

# **STRATEGIES TO PREVENT INHIBITORS**

## **Choice of products: a personal view**

**P.M. Mannucci**

**Scientific Direction, IRCCS Ca' Granda  
Foundation Maggiore Hospital, Milan, Italy**

## **THE CURRENT PROBLEM**

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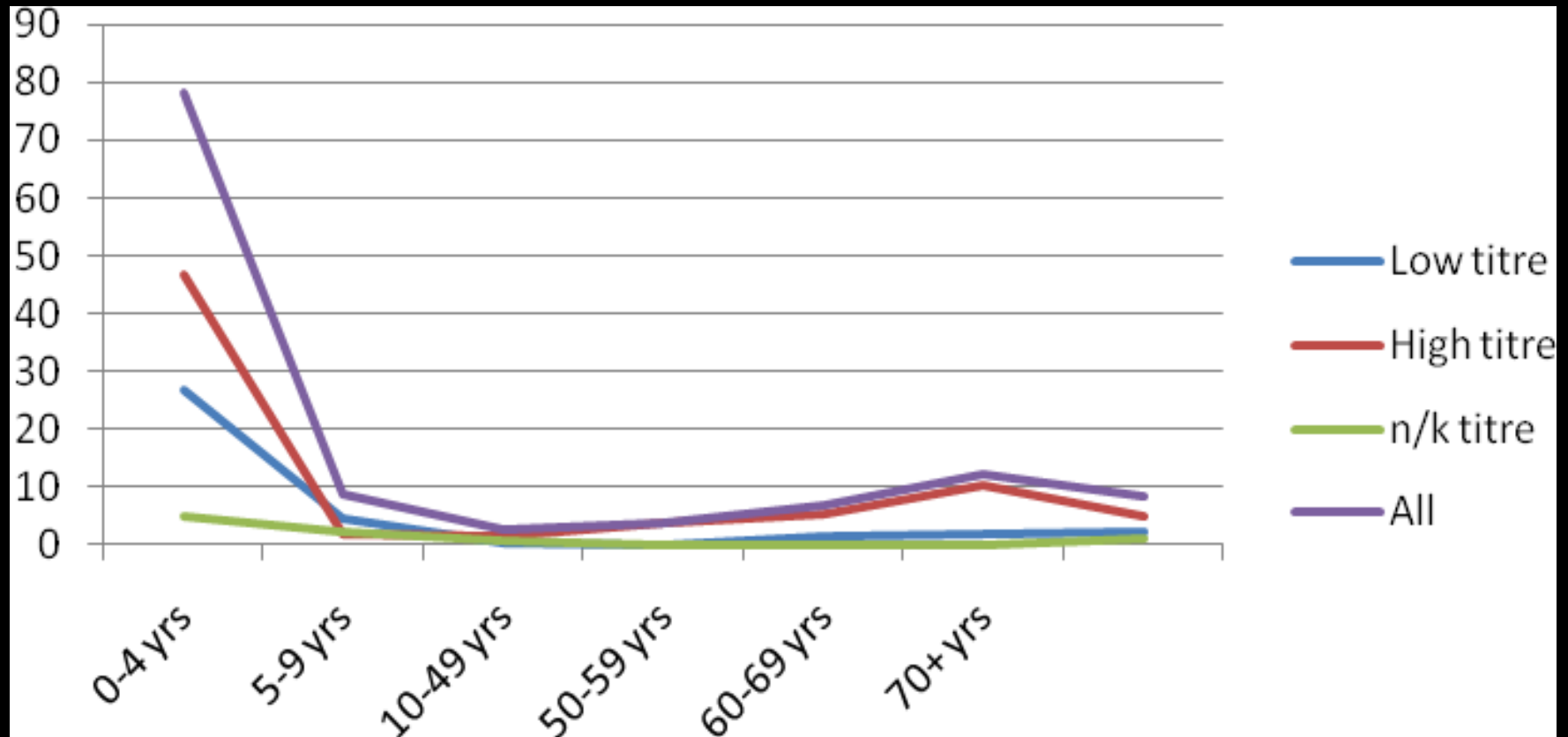
- **Inhibitors are the most cogent unresolved problem in patients with severe hemophilia A**
- **They replace pathogen risk as the most significant current problem**

