IL BAMBINO CON EMOFILIA

CORSO DI FORMAZIONE AD ALTA SPECIALIZZAZIONE SULLA GESTIONE DEL BAMBINO CON EMOFILIA

PADOVA 13-14 MAGGIO 2016

Massimo Morfini

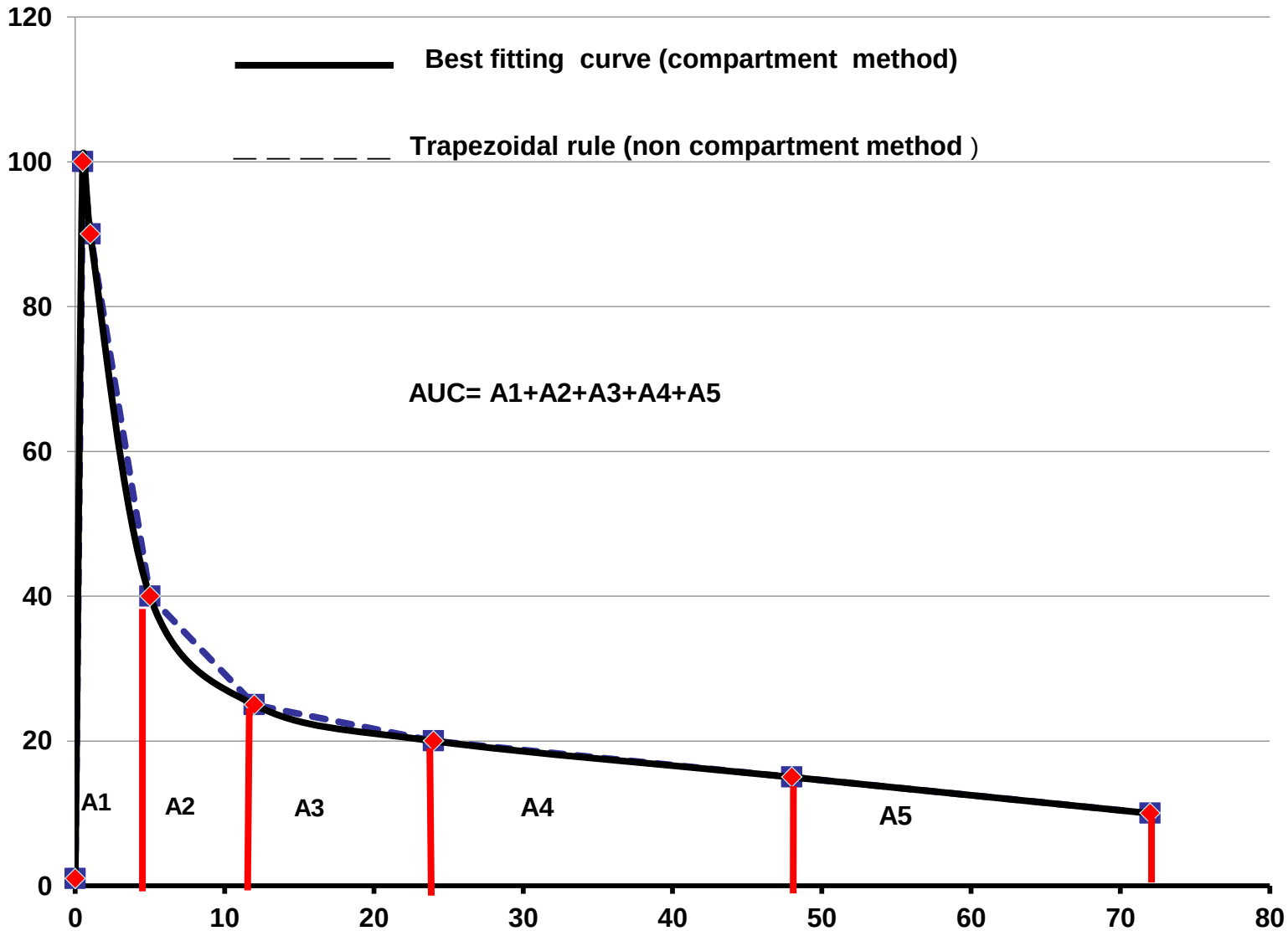
Farmacocinetica e profilassi

Pharmacokinetics is the study of effects of the body on the drugs. It is dealing with the time course of

