Cost-effectiveness of treatment strategies for Severe Haemophilia

Mart Janssen PhD[1,2] & Kathelijn Fischer MD PhD[1,3]

1 - Julius Center for Health Sciences and Primary Care, UMC Utrecht, The Netherlands
2 - Sanquin Blood Supply Foundation, Amsterdam, The Netherlands
3 - Van Creveldkliniek, Utrecht, The Netherlands

Malta, October 8, 2015

University Medical Center Utrecht

Severe haemophilia

University Medical Center Utrecht

- Congenital absence of clotting factor FVIII or IX (single protein deficiency)
- Rare disease: 660 patients in the Netherlands
  (1 in every 5,000-10,000 males, 1 in 5,000 cases are severe bleeders)

- Clinical phenotype:
  Spontaneous and trauma related bleeding
  Soft tissue → intracranial, post surgery, post trauma
  → life expectancy reduced
  Elbows, knees, ankles → crippling arthropathy

Severe haemophilia: treatment options

University Medical Center Utrecht

Treatment: intravenous clotting factor concentrate (life-long, since mid 1960s)

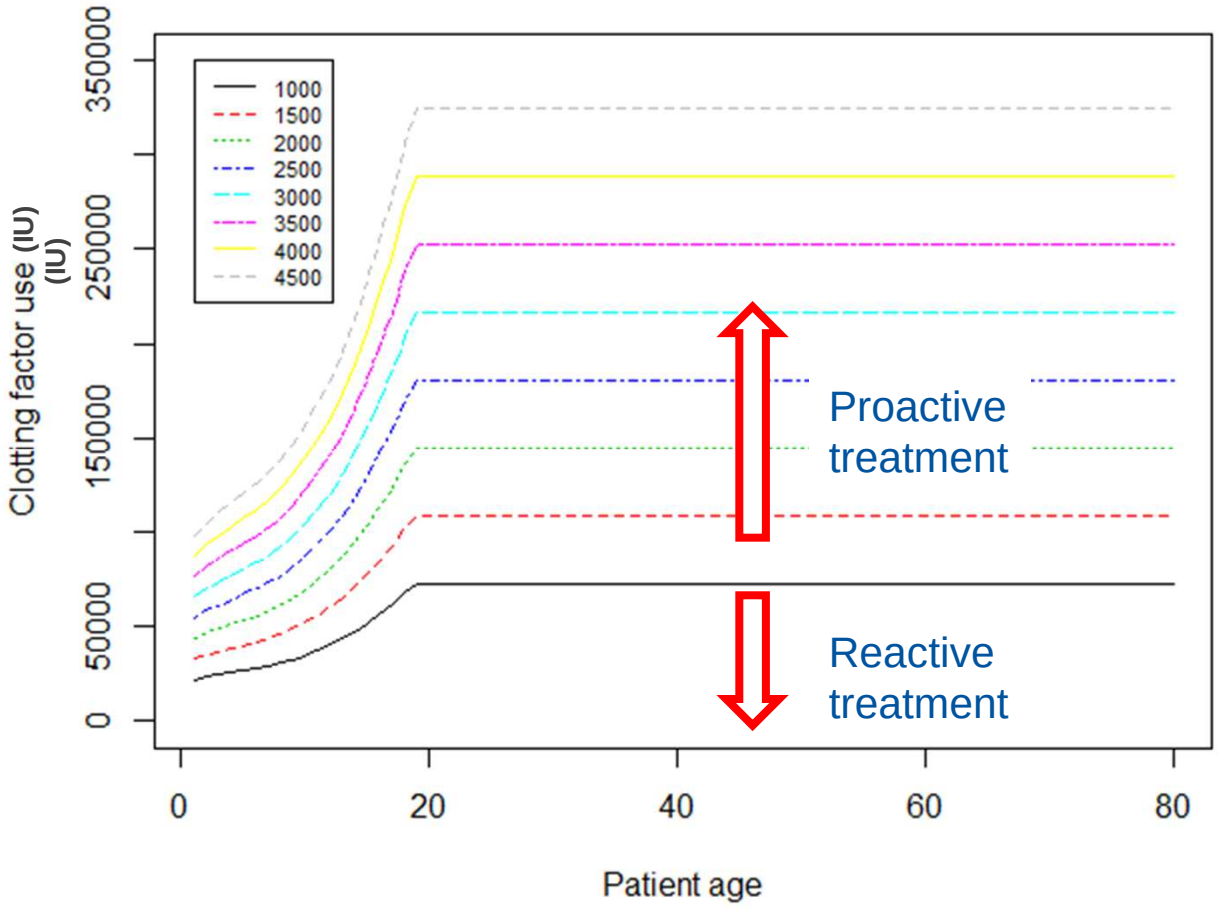
1. prophylaxis: regular infusions to prevent bleeding

2. on demand: in case of bleeding only (will not prevent arthropathy)

Medication is titrated dynamically on basis of perceived individual efficacy

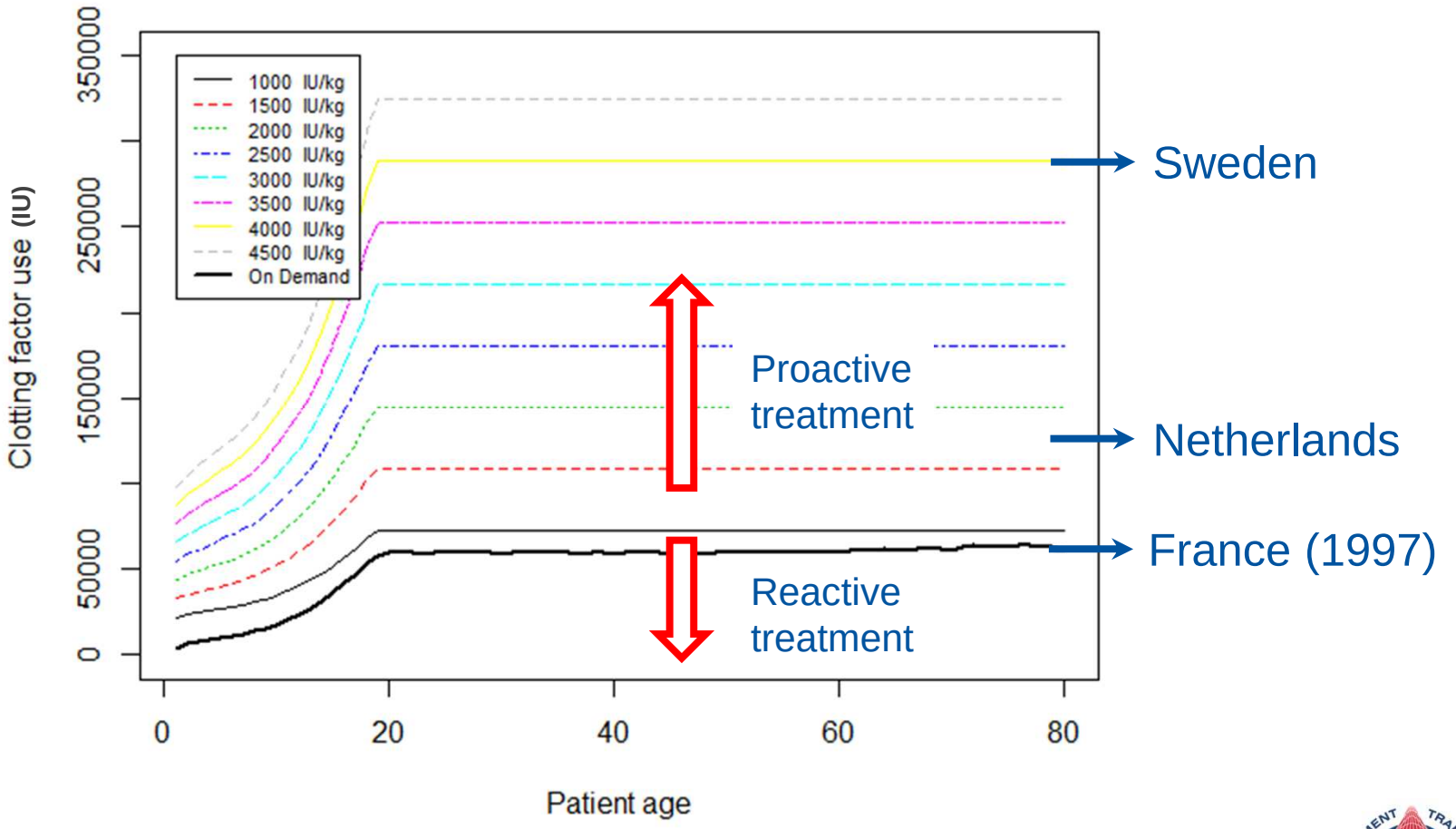
Clotting factor use: prophylaxis patients

