SIPPET 3 years later – what impact in clinical practice?

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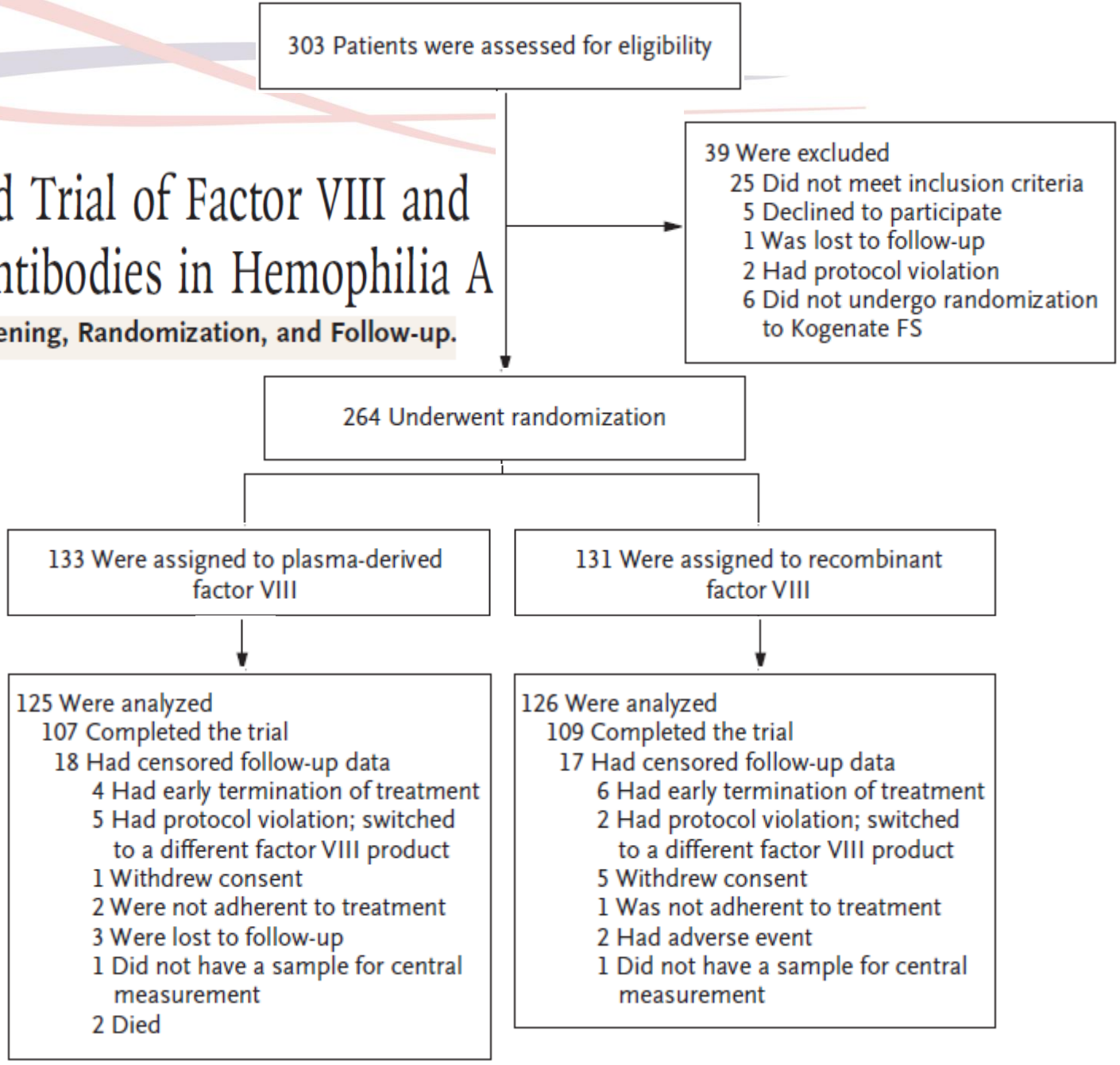
A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

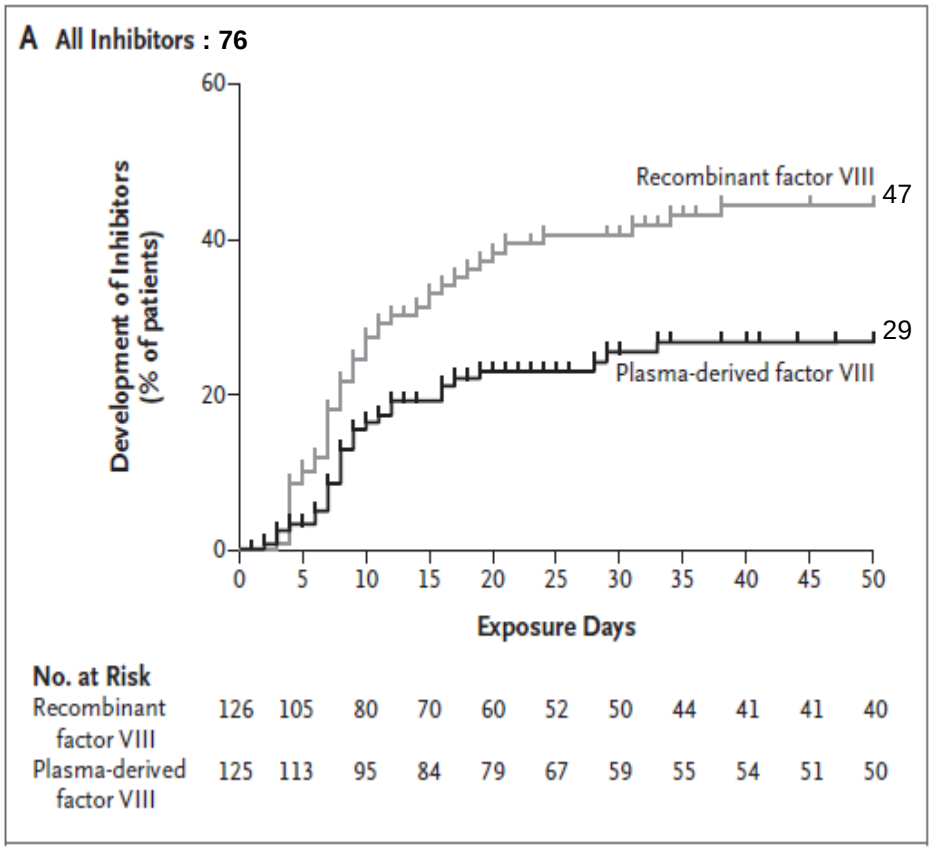
Figure 1. Screening, Randomization, and Follow-up.

