The SIPPET study

N Engl J Med 2016;374:2054-64.
DOI: 10.1056/NEJMoa1516437

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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The SIPPET study

- **The first** investigator-initiated, multicenter, **randomized**, open-label **clinical trial** in hemophilia with the aim to compare the immunogenicity of FVIII product classes:
  - Plasma-derived FVIII products with Von Willebrand factor
  - Recombinant FVIII products

- Primary outcome: incidence of all inhibitor
- Secondary outcome: incidence of high-titer inhibitors ($\geq$ 5 BU)

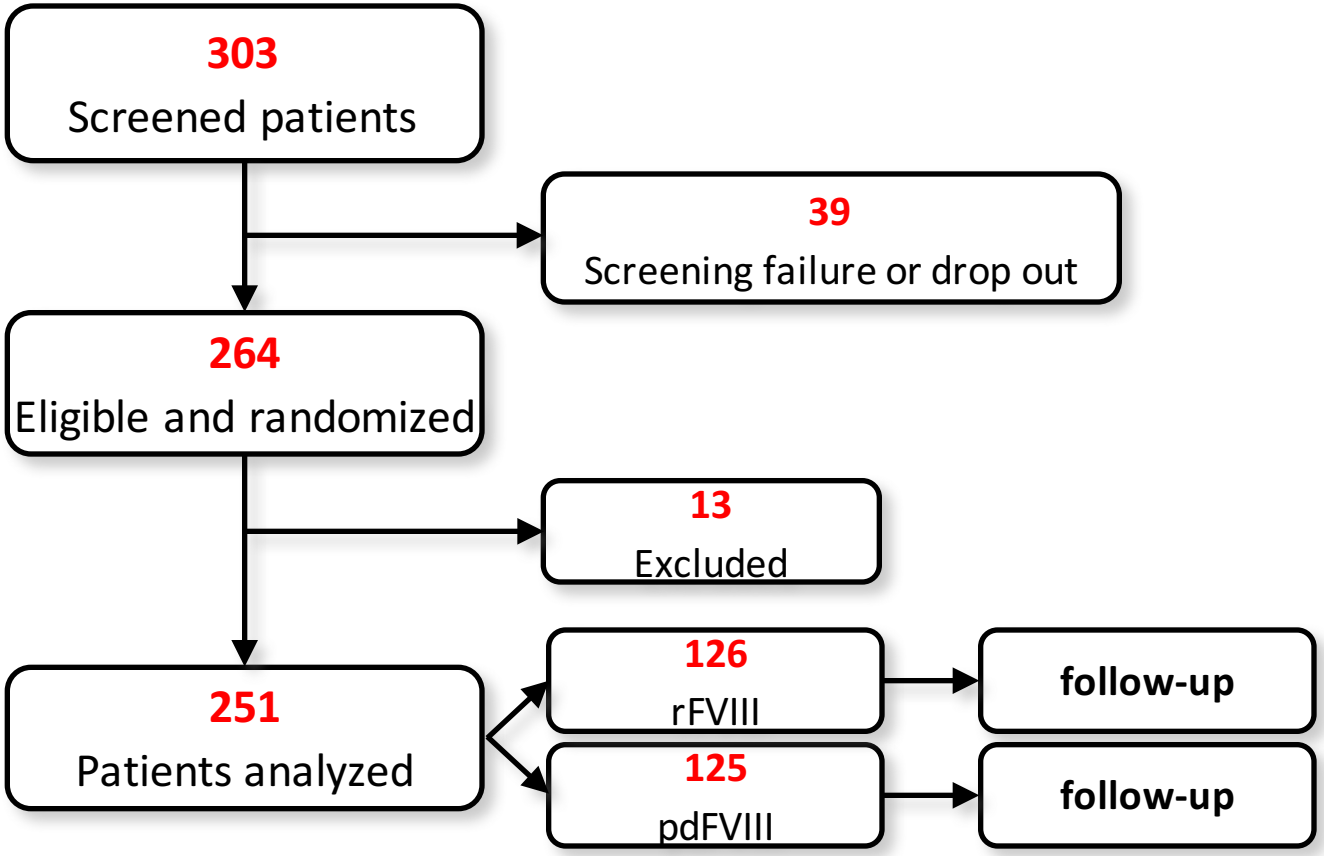
Contrast

- Per country only one brand of pdFVIII and rFVIII available (only licensed brands)
- Per center randomization between pdFVIII and rFVIII
- Ties brand, treatment preferences and ethnicity to country
- Balances all factors optimally between rFVIII and pdFVIII