University Medical Center Utrecht



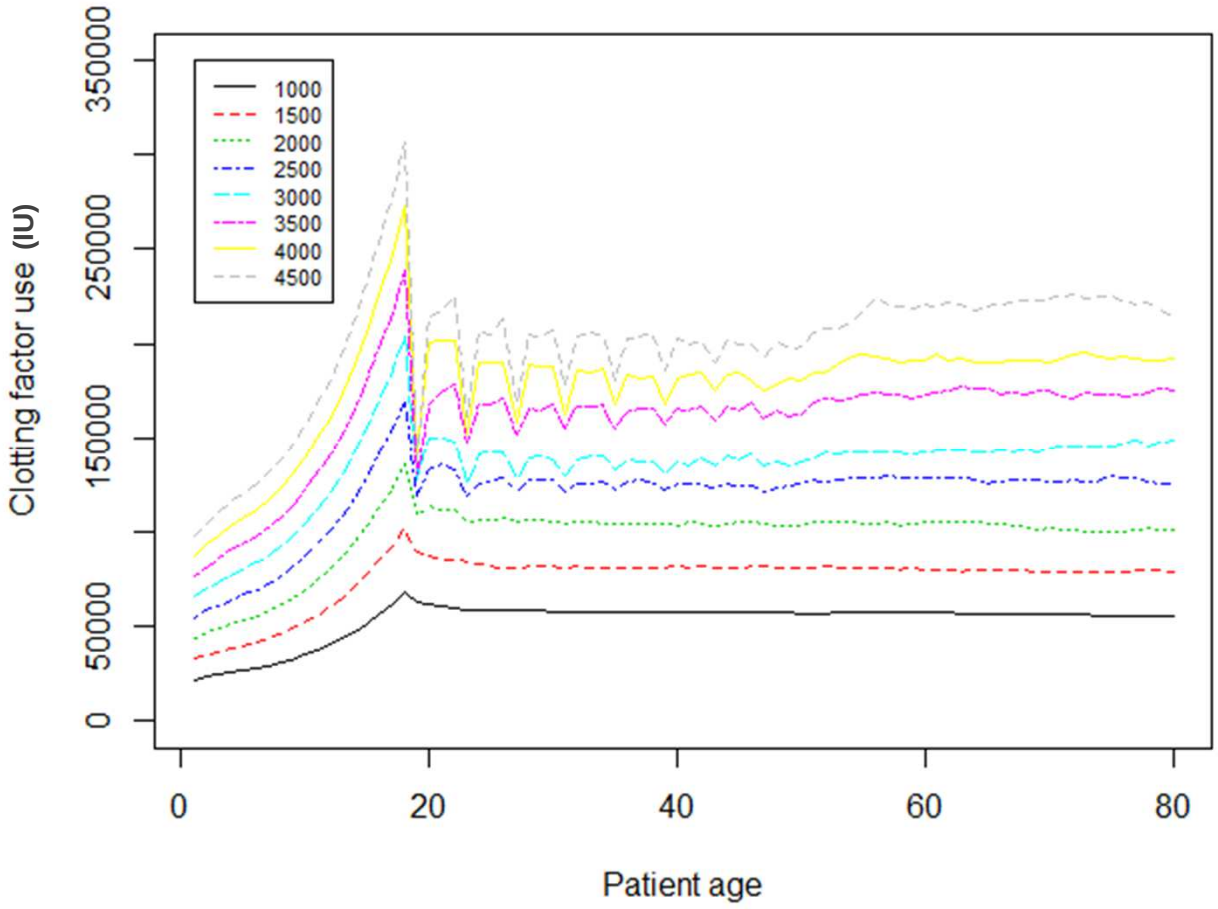
Clotting factor use: prophylaxis and on demand patients

University Medical Center Utrecht



Clotting factor use: multiple switch patients

University Medical Center Utrecht



Research Question & Study design

University Medical Center Utrecht

Question:

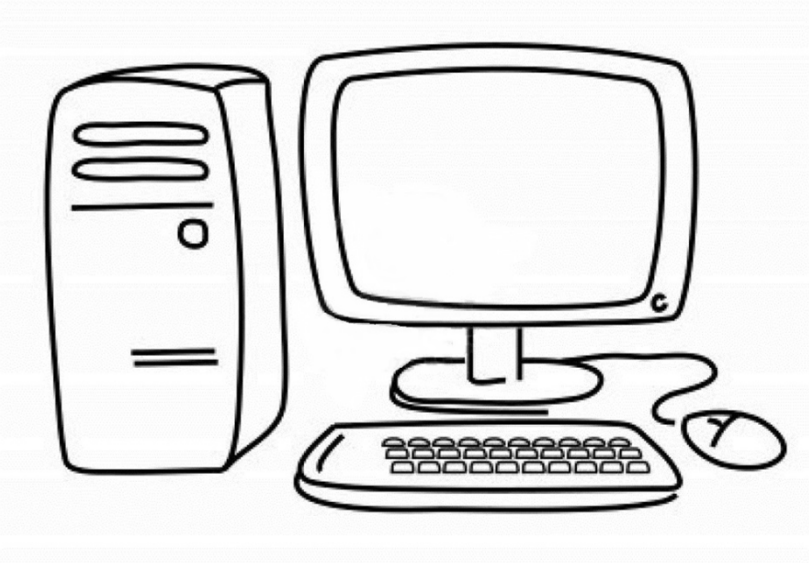
What is the optimal switching strategy between prophylaxis and on demand treatment?