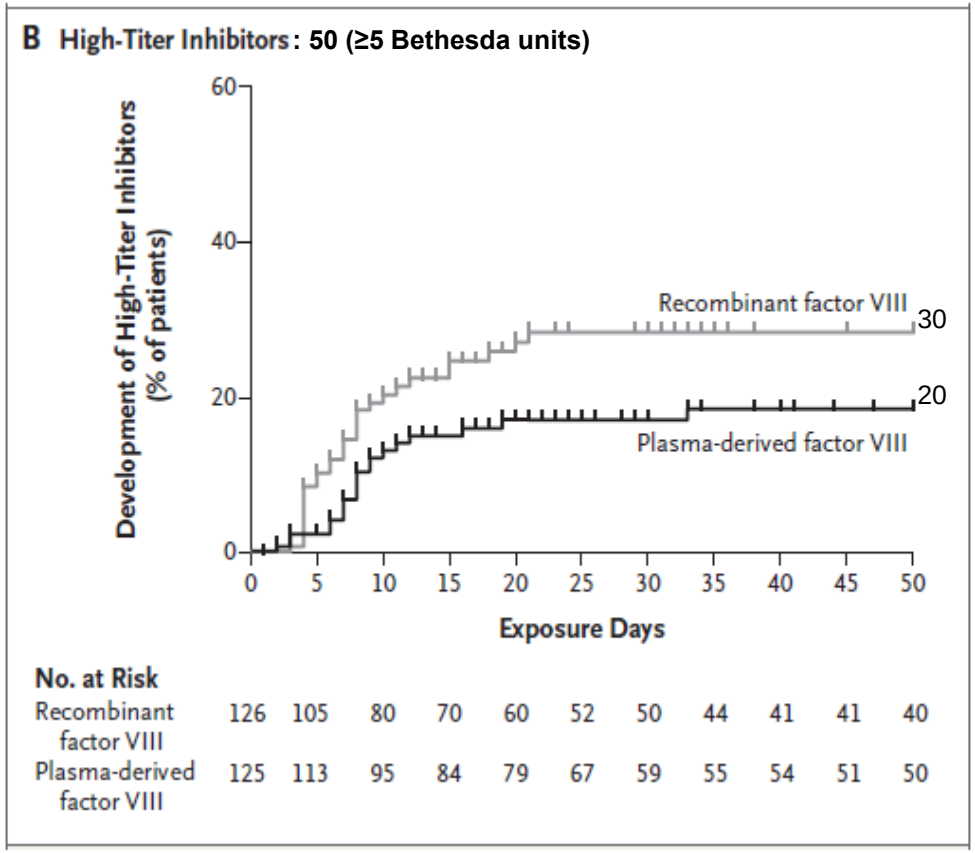


SIPPET

Figure 2. Cumulative Incidence of Inhibitors According to Treatment Group.

Shown are Kaplan–Meier curves of inhibitor development for all inhibitors (≥0.4 Bethesda units; Panel A) and high-titer inhibitors (≥5 Bethesda units; Panel B). The curves depict the cumulative incidence of inhibitor development over time, which is counted as exposure days. Patients who did not complete 50 exposure days before trial termination are indicated by tick marks.





Genetic risk stratification to reduce inhibitor development in the early treatment of hemophilia A: a SIPPET analysis

Frits R. Rosendaal,[1,2] Roberta Palla,[2,3] Isabella Garagiola,[2,3] Pier M. Mannucci,[2,3] and Flora Peyvandi,[2-4] for the SIPPET Study Group

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [2]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Milan, Italy; [3]Luigi Villa Foundation, Milan, Italy; and [4]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Table 1. Inhibitor development for patients with low and high genetic risk, by product class

	pdFVIII				rFVIII				
	No. per group	Inhibitor count	Cumulative incidence, %	95% CI, %	No. per group	Inhibitor count	Cumulative incidence, %	95% CI, %	NNH
All inhibitors									
Low risk	16	0	0	0-21	22	7	43	23-71	2.3
High risk	101	27	31	22-41	96	38	47	36-58	6.3
High-titer inhibitors									
Low risk	16	0	0	0-21	22	4	24	10-52	4.1
High risk	101	19	22	14-32	96	25	30	21-42	11.6

For the zero observations in the low-risk pdFVIII group, the 95% CI was based on a binomial distribution, ignoring censoring. Median number of exposure days was 45.4 in the low-risk pdFVIII group, 29 in the low-risk rFVIII group, 15.5 in the high-risk pdFVIII group, and 17.5 in the high-risk rFVIII group.

NNH, number needed to harm when treated with rFVIII instead of pdFVIII.

Genetic risk stratification to reduce inhibitor development in the early treatment of hemophilia A: a SIPPET analysis

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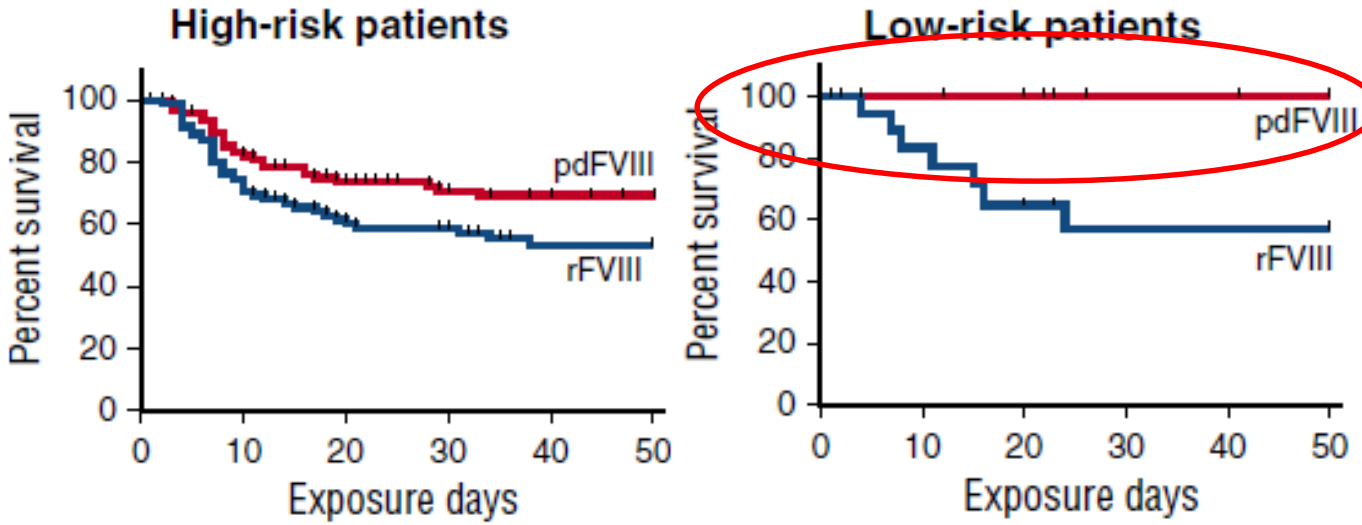

ED	0	10	20	30	40	50
pdFVIII	101	76	61	47	42	39
rFVIII	96	61	45	38	29	29

ED	0	10	20	30	40	50
pdFVIII	16	14	13	9	9	8
rFVIII	22	14	10	7	7	7

Figure 1. Survival by genetic risk and treatment class. Kaplan-Meier survival curves show the cumulative incidence of inhibitors in 4 groups, with low (A) and high (B)' genetic risk based on the F8 mutation, treated with either pdFVIII and rFVIII. Below the curves are the number of patients at risk at the start of each 10-day exposure day (ED) interval.

