Iceland Liechtenstein Norway grants

"Working together for
a green, competitive and inclusive Europe"

"HE-RO-IS strategic cooperation in hematology"

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Curricula in hemophilia

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The concept of prophylaxis

Prophylaxis (revised definition consensus in London 2002)

- Primary prophylaxis determined by age
  - Long-term continuous treatment started before the age of 2 years and *prior to any clinically evident joint bleeding*
- Primary prophylaxis determined by first bleed
  - Long-term continuous treatment started *prior to the onset of joint damage* (presumptively defined as having had no more than one joint bleed) irrespective of age
- Secondary prophylaxis
  - Long-term continuous treatment not fulfilling the criteria for primary prophylaxis

Berntorp et al 2003

Use of prophylaxis in Europe

Haemophilia 2005

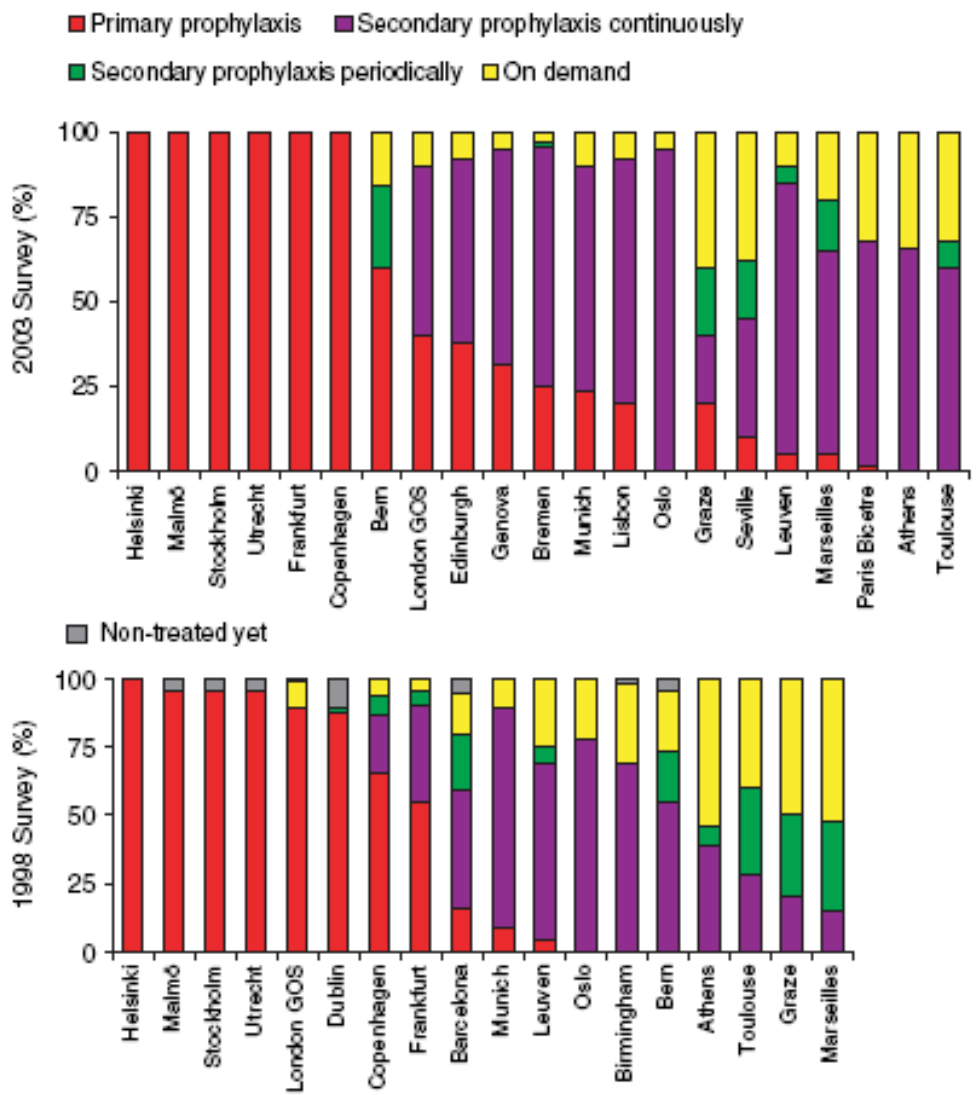


Fig. 1. Therapeutic regimen patterns in boys treated for severe haemophilia in 22 European centres: comparison of the 1998 and 2003 surveys. Therapeutic models according to the definitions acknowledged by the PedNet [26]: prophylactic continuous (long-term) treatment includes primary prophylaxis (starting before 2 years or after the first joint bleed); secondary prophylaxis type A (starting after 2 years, or after two joint bleeds or more); secondary prophylaxis type B is defined as periodic prophylaxis, because of frequent bleeds.

