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ORIGINAL ARTICLE

Inhibitor development according to concentrate in severe hemophilia: reporting on 1392 Previously Untreated Patients from Europe and Canada

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Abstract

Background: Clotting factor concentrates have been the mainstay of severe hemophilia treatment over the last 50 years. Differences in risk of neutralizing antibody (inhibitor) formation according to concentrate used remain clinically relevant.

Objectives: To assess inhibitor development according to type of clotting factor concentrate in previously untreated patients (PUPs) with severe hemophilia A and B.

Methods: The European Haemophilia Safety Surveillance (EUHASS) and Canadian Bleeding Disorders Registry (CBDR) have been monitoring adverse events overall and according to concentrate for 11 and 8 years, respectively. Inhibitors were reported quarterly, and PUPs completed 50 exposure days without inhibitor development annually. Cumulative inhibitor incidences and 95% confidence intervals (CIs) were compared without adjustment for other risk factors.

Results: Fifty-six European and 23 Canadian centers reported inhibitor development in 312 of 1219 (26%; CI, 23%-28%) PUPs with severe hemophilia A and 14 of 173 (8%; CI, 5%-13%) PUPs with severe hemophilia B. Inhibitor development was lower on plasma-derived factor (F)VIII (pdFVIII, 20%; CI, 14%-26%) than on standard half-life recombinant FVIII (SHL-rFVIII, 27%; CI, 24%-30% and odds ratio, 0.67; CI, 0.45%-0.98%; P = .04). Extended half-life recombinant FVIII (EHL-rFVIII, 22%; CI, 12%-36%) showed an intermediate inhibitor rate, while inhibitor rates for Advate (26%; CI, 22%-31%) and Kogenate/Helixate (30%; CI, 24%-36%) overlapped. For other SHL-rFVIII concentrates, inhibitor rates varied from 3% to 43%. Inhibitor development was similar for pdFIX (11%; CI, 3%-25%), SHL-rFIX (8%; CI, 3%-15%), and EHL-rFIX (7%; CI, 1%-22%).

Conclusion: While confirming expected rates of inhibitors in PUPs, inhibitor development was lower in pdFVIII than in SHL-rFVIII. Preliminary data suggest variation in inhibitor development among different SHL-rFVIII and EHL-rFVIII concentrates.

KEYWORDS
antibodies, factor VIII, hemophilia A, hemophilia B, neutralizing, registries

Essentials

- Development of neutralizing antibodies (inhibitors) may vary between factor (F)VIII/IX concentrates.
- Inhibitor risk according to concentrate was assessed in 1390 previously untreated patients with severe hemophilia.
- Inhibitor development risk was significantly lower on plasma-derived FVIII (20%) than on recombinant FVIII (27%).
- Inhibitor risk seems to vary between recombinant FVIII concentrates.

1 | INTRODUCTION

Severe hemophilia is an inherited bleeding disorder caused by the absence of coagulation factor (F)VIII in hemophilia A or FIX in hemophilia B, resulting in a FVIII/FIX activity of <0.01 IU/mL. Modern treatment with regular prophylactic intravenous (i.v.) infusion of clotting factor concentrates (CFCs) effectively minimizes bleeding. Consequently, patients are able to live a normal and productive life, albeit needing frequent i.v. infusions [1–3]. Although the recent introduction of nonreplacement therapy emicizumab (Hemlibra) will affect prophylactic treatment in the next decade, classic factor replacement therapies will still be used [4,5].

The development of neutralizing antibodies (inhibitors) against infused CFCs prevents effective prophylaxis and bleeding control and remains the major complication of replacement therapy. Inhibitors develop in about 30% of severe hemophilia A (SHA) cases and 10% of severe hemophilia B (SHB) cases, mostly during the first 50 exposure days (EDs) [6,7].

Although emicizumab prophylaxis is very effective in prevention of bleeding in SHA, it is currently not accessible for all, while trauma-related bleeding and surgeries requiring treatment with FVIII still occur. For SHB, nonreplacement therapy will soon become clinically available. Consequently, treatment and prevention of bleeding in patients with inhibitors and inhibitor eradication remain an important challenge in hemophilia care, making inhibitor prevention an important target.

Many endogenous and treatment-related (exogenous) factors for inhibitor development in previously untreated patients (PUPs) with severe hemophilia have been identified. Especially, the role of different FVIII concentrates in inhibitor development has been debated [8,9]. For FIX concentrates, this is much less established due to low patient numbers [10].