Study protocol

STUDY DESIGN	
Inclusion criteria	– male, age <6 years – severe hemophilia A (FVIII:C < 1%) – negative inhibitor measurement at enrolment – no or minimal treatment (< 5 ED) exposure to blood products
Treatment allocation	randomized to either a single pdFVIII containing VWF or rFVIII
Follow up	50 ED, or 3 years, or until inhibitor development
Treatment regimen	at the discretion of local physicians
INHIBITOR DEFINITIONS	
Positivity	≥ 0.4 BU
High-titer	≥ 5 BU
Transient	spontaneously disappearing within 6 months
INHIBITOR DETERMINATION	
Sampling time	every 3-5 ED within the first 20 ED, then every 10 ED or every 3 months and every two weeks during prophylaxis

SIPPET Flow-chart



Analysis

- Check if randomization worked
  - no differences between groups
- Estimate risk of inhibitor over time (survival curves)
- Quantify differences between arms (Cox)
  - adjust for confounding by chance
- Quantify random error (confidence interval)
- Repeat for high-titer inhibitors

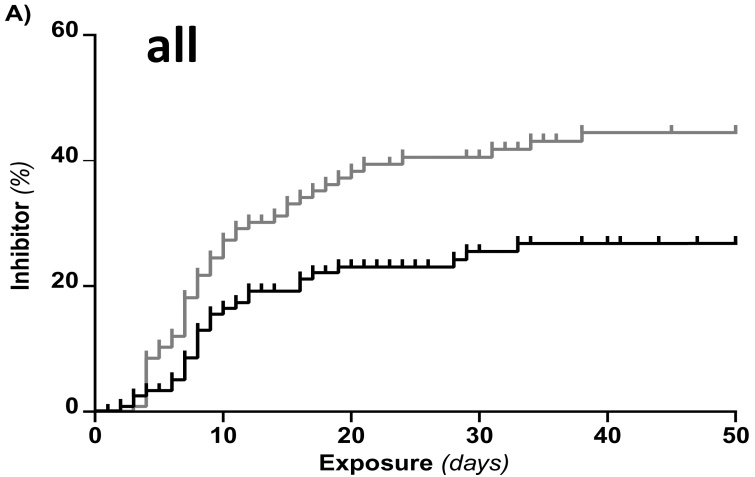
Baseline Characteristics

		rFVIII (n = 126)	pdFVIII (n = 125)
Age at first treatment *(months)*	*range*	0-75	0-67
	median	16.0	15.0
		n *(%)*	**n** *(%)*
Family history	*of hemophilia*	52 *(42.6)*	59 *(47.6)*
	of inhibitor	12 *(10.1)*	13 *(11.5)*
Null mutation		96 *(81.4)*	101 *(86.3)*
Previous exposure		53 *(42.1)*	56 *(44.8)*
Treatment regimen			
	on-demand	56 *(44.4)*	61 *(48.8)*
	standard prophylaxis	19 *(15.1)*	21 *(16.8)*
	modified prophylaxis	51 *(40.5)*	43 *(34.3)*

Risk of Inhibitor Development

	Number	Cumulative Incidence *(%)*	CI95
All	76	**35.4**	28.9-41.9
High titre	50	**23.3**	17.6-30.0

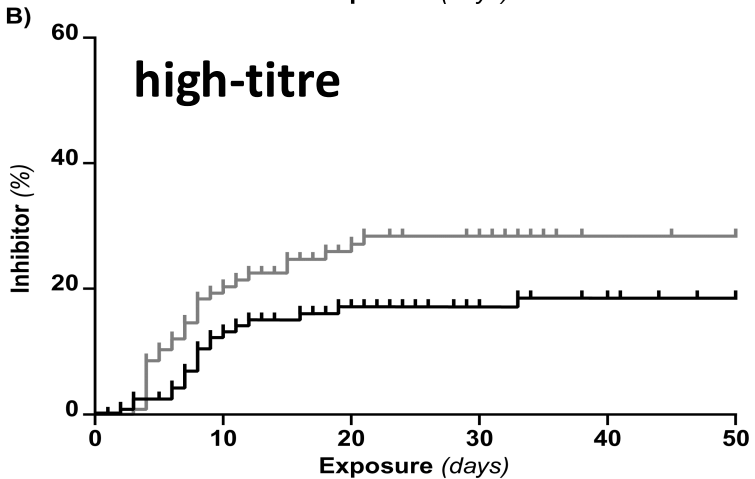
Risk per Treatment Arm



rFVIII: 44.5% (CI95 34.7-54.3)

pdFVIII: 26.8% (CI95 18.3-35.2)

