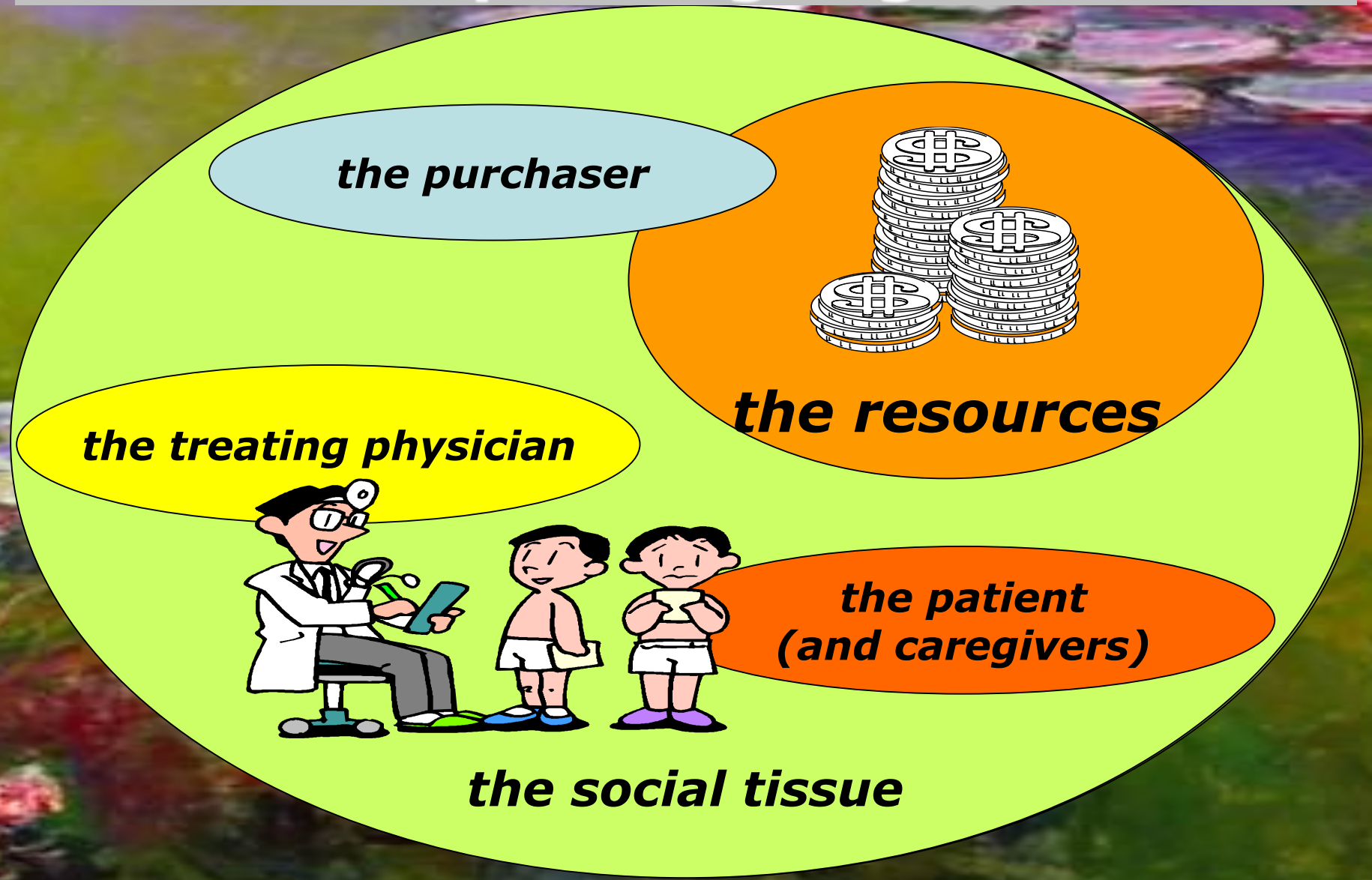
Choicing therapeutic goals and accomplishing regimens



Identifying challenges and barriers

Previous clinical experience

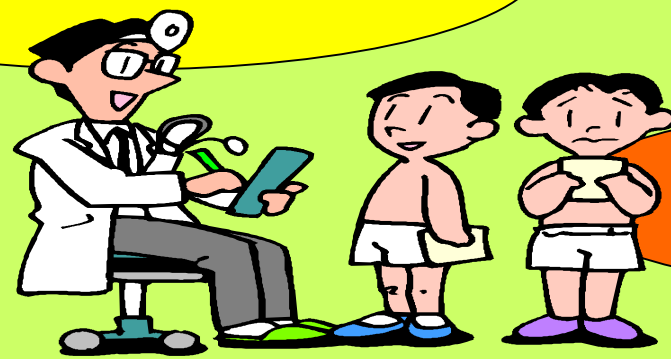
Previous clinical history

Evidence

Perceived need

Physical and psycho-social need

the treating physician



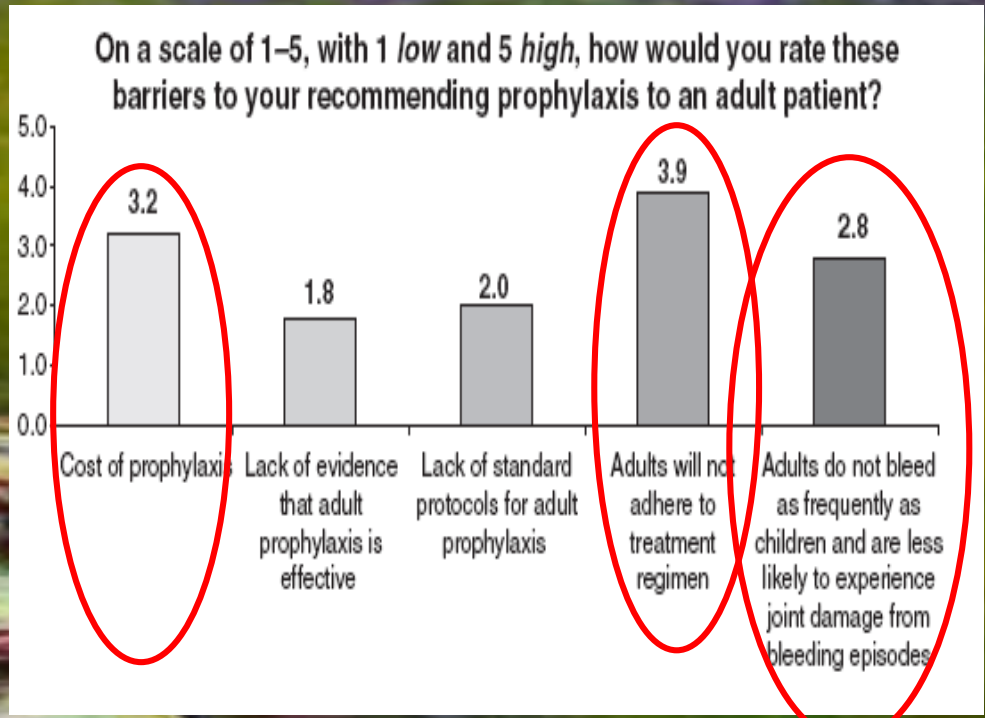
the patient (and caregivers)

How are adults treated ?

Prophylaxis most likely recommended to:

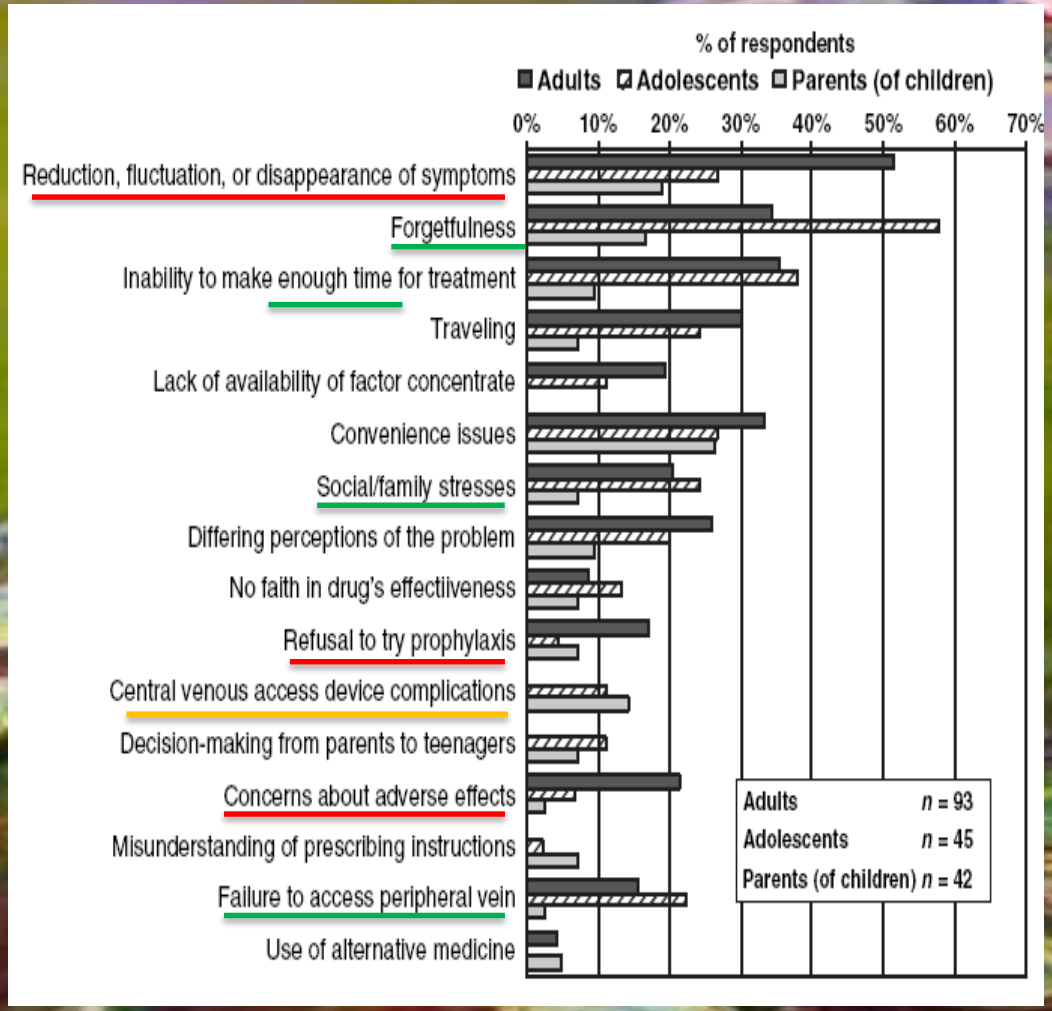
- Patients on primary prophylaxis with no or little joint damage
- Patients never received prophylaxis and experience life- or limb- threatening bleeding
- Patients never received prophylaxis and experience frequent joint bleeding

Perceived barriers



Walsh and Valentino, Haemophilia 2009

Adherence according to the age…



De Moerloose et al, Haemophilia 2008

Haemophilia

Haemophilia (2012), 18 (Suppl. 5), 27–32 DOI: 10.1111/j.1365-2516.2012.028

ORIGINAL ARTICLE

From boy to man: recommendations for the transition process in haemophilia

GUY YOUNG
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'transition of care' [1]. Transition of care can be thought of as the developmental changes in disease management resulting from a combination of the natural medical history of the disorder, the cognitive and social development of the child with the disorder, and the psychosocial dynamics of the family setting. The particular aspects of

(HTC) [2]. An HTC has not only physicians with specific medical expertise in haemophilia, but also highly skilled and trained staff members including nurses, social workers, physical therapists and, in some centres, psychologists to help navigate through the transition process.