The randomized SIPPET study was designed to compare inhibitor development between plasma-derived FVIII (pdFVIII) and recombinant FVIII (rFVIII) concentrates in PUPs with SHA [11]. It compared inhibitor incidence of 4 pdFVIII and 4 rFVIII concentrates and reported a significant reduction of inhibitor incidence in patients treated with pdFVIII but did not report inhibitor incidence according to individual concentrates. An updated systematic review recently confirmed increased overall inhibitor development for PUPs with SHA treated with rFVIII compared with pdFVIII (hazard ratio, 1.89; 95% CI, 1.15-2.70; but odds ratio, 1.57; 95% CI, 0.95-2.59) and a trend for more high-responding inhibitor development [12].

Studies assessing inhibitor incidence for individual rFVIII concentrates, even those originating from (inter)national registries, pooled studies, or meta-analyses, have suffered from a lack of

statistical power due to low patient numbers [9,13–19]. A further complicating factor is the introduction of many new CFCs, including both standard half-life (SHL-FVIII/FIX) and extended half-life (EHL-FVIII/FIX) concentrates. For example, the recent report of inhibitor development in 1076 PUPs with SHA from the 31 centers of the international PedNet registry included only 5 of 23 concentrates used by a minimum of 50 PUPs [16].

Early identification of risks of transmission of blood-borne pathogens or inhibitor development is best addressed by prospective surveillance systems or (inter)national cohort studies or registries. Since October 2008, the European Haemophilia Safety Surveillance (EUHASS) has monitored inhibitor development and treatment safety according to individual CFCs and is now present in 94 centers. From 2013 to 2018, the Canadian Hemophilia Surveillance System (CHESS) used the same data capture system as EUHASS; from 2018 onward, an identical EUHASS data capture system has been integrated into the Canadian Bleeding Disorders Registry (CBDR).

The present study evaluates the 11-year results of EUHASS and 8-year results of CHESS monitoring for inhibitor development according to FVIII/FIX concentrates in PUPs with severe hemophilia.

2 | METHODS

The design of the EUHASS study has already been reported [20,21]. Its aim was to assess side effects of treatment and adverse events in patients receiving CFCs. Data collection started on October 1, 2008, or subsequent years for centers that joined EUHASS later. Subsequently, centers provided reports on all new inhibitors diagnosed at the center every 3 months using a secure web-based data entry system. Inhibitors were defined by 2 consecutive tests above the local laboratory threshold. For each patient with an inhibitor, anonymized data on age, type, and severity of hemophilia; cumulative number of EDs to FVIII/FIX concentrate before inhibitor development (for each concentrate used); date of the last negative inhibitor titer; dates and titers of the first 2 positive inhibitor titers; type of inhibitor test used; and local threshold for positive inhibitor testing were collected. Only new inhibitors with positive titers on 2 occasions were considered.

For each year, the number of PUPs with SHA and SHB at risk for inhibitor development was established by collecting the number of PUPs reaching 50 EDs without developing an inhibitor in the previous year. These data were captured according to the concentrate used at the time of reaching 50 EDs. As data collection was anonymized for inhibitor cases and collected at group level only for noninhibitor cases, data on ethnicity were unavailable in EUHASS.

The CBDR was developed by the Association of Hemophilia Directors of Canada (AHCDC) and commenced in 2012 to replace the former Canadian Hemophilia Registry and Canadian Hemophilia A Risk Management System by merging their functions. In 2013, the AHCDC launched CHESS, supported by a dedicated instance of the EUHASS data capture system in 2013 [22,23]. Of note, Canadian data were collected with a direct linkage the individual patient record in CBDR so that precise EDs are known for Canadian patients both with and without inhibitors.

The present analysis was based on data in patients with SHA and SHB from October 1, 2008, to January 1, 2020, for EUHASS and from January 1, 2013, to December 31, 2020, for CBDR. Logical checks, as well as checks for completeness of data, are performed on each adverse event at the time of reporting. In 2021, all centers were asked to confirm accuracy and completeness of their data. Only data from centers with fully checked data and resolution of all queries were included in this analysis. Regulations in the 26 European Countries participating vary, and for the majority of centers, no formal ethics approval was required. If required, institutional review board approval was obtained before study participation.

2.1 | Statistical analysis

The cumulative incidence of inhibitor development according to concentrate in PUPs was calculated at the time of reaching 50 EDs. For the assessment of inhibitor development according to FVIII/FIX concentrates, only complete data were analyzed. In case of switching concentrates, patients with inhibitors were classified according to the last concentrate used. The validity of the calculation method was established by simulation studies [21]. The exact method (Wilson modification) was used to calculate 95% CIs for data on PUPs [24]. Odds ratios (ORs) were calculated from the contingency tables using https://select-statistics.co.uk/calculators/confidence-interval-calculator-odds-ratio/. All analyses were performed separately according to diagnosis (hemophilia A or B). A subgroup analysis compared data reported to EUHASS or CHESS only to those reported to the PedNet registry (www.pednet.eu). Within these groups, inhibitor development was compared according to concentrate type (plasma-derived vs recombinant) and the different concentrates. Inhibitor rates were compared using chi-squared or Fisher exact tests, whichever was appropriate. All analyses were performed using SPSS version 26.

