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The uptake of recombinant Factor VIII in the Netherlands

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Summary. In comparison with other biotechnology substitutions, the adoption of recombinant Factor VIII (rFVIII) has been relatively slow. We sent a postal questionnaire to all Dutch haemophilia patients and haemophilia-treating physicians, to determine which factors predict whether a patient uses plasma-derived FVIII (pdFVIII) or rFVIII and to investigate patients' and doctors' opinions on both products. Fifty-six per cent of patients received rFVIII. This percentage varied widely between centres. Only one doctor would choose to use pdFVIII if he suffered from haemophilia A himself, and 74% would choose to use rFVIII. Younger patients, those not infected with the human immunodeficiency virus or hepatitis C, and those who did not have family members who used pdFVIII switched more often from pdFVIII to rFVIII. Patients who rated themselves as innovative, who had family members who used rFVIII, and those who were treated in a large haemophilia treatment centre were also more likely to have switched. For physicians and patients alike, the respondents generally did not see large differences between rFVIII and pdFVIII, except for the risk of infections and the knowledge of long-term effects (both larger for pdFVIII). Although haemophilia patients represent one of the most empowered patient groups, physicians appear to have been influential in choosing between pdFVIII and rFVIII.

Keywords: haemophilia, recombinant Factor VIII, product choice, patient preference, physician preference.

In 1995, recombinant Factor VIII (rFVIII) was introduced in The Netherlands for the treatment of patients with haemophilia A, as a substitute for plasma-derived Factor VIII (pdFVIII). Of the Dutch haemophilia patients who were treated with plasma-derived clotting factors before 1985, 16–17% had become infected with the human immunodeficiency virus (HIV) (Rosendaal *et al*, 1991; Mauser-Bunschoten, 1995). In addition, the large majority (about 80%) of patients had been infected with hepatitis C (Mauser-Bunschoten *et al*, 1995; Triemstra, 1996).

Because of this history of infectivity with plasma-derived clotting factors, one might have expected that rFVIII would have been quickly adopted by the market. This, however, has not been the case. In 2001, 6 years after its introduction, rFVIII was used by 50% of the Dutch haemophilia patients, while the other 50% continued to use pdFVIII (Mauser-Bunschoten *et al,* 2001). Compared with other biotechnology substitutions, the uptake of rFVIII is slow. In The Netherlands, both recombinant human growth hormone and recombinant human insulin quickly completely replaced their organic counterparts, and the recombinant follitropins have captured an 80% market share within 4 years (Gale, 1989; Wolff, 1992; van Rijkom *et al*, 1999). The uptake of rFVIII in The Netherlands has also been slower than in other countries. Ireland, Scotland and Denmark have completely switched from pdFVIII to rFVIII as a matter of health policy. In France, rFVIII represents 80% of all FVIII used [Agence Francaise de Sécurité Sanitaire des Produits de Santé (AFSSAPS), 2000] and in Germany it represents 50%.

Apparently, doctors and/or patients have been hesitant to adopt rFVIII. Explanations may be that they fear some unforeseen long-term negative effect caused by the use of rFVIII or that they are concerned about increased antigenicity of rFVIII, as this was debated in the early 1990s (Lusher *et al*, 1993; Hoyer, 1994; de Wit & Mauser-Bunschoten, 1995), even though the current scientific belief is that this is not the case (Addiego *et al*, 1993; Briët & Mauser-Bunschoten, 1997; Mannucci & Tuddenham, 2001). The Central Laboratory of The Netherlands Red Cross Blood Transfusion Service (CLB) is the major provider of pdFVIII in The Netherlands. Loyalty towards this

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organization might be another reason for the hesitation. As in the past the prevalence of HIV positivity was highest in countries that predominantly used FVIII preparations derived from the plasma of paid donors from the USA (Rosendaal *et al*, 1991), there might be a preference for a Dutch non-profit organization that relies on unpaid donors. Also, it has been argued that it is not possible to switch all patients to rFVIII, even if they wanted to, because the supply of rFVIII is not sufficient. (Mauser-Bunschoten *et al,* 2001). Indeed, at the time of our study, there was a sudden shortage of rFVIII, as Bayer, one of the major producers of rFVIII, had suspended the market release for its world-wide market (Anonymous, 2001). In addition, there may have been doubts about the advertised increased safety of rFVIII with regard to transmission of infections. The first rFVIII preparations contained plasma-derived albumin as a stabilizer. In 1999 and 2000, three virtually albumin-free formulations (Refacto®, Kogenate Bayer® and Helixate NexGen®) were introduced. They contain 1000-times less plasma-derived albumin than the former formulations and have an additional detergent-based purification step, aimed at further reducing the potential for transmission of infectious agents (Anonymous, 2000).

