

THE USE OF FVIII AND FIX

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CRYOPRECIPITATE

**The mainstay of hemophilia A
treatment in the late 1960s!**



Judith Pool, the inventor of cryoprecipitate

THE 1970s: THE SUCCESS STORY OF THE DECADE

- **Lyophilized coagulation factors**
- **Desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease**
- **Comprehensive treatment centers**
- **Home treatment**
- **Prophylaxis programs**

THE 1980s: MANY SHADOWS, SOME LIGHTS

- **AIDS and hepatitis**
- **Factor VIII and IX genes are cloned**
- **Viral inactivation makes plasma factors safe**

THE 1990s: A NEW GOLDEN ERA

- **Recombinant factor VIII and factor IX**
- **Patients with inhibitory alloantibodies: immune tolerance and bypassing products (FEIBA, factor VIIa)**
- **cART for HIV, interferon for hepatitis**

Changes in life expectancy of patients with haemophilia

Publication	Country	Study period	Life expectancy (years)					
			All patients	Severe disease	Unaffected males			
Plug <i>et al</i> , 2006 ¹	The Netherlands	1992–2001: HIV and HCV negative	74	↑	71	↑	76	↑
		1992–2001: HIV negative	70		70		76	
		1992–2001: all patients	67		59		76	
		1985–1992	68		61		74	
		1972–1985	66		63		71	
Chorba <i>et al</i> , 2001 ²	USA	1995–1998: HIV negative	72	↑				
		1995–1998: HIV positive	33					
		1995–1998: all patients	46					
		1987–1990	40.5					
		1979–1982	55					
Tagliaferri <i>et al</i> , 2008 ³	Italy	2000–2007	71.2	↑				
		1990–1999	64.0					

1. Plug I, *et al*. *J Thromb Haemost* 2006;**4**:510–6.
2. Chorba TL, *et al*. *Am J Hematol* 2001;**66**:229–40.
3. Tagliaferri A, *et al*. *Haemophilia* 2008;**14**:945–51.

LIFE EXPECTANCY FOR THE MOST FREQUENT MONOGENIC DISEASES

- Hemophilia
- Cystic fibrosis
- Thalassemia major
- Muscular dystrophy



THE NEXT YEARS BUILDING ON STRENGTH: THE ISSUES

- **More and younger hemophilia experts**
- **Greater and wider factor availability**
- **Longer-acting recombinant factors**
- **Less alloantibodies (inhibitors), and their improved treatment**
- **The elderly patient with hemophilia**
- **Towards cure: gene transfer therapy**

GREATER AND WIDER FACTOR AVAILABILITY:

**no treatment for at least two thirds of
persons with hemophilia in the world!**

AVAILABLE PRODUCTS FOR HEMOPHLIA A AND B



- **Recombinant**
 - safe and efficacious
 - why is cost not decreasing?



- **Plasma derived**
 - safe from HIV/HAV/HBV/HCV
 - Prion-related disease?
 - Continued surveillance: EAHAD - EUHASS

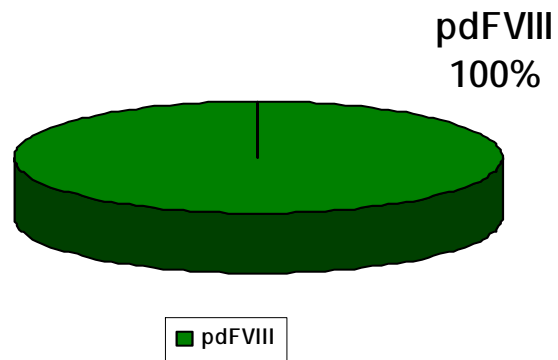
SPECIFIC REPLACEMENT PRODUCTS FOR RARE COAGULATION DISORDERS

- A very neglected issue!**
- Only fibrinogen, factor VII, XI and XIII concentrates are available (and not in many countries!)**
- Factor X products are in the pipeline**
- Only fresh-frozen plasma available for factor V deficiency and other diseases!**

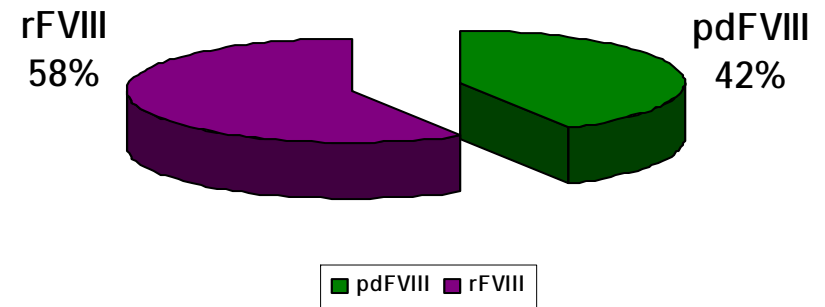
Worldwide Factor VIII market

Evolution of product distribution based on its origin

Year 1992



Year 2008

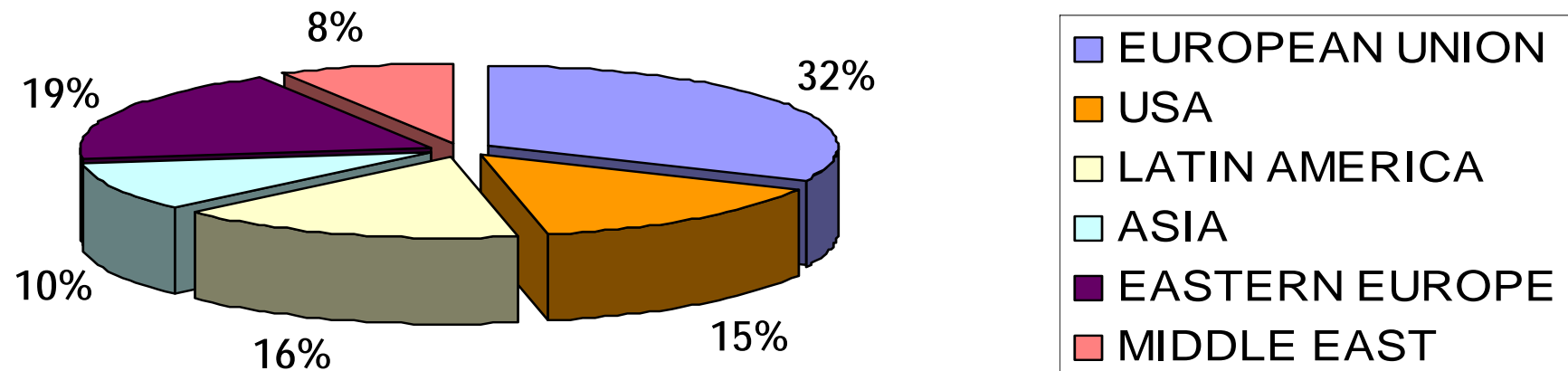


Total FVIII market in 1992 \Rightarrow 1.837 Mio IUs

Total FVIII market in 2008 \Rightarrow 7.431 Mio IUs

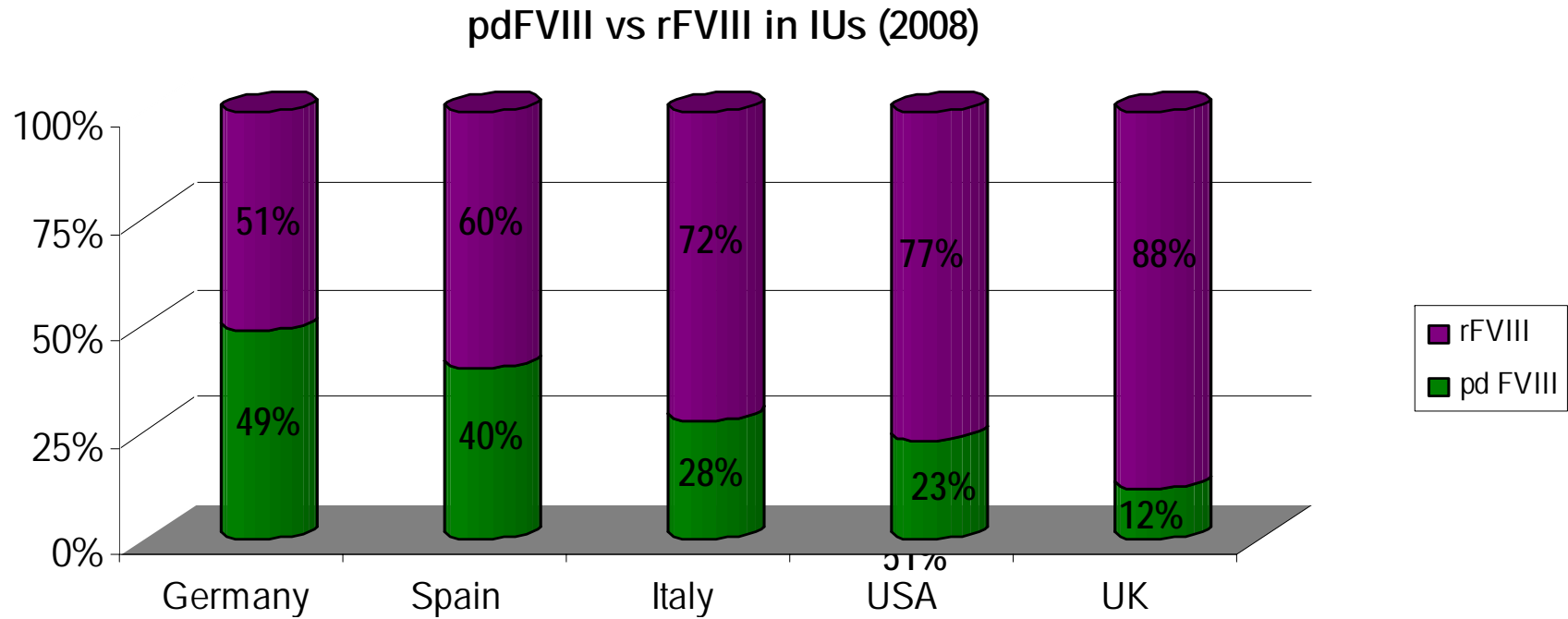
Worldwide plasma derived Factor VIII market (2008)

pdFVIII market by geographical zone



Worldwide pdFVIII market (2008): 3157 Mio UIs

Product distribution pdFVIII vs rFVIII per country (2008)



