HEMOSTASIS

EQOFIX: a combined economic and quality-of-life study of hemophilia B treatments in France

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BACKGROUND: EQOFIX is a medicoeconomic study that analyzed the health-related quality of life (HRQoL) and costs of care of the moderate and severe forms of hemophilia B, treated on demand or by prophylaxis with either plasma-derived Factor IX (pdFIX) or recombinant FIX (rFIX).

STUDY DESIGN AND METHODS: The primary objectives were evaluations of the impact of hemophilia B on HRQoL and of the costs associated with its management. The secondary objectives were evaluations of the clinical efficacy and costs of care of pdFIX and rFIX. In this observational study we included and followed for 1 year severe and moderate hemophilia B patients without inhibitor. HRQoL was evaluated through generic and disease-specific questionnaires. Information on the health resources consumed was collected every 3 months.

RESULTS: The EQOFIX cohort was composed of 155 patients, including 51 children and 104 adults, with 114 having severe disease and 41 having moderate disease. The regimens were prophylactic for 61 and on demand for 94. Altogether, 78 were treated with rFIX and 77 with pdFIX. There was no difference in the QoL between the pdFIX and rFIX treatments. The extra cost of prophylaxis was €22,605 per bleeding event prevented. The consumption of FIX was 1.4-fold higher for the patients treated with rFIX than for the patients treated with pdFIX.

CONCLUSION: Our findings in a cohort composed of 25% of the French population of moderate and severe hemophilia B patients show, with similar clinical and HRQoL results, that treatment with rFIX is more expensive than treatment with pdFIX.

ABBREVIATIONS: DRG(s) = diagnosis-related group(s); HRQoL = health-related quality of life; pdFIX = plasma-derived Factor IX; QoL = quality of life; rFIX = recombinant Factor IX; WFH = World Federation of Hemophilia.
For patients suffering from hemophilia, bleeding and musculoskeletal complications are causes of chronic pain and handicap impeding their quality of life (QoL).\textsuperscript{1,2} The availability of efficacious treatment has substantially improved the therapeutic management of hemophilia patients. However, because the disease necessitates multidisciplinary care and due to the cost of medicinal products, the treatment of persons with hemophilia illustrates the impact of biotechnology on the management of patients with orphan diseases.\textsuperscript{3-6}

Hemophilia B, caused by a deficiency in blood clotting Factor IX (FIX), is a recessive X-linked bleeding diathesis occurring in approximately one out of 30,000 male births.\textsuperscript{7} Because the number of patients with hemophilia A is approximately five times lower than that for hemophilia A, hemophilia B is less studied and less well understood.\textsuperscript{8,9}

In the EQOFIX study, we aimed to determine whether different FIX products are associated with differences in QoL or cost of care. To achieve that aim, an observational, longitudinal, multicenter quality-of-life and cost-of-care study was designed and conducted in France in agreement with published guidelines.\textsuperscript{10}

The primary objectives were to evaluate the impact of the disease on health-related quality of life (HRQoL) and to estimate the costs associated with management of the moderate and severe forms of hemophilia B, treated either by prophylaxis or on-demand regimens in France. The secondary objectives were to evaluate under similar conditions 1) the efficacy of recombinant and plasma-derived FIX (rFIX and pdFIX, respectively) in terms of therapeutic results and QoL and 2) the costs of care associated with rFIX and pdFIX.

**MATERIALS AND METHODS**

**Study cohort**

The study was proposed to all French hemophilia treatment centers participating in the French National Survey of Bleeding Disorders, FranceCoag Network. After informed consent was obtained, patients were consecutively enrolled from July 2008 to July 2010. The participants had to satisfy the following inclusion criteria: moderate (baseline level of FIX between 1 and 5%) or severe (FIX < 1%) hemophilia B, without inhibitor, and with or without treatment with FIX. Prophylaxis or on-demand regimens were defined by the investigators. The study was approved by a national ethical committee (CPP S-E).

**Observation period**

The enrolled patients were observed for 12 months. The last visit occurred in November 2011. The patients or the parents of children with hemophilia were asked to provide information on the resources used at the time of inclusion and then every 3 months during the study period.

**Data collection**

To evaluate the cost of care and the HRQoL, patients were interviewed by means of a specially designed semistructured questionnaire administered to them by a physician at the time of enrollment and at the end of the study. The clinical research organization in charge of the study realized the telephonic trimestral follow-up. At the first visit, information was obtained on demographic and socioeconomic characteristics, replacement therapy, and concomitant diseases. For this observational study, on-demand or prophylaxis regimen, and nature of FIX (rFIX or pdFIX) were according to investigators’ and patients’ choices. During the follow-up period information on number and sites of bleeding episodes, replacement therapy, surgical procedures, concomitant diseases, physicians’ visits, hospitalizations, and all events leading to hemophilia-related absorption of health care resources was collected every 3 months.