3 | RESULTS

The number of PUPs included in the analyses is shown in the Figure. By 2020, 59 EUHASS and 23 Canadian centers had provided both summary and inhibitor data on a total of 1244 PUPs with SHA and 173 PUPs with SHB as well as on 54 PUPs treated with unlicensed clinical concentrates without specification of the diagnosis SHA or SHB. Failure to confirm the accuracy of submitted data resulted in exclusion of events and at-risk PUPs from 3 European centers that reported a total of 3 inhibitors and an unknown number of noninhibitors, resulting in the inclusion of 99% of all inhibitors in PUPs receiving licensed concentrates. No Canadian data were excluded. For the analyses of inhibitor development according to concentrate, data on 54 PUPs treated with unlicensed FVIII/IX concentrates (including 27 with inhibitors) were excluded. In addition, data on 25 PUPs with SHA who were receiving emicizumab (no inhibitors) were excluded. Eventually, 312 inhibitors in 1219 PUPs with SHA and 14 inhibitors in

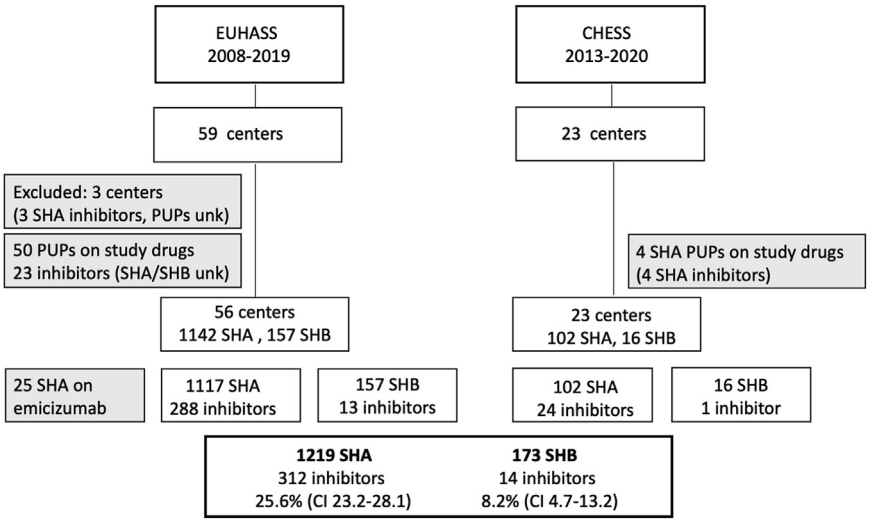

FIGURE Flowchart of inclusion and exclusion of patients. CHESS, Canadian Hemophilia Surveillance System; EUHASS, European Haemophilia Safety Surveillance; PUPs, previously untreated patients; SHA, severe hemophilia A; SHB, severe hemophilia B; unk, unknown.

173 PUPs with SHB were analyzed. These included data of 102 PUPs with SHA and 16 PUPs with SHB from the Canadian CHESS registry.

3.1 | Inhibitor characteristics

Characteristics of all inhibitor patients analyzed are shown in Table 1. For 10 of 326 (3.1%) European PUPs with SHA and inhibitors, data on age and EDs were missing, and data on titers were missing in 1 additional PUP with SHA. Inhibitors developed very early, at a median age of 1.2 years and 13 EDs for PUPs with hemophilia A and 1.6 years and 10 EDs for PUPs with hemophilia B. As only the first 2 positive inhibitor titers were reported to EUHASS, the reported proportions of high-titer inhibitors (51.8% for hemophilia A and 41.9% for hemophilia B) likely represent an underestimation. Inhibitor characteristics were similar in European and Canadian PUPs.

3.2 | Inhibitor development according to factor VIII concentrates

Overall, 312 inhibitors were observed in 1219 PUPs with SHA treated with licensed FVIII concentrates (25.6%; 95% CI, 23.2%-28.1%). FVIII concentrates used included 10 SHL-rFVIII (used by 80.1% cases), 2 EHL-rFVIII (used by 4.4% cases), and 11 pdFVIII concentrates (used by 15.4% cases). In addition, 25 PUPs reported using Hemlibra non-replacement therapy. Concomitant FVIII treatment was not recorded for these PUPs. Inhibitor development in PUPs with SHA according to concentrate type is shown in Table 2. In this unadjusted analysis, inhibitor development was lower on pdFVIII concentrates (19.7%) than on SHL-rFVIII concentrates (26.9%; OR, 0.67; 95% CI, 0.45-0.98; P = .038) or all rFVIII combined (26.7%; OR, 0.67; 95% CI, 0.46-0.99; P = .04).

