CaSS | Clinical and Statewide Services

safe | sustainable | appropriate

Current understanding of why inhibitors develop.

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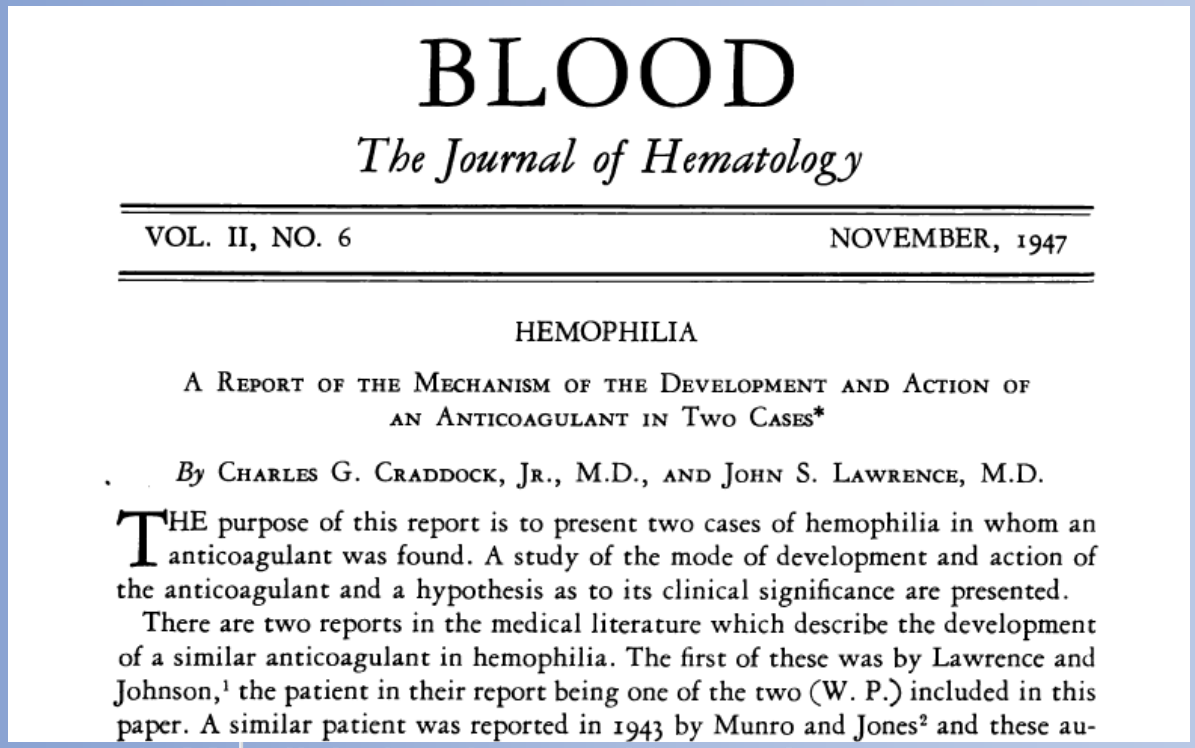
Definitions

- Inhibitor – antibody that neutralises the haemostatic effect of clotting factor (e.g. FVIII and FIX)

- Inhibitor level (titre)
  - Measured in Bethesda units per millilitre (BU/mL)
  - 1 BU/mL is amount of antibody (inhibitor) in 1mL of plasma that will neutralise 50% clotting activity
  - Low titre inhibitor <5 BU/mL
  - High titre inhibitor >5BU/mL

Inhibitors in haemophilia

- First case reports in 1940's
- Development of antibody to infused factor
  - same response body uses to fight infection



BLOOD

The Journal of Hematology

VOL. II, NO. 6 NOVEMBER, 1947

HEMOPHILIA

A Report of the Mechanism of the Development and Action of an Anticoagulant in Two Cases*

By Charles G. Craddock, Jr., M.D., and John S. Lawrence, M.D.

THE purpose of this report is to present two cases of hemophilia in whom an anticoagulant was found. A study of the mode of development and action of the anticoagulant and a hypothesis as to its clinical significance are presented.

There are two reports in the medical literature which describe the development of a similar anticoagulant in hemophilia. The first of these was by Lawrence and Johnson,[1] the patient in their report being one of the two (W. P.) included in this paper. A similar patient was reported in 1943 by Munro and Jones[2] and these au-

Consequences

- Associated with higher morbidity – increased risk of impaired range of movement of joints ***(Soucie JM et al. Blood 2004, 103)***
- Associated with decreased quality of life
- Improved treatment has improved outlook for individuals with inhibitors
  - after 1992 there was no difference in mortality when compared to individuals without inhibitors ***(UKHCDO J Thromb Haemost 2004, 2)***

How often?