Starting prophylaxis in adulthood
OPEN ISSUES

- **Clinical efficacy**
  - → Bleeds
  - → Joint deterioration
- **Long-term feasibility and patients' compliance**
- **Health-related Quality of Life**
- **Costs**
  - → Concentrates
  - → other social and health-related costs

Evidenze sulla profilassi 'terziaria'

Author, year [Ref]	Type of publication	Patients	Mean age (range), years	Main results
Rocino [20]	Abstract	27 HA	17 (4–43)	80% of patients stopped bleeding, radiographic scores remained stable in all evaluable joints; improved activity capability and sense of well-being in all patients
Miners [21]	Full paper	19 HA		65% reduction of bleeding from median 37 (range 11–132) to 13 (range 0–92) bleeds per year, but 350% higher factor consumption
Loverin [22]	Abstract	4 HA		89% mean reduction of joint bleeds, better joint status, lower annual factor usage
Saba [23]	Abstract	6 HA,		Decreased number of joint bleeds/month (4.16 → 0.48) with increase of costs (+$10,979 per patient/month)
Schramm [24]	Full paper	281 HA, 53 HB	34 (12–83)	5.15 times more joint bleeds than 669 patients treated on-demand and better quality of life, but costs were significantly higher
Fischer [25]	Abstract	61 HA	26 (19–43)	Decreased number of joint bleeds/year (9.1 → 3.6) on long-term prophylaxis slows, but does not stop progression of haemophilic arthropathy
Coppola [26]	Abstract	19 HA	29 (17–46)	71% mean reduction of total bleeds, increased costs (23 645 € per patient/month), improved quality of life
Tagliaferri [27]	Letter	17 HA, 3 HB	27 (12–74)	Decreased mean number of joint bleeds/year (26.1 → 3.4), improved orthopaedic scores and well-being, 31% increase of factor use and costs
Tagliaferri [28]	Full paper	76 HA, 8 HB	28 (13–76)	Decreased mean number of joint bleeds (32.4 → 3.3) and work/school s lost (32.4 → 3.0), improved orthopaedic scores and higher
Collins [29]	Full paper	19 HA	36 (30–45)	Decreased mean number of joint bleeds (15 → 0) and imp orthopaedic scores (25 → 18)
Valentino [30]	Full paper	66 H	7–59	Decreased median annualized bleeding rate (43.9 → 1

Pochi studi retrospettivi

2 studi prospettici

Breve follow-up

6 mesi

12 mesi

Gringeri et al, Haemophilia 2012

The Italian experience

Characteristics	Adolescents (n = 30)	Adults (n = 54)	Total (n = 84)
Haemophilia A/haemophilia B	26/4	50/4	76/8
Median age at start of prophylaxis, years (range)	12.0 (10–17)	30.0 (18–72)	23.6 (10–72)
Median age at the time of this evaluation, years (range)	18.0 (13–24)	33.0 (23–76)	28.0 (13–76)
Median duration of prophylaxis, years (range)	5.8 (2–14.7)	4.2 (2–12)	4.8 (2–14.7)

Reasons for starting prophylaxis in adults

- **Target joint or worsening of joint status (59,5%)**
- **Increased bleeding tendency and target joint (11%)**
- **Increased FVIII consumption (25%)**
- **High-risk activities, including physiotherapy (4, 8%)**

Tagliaferri et al, Haemophilia 2008

The Italian experience

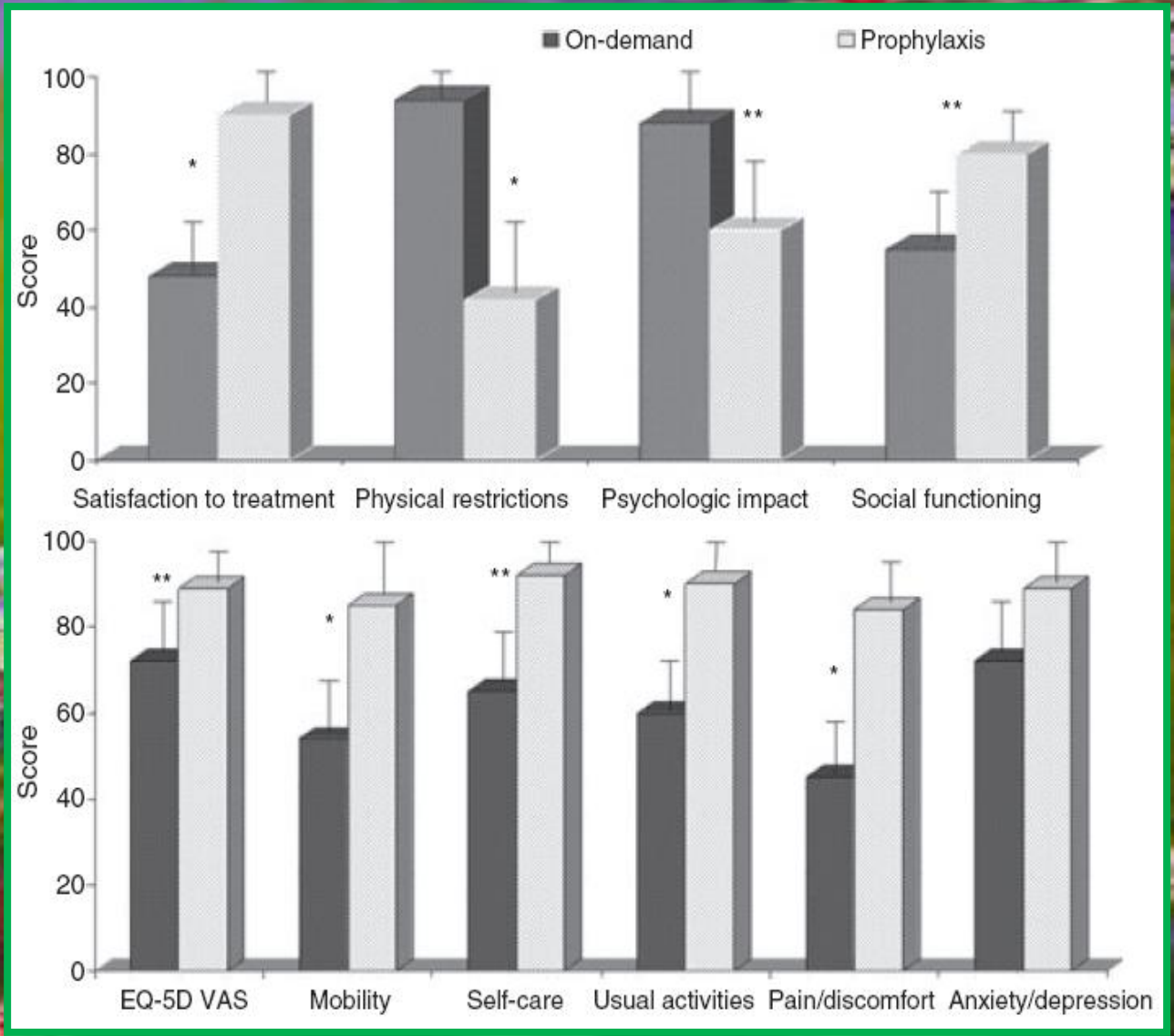
Parameters	Adolescents (n = 30)		Adults (n = 54)		Total (n = 84)		
	On-demand*	Prophylaxis	On-demand*	Prophylaxis	On-demand*	Prophylaxis	P
Total bleeds/year	33.7 (26.5)	2.5 (2.6)	36.9 (23.6)	5.4 (4.8)	35.8 (24.8)	4.2 (3.7)	<0.01
Joint bleeds/year	29.3 (23.6)	1.8 (2.3)	33.9 (22.6)	4.1 (3.7)	32.4 (23.1)	3.3 (3.1)	<0.01
Orthopaedic score†	7.3 (6.4)	3.5 (2.8)	23.4 (12.3)	19.9 (13.1)	18.1 (13.1)	13.8 (12.6)	0.13
Pettersson score‡	5.7 (3.3)	6.2 (2.6)	23.3 (20.1)	22.3 (19.9)	13.9 (16.9)	13.7 (16.0)	0.73
Work-school days lost/year	33.9 (30.8)	1.3 (1.8)	35.0 (23.4)	4.0 (4.8)	34.6 (25.6)	3.0 (2.6)	<0.01
Concentrate consumption§	2352 (1584)	3848 (808)	3135 (2185)	4065 (895)	2871 (2049)	3987 (876)	<0.01
Overall cost of concentrate¶	1858 (1251)	2886 (638)	2476 (1639)	3049 (671)	2153 (1537)	2990 (657)	0.01
Days of hospitalization/year	1.3 (1.7)	0.1 (0.3)	0.5 (0.7)	0.1 (0.4)	0.8 (0.6)	0.1 (0.3)	0.01
Medical visits at haemophilia centre/year	8.5 (6.4)	3.0 (1.4)	5.8 (6.5)	2.9 (1.2)	6.8 (6.4)	2.9 (1.3)	0.03
Physiotherapy cycles/year**	0.8 (1.1)	0.5 (0.6)	1.1 (1.2)	1.0 (0.8)	1.0 (1.1)	0.8 (0.9)	0.41
Orthopaedic visits††	3.2 (4.2)	1.0 (0.6)	2.3 (2.5)	1.1 (0.5)	2.6 (3.3)	1.1 (0.5)	0.01
Instrumental exams/year‡‡	2.2 (2.2)	0.7 (0.6)	1.6 (1.6)	0.9 (0.8)	1.8 (1.8)	0.8 (0.7)	0.01

Long-term adherence

Interruptions of treatment, 1-3 mo. (4, 7%)

Tagliaferri et al, Haemophilia 2008

The Italian experience



Tagliaferri et al, Haemophilia 2008

COST-EFFECTIVENESS

HR
QoL

COST-UTILITY

Haemophilia

Awaiting evidence-based recommendations on prophylaxis in adult patients

A. TAGLIAFERRI
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In conclusion, long-term prospective trial on adult prophylaxis has been yet completed. The final results of the POTTER study and the rigorous data that the SPINART trial is collecting with a randomized design and the evaluation of joint status by Magnetic Resonance Imaging are expected to provide significant insights for addressing the numerous unsolved questions and evaluating the long-term outcome (i.e., joint status, quality of life and economic impact) of secondary prophylaxis vs. episodic treatment in adult haemophiliacs.

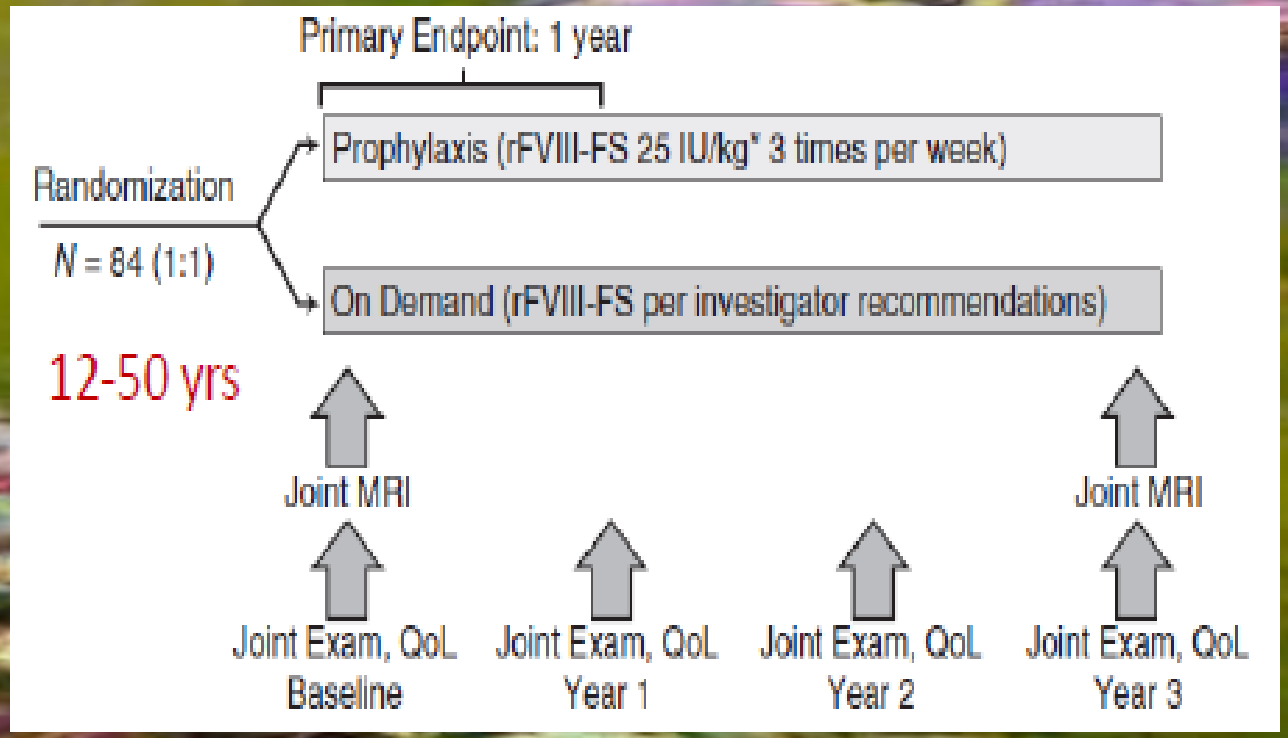
Haemophilia (2010), **16**, 952–971

Prospective studies on prophylaxis in adults

Author, yr	Type of study	Patients	Follow-up	Main results
Collins, 2010	Cross-over (6 mo. OD then 7 mo prophylaxis 20-40 IUKg t.i.w., including 1 mo. run-in)	19 HA (30-45 yrs) 2 bleeds per mo.	6 mo.	⬇ median number of joint bleeds (15 → 0), ⬇ Gilbert scores (mainly due to ⬇ bleeding) ~ 3-fold ⬆ factor infusions and consumption) No significant difference in health economic parameters and HRQoL. 48- and 72 hrs trough levels on prophylaxis consistently >6 and 4 IU/dl
Valentino, 2012	Randomization after 6 mo. OD to standard (20-40 IU/Kg e.o.d.) or PK-tailored (20-80 IU/Kg every third day) prophylaxis	66 HA (7-59 yrs), 57 (86%) >16 yrs	12 mo.	⬇ Median annual bleeding rate (44 OD → 1 standard, 2 PK-tailored P). Improvement of HRQoL (pain and physical components). No significant difference in ABR, FVIII consumption and HRQoL between the two prophylaxis regimens. Median trough levels 3 and 1 IU/dl on standard and PK-tailored prophylaxis, respectively

