



# Plasma FVIII beter dan recombinant FVIII?


## Duiding SIPPET resultaten

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([www.cctr.org](http://www.cctr.org))

# SIPPET studie

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-Author name in bold denotes the presenting author  
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 denotes an abstract that is clinically relevant.  
 denotes that this is a recommended PHD Trainee Session.

**5 Source of Factor VIII Replacement (PLASMATIC OR RECOMBINANT) and Incidence of Inhibitory Alloantibodies in Previously Untreated Patients with Severe Hemophilia a: The Multicenter Randomized Sippet Study**

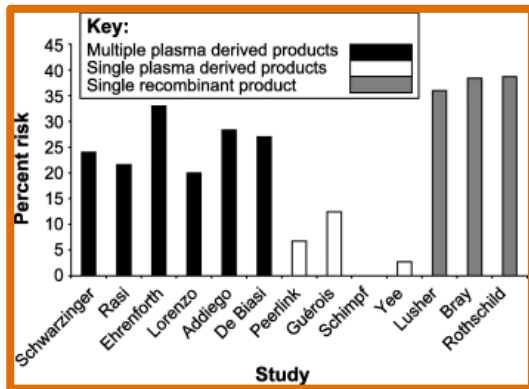
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Plenary  
 Program: General Sessions  
 Session: Plenary Scientific Session

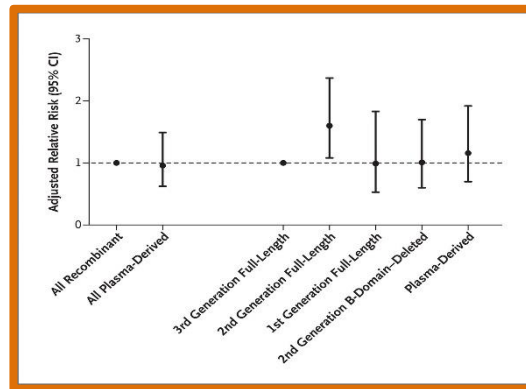
Sunday, December 6, 2015, 2:00 PM-4:00 PM  
 Hall D, Level 2 (Orange County Convention Center)

*Flora Peyvandi, MD, PhD<sup>1</sup>, Pier Mannuccio Mannucci, MD<sup>2</sup>, Isabella Garagiola, PhD<sup>3\*</sup>, Mohsen Elalfy, MD<sup>4\*</sup>, Amal El-Beshlawy, MD<sup>5</sup>, Madatha V. Ramanan, MD<sup>6\*</sup>, Peyman Eshghi, MD<sup>7\*</sup>, Suresh Hanagavad<sup>8\*</sup>, Ramabadran Varadarajan, MD<sup>9\*</sup>, Mehran Karimi, MD<sup>10</sup>, Mamta V. Manglani, MD<sup>11\*</sup>, Cecil Ross, MD<sup>12\*</sup>, Guy Young, MD<sup>13</sup>, Tulika Seth, MD<sup>14\*</sup>, Shashikant Apte, MD, FRCPA<sup>15</sup>, Dinesh M. Nayak, MD<sup>16\*</sup>, Adriana C. Sandoval Gonzales, MD<sup>17\*</sup>, Elena Santagostino, MD, PhD<sup>18</sup>, Maria Elisa Mancuso, MD, PhD<sup>18</sup>, Johnny N. Majlangu, MD<sup>19\*</sup>, Santiago Bonanad, PhD<sup>20\*</sup>, Monica Cerqueira, MD<sup>21\*</sup>, Nadia P. Ewing, MD<sup>22</sup>, Christoph Male, MD, MSC<sup>23\*</sup>, Tarek Owaidah, MD, FRCPA<sup>24</sup>, Veronica Soto Arellano, MD<sup>25\*</sup>, Nathan L. Kobrinsky, MD, FRCP<sup>26\*</sup>, Suvankar Majumdar, MD<sup>27</sup>, Rosario Perez Garrido, MD<sup>28\*</sup>, Anupam Sachdeva<sup>29</sup>, Mindy Simpson, MD, FAAP<sup>30</sup>, Mathew Thomas<sup>31\*</sup>, Ezio Zanon, MD<sup>32\*</sup>, ALI Bulent Antmen<sup>33\*</sup>, Kaan Kavakli,*