Inhibitor development according to individual rFVIII concentrates used by at least 50 PUPs was compared with Advate as a reference (n = 417; inhibitors in 26.1%; 95% CI, 22.0%-30.6%). Inhibitor development for Kogenate Bayer/Helixate NexGen (Kogenate, 30.0%; 95% CI, 24.1%-36.4%; P = .30) and Refacto AF/Xyntha (26.0%; 95% CI, 20.0%-32.9%; P = .98) was similar to that for Advate. Nuwiq, which was introduced in Europe in August 2014 and in Canada in March 2017, was used by 58 PUPs, of which 43.1% (95% CI, 30.2%-56.8%) developed inhibitors; this rate was significantly more frequent than for Advate (OR 2.15; 95% CI, 1.22-3.76; P = .007). Elocta(te), approved in Canada since August 2014 and in Europe since November 2015, was used by 51 PUPs, showing inhibitors in 23.5% (95% CI, 12.8%-37.5%); this rate was similar to that for inhibitor development on Advate (P = .688). Only 1 pdFVIII concentrate, Factane (n = 64), was used by more than 50 PUPs. Inhibitor development on Factane (20.3%; 95% CI, 11.3%-32.2%) was similar to that on Advate (P = .319). No inhibitors were reported for the 25 PUPs completing 50 EDs of Hemlibra treatment.

3.3 | Subgroup analysis for inhibitor development on plasma-derived factor VIII compared with recombinant factor VIII

To address the conflicting results between the present analysis and the recent PedNet report showing no protective effect of pdFVIII on inhibitor development [16], a subgroup analysis was performed comparing data according to their origin. In total, 17 of 59 European centers (29%) and 2 of 23 Canadian centers (9%) reported to both EUHASS or CHESS and PedNet. Table 3 shows that PedNet centers contributed 30.3% (57/188) of PUPs treated with pdFVIII and 38.3% (395/1031) of PUPs treated with rFVIII. Table 3 shows that the contradictory results may be attributed to center-specific differences: in the non-PedNet centers, inhibitor development was significantly lower in pdFVIII/increased in rFVIII at 13.7% vs 26.1% (OR, 0.45; 95% CI, 0.26-0.76)/(OR, 2.23; 95% CI, 1.32-3.78; P = .002), whereas inhibitor development on pdFVIII was much higher (33.3%) and similar

TABLE 1 Characteristics of inhibitor patients among previously untreated patients according to hemophilia type and registry.

Patient characteristics	Hemophilia A			Hemophilia B		
	Total	EUHASS	CHESS	Total	EUHASS	CHESS
	N (%) or median (P25-P75)			*N* (%) or median (P25-P75)		
No.	312	288[a]	24	14	13	1
Age (y)	1.2 (0.9-1.8)	1.2[a] (0.9-1.8)	1.3 (1.2-1.7)	2.0 (1.6-2.3)	2.1 (1.5-2.4)	1.9
No. of EDs at inhibitor development	13 (9-20)	13[a] (9-20)	15 (9-20)	10 (6-15)	8 (6-14)	23
Maximum titer within the first 2 tests	5.6 (1.8-21.1)	5.6[b] (1.8-22.0)	6.0 (2.7-20.0)	4.0 (1.5-18.5)	4.5 (1.8-2.7)	0.7
High titer within the first 2 tests (valid %)	156 (51.7)	144[b] (52.0)	12 (50.0)	6 (42.9)	6 (46.2)	0 (0)

CHESS, Canadian Hemophilia Surveillance System; EDs, exposure days; EUHASS, European Haemophilia Safety Surveillance.
[a]Missing data for 10 previously untreated patients with severe hemophilia A (3.5%).
[b]Missing data for 11 previously untreated patients with severe hemophilia A (3.8%).

TABLE 2 Inhibitor development in previously untreated patients with severe hemophilia A according to factor VIII concentrate.