Use of prophylaxis United States

- 48 % of patients with severe hemophilia A and 39 % with severe hemophilia B receive prophylaxis (CDC 2008)

Use of prophylaxis Worldwide

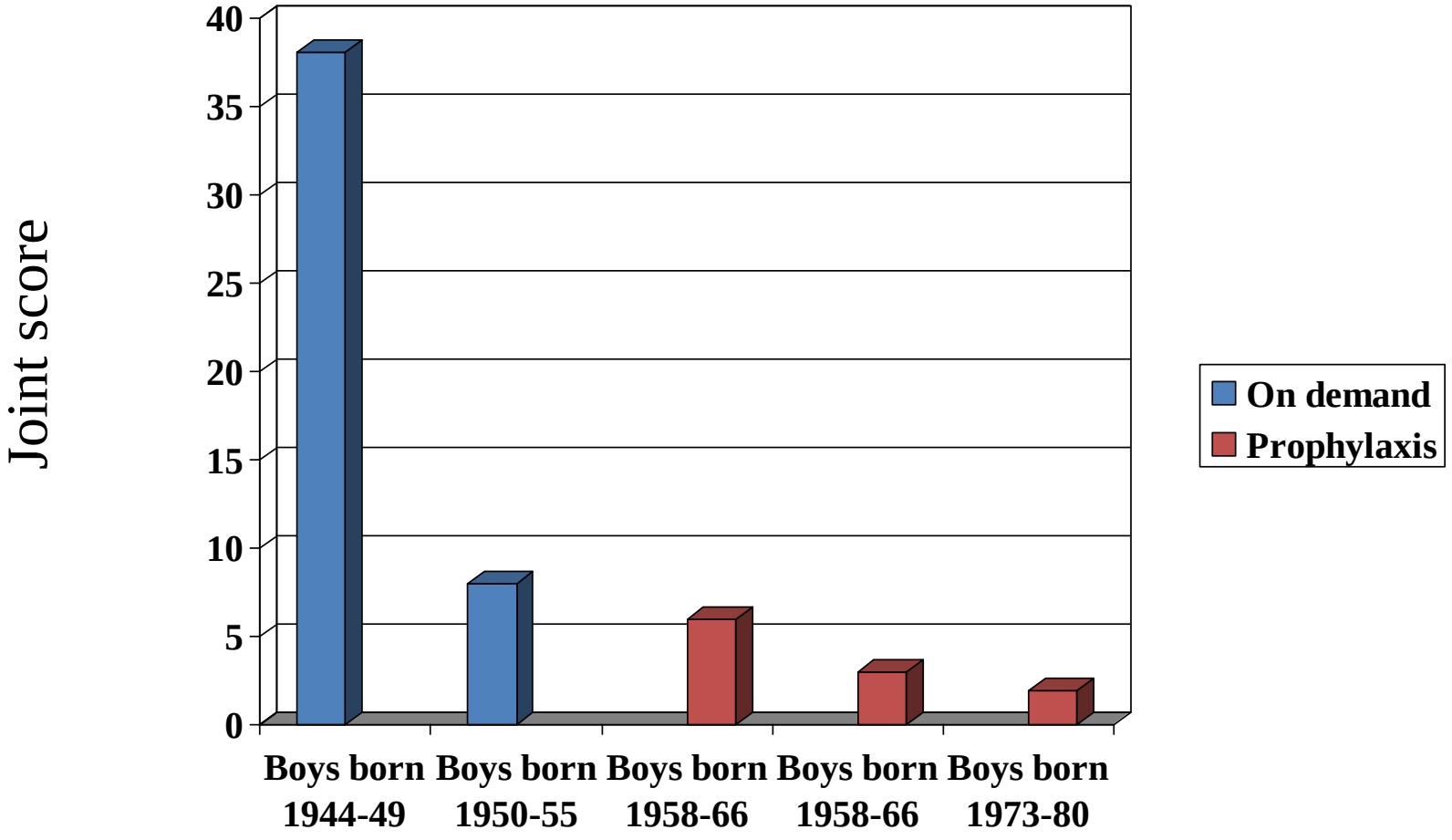
- 19 % receive “primary” prophylaxis
- 54 % treated on demand

Geraghty et al 2006

Rationale behind prophylaxis

Ramgren (1962) and Ahlberg (1965) showed that hemophiliacs with factor VIII or IX levels above 1% of normal rarely develop severe arthropathy. The possibility to convert severe hemophilia to a mild form by prophylaxis was hypothesized.

Orthopedic joint score at different age groups in patients with or without prophylaxis



Nilsson et al 1992

Conclusion Swedish experience

- If started early, high-dose prophylactic treatment, i.e 3000-5000 IU/kg annually, maintaining a level of at least 1%, virtually eliminates bleeds and joint defects
- Side effects not more frequent than for on-demand treatment
- Patients can live normal lives, both physically and socially

Is prophylaxis superior to treatment on demand?

