Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A

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Supplementary methods

FranceCoag Network

FranceCoag is a health surveillance network established by the French public health authorities and coordinated by the national public health agency. It includes a cohort of patients with inherited deficiencies in coagulation proteins, such as hemophilia A and B, von Willebrand's disease, and other rare inherited bleeding disorders. Thirty-five French hemophilia treatment centers participate in FranceCoag. It was set up in France in 2003, as the continuation of a project called *Suivi thérapeutique national des Hémophiles* (national therapeutic follow-up of hemophiliacs) which started in 1994 and only concerned hemophilia. The FranceCoag protocol, along with dedicated forms, summary results, and other information, is available at http://www.francecoag.org/.

Additional data collection of treatment details

Independently of the FranceCoag Network, the French Hemophilia Association publishes a customized booklet for collecting the adhesive labels of all injected factor VIII (FVIII) or factor IX products in order to obtain details of home treatment. For several decades, this tool has been distributed to hemophilia patients in all French centers. In addition to data collected during hospitalization, this booklet allowed us to record the first 75 exposure days (EDs) with the infusion dates, FVIII product brands and doses, indications, bleeding events, and types of surgery. These additional data were collected by clinical research assistants independently of the basic data collection. Thus, any discrepancy between the two recording systems (regarding the date of the first infusion, FVIII products received, number of EDs at the date of inhibitor detection, initiation of regular prophylaxis, surgical procedures, and severe bleeding episodes) triggered extensive investigations based on the original files.

Definitions of severity classes of hemophilia A

Severe HA is defined as a baseline FVIII coagulant activity level <1 IU/dL.[1] To estimate the baseline FVIII coagulant activity level, the average of all results of one-stage functional assays performed at least three days after the previous injection was considered. In addition, for patients with a low-risk *F8* gene defect (small deletions/insertions without stop codon, missense mutations, and splice-site mutations) referenced in the European database EAHAD (www.factorviii-db.org) and/or in the US database CHAMP (www.cdc.gov/ncbddd/hemophilia/champs.html), the existence of severe forms of HA was checked.

Moderate HA is defined as a baseline FVIII coagulant activity level ≥1 and ≤5 IU/dL. This baseline FVIII coagulant activity level was also based on the average of all valid results of one-stage functional assays. In addition, the absence of high-risk *F8* gene defect (large deletions [at least 1 exon], intron 1 and 22 inversions, small deletions/insertions with stop codon [out of A-run] and nonsense mutations) was checked.

Definition of inhibitor development

In order to classify the patients as having or not having inhibitors, all cases were reviewed by an *ad hoc* clinical committee of four physicians, in a precise and uniform process. Inhibitor tests were considered positive if the value

was greater than 0.6 Bethesda units, using the standardized Bethesda method or the Nijmegen modified assay. The presence of an inhibitor was defined either by: (1) a first-order criterion, ie, at least two positive inhibitor assays of two different samples taken on two different dates, or (2) one positive inhibitor assay plus at least one of the following second-order criteria:

- an infused FVIII recovery of less than 1.3%/IU/kg. As no standardized definition was available, this cutoff was based on the criterion used to define success in the international immune tolerance study;[2]
- a reduced half-life (<6 hours) of infused FVIII;[2–4]
- administration of immune tolerance induction;[3]
- use of bypassing agents (recombinant activated factor VII or activated prothrombin complex concentrates);
- a significant increase in the FVIII concentrate dosage (chosen at the clinician's discretion) required to achieve adequate FVIII:C levels during intensive treatment; and, finally
- clinical inefficacy of FVIII treatment during a bleeding episode.

In the case of two positive inhibitor assays but normal FVIII recovery and/or a normal FVIII half-life, the first-order criterion was considered unmet and the patient's inhibitor status was classified as: 1) "questionable" if the inhibitor titer was less than 5 Bethesda units and if the interval between the inhibitor assay and the contradictory data was less than 15 days; or 2) "proven" if the inhibitor titer was higher than 5 Bethesda units.

Cofactor definitions and grouping procedures

Fixed risk factors were defined as follows:

- *F8* gene defects were classified into two groups, namely "low-risk" and "high-risk" mutations. High-risk mutations included large deletions (at least one exon), intron 1 and 22 inversions, small deletions/insertions with a stop codon (out of A-run) and nonsense mutations.
- The family history of hemophilia and inhibitors was classified in three ways: family history of hemophilia but not of inhibitors; family history of both hemophilia and inhibitors; and no family history of hemophilia.
- Up to four ethnic origins per patient (one for each grandparent) were recorded during an interview between the clinician and the PUP's parents. Ethnic origin was first classified into five groups: (1) White only; (2) mixed White and other non-African origin; (3) non-White, non-African; (4) mixed African or Afro-American and other non-African origin; and (5) African or Afro-American origin only. Because of the small numbers of patients in the non-White groups, the classification was simplified into 3 groups: 1) White only; 2) mixed and/or other non-African origin; and 3) African or Afro-American (at least one grandparent).
- Age at first exposure to a FVIII product was split into three roughly equal classes: less than 6 months old; 6 to 11 months old; and 12 months or older.

Time-varying risk factors were defined as follows:

- the calendar period of EDs was split into five classes yielding similar number of EDs in each period: 2001 to 2003; 2004 to 2006; 2007 to 2009; 2010 to 2012, and 2013 to 2016.

- Peak treatment episodes were defined as FVIII treatments, for bleeding or surgery, on at least 3, 5 or 10 consecutive days. For each of these peak types, five limited effect durations were tested (21, 45, 91, 183, 365 days), in addition to persistent effect until the end of follow-up. Finally, the 183-day duration (6 months) was selected for the three peak types because it maximized the HR for the relation with inhibitor development. Peak treatment episodes were associated with inhibitor development regardless of when they occurred during the observational period (ie, at first exposure to FVIII or after). Thus, we considered all peak treatment episodes as time-varying risk factors.
- Surgical procedures were taken into account if they were associated with at least three consecutive days of FVIII treatment (RODIN definition).[5] Five limited effect durations were tested (21, 45, 91, 183, 365 days) in addition to persistent effect until the end of follow-up. The observed association between surgical procedures and inhibitor development was weak, regardless of the effect duration, and this factor was not used in the final multivariate analyses.
- Severe bleeding episodes were defined as central nervous system hemorrhage or other life-threatening hemorrhage (eg, intraperitoneal, retroperitoneal or gastrointestinal bleeding). Five limited effect durations were tested (21, 45, 91, 183, 365 days) in addition to persistent effect until the end of follow-up. Finally, the 183-day duration (6 months) was selected because it maximized the HR for the association with inhibitor development. Severe bleeding episodes were associated with inhibitor development regardless of when they occurred during the observational period (ie, at the first exposure to FVIII or after) Thus, we considered all severe bleeding episodes as time-varying risk factors.
- The date of regular prophylaxis initiation was defined as the date when at least three consecutive prophylactic FVIII infusions were given within a period of at least 15 days (RODIN definition).[5] The effect of prophylaxis on inhibitor development was assumed to be consistent from its outset until the end of the follow-up.

Missing data procedures

Twenty-nine patients with insufficient data for the first EDs were excluded from the analyses (Figure 1). The *F8* gene defect was undetermined for 18 of the 395 selected boys. This group formed an additional category in the *F8* gene defect analyses. Ethnic information was missing for three of the 395 selected boys, who were assigned the most prevalent ethnic origin (White). All other required information was complete.