Short follow-up ! → **No data on long-term outcomes**

The first randomized study: SPINART



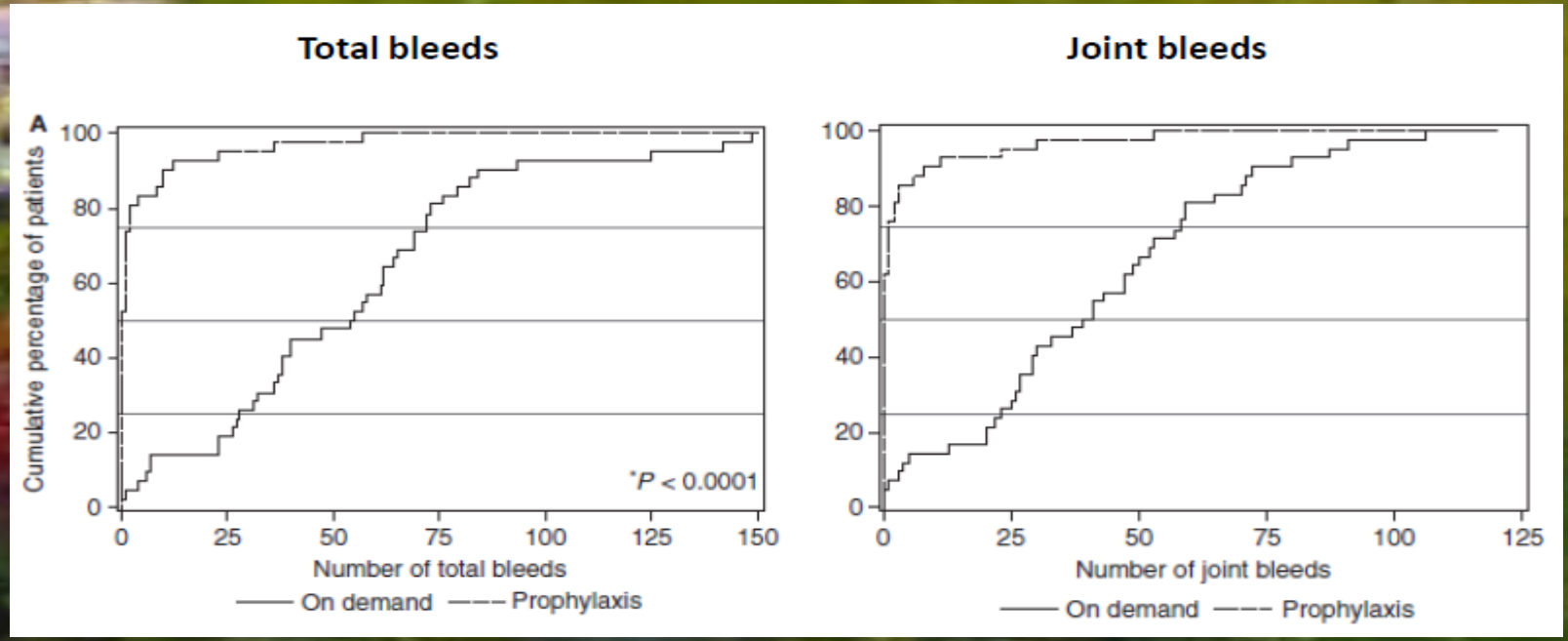
Ongoing, 1-yr interim analysis published

- Manco-Johnson et al, J Thromb Haemost 2013

SPINART: 1-yr results

	Prophylaxis (n=42)	On-demand (n=42)
Age*	29 (15-50)	29 (17-48)
Severe (<1%)	39	42
Target Joints (yes/no)	28/14	31/11
Bleeds in last 12 mo.*	17 (6-42)	19.5 (8-47)
Annual bleeding rate*	**0 (0-9)**	**27.9 (16.5-45.7)**

*median (range)



Prophylaxis vs

On demand

Therapy

Through

Economic

Report

A. Tagliaferri et al, WFH 2012

Study design and aims

- ✓ **Observational**
- ✓ **Prospective**
- ✓ **Multi-centre**
- ✓ **Open label**
- ✓ **Two arms**

STUDY

➢ To evaluate the **clinical effects** and **pharmaco-economic impact of long-term secondary prophylaxis** with **rFVIII (octocog-alfa)** in **adolescents** and **adults** (12-55 yrs) with **severe haemophilia A.**

➢ **To compare long-term secondary prophylaxis vs. on-demand treatment.**

End-points

Primary end-point:

- **Number of joint bleeds/year**

Other evaluations:

- **Number of total bleeds/year**
- **Joint status (Orthopaedic Joint Score and Pettersson Score)**
- **Pharmacoeconomic assessment**
- **Health-Related Quality of Life (HRQoL)**
- **Patients' compliance to treatment**
- **Adverse events**

Inclusion Criteria

- Adolescents or adults (age ≥12 and ≤55 yrs)
- Severe haemophilia A (FVIII < 1%)
- Absence of Inhibitor
- PTP > 200 Exposure days
- Treatment with rFVIII (octocog-alfa)
  - **Prophylaxis**: 20-30 IU/Kg t.i.w.
  - **On-demand**: ≥ 6 joint bleeds in the last 6 months prior to the study
- Written informed consent

Follow-up

- **Clinical assessment:** ***every 6 months***
  - bleeding episodes
  - treatments and rFVIII (octocog-alfa) consumption
  - work/school days lost
  - medical visits, days in hospital, physiotherapy, radiological and other exams, other drugs.
- **Evaluation of Orthopaedic Joint Score and HRQoL (Haemo-QoL, SF-36, EQ 5D):** ***every 12 months*****.**
- **Pettersson score:** ***baseline, study end (if available)***
- **Follow-up: 3 yrs planned, extended to 5 yrs**

1st pt enrolled: 31 July 2004 - Enrolment end: 30 September 2005

Study end: December 2010 (Sept-Dec)

Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study

Annarita Tagliaferri[1]; Giulio Feola[2]; Angelo Claudio Molinari[3]; Cristina Santoro[4]; Gianna Franca Rivolta[1]; Dorina Bianca Cultrera[5]; Fabio Gagliano[6]; Ezio Zanon[7]; Maria Elisa Mancuso[8]; Lelia Valdrè[9]; Luciana Mameli[10]; Susanna Amoresano[11]; Prasad Mathew[12]; Antonio Coppola[13]; for the POTTER Study Group*

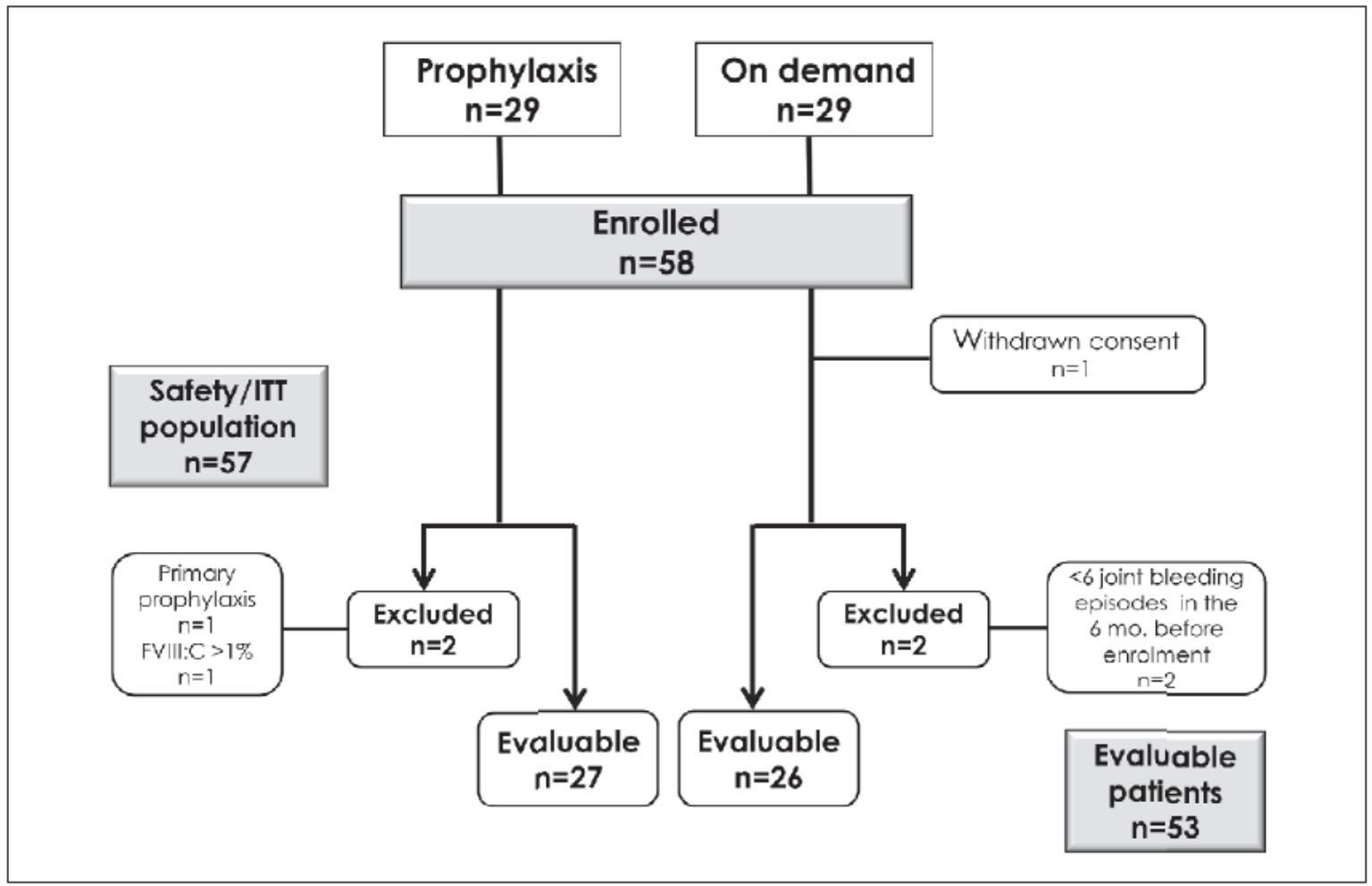


Figure 1: Patient disposition according to treatment regimen at study enrollment.
ITT=intent to treat.

Table 1: Baseline patient characteristics by treatment regimen* and age subgroup.

	Prophylaxis		On demand	
	Age 12–25 years (n=14)	Age 26–55 years (n=13)	Age 12–25 years (n=11)	Age 26–55 years (n=15)
Age, years				
Mean (SD)	17.0 (3.8)	31.1 (3.9)	18.1 (5.5)	36.9 (7.5)
Median (range)	17.5 (12–23)	30.0 (27–39)	17.0 (11–25)	37.0 (26–49)
Age at diagnosis, years				
Mean (SD)	1.0 (1.4)	2.0 (1.5)	0.6 (1.2)	3.9 (4.9)
Median (range)	0.5 (0–4)	2.0 (0–4)	0.0 (0–4)	2.0 (0–16)
Age at start of prophylaxis, years†			–	–
Mean (SD)	11.5 (4.1)	27.7 (5.5)	–	
Median (range)	12.2 (8–19)	27.0 (20–38)		
Duration of prophylaxis before study entry, years‡			–	–
Mean (SD)	4.8 (2.7)	2.9 (2.7)	–	
Median (range)	4.0 (1–9)	1.0 (0.5–7)		
Prophylaxis dose, IU/kg			–	–
Mean (SD)	27.5 (3.6)	25.0 (4.2)		
Median (range)	27.0 (20–35)	26.0 (15–30)	–	–
Frequency (times/week), mean	3	3	–	–

8 shifter patients

5 OD → prophy

1 OD ↔ prophy

2 prophy ↔ OD

*Forty-five patients maintained the same regimen of treatment throughout the study, whereas 8 patients shifted from one regimen to the other once (4 patients in the subgroup aged 26–55 years and 1 in the subgroup aged 12–25 years) or more than once (2 patients in the older and 1 in the younger subgroup). All five patients who changed regimen only once shifted from the on-demand to the prophylaxis regimen. The remaining three patients (1 on-demand patient and 2 prophylaxis patients) had 3 to 4 regimen changes, all concluding at the study follow-up on prophylaxis. †$P<0.0001$ between age groups (analysis of variance model). ‡$P=0.0354$ between age groups (analysis of variance model).

Table 2: Efficacy outcomes by treatment regimen and age subgroup.

