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On-demand vs. prophylactic treatment for severe haemophilia in Norway and Sweden: differences in treatment characteristics and outcome

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Summary. Using an 11-year panel of 156 Norwegian and Swedish patients with severe haemophilia, and including retrospective case-book data from birth, we compared the differences in the haemophilia-related resource use between on-demand and prophylactic treatment. Patients treated on-demand had more surgery (arthrodeses, prostheses implantations and synovectomies) and more days lost from work. Median annual factor-concentrate consumption among adults (18+) was 211 000 IU [interquartile range (IQR) 154 000–268 000] or 3 024 IU kg^{-1} $year^{-1}$ for patients on prophylactic treatment and 55 000 IU (IQR 28 000–91 000) for on-demand patients (780 IU kg^{-1} $year^{-1}$). This was partly explained by the fact that the median dose per kg body weight was twice as great 28, (IQR 24–32) for prophylaxis compared with 14 (IQR 12–16) for on-demand. Prescribed dose per kg body weight was found to be an important factor explaining the variation in total annual factor-concentrate consumption per patient for both types of treatment. Other variables included in the panel-data regression analysis were the number of weeks on secondary prophylaxis for on-demand patients and age, body weight and type of haemophilia for children (0–17 years) on prophylaxis. Differences were consistently substantial and will affect both costs and benefits of the two treatment strategies.

Keywords: days lost from work, factor-concentrate consumption, haemophilia-related surgery, longitudinal data, treatment characteristics, treatment strategy

Introduction

The introduction of replacement therapy with factor concentrate in the mid-1950s changed the prospects for patients with haemophilia A and B, especially for patients with severe haemophilia (factor VIII/IX activity <1%). Replacement therapy increases both life-expectancy and quality of life [1–4]. It may also expand the individual's range of choices, i.e. increase both the possibilities of participating in the labour market and the range of possible professions. Two alternative treatment strategies have developed: on-demand treatment and prophylactic treatment. Both strategies can be hospital-based or home-based when the latter may be more convenient for the patient.

On-demand treatment implies that the patient is given concentrates of the deficient factor as soon as a haemorrhage occurs [5,6]. This can stop smaller haemorrhages from developing into larger ones, but cannot fully prevent the development of haemophilic arthropathy with chronic clinical symptoms [5]. On-demand treatment also includes limited periods of prophylactic treatment (secondary prophylaxis) in connection with operations, physiotherapy, during periods with severe haemorrhages, and sometimes also in connection with patient-initiated activity.

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Under *prophylactic treatment*, the patient receives doses of factor concentrate on a regular basis, starting early in life and continuing into adulthood. If successful, this strategy could change the status of the disease to a milder form, thereby preventing spontaneous joint haemorrhages and subsequent arthropathy [5]. In both cases the intensity [IU per kg bodyweight per injection (kg^{-1})] may vary. Two types of prophylactic treatment may also be distinguished: high-dose treatment (25–40 IU kg^{-1} per injection) and intermediate-dose treatment (15–25 IU kg^{-1}) [6–10].

On-demand treatment seems to be standard practice in most countries [1,6,11,12]. However, several studies have shown that patients on prophylactic treatment have fewer haemorrhagic episodes, less-rapid deterioration of joints, fewer days spent in hospital, and fewer days lost from work or school [1,5,6,11,13–20]. Hence, it has been suggested that the main reason for the choice of strategy is the high costs of factor-concentrate consumption under prophylactic treatment [6,21–23]. Nevertheless, it has been found that the amounts of factor concentrate vary considerably in both strategies, and that patients with on-demand treatment in some cases consume annual amounts of factor concentrate as large as those received by patients on prophylaxis [6,11,20,24]. There may be several reasons for these diverging results. Some studies included patients with milder forms of haemophilia. Moreover, even if only patients with severe haemophilia were included, they may have been selected into a particular strategy because of their haemorrhage pattern or other personal characteristics. Finally, both strategies may vary in design (home or hospital treatment, intensity of dosage and, for prophylaxis, frequency of prescribed injections).

Accordingly, there is a continuous interest in evaluating the on-demand and prophylactic treatment strategies with respect to treatment characteristics, outcomes, and costs. Our on-going project 'Treatment strategies for severe haemophilia – on demand versus prophylaxis' was formed with the overall aim of evaluating the costs and benefits of on-demand and prophylactic treatment. To do this, (i) we included only patients with severe haemophilia; (ii) used strict definitions of on-demand and prophylactic treatment; (iii) used population data from two countries to avoid selection bias; (iv) collected detailed data from birth up to 1999 (treatment characteristics and resource use) on each patient; and finally (v) used panel-data regression models to account simultaneously for several factors in the statistical analysis.

This article focuses on the differences in resource use measured in *physical quantities*. Future articles will calculate and analyse the costs of these resource-use differences, as well as relating it to estimated benefits in monetary terms. Adopting the societal perspective, differences both in the amount of resources consumed within the health-care sector (factor concentrate, surgery, etc.) and in the effects on other sectors of society (labour-market participation, absence from work or school due to haemorrhaging, consumption of community services, etc.) were studied. In addition, variations within each strategy with respect to detailed treatment and patient characteristics were analysed.