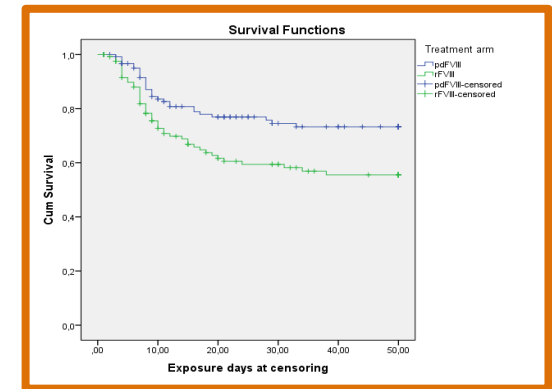
# Recombinant vs Plasma FVIII: vroeger was alles beter...



Wight, 2003



RODIN, 2013



SIPPET, 2015

## Inhoud

1. SIPPET opzet en resultaten
2. Verklaringen: confounding, selectiebias, misclassificatie, toeval
3. In het licht van wat we eerder zagen
4. Duiding van experts
5. Gevolgen voor huidige patient
6. Persoonlijke mening
7. Volgend onderzoek



Piere M. Mannucci

## 1. SIPPET opzet

- Survey of Inhibitors in Plasma Product Exposed Toddlers
- Vergelijking von Willebrand factor-bevattend factor VIII concentraten & Recombinant factor VIII concentraten
- Design: Randomized 1:1 block, Open-label
- Setting: 5 continenten, 19 landen, 77 behandelcentra
- Previously Untreated Patients (PUPs) or Minimally Blood Component-Treated Patients (MBCTPs) (n=300)
- Eindpunt: Remmer, 50 behandel dagen, of 3 jaar follow-up



