Developments in modern hemophilia care

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Chapter 4

Factor VIII products and inhibitor development in previously treated patients with severe or moderately severe haemophilia A: a systematic review

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Journal of Thrombosis and Haemostasis. 2018;16(6):1055-1068

Summary

Background

Patients with severe haemophilia A who have been treated extensively with factor VIII (FVIII) products face a low but potentially serious risk of inhibitor development. It is unknown why these patients break immunological tolerance and data on product-related immunogenicity is scarce.

Aims

To summarize the currently available evidence on the relationship between inhibitor development and recombinant FVIII product type in previously treated patients with severe haemophilia A.

Methods

Longitudinal studies were included that reported on de novo inhibitor formation in patients with baseline FVIII activity levels less than 0.02 IU/ml who had been treated with FVIII for at least 50 days. Pooled incidence rates of inhibitor development according to product types were calculated using a random intercept Poisson regression model.

Results

Forty-one independent cohorts were included, 39 patients developed de novo inhibitors during 19,157 person-years of observation. The overall incidence rate was 2.06 per 1000 person-years (p-y) with a 95% confidence interval (CI95) of 1.06-4.01. According to product type, the pooled incidence rate was 0.99 (CI95: 0.37-2.70) per 1000 p-y for patients treated with Advate, 5.86 (CI95: 0.25-134.92) per 1000 p-y for those treated with Kogenate/Helixate, 1.35 (CI95: 0.66-2.77) per 1000 p-y for Kogenate FS/Helixate NexGen, 12.05 (CI95: 1.53-94.78) per 1000 p-y for Refacto and 4.64 (CI95: 0.82-26.43) per 1000 p-y for Refacto AF.

Conclusion

These results suggest that some products may be associated with increased immunogenicity. However, the low incidence of inhibitors in PTPs and the differences in study design may cause significant variation in estimates of risk.

Introduction

The development of factor VIII (FVIII)-specific neutralizing antibodies (inhibitors) remains the most important treatment complication in patients with congenital haemophilia A. Inhibitor development is associated with increased morbidity and mortality[1-3] and occurs primarily during the first 50 days of treatment with FVIII[4,5] after a median of 14.5 days of exposure to FVIII (IQR: 9.75-20.0)[6]. Patients who have been treated with FVIII for more than 50 days, also termed previously treated patients (PTPs), are relatively tolerant to FVIII and inhibitor development is rare[7], with a reported rate of 2.14 per 1000 person-years[8]. It has been suggested that inhibitor incidence follows a bimodal distribution and that at older age the risk of developing inhibitors increases again[9].

Knowledge about immunogenicity of recombinant FVIII (rFVIII) products in PTPs is scarce, which is largely due to the rarity of inhibitor development during this phase of replacement therapy. In addition, findings on a differential inhibitor rate among rFVIII products in PTPs might seem conflicting[7, 10]. The observed differences in immunogenicity between rFVIII products may be explained by product characteristics such as the specific amino acid sequence, culture conditions, stabilizing agents and/or post-translational modifications.[11]

Two previous meta-analyses have assessed product-related immunogenicity in previously treated haemophilia A patients.[7, 10] Several new studies have been published since the latest review (published in 2013), which is one of the reasons to perform a new meta-analysis. Moreover, a new meta-analysis is needed with methods that can appropriately handle rare event situations and differences in follow-up time among included studies.

The objective of this systematic review and meta-analysis was to quantify and compare the current knowledge on incidences of inhibitor formation according to rFVIII product type among PTPs affected with severe or moderately severe haemophilia A.

Methods

A systematic literature review was performed to identify studies that assessed de novo inhibitor development in PTPs with severe or moderately severe haemophilia A who were treated exclusively with one brand of rFVIII. The Meta-analysis of Observational Studies in Epidemiology (MOOSE)[12] and Strengthening of Reporting of Observational Studies in Epidemiology (STROBE)[13] guidelines were followed.

Inclusion/exclusion criteria

Types of studies
All longitudinal studies that assessed de novo inhibitor development and that reported total, mean or median follow-up time in person-years were eligible. Original articles, letters published in peer-reviewed journals and meeting abstracts were eligible for inclusion. There was no restriction on date of publication or language. We excluded case-control studies, case-series, cross-sectional studies, studies with a follow-up time of less than 3 months, studies with fewer than 10 patients, studies in which treatment for surgery was the main goal, pharmacokinetic studies and studies with duplicate data. Authors of studies in which inhibitor incidences were not reported separately for PTPs were asked to provide these data. In case these data were not provided, these studies were excluded.

Type of patients
All patients with severe moderately severe haemophilia A (baseline FVIII activity ‹ 0.02 IU/ml) with at least 50 days of prior exposure to FVIII, were eligible. Furthermore, only patients that were exclusively treated with one brand of rFVIII during the observation period were eligible. Studies that also included patients with fewer than 50 days of exposure to FVIII were only included when separate results were available for the subset of patients with more than 50 days of exposure to FVIII.

Types of rFVIII products
rFVIII product type (analysed according to brand) was the determinant in the primary analysis. The following brands were included; Advate (Shire), Kogenate (Bayer), Kogenate FS/Bayer (Bayer), Helixate (Bayer), Helixate FS/NexGen (CSL Behring), Refacto (Wyeth), Refacto AF (Pfizer). Also included were GreenGene F (Green Cross), Kovaltry/Iblias (Bayer), NovoEight (Novo Nordisk), Nuwiq (Octapharma) and Recombinate (Baxter). Kogenate and Helixate users were grouped into one category. Similarly, Kogenate FS/Bayer and Helixate FS/NexGen users were grouped together.

For the secondary analyses, rFVIII products were also categorised according to length (full-length vs B-domain deleted) and the cell line used for production (Chinese hamster ovary cells, baby hamster kidney cells or human embryonic kidney cells). Lastly, rFVIII products were also categorised according to generation; first-generation products (human/animal proteins in production and final formulation), second-generation products (human/animal proteins in production but not in final formulation), third-generation products (no human/animal proteins used in production or final

formulation) and fourth-generation products (no human/animal proteins used in production or final formulation and human embryonic kidney cells used as cell line). Studies performed with extended half-life rFVIII products were excluded, mainly since there were not enough studies done with these products.

Type of endpoints

The primary endpoint was de novo inhibitor development defined as the first occurrence of an inhibitor according to the cut-off used by the investigators of the original studies. The secondary outcome was high titre de novo inhibitor formation, defined as a peak inhibitor titre of at least 5 Bethesda Units (BU)/mL.

Search strategy

We searched the following databases; PubMed, Embase, Web of Science, Cochrane database and CINAHL. The search strategy was designed and supervised by an experienced librarian (J.W. Schoones, MA, Walaeus Library, Leiden University Medical Center). The initial search was performed in February 2016. Additional studies were included by monthly searches in PubMed up to November 2017. (search terms are reported in supplemental figure S1)

Study selection and data extraction

Two reviewers (S. Hassan and A. Cannavò) independently scanned all titles and abstracts to select articles for further scrutiny. Full text versions of each selected article were reviewed to assess eligibility. Inclusion of an article was determined by consensus between the two reviewers. Consultation of a third reviewer (J.G. van der Bom) was carried out in case of disagreement. To avoid multiple counting of patients included in more than one study, recruitment periods and catchment areas were recorded and, if needed, authors were contacted for clarification. Data were extracted independently by two investigators (S. Hassan and A. Cannavò). A structured electronic data extraction form was used. When the required data were missing, the original investigator(s) were contacted for further information.

Quality assessment

The methodological quality of each article was assessed using the Downs and Black checklist[14]. For the non-comparative studies in our systematic review, only items relevant to this study design were scored (18 of the 27 items from the original checklist[14]). The modified Downs and Black checklist contained 8 items about reporting accuracy, 3 items about external validity, 6 items concerning internal validity and 1 item about study power. Eight items that were only applicable to comparative studies

(i.e. all items about randomisation, blinding, concealment of treatment allocation and confounding) and one item about the use of p-values were removed. The wording of some questions was modified to provide clearer scoring criteria to improve consistency among raters. (supplemental table S2) Each item could be scored as "no" or "unknown" which yielded 0 points or "yes" which yielded 1 point. The overall score was derived by adding up each item score, each study could score between 0-18 points. Two reviewers (A. Cannavò and S. Hassan) evaluated each article independently and a third reviewer (J.G. van der Bom) was consulted in case of any discrepancy.

Data analysis

Statistical analysis

The total inhibitor incidence rate and high titre inhibitor incidence rate in PTPs was estimated for each study as the number of de novo inhibitors divided by the number of person-years on a given rFVIII product. Conventional random effects meta-analysis methods (such as the DerSimonian-Laird random-effects method) are biased when the outcome of interest is rare, also when continuity corrections are applied[15]. Therefore, we pooled the incidence rates of the individual studies and calculated the pooled incidence rate ratio (IRR) of inhibitor development according to product type using a random intercept Poisson regression model[16]. Heterogeneity was explored by estimating the between-study variance (^{2}) as well as visually assessing the extent to which the confidence intervals of the individual studies overlapped. As the most frequently used product, we used Advate as the reference category in the analysis according to product type.

Sensitivity analysis

To verify whether the results were robust to changes in methodology two sensitivity analyses were conducted. In the first sensitivity analysis, we restricted the main analysis to studies that only reported information for severe patients (baseline FVIII activity ‹ 0.01 IU/ml). In the second sensitivity analysis, we restricted the main analysis to large studies (i.e. studies with › 150 person-years of follow-up time).

Summary of findings

The main results of the product comparisons (including an overall quality assessment) are also summarized in a "summary of findings" table (table 3), according to the GRADE approach.[17]

Results

Included studies

A flowchart of the literature search is reported in figure 1 and the search terms are reported in supplemental figure S1 (see appendix). In total, 1605 articles were screened on their title and abstract. Eighty-two unique articles were reviewed in full, of these, 52 articles were excluded. Thirty articles[18-47] were selected for the analysis, four additional articles[48-51] were included after monthly searches on PubMed. Most articles reported on a single cohort of patients using one brand of rFVIII product, whereas three articles[23, 25, 26] provided information on multiple cohorts. Fischer et al[23] reported on five cohorts using different rFVIII products, Recht et al[26] reported on 2 cohorts with slightly different inclusion criteria and Hay et al[25] reported on three cohorts using different rFVIII products. In total, 34 articles reporting on 41 cohorts were included[18-51]. Characteristics of the 52 excluded papers are reported in supplemental table S1, references to the 52 excluded papers (labelled S1-S52) are also reported in supplemental table S1. Eighteen articles did not separately report inhibitor incidence and follow-up time for severe or moderately severe PTPs (but were otherwise eligible for inclusion). The corresponding authors were contacted but did not provide additional data. Consequently, these 18 articles were excluded from the meta-analysis. (supplemental table S1)

Study characteristics

Overall, 39 patients developed inhibitors during 19,157 person-years of observation. (table 1) One study did not provide information on the total number of patients[23], therefore, the overall number of patients included in this meta-analysis is unknown. Seven studies evaluated Advate (6043 person-years, 6 inhibitors), four studies evaluated Kogenate or Helixate (537 person-years, 5 inhibitors), ten studies evaluated Kogenate FS/Bayer or Helixate FS/NexGen (7386 person-years, 10 inhibitors), three studies evaluated Refacto (609 person-years, 7 inhibitors) and four studies (containing 5 cohorts) evaluated Refacto AF (3226 person-years, 10 inhibitors).

Furthermore, one study used GreenGene F (56 person-years, 1 inhibitor), three studies used Kovaltry/Iblias (165 person-years, 0 inhibitors), three studies used NovoEight (551 person-years, 0 inhibitors), three studies used Nuwiq (85 person-years, 0 inhibitors) and two studies evaluated Recombinate (499 person-years, 0 inhibitors). Because of the small sample sizes, studies evaluating GreenGene F, Kovaltry/Iblias, NovoEight, Nuwiq and Recombinate were only included when calculating the overall incidence rate but were excluded from product-specific analyses. In total, 12 studies were excluded (1356 person-years, 1 inhibitor).

Table 1. Study characteristics.