THE ISSUE

- **Inhibitors are the most cogent unresolved problem in patients with severe hemophilia A**

RESOURCE ABSORPTION

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group

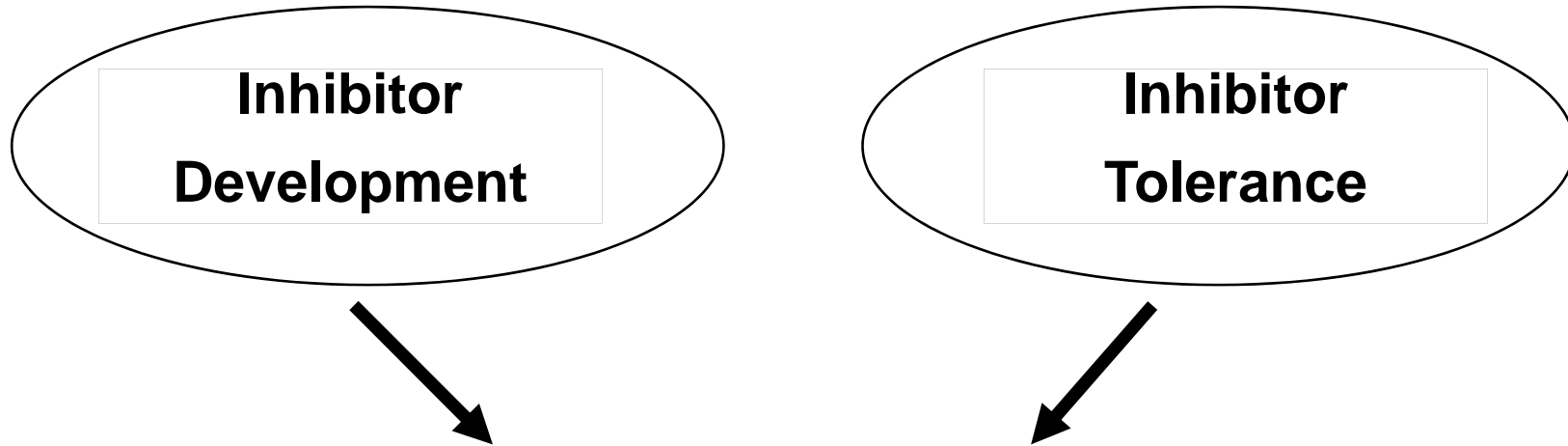
Alessandro Gringeri, Lorenzo G. Mantovani, Luciana Scalone, and Pier Mannuccio Mannucci, for the COCIS Study Group

BLOOD, 1 OCTOBER 2003 • VOLUME 102, NUMBER 7

Table 4. Health care costs

Resource	Cost per patient per month, in euros	% of total cost
rFVIIa	8491.9	47.3
rFVIII	3174.2	17.7
Human plasma-derived FVIII	3077.1	17.2
Activated prothrombin		

**Average cost of care of a patient with inhibitors:
220,000 Euro a year!**



**Influenced by
multiple genetic and exogenous variables**



**? Source of concentrates ?
? Content of VWF ?**

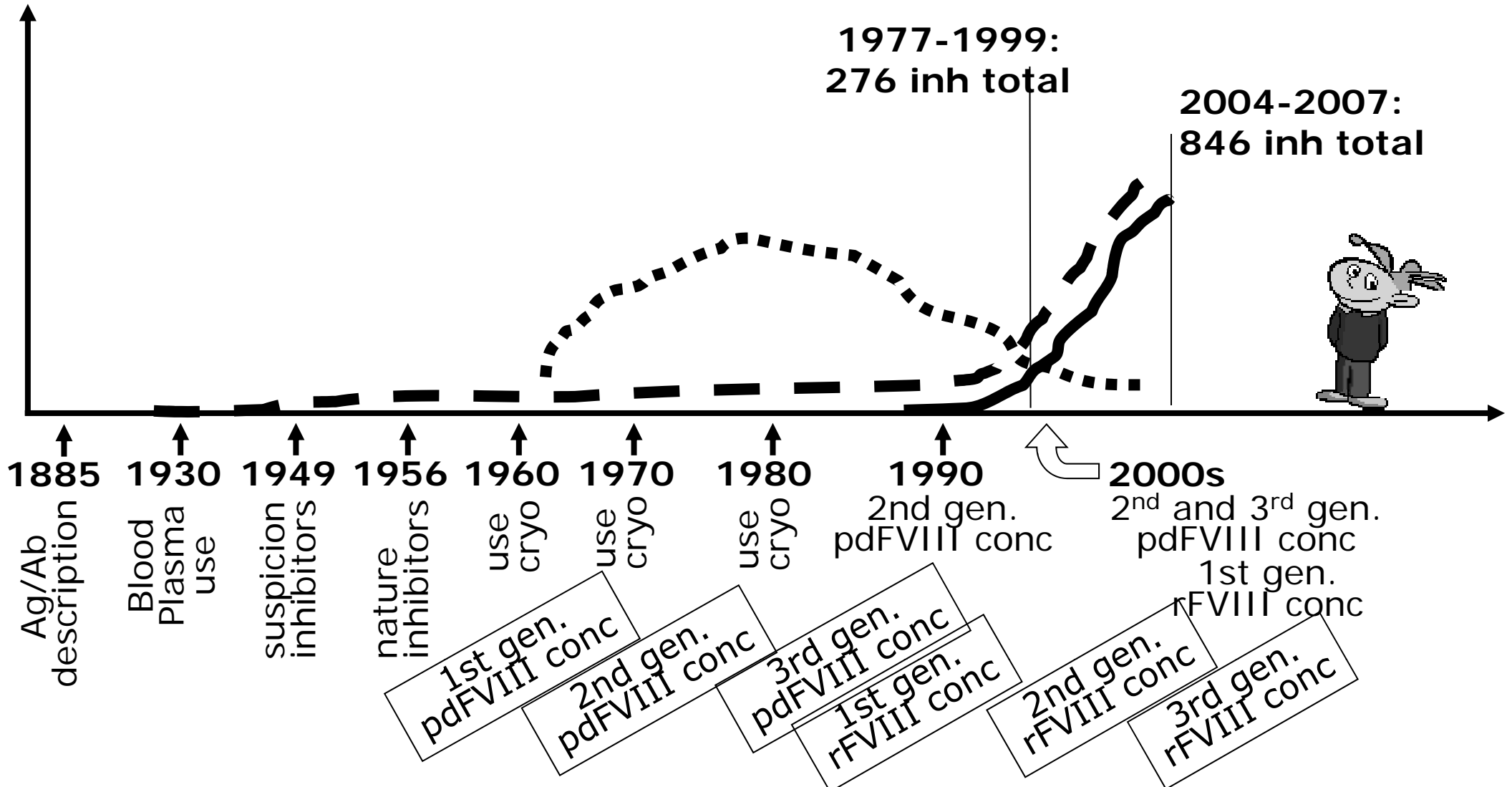
PLASMA-DERIVED, VWF-CONTAINING FVIII PRODUCTS AND INHIBITOR INCIDENCE

Clinical data

Ref:

- 1.UKHCDO 2004, J. Thromb Haem
- 2.UKHCDO report 2007

- ▬ inhibitors
- ⋯ pd prods infusions
- ▬ rec prods infusions



IS INHIBITOR INCIDENCE INCREASING?

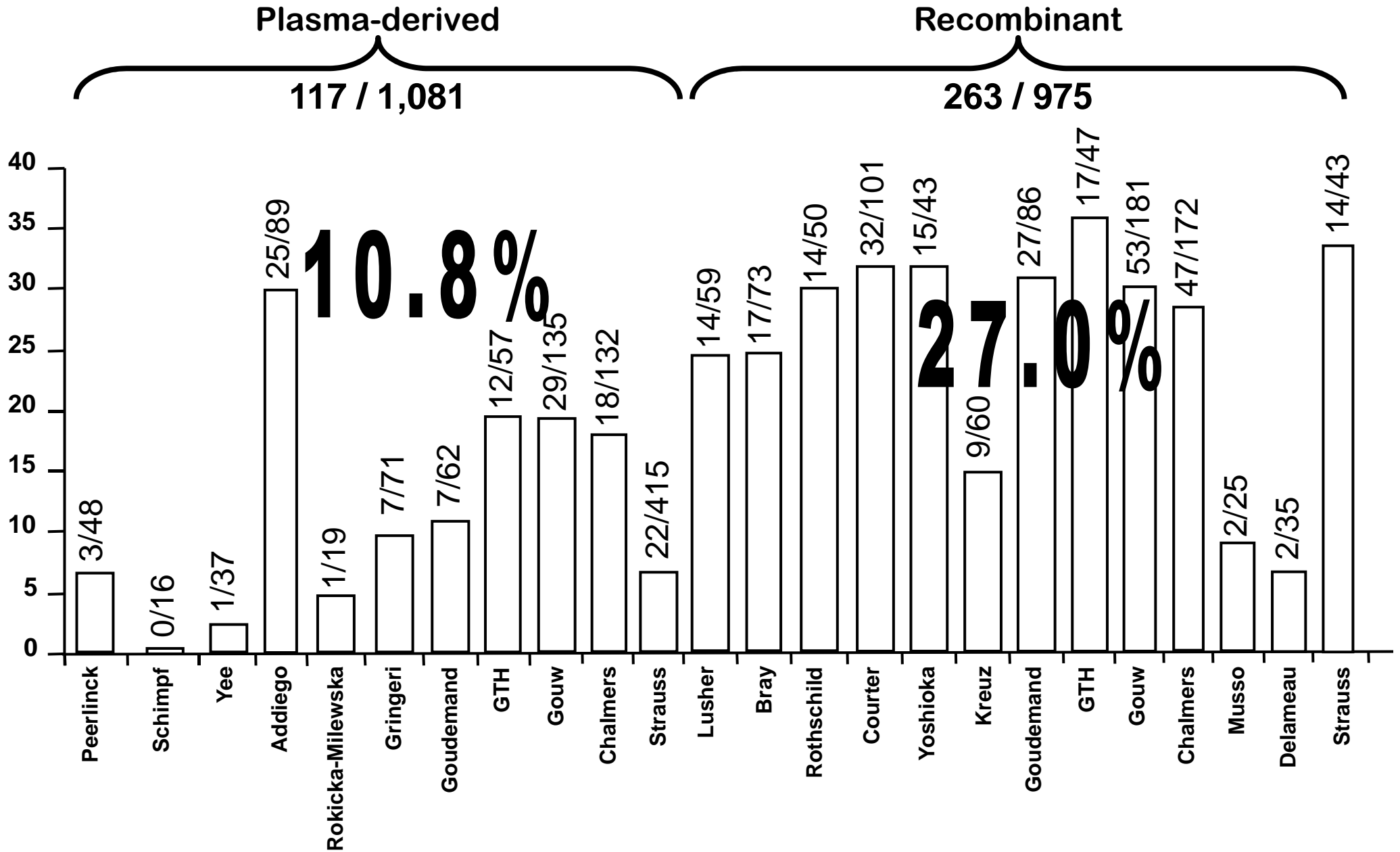
- **More testing & awareness**
- **Previous studies may have underestimated incidence**
- **Higher incidence with rFVIII vs. pdFVIII**