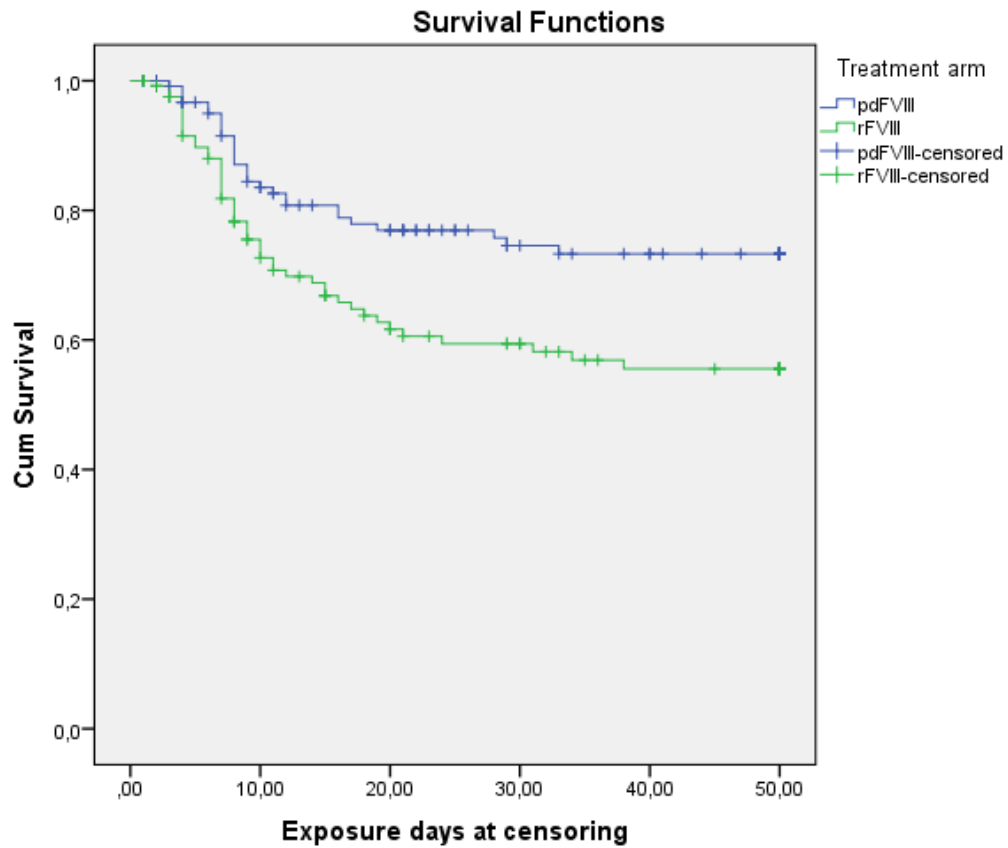
Flora Peyvandi

## 1. SIPPET resultaten

- Vroegtijdig beëindigd (303 geïncludeerd)
- 251 patiënten, 14 landen, 42 behandelcentra
- Mediaan aantal infusies = 22
- 76 remmers (30%), KM cumulative incidentie: 35%

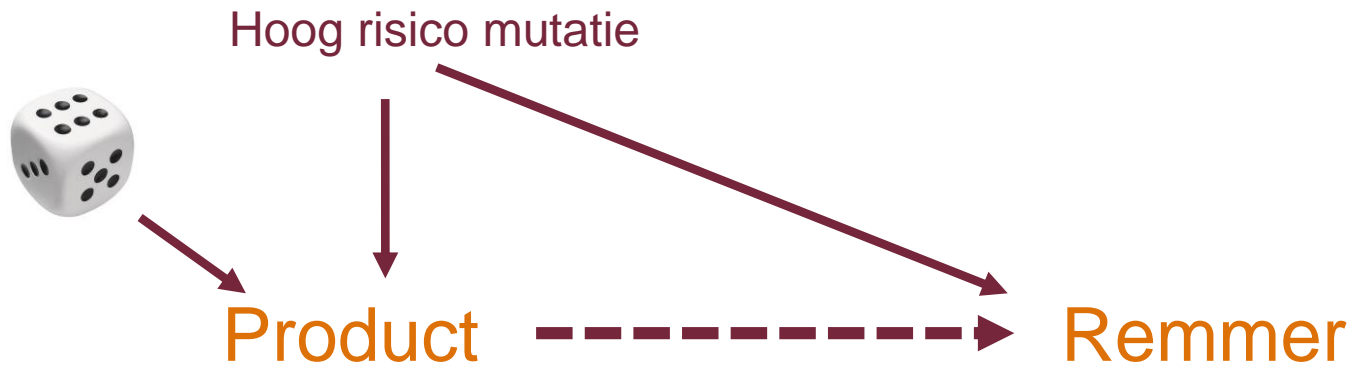
Product	Recombinant FVIII	Plasma FVIII
Aantal patiënten	126	125
Remmers	47 (37%)	29 (23%)
KM Incidentie	45%	27%

# 1. SIPPET resultaten



## 2. Verklaringen: confounding, selectiebias, misclassificatie, toeval

Confounding (andere oorzaak remmers)



Zwakte 1) 1:1 blocks; hoog risico bekend dan liever recombinant?  
2) niet geblindeerd; profylaxe afstemming op risico, vaker remmer testen bij recombinant?