# OUTLINE

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- **Epidemiology of factor VIII inhibitors**
- **Risk factors in previously untreated patients and possible prevention strategies**
- **Risk factors in previously treated patients and possible prevention strategies**

# INCIDENCE OF NEW INHIBITORS BY AGE: SEVERE HEMOPHILIA A IN THE UK 1990-2010 PER 100/TREATMENT YEARS



# INHIBITOR INCIDENCE BY AGE: UKHCDO 1990-2009

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Age (yrs)	Incidence (per 1,000 pt yrs)
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0 – 4

64.3

5 – 9

9.4

10 – 49

5.3

50 – 59

5.2

>60

10.5

**(both high and low titer inhibitors)**

Hay et al. Blood 2011; 117: 6367

## **INHIBITOR EPIDEMIOLOGY**

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- **The highest risk of inhibitor pertains to children previously untreated (or minimally treated) with factor replacement therapy**
- **However, de novo inhibitors develop lifelong also in previously treated patients, peaking in the elderly**

## LATE DE NOVO INHIBITORS: WHY?

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- **Delayed detection (low titre).**
- **Loss of immunological tolerance.**
  - **Increasing age ( $p=0.01$ )\*.**
  - **Peak treatment moments?**
  - **Change of replacement products (switching)?**

# **FVIII INHIBITOR RISK FACTORS IN PREVIOUSLY UNTREATED PATIENTS (PUPs)**

**patient-related\_**

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**Genotype**            **80% in multiple-domain deletions**

**Family history of inhibitor**  
**70% sibling concordance**

**American Black/Hispanic**  
**2 to 4-fold higher**

# **FVIII INHIBITOR PREDICTIVE FACTORS IN PUPs**

## **enviroment-related**

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**1. Coincident inflammation**

**2. Treatment intensity**

**3. Surgery**

**4. Source/type of factor VIII: recombinant  
vs plasma derived products**

# **FVIII INHIBITOR PREDICTIVE FACTORS IN PUPs**

## **enviroment-related**

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- 1. Inhibitors are a multi-factorial event**
- 2. A single targeted approach cannot expect to fully abolish the onset of the event**

# IS RECOMBINANT FVIII MORE IMMUNOGENIC THAN PLASMA-DERIVED FVIII?

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**Some preliminary evidence from**

**1. Animal model data**

**2. Previously published clinical data**

**3. Recently published clinical data**

# WHY WOULD RECOMBINANT FVIII BE MORE IMMUNOGENIC?

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- 1. Post-translational modifications**  
- eg. glycosylation
- 2. Population of “free” FVIII unable to bind VWF**
- 3. Missing immunosuppressive molecules**  
(eg. TGF $\beta$ )