HR 1.87 *(CI95 1.17-2.96)*



rFVIII: 28.4% (CI95 19.6-37.2)

pdFVIII: 18.6% (CI95 11.1-26.9)

HR 1.69 *(CI95 0.96-2.98)*

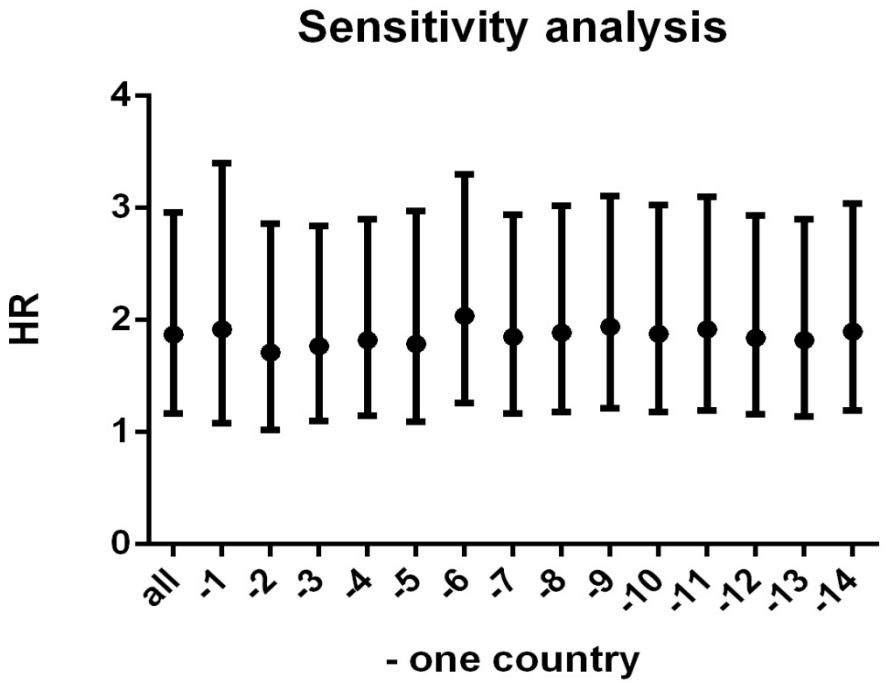
Adjusted Estimates

Adjustment variable	Hazard ratio (95% confidence interval)
None	1.87 (1.17-2.96)
Age	1.88 (1.18-2.99)
Mutation	1.97 (1.22-3.17)
Country	
5 categories	1.89 (1.19-3.00)
14 categories	1.88 (1.17-3.01)
Ethnicity	1.87 (1.18-2.97)
Family history of hemophilia	1.82 (1.14-2.89)
Family history of inhibitor	1.66 (1.03-2.67)
Previous exposure blood components	1.86 (1.17-2.95)
Treatment regimen	1.82 (1.15-2.90)
Treatment intensity	1.87 (1.17-2.97)
Surgery	1.80 (1.13-2.86)

Cox regression

Results are not country-driven

A sensitive analysis looking at HR results every time that a given country is left out shows no change



Restricted Analysis

exclusion of 2nd generation full-length rFVIII

	With *2nd generation FL rFVIII*		Without *2nd generation FL rFVIII*	
	HR	**CI95**	**HR**	**CI95**
All inhibitors	1.87	1.17-2.96	1.98	0.99-3.97
High-titre	1.69	0.96-2.98	2.59	1.11-6.00

Conclusion

- Patients treated with rFVIII have an 87% higher risk to develop inhibitors than those treated with pdFVIII containing VWF
- This difference remained even when second generation full length rFVIII concentrate was excluded from the analyses
- These findings are clinically important, because the development of FVIII alloantibodies is currently the major therapeutic complication in hemophilia A, that causes a marked increase in morbidity, mortality and treatment costs

Acknowledgments

ALL PATIENTS, THEIR PARENTS AND FAMILIES

42 PARTICIPATING CENTERS FROM 4 CONTINENTS

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Vijay Ramanan
Cecil Ross
Anupam Sachdeva
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Rosario Perez Garrido

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Bulent Antmen
Kaan Kavakli
Bulent Zulfikar

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SPONSORS

SPONSORS OF THE STUDY

FONDAZIONE ANGELO BIANCHI BONOMI
Per lo studio e la ricerca nel campo dell'emofilia, della trombosi e delle malattie emorragiche

Ministero della Salute

UNRESTRICTED GRANTS

Grifols, Spain

Kedrion Biopharma, Italy

LFB, France