## 2. Verklaringen: confounding, selectiebias, misclassificatie, toeval

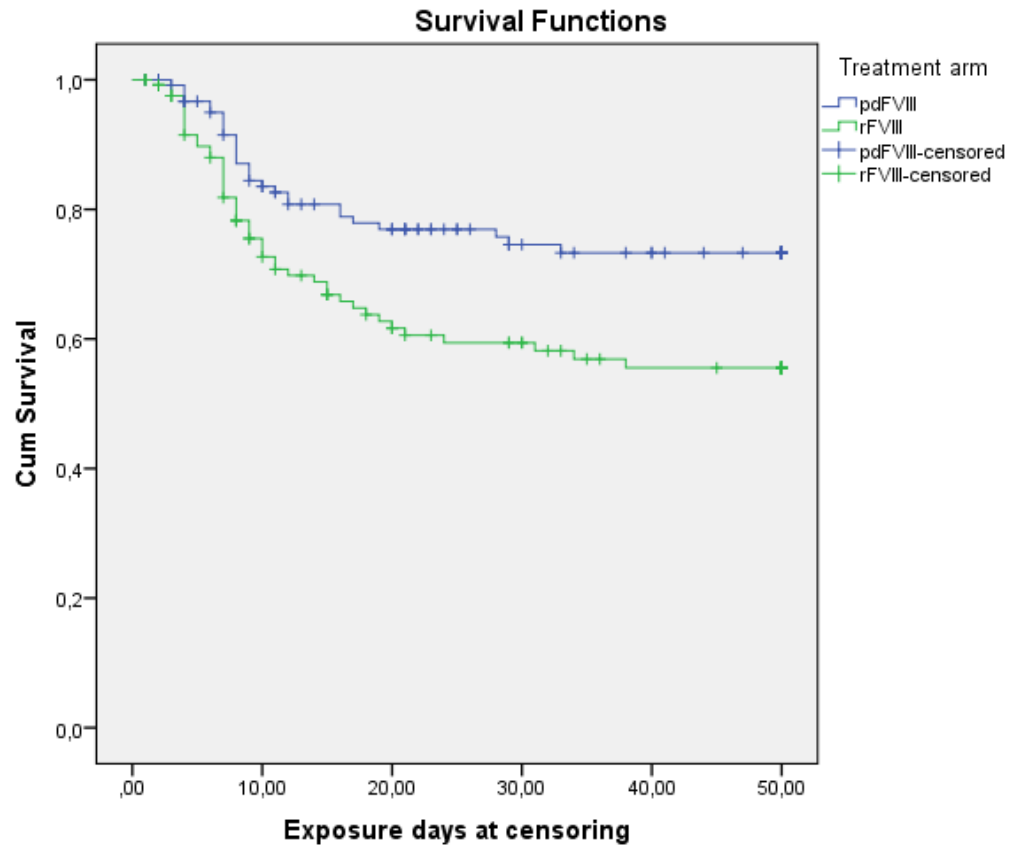
Selectie bias (incomplete, differentiele follow-up)

Plasma 

Recomb 

Zwakte 1) 35 patienten drop out; meer bij plasma?  
2) studie vroeg gestopt; loss to FU random?

## 2. Verklaringen: confounding, selectiebias, misclassificatie, toeval



## 2. Verklaringen: confounding, selectiebias, misclassificatie, toeval

Misclassificatie (uitkomst meting afhankelijk van interventie)

Test frequentie remmers (niet blind)  
Centraal laboratorium

Zwakte vaker/sneller meten bij recombinant?

