Comparison studies on safety and efficacy different generations of recombinant products

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Parsian Azadi Hotel-Tehran-Iran , October 23th 2014

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- **Chair Canadian Hemophilia Registry Program**

- **Associate Editor: Blood Coagulation Disorders of the Cystic Fibrosis and Genetic Disorders Review Group of the Cochrane Collaboration**

References

- Iorio, A. CDRS, 9, CD003429
- Iorio A. Haemophilia, 2014 doi:10.1111/hae.12480
- Fischer, K. Blood, 2013: 122(7), 1129–36.
- Xi, M. JTH, 2013; 11(9), 1655–62.
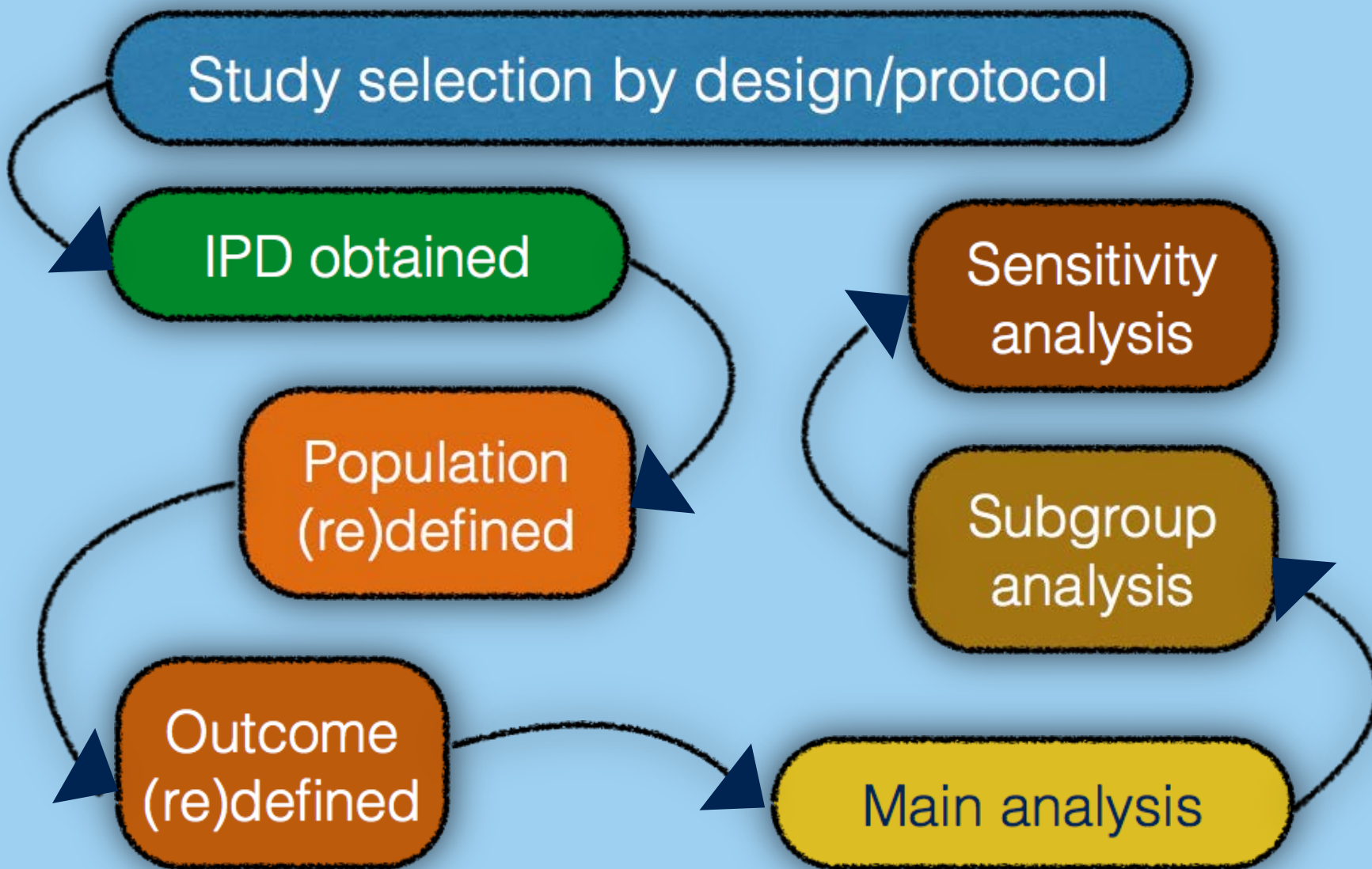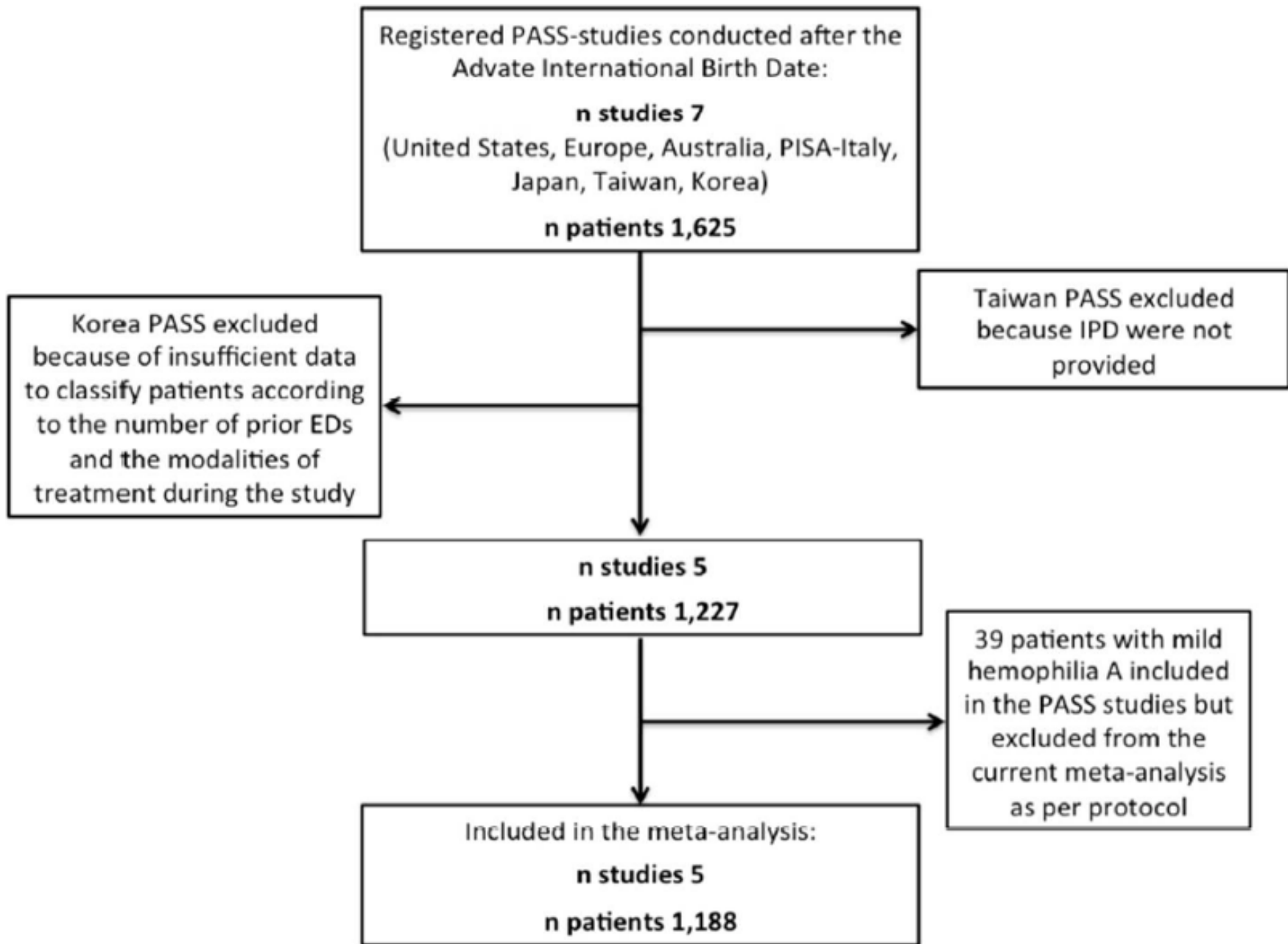- Iorio A. *JTH* 2010;8:1256–65.

Efficacy

Evidence about efficacy

- Level I: Prophylaxis reduces bleeding rate by 10
  - Cochrane Collaboration SR:

- Level II: Higher intensity produces better results
  - Swedish vs Dutch Regimen
  - Canadian escalating dose study

- Level II: Tailoring to the individual need reduces wastage and costs
 - Collins
  - MUSFIT

Post Authorization Safety Studies

Registered PASS-studies conducted after the Advate International Birth Date:

n studies 7
(United States, Europe, Australia, PISA-Italy, Japan, Taiwan, Korea)

n patients 1,625

Taiwan PASS excluded because IPD were not provided

Korea PASS excluded because of insufficient data to classify patients according to the number of prior EDs and the modalities of treatment during the study

n studies 5

n patients 1,227

39 patients with mild hemophilia A included in the PASS studies but excluded from the current meta-analysis as per protocol

Included in the meta-analysis:

n studies 5

n patients 1,188

Iorio A. Haemophilia, 2014 doi:10.1111/hae.12480

PASS Effectiveness Outcomes

Secondary Analyses	Patient Number	
Annualized Bleeding Rate		**median (Q1, Q3)**
All patients	1,140	3.83 (0.60, 12.90)
Patients prescribed OD at enrolment	421	10.38 (2.27, 27.29)
Prophylaxis (on study, any frequency)	707	2.00 (0, 6.73)
Prophylaxis (on study, ≥twice/week)	560	1.67 (0, 4.80)

