regressions of the annual costs on factor-concentrate price, prescribed dose kg^{-1}, and individual and treatment characteristics as independent variables.

Results

Descriptive statistics

The mean cost for an adult (18+) patient-year for on-demand was EUR 51 518 ± 36 035 (mean ± SD) and for prophylaxis EUR 147 939 ± 65 963 (590 and 504 patient-years for on-demand and prophylaxis, respectively). In Fig. 1, the mean cost is divided into three main sources of cost: factor concentrate, other health-care sector costs and costs in other sectors. It is evident that, for both strategies, factor concentrate was the major source of costs (74 and 94%, respectively). Both other health-care costs and costs in other sectors were greater for on-demand (EUR 1807 and 11 358, respectively) than for prophylaxis (EUR 1126 and 7530, respectively).

To illustrate the weight of the different costs sources, we ranked all adult (18+) patient-years according to their ratio of factor-concentrate costs to total costs for each strategy. We found that the median and interquartile range (IQR) of factor-concentrate costs to total costs were 89% (66–97%) for on-demand and 99% (94–100%) for prophylaxis. Table 4 shows the distribution of cost sources

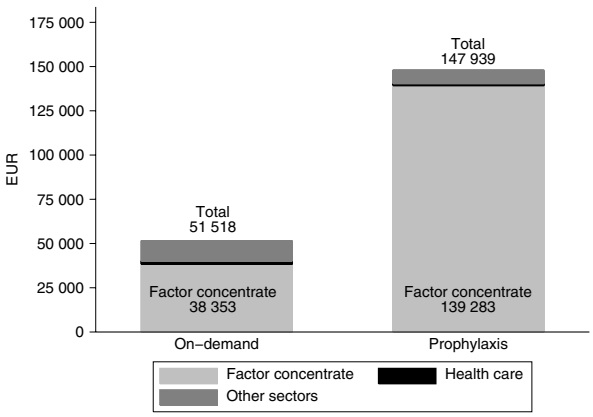

Fig. 1. Mean annual cost per patient-year for adults (18+) by different sources of cost.

Table 4. Mean costs within *first* quartile when patients were ranked by the proportion of factor-concentrate costs in total costs, i.e. patients with the lowest percentage of factor-concentrate costs to other costs; by different sources of costs.

	On-demand [EUR (%)]	Prophylaxis [EUR (%)]
Factor concentrate	30 835 (46.5)	97 615 (80.5)
Other health-care costs	2523 (3.8)	2127 (1.8)
Lost production	31 096 (46.9)	13 004 (10.7)
Other non-health-care costs	1874 (2.8)	8516 (7.0)
Total	66 327 (100)	121 263 (100)

in the quartile of patient-years with the *lowest* ratio of factor-concentrate costs to total costs. Also in this group where factor concentrate cost had the lowest relative importance, it was still dominant for prophylaxis. However, for on-demand patients, the cost of lost production was equal to that of factor-concentrate consumption. We also note that the cost of lost production for prophylaxis was 42% of that for on-demand patients.

Table 5 presents the costs of six major invasive procedures. As reported in our previous publication [5], most of the reconstructive surgery was performed on on-demand patients. In Table 5, we do not distinguish between treatment strategies, but report the cost of surgery by specific types of procedures. It may be noted that factor concentrate represented the major source of costs for five of the six procedures, ranging from 69% for knee and elbow prostheses to 81% for radioactive isotopes. This was true also for procedures where the median length of stay exceeded 11 days.

Panel-data analysis

Figure 2 shows the average predicted annual cost for on-demand and prophylactic treatment. For both strategies, there was a rather wide 95% prediction interval illustrating the within- and between-patient variation in the material. However, this may be compared with the precision in the *mean estimates* for a typical patient on either strategy. The average predicted annual cost for, for example, a 30-year-old on-demand patient was EUR 51 832 (95% CI: 44 324–59 341). The corresponding figures for the typical 30-year-old prophylaxis patient were EUR 146 118 (95% CI: 129 965–162 271). Hence, the expected annual costs were nearly three times higher for prophylaxis than for on-demand treatment.