Adsorption
Distribution
Metabolism
Elimination

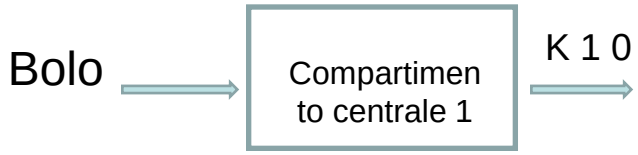
Pharmacodinamics is the study of the biochemical and physiological effects of drugs on the body

The majority of drugs either mimic or inhibit normal physiological/biochemical processes or inhibit pathological processes

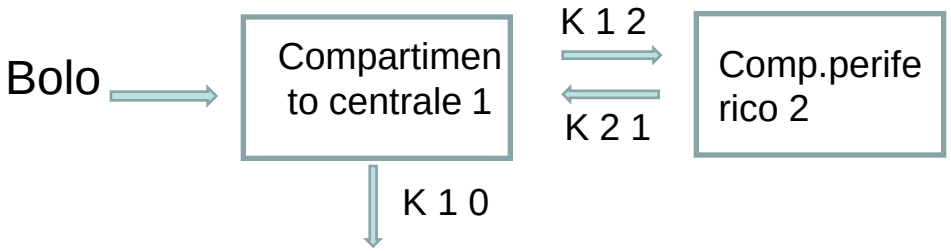

Best fitting curve (compartment method)
Trapezoidal rule (non compartment method)
AUC= A1+A2+A3+A4+A5
A1
A2
A3
A4
A5
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80

Parameters of Non-Compartment Analysis (NCA)

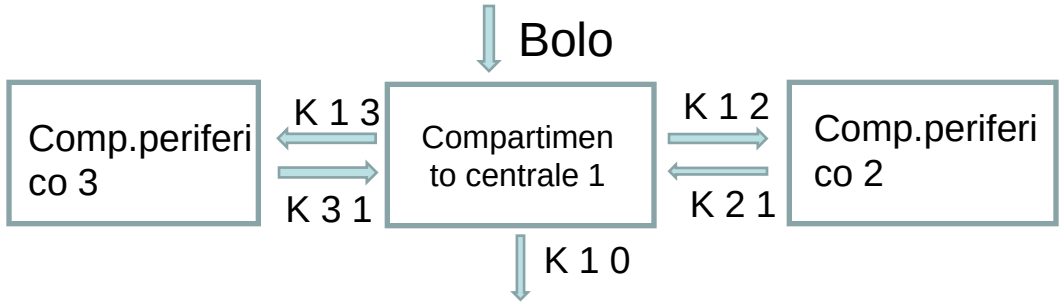
Parametro	Unità di misura
AUC (Area sotto la curva)	U*h/dL
AUMC (Momento dell'AUC)	U*h^2/L
Clearance	dL/h o dL/h/kg
Mean Residence Time	h
Half life	h
Lambda $_z$	h^{-1}
Numero di punti usati per il calcolo della Lambda $_z$	n
Terminal Half Life	h
Vz, Volume di distribuzione	dL o dL/kg
Vss, Volume allo steady state	dL o dL/kg



Modello a 1 compartimento , C (T) = (D/V) exp(-K10 * T)