Safety
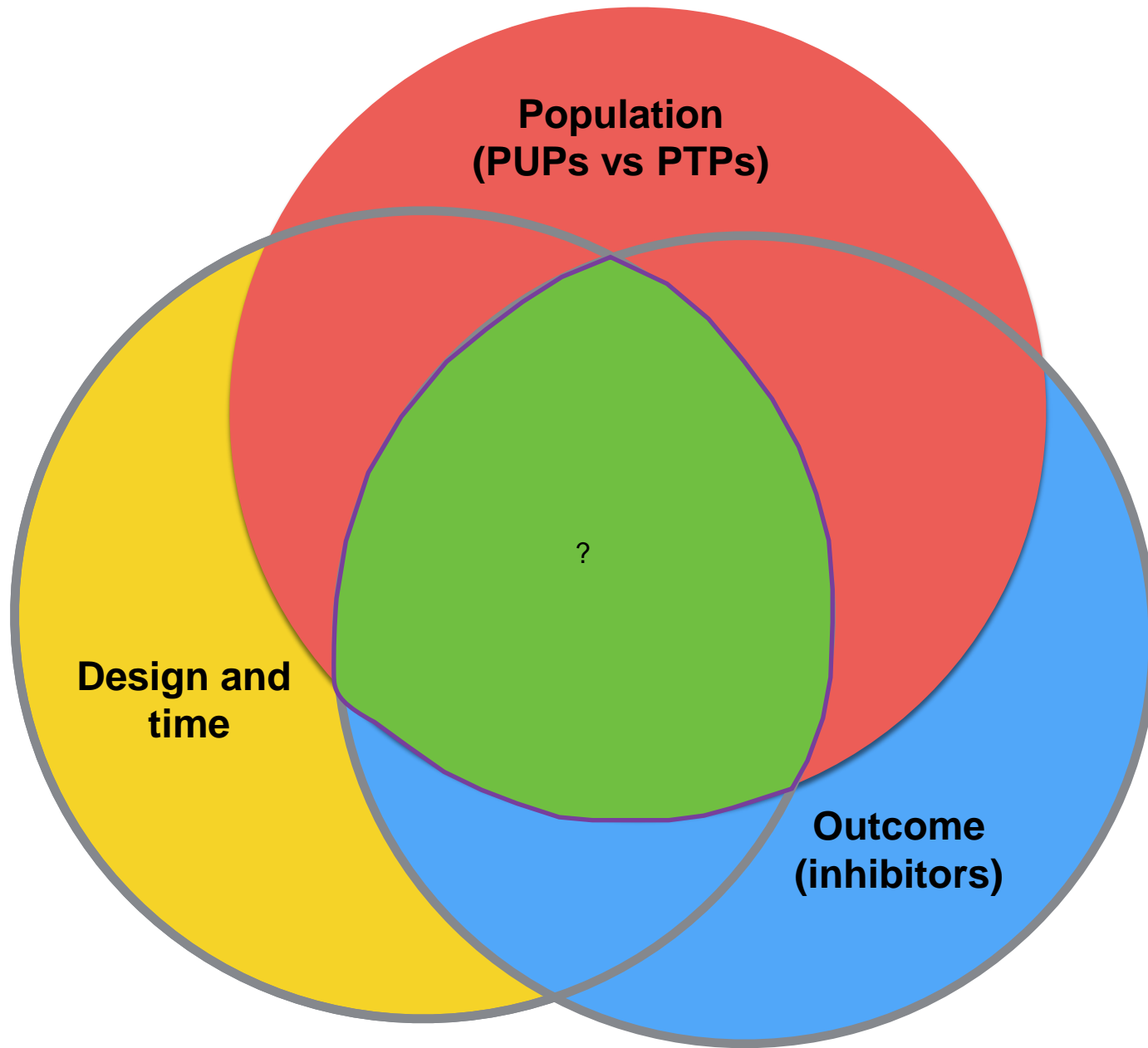
PTPs (vs PUPs) as a model to study immunogenicity

- **Strenghts**

  - Already tolerized

  - No other con causes

  - Easier to recruit

    - adults

    - low, if any, risk of events

- **Weaknesses**

  - ..to a specific FVIII

  - Assumptions!!

  - Easy and optimal are enemies

    - Low prevalence

    - BU? NIAb? threshold?

Characteristics of inhibitors in PTPs

As a result of our systematic review, we identified:

- **39 de novo inhibitors** reported in **19 publications.**

Individual patient data has been collected for:
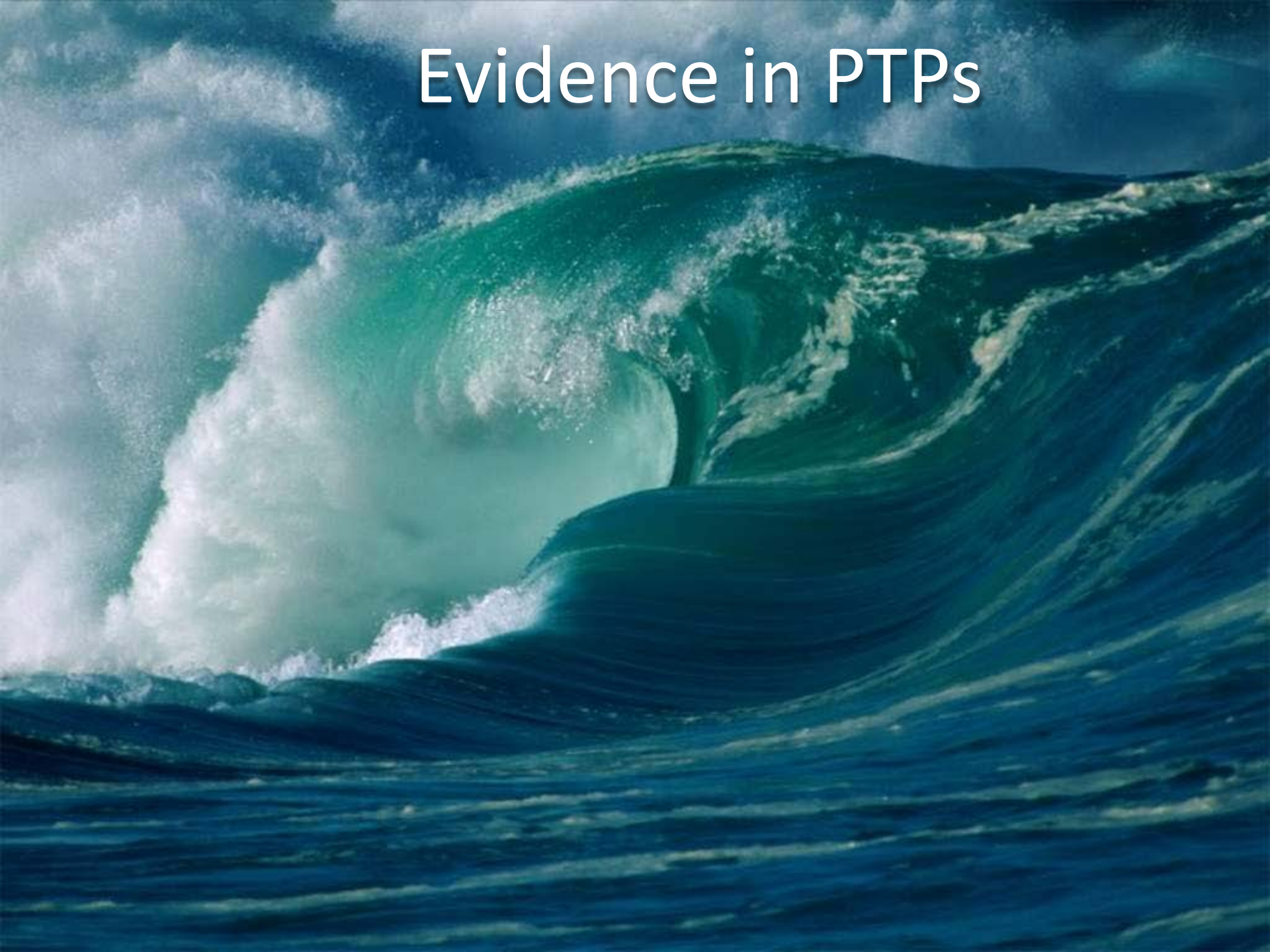
- **29 (74%) inhibitor cases overall**

  - **14 (36%) from CRFs** completed by study investigators

  - **15 (39%) extracted** from patient-level information available in the published reports.
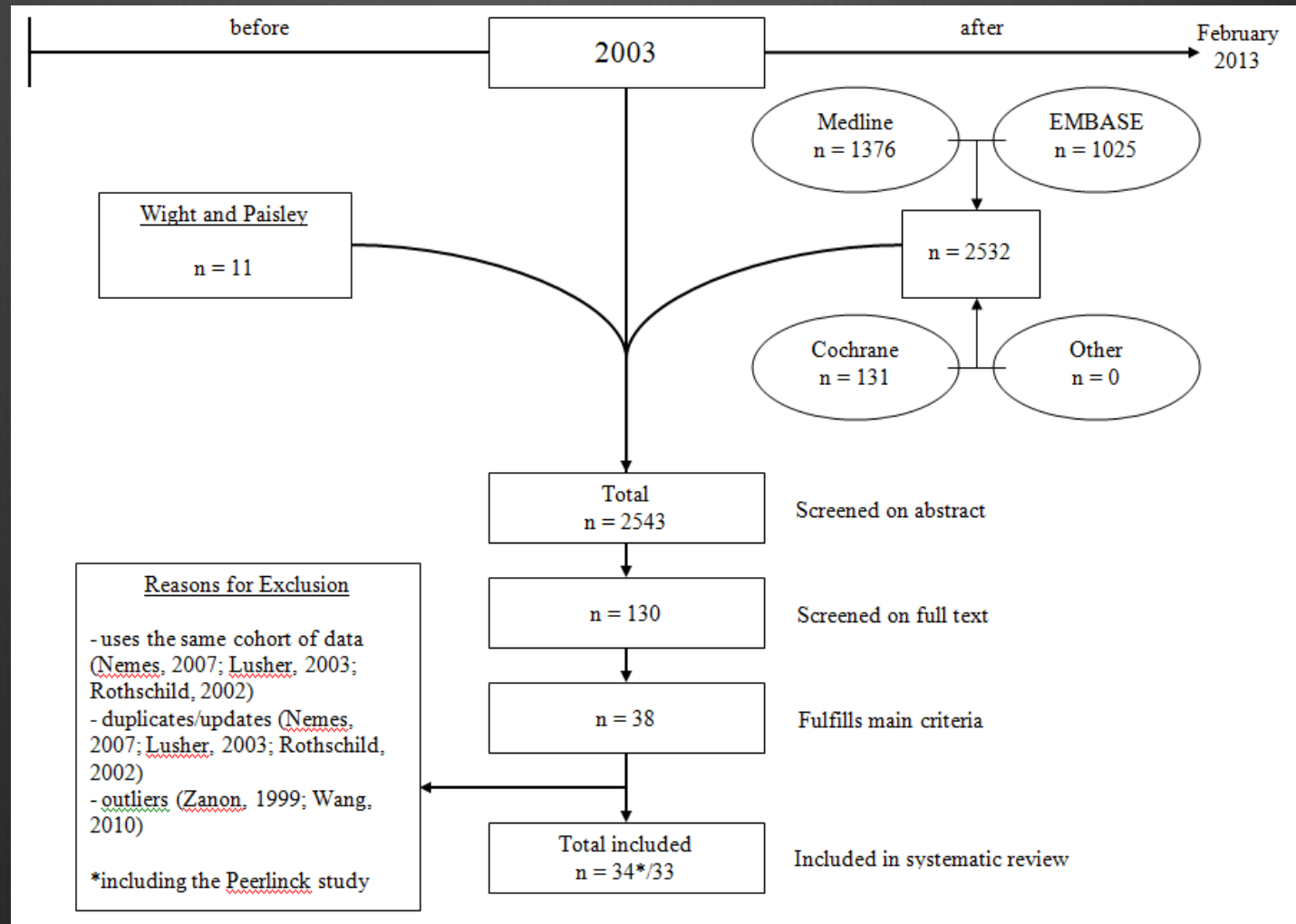
Interim results - inhibitor characteristics

