Impact of being underweight or overweight on factor VIII dosing in hemophilia A patients

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ABSTRACT

Since 1981, the number of factor VIII units to infuse into patients with hemophilia A in order to achieve adequate circulating factor VIII levels has been calculated using the formula: [body weight(kg)×desired factor VIII increase(%)]/2, assuming a factor VIII recovery value of 2 for all patients. This study's aim was to evaluate the impact of several morphometric parameters and various coagulation factor concentrates on factor VIII recovery. The analysis included 201 hemophilia A adults (>18 years of age) who were carefully selected from eight pharmacokinetic clinical trials using three recombinant factor VIII concentrates (Advate®, Kogenate® FS, or ReFacto AF®/Xyntha®). Regression tree analysis was used to identify factor VIII recovery predictors. The median factor VIII recovery was 2.16 for all patients. Using regression tree analysis, patients were separated into three groups on the basis of body mass index: below 20.3 kg/m^2, between 20.3 and 29.5 kg/m^2, and 29.6 kg/m^2 or more. Each group had a significantly different median factor VIII recovery (P<0.001): 1.60, 2.14, and 2.70, respectively. The type of coagulation factor concentrate had no influence on recovery in the regression tree. In conclusion, factor VIII dosing should be adapted to underweight and overweight patients, as a factor VIII recovery of 2 does not apply to these patients. Ideal body weight should be considered instead of actual body weight in the dose calculations.

Introduction

Hemophilia A is a hereditary hemorrhagic disease characterized by partial or complete deficiency of circulating factor VIII (FVIII).[1] Therapy with intravenous infusions of FVIII clotting concentrates may be preventive or curative in cases of bleeding episodes. Under-treatment exposes patients to hemorrhages, and over-treatment results in a waste of costly concentrates. Therefore, correct FVIII dosing is vital.

The number of FVIII units required to obtain adequate circulating FVIII levels is calculated using the following formula: [body weight (BW)(kg) × desired FVIII increase(%)]/2. This formula is based on a FVIII *in vivo* recovery value of 2 (IU dL^{-1}/IU kg^{-1}), so each FVIII unit infused per kilogram of BW increases the circulating FVIII level by 2%. Since only a small fraction of FVIII circulates outside the vascular system,[2] we hypothesized that the FVIII recovery increases with respect to patient's BW and fat mass, and is not 2% for all patients.

We previously reported the influence of several morphometric parameters on FVIII *in vivo* recovery in a small number of hemophilia A patients.[3] In brief, FVIII recovery was found to be dependent on both BW and fat mass index (FMI), suggesting that FVIII dosing should be adapted specifically to underweight and overweight patients.

This study aimed to describe the impact of several morphometric parameters [BW, FMI, and body mass index (BMI), difference between BW and ideal BW, and height], as well as patient's age, and type of recombinant coagulation concentrate (Advate®, Kogenate® FS, and ReFacto AF®/Xyntha®) on FVIII recovery in a large sample of patients who had previously been enrolled in different clinical pharmacokinetic trials.

Methods

Patients

The study included 201 adult people with hemophilia A who had previously participated in a clinical trial designed to evaluate the pharmacokinetic and hemostatic efficacy of several commercially available recombinant FVIII concentrates, namely Advate® (n=144), Kogenate® FS (n=31), and ReFacto AF®/Xyntha® (n=26) (Figure 1).

The inclusion criteria were age >18 years, available values of FVIII concentrations measured by a one-stage clotting assay at the time of infusion and 15 and 30 minutes after infusion, and recorded data on the infused dose, as well as the patient's height and BW at the time of the pharmacokinetic study (Figure 1). For patients who took part in repeated pharmacokinetic assessments, the FVIII values and corresponding morphometric variables from the first evaluation were considered.