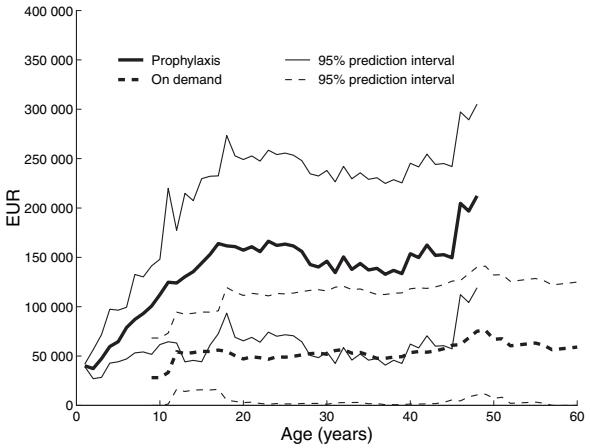

Fig. 2. Predicted average annual cost of on-demand and prophylaxis for patients with average individual and treatment characteristics. 95% prediction intervals illustrate the within- and between-patient variations.

Table 6 presents the final results from our four panel-data regressions. The coefficients are the variables' marginal effects in EUR on the predicted annual cost, i.e. the effect of increasing the variable by one unit, on average, holding all else constant. Hence, for children on prophylaxis and for adults treated on-demand, increasing a person's age by 1 year, would raise the costs by EUR 4213 and 919, respectively. In addition, weighing more than

Table 5. Costs and days of hospitalisation for major invasive procedures.

	Median (IQR)			
	Total cost	Surgery cost*	Factor-concentrate cost	Number of hospital days
Arthrodeses (ankle joint) ($n = 23$)	29 725 (23 642–33 257)	2296 (2155–2501)	22 050 (17 604–26 355)	15 (11–16)
Knee prostheses ($n = 31$)	31 580 (28 670–38 754)	2847 (2463–3078)	21 894 (19 231–28 847)	16 (14–16)
Elbow prostheses ($n = 9$)	26 659 (25 439–30 223)	2309 (2 155–2463)	18 343 (17 752–23 373)	11 (10–14)
Radioactive isotope ($n = 11$)	3673 (3612–4468)	NA	2959 (2367–3325)	3 (2–4))
Synovectomy ($n = 15$)	22 568 (21 841–25 804)	2155 (1885–2578)	17 160 (16 568–20 911)	10 (10–13)
Port-à-Cath† ($n = 13$)	5319 (5117–7991)	2252 (2252–2252)‡	2238 (1479–4413)	3 (3–3)

*Surgery cost for invasive procedures under anaesthesia based on time under anaesthesia.

†Both implantations and extractions.

‡The anaesthesia time for eight observations was missing and the average anaesthesia time in our sample was imputed for these.

Table 6. Panel-data regression of annual costs by generalized estimating equations (GEE) estimation procedure. Regressions estimated for on-demand treatment of children (8–17 years) in column (1) and of adults in column (2); and for prophylactic treatment of children (0–17 years) in column (3) and of adults in column (4). The coefficients reported in columns (1)–(4) are the respective estimates of the marginal effect in EUR on the predicted annual cost when the variable in the left column changes one unit. The starting model included in addition to the variables in the final model: dummy variables for haemophilia A and surgery during the year, and the continuous variables age at diagnosis and number of years since diagnosis as well as interactions between haemophilia A and all other variables. None of these were however significant at conventional levels.

	On-demand		Prophylaxis	
Variable	Children (1)	Adults (2)	Children (3)	Adults (4)
Age (years)		919.4***	4212.7***	
Residual body weight† (kg)			1210.0***	
Prescribed dose per infusion (in IU)	30.9***	33.9***	−39.7***	
Prescribed dose in IU per week			27.4***	24.9***
Low-frequency prophylaxis‡				23 495.3**
Prescribed dose per kg body weight (in IU)			546.4*	−1381.7**
Secondary prophylaxis‡	31 997.1***	35 073.1***		
Number of months between age 2 and 18 years old *without* factor-concentrate treatment		−125.7*		
Percentage of time between age 2 and 18 *without* replacement therapy for haemophilia A			30 143.3*	
Percentage of time between age 2 and 18 with old prophylaxis§				−69 289.9*
Constant	12 714.3	−10 406.2	2592.7	69 656.2***
Total number of observations	81	584	480	389
Number of patients	18	61	62	57
Average number of observations per patient	4.5	9.6	7.7	6.8
Wald	106.3***	104.9***	1571.0***	195.26***