	Prophylaxis		On Demand		P between treatment cohorts
	Age 12–25 years (n=14)	Age 26–55 years (n=13)	Age 12–25 years (n=11)	Age 26–55 years (n=15)	
Follow-up duration, years					
Median (range)	5.4 (4.0–6.0)	5.7 (4.0–6.0)	5.7 (5.0–6.0)	5.3 (0.5–6.0)	
Joint bleeding episodes					
Mean^ (SD)	2.0 (2.0)	3.4 (4.6)	16.6 (12.4)	13.7 (11.2)	0.0043†
Median^ (range)	1.1 (0.2–5.6)	2.0 (0.0–17.6)	14.2 (2.4–48.6)	9.2 (1.6–40.6)	
Annualised bleeding rate*					
Observed	1.97	2.46	16.80	16.71	
Estimated by model (95% CI)	1.92 (1.2–3.2)	2.46 (1.5–4.1)	16.05 (10.2–25.3)	18.04 (12.5–26.1)	
Total bleeding episodes					
Mean (SD)	2.6 (2.2)	4.5 (7.1)	19.5 (15.0)	17.7 (11.7)	0.0048†
Median (range)	2.1 (0.2–6.8)	2.2 (0.0–27.4)	15.6 (6.0–60.8)	15.0 (2.2–47.6)	
Annualised bleeding rate*					
Observed	2.54	2.95	19.77	21.49	
Estimated by model (95% CI)	2.47 (1.6–3.8)	2.95 (1.8–4.7)	19.14 (12.2–30.1)	22.40 (16.3–30.8)	
Target joints°					
Number of patients (%)	2 (14.3)	5 (38.5)	9 (81.8)	12 (80.0)	<0.001**
Mean number per patient (total number)	0.14 (2)	0.77 (10)	1.64 (18)	1.93 (29)	
Orthopaedic Joint Score (pain + physical examination), mean (SD)					
Baseline	3.2 (3.3)	13.3 (15.4)	5.4 (3.0)	17.1 (10.3)	0.0019§
Last evaluation‡	3.0 (2.4)	10.1 (12.5)	8. 8 (4.4)	21.5 (12.8)	
Change last evaluation vs baseline	–0.2 (3.4)	–3.2 (9.7)	+3.6 (4.8)	+4.4 (6.2)	
Pettersson score, mean (SD)‖					
Baseline	4.3 (4.5)	20.0 (18.9)	3.3 (4.9)	22.2 (15.1)	0.0177§
Last evaluation¶	5.5 (4.9)	22.2 (18.5)	5.7 (6.7)	35.0 (17.2)	
Change last evaluation vs baseline	+1.2 (1.6)	+2.2 (2.8)	+2.3 (2.1)	+12.8 (12.3)	
Total average consumption rFVIII, IU/kg/year					
Mean (SD)	3795.8 (1030.7)	3664.5 (763.8)	1367.7 (1330.1)	2004.2 (1321.1)	<0.0001#
Median	3998.0	3844.4	786.4	1651.3	
Range	887.8–4858.0	2259.3–5261.2	432.3–4305.1	211.8–4562.3	
Mean number of days of everyday activities lost/ patient-/caregiver-year	10.6	13.8	43.0	35.6	<0.001**

Pts in prop vs OD
Young 8.1 } time
Old 7.3 } less

67% P vs 19% OD free TJ

Greater effect Pr in older than younger
87% reduction vs 48%

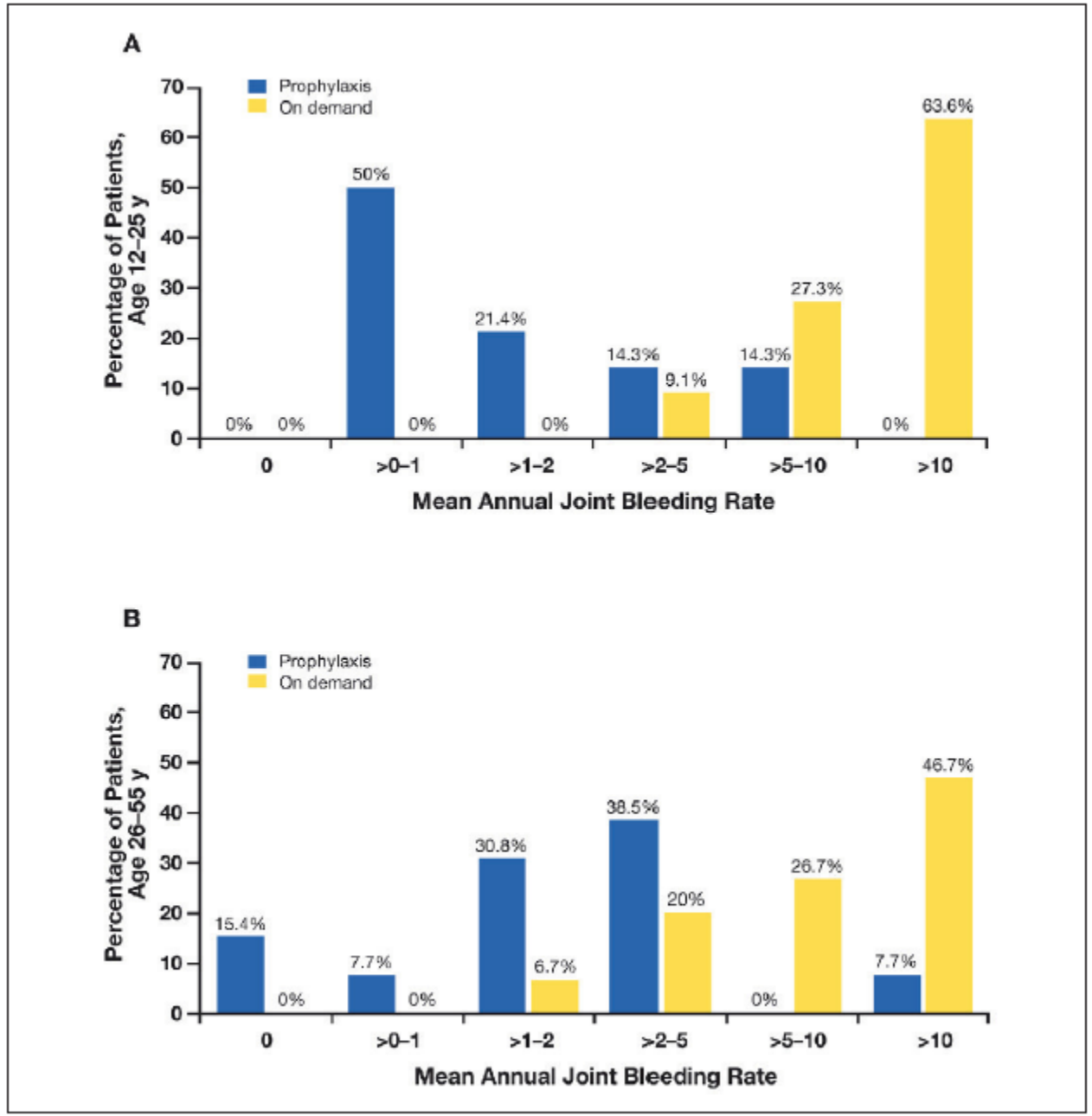


Figure 2: Distribution of patients according to mean annual number of joint bleeding episodes in the two treatment regimens (prophylaxis and on demand) in the (A) 12– to 25-year age group and (B) 26– to 55-year age group. Overall, among patients on prophylaxis, annual joint bleeding rates >5 were reported by 2 patients in the younger group (5.2 and 5.6, respectively) and by a single patient in the older group (17.6).

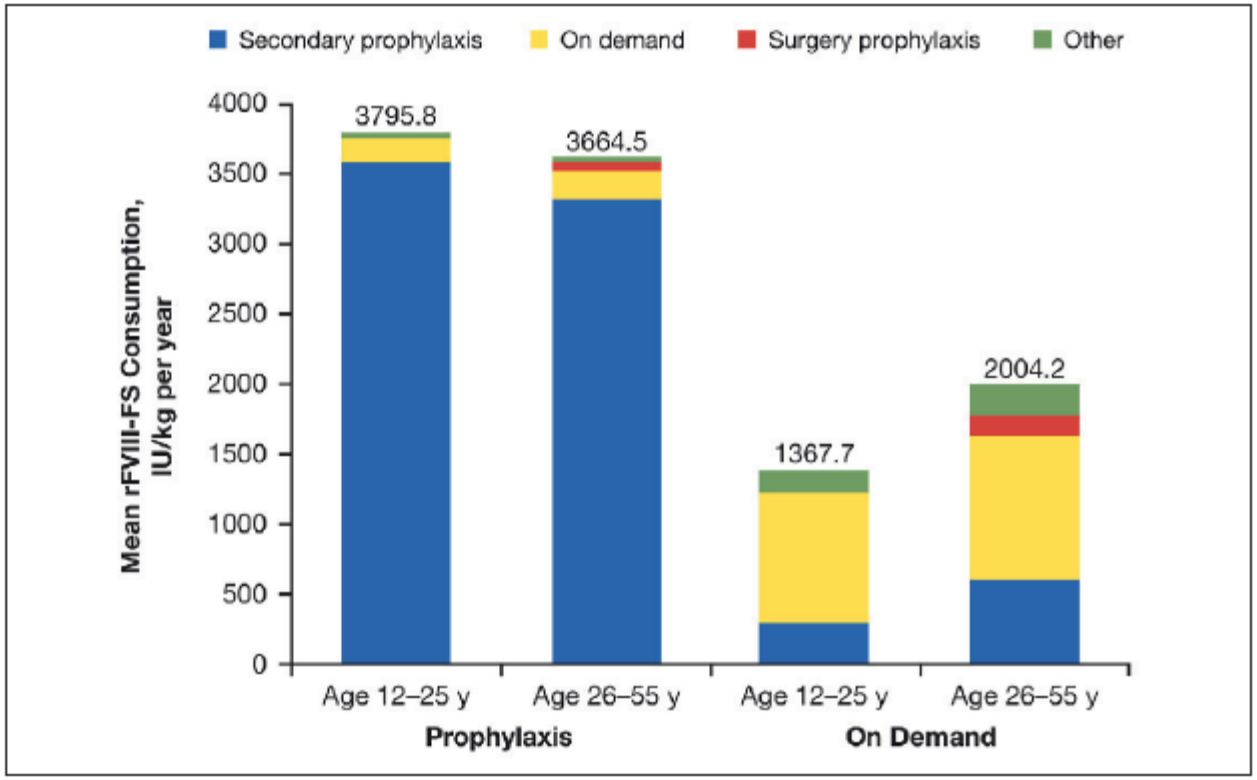


Figure 3: Annual rFVIII-FS consumption based on reason for treatment. Mean values of annual rFVIII-FS consumption (IU/kg per year) according to reason for treatment ($p<0.0001$, ANOVA model treatment regimen effect). ANOVA=analysis of variance; rFVIII-FS=recombinant full-length factor VIII product formulated in sucrose.