**Orthopedic status**

A hemophilia specialist evaluated at enrollment or at the end of the study the orthopedic status of patients using the World Federation of Hemophilia (WFH) orthopedic joint score.\textsuperscript{11} Specifically, for each joint, a number representing pain, bleeding, and physical examination was assigned as the score. The orthopedic joint score per joint (ankles, knees, and elbows) ranged from 0 (the best orthopedic condition) to 17 (the worst). The total score was calculated as the mean of the scored joints.

**Evaluations of HRQoL**

HRQoL was evaluated using generic and hemophilia-specific questionnaires. The SF-36 generic instrument for adults explores physical, emotional, and social health through measuring eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health.\textsuperscript{12} A scoring algorithm allows for aggregating the eight subscale scores in two distinct summary scores: Physical Component Summary and Mental Component Summary. Subscale scores and summary scores range from 0 to 100. A score of 100 is equivalent to the best possible state.

The KIDSCREEN generic questionnaires assess children’s and adolescent’s subjective health and well-being.\textsuperscript{13} Two versions were used: one for children and adolescents (from 8 to 18 years old) and one for parents. Both are composed of 52 self-reported items using a five-point Likert scale and are categorized into 10 dimensions: physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, parent relations and home life, financial resources,
social support and peers, school environment, and social acceptance and bullying. The score for each dimension is then transformed to a 0- to 100-point scale. Higher scores indicate better HRQoL.

The disease-specific instrument QUAL-HEMO was developed in French after literature review and in-depth interviews of hemophilia adults, parents of children, and clinicians. Four QUAL-HEMO versions are available: adult (61 items, eight dimensions with synthetic scores, and eight descriptive questions), adolescent (13-17 years old, 52 items, six dimensions with synthetic scores, seven descriptive questions, and 17 other items to be treated separately), child (8-12 years old, nine items, and three dimensions), and parents of children of 2 to 12 years old (38 items, five dimensions with synthetic scores, and three descriptive questions). Note that the adolescent version is not yet validated. Synthetic scores vary between 1 and 5 (except for children for which the range is 1-3). Higher scores represent better HRQoL. Between age groups, reduced dimensions of those questionnaires are not comparable, even if they share the same title, as they are not derived from similar questions. Descriptive questions are not reported in this study.

Cost-of-care analysis
Direct medical costs supported by the French National Health Insurance System (Caisse Nationale d’Assurance Maladie [CNAM]) were calculated by multiplying resources absorbed by their official unit cost (reference year 2011). They included the following health resources used by patients over a 1-year period: therapy with FIX, other medications, hospitalizations for bleeding or other reasons, laboratory and other diagnostic examinations, surgeries, rehabilitation care, physicians’ visits (general practitioners and specialists), skilled nursing, purchase or lease of medical devices, and transportation to and from the treatment center. Diagnosis-related group (DRG) tariffs were applied to estimate the cost of hospitalizations. For each specific hospitalization, the corresponding DRG was applied and the different levels of severity applying to hemophilia were introduced in the tariff. As DRG tariffs do not include the costs of FIX during hospitalization, they were considered separately in our analysis. It must be stressed that, in France, there is a unique tariff for rFIX and pdFIX: €0.72 per IU. All medical, biological, or paramedical costs specific for hemophilia care such as physiotherapy, medical visits at the hemophilia centers, and paramedical acts were calculated from conventional costs of the National Health Insurance. All costs are expressed in euros (€): at the time of analysis, €1 was roughly equivalent to US$1.3. Sources of costs are indicated in Data Supplement S1 (available as supporting information in the online version of this paper).

Statistical analysis
Statistical analysis was performed using computer software (SAS, Version 9.2, SAS Institute, Inc., Cary, NC).

Descriptive statistics
All the patients meeting the eligibility criteria were considered. The population analyzed was restricted to the patients with the required information. Concurrently, complementary analyses were performed to demonstrate the lack of bias due to nonevaluable patients (lost to follow-up, withdrawals, missing values). Since data were missing completely at random, no missing values were replaced. All variables were analyzed in the global population and by subgroups defined on severity status ("severe" vs. "moderate"), treatment regimen ("on demand" vs. "prophylaxis"), and type of FIX (pdFIX vs. rFIX).

Differences in mean values between study subgroups were evaluated by the t test (two subgroups), analysis of variance (more than two subgroups), or their nonparametric analogues (Mann-Whitney/Kruskal-Wallis tests) when the measurement variable does not meet the normality assumption. Differences in proportions were evaluated by the chi-square or Fisher’s exact test, according to the conditions of statistical validity (i.e., group size strictly lower than 5). Two-sided p values were calculated, with significance set at 0.05 level.