Materials and methods

Study population

All patients with severe haemophilia (factor VIII/IV activity < 1%) in Norway and Sweden meeting the inclusion and exclusion criteria (Table 1) were included in the study; i.e. it is a population study. To avoid selection bias (confounding factors) from patients being selected into a particular treatment strategy because of their haemorrhage patterns, we used data from Norway where on-demand has been the standard treatment for severe haemophilia, and

Table 1. Selection criteria for Swedish and Norwegian patients, respectively. Patients were excluded if at least one inclusion criteria was *not* met or at least one exclusion criteria was met.

	Answer
Prophylaxis patients	
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 31-12-1988	Yes
Patient had developed inhibitors against factor VIII or IX	Yes
On-demand patients	
Inclusion criteria	
Severe haemophilia A or B	Yes
Born between 1939 and 1981	Yes
Treated on demand	Yes
Signed patient information	Yes
Exclusion criteria	
Ad mortem after 31-12-1988	Yes
Patient had developed inhibitors against factor VIII or IX	Yes

from Sweden, which has a long history of prophylaxis as the standard treatment. Sweden and Norway were chosen also because of the similarities in the institutional framework (social services, health-care organization, labour-market structure, etc.). This was important, particularly as we included resource use outside the health-care sector.

Prophylactic treatment was defined as primary prophylaxis, meaning regular injections of factor concentrate at least twice weekly for haemophilia A patients and at least once weekly for haemophilia B patients. On-demand treatment was defined as injections when haemorrhaging occurred but also included periods of prescribed secondary prophylaxis. Swedish patients born before 1949 were excluded because of their initial long period of non-prophylactic treatment. Norwegian patients born after 1981 were excluded because prophylaxis was introduced for younger patients in the early 1990s. Patients born before 1939 were excluded because we wanted to reduce the impact of age differences on resource use.

Patients who had developed inhibitors were excluded, as their use of factor concentrate was not representative for either type of treatment. The incidence of long-standing, high-titre inhibitors seems to be comparable in most major studies whereas more low-titre and transient inhibitors are detected in prospective studies with a more frequent sampling schedule [25–28].

Patients with hepatitis C and HIV/AIDS were not excluded, as the treatment of haemophilia *per se* does not change according to our experience. There seems to be no difference between the strategies in the risk of contracting these diseases [16,29]. Rather, the risk of infection has been associated with the brand of factor concentrate and the time period when the concentrate was produced. The heat inactivation of FVIII concentrates was introduced in 1983 and no patient has been infected with HIV since 1985 [29].

We screened 85 patients in Norway and 168 patients in Sweden (Table 2). Fourteen patients in Norway were excluded because they were not prescribed on-demand treatment during the whole period, had developed inhibitors or had migrated during the period. Fifty-eight patients were excluded for the corresponding reasons in Sweden. A few patients declined participation, 10 in Norway and 15 in Sweden.

Table 2. Included patients, excluded patients and drop-outs due to different reasons.

	On demand	Prophylaxis
Number of patients screened	85	168
Final number of patients	61	95
Exclusions and drop-outs		
Inhibitors	8	21
Not prophylaxis/on demand according to inclusion criteria	4	20
Not willing to participate	10	15
Other	2*	17†
Total	17	73

*Migration (1) and other complicating factors that affect treatment contents (1).

†Migration (12); other complicating factors that affect treatment content (3) and liver transplantation removing haemophilia (2).

Patient and treatment data

Table 3 shows the standardized protocol we used in the data collection. We collected detailed annual data on resource use within the health-care sector for the period 1989–1999 retrospectively from clinical records. The relatively long period of 11 years was chosen because single rare events (such as invasive procedures) for individual patients might have a large impact on the resource use for a given year. Data on treatment history from birth to 1989 was collected to enable the analysis of the effect of treatment characteristics at all stages in life on present resource use. Detailed annual data on resource use outside the health-care sector for the period 1989–1999 was generated by telephone interviews with the patients and their relatives (Table 3, part 3 and 4).

All data was registered by research nurses at each participating centre: Karolinska Hospital (Stockholm), Malmö University Hospital (Malmö) and Sahlgrenska University Hospital (Gothenburg), all in Sweden, and the Institute for Hemophilia (Oslo) in Norway. To assure that data was generated in a coherent way across the centres and to reduce the potential sources of errors, a new electronic data input form was developed for the project.

Finally, the data-generation process was continuously monitored by two research nurses at Malmö University Hospital in collaboration with health economists at Luche.

The study was approved by Ethics committees at all the participating centres.

Statistical methods

We used standard descriptive techniques to report on mean, median, standard deviations and quantiles, and non-parametric Mann–Whitney tests [30] of differences in distributions. Panel-data methods [31] were used in the analysis of variations in factor-concentrate consumption in order to account for the

Table 3. 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 injection when bleeding) during on-demand treatment
4 Prescribed dose of factor concentrate (IU per injection) during prophylaxis
5 Frequency of prophylaxis (injections 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, who is interviewed
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) due to 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 due to the patient's haemorrhagic episodes

fact that characteristics may vary both between patients and, for a given patient, over the study period.