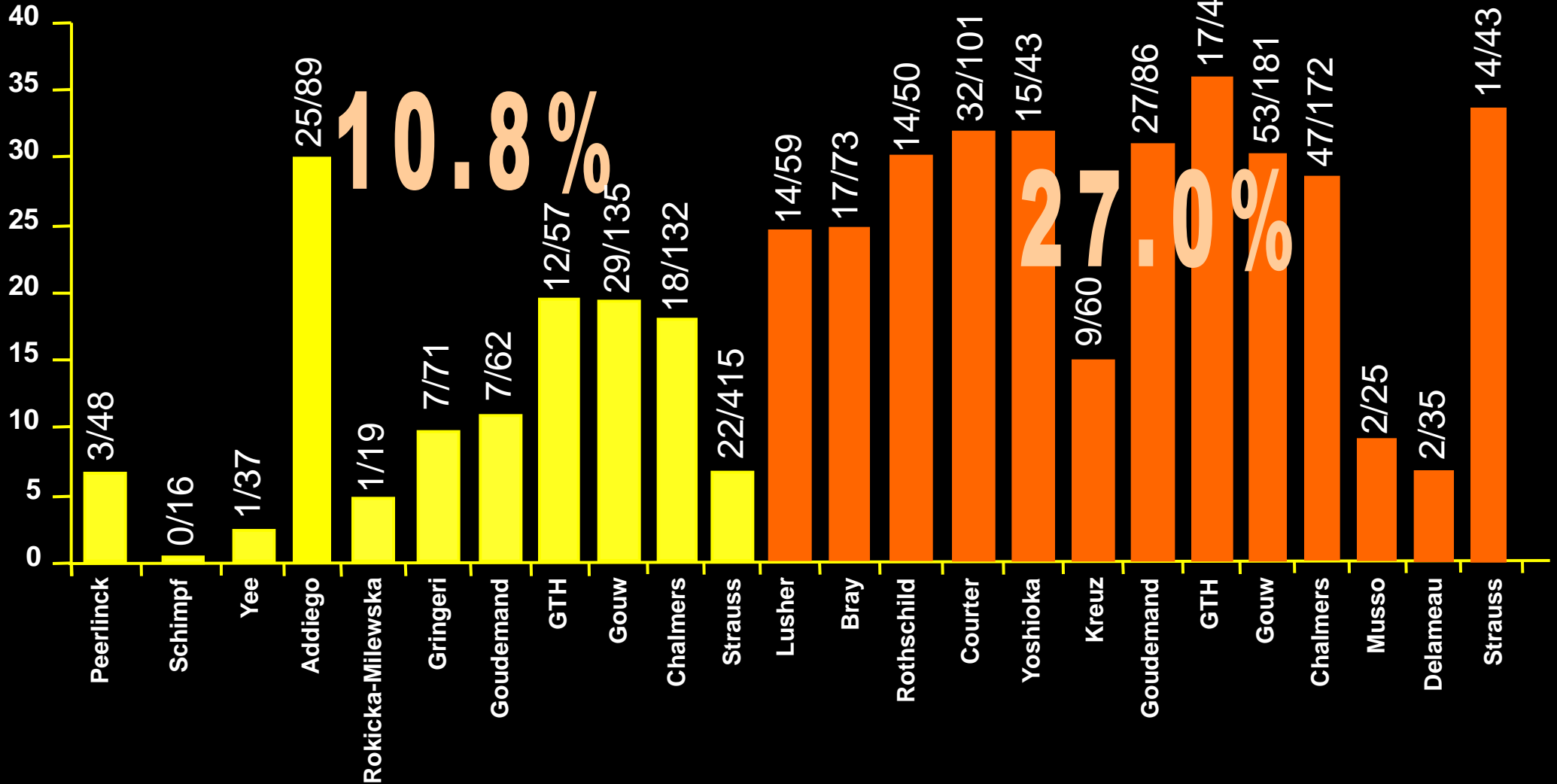
# Crude incidence of inhibitors in PUPs

Plasma-derived

Recombinant

117 / 1,081

263 / 975



# **COMPARATIVE IMMUNOGENICITY OF FVIII PRODUCT SOURCE (retrospective cohort studies)**

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**Goudemand et al. Blood 2006**