Multivariate analysis of HRQoL and cost of care
Patients were divided by age groups as used scales are age-dependent and nonhomogeneous among themselves. Predictors of generic HRQoL modification (physical or mental SF-36 composite scores for the adult population) and annual medical costs drivers were identified by multivariate regression models. As the distributions of these dependent variables were highly nonnormal (right skewed) and no common data transformations had improved their normality, we discretized the outcome variables into three levels based on lower and upper tertiles and ran an ordered logistic regression like a proportional odds model.

All the predictive factors potentially related to an impairment of generic HRQoL or to an increase of costs and listed by physicians were tested. Univariate models for each independent variable were performed and a p value threshold of 0.05 was applied for selecting variables to be included into the multivariate model. A multicollinearity diagnostic was produced by linear regression analysis with the tolerance (values < 0.6) and the variance inflation factor (values > 2) for each selected independent variable. In case of multicollinearity, practical aspects and importance of the variables were taken into account to make a decision what variables to drop from the model. A forward selection and a potential backward elimination method (threshold fixed at 0.2) was finally used to select the best.
model to fit the HRQoL alteration or annual medical costs increase as measured by the Akaike information criteria.

RESULTS

Demographics

Altogether, 31 of the 35 hemophilia treatment centers in metropolitan France were contacted. Two centers declined participation, and two centers did not include any patients, resulting in 27 active centers. Therefore, the coverage rate was of 77% (27/35) of the overall French centers. These centers included 155 patients of the 639 severe and moderate hemophilia B patients referenced in the FranceCoag cohort at the time of the study. As a result, we included 24.3% of the French cohort. Four patients were lost to follow-up, and one died during the study. In addition, the last visit was missing for four patients and was not reported for one additional patient. The assignments by subgroup were as follows: 51 children and 104 adults, 114 with severe disease and 41 with moderate disease, 61 with a prophylactic regimen and 94 with on-demand regimen, and 78 treated with rFIX and 77 treated with pdFIX. The demographics and main characteristics of the cohort are summarized in Table 1.

There were no significant differences in age or weight between the patients with moderate and severe disease and between the patients treated with pdFIX and rFIX. Viral status was not different between the patients with moderate and severe disease; however, there were significantly more human immunodeficiency virus (HIV)-positive patients treated with rFIX than with pdFIX. The patients on prophylaxis were younger and had a lower number of comorbidities compared with those on on-demand therapy. Finally, among the 77 patients receiving pdFIX, 64 (83.1%) were treated with Betafact (LFB, Les Ulis, France), nine (11.7%) with Mononine (CSL Behring, Paris, France), and four (5.2%) with Octafix (Octapharma, Lingolsheim, France).

Follow-up of patients

During the 1-year follow-up period, 89 patients of the 145 evaluable reported at least one bleeding episode, including five life-threatening ones (Table S1, available as supporting information in the online version of this paper). There were significantly more hemorrhages in the severely affected population than in the moderately affected one and in the population of patients receiving on-demand therapy than in the one receiving a prophylactic treatment regimen. All events were directly included in the medico-economic analysis.

Orthopedic score

The WFH orthopedic score was available for 142 of 155 patients (91.6%). The mean score was 1.77 ± 2.39, with a median of 0.67 and a range from 0 to 11. The scores according to subgroup are detailed in Fig. S1 (available as supporting information in the online version of this paper). The score was significantly different between the patients with severe (2.09 ± 2.51) and moderate (0.70 ± 1.48, p = 0.003) disease; this difference was present for all of the joints, with the exception of the right knee. There was no significant difference between the prophylactic and on-demand treatment regimens in this population of patients. Furthermore, there was no significant difference between severe patients treated by prophylaxis or on-demand regimens (data not shown). In addition, there was no difference between the scores obtained from the patients treated with rFIX (1.53 ± 2.11) and those treated with pdFIX (2.03 ± 2.49, p = 0.211), despite a significant difference in the scores for the left ankle (p = 0.047), which was caused by a single outlier patient (p = 0.091 without this patient). It must be stressed that the distributions of all the scores were largely skewed.

QoL

QoL was analyzed separately for adults and children. There were no statistical differences between questionnaires at inclusion or at the end of the study.

For adults, the SF-36 generic scale was available for 92% (96/104) of the included adults (Fig. S2, available as supporting information in the online version of this paper). The broadest physical score, that is, for “general health,” was slightly higher than the theoretical mean of the scale at 52.7 but much lower than the score of 69.1 for the French reference population (Data Supplement S1, Table S2, available as supporting information in the online version of this paper).