Patients' characteristics and clinical variables

Baseline characteristics, including age, height, BW, coagulation factor dose, coagulation factor concentrate type (Advate®, Kogenate® FS or ReFacto AF®/Xyntha®), as well as FVIII levels before and after FVIII administration, and after FVIII recovery, were obtained from the pharmaceutical companies. FVIII recovery was calculated according to the following formula: [body weight(kg)×observed FVIII increase(%)]/administrated dose(IU). The FVIII value used to calculate the observed FVIII increase was the larger of the two measurements obtained at 15 and 30 minutes after infusion. FVIII recovery was expressed as the percentage rise of FVIII per unit of FVIII per kg infused. BMI was calculated according to the following formula: body weight (kg)/height (m)^2. Ideal body weight (IBW) was calculated using the Lorentz formula: height(cm)–100–[(height(cm)–150)/4]. The

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FMI(%) was calculated using the Deurenberg formula: (1.2×BMI(kg.m^{-2}))+(0.23×age(years))–(10.8×gender)–5.4, where the gender was replaced by 1 for men.[4]

Statistical analysis

Variables were analyzed using means and standard deviations when the data were normally distributed, and medians (P_{25} and P_{75}) when data were not normally distributed. Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using Pearson's chi-squared test.

Regression tree analysis was used to create homogeneous groups of patients regarding BW, as well as differences between BW and IBW, in order to compare FVIII recovery between groups. With respect to BMI and FMI, cut-off values to form the groups were obtained from the literature. In addition, regression tree analysis was used to analyze the relationship between several determinants, such as morphometric variables, age, coagulation factor type, and FVIII recovery. The regression tree-based models used were non-linear and non-parametric alternatives to linear models for regression problems.[5,6] The regression tree models were fitted using recursive partitioning of a multidimensional covariate space, in which the dataset was successively split into homogeneous subgroups. The selected split maximized the homogeneity of the two resulting nodes with regard to the response variable. The one-standard error rule was used to select the best tree. A random forest provided a ranking based on each variable's overall contribution that was included in the tree's construction. Statistical analyses were performed using R software version 2.12.0 (Free Software Foundation, Inc., Boston, Massachusetts, USA) and Salford Predictive Modeler Builder version 6.6 (Salford Systems, San Diego, CA, USA). A P value <0.05 was considered statistically significant.