**Gouw et al. Blood 2007**

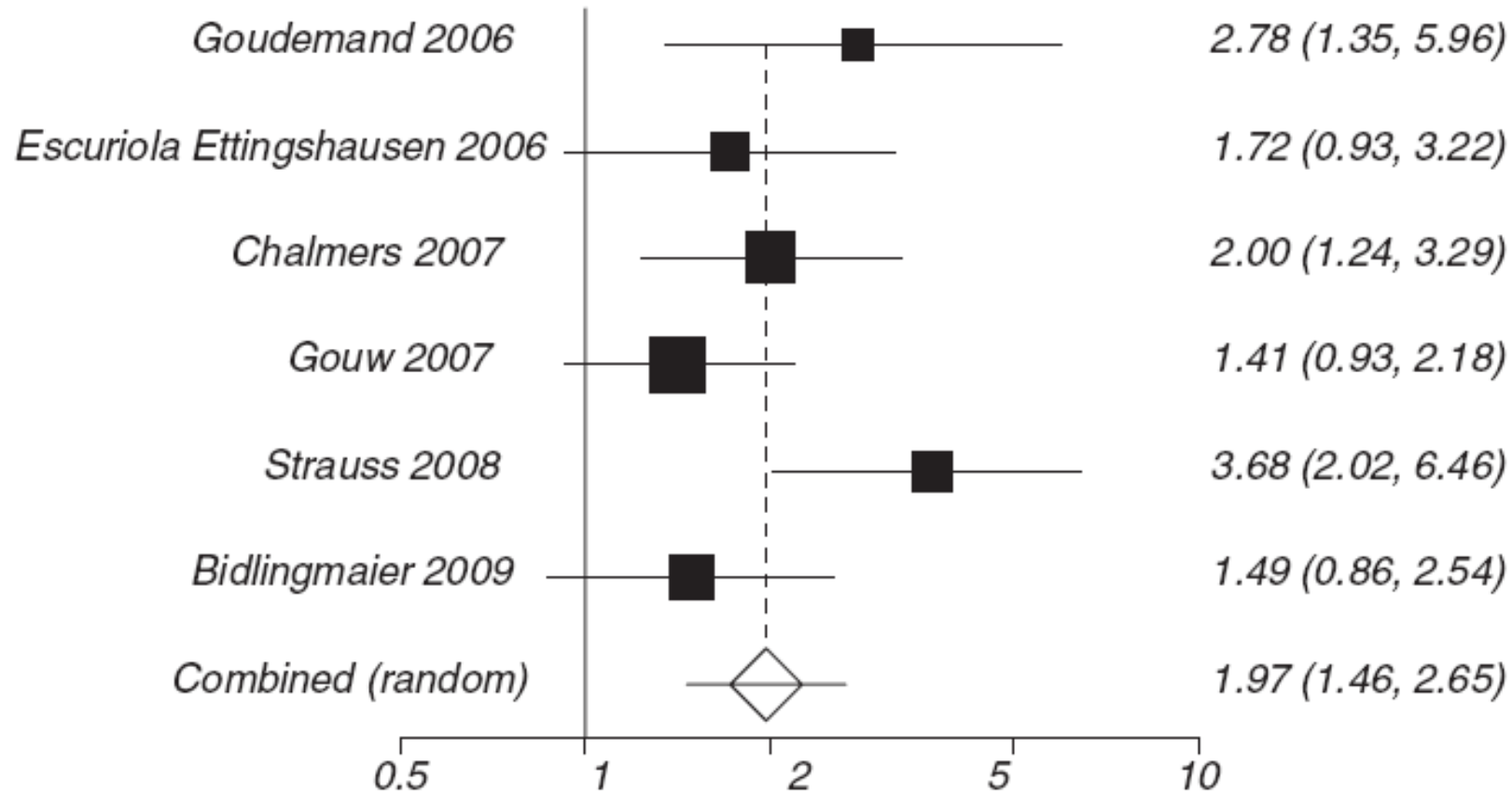
**Chalmers et al. Haemophilia 2007**

**Strauss et al. Haemophilia 2011**

**Mancuso et al, published as abstract**

# A META-ANALYSIS

## Measurement of risk (rFVIII vs pd FVIII)



RELATIVE RISK (95% CI) rFVIII vs pd FVIII

**Iorio et al, J Thromb Haemost 2010; 8:1256-65**

# PD-FVIII VS rFVIII INHIBITOR INCIDENCE (META-ANALYSIS)

lorio et al. JTH 2010;8:1256-65

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**24 studies - 2,094 patients (1,965 pd-FVIII: 887 rFVIII)**

**pd-FVIII 14.3 % (10.4 – 19.4)**

**rFVIII 27.4% (23.6 – 31.5)**

**After multi-way ANOVA -**

**Significant differences: study design, study period, testing frequency**

**Type of concentrate lost statistical significance**

# INHIBITOR INCIDENCE IN PUPs

## Limits of available studies (and thus of meta-analysis)

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### Non-homogenous study populations

- Severity (<1/≤2%)
- mutation type
- ethnicity
- pre-treatment (previously untreated minimally pretreated)
- therapy regimen (early vs late prophylaxis, prophylaxis vs on demand)

### Non-homogenous study designs

- frequency of inhibitor testing
- prospective/retrospective
- Length of observation periods

**Randomized studies needed !**

# CLINICAL EQUIPOISE

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- **A randomized clinical trial is justified when there is uncertainty on the relative efficacy of two competing interventions**
- **This state of uncertainty is referred to as clinical equipoise**
- **Clinical equipoise applies at the moment to the issue of the role of FVIII source on inhibitor incidence, providing a justification for randomizing patients to competing therapies**