PUPs with severe hemophilia A	Inhibitors	At risk	Cumulative incidence, %	Lower CI, %	Upper CI, %	*P* value
Plasma-derived FVIII	37	188	19.7	14.3	26.1%	Ref
SHL recombinant FVIII	263	977	26.9	24.2	29.8%	.038
EHL recombinant FVIII	12	54	26.9	24.2	29.8%	.682
Advate	109	417	26.1	22.0	30.6	Ref
Kogenate Bayer/Helixate NexGen	68	227	30.0	24.1	36.4	.300
Recombinate	1	39	2.6	0.1	13.5	
Refacto	1	8	12.5	0.3	52.7	
Refacto AF/Xyntha	50	192	26.0	20.0	32.9	.978
Afstyla	1	3	33.3	0.8	90.6	
Kovaltry	4	18	22.2	6.4	47.6	
Novoeight	4	15	26.7	7.8	55.1	
Nuwiq	25	58	43.1	30.2	56.8	.007
Elocta(te)	12	51	23.5	12.8	37.5	.546
Adynovate	0	3	0.0	0.0	70.8	
Beriate	0	9	0.0	0.0	33.6	
Emoclot	0	6	0.0	0.0	45.9	
Factane (LFB)	13	64	20.3	11.3	32.2	.312
Fanhdi	6	23	26.1	10.2	48.4	
Haemoctin SDH	4	17	23.5	6.8	49.9	
Immunate	2	10	20.0	2.5	55.6	
Octanate (LV)	5	27	18.5	6.3	38.1	
Haemate P	1	9	11.1	0.3	48.2	
Hemophil M	1	1	100.0	2.5	100.0	
Voncento	0	2	0.0	0.0	84.2	
Wilate	5	20	25.0	8.7	49.1	

EHL, extended half-life; PUPs, previously untreated patients; ref, reference category; SHL, standard half-life.

TABLE 3 Inhibitor development according to factor VIII concentrate type compared between centers participating in PedNet or European Haemophilia Safety Surveillance only (subgroup analysis).

FVIII concentrate type	Inhibitor (*N*)	At risk (*N*)	Inhibitor incidence, %	Lower CI, %	Upper CI, %	Odds ratio	95% CI	*P* value
EUHASS & CHESS-all data								
Plasma-derived FVIII	37	188	19.7	14.3	26.1	Ref		
SHL recombinant FVIII	263	977	26.9	24.2	29.8	1.50	(1.02-2.21)	.038
SHL + EHL recombinant FVIII	275	1031	26.7	24.0	29.5	1.48	(1.01-2.18)	.043
EUHASS & CHESS without overlap with the PedNet registry								
Plasma-derived FVIII	18	131	13.7	8.4	20.8	Ref		
SHL recombinant FVIII	159	610	26.1	22.6	29.7	2.21	(1.30-3.76)	.003
SHL + EHL recombinant FVIII	166	636	26.1	22.7	29.7	2.23	(1.32-3.78)	.002
EUHASS & Canada overlapping data with PedNet registry								
Plasma-derived FVIII	19	57	33.3	21.4	47.1	Ref		
SHL recombinant FVIII	104	367	28.3	23.8	33.2	0.79	(0.44-1.43)	.439
SHL + EHL recombinant FVIII	109	395	27.6	23.2	32.3	0.76	(0.42-1.38)	.369

CHESS, Canadian Hemophilia Surveillance System; EHL, extended half-life; EUHASS, European Haemophilia Safety Surveillance; F, factor; SHL, standard half-life; Ref, reference category.

to inhibitor development on rFVIII (27.6%; *P* = .369) in the PedNet centers. FVIII inhibitor characteristics were similar between these groups (data not shown).

3.4 | Inhibitor development according to factor IX concentrates

Overall, 14 inhibitors were observed in 183 PUPs with SHB, resulting in an overall inhibitor incidence of 8.1% (95% CI, 4.5%-13.2%). The majority of these PUPs were treated with Benefix (55.2%), but due to the recent development of new concentrates, 1 additional SHL-rFIX, used by 2.3% of PUPs, and 4 EHL-rFIX concentrates (used by 16.4%) were reported. The remaining 38 PUPs (20.7%) used any of the 9 pdFIX concentrates. Inhibitor development according to individual FIX concentrates is shown in Table 4. Similar inhibitor development was observed across plasma-derived and recombinant concentrates, at 10.5% (95% CI, 2.9%-24.8%) for pdFIX (*N* = 38) compared with 7.6% (95% CI, 3.3%-14.5%; *P* = .58) for the group of SHL-rFIX concentrates (*N* = 105) and 6.7% (95% CI, 0.8%-22.1%; *P* = .68) for the 30 PUPs using EHL-rFIX. Due to the low patient numbers, it was impossible to reliably compare inhibitor development for individual FIX concentrates.

