Il bambino con emofilia

corso di formazione ad alta specializzazione sulla gestione del bambino con emofilia

Padova 13-14 maggio 2016

LA PROFILASSI NEL BAMBINO CON EMOFILIA

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Centro Regionale multidisciplinare per la prevenzione, profilassi e trattamento avanzato dell'artropatia emofilica

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DEFINIZIONE PROFILASSI

PRIMARIA

trattamento continuativo* iniziato, in assenza di un danno osteocondrale, prima di un secondo emartro o dei tre anni di età

SECONDARIA

trattamento continuativo* iniziato dopo due o più emartri

TERZIARIA

trattamento continuativo * iniziato dopo la comparsa di malattia articolare

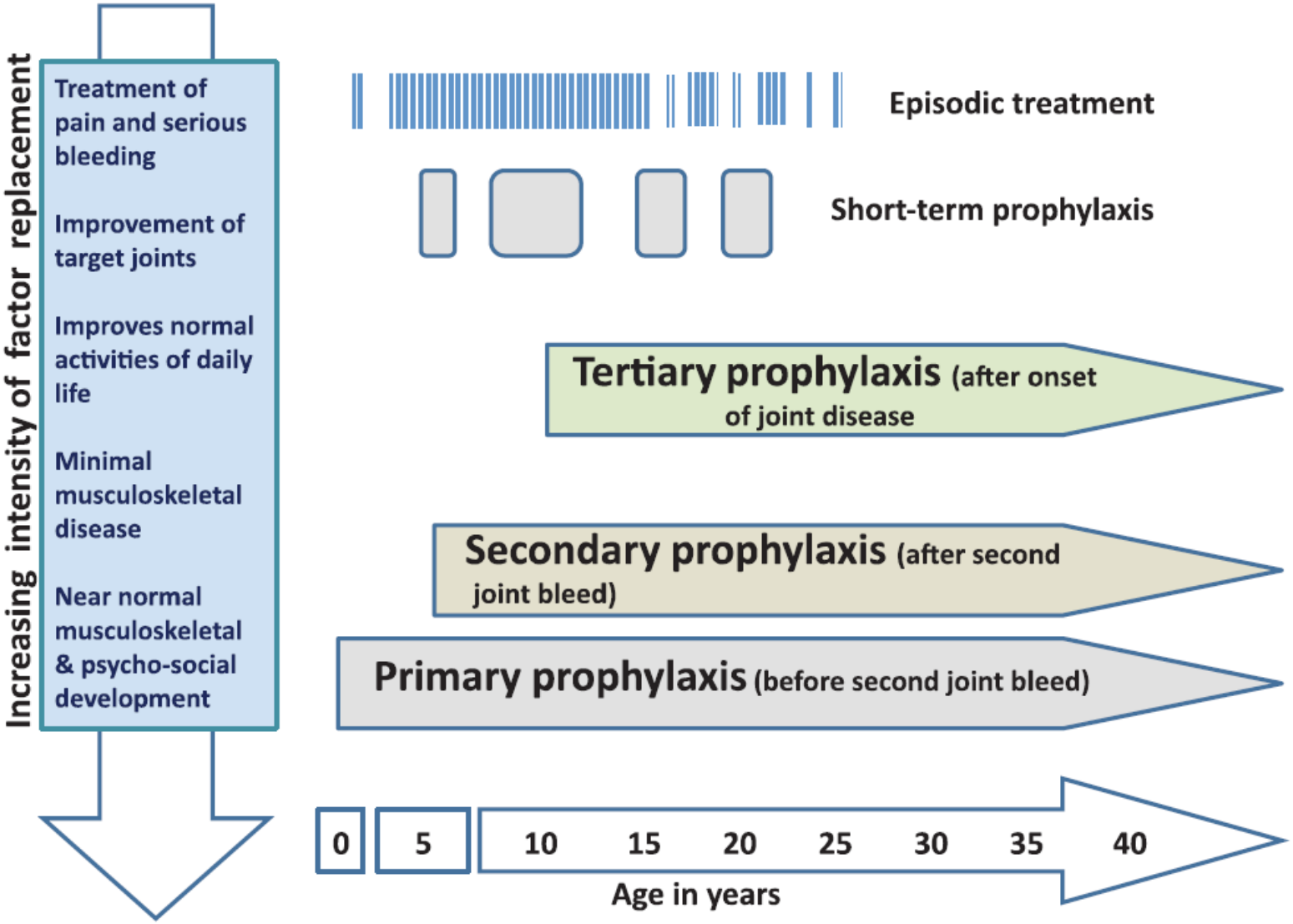
***** Almeno 46 settimane/anno

Srivastava A Haemophilia 2013

PROFILASSI: OBIETTIVI

Trasformare un' emofilia grave in un'emofilia moderata in modo da prevenire gli episodi emorragici articolari e le loro sequele