Propensity scores analyses

Propensity scores (PS) analyses are useful to account for imbalance in fixed risk factors between product groups.[6] PS represent the probability of receiving a treatment, conditionally on a set of measured covariates. We used PS in our analyses according to two well-acknowledged methods: stratifying by PS quintiles and inverse probability of treatment weighting (IPTW). PS were calculated by logistic regression using received treatment as the dependent variable. The four following sets of fixed risk factors were successively used as independent variables:

- Model 1: High-risk *F8* gene defect known at first FVIII infusion; family history of hemophilia and inhibitor known at first FVIII infusion.
- Model 2: Cofactors of Model 1 + Ethnic origin; calendar period of first exposure to FVIII; age at first exposure to FVIII.
- Model 3: Cofactors of Model 2 + Peak treatment episodes ≥3, ≥5 and ≥10 consecutive EDs at first exposure; first exposure linked to surgical procedure (with at least 3 EDs); first exposure linked to severe bleeding episode.
- Model 4: *F8* gene defect; family history of hemophilia and inhibitor; ethnic origin; calendar period of first exposure to FVIII; age at first exposure to FVIII; peak treatment episodes ≥3, ≥5 and ≥10 consecutive EDs at first exposure; first exposure linked to surgical procedure (with at least 3 EDs); first exposure linked to severe bleeding episode.

For each model, global and intra-quintile PS distributions were checked with histograms and box plots, respectively. Stabilized weights were calculated for each model. The imbalance of all fixed risk factors between product groups was checked using standardized differences before and after weighting.[7] Finally, we performed weighted Cox model analyses with PS of the chosen model.[8] The cumulative inhibitor incidences according to the FVIII products received were represented by weighted Kaplan-Meier curves for the three outcomes (PS of the three product groups were simultaneously calculated with multinomial logistic regression).

For each comparison (Advate versus Factane and Kogenate versus Factane) and each outcome (ie, all inhibitors, high-titer inhibitors and treated inhibitors), HRs were estimated using PS by stratifying on PS quintiles and IPTW. Results without and with adjustment for time-varying risk factors (ie, calendar period, peak treatment episodes ≥5 and ≥10 consecutive EDs after first exposure to FVIII, severe bleeding episodes after first exposure to FVIII, and regular prophylaxis) were shown. We chose the results of the last method (IPTW and adjustment for time-varying risk factors) as the most accurate of the PS analyses (in bold in Figure 4).

Supplementary results

Verification of the proportional hazards assumption of the Cox model

The proportional hazards assumption was checked by testing the correlation between the scaled Schoenfeld residuals and time.[9] The null hypothesis of zero slope was not rejected for the "all inhibitors" outcome (*P* global test = 0.287), or for the high-titer inhibitors (*P* global test = 0.518), or the treated inhibitors (*P* global test = 0.889). The proportional hazards assumption was also checked for each cofactor by plotting the curves of ln(-ln(S(t)). The curves of unadjusted estimates and estimates adjusted for all cofactors were nearly parallel for Factane, Advate, and Kogenate.

Assessing propensity scores

Patients first treated before 2004 were excluded from the comparisons between Advate and Factane using PS. After checking PS distributions and fixed risk factor imbalance, PS calculated with the Model 4 were chosen (Figures S2, S3 and S4).

Patients first treated after 2012 were excluded from the comparisons between Kogenate and Factane using PS. After checking PS distributions and fixed risk factors imbalance, PS calculated with the Model 4 were chosen (Figures S2, S3 and S5).

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Supplementary tables

Table S1. Year of first exposure to factor VIII according to the factor VIII product received.

	Factane (N=131)	Advate (N=137)	Kogenate (N=127)	*P*
Year of first exposure to factor VIII — no. (%)				<0.001
2001	8 (6.1)	0	3 (2.4)	
2002	9 (6.9)	0	17 (13.4)	
2003	4 (3.1)	0	14 (11.0)	
2004	6 (4.6)	5 (3.6)	9 (7.1)	
2005	4 (3.1)	16 (11.7)	6 (4.7)	
2006	6 (4.6)	14 (10.2)	7 (5.5)	
2007	11 (8.4)	11 (8.0)	10 (7.9)	
2008	13 (9.9)	15 (10.9)	10 (7.9)	
2009	13 (9.9)	10 (7.3)	15 (11.8)	
2010	9 (6.9)	8 (5.8)	10 (7.9)	
2011	8 (6.1)	11 (8.0)	6 (4.7)	
2012	1 (0.8)	12 (8.8)	15 (11.8)	
2013	7 (5.3)	12 (8.8)	5 (3.9)	
2014	11 (8.4)	9 (6.6)	0	
2015	14 (10.7)	11 (8.0)	0	
2016	7 (5.3)	3 (2.2)	0	

Table S2. Overall and individual follow-up of patients with and without inhibitors according to the factor VIII product received.

Overall follow-up	**Factane (N=131)**	**Advate (N=137)**	**Kogenate (N=127)**	**All Patients (N=395)**
Total number of person-years [a]	199.7	182.0	177.8	559.5
Total number of exposure days (EDs) [b]	6,540	6,426	5,278	18,244
Mean interval between EDs in days [a/b]	11.2	10.3	12.3	11.2
Median dose of factor VIII per ED (IU/kg) — med. (IQR)	46.1 (38.5-57.7)	43.5 (37.2-55.1)	44.2 (37.3-53.3)	44.7 (37.6-55.3)
Patients with inhibitors — no.	**25**	**36**	**60**	**121**
Total number of person-years [c]	18.7	28.3	35.7	82.7
Total number of EDs [d]	473	742	923	2,138
Mean interval between EDs in days [c/d]	14.4	13.9	14.1	14.1
Median individual follow-up in EDs — med. (IQR)	14 (9-19)	16 (10-24)	14 (8-19)	14 (8-20)
Patients without inhibitors — no.	**106**	**101**	**67**	**274**
Total number of person-years [e]	181.0	153.7	142.1	476.8
Total number of EDs [f]	6,067	5,684	4,355	16,106
Mean interval between EDs in days [e/f]	10.9	9.9	11.9	10.8
Patients who reached ED-25 — no. (%)	84 (79.2)	74 (73.3)	58 (86.6)	216 (78.8)
Patients who reached ED-50 — no. (%)	77 (72.6)	73 (72.3)	56 (83.6)	206 (75.2)
Patients who reached ED-75 — no. (%)	69 (65.1)	69 (68.3)	56 (83.6)	194 (70.8)
Patients who had not reached ED-75 (censored follow-up) — no. (%)	37 (34.9)	32 (31.7)	11 (16.4)	80 (29.2)
Reasons for censoring follow-up:				
Died (of intracranial hemorrhage) before ED-75 — no.	1	1	0	2
Switch to another factor VIII product before ED-75 — no.	12	7	5	24
Had not reached ED-75 at the last clinical visit (date <2015) — no.	3	6	5	14
Had not reached ED-75 at the last clinical visit (date ≥2015) — no.	21	18	1	40

Table S3. Switches from one factor VIII product to another during the first 75 exposure days according to the first factor VIII product received.