**Inhibitor Development in Previously Untreated Patients (PUPs) or Minimally Blood component-Exposed Patients (MBEPs) when Exposed to von Willebrand Factor-Containing Factor VIII Concentrates and to Recombinant Factor VIII Concentrates:  
An International, Randomised, Clinical Trial**

**Steering Committee: *P.M. Mannucci, A. Gringeri, S. Apte, J. Aznar, H. Chambost, D. Di Michele, J. Goudemand, W. Kreuz, R. Kruse-Jarres, J. Mahlangu, C. Negrier, F. Peyvandi, E. Santagostino, M. Tarantino***

**Study acronym: SIPPET**

**(Sudy on Inhibitors in Plasma-Product Exposed Toddlers)**

# STUDY TREATMENT

Patients are randomised to receive  
one product of 2 classes  
up to 50 exposure days (EDs):

The class of  
recombinant FVIII  
products, not  
containing von  
Willebrand factor:

- Recombinate (Baxter)
- Advate (Baxter)
- Kogenate SF (Bayer)
- Refacto AF (Pfizer)

Recombinant arm

The class of plasma-  
derived FVIII products,  
containing von Willebrand  
factor:

- Alphanate (Grifols)
- Fandhi (Grifols)
- Emoclot (Kedrion)
- Factane (LFB)

Plasma-derived arm

# CRITERIA FOR INCLUSION

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- Age <6 years, any ethnicity
- Severe hemophilia A (FVIII:C <1%)
- Negative inhibitor at screening
- ➔ Previously untreated patients
  - no exposure to any blood product, or
- ➔ minimally exposed to blood components
  - 5 less than 5 EDs to blood components, namely whole blood, fresh frozen plasma, cryoprecipitate, red blood cells (concentrate exposure leads to exclusion)

# **SAMPLE SIZE**

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**300 patients**

- **Assuming a cumulative inhibitor incidence of 25% in recombinant FVIII-treated patients, and a 50% decreased incidence with plasma-derived VWF/FVIII, 136 in each arm (plus 10% drop-out patients) should be enrolled to provide 80% power to detect a significant difference ( $p < 0.05$ ).**
- **A futility analysis is to be carried out when 150 patients are exposed to FVIII for at least 20 EDs**