PROFILASSI IN EMOFILIA



Adapted from Blood Transfus 2008 Sep;6 Suppl 2:s4-11

PROFILASSI IN EMOFILIA

- 1968: Direttori dei Centri Emofilia, Svezia
- 1987: Direttori dei Centri Emofilia, Olanda
- 1994: Direttori dei Centri Emofilia, UK
- 1994: M.A.S.A.C. - Consiglio Medico Scientifico National Hemophilia Foundation (NHF) USA
- 1994: Organizzazione Mondiale della Sanità (OMS) e World Federation Haemophilia (WFH)
- 2001: estesa agli emofilici gravi di ogni età
- 2006: terapia ottimale da istituire precocemente

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding and clotting disorders

MASAC Document #170
(Replaces #117)

PIONIERI DELLA PROFILASSI

- **1962: Ramgren livelli FVIII>1% proteggono il paziente emofilico dallo sviluppo dell'artropatia emofilica (Acta Med Scand 1962; 379:11-90)**
- **1968: Van Creveld introduce la profilassi nella prevenzione del sanguinamento articolare (Acta Hematol 1971; 45:120-7)**

Kasper CK et al.	**5HA ; 250-500IU/kg die**	**Arch Inter Med 1970**
Schimpf K. et al.	36 IU/Kg/week 1x36 IU/KG, 2x18IU/KG, 3x12 IU/KG	Dtsch Med Woch 1976
Aronstam et al.	Personalizzata 0.25IU/ml week	Br J Hematol 1976
Morfini M et al.	**FIX 7.5 IU/kg bi-week 15 IU/ kg week**	**Scan J Hematol 1976**

L'ESPERIENZA SVEDESE

Età attuale	3-6 anni	7-12 anni	13-17 anni	18-23 anni	24-32 anni
No. pazienti	6	9	20	10	15
Età di inizio (anni)	1.1 (1-1.5)	1.2 (0.5-2)	2.6 (1-4.5)	4.9 (3-7)	7.0 (3-13)
Emorragie articolari (per anno)	0.1 (0.0-6)	0.1 (0.0-4)	3 (0.1-16.6)	5.6 (0.5-14)	5.0 (1.6-16)
Dose Totale FVIII/FIX per kg/anno (x 103)	4.3 (3.0-7.0)	4.0-7.4 (1.7-9.0)	1.5-4.9 (0.8-6.6)	1.2-3.8 (0.5-5)	0.4-2.6 (0.2-6)
Livello pre-infusione VIII:C/IX:C	2 (1-5)	1 (1-4)	<1-3	1-2.5	<1-2.5
Orthopaedic joint score	0	0	1.2 (0-7)	2.9 (0-7)	6.6 (0-15)
Pettersson score	0	0	4.8 (0-22)	14.2 (0-22)	20.6 (0-41)
Giorni di lavoro/scuola persi (per anno)	0	0	0.9 (0.6-7)	2.8 (0-9.8)	5.8 (1-20)

Nilsson et al. J Intern Med 1992

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D.

Journal of Thrombosis and Haemostasis, **9**: 700–710 DOI: 10.1111/j.1538-7836.2011.04214.x

ORIGINAL ARTICLE

A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study)

A. GRINGERI,* B. LUNDIN,† S. VON MACKENSEN,*‡ L. MANTOVANI,§ P. M. MANNUCCI*¶ and THE ESPRIT STUDY GROUP[1]

Table 1. Baseline Demographic and Clinical Characteristics of All Randomized Participants.

Characteristic	Prophylaxis (N = 32)	Enhanced Episodic Therapy (N = 33)	P Value
Mean age (yr)	1.6	1.6	0.78
Race or ethnic group — no. (%)*			0.33
White	24 (75)	25 (76)	
Black	0	3 (9)	
Hispanic	4 (13)	4 (12)	
Asian or Pacific Islander	1 (3)	1 (3)	
American Indian or Alaskan native	1 (3)	0	
Other	2 (6)	0	
Educational level of parent or guardian — no. (%)			0.06
≤12 yr	20 (63)	13 (39)	
>12 yr	12 (37)	20 (61)	
First index-joint hemorrhage before enrollment — no. (%)			0.17
Yes	18 (56)	13 (39)	
No	14 (44)	20 (61)	
No. of previous index-joint hemorrhages			0.17
Mean	1.0	0.6	
Range	0–5	0–3	
No. of previous total hemorrhages			0.74
Mean	6.2	6.8	
Range	0–35	0–32	

* Race and ethnic group were reported by the parent or guardian of each child.