Panel-data methods differ from ordinary multiple regressions in that they do not require the observations to be independent. The random-effects model is a special one in which each individual has his own random level around which the annual amount of factor concentrate varies independently. This leads to a covariance structure, where the annual variations for different individuals are independent but where a particular individual's annual amounts of factor concentrate are dependent on each other with a correlation term that is constant, regardless of distance in time.

The probit-regression technique was used when the analysis included a binary dependent variable [32]. Both having had major surgery at least once during the 11-year period and having had at least one long period of loss of working time were defined as binary variables.

The aim of both the panel-data and the probit analysis was to analyse the effect of a factor believed to influence the dependent variable (for instance, annual factor-concentrate consumption or having had major surgery) in the presence of all other factors. The regression methods were then used to disentangle, for instance, how much an increase in the patient's age would affect annual factor-concentrate consumption when type of haemophilia, body weight and dose per kg were also accounted for.

We used an explorative design, so that all panel-data and probit estimations started with a very general model, where we allowed all collected patient and treatment characteristics, past and present, to influence (Table 3). The least significant variable was then rejected and the model re-run. The procedure was repeated until all remaining variables were significant at conventional levels. For the panel-data models, we used a Hausman specification test [33] of parameter stability to check whether the model could be rejected because of specification error/correlation between independent variables and error term.

Results

Patient characteristics

Table 4 gives some background characteristics for the included patients. The majority of patients had haemophilia A. The median age at diagnosis was

Table 4. Background characteristics for the 156 patients.

	On demand	Prophylaxis
	Number of patients	
Total	61	95
Haemophilia A	52	81
Haemophilia B	9	14
	Median (IQR)	
Age as on 31-12-1999	35 (27–46)	23 (14–33)
Age at diagnosis	1 (0.5–1.6)	0.8 (0.4–1.2)
Age at start of factor-concentrate treatment	1.5 (0.8–5.3)	1.1 (0.7–3)
Age at start of prophylactic treatment	–	2.9 (1.8–6.5)
Body-weight (adult individuals 19+ as on 31-12-1999)	78 (68–85)	75 (69–82)

IQR, interquartile range.

about 3 months lower in the prophylaxis population, but as there was a large variation in both populations, the difference was not statistically significant. Nearly all prophylaxis patients had had an initial period of on-demand treatment and the median age at the start of treatment was lower in the prophylaxis population. However, the median age for start of prophylactic treatment in the prophylaxis group was about 3 years [interquartile range (IQR) 1.75–6.5]. Finally, the median body weight in the adult part of the respective population was very similar.

Physical quantities

Prophylactic treatment was associated with a higher annual consumption of factor concentrate (Figs 1–3); fewer and different types of invasive procedures as well as less hospitalization (Table 5) and less/no time lost from work (Table 6, Fig. 4).

Figure 1 shows the distributions of total annual factor-concentrate consumption per patient in the

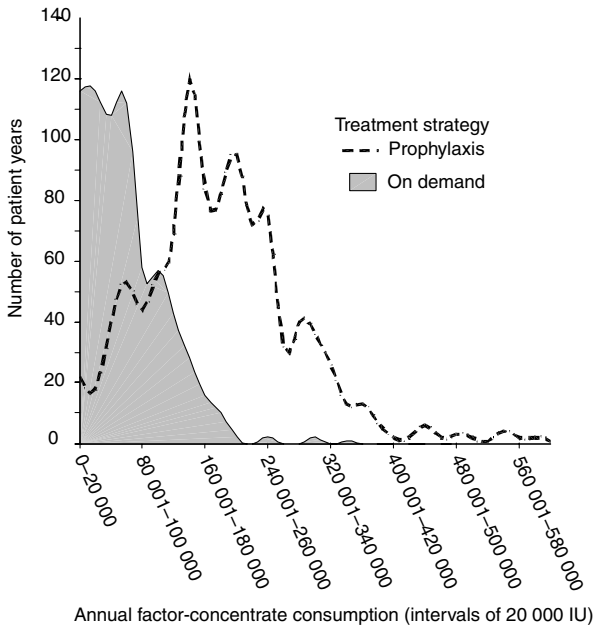

Fig. 1. Distributions of total annual factor-concentrate consumption in international units (data pooled for 1989–1999).