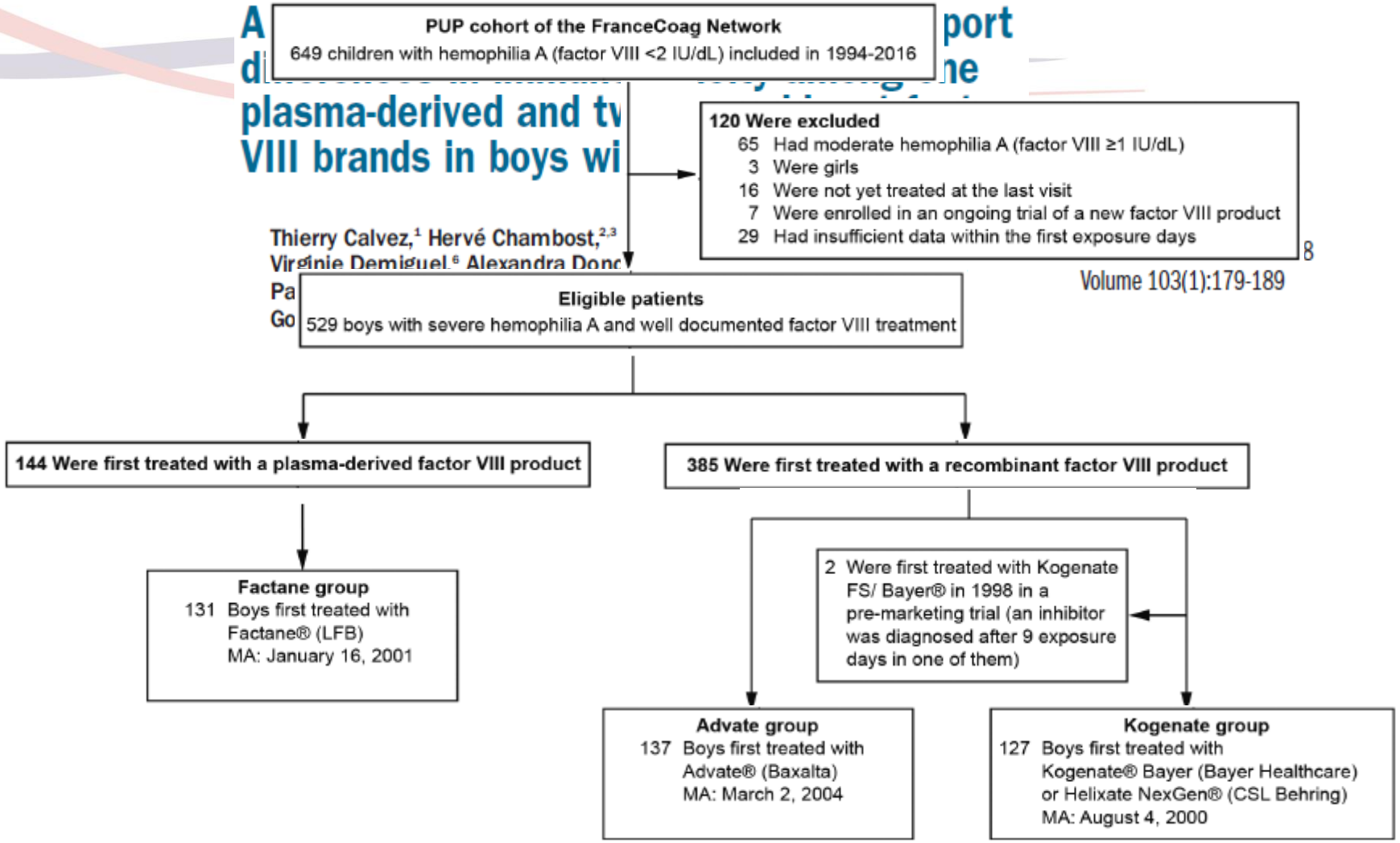

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Figure 1. Patient selection process. At the cutoff date (December 6, 2016), 649 previously untreated patients (PUPs) with hemophilia A (factor VIII <2 IU/dL) had been included in the dedicated cohort of FranceCoag. After the selection process, three groups of boys with severe hemophilia A (factor VIII <1 IU/dL) were formed based on the first factor VIII product received. MA: marketing authorization dates in European Union (or in France for Factane®).

Kaplan-Meier estimates

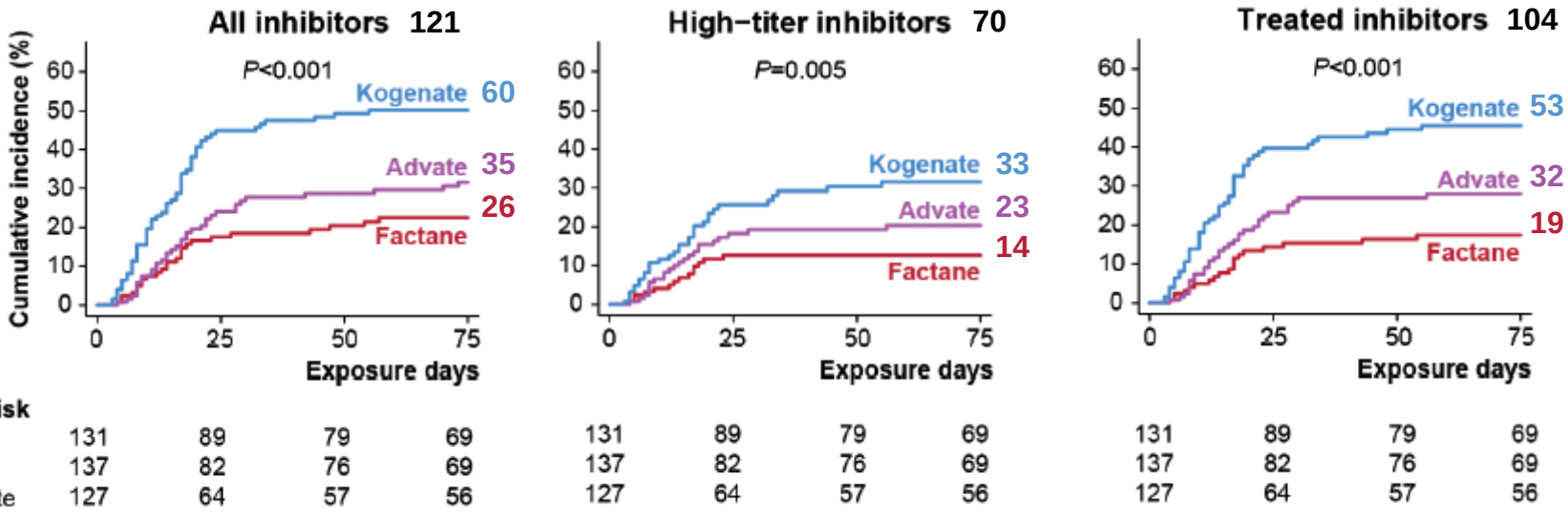

Figure 2. Kaplan-Meier representation of the cumulative incidence of inhibitors, with exposure day as the observational time unit, according to the factor VIII product received. Three outcomes are shown: all inhibitors, high-titer inhibitors and inhibitors subsequently treated with a bypassing agent and/or immune tolerance induction. Kaplan-Meier estimates are shown for all patients. Tests used Cox proportional hazards model.