Table 2. Outcome Data.*

Variable	Prophylaxis (N=32)	Enhanced Episodic Therapy (N=33)	P Value
MRI findings			
No. of participants with primary outcome data	27	29	0.73
Joint damage — no. (%)	2 (7)	13 (45)	0.002
No joint damage — no. (%)	25 (93)	16 (55)	
Radiographic findings			
No. of participants with primary outcome data	28	27	0.73
Joint damage — no. (%)	1 (4)	5 (19)	0.10
No joint damage — no. (%)	27 (96)	22 (81)	
No. of days in study			
Mean	1,497	1,490	0.95
Total	47,895	49,179	
Reported no. of factor VIII infusions			
Mean	653±246	187±100	<0.001
Total	20,896	6,176	
Reported no. of factor VIII units infused			
Mean	352,793±150,454	113,237±65,494	<0.001
Total	11,289,372	3,736,807	
Joint hemorrhages (no./participant/yr)			
Mean	0.63±1.35	4.89±3.57	<0.001
Median	0.20	4.35	
Total hemorrhages (no./participant/yr)			
Mean	3.27±6.24	17.69±9.25	<0.001
Median	1.15	17.13	

* Plus–minus values are means ±SD. The data on MRI and radiographic findings include interim-analysis data for children who were removed from the study because of early joint failure.

STUDIO ESPRIT

Table 1 Baseline demographic characteristics of trial groups

Characteristic	Prophylaxis (n = 21)	Episodic treatment (n = 19)	P value
Age, months			
Mean ± SD	49.7 ± 26.9	48.8 ± 21.2	ns
Median (min–max)	50 (10–84)	48 (14–84)	
Age groups, n (%)			
≤36 months	8 (38)	7 (38)	ns
37–60 months	6 (29)	6 (32)	
>60 months	7 (33)	6 (32)	
Age at diagnosis, months			
Mean ± SD	5.7 ± 6.2	8.8 ± 10.1	ns
Median (min–max)	6 (0–23)	6 (0–32)	
Body mass index, kg m^{-2}			
Mean ± SD	16.4 ± 0.8	16.4 ± 0.7	ns
Median (min–max)	16.2 (15.5–18.2)	15.5 (15.5–17.9)	

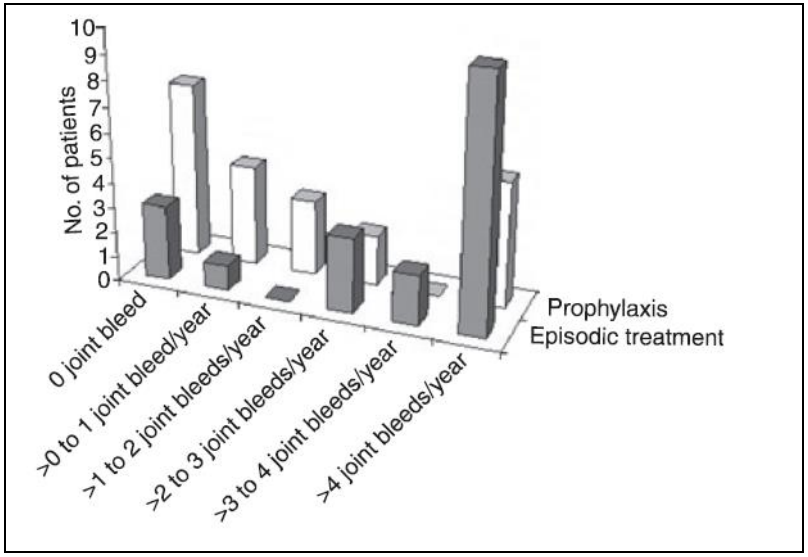
SD, standard deviation.
ns, not significant.

Gringeri al. J Thromb Haemost 2011

STUDIO ESPRIT

Variable	Prophylaxis (n = 21)	Episodic Treatment (n = 19)	P value
No. of months in randomization arm			
Mean	46.2	51.8	ns
Median (min–max)	54.5	58.6	
No. of patient years	81	82	
Total bleeding events per patient			
Mean	5.0	24.9	< 0.01
Median (min–max)	1	7.5	
No. of events per patient per month	0.11	0.48	
No. of hemarthroses per patient			
Mean	2.48	12.42	< 0.01
Median (min–max)	0	4	
No. of events per patient per month	0.05	0.24	
Radiographic findings			
Joint damage, no. (%)	0	5	ns
No joint damage, no. (%)	21	14	

ns, not significant.



Gringeri al. J Thromb Haemost 2011

BARRIERE ALLA PROFILASSI IN EMOFILIA

1. Mancata percezione della necessità
2. Accesso venoso
3. Età
4. Periodicità delle infusioni
5. Compliance e tempo disponibile da parte genitori
6. Costi e disponibilità farmaci

Petrini, Haemophilia 2007

BARRIERE ALLA PROFILASSI IN EMOFILIA

Categories		Score†	
		Median	Quartile 1
Age 0–2 years	Parents' acceptance	89	59
	Venous access	85	70
	Compliance to therapy	78	57
	Social and cultural level of parents	75	38
	Geographical, cultural and psychological barriers	70	50
Age >2–6 years	Venous access	96	90
	Parents' acceptance	94	78
	Compliance to therapy	88	78
	Geographical, cultural and psychological barriers	80	75
	Social and cultural level of parents	75	63
Age >6–12 years	Compliance to therapy	80	69
	Venous access	78	61
	Geographical, cultural and psychological barriers	75	67
	Parents' acceptance	73	60
	Social and cultural level of parents	65	54
Age >12–18 years	Compliance to therapy	76	53
	Geographical, cultural and psychological barriers	65	38
	Occupation type	63	34
	Venous access	61	40
	Parents' acceptance	52	28