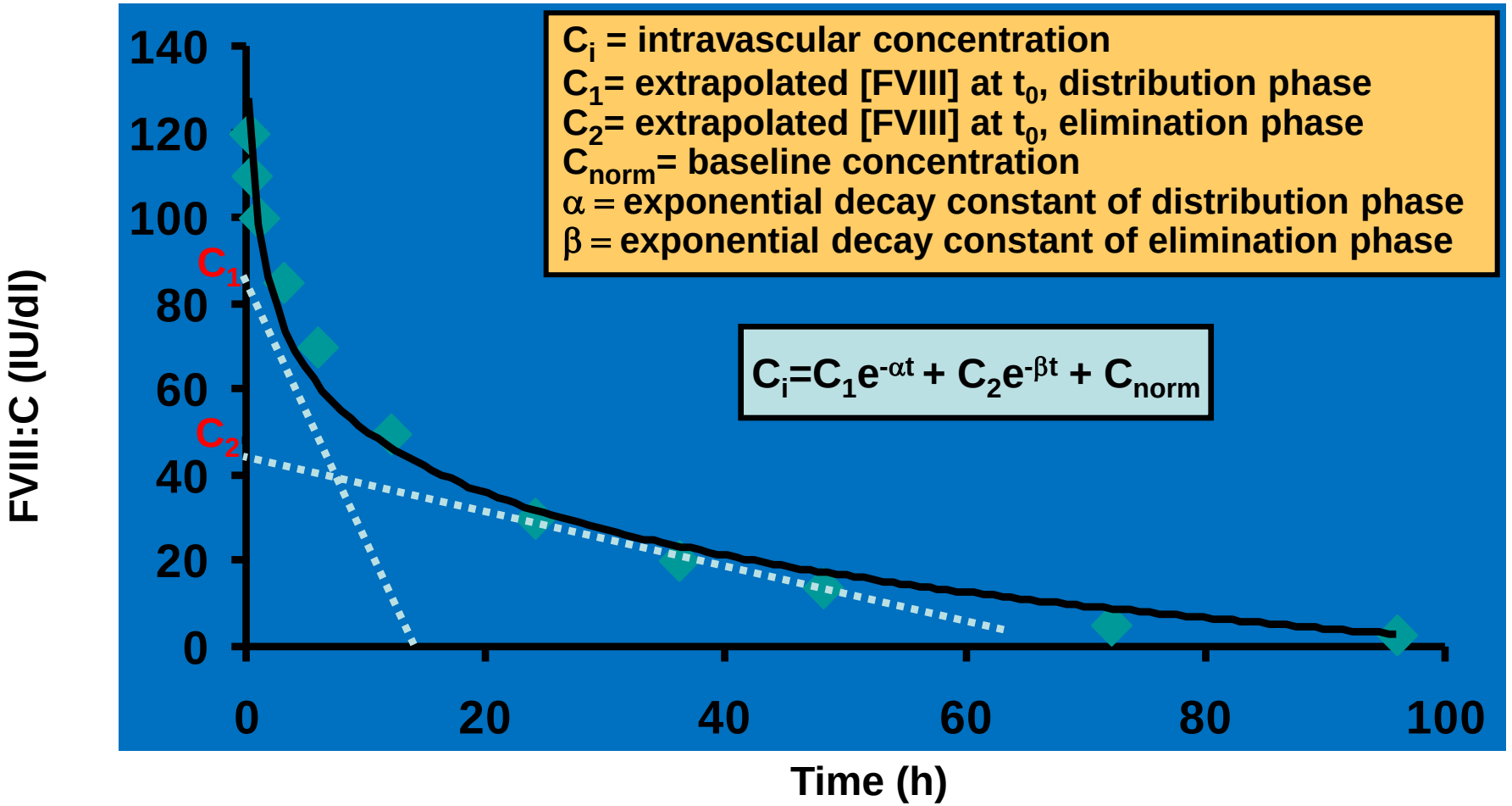


Modello a 2 compartimenti , C (T) = A exp(-ALPHA * T)+B exp(-BETA * T)



Modello a 3 compartimenti, C (T) = A exp(-ALPHA · T) + B exp(-BETA · T) + C exp(-GAMMA · T)

Biphasic decay



Primary and Secondary parameters TCM

Parameter	Units	Estimate	StdError	CV%
Cmax	U/dL			
A	U/dL			
B	U/dL			
Alpha	$hour^{-1}$			
Beta	$hour^{-1}$			
Alpha_HL	hour			
Beta_HL	hour			
K 1 0 HL	Hour			
AUC	U*h/dL			
AUMC	U^2*h/dL			
CL	dL/h o dL/h/kg			
MRT	hour			
V1	dL o dL/kg			
V2	dL o dL/kg			
Vss	dL o dL/kg			
K 1 2	$hour^{-1}$			
K 2 1	$hour^{-1}$			