The patients with severe disease reported a poorer QoL on this dimension than the patients with moderate disease. Similarly, the patients treated by prophylaxis described a poorer QoL than the patients with on-demand treatment. Conversely, there was no difference between severe patients treated with on-demand or prophylaxis regimens (data not shown). However, there was no difference in the QoL between the patients treated with rFIX and pdFIX (Fig. S2, available as supporting information in the online version of this paper). A multivariate analysis showed that the most relevant parameters explaining the difference in the “physical component summary scale” were the number of altered joints (odds ratio [OR], 0.453 per joint; 95% confidence interval [CI], 0.329-0.623; p < 0.0001) and the presence of comorbidities (Data Supplement S1, Table S3, available as supporting information in the online version of this paper). Conversely, no differences between groups were reported on the emotional-related part of the questionnaire (Fig. S2, available as supporting information in the online version of this paper).

A comparison of SF-36 scores between hemophilia B patients and the French general population showed roughly no important differences for the patients with

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| Variable       | Total (n = 155) | Moderate (n = 41) | Severe (n = 114) | p value | On demand (n = 94) | Prophylaxis (n = 61) | p value | rFIX (n = 78) | p value | pdFIX (n = 77) | p value |
|----------------|-----------------|------------------|------------------|---------|-------------------|---------------------|---------|---------------|---------|---------------|---------|
| Age (years)    |                 |                  |                  |         |                   |                     |         |               |         |               |         |
| Mean ± SD      | 29 ± 18.1       | 32 ± 20          | 28 ± 17.3        | 0.238   | 34 ± 17.1         | 21 ± 16.8           | <0.001* | 29 ± 17.1     | 30 ± 19.1 | 0.673         |
| Median [range] | 26 [3-73]       | 26 [5-69]        | 27 [3-73]        |         | 33 [4-73]         | 14 [3-73]           |         | 27 [4-68]     | 26 [3-73] |               |
| ≥ 18           | 104 (67%)       | 30 (73%)         | 74 (65%)         | 0.334   | 19 (84%)          | 25 (41%)            | <0.001* | 51 (65%)      | 53 (69%)  | 0.648         |
| < 18           | 51 (33%)        | 11 (27%)         | 40 (35%)         |         | 15 (16%)          | 36 (59%)            |         | 27 (35%)      | 24 (31%)  |               |
| Weight (kg)    |                 |                  |                  |         |                   |                     |         |               |         |               |         |
| Mean ± SD      | 61 ± 23.7       | 61 ± 24.0        | 64 ± 22.8        | 0.435   | 67 ± 19.8         | 52 ± 26.4           | <0.001* | 63 ± 24.2     | 60 ± 23.2 | 0.403         |
| Median [range] | 64 [14-118]     | 63 [14-117]      | 70 [19-118]      |         | 69 [14-118]       | 53 [1-117]          |         | 65 [14-118]   | 63 [14-117]|               |
| Viral status   |                 |                  |                  |         |                   |                     |         |               |         |               |         |
| HIV            | 24 (15.5%)      | 3 (7.3%)         | 21 (18.4%)       | 0.092   | 17 (18.1%)        | 7 (11.5%)           | 0.266   | 17 (21.8%)    | 7 (9.1%)  | 0.029*        |
| HCV            | 66 (42.6%)      | 13 (31.7%)       | 53 (46.5%)       | 0.101   | 50 (53.2%)        | 16 (26.2%)          | <0.001* | 34 (43.6%)    | 32 (41.6%)| 0.798         |
| HIV and HCV    | 23 (14.8%)      | 3 (7.3%)         | 20 (17.5%)       | 0.114   | 17 (18.1%)        | 6 (9.8%)            | 0.156   | 16 (20.5%)    | 7 (9.1%)  | 0.046*        |
| Comorbidities  |                 |                  |                  |         |                   |                     |         |               |         |               |         |
| At least one other comorbidity | 35 (22.6%) | 9 (22.0%) | 26 (22.8%) | 0.911 | 28 (29.8%) | 7 (11.5%) | 0.008* | 20 (25.6%) | 15 (19.5%) | 0.359 |
| Mean ± SD      | 0.4 ± 0.78      | 0.4 ± 0.83       | 0.3 ± 0.65       | 0.630   | 0.5 ± 0.83        | 0.2 ± 0.69           | 0.047*  | 0.4 ± 0.76    | 0.3 ± 0.80 | 0.497 |
| Median [range] | 0 [0-4]         | 0 [0-4]          | 0 [0-2]          |         | 0 [0-4]           | 0 [0-4]             |         | 0 [0-3]      | 0 [0-4]   |               |
| Joint lesions  |                 |                  |                  |         |                   |                     |         |               |         |               |         |
| Orthopedic manifestations | 83 (53.9%) | 13 (31.7%) | 70 (61.9%) | <0.001* | 54 (57.4%) | 29 (48.3%) | 0.269 | 41 (53.2%) | 42 (54.5%) | 0.872 |
| Affected joints/relevant patient | 3.6 ± 2.47 | 1.9 ± 1.55 | 3.9 ± 2.49 | 0.006* | 3.6 ± 2.08 | 3.7 ± 3.12 | 0.794 | 3.5 ± 2.50 | 3.7 ± 2.47 | 0.680 |
| Target joints/relevant patient | 1.3 ± 1.71 | 0.5 ± 0.88 | 1.4 ± 1.80 | 0.096 | 1.3 ± 1.29 | 1.2 ± 2.32 | 0.927 | 1.2 ± 20.5 | 1.3 ± 1.33 | 0.912 |
| WFH score‡ (mean ± SD) | 1.8 ± 2.4 | 0.7 ± 1.5 | 2.1 ± 2.5 | 0.003* | 1.8 ± 2.3 | 1.7 ± 2.5 | 0.925 | 1.5 ± 2.1 | 2.0 ± 2.6 | 0.211 |
| Median [range] | 0.67 [0-11]     | 0 [0-6]          | 1 [0-11]         |         | 0.63 [0-11]       | 0.4 [0-10.7]         |         | 0.67 [0-7.7] | 0.63 [0-11]|               |