†Residual body weight = individuals' actual bodyweight – predicted average bodyweight for that age (within sample).
‡Dummy variable taking the value 1 when the observation has the characteristic and 0 otherwise.
§Old prophylaxis defined as less than twice weekly for haemophilia A and less than once weekly for haemophilia B.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

children of the same age ('residual body weight') would increase the costs by EUR 1210 per extra kg for children on prophylaxis.

Several variables describing the prescription pattern were associated with the variation in the annual costs. For on-demand patients, increasing the prescribed dose per infusion by one IU raises annual costs by EUR 31 (children) and EUR 34 (adults). Also, patients on secondary prophylaxis have higher annual costs than other on-demand patients.

For prophylaxis patients, a combination of variables best described the association between prescription pattern and annual cost. For children, both a higher the dose per week and higher dose kg^{-1} were associated with higher annual costs, but those effects were balanced by the dose per infusion. Given a certain prescribed dose kg^{-1} and total dose per week, a higher dose *per infusion* (which would then be equivalent to being prescribed a fewer number of infusions per week) would reduce costs. The result may be illustrated by the following hypothetical example. Assume that an adolescent, who weighs 50 kg and takes infusions twice weekly, were to be prescribed an increase in the dose per infusion from 1250 to 1750 IU, all else being equal. This increase would also imply an increase from 25 to 35 IU kg^{-1} and an increase in the weekly prescribed dose by 1000 IU. Multiplying these changes with the coefficients for prescribed dose in column (3) in Table 6, we would obtain the predicted total effect on annual costs, $-39.7 \times 500 + 27.4 \times 1000 + 546.4 \times 10$, or an increase of EUR 13 014.

For adults on prophylaxis, increasing the dose per week would increase costs. Also, patients on low frequency prophylaxis (infusions only twice weekly for haemophilia A and only once weekly for haemophilia B) had higher costs than those prescribed more infusions per week, all else being equal. These two effects were balanced by the fact that adult patients who were prescribed a higher dose kg^{-1} had lower costs, all else being equal. Assume that an adult patient with haemophilia A, weighing 70 kg and prescribed 2000 IU per infusion twice weekly (i.e. low-frequency prophylaxis for haemophilia A), were to be prescribed 2500 IU per infusion instead. The predicted total effect on annual costs would then be an increase of EUR 38 526 ($24.9 \times 1000 + 23\,495.3 \times 1 - 1381.7 \times 7.14$).

	On-demand (SD)	Prophylaxis (SD)
Total annual cost	51 518 (36 035)	147 939 (65 963)
Double prices in health-care sector (not factor concentrate)	53 325 (37 662)	149 065 (66 195)
Double prices in other sectors	62 876 (47 050)	155 469 (71 782)
All patients use most expensive factor-concentrate brand	65 811 (45 777)	190 736 (83 481)
All patients use cheapest factor-concentrate brand	45 013 (31 656)	118 835 (52 328)

Table 7. Sensitivity analysis of prices for adults only: mean annual total costs by different prices, all else equal (in EUR).

Treatment between ages 2 and 18 affected present costs, but in ambiguous directions. For adult on-demand patients, each month without replacement therapy between age 2 and age 18 reduced the annual present costs by EUR 126. For children with haemophilia A, on prophylaxis, present costs would fall by EUR 301.4 for each percentage unit of time between age 2 and age 18 that they received replacement therapy (1/100 of 30 143.3). For adults on prophylaxis, present costs fell by EUR 692.9 with each percentage unit of time between age 2 and age 18 that they had been on 'old' prophylaxis.

Sensitivity analyses

Regressions were re-run with age-matched samples. The estimated coefficients for adult on-demand patients were in all essentials equal when we excluded the five on-demand patients born before 1949. Excluding prophylaxis patients born after 1981 reduced the sample for children on prophylaxis from 480 to 134 observations and, as expected, several of the variables became insignificant. However, the dominant variable, 'prescribed dose in IU per week' did not change. Moreover, the plotted predictions were virtually indistinguishable from those in Fig. 2.