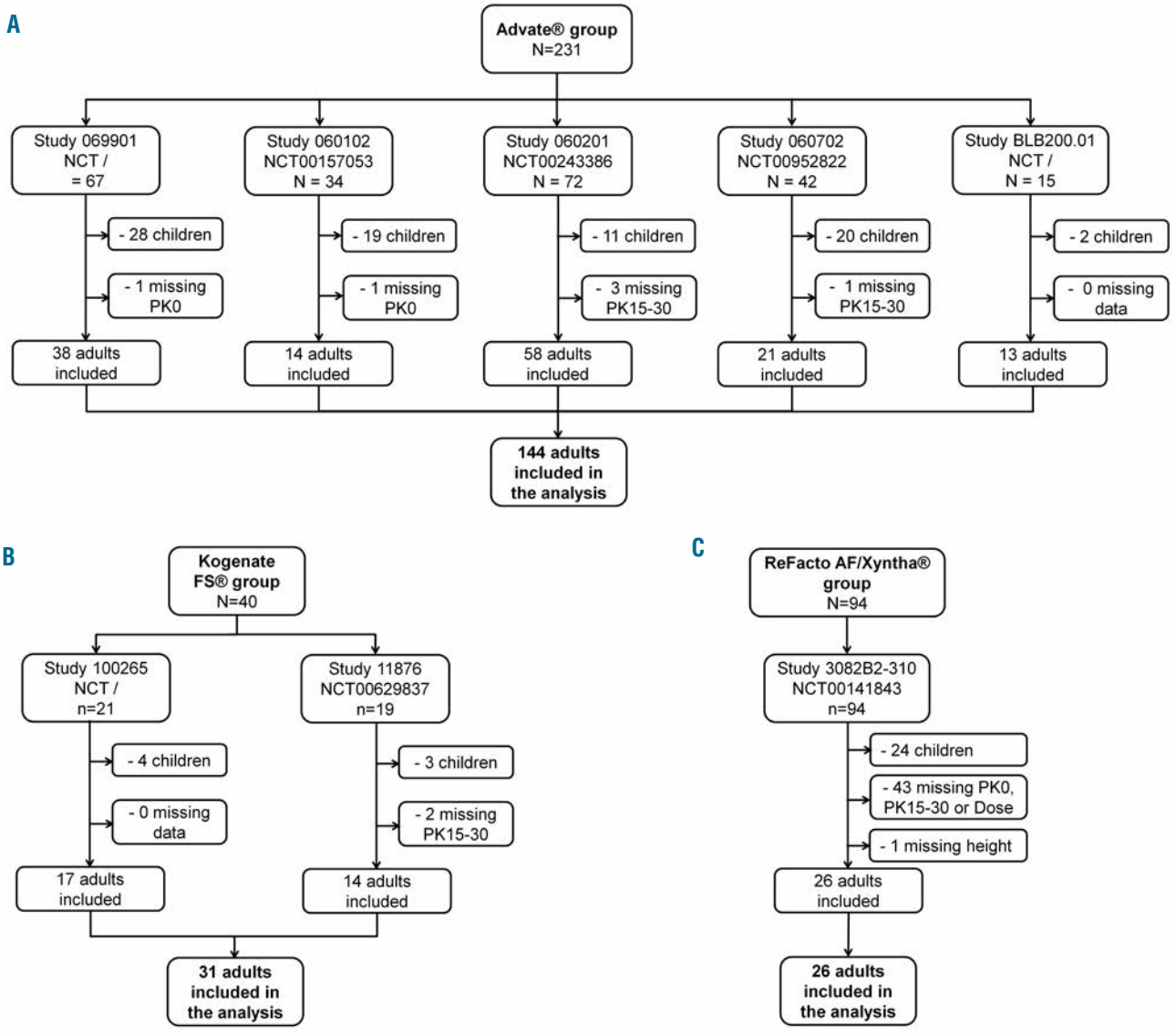

Figure 1. Description of selection of patients in the Advate® group (A), Kogenate® FS group (B), and ReFacto AF®/Xyntha® group (C). NTC: unique identifier in ClinicalTrials.gov; PK0: measure of factor VIII at the time of infusion; PK15-30: measure of factor VIII at 15 and 30 minutes; Dose: dose of factor VIII infused; Height: height of the patient.

Results

Patients' characteristics

The median [P_{25}; P_{75}] age of the 201 patients was 26.0 [21.0; 38.0] years (Table 1), with no significant difference in age distribution between the groups treated with Advate®, Kogenate® FS, or ReFacto AF®/Xyntha® (P=0.735) (Table 1). Patients received a median FVIII dose of 3745 IU, with a minimum of 1953 IU and maximum of 8794 IU (Table 1).

A small proportion of the patients (n=9/201, 4.5%) were underweight (BMI <18.5 kg/m^2); 52.2% (n=105/201) had a normal BMI between 18.5 and 24.9 kg/m^2; 25.9% were pre-obese (n=52/201), with a BMI between 25.0 and 29.9 kg/m^2; and 17.4% were obese (n=35/201), with a BMI ≥30.0kg/m^2. Regarding FMI, 33.8% (n=68/201) had a normal FMI between 15 and 20%, 17.4% (n=35/201) had a FMI below 15%, while 48.8% (n=98/201) were obese, with a FMI ≥20% (Table 1). In total, 144 patients had been enrolled in Advate® (n = 144/201, 71.6%), 31 in Kogenate® (n=31/201, 15.4%), and 26 in ReFacto AF®/Xyntha® clinical trials (12.9%) (Table 1).

The median FVIII recovery was 2.16 IU/dL/IU/kg (Table 1), with a significant difference between the three clotting factor groups in univariate analysis (Table 1). The median FVIII recovery was 2.14 IU/dL/IU/kg in the Advate® group, 2.49 IU/dL/IU/kg in the Kogenate® FS group, and 1.80 IU/dL/IU/kg in the ReFacto AF®/Xyntha® group (P<0.001). Median BW, median difference between BW and IBW, median BMI, and median FMI were significantly higher in the Kogenate® FS group than in the Advate® one (Table 1).

Factor VIII recovery and morphometric predictors (univariate analysis)

Using the regression tree method, patients were divided into four groups according to BW: low (<66.5 kg; n=46), medium (66.5-83.3 kg; n=90), high (83.4-102.2 kg; n=46), and very high (≥102.3 kg; n=19). The median FVIII recovery was 1.84, 2.12, 2.37, and 2.64 for each group, respectively. FVIII recovery differed significantly between the four BW groups (P<0.001), except between the high and the very high BW group. The median FVIII recovery in the different BW groups is illustrated in a box plot (Figure 2A).