Yes, definitively

Treatment Strategies for Severe Hemophilia: On demand versus prophylaxis ”Norway vs. Sweden”

A comparison of two different strategies during 11 years in 61 patients treated on-demand and 95 treated with prophylaxis

Treatment data 1989-1999

- All haemophilia related treatment costs within the health care sector
  - Factor concentrate consumption
  - Doctors' and nurses' visits
  - Diagnostic procedures
  - Hospitalisations and invasive procedures
- Cost for haemophilia-related resource use outside the health care sector
  - Loss of productive time (incl. relatives)
  - The use of special equipment
  - Adaptation of work place and domicile

Total number of surgical procedures

	On Demand n=61	Prophylaxis n=95
Arthrodeses **Prostheses**	63	7
Synovectomies	25	2
Miscellaneous minor surgeries including tooth extractions	33	23
Port implantations/extractions		16
Total number of procedures 1989-1999	121	48
Number of procedures divided by group size	1.98	0.51

On demand vs. Prophylactic treatment in Norway and Sweden. General Conclusions.

- Strong support for prophylaxis
  - Less resource use (surgery, loss of production etc.) indicates better quality of life. This finding corroborates with other studies
  - Willingness-to-pay exceeds costs for both treatments

”The joint outcome Study”

- Open-label, prospective, randomized trial in children
- 25 U/kg FVIII every other day vs. ≥ 3 infusions totaling ≥ 80 U/kg FVIII given on-demand
- Primary outcome: proportion of boys in each arm with bone or cartilage damage (MRI and plain-film radiography)
- Followed between 12 and 30 months until age 6 years
- Normal joints at entry and ≤ 2 bleeds in any one joint

Manco-Johnson et al 2007

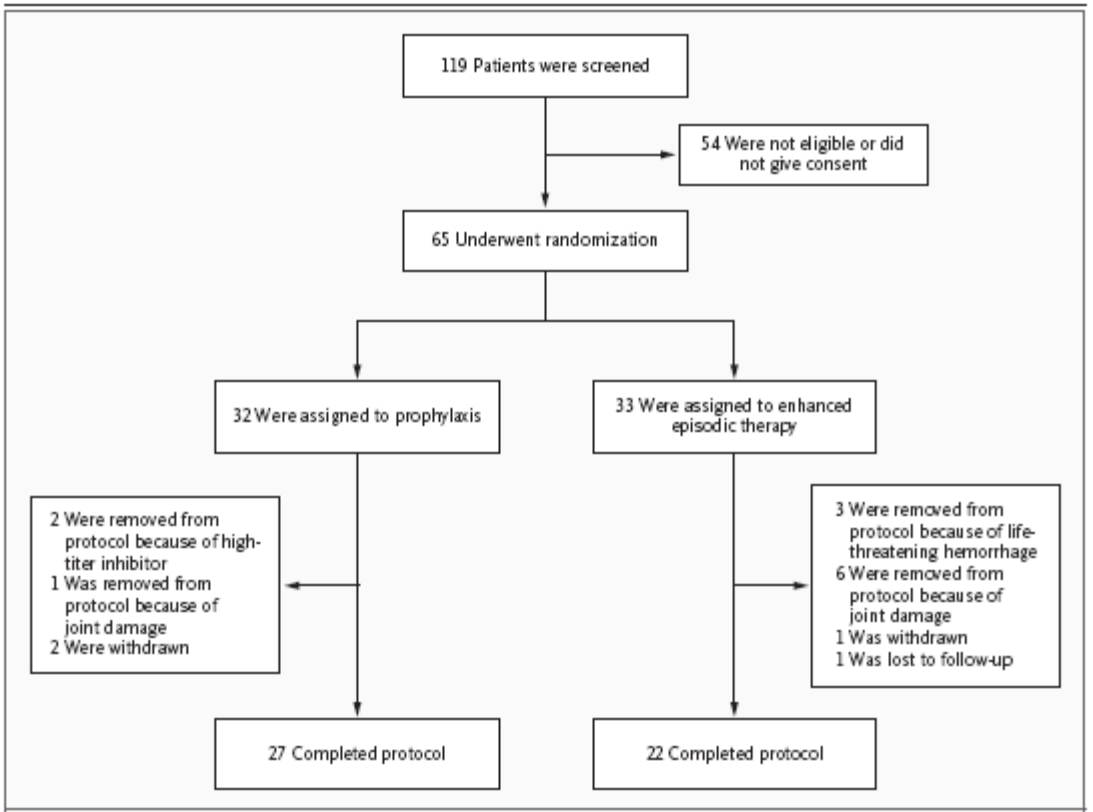
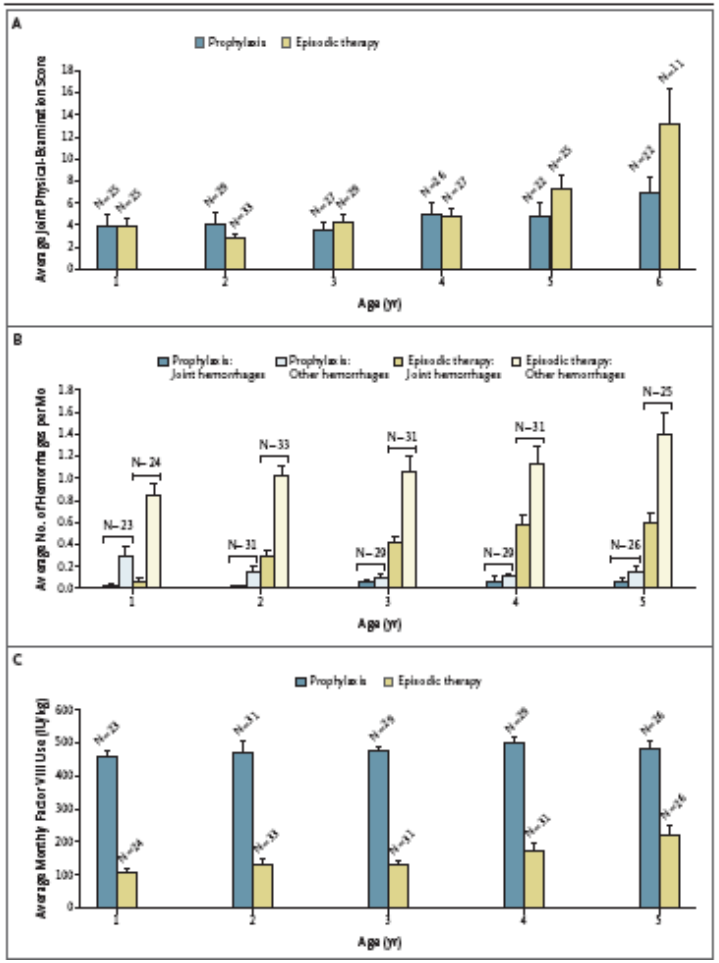