## 2. Verklaringen: confounding, selectiebias, misclassificatie, toeval

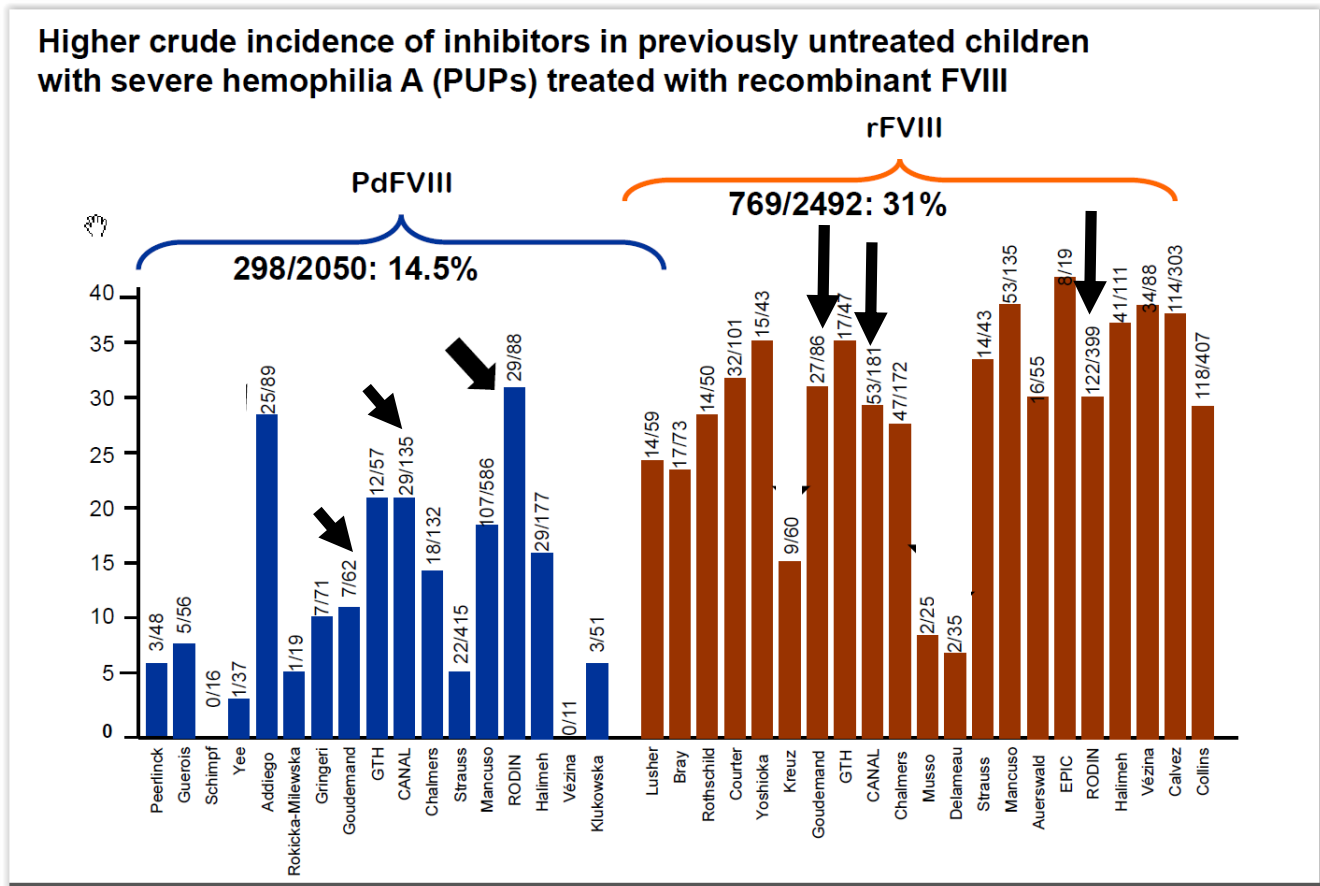
Toeval (interim-analyse gestopt wegens mooie resultaten?)

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### 3. In het licht van eerdere resultaten



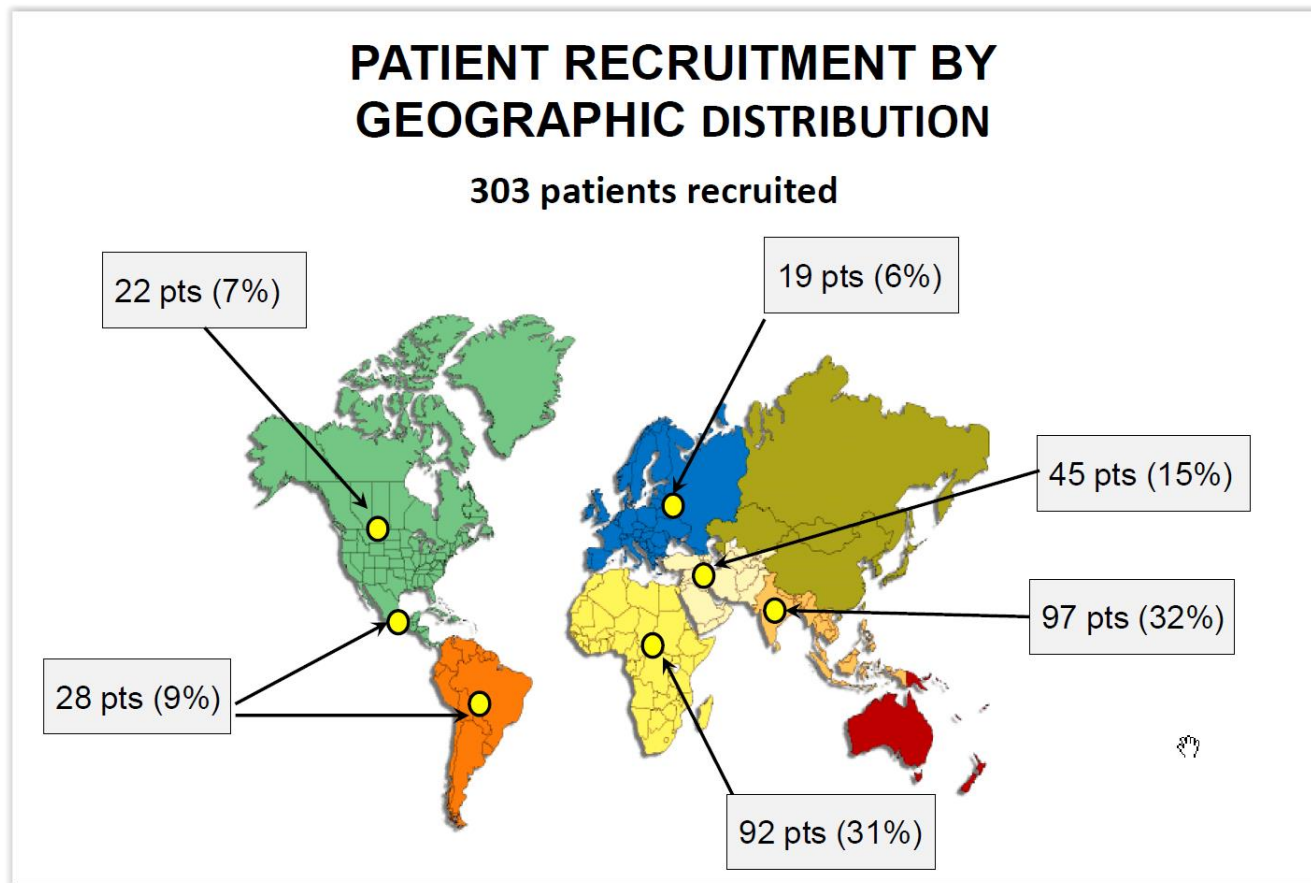
### 3. In het licht van andere resultaten