As far as we know, the factors that underlie the choice for either pdFVIII or rFVIII have never been systematically studied. Who is the most influential in choosing between pdFVIII and rFVIII: the doctor or the patient? Can the adoption of rFVIII be predicted from medical characteristics such as severity of the disease, treatment modality or infections contracted through the use of clotting factors (HIV, hepatitis C)? What do patients actually think of the safety and antigenicity of rFVIII and pdFVIII? To address these questions, we sent a postal questionnaire to all haemophilia patients and all haemophilia therapists in The Netherlands. The objective was to investigate the opinions of patients and doctors on the choice between pdFVIII and rFVIII, and to determine which factors predict whether a patient uses pdFVIII or rFVIII.

PATIENTS AND METHODS

Mailing procedures. The study in patients was carried out as part of the Haemophilia in The Netherlands 5 (HiN-5) project. During the past 30 years, the effects of changes in haemophilia treatment have been monitored by four nation-wide postal surveys among Dutch haemophilia patients conducted in 1972, 1978, 1985 and 1992. In April 2001, patients received a letter about the forthcoming HiN-5 study on haemophilia. Where possible, this announcement was sent by their physician. Other patients were first informed by the Dutch Haemophilia Patients' Society or directly by the Study Group HiN-5. All haemophilia patients who were listed with the haemophilia treatment centres, with the Dutch Haemophilia Patients' Society or on updated mailing lists from previous survey(s) were included in the mailing. After an extensive search for addresses, the questionnaire was sent to 1566 patients in May 2001. The closing date for data collection for the current study was set at 12 September 2001.

In addition, in May 2001, we sent a postal questionnaire to the 26 directors of the licensed haemophilia care centres in The Netherlands. Supplementary questionnaires were included, which they were asked to distribute among colleagues in their department who autonomously treated haemophilia patients as well. To enable us to measure the response, we requested the directors to report how many of their colleagues had been given a questionnaire. Reminders were sent after 2 weeks.

Content. The prestructured patient questionnaire in 2001 was largely based on the four previous HiN questionnaires. For this study, we added specific questions, which followed from a prior model that we had developed and that incorporated all factors we assumed to be predictive of the choice between recombinant and plasma-derived clotting factors. To formulate this model and these questions, literature on clotting factors was consulted, and interviews were held with patients and representatives of the Dutch Haemophilia Patients' Society, haemophilia-treating physicians and clotting factor producers. Before the questionnaire was actually sent out, a small number of patients and a panel of experts were asked to complete the questionnaire and to give their comments. These 'pilots' were helpful in optimizing the structure and content of the questionnaire.

Questions on age, type of haemophilia, severity of disease, treatment modality, inhibitor formation, infectious diseases (HIV, hepatitis C), treatment centre, membership of the Dutch Haemophilia Patients' Society, education level and net income were included in the HiN questionnaires. For this study, items were added: attitude towards innovations (innovativeness), aversion against switching, empowerment, first clotting factor used, current product used, consideration of future product switch, clotting factor used by family members, number of family members with HIV or hepatitis C through the use of clotting factors, most important influence in clotting factor choice (respondent himself, physician or both equally influential), physician's advice (recombinant, plasma derived or neutral), preference for a specific producer (Dutch over foreign, non-profit over profit-making), and opinion on albumin-free formulations of rFVIII (5 point scale: large deterioration, deterioration, no difference, improvement, large improvement). The first three items are described in Table I and were included at the beginning of the questionnaire, before the issue of recombinant versus plasma-derived clotting factors was introduced.

From a list of eight characteristics which may be important to patients in choosing between different clotting factor products (price, effectiveness, user-friendliness, producer's image, knowledge on long-term effects, risk of infections, risk of product shortages and risk of inhibitor formation), respondents were asked to rank the five most important characteristics (between 1 and 5 points). The average rating for a product characteristic could be a maximum of 5 (if all respondents ranked the characteristic as the most important one) and a minimum of 0 (if none of the respondents selected the characteristic in the top five most important). In addition, their opinion on the eight characteristics was asked on a five-point scale (−2 very

Table I. Selection of items included in the questionnaires for patients and physicians.