Aim:

Balancing benefits and burden of combining these treatment options by targeted selection and monitoring of patients

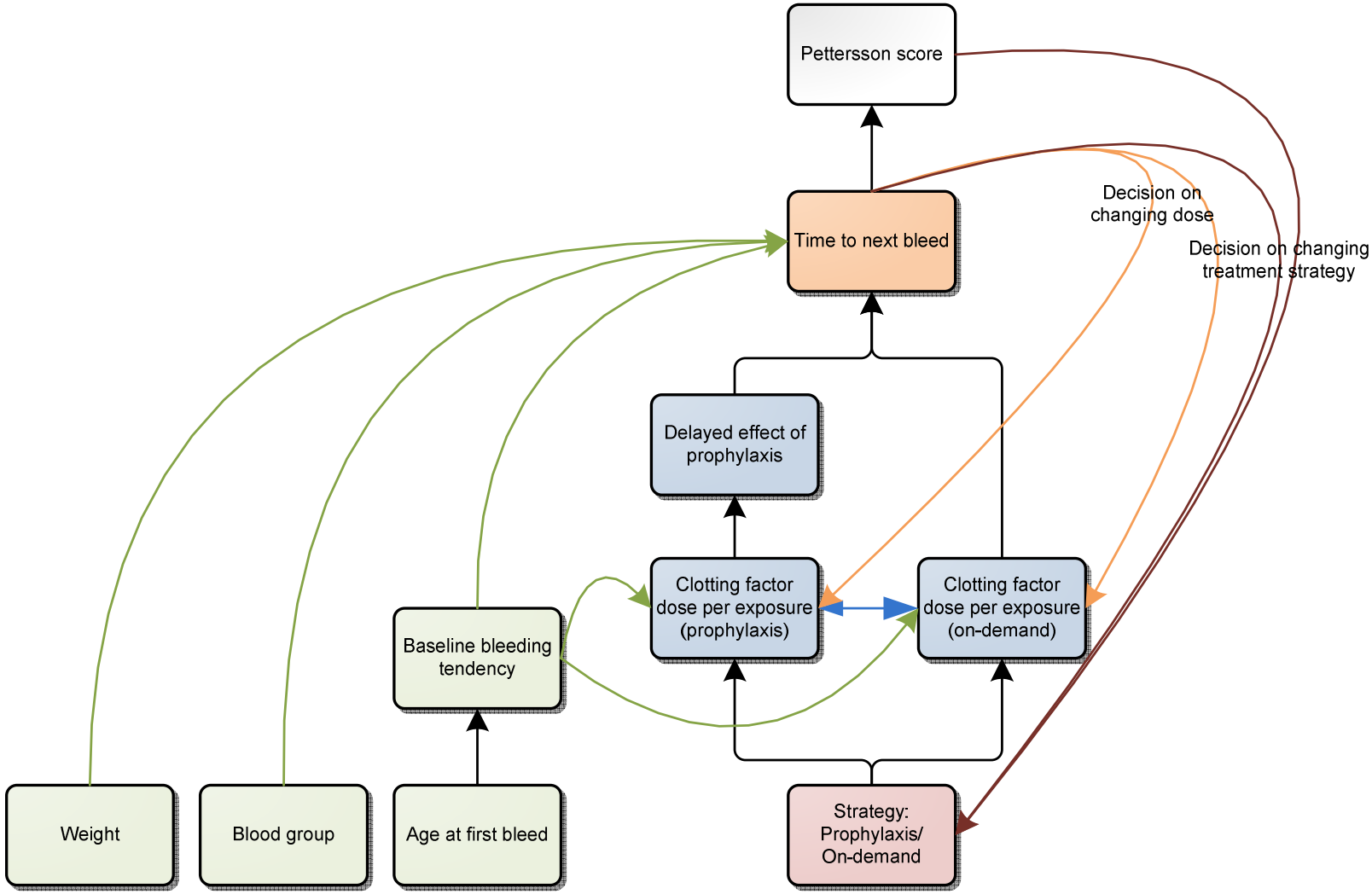
Design:

Discrete Event Modeling



How does the model work?

University Medical Center Utrecht



A first modelling attempt

University Medical Center Utrecht

A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A

Table 2. Characteristics of the datasets. The simulation model is based on both the original prophylaxis and on demand datasets as reported by Fischer[4] and Molho.[7]

		Prophylaxis[4]	On Demand[7]
Study Design			
	Number of patients	111	69
	Dataset	Longitudinal 1988-1997	Cross-sectional 1997
	Total years of follow up	610	69
Data			
	Mean age	16.4 (1.3-33.4)	22.47 (16.7-28.0)
	Mean age at first joint bleed	2.43 (0.17-13.18)	Not Available
	Mean annual number of joint bleeds per patient	4.91 (0-37.7)	20.91 (0-104)
	Mean clotting factor use (IU/kg/year)	2100 (251-6277)	1369 (0-6352)

Data are means (range).

Citation: Fischer K, Pouw ME, Lewandowski D, Janssen MP, van den Berg HM, and van Hout BA. A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A. Haematologica 2011;96(5):738-743. doi:10.3324/haematol.2010.029868

Results

University Medical Center Utrecht

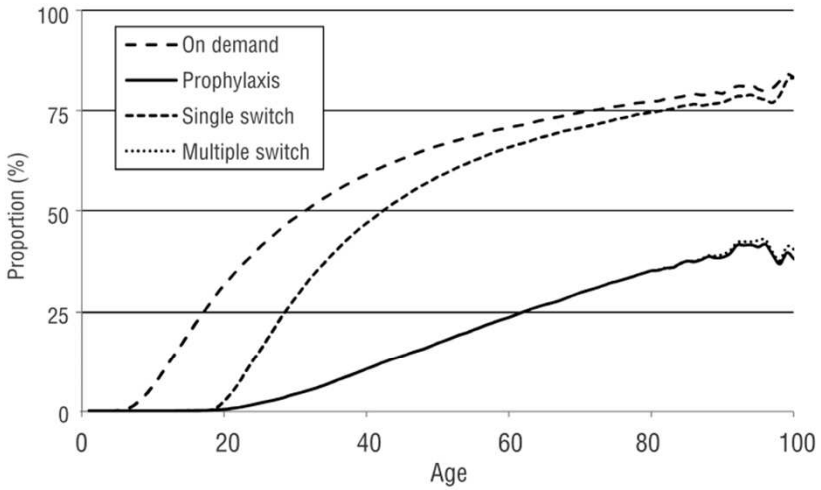


Figure 1. Proportion of patients with a Pettersson score > 28 according to age and therapeutic strategy. The single switch strategy and the on demand (years) strategy curves stay close together, while the multiple switch strategy and the pure prophylaxis strategy results are almost identical. These results suggest that the multiple switch strategy is very effective at preventing arthropathy.