# COUNTRIES

23 countries involved  
17 centrally approved  
14 countries active

ARGENTINA 
AUSTRIA
BELGIUM
BRAZIL
CZECH REP 
COLOMBIA 
CHILE 
EGYPT
FRANCE
GERMANY
ITALY
INDIA

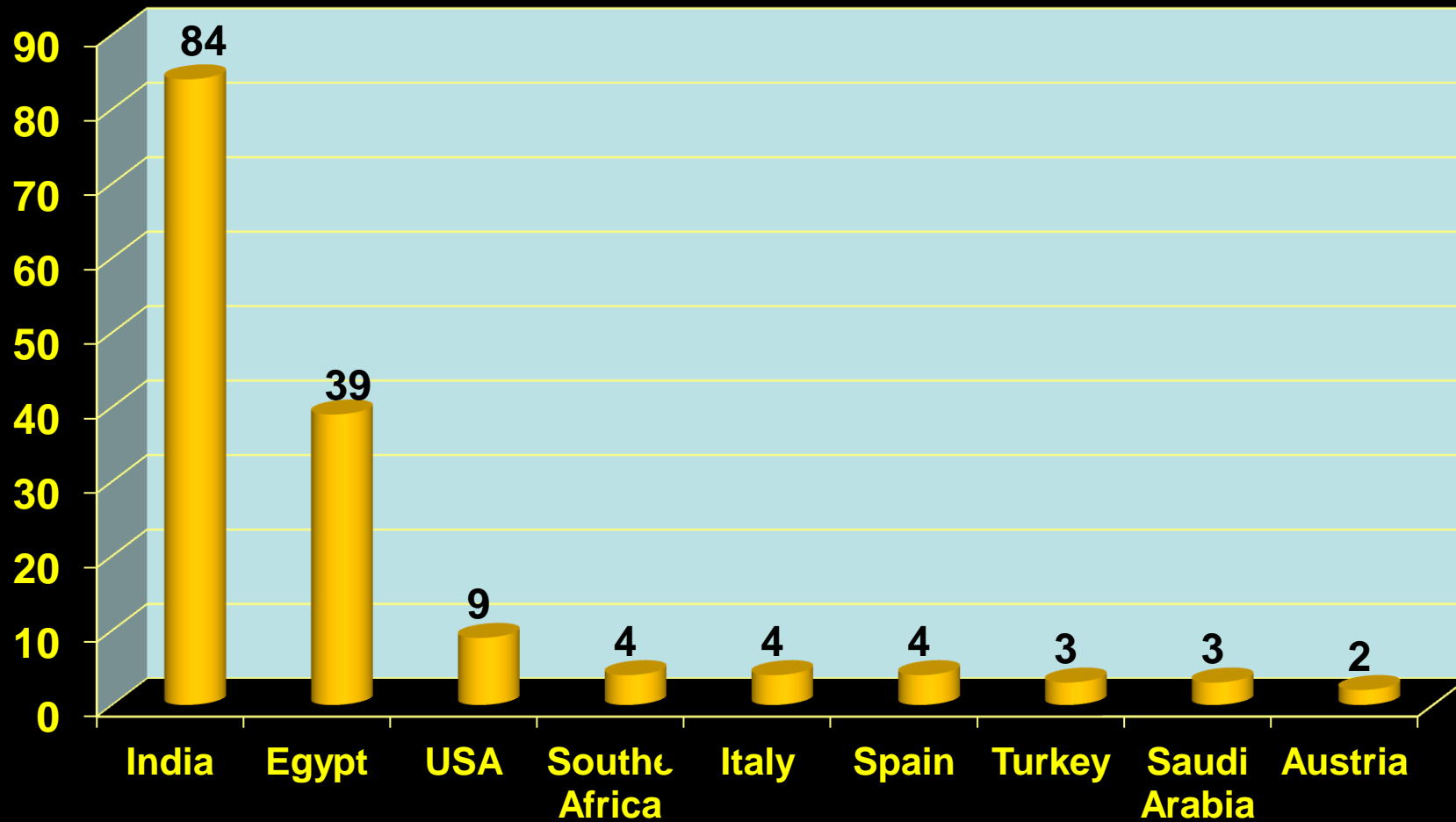
IRAN
MEXICO
PORTOGALLO
SAUDI ARABIA
SLOVAKIA 
SOUTH AFRICA
SPAIN
TURKEY
UK
URUGUAY 
USA