Advate						
Author	**Year**	**Study design**	**Country**	**Inclusion criteria**	**INH testing**	
Blanchette [33]	2008	Clinical trial	US, Europe	≤ 2%, EDs ≥ 50	3 months	
Den Uijl [36]	2009	Registry	The Netherlands	Any severity, EDs ≥ 50	12 months	
Valentino [38]	2012	Clinical trial	US, Europe	≤ 2%, EDs ≥ 150	3 months	
Fukutake [19]	2014	Surveillance	Japan	Any severity, EDs ≥ 4	Unknown	
Hay (cohort 2) [25*]	2015	Surveillance	UK	≤ 1%, 12 months of prior treatment	6 months	
Oldenburg [21**]	2010	Surveillance	US, Europe	Any severity, All previous EDs	routine detection	
Fischer (cohort 1) [23]	2015	Registry	Europe	‹1%, EDs› 50	routine detection	
Kogenate, Helixate						
Aygören-Pürsün [8]	1997	Clinical trial	Germany	‹ 15%, EDs› 100	3 months	
Seremetis[20]	1999	Clinical trial	US, Europe	‹5%, EDs › 50	Monthly (at beginning), every 6 months (at end)	
Yoshioka[30]	2006	Clinical trial	Japan	Any, EDs › 50	At months 0-3-6-9-12-18-24	
Singleton[32]	2007	Retrospective survey	Ireland	Any severity, All previous EDs	routine detection	
Kogenate FS/Bayer, Helixate FS/Nexgen						
Abshire[22]	2000	Clinical trial	North America, Europe	‹2%, EDs≥ 100	week 0-4-12-24, months 12-18-24	
Musso[34]	2008	Surveillance	Europe	‹2%, EDs› 0	routine detection	
Delumeau[35]	2008	Surveillance	Japan	Any severity, All previous EDs	routine detection	
Youn [18]	2009	Surveillance	Taiwan	Any severity, All previous EDs	routine detection	
Collins[37]	2010	Clinical trial	US, Europe	‹1%, EDs› 100	baseline and 13 months	
Manco-Johnson[41*]	2013	Clinical trial	Worldwide	‹2%, EDs≥ 150	0 and 3 months, 1, 2 and 3 years	
Lalezari [27*]	2014	Clinical trial	Worldwide	‹1%, EDs≥ 150	Week 1-2-3-7-12-26-38-52	
Gouider [45]	2015	Surveillance	Worldwide	‹4%, all previous EDs	routine detection	
Hay (cohort 3) [25*]	2015	Surveillance	UK	≤ 1%, 12 months of prior treatment	6 months	
Fischer (cohort 2) [23]	2015	Registry	Europe	‹1%, EDs› 50	routine detection	

	Sample size	Follow-up (person-years)	Follow-up (exposure days)	Inhibitors	Age
	53	56	8268	0/0	Mean 3.1 years (SD, 1.5)
	71	213	-	0/0	Median 25 years (range, 0.5-67)
	73	97	-	0/0	Median 26 years (range, 7-59)
	271	542	.	0/0	Median 24 years (range, 0-81)
	118	118	-	0/0	Switchers: mean 25 years (IQR 13-44) Non-switchers: mean 22 years (IQR 14-33)
	348	361	30972	1/0	29.9% ‹ 12 years 10.4% 12-16 years 59.3% ≥ 16 years
	-	4656	-	5/-	-
	22	22	1507	0/0	Median 27 years (range:2-62)
	54	254	12204	1/1	Median 25 years (range:1-72)
	74	121	7134	4/0	Mean 24 years (range:1-73)
	84	140	-	0/0	51.1%: › 18 years 11.7%: 13-18 years 37.2%: ≤ 12 years
	71	119	11867	0/0	NA: mean 22.6 years (SD: 10.2) EU: mean 32.6 years (SD: 13.3)
	181	352	33847	0/0	Mean 23.6 years (range:0.1-71)
	323	409	-	1/0	Mean 23.7 years (SD, 16.6)
	38	34	-	0/0	Mean 20.3 years (SD, 15.6)
	20	22	2231	0/0	Mean 36.4 years (SD, 3.5)
	84	143	11676	0/0	Median 30.6 years (range, 15-50)
	72	56	8834	0/0	Mean 34.4 years (range, 13-64)
	118	236	-	1/0	Mean 13.8 years (SD, 13.6)
	509	509	-	1/1	Switchers: mean 25 years (IQR 13-44) Non-switchers: mean 22 years (IQR 14-33)
		5506	-	7/-	-

Refacto						
Author	**Year**	**Study design**	**Country**	**Inclusion criteria**	**INH testing**	
Gringeri [24]	2004	Cohort study	Italy	‹1%, EDs≥ 50	3 months	
Pollmann [31]	2007	Surveillance	Germany, Austria	Any severity, All previous EDs	routine detection	
Fischer (cohort 3) [23]	2015	Registry	Europe	‹1%, EDs› 50	routine detection	
Refacto AF						
Recht (cohort 1) [26]	2009	Clinical trial	Worldwide	≤ 2%, EDs≥ 150	Months 0-1-3-6	
Recht (cohort 2) [26]	2009	Clinical trial	Worldwide	≤ 2%, EDs≥ 250	Months 0-1-3-6	
Lopez [43*]	2015	Clinical trial	Europe	‹1%, EDs› 150	At 1, 10-15, 50 EDs and then every 6 months	
Hay (cohort 1) [25*]	2015	Registry	UK	≤ 1%, EDs› 50 or 12 months of prior treatment	6 months	
Fischer (cohort 4) [23]	2015	Registry	Europe	‹1%, EDs› 50	routine detection	
GreenGene F						
Hyun [44]	2015	Clinical trial	Korea	≤ 2%, EDs› 150	3 months	
Kovaltry, Iblias						
Kavakli [46]	2015	Clinical trial	Worldwide	‹1%, EDs≥ 150	-	
Ljung [47]	2016	Clinical trial	Worldwide	‹1%, EDs≥ 50	Months 0-1-2-6	
Saxena [50]	2016	Clinical trial	Worlwide	‹1%, EDs≥ 150	-	
NovoEight						
Kulkarni [39]	2013	Clinical trial	Worldwide	≤ 1%, EDs› 50	At 6/8 study visits	
Lentz [40]	2013	Clinical trial	Worldwide	≤ 1%, EDs› 150	At 8/9 study visits	
Lentz [49]	2016	Clinical trial	Worldwide	≤ 1%, EDs› 50	Every 6 months	
Nuwiq						
Lissitchkov [42]	2015	Clinical trial	Europe	≤ 1%, EDs› 150	EDs 1, 2, 10–15, months 3 and 6.	
Tiede [48]	2016	Clinical trial	Europe	≤ 1%, EDs› 150	-	
Lissitchkov [51]	2017	Clinical trial	Europe	≤ 1%, EDs› 150	At baseline and study completion	

	Sample size	Follow-up (person-years)	Follow-up (exposure days)	Inhibitors	Age
	25	12.5	610	1/1	Median 31 years (range:6-60)
	188	387	55259	2/1	Mean 26.3 years (range:0-67)
	-	209	-	4/-	-
	94	62	6741	2/0	Median 24 years (range: 12-60)
	110	48	6860	1/0	Median 19 years (range: 7-70)
	208	207	19552	0/0	Mean 30.5 years (SD:13)
	571	571	-	4/1	Switchers: mean 25 years (IQR 13-44) Non-switchers: mean 22 years (IQR 14-33)
	-	2338	-	3/-	-
	70	56	6397	1/-	Mean 31.9 years (SD, 9.6)
	79	79	-	0/0	Median 28.5 years (range: 14-59)
	50	25	3650	0/0	Mean 6.4 years (SD, 3.0)
	61	61	-	0/0	Mean 31.5 years (SD, 12.7)
	63	24	3780	0/0	Mean 6.1 years (SD, 2.9)
	150	75	12750	0/0	Mean 28 years (SD, 11.8)
	199	452	72320	0/0	
	32	16	2723	0/0	Mean 37.3 years (SD, 13.6)
	22	20	1030	0/0	Mean 39.6 years (SD, 14.1)
	66	49	6612	0/0	Mean 33.6 years (SD, 9.89)

Recombinate						
Author		**Study design**	**Country**	**Inclusion criteria**	**INH testing**	
White [29]		Clinical trial	Worldwide	≤ 5%, EDs›200	-	
Fischer (cohort 5) [23]		Registry	Europe	‹1%, EDs› 50	routine detection	

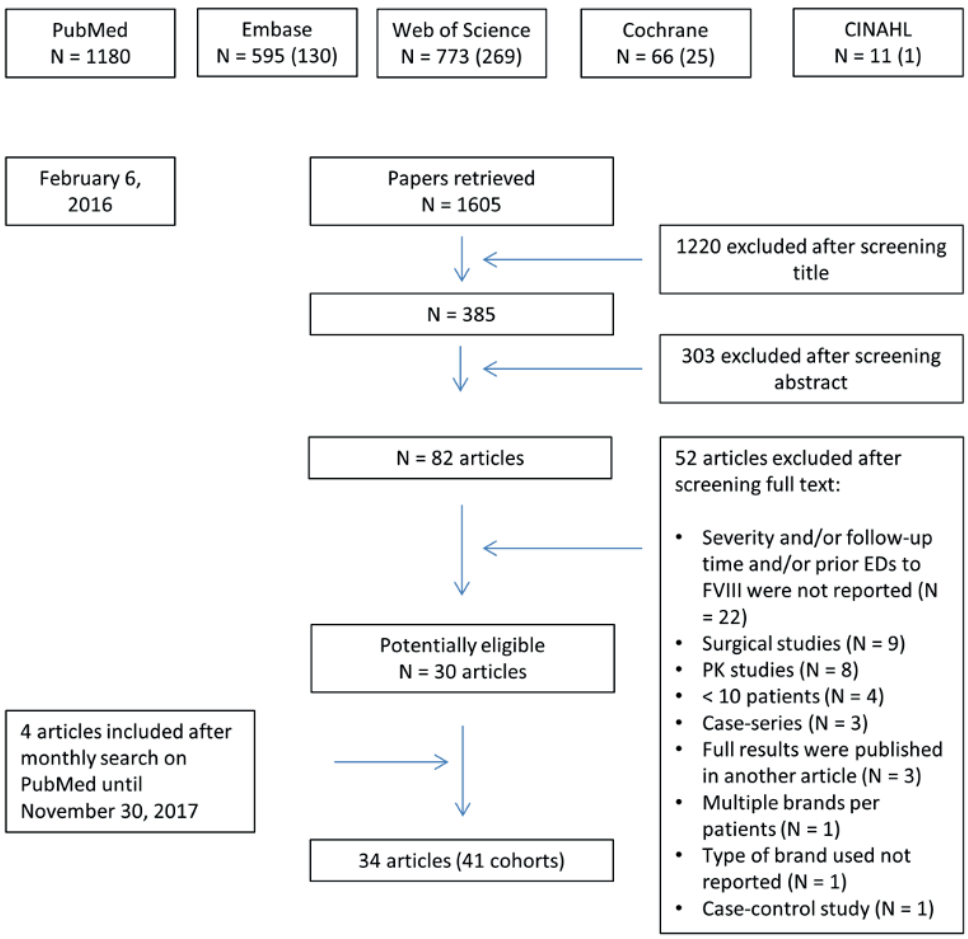
* Possible overlap with EUHASS registry.[21]

** Patient recruitment period not reported, unclear if there is any overlap with EUHASS registry.[21]

	Sample size	Follow-up (person-years)	Follow-up (exposure days)	All Inhibitors / High-titre inhibitors	Age
	67	248	-	0/0	33% › 18 years 67% ≥ 18 years
		251	-	0/-	-

Figure 1. Flowchart of the search strategy (number of unique reports are indicated in parentheses).

The search was run on February 6, 2016. Two additional studies were included by performing monthly searches on Pubmed until November 30, 2017.



We found similar methodological quality across studies with the modified Downs and Black checklist (median score: 11, range: 6-16), except for two studies with a high risk of bias which were published as a letter to the editor[18] (score: 6) and a conference poster[19] (score: 8). (supplemental table S2) The majority of studies were similar in quality, therefore, we did not perform a sensitivity analysis based on methodological quality.

Risk of inhibitor formation according to recombinant rFVIII product

Overall incidence rate and incidence rate per rFVIII product

The overall inhibitor incidence rate among previously treated patients was 2.06 per 1000 person-years with a 95% confidence interval (CI95) of 1.06-4.01). The incidence rate of inhibitor formation was 0.99 (CI95: 0.37-2.70) per 1000 person-years for Advate, 5.86 (CI95: 0.25-134.92) per 1000 person-years for Kogenate/Helixate, 1.35 (CI95: 0.66-2.77) per 1000 person-years for Kogenate FS/Helixate NexGen, 12.05 (CI95: 1.53-94.78) per 1000 person-years for Refacto and 4.64 (CI95: 0.82-26.43) per 1000 person-years for Refacto AF (figure 2).