The impact of changes in the prices is reported in Table 7. The first row reproduces the results in our base case: mean total annual cost for adults on on-demand and prophylactic treatment, respectively. The result that prophylaxis is the more costly of the strategies is apparently unaffected by these rather substantial hypothetical price changes.

However, the cost relations might change if the risk of premature death were higher for patients under on-demand than under prophylaxis. Using our benchmark results [row (1) in Table 7], the annual risk of premature death under on-demand treatment would have to be 3.7 percentage units larger than under prophylaxis to equalize the expected annual costs of treatment between the strategies, given that the VOSL [22] is EUR 2.61 million [23].

Table 8. The elasticity (sensitivity) of annual costs with respect to the price of factor concentrate and to the prescribed dose kg^{-1}.

	Cost-elasticities	
	On-demand (95% CI)	Prophylaxis (95% CI)
Price of factor concentrate	NA*	1.11 (0.66–1.58)
Prescribed dose kg^{-1}	0.90 (0.57–1.22)	0.47 (0.35–0.60)

*Elasticitity could not be estimated since 99.5% used the same brand of factor concentrate.

The cost-elasticities with respect to price and prescribed dose of factor concentrate are reported in Table 8. For prophylaxis, the cost-elasticity with respect to the prescribed dose kg^{-1} was smaller than one implying that the proportionate change in costs would be smaller than that in the prescribed dose kg^{-1}. For example, reducing the prescribed dose kg^{-1} by 10% from the average 27.9–25.1 IU kg^{-1}, would reduce the annual cost by about 5%. For on-demand, this elasticity was not significantly different from one indicating proportionate changes in costs and dose kg^{-1}. The cost-elasticity with respect to the *price of factor concentrate* could not be estimated for on-demand since in principle all patients used the same brand of FVIII and FIX concentrate, respectively. For prophylaxis, this elasticity was not significantly different from one, implying that a 10% reduction in factor-concentrate prices would lead to a 10% reduction in annual treatment costs.

For neither treatment we could establish any significant effect of the price of factor concentrate on the number of IUs of factor concentrate consumed.

Discussion

The main result from our analysis was that Swedish prophylactic treatment was significantly more costly than Norwegian on-demand treatment. The magnitude of the overall difference may be captured by the respective predictive average costs (obtained from panel-data regressions) of treating a 30-year-old

patient with typical individual and treatment characteristics: EUR 51 832 (on-demand) and EUR 146 118 (prophylaxis).

Factor concentrate was the single greatest source of costs for both treatments: 77% for on-demand and 95% for prophylaxis, respectively, based on all patient-years. However, on-demand treatment as described from Norway and prophylaxis as described from Sweden, differed both in the prescribed dose kg^{-1} (median for adults 14 and 28 IU kg^{-1}, respectively); and in total annual consumption of replacement factor (median for adults 55 000 and 211 000 IU, respectively) [5]. Thus, we apparently compared high-dose prophylaxis with a relatively low-dose on-demand treatment. Given the role of factor concentrate costs in total costs, the cost differences reported here were bigger than, for instance, what would be expected for intermediate prophylaxis and a more intensive on-demand therapy [24].

Costs for other resources than factor concentrate within the health-care sector (other than factor concentrate), as well as costs in other sectors, were greater for on-demand than for prophylaxis. The most important source of costs in other sectors was lost production: 92% for on-demand and 60% for prophylaxis. Thus, our results confirmed those of previous studies [2,12,14]. However, the results on the size of different cost sources reported from simulations by Miners *et al.* [14] are not directly comparable to ours, since their analysis did not separate the factor-concentrate cost from surgery cost as we have done. Nevertheless, since other costs were small in comparison for both treatments, the greater costs of resources other than factor concentrates incurred under on-demand did not match up to the higher factor-concentrate costs under prophylactic treatment. Our results were robust in that our sensitivity analysis did not change the overall ranking of the treatment alternatives.