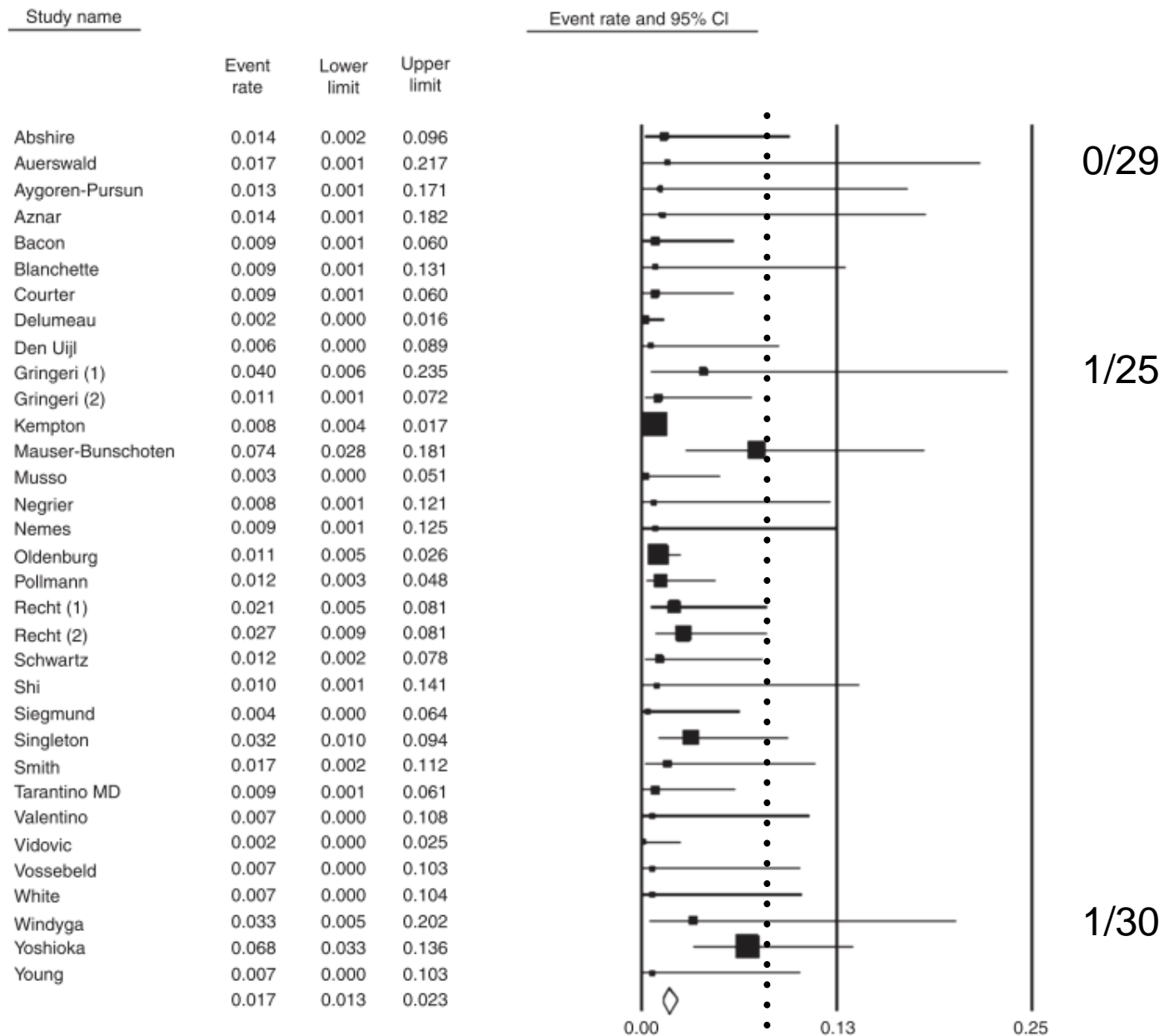| Characteristic	Range (*n* =29)
Age at inhibitor diagnosis (years)	2 - 67
Peak titre level (BU/ml)	0.5 - 75
Last known titre level (BU/ml)	0 – 10.4
Patient follow-up (months)	1 - 143

Evidence in PTPs

PTP meta-analysis

Xi, M et al. Journal of Thrombosis and Haemostasis : JTH, 2013; 11(9), 1655–62.

Study name	Event rate	Lower limit	Upper limit	Event rate and 95% CI
Abshire	0.014	0.002	0.096	
Auerswald	0.017	0.001	0.217	
Aygoren-Pursun	0.013	0.001	0.171	
Aznar	0.014	0.001	0.182	
Bacon	0.009	0.001	0.060	
Blanchette	0.009	0.001	0.131	
Courter	0.009	0.001	0.060	
Delumeau	0.002	0.000	0.016	
Den Uijl	0.006	0.000	0.089	
Gringeri (1)	0.040	0.006	0.235	
Gringeri (2)	0.011	0.001	0.072	
Kempton	0.008	0.004	0.017	
Mauser-Bunschoten	0.074	0.028	0.181	
Musso	0.003	0.000	0.051	
Negrier	0.008	0.001	0.121	
Nemes	0.009	0.001	0.125	
Oldenburg	0.011	0.005	0.026	
Pollmann	0.012	0.003	0.048	
Recht (1)	0.021	0.005	0.081	
Recht (2)	0.027	0.009	0.081	
Schwartz	0.012	0.002	0.078	
Shi	0.010	0.001	0.141	
Siegmund	0.004	0.000	0.064	
Singleton	0.032	0.010	0.094	
Smith	0.017	0.002	0.112	
Tarantino MD	0.009	0.001	0.061	
Valentino	0.007	0.000	0.108	
Vidovic	0.002	0.000	0.025	
Vossebeld	0.007	0.000	0.103	
White	0.007	0.000	0.104	
Windyga	0.033	0.005	0.202	
Yoshioka	0.068	0.033	0.136	
Young	0.007	0.000	0.103	
	0.017	0.013	0.023	

0/29

1/25

1/30

0.00   0.13   0.25

Xi, M et al. Journal of Thrombosis and Haemostasis : JTH, 2013; 11(9), 1655–62.

Inhibitor rates, selected recombinant FVIII

Product	Studies	Rate (x 100 py)	95% CI
Advate	9	0.10	0.05-0.18
Kogenate	9	0.12	(0.04-0.33)*
Refacto	8	0.19	0.11-0.34
PD factor VIII	4	0.09	0.02-0.45

* 0.26 (0.16 - 0.44) at fixed effect model

Xi, M et al. Journal of Thrombosis and Haemostasis : JTH, 2013; 11(9), 1655–62.

Sensitivity analysis

Variable	Proportion	Heterogeneity	
Design		within	between
RCT(4)	0.012 (0.009-0.041)	Low	P=0.231
Prosp (20)	0.015 (0.011-0.027)	Low 0.013	
Retrosp (8)	0.019 (0.012-0.030)	Moderate 0.020	
Other (3)	0.010 (0.04-0.029)	Low	

Xi, M et al. Journal of Thrombosis and Haemostasis : JTH, 2013; 11(9), 1655–62.

Study

FL-rFVIII
Schwartz et al., 1990 [10,34]
Aygören-Pürsün and Scharrer, 19
White et al., 1997 [33]
Abshire et al., 2000 [35,37]
Tarantino et al., 2004 [41]
Keeling, 2006 [44]
Yoshioka et al., 2006 [14]
Shi et al., 2007 [46]
Blanchette et al., 2008 [47]
Delumeau et al., 2008 [48]
Musso et al., 2008 [49]
Négrier et al., 2008 [15]
Auerswald et al., 2009 [50]
Collins et al., 2009 [51]
den Uijl et al., 2009 [52]
Fukutake et al., 2009 [53]
Shapiro et al., 2009 [16]
Taki et al., 2009 [56]
Young et al., 2009 [57]
Oldenburg et al., 2010 [58]
Vidovic et al., 2010 [59]
 Pooled FL-rFVIII
BDD-rFVIII
Courter and Bedrosian, 2001 [36,
Roussel-Robert et al., 2003 [39]
Gringeri et al., 2004 [40]
Smith et al., 2005 [43]
Keeling, 2006 [44]
Pollmann et al., 2007 [45]
Auerswald et al., 2009 [50]
Petrini and Rylander, 2009 [54]
Recht et al., 2009 [55]
Windyga et al., 2010 [60]
 Pooled BDD-rFVIII
Pooled FL-rFVIII and BDD-rFVIII

All Inhibitors

ED	Cumulative Hazard (CI), %		
	BDD-rFVIII	FL-rFVIII	Total
50	2.46 (1.32-3.60)	0.34 (0.12-0.55)	0.55 (0.26-0.84)
100	3.52 (2.03-5.02)	0.49 (0.19-0.78)	0.79 (0.40-1.18)
150	4.48 (2.65-6.31)	0.62 (0.24-0.99)	1.00 (0.51-1.49)
200	4.82 (2.85-6.79)	0.66 (0.26-1.07)	1.08 (0.55-1.60)
250	5.60 (3.31-7.90)	0.77 (0.29-1.25)	1.25 (0.63-1.88)

Patients at Risk

	0	50	100	150	200	250
FL-rFVIII	2277	1604	1144	669	669	360
BDD-rFVIII	735	549	370	296	235	235

Cumulative Hazard (%)

Time at Risk (ED)

Aledort LM et al. *JTH* 2011;9:2180–92.
Iorio A et al. *JTH* 2011;9:2176–9.
Aledort LM et al. *JTH* 2011;9:2325–7.