Inhibitor formation by product

Compared with Advate, the pooled incidence rate ratio (IRR) was 9.77 (95%CI: 1.97-48.41) for Kogenate/Helixate, 1.51 (95%CI: 0.34-6.69) for Kogenate FS/Helixate NexGen, 14.40 (95%CI: 2.84-72.94) for Refacto and 4.81 (95%CI: 0.99-23.34) for Refacto AF. (table 2). Compared with full-length rFVIII, the pooled IRR for B-domain-deleted rFVIII was 4.80 (CI95: 1.32-17.40). Compared to rFVIII products derived from Chinese hamster ovary (CHO) cells, the pooled IRR was 0.62 (CI95: 0.17-2.34) for rFVIII products derived from baby hamster kidney (BHK) cells. Compared to second generation rFVIII products, the pooled IRR was 2.54 (CI95: 0.45-14.27) for first generation rFVIII products and 0.75 (CI95: 0.21-2.66) for third-generation rFVIII products. (table 2)

Sensitivity analysis

The sensitivity analyses showed that the results for each rFVIII brand varied significantly with changes to methodology. (supplemental table S4 and S5) However, this can be partly explained by the low number of studies per brand. Furthermore, the results of the sensitivity analyses were roughly in line with the results of the main analysis with regards to the overall incidence rate and when rFVIII products were analysed according to length, cell line and generation. Nevertheless, this shows that that the most important results of the main analysis are not very robust to changes in methodology. (supplemental table S4 and S5)

Discussion

This meta-analysis comprehensively reviews published reports of rFVIII products in relation to immunogenicity among previously treated patients with haemophilia. In total, 34 studies reporting on 41 cohorts were included with 39 inhibitor events and

19,157 person-years of observation. The incidence rate among PTPs was 2.06 per 1000 person-years (CI95: 1.06-4.01).

Formal comparisons of products yielded a statistically significant higher incidence of inhibitors among patients using Kogenate/Helixate and Refacto when compared with Advate, but not Kogenate FS/Helixate NexGen or Refacto AF. Taken as a whole, B-domain deleted rFVIII products were associated with an increased risk of inhibitor formation when compared to full-length rFVIII products. However, the overall quality of evidence was low, mainly due to the high risk of bias and confounding, lack of power to detect an effect in most studies (given the rare outcome) and the lack of consistency among studies evaluating the same rFVIII product. Therefore, the aforementioned results have to be interpreted with caution (Table 3).

Comparison with previous reviews

The overall incidence of inhibitors in PTPs in our study corroborates earlier findings[8, 52-55]. Recently, two previous systematic reviews have evaluated the association between rFVIII product type and inhibitor formation in PTPs[7, 10].

In 2011, the first of the two meta-analyses was published, its focus was mainly on the risk of inhibitor formation with B-domain deleted rFVIII products compared to full-length rFVIII products[10]. This meta-analysis included prospective studies of patients who were treated for more than 50 exposure days at baseline. A mixed effects Cox proportional hazards model with study as a random effect was used to pool and compare studies. Due to incomplete reporting, individual follow-up time was estimated for most non-inhibitor patients. Fourteen out of 29 studies in the previous meta-analysis were also included in our current meta-analysis. The following 9 studies were included in the previous meta-analysis but excluded from the current meta-analysis; 3 surgical studies [S7, S27, S28], 1 case-series [S2], 2 studies that did not adequately report prior exposure to FVIII [S49, S51] and 3 studies that did not adequately report follow-up time [S39, S41, S46] (see supplemental table S1 for references of excluded studies). Similar to our study, this meta-analysis found a statistically significantly higher risk of inhibitor formation in previously treated patients using B-domain deleted rFVIII, compared to previously treated patients using full-length rFVIII (HR: 7.26, CI95: 2.12–24.9).

A more recent meta-analysis from 2013 did not report any differences in immunogenicity[7]. Thirteen out of 33 studies in this previous meta-analysis were also included in the current meta-analysis. The following 11 studies were included in the previous

Figure 2. Incidence rates of inhibitor development per study.

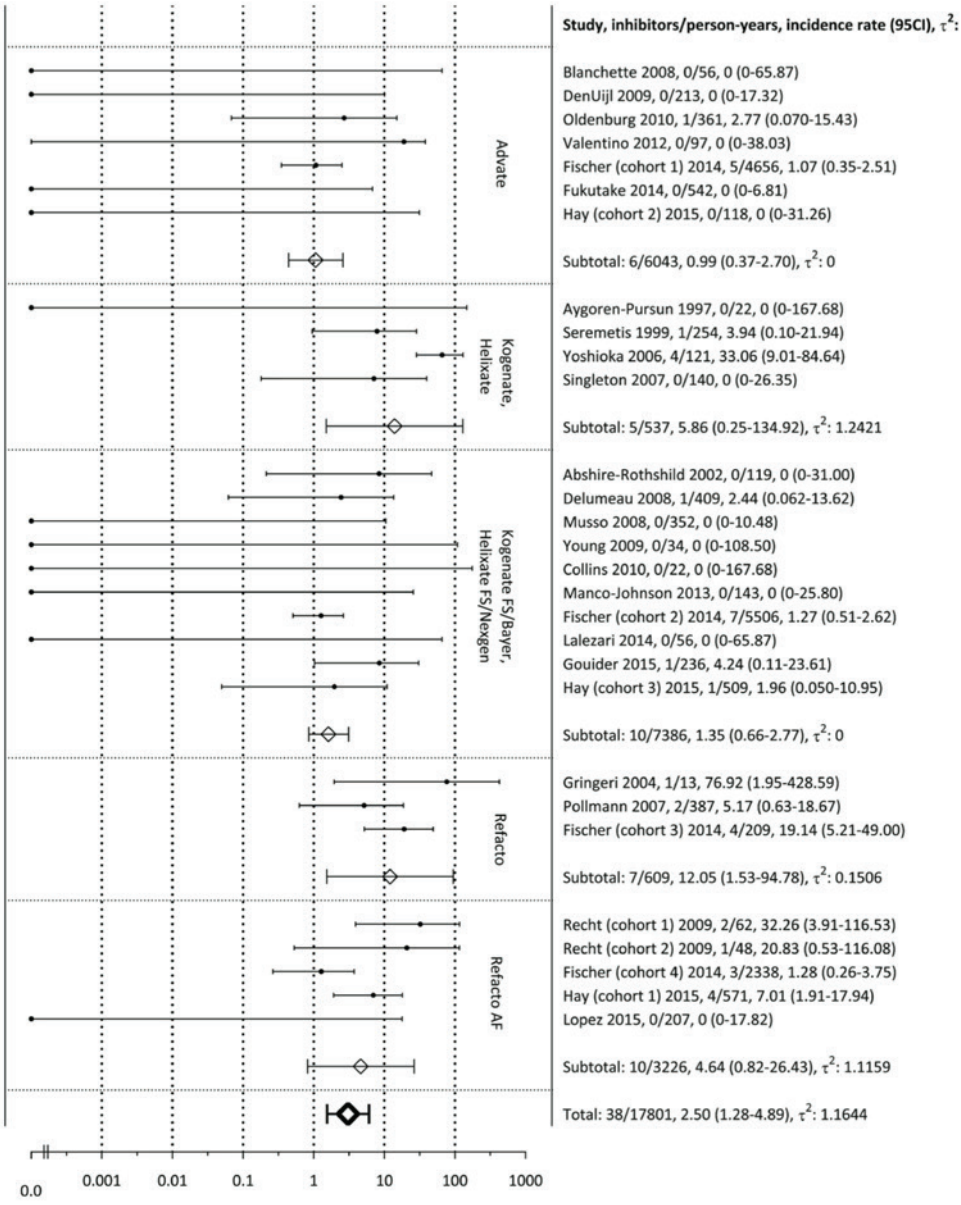


Table 2. Pooled incidence rates and incidence rate ratios of inhibitor development by product type.

Variable	N	Inhibitors/ p-y	Pooled inhibitor incidence rate per 1000 p-y (CI95)	between-study variance (^{2})	Incidence rate ratio (CI95)
Overall (main products only):	29	38/17801	2.50 (CI95: 1.28-4.89)	1.1644	
Product					
Advate	7	6/6043	0.99 (CI95: 0.37-2.70)	0	Ref
Kogenate/Helixate	4	5/537	5.86 (CI95: 0.25-134.92)	1.2421	9.77 (CI95: 1.97-48.41)
Kogenate FS/Helixate NexGen	10	10/7386	1.35 (CI95: 0.66-2.77)	0	1.51 (CI95: 0.34-6.69)
Refacto	3	7/609	12.05 (CI95: 1.53-94.78)	0.1506	14.40 (CI95: 2.84-72.94)
Refacto AF	5	10/3226	4.64 (CI95: 0.82-26.43)	1.1159	4.81 (CI95: 0.99-23.34)
rFVIII length[1]					
Full-length rFVIII	21	21/13966	1.46 (CI95: 0.59-3.59)	0.8967	Ref
B-domain deleted rFVIII	8	17/3835	6.93 (CI95: 2.28-21.08)	0.9980	4.80 (CI95: 1.32-17.40)
Cell line[2]					
CHO-cells	15	23/9878	3.01 (CI95: 1.20-7.54)	1.3115	Ref
BHK-cells	14	15/7923	1.96 (CI95: 0.63-6.15)	1.0564	0.62 (CI95: 0.17-2.34)
rFVIII generation[3]					
Second-generation rFVIII	13	17/7995	2.66 (CI95: 1.06-6.66)	0.7128	Ref
First-generation rFVIII	4	5/537	5.86 (CI95: 0.25-134.92)	1.2421	2.54 (CI95: 0.45-14.27)
Third-generation rFVIII	12	16/9269	1.95 (CI95: 0.70-5.40)	0.9157	0.75 (CI95: 0.21-2.66)

[1] Full-length rFVIII (Kogenate/Helixate, Kogenate FS/Helixate NexGen and Advate) is compared with B-domain deleted rFVIII (Refacto and Refacto AF).

[2] rFVIII derived from CHO-cells (Refacto, Refacto AF and Advate) is compared with rFVIII derived from BHK-cells (Kogenate/Helixate and Kogenate FS/Helixate NexGen).

[3] First Generation rFVIII (Kogenate/Helixate) is compared with second generation rFVIII (Refacto and Kogenate FS/Helixate NexGen) and third generation rFVIII (Advate and Refacto AF).

meta-analysis but excluded from the current meta-analysis; 3 surgical studies [S7, S27, S28], 3 studies that did not report haemophilia severity and/or prior EDs to FVIII [S43, S49, S9], 4 studies that did not report follow-up time [S40, S41, S46, S47] and 1 study in which the type of FVIII brand used was not specified [S10] (see supplemental table S1 for references of excluded studies). The method of Laird and Mosteller was used to pool study results. Crude proportions of inhibitor development for each FVIII product were indirectly compared by evaluating whether statistically significant between-groups heterogeneity existed according to the Cochran's Q statistic. The crude proportion of inhibitor development was 1.0% (CI95: 0.5%-1.8%) for Advate, 2.6% (CI95: 1.6%-4.4%) for Kogenate (first generation) and 1.9% (CI95: 1.1%-3.4%) for Refacto (first generation).

No statistically significant Q-statistic was found based on the type of FVIII concentrate (Q statistic = 6.854, P = 0.077), this was confirmed by a univariate meta-regression analysis (these results were not shown). Cochran's Q, however, is not a sensitive tool for assessing heterogeneity as it has low power to detect heterogeneity if the event rate is very low[56], and hence this meta-analysis at most indicated the absence of gross differences by product.

In this meta-analysis Kogenate/Helixate and Kogenate FS/Helixate NexGen were categorized and analysed as one product group, complicating comparisons between individual rFVIII products. Further, only information on the cumulative incidence of inhibitor formation (i.e., the numbers of events per persons) per product was provided without correcting for study follow-up time. It is mentioned in the article that "similar results were obtained when the incidence rate was calculated as events per person-years" (however, these data were not shown). As development of inhibitors to FVIII is dependent on exposure to FVIII and therefore follow-up time, the reporting of incidence rates is preferred over proportions of inhibitor patients. In addition, conventional data pooling methods (such as the one used in the aforementioned meta-analysis) are based on large sample approximations which produce biased estimates when applied to studies with very low event rates[56], which is the case in inhibitor development in PTPs.

Study strengths and limitations

Study strengths

The last review included studies up to January 2013. Of the 41 cohorts included in this analysis, 14 cohorts were published after this date.

In contrast to previous reviews, the inhibitor incidence rate was the main study outcome. This was preferred over the cumulative inhibitor incidence as the main outcome because the study duration was not identical across studies and over the hazard rate as the main outcome because most studies did not report the follow-up time of non-inhibitor patients. Unlike earlier reviews, we also directly compared the pooled inhibitor incidence rates of all major rFVIII products with each other.

Standard meta-analysis methods (e.g. the DerSimonian-Laird random effects method) can give biased results when applied inappropriately. Firstly, the effect estimate and standard error of each study are usually correlated. Secondly, pooling studies with zero events leads to computational errors, this is often avoided by applying a continuity correction. Lastly, the within-study distribution of the effect estimate is assumed to be normal, this assumption is often violated when the event rate is very rare. The meta-analysis model used in this review, a random intercept Poisson regression model, avoids the aforementioned problems[16].

Table 3. Summary of findings.