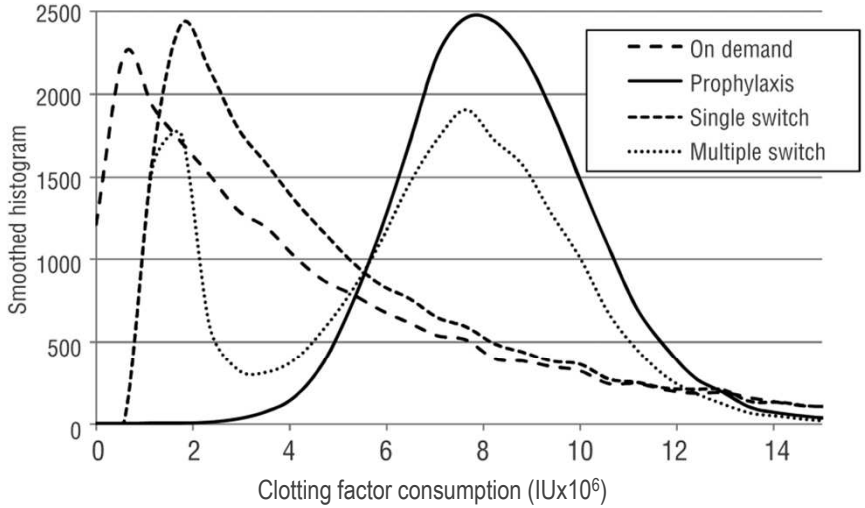


Figure 2. Distribution of the lifetime clotting factor consumption according to treatment strategy. Note the double peak pattern for the multiple switch strategy as a result of mixing the prophylaxis and on-demand treatment strategies.

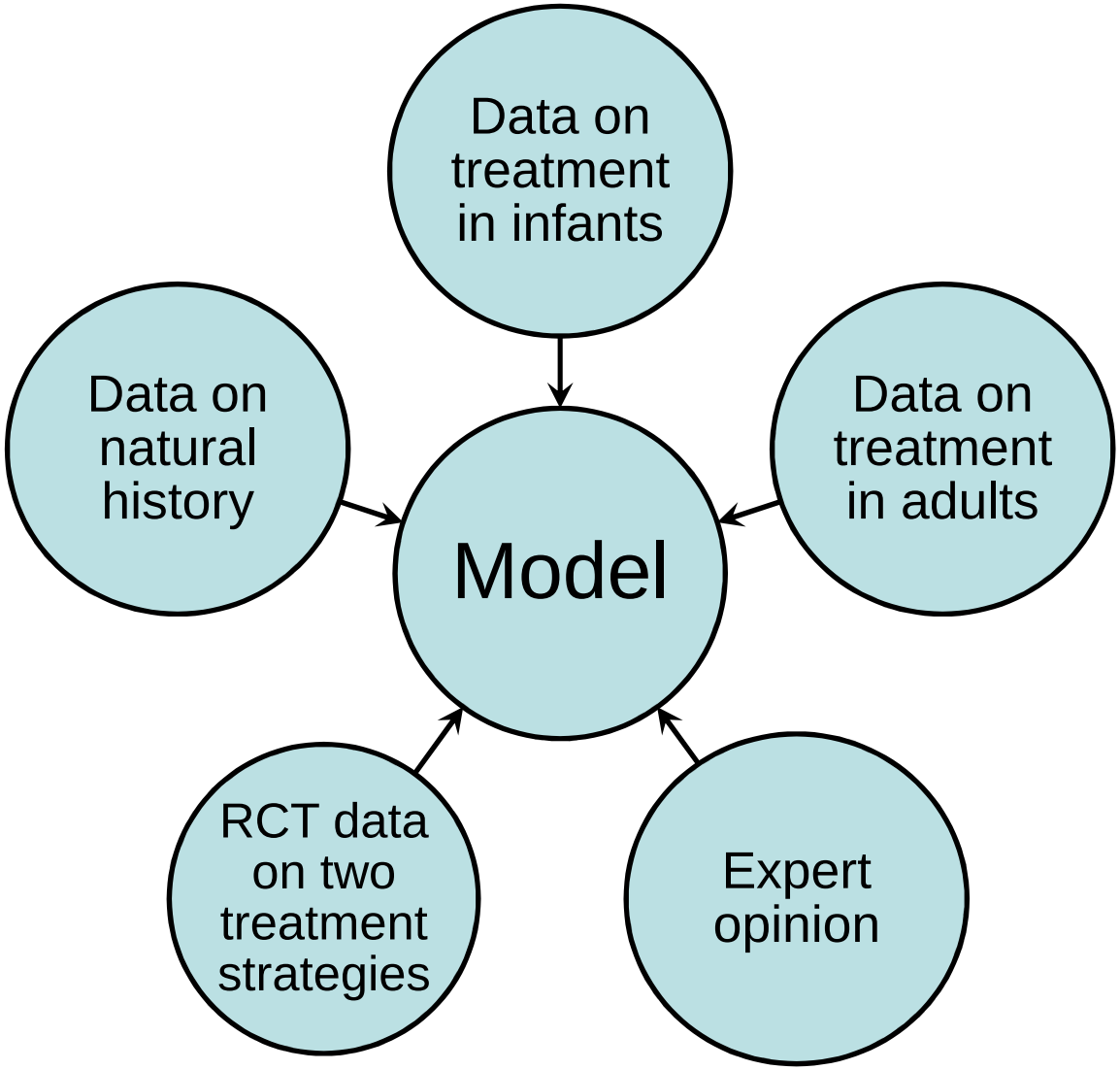
Table 3. Results of the simulation according to age and treatment strategy.

Age	On demand	Prophylaxis	Single-switch strategy	Multiple-switch strategy
Lifetime				
Cumulative joint bleeds	1494 (32-5754)	357 (14-1333)	1258 (40-4826)	395 (40-1333)
Pettersson score	55 (0-78)	23 (0-78)	52 (0-78)	26 (0-78)
Cumulative clotting factor use (IU×10⁶)	4.9 (1-18.7)	8.3 (4.8-12.5)	5.4 (1.2-17.8)	6.6 (1.2-12.9)

Data are mean values (95% CI) excluding patients who died before reaching the presented age.

Combining data from different sources to derive optimal treatment strategy

University Medical Center Utrecht



Lack of information

University Medical Center Utrecht

Use expert elicitation to obtain data on:

1. Patient/treatment characteristics:
   - Bleeding frequency for on-demand treatment (according to age and onset of bleeding);
   - Life expectancy of haemophilia patients as compared to general population;
   - Treatment of minor bleeds;

2. Patient response to treatment:
   - Dose of prophylaxis required to control bleeding tendency;
   - Time needed to achieve control of bleeding after starting prophylactic treatment.