Innovativeness	
If a new treatment for haemophilia would become available, e.g. gene therapy, how would you react to that?	
1	Very negative
2	Negative
3	Neutral
4	Positive
5	Very positive
In general, if a new treatment for haemophilia became available, when would you adopt it?	
1	Never
2	When the treatment can hardly be escaped anymore
3	When the treatment is proven superior in a large number of patients
4	When the treatment is successful in some other patients
5	Immediately
With regard to the adoption of the latest insights and treatments in health care, patients can be categorized into five groups. In which group would you place yourself?	
1	Laggards (10%)
2	Late majority (35%)
3	Early majority (35%)
4	Early adopters (15%)
5	Innovators (5%)
*Empowerment**	
I always make clear to my physician which treatment I prefer myself.	
I am well informed about the different treatment possibilities for haemophilia.	
I follow my physician's advice without questioning.†	
Besides the information my physician gives me, I also look for information about clotting factors myself.	
When my physician proposes a certain treatment, I ask if there are other treatment options as well.	
1	Not at all
2	A little bit
3	Quite a lot
4	Very much
Aversion against switching	
Switching from one clotting factor product to another may cause problems (e.g. inhibitor formation).	
If you are doing well with your current treatment, you should never change to another clotting factor product.	
1	Totally disagree
2	Disagree
3	Neither agree nor disagree
4	Agree
5	Totally agree

*The items on empowerment were included in the patient questionnaire only.
†Reverse coding.

favourable for plasma, −1 favourable for plasma, 0 the same for plasma and recombinant, 1 favourable for recombinant, 2 very favourable for recombinant).

The questionnaire for doctors mainly contained the same items as the patients questionnaire. Items were added on the personal characteristics of the responding doctor, such as age, sex, year of graduation from medical school, medical specialism, and whether they treated mainly adults, children, or both. In addition, the respondents were asked which type of clotting factor they would choose for themselves if they had severe haemophilia (plasma derived, recombinant or no preference). Only the directors and not their colleagues were asked to fill the characteristics of their department's patient population: number of patients with haemophilia A and B, severity, number of patients on plasma-derived and recombinant clotting factors, number of patients with inhibitors, and number of infections with HIV and hepatitis C. Before the questionnaire was actually sent out, two doctors were asked to complete the questionnaire and to give their comments. This 'pilot' was helpful in optimizing the structure and the content of the questionnaire.

Analysis. As we were interested in the choice between and the opinions about rFVIII and pdFVIII, we included in the analysis only patients with haemophilia A who had used FVIII during the 18 months preceding our questionnaire, and for whom we knew whether the first clotting factor product used had been recombinant or plasma derived. The type of first clotting factor used (recombinant or plasma derived) was investigated in relation to year of birth. In this

analysis, year of birth was used as a proxy for the year of first treatment.

Subsequently, to study switching behaviour, we included only those respondents who had started on plasma-derived clotting factor and excluded the respondents who had started on rFVIII, as switching from rFVIII to pdFVIII is very rare. Odds ratios (OR) for the association with switching from pdFVIII to rFVIII were calculated by logistic regression for all factors in our prior model. The factors that were statistically significantly associated with switching in these univariate analyses were subsequently included in a multivariate logistic regression model to calculate the adjusted ORs. The severity of haemophilia was classified according to the residual percentage of FVIII clotting activity: severe (< 1%, i.e. < 1 IU/dl), moderate (1–5%), or mild (> 5–40%). Haemophilia treatment centres were categorized into 'small' and 'large' centres according to the number of patients ($n \leq 10$, $n > 10$ respondents respectively). Different items that were designed to measure one common factor, such as the three items on innovativeness, were clustered together (as the average over the items), if Crohnbach's alpha for correlation was ≥ 0·70.

To calculate the response in the physicians' questionnaire, we assumed that directors who, after the reminder, did not respond to our questionnaire had not distributed it among colleagues either. The departments were categorized into three groups: departments treating mainly adults, departments treating mainly children and those treating both. Personal characteristics of the respondents were described, as were the influences of patient characteristics on the doctor's advice about rFVIII versus pdFVIII. The personal opinions of doctors on matters related to the choice between pdFVIII and rFVIII were noted and compared with the opinions of patients. For each respondent (both patients and doctors), the opinion on each of the eight product characteristics was multiplied by the importance attached to that characteristic. The sum of these eight multiplications was used as a summarizing measure of the respondent's opinion on recombinant versus plasma-derived clotting factor (range from −30 to 30).