By peak treatment episode at first exposure

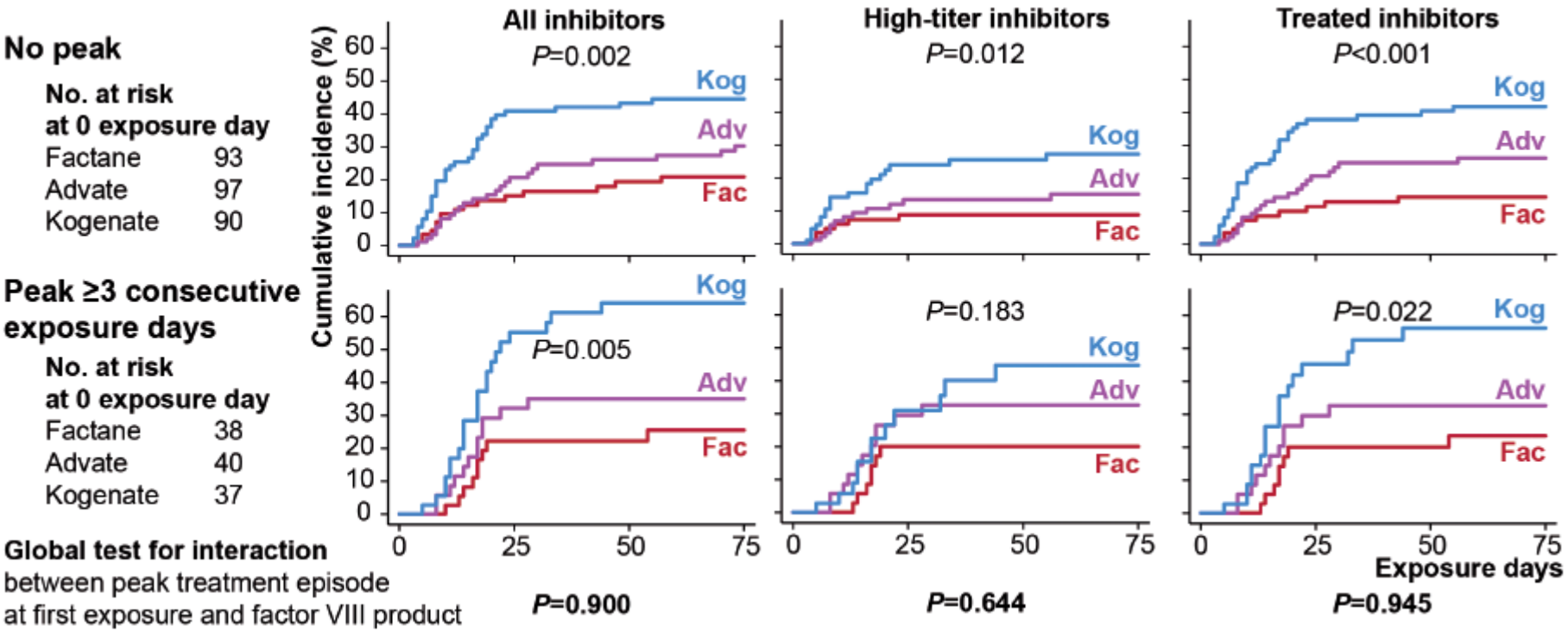

Figure 3. Kaplan-Meier representation of the cumulative incidence of inhibitors, with exposure day as the observational time unit, according to the factor VIII product received. Three outcomes are shown: all inhibitors, high-titer inhibitors and inhibitors subsequently treated with a bypassing agent and/or immune tolerance induction. Tests used Cox proportional hazards model. (A) Kaplan-Meier estimates according to calendar period of first exposure to factor VIII. (B) Kaplan-Meier estimates according to treatment intensity at first exposure (peak treatment episode ≥ 3 consecutive exposure days).

SIPPET: methodology, analysis and generalizability

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Haemophilia (2017), **23**, 353–361

17 Questions and answers in 5 Clusters

- Generally: 1 – 6 of 17
- Analysis: 7 – 8 of 17
- Comparability and confounding: 9 -11 of 17
- Generalizability: 12-15 of 17
- Formal aspects: 16-17 of 17

SIPPET: methodology, analysis and generalizability

Generally

Question 1: Is the inhibitor risk higher in SIPPET than in previous reports?

Short answer: No.

Long answer:
Cumulative incidence in SIPPET: 44,5%rFVIII / 26,8 pdFVIII - in metanalysis by Marcucci et al. 2015 44% / 22% (including 14,37% with only light haemophilia a)

Type and intensity of FVIII exposure on inhibitor development in PUI with haemophilia A

A patient-level meta-analysis

Maura Marcucci[1,2]; Maria Elisa Mancuso[3]; Elena Santagostino[3]; Gili Kenet[4]; Mohssen Elalfy[5]; Susanne Holzhauer[6]; Christoph Bidlingmaier[7]; Carmen Escuriola Ettingshausen[8]; Alfonso Iorio*[1,9]; Ulrike Nowak-Göttl*[10]

SIPPET: methodology, analysis and generalizability

Generally

Question 2: Some of the patients had been exposed to various blood components prior to enrolment, and so they were not all previously untreated patients (PUPs). Does this affect the outcome?

Short answer: No.

Long answer:

- Never exposed: 142 patients, minimally exposed: 109.

- no difference in inhibitor incidence between patients previously exposed and those never exposed - hazard ratio (HR) of 0.80 [95% confidence interval (CI95) 0.51–1.26]

SIPPET: methodology, analysis and generalizability

Generally

Question 3: Among patients treated with pdFVIII the cumulative incidence of high-titre inhibitors was 18.6%, which is a substantial risk. How many fewer inhibitors develop when patients are treated with pdFVIII than rFVIII?

- Number Needed to Treat (NNT) all inhibitors 5,6, high-titre inhibitors 10,2

- treating six PUPs with pdFVIII instead of rFVIII will prevent one inhibitor

SIPPET: methodology, analysis and generalizability

Generally

Question 4: SIPPET used a cut-off of 0.4 BU, which is lower than in most previous studies. Could this have contributed to a high proportion of low-titre inhibitors?

- Yes– but in both arms of the study
- data for the endpoint of >1.0 BU, i.e. considering the three SIPPET-patients with peaks between 0.7 and 1.0 BU as not having developed an inhibitor: the HR for rFVIIII vs. pdFVIII became 1.96, CI95: 1.22–3.16
- even with the ISTH definition cut-off of 0.6 BU, results would have been the same

SIPPET: methodology, analysis and generalizability

Generally

Question 5: The study was stopped early, after publication of an increased risk of inhibitors with second generation full-length rFVIII. Did this increase the probability of a chance finding, since the number of inhibitors is relatively low?

- Reason for stopping early: exposing newly diagnosed patients to full-length rFVIII, after findings of increased inhibitor-risk would have been unethical
- continuing after adjustments of the study would have been too costly
- planned sample size was achieved, including a few more patients would not have changed the results
- nearly every study in haemophilia, including registration trials for efficacy and safety, include fewer than 100 cases
- SIPPET is the largest randomized trial ever performed in patients with such a rare disease as haemophilia

SIPPET: methodology, analysis and generalizability

Generally

Question 6: Will the risk for those who started with pdFVIII remain low when switched back to rFVIII after 50 exposure days?

SIPPET can´t answer this

SIPPET: methodology, analysis and generalizability

Analysis

Question 7: Not all patients were followed until 50 ED: does this affect the estimated risk of inhibitor development?

- only effect early termination could have is an underestimation of overall inhibitor development, but since it only concerned a fraction of all patients, there was no such effect

- sensitivity analyses yielded essentially the same results as the actual analysis

SIPPET: methodology, analysis and generalizability

Analysis

Question 8: How should the results on high-titre inhibitors be interpreted, since these were not statistically significant?

Since there is no likely mechanism by which a particular product would increase the risk of all inhibitors but not of the subgroup of high-titre inhibitors, and given the consistency of effect estimates for all and high-titre inhibitors, we feel confident to conclude that rFVIII is associated with an increased rate of high-titre inhibitors.