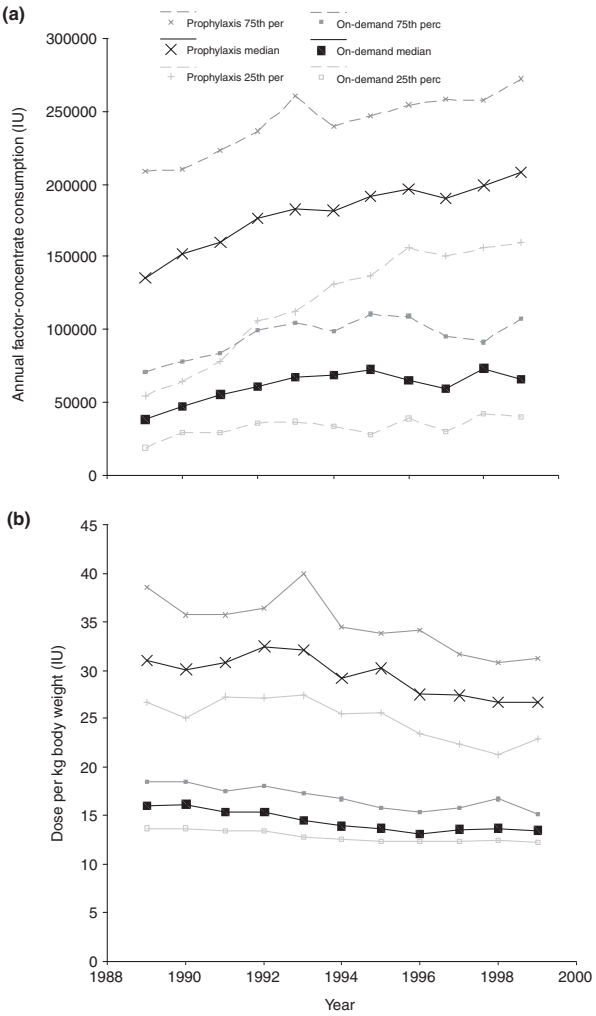

Fig. 2. (a) Annual total factor-concentrate consumption for all individuals. (b) Dose per kilogram body weight in the pooled sample.

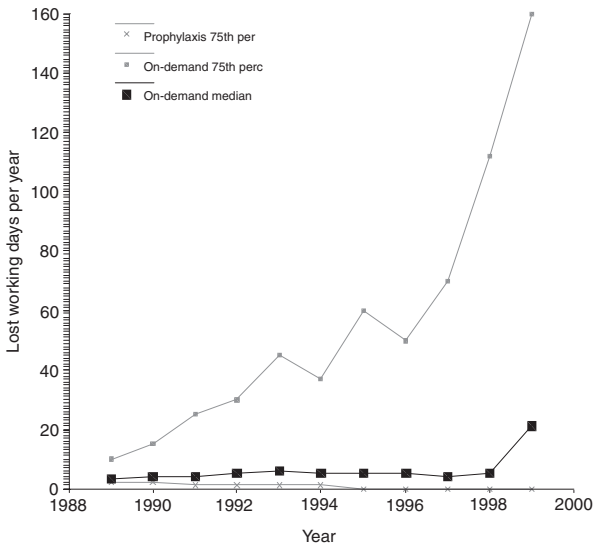

Fig. 3. Number of days lost from work or school.

pooled data-set for the respective treatment strategies. Both distributions were skewed to the left with a thin tail out on the right, representing a few observations with very high consumption. The two distributions were significantly different ($Z = -26.35$; $P < 0.001$).

Figure 2a shows the median and 25th and 75th percentiles of annual consumption of factor concentrate over the period 1989–1999. The two treatment strategies were significantly different both for every single year and jointly for the whole period ($P < 0.001$). The median annual factor-concentrate consumption in the prophylaxis population was about three times as large as for the on-demand patients when we pooled children and adults. In most years, 75% of the on-demand population had lower annual factor-concentrate consumption than the lowest 25% of the prophylaxis population.

The median dose per kg per injection for prophylaxis patients was about twice as great as that for on-demand patients, which is illustrated in Fig. 2b. The differences were again significant for each year as well as jointly ($P < 0.001$). For adults, the median total IU kg^{-1} per annum was for prophylaxis 3 024 IU (IQR 2 328–3 864) and for on demand 780 IU (IQR 400–1 303).

Table 5 presents the pooled number of days of hospitalization (without invasive procedures) and the pooled number of invasive procedures for the respective treatment strategies for the period 1989–1999. Dividing hospital days and invasive procedures by group size, we found half as many hospital days per patient in the prophylaxis group compared with the on-demand group. The number of invasive procedures divided by group size was also lower in the prophylaxis group (0.51) than in the on-demand group (1.98). The number of major surgical procedures occasioned by haemophilia was, for prophy-

Table 5. Total number of days of hospitalization (without invasive procedures) and total number of invasive procedures in the data set pooled for the whole period 1989–1999 by different types*.