First factor VIII product received	Non-switcher patients	Switcher patients	
	No.	No.	Switch details *
Factane (N=131)	**119**	**12**	1*F -> 6*A -> 68*F 10*F -> 12*R -> 2*F -> 5*R -> 5*A -> 3*F -> 2*R -> 3*A -> 1*F -> 6*A -> 1*F -> 25*A 12*F -> 63*K 12*F -> 63*K 29*F -> 46*K 42*F -> 1*A -> 4*F -> 28*A 45*F -> 9*K -> 6*F -> 15*K 46*F -> 29*K 56*F -> 19*A 62*F -> 13*A 63*F -> 12*A 68*F -> 7*A
Advate (N=137)	**130**	**7**	1*A -> 17*F (-> inhibitor discovered 142 calendar days after the switch) † 1*A -> 73*F 2*A -> 10*K (-> inhibitor discovered 44 calendar days after the switch) † 5*A -> 3*ND (-> inhibitor discovered 32 calendar days after the switch) † 7*A -> 68*K 11*A -> 1*K -> 63*A 21*A -> 1*ND (-> inhibitor discovered 10 calendar days after the switch) †
Kogenate (N=127)	**122**	**5**	1*K -> 22*A -> 10*K -> 42*A 1*K -> 5*F (-> inhibitor discovered 115 calendar days after the switch) † 2*K -> 73*P 4*K -> 71*A 6*K -> 6*F
Total	**371**	**24**	

* Product exposure day sequence is shown for each patient. For example, "1*F -> 6*A -> 68*F" means 1 exposure day with Factane followed by 6 exposure days with Advate and lastly 68 exposure days with Factane.
Product R=Recombinate™ (Baxter Healthcare) or Bioclate™ (Aventis Behring); Product P=Refacto AF® (Pfizer); Product ND=unidentified.

† Five boys experienced inhibitor development after a product switch. These inhibitors were discovered far more than 7 calendar days after the switch. According to the rule defined in the statistical analyses section of this supplemental Data, these five inhibitors were not attributed to the first received product and thus were not considered in the analyses.

Table S4. Contribution in exposure days according to the factor VIII product received and the studied time-varying risk factors.

Time-varying risk factors	Factane (N=131)	Advate (N=137)	Kogenate (N=127)	All Patients (N=395)
Calendar period				
2001-2003	667	0	599	1,266
2004-2006	1,064	670	1,569	3,303
2007-2009	1,429	2,304	970	4,703
2010-2012	1,782	1,536	1,540	4,858
2013-2016	1,598	1,916	600	4,114
Peak treatment episodes				
No	3,498	3,540	3,026	10,064
At least 3 consecutive exposure days (EDs)	3,042	2,886	2,252	8,180
At least 5 consecutive EDs	1,622	1,275	1,025	3,922
At least 10 consecutive EDs	597	532	304	1,433
Surgical procedures associated with at least 3 consecutive EDs				
No	5,816	5,866	5,004	16,686
Yes	724	560	274	1,558
Severe bleeding episodes				
No	6,070	5,977	4,892	16,939
Yes	470	449	386	1,305
Regular prophylaxis *				
No	2,824	2,610	2,460	7,894
Yes	3,716	3,816	2,818	10,350
Total contribution	**6,540**	**6,426**	**5,278**	**18,244**

* The initiation of regular prophylaxis was defined as the moment at which at least three consecutive prophylactic infusions of factor VIII had been given within a period of at least 15 days (RODIN definition).[5]

Table S5. Inhibitor assay frequency according to the factor VIII product received.

Time-varying risk factors	Factane (N=131)	Advate (N=137)	Kogenate (N=127)	All Patients (N=395)
Total number of inhibitor assays	646	737	619	2,002
Total contribution — (Exposure days)	6,540	6,426	5,278	18,244
Mean number of exposure days between two inhibitor assays during the first 25 exposure days	6.5	5.7	5.8	6.0
Mean number of exposure days between two inhibitor assays for the entire follow-up period	10.1	8.7	8.5	9.1

Table S6. Associations between factor VIII (FVIII) product received, cofactors and occurrence of all inhibitors.

Population: Boys with severe HA (FVIII activity <1 IU/dL) treated with Factane, Advate or Kogenate within the first 75 exposure days (n=395). Main studied factor: FVIII product received during the first 75 exposure days (fixed factor). Statistical method: Cox proportional hazards model with exposure day as observational time. Adjusted hazard ratio (HR) took into account the following cofactors: four fixed factors (*F8* gene defect, family history of hemophilia and inhibitor, ethnic origin, and age at first exposure to FVIII) and five time-varying factors (calendar period, history of peak treatment episodes ≥5 and ≥10 consecutive exposure days, history of severe bleeding episodes, and regular prophylaxis initiation).

	Number of	Unadjusted analysis			Multivariate analysis		
Fixed risk factors	**exposure days**	**Crude HR**	**(95% CI)**	***P***	**Adjusted HR**	**(95% CI)**	***P***
FVIII product received				<0.001§			<0.001§
Factane	6,540	1.00			1.00		
Advate	6,426	1.44	(0.86-2.40)	0.162	1.41	(0.83-2.38)	0.199
Kogenate	5,278	2.77	(1.74-4.42)	<0.001	2.74	(1.67-4.48)	<0.001
***F8* gene defect**				<0.001§			<0.001§
Low risk	5,495	1.00			1.00		
High risk *	12,389	3.37	(1.89-5.99)	<0.001	3.11	(1.73-5.58)	<0.001
Undetermined (eg, not yet tested, unidentified)	360	1.93	(0.43-8.56)	0.387	2.41	(0.52-11.14)	0.262
Family history				0.016§			0.378§
Hemophilia without inhibitor	6,420	1.00			1.00		
Hemophilia with inhibitor	1,108	2.01	(1.15-3.54)	0.015	1.41	(0.79-2.54)	0.245
No family history of hemophilia	10,716	0.93	(0.63-1.37)	0.697	0.94	(0.62-1.42)	0.768
Ethnic origin †				0.025§			0.046§
White only (both parents)	14,046	1.00			1.00		
Other, not African or Afro-American	3,323	1.34	(0.87-2.06)	0.182	1.22	(0.78-1.92)	0.384
African or Afro-American (at least one grandparent)	875	2.16	(1.20-3.89)	0.010	2.13	(1.16-3.91)	0.015
Age at first exposure to FVIII				0.729§			0.266§
Less than 6 months	4,830	1.00			1.00		
6-11 months	6,434	0.84	(0.53-1.34)	0.472	1.08	(0.66-1.75)	0.765
At least 12 months	6,980	0.98	(0.63-1.51)	0.911	1.45	(0.88-2.37)	0.141
Time-varying risk factors							
Calendar period				0.225§			0.196§
2001-2003	1,266	1.00			1.00		
2004-2006	3,303	0.86	(0.43-1.73)	0.678	0.97	(0.47-2.00)	0.940
2007-2009	4,703	1.08	(0.57-2.06)	0.818	1.63	(0.82-3.24)	0.163
2010-2012	4,858	0.73	(0.37-1.45)	0.375	1.02	(0.50-2.06)	0.964
2013-2016	4,114	0.58	(0.28-1.22)	0.151	0.98	(0.45-2.15)	0.955
Peak treatment episode ≥5 consecutive exposure days							
No	14,322	1.00			1.00		
Yes	3,922	1.99	(1.37-2.91)	<0.001	1.29	(0.76-2.18)	0.352
Peak treatment episode ≥10 consecutive exposure days							
No	16,811	1.00			1.00		
Yes	1,433	3.51	(2.20-5.61)	<0.001	2.75	(1.34-5.65)	0.006
Severe bleeding episodes							
No	16,939	1.00			1.00		
Yes	1,305	2.38	(1.51-3.76)	<0.001	1.05	(0.54-2.02)	0.896
Initiation of regular prophylaxis ‡							
No	7,894	1.00			1.00		
Yes	10,350	0.58	(0.37-0.92)	0.022	0.79	(0.48-1.31)	0.364

* High-risk *F8* gene defects include large deletions (at least 1 exon), intron 1 and 22 inversions, small deletions/insertions with stop codon (out of A-run) and nonsense mutations.