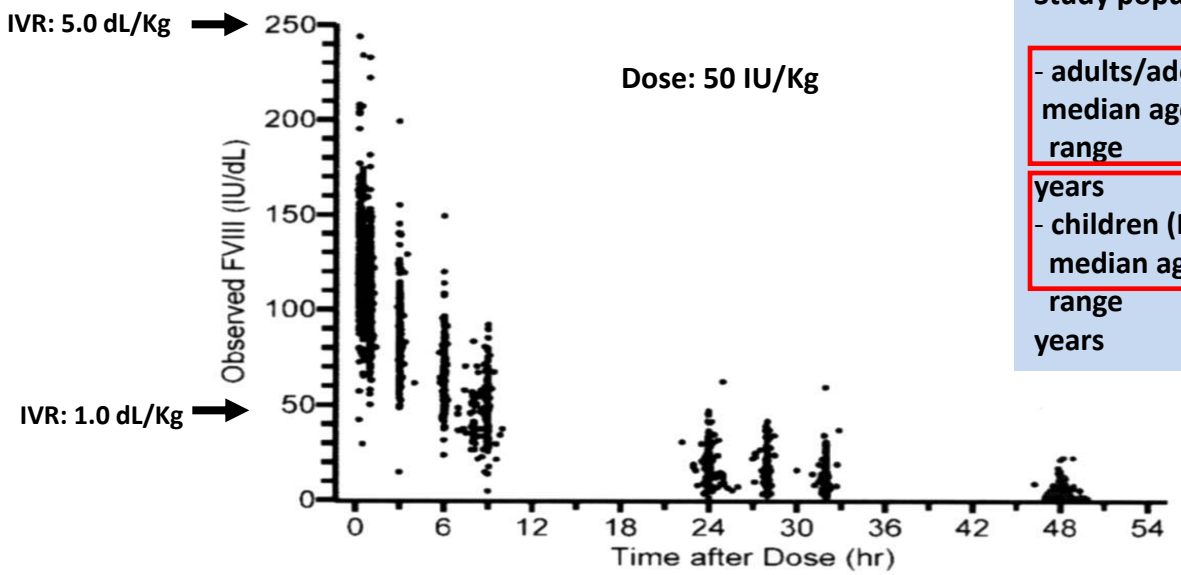
ESTIMATE OF THREE PHARMACOKINETIC PARAMETERS BY MODEL-INDEPENDENT METHOD

1. **Clearance** (ml/h/kg) : the volume of plasma made free of the drug, an overall measure.
2. **Mean Residence Time** (h): the rate at which the drug concentration declines after the dose (HL=MRT/1.443), independently of the shape (monophasic or biphasic).
3. **Volume of distribution Area**: indicates if the ***entire*** decay curve is high, normal or low with respect to the dose. Not affected by the fitting errors of the first part of the curve, as IVR.

blood

Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight

Sven Björkman, MyungShin Oh, Gerald Spotts, Phillip Schroth, Sandor Fritsch, Bruce M. Ewenstein, Kathleen Casey, Kathelijn Fischer, Victor S. Blanchette and Peter W. Collins