RESULTS

Response, participants and first use

The total response to the patient questionnaire was 69% ($n = 1084$). Respondents who were excluded from the analysis were patients who did not have haemophilia A ($n = 188$), patients who had not used FVIII in the past 18 months ($n = 337$, mainly mild haemophilia A) and patients for whom the type of first clotting factor used was not known ($n = 22$). In total, 537 respondents were eligible for analysis. Characteristics of the responding patients are presented in Table II. First treatment had been with rFVIII for 16% ($n = 84$) of the participants and with plasma-derived clotting factor for 84% ($n = 453$). Because of the consensus among the Dutch haemophilia therapists to treat previously untreated patients (PUPs) with rFVIII, we expected that the large majority of respondents who started using clotting factor treatment after 1994 would start on rFVIII. As we did not have data on the year of first treatment, we used year of birth as a proxy. Of all 537 respondents, 12% ($n = 67$) was born after 1994. Figure 1 shows that these young patients had generally started on rFVIII.

Eighteen directors returned the questionnaire (response 69%). They reported that they had forwarded the questionnaire to 18 colleagues. Overall, including colleagues, we received 30 completed questionnaires (response 30/44 = 68%). Together, the directors reported 1316 patients with haemophilia A and 169 patients with haemophilia B in their care. As such, our sample represents the treating physicians of > 95% of all Dutch haemophilia patients. One director was excluded who no longer treated haemophilia patients. A total of 29 participating physicians, from 17 departments, remained for analysis.

Mean age of the physicians was 47 years (range 35–61 years). Fifty-nine per cent were men and the average year of graduation from medical school was 1980. Seven per cent ($n = 2$) were general practitioners, 11% ($n = 3$) internists, 46% ($n = 13$) haematologists, 21% ($n = 6$) paediatricians and 14% ($n = 4$) paediatric haematologists.

Switching behaviour

For the analysis of switching behaviour, we included the 453 responding patients whose first treatment had been with plasma-derived clotting factors. Of these, 45% ($n = 206$, switchers) had switched from pdFVIII to rFVIII and 55% ($n = 247$, non-switchers) continued to use pdFVIII at the time of our questionnaire.

Influence of treating physician

The 453 responding switchers and non-switchers were treated in 30 different treatment centres. Eighty-eight per cent of these patients were treated in seven large centres (median number of respondents per centre was 31). In these large centres, the percentage of respondents who had switched from pdFVIII to rFVIII varied from 26% to 71% (median 40%). In the small centres ($n = 23$, median number of respondents per centre was one), the percentage of switchers varied from 0% to 100% (median 0%). As such, treatment in a large haemophilia treatment centre was positively associated with switching from pdFVIII to rFVIII (OR_{adj} 3·2, 95% CI 1·1–9·8).

In the responding departments that treated mainly adults ($n = 8$; 501 patients), the proportion of patients using rFVIII ranged from 0% to 75% (median 12%) and, in the departments that treated mainly children ($n = 6$; 167 patients), it varied between 0% and 100% (median 84%). On average the proportion of patients using rFVIII was three times higher in departments treating children than in departments treating adults ($P = 0{\cdot}02$).

To the question 'Who was the most influential in the choice of the type of FVIII product used?', 54% of the patients answered 'my treating physician', 25% answered 'both myself and my physician' and 21% answered 'myself'. There was no difference between switchers and non-switchers in this respect. Quite similarly, in the group of

Table II. Characteristics of the participating patients.

	First use was rFVIII ($n = 84$)	First use was pdFVIII ($n = 453$)
Mean age, years (95% CI)	9 (6–11)	37 (35–38)
Male	84 (100)	444 (99)
Severity of disease		
Mild	25 (31)	85 (19)
Moderate	16 (20)	81 (18)
Severe	41 (50)	277 (63)
Treatment modality		
Home treatment	27 (33)	318 (72)
Prophylactic treatment	37 (45)	234 (53)
Infectious diseases		
HIV positive	0 (0)	26 (6)
Hepatitis C	4 (5)	284 (67)
(Past) development of inhibitor	5 (7)	51 (13)
Member of Haemophilia Society	72 (86)	344 (77)
High income	39 (62)	215 (52)
Higher education	30 (37)	167 (39)

All values are number (%) except where otherwise indicated. 95% CI, 95% confidence interval.