Patients were divided into four analysis groups on the basis of their BMI: those with a BMI <18.5 kg/m^2 [underweight patients (n=9); median FVIII recovery=1.72], those with a BMI between 18.5 and 24.9 kg/m^2 [normal patients (n=105); median FVIII recovery=2.03], those with a BMI between 25.0 and 29.9 kg/m^2 [overweight patients (n=52); median FVIII recovery=2.18], and those with a BMI ≥30.0 kg/m^2 [obese patients (n=35); median FVIII recovery=2.68] (Figure 2B). FVIII recovery was significantly lower in the underweight, normal, and overweight groups than in the obese group (P<0.001).

Patients were divided into three groups based on FMI: FMI <15.0% (n=35), between 15.0 and 19.9% (normal; n=68), and ≥20.0% (n=98). The median FVIII recovery for the three groups was 1.72, 2.13, and 2.37, respectively. FVIII recovery was significantly different between the three groups (P<0.001) (Figure 2C).

To evaluate the impact of the difference between BW and IBW, four groups were created using the regression tree: patients with a BW difference <0.4 kg (median FVIII recovery: 1.86; n=61), between 0.4 and 15.0 kg (median FVIII recovery: 2.16; n=87), between 15.1 and 31.5 kg (median FVIII recovery: 2.35; n=35), and ≥31.6 kg (median FVIII recovery: 2.66; n=18). FVIII recovery differed significantly between these four groups (P<0.001), except between the second and third groups, and between the third and last groups (Figure 2D).

Table 1. Patients' baseline and clinical characteristics for the whole cohort (N=201) and comparison between the patients in the Advate®, Kogenate® FS, and ReFacto AF®/Xyntha® groups.

Variables	Whole cohort (N=201) Median [P25; P75] or N. (%)	Type of coagulation factor: Advate® (n=144) Median [P25; P75] or N. (%)	Kogenate® FS (n=31) Median [P25; P75] or N. (%)	ReFacto AF®/ Xyntha® (n=26) Median [P25; P75] or N. (%)	P
FVIII recovery, IU dL^{-1}/IU kg-1	2.16 [1.81; 2.51]	2.14 [1.80; 2.50]	2.49 [2.20; 2.89]	1.80 [1.57; 2.28]	<0.001
FVIII dose, IU	3745 [3328; 4319]	3727 [3306; 4201]	3731 [3388; 4333]	3952 [3724; 4641]	0.20
Age, years	26.0 [21.0; 38.0]	27.0 [21.0; 39.3]	27.0 [21.0; 36.5]	25.5 [22.0; 34.8]	0.74
Height, cm	176.1 ± 7.7*	176.0 [170.2; 180.1]	175.3 [170.2; 180.6]	182.0 [173.6; 184.8]	0.04
BW, kg	75.0 [67.5; 88.0]	74.3 [66.8; 83.9]	85.6 [69.2; 109.7]	79.8 [74.1; 88.8]	0.008
IBW difference, kg	6.1 [-1.3; 16.2]	3.6 [-1.5; 10.7]	20.1 [1.9; 33.1]	8.6 [1.8; 13.9]	0.006
BMI, kg m^{-2}	24.3 [22.0; 27.4]	23.7 [21.9; 26.1]	29.4 [23.1; 32.3]	25.2 [22.8; 27.1]	0.005
<18.5	9 (4.5)	7 (4.9)	0 (0.0)	2 (7.7)	
18.5-24.9	105 (52.2)	83 (57.6)	12 (38.7)	10 (38.5)	
25.0-29.9	52 (25.9)	37 (25.7)	5 (16.1)	10 (38.5)	
≥30.0	35 (17.4)	17 (11.8)	14 (45.2)	4 (15.4)	
FMI, %	19.8 [16.8; 24.6]	19.5 [16.6; 24.2]	23.7 [19.2; 29.8]	20.0 [16.6; 24.3]	0.02
<15.0	35 (17.4)	26 (18.1)	4 (12.9)	5 (19.2)	
15.0-19.9	68 (33.8)	54 (37.5)	6 (19.4)	8 (30.8)	
≥20.0	98 (48.8)	64 (44.4)	21 (67.7)	13 (50.0)	

Mean ± standard deviation, FVIII: factor VIII; BW: body weight of the patient; IBW difference: difference between body weight and ideal body weight; BMI: body mass index; FMI: fat mass index

Morphometric predictors of factor VIII recovery (multivariate analysis)

Regression tree analysis was employed to create homogeneous groups of patients with respect to FVIII recovery (Figure 3). Potential predictors of FVIII recovery used in the analysis were coagulation factor concentrate and morphometric variables, such as BW, the difference between BW and IBW, BMI, FMI, and height and age of the patients.