Dose: 50 IU/Kg

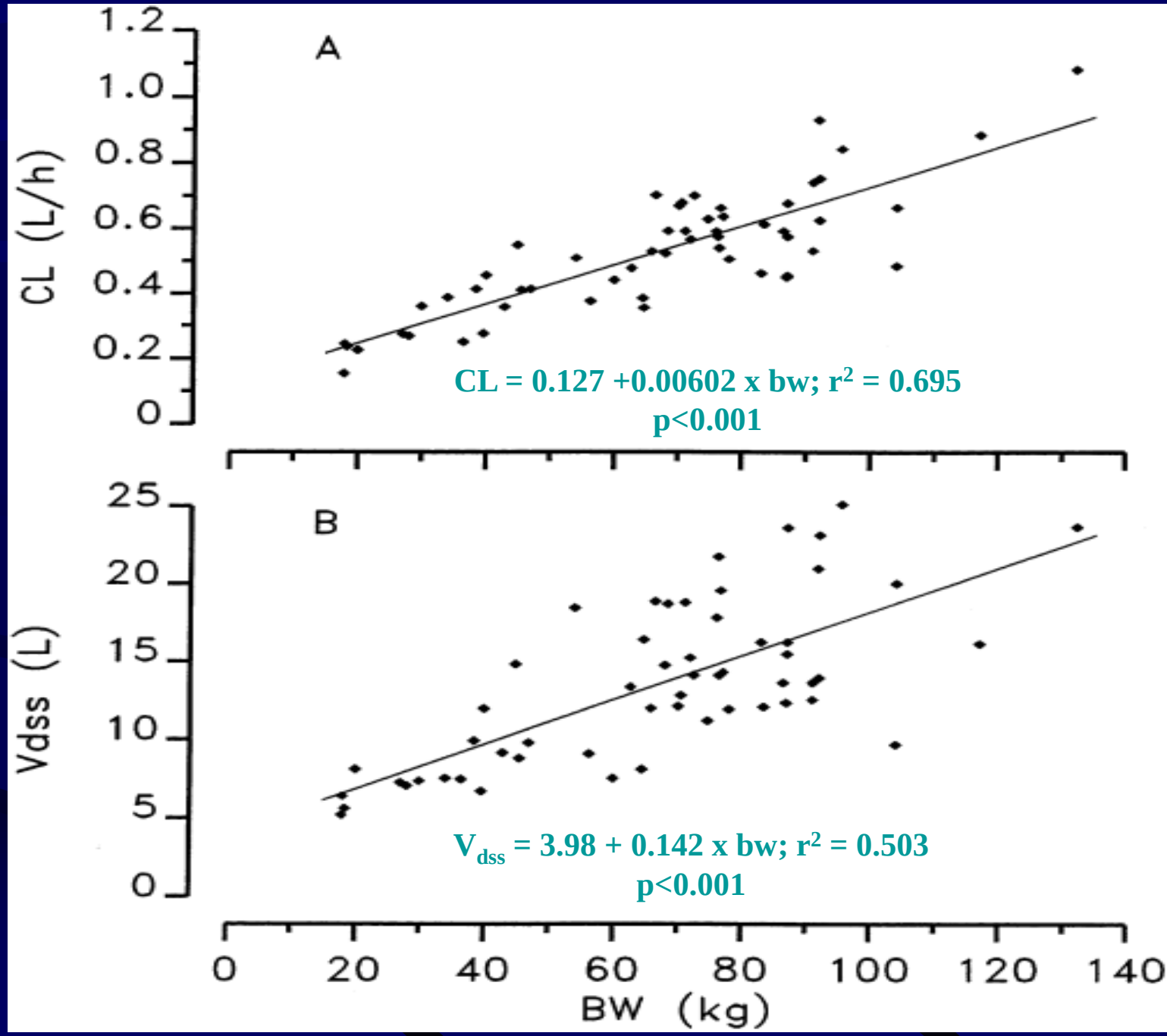
Study population

- **adults/adolescents (N=100)**
  median age 19 years
  range 10-66 years
- **children (N=52)**
  median age 3.5 years
  range 1-6 years

Björkman et al Blood 2012;119(2):612-618

rFIX (n=56)

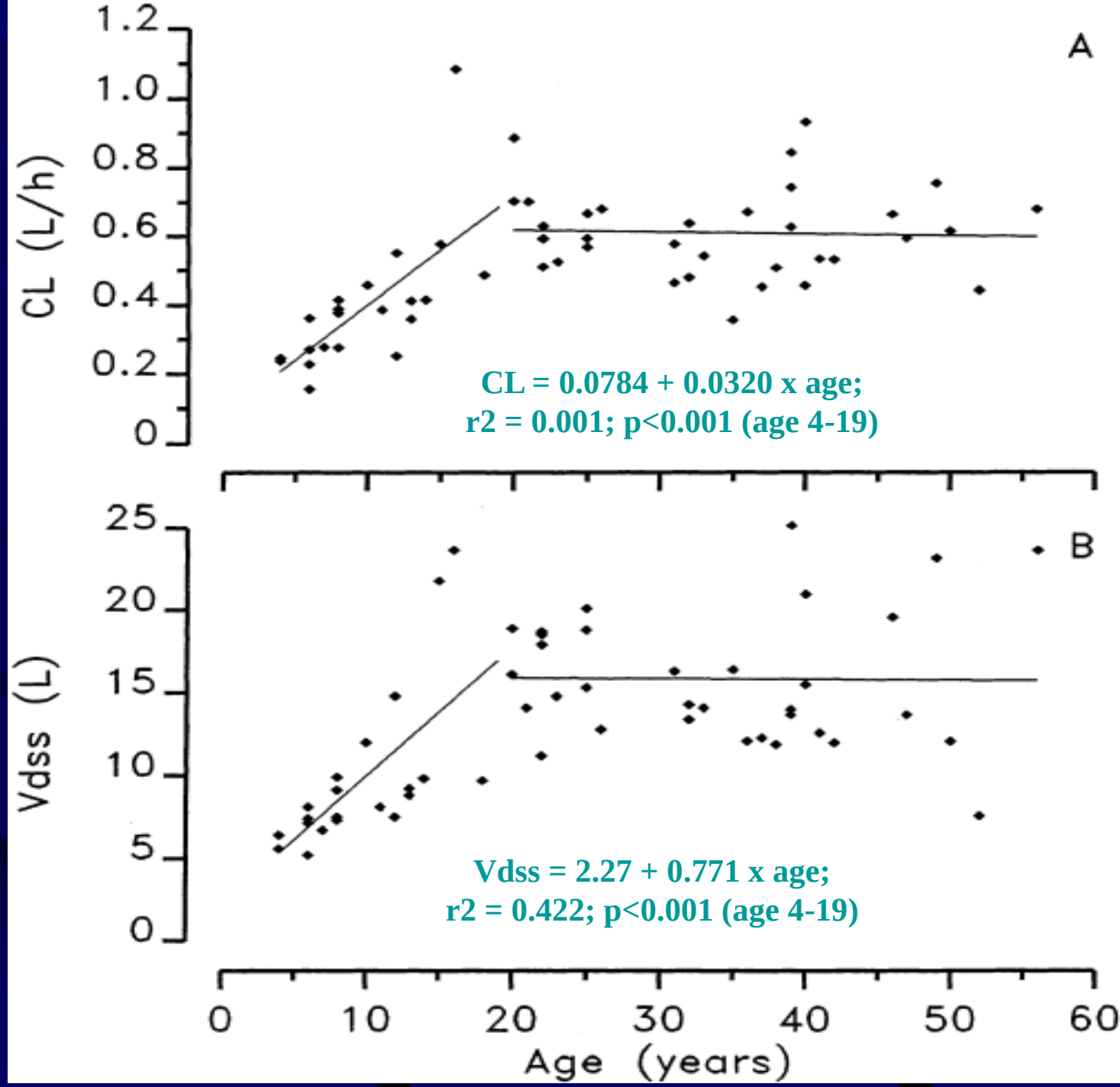
absolute CL (L/h)
and
absolute V_{dss} (L) vs. BW