Science is built up of facts, as a house is built up of stones; but an accumulation of facts is no more science than a heap of stones is a house

Henri Poncare, 1854–1912

The EUHASS study

Strengths

- Prospective, very large inception cohort

- Controlled (parallel, head-to-head)

Limitations

- Minimal information collected

- No multivariable approach

- Confounding still possible

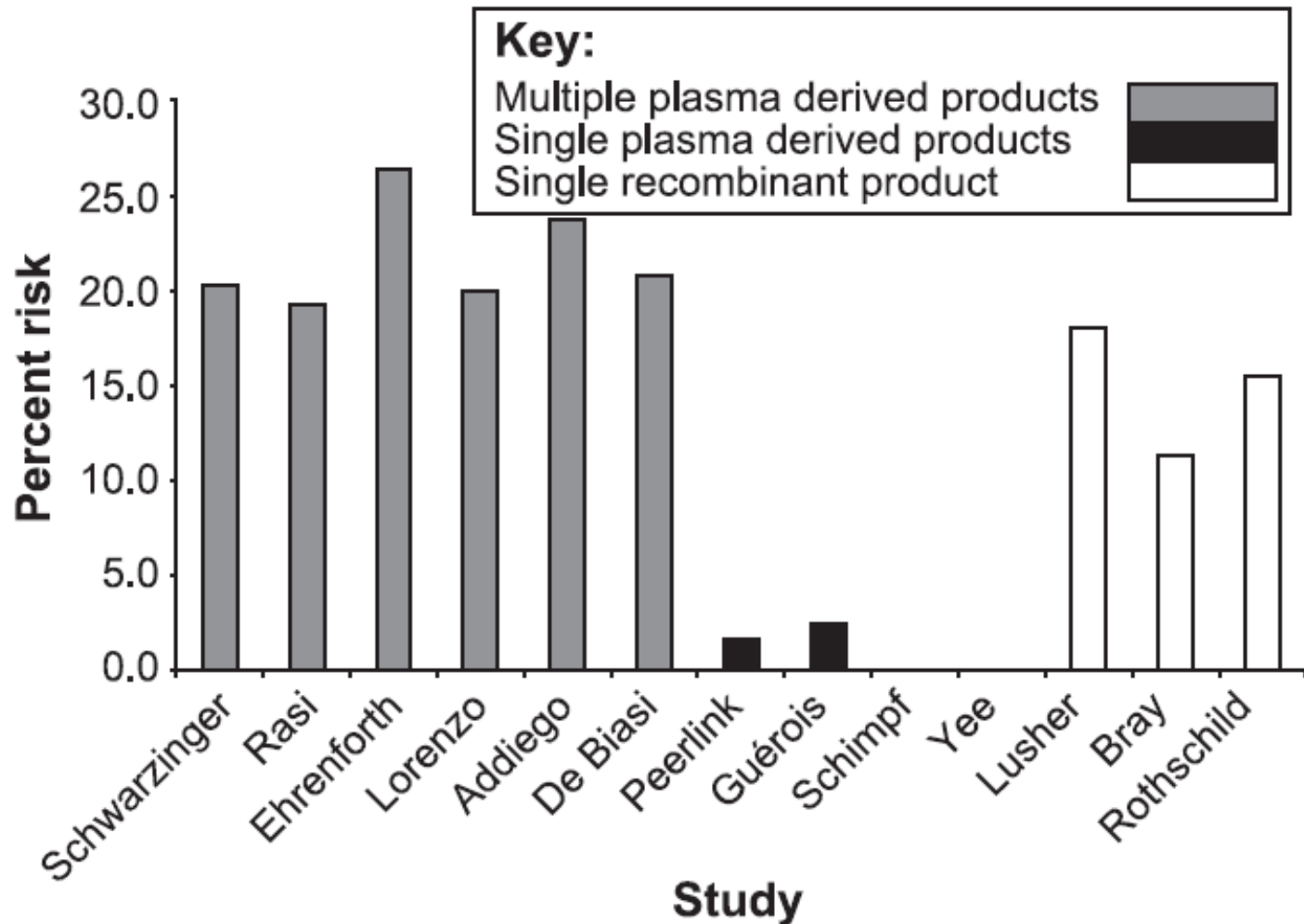- Dynamic cohort not always at steady-state

EUHASS: Inhibitors in PTPs

Product	Inhibitors	Pt/yr	Rate	(95% C.I.)
1	5	4656	0.11	(0.03-0.25)
2	1	1987	0.05	(0.00 - 0.28)
3	6	3519	0.17	(0.06 - 0.37)
4	3	2338	0.13	(0.03 - 0.37)

Data from the EUHASS annual reports to the Investigators

Findings in PTPs

- No difference in inhbitor rates between

    - Plasma derived and recombinants

    - Different recombinants

- When the proper analysis method is used

Evidence in PUPs

Key:
Multiple plasma derived products
Single plasma derived products
Single recombinant product

..”homogeneous results”

Univariate

Multivariate

Calvez T et al J Thromb Haemost 2008
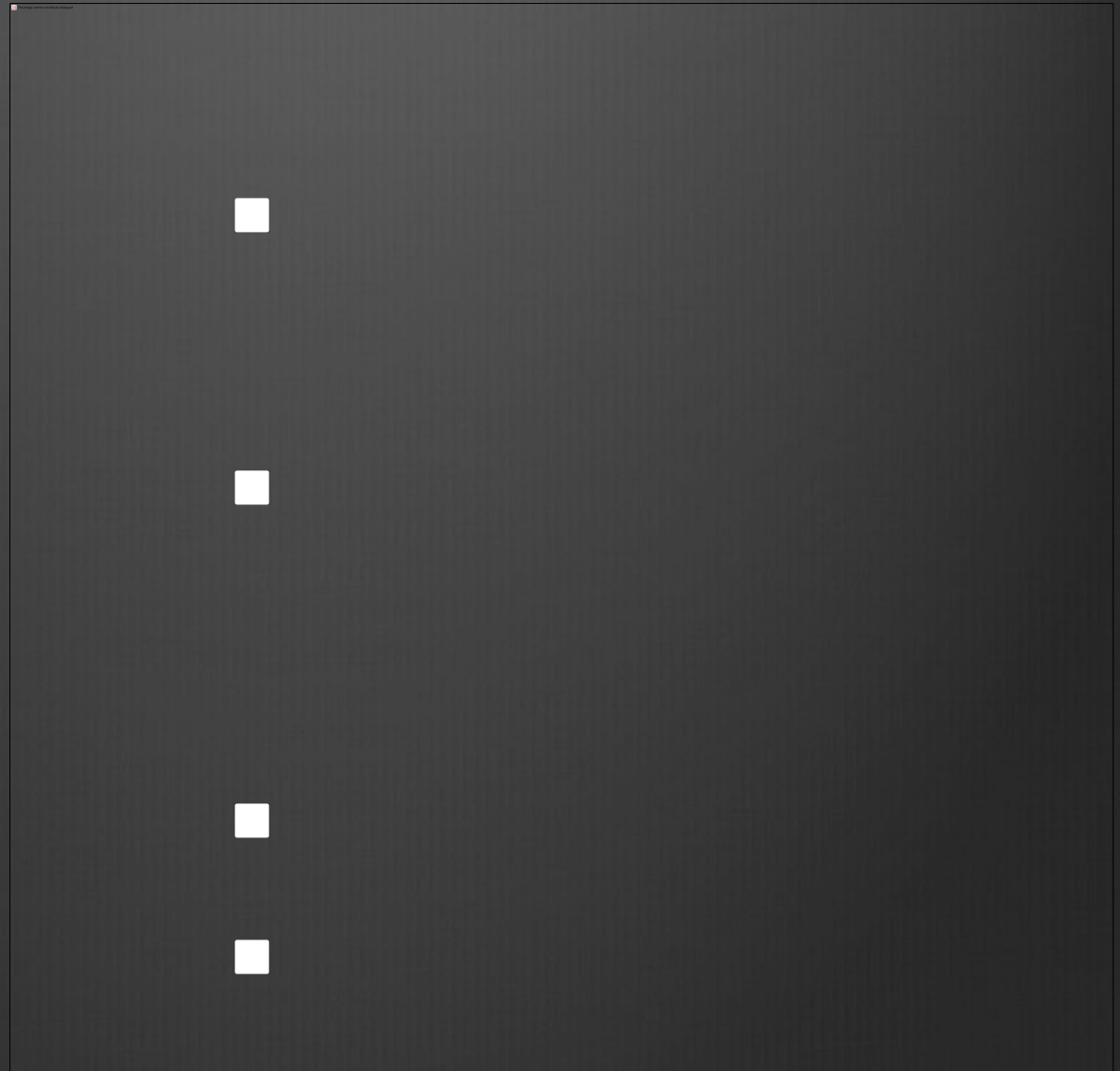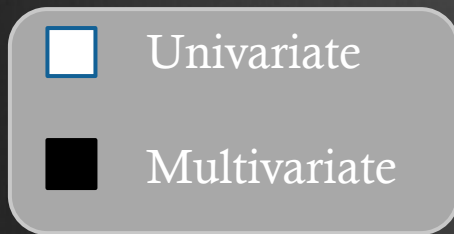
Inhibitor risk in PUPs: a meta-analysis