Main recombinant FVIII products compared to Advate in previously treated patients with severe haemophilia A					
Intervention: Kogenate/Helixate					
Outcomes	**Absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of person-years (studies)	Certainty of the evidence (GRADE)
	Risk with Advate	**Risk with Kogenate/ Helixate**			
Inhibitor incidence assessed with: Bethesda assay	0.99 per 1,000	**5.86 per 1,000** (0.25 to 134.92)	**RR 9.77** (1.97 to 48.41)	6580 (11 non-comparative observational studies)	⨁◯◯◯ VERY LOW
Intervention: Kogenate FS/Helixate NexGen					
Outcomes	**Absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of person-years (studies)	Certainty of the evidence (GRADE)
	Risk with Advate	**Risk with Kogenate FS/Helixate NexGen**			
Inhibitor incidence assessed with: Bethesda assay	0.99 per 1,000	**1.35 per 1,000** (0.66 to 2.77)	**RR 1.51** (0.34 to 6.69)	13429 (17 non-comparative observational studies)	⨁◯◯◯ VERY LOW

Intervention: Refacto					
Outcomes	**Absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of person-years (studies)	Certainty of the evidence (GRADE)
	Risk with Advate	**Risk with Refacto**			
Inhibitor incidence assessed with: Bethesda assay	0.99 per 1,000	**12.05 per 1,000** (1.53 to 94.78)	**RR 14.40** (2.84 to 72.94)	6652 (10 non-comparative observational studies)	⨁◯◯◯ VERY LOW
Intervention: Refacto AF					
Outcomes	**Absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of person-years (studies)	Certainty of the evidence (GRADE)
	Risk with Advate	**Risk with Refacto AF**			
Inhibitor incidence assessed with: Bethesda assay	0.99 per 1,000	**4.64 per 1,000** (0.82 to 26.43)	**RR 4.81** (0.99 to 23.34)	9269 (12 non-comparative observational studies)	⨁◯◯◯ VERY LOW

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Limitations - Random variation

The pooled results have to be interpreted with caution due to the low number of inhibitors within each product type, which give rise to significant random variation as indicated by the broad confidence intervals. Furthermore, haemophilia severity, follow-up time and the prior number of exposure days to FVIII were not accurately reported in several studies (supplemental table S1), these studies were excluded (after attempts to retrieve this information by contacting the corresponding authors). Due to the low event rate overall, the absence of these studies in the meta-analysis may have significantly impacted our results.

Limitations - Confounding

As no comparative studies were found, we could only compare single-arm trials in our analysis of inhibitor formation by product type. Due to differences in the distri-

bution of genetic/treatment-related risk factors, comparing single-arm trials may be misleading.

Many studies also included moderately severe patients (the exact proportion varied per study). If moderately severe patients are at a significantly lower risk of inhibitor formation, then this could have confounded our results.

Compared to on-demand treatment, patients on prophylactic treatment are exposed to more units of FVIII over a given time period and are therefore at a higher risk of inhibitor formation. Correcting for this problem by using exposure days to FVIII instead of person-years as the unit of time in the main analysis was not feasible due to the low number of studies that accurately reported the total number of exposure days to FVIII.

Adjustment for other potential confounders such as F8 genotype, ethnicity, family history and surgery was not possible due to incomplete reporting (supplemental table S3). Overall, there is a moderate chance of confounding, mainly due to variables that may have influenced the physician's choice of rFVIII product (F8 genotype, family history of inhibitors).

Limitations - Bias
The cut-off level and screening frequency of the inhibitor assays, which could have influenced the reported number of low-titre inhibitors, varied across studies. This could have introduced misclassification bias and consequently over- or underestimation of inhibitor incidences. Patients in market approval studies undergo more intensive screening for inhibitors. (Transient) low-titre inhibitors that were not detected before the study or at study baseline may be detected after inclusion. Due to this, newer products for which data is mainly available from market approval studies may seem more immunogenic than older products which have also been evaluated in post-approval studies.

Over time, the screening intensity has increased, possibly leading to an increased detection of low-titre inhibitors in newer studies. However, screening intensity was slightly higher among older products (Kogenate/Helixate and Refacto) when compared to newer products (Kogenate FS/Helixate NexGen and Refacto AF). (table 1) This observation is in line with our results, as Kogenate/Helixate and Refacto were also the most immunogenic products in our analysis. Correcting for this problem by only analysing high-titre inhibitors was not feasible due to the very low number of high-titre inhibitors overall.

In addition, there could have been some overlap between 5 studies (that evaluated Advate, Kogenate FS/Helixate NexGen or Refacto AF) and the EUHASS registry[23] (table 1) Double counting could have led to over- or underestimating inhibitor incidences and producing overly narrow confidence intervals. Because Advate was used as the reference product, reported incidence rate ratios for all product types would also be biased. Overall, double counting could have influenced the main results.

Many patients were treated with a different FVIII product before study inclusion (especially in market approval trials). Consequently, increased immunogenicity due to product switching could have biased the results. However, there have been several national product switches and there was no evidence of increased immunogenicity.[57]

Biological explanation of a causal effect

Several differences between rFVIII products could explain the reported results. Second- and third generation full length rFVIII products vary slightly in their FVIII amino acid sequence. Furthermore, differences in product formulation such as culture conditions and stabilizing agents could also be relevant. Lastly, the type of cell culture used for production such as CHO cells, BHK cells or, more recently HEK 293 cells, leads to rFVIII products with different post-translational modifications that may influence immunogenic potential[11].

Implications of these results for future research

Comparing single-arm trials may be misleading due to bias and confounding. Single-arm trials are useful for identifying extremely immunogenic products but less suitable for detecting smaller effects (e.g. the difference in inhibitor risk found in the studies by Peyvandi et al[2] or Gouw et al[58]). Nevertheless, these studies could be used more effectively if a standardized data reporting system was used. This system should include all relevant variables such as known genetic/treatment-related confounders.[59] Lastly, future research should focus on using study designs that are appropriate for evaluating rare outcomes (i.e. case control studies).

Conclusion

These results suggest that some products may be associated with increased immunogenicity. However, these findings should be interpreted with caution, both the low incidence of inhibitors in PTPs and the differences in study design may cause significant variation in estimates of risk.

Acknowledgements

The authors thank J. W. Schoones of the Walaeus Library (Leiden University Medical Center, Leiden, The Netherlands) for expert support in designing the literature research, and S. le Cessie for expert statistical advice.

References

1. Mannucci PM, Tuddenham EG. The hemophilias--from royal genes to gene therapy. *The New England journal of medicine*. Jun 07 2001;344(23):1773-9. doi:10.1056/nejm200106073442307
2. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet (London, England)*. Feb 17 2016;doi:10.1016/s0140-6736(15)01123-x
3. Walsh CE, Soucie JM, Miller CH. Impact of inhibitors on hemophilia A mortality in the United States. *American journal of hematology*. May 2015;90(5):400-5. doi:10.1002/ajh.23957
4. Iorio A, Halimeh S, Holzhauer S, et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. *Journal of thrombosis and haemostasis : JTH*. Jun 2010;8(6):1256-65. doi:10.1111/j.1538-7836.2010.03823.x
5. Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *The New England journal of medicine*. May 26 2016;374(21):2054-64. doi:10.1056/NEJMoa1516437
6. Gouw SC, van den Berg HM, Fischer K, et al. Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. *Blood*. May 16 2013;121(20):4046-55. doi:10.1182/blood-2012-09-457036
7. Xi M, Makris M, Marcucci M, Santagostino E, Mannucci PM, Iorio A. Inhibitor development in previously treated hemophilia A patients: a systematic review, meta-analysis, and meta-regression. *Journal of thrombosis and haemostasis : JTH*. Sep 2013;11(9):1655-62. doi:10.1111/jth.12335
8. Kempton CL, Soucie JM, Abshire TC. Incidence of inhibitors in a cohort of 838 males with hemophilia A previously treated with factor VIII concentrates. *Journal of thrombosis and haemostasis : JTH*. Dec 2006;4(12):2576-81. doi:10.1111/j.1538-7836.2006.02233.x
9. Hay CR, Palmer B, Chalmers E, et al. Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. *Blood*. Jun 9 2011;117(23):6367-70. doi:10.1182/blood-2010-09-308668
10. Aledort LM, Navickis RJ, Wilkes MM. Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A meta-analysis of prospective clinical studies. *Journal of thrombosis and haemostasis : JTH*. Nov 2011;9(11):2180-92. doi:10.1111/j.1538-7836.2011.04472.x

11. Lai J, Hough C, Tarrant J, Lillicrap D. Biological considerations of plasma-derived and recombinant factor VIII immunogenicity. *Blood*. Jun 15 2017;129(24):3147-3154. doi:10.1182/blood-2016-11-750885
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama*. Apr 19 2000;283(15):2008-12.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ (Clinical research ed)*. Oct 20 2007;335(7624):806-8. doi:10.1136/bmj.39335.541782.AD
14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of epidemiology and community health*. Jun 1998;52(6):377-84.
15. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statistics in medicine*. May 15 2004;23(9):1351-75. doi:10.1002/sim.1761
16. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Statistics in medicine*. Dec 20 2010;29(29):3046-67. doi:10.1002/sim.4040
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*. Apr 26 2008;336(7650):924-6. doi:10.1136/bmj.39489.470347.AD
18. Young JH, Liu HC, Hsueh EJ, et al. Efficacy and safety evaluation of sucrose-formulated recombinant factor VIII for Taiwanese patients with haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia*. Jul 2009;15(4):968-70. doi:10.1111/j.1365-2516.2009.02024.x
19. Fukutake K, Hanabusa H, Taki M, Matsushita T, Nogami K, Shirahata A. Data from a prospective post-authorization safety surveillance study in 384 hemophilia A patients in Japan with the antihemophilic factor (recombinant) plasma/albumin-free method demonstrates safety and efficacy. *Haemophilia : the official journal of the World Federation of Hemophilia*. 2014:Conference:18.
20. Seremetis S, Lusher JM, Abildgaard CF, Kasper CK, Allred R, Hurst D. Human recombinant DNA-derived antihaemophilic factor (factor VIII) in the treatment of haemophilia A: conclusions of a 5-year study of home therapy. The KOGENATE Study Group. *Haemophilia : the official journal of the World Federation of Hemophilia*. Jan 1999;5(1):9-16.

21. Oldenburg J, Goudemand J, Valentino L, et al. Postauthorization safety surveillance of ADVATE [antihaemophilic factor (recombinant), plasma/albumin-free method] demonstrates efficacy, safety and low-risk for immunogenicity in routine clinical practice. *Haemophilia : the official journal of the World Federation of Hemophilia*. Nov 2010;16(6):866-77. doi:10.1111/j.1365-2516.2010.02332.x
22. Abshire TC, Brackmann HH, Scharrer I, et al. Sucrose formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia A in home therapy--International Kogenate-FS Study Group. *Thrombosis and haemostasis*. Jun 2000;83(6):811-6.
23. Fischer K, Lassila R, Peyvandi F, et al. Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. *Thrombosis and haemostasis*. May 2015;113(5):968-75. doi:10.1160/th14-10-0826
24. Gringeri A, Tagliaferri A, Tagariello G, Morfini M, Santagostino E, Mannucci P. Efficacy and inhibitor development in previously treated patients with haemophilia A switched to a B domain-deleted recombinant factor VIII. *British journal of haematology*. Aug 2004;126(3):398-404. doi:10.1111/j.1365-2141.2004.05058.x
25. Hay CR, Palmer BP, Chalmers EA, et al. The incidence of factor VIII inhibitors in severe haemophilia A following a major switch from full-length to B-domain-deleted factor VIII: a prospective cohort comparison. *Haemophilia : the official journal of the World Federation of Hemophilia*. Mar 2015;21(2):219-26. doi:10.1111/hae.12563
26. Recht M, Nemes L, Matysiak M, et al. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII. *Haemophilia : the official journal of the World Federation of Hemophilia*. Jul 2009;15(4):869-80. doi:10.1111/j.1365-2516.2009.02027.x
27. Lalezari S, Coppola A, Lin J, et al. Patient characteristics that influence efficacy of prophylaxis with rFVIII-FS three times per week: a subgroup analysis of the LIPLONG study. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2014;20(3):354-61.
28. Aygoren-Pursun E, Scharrer I. A multicenter pharmacosurveillance study for the evaluation of the efficacy and safety of recombinant factor VIII in the treatment of patients with hemophilia A. German Kogenate Study Group. *Thrombosis and haemostasis*. Nov 1997;78(5):1352-6.
29. White GC, 2nd, Courter S, Bray GL, Lee M, Gomperts ED. A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemo-

philia A. The Recombinate Previously Treated Patient Study Group. *Thrombosis and haemostasis*. Apr 1997;77(4):660-7.
30. Yoshioka A, Shima M, Fukutake K, Takamatsu J, Shirahata A. Safety and efficacy of a new recombinant FVIII formulated with sucrose (rFVIII-FS) in patients with haemophilia A: a long-term, multicentre clinical study in Japan. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2001;7(3):242-9.
31. Pollmann H, Externest D, Ganser A, et al. Efficacy, safety and tolerability of recombinant factor VIII (REFACTO) in patients with haemophilia A: interim data from a postmarketing surveillance study in Germany and Austria. *Haemophilia : the official journal of the World Federation of Hemophilia*. Mar 2007;13(2):131-43. doi:10.1111/j.1365-2516.2006.01416.x
32. Singleton E, Smith J, Kavanagh M, Nolan B, White B. Low risk of inhibitor formation in haemophilia patients after a change in treatment from Chinese hamster ovary cell-produced to baby hamster kidney cell-produced recombinant factor VIII. *Thrombosis and haemostasis*. Dec 2007;98(6):1188-92.
33. Blanchette VS, Shapiro AD, Liesner RJ, et al. Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients. *Journal of thrombosis and haemostasis : JTH*. Aug 2008;6(8):1319-26. doi:10.1111/j.1538-7836.2008.03032.x
34. Musso R, Santagostino E, Faradji A, et al. Safety and efficacy of sucrose-formulated full-length recombinant factor VIII: experience in the standard clinical setting. *Thrombosis and haemostasis*. Jan 2008;99(1):52-8. doi:10.1160/th07-06-0409
35. Delumeau JC, Ikegawa C, Yokoyama C, Haupt V. An observational study of sucrose-formulated recombinant factor VIII for Japanese patients with haemophilia A. *Thrombosis and haemostasis*. Jul 2008;100(1):32-7. doi:10.1160/th07-12-0724
36. Den Uijl I, Mauser-Bunschoten EP, Roosendaal G, Schutgens R, Fischer K. Efficacy assessment of a new clotting factor concentrate in haemophilia A patients, including prophylactic treatment. *Haemophilia : the official journal of the World Federation of Hemophilia*. Nov 2009;15(6):1215-8. doi:10.1111/j.1365-2516.2009.02079.x
37. Collins P, Faradji A, Morfini M, Enriquez MM, Schwartz L. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month cross-over study. *Journal of thrombosis and haemostasis : JTH*. Jan 2010;8(1):83-9. doi:10.1111/j.1538-7836.2009.03650.x

38. Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *Journal of thrombosis and haemostasis : JTH*. Mar 2012;10(3):359-67. doi:10.1111/j.1538-7836.2011.04611.x
39. Kulkarni R, Karim FA, Glamocanin S, et al. Results from a large multinational clinical trial (guardian3) using prophylactic treatment with turoctocog alfa in paediatric patients with severe haemophilia A: safety, efficacy and pharmacokinetics. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2013;19(5):698-705. doi:10.1111/hae.12165
40. Lentz SR, Misgav M, Ozelo M, et al. Results from a large multinational clinical trial (guardian1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2013;19(5):691-7. doi:10.1111/hae.12159
41. Manco-Johnson MJ, Kempton CL, Reding MT, et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *Journal of thrombosis and haemostasis : JTH*. Jun 2013;11(6):1119-27. doi:10.1111/jth.12202
42. Lissitchkov T, Hampton K, von Depka M, et al. Novel, human cell line-derived recombinant factor VIII (human-cl rhFVIII; Nuwiq(R)) in adults with severe haemophilia A: efficacy and safety. *Haemophilia : the official journal of the World Federation of Hemophilia*. Aug 28 2015;doi:10.1111/hae.12793
43. Parra Lopez R, Nemes L, Jimenez-Yuste V, et al. Prospective surveillance study of haemophilia A patients switching from moroctocog alfa or other factor VIII products to moroctocog alfa albumin-free cell culture (AF-CC) in usual care settings. *Thrombosis and haemostasis*. Oct 2015;114(4):676-84. doi:10.1160/th14-09-0760
44. Hyun SY, Park SY, Lee SY, et al. Efficacy, Safety, and Pharmacokinetics of Beroctocog Alfa in Patients Previously Treated for Hemophilia A. *Yonsei medical journal*. Jul 2015;56(4):935-43. doi:10.3349/ymj.2015.56.4.935
45. Gouider E, Rauchensteiner S, Andreeva T, et al. Real-life evidence in evaluating effectiveness of treatment in Haemophilia A with a recombinant FVIII concentrate: a non-interventional study in emerging countries. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2015;21(3):e167-75. doi:10.1111/hae.12631
46. Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma

protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). *Journal of thrombosis and haemostasis : JTH*. Mar 2015;13(3):360-9. doi:10.1111/jth.12828

47. Ljung R, Kenet G, Mancuso ME, et al. BAY 81-8973 safety and efficacy for prophylaxis and treatment of bleeds in previously treated children with severe haemophilia A: results of the LEOPOLD Kids Trial. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2016;22(3):354-60. doi:10.1111/hae.12866
48. Tiede A, Oldenburg J, Lissitchkov T, Knaub S, Bichler J, Manco-Johnson MJ. Prophylaxis vs. on-demand treatment with Nuwiq((R)) (Human-cl rhFVIII) in adults with severe haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2016;22(3):374-80. doi:10.1111/hae.12859
49. Lentz SR, Cerqueira M, Janic D, et al. Interim results from a large multinational extension trial (guardian() 2) using turoctocog alfa for prophylaxis and treatment of bleeding in patients with severe haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2016;22(5):e445-9. doi:10.1111/hae.12990
50. Saxena K, Lalezari S, Oldenburg J, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2016;22(5):706-12. doi:10.1111/hae.12952
51. Lissitchkov T, Rusen L, Georgiev P, et al. PK-guided personalized prophylaxis with Nuwiq(R) (human-cl rhFVIII) in adults with severe haemophilia A. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2017;23(5):697-704. doi:10.1111/hae.13251
52. Rosendaal FR, Nieuwenhuis HK, van den Berg HM, et al. A sudden increase in factor VIII inhibitor development in multitransfused hemophilia A patients in The Netherlands. Dutch Hemophilia Study Group. *Blood*. Apr 15 1993;81(8):2180-6.
53. McMillan CW, Shapiro SS, Whitehurst D, Hoyer LW, Rao AV, Lazerson J. The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. *Blood*. Feb 1988;71(2):344-8.
54. Rasi V, Ikkala E. Haemophiliacs with factor VIII inhibitors in Finland: prevalence, incidence and outcome. *British journal of haematology*. Nov 1990;76(3):369-71.
55. Darby SC, Keeling DM, Spooner RJ, et al. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977-99. *Journal of thrombosis and haemostasis : JTH*. Jul 2004;2(7):1047-54. doi:10.1046/j.1538-7836.2004.00710.x

56. Shuster JJ, Walker MA. Low-event-rate meta-analyses of clinical trials: implementing good practices. *Statistics in medicine*. Jun 30 2016;35(14):2467-78. doi:10.1002/sim.6844
57. Coppola A, Marrone E, Conca P, et al. Safety of Switching Factor VIII Products in the Era of Evolving Concentrates: Myths and Facts. *Seminars in thrombosis and hemostasis*. Jul 2016;42(5):563-76. doi:10.1055/s-0036-1581102
58. Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. *The New England journal of medicine*. Jan 17 2013;368(3):231-9. doi:10.1056/NEJMoa1208024
59. Iorio A, Barbara AM, Bernardi F, et al. Recommendations for authors of manuscripts reporting inhibitor cases developed in previously treated patients with hemophilia: communication from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH*. Aug 2016;14(8):1668-72. doi:10.1111/jth.13382

Supplemental Table S1. List of excluded papers (including references).

First author	Year	Reason for exclusion	Product	Patients	Inhibitors
Sennet [S1]	2004	Case series	Refacto	2	0
Keeling [S2]	2006	Case series	Refacto	3	3
Ishaku [S3]	2015	Case-control study	-	48	3
Kocher [S4]	2012	Multiple brands per patient	rFVIII and pdFVIII	119	0
Von Auer [S5]	2005	Case series	-	10	10
Giles [S6]	1998	Severity and prior exposure to FVIII were not reported	rFVIII	-	-
Auerswald [S7]	2013	Surgery	rFVIII and pdFVIII	29	0
Batorova [S8]	2012	Surgery, cross-sectional study	-	742	9
Siegmund [S9]	2010	Prior exposure to FVIII was not reported	rFVIII and pdFVIII	118	0
Aznar [S10]	2014	Type of brand used not accurately reported	rFVIII and pdFVIII	97	9
Xuan [S11]	2014	Prior exposure to FVIII and follow-up were not reported.	-	926	40
Martinowitz [S12]	2011	Study on pharmacokinetics	Novoeight, Advate	23	-
Lambert [S13]	2007	Study on pharmacokinetics	Refacto	14	-
Di Paola [S14]	2007	Study on pharmacokinetics	Refacto, Advate	18	0
Kelly [S15]	1997	Study on pharmacokinetics	rFVIII	10	-
Barnes [S16]	2006	Study on pharmacokinetics	Kogenate-FS	20	-
Kessler [S17]	2005	Study on pharmacokinetics	BDD rFVIII, pdFVIII	18	-
Mulcahy [S18]	2005	Only treatment during surgery and/or severe bleeding	rFVIII	12	2
Mannucci [S19]	1994	Prior exposure to FVIII was not reported	Kogenate	51	0
Lalezari [S20]	2013	Follow-up and inhibitor information not reported	Kogenate FS	68	-
Shah [S21]	2015	Study on pharmacokinetics	Kovaltry	45	-
Tuddenham [S22]	2010	Early findings of a study, results of full study were published later	-	-	-
Oldenburg [S23]	1995	Prior exposure to FVIII, severity and follow-up were not reported	Kogenate, Recombinate	112	-
Ewenstein [S24]	2004	Prior exposure to FVIII and follow-up were not accurately reported	Recombinate/ Bioclate	-	-
Lusher [S25]	2005	Follow-up was not reported	Refacto	218	33
Jiménez-Yuste [S26]	2015	Study on pharmacokinetics	NovoEight	76	0

Windyga [S27]	2010	Surgery	Refacto AF	30	1
Négrier [S28]	2008	Surgery	Advate	58	0
Meijer [S29]	2015	Surgery	Kogenate FS	25	0
Santagostino [S30]	2015	Surgery	Novoeight	33	0
Scharrer [S31]	2000	Surgery	Kogenate FS	15	1
Martinowitz [S32]	2009	Surgery	Kogenate FS	14	0
Shirahata [S33]	2000	< 10 patients	Kogenate FS	5	0
Zanon [S34]	1999	< 10 patients treated with rFVIII products	rFVIII and pdFVIII	62	7
Fukui [S35]	1991	< 10 patients	Kogenate	5	0
Prezotti [S36]	2015	Follow-up and prior exposure to FVIII were not reported	Advate	346	5
Chen [S37]	2012	Prior exposure to FVIII was not reported	Advate	40	0
Rubinger [S38]	2008	Prior exposure to FVIII was not reported	Kogenate-FS	274	0
Roussel-Robert [S39]	2003	Follow-up was not reported	Refacto	70	4
Tarantino [S40]	2004	Follow-up was not reported	Advate	108	1
Shi [S41]	2007	Follow-up was not reported	Kogenate-FS	49	0
Rea [S42]	2009	Prior exposure to FVIII was not reported	Refacto	33	1
Bacon [S43]	2011	Prior exposure to FVIII was not reported	Advate	96	1
Zhang [S44]	2011	Prior exposure to FVIII was not reported	Advate	58	1
Chang [S45]	2015	< 10 patients	Refacto AF	8	4
Smith [S46]	2005	Follow-up was not reported	Refacto	60	3
Vidovic [S47]	2010	Follow-up was not reported	Kogenate-FS	306	0
Pollmann [S48]	2013	Subanalysis of earlier report (duplicate data)	-	-	-
Schwartz [S49]	1990	Prior exposure to FVIII was not reported accurately, long-term results are published in later report	Kogenate	107	8
Rothschild [S50]	2002	Subanalysis of earlier report (duplicate data)	-	-	-
Petrini [S51]	2009	Prior exposure to FVIII was not reported	Refacto	57	0
Klukowska [S52]	2015	Follow-up not reported	Nuwiq	59	0

References of excluded papers

S1. Sennett MM, de Alarcon PA. Successful use of ReFacto continuous infusion in two paediatric patients with severe haemophilia A undergoing orthopaedic surgery. *Haemophilia* 2004; **10**: 655-60.

S2. Keeling D. Switching between full-length and B-domain-deleted factor VIII and the risk of inhibitors. *Haemophilia* 2006; **12**: 690-1.

S3. Ishaku NG, Key NS, Miller CH, Nielsen B, Buckner T, Chen SL, Hooper WC, Soucie JM. Cluster of inhibitors among adult inpatients with haemophilia in a single institution. *Haemophilia* 2015; **21**: e325-8.

S4. Kocher S, Asmelash G, Makki V, Muller S, Krekeler S, Alesci S, Miesbach W. [Inhibitor development after changing FVIII/IX products in patients with haemophilia]. *Hamostaseologie* 2012; **32 Suppl 1**: S39-42.

S5. von Auer C, Oldenburg J, von Depka M, Escuriola-Ettinghausen C, Kurnik K, Lenk H, Scharrer I. Inhibitor development in patients with hemophilia A after continuous infusion of FVIII concentrates. *Ann N Y Acad Sci* 2005; **1051**: 498-505.