Björkman S, et al.-Pharmacokinetics of recombinant factor IX in relation to age of the patient: implication for dosing in prophylaxis Haemophilia 2001;7:133-9 (Data supplied by Gentics Institute Inc,)

rFIX (n=56)

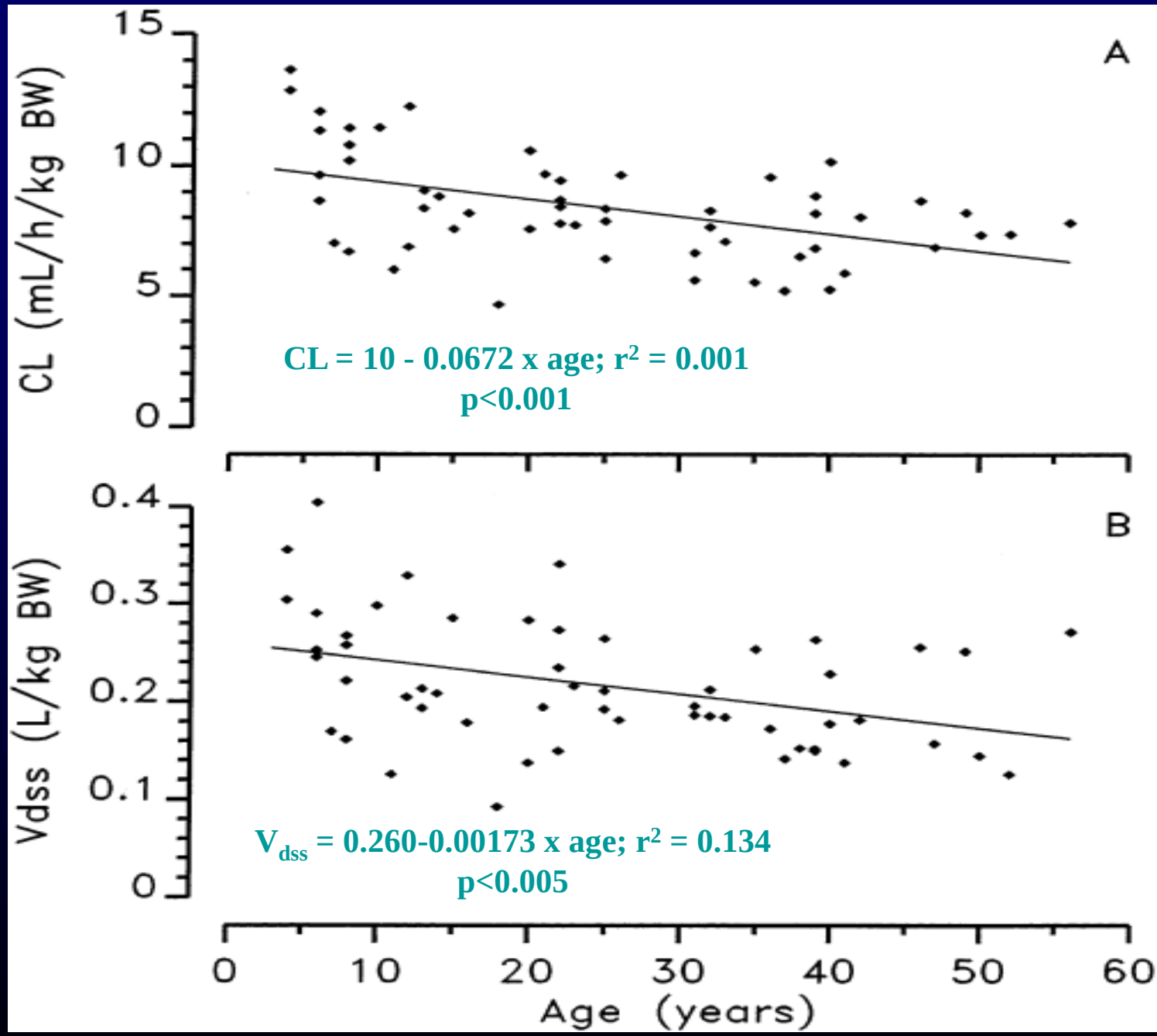
absolute CL (L/h)
and
absolute V_{dss} (L) vs. Age