6 Countries pending

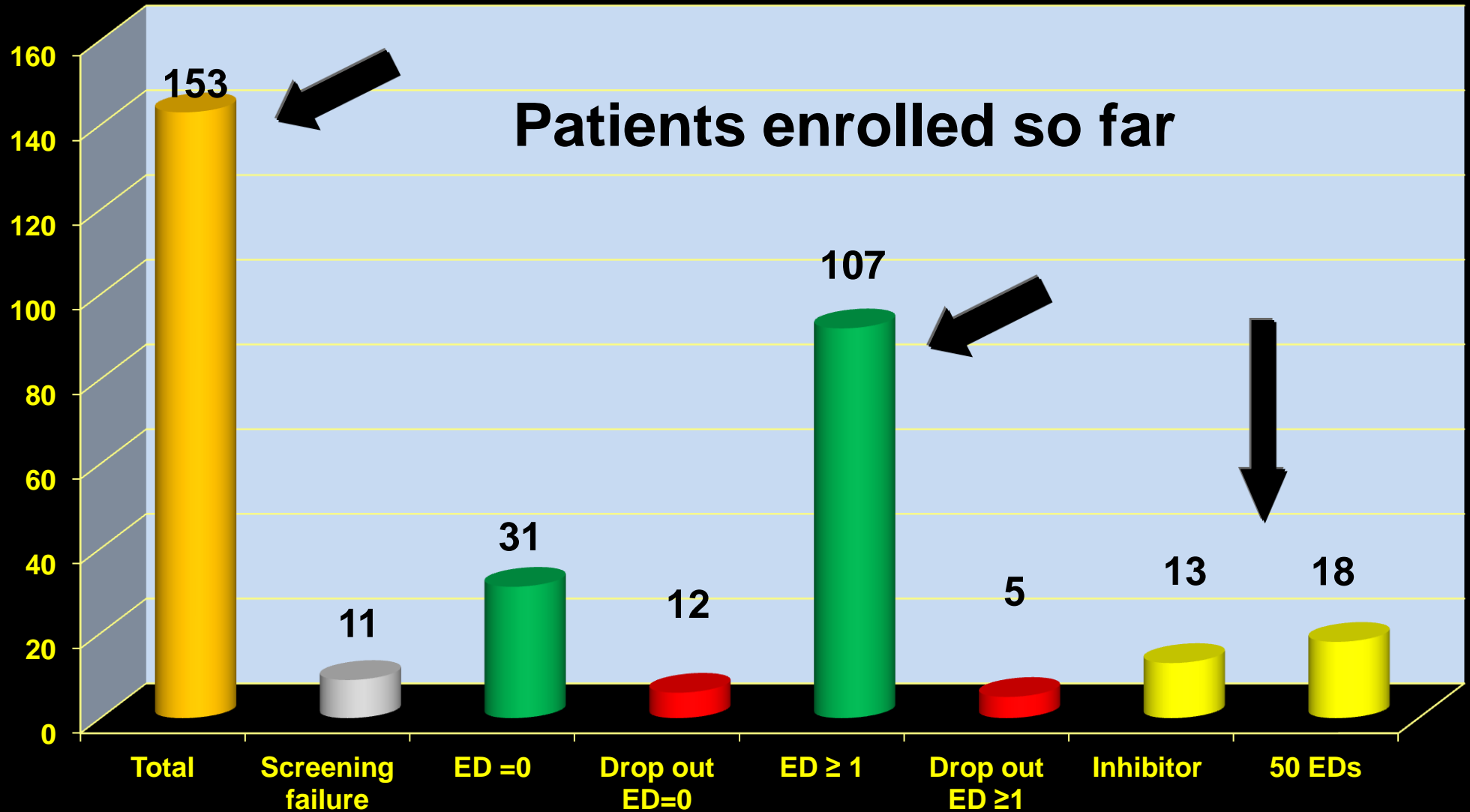
# SIPPET STUDY

(Survey of Inhibitors in Plasma-Product Exposed Toddlers)



# SIPPET STUDY

(Survey of Inhibitors in Plasma-Product Exposed Toddlers)



# **STRENGTHS OF SIPPET: IT IS A NATURALISTIC STUDY!**

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- **Naturalistic studies are meant to compare medical interventions in the frame of real-world practice:**
  - **SIPPET compares FVIII products as belonging to two classes (recombinant and plasma derived)**
  - **SIPPET enrolls patients treated with prophylaxis or on demand (the latter still the most widely used regimen worldwide)**
  - **SIPPET enrolls patients in 23 countries from 5 continents**

# LIMITATIONS OF THE SIPPET STUDY

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- Different products brands considered as belonging to one class (recombinant or FVIII/VWF)
- Inclusion of patients minimally exposed to blood components

# **PUTATIVE RISK FACTOR OF DE NOVO INHIBITORS IN PREVIOUSLY TREATED PATIENTS (PTP)**

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- **Aging**
- **Change of FVIII product (switching)**

# NEW FVIII INHIBITORS IN THE FRAME OF RECOMBINANT FVIII LICENSING STUDIES IN PTP

<u>Product</u>	<u>Patient #</u>	<u>Inhibitors</u>
Kogenate	86	2 (2%)
Recombinate	69	2 (3%)
ReFacto	113	1 (1%)
Kogenate-FS	71	1 (1%)
Advate	521	1 (0.9%)

# INCIDENCE OF FVIII INHIBITORS IN PTPs

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- **2.6 cases per 1000 person year  
(McMillan, USA 1988 data)**
- **2.14 cases per 1,000 person years  
(Kempton et al. UDC data)**
- **3.2 cases per 1,000 person years  
(Darby et al. UK Registry)**

# CANADIAN SURVEILLANCE SYSTEM: SWITCH FROM PDFVIII TO 1° OR 2° GENERATION RFVIII

## Giles et al 1998

- 478 “inhibitor free” pts.
- Switched to 1<sup>st</sup> gen. rFVIII.
- 2 yrs follow-up.



## RESULTS:

- 2-3% *de-novo* inhibitors.

## Rubinger et al 2008

- 274 “inhibitor free” pts.
- Switched to 2<sup>nd</sup> gen rVIII
- 2 yrs follow-up.