Using regression tree analysis, five groups were created, two of which included an outlier patient (groups 1 and 3); among the three other groups, BMI appeared to be the strongest predictor of FVIII recovery with cut-off values of 20.3 and 29.6 kg/m^2 (Figure 3). The remaining three groups were composed of patients with BMI <20.3 kg/m^2 (group 2), between 20.3 and 29.5 kg/m^2 (group 4), and ≥29.6 kg/m^2 (group 5) (Figures 3 and 4). Based on the box plot (Figure 4) of the FVIII recovery of the five random tree-generated groups, FVIII recovery was significantly higher in group 4 than in group 2, in group 5 than in group 2, and in group 5 than in group 4 (P<0.001). The median FVIII recovery [P_{25}; P_{75}] was 1.60 [1.42; 1.79] in group 2, 2.14 [1.83; 2.43] in group 4, and 2.70 [2.36; 2.92] in group 5. Groups 1 and 3 were both compounded by one outlier patient.

Concerning the associated random forest, BMI and FMI had a discriminatory power of 91.3 and 56.9, respectively. Although BW and the difference between BW and IBW were important predictors for FVIII recovery in the associated random forest, as evidenced by their discriminatory power ranking of 100.0 and 75.9, respectively, they did not appear to be main splitters in the final tree. Height had a minor influence, yet age and coagulation factor concentrate had no influence (power of 0.0) in the final tree.

In group 2, which was created by the regression tree, 82.6% (n=19/23) of patients were undertreated (FVIII recovery <2), compared to 37.1% (n=52/140) in group 4, and 11.1% (n=4/36) in group 5. The proportion of undertreated patients differed significantly between the three groups (P<0.001).

Discussion

In this study, we investigated the relationship between FVIII recovery and several morphometric variables, such as age, and recombinant factor type (Advate®, Kogenate® FS and ReFacto AF®/Xyntha®), in 201 patients who had been enrolled in pharmaceutical clinical trials. To our knowledge, this is the first study to assess the value of