Björkman S, et al.-Pharmacokinetics of recombinant factor IX in relation to age of the patient: implication for dosing in prophylaxis Haemophilia 2001;7:133-9
(Data supplied by Gentics Institute Inc,)

rFIX (n=56)

BW-adjusted
CL (mL/h/kg)
and
V_{dss} (L/kg) vs. Age



Björkman S, et al.-Pharmacokinetics of recombinant factor IX in relation to age of the patient: implication for dosing in prophylaxis Haemophilia 2001;7:133-9
(Data supplied by Gentics Institute Inc,)

Björkman S, - Comparison pharmacokinetics of factor VIII and recombinant factor IX: for which coagulation factors should half-life change with age?
Haemophilia, 2013, 19, 882-886.

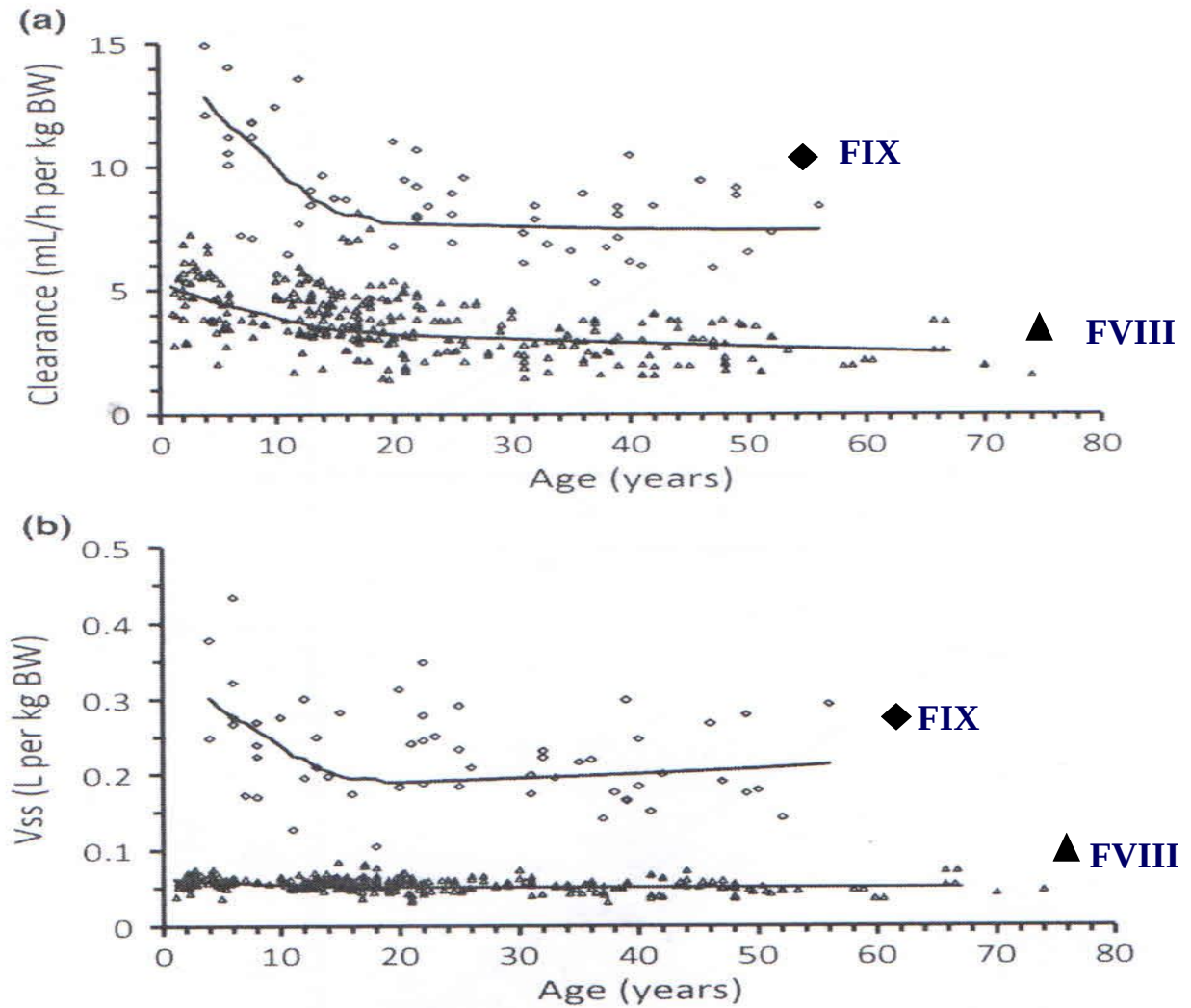
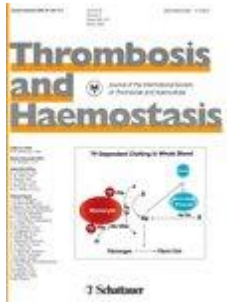