† Up to four ethnic origins per patient could be recorded (one for each grandparent).

‡ The initiation of regular prophylaxis was defined as the moment at which at least three consecutive prophylactic infusions of factor VIII were given within a period of at least 15 days (RODIN definition).[5]

§ P value for global test.

Table S7. Associations between factor VIII (FVIII) product received, cofactors and occurrence of high-titer inhibitors.

Population: Boys with severe HA (FVIII activity <1 IU/dL) treated with Factane, Advate or Kogenate within the first 75 exposure days (n=395). Main studied factor: FVIII product received during the first 75 exposure days (fixed factor). Statistical method: Cox proportional hazards model with exposure day as observational time. Adjusted hazard ratio (HR) took into account the following cofactors: four fixed factors (*F8* gene defect, family history of hemophilia and inhibitor, ethnic origin, and age at first exposure to FVIII) and five time-varying factors (calendar period, history of peak treatment episodes ≥5 and ≥10 consecutive exposure days, history of severe bleeding episodes, and regular prophylaxis initiation).

	Number of	Unadjusted analysis			Multivariate analysis		
Fixed risk factors	**exposure days**	**Crude HR**	**(95% CI)**	***P***	**Adjusted HR**	**(95% CI)**	***P***
FVIII product received				0.005§			0.009§
Factane	6,540	1.00			1.00		
Advate	6,426	1.63	(0.84-3.17)	0.148	1.64	(0.82-3.25)	0.160
Kogenate	5,278	2.68	(1.43-5.00)	0.002	2.81	(1.44-5.49)	0.003
***F8* gene defect**				.003§			0.004§
Low risk	5,495	1.00			1.00		
High risk *	12,389	4.27	(1.85-9.86)	<0.001	4.20	(1.80-9.83)	<0.001
Undetermined (eg, not yet tested, unidentified)	360	1.99	(0.24-16.57)	0.524	1.93	(0.22-17.10)	0.555
Family history				0.338§			0.433§
Hemophilia without inhibitor	6,420	1.00			1.00		
Hemophilia with inhibitor	1,108	1.84	(0.81-4.15)	0.144	1.15	(0.50-2.66)	0.749
No family history of hemophilia	10,716	1.23	(0.73-2.09)	0.432	1.44	(0.83-2.50)	0.199
Ethnic origin †				0.075§			0.125§
White only (both parents)	14,046	1.00			1.00		
Other, not African or Afro-American	3,323	1.63	(0.95-2.79)	0.076	1.67	(0.94-2.97)	0.079
African or Afro-American (at least one grandparent)	875	2.05	(0.92-4.55)	0.079	1.76	(0.77-4.03)	0.184
Age at first exposure to FVIII				0.408§			0.796§
Less than 6 months	4,830	1.00			1.00		
6-11 months	6,434	0.72	(0.40-1.28)	0.256	0.92	(0.49-1.73)	0.801
At least 12 months	6,980	0.71	(0.40-1.25)	0.240	1.14	(0.59-2.20)	0.701
Time-varying risk factors							
Calendar period				0.672§			0.425§
2001-2003	1,266	1.00			1.00		
2004-2006	3,303	0.98	(0.37-2.57)	0.962	1.45	(0.53-3.96)	0.472
2007-2009	4,703	1.30	(0.53-3.19)	0.569	2.29	(0.88-5.97)	0.088
2010-2012	4,858	0.99	(0.39-2.51)	0.978	1.57	(0.59-4.18)	0.368
2013-2016	4,114	0.76	(0.28-2.05)	0.583	1.53	(0.52-4.48)	0.434
Peak treatment episode ≥5 consecutive exposure days							
No	14,322	1.00			1.00		
Yes	3,922	2.34	(1.42-3.85)	<0.001	1.09	(0.49-2.41)	0.832
Peak treatment episode ≥10 consecutive exposure days							
No	16,811	1.00			1.00		
Yes	1,433	6.31	(3.47-11.46)	<0.001	6.66	(2.47-18.01)	<0.001
Severe bleeding episodes							
No	16,939	1.00			1.00		
Yes	1,305	2.93	(1.67-5.12)	<0.001	0.87	(0.38-2.02)	0.750
Initiation of regular prophylaxis ‡							
No	7,894	1.00			1.00		
Yes	10,350	0.62	(0.34-1.15)	0.133	0.93	(0.48-1.82)	0.835

* High-risk *F8* gene defects include large deletions (at least 1 exon), intron 1 and 22 inversions, small deletions/insertions with stop codon (out of A-run) and nonsense mutations.

† Up to four ethnic origins per patient could be recorded (one for each grandparent).

‡ The initiation of regular prophylaxis was defined as the moment at which at least three consecutive prophylactic infusions of factor VIII were given within a period of at least 15 days (RODIN definition).[5]

§ P value for global test.

Table S8. Associations between factor VIII (FVIII) product received, cofactors and occurrence of treated inhibitors.

Population: Boys with severe HA (FVIII activity <1 IU/dL) treated with Factane, Advate or Kogenate within the first 75 exposure days (n=395). Main studied factor: FVIII product received during the first 75 exposure days (fixed factor). Statistical method: Cox proportional hazards model with exposure day as observational time. Adjusted hazard ratio (HR) took into account the following cofactors: four fixed factors (*F8* gene defect, family history of hemophilia and inhibitor, ethnic origin, and age at first exposure to FVIII) and five time-varying factors (calendar period, history of peak treatment episodes ≥5 and ≥10 consecutive exposure days, history of severe bleeding episodes, and regular prophylaxis initiation).