* Significant probabilities (p < 0.05).
† More than two bleeds into a single joint over 6 months.
‡ Level of disability.
HCV = hepatitis C virus.
moderate disease. Conversely, noticeable differences were present between the severe hemophilia B patients and the general population for all of the four “physical component” items, whereas the only markedly lower “mental component” was “role-emotional” (Table S2, available as supporting information in the online version of this paper).

The disease-specific QUAL-HEMO questionnaire for adults yielded similar results (Fig. S3, available as supporting information in the online version of this paper). All items were significantly different between the patients with moderate and severe disease except for the items entitled “relevance of information received” and “reason for concern.” In addition, there was no difference between the treatment regimens or the types of FIX.

The KIDSCREEN self-administered generic questionnaire for children and adolescents between 8 and 18 years old was completed by 35 boys of the 51 included (2/3). Two additional questionnaires were included because they were from children who were 8 years old by the end of the study. One questionnaire was not usable, and thus the results are given for 35 children. The results were markedly different from those of adults, even if no direct comparisons are possible as the dimensions are not the same, because the only significant difference in scoring between the patients with severe and moderate disease was for “social acceptance” (Fig. S4, available as supporting information in the online version of this paper). There was no difference between the patients treated on demand and by prophylaxis or between the rFIX and pdFIX treatments.

The parents’ version of the KIDSCREEN generic questionnaire was available for 49 children and adolescents. The only significant differences reported concerned the “school” dimension between the children treated on demand and by prophylaxis (45.1 ± 7.0 and 51.0 ± 9.0, respectively; p = 0.034) and the “financial resources” dimension between rFIX and pdFIX (48.3 ± 12.1 and 40.7 ± 10.6, respectively; p = 0.042). Furthermore, the parents’ versions of the KIDSCREEN were available for the 35 children. Because the dimensions are identical, we compared the two questionnaires. Interestingly, the perception of the disease by children was more optimistic than that of their parents (data not shown).

The QUAL-HEMO hemophilia-specific scores are presented by age groups. The subgroups had to be analyzed with caution because of their size. For children between 8 and 12 years old, the only significant differences were observed between the patients with moderate and severe disease and between the on-demand and prophylactic treatment regimens for the dimension “absence of anxiety” (Data Supplement S1, Fig. S5, available as supporting information in the online version of this paper). For the parents of children between 2 and 12 years old, there was no difference according to subgroup (Data Supplement S1, Fig. S6, available as supporting information in the online version of this paper). Finally, for adolescents between 13 and 18 years old, the results were difficult to interpret due to an imbalance in the groups (Data Supplement S1, Fig. S7, available as supporting information in the online version of this paper).

Medicoeconomic analysis

The medicoeconomic study involved 126 of the 155 patients included (81.3%). One patient (0.6%) died during the follow-up, and 28 (18.1%) with incomplete data were excluded. These 126 patients were not significantly different in terms of age, treatment regimen, FIX type, QoL scores, and WFH joint score (data not shown). Of these patients, 93 (73.8%) and 33 (26.2%) had severe and moderate hemophilia, respectively, and 76 (60.3%) and 50 (39.7%) were receiving an on-demand and prophylactic treatment regimen, respectively. Additionally, there was an equal repartition between rFIX and pdFIX. Among these 126 patients, two with a complete follow-up used no medical resources, including FIX, during the 1-year follow-up. They were two young adults of 18 and 26 years of age with moderate hemophilia B who were usually treated with rFIX and pdFIX, respectively.