S6. Giles AR, Rivard GE, Teitel J, Walker I. Surveillance for factor VIII inhibitor development in the Canadian Hemophilia A population following the widespread introduction of recombinant factor VIII replacement therapy. *Transfus Sci* 1998; **19**: 139-48.

S7. Auerswald G, Bade A, Haubold K, Overberg D, Masurat S, Moorthi C. No inhibitor development after continuous infusion of factor concentrates in subjects with bleeding disorders undergoing surgery: a prospective study. *Haemophilia* 2013; **19**: 438-44.

S8. Batorova A, Holme P, Gringeri A, Richards M, Hermans C, Altisent C, Lopez-Fernandez M, Fijnvandraat K. Continuous infusion in haemophilia: current practice in Europe. *Haemophilia* 2012; **18**: 753-9.

S9. Siegmund B, Pollmann H, Richter H, Orlovic M, Gottstein S, Klamroth R. [Inhibitor development against FVIII in previously treated patients with haemophilia A. A retrospective data collection]. *Hamostaseologie* 2010; **30 Suppl 1**: S37-9.

S10. Aznar JA, Moret A, Ibanez F, Vila C, Cabrera N, Mesa E, Bonanad S. Inhibitor development after switching of FVIII concentrate in multitransfused patients with severe haemophilia A. *Haemophilia* 2014; **20**: 624-9.

S11. Xuan M, Xue F, Fu R, Yang Y, Zhang L, Tian M, Yang R. Retrospective analysis of 1,226 Chinese patients with haemophilia in a single medical centre. *J Thromb Thrombolysis* 2014; **38**: 92-7.

S12. Martinowitz U, Bjerre J, Brand B, Klamroth R, Misgav M, Morfini M, Santagostino E, Tiede A, Viuff D. Bioequivalence between two serum-free recombinant

factor VIII preparations (N8 and ADVATE(R))--an open-label, sequential dosing pharmacokinetic study in patients with severe haemophilia A. *Haemophilia* 2011; **17**: 854-9.

S13. Lambert T, Guerois C, Gay V, Stieltjes N, Bertrand MA, Derlon A, Sigaud M, Hassoun A, Negrier C, Coatmelec B, Dreyfus M, Dubanchet A. Factor VIII recovery after a single infusion of recalibrated ReFacto in 14 severe haemophilia A patients. *Haemophilia* 2007; **13**: 357-60.

S14. Di Paola J, Smith MP, Klamroth R, Mannucci PM, Kollmer C, Feingold J, Kessler C, Pollmann H, Morfini M, Udata C, Rothschild C, Hermans C, Janco R. ReFacto and Advate: a single-dose, randomized, two-period crossover pharmacokinetics study in subjects with haemophilia A. *Haemophilia* 2007; **13**: 124-30.

S15. Kelly KM, Butler RB, Farace L, Cohen AR, Manno CS. Superior in vivo response of recombinant factor VIII concentrate in children with hemophilia A. *J Pediatr* 1997; **130**: 537-40.

S16. Barnes C, Lillicrap D, Pazmino-Canizares J, Blanchette VS, Stain AM, Clark D, Hensmen C, Carcao M. Pharmacokinetics of recombinant factor VIII (Kogenate-FS®) in children and causes of inter-patient pharmacokinetic variability. *Haemophilia* 2006; **12**: 40-9.

S17. Kessler CM, Gill JC, White GC, 2nd, Shapiro A, Arkin S, Roth DA, Meng X, Lusher JM. B-domain deleted recombinant factor VIII preparations are bioequivalent to a monoclonal antibody purified plasma-derived factor VIII concentrate: a randomized, three-way crossover study. *Haemophilia* 2005; **11**: 84-91.

S18. Mulcahy R, Walsh M, Scully MF. Retrospective audit of a continuous infusion protocol for haemophilia A at a single haemophilia treatment centre. *Haemophilia* 2005; **11**: 208-15.

S19. Mannucci PM, Brettler DB, Aledort LM, Lusher JM, Abildgaard CF, Schwartz RS, Hurst D. Immune status of human immunodeficiency virus seropositive and seronegative hemophiliacs infused for 3.5 years with recombinant factor VIII. The Kogenate Study Group. *Blood* 1994; **83**: 1958-62.

S20. Lalezari S, Martinowitz U, Windyga J, Enriquez MM, Delesen H, Schwartz L, Scharrer I. Correlation between endogenous VWF:Ag and PK parameters and bleeding frequency in severe haemophilia A subjects during three-times-weekly prophylaxis with rFVIII-FS. *Haemophilia* 2014; **20**: e15-22.

S21. Shah A, Delesen H, Garger S, Lalezari S. Pharmacokinetic properties of BAY 81-8973, a full-length recombinant factor VIII. *Haemophilia* 2015; **21**: 766-71.

S22. Tuddenham EGD, Kannicht C, Agerkvist I, Sandberg H, Knaub S, Zozulya N. From human to humans - Introducing the first recombinant human FVIII product produced from a human cell line. *Thrombosis and Haemostasis* 2010; **103**: 4-14.

S23. Oldenburg J, Effenberger W, Hammerstein U, Brackmann HH. Report on Experiences with Two Recombinant Factor VIII Concentrates: Kogenate‹sup›®‹/sup› (Bayer) and Recombinate‹sup›®‹/sup› (Baxter). *Transfusion Medicine and Hemotherapy* 1995; **22(suppl 1)**: 60-2.
S24. Ewenstein BM, Gomperts ED, Pearson S, O'Banion ME. Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclate): a prospective pharmacovigilance study. *Haemophilia* 2004; **10**: 491-8.
S25. Lusher JM, Roth DA. The safety and efficacy of B-domain deleted recombinant factor VIII concentrates in patients with severe haemophilia A: an update. *Haemophilia* 2005; **11**: 292-3.
S26. Jimenez-Yuste V, Lejniece S, Klamroth R, Suzuki T, Santagostino E, Karim FA, Saugstrup T, Moss J. The pharmacokinetics of a B-domain truncated recombinant factor VIII, turoctocog alfa (NovoEight(R)), in patients with hemophilia A. *J Thromb Haemost* 2015; **13**: 370-9.
S27. Windyga J, Rusen L, Gruppo R, O'Brien AC, Kelly P, Roth DA, Arkin S. BDDrFVIII (Moroctocog alfa [AF-CC]) for surgical haemostasis in patients with haemophilia A: results of a pivotal study. *Haemophilia* 2010; **16**: 731-9.
S28. Negrier C, Shapiro A, Berntorp E, Pabinger I, Tarantino M, Retzios A, Schroth P, Ewenstein B. Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of Advate in previously treated patients. *Thromb Haemost* 2008; **100**: 217-23.
S29. Meijer K, Rauchensteiner S, Santagostino E, Platokouki H, Schutgens RE, Brunn M, Tueckmantel C, Valeri F, Schinco PC. Continuous infusion of recombinant factor VIII formulated with sucrose in surgery: non-interventional, observational study in patients with severe haemophilia A. *Haemophilia* 2015; **21**: e19-25.
S30. Santagostino E, Lentz SR, Misgav M, Brand B, Chowdary P, Savic A, Kilinc Y, Amit Y, Amendola A, Solimeno LP, Saugstrup T, Matytsina I. Safety and efficacy of turoctocog alfa (NovoEight(R)) during surgery in patients with haemophilia A: results from the multinational guardian clinical trials. *Haemophilia* 2015; **21**: 34-40.
S31. Scharrer I, Brackmann HH, Sultan Y, Abshire T, Gazengel C, Ragni M, Gorina E, Vosburgh E, Kellermann E. Efficacy of a sucrose-formulated recombinant factor VIII used for 22 surgical procedures in patients with severe haemophilia A. *Haemophilia* 2000; **6**: 614-8.
S32. Martinowitz U, Luboshitz J, Bashari D, Ravid B, Gorina E, Regan L, Stass H, Lubetsky A. Stability, efficacy, and safety of continuously infused sucrose-formulated recombinant factor VIII (rFVIII-FS) during surgery in patients with severe haemophilia. *Haemophilia* 2009; **15**: 676-85.

S33. Shirahata A, Fukutake K, Takamatsu J, Shima M, Yoshioka A. Pharmacokinetics, prophylactic effects, and safety of a new recombinant FVIII formulated with sucrose (BAY 14-2222) in Japanese patients with hemophilia A. *Int J Hematol* 2000; **72**: 101-7.

S34. Zanon E, Zerbinati P, Girolami B, Bertomoro A, Girolami A. Frequent but low titre factor VIII inhibitors in haemophilia A patients treated with high purity concentrates. *Blood Coagul Fibrinolysis* 1999; **10**: 117-20.

S35. Fukui H, Yoshioka A, Shima M, Tanaka I, Koshihara K, Fukutake K, Fujimaki M. Clinical evaluation of recombinant human factor VIII (BAY w 6240) in the treatment of hemophilia A. *Int J Hematol* 1991; **54**: 419-27.

S36. Prezotti A, Montalvao S, Marques A, Ferreira C, Oliveira L, Villaca P, Ferreira FL, Lorenzato C, Medina S, Araujo F, Ozelo M. Assessment of inhibitor risk after switching from plasma-derived factor VIII concentrate to recombinant factor VIII (Brasil-RFVIII: Brazilian study of inhibitor linked to recombinant factor VIII). *Journal of Thrombosis and Haemostasis* 2015: Conference:366.

S37. Chen Y, Cheng S, Chang P. The safety and efficacy surveillance study of full-length plasma and albumin-free recombinant factor VIII for previously treated patients with hemophilia A in Taiwan. *Haemophilia* 2012: Conference:143.

S38. Rubinger M, Lillicrap D, Rivard GE, Teitel J, Carcao M, Hensman C, Walker I. A prospective surveillance study of factor VIII inhibitor development in the Canadian haemophilia A population following the switch to a recombinant factor VIII product formulated with sucrose. *Haemophilia* 2008; **14**: 281-6.

S39. Roussel-Robert V, Torchet MF, Legrand F, Rothschild C, Stieltjes N. Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four hemophilia A previously treated patients. *J Thromb Haemost* 2003; **1**: 2450-1.

S40. Tarantino MD, Collins PW, Hay CR, Shapiro AD, Gruppo RA, Berntorp E, Bray GL, Tonetta SA, Schroth PC, Retzios AD, Rogy SS, Sensel MG, Ewenstein BM. Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia* 2004; **10**: 428-37.

S41. Shi J, Zhao Y, Wu J, Sun J, Wang L, Yang R. Safety and efficacy of a sucrose-formulated recombinant factor VIII product for the treatment of previously treated patients with haemophilia A in China. *Haemophilia* 2007; **13**: 351-6.

S42. Rea C, Dunkerley A, Sorensen B, Rangarajan S. Pharmacokinetics, coagulation factor consumption and clinical efficacy in patients being switched from full-length FVIII treatment to B-domain-deleted r-FVIII and back to full-length FVIII. *Haemophilia* 2009; **15**: 1237-42.

S43. Bacon CL, Singleton E, Brady B, White B, Nolan B, Gilmore RM, Ryan C, Keohane C, Jenkins PV, O'Donnell JS. Low risk of inhibitor formation in haemophilia A patients following en masse switch in treatment to a third generation full length plasma and albumin-free recombinant factor VIII product (ADVATE(R)). *Haemophilia* 2011; **17**: 407-11.

S44. Zhang L, Zhao Y, Sun J, Wang X, Yu M, Yang R. Clinical observation on safety and efficacy of a plasma- and albumin-free recombinant factor VIII for on-demand treatment of Chinese patients with haemophilia A. *Haemophilia* 2011; **17**: 191-5.

S45. Chang C-Y, Chen S-H, Yeh G-C, Tsai C-H, Tsai J-R, Liu Y-L. Inhibitor development as switching full-length recombinant FVIII to B-domain deleted recombinant FVIII in previously treated patients with hemophilia A: Taiwan's experience. *Journal of Thrombosis and Haemostasis* 2015: Conference:856-7.

S46. Smith MP, Giangrande P, Pollman H, Littlewood R, Kollmer C, Feingold J. A post-marketing surveillance study of the safety and efficacy of ReFacto (St Louis-derived active substance) in patients with haemophilia A. *Haemophilia* 2005; **11**: 444-51.

S47. Vidovic N, Musso R, Klamroth R, Enriquez MM, Achilles K. Postmarketing surveillance study of KOGENATE Bayer with Bio-Set in patients with haemophilia A: evaluation of patients' satisfaction after switch to the new reconstitution system. *Haemophilia* 2010; **16**: 66-71.

S48. Pollmann H, Klamroth R, Vidovic N, Kriukov AY, Epstein J, Abraham I, Spotts G, Oldenburg J. Prophylaxis and quality of life in patients with hemophilia A during routine treatment with ADVATE [antihemophilic factor (recombinant), plasma/albumin-free method] in Germany: a subgroup analysis of the ADVATE PASS post-approval, non-interventional study. *Ann Hematol* 2013; **92**: 689-98.