Prophylaxis 2.8 vs 1.8 fold higher r-FVIII use for younger vs older ($p<0.0001$)

However FVIII use for bleeding episodes, surgical proph, and other events had a greater impact in pts OD

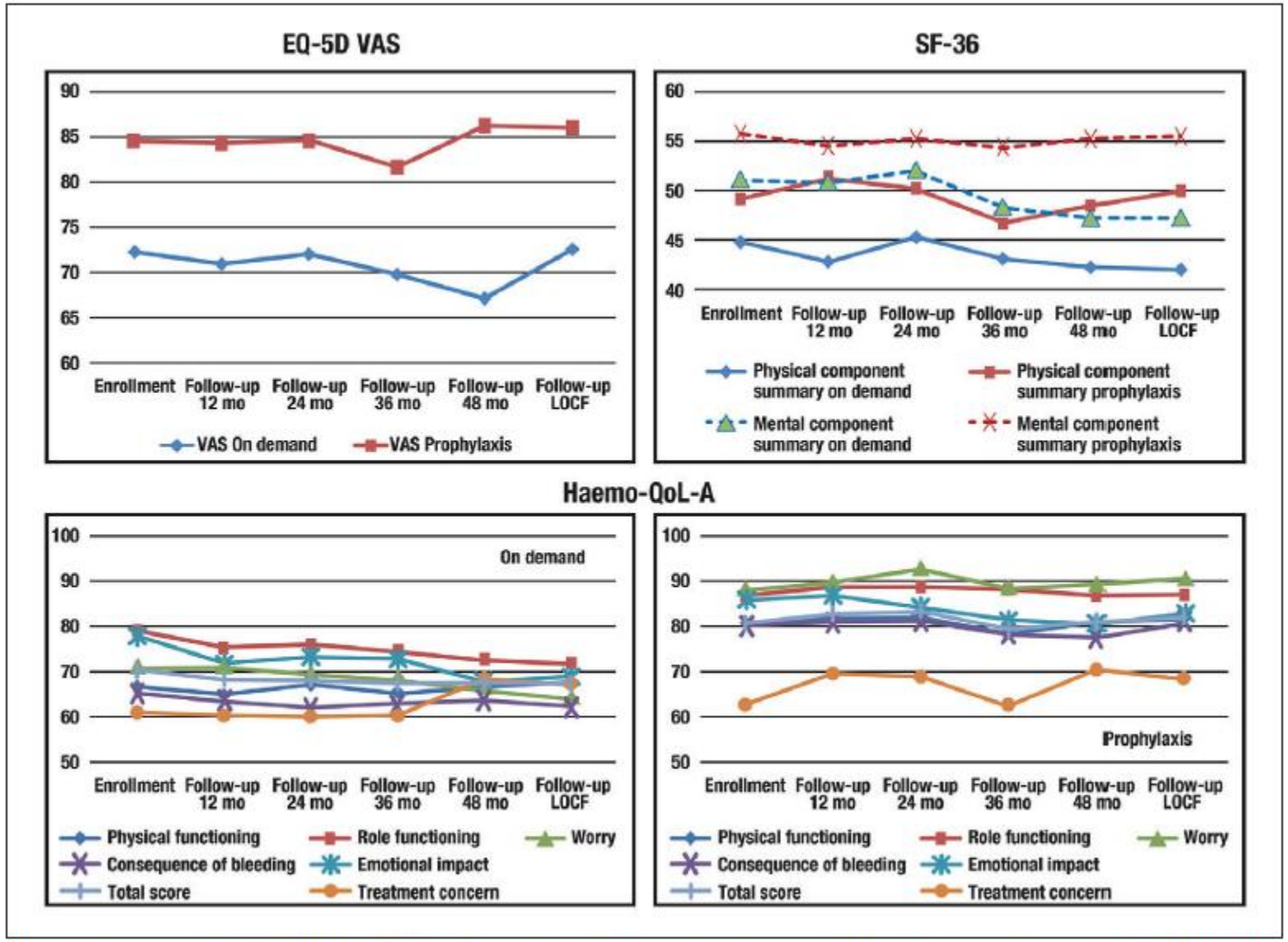


Figure 4: Assessment of health-related quality of life in the two treatment regimens (prophylaxis and on demand) according to EQ-5D (VAS), SF-36 (physical and mental component summaries), and Haemo-QoL-A questionnaires. EQ-5D=5-dimension EuroQoL; LOCF=last observation carried forward (data collected between 54 and 72 months); SF-36=36-item Short Form; VAS=visual analogue scale.

Pts in prophylaxis reported better HRQoL than pts OD. Differences at baseline were significant in SF36, EQ-5D, 4 Haemo-QoL domanin (physical f, role f, worry, consequence of bleeding). Haemo-QoL total score persisted throught the study.
Worse HRQoL was associated with higher mean of bleeds

Conclusions

The POTTER study is the **first long-term prospective study, controlled trial** to document, over a **5-yr follow-up,** the **clinical benefits of late secondary/tertiary prophylaxis**

Significant decreases in **total** and **joint bleeds**, **target joint** and improve **joint status** as revealed by orthopaedic scores

Pettersson scores → prophylaxis may actually **delay progression of arthropaty** even in patients with clinically relevant joint damage

Conclusions

clinical benefits of late secondary/tertiary prophylaxis

Improved **HRQoL**

Impr… → …ies lost

Clinical a… … **…mption**

…crease … **…re costs** … **…ost**

Mean adherence to prophylaxis in our long-term study was even higher than that reported in short-term trials (14, 15). These data seem to dispute the poor adherence to prophylaxis that is often reported in adolescents and adults (26–29), which is perceived as a major barrier for extending or starting prophylaxis later in life (27, 30). Patients with a significant bleeding tendency and long previous experience of on-demand treatment are well aware of clinical benefits of prophylaxis and are highly motivated to adhere to such regimens.

Addressing challenges from prospective studies

Mean FVIII consumption IU/Kg/yr	Prophylaxis	On-demand
JOS (children)	6000	2500
Collins 2010 (6 mo.)	**4552**	**1630**
SPINART (1 yr)	**3298**	**1363**
POTTER (5 yrs) 12-25 yrs	**3796**	**1368**
26-55 yrs	**3665**	**2004**

Study	Mean adherence
SPINART	75%
POTTER (26-55 yrs)	90%

Cost-effectiveness and cost-utility of prophylaxis in adults

- So far no rigorous study available (lack of long-term prospective data concerning joint status and HRQoL → expected from POTTER)
- Economic models only from studies in children.
- Cost-effectiveness improvement
  - from tailored prophylaxis regimens (PK- or bleeding phenotype-driven) ?
  - from switching strategies (OD→P →OD…) ?

ORIGINAL ARTICLE

Haemophilia (2013), 1–11

Treatment for life for severe haemophilia A– A cost-utility model for prophylaxis vs. on-demand treatment

A. FARRUGIA,*†‡ J. CASSAR,§ M. C. KIMBER,* M. BANSAL,* K. FISCHER,¶ G. AUSERSWALD,** B. O'MAHONY,†† K. TOLLEY,‡‡ D. NOONE†† and S. BALBONI*

Older adults

- 64% respondents consider prophylaxis in patients >50 yrs but no consensus on the managment
- 23% patients (58/251) were on a form of regular concentrate administration

EU Survey, Richards et al, Haemophilia 2007

Newer bleeding risks ?

- Thrombocytopenia and advanced liver disease
- Risks of falls
- Rehabilitation (after orthopedic surgery)
- Antithrombotic treatment in patients with cardiovascular disease

WFH GUIDELINES

Haemophilia (2013), 19, e1–e47

Guidelines for the management of hemophilia

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Table 1-4. Definitions of factor replacement therapy protocols [64].

Protocol	Definition
Episodic (on-demand treatment)	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis	
Primary prophylaxis	Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years**
Secondary prophylaxis	Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent (periodic) prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

3. Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2)

Early PROPHYLAXIS

7. Prophylaxis does not reverse established joint damage; however, it decreases frequency of bleeding and may slow progression of joint disease and improve quality of life.

PROPHYLAXIS started later in life

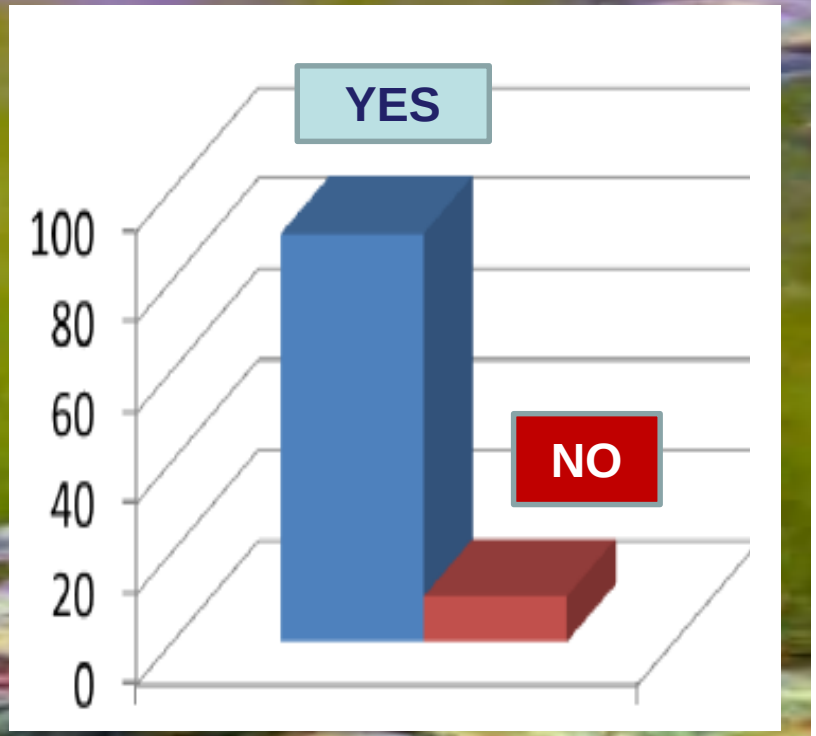
Prophylaxis: 'age-specific' objectives

Table 2. Types of prophylaxis and goals.

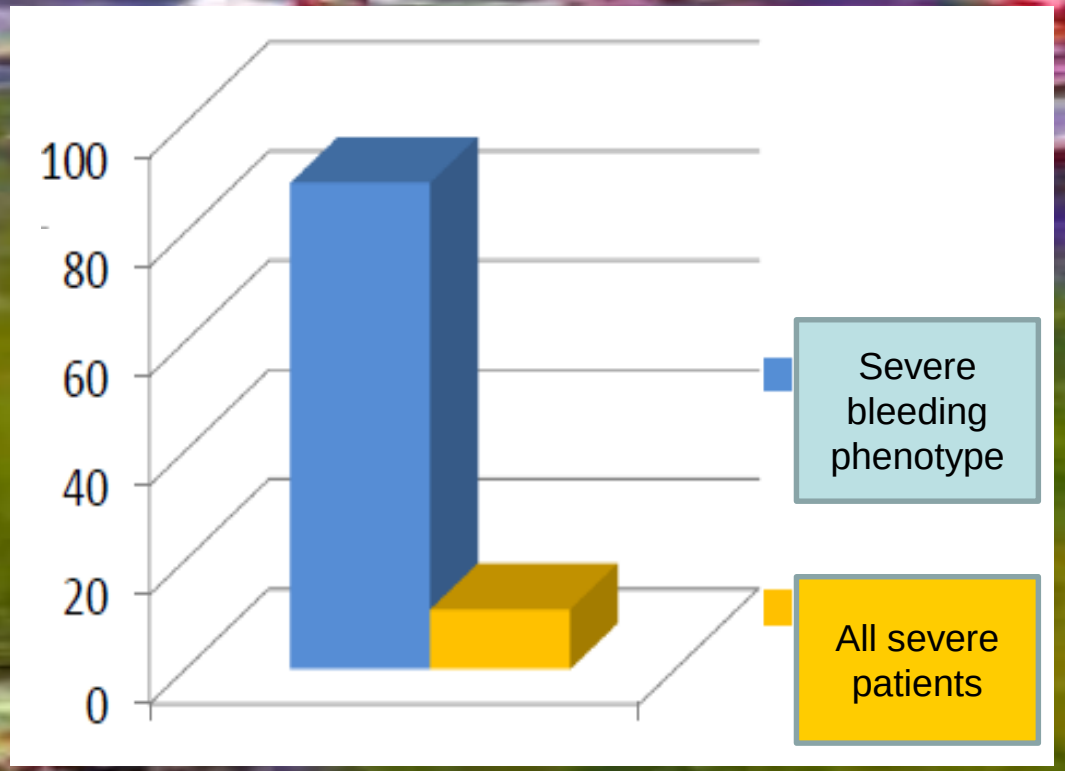
Primary prophylaxis	Secondary prophylaxis	Tertiary prophylaxis
Prevent life-threatening bleeds	Prevent life-threatening bleeds	Prevent life-threatening bleeds
Preserve pristine joints	Reduce the risk of arthropathy	Reduce the worsening of arthropathy
Minimize bleeding occurrence	Reduce bleeding frequency	Reduce bleeding frequency
Maintain high levels of QoL	Maintain high levels of QoL	Improve QoL
Support normal social participation and studying/working life	Support normal social participation and studying/working life	Improve social participation and maintain working activity and independence
Allow physical activities	Allow physical activities	Improve activity/autonomy levels
–	Prevent target joints	Reduce bleeding in target joints
–	–	Control pain
–	–	Permit physiotherapy
–	–	Reduce bleeding risk due to comorbidities

Gringeri et al, Haemophilia 2012

The opinion of Italian treaters



Use of prophylaxis in adults



In which patients ?