Castaman , Blood Transfusion 2015

PROFILASSI: MODALITA'

Prophylactic dosing regimen	Dose	Dosing frequency	Dosing adjustments
Swedish (Malmö) high-dose protocol (24, 50, 51)	25–40 IU/kg	3 times weekly or every other day	Dosing adjusted to maintain FVIII levels >1 %
Utrecht (intermediate-dose) protocol (2, 52)	15–30 IU/kg	2 or 3 times weekly	Dosing adjusted based on patient's bleeding pattern
Canadian dose-escalation protocol (27)	50 IU/kg	Once weekly	Escalate to 30 IU/kg twice weekly or 25 IU/kg on alternate days based on patient's bleeding frequency

Ljung R. et al. Thromb Haemost 2016

INDICAZIONI ALLA PROFILASSI IN EMOFILIA

Categories		Score†	
		Median	Quartile 1
Age 0–2 years	Bleeding frequency	97	95
	Bleeding severity	97	96
	Severity of coagulation defect	95	90
	High risk genetic mutation	83	60
	Intensive treatment at the beginning of transfusional history	83	76
Age >2–6 years	Bleeding severity	99	98
	Bleeding frequency	99	98
	Presence of target joints	97	91
	Severity of coagulation defect	94	90
	Orthopaedic score	86	80
Age >6–12 years	Bleeding severity	99	98
	Bleeding frequency	98	96
	Presence of target joints	96	90
	Orthopaedic score	93	84
	Severity of coagulation defect	90	86
Age >12–18 years	Bleeding frequency	98	96
	Bleeding severity	97	97
	Presence of target joints	96	95
	Orthopaedic score	94	89
	Quality of life	92	86