S49. Schwartz RS, Abildgaard CF, Aledort LM, Arkin S, Bloom AL, Brackmann HH, Brettler DB, Fukui H, Hilgartner MW, Inwood MJ, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. recombinant Factor VIII Study Group. *N Engl J Med* 1990; **323**: 1800-5.

S50. Rothschild C, Scharrer I, Brackmann HH, Stieltjes N, Vicariot M, Torchet MF, Effenberger W. European data of a clinical trial with a sucrose formulated recombinant factor VIII in previously treated haemophilia A patients. *Haemophilia* 2002; **8 Suppl 2**: 10-4.

S51. Petrini P, Rylander C. Clinical safety surveillance study of the safety and efficacy of long-term home treatment with ReFacto utilizing a computer-aided diary: a Nordic multicentre study. *Haemophilia* 2009; **15**: 175-83.

S52. Klukowska A, Szczepanski T, Vdovin V, Knaub S, Jansen M, Liesner R. Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq(R)) in children with severe haemophilia A: efficacy, safety and pharmacokinetics. *Haemophilia* 2015.

Supplemental Table S2. Quality assessment score. The methodological quality of each article was assessed using a modified Downs and Black checklist.

Study	REPORTING	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
		Is the aim clearly described?	Are the main outcomes clearly described in the methods?	Are the characteristic of the patients clearly described?	Are the interventions of interest clearly described?	Are the main study findings clearly described?	Does the study provide estimates of the random variability in the data for the main outcomes?	Have all important adverse events that may be a consequence of the intervention been reported?	Have the characteristics of patients lost to follow-up been described?
Abshire [22]		*	*	*	*	*		*	
Aygören-Pürsün [28]		*	*	*	*	*		*	*
Blanchette [33]		*	*	*	*	*		*	*
Collins [37]		*	*	*	*	*		*	*
Delumeau [35]		*	*	*	*	*		*	
Den Uijl [36]		*	*	*	*	*		*	
Fischer [23]		*	*	*	*	*	*		*
Fukutake [19]		*	*	*		*	*		
Gouider [45]		*	*	*	*	*		*	*
Gringeri [24]		*	*	*	*	*			
Hay [25]		*	*	*	*	*	*	*	
Hyun [44]		*	*	*	*	*		*	*
Kavakli [46]		*	*	*	*	*		*	*
Kulkarni [39]		*	*	*	*	*		*	*
Lalezari [27]		*	*	*	*	*		*	
Lentz [40]		*	*	*	*	*	*	*	*
Lentz [49]		*	*		*	*		*	

	EXTERNAL VALIDITY				INTERNAL VALIDITY						POWER		
	Q9	Q10	Q11		Q12	Q13	Q14	Q15	Q16	Q17		Q18	
	Were the subjects asked to participate representative of the entire population?	Were those subjects who were prepared to participate representative of the entire population from which they were recruited ?	Were the staff, places and facilities representative of the treatment the majority of patients receive?		If any of the results of the study were based on *data dredging*, was this made clear?	Do the analyses adjust for different lengths of folluw-up of patients?	Were the statistical tests used to assess the main outcomes appropriate?	Was compliance with the interventions reliable?	Were the main outcome measures used accurate (valid and reliable)?	Were losses of patients to follow-up taken into account?		Did the study have sufficient power? (>100 person-years)	SCORE
	*		*		*				*			*	11
	*		*		*				*				11
	*		*		*				*	*			12
	*		*		*				*				11
			*		*				*			*	10
	*		*		*			*	*	*		*	13
	*	*	*		*	*	*		*	*		*	16
	*		*									*	8
	*		*		*			*	*			*	13
	*		*		*				*				9
	*		*		*	*	*	*	*			*	15
			*		*			*	*				10
	*		*		*			*	*				12
	*		*		*	*	*	*	*	*			15
	*		*		*			*	*				11
	*		*		*			*	*	*		*	15
	*		*		*			*	*			*	11

Study	REPORTING	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
		Is the aim clearly described?	Are the main outcomes clearly described in the methods?	Are the characteristic of the patients clearly described?	Are the interventions of interest clearly described?	Are the main study findings clearly described?	Does the study provide estimates of the random variability in the data for the main outcomes?	Have all important adverse events that may be a consequence of the intervention been reported?	Have the characteristics of patients lost to follow-up been described?
Lissitchkov (2015) [42]		*	*	*	*	*		*	*
Lissitchkov (2017) [51]		*	*	*	*	*		*	*
Ljung [47]		*	*	*	*	*		*	
Lopez [43]		*	*	*	*	*		*	
Manco-Johnson [41]		*	*	*	*	*		*	*
Musso [34]		*	*	*	*	*		*	
Oldenburg [21]		*	*	*	*	*	*	*	*
Pollmann [31]		*	*	*	*	*		*	
Recht [26]		*	*	*	*	*		*	
Saxena [50]		*	*	*	*	*		*	*
Seremetis [20]		*	*	*	*	*		*	
Singleton [32]		*	*	*	*	*			
Tiede [48]		*	*	*	*	*		*	*
Valentino [38]		*	*	*	*	*		*	*
White [29]		*	*	*	*	*		*	
Yoshioka [30]		*	*	*	*	*		*	
Young [18]		*	*	*					

	EXTERNAL VALIDITY				INTERNAL VALIDITY							POWER		
	Q9	Q10	Q11		Q12	Q13	Q14	Q15	Q16	Q17		Q18	
	Were the subjects asked to participate representative of the entire population?	Were those subjects who were prepared to participate representative of the entire population from which they were recruited ?	Were the staff, places and facilities representative of the treatment the majority of patients receive?		If any of the results of the study were based on *data dredging*, was this made clear?	Do the analyses adjust for different lengths of folluw-up of patients?	Were the statistical tests used to assess the main outcomes appropriate?	Was compliance with the interventions reliable?	Were the main outcome measures used accurate (valid and reliable)?	Were losses of patients to follow-up taken into account?		Did the study have sufficient power? (>100 person-years)	SCORE
	*		*		*				*				11
	*		*		*			*	*				12
	*		*		*			*	*				10
	*		*		*				*			*	11
	*		*		*			*	*			*	13
	*		*		*				*			*	11
	*		*		*			*	*			*	14
	*		*		*			*	*			*	12
	*		*		*				*			*	11
	*		*		*			*	*				12
	*		*		*				*			*	11
	*		*		*			*	*			*	11
	*		*		*				*				11
	*		*		*			*	*	*			13
	*		*		*				*			*	11
			*		*				*			*	10
			*		*				*				6

Supplemental table S3. information on the distribution of potential confounders in the studies that were included in the main analysis.

Author	Family history of inhibitors	Treatment type (prophylaxis/on-demand)
Advate		
Blanchette [33]	-	90.6% prophylaxis 3.8% on-demand 5.7% on-demand/prophylaxis
Den Uijl [36]	-	65.9% prophylaxis, 34.1% on-demand
Valentino [38]	-	Patients were treated with on-demand regimen during the first 6 months, and then with a prophylactic regimen for the following 6 months
Fukutake [19]	-	53.4% Prophylaxis 30.7% On-demand 15.9% Mixed
Hay (cohort 2) [25]	-	-
Oldenburg [21]	-	57.0% Prophylaxis 43.0% On-demand
Fischer (cohort 1) [23]	-	-
Kogenate, Helixate		
Aygören-Pürsün [28]	-	-
Seremetis [20]	-	-
Yoshioka [30]	-	-
Singleton [32]	-	52.1% Prophylaxis 38.3% On-demand 9.6 % Unknown
Kogenate FS/Bayer, Helixate FS/NexGen		
Abshire [22]	-	Prophylaxis: 43.8% N. America, 60.7% EU On-demand: 12.1% N. America, 12.9% EU
Musso [34]	-	31.8% Prophylaxis

	F8 genotype	Ethnicity	Surgery during follow-up
	40% intron 22 inversion 27% missense mutation 13% nonsense mutation 11% frameshift mutation 5% deletion 2% intron 1 inversion 2% splice defect	90.6% Caucasian 5.6% African-American 3.8% Unspecified	5 patients underwent a surgical procedure
	-	-	27 surgical procedures
	-	87.7% White 5.5% Hispanic 4.1% Black/African-American 1.4% Asian 1.4% Other	-
	-	100% Asian	-
	-	-	-
	-	90.8% Caucasian 3.3% Black 1.5% Asian 3.6% Other	16 surgical procedures (15 patients)
	-	-	-
	-	-	-
	-	-	25 surgical procedures (22 patients)
	-	100% Asian	10 patients underwent at least one surgical procedure (not included in analysis)
	-	-	-
	-	-	22 surgical procedures (15 patients)
	-	81.8% White 1.4% Black 0.9% Asian 3.6% other	46 surgical procedures (37 patients)

Author	Family history of inhibitors	Treatment type (prophylaxis/on-demand)
Delumeau [35]	-	17.6% prophylaxis
Young [18]	-	12.9% regular prophylaxis 87.1% Other
Collins [37]	-	Patients were treated on-demand for 6 months, followed by 7 months prophylaxis
Manco-Johnson [41]	-	50% prophylaxis 50% on-demand
Lalezari [27]	-	100% prophylaxis
Gouider [45]	-	60.2% prophylaxis
Hay (cohort 3) [25]	-	-
Fischer (cohort 2) [23]	-	-
Refacto		
Gringeri [24]	-	100% on demand
Pollmann [31]	-	81 patients treated on prophylaxis for at least one treatment-year 39 patients treated on-demand for at least one treatment-year
Fischer (cohort 3) [23]	-	-
Refacto AF		
Recht (cohort 1) [26]	-	100% prophylaxis
Recht (cohort 2) [26]	-	100% prophylaxis
Lopez [43]	-	74% prophylaxis, 25% on-demand, 1% Other
Hay (cohort 1) [25]	-	-
Fischer (cohort 4) [23]	-	-

	F8 genotype	Ethnicity	Surgery during follow-up
	-	100% Asian	-
	-	98.6% Asian 1.4% Caucasian	-
	-	95% White 5% Hispanic	-
	-	90.5% White 2.4% Asian 7.1% Hispanic	-
	-	-	-
	-	81.2% Caucasian 2.2% Black 5.4% Asian 5.9% Other	18 surgical procedures (15 patients)
	-	-	-
	-	-	-
	-	-	-
	47.0% Intron 22 inversion 16.7% Missense mutation 10.8% Small deletion or insertion	100% Caucasian	-
	-	-	-
	-	94.7% White 5.3% Other	Surgery during study was not permitted
	-	86.4% White 13.6% Other	9 patients underwent at least one surgical procedure
	-	96.6% White 1.0% Asian 0.5% Black 1.9% Other	-
	-	-	-
	-	-	-

Supplemental Table S4. Sensitivity analysis. Main analysis restricted to studies that only reported information for severe patients (baseline FVIII activity <0.01 IU/ml).

Variable	N	Inhibitors/ p-y	Pooled inhibitor incidence rate per 1000 p-y (CI95)	Between-study variance (τ^2)	Incidence rate ratio (CI95)
Overall (main products only)	20	30/16181	1.88 (CI95: 0.72-4.92)	1.6120	
Product					
Advate	4	5/5529	0.62 (CI95: 0.11-3.46)	0	Ref
Kogenate/Helixate	3	4/283	6.34 (CI95: 0.01-7819.34)	1.8502	15.63 (CI95: 3.84-63.63)
Kogenate FS/Helixate NexGen	8	9/7031	1.28 (CI95: 0.58-2.82)	0	1.42 (CI95: 0.44-4.55)
Refacto*	2	5/222	-	-	-
Refacto AF	3	7/3116	2.30 (CI95: 0.19-28.48)	0.4149	2.48 (CI95: 0.73-8.45)
rFVIII length[1]					
Full-length rFVIII	15	18/12843	1.14 (CI95: 0.30-4.33)	1.4962	Ref
B-domain deleted rFVIII	5	12/3338	5.19 (CI95: 0.85-31.77)	1.3310	4.49 (CI95: 0.70-28.58)
Cell line[2]					
CHO-cells	9	17/8867	2.13 (CI95: 0.52-8.67)	1.7264	Ref
BHK-cells	11	13/7314	1.62 (CI95: 0.32-8.09)	1.5944	0.74 (CI95: 0.12-4.53)
rFVIII generation[3]					
Second-generation rFVIII	10	14/7253	2.40 (CI95: 0.65-8.83)	1.1894	Ref
First-generation rFVIII	3	4/283	6.34 (CI95: 0.01-7819.34)	1.8502	3.56 (CI95: 0.44-28.77)
Third-generation rFVIII	7	12/8645	1.35 (CI95: 0.44-4.12)	0.3568	0.47 (CI95: 0.10-2.23)

[1] Full-length rFVIII (Kogenate/Helixate, Kogenate FS/Helixate NexGen and Advate) is compared with B-domain deleted rFVIII (Refacto and Refacto AF).

[2] rFVIII derived from CHO-cells (Refacto, Refacto AF and Advate) is compared with rFVIII derived from BHK-cells (Kogenate/Helixate and Kogenate FS/Helixate NexGen).