Fig. 2. The relationships of a: clearance and b: volume of distribution at steady state (V_{ss}), both per kg body weight (BW), with age for factor VIII and recombinant factor IX. The curves are model-calculated average clearance and V_{ss} in subjects with median BW for age. Keys to symbols are as in Fig. 1.



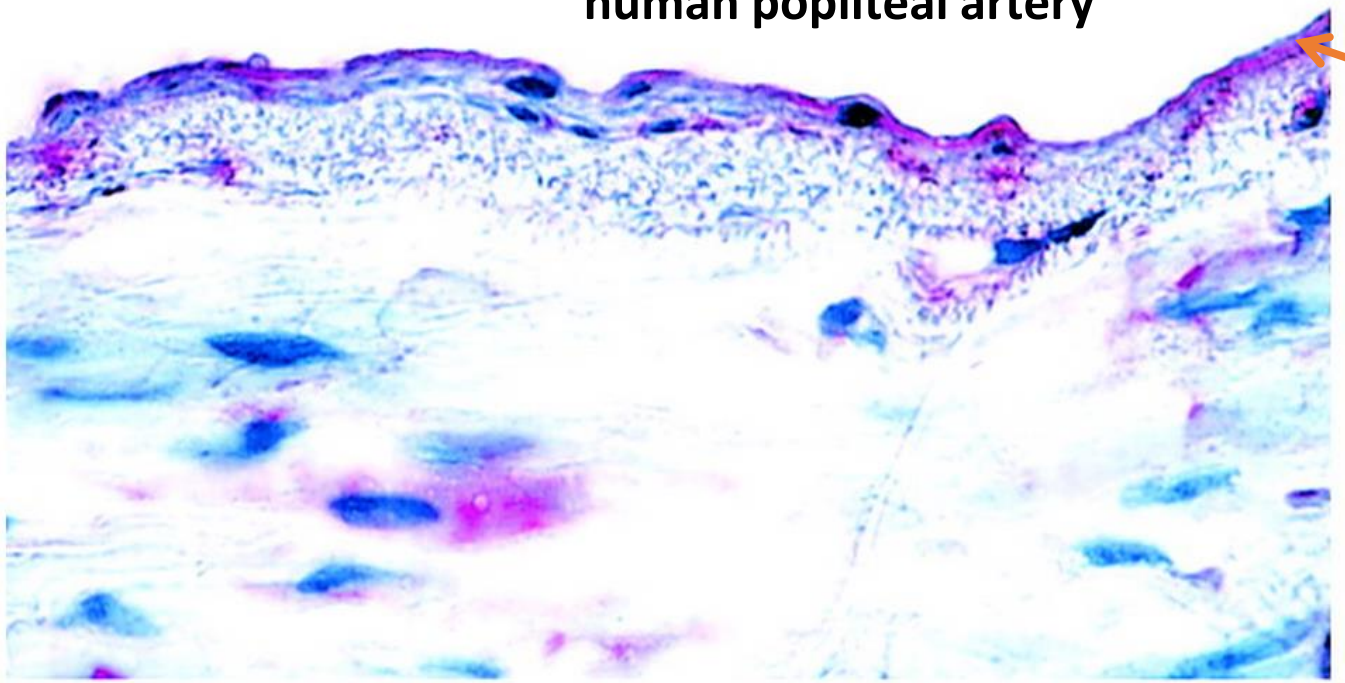
Haemostatic factors in human peripheral afferent lymph.

Miller GJ, Howarth DJ, Attfield JC, Cooke CJ, Nanjee MN, Olszewski WL, Morrissey JH, Miller NE.

Healthy volunteers			
N= 17	**Mean lymph:plasma concentration ratio**	**Interstitial fluid:plasma volume ratio**	**% located extravascularly at steady state**
FVIII	**4:100**	**4:1**	**16%