- Aim of the study

  - To produce an updated systematic review of the evidence regarding the role of PD versus R factor concentrates in modulating inhibitor incident rate

  - To investigate the role of study- and patient-level characteristics on the estimated effect

Results

STUDY SELECTION
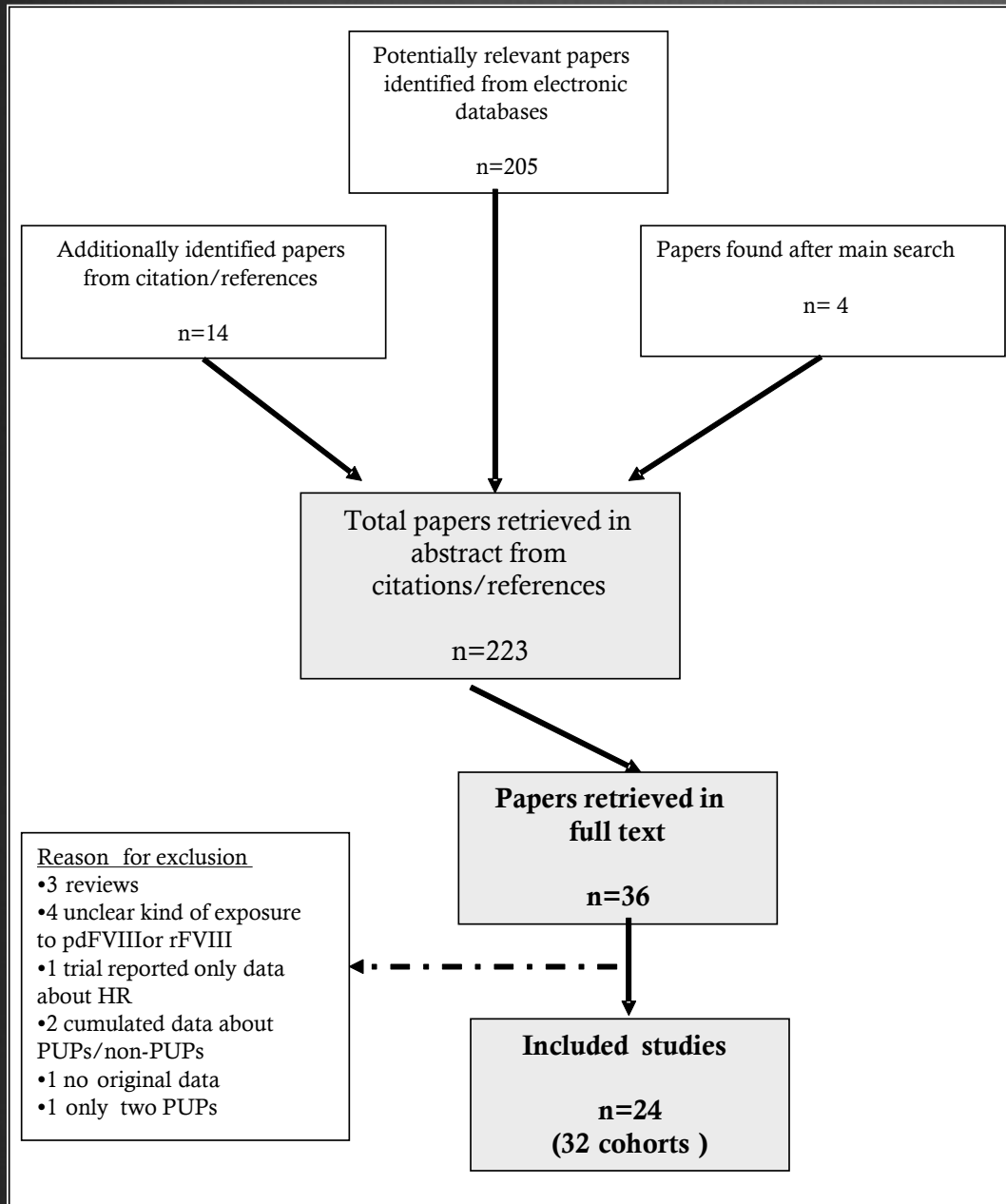
17 pdFVIII cohorts
15 rFVIII cohorts

19 prospective cohorts
13 retrospective cohorts

2094 pts / 420 inhibitors

+13 over Wight and Paisley

Pooled Analysis of Single Arm Studies
(Pooled incidence rates)

pdFVIII	rFVIII	P value (Cochrane Q)
14.3 (10.4-19.4)	27.4 (23.6-31.5)	<0.001

Iorio A *et al. JTH* 2010; 8: 1256–65.
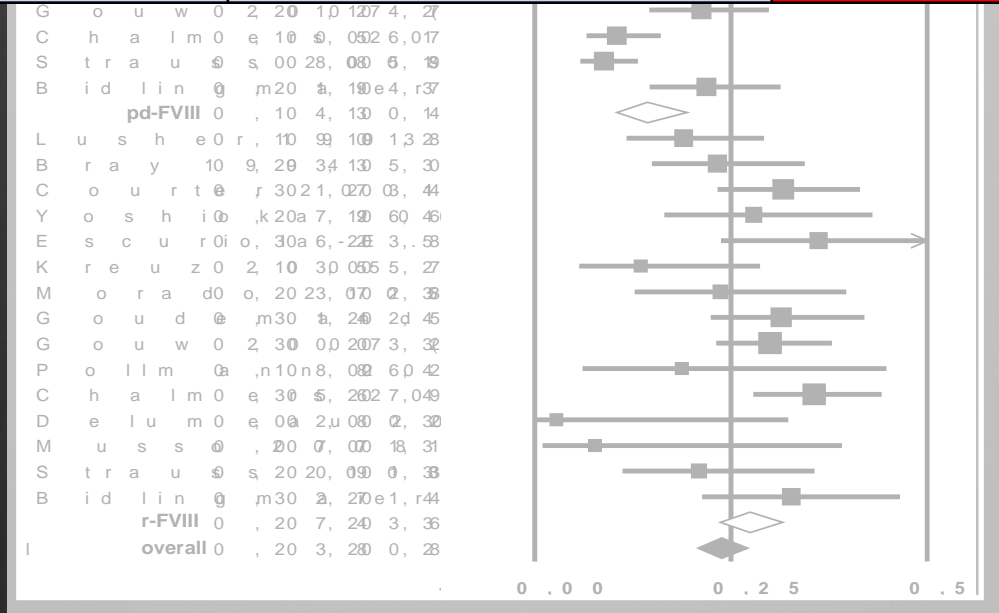
ANOVA

	F	Prob > F	Adjusted R^2
Univariable Models			
kind of concentrate	17.51	0.0002	0.35
study design	7.96	0.0248	
Multivariable Model			
MODEL	7.26	0.0123	0.80
kind of concentrate	0.26	0.6287	
study design	0.08	0.7903	
kind of conc*test freq	0.41	0.5445	
Kind* of conc*study period	0.25	0.6355	
Kind of conc*FUP	0.93	0.3721	
study design * test freq	2.75	0.1485	
study design * study period	0.08	0.7914	
study design * FUP	-	-	

Iorio A *et al. JTH* 2010; 8: 1256–65.

Meta-regression
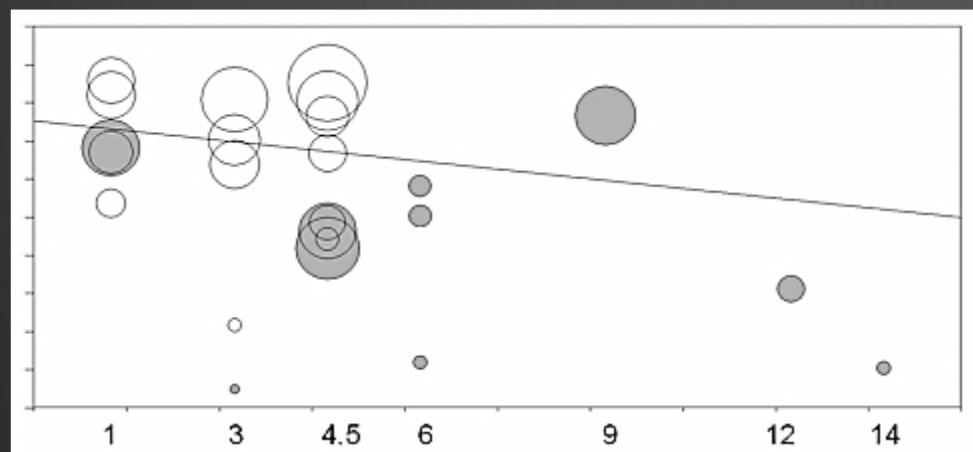
a) **Testing frequency (months)**

White = rFVIII

Grey = pdFVIII
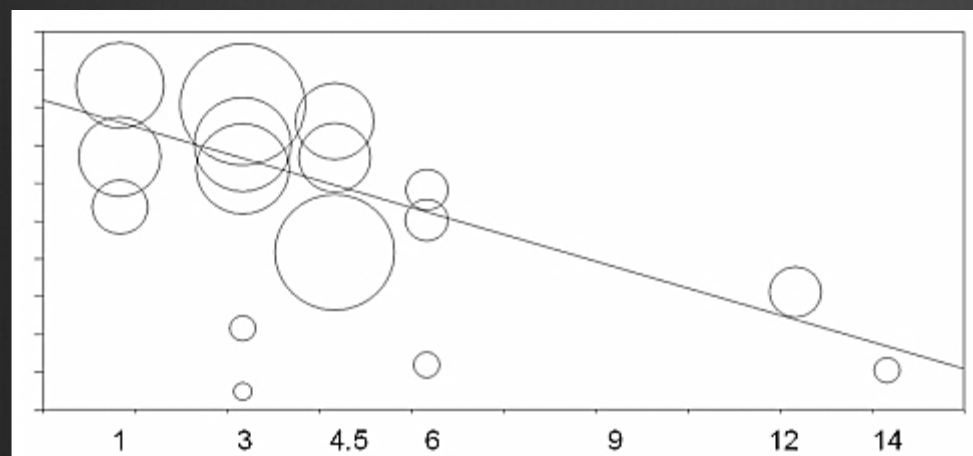
b) **Testing frequency (months)**

Only prospective studies

Y-axis shows the logit of the incidence rate of inhibitor. Each bubble represents a single study, the diameter being inversely proportional to the variance of the study.