CUMULATIVE INCIDENCE IN PUPs SEVERELY AFFECTED

- **Single *plasma* products**
 - **Mean 6.8% (range 0%-12.4%)**
- **Single *recombinant* products**
 - **Mean 37.5% (range 36.0%-38.7%)***

Wight and Paisley, Haemophilia, 2003

Crude incidence of inhibitors in PUPs



SYSTEMATIC REVIEW

**Journal of Thrombosis and Haemostasis, 2010; 8:
1256–65**

Journal of Thrombosis and Haemostasis, 8: 1256–1265

DOI: 10.1111/j.1538-7836.2010.03823.x

ORIGINAL ARTICLE

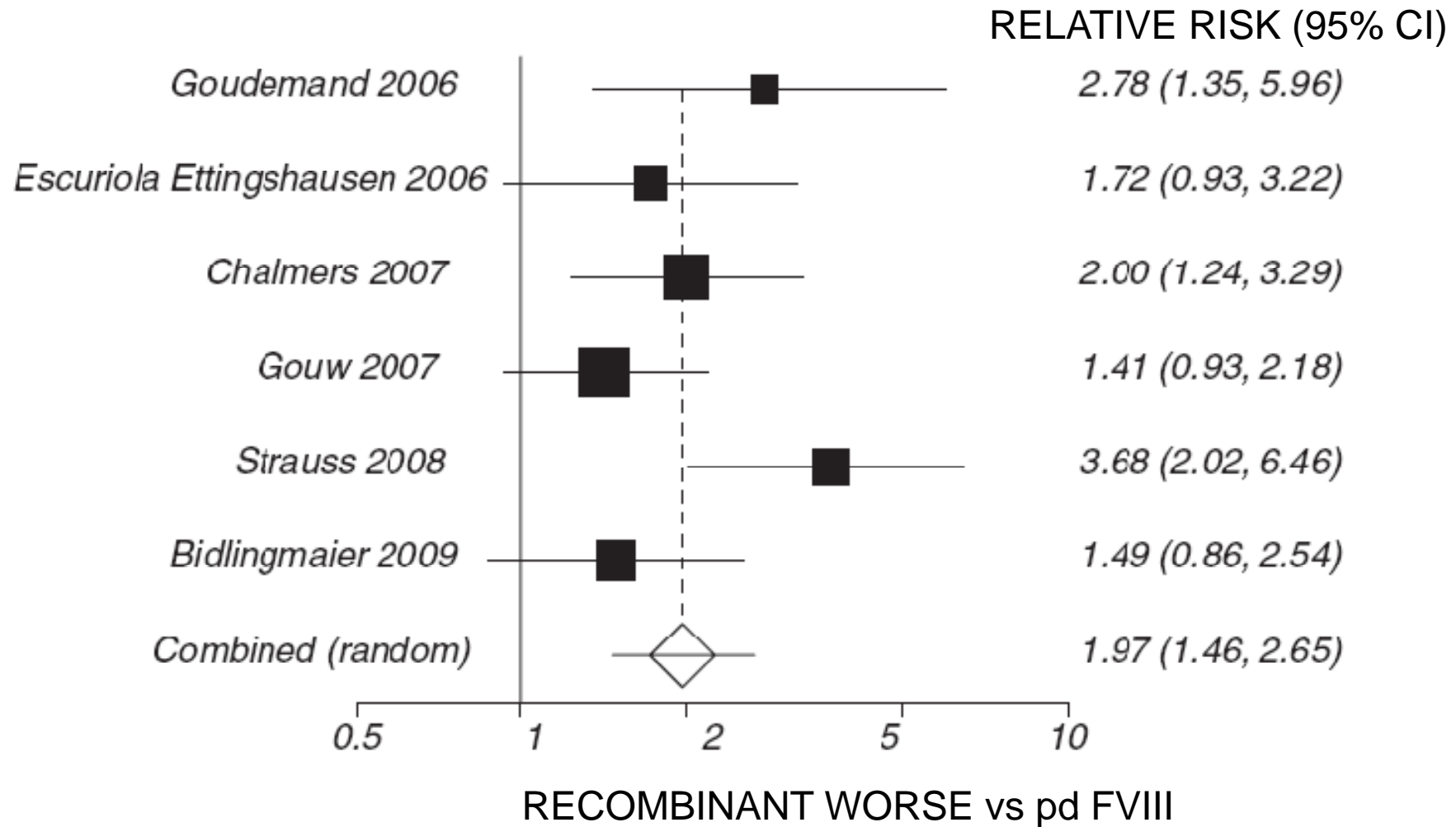
Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review

A. IORIO,* S. HALIMEH,† S. HOLZHAUER,‡ N. GOLDENBERG,§ E. MARCHESINI,* M. MARCUCCI,* G. YOUNG,¶ C. BIDLINGMAIER,‡‡ L. R. BRANDAO,§§ C. E. ETTINGSHAUSEN,¶¶ A. GRINGERI,** G. KENET,*** R. KNÖFLER,††† W. KREUZ,¶¶ K. KURNIK,‡‡ D. MANNER,†† E. SANTAGOSTINO,** P. M. MANNUCCI** and U. NOWAK-GÖTTL††

- **The systematic review was performed to compare the incident rate of inhibitors in PUPs with haemophilia A treated with pd- or r-FVIII.**
 - **2 113 patients from 24 studies were included**
 - **1 170 treated exclusively with pd-FVIII,**
 - **943 with r-FVIII;**
 - **median age: 9.6 months**

A META-ANALYSIS OF ALL OBSERVATIONAL STUDIES

Measurement of risk (rFVIII vs pd FVIII)



INHIBITOR INCIDENCE IN PUPs

Limits of available observational studies

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 !

**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**

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

STUDY OBJECTIVE AND DESIGN

- To compare the immunogenicity of the class of plasma-derived VWF-FVIII concentrates with that of the class of recombinant FVIII, by determining the rate of inhibitor development in previously untreated or minimally treated hemophiliacs exposed to study products for at least 50 EDs.

The study is:

- independent
- international (Europe, Africa, America, Asia)
- prospective
- controlled (open-label)
- randomized

TREATMENT

- **Each patient with severe hemophilia A will be randomly assigned to treatment with a single product of the class of plasma FVIII/VWF concentrates or to a single product of the class of recombinant FVIII (second or third generation)**
- **Prophylaxis or on-demand regimens can be chosen by the clinicians according to patients' status and his/her guidelines and preferences**

VWF/FVIII PLASMA-DERIVED PRODUCTS IN THE SIPPET STUDY

Name	Purification procedures	Virucidal Rx	VWF: RCo/Ag*	VWF: RCo/FVIII*	Manufacturer
Alphanate	Heparin ligand CT	SD; Dry heat	0.6	1.2	Grifols (US)
Fanhdi	Precipitation, heparin ligand CT	SD; Dry heat	0.6	1.6	Grifols (Sp)
Emoclot	Ion-exchange CT	SD; Dry heat	0.5	1.2	Kedrion (Italy)
Factane	Ion-exchange CT	SD; Vapor heat	0.2	0.3	LFB (France)

***Values declared by manufacturers**

RECOMBINANT PRODUCTS IN THE SIPPET STUDY

- **Advate (Baxter)**
- **Helixate (CSL Behring)**
- **Kogenate (Bayer)**
- **Refacto (Wyeth)**

SAMPLE SIZE

Assuming a 50% decrease of cumulative inhibitor incidence in patients treated with VWF/FVIII and an incidence of 30% in recombinant FVIII- treated patients, 230 patients (115 in each arm) should be enrolled to provide 80% power to detect a significant difference ($P < 0,05$)

COUNTRIES INVOLVED

COUNTRY	Sites		COUNTRY	Sites
Austria	2		Italy	7
Belgium	1		Mexico	4
Brazil	4		Portugal	2
Colombia	1		Saudi Arabia	1
Egypt	3		South Africa	6
France	5		Spain	3
Germany	5		Turkey	5
India	10		UK	1
Iran	2		USA	15