## RESULTS:

- No *de-novo* inhibitors.

1.) Giles et al. Transfusion Science 1998, 19 (2) 139-8.

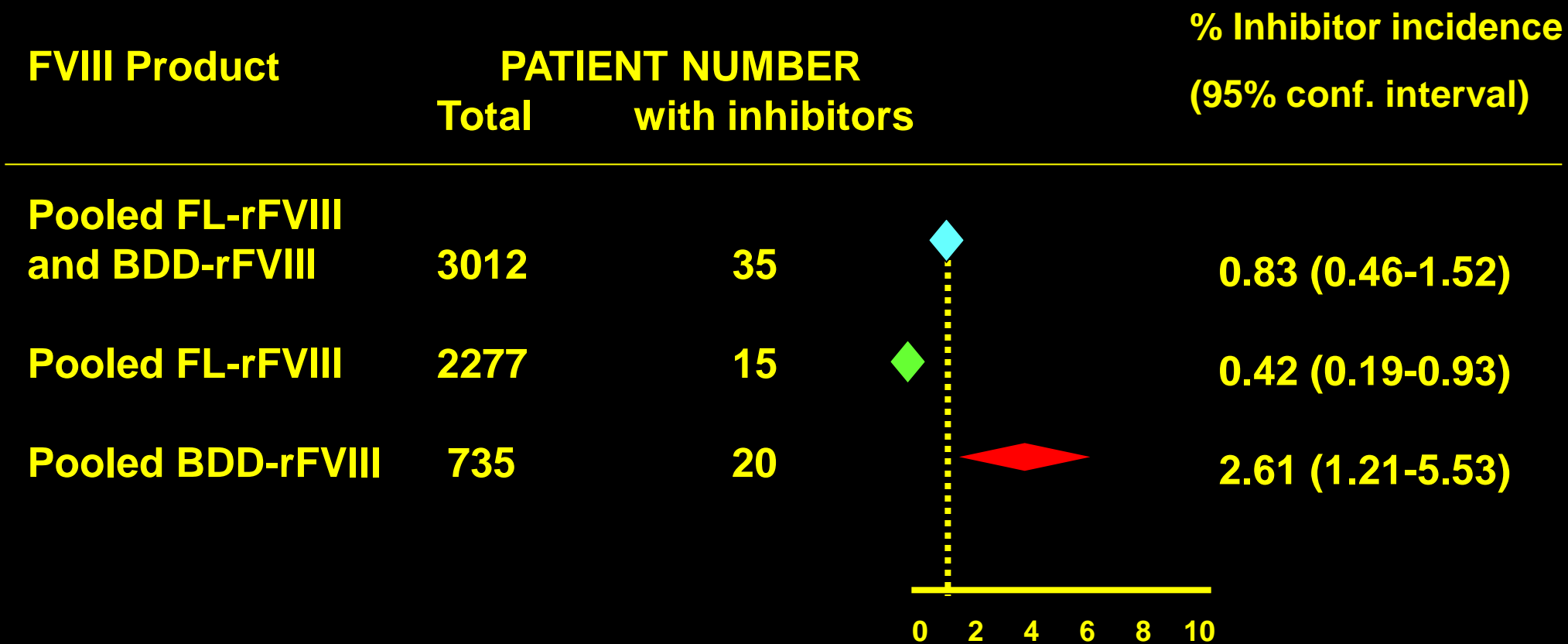
2.) Rubinger et al. Haemophilia 2008, 1-6.

- **Available data suggests no excess of new inhibitors in “switchers”**
- **No excess of new inhibitors with any particular switch type**

**Can B-domain deletion alter the immunogenicity of recombinant factor VIII?**

**L. Aledort, et al**

**JTH, 2011 - accepted for publication**



**Concentrate-related inhibitor risk: is a  
difference always real?**

**A.lorio, et al**

**JTH, 2011 – accepted for publication**

# CONCLUSIONS

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- **It is still unsettled whether or not the source of FVIII (plasma-derived or recombinant) affects the incidence of inhibitors in PUPs (randomized SIPPET study ongoing!)**
- **The risk of de novo inhibitors in PTPs is small (also in switchers)**
- **It is still unsettled whether the different types of FVIII molecule (full-length or B-domain deleted) affect the incidence of de novo inhibitors**

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