Iorio A *et al. JTH* 2010;8:1256–65.

EAHAD

COLLABORATIVE GROUP
ON TREATMENT RELATED INHIBITOR RISK

Predictors of inhibitor development in Hemophilia A previously untreated patients: the role of factor concentrate type.

An individual patient data meta-analysis.

Study design

Pooled cohort of consecutive patients from 6 Hemophilia Centres (5 European, 1 Israeli)

284 PUPs born between 1967 and 2011

Moderate-Severe[1] Hemophilia A

Treated with pdFVIII or rFVIII concentrates, with high-dose[2] or low-dose regimen

Followed up until =>200 ED

[1]Baseline FVIII level ≤ 0.05 IU/dl
[2]Median single dose received within 8 to 12 weeks after therapy start > 30 IU/kg of body weight

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Sunday, July 8 - Thursday, July 12

Study methods

- Cox regression analysis

- CART

- Propensity score matching
  - To adjust a Cox model
  - To calculate the Average effect of Treatment on the Treated (ATT)

Classification and Regression Tree (CART)

	N	F	RHR
pdFVIII	82	1	.04
rFVIII	47	14	1.18
high-dose	155	55	1.59
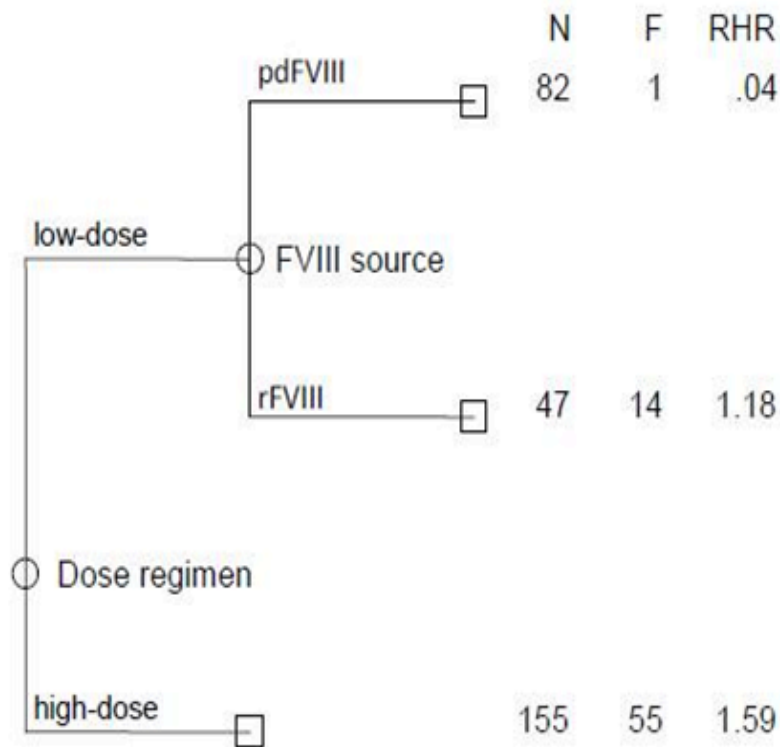
Legend: N, number; F, Failures; RHR, Relative Hazard Ratio.
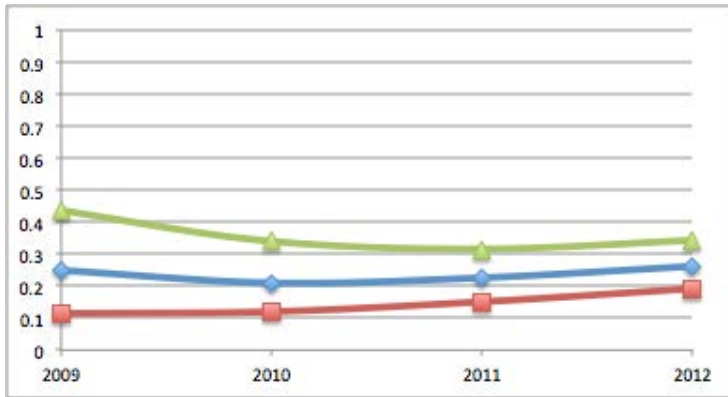
Variables included :

- FVIII source
- dose regimen

Unpublished data omitted

⚙ Analysis results did show that, when adjusting for covariates, there is no difference between plasma derived and recombinant
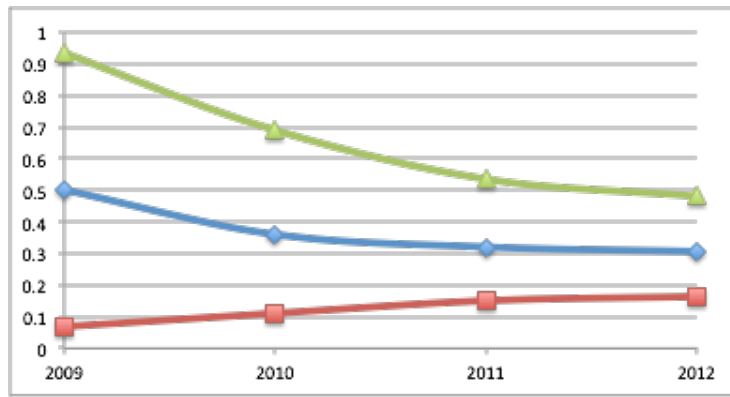
⚙ Paper submitted to Thrombosis and Haemstasis

Inhibitors in PUPs (rate and 95% CI)
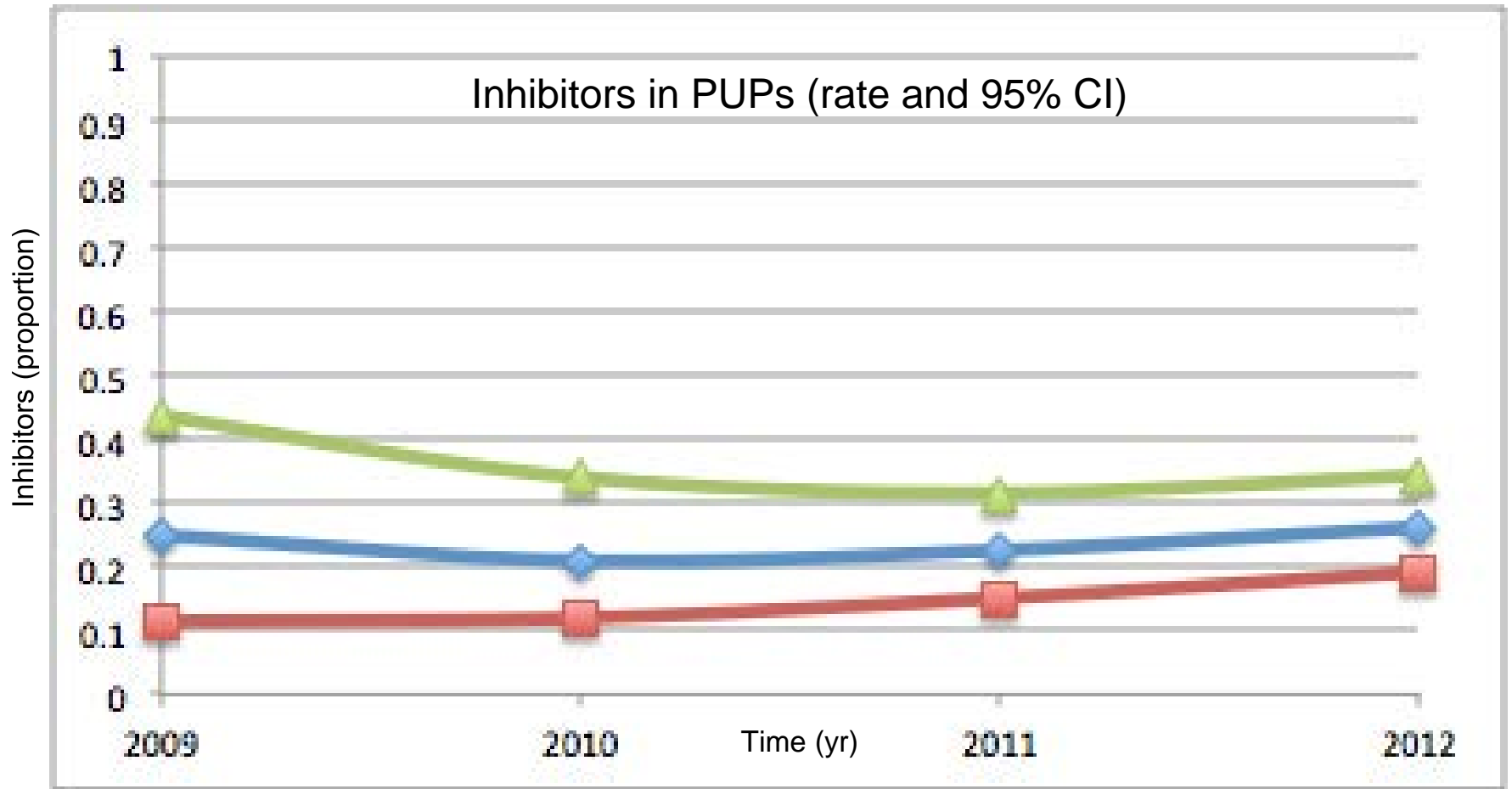
	2009	2010	2011	2012
Cases	8	12	24	37
At risk	32	56	106	141