Survey AICE 2013, Franchini et al, Haemophilia 2013

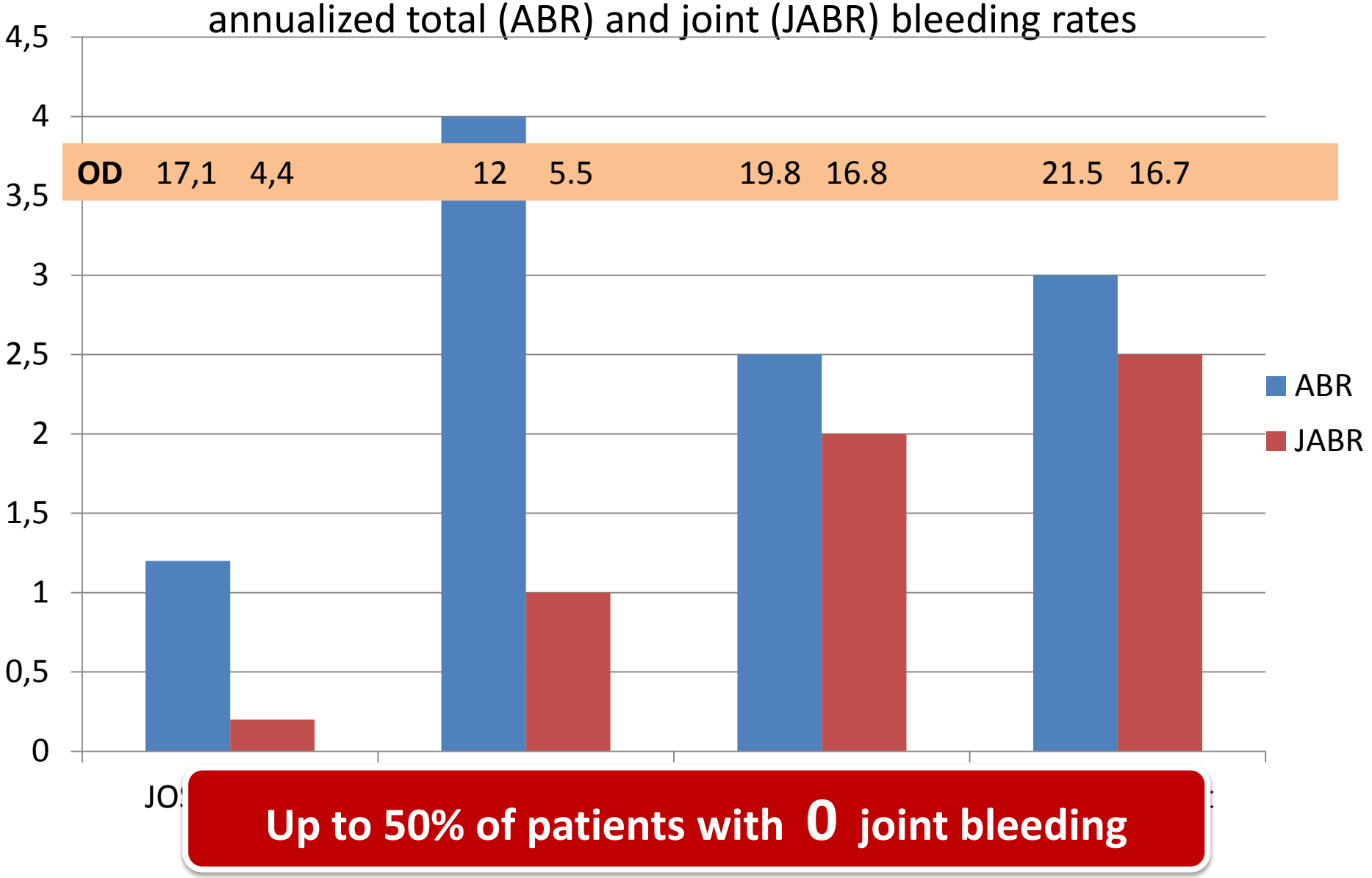
Addressing challenges for adult prophylaxis

- Elucidating determinants of bleeding phenotype in young-adults potentially discontinuing treatment.
- Elucidating long-term outcomes (joint bleeds, impact on joint disease) in these patients.
- Providing evidence of the global clinical impact of starting prophylaxis in adults, beyond reduction of frequency of bleeding (joint status, HRQoL, cost-utility).
- Defining and experiencing tailored adult (and individualized?) prophylaxis regimens.

Personalizzare la terapia:

fenotipo, PK, stile di vita, aderenza….

Prophylaxis: current achivements



Un regime per tutti ?

Pivotal approaches

- Swedish

High dose (25-40 IU three times per week, **adjusted if spontaneous breakthrough bleeds**)

Fast escalation after start

Trough levels measured

- Dutch

Intermediate dose (15-25 IU/Kg, two-three times per week, **adjusted if spontaneous breakthrough bleeds**)

Trough levels not measured

No direct comparison available!

Assessment:

- Efficacy / safety
- Convenience
- Costs

cost-effectiveness

cost-utility

Assessing '**values**' of prophylaxis

	Dosing principle	Convenience	Efficacy	Cost
Dutch regimen (intermediate dose)[26]	15–25 IU/kg Start early after occurrence of joint bleeds	+/–	+	–/+
Traditional Swedish regimen (high dose)[25]	25–40 IU/kg Start before joint bleeds	+/–	++	––
Pharmacokinetic (Swedish) dosing[27]	Individualised from high-dose by reducing dose interval and total dose	–	+++	+++
Canadian regimen (dose escalation)[28]	50 IU/kg weekly Intensify stepwise depending on bleeding frequency Start early after occurrence of joint bleeds.	+	+	+

+=superior. –=inferior.

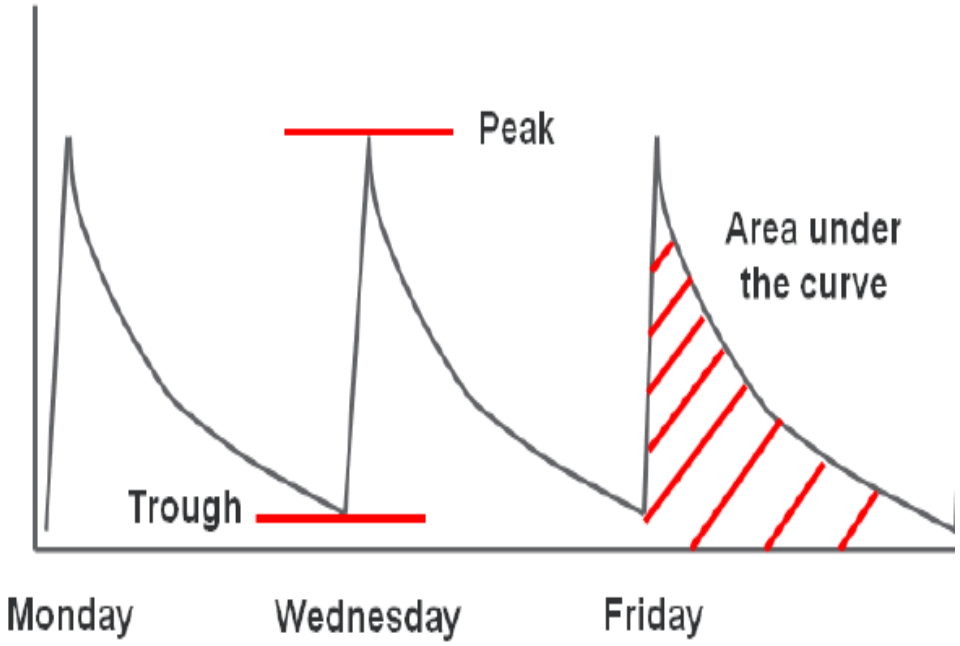
***Table 2*: Main dosing strategies for long-term prophylaxis**

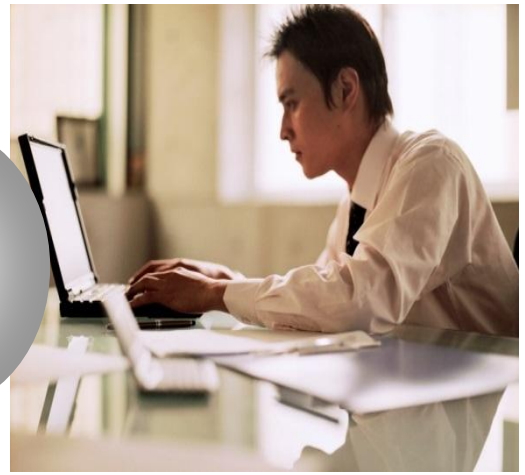
Berntorp & Shapiro, Lancet 2012

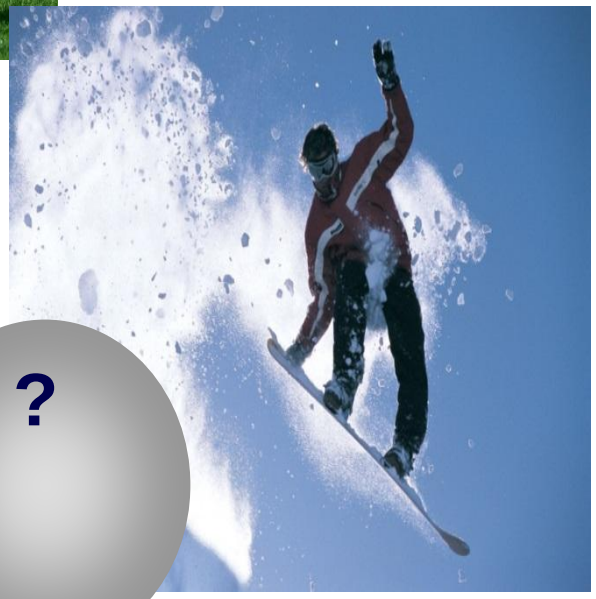
«Ottimizzare» la profilassi ?

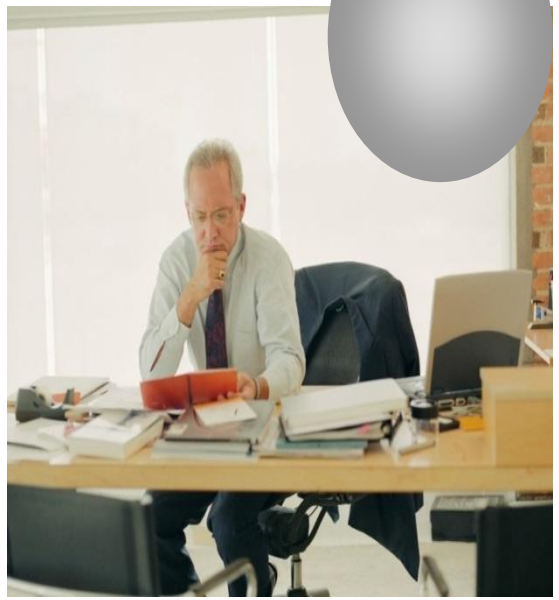
Breakthrough bleeding: why ?

- Trauma
- Activity (lifestyle)
- Joint status
- FVIII levels (trough)
- Adherence
- ……





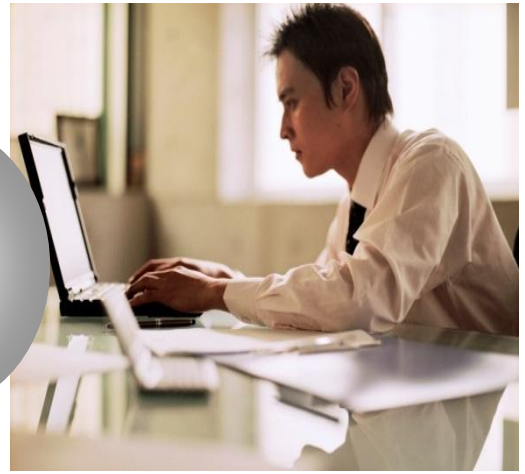




Which Trough Level ?

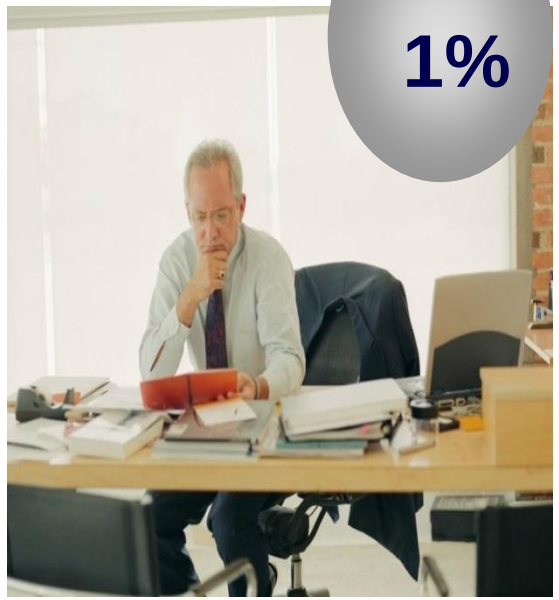
ins PW et al. *J Thromb Haemost*. 2010;8(2):269-275.

?
10%



?
2%

?
30%



?
1%

Which Trough Level ?

ins PW et al. *J Thromb Haemost*. 2010;8(2):269-275.

The dilemma

- What is affordable….

- What is desirable….