- Haemophilia A
  - Severe haemophilia A
    - 30% incidence in rFVIII studies ***(Schwartz et al. NEJM 1990, Bray et al. Blood 1994, Lusher et al. Thromb Haemost 1999)***
    - High titre 40-53% of these
    - Transient (disappearing) 27-55%
  - Mild and moderate haemophilia
    - Only 6% of all inhibitors in haemophilia A
- Haemophilia B
  - 1-2% of patients with haemophilia B have an inhibitor to factor IX

When?

- Inhibitors occur early – 50% before the 15th exposure day.
  - At 50 exposure days risk of inhibitor development is <1%

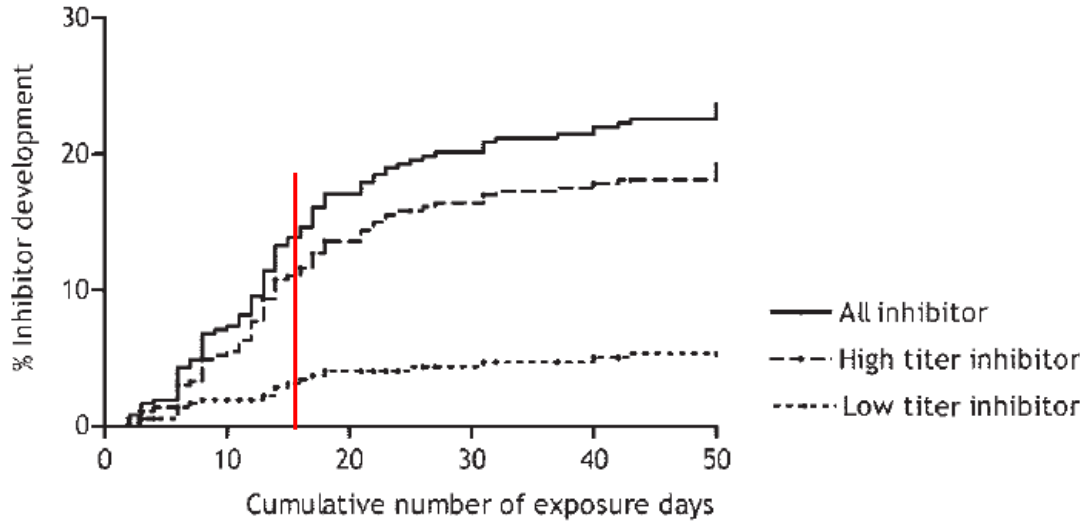
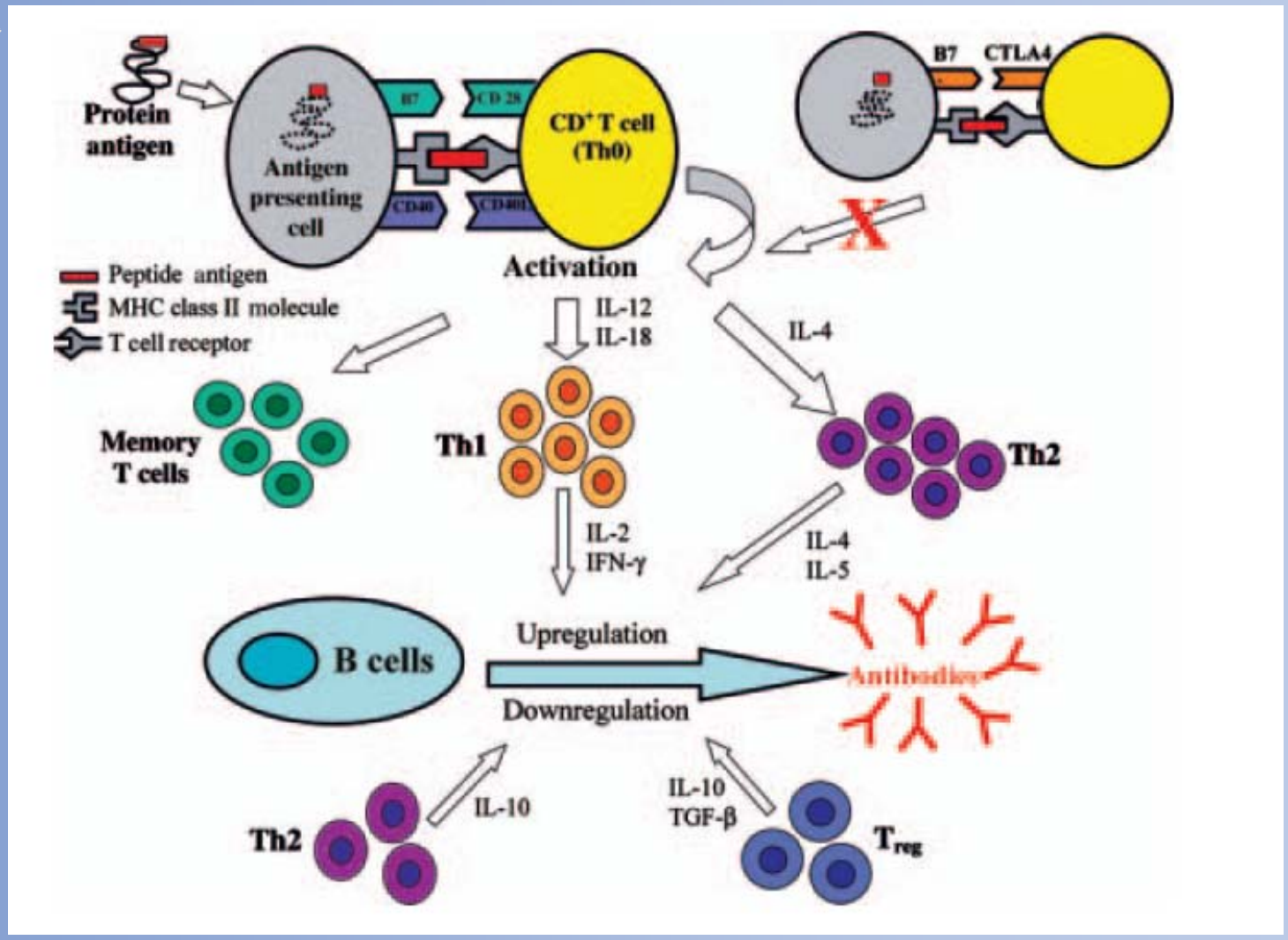