Castaman , Blood Transfusion 2015

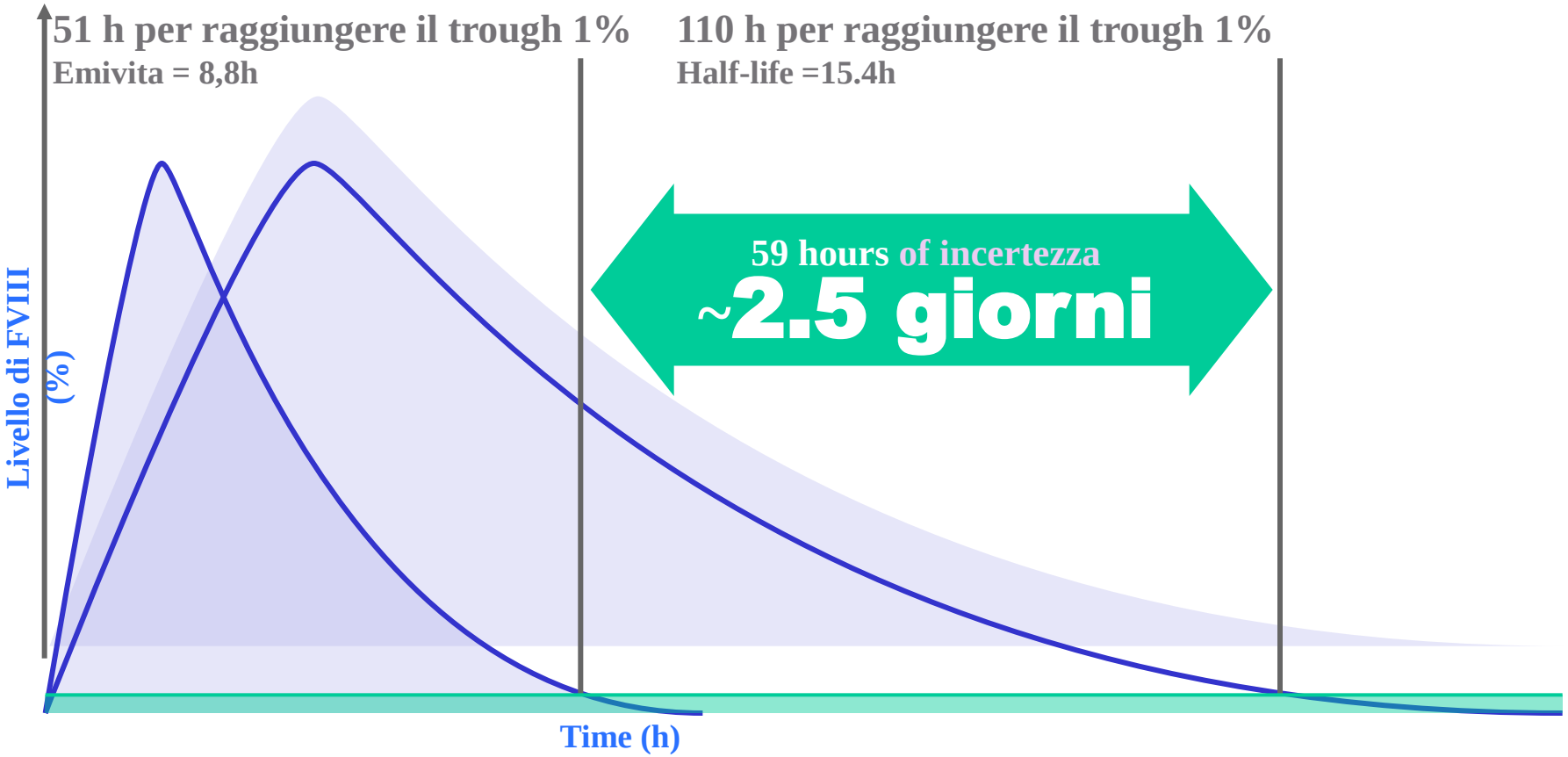
ALTRI FATTORI CHE INFLUENZANO IL REGIME DI PROFILASSI

1. Trough levels
2. Farmacocinetica (PK)

FARMACOCINETICA