The mean total medical cost per year was €95,619 ± €83,142 (Table 2). FIX was the major cost driver (90%). The total annual cost was higher for severe than for moderate disease (€117,012 ± €82,318 and €35,329 ± €49,419, respectively; p < 0.001), with an identical contribution of FIX. There was also a significant difference in cost according to treatment regimen: €69,425 ± €80,363 for the patients treated on demand and €135,433 ± €71,126 for the patients receiving prophylaxis (p < 0.001). Nevertheless, the contributions of FIX to the cost were different: 82% for the patients treated on demand and 96% for the patients receiving prophylaxis (Table 2). There was also a significant difference in cost between patients treated with rFIX (€110,874 ± €95,167) and pdFIX (€80,363 ± €66,385, p = 0.039), whereas the contributions of FIX to the cost were nearly the same (91 and 88%, respectively).

A cost-effectiveness analysis was then performed to compare the on-demand and prophylactic treatment regimens. As shown previously, there were more hemorrhages in the patients treated on demand than in those receiving prophylaxis, with a difference in the annual number of hemorrhages of 2.9. However, the cost of prophylaxis was €66,008 higher. The ratio of the difference in cost to effectiveness showed that the cost to prevent one hemorrhage event per year was €22,605 (Table 3). However, a cost-minimization analysis, a pharmacoeconomic method for comparing drugs of equal efficacy and tolerability, indicated no difference in cost between rFIX and pdFIX (data not shown).

In addition, a multivariate analysis of annual medical costs was performed for 118 patients because eight patients had missing data for important covariates (Table 4). The model was significant (p < 0.0001) and explained...
| Variable                                      | Total (n = 126) | Severe (n = 93) | Moderate (n = 33) | p value | On demand (n = 76) | Prophylaxis (n = 50) | p value | rFIX (n = 63) | pdFIX (n = 63) | p value |
|-----------------------------------------------|----------------|----------------|------------------|---------|-------------------|---------------------|---------|---------------|---------------|---------|
| Total medical cost per year                   |                |                |                  |         |                   |                     |         |               |               |         |
| Mean ± SD                                     | €95,618.6 ±    | €117,011.7 ±   | €35,329.1 ±      | <0.001*| €69,425.0 ±       | €135,432.9 ±       | <0.001*| €110,874.3 ± | €80,362.9 ±   | 0.039*  |
| Median                                        | €83,297.2      | €106,885.2     | €142,959.9       |         | €39,821.1         | €119,790.3         |         | €99,661.9     | €77,699.6     |         |
| Range                                         | [€385,685.4]   | [€385,685.4]   | [€157,000.5]     |         | [€385,685.4]      | [€349,935.0]       |         | [€385,685.4]  | [€286,974.0]  |         |
| Cost distribution (%)                         |                |                |                  |         |                   |                     |         |               |               |         |
| FIX†                                          | 89.96          | 89.99          | 89.71            |         | 81.89             | 96.25               |         | 91.09         | 88.40         |         |
| Viral infectious drug                         | 2.62           | 2.59           | 2.93             |         | 4.93              | 0.82                |         | 2.50          | 2.78          |         |
| Antalgic                                      | 0.09           | 0.08           | 0.10             |         | 0.12              | 0.06                |         | 0.09          | 0.08          |         |
| All drugs (subtotals)                         | 92.67          | 92.66          | 92.74            |         | 86.93             | 97.13               |         | 93.68         | 91.26         |         |
| Hospitalizations                              | 1.13           | 1.09           | 1.50             |         | 2.06              | 0.39                |         | 1.36          | 0.81          |         |
| Life-threatening hemorrhages                  | 0.44           | 0.45           | 0.35             |         | 1.00              | 0.00                |         | 0.00          | 1.05          |         |
| Non-life-threatening hemorrhages              | 4.97           | 5.05           | 4.15             |         | 8.96              | 1.85                |         | 4.08          | 6.18          |         |
| All hemorrhages (subtotals)                   | 5.41           | 5.50           | 4.50             |         | 9.97              | 1.85                |         | 4.08          | 7.23          |         |
| All hospital costs including                  | 6.53           | 6.59           | 6.00             |         | 12.04             | 2.24                |         | 5.44          | 8.04          |         |
| hemorraghes (subtotals)                       |                |                |                  |         |                   |                     |         |               |               |         |
| Hemostasis investigations                    | 0.05           | 0.04           | 0.08             |         | 0.05              | 0.04                |         | 0.04          | 0.05          |         |
| General practitioner and specialist visits    | 0.12           | 0.10           | 0.25             |         | 0.17              | 0.07                |         | 0.11          | 0.12          |         |
| Medical auxiliaries                           | 0.17           | 0.17           | 0.21             |         | 0.21              | 0.14                |         | 0.17          | 0.17          |         |
| Medical devices                               | 0.05           | 0.06           | 0.03             |         | 0.07              | 0.04                |         | 0.05          | 0.05          |         |
| Transport                                     | 0.42           | 0.39           | 0.69             |         | 0.52              | 0.33                |         | 0.50          | 0.30          |         |
| All (subtotal excluded)                       | 100            | 100            | 100              |         | 100               | 100                  |         | 100.00        | 100.00        |         |