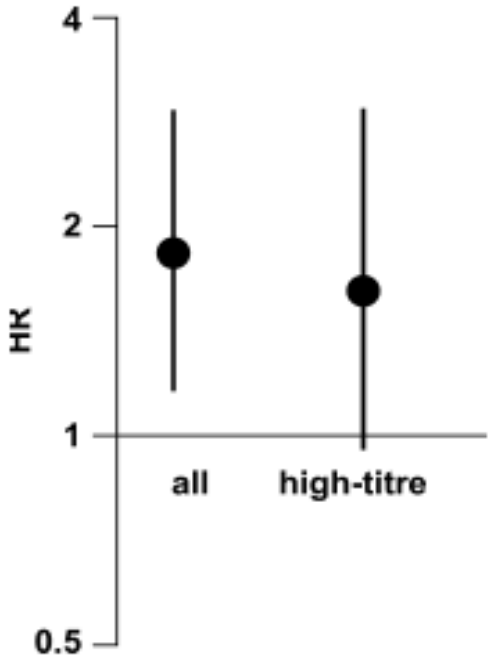


Fig. 1. All and high-titre inhibitors in SIPPET. 95% confidence interval for the hazard ratio of inhibitor development of rFVIII vs. pdFVIII for all (left) and high-titre (right) inhibitors in SIPPET.

SIPPET: methodology, analysis and generalizability

Comparability and confounding

Question 9: How did the authors in SIPPET account for differences between study sites in ethnicity, treatment modalities and other potential differences?

- Patients were randomized between pdFVIII and rFVIII, and such randomization is done to balance all differences

- No adjustments or sensitivityanalyses [for all kinds of varibles] led to any different result than the overall unadjusted analysis

SIPPET: methodology, analysis and generalizability

Comparability and confounding

Question 10: Could differences in treatment modalities between countries have affected the results?

- No – randomisation cancelled that out
- adjustments were done for "[…] country and treatment regimens, which did not change the results at all."

SIPPET: methodology, analysis and generalizability

Comparability and confounding

Question 11: The randomization used a block size of two per centre. Could this have affected results?

Short answer: No

Long answer:

- Blocking is used to prevent uncontrollable centre effects (confounding by centre)
- block size of two, meaning that for every block of two patients one will receive pdFVIII and one rFVIII, leads to the highest degree of balance between the two arms
- since within a centre the number of patients in each arm cannot differ more than one the small block size guaranteed the observed maximal similarity between the two treatment arms, and was a strength of the study

SIPPET: methodology, analysis and generalizability

Generalizability

Question 12: How should the results of SIPPET be interpreted in the context of other observational studies?

- randomized trials offer the highest level of evidence for effects, their generalizability is sometimes questioned, since they often only include highly selected patients

- major strength of SIPPET is its randomized design in a real world setting

SIPPET: methodology, analysis and generalizability

Generalizability

Question 13: The majority of patients were enrolled from Egypt, India and Iran, and is it therefore possible to extrapolate to European and North American populations: for instance because in them treatment was less intense or more patients used on demand vs. prophylactic treatment?

- doubting generalizability requires a valid and reasonable argument, in this case why a differential in inhibitor

- development between rFVIII and pdFVIII would depend on nationality, ethnicity or treatment modality. There is no such argument

SIPPET: methodology, analysis and generalizability

Generalizability

Question 14: SIPPET included mainly 1st and 2nd generation rFVIII: do the results also apply to other rFVIII?

- rFVIII products analysed in SIPPET are still licensed and used widely and globally.
- The results do not include human rFVIII, rFVIII-Fc nor PEG-FVIII
- four rFVIII and four pdFVIII concentrates were included
- We examined whether the higher risk with rFVIII was the result of an excess risk of only one of the rFVIII by repeating the analysis after excluding each time one of the four recombinant products (which every time included the other three products), and the pdFVIII using patients in the same centres. Results remained essentially unchanged (Fig. 2).

SIPPET: methodology, analysis and generalizability

Generalizability

Question 14

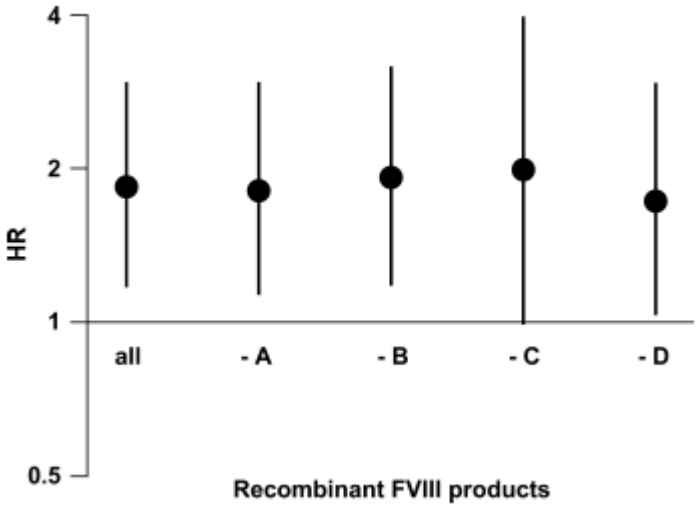


Fig. 2. Sensitivity analysis of product-related inhibitor development in SIPPET. Hazard ratio and 95% confidence interval for inhibitor development of rFVIII vs. pdFVIII with five different analyses. First, on the left, the overall analysis. Then analyses in which subsequently sites in which one of the four brands of rFVIII were used, were completely (i.e. all patients from these sites, including those using pdFVIII) left out, repeated for each of the four brands of rFVIII. This analysis maintains a randomized comparison. While it does not give information on brand-specific risk, it shows that the difference between rFVIII and pdFVIII in SIPPET is not caused by one brand.

SIPPET: methodology, analysis and generalizability

Generalizability

Question 15: Were there more patients with null mutations than expected in SIPPET and could this have affected the interpretation?

prevalence is not vastly different from that reported in the literature, i.e. in a meta-analysis 76% of patients had inversions, large deletions, nonsense and small deletions/insertions that usually lead to frameshifts

prevalence of null mutations is irrelevant to the primary research outcome, which is the risk differential

F8 gene mutation type and inhibitor development in patients with severe hemophilia A: systematic review and meta-analysis

Samantha C. Gouw,[1,2] H. Marijke van den Berg,[2] Johannes Oldenburg,[3] Jan Astermark,[4] Philip G. de Groot,[2] Maurizio Margaglione,[5] Arthur R. Thompson,[6] Waander van Heerde,[7] Jorien Boekhorst,[7] Connie H. Miller,[8] Saskia le Cessie,[9,10] and Johanna G. van der Bom[10,11]

BLOOD, 22 MARCH 2012 • VOLUME 119, NUMBER 12

SIPPET: methodology, analysis and generalizability

Formal aspects

Question 16: How were changes to the statistical plan made, and did it change the conclusions?