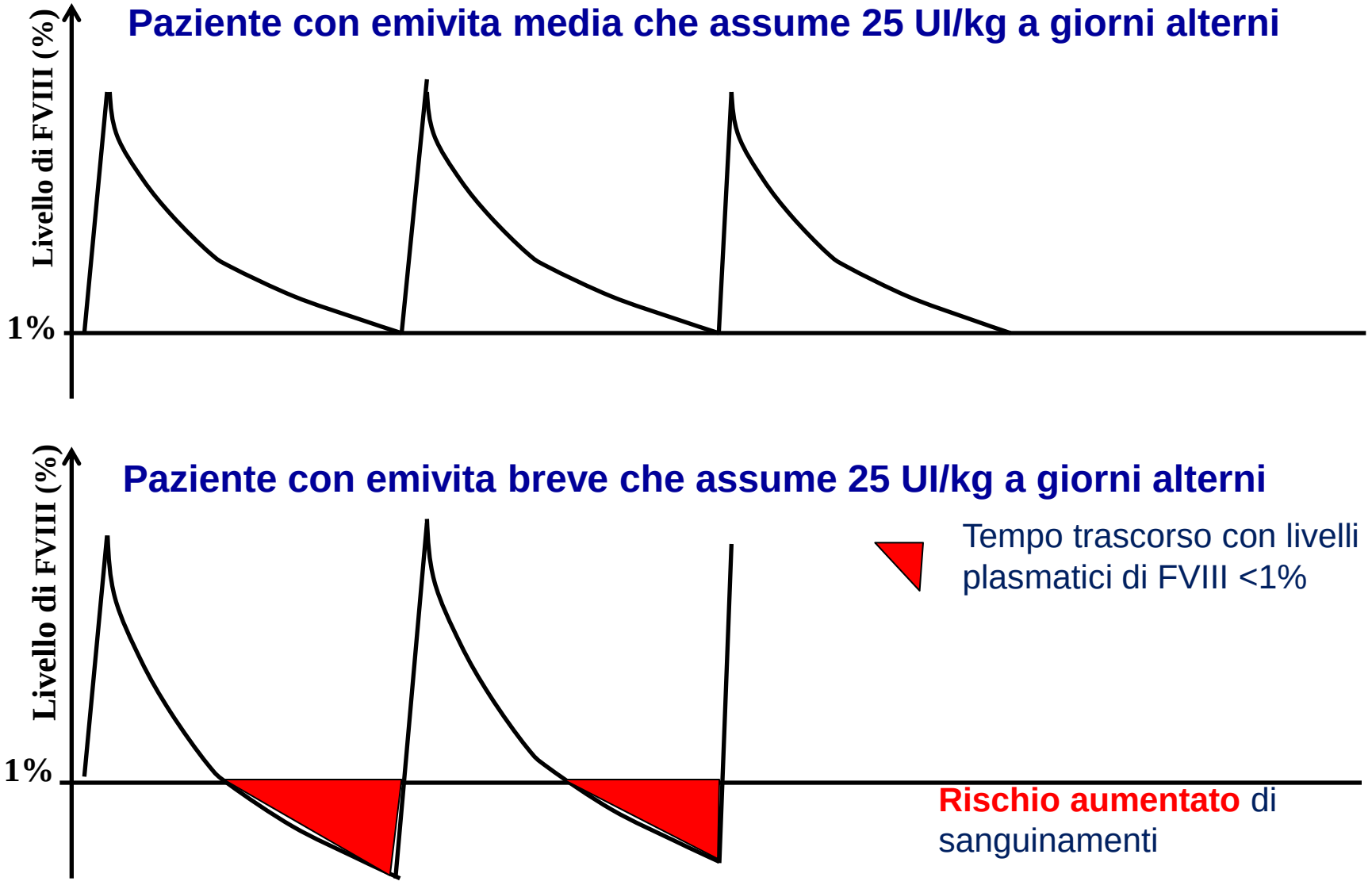
POSSIBILE VARIANZA

Adolescenti e adulti 10-65 anni; es. 70kg, 30 IU/kg dello stesso FVIII

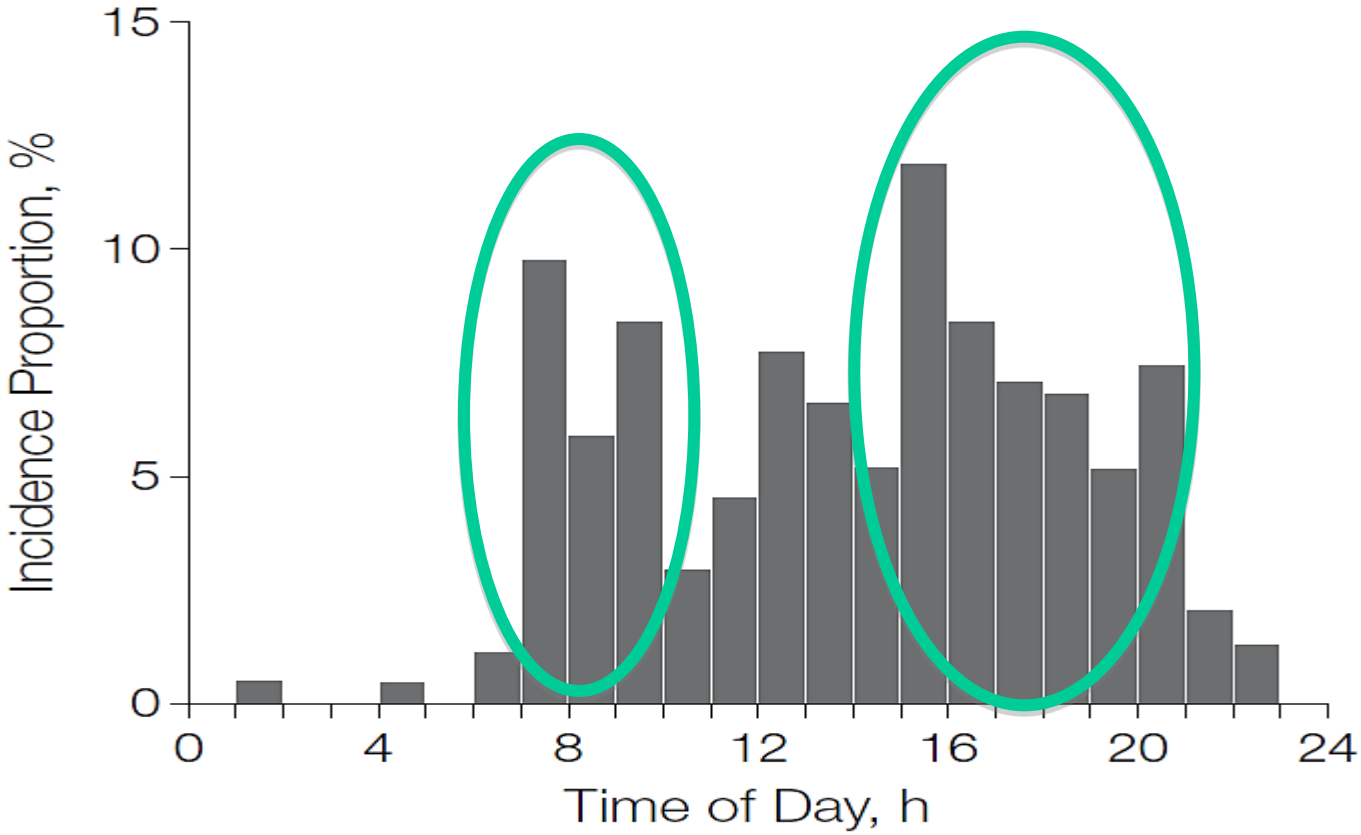


Collins PW et al. Haemophilia. 2011;17:2-10.