Figure 1. Randomization and Follow-up of Study Participants.

Although just 27 boys in the prophylaxis group and 22 boys in the episodic-therapy group remained on the protocol until the age of 6 years, primary outcome data were available for boys who were removed from the protocol before the age of 6 years.

Manco-Johnson et al 2007



PE score

bleeds

consumption

Manco-Johnson et al 2007

Conclusions Joint Outcome Study

Conclusion: prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A

Further evidence

Reference	Study design	N	Duration of PX	Median no. of bleeds px vs. on demand
Liesner et al 1996	Retrospective, noncomparative	27	2.5 y	1.5/y vs. 14.7/y
Fischer et al 2002	Retrospective, comparative	PX=49; On-demand=106	12.7 y	2.8/y vs. 11.5/y
Gringeri 2002,2003	Randomized, prospective, comparative	PX=21; On-demand=19	NR	0.24/month vs. 1.3/month

Prophylaxis

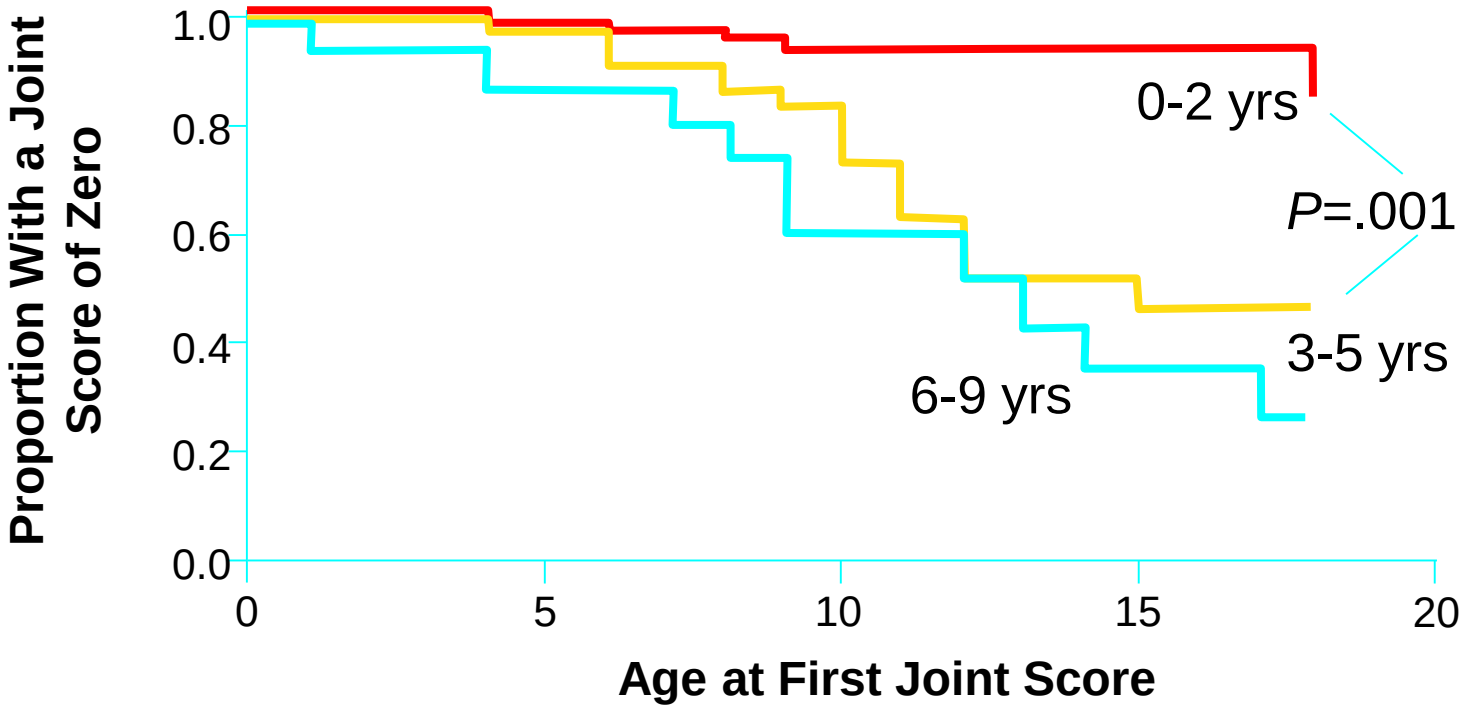
Unresolved issues/problems:

- When to start?
- How to dose?
- When (if) to stop?
- How to evaluate?
- Convenience
- Economy

Starting prophylaxis – the dilemma of timing

- Not all patients with severe hemophilia develop arthropathy (Aledort et al., 1994; Aznar et al., 2000)
- Only a few joint bleeds may cause damage (Kreuz et al. 1998)
- Three hemarthrosis cause chronic joint changes in a murine hemophilia A model (Hakobyan et al., 2005)
- Number of clinical hemarthroses correlates weekly with MRI outcome (Manco-Johnson et al 2007)

When to Start: The Swedish Experience



Conclusion: Prophylaxis should be started in the first years of life, before age 3.

Astermark et al. *Br J Haematol*.1999;105:1109-1113.

Dosing strategies

- Dutch regimen (intermediate dose)
- Traditional Swedish regimen (high dose)
- Canadian regimen (dose escalation)
- Pharmacokinetic (Swedish) dosing

Dose regimen comparisons

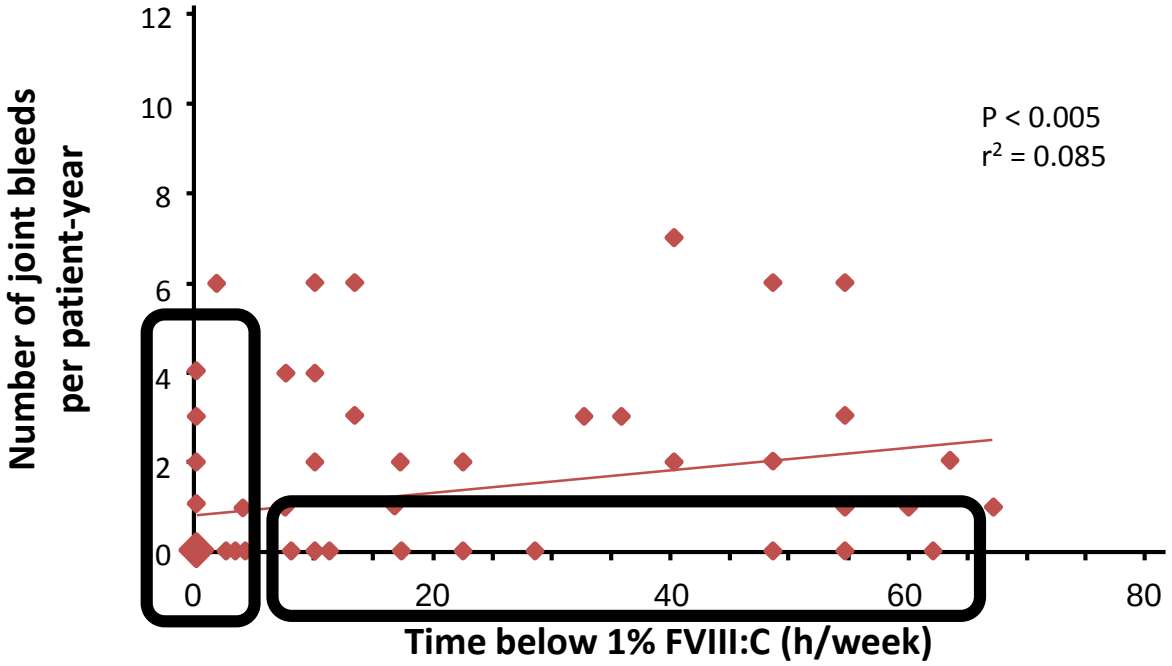
	Convenience	Overall efficacy	Cost
Dutch	+/-	+	-/+
Swedish	+/-	++	--
Canadian	+	+	+
PK	-	+++	+++