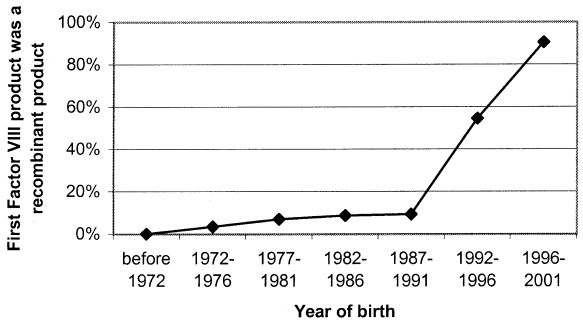

Fig 1. Percentage of patients who started on rFVIII versus year of birth.

physicians, only one doctor indicated the patient to be the most influential in choosing a FVIII product. Forty-four per cent of the non-switchers had spoken with their physician about the choice between rFVIII and pdFVIII. Only 21% of all patients who discussed the topic with their physician (switchers and non-switchers) initiated the conversation themselves. Eight per cent of the non-switchers and 52% of the switchers had been advised by their physician to use rFVIII.

Five of the 29 physicians (17%) gave the same advice to all patients (either pro-pdFVIII, pro-rFVIII or neutral), while the other 22 doctors gave different advice to different patients. The reasons for this differential advice were the limited availability of rFVIII (23%), differences between patients (32%) or both (46%). Young patients were preferentially advised to use rFVIII by 81% of these physicians and PUPs by 95% (Table III). Thirty per cent preferred to give rFVIII to HIV-negative patients. Twenty-nine per cent of the doctors were more inclined to advise rFVIII to patients who were afraid of bovine spongiform encephalopathy (BSE) than to patients who were not afraid of BSE. Twenty-four per cent took into consideration whether family members of the patient were already using rFVIII.

Patient characteristics

The average age of the switchers (31 years, range 2–78) was lower than of the non-switchers (41 years, 5–83). Switching was not associated with severity of disease, history of inhibitor formation or home treatment (Table IV). Patients who had been infected with HIV or hepatitis C switched less to rFVIII than patients who had not been infected (OR_{adj} 0·3, 95% CI 0·1–1·0). The fact whether patients did or did not have family members who had been infected with HIV or hepatitis C through the use of clotting factors was not associated with switching behaviour. The more family members were using pdFVIII, the less the patients themselves had switched from pdFVIII to rFVIII (OR_{adj} 0·7, 95% CI 0·5–0·9). On the other hand, the more family members who used rFVIII, the more the patients had switched to rFVIII (OR_{adj} 2·7, 95% CI 1·6–4·3).

The three items on innovativeness (Crohnbach's alpha 0·70), as well as the five items on empowerment (Crohnbach's alpha 0·75) were clustered together in the analysis. In univariate analyses both were positively associated with switching from pdFVIII to rFVIII.

Membership of the Dutch Haemophilia Patients' Society was also higher in the switchers than in the non-switchers (81% *vs* 73%). Net income and education correlated only weakly (Crohnbach's alpha 0·49), and therefore they were not clustered together as one measure of socio-economic status. In univariate analysis, high income was positively associated with switching, while higher education was not.

Table III. To which patients do you tend to advise treatment with rFVIII instead of pdFVIII?

Patient characteristic	Doctor's preference to advise rFVIII instead of pdFVIII		
Severity of the disease	Severe haemophiliacs	No preference	Mild haemophiliacs
	14	76	10
Previously untreated patients (PUPs)	PUPs	No preference	Previously treated patients
	95	5	0
Age	Young patients	No preference	Old patients
	81	19	0
HIV status	HIV positive	No preference	HIV negative
	15	55	30
Prophylaxis status	Patients on prophylaxis	No preference	Patients not on prophylaxis
	5	91	5
Home treatment	Patients on home treatment	No preference	Patients not on home treatment
	0	100	0
Family members using rFVIII	Patients with family members using rFVIII	No preference	Patients without family members using rFVIII
	24	76	0
Compliance	Compliant patients	No preference	Non-compliant patients
	5	95	0
Inquiry about rFVIII	Patients who do inquire about rFVIII	No preference	Patients who do not inquire about rFVIII
	10	90	0
Fear of BSE	Patients afraid of BSE	No preference	Patients not afraid of BSE
	29	71	0

Results are given in percentages ($n = 22$ physicians). HIV, human immunodeficiency virus; BSE, bovine spongiform encephalopathy.

After adjustment for the other parameters in the model (see Table IV), the point estimates for the influence on switching of empowerment, income and membership of the Dutch Haemophilia Patients' Society stayed very much the same, only the confidence intervals were broader. The influence of innovativeness increased after adjustment.