Elicitation process

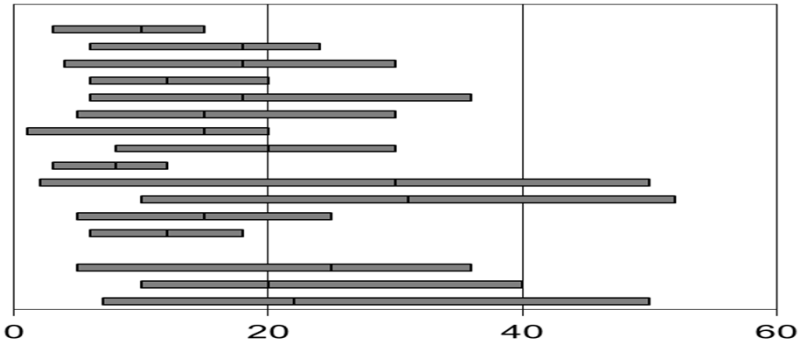
University Medical Center Utrecht

- Session during a haemophilia conference
- 18 experts participated
- 15 items, 7 calibration questions
- Instruction manual and introduction exercises

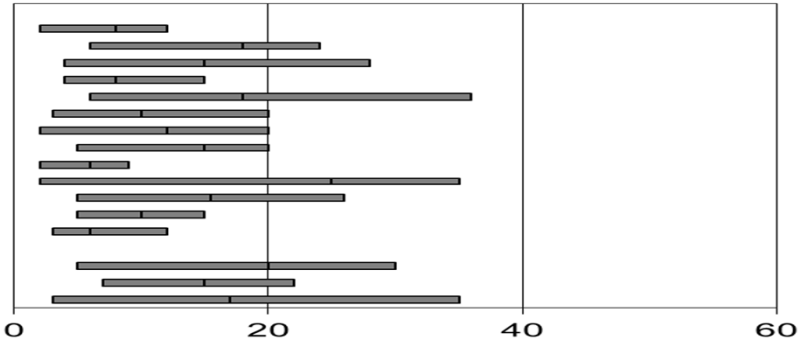
Question 1	**Joint bleed frequency on ON-DEMAND treatment** During **teen years** (≤ 18 years) According to onset of joint bleeding	
Consider patients with severe hemophilia A during their teenage years (≤ 18 years old). Treatment is on demand, but readily available. According to you, what is the distribution of the number of joint bleeds per year if the age at first joint bleed is 0.7, 1.7 or 3 years? Please enter your assessments in the table below. *(if you don't consider age at first joint bleed of any importance here, you just enter the same answers in questions 1a, 1b, and 1c)*		
Question 1a	**Age at first spontaneous joint bleed is 0.7 years**	
	joint bleeds/year	
10%	50%	90%

Expert estimates

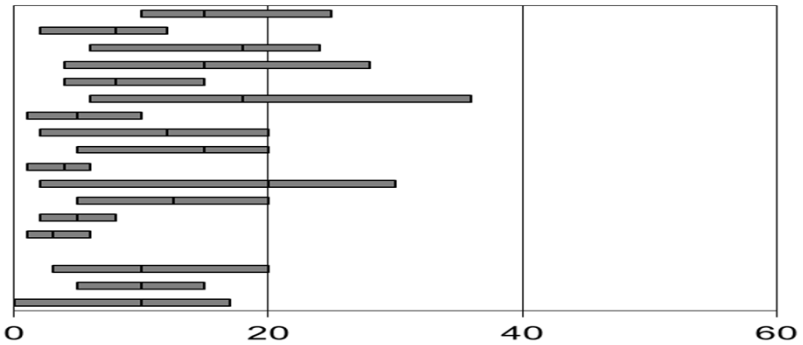
University Medical Center Utrecht



Joint bleed frequency when age at first spontaneous joint bleed is 0.7 years.



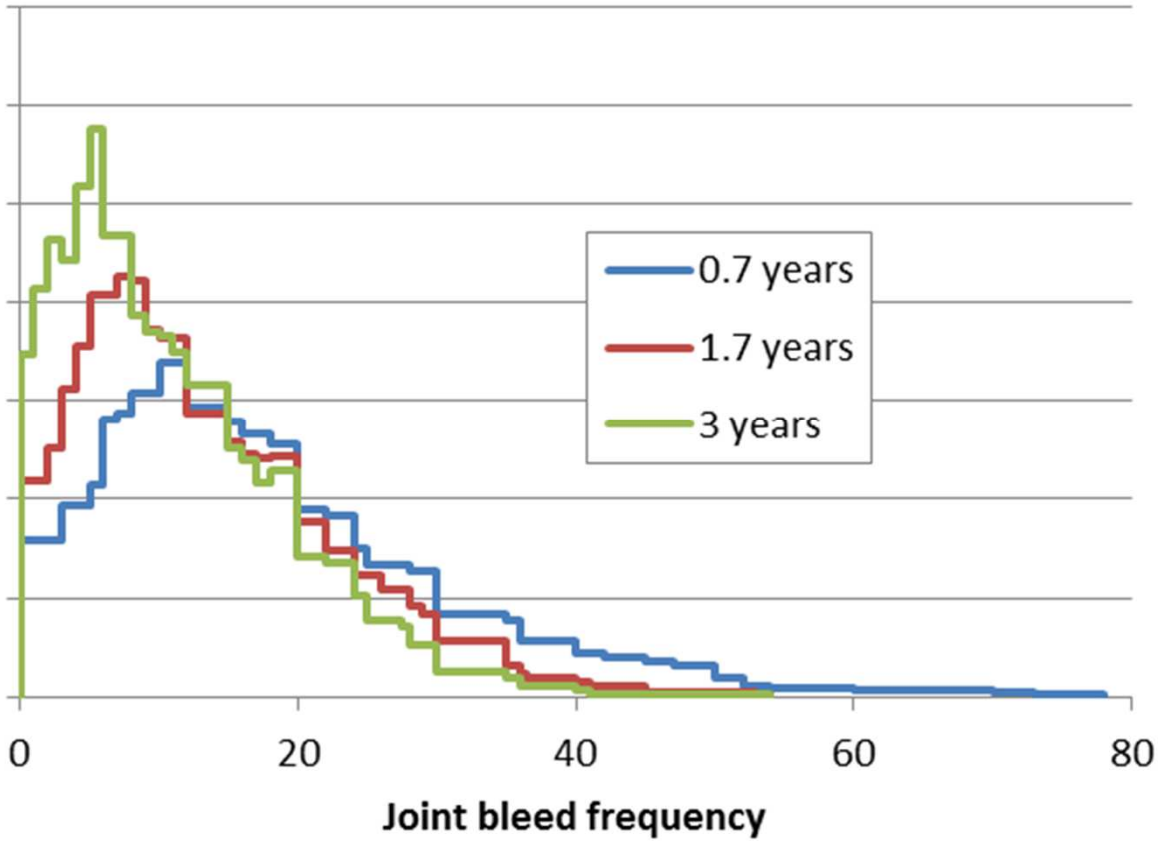
Joint bleed frequency when age at first spontaneous joint bleed is 1.7 years.



Joint bleed frequency when age at first spontaneous joint bleed is 3 years.