Data from the EUHASS annual reports to the Investigators

Data from the EUHASS annual reports to the Investigators
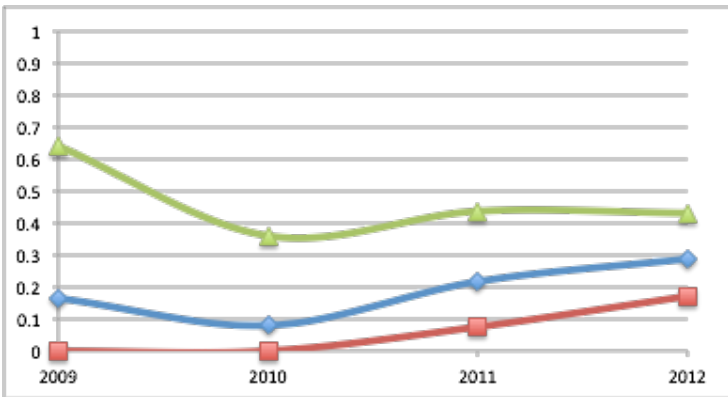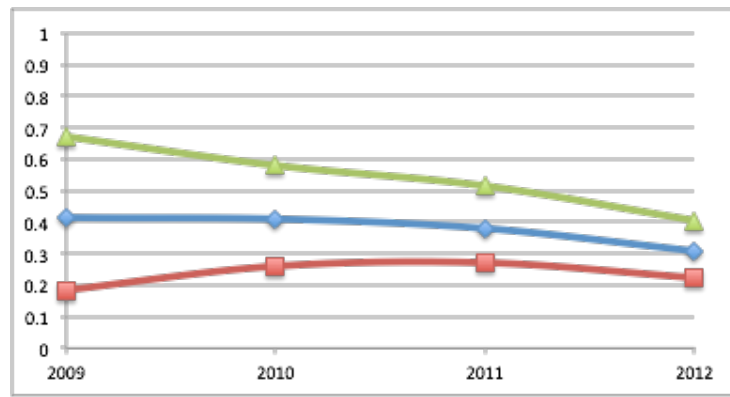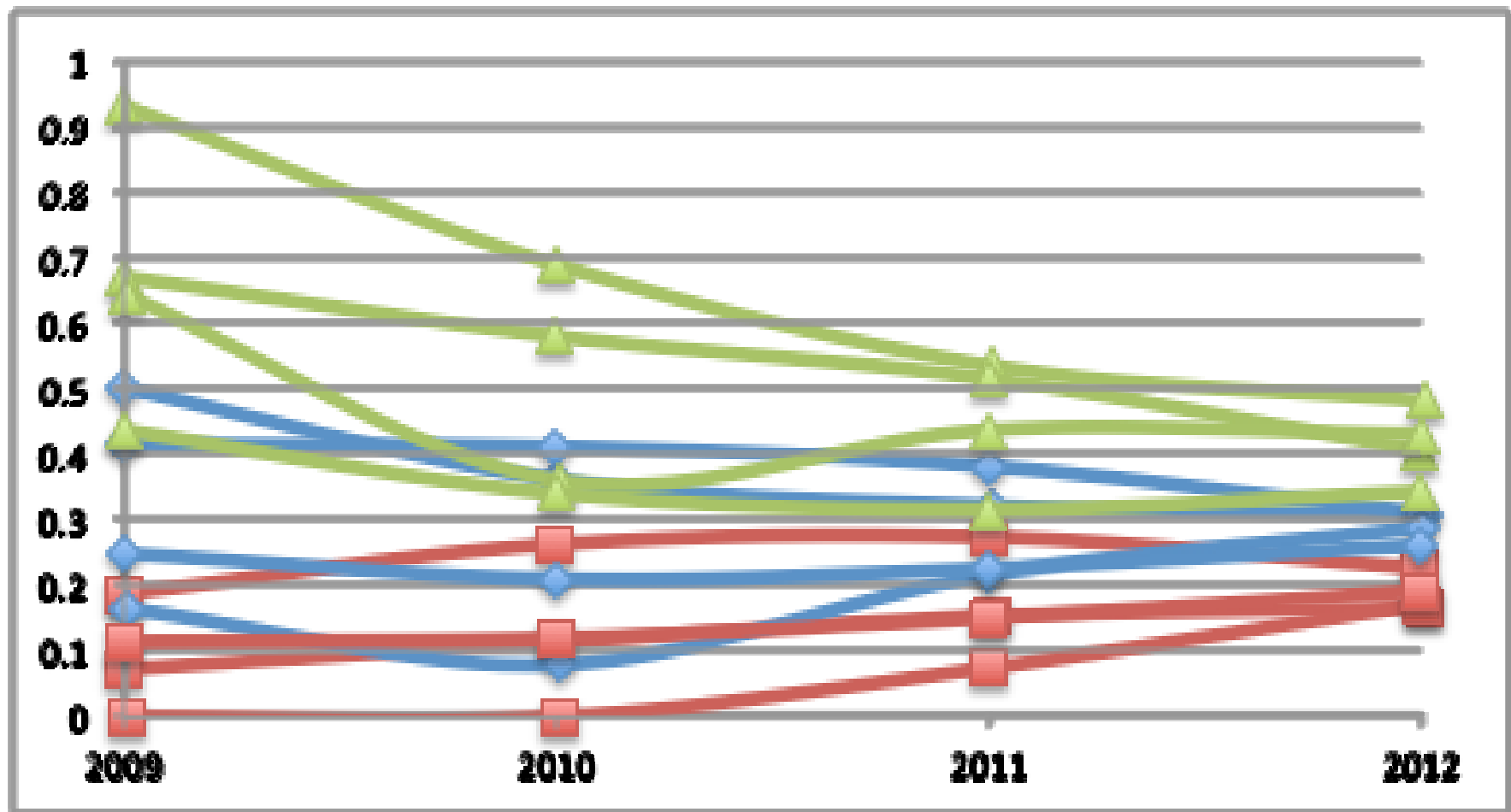
Year	2009	2010	2011	2012
Inhib	8	34	63	96
Exposed	59	121	221	336
Proportion	**0.31**	**0.28**	**0.29**	**0.29**

Data from the EUHASS annual reports to the Investigators

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

Samantha C. Gouw, M.D., Ph.D., Johanna G. van der Bom, M.D., Ph.D.,
Rolf Ljung, M.D., Ph.D., Carmen Escuriola, M.D., Ana R. Cid, M.D.,
Ségolène Claeyssens-Donadel, M.D., Christel van Geet, M.D., Ph.D.,
Gili Kenet, M.D., Anne Mäkipernaa, M.D., Ph.D., Angelo Claudio Molinari, M.D.,
Wolfgang Muntean, M.D., Rainer Kobelt, M.D., George Rivard, M.D.,
Elena Santagostino, M.D., Ph.D., Angela Thomas, M.D., Ph.D.,
and H. Marijke van den Berg, M.D., Ph.D.,
for the PedNet and RODIN Study Group*
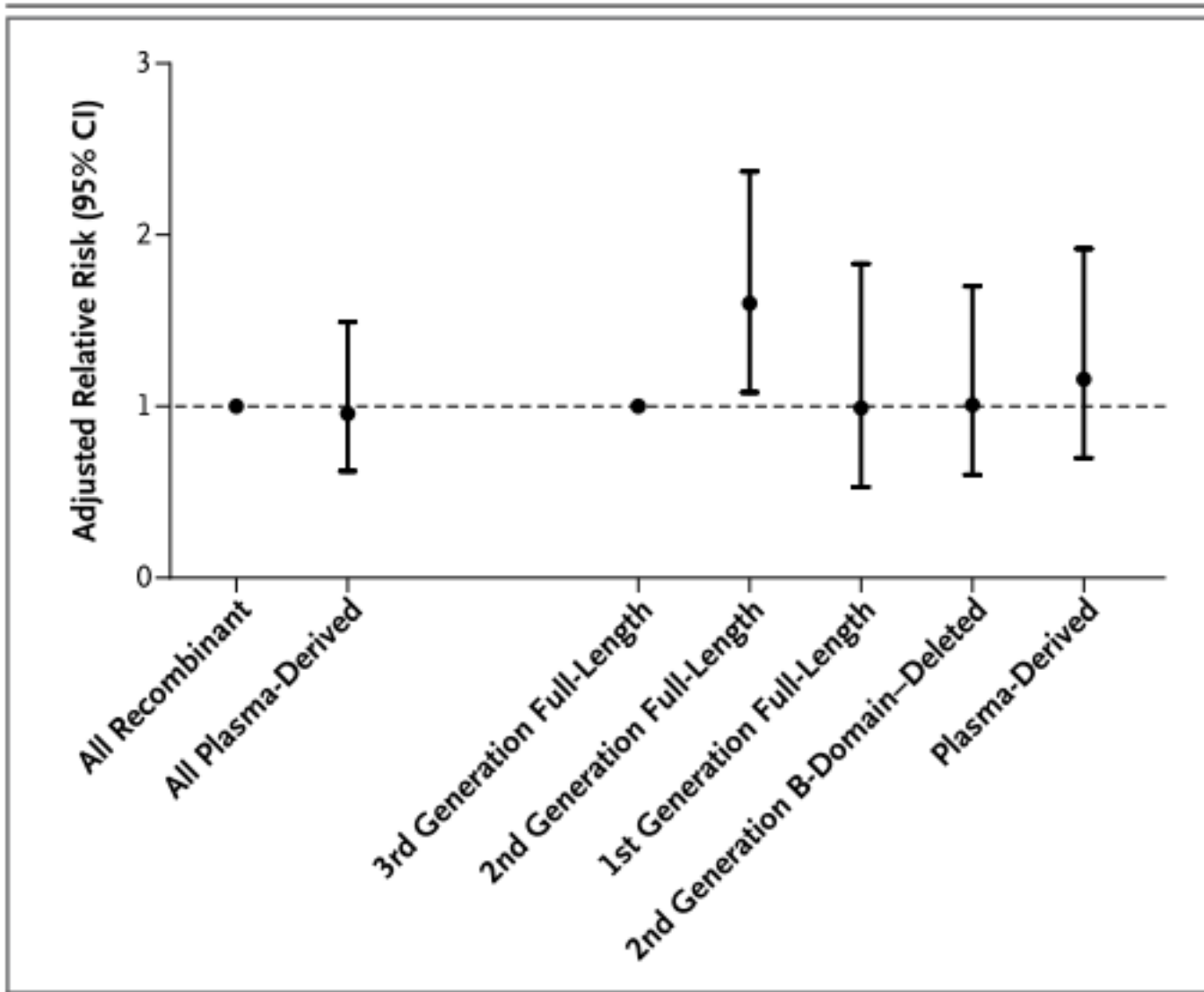