Figure 1. Cumulative incidence of inhibitor development: all inhibitors, and high- and low-titer inhibitors.

(Gouw et al. Blood 2007, 109)

Why?

- Natural response of bodies immune system to presence of a “foreign” protein
  - Complex pathway of interactions
  - Main cells involved:
    - Dendritic cells (present foreign protein to lymphocytes)
    - T cell lymphocytes
    - B cell lymphocytes (produce inhibitor)
  - ? role of danger signal(s)



(Key NS. B J Haem 2004)

Risk factors for inhibitor development

- If we understand why some people develop inhibitors could we prevent or reduce their occurrence?

- Inherited factors are important:
  - 48% risk off developing inhibitor with positive family history
  - compared with just 15% if no family history.

- But other non-inherited factors are important
  - Discordance seen with monozygotic twins

Inherited risk factors

- Immune system (MIBS study)
  - HLA **?**
  - TNF-a (G/**A** at -308)⇑
  - IL10 (134 bp variant of CA repeat in promoter) ⇑
  - CTLA-4 (C/**T** at -318) ⇓
- Factor VIII
  - High risk mutations (large deletions, nonsense mutations and inversions of introns 22 & 1)
  - Specific mutations in mild haemophilia A
- Ethnicity
  - Higher incidence in African Americans ***(Astermark J et al. Haemophilia 2001)***

Non-inherited risk factors

- Age at first treatment — NO
- Intensity of first treatment — YES
  - Surgery (includes port insertion)
  - 5 consecutive days (plus effect of dose of FVIII)
- Breast feeding — NO
  - ***(Gouw et al Blood 2007, Santagostino et al B J Haem 2005)***
- Immunisations/infections — NO
  - ***(Santagostino et al B J Haem 2005)***
- Prophylaxis — Protective
- Product type — ?