Tailoring prophylaxis

- May change:
  - Dose
  - infusion frequency
  - Timing
  - Target trough levels

Factor levels depends on

- Regimen (dose, frequency)
- PK
- Adherence

Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens

- breakthrough bleedings are related to the time per week spent with FVIII<1%
- the frequency of infusion and half-life FVIII have a much bigger effect on trough level than altering the dose or the *in vivo* recovery

Table 3 Effect of half-life and frequency of dosing on weekly factor (F)VIII requirement

	Amount of FVIII per week to maintain a trough level above 1 IU dL^{-1} (IU kg^{-1})							
	Daily dosing		Alternate day dosing		Every third day dosing		Mon/Wed/Fri dosing	
Half-life	1–6 years	10–65 years	1–6 years	10–65 years	1–6 years	10–65 years	1–6 years	10–65 years
5th percentile	29	24	153	121	967	747	497	386
Median	17	12	59	35	236	119	132	69
95th percentile	9	5	21	10	54	20	34	14

- knowledge of patient's half-life:
  - will be more useful than IVR when tailoring prophylactic regimens
  - migh allow more cost effective prophilaxis regimens to be prescribed

Collins P et al,Journal of Thrombosis and Haemostasis 2010, 8: 269–275

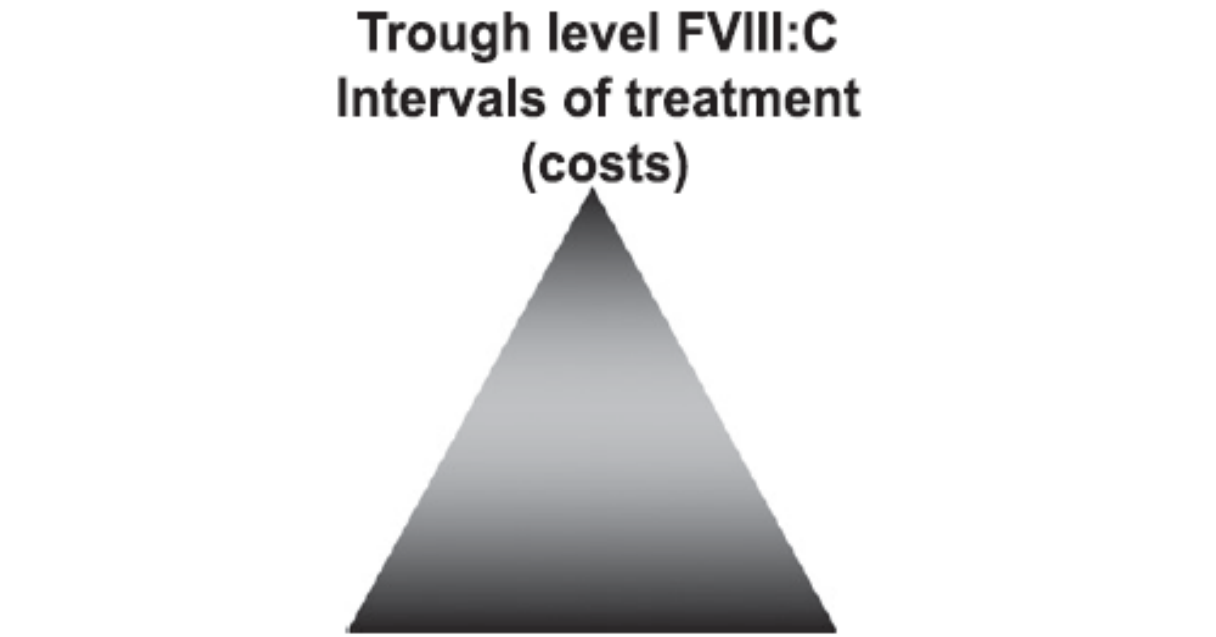
Tailoring prophylaxis

- Personalized regimens, based not only on weight, but using all information available:

  Better and actually tailored to the individual

  More cost-effective

Determinants of prophylaxis regimen



Oldenburg J. *Blood* 2015; 125: 2038-2044

Indicatori di efficacia della profilassi

- Clinici: ABR, score ortopedici (Gilbert, HJHS)
- Laboratoristici: Trough levels, inhibitor
- Strumentali: Rx, ecografia, RMN
- HRQoL, aderenza
- Consumo di FVIII, costi

Come seguire (e personalizzare) la profilassi ?

Haemophilia (2003), 9, 376–381

Prophylaxis for severe haemophilia: clinical and economical issues

K. FISCHER*† and M. VAN DEN BERG†

Table 1. Treatment according to strategy.

	On demand $n = 106$	Prophylaxis	
		Interm. dose $n = 49$	High dose $n = 24$
Age at evaluation (year)	22.3 (18.9–25.4)	22.3 (18.5–24.5)	17.2 (15.2–20.4)
Past treatment			
Age at start prophylaxis (year)	NA	5.4 (4.1–8.7)	3.1 (2.0–3.9)
Current treatment			
Weekly dose (IU kg^{-1} $week^{-1}$)	NA	35 (24–44)	82 (57–90)
Clotting factor consumption (IU kg^{-1} $year^{-1}$)	1260 (630–2130)	1550 (824–1968)	4301 (3034–4726)

Values are medians (interquartile ranges).

Table 2. Outcome according to treatment strategy.

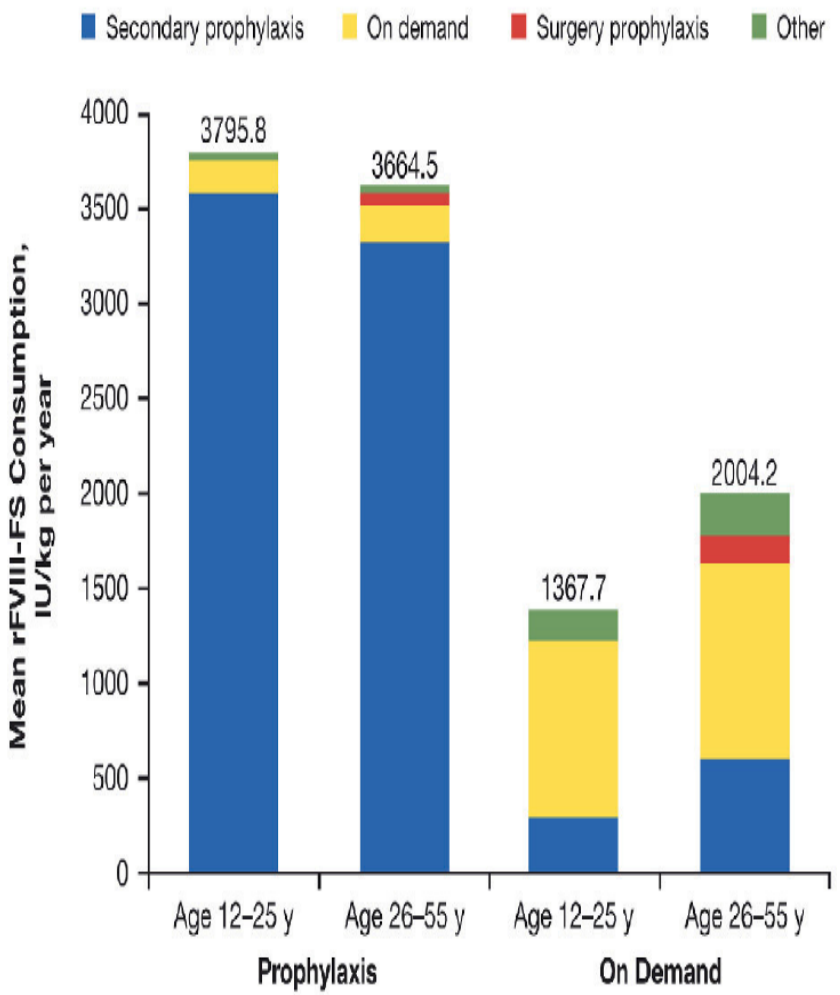
	On demand $n = 106$	Prophylaxis	
		Interm. dose $n = 49$	High dose $n = 24$
Joint bleeds/year (*n*)	11.5 (3.8–24.0)	2.8 (0–7.8)	0.5 (0.2–1.8)
Clinical score (max. 90)	8.0 (3.3–14.0)	2.0 (0.3–5.0)	0 (0–1.0)
Pettersson score (max. 78)	16 (8–28)	7 (3–15)	4 (0–15)
Pettersson = 0 (%)	2%	14%	46%

Values are medians (interquartile ranges).

Quali sono i costi della profilassi ?

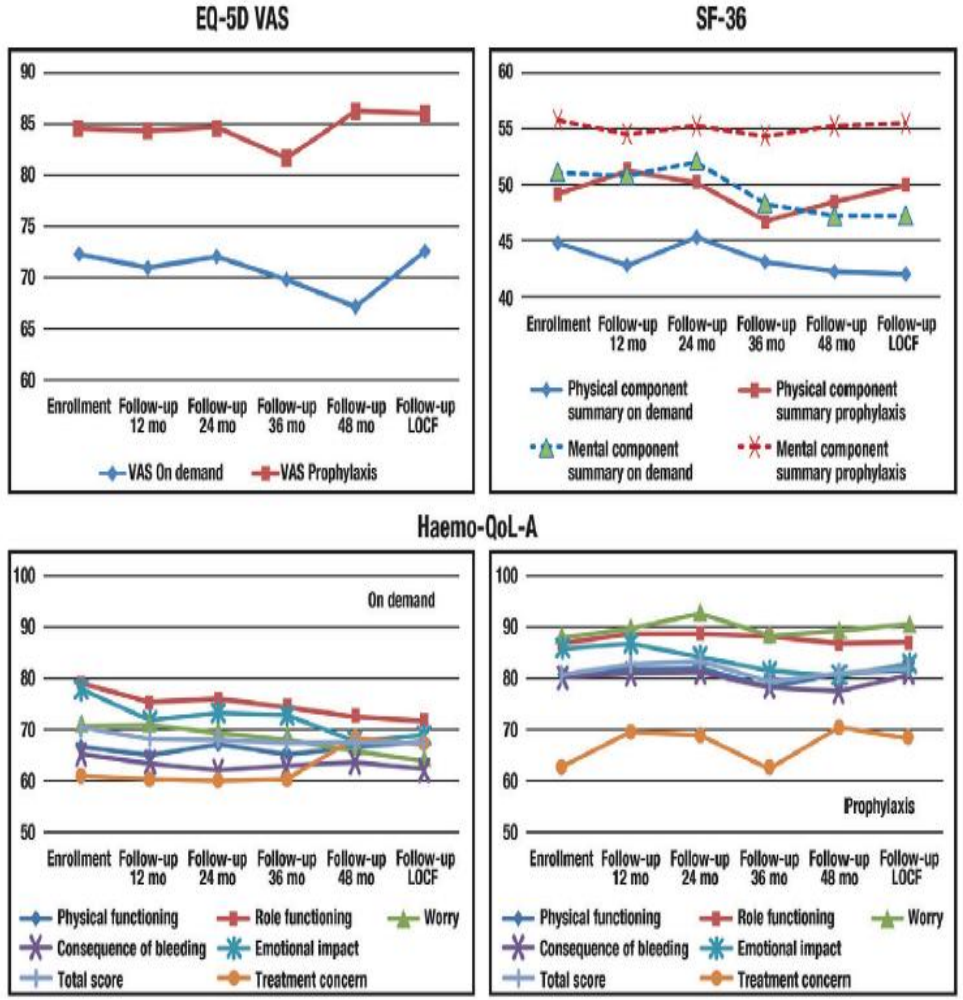
Costo-utilità

Consumo FVIII



POTTER Study

HRQoL



Tagliaferri et al, Thromb Haemost 2015

Il futuro……. prossimo…….

bjh review

New products for the treatment of haemophilia

Laffan, Oct 2015

Table II. Extended half-life products.