LIMITI DELLA PROFILASSI STANDARD

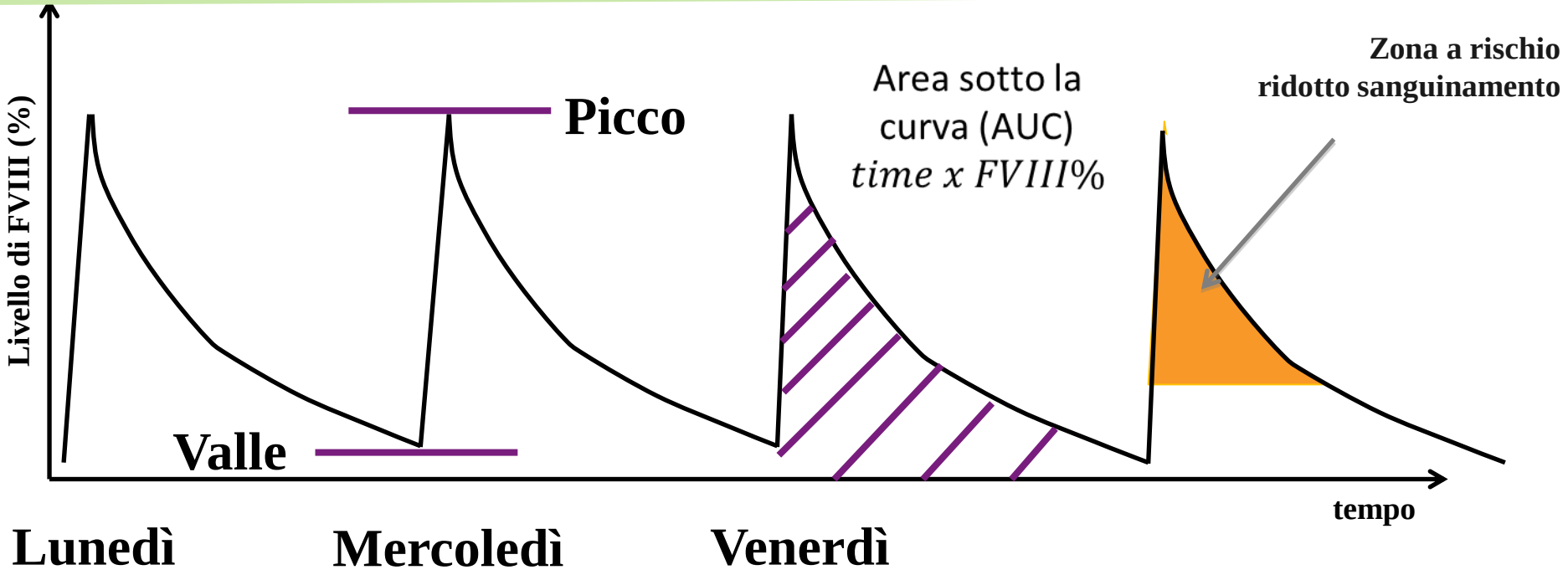


INSORGENZA DI SANGUINAMENTI E ORA DEL GIORNO



Broderick CR et al. JAMA. 2012;308(14):1452-1459

QUALI FATTORI SONO IMPORTANTI?



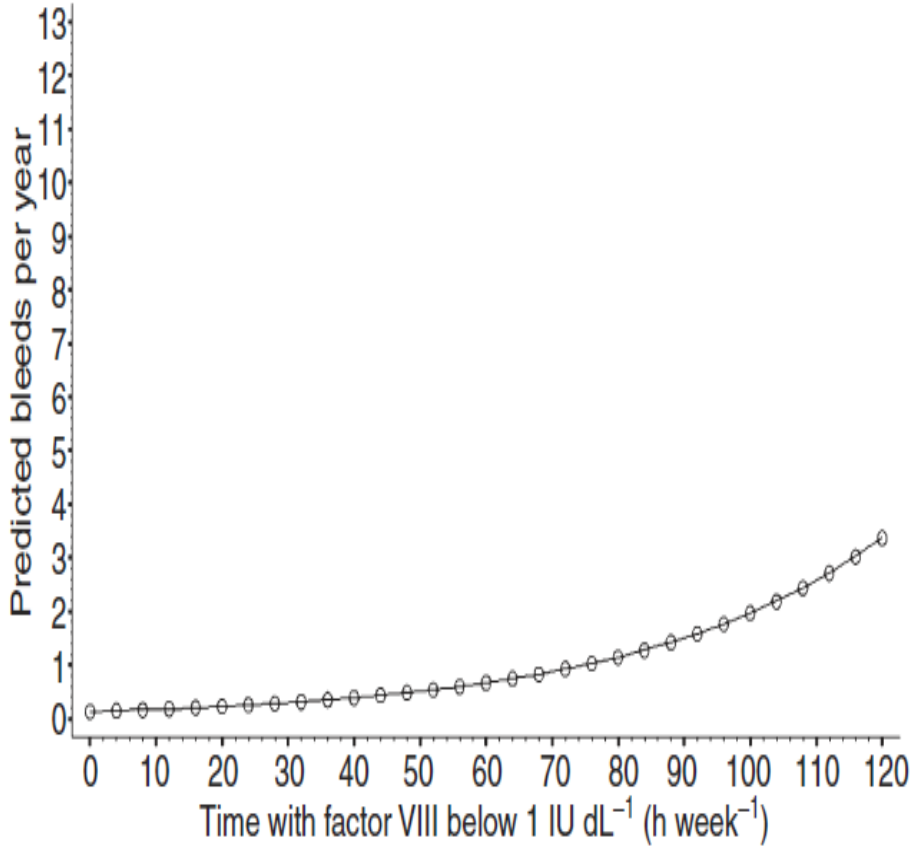
Picco e Tempo e nella zona a rischio ridotto sanguinamento:
importante per prevenire i sanguinamenti correlati all'attività e ai traumi