* Significant probabilities (p < 0.05).
† Costs calculated for the French case; with identical prices for rFIX or pdFIX: 1 IU = €0.72. At the time of inclusion, 1€ ~ US$1.3.
62.5% of the variance. The factors with the highest impact on cost were the treatment regimen (OR, 106.1; 95% CI, 22.5-499.2; p < 0.0001), HIV infection (OR, 15.9; 95% CI, 3.8-67.3; p < 0.0002), the presence of a target joint (at least two bleeds into a single joint over 6 months; OR, 15.3; 95% CI, 3.6-65.7; p = 0.0002), or a WFH joint score in the upper third of the range (OR, 8.3; 95% CI, 1.0-6.9; p = 0.0440), and patient’s weight (per 10-kg step, OR, 1.5; 95% CI, 1.1-2.1; p = 0.0265).

Finally, we analyzed the consumption of FIX by subgroup restricted to the 112 patients who received a FIX infusion during the study. FIX use was expressed in IU/kg body weight and converted into € given that both rFIX and pdFIX are priced at €0.72/IU in France (Table 5). Obviously, the cost of FIX was higher for severe disease than for moderate disease with a 2.5-fold higher FIX consumption and cost. Similarly, the patients treated by prophylaxis had a threefold higher FIX consumption and cost, whereas patient weight was significantly higher for the on-demand regimen than for prophylaxis. The consumption and cost of FIX were 1.4-fold higher for the patients treated with rFIX than for the patients receiving pdFIX, despite an absence of significant differences in the patients’ weight and annual number of infusions. The main difference was between the amounts of FIX used per infusion: 51.5±15.7 IU/kg per infusion for rFIX versus 43.1±17.9 IU/kg per infusion for pdFIX (p = 0.009, Table 5).

Therefore, a patient treated with rFIX will consume 811 IU/kg more each year than one treated with pdFIX. However, the analysis could not be sharpened because of the numbers of patients in subgroups.

### DISCUSSION

The available literature has established that hemophilia, similar to many chronic diseases, is a condition associated with a considerable burden on the patient and society. However, because of its higher prevalence, there is bias toward hemophilia A with only a limited number of studies focused exclusively on or presenting results separately for hemophilia B. In addition, the only published comparison of costs between rFIX and pdFIX treatments used a model based on pharmacokinetics differences.
### TABLE 5. Consumption and cost of FIX by subgroup

| Variable                          | 
|-----------------------------------|
| **Severity status**               | **Treatment regimen** |
| **On demand**                     | **Prophylaxis**       |
| **Type of FIX**                   | **p value**           |
| **FIX cost per kg/year**          | $\text{Mean} \pm \text{SD}$ | $\text{Median}$ | $\text{Range}$ | $\text{p value}$ |
| **Mean ± SD**                     | $1803.38 \pm 1787.77$ | $1559.16$ | $13.87-17302.79$ | $<0.001\dagger$ |
| **Median**                        | $1803.38 \pm 1787.77$ | $1559.16$ | $13.87-17302.79$ | $<0.001\dagger$ |
| **Range**                         | $1803.38 \pm 1787.77$ | $1559.16$ | $13.87-17302.79$ | $<0.001\dagger$ |
| Total amount of FIX in IU/kg/year | $2453.7 \pm 2432.4$   | $2122.0$ | $18.9-9934.2$ | $<0.001\dagger$ |
| **Mean ± SD**                     | $2453.7 \pm 2432.4$   | $2122.0$ | $18.9-9934.2$ | $<0.001\dagger$ |
| **Median**                        | $2453.7 \pm 2432.4$   | $2122.0$ | $18.9-9934.2$ | $<0.001\dagger$ |
| **Range**                         | $2453.7 \pm 2432.4$   | $2122.0$ | $18.9-9934.2$ | $<0.001\dagger$ |
| Total number of FIX infusions per year | $53.5 \pm 46.1$ | $46.1$ | $0.4-147.9$ | $<0.001\dagger$ |
| **Mean ± SD**                     | $53.5 \pm 46.1$ | $46.1$ | $0.4-147.9$ | $<0.001\dagger$ |
| **Median**                        | $53.5 \pm 46.1$ | $46.1$ | $0.4-147.9$ | $<0.001\dagger$ |
| **Range**                         | $53.5 \pm 46.1$ | $46.1$ | $0.4-147.9$ | $<0.001\dagger$ |
| Mean amount of FIX in IU per infusion per year | $47.3 \pm 63.3$ | $63.3$ | $7.6-98.7$ | $0.541$ |
| **Mean ± SD**                     | $47.3 \pm 63.3$ | $63.3$ | $7.6-98.7$ | $0.541$ |
| **Median**                        | $47.3 \pm 63.3$ | $63.3$ | $7.6-98.7$ | $0.541$ |
| **Range**                         | $47.3 \pm 63.3$ | $63.3$ | $7.6-98.7$ | $0.541$ |
| Patients' weight (kg)             | $60.8 \pm 63.3$ | $63.3$ | $64.8$ | $0.016$ |
| **Mean ± SD**                     | $60.8 \pm 63.3$ | $63.3$ | $64.8$ | $0.016$ |
| **Median**                        | $60.8 \pm 63.3$ | $63.3$ | $64.8$ | $0.016$ |
| **Range**                         | $60.8 \pm 63.3$ | $63.3$ | $64.8$ | $0.016$ |