Vergelijkende studies: France (2006), CANAL (2007), RODIN (2013)

	SIPPET 2016		France 2006		CANAL 2007		RODIN 2013	
Product	rec	pd	rec	pd	rec	pd	rec	pd
Aantal	126	125	86	62	181	135	476	88
Remmer	47 <b>(37)</b>	29 <b>(23)</b>						
KM Inc	45%	27%						

37 % hoog door: on-demand ipv profylaxe?

### 3. In het licht van eerdere resultaten





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KM Inc	45%	27%						

37 % hoog door: on-demand ipv profylaxe?

23 % laag door: vroegtijdig stoppen follow-up?

45 % hoog door: oververtegenwoordiging van hoog risico “periodes”

## 4. Duiding van experts

WFH

EMA

FDA

## 4. Duiding van experts:WFH



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- Epidemiological Research
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  - [Bad Blood Documentary](#)
  - [Global Forum](#)
- Data Collection

### WFH statements, advisories, and letters

The WFH will make further comments after the publication of the complete study in a peer reviewed journal.

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**SIPPET study results released**  
**November 11, 2015** – Some results of the SIPPET (Survey of Inhibitors in Plasma-Products Exposed Toddlers) study were published last week as a conference abstract in advance of the American Society of Hematology (ASH) Annual Meeting this December. The abstract suggests that, in previously untreated patients, the risk of developing an inhibitor when using recombinant factors is significantly higher than when using plasma derived factor concentrates. This is an important study and the results may prove to be significant.

The WFH will make further comments after the publication of the complete study in a peer-reviewed journal. [The abstract can be viewed here >](#)

## 4. Duiding van experts

WFH

EMA

FDA

NVHP

Professionals

Farmaceuten

## 5. Gevolgen voor huidige patiënt

## 6. Persoonlijke mening

- Zinnige vergelijking?

BLOOD, 15 OCTOBER 2007 • VOLUME 110, NUMBER 8

CORRESPONDENCE 3085

Gringeri and Mannucci suggest that a randomized clinical trial will provide a definite answer on the comparison of immunogenicities of factor VIII products. In our view, the next relevant question is not whether plasma-derived products have a lower risk of inhibitors but rather which plasma-derived products carry a lower risk of inhibitors and why. It may be worth reanalyzing the CANAL study<sup>3</sup> data in order to explore the potential effects