	Number of	Unadjusted analysis			Multivariate analysis		
Fixed risk factors	**exposure days**	**Crude HR**	**(95% CI)**	***P***	**Adjusted HR**	**(95% CI)**	***P***
FVIII product received				<0.001§			<0.001§
Factane	6,540	1.00			1.00		
Advate	6,426	1.68	(0.95-2.97)	0.072	1.62	(0.91-2.90)	0.104
Kogenate	5,278	3.20	(1.89-5.41)	<0.001	3.12	(1.79-5.43)	<0.001
***F8* gene defect**				<0.001§			<0.001§
Low risk	5,495	1.00			1.00		
High risk *	12,389	4.23	(2.13-8.38)	<0.001	3.87	(1.94-7.74)	<0.001
Undetermined (eg, not yet tested, unidentified)	360	2.71	(0.58-12.55)	0.203	3.34	(0.69-16.20)	0.135
Family history				0.061§			0.759§
Hemophilia without inhibitor	6,420	1.00			1.00		
Hemophilia with inhibitor	1,108	1.96	(1.05-3.65)	0.033	1.27	(0.67-2.42)	0.460
No family history of hemophilia	10,716	0.99	(0.65-1.51)	0.955	1.04	(0.67-1.64)	0.850
Ethnic origin †				0.004§			0.009§
White only (both parents)	14,046	1.00			1.00		
Other, not African or Afro-American	3,323	1.66	(1.07-2.59)	0.025	1.59	(1.00-2.55)	0.052
African or Afro-American (at least one grandparent)	875	2.46	(1.32-4.56)	0.004	2.41	(1.27-4.59)	0.007
Age at first exposure to FVIII				0.904§			0.341§
Less than 6 months	4,830	1.00			1.00		
6-11 months	6,434	0.91	(0.56-1.50)	0.725	1.20	(0.71-2.03)	0.500
At least 12 months	6,980	1.01	(0.63-1.62)	0.972	1.49	(0.87-2.58)	0.148
Time-varying risk factors							
Calendar period				0.281§			0.159§
2001-2003	1,266	1.00			1.00		
2004-2006	3,303	1.08	(0.49-2.34)	0.855	1.32	(0.59-2.96)	0.504
2007-2009	4,703	1.25	(0.60-2.61)	0.551	2.06	(0.95-4.51)	0.069
2010-2012	4,858	0.93	(0.43-2.01)	0.859	1.35	(0.61-3.00)	0.458
2013-2016	4,114	0.62	(0.27-1.44)	0.269	1.06	(0.43-2.60)	0.901
Peak treatment episode ≥5 consecutive exposure days							
No	14,322	1.00			1.00		
Yes	3,922	1.87	(1.24-2.82)	0.003	1.13	(0.62-2.07)	0.690
Peak treatment episode ≥10 consecutive exposure days							
No	16,811	1.00			1.00		
Yes	1,433	3.67	(2.22-6.06)	<0.001	3.36	(1.50-7.51)	0.003
Severe bleeding episodes							
No	16,939	1.00			1.00		
Yes	1,305	2.38	(1.46-3.88)	<0.001	1.06	(0.51-2.17)	0.881
Initiation of regular prophylaxis ‡							
No	7,894	1.00			1.00		
Yes	10,350	0.64	(0.39-1.05)	0.075	0.88	(0.52-1.50)	0.639

* High-risk *F8* gene defects include large deletions (at least 1 exon), intron 1 and 22 inversions, small deletions/insertions with stop codon (out of A-run) and nonsense mutations.

† Up to four ethnic origins per patient could be recorded (one for each grandparent).

‡ The initiation of regular prophylaxis was defined as the moment at which at least three consecutive prophylactic infusions of factor VIII were given within a period of at least 15 days (RODIN definition).[2]

§ P value for global test.

Table S9. Number of patients by hemophilia treatment center (HTC) and factor VIII product received.
The 32 hemophilia treatment centers were sorted by number of analyzed patients and classified in three size groups according to this number, so that the total numbers of patients by group were similar.

Center	Factor VIII product received			Number of patients
	Factane	Advate	Kogenate	
Larger centers (number of patients ≥38)				
HTC-1	13	17	26	**56**
HTC-2	18	21	9	**48**
HTC-3	21	8	9	**38**
Total	**52**	**46**	**44**	**142**
Intermediate centers (number of patients ≥14 and ≤35)				
HTC-4	30	0	5	**35**
HTC-5	3	17	7	**27**
HTC-6	13	2	4	**19**
HTC-7	8	3	8	**19**
HTC-8	1	6	7	**14**
Total	**55**	**28**	**31**	**114**
Smaller centers (number of patients ≤13)				
HTC-9	2	7	4	**13**
HTC-10	0	11	2	**13**
HTC-11	0	2	11	**13**
HTC-12	3	4	5	**12**
HTC-13	5	2	3	**10**
HTC-14	2	3	4	**9**
HTC-15	1	5	2	**8**
HTC-16	0	5	2	**7**
HTC-17	0	4	3	**7**
HTC-18	3	1	2	**6**
HTC-19	0	5	0	**5**
HTC-20	0	4	1	**5**
HTC-21	0	2	2	**4**
HTC-22	2	1	1	**4**
HTC-23	0	2	2	**4**
HTC-24	3	0	1	**4**
HTC-25	0	1	3	**4**
HTC-26	2	0	1	**3**
HTC-27	0	2	0	**2**
HTC-28	0	1	1	**2**
HTC-29	0	0	1	**1**
HTC-30	0	1	0	**1**
HTC-31	1	0	0	**1**
HTC-32	0	0	1	**1**
Total	**24**	**63**	**52**	**139**
TOTAL	**131**	**137**	**127**	**395**

Supplementary figures

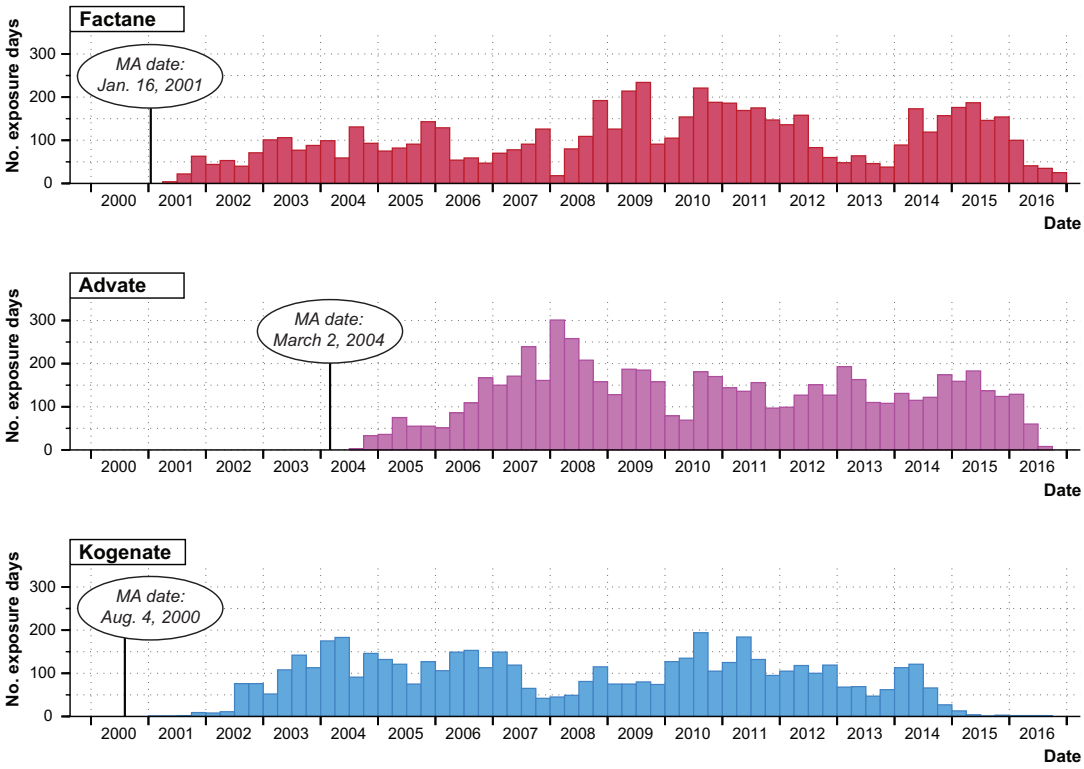
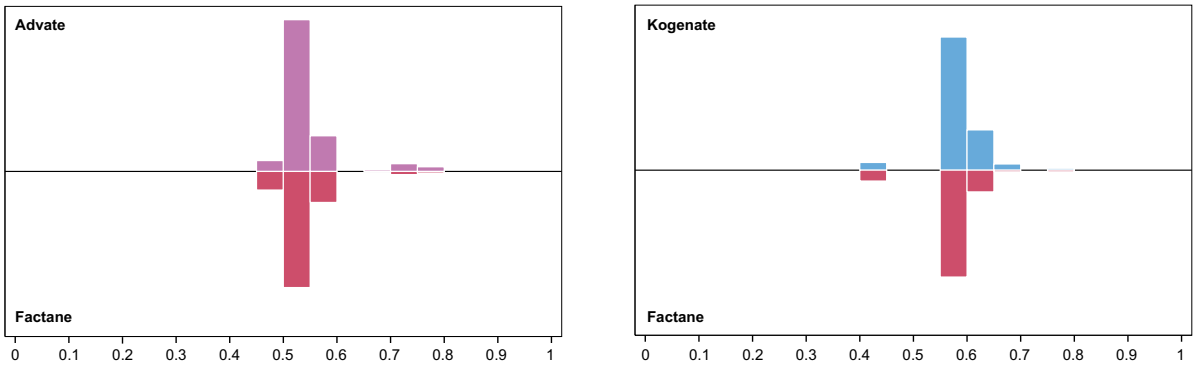
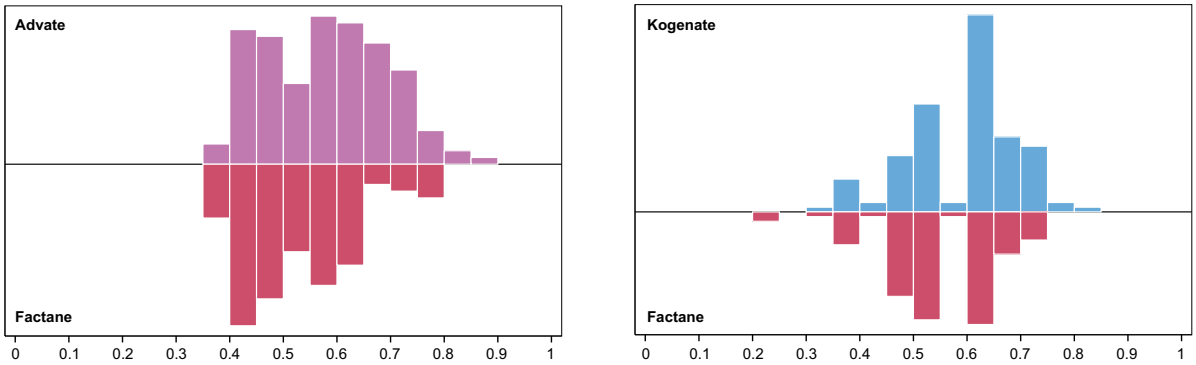