	On demand	Prophylaxis
Total number of hospital days (all patients)	320	246
Number of days divided by group size	5.25	2.59
Total number of invasive procedures		
Arthrodeses	21	3
Prostheses implantations/extractions	42	4
Synovectomies	13	2
Radioactive isotope	12	
Port-á-Cath implantations/extractions		13
Percuseal port implantations/ extractions		3
Arthroscopies	1	3
CAP. Radii. resections	3	
Tooth extractions	21	8
Nose surgery	1	2
Extraction of osteophytes and free bodies	4	3
Others	3†	7‡
Total number of procedures 1989–1999	121	48
Number of procedures divided by group size	1.98	0.51

*During our period of investigation, 15 liver biopsies were made on prophylaxis patients as part of another study [35] but were not here considered as a consequence of the chosen treatment strategy.
†Others included arthrolysis (1), fistula operation (1), knee surgery (1), knee injections (2) and extraction of Hoffman's instrument (2).
‡Others included extirpation of pseudo tumour (1), hand surgery (1) and revision of pseudo aneurysm in elbow (1).

Table 6. Employment status per 31 December 1999 in numbers and as percentage of adult population (19+).

Employment status as on 31-12-1999	On demand, *n* (%)	Prophylaxis, *n* (%)
Employed	34* (57)	36† (68)
Student	4 (7)	8 (15)
Unemployed	2 (3)	2 (4)
100% sick leave‡/early retired	20 (33)	5 (9)
Total	60 (100)	51 (96)§

*Includes five patients who were 50% early retired or on 50% sick leave.
†Includes two patients who were 50% early retired or on 50% sick leave.
‡'Sick leave' only includes spells with a duration of at least 2 months.
§We lack information on two patients; one of whom died in 2000.

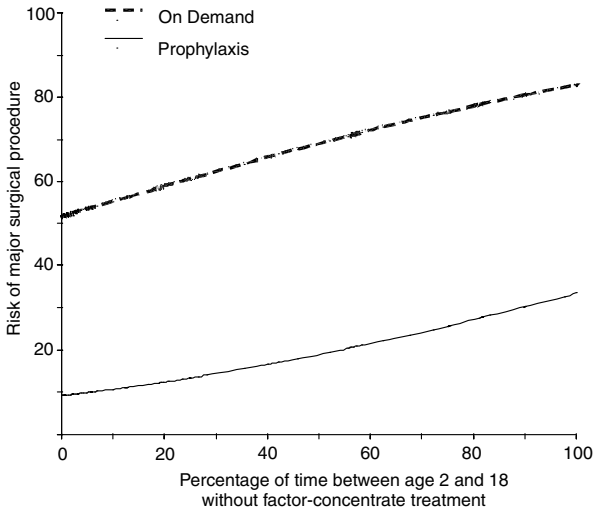

Fig. 4. The difference in risk of undergoing at least one corrective major surgical procedure during the 11-year period (1989–1999) for on-demand and prophylaxis patients, when accounting for the percentage of time the individual had been without factor-concentrate treatment.

laxis patients (9), only about one-eighth of that for on-demand patients (76). The mean age was about 33.2 years (SD 9.9, median 34 and range 18–50 years) for the arthrodeses; 38.5 years (SD 9.2, median 39 and range 22–57 years) for the prostheses procedures; 26.9 years (SD 14.1, median 21 and range 11–58 years) for the radioactive isotopes; and 27.5 years (SD 9.5, median 26 and range 19–51 years) for the synovectomies.

A greater share of the on-demand patients (20–58 years old), were on 100% sick leave/early retirement in 1999 (33% vs. 9% in prophylaxis group) (Table 6). Only three of the on-demand patients, who were on 100% sick leave or had retired early were over 50 years of age in 1999 (the maximum age of prophylaxis patients). Both the employment rate and the proportion of students were higher in the prophylaxis (68 and 15%, respectively) than in the on-demand group (57 and 7%). Moreover, among the on-demand patients who were recorded as employed on 31 December 1999, four were actually 50% early retired or on 50% sick leave, and another one was 60% unemployed. In the prophylaxis group, only two of those recorded as employed were part-time early retired or on part-time sick leave.

Figure 3 illustrates differences in the annual number of days lost from work from 1989 to 1999. This includes haemophilia-related sick days for employed persons and people at school, as well as all normal workdays for people on long-term sick leave or early retirement (measured by 226 days per annum full sick leave). For those on prophylactic treatment, the median was equal to zero and only the borderline for the 75th percentile is shown in Fig. 3. The differences were statistically significant by the Mann–Whitney test both for all single years ($P < 0.01$) and jointly ($P < 0.05$).

Table 7. Number of pieces of special equipment, workplace and domicile adaptations by type and treatment strategy based on pooled data for the whole period 1989–1999.

	On demand	Prophylaxis
Equipment		
Cars	31	3
Wheel chairs	13	6
Adjustable furniture	6	
Other minor aids	28	46
Adaptations		
Adaptation of workplace	5	4
Handicap adaptation of domicile	6	3
Other minor adaptations	1	22

Both patient groups consumed resources to compensate for disabilities caused by haemophilia-related problems (Table 7). On-demand patients had relatively more specially equipped cars, wheel chairs, adjustable furniture and adaptations of domicile and workplace. The entry 'other minor aids', under the heading of equipment, includes items such as ankle, knee and neck cushions, crutches, bicycle helmets, specially adapted shoes, etc. The entry 'other minor adaptations' includes installation of specially designed bathtub, fences and ramps for facilitating the use of wheel chairs, removal of doorsteps and installation of carpets and devices to cushion sharp edges, which made measures to adapt the domicile more common among prophylaxis patients.