Joint bleed frequency as a function of age of first joint bleed

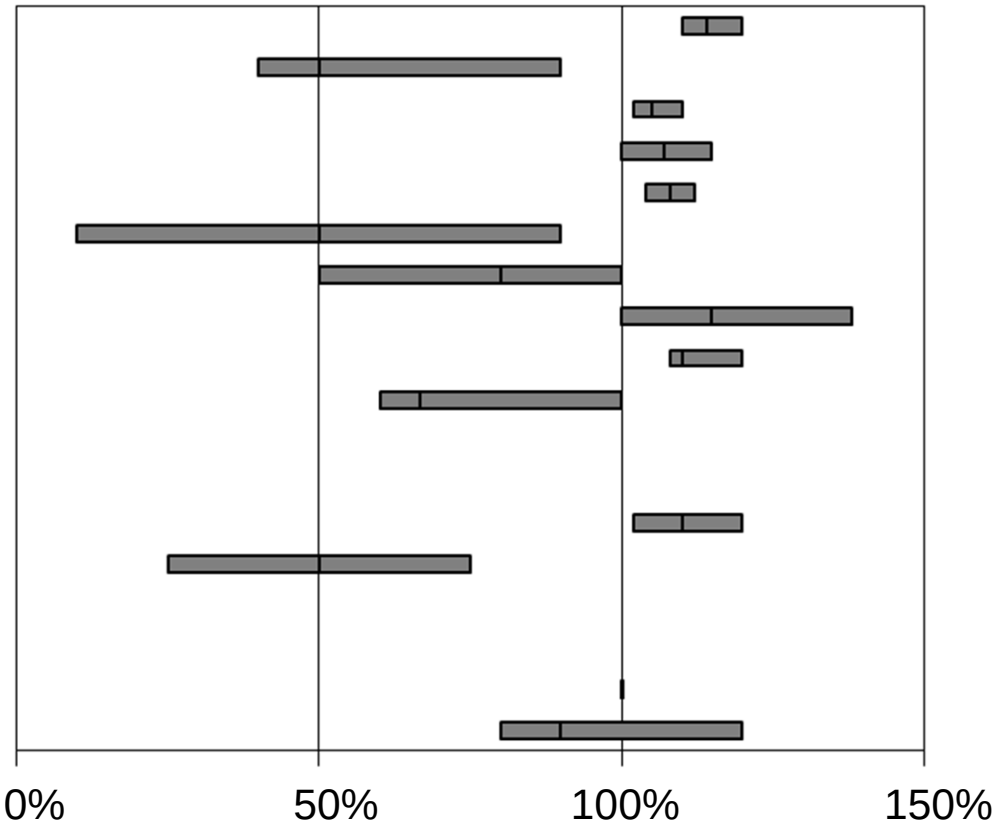
University Medical Center Utrecht



Proportional change in late adulthood bleeding frequency

University Medical Center Utrecht

Long term patient characteristic



Expert scores

University Medical Center Utrecht

Expert ID	Calibration	Relative Information	Un-normalized Weight	Normalized Weight
14	0.85	1.07	0.91	0.17
11	0.85	0.98	0.84	0.16
5	0.85	0.77	0.66	0.13
3	0.61	0.97	0.59	0.11
9	0.61	0.80	0.49	0.09
18	0.61	0.72	0.44	0.08
10	0.41	0.74	0.30	0.06
7	0.39	0.64	0.25	0.05
2	0.31	0.65	0.20	0.04
16	0.31	0.62	0.19	0.04
6	0.20	0.78	0.16	0.03
15	0.13	0.69	0.09	0.02
8	0.03	1.54	0.04	0.01
17	0.04	0.62	0.02	0.00
12	0.01	1.64	0.02	0.00
1	0.01	1.39	0.01	0.00
4	0.01	1.09	0.01	0.00
13	0.01	1.03	0.01	0.00
Performance Weights	**0.31**	**0.27**	**0.085**	
Optimal Performance Weights	**0.31**	**0.49**	**0.154**	
User Weights	**0.25**	**0.23**	**0.058**	
Equal Weights	**0.25**	**0.20**	**0.051**	

Top 3 selected

Expert opinion results published

University Medical Center Utrecht

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Table 1. Experts' estimates of parameters of bleeding, treatment and life-expectancy in severe haemophilia A.

		P50	P2.5	P97.5	% overlap in P10–P90 intervals	No. of experts
Joint bleeding ON DEMAND						
Age 10–18	1st joint bleed 0.7 years	16	1.3	50	100%	16
	1st joint bleed 1.7 years	12	0.9	36	100%	16
	1st joint bleed 3.0 years	9	0.6			
Age 18–50	1st joint bleed 0.7 years	14	1.1			
	1st joint bleed 1.7 years	11	0.8			
	1st joint bleed 3.0 years	9.5	0.6	60	70%	17
After age 50 years, proportional change		−2.1%	−76%	29%	37%	14
Concerning a model patient: Weight 85 kg, recovery 2%/IU/kg, half-life 12 h						
Treatment DOSE						
Secondary prophylaxis, started at age 15 years, dose needed to suppress bleeding < three joint bleeds per year, frequency every other day						
Previous bleeding frequency		Dose/infusion (IU)				
5 joint bleeds per day		1534	0.7	3542	53%	17
15 joint bleeds per day		1975	499			
30 joint bleeds per day		2229	555			
50 joint bleeds per day		2584	899			
Time (years) needed to reduce joint bleeds to <3 per day, in patient who first starts prophylaxis at age 20, dose 3000 IU EOD		0.25	0.0	1.82	78%	18
Treatment of minor joint bleed						
Initial dose(IU)		1885	532			
No. of infusions		1.4	0.4			
Life expectancy, treated on demand, HCV and HIV negative (% of normal)		89	58			

Interpretation: P50 reflects the median estimate for the parameter, the 95% confidence interval of the combined estimate (P2.5–P97.5) reflects the uncertainty of the combined experts, the % overlap in agreement of the P10–P90 intervals provided reflects the agreement between the estimates of the individual experts.