Figure S1. Number of exposure days according to the factor VIII product received and quarter periods for the 395 boys included in the analyses, and marketing authorization (MA) dates in France for Factane, and in European Union for Advate and Kogenate.

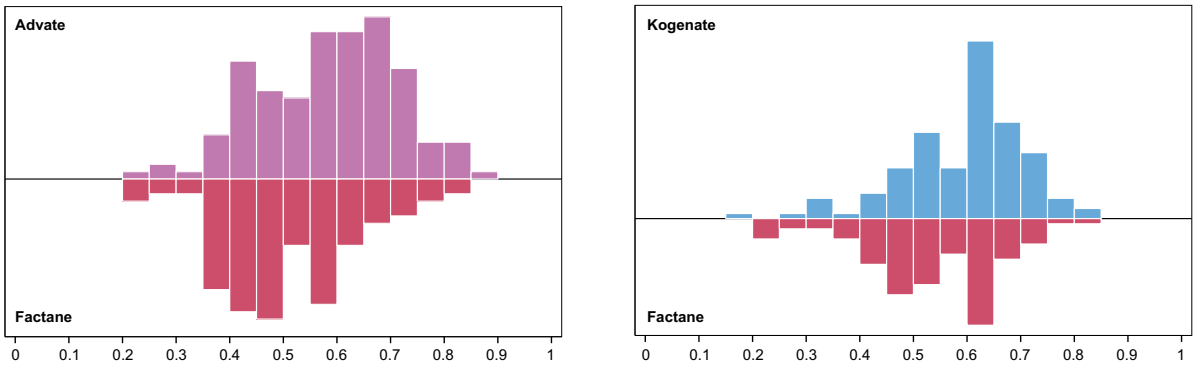
Model 1: High-risk *F8* gene defect known at first factor VIII infusion; family history of hemophilia and inhibitor known at first factor VIII infusion



Model 2: Cofactors of Model 1 + Ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII



Model 3: Cofactors of Model 2 + Peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode



Model 4: *F8* gene defect; family history of hemophilia and inhibitor; ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII; peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode

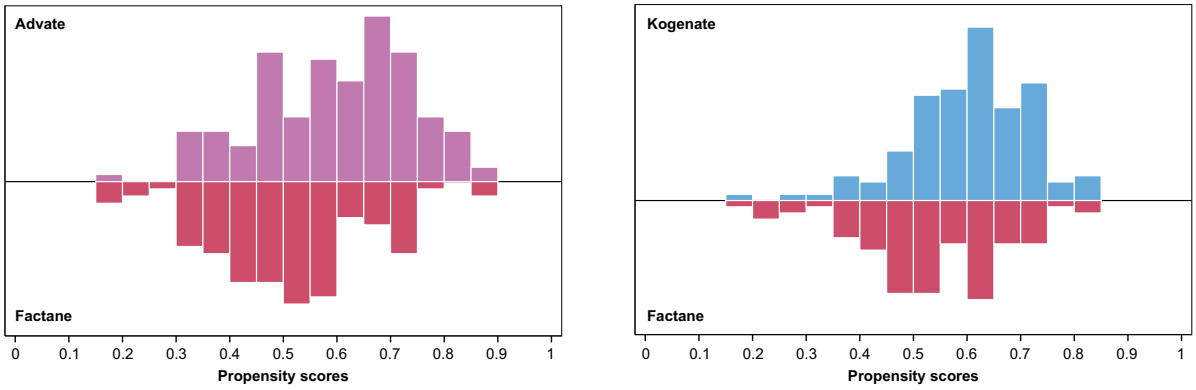


Figure S2. Histograms of propensity scores according to the factor VIII product received and four sets of fixed risk factors (Models 1 to 4).