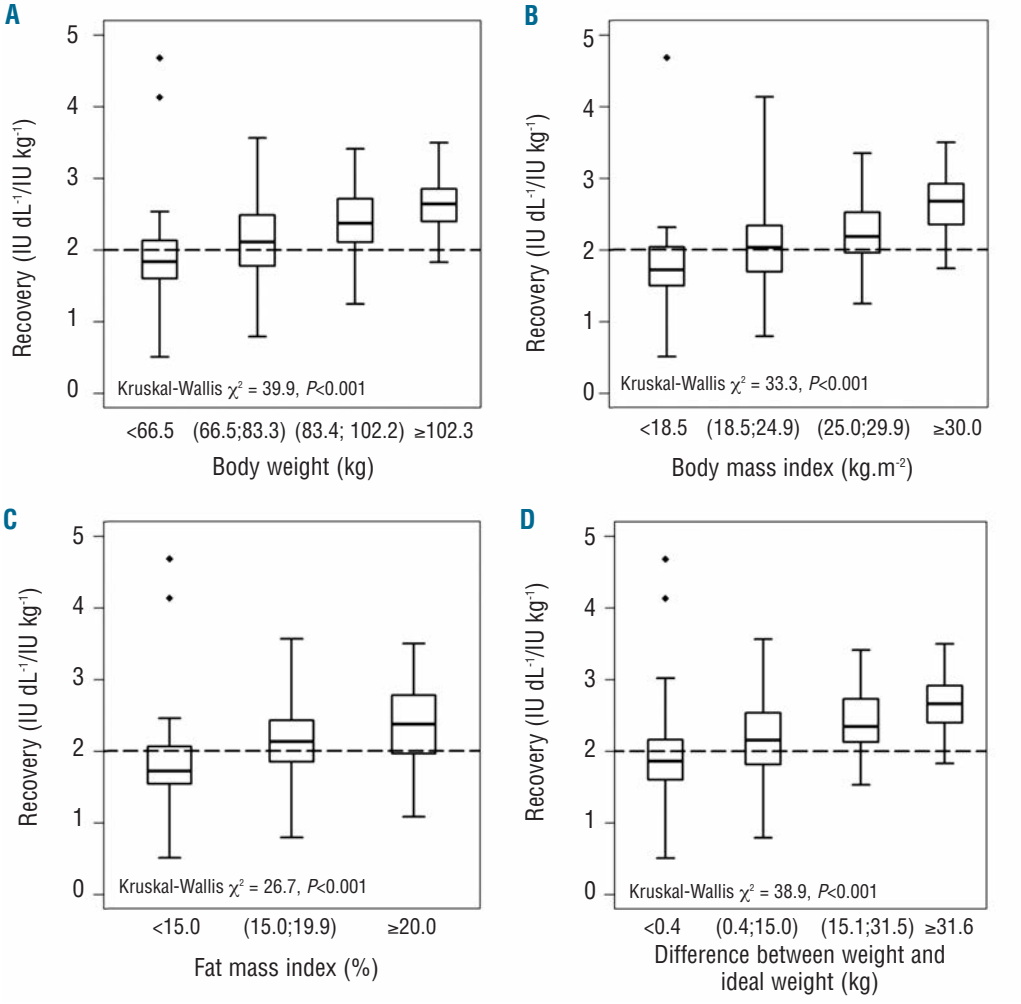

Figure 2. Box plot of factor VIII recovery according to body weight (A), body mass index (B), fat mass index (C), and difference between body weight and ideal body weight (D).

FVIII recovery in a large sample of patients since the 1981 implementation of FVIII dosing. As demonstrated by regression tree analysis (Figure 3), BMI was the strongest predictor of FVIII recovery, whereas recombinant factor type and age had no influence in the regression tree analysis. Regression tree analysis defined three important groups of patients: those with a BMI <20 kg/m^2 and median FVIII recovery of 1.60; those with a BMI between 20 and 30 kg/m^2 and median FVIII recovery of 2.14; and those with a BMI ≥30 kg/m^2 and a median FVIII recovery of 2.70. The median FVIII recovery differed significantly between these three groups (P<0.001).

The FVIII dose administered to people with hemophilia A has long been considered equal to the desired FVIII increase in IU/dL multiplied by the plasma volume (dL). In 1981, Ingram[7] evaluated three different methods for calculating the infused FVIII dose based on data from 19 people with hemophilia and a BW between 27 and 91 kg. According to Ingram's[7] conclusion, the dose calculation using a plasma volume of 0.5 dL/kg could be applied as long as the patient's physical build did not differ markedly from the average. The author recommended that in the case of underweight or overweight patients, plasma volume calculations should consider BW and height. In spite of these warnings and previously reported differences in FVIII recovery,[3] the validity of FVIII dosing based on the universal FVIII recovery value of 2 has never been reassessed.

A small fraction of FVIII, approximately 14% of the body load of FVIII, is currently known to circulate outside the vascular system.[2] However, only a few studies have evaluated the dependence of FVIII recovery on several morphometric variables.[8-10]. Blanchette *et al.*[9] concluded that BMI was a significant anthropometric predictor of adjusted *in vivo* recovery. Björkman *et al.*[8] showed that recovery significantly increased with the weight ratio, which is defined by the actual/ideal weight for age among hemophiliacs aged 10-65 years old. Furthermore, Collins *et al.*[10] reported that *in vivo* recovery increased with the patient's BW and suggested using ideal weight rather than actual weight in FVIII dose calculations.

In our study, FVIII recovery was found to be significantly dependent on BMI. Therefore, a standard rise of 2%/IU in FVIII/kg infused dose does not apply to patients with a BMI <20 or ≥30kg/m^2. Moreover, of the 201 patients, 43.3% were overweight and 17.4% obese. Adapting the FVIII dose to individual morphometric parameters appears to be relevant because of the large number of obese people with hemophilia A.[11]

One of this study's limitations was not having evaluated FMI using accurate techniques, as the data necessary were unavailable, but only by means of the Deurenberg formula: [1.2 × BMI (kg.m^{-2})] + [0.23 × age(years)] - [10.8 × gender] – 5.4, where gender was replaced by 1 for men.[4] It might be of interest to evaluate FMI by impedance in future studies designed to assess the pharmacokinetic properties of FVIII concentrates. Another limitation of our study is that it only included patients treated with recombinant FVIII concentrates because a group of patients of similar size and profile treated with plasma-derived concentrate was not available for comparison. Although unlikely, one cannot rule out that the impact of morphometric variables on recovery would be different in patients treated with plasma-derived FVIII concentrates.