Effect of prophylaxis

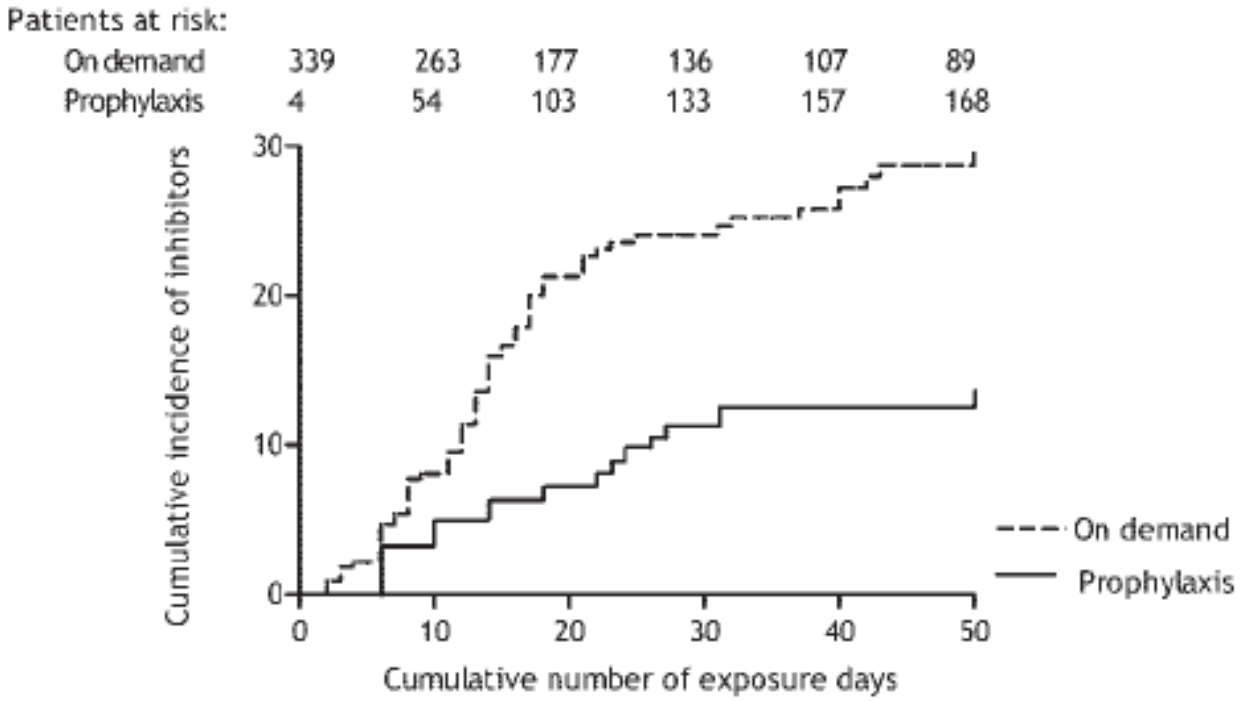


Figure 2. Cumulative incidence of inhibitor development according to treatment regimen: prophylaxis versus on demand.

(Gouw et al. Blood 2007, 109)

Product

- Neoantigens
  - Outbreak of inhibitors in Netherlands and Belgium in multiply transfused patients approx. 5% developed inhibitor ***(Rosendaal et al. Blood 1993)***
  - ? implications for new rFVIII molecules
- Product type
  - Unresolved issue
  - Quality of data – prospective studies needed.

A systematic review

(Wight & Paisley Haemophilia 2003)