+ = superior; - = inferior

FVIII level is not a good predictor of bleeding during prophylaxis

- Bleeding phenotype is not only a function of FVIII genotype or FVIII levels
- Dose regimen strategy should be based primarily on clinical response, cost considerations and convenience, and not strictly on FVIII values

Number of joint bleeds per year in patients with joint score 0 (WFH/Gilbert) as a function of predicted time below 1% VIII:C

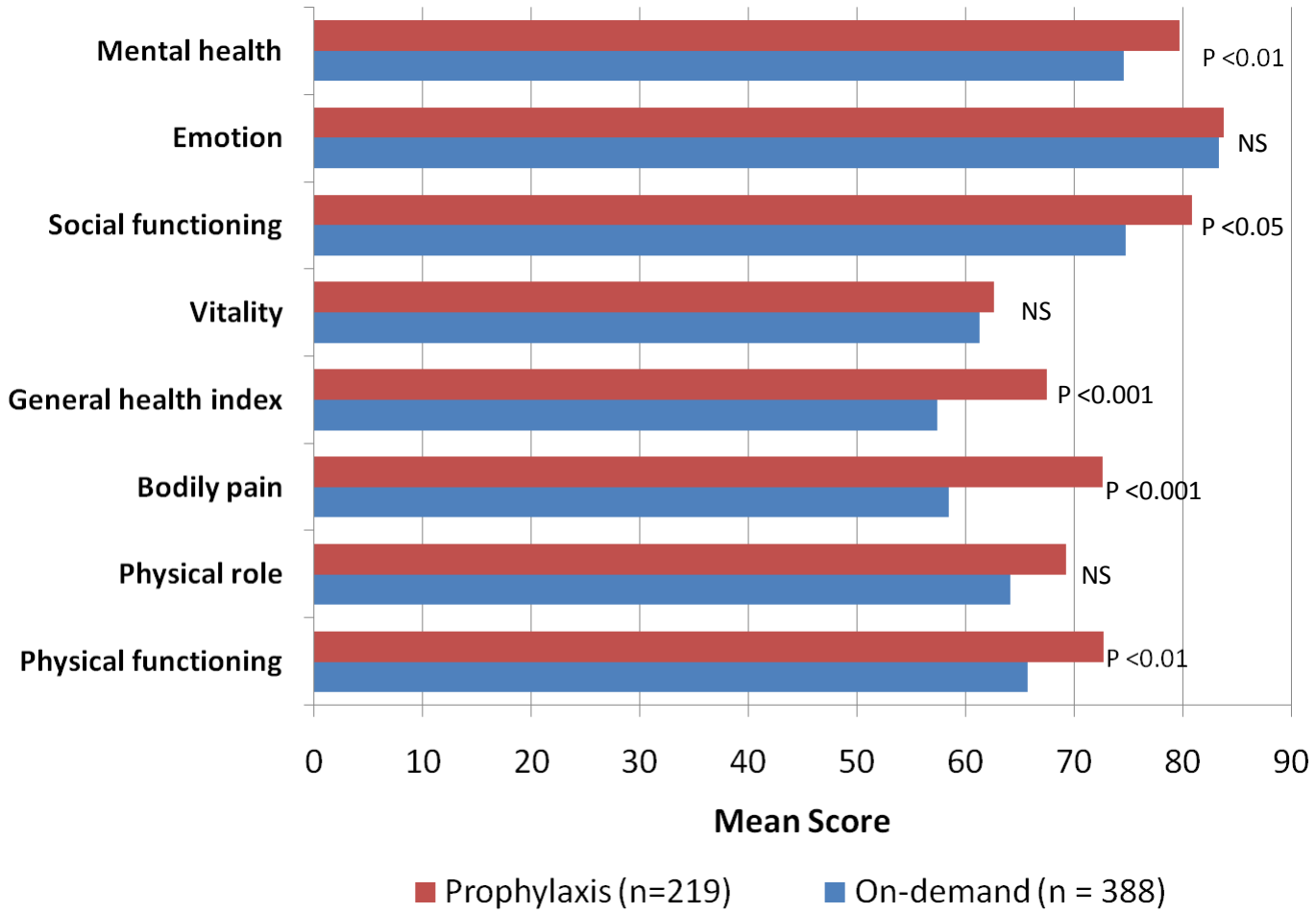


Ahnström et al . Haemophilia 2004 Nov;10(6):689-97

Assessment of prophylaxis in hemophilia – important for optimized cost-effectiveness

- Registries
- Pharmacokinetics
  - Survival studies
  - Computerized dose simulations
- Physical score
  - WFH score
  - HJHS
- Functional score
- Imaging score
  - Not compulsory
    - Pettersson score
    - MRI score
    - Ultrasound (HEAD-US)
- Health-economy
- Quality of life

SF-36 Severe and moderate hemophilia. HIV neg.