The panel-data analysis showed, among other things, that adult on-demand patients cost less the longer the period *without* replacement therapy during childhood and adolescence. One explanation for this less intuitive result may be that patients who started replacement therapy later have a mild bleeding phenotype and therefore also had fewer costly haemorrhages during our period of investigation.

Adult prophylaxis patients cost less the longer their period of old prophylaxis (defined as infusions less than twice weekly for haemophilia A and less than once weekly for haemophilia B) during childhood and adolescence. These could similarly belong to a mild bleeding phenotype, although it has to be underlined that when most adult prophylaxis patients were young, modern 'high-dose' prophylaxis was not yet developed.

We were unable to demonstrate any significant effect of modern prophylaxis during childhood and adolescence on annual costs when the patients became adult, probably because of the fact that few of the adult patients were young enough to have experienced any longer periods of modern prophylaxis during childhood and adolescence. Alternatively, patients with a more severe bleeding phenotype may have been over-represented among patients who were the first to be treated with modern prophylaxis. In that case, an early start of modern prophylaxis may be a marker for phenotype that, *per se*, would be associated with higher factor-concentrate consumption and cost.

Our sensitivity analysis showed that the main patterns did not change when the oldest on-demand patients and youngest prophylaxis patients were omitted. Hence, the study design with a non–age matched sample did not affect the results.

We have not found any evidence of potential differences in life expectancy between on-demand and prophylaxis. The life-long effects of replacement therapy are obviously not yet fully analysable although one study from Canada found a life expectancy close to that of the general population for HIV-negative haemophiliacs [25]. Our figure for the hypothetical difference in mortality between the treatment strategies at which the average cost of treatment would balance may then be compared to future evidence on actual mortality.

Our results may have important consequences for medical decision-making. Individual tailoring of dose [7] has a clear potential to reduce factor-concentrate consumption and cost. A later start of prophylaxis in patients with mild bleeding phenotype and a change to on-demand treatment in some adult prophylaxis patients would be other important considerations in order to reduce cost without jeopardizing quality [1]. Brands with the lowest price might also be used, provided that the quality of the products is not compromised; looking at the data, there was a clear tendency to prescribe low- or medium-priced brands of replacement factor.

A thought-experiment with respect to prices following our results is: 'At what price of factor concentrate would the average cost of on-demand and prophylaxis be equal?' Assuming that patients consume the number of IUs they do in our material, the price would then have to be 6 Euro cents per IU, which does not seem very realistic today. The actual Swedish (year 2000) price range was 49–81 Euro cents.

The cost-per-patient estimates were based on successful long-term continuous treatment. Hence, inhibitor patients were excluded. The risk of developing inhibitors should not differ between the strategies [26–29] implying that the exclusion of these patients would not affect the cost-differences. Patients who had developed HIV/AIDS and hepatitis C were included, although the costs of treating these diseases *per se*, were not. This was partly because there seems to be no difference between the strategies in the risk of contracting HIV/AIDS (thus, these costs would not affect the cost-differences), and partly because of new viral-safe factor concentrates [5,10,30].

Health care is tax financed in Norway and Sweden. To get an idea of how much treatment of haemophilia costs per taxpayer, we have made an illustrative example where we only consider the costs that arise within the health-care sector (78% for on-demand and 95% for prophylaxis) since they may be related to the health-care taxes paid. We also assume for simplicity that all taxpayers would pay an equal share of the cost of haemophilia treatment. What would then each taxpayer pay for haemophilia treatment and what would the share of the tax on the median income allocated to haemophilia treatment? There were 7 million taxpayers in 2002 and 254 persons were diagnosed with severe haemophilia in Sweden (spring 2003). Providing on-demand treatment for all 254 patients would cost the health-care sector EUR 10.3 million while prophylaxis would cost EUR 35.2 million per year. The lump sum cost per taxpayer would then be EUR 1.5 (on-demand) or EUR 5 (prophylaxis). The median income for men and women aged 20+ was EUR 22 187 (year 2002, Statistics Sweden) and the average health-care tax rate was 10.71% (year 2002, Statistics Sweden). The proportion of health-care taxes for the median income person would then be 0.06% for on-demand and 0.21% for prophylaxis.