Factors associated with variations in annual factor-concentrate use

Using panel-data regression analysis, we explored what individual and treatment characteristics were associated with variations in total annual factor-concentrate consumption (i.e. the sum of consumption in regular prophylactic treatment, during haemorrhages, surgery and physiotherapy sessions, etc). Results are reported in Table 8. We started the analysis with full-sample models where we employed dummy variables (and their interactions) as indicators of different characteristics of the two treatment strategies. However, these models failed the Hausman specification test. Thus, we divided the total sample into three sub-samples: (i) all on-demand patients, (ii) young patients (age 0–17 years) on

Table 8. Panel-data regression of annual factor-concentrate consumption by random-effects for three subsamples: (1) all on-demand patients, (2) children (0–17 years) on prophylaxis and (3) adults on prophylaxis†.

	On-demand‡	Prophylaxis‡	
	All	Children	Adults
Age		15948.4**	
Adult (18+)	22671.5**		
Prescribed dose (kg^{-1})	2141.6	2681.2**	4401.1**
Weeks on secondary prophylaxis	1660.6**		
Low-frequency prophylaxis		−30209.4**	
Residual body weight		2917.5**	
Type A		68712.1**	
Constant	1733.4	−134660.3**	113138.2**
Number of observations	552	480	384
Number of patients	59	62	57
R^2 (overall)	0.43	0.74	0.11
Wald $\chi^2(7)$	334.42**	1220.44**	63.96**
Hausman§	4.76	7.30	0.87

**$P < 0.001$.

†The starting model included for both treatments age, prescribed dose per kg body weight, type A, residual body weight, age at diagnosis. In addition, for on-demand it included adult (dummy age 18+), weeks on secondary prophylaxis and time period between 2 and 18 years without any factor-concentrate treatment; and for prophylaxis the corresponding variables were dummy variables indicating treatment centre, age polynomials up to 4, low-frequency treatment (maximum twice weekly for type A and once weekly for type B) and the percentage time between 2 and 18 years of age with prophylactic treatment.

‡The coefficients are interpreted as the independent variable's (individual and treatment characteristics) marginal effect in number of IUs on annual factor-concentrate consumption (dependent variable), or extra factor-concentrate consumption due to one 'unit' increase in the independent variable, *ceteris paribus*.

§Test of systematic differences in coefficients compared with a fixed-effect model, which if significant implies that the model is either misspecified or has a correlation between independent variables and error terms.

prophylaxis and (iii) adult patients (18+) on prophylaxis; and searched for the model in each sub-sample that fitted the data best.

For all on-demand patients, three characteristics were significantly associated with the variation in annual factor-concentrate consumption: being adult (18+), the prescribed dose per kg when haemorrhaging and the number of weeks on secondary prophylaxis during the year (Table 8, column 1). Adults consumed on average 22 671 IU more than children. An increase in the prescribed dose per kg by 1 IU (from, for instance, 14 to 15 IU) increased the annual consumption by 2 141 IU. Finally, increasing the number of weeks on secondary prophylaxis by 1 week increased the annual factor-concentrate consumption by 1 661 IU.

Column (2) in Table 8 presents the results for young patients (age 0–17 years) on prophylaxis. We included all children who fit the inclusion criteria for prophylaxis (Table 1). However, for very young children (age 1–2 years) who had not yet started the regular prophylactic treatment (cf. Table 4), we excluded from the analysis the years when the child was treated on demand. These years were not representative of prophylactic treatment and typically involved considerably lower levels of factor-concentrate consumption. Therefore, the child was included as soon as regular prophylactic treatment was started. For children then, having haemophilia A was associated with a higher factor-concentrate consumption, 68 712 IU, and an increase in age by 1 year was associated with 15 948 IU more per annum. We also found that children who weighed relatively more than other children at the same age consumed more, i.e. an additional 2 918 IU per kg above the average weight for that age. The variable 'residual body weight' consisted of the residuals from a regression of body weight on age, i.e. every patient was assigned his deviation from the predicted weight for a person of his age. This construction avoids multicollinearity. Moreover, increasing the dose per kg by 1 IU increased annual consumption by 2 681 IU. However, children who were prescribed a less-frequent prophylaxis (twice weekly for haemophilia A and once weekly for haemophilia B) consumed 30 209 IU less per year.

Column (3) in Table 8 presents the results for adult patients (18+) on prophylaxis. Only one variable remained significant when we had eliminated the insignificant variables. Increasing the dose per kg bodyweight by 1 IU increased annual consumption of factor concentrate by 2 580 IU.