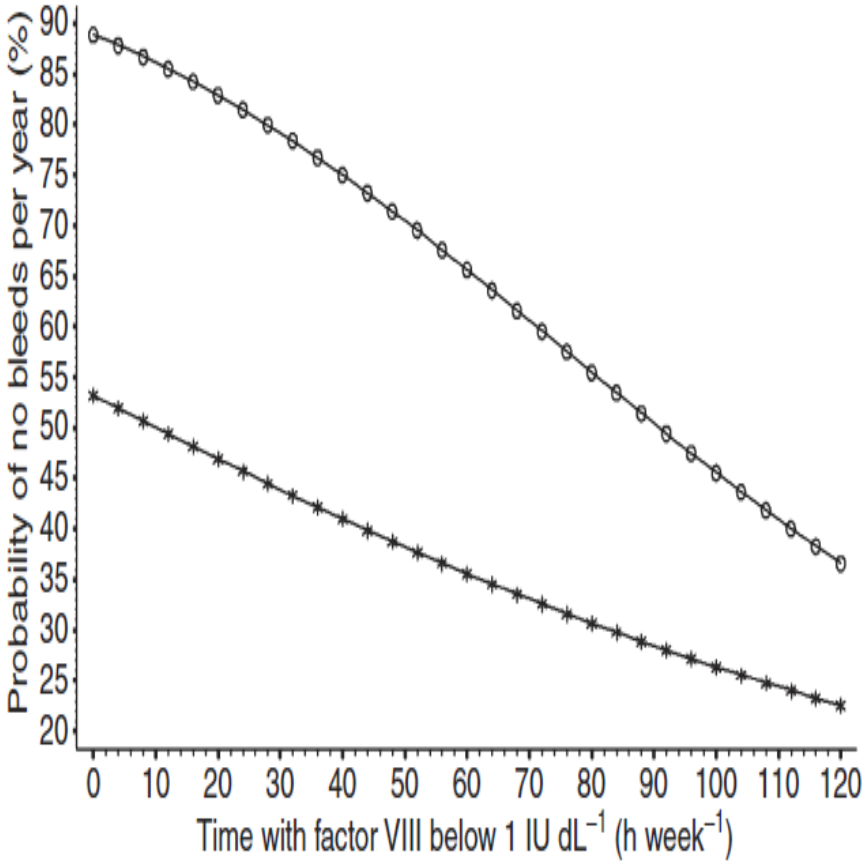
Valle: importante per prevenire i sanguinamenti spontanei

AUC: importante per prevenire i sanguinamenti subclinici, massimizzando la finestra di protezione

Collins PW: lettura della Sessione plenaria «Profilassi personalizzata» tenuta al Congresso WFH 10 Luglio 2012

INSORGENZA DI SANGUINAMENTI E LIVELLI DI FVIII < 1%





Collins PW et al. J Thromb Haemost 2009;7:413-20

ABR* IN PAZIENTI PEDIATRICI IN PROFILASSI

Paper	Paz (n)	Età (anni)	Regime	ABR All bleeds	ABR Spontaneous Bleeds	ABR Traumatic Bleeds
Klukowka et al. Haemophilia 2016	59	2-12	30-40 UI/kg/3 w giorni alterni	4.12 (3.03-5.28) 1.90 (0-20.7)	1.50 (3.32) 0 (0-13.8)	2.31 (1.61-3.31) 1.57 (0-18.6)
	29	2-5		2.60 (1.46-4.66) 0 (0-12.2)	n.a. n.a.	n.a. n.a.
	30	6-12		5.59 (3.59-8.17) 3.63 (0-20.7)	n.a. n.a.	n.a. n.a
Kulkarni et al. Haemophilia 2013	63	0-11	25-60 UI/Kg/x 3 w	5.33 (3.9-7.28) 3.02 (8.50)	1.69 (0.94-3.03) 0.00 (2.53)	3.55 (2.51-5.33) 2.53 (5.89)
	31	0-5	20-50 UI/kg giorni alterni	4.73 (3.06-7.30) 2.95 (6.14)	0.8 (0.43-1.49) 0.00 (0.00)	3.93 (2.29-6.72) 1.90 (6.14)
	32	6-11		5.86(3.76-9.13) 3.57 (8.68)	2.49 (1.2-5.17) 0.00 (2.94)	3.21(2.09-4.93) 2.70 (5.67)

***annualized bleeding rate**

SUGGERIMENTI PER LA PROFILASSI IN EMOFILIA

1. Profilassi deve essere avviata prima possibile
2. Frequenti infusioni sono più protettive
3. Picco e trough level sono importanti per prevenire i sanguinamenti spontanei e traumatici
4. Meglio infondere il fattore al mattino
5. La profilassi va modificata nel tempo se il paziente modifica le sue attività
6. La profilassi dovrebbe essere personalizzata sulla base del PK e del sanguinamento.

Ljung R. et al. Thromb Haemost 2016

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