- change was only to use two-sided testing rather than one-sided as in the protocol, which obviously increased the bar for statistical significance

- results would have led to the same conclusion: the proportions were 29/125 vs. 47/ 126, chi-square = 5.91, P = 0.015. For the full intention-to-treat analysis: P = 0.011

SIPPET: methodology, analysis and generalizability

Formal aspects

Question 17: Is there a difference in inhibitor risk between the different brands within the plasma and recombinant groups?

all centre-specific factors were equal in the two groups

Centre- and country-specific factors would be different for different brands, confounding the comparison

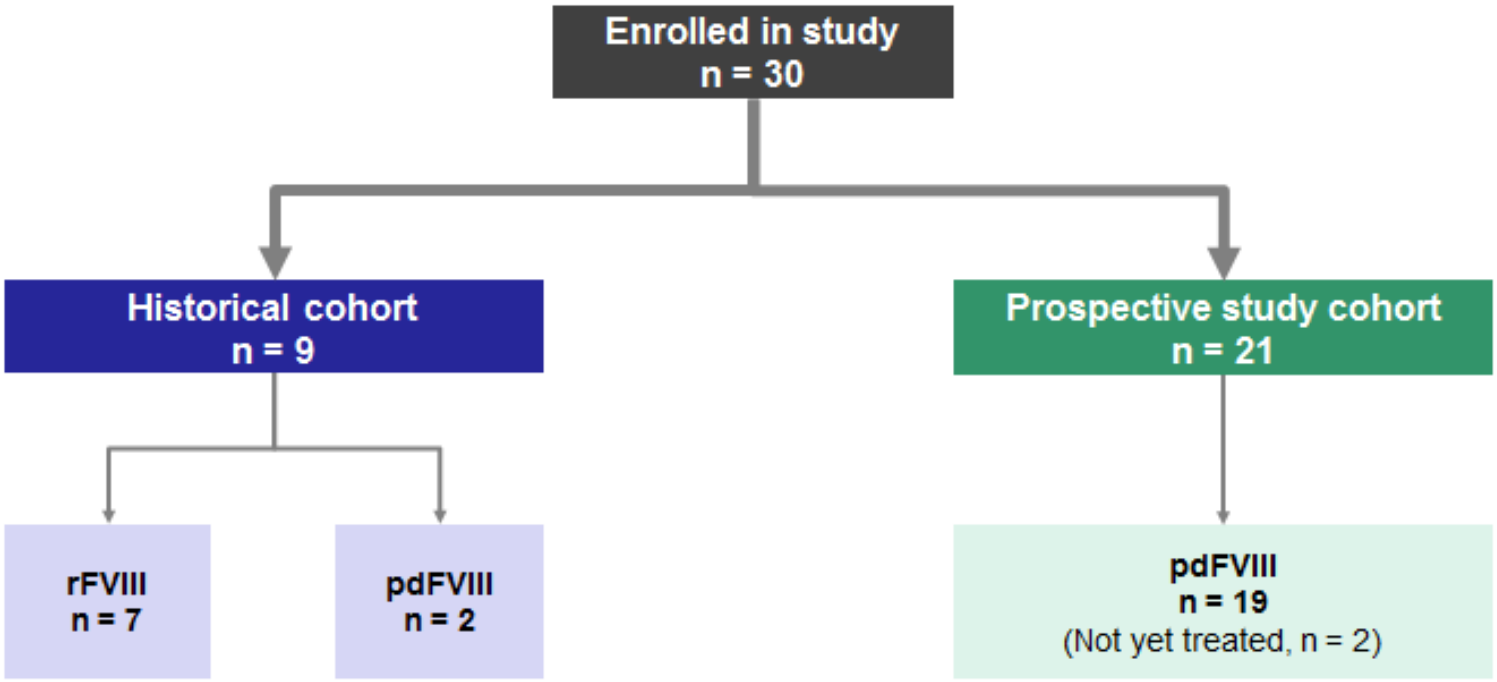
Personalised approach to the management of PUPs with severe haemophilia A

- Inhibitors occur in 25–30% PUPs, and usually develop within the first 50 exposure days (EDs)[1]
- Risk factors for inhibitor development include ethnicity, *F8* genotype, family history of inhibitors, and product type[1,2]
- Treatment approach may also influence inhibitor development
  - **SIPPET** study found an 87% higher inhibitor incidence with rFVIII produced in hamster cell lines than with plasma-derived (pd)FVIII[2]
- Estimated average annual cost per haemophilia patient in Germany: €40000–120000[3]
  - Immune tolerance induction (ITI) costs in inhibitor cases estimated at **€570000** per patient
- This study investigated a personalised treatment approach in PUPs, using low-dose prophylaxis with pdFVIII/VWF for the first 100 EDs, with the aim of minimising the risk of **inhibitor development** and **joint bleeds**
- Study cohort was compared with a historical cohort treated with early prophylaxis with hamster cell-derived rFVIII or pdFVII

Study design: Personalised treatment approach

	FVIII treatment	Inhibitor levels	Monitoring	Joint monitoring and protection
Diagnosis	Parents trained in bleed detection	Measured Every 3-4 EDs	**Observation period** Recording of • Bleeding events • Activity levels • Trauma Surgery avoided during peak treatment moments (where possible)	Individual physiotherapy schedule
	pdFVIII/VWF prophylaxis initiated at ~10 months of age Dose tailored to each patient. Initial dose < 30 IU/kg where possible			Age 3 years: Joint ultrasound
20 ED	Optional dose increase to full prophylaxis schedule (n = 8)			Prophylactic physiotherapy (2–4 months)
100 ED	Home treatment permitted	Every 3 months (for 2 years)		Age 6 years: Ankle MRI (and every 4 years thereafter)

Patient disposition



Baseline characteristics: Historical cohort

Patient no.	Date of birth	Reason for diagnosis	Age at diagnosis	Age at start of prophylaxis, months	Gene mutation	*F8* genotype	Product choice
1	Jun 2003	Mother carrier	1 day	10	Deletion c.3385del1C;Gln1110fs	High-risk	rFVIII
2	Dec 2004	Mother carrier	1 day	11	Missense mutation c.541G>A,Val162Met	Low-risk	rFVIII
3	Jun 2007	Frenulum bleeding	9 months	5	Missense mutation c.1654T>C p.Tyr533His	Low-risk	rFVIII
4	Jun 2007	Frenulum bleeding	9 months	5	Missense mutation c.1654T>C p.Tyr533His	Low-risk	rFVIII
5	May 2008	Mother carrier	1 day	5	Stop mutation c.3155T>A p.Leu1033Stop	High-risk	pdFVIII
6	Jun 2009	Mother carrier	2 days	12	Intron 22 inversion	High-risk	rFVIII
7	Oct 2009	Mother carrier	1 day	12	Splice mutation c.1010-2A>C	High-risk	rFVIII
8	Jan 2010	Mother carrier	1 day	9	Intron 22 inversion	High-risk	rFVIII
9	May 2010	Mother carrier	1 day	5	Deletion c.3385del1C;Gln1110fs	High-risk	pdFVIII

Baseline characteristics: Study cohort

Patient no.	Date of birth	Reason for diagnosis	Age at diagnosis	Age at start of prophylaxis, months	Gene mutation	*F8* genotype	Product choice
1	May 2010	Mother carrier	6 months	45	Nonsense mutation c.1336C>T,p.Arg466	High-risk	pdFVIII
2	Dec 2012	GI bleeding	12 months	12	Missense mutation c.6038G>A,p.Gly2013Glu	Low-risk	pdFVIII
3	May 2013	Mother carrier	1 day	8	Nonsense mutation c.5677,p.Gln1893Ter	High-risk	pdFVIII
4	Sept 2013	Light bruising	8 months	15	Missense mutation c.2057C>A	Low-risk	pdFVIII
5	Jan 2014	Oral bleeding	11 months	11	Missense mutation c.6167T>Ap.Ile2056Asn	Low-risk	pdFVIII
6	Feb 2014	Light bruising	9 months	9	Intron 22 inversion	High-risk	pdFVIII
7	May 2014	Mother carrier	1 day	8	Intron 22 inversion	High-risk	pdFVIII
8	Sept 2014	Mother carrier	14 days	7	Intron 22 inversion	High-risk	pdFVIII
9	Oct 2014	Forehead bleeding	14 months	14	Nonsense mutation c.6793C>T,p.Gln2265	High-risk	pdFVIII
10	Nov 2015	Mother carrier	11 days	16	Nonsense mutation c.3875T>A,p.Leu1052	High-rsk	pdFVIII