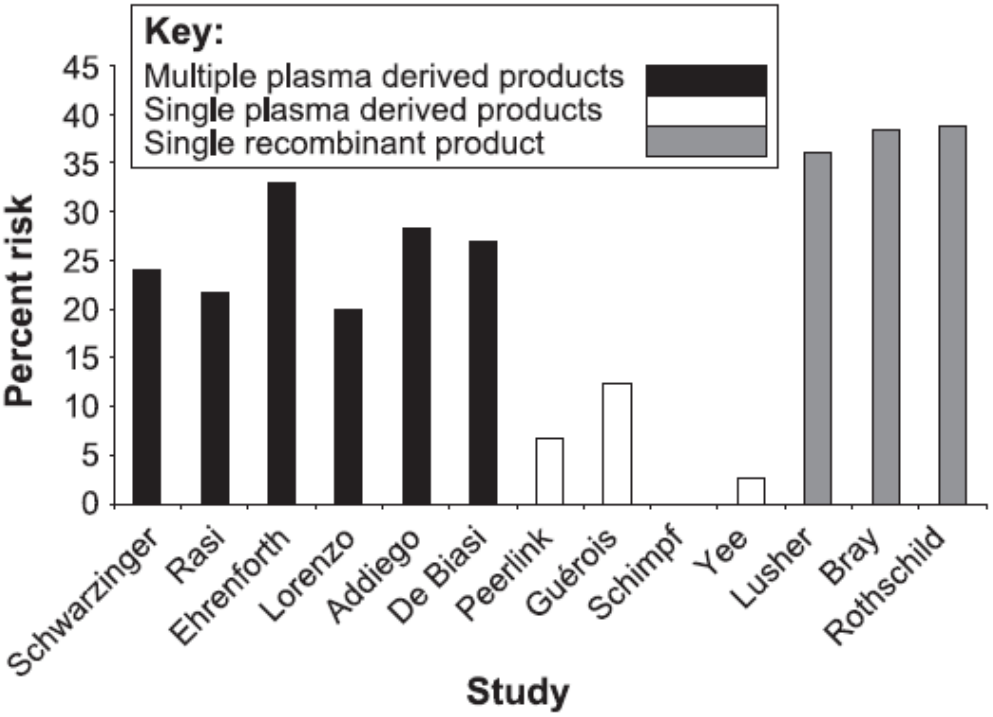
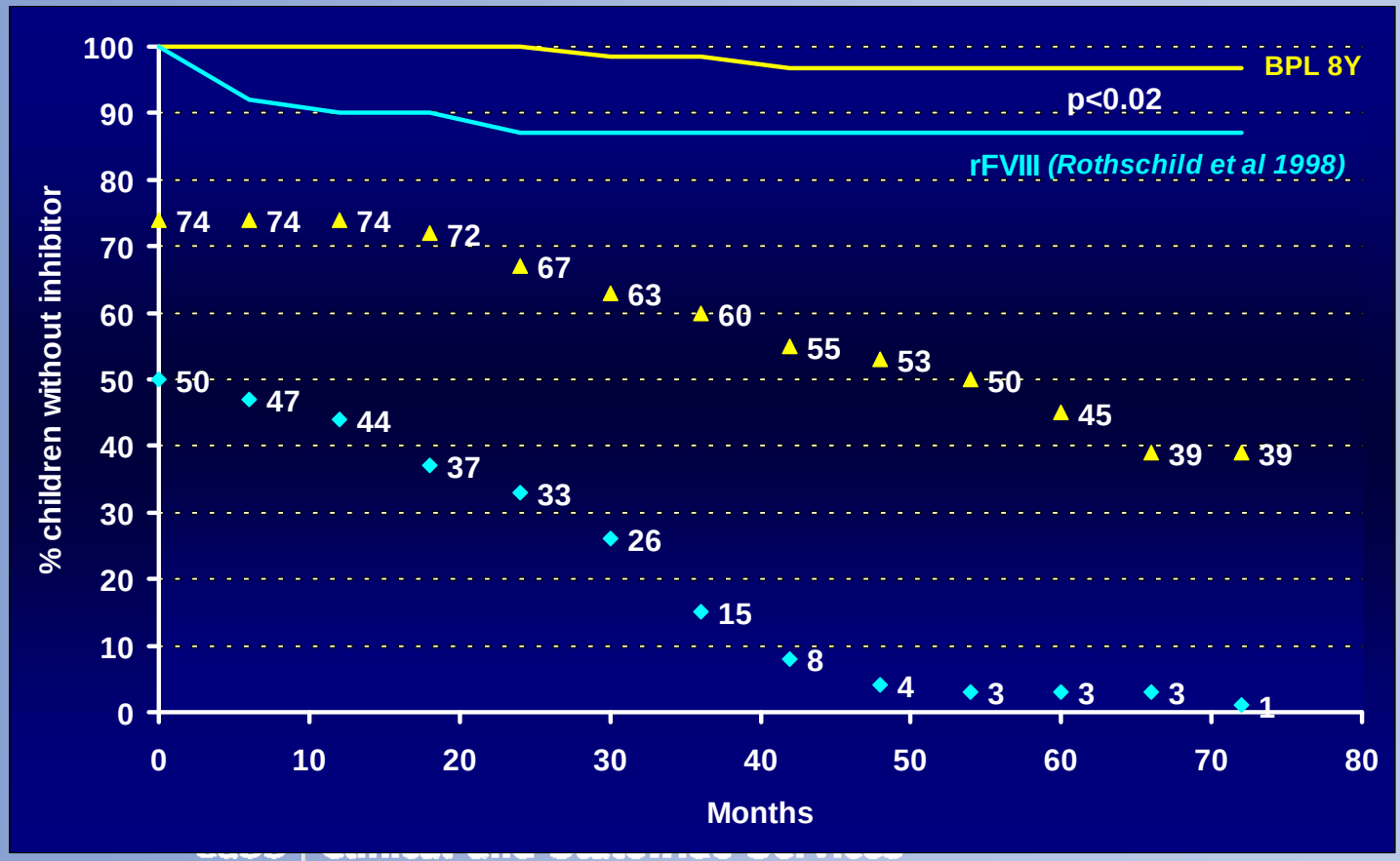


Fig. 5. Cumulative risk of inhibitor – all inhibitors.