Total countries: 18

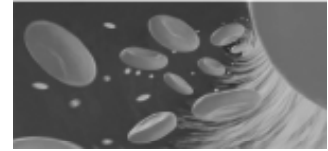
Total sites: 77

CURRENT SITUATION

Countries approved:	16
Sites approved:	54
Sites activated:	20
Sites ready to start:	15
First patient in:	14 January 2010

STUDY DURATION: APPROXIMATELY 5 YEARS 2014

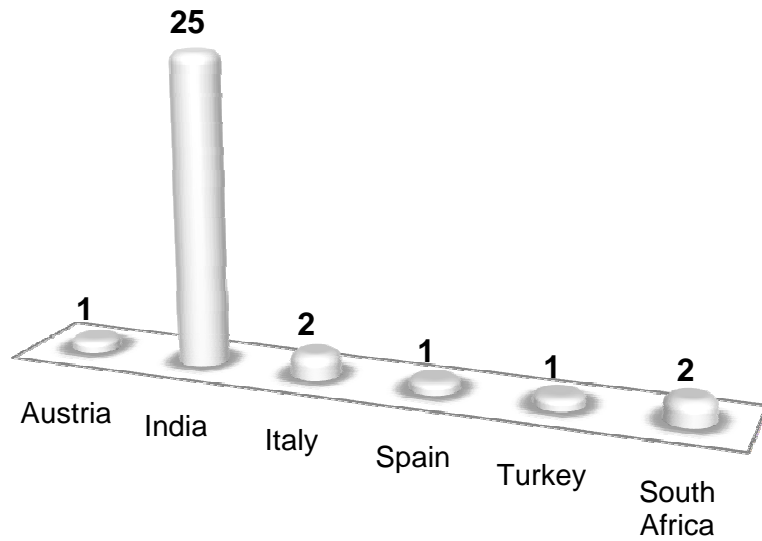
SUMMARY



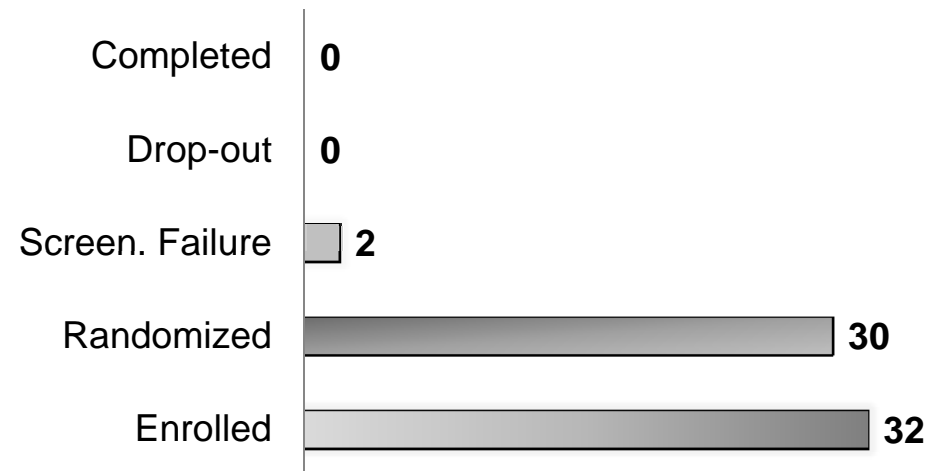
PATIENT ENROLLED:

32

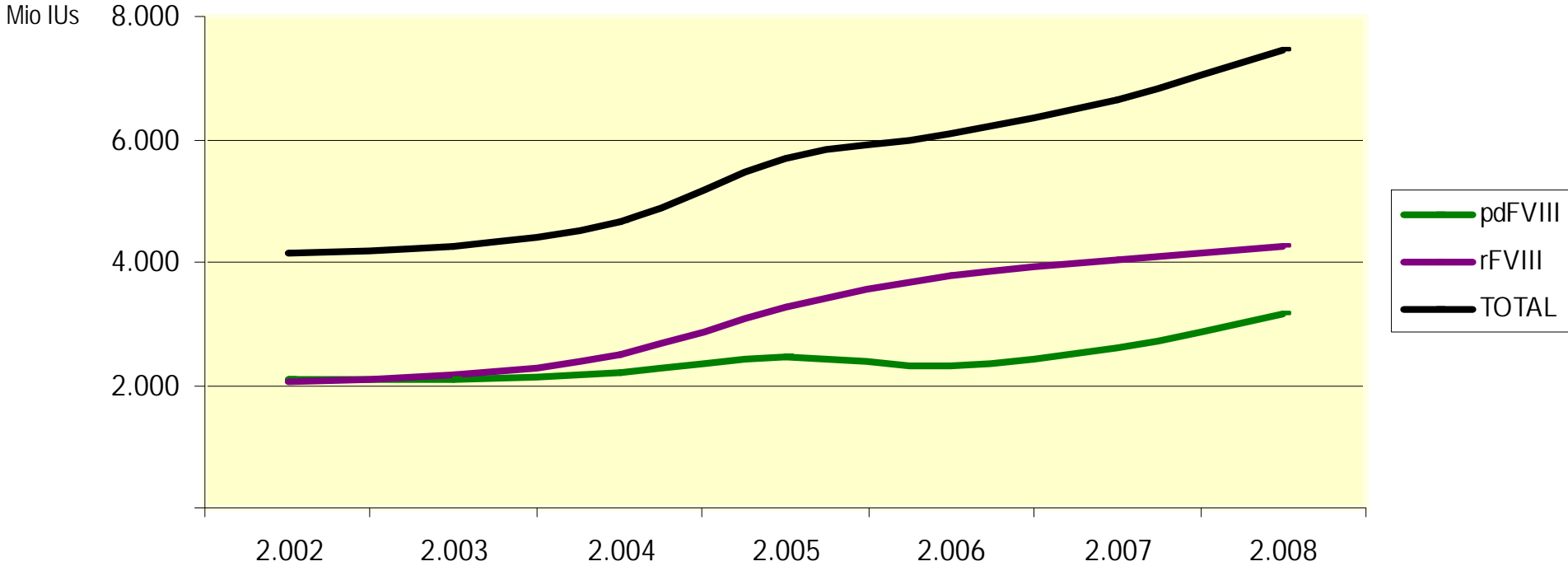
Best Enroller Countries



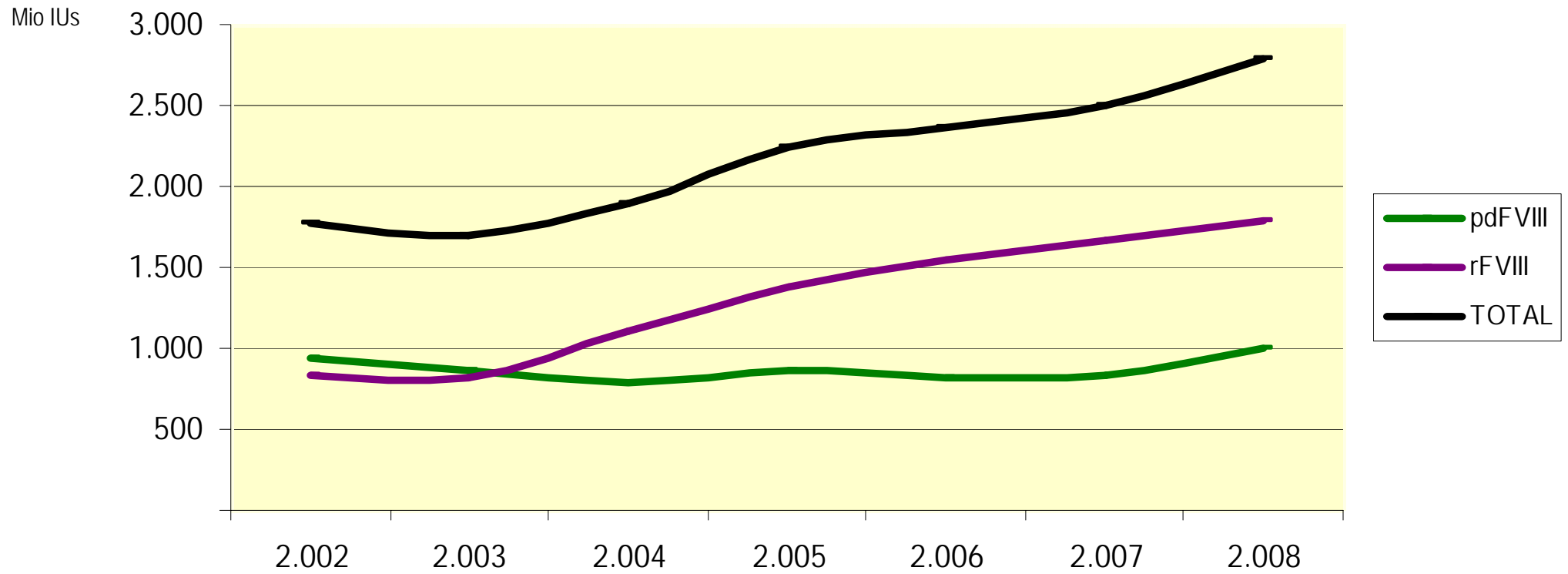
Patients Enrolment



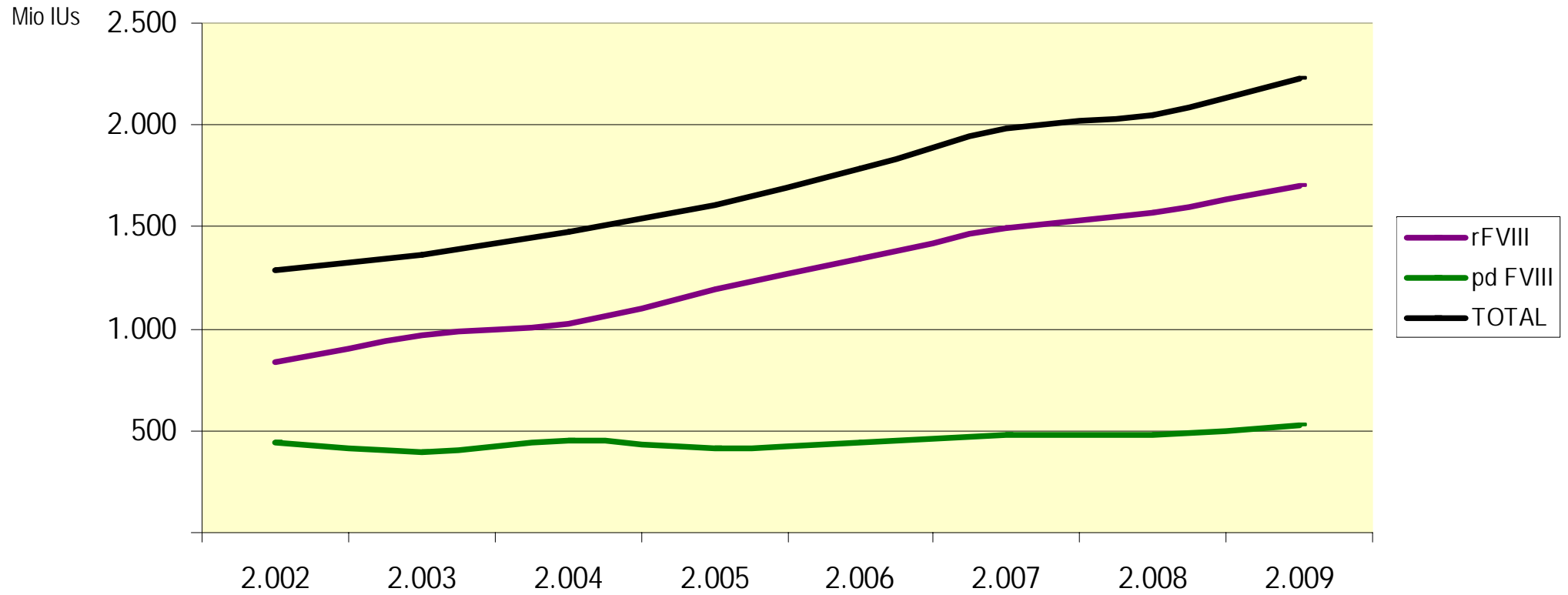
Worldwide Factor VIII market



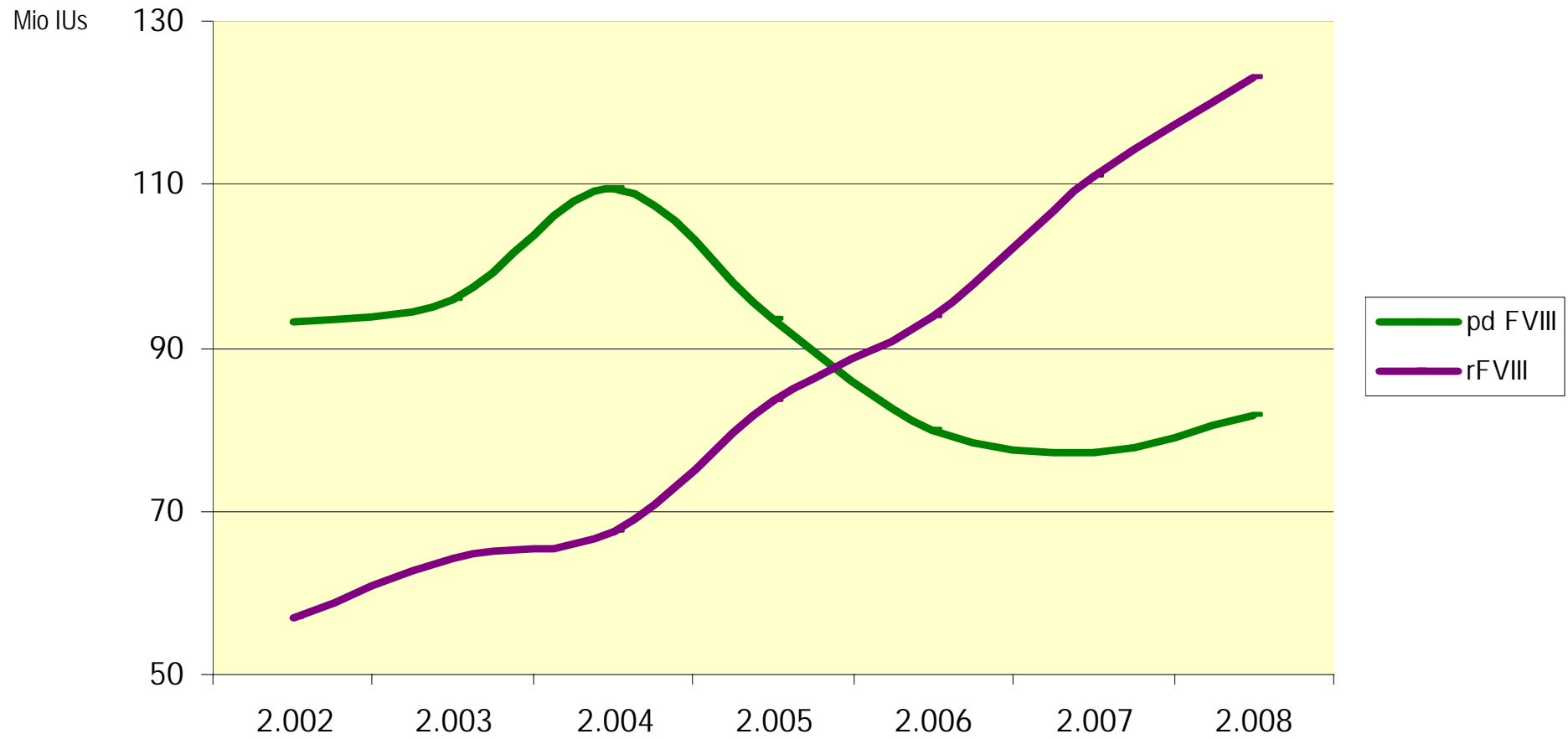
Factor VIII market in Europe



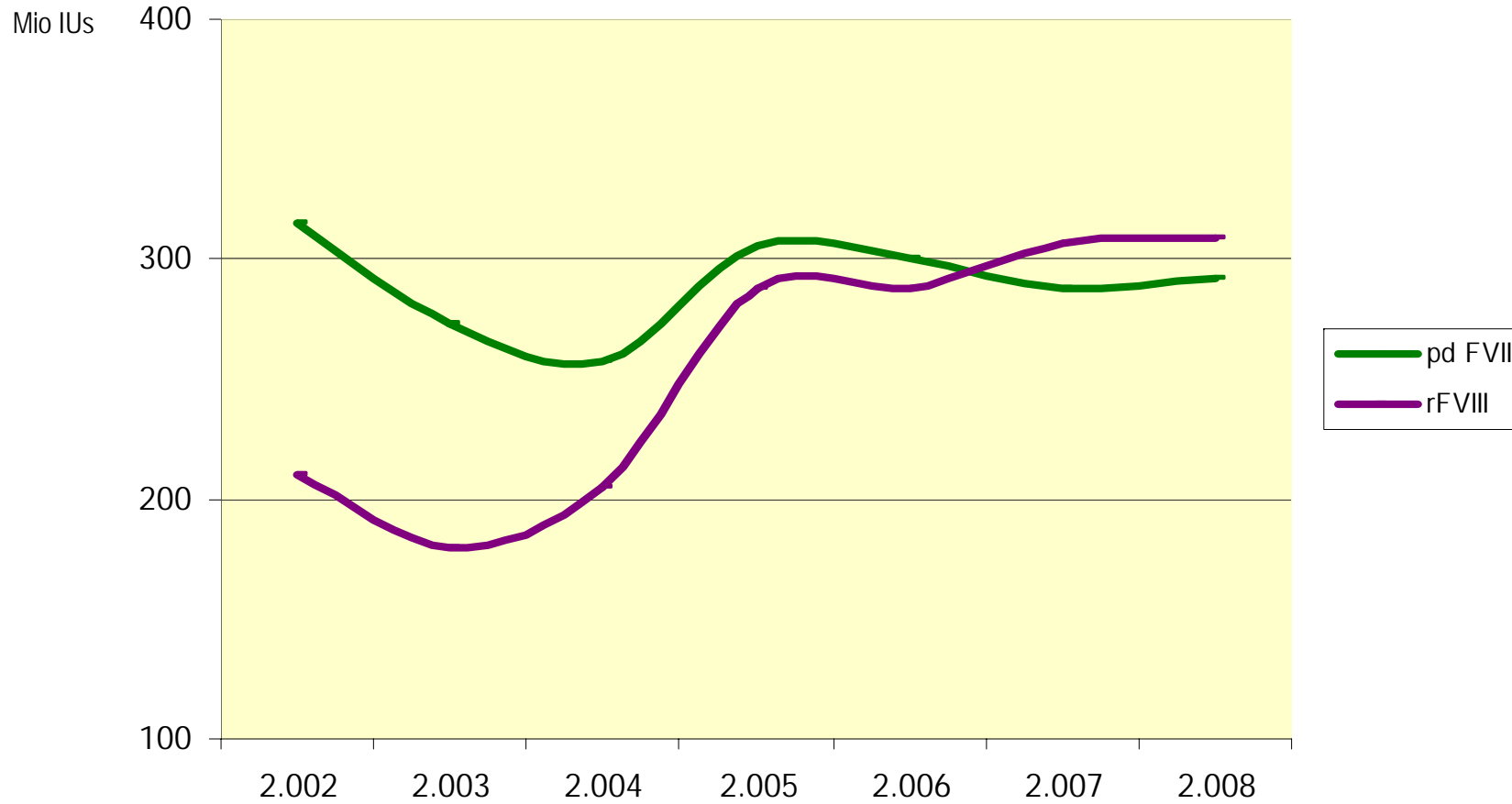
Factor VIII market in USA



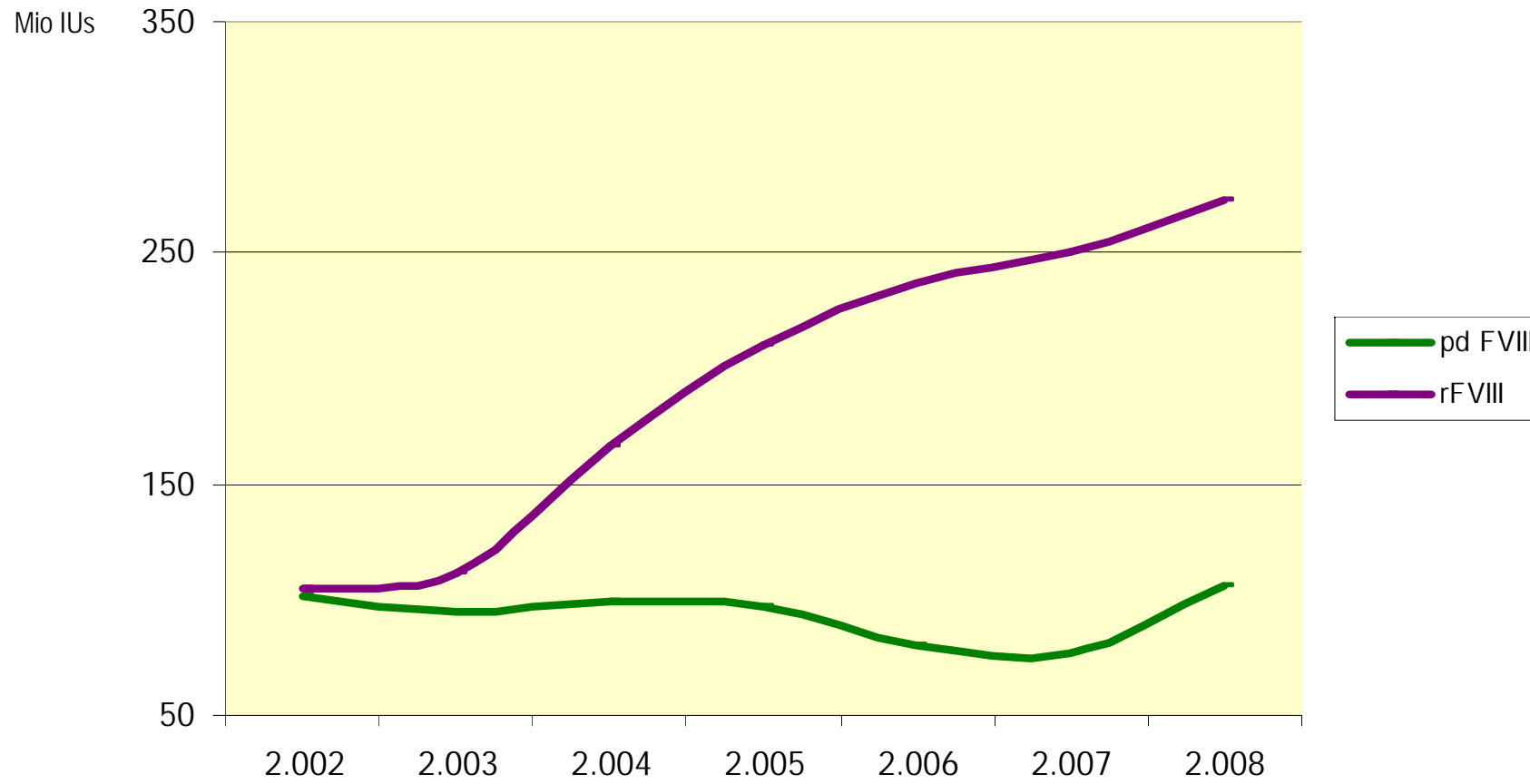
Factor VIII market - Spain



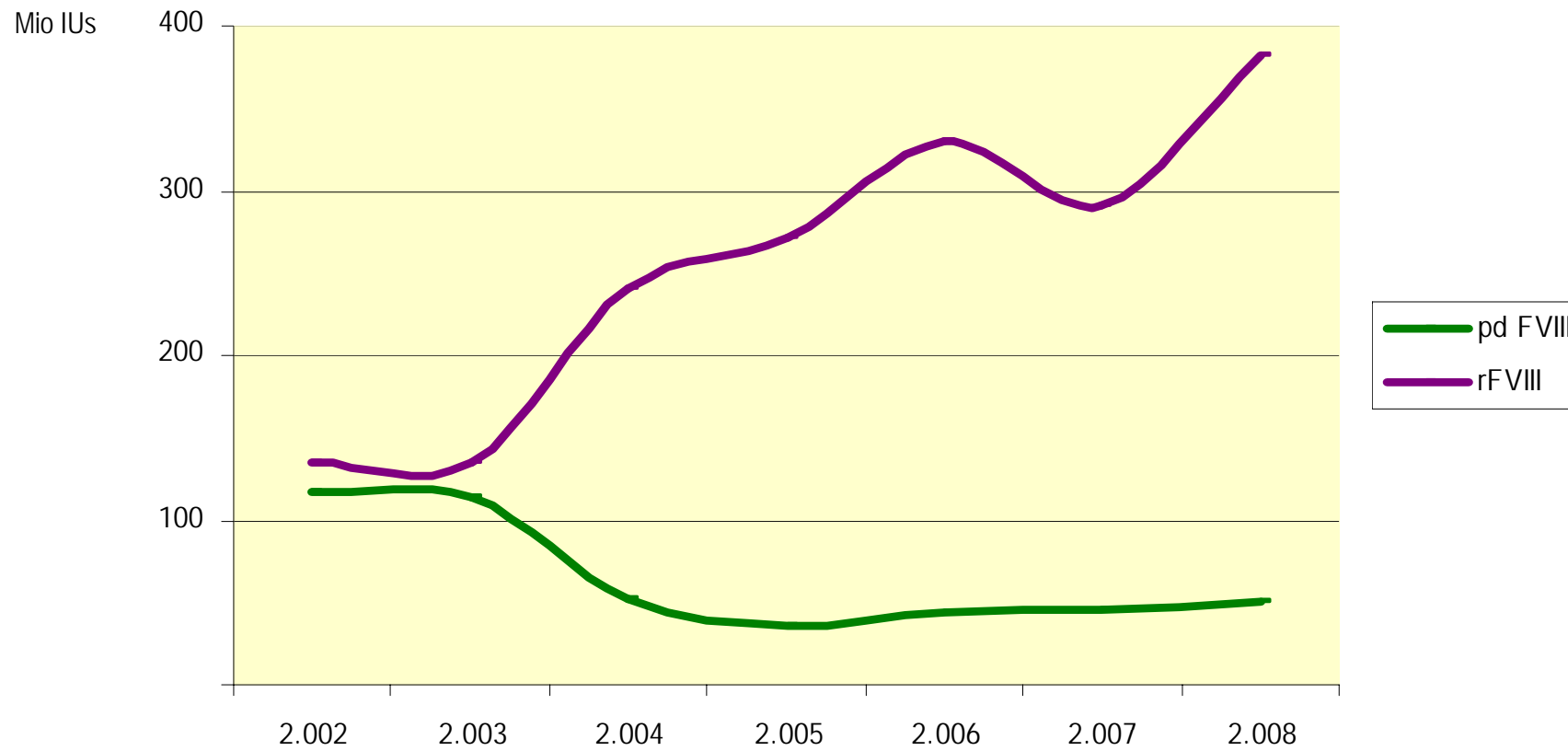
Factor VIII market - Germany



Factor VIII market - Italy

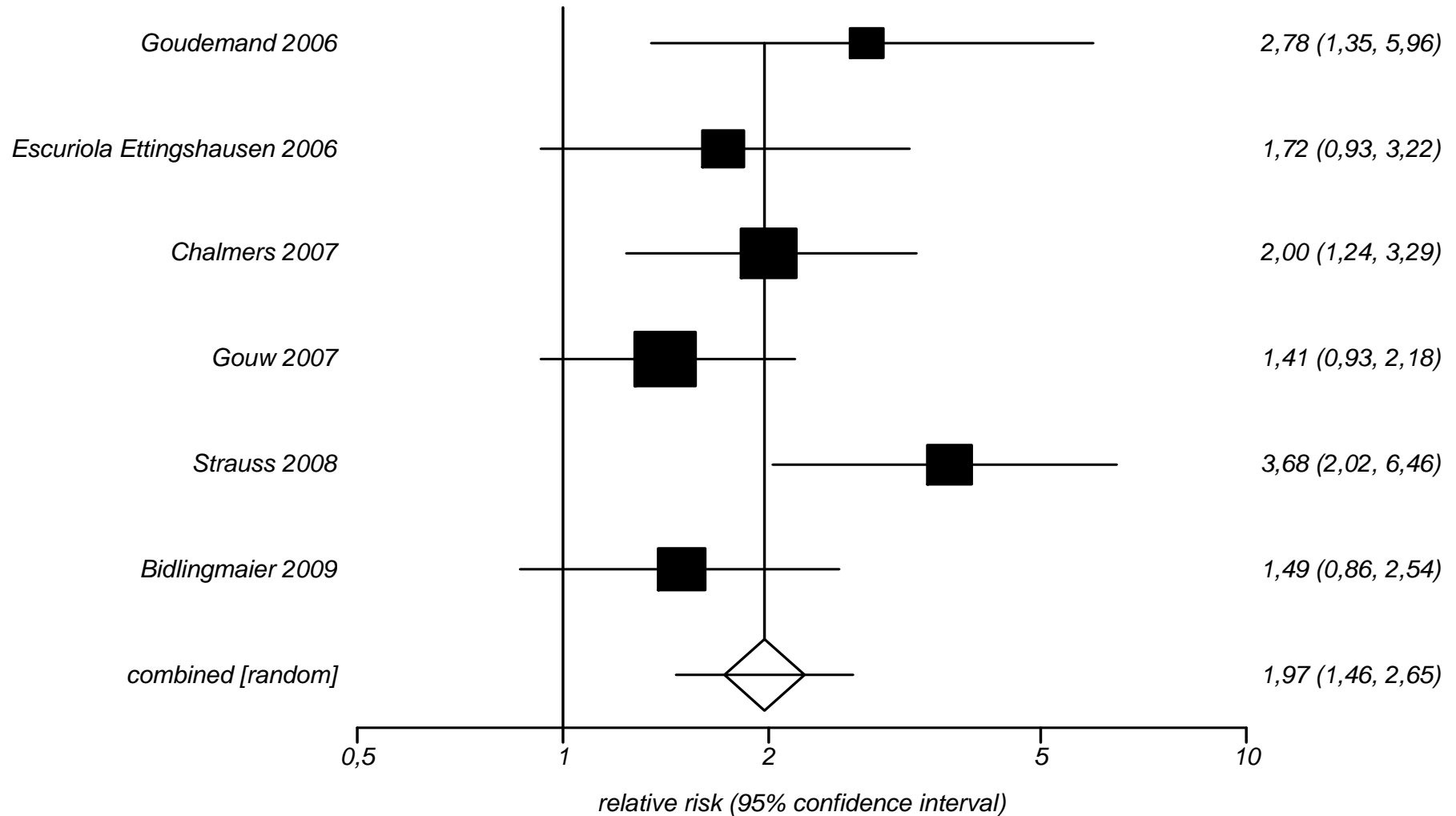


Factor VIII market - United Kingdom



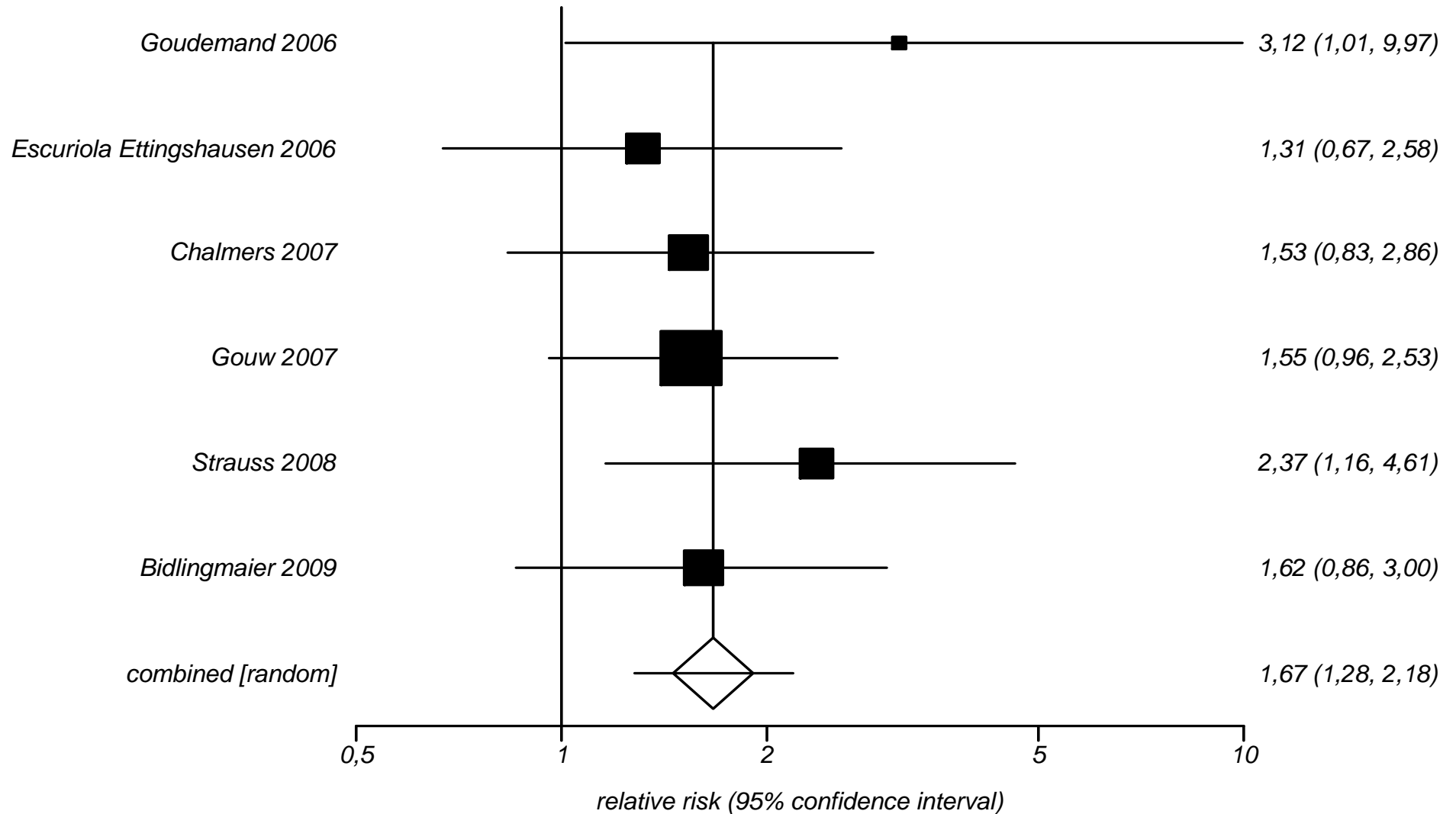
RELATIVE RISK METANALYSIS PLOT

Incidence of all inhibitors



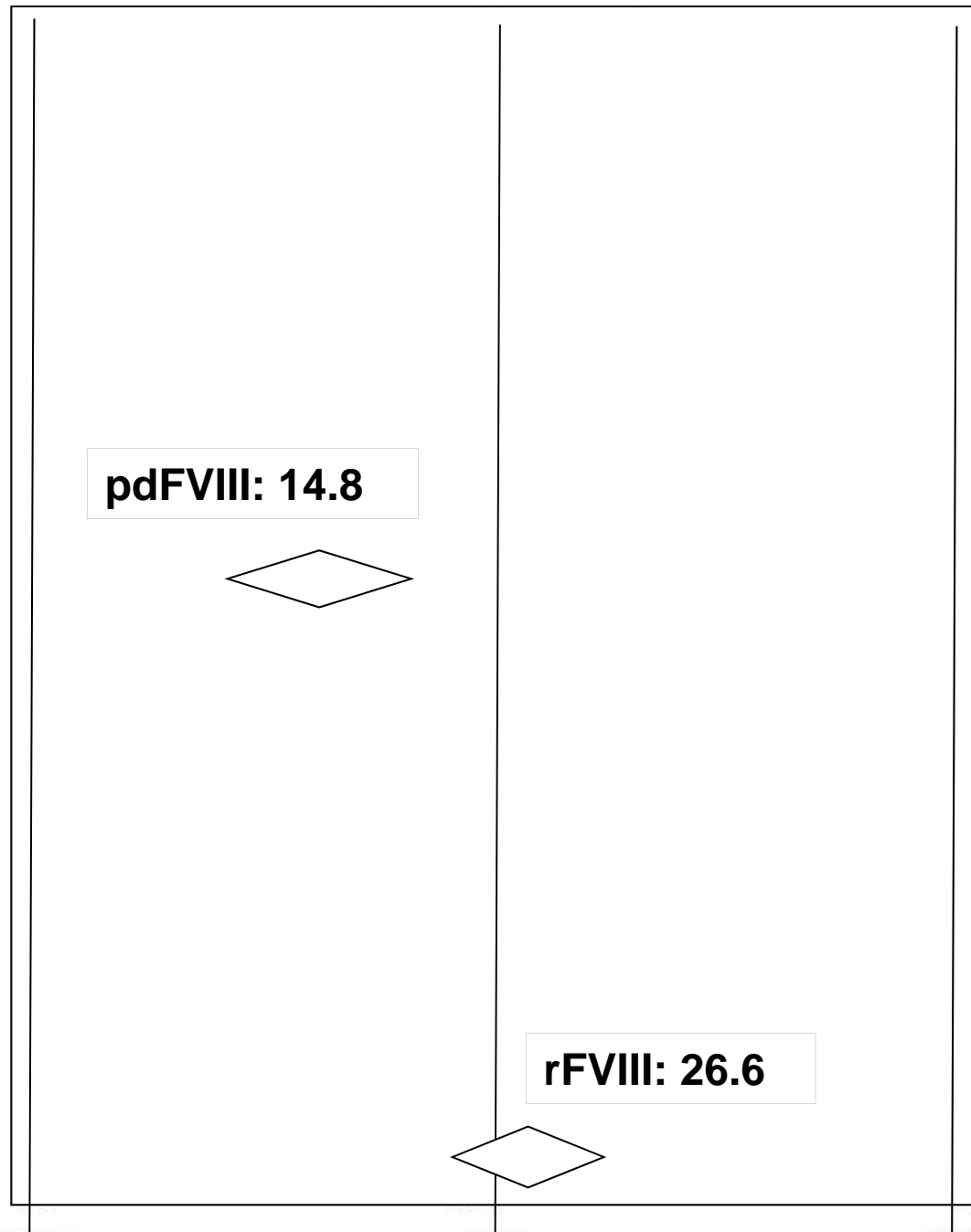