Baseline characteristics: Study cohort

Patient no.	Date of birth	Reason for diagnosis	Age at diagnosis	Age at start of prophylaxis, months	Gene mutation	*F8* genotype	Product choice
11	April 2016	Umbilical bleeding	14 days	12	Missense mutation c.5815G>A,p.Ala1939Thr	Low-risk	pdFVIII
12	Jan 2017	Mother carrier	1 day	14	Nonsense mutation c.6793C>T,p.Gln2265	High-risk	pdFVIII
13	Jul 2017	Mother carrier	13 days	10	Missense mutation c.6167T>Ap.Ile2056Asn	High-risk	pdFVIII
14	Feb 2018	Mother carrrier	1 day	6	Intron 22 inversion	High-risk	pdFVIII
15	Aug 2017	Bruising	8 months	10	Intron 22 inversion	High-risk	pdFVIII
16	Jun 2016	Frenulum bleeding	24 months	25	Splice site mutation c.1271G>A	Low-risk	pdFVIII
17	Jan 2017	Haematoma	20 months	20	Missense mutation c.1457A>G,p.Asn486Ser	Low-risk	pdFVIII
18	Aug 2018	Haematoma	3 months	9	Intron 22 inversion	High-risk	pdFVIII
19	Aug 2018	Bleeding after circumcision	3 months	3	Intron 22 inversion	High-risk	pdFVIII
20	Dec 2018	Uncle severe haemophilia	4 months	N/A*	Unknown	-	N/A*
21	Jun 2019	Mother carrier	10 days	N/A*	Unknown	-	N/A*

Baseline characteristics: Study and historical cohorts

Family history

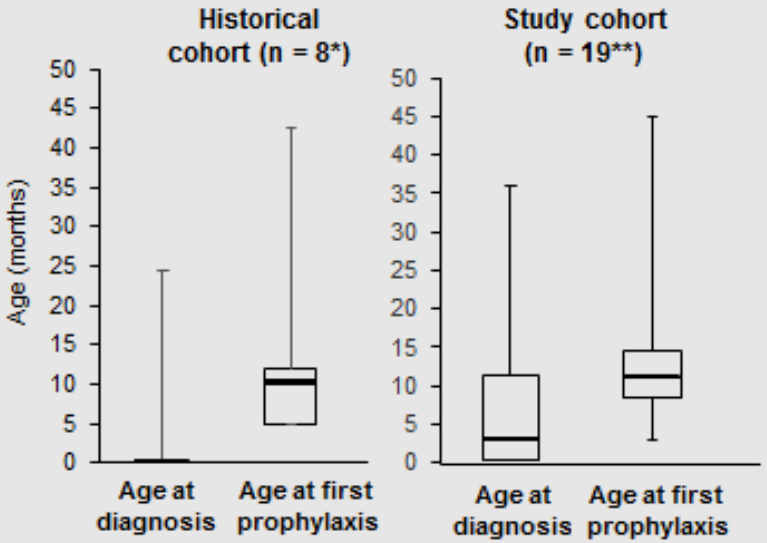
Haemophilia

Historical cohort (n = 9)	Study cohort (n = 21)
88.8%	47.4%

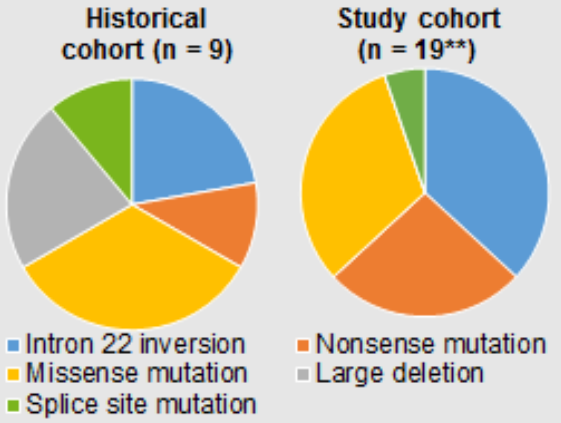
Inhibitors

Historical cohort (n = 9)	Study cohort (n = 21)
22.2%	0%

Age at diagnosis vs age at first prophylaxis



F8 mutation



Historical cohort (n = 9)	Study cohort (n = 19**)
High-risk mutations 66.6%	High-risk mutations 68.4%
Low-risk mutations 33.3%	Low-risk mutations 31.6%

Results: Bleeding events

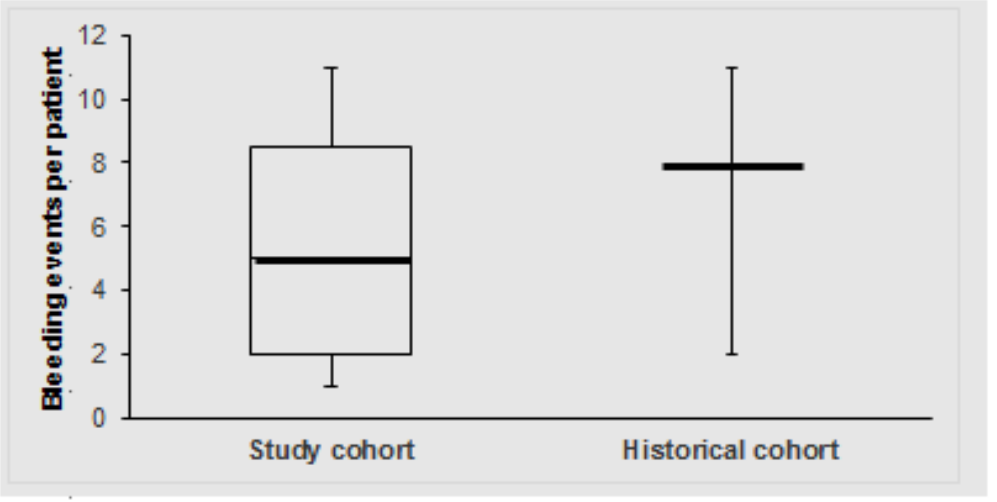
Number of bleeds

Study cohort

- 100 bleeding events in 19/19* patients
  - **Median age** at first bleed: 14 months (range 0.25–41)
  - **Median no. of EDs** at first bleed: 6 (range 1–53)

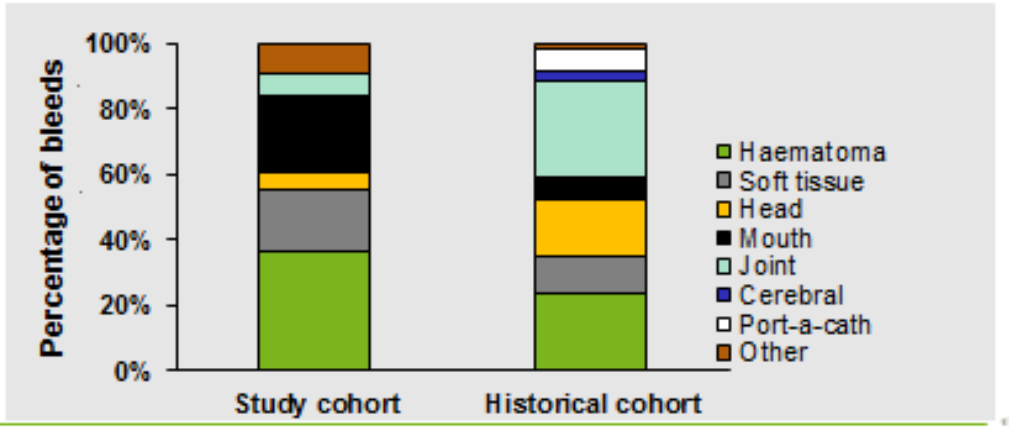
Historical cohort

- All 9 patients experienced bleeds (total 66 events)
  - **Median age** at first bleed:10 months (range 3–14)
  - **Median no. of EDs** at first bleed: 4 (range 1–24)