Opinions

Of the non-switchers, 21% ($n = 45$) was thinking about switching to rFVIII in the future and 79% ($n = 167$) wanted to continue using pdFVIII. In 2000, two virtually albumin-free formulations of rFVIII were introduced. Forty per cent of the switchers, 23% of the non-switchers and 90% of the physicians knew about the introduction of these albumin-free formulations of rFVIII. Only 35% of the patients gave an opinion on this development, the large majority of whom (89%) thought that it was an improvement. Of the 45 non-switchers who indicated that they were thinking about switching to rFVIII, 21 (47%) had done so since the introduction of the albumin-free formulations and 25 (53%) before this introduction. The large majority of physicians reported that the introduction of albumin-free products had not influenced their prescribing behaviour. Eleven per cent had started to prescribe rFVIII more often.

Figure 2 shows how doctors and patients, respectively, rated the importance of the eight predefined product characteristics in choosing between rFVIII and pdFVIII. Risk of infections was a very important characteristic to both patients and physicians. Doctors attached a lot of importance to the knowledge of long-term effects, while patients, especially the non-switchers, were very much concerned with the effectiveness. If the physicians hypothetically suffered from severe haemophilia A themselves, 74% would choose to use rFVIII, 4% pdFVIII and 22% had no preference.

The majority of both doctors and patients thought that the risk of infection was larger with pdFVIII than with rFVIII (Fig 3A). On the other hand, they were also of the opinion that for rFVIII, less is known about the long-term effects (Fig 3B). Switchers answered these questions more favourably for rFVIII than non-switchers. All doctors and the large majority of the patients (73%) considered rFVIII and pdFVIII equally effective. The remaining minority of patients was divided: switchers believed rFVIII to be more effective, while non-switchers believed the opposite. Also on the topic of inhibitor formation, the majority of the patients (57%) and doctors (82%) did not perceive a difference between rFVIII and pdFVIII (Fig 3C). With respect to the risk of product shortages, the respondents were divided (Fig 3D). To the question 'Have you been troubled by shortages of FVIII product during this year or last year (2000 + 2001)?', 27% ($n = 56$) of switchers and 7% ($n = 16$) of non-switchers answered in the affirmative. The large majority of the participants (67% and 75%, respectively, of patients and doctors) rated the image of the producers of rFVIII and of pdFVIII as equally good. To the remaining switchers, the image of rFVIII producers was better, while the opposite was true for the remaining non-switchers. Non-switchers expressed the strongest preference for a Dutch, non-profit-making producer (Fig 3E and F). On average, switchers were more positive about rFVIII [summarized score 6 (5–7)] than non-switchers [−0·3 (−1 to 1)].

Table IV. Univariate and multivariate logistic regression model of switching versus non-switching in patients.

	OR_{crude}	(95% CI)	OR_{adj}*	(95% CI)
Parameters included in the multivariate model				
Patient characteristics				
Age	0·97	(0·96–0·98)	0·98	(0·96–1·0)
HIV positivity	0·4	(0·2–1·0)	0·3	(0·1–0·9)
Hepatitis C infection	0·4	(0·3–0·6)	0·4	(0·2–1·0)
Number of family members on plasma	0·7	(0·6–0·9)	0·6	(0·5–0·9)
Number of family members on recombinant	2·0	(1·4–2·6)	2·7	(1·6–4·4)
Innovativeness (1–5)	1·3	(1·0–1·8)	1·8	(1·1–3·1)
Prophylactic treatment	1·5	(1·0–2·2)	1·4	(0·7–2·8)
Membership of Haemophilia Patients' Society	1·6	(1·0–2·6)	1·4	(0·6–3·4)
Empowerment (1–4)	1·3	(1·0–1·8)	1·2	(0·7–2·1)
High income	1·4	(1·0–2·1)	1·4	(0·8–2·7)
Treatment centre				
Size of treatment centre (small/large)	5·6	(2·6–12·2)	3·2	(1·1–9·8)
Opinions				
Pro-recombinant opinion (−30 through 30)	1·1	(1·1–1·2)	1·1	(1·1–1·2)
'Never change a winning team' (1–5)	0·7	(0·6–0·9)	0·8	(0·6–1·1)
Preference for Dutch over foreign producer (1–5)	0·6	(0·5–0·7)	0·8	(0·5–1·1)
Preference for not-for-profit producer (1–5)	0·7	(0·6–0·8)	0·8	(0·6–1·1)
Other parameters from our prior model				
Severity of disease	1·1	(0·9–1·4)		
(Past) development of inhibitor	1·5	(0·8–2·7)		
Home treatment	1·4	(0·9–2·2)		
Number of HIV-positive family members	0·7	(0·3–1·3)		
Number of family members with hepatitis C	1·2	(0·8–1·8)		
High education	1·0	(0·7–1·5)		
Agreement with 'Switching might cause problems, e.g. inhibitors' (1–5)	0·9	(0·8–1·2)		

*Adjusted for all other parameters in the model.
95% CI, 95% confidence interval.