	Source/Comments	Effect on half life		Assay*
		Measured half-life	Fold increase over control	
FACTOR VIII				
Factor VIII-Fc	Human HEK293 cell line BDD	11–18·8 h	1·7	One stage + normal plasma standard and chromogenic
Factor VIII-random PEG	CHO cells Full length	Not stated	1·5	One stage assay
Factor VIII-O-glycopegylation	CHO cells BDD	18·4 h	1·6	–
Factor VIII-site specific pegylation (K1804C)	BHK 21 BDD	13–19 h	1·5	–
FACTOR IX				
Factor IX-Fc	Human HEK293 cell line	60 h	3	One stage + normal plasma standard
Factor IX-glycopegylation	CHO cell line	93 h	5	One stage + product-specific standard
Factor IX-albumin	CHO cell line	92 h	5	Company-specific method

PEG, polyethylene glycol; BDD, B-domain deleted; CHO, Chinese hamster ovary.
*Assay technique reported in phase II/III studies.

rFVIII

Giugno 2016

Lunedì	Martedì	Mercoledì	Giovedì	Venerdì	Sabato	Domenica
		1 	2	3 	4	5
6 	7	8 	9	10 	11	12
13 	14	15 	16	17 	18	19
20 	21	22 	23	24 	25	26
27 	28	29 	30			

icalendario.it

13 infusioni/mese

rFVIII-Fc

Ottobre 2016

Lunedì	Martedì	Mercoledì	Giovedì	Venerdì	Sabato	Domenica
					1	2
3 ✓	4	5	6 ✓	7	8	9
10 ✓	11	12	13 ✓	14	15	16
17 ✓	18	19	20 ✓	21	22	23
24 ✓	25	26	27 ✓	28	29	30
31 ✓						

icalendario.it

9 infusioni/mese

rFVIII-Fc

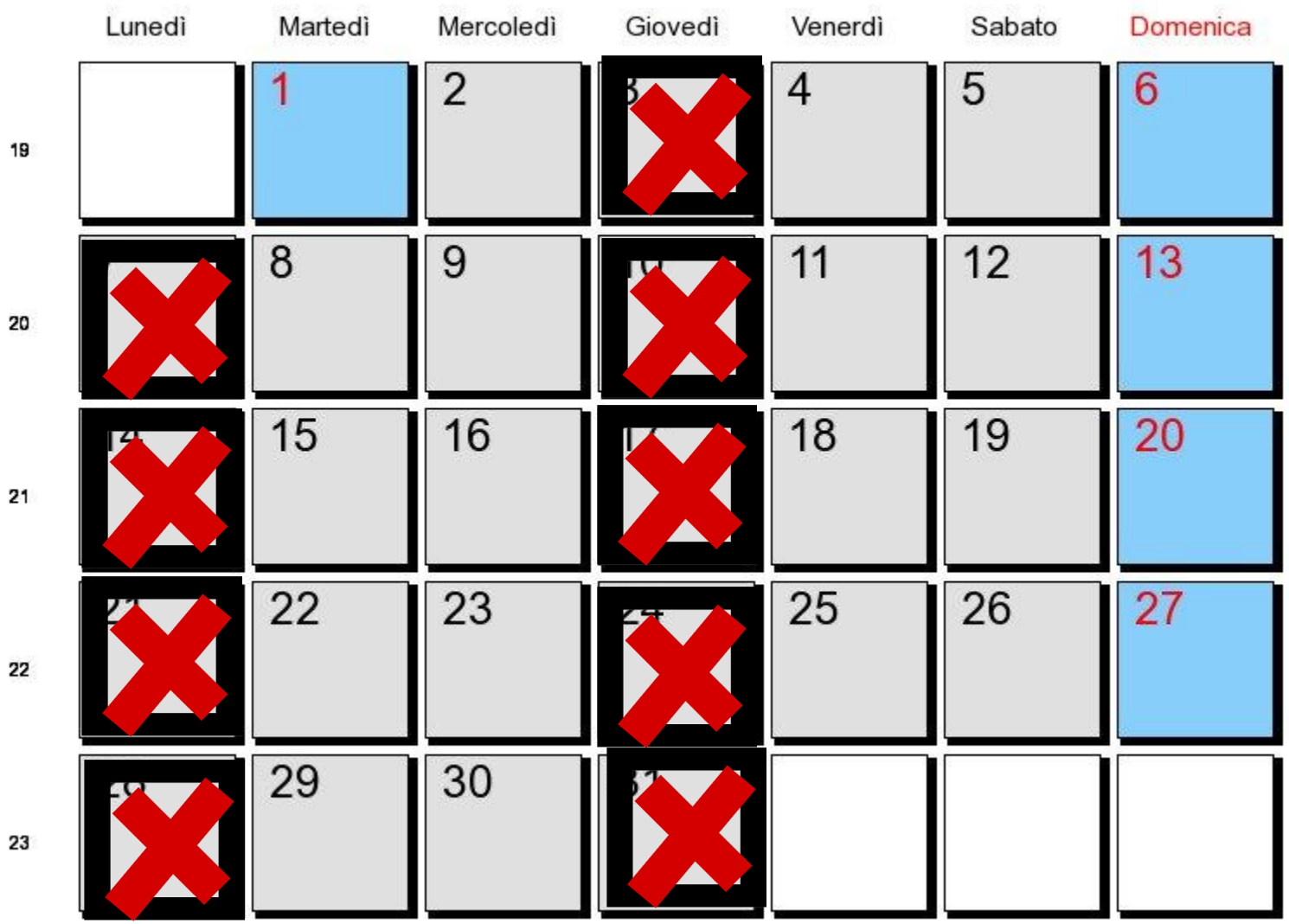
Ottobre 2016

Lunedì	Martedì	Mercoledì	Giovedì	Venerdì	Sabato	Domenica
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

icalendario.it

7 infusioni/mese

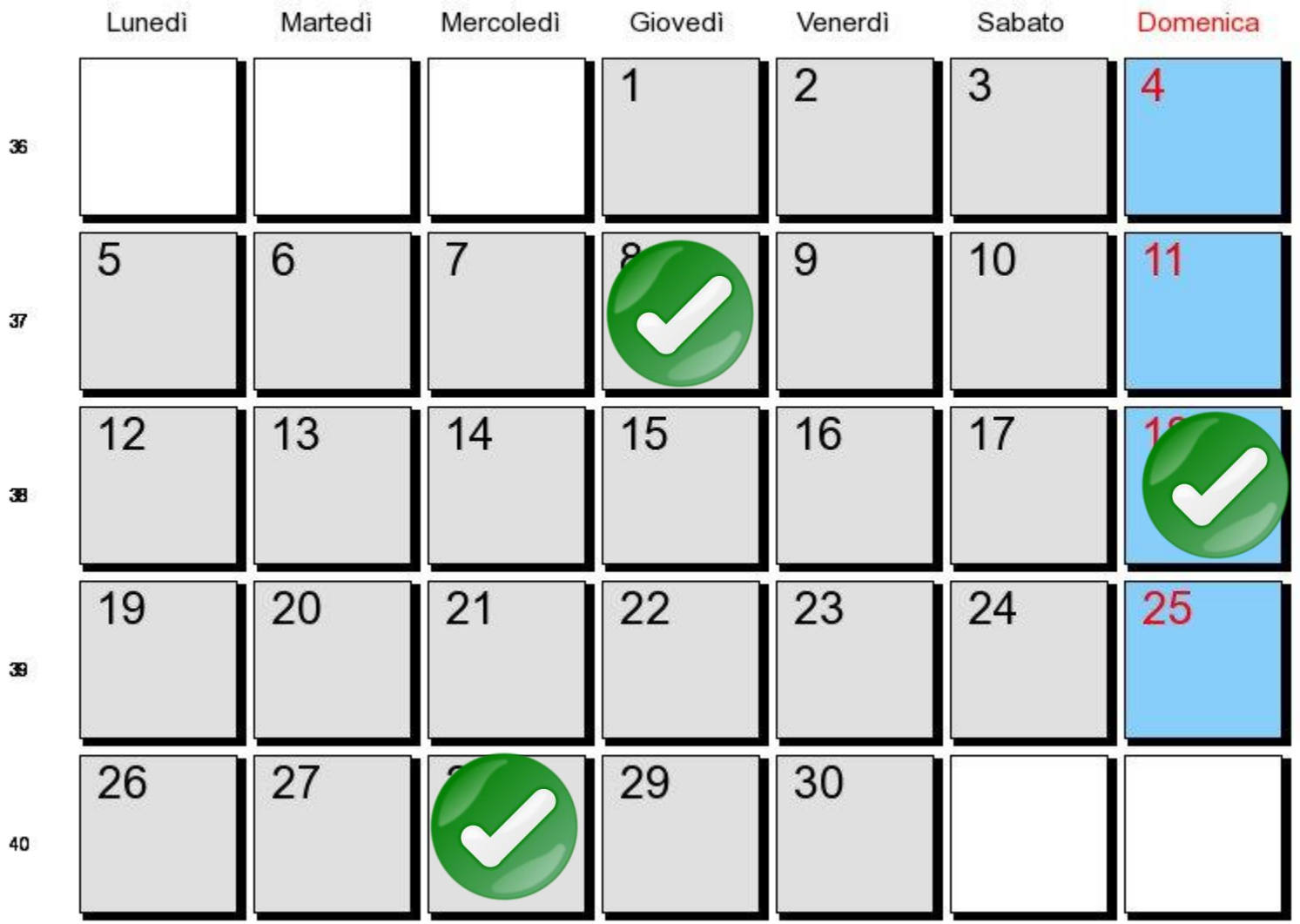
rFIX



9 infusioni/mese

rFIX-long acting

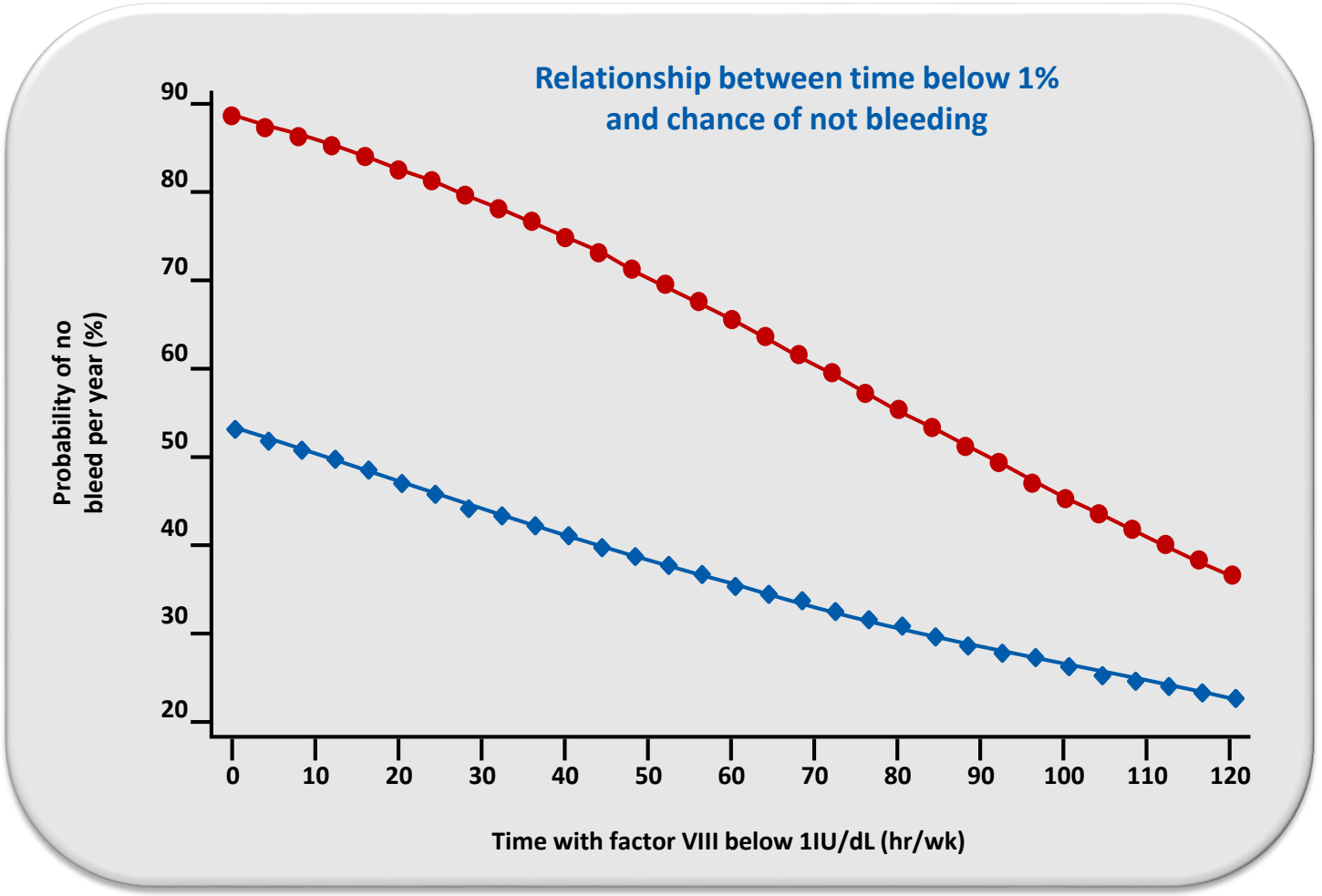
2017



3 infusioni/mese


GRAZIE

Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A



Red: age 1-6 years; **Blue:** age 10-65 years Collins et al, JTH 2009

A Randomized comparison of two prophylaxis regimens and a paired comparison of on-demad and prophylaxis treatments in hemophilia A management

Objectives

Primary: to compare the efficacy of two prophylaxis regimens

Secondary: to compare on-demad teatments and prophylaxis and to continue evaluation of immunogenicity and overall safety of the Advate

On demand tretment for 6 months

69 pts

12 months

Standard prophylaxis
20-40 IU/Kg ***every other day***
32 pts (30pts)

PK-tailored prophylaxis
20-80 IU/Kg ***every third day***
4 pts (23 pts)

Valentino L.A., JTH feb 2012

A Randomized comparison of two prophylaxis regimens and a paired comparison of on-demad and prophylaxis treatments in hemophilia A management

Results

- 22 pts on prophylaxis (33%) no bleeding episodes
- None treated on-demand free from an episode of bleeding
- No difference in FVIII consumption or adverse event rates between prophylaxis regimens
- No subject developed inhibitor

Conclusions

- The study demonstrates comparable safety and effictiveness for two prophylaxis regimens
- Prophylaxis significantly reduces bleeding compared with on-demand
- PK-tailored prophylaxis offers an alternative to standard prophylaxis

Valentino LA, JTH 2012