Our results may, after some adjustments, be used in other countries. For instance, the prices and prescribed quantities of factor concentrates may differ and, therefore, the elasticities derived here are useful. For *prophylaxis*, the cost-elasticity with respect to factor price indicates that if prices were 10% higher than in Sweden (i.e. 68 Euro cents per IU instead of the Swedish average of 62 Euro cents per IU), the annual costs of prophylaxis would be 11% higher than our reported estimate (i.e. EUR 162 191 instead of EUR 146 118) provided that the prophylaxis regime was otherwise the same as in Sweden. It was not possible to estimate the cost-elasticity with respect to the price of factor concentrate for *on-demand treatment*, since prices did not vary enough as only 0.5% used a brand other than the dominant FVIII and FIX concentrates.

Cost-elasticities with respect to dose kg^{-1} per infusion could be estimated for both treatments. Increasing the dose kg^{-1} per infusion for on-demand, would increase the cost of treatment by nearly the same proportion, at least within the ranges of IU kg^{-1} per infusion reported from Norway (IQR 12.5–16.3 IU kg^{-1}). Care is needed when extrapolating outside these limits.

Twenty-five percent of the Swedish adult prophylaxis patients were prescribed doses equivalent to those on intermediate-dose prophylaxis. For prophylaxis, a reduction in the average prescribed dose kg^{-1} from the Swedish median 28 IU kg^{-1} to, for instance, 21 (i.e. a reduction by 25%), would reduce total cost by about 12%, all else being equal. The proportionally smaller cost-reduction might then be a result of an increase in haemorrhaging, thereby causing costs both within the health-care sector and in other sectors.

A study by Fischer *et al.* [31] compared the intermediate dose prophylaxis in the Netherlands with the Swedish regimen and, although the low-dose prophylaxis implied significantly more haemorrhages, they were unable to detect any significant difference in joint status. However, a longer follow-up period might change the latter result. An on-going study in Canada may in the future provide more evidence of the extent of differences in joint status between different prophylaxis regimens [32].

We conclude that the cost of prophylaxis was nearly three times higher than those of on-demand treatment. However, costs alone do not provide sufficient information for a choice between the two strategies, since we know from the literature [5–13] that prophylaxis also produces better health and improved quality of life. Combining this cost analysis with an estimated value of quality of life produced by the respective treatment strategies, as reported from the contingent valuation study in our project [16], then provides a comprehensive health-economic analysis of on-demand and prophylactic treatment strategies for severe haemophilia.