4 | DISCUSSION

4.1 | Main findings

Combining 11 years of European data and 8 years of Canadian data, the present study observed a cumulative inhibitor incidence of 25.6% (95% CI, 23.2%-28.1%) in 1219 PUPs with SHA and 8.1% (95% CI, 4.5%-13.2%) in 188 PUPs with SHB. Reliable comparisons between FIX concentrates were impossible due to low patient count. For FVIII concentrates, however, univariable comparison of inhibitor rates showed less inhibitor development on pdFVIII concentrates (19.7%; 95% CI, 14.3%-26.1%) than on SHL-rFVIII concentrates (26.9%; 95% CI, 24.1%-29.8%; *P* = .038). Comparisons between individual SHL-rFVIII concentrates did not confirm increased inhibitor development on Kogenate but pointed toward increased inhibitor development on the first human cell line–derived SHL-rFVIII. However, data from newly introduced rFVIII concentrates reported to EUHASS need to be interpreted with caution because inhibitors occur early, and these are reported before the majority of the cohort reaches 50 EDs without inhibitor development [21]. Further, although this international registry is able to achieve a sample size that is sufficient to evaluate inhibitor development according to individual concentrates, the EUHASS data collection method needs a relatively long follow-up to reliably evaluate new concentrates.

4.2 | Strengths and limitations

The strength of the EUHASS registry is the homogenous data collection involving a large number of centers throughout Europe, representing different countries, all sizes of treatment centers, and a variation of treatment strategies. The Canadian data reflect an entire country and may include different treatment choices. Use of the same data capture platform allowed addition of data from the CBDR. This variability increases the generalizability of the results, especially in comparison with national studies with more homogeneous treatment strategies [13,14,19], international studies including mostly large centers [16,25], or single-concentrate PUP studies conducted by

TABLE 4 Inhibitor development in previously untreated patients with severe hemophilia B according to factor IX concentrate.

PUPs with severe hemophilia B	Inhibitors	At risk	Cumulative incidence, %	Lower CI, %	Upper CI, %	*P* value
Plasma-derived FIX	4	38	10.5	2.9	24.8	Ref
SHL recombinant FIX	8	105	7.6	3.3	14.5	.580
EHL recombinant FIX	2	30	6.7	0.8	22.1	.577
Benefix	8	110	7.9	3.5	15.0	
Rixubis	0	4	0.0	0.0	60.2	
Alprolix	2	21	9.5	1.2	30.4	
Idelvion	0	7	0.0	0.0	41.0	
Refixia/Rebinyn	0	2	0.0	0.0	84.2	
Berinin	0	1	0.0	0.0	97.5	
BETAFACT	2	16	12.5	1.6	38.3	
FIX Grifols	0	1	0.0	0.0	97.5	
Haemonine	0	1	0.0	0.0	97.5	
Immunine	1	5	20.0	0.5	71.6	
Mononine	0	3	0.0	0.0	70.8	
Nanovix	0	1	0.0	0.0	97.5	
Octanine (HB)	0	9	0.0	0.0	33.6	
Replenine VF	1	1	100.0	2.5	100.0	

EHL, extended half-life; F, factor; PUPs, previously untreated patients; SHL, standard half-life.

manufacturers. This is also reflected in the results from the subgroup analysis: centers reporting to EUHASS/CHESS showed very different results than those reporting to both PedNet and EUHASS/CHESS. In addition, EUHASS and CHESS included a larger number of recently introduced concentrates, thus providing more timely information for clinicians. Limitations of the EUHASS study are dependent on the design and anonymous data collection. As denominator data are only collected at reaching 50 EDs, inhibitor development is expected to be overestimated for recently introduced concentrates, as the 95th percentile of reaching 50 EDs was estimated to occur 3 to 4 years after the introduction of a new concentrate [19]. This is in contrast with the Canadian registry, which assesses the number of EDs for noninhibitor patients, but its numbers are currently too low to compare inhibitor development according to individual concentrates. In addition, anonymous data collection at the group level precludes the evaluation of other risk factors for inhibitor development, including ethnicity. Consequently, inhibitor development according to individual concentrates could only be compared by a simple comparison of cumulative incidences. Although only multivariable regression can adjust for other known risk factors, the present analysis provides the first step to assess the presence or absence of an association with inhibitor development. Lack of source data monitoring or central inhibitor testing is not expected to have significantly affected our results as all reports of side effects are being checked for inconsistencies, and all European centers were asked to review their data and answer queries before analysis. For the Canadian centers, all data are reviewed and confirmed annually. Centers were asked to report all inhibitors diagnosed, and all patients treated according to diagnosis and concentrate. Most European centers (95%) answered our queries, resulting in inclusion of 99% of inhibitors reported.