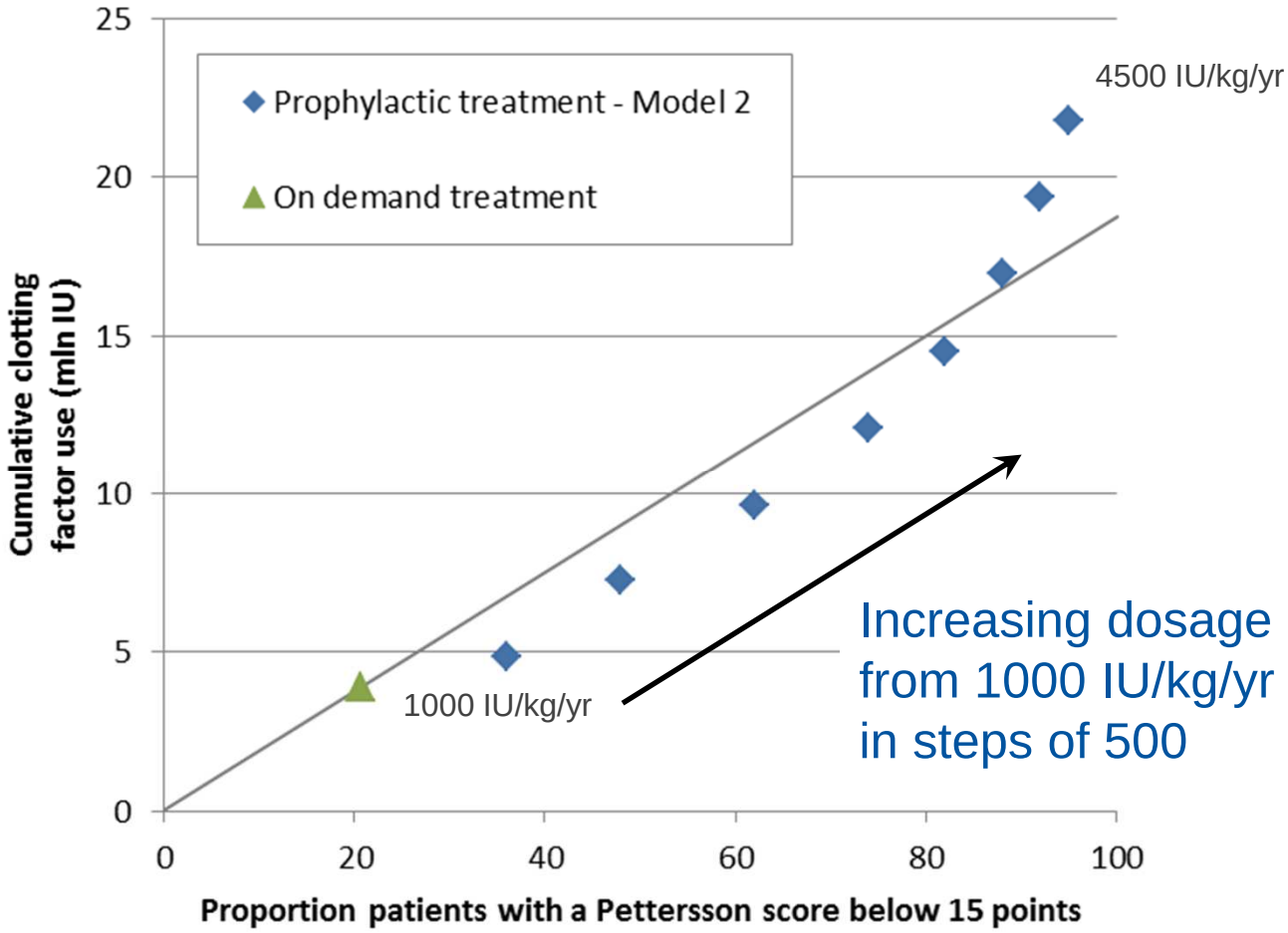
BLEEDING FREQUENCIES

EFFICACY OF TREATMENT

PATIENT LIFE EXPECTANCY

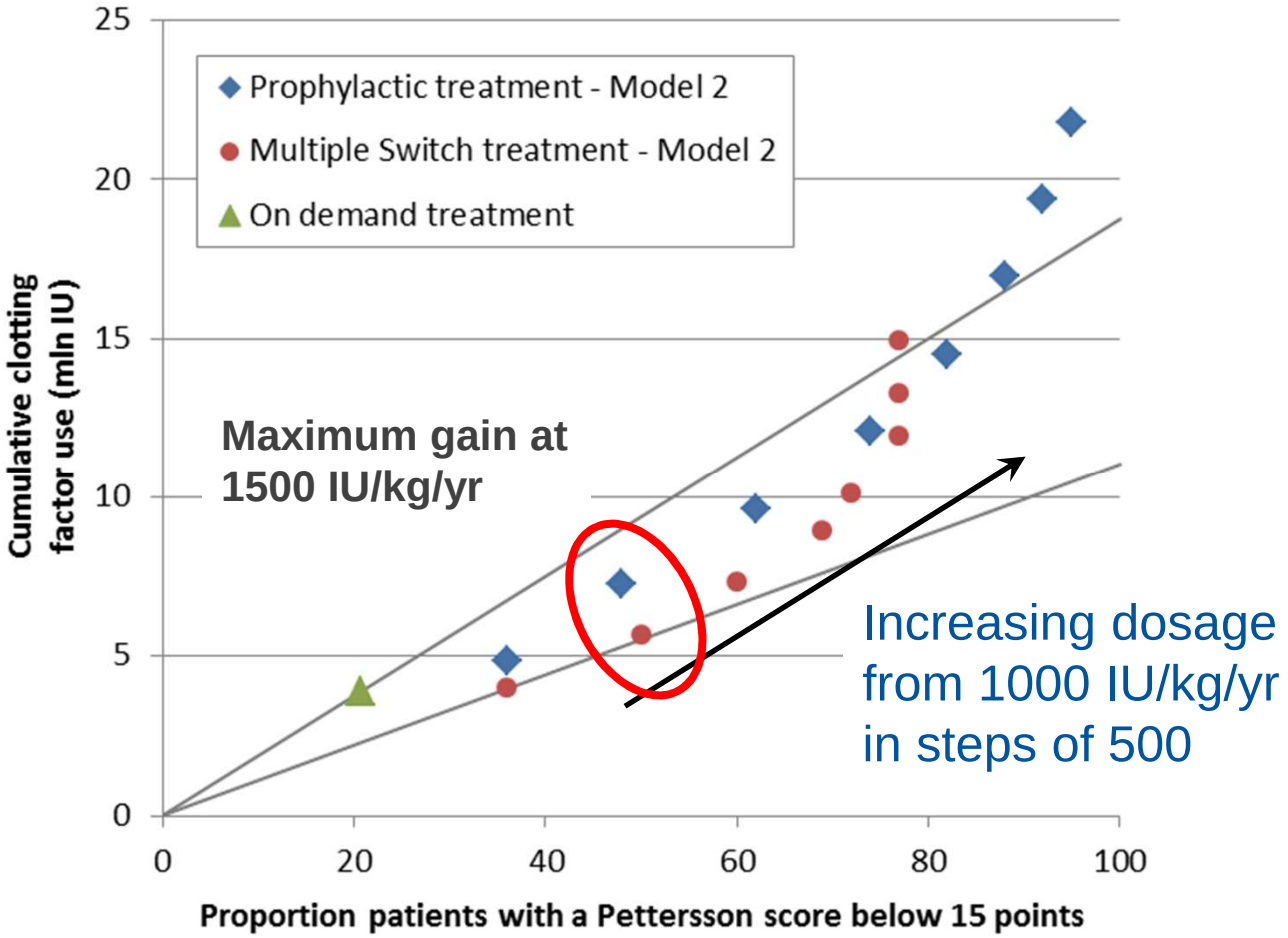
Costs and effects of treatment strategy and dosage