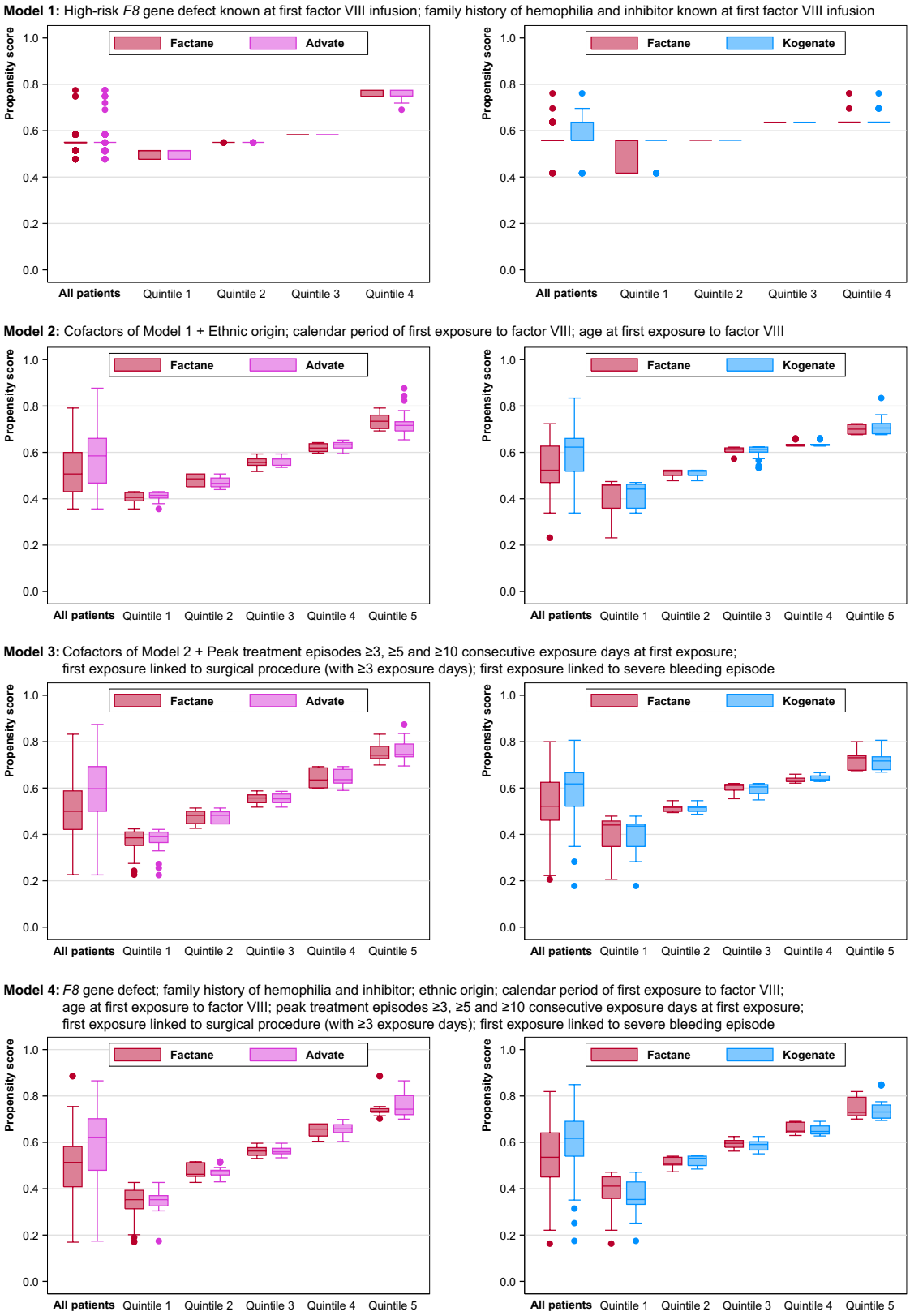
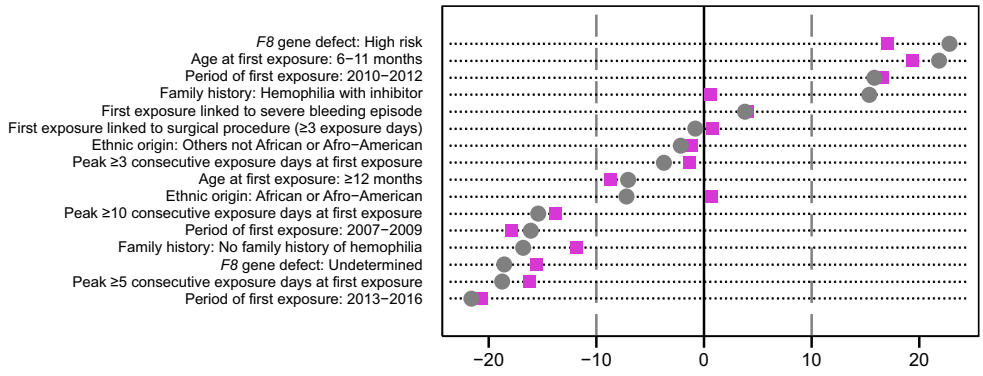
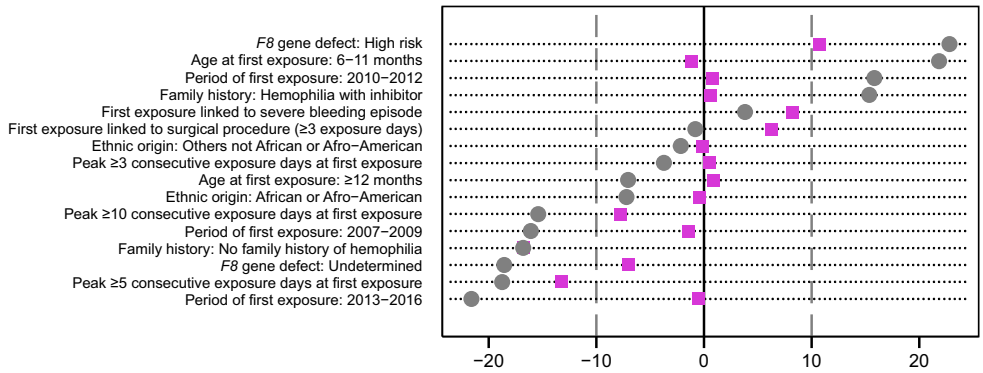


Figure S3. Box plots of propensity scores (PS) according to the factor VIII received, four sets of fixed risk factors (Models 1 to 4) and PS quintiles. Boxes represent 25th and 75th percentiles (Q1 and Q3) of PS, middle bars represent the median, and whiskers represent the lower and upper adjacent values (which are the most extreme values within Q1-1.5*(Q3-Q1) and Q3+1.5(Q3-Q1), respectively). Dots represent extreme outliers.

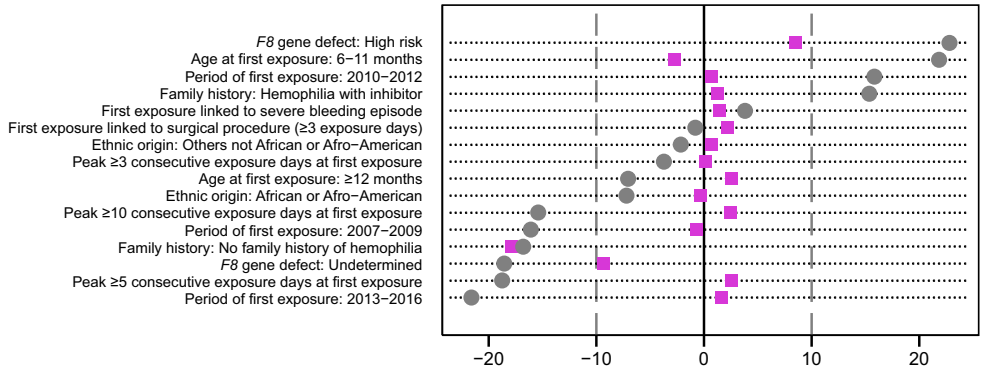
Model 1: High-risk *F8* gene defect known at first factor VIII infusion; family history of hemophilia and inhibitor known at first factor VIII infusion



Model 2: Cofactors of Model 1 + Ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII



Model 3: Cofactors of Model 2 + Peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode



Model 4: *F8* gene defect; family history of hemophilia and inhibitor; ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII; peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode