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References

1 Berntorp E, Astermark J, Björkman S *et al.* Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; **9**(Suppl. 1): 1–4.
2 Aledort L, Hashmeyer R, Pettersson H, Group at OOS. A longitudinal study of orthopaedic outcomes for severe factor VIII-deficient haemophiliacs. *J Intern Med* 1994; **236**: 391–9.
3 Nilsson I-M. *Hemophilia*. Stockholm, Sweden: Pharmacia Plasma Products, 1994.
4 Ljung R, Aronis-Vournas S, Kurnik-Auberger K *et al.* Treatment of children with haemophilia in Europe: a survey of 20 centres in 16 countries. *Haemophilia* 2000; **6**: 619–24.
5 Steen Carlsson K, Höjgård S, Glomstein A *et al.* On-demand vs. prophylactic treatment for severe haemophilia in Norway and Sweden: differences in treatment characteristics and outcome. *Haemophilia* 2003; **9**: 555–66.
6 Berntorp E. Methods of haemophilia care delivery: regular prophylaxis versus episodic treatment. *Haemophilia* 1995; **1**(Suppl. 1): 3–7.
7 Carlsson M. *Pharmacokinetic Dosing of Factor VIII and Factor IX in Prophylactic Treatment of Haemophilia, in Department for Coagulation Disorders (Department of Medicine)*. Malmö, Sweden: Lund University, 1997.
8 Kasper C, Dietrich S, Rapaport S. Hemophilia prophylaxis with factor VIII concentrate. *Arch Intern Med* 1970; **125**: 1004–9.
9 Petrini P, Lindwall N, Blombäck M. Prophylaxis with factor concentrates in preventing hemophilic arthropathy. *Am J Pediatr Hematol Oncol* 1991; **13**: 280–7.
10 Nilsson I, Berntorp E, Ljung R, Löfqvist T, Pettersson H. Prophylactic treatment of severe hemophilia A and B can prevent joint disability. *Semin Hematol* 1994; **31**(Suppl. 2): 5–9.
11 Ross-Degnan D, Soumerai S, Avorn J, Bohn R, Bright R, Aledort L. Hemophilia home treatment. Economic analysis and implications for health policy. *Int J Technol Assess Health Care* 1995; **11**: 327–44.
12 Miners A, Sabin C, Tolley K, Lee C. Primary prophylaxis for individuals with severe haemophilia: how many hospital visits could treatment prevent? *J Intern Med* 2000; **247**: 493–9.
13 Schramm W, Royal S, Kroner B *et al.* Clinical outcomes and resource utilization associated with haemophilia care in Europe. *Haemophilia* 2002; **8**: 33–43.
14 Miners A, Sabin CA, Tolley K, Lee C. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. *Pharmacoeconomics* 2002; **20**: 759–74.
15 Steen Carlsson K, Höjgård S, Lethagen S, Berntorp E, Lindgren B. Economic evaluation: What are we looking for and how do we get there? *Haemophilia* 2004; **10**(Suppl. 1): 44–9.
16 Steen Carlsson K, Höjgård S, Lethagen S, Lindgren A, Berntorp E, Lindgren B. Willingness to pay for on-demand and prophylactic treatment for severe haemophilia in Sweden. *Haemophilia* 2004; **10**: 527–41.
17 Goudemand J. Treatment of patient with inhibitors: cost issues. *Haemophilia* 1999; **5**: 397–401.
18 Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford Medical Publications, Oxford, UK: Oxford University Press, 1997.
19 Becker G. *Human Capital. A Theoretical and Empirical Analysis, with Special Reference to Education*, 2nd edn. New York, NY: National Bureau of Economic Research, 1975.
20 Baltagi B. *Econometric Analysis of Panel Data*. New York, NY: Wiley and Sons, 1995.
21 Zerbe R, Dively D. *Benefit-Cost Analysis in Theory and Practice*. New York: Harper Collins, 1994.
22 Viscusi K. *Fatal Tradeoffs: Public and Private Responsibilities for Risk*. Oxford, UK: Oxford University Press, 1992.
23 Persson U, Norinder A, Hjalte K, Gralén K. The value of a statistical life in transport: findings from a new contingent valuation study in Sweden. *J Risk Uncertainty* 2001; **23**: 121–34.
24 Fischer K, van der Bom J, Molho P *et al.* Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia* 2002; **8**: 745–52.
25 Walker I, Julian J. Causes of death in Canadians with haemophilia 1980–1995. *Haemophilia* 1998; **4**: 714–20.
26 Addiego J, Kasper C, Abildgaard C *et al.* Frequency of inhibitor development in hemophiliacs treated with low-purity factor VIII. *Lancet* 1993; **343**: 462–4.
27 Bray G, Gomperts E, Courter S, Gruppo R, Gordon E, Manco-Johnson M, *et al.* A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with

hemophilia A. The Recombinate Study Group. *Blood* 1994; **83**: 2428–35.
28 Lusher JM, Arkin S, Abildgaard CF, Schwartz RS, The Kogenate Previously Untreated Patient Study Group. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A – safety, efficacy, and development of inhibitors. *N Engl J Med* 1993; **328**: 453–9.
29 Nilsson I, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Inter Med* 1992; **232**: 25–32.
30 Berntorp E, Hansson B, Böttiger B *et al.* HIV seroconversion in Swedish haemophiliacs: relation to type and dosage of factor concentrate. *Eur J Haematol* 1987; **38**: 256–60.
31 Fischer K, Astermark J, Van Der Bom JG *et al.* Prophylactic treatment for severe haemophilia: comparison of an intermediate-dose to a high-dose regimen. *Haemophilia* 2002; **8**: 753–60.
32 Manco-Johnson MJ, Blanchette VS. North American prophylaxis studies for persons with severe haemophilia: background, rationale and design. *Haemophilia* 2003; **9**(Suppl. 1): 44–9.