Probability of major surgical procedure

The probability of undergoing at least one haemophilia-related major surgical procedure (corrective procedures arthrodeses, prostheses implantation and extraction, synovectomy, etc.) during the period 1989–1999 was estimated using explanatory variables treatment history, type of haemophilia, present treatment strategy, age and residual bodyweight. Treatment history was defined for the years between 2 and 18 years of age and included the percentage of that time period that the patient (i) did not have any factor-concentrate treatment, (ii) had on-demand treatment and (iii) had prophylactic treatment. For this analysis, we used only patients born between

1949 and 1981, i.e. we used the same age interval for the two treatment strategies ($n = 111$).

Patients on prophylactic treatment had 50 percentage units lower probability of undergoing a major surgical procedure ($P < 0.001$). Increasing the percentage of time between ages 2 and 18 years without any factor-concentrate treatment at all increased the probability of surgery under both treatment strategies. Remember, the oldest Swedish patients also started their factor-concentrate treatment later than is common practice today. For example, a person who did not start factor-concentrate treatment before he was 11 years old (half the period between 2 and 18 years) had 16 percentage units higher probability of undergoing a major surgical procedure ($P < 0.05$)

The results from the probit regression are illustrated in Fig. 4, where we have plotted the predicted risk of a major surgical procedure for patients with prophylactic and on-demand treatment, respectively, against the percentage of time without any factor-concentrate treatment between ages 2 and 18 years. The difference between treatment strategies in absolute risk was stable and about 50 percentage units, irrespective of when factor-concentrate treatment started.

Probability of longer loss of working days

We also investigated which individual and treatment characteristics affected the probability of having a longer period of loss of working days (at least one period of more than half a year) due to haemophilia during the period 1989 to 1999 using the same explanatory variables. This analysis was confined to the adult population born 1969 and earlier as they were potentially active on the labour market already in 1989 ($n = 65$).

After eliminating insignificant variables, the reduced model included only the percentage of time on prophylactic treatment between 2 and 18 years of age. A person who had been on prophylactic treatment all the time between 2 and 18 years old had a 74 percentage units lower risk of having a longer period of loss of working days due to haemophilia compared with a person who did not have any prophylaxis between 2 and 18 years ($P < 0.01$). In a sensitivity analysis, we repeated the analysis in the age-matched sample (born 1949–1969, $n = 60$) and hence excluded the oldest on-demand patients. The results barely changed. In the same final model the marginal effect was 73 percentage units lower risk ($P < 0.01$) if the patient had prophylactic treatment all the time (cp. 74 percentage units above).

Discussion

We have combined medical expertise on haemophilia treatment with health-economics methodology in order to identify what, from a societal point of view, constitutes differences in resource use between on-demand and prophylactic treatment for severe haemophilia. To do this we made a very thorough investigation of all kinds of resource use associated with the two treatment strategies. In our analysis we used both retrospective information on treatment history from birth to 1988 and a detailed retrospective registration of resource use within, as well as outside, the health-care sector during the period 1989–1999. Such a long period of investigation makes our results less sensitive to rare events such as surgery or adaptation of domicile that may have great impact on results from cross-sectional analysis. The long period may also imply a trade-off in terms of recollection bias for patient interviews. However, we asked about major events, such as change of work or school and adaptation of domicile, that are easier to remember. Moreover, reported days lost from work or school were also checked against clinical records.

The regression methods used here compensate for the fact that the number of patients was restricted by the size of the population with severe haemophilia and also allowed inference despite the difference in age structure between the two patient groups. Our primary interest in the regression analyses was to identify variation attributable to individual and treatment characteristics. The organization of society in Norway and Sweden is very similar, but we cannot rule out that some of the variation in resource use could be attributed to small differences existing between Sweden and Norway, for instance in the organization of the health-care sector. The study compared prophylactic treatment according to the Swedish regime with on-demand treatment as described from Norway. The implicit assumption was then that if on-demand treatment had been the standard practice in Sweden, Swedish patients would have followed the same treatment and experienced the same consequences as the Norwegian sub-population in this study actually did.

Our study confirmed the great variation in annual factor-concentrate consumption between patients on the same treatment regimen found in previous studies [6,11,17,20,23,24]. However, we also found that prophylactic treatment according to the Swedish regimen involved higher amounts of factor-concentrate consumption. The median was 211 000 IU

(IQR 154 000 IU–268 000 IU) for adults on prophylaxis compared with 55 000 IU (IQR 28 000–91 000 IU) for on-demand treatment. The corresponding figures for median total IU kg^{-1} per annum for adults were 3 024 (IQR 2 328–3 864) for prophylaxis and 780 (IQR 400–1 303) for on-demand. The panel-data analysis showed that the prescribed dose per kg was significantly associated with the variation in annual factor-concentrate consumption for both treatment strategies. The median prescribed dose per kg was for prophylaxis 28 IU (IQR 24–32) and 14 IU (IQR 12–16) for on demand.