RELATIVE RISK METANALYSIS PLOT

Incidence of high titre inhibitors

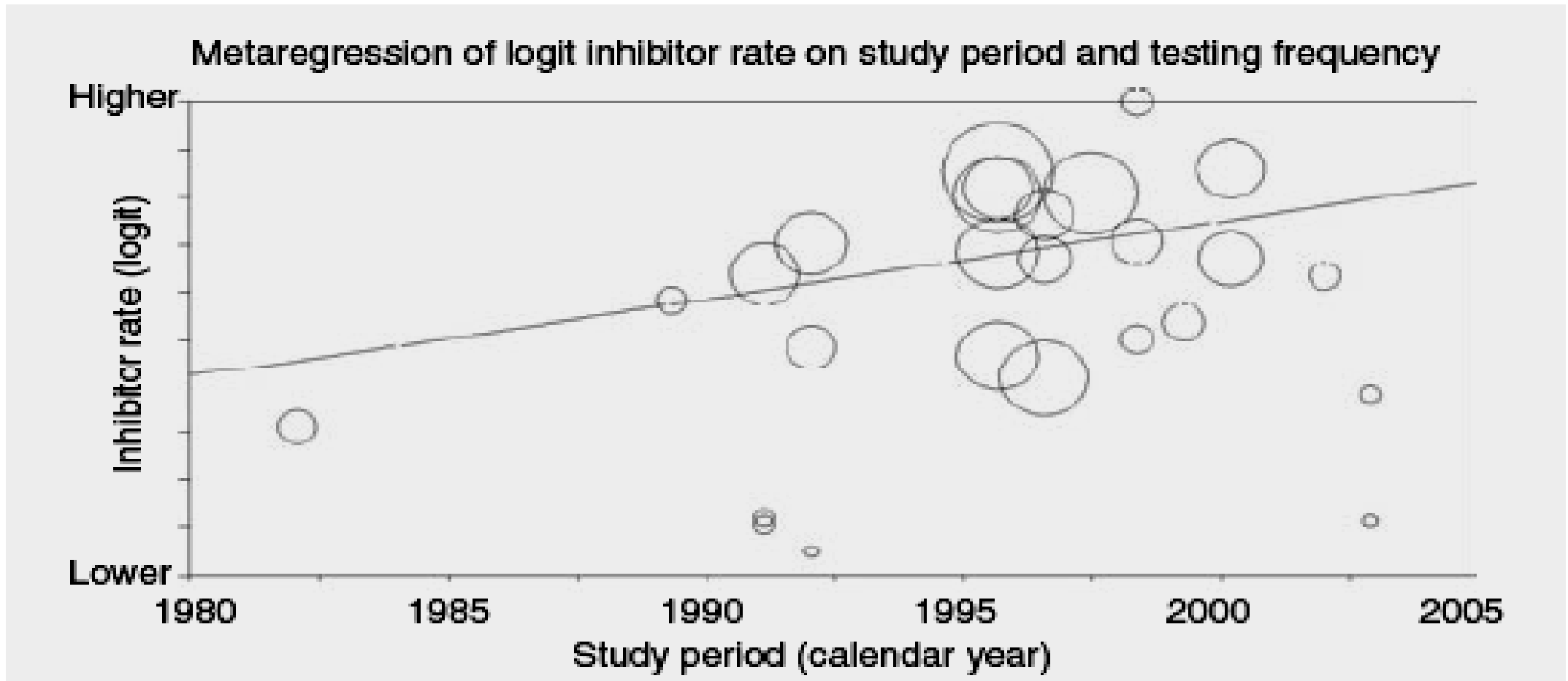


Study name	Statistics for each study		
	Event rate	Lower limit	Upper limit
Lusher 1990 (A)	0,029	0,004	0,177
Lusher 1990 (B)	0,158	0,052	0,392
Addiego 1993	0,281	0,197	0,383
Peerlink 1993	0,060	0,023	0,149
Schimpf 1995	0,022	0,001	0,268
Yee 1997	0,027	0,004	0,168
El Alfy 2000	0,120	0,039	0,313
Mauser-B. 2001	0,237	0,146	0,362
Escuriola-E. 2004 (PD)	0,211	0,124	0,335
Morado 2005 (PD)	0,500	0,225	0,775
Goudemand 2006 (PD)	0,113	0,055	0,218
Gringeri 2006	0,097	0,032	0,261
Gouw 2007 (PD)	0,212	0,147	0,297
Chalmers 2008 (PD)	0,105	0,067	0,160
Strauss 2008 (PD)	0,088	0,059	0,131
Bidlingmaier 2009 (PD)	0,219	0,147	0,312
pd-FVIII	0,148	0,108	0,200