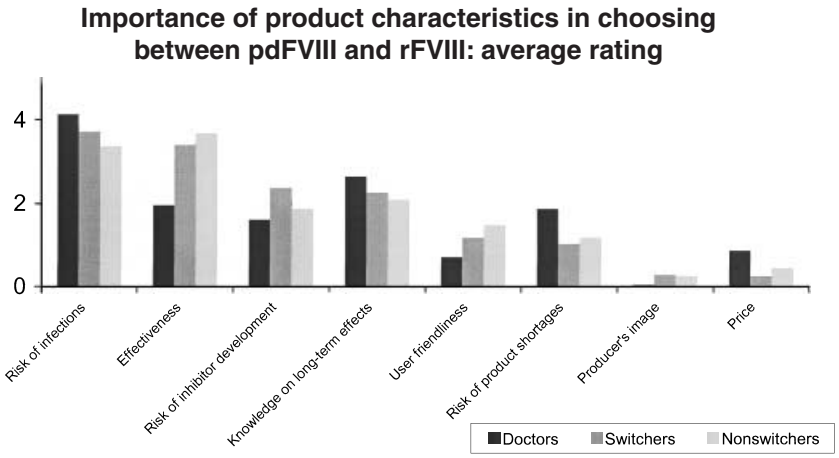

Fig 2. Importance of different product characteristics in choosing between pdFVIII and rFVIII: average ratings of switchers and non-switchers.

The correlation between the two items measuring aversion against switching of clotting factor in general was too low (Crohnbach's alpha 0·42) to cluster them together in the regression analysis for patients (Table IV). With the statement 'Switching from one clotting factor product to another may cause problems', most patients neither agreed nor disagreed while most doctors (48%) disagreed (Fig 3G). Thirty-nine per cent of the switchers and 51% of the non-switchers agreed with the notion to 'never change a winning team' (Fig 3H).

DISCUSSION

From 1995 onwards, nearly all children who received FVIII for the first time (PUPs) were prescribed rFVIII. From all responding patients who had started using pdFVIII in the