In this study, only the dependency of FVIII recovery on morphometric variables was analyzed, yet the variables' influence on concentrate half-life or clearance was not considered. However, concentrate clearance was reported to significantly affect the frequency of FVIII administrations when given either in a preventive or curative manner. Major efforts are currently underway to prolong the half-lives of FVIII products and thereby reduce infusion frequency. The recovery impact on FVIII kinetic behavior should not be underestimated. In patients with a recovery >2, higher and longer FVIII level corrections were obtained following FVIII infusion compared to patients with a recovery <2. Although the impact of morphometric variables, such as BMI, on concentrate half-life has not been

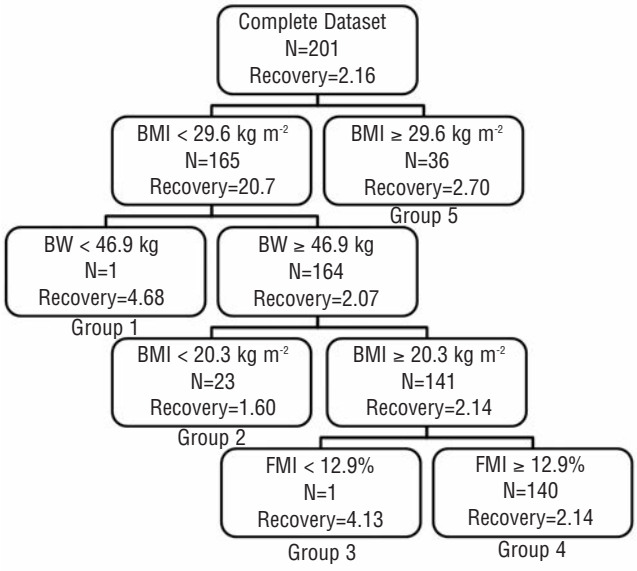

Figure 3. Regression tree representing the predictors for FVIII recovery. The selected splitting variables (BMI: body mass index; BW: body weight; FMI: fat mass index) are shown in the nodes.

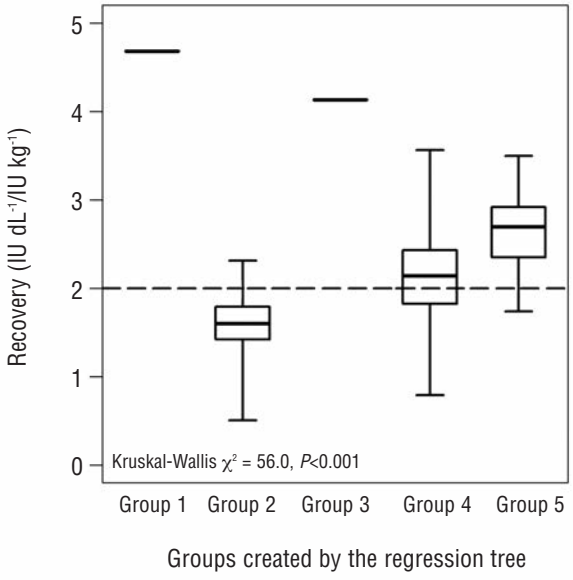

Figure 4. Box plot of factor VIII recovery according to groups created using a regression tree.

extensively studied, it is likely minor. Since our study only included rather young patients (median age, 26 years), one cannot rule out that the recovery could change with aging. In a previous study involving a much smaller group of patients of different ages (mean age, 40.4±12.3 years), no impact of age on the recovery was identified by regression tree analysis.[3]

In conclusion, based on our findings, the clinical practice of FVIII dose calculations aimed at reaching adequate FVIII target levels should be adapted for underweight and overweight patients. The ideal BW rather than the actual BW should be considered in the dose calculations, given that only a small fraction of FVIII circulates outside the vascular system.[2] The long-held and current practice of applying an arbitrary and universal recovery of 2 to the calculations of FVIII dosage should be abolished. Moreover, our data support crossover studies that exhibit the ideal design for validating and comparing pharmacokinetic properties of several FVIII concentrates. When comparing recovery of different concentrates in non-cross-over studies, the participants' morphometric characteristics must be taken into account. In addition, we hypothesize that new coagulation factors developed using pegylation, liposomal formulations, or fusion proteins would be subject to the same morphometric influences due to their larger size.[12]

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Authorship and Disclosures

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