Lusher 1993	0,190	0,118	0,291
Bray 1994	0,233	0,150	0,343
Rokicka-M. 1999	0,042	0,006	0,244
Courter 2001	0,317	0,234	0,414
Yoshioka 2003	0,279	0,166	0,430
Escuriola-E. 2004 (R)	0,362	0,238	0,507
Kreuz 2005	0,135	0,057	0,286
Morado 2005 (R)	0,237	0,128	0,396
Goudemand 2006 (R)	0,314	0,225	0,419
Gouw 2007 (R)	0,300	0,232	0,378
Pollmann 2007	0,188	0,062	0,447
Chalmers 2008 (R)	0,356	0,279	0,441
Delumeau 2008	0,028	0,002	0,322
Musso 2008	0,077	0,011	0,391
Strauss 2008 (R)	0,209	0,113	0,356
Bidlingmaier 2009 (R)	0,327	0,214	0,464
r-FVIII	0,266	0,226	0,310
Overall	0,230	0,199	0,265

Inhibitor incident rate



METAREGRESSION OF LOGIT INHIBITOR RATE ON STUDY PERIOD





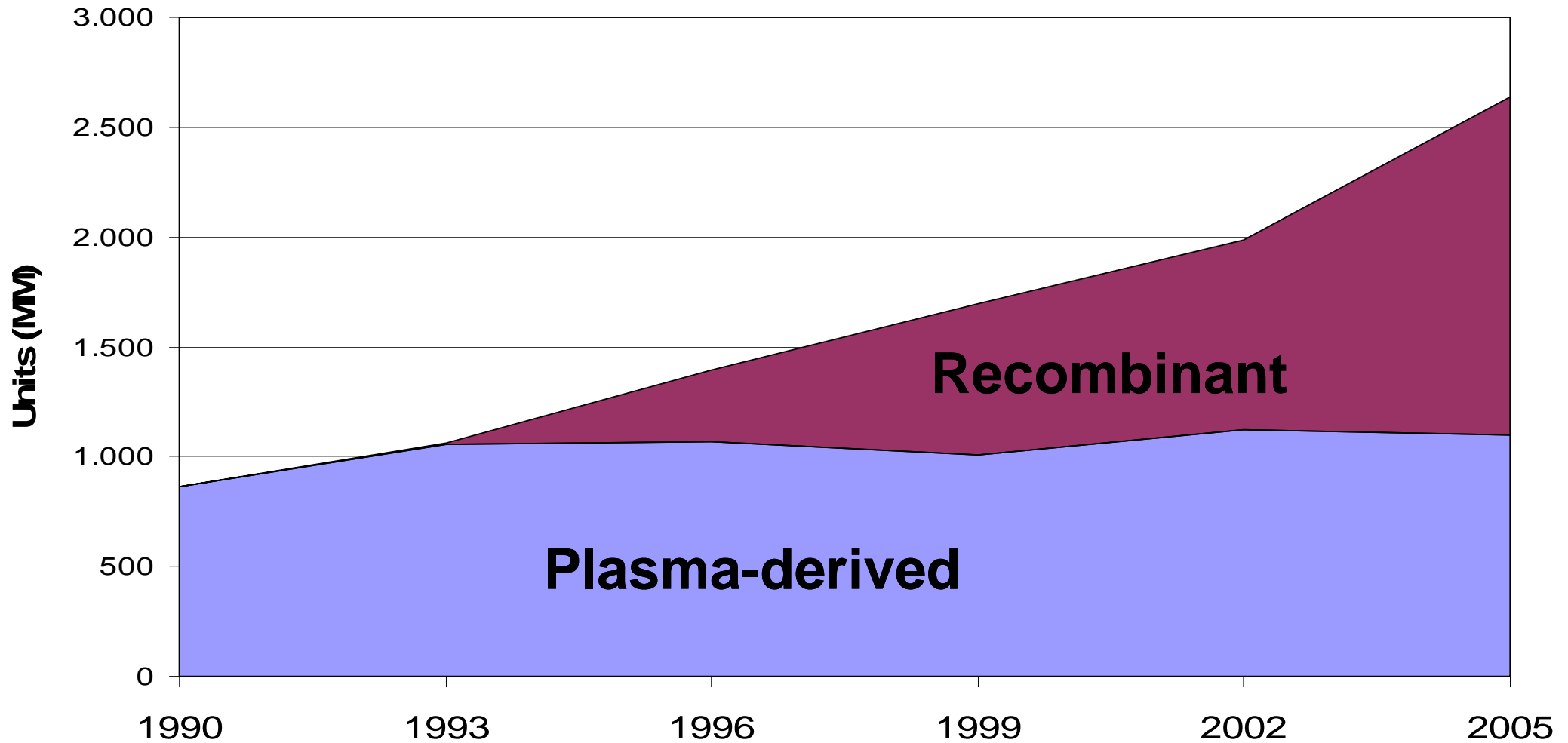
“The global economic downturn is likely to have ripple effects on health and social spending, especially in developing countries.

Protecting investments in health and social structures is essential to maintain stability and security, and accelerate economic recovery.

The challenge facing the world now is to prevent an economic crisis becoming a social and health crisis.”



1990-2005 consumption in Europe of Plasma-derived Recombinant FVIII/FIX: IUx10⁶



Adapted from W. Schramm, WFH Global Forum, Montreal 2007

A SPECTRE IS HAUNTING EUROPE – THE SPECTRE OF ... REDUCTION OF RESOURCES FOR HEALTH CARE

- Belgium: Mandatory Price Cuts
- Germany: Haemophilia Budget Capitation
- UK and Ireland: National Tenders for Coagulation Factors
- Sweden: Health Technology Assessment (TLV November 2009)