University Medical Center Utrecht

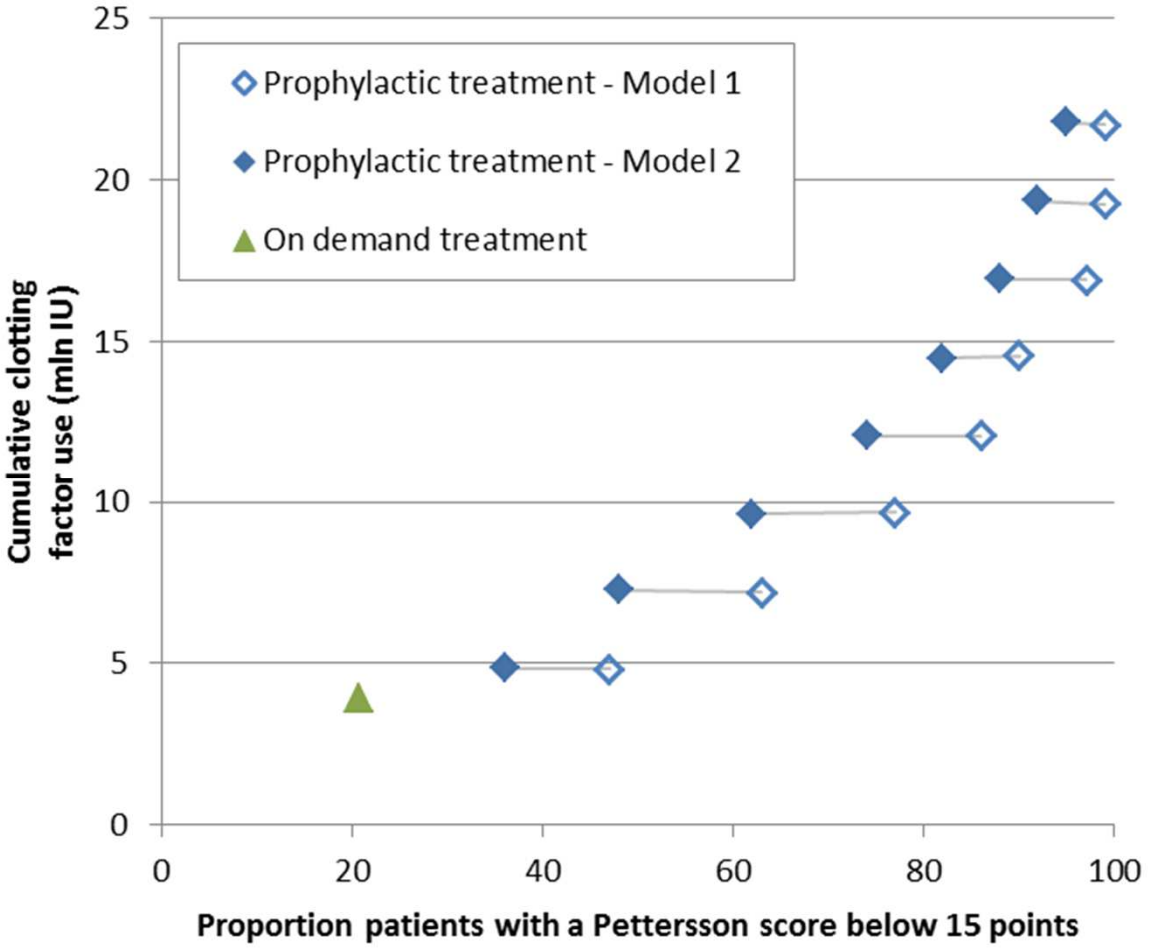


Costs and effects of treatment strategy and dosage

University Medical Center Utrecht

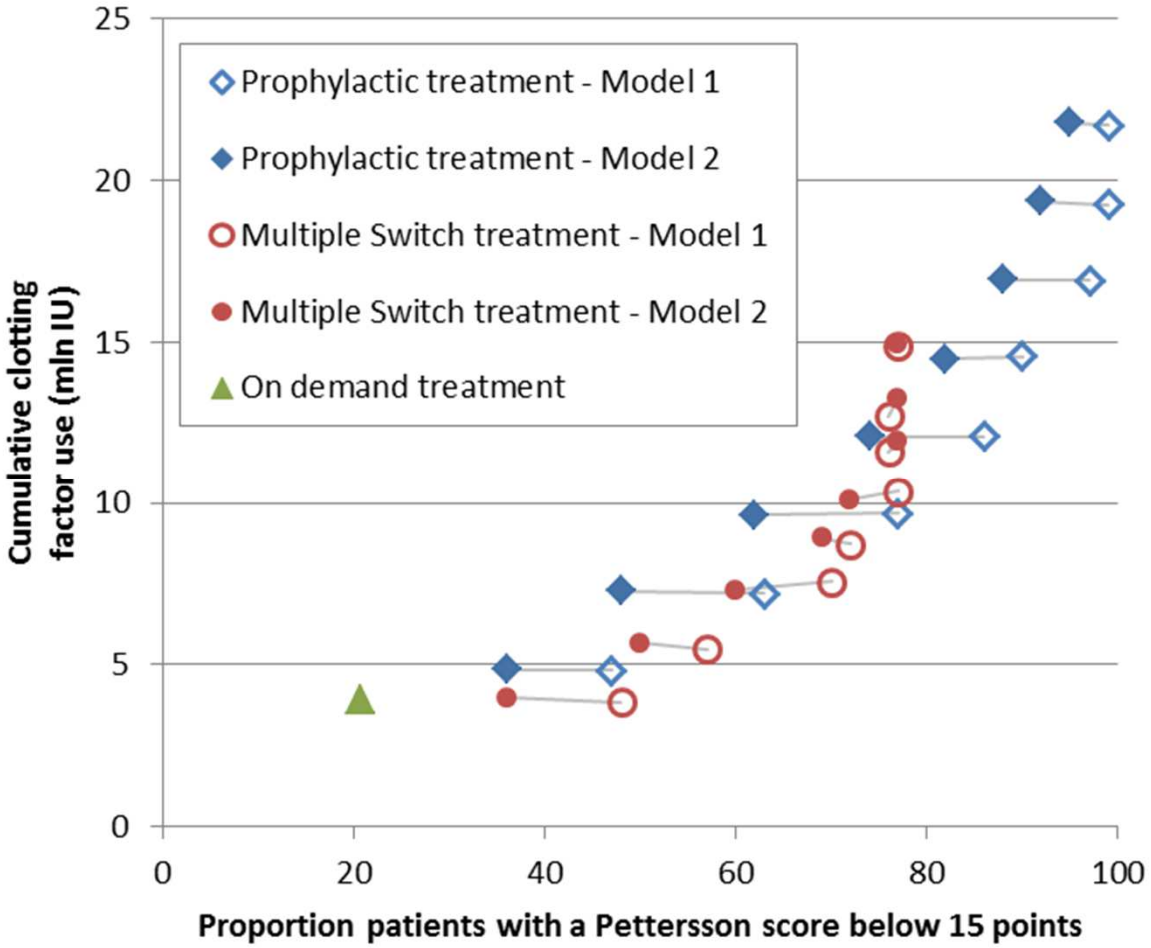


Substantial decrease in efficacy of treatment



Similar change for MS strategy

University Medical Center Utrecht



Conclusions

University Medical Center Utrecht

1. Expert opinion based model predicts less favourable outcomes in patients
2. Including expert opinion helps acceptance of the model by clinicians
3. Primary MS strategy applied is near the optimum found, and is similar for all dosage levels !!
4. Multiple-Switch strategy primarily prevents damage in high bleeders and therefore loses efficacy when applying higher prophylactic doses

Further research

University Medical Center Utrecht

- Further explore the impact of various modelling assumptions
- Identify other relevant gaps in knowledge
- Evaluation of alternative strategies that incorporate:
  - Within patient modification of prophylactic dose
  - Longer history of bleedings

- Most importantly:
  - Collecting consistent and complete ***patient follow-up data***

Thanks also to my colleagues and sponsor

University Medical Center Utrecht

- Kathelijn Fischer
- Daniel Lewandowski
- Ben van Hout
- Maurice Pouw

ZonMw

Questions?

University Medical Center Utrecht