Even with 11 years of follow-up, the present analyses were limited by low patient numbers; this was partly due to the introduction of many new concentrates combined with the introduction of the bispecific antibody Hemlibra prophylaxis.

4.3 | Comparison with other studies

The cumulative incidence of inhibitors at 50 EDs in PUPs with SHA of 25.6% (95% CI, 23.2%-28.1%) observed in EUHASS appears slightly lower but is still within the 95% CIs of the reports on 1109 PUPs with SHA from the combined European registries (29.0%; 95% CI, 26.4%-31.8%) [9] and just below the incidence based on survival analysis in the recent update on 1076 PUPs with SHA from the PedNet group (31.0%; 95% CI, 28.3%-33.7%) [16].

Compared with the 4-year analysis of EUHASS data [10], the number of PUPs with SHA increased by 190%, while inhibitor incidence remained stable, ie, from 25.9% (108/417) in the first analysis to 25.6% (312/1217) in the present analysis. Accordingly, the overall inhibitor development remained stable for both pdFVIII (from 21.6% to 19.7%) and SHL-rFVIII (from 26.5% to 26.9%), but the 95% CIs were smaller due to the larger sample size, and the difference was statistically significant ($P = .038$). Our data are in accordance with data from a systematic review, which showed a significantly reduced

inhibitor development in 1018 PUPs treated with pdFVIII (19.3% inhibitors; 95% CI, 16.8%-21.7%) compared with 1406 PUPs treated with SHL-rFVIII (28.4% inhibitors; 95% CI, 26.1%-30.9%) [12]. However, these results still contrast with the recent report from the international PedNet registry, showing only a nonsignificant trend of inhibitor development on pdFVIII vs rSHL FVIII (adjusted hazard ratio, 0.90; 95% CI, 0.67-1.21) after adjustment for all known other risk factors for inhibitor development in 1076 PUPs with SHA [16]. To study this discrepancy, we performed a subgroup analysis, which showed that the lower inhibitor rate on pdFVIII compared with that on rFVIII was only observed in the centers outside the PedNet registry. This finding may help generate hypotheses regarding other center-related factors explaining these results, which corroborate the SIPPET study as well as the PedNet findings, which do not corroborate the SIPPET study [11,16].

The comparison of inhibitor development according to individual FVIII concentrates was hampered by the introduction of 4 SHL-rFVIII, 2 EHL-rFVIII, and 2 pdFVIII concentrates. The comparison between Advate and Kogenate was affected by the lower use of Kogenate following the publications on increased inhibitor risk. Compared with the first 4 years of EUHASS, the use of Advate increased from 143 to 417 PUPs (192%), while the use of Kogenate increased from 141 to 227 PUPs (61%) only. Although patients treated with Kogenate possibly had a favorable inhibitor risk profile, the proportion of inhibitors observed shifted only slightly from 31.2% to 30.0%. Most striking is that the inhibitor rate on Advate in the present analysis was equal to the combined analysis by Volkers et al. [9,10] (both 26.1%), but EUHASS showed fewer inhibitors on Kogenate: 30.8% in the first EUHASS analysis and 30.0% in the second vs 36.7% reported by Volkers et al. [9,10]. We have no explanation for this discrepancy. In contrast, the PedNet data showed a significantly increased inhibitor risk for Kogenate compared with Advate (adjusted hazard ratio, 1.41; 95% CI, 1.05-1.90) after adjustment for other risk factors for inhibitor development [16].

The observed inhibitor development on Nuwiq (25/58 [43.1%]; 95% CI, 30.2%-56.8%) was significantly higher than reported in the study by Liesner et al. [26] (28/105 [26.7%]; 95% CI, 18.5%-36.2%; P = .03). The EUHASS findings, however, must be interpreted with caution, as the EUHASS methodology leads to overestimation of the inhibitor rate in the first years after the introduction of a new concentrate [21]. In addition, following the first reports on lower inhibitor development on Nuwiq [27], treaters could have preferentially prescribed Nuwiq to PUPs with known risk factors for increased inhibitor development. This could not be adjusted for in the present analysis.

After 11 years of collecting data, 1 of the pdFVIII concentrates, Factane, was used in 64 PUPs, allowing for individual analysis. Factane had a relatively low inhibitor incidence of 20.3%, with a wide 95% CI of 11.3%-32.2%; these data are very similar to the ±20% inhibitor development in 127 PUPs (estimated 95% CI, 13.2%-27.7%) on Factane reported by Calvez et al. [15].