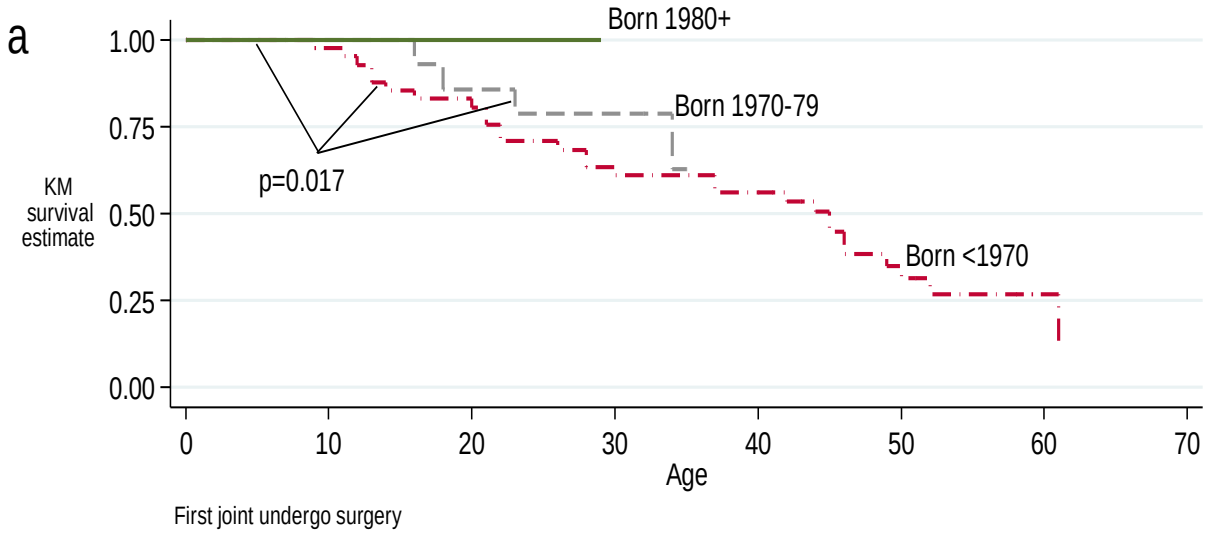


Adopted from Royal et al 2002

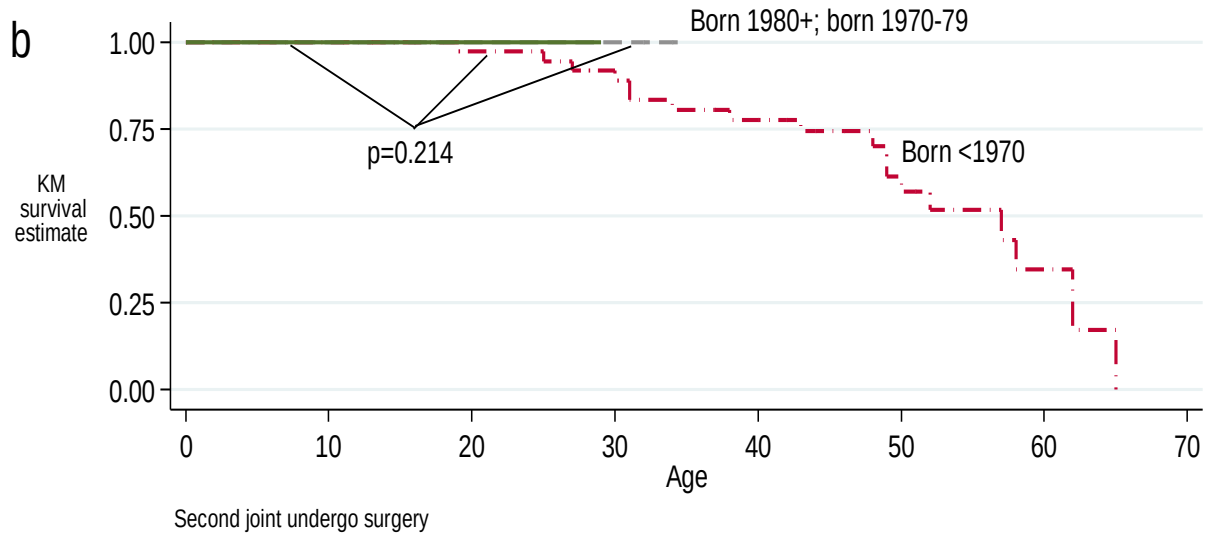
Cost!

THE MAJOR SIDE EFFECT OF PROPHYLAXIS IS……..