[3] First Generation rFVIII (Kogenate/Helixate) is compared with second generation rFVIII (Refacto and Kogenate FS/Helixate NexGen) and third generation rFVIII (Advate and Refacto AF).

* Not enough studies for analysis.

Supplemental Table S5. Sensitivity analysis. Main analysis restricted to large studies (i.e. studies with › 150 person-years of follow-up time).

Variable	N	Inhibitors/ p-y	Pooled inhibitor incidence rate per 1000 p-y (CI95)	Between-study variance (τ^2)	Incidence rate ratio (CI95)
Overall (main products only)	15	30/16750	2.06 (CI95: 1.09-3.91)	0.5248	
Product					
Advate	4	6/5772	1.04 (CI95: 0.28-3.81)	0	Ref
Kogenate/Helixate*	1	1/254	-	-	-
Kogenate FS/Helixate NexGen	5	10/7012	0.88 (CI95: 0.29-2.69)	0	1.37 (CI95: 0.33-5.75)
Refacto*	2	6/596	-	-	-
Refacto AF	3	7/3116	2.30 (CI95: 0.19-28.48)	0.4149	2.16 (CI95: 0.47-9.86)
rFVIII length[1]					
Full-length rFVIII	10	17/13038	1.83 (CI95: 1.15-2.91)	0	Ref
B-domain deleted rFVIII	5	13/3712	4.07 (CI95: 1.01-16.39)	0.7253	3.20 (CI95: 1.09-9.40)
Cell line[2]					
CHO-cells	9	19/9484	2.23 (CI95: 0.79-6.28)	0.9128	Ref
BHK-cells	6	11/7266	1.51 (CI95: 0.70-3.29)	0	0.68 (CI95: 0.18-2.51)
rFVIII generation[3]					
Second-generation rFVIII	7	16/7608	2.77 (CI95: 0.94-8.18)	0.6663	Ref
First-generation rFVIII	1	1/254	-	-	-
Third-generation rFVIII	7	13/8888	1.49 (CI95: 0.58-3.86)	0.2716	0.51 (CI95: 0.14-1.83)

[1] Full-length rFVIII (Kogenate/Helixate, Kogenate FS/Helixate NexGen and Advate) is compared with B-domain deleted rFVIII (Refacto and Refacto AF).

[2] rFVIII derived from CHO-cells (Refacto, Refacto AF and Advate) is compared with rFVIII derived from BHK-cells (Kogenate/Helixate and Kogenate FS/Helixate NexGen).

[3] First Generation rFVIII (Kogenate/Helixate) is compared with second generation rFVIII (Refacto and Kogenate FS/Helixate NexGen) and third generation rFVIII (Advate and Refacto AF).

* Not enough studies for analysis.

Supplemental Figure S1. Search strategy

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(((“Factor VIII”[Mesh] OR “Factor VIII”[tw] OR “Factor 8”[tw] OR “Thromboplastinogen”[tw] OR “Hyate-C”[tw] OR “Hyate C”[tw] OR “Factor VIIIC”[tw] OR “F VIII-C”[tw] OR “F VIII C”[tw] OR “FVIII”[tw] OR antihemophilic factor*[tw] OR anti-hemophilic factor*[tw] OR antihaemophilic factor*[tw] OR anti-haemophilic factor*[tw] OR “Factor VIIIa”[tw] OR “Coagulation Factor VIIIa”[tw]) AND (“recombinant”[tw] OR “Recombinant Proteins”[Mesh]) AND (“INH”[tw] OR “inhibitor development”[tw] OR “inhibitors development”[tw] OR (inhibitor*[tw] AND (develop*[tw] OR occurence*[tw])) OR inhibitor*[tw] OR “inhibitory”[tw])) **OR** (“Factor VIII/antagonists and inhibitors”[Mesh] AND (“recombinant”[tw] OR “Recombinant Proteins”[Mesh])) **OR** ((“Advate”[tw] OR “rAHF-PFM”[tw] OR “Refacto”[tw] OR “Refacto AF”[tw] OR “Kogenate-FS”[tw] OR “Kogenate”[tw] OR “Helixate”[tw] OR “Helixate-FS”[tw] OR “Recombinate”[tw] OR “Xyntha”[tw]) AND (“INH”[tw] OR “inhibitor development”[tw] OR “inhibitors development”[tw] OR (inhibitor*[tw] AND develop*[tw]) OR inhibitor*[tw] OR “inhibitory”[tw] OR “antagonists and inhibitors”[Subheading])) **OR** ((“Advate”[ti] OR “rAHF-PFM”[ti] OR “Refacto”[ti] OR “Refacto AF”[ti] OR “Kogenate-FS”[ti] OR “Kogenate”[ti] OR Helixat*[ti] OR “Recombinate”[ti] OR “Xyntha”[ti] OR recombinant factor VIII*[ti])) **OR** ((“Factor VIII”[majr] OR “Factor VIII”[ti] OR “Factor 8”[ti] OR “Thromboplastinogen”[ti] OR “Hyate-C”[ti] OR “Hyate C”[ti] OR “Factor VIIIC”[ti] OR “F VIII-C”[ti] OR “F VIII C”[ti] OR “FVIII”[ti] OR antihemophilic factor*[ti] OR anti-hemophilic factor*[ti] OR antihaemophilic factor*[ti] OR anti-haemophilic factor*[ti] OR “Factor VIIIa”[ti] OR “Coagulation Factor VIIIa”[ti]) AND (“concentrates”[tw] OR “concentrate”[tw]) AND (“INH”[ti] OR “inhibitor development”[ti] OR “inhibitors development”[ti] OR (inhibitor*[ti] AND (develop*[ti] OR occurence*[ti])) OR inhibitor*[ti] OR “inhibitory”[ti]) AND (“Clinical Study”[Publication Type] OR “Epidemiologic Studies”[Mesh] OR “Support of Research”[Publication Type]))) AND (“Hemophilia A”[Mesh] OR “hemophilia”[tw] OR “haemophilia”[tw] OR hemophil*[tw] OR haemophil*[tw]) NOT (“Animals”[mesh] NOT “Humans”[mesh]) NOT ((acquired haemophil*[ti] OR acquired haemophil*[ti]) NOT Congenital*[ti])

Embase

(((*”blood clotting factor 8”/ OR “Factor VIII”.ti,ab OR “Factor 8”.ti,ab OR “Thromboplastinogen”.ti,ab OR “Hyate-C”.ti,ab OR “Hyate C”.ti,ab OR “Factor VIIIC”.ti,ab OR “F VIII-C”.ti,ab OR “F VIII C”.ti,ab OR “FVIII”.ti,ab OR antihemophilic factor*.ti,ab OR anti-hemophilic factor*.ti,ab OR antihaemophilic factor*.ti,ab OR anti-haemophilic factor*.ti,ab OR “Factor VIIIa”.ti,ab OR “Coagulation Factor VIIIa”.ti,ab) AND (“recom-

binant".ti,ab OR exp *"Recombinant Protein"/) AND ("INH".ti,ab OR "inhibitor development".ti,ab OR "inhibitors development".ti,ab OR (inhibitor*.ti,ab ADJ5 (develop*.ti,ab OR occurence*.ti,ab)) OR inhibitor*.ti OR "inhibitory".ti OR *"blood clotting factor 8 inhibitor"/)) OR ((*"recombinant blood clotting factor 8"/ OR "Advate".ti,ab OR "rAHF-PFM".ti,ab OR "Refacto".ti,ab OR "Refacto AF".ti,ab OR "Kogenate-FS".ti,ab OR "Kogenate".ti,ab OR "Helixate".ti,ab OR "Helixate-FS".ti,ab OR "Recombinate".ti,ab OR "Xyntha".ti,ab) AND ("INH".ti,ab OR "inhibitor development".ti,ab OR "inhibitors development".ti,ab OR (inhibitor*.ti,ab ADJ5 develop*.ti,ab) OR inhibitor*.ti OR "inhibitory".ti OR *"blood clotting factor 8 inhibitor"/))) AND ("Hemophilia A"/ OR "Hemophilia"/ OR "hemophilia".ti,ab OR "haemophilia".ti,ab OR hemophil*.ti,ab OR haemophil*.ti,ab) AND exp "Humans"/ NOT ((acquired haemophil*.ti OR acquired haemophil*.ti) NOT Congenital*.ti) NOT "conference review".pt NOT "conference abstract".pt

Web of Science

(((TS=("blood clotting factor 8" OR "Factor VIII" OR "Factor 8" OR "Thromboplastinogen" OR "Hyate-C" OR "Hyate C" OR "Factor VIIIC" OR "F VIII-C" OR "F VIII C" OR "FVIII" OR antihemophilic factor* OR anti-hemophilic factor* OR antihaemophilic factor* OR anti-haemophilic factor* OR "Factor VIIIa" OR "Coagulation Factor VIIIa") AND TS=("recombinant" OR "Recombinant Protein") AND TI=("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 (develop* OR occurence*)) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor")) **OR** (TS=("recombinant blood clotting factor 8" OR "Advate" OR "rAHF-PFM" OR "Refacto" OR "Refacto AF" OR "Kogenate-FS" OR "Kogenate" OR "Helixate" OR "Helixate-FS" OR "Recombinate" OR "Xyntha") AND TI=("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 develop*) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor"))) AND TS=("Hemophilia A" OR "Hemophilia" OR "hemophilia" OR "haemophilia" OR hemophil* OR haemophil*) NOT TI=(animal* OR "rat" OR "rats" OR "mice" OR "mouse") NOT TI=((acquired haemophil* OR acquired haemophil*) NOT Congenital*)) OR (((TI=("blood clotting factor 8" OR "Factor VIII" OR "Factor 8" OR "Thromboplastinogen" OR "Hyate-C" OR "Hyate C" OR "Factor VIIIC" OR "F VIII-C" OR "F VIII C" OR "FVIII" OR antihemophilic factor* OR anti-hemophilic factor* OR antihaemophilic factor* OR anti-haemophilic factor* OR "Factor VIIIa" OR "Coagulation Factor VIIIa") AND TS=("recombinant" OR "Recombinant Protein") AND TS=("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 (develop* OR occurence*)) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor")) **OR** (TI=("recombinant blood clotting factor 8" OR "Advate" OR "rAHF-PFM" OR "Refacto" OR "Refacto AF" OR "Kogenate-FS" OR "Kogenate" OR "Helixate" OR "Helixate-FS" OR

"Recombinate" OR "Xyntha") AND TS=("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 develop*) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor"))) AND TS=("Hemophilia A" OR "Hemophilia" OR "hemophilia" OR "haemophilia" OR hemophil* OR haemophil*) NOT TI=(animal* OR "rat" OR "rats" OR "mice" OR "mouse") NOT TI=((acquired haemophil* OR acquired haemophil*) NOT Congenital*))

Cochrane
(((("blood clotting factor 8" OR "Factor VIII" OR "Factor 8" OR "Thromboplastinogen" OR "Hyate-C" OR "Hyate C" OR "Factor VIIIC" OR "F VIII-C" OR "F VIII C" OR "FVIII" OR antihemophilic factor* OR anti-hemophilic factor* OR antihaemophilic factor* OR anti-haemophilic factor* OR "Factor VIIIa" OR "Coagulation Factor VIIIa") AND ("recombinant" OR "Recombinant Protein") AND ("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 (develop* OR occurence*)) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor")) **OR** (("recombinant blood clotting factor 8" OR "Advate" OR "rAHF-PFM" OR "Refacto" OR "Refacto AF" OR "Kogenate-FS" OR "Kogenate" OR "Helixate" OR "Helixate-FS" OR "Recombinate" OR "Xyntha") AND ("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 develop*) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor"))) AND ("Hemophilia A" OR "Hemophilia" OR "hemophilia" OR "haemophilia" OR hemophil* OR haemophil*)

CINAHL
(((("blood clotting factor 8" OR "Factor VIII" OR "Factor 8" OR "Thromboplastinogen" OR "Hyate-C" OR "Hyate C" OR "Factor VIIIC" OR "F VIII-C" OR "F VIII C" OR "FVIII" OR antihemophilic factor* OR anti-hemophilic factor* OR antihaemophilic factor* OR anti-haemophilic factor* OR "Factor VIIIa" OR "Coagulation Factor VIIIa") AND ("recombinant" OR "Recombinant Protein") AND ("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 (develop* OR occurence*)) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor")) **OR** (("recombinant blood clotting factor 8" OR "Advate" OR "rAHF-PFM" OR "Refacto" OR "Refacto AF" OR "Kogenate-FS" OR "Kogenate" OR "Helixate" OR "Helixate-FS" OR "Recombinate" OR "Xyntha") AND ("INH" OR "inhibitor development" OR "inhibitors development" OR (inhibitor* ADJ5 develop*) OR inhibitor* OR "inhibitory" OR "blood clotting factor 8 inhibitor"))) AND ("Hemophilia A" OR "Hemophilia" OR "hemophilia" OR "haemophilia" OR hemophil* OR haemophil*)