Compared with the 4-year analysis of the EUHASS data, the number of PUPs with SHB increased by 140% (from 72 to 173), with a slight shift in overall inhibitor development from 6.9% to 8.1%. Concomitantly, 1 SHL-rFIX, 4 EHL-rFIX, and 3 pdFIX concentrates were introduced, which further reduces the number of PUPs per concentrate and complicates the comparison of inhibitor development between concentrates. The overall inhibitor incidence was in accordance with the data on 154 PUPs from PedNet, which observed 9.3% (95% CI, 4.4%-14.1%) inhibitors at 75 EDs [7].

4.4 | Clinical relevance

In clinical practice, any medical professional will have to choose a FVIII/FIX concentrate. Consequently, the inhibitor risk associated with individual FVIII/IX concentrates remains an important target for studies. Regarding the discussion on inhibitor risk associated with pdFVIII, currently, only data for a potentially lower inhibitor risk for Factane are beginning to emerge. At the same time, the landscape of hemophilia treatment is rapidly changing: particularly, new SHL- and EHL-rFVIII/FIX concentrates have been developed, and their inhibitor risk in PUPs needs to be established. This is a challenge as the number of PUPs needed to reliably establish reduced or increased inhibitor development is considerable. With the introduction of numerous new concentrates, even international registries struggle to collect sufficient numbers. On the other hand, concentrates, including Kogenate, are taken off the market, and analyses lose their clinical relevance. The other main development is the introduction of prophylaxis with nonreplacement therapy, which is so far only available for hemophilia A (emicizumab: Hemlibra). The use of Hemlibra is expected to increase as preliminary results show that prophylaxis with Hemlibra is superior to FVIII prophylaxis in both inhibitor and noninhibitor SHA patients [4,28,29]. During Hemlibra prophylaxis, exposure to FVIII is much less frequent, thus reaching 50 EDs, and inhibitor development is expected to be delayed; the international INSIGHT studies in nonsevere hemophilia reported reaching 20 EDs around the age of 10 years only [30]. It is unknown if this will affect inhibitor incidence itself, but it is expected to affect the power of the current EUHASS methodology to assess inhibitor development according to individual concentrates. This was the reason to analyze data until January 2020 only.

5 | CONCLUSION

The cumulative incidence of inhibitors in PUPs with SH A was 25.6%, and 8.1% in PUPs with SHB. Nonadjusted analyses suggested lower inhibitor incidences for pdFVIII compared with rFVIII and varying inhibitor incidences for several newly introduced FVIII concentrates. A subgroup analysis showed that the protective effect of pdFVIII was observed only in centers outside the PedNet registry. These findings need confirmation by additional data collection and longer follow-up of cohorts.

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ETHICS STATEMENT

Regulations in the 26 European Countries participating vary, and for the majority of centers, no formal ethics approval was required. If required, institutional review board approval was obtained before study participation.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the study. M.M. secured funding. M.M., R.H., and K.F. coordinated and performed data checking for the European data. A.I. proposed, implemented, and performed data checking for the Canadian data. K.F. planned and undertook the statistical analyses. All authors performed data interpretation. K.F. drafted the manuscript, which was completed with input from all authors. All the authors approved the final manuscript. Data collection was performed by K.F., R.L., F.P., A.G., T.L., A.B., N.S., G.É.R., M.C., A.I., M.M., and all centers collaborating in the EUHASS and CHESS projects.

The lists of collaborators in the EUHASS and CHESS projects are available in the supplementary material.

RELATIONSHIP DISCLOSURE

K.F. has acted as a consultant and participated in expert groups for Bayer, Biogen, CSL Behring, Novo Nordisk, and SOBI; has received research grants from Bayer, Novo Nordisk, and Pfizer; has given invited educational lectures for Bayer, Novo Nordisk, and Pfizer; and has received travel support from SOBI and Bayer. R.L. has received honoraria for advisory board participation for Novo Nordisk, Pfizer, and Sanquin. F.P. has received honoraria for invited educational lectures from Novo Nordisk, CSL Behring, Bayer, and Baxter and has received research support from Novo Nordisk. R.H. is the chief executive officer at MDSAS. T.L. has received honoraria for consultancy, advisory board participation, and/or invited educational lectures from Baxter, Bayer, CSL Behring, and Pfizer. R.K. has received research funding from Bayer. M.C. has received research support from Bayer, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Shire/Takeda; speakers/consultancy fees from Bayer, Bioverativ/Sanofi, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire/Takeda. A.I.'s Institution (McMaster University) has received funding as research grants, research service agreements, and consultancy services from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. M.M. has received honoraria for lecturing, grant reviewing, and advisory committee participation from Novo Nordisk, Takeda, Grifols, and Sanofi. A.G., A.B., N.S., and G.É.R. disclose no competing interests.

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