We used actual recorded factor-concentrate consumption, which of course may deviate from the prescribed dose. A few patients on prophylaxis reported consumption levels that sometimes deviated considerably from what would be expected, given the prescribed dose and frequency of injections. In these cases, we cross-checked the reported consumption against pharmacy records and found that the reported consumption in most of these cases corresponded with pharmacy records. In a sensitivity analysis, we replaced the remaining possibly 'truly' under-reported figures by the figures from the pharmacy records. The resulting final models included the same set of variables with only marginal differences in the coefficients. Thus, the possible under-reporting did not change the overall results or implications. Why patients chose other consumption levels than prescribed were beyond the scope of this study. Moreover, in the on-demand group we found patients with very low factor-concentrate consumption in some years, but these observations could be explained by other factors than under-reporting (for instance, consistently restrictive consumption, joints with a high degree of arthropathy that did not bleed, etc.).

There was a striking difference in type of invasive procedures for the on-demand and prophylaxis. Fifty-nine per cent of the on-demand patients underwent at least one major corrective surgical procedure during 1989–1999, compared with 8% for prophylaxis patients. Some patients had more than one corrective procedure and there were 13 times as many corrective procedures among on-demand patients relative to group size. The results from the probit analysis illustrated in Fig. 4 may be seen as an argument for the benefits of present prophylactic treatment also for patients who did not start with factor-concentrate treatment until later in life. Present prophylactic treatment shifts the probability of a major surgical procedure to a lower level. It should also be noted that one-third of the invasive procedures in the prophylaxis group were associated with port-á-caths or percuseal ports, devices used to facilitate injections mainly used for young children. Although an integral part of prophylactic treatment for young children, these devices are themselves of a preventive rather than corrective character. Hence, the differences between the treatment strategies with respect to outcomes are bigger than a first glance at Table 5 may indicate.

When one adopts the societal perspective, it is also important to account for differences in resource use and other effects outside the health-care sector (including lost working days, special equipment and adaptations because of haemophilia). Lost working days when people are unable to work or go to school due to severe haemophilia constitute a welfare loss to society. We found that 9% of all adult prophylactic patients were on 100% early retirement/long-term sick leave. This was not far from the same figure for the general population (7%), while the figure for on-demand treatment was 33%. The probability of at least half-a-year of lost working days during 1989–1999 was reduced considerably (74%), if the patient had been on prophylaxis all the time between 2 and 18 years of age, which demonstrates the long-run positive effect of early prophylactic treatment.

There were also qualitative differences between the two treatment strategies regarding kinds of special equipment and adaptations of workplace and domicile. Major equipment (cars, etc.) and major adaptations (full handicap-adjustment of domicile, etc.) were relatively more common among on-demand patients. Such measures were then a consequence of some degree of disability in the patient. We also found that minor aids and minor adaptations in the prophylaxis group stem mainly from young children where preventive measures were taken to reduce the risk of haemorrhages. The on-demand population did not include young children for reasons given above, but we find it reasonable to assume that minor preventive measures would be as frequent if on-demand was standard treatment in Sweden. Even if we found a difference in equipments, adaptations and preventive measures depending on treatment strategy, it is important to stress that haemophilia patients, irrespective of disease severity and mode of treatment, have a chronic disease and require lifelong surveillance.

It is clear from our results that patients treated according to the Swedish prophylactic strategy needed significantly less orthopaedic surgery. This indicates that the Norwegian on-demand patients have more severe haemophilic arthropathy, a

destructive joint condition caused by repeated joint haemorrhages, than the Swedish patients. More hospitalization, more need for aids and more days lost from work are other signs of a higher degree of disability in the on-demand patients. Furthermore, joint haemorrhages not only disable the patient but are also extremely painful. A patient with severe haemophilia who is not on prophylaxis will restrict his way of life in order to avoid further haemorrhages. The reason for treating haemophilia patients with factor concentrates is not only to prevent lethal haemorrhages. The primary aim is to prevent joint haemorrhages and the development of haemophilic arthropathy. Our data clearly showed that the early regular prophylactic treatment continuing into adulthood achieved this aim.

The annual consumption of factor concentrate increased over the period 1989–1999 for both treatment strategies. At the same time, the prescribed dose per kg bodyweight remained quite the same, or even showed a tendency to be a little lower in 1999 than in 1989. The latter fact may be explained by the ageing of our population and also, to some extent, by the fact that small children had larger doses than necessary, as the smallest available dose on the market is normally 500 IU.

This comparison of on-demand and prophylaxis treatment used data from Sweden, where prophylaxis has been used for several decades, mainly as a high-dose regimen, and Norway, where many patients, according to our results, had quite low levels of annual factor-concentrate consumption, also compared with other countries and with the guidelines issued by the World Health Organisation and the World Federation of Haemophilia [20,34]. Hence, the results cannot be directly transferred to countries with somewhat different treatment regimes. We can neither rule out that the study design *per se* may impact on the results. The lack of randomization may introduce a bias. Although the two countries are very similar in terms of socio-economic and cultural issues, differences in health care systems and in the tradition and organization of haemophilia care, may give differences in outcome not related to the mode of clotting factor therapy.

The large differences in most aspects of resource use were probably caused by the different treatment strategies. These differences will, of course, affect both costs and benefits. Further studies from this project will evaluate costs and benefits in monetary terms and discuss the possible trade-offs between different types of resource use.

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