MODERN PROPHYLAXIS IS FANTASTIC

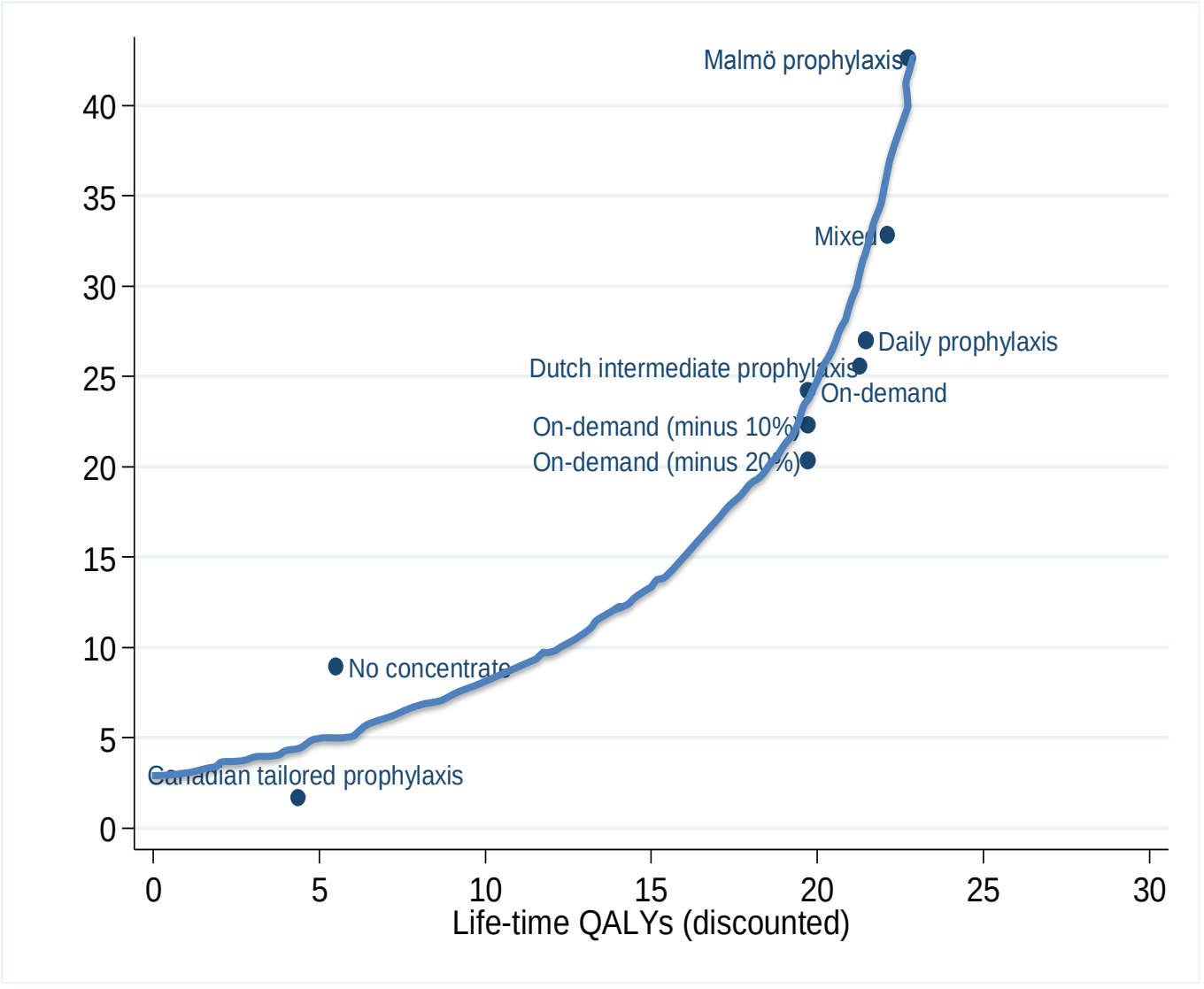


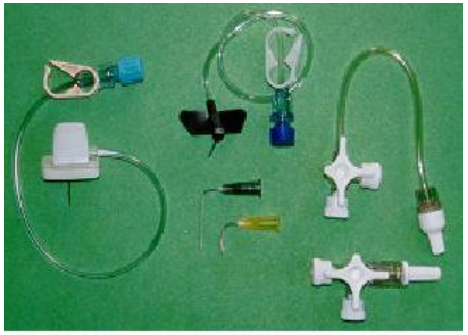
First joint undergo surgery

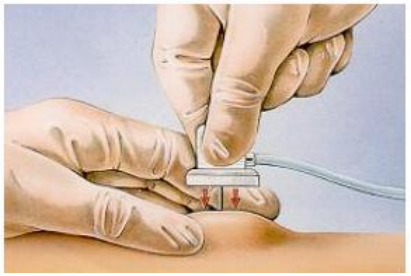


Second joint undergo surgery

BUT EXPENSIVE


Malmö prophylaxis
Mixed
Daily prophylaxis
Dutch intermediate prophylaxis
On-demand
On-demand (minus 10%)
On-demand (minus 20%)
No concentrate
Canadian tailored prophylaxis
0
5
10
15
20
25
30
35
40
Life-time QALYs (discounted)





AND SOMETIMES DIFFICULT

….and that is another history

THEN WE HAVE THE ISSUE OF PROPHYLAXIS IN INHIBITOR PATIENTS