UK experience with BPL 8Y

- **Inhibitors:**
  - **2 high titre inhibitors (2.7%) – 96.8% inhibitor free (compared with 87% for rFVIII) at 48 months**
  - **1 low titre inhibitor**



Product type

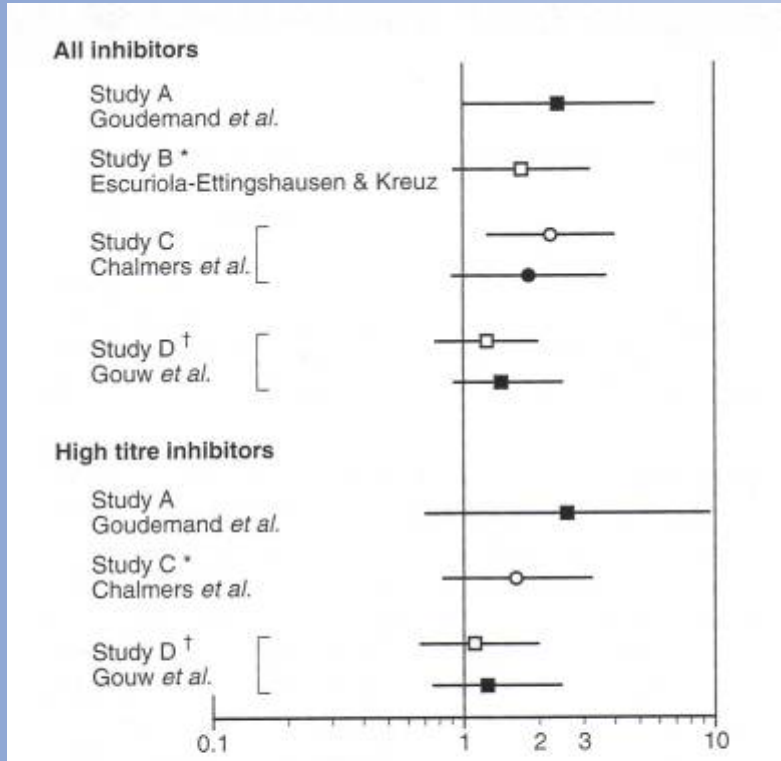


Fig. 1. Measurements of risk (rFVIII vs. pdFVIII) and 95% confidence interval drawn from the four observational studies comparing inhibitor incidence in previously untreated patients with severe hemophilia A. □ relative risk (RR); ■ adjusted RR; ○ odds ratio (OR); ● adjusted OR. *Crude RR or OR calculated according to the hypothesis of equal follow-up time per subject. †Transformed RR (with inverse function) from article of Gouw *et al.* [4].

Calvez et al. J Thromb Haemost 2008

Can we modify risk?

- Models for predicting risk have been proposed
  - Positive FH, high risk mutation and >5 days therapy
- What could be modified?
  - Intensity of initial therapy – dose and duration
  - Early prophylaxis
    - Note - US study of on demand *vs* prophylaxis (NEJM 2007)
    - Inhibitors - 2/32 prophylaxis *vs* 0/33 on demand (p=0.24)
  - Product type (?)

Attempt to modify risk

- Canadian study ***(Rivard et al. Haemophilia 2005)***
  - Try to postpone FVIII exposure until after 2 years (based on observations of age at first treatment)
  - Used rFVIIa on demand
  - 11 infants
  - Only 3 had first exposure to FVIII delayed to > 2 years of age
  - 5 of the 11 developed inhibitors

Summary

- Inhibitors remain a major complication of haemophilia.
- Considerable progress has been made in understanding risk factors for inhibitor development
- It may be too easy to modify practice without waiting for studies to:
  - confirm benefits or
  - clarify risk factors (e.g. product type)
- What about Australian cohorts on plasma derived and recombinant FVIII?