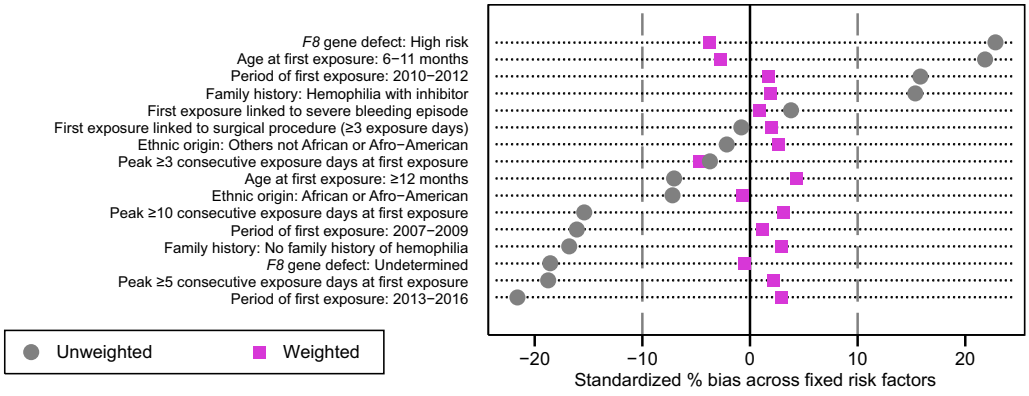
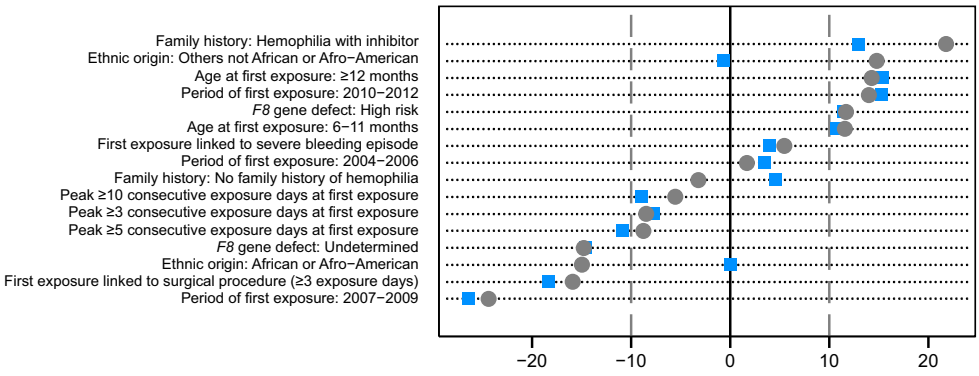
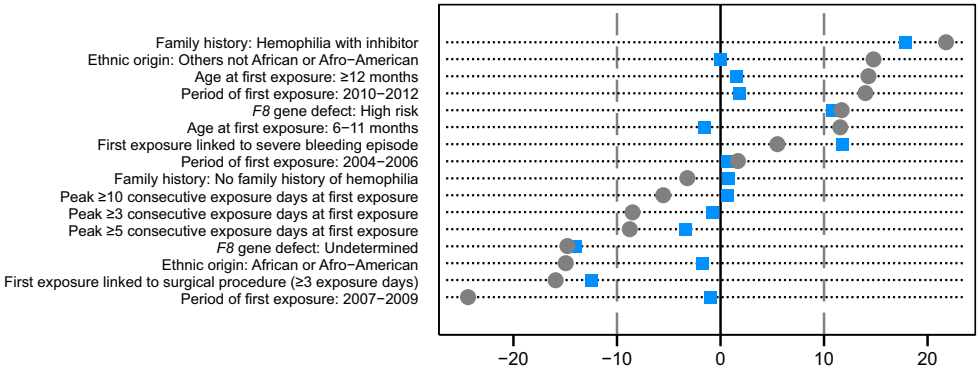


Figure S4. Standardized differences in fixed risk factors between Advate and Factane groups in unweighted and weighted samples according to four sets of fixed risk factors (Models 1 to 4).

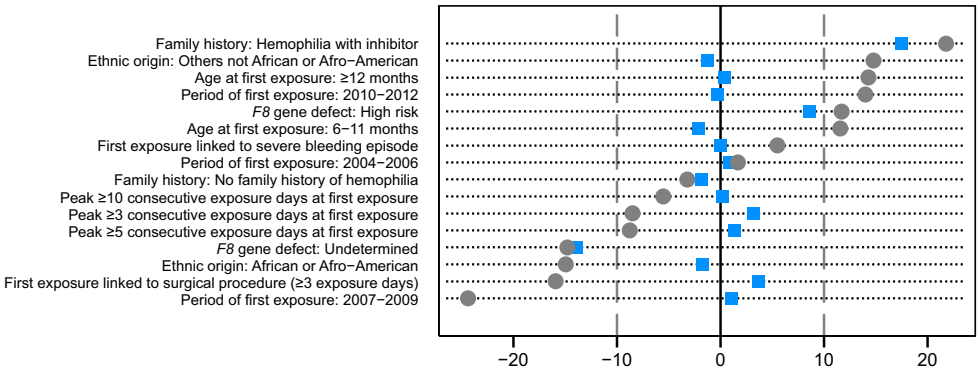
Model 1: High-risk *F8* gene defect known at first factor VIII infusion; family history of hemophilia and inhibitor known at first factor VIII infusion



Model 2: Cofactors of Model 1 + Ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII



Model 3: Cofactors of Model 2 + Peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode



Model 4: *F8* gene defect; family history of hemophilia and inhibitor; ethnic origin; calendar period of first exposure to factor VIII; age at first exposure to factor VIII; peak treatment episodes ≥3, ≥5 and ≥10 consecutive exposure days at first exposure; first exposure linked to surgical procedure (with ≥3 exposure days); first exposure linked to severe bleeding episode

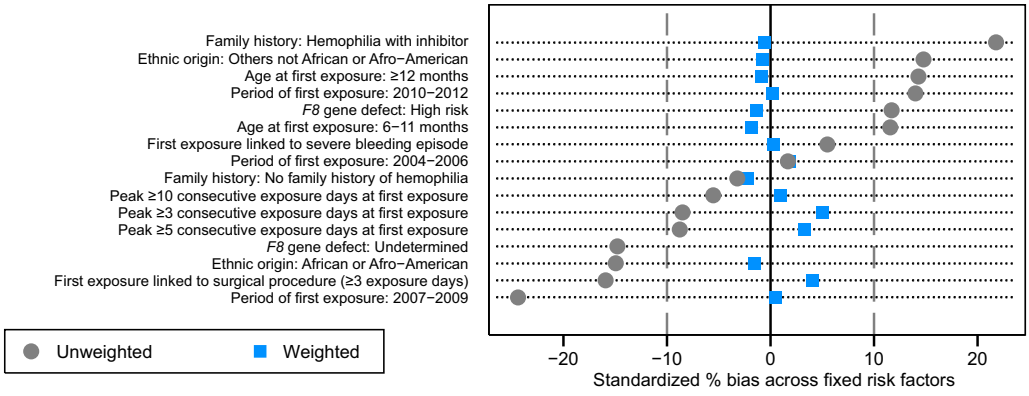


Figure S5. Standardized differences in fixed risk factors between Kogenate and Factane groups in unweighted and weighted samples according to four sets of fixed risk factors (Models 1 to 4).