ABSTRACT

The RODIN study

- **Strengths**

  - Naturalistic, large

  - Controlled (parallel, head-to-head)

  - Very high data quality

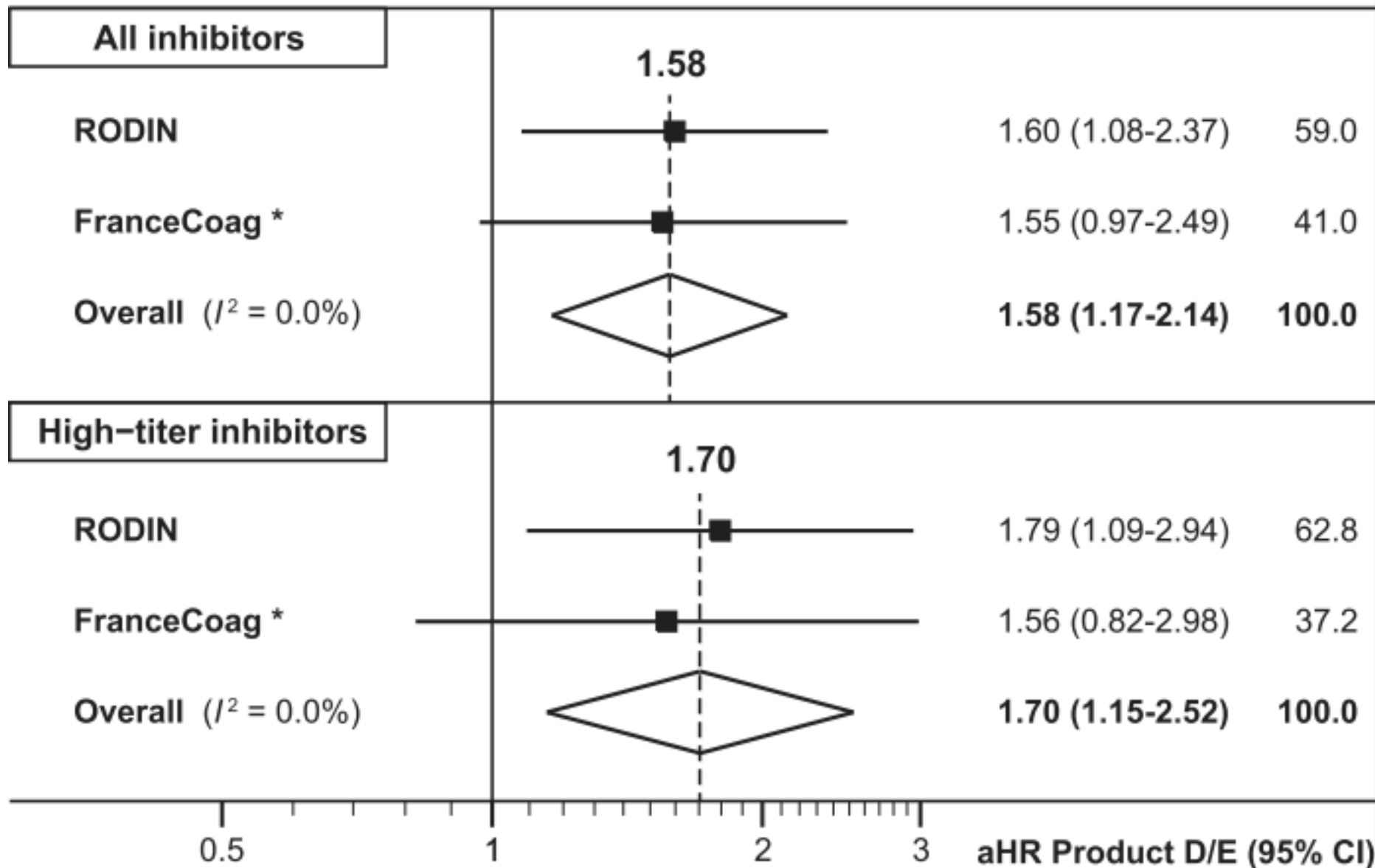- **Weaknesses**

  - Residual confounding

  - Intrinsic to the design

  - Analytical approach

Gouw, SC et al. The New England Journal of Medicine, 368(3), 231–9.

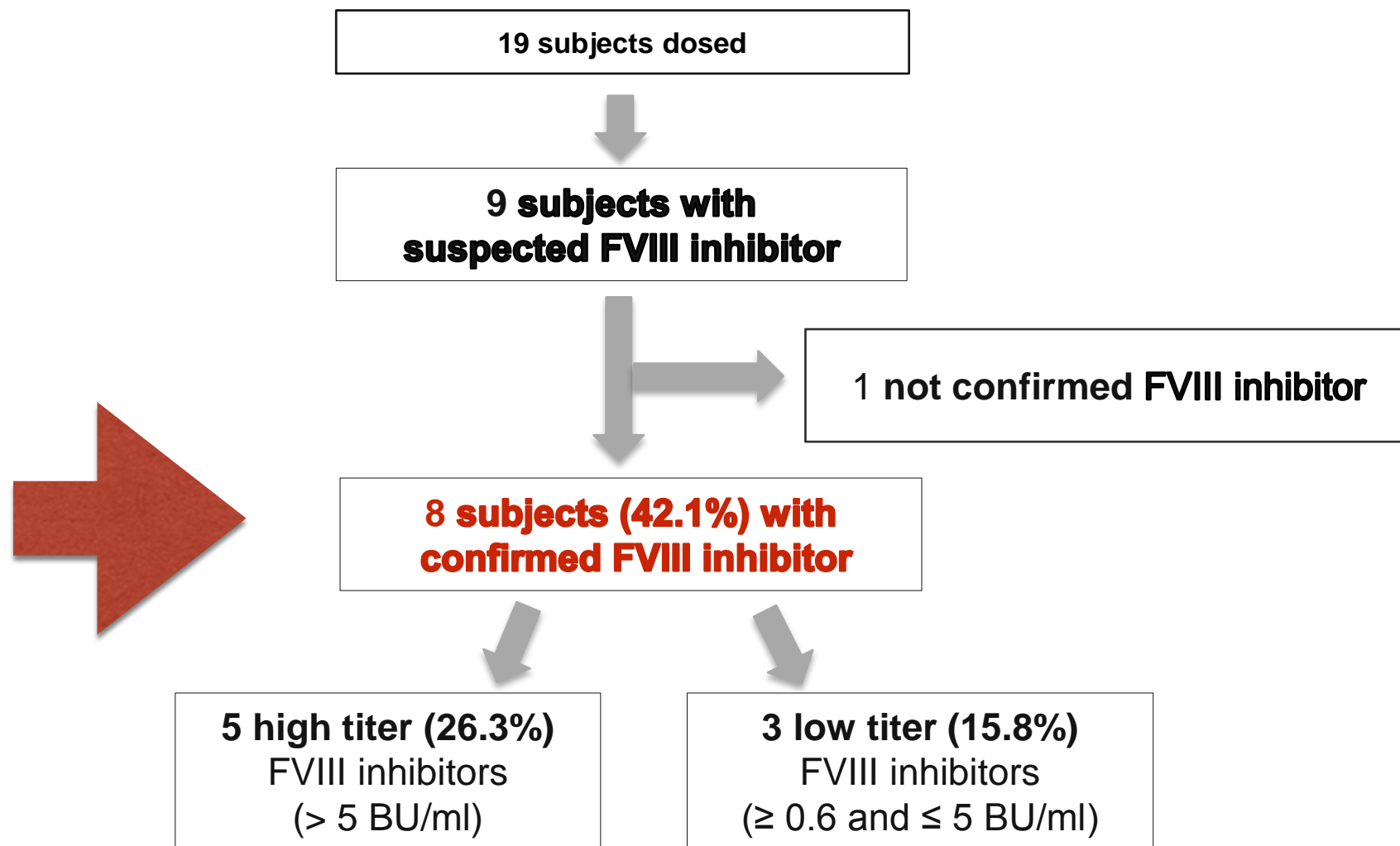| Outcome and study	aHR (95% CI)	Weight (%)
All inhibitors		
1.58		
RODIN	1.60 (1.08-2.37)	59.0
FranceCoag *	1.55 (0.97-2.49)	41.0
Overall ($I^2 = 0.0\%$)	**1.58 (1.17-2.14)**	**100.0**
High−titer inhibitors		
1.70		
RODIN	1.79 (1.09-2.94)	62.8
FranceCoag *	1.56 (0.82-2.98)	37.2
Overall ($I^2 = 0.0\%$)	**1.70 (1.15-2.52)**	**100.0**

0.5   1   2   3   aHR Product D/E (95% CI)

* After exclusion of the 50 boys who were also included in the RODIN study

Unpublished data omitted

- Sensitivity analysis of the French data show that all the effect is due to 3 centers

- These were those observing low inhbitor rate with Kogenate in the early 2000, and likely selected high risk patients to be treated with kogenate

19 subjects dosed

↓

9 **subjects with suspected FVIII inhibitor**

→ 1 **not confirmed FVIII inhibitor**

↓

8 **subjects (42.1%) with confirmed FVIII inhibitor**

5 high titer (26.3%)
FVIII inhibitors
(> 5 BU/ml)

3 low titer (15.8%)
FVIII inhibitors
(≥ 0.6 and ≤ 5 BU/ml)

Courtesy of Guenter Auesrwald: ASH, New Orleans, 2013.

Role of concentrate type: PUPs

Not any important difference

suggested by assessment of

the overall body of evidence

Summary .1

- The risk of inhibitors associated with treatment (source / dose)
  - Cannot be estimated from observational studies without accounting for the effect of confounders
  - The interaction between the candidate predictor and the confounders should always be tested

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Summary .2

- The risk of inhibitors associated with treatment (source / dose)
  - Might benefit from use of sophisticated statistical analysis tecniques, eg propensity score analysis
  - This might:
    - Increase consistency of evidence from imperfect observation
    - Help in better planning future studies

Thank You

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