Localisation of bleeds

Reduction in joint bleeds
in study cohort compared with historical cohort (6.9% vs 29.0%)



Results: Prophylaxis and inhibitor development

Study cohort

- 19 patients were started on prophylaxis with pdFVIII/VWF
- 17 patients started on early prophylaxis
  - Initial dose range: **21 IU/kg every 10 days to 40 IU/kg 2X/week**
- No patient developed inhibitors to FVIII
  - Median observation time 25.6 months (mean 26.5; range 1 day to 36 months)

Historical cohort

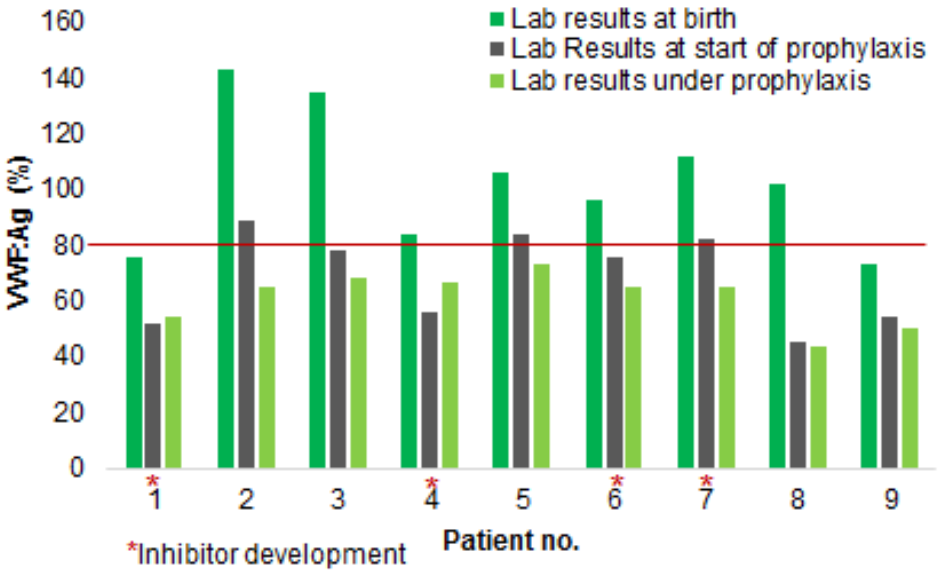
- 9 patients started early prophylaxis
  - Initial dose range: **25 IU/kg/10 days to 60 IU/kg/week**
- 44% (4/9) of patients developed high-titre inhibitors during the first 20 EDs with rFVIII

Should we treat all PUPs with pdFVIII?

Not necessarily

Patients' **VWF level** may provide a tool for decision on product choice

VWF levels: Historical cohort

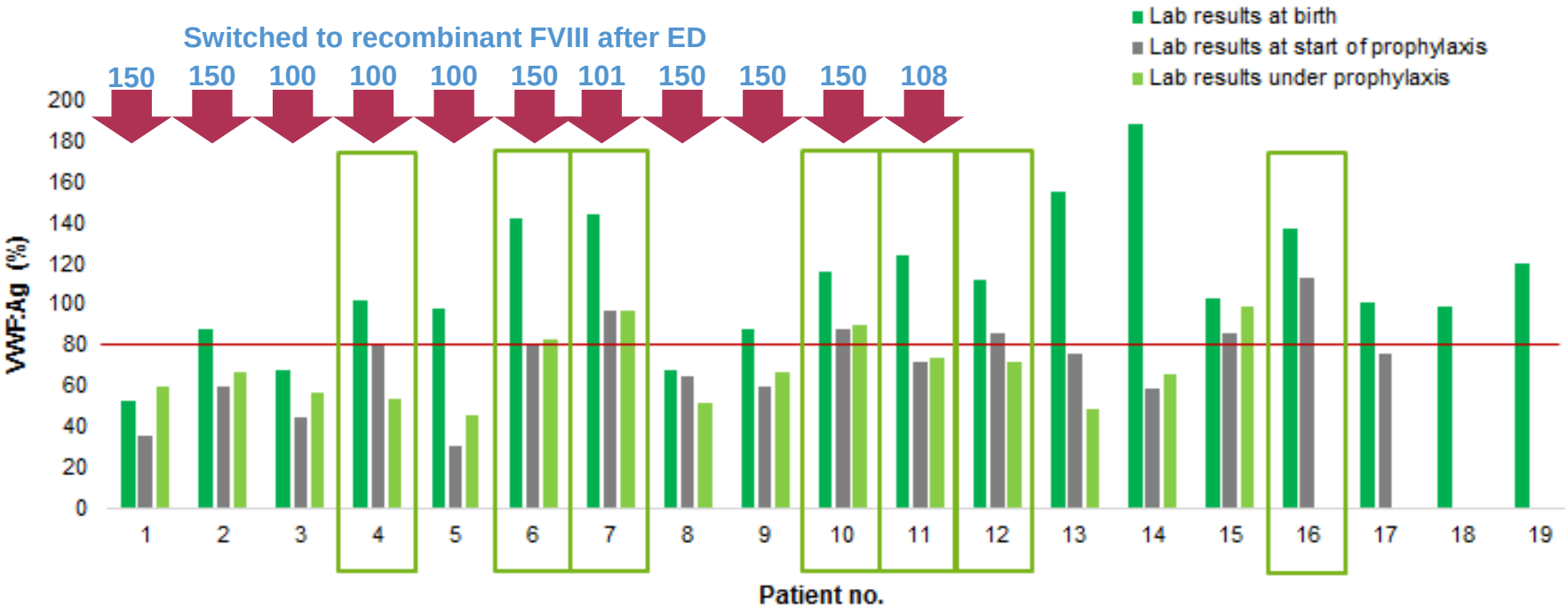


Average VWF:Ag levels

	At birth	At start of prophylaxis	Under prophylaxis
Inhibitor positive, %	89.5	57.25	57.5
Inhibitor negative, %	113.8	77.4	64.2

Inhibitor patients seem to have **lower VWF:Ag** levels
Can we treat patients with **VWF:Ag above 80%** with **rFVIII** from ED 1 onwards?

VWF levels: Study cohort



Could we have started treatment with **rFVIII** in patients **4, 6, 7, 10, 11, 12, 16**?

Conclusions

PUPs who received low-dose pdFVIII prophylaxis for the first 100 EDs with a personalised physiotherapy regime and regular joint function testing had

- No inhibitors
- Good bleed protection and few joint bleeds

Hypothesis: patients with normal to high VWF may be treated safely with rFVIII

Inhibitor risk in PUPs – when to use pdFVIII?

- Proposed **risk scoring system**
- Treat patients with **high risk score** with **pdFVIII** to reduce inhibitor risk

High-risk mutation	= 2	
Intensive treatment	= 1	**≥ 3 points**
Family history of inhibitors	= 1	**→ use pdFVIII**
VWF values	**= 1**