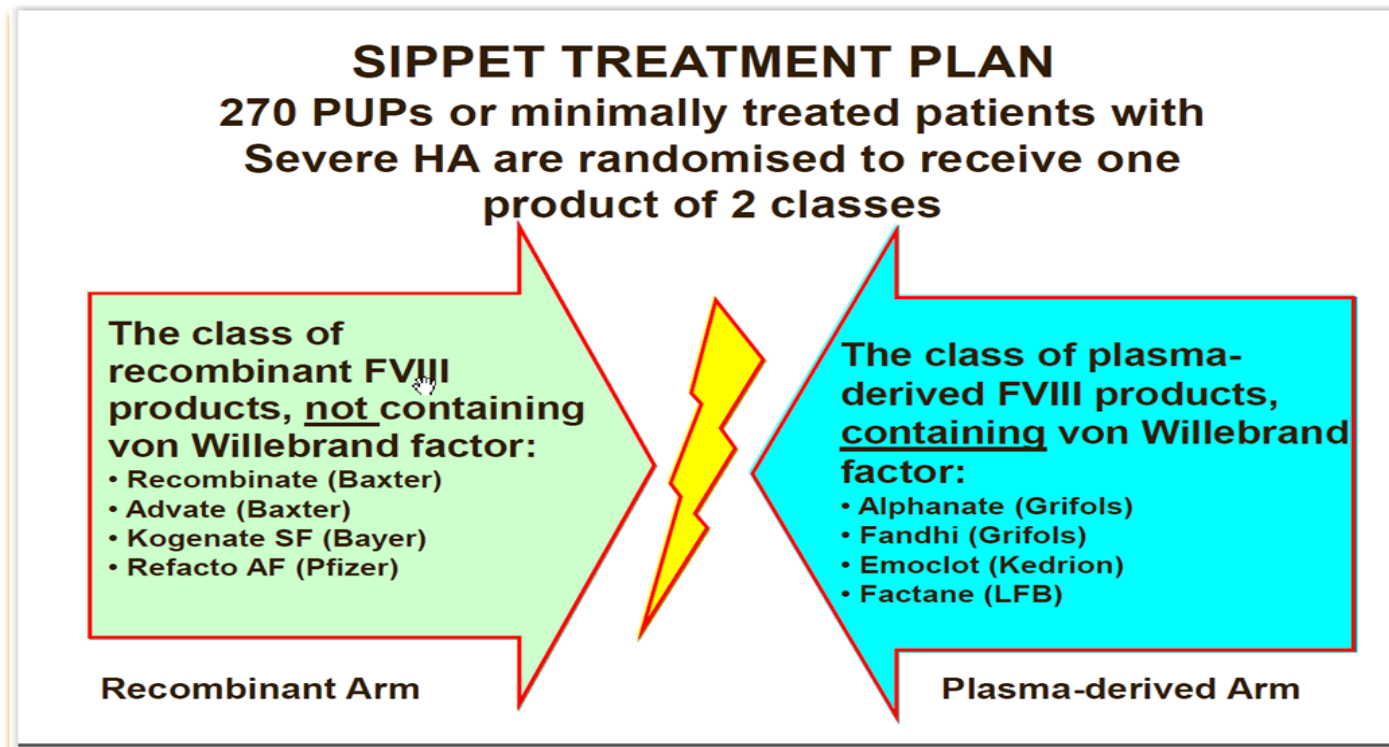
more sensitive testing for the presence of inhibitors in the cohorts on recombinant products. At present, the clinical significance of these otherwise undetected inhibitors is unclear.

Patients are categorized according to the products of their first exposure to factor VIII.

p  
with that  
inant  
s (%)  
(11)  
(14)  
(21)

## 6. Persoonlijke mening

- Zinnige vergelijking?



## 6. Persoonlijke mening

- Zinnige vergelijking?

Er zit “iets beschermends” in sommige plasma derived producten.

- Groote van het effect verschilt per product en moet per product onderzocht worden.
- “iets beschermends” is niet VWF.
- Wat is “iets beschermends”?



## 7. Volgend onderzoek

Plan van SIPPET onderzoekers: Vergelijken pdFVIII gevolgd door rFVIII met rFVIII.

Nodig:

Uitzoeken wat “iets beschermends” is.

Immunogeniciteit van nieuwe factor VIII producten monitoren.



Dank voor uw aandacht!

### 3. In het licht van andere resultaten

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KM Inc	45%	27%						
Hoge ttr	66%		47%		80%		66%	