* On the basis of patients with a positive consumption of FIX. Costs calculated for the French case with identical prices for rFIX or pdFIX: 1 IU = €0.72. At the time of inclusion, 1€ ~ US$1.3.
† Significant probabilities (p < 0.05).
Therefore, our work is the first focused only on hemophilia B and extensively analyzing the cost of this disease in real practice from the point of view of the third-party payer.

EQOFIX is the first prospective study of hemophilia B in which the overall burden of disease was associated with a medicoeconomic analysis. Therefore, with the inclusion of nearly 25% of the registered French population of severe and moderate hemophilia B patients, the EQOFIX study provides a genuine description of the care of hemophilia B in France. Moreover, with 155 patients included, EQOFIX is the largest prospective study of hemophilia B.

Analysis confirmed that the QoL is worse for people with severe than moderate hemophilia, especially on the physical dimensions.20,21 Furthermore, the analysis showed a worse QoL for patients treated prophylactically compared with those treated with an on-demand regimen, which was confirmed by multivariate analysis. Because there was no difference in articulare scores, we speculate that this difference may be linked to the burden of the regular infusion of FIX. However, for severe patients, there was no difference between treatment regimens. Therefore, this poorer QoL in patients treated by prophylaxis may also originate from the bias of reapportionment of treatment regimen in moderate patients, as 36 of 41 are treated on demand. Other main contributors to the physical components of the QoL were the number of joint lesions, presence of a target joint, and presence of associated pathologies. Conversely, there was no difference in the emotional scores. Moreover, no difference in the QoL, regardless of which scale was used, was observed between the types of FIX, whether recombinant or plasma derived.

Similar to the majority of previously published studies, the mean cost of clotting factor concentrates represented approximately 90% of the overall cost compared with approximately 99% for patients with inhibitors.23,24 However, in this study, this cost reached 96% of the total cost in patients treated by prophylaxis. In addition, whereas the total hospital cost was 12% of the total cost for patients treated on demand, the cost was only 2.2% for patients treated by prophylaxis. As this difference was mainly due to a reduction in hemorrhages, showing the efficacy of prophylaxis in hemophilia B,9 we calculated that the annual mean cost of one hemorrhage prevented by prophylactic treatment was €22,005, therefore, less than the usual threshold of $50,000 per quality-adjusted life-year.25 Because of the low total number of life-threatening hemorrhages (n = 5), we were not able to evaluate the annual cost of their prevention.

Finally, for the first time, we demonstrated that treatment with rFIX consumes 1.4-fold more clotting factor than with pdFIX. Indeed, this concept has been previously suggested by pharmacokinetics analysis or modeling of the consumption of FIX.18,19,26,27 However, it is lower that the approximately 1.6-fold increase in FIX needs modeled by Kisker and coworkers.19 Moreover, in contrast to France, in most countries, rFIX is more expensive than pdFIX on a per-IU basis. Therefore, in most countries, the real difference in annual cost may be higher than that described in France: €2859/kg/year of treatment for rFIX versus €2048 for pdFIX, respectively. However, this must be put into the perspective of the theoretical infectious safety of rFIX compared to pdFIX keeping in view that 1) cell lines used for recombinant protein production also produce viruses28 and 2) the question of interchangeability between therapeutic proteins is neither totally innocuous nor totally validated.

In conclusion, based on French patients with identical clinical outcomes, QoL, and WFH joint scores, EQOFIX, the largest medicoeconomic and QoL study of hemophilia B treatment, demonstrated that rFIX treatment is more expensive than pdFIX treatment with no difference in QoL or clinical results. This finding must be considered as FIX represents more than 90% of the total cost of the pathology and as the overall health care resources are becoming more and more restrained worldwide.4,6

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**CONFLICT OF INTEREST**

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Data Supplement S1. EQOFIX: a combined economic and quality of life study of hemophilia B treatments in France.