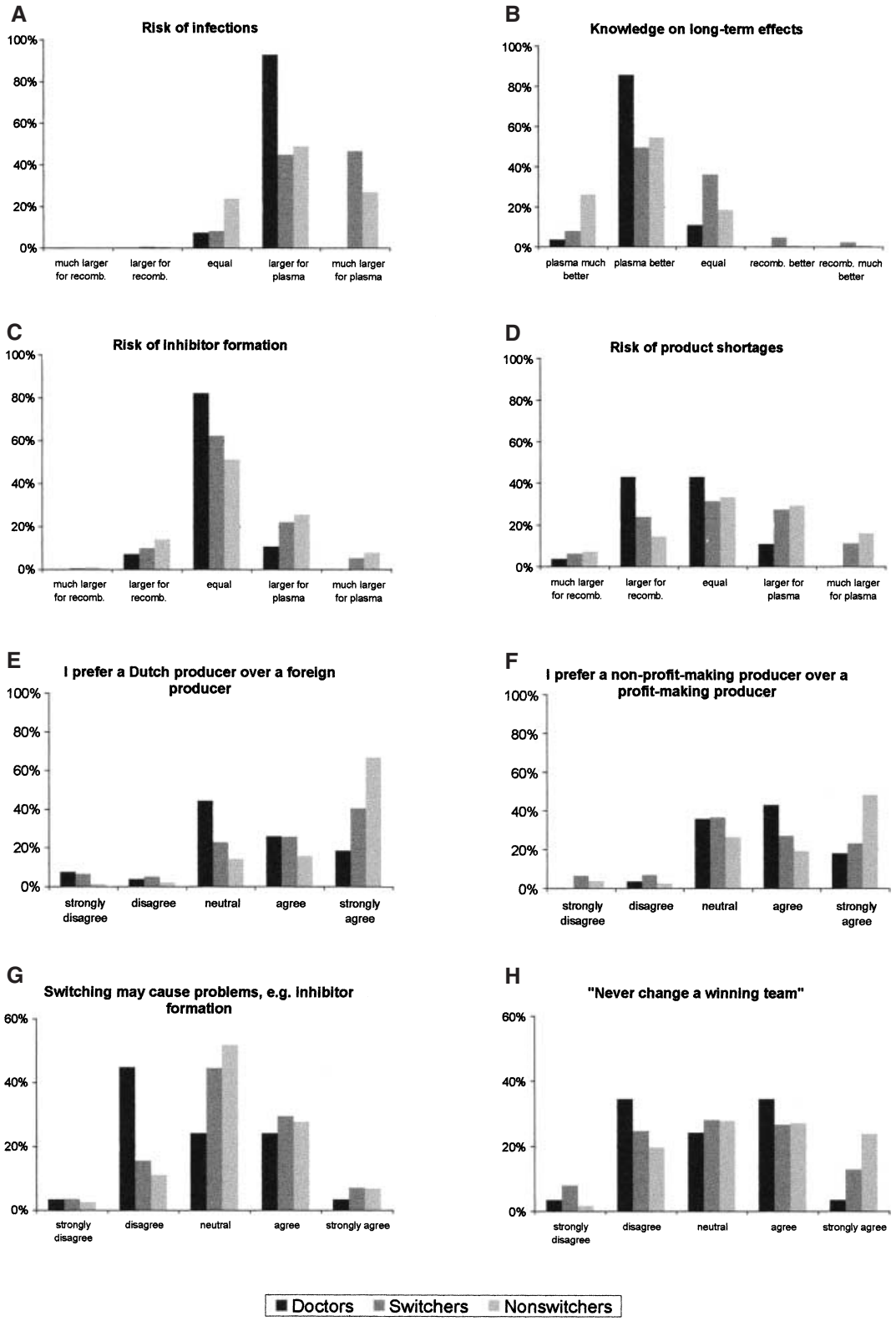

Fig 3. Opinions of doctors and patients (switchers and non-switchers) on various topics.

past, 45% had switched to rFVIII and 55% continued to use pdFVIII at the time of our questionnaire.

The percentage of patients who had switched from pdFVIII to rFVIII varied from 0% to 100% in small centres and from 26% to 71% in large centres. The proportion of patients using rFVIII was on average 2·9 times higher in those departments treating mainly children than in those treating mainly adults. Even within the groups of child departments and adult departments, the proportion of patients using rFVIII varied tremendously. From this large variability, one may conclude that the treating physician strongly influences product choice. This conclusion is further strengthened by 41% of the doctors and 54% of the patients, regarding the treating physician as the most influential person in choosing a clotting product. Unfortunately, the number of departments was too small to investigate whether the opinions or the innovativeness of the physicians within a department were predictive of the proportion of patients on rFVIII.

Notwithstanding the physicians' strong influence, our results showed a small influence of the patients as well in the choice between pdFVIII and rFVIII. The majority of physicians reported that their advice to a specific patient was not influenced by HIV status or product choice of other family members. Therefore, the association of these factors must go largely through patient preferences and not through physicians' policies. The same holds true for innovativeness of patients and opinion on rFVIII. Also, there seems to be a weak association in patients between preferring a Dutch or a non-profit-making producer and continued use of pdFVIII. The interpretation of these results is, of course, complicated by the cross-sectional characteristics of our data. We cannot determine, for example, whether a favourable opinion on rFVIII caused people to switch or whether the switch caused the favourable opinion. As there are no clear guidelines on which patients should switch from pdFVIII to rFVIII, we hypothesized that physicians mainly switched those patients who especially asked to be treated with rFVIII, which we expected to be the most empowered patients, members of the Dutch Haemophilia Patients' Society or patients with a higher social economic status. Except for the absence of an effect of higher education, our hypothesis was confirmed by the data. After the many years of discussion about the perceived increased antigenicity of rFVIII, it is remarkable that only 13% of the patients thought rFVIII to be more antigenic than pdFVIII.

In the preparatory interviews, which we conducted to construct the questionnaire for patients, we learned that the haemophilia-treating physicians, jointly with the Dutch Haemophilia Treatment Society, had agreed at the launch of rFVIII to introduce this new product very gradually to build up experience and to minimize the risk of shortages. They reasoned that a sudden and complete switch to rFVIII would mean the end of the production of pdFVIII by the Central Laboratory of The Netherlands Red Cross Blood Transfusion Service (CLB), the major provider of pdFVIII in The Netherlands. They preferred to keep both the CLB and the producers of rFVIII in business, as history had showed that dependence on a single producer makes one vulnerable. The physicians have indeed adhered to this agreement. Still, if they had suffered from haemophilia A themselves, only one doctor would choose to use pdFVIII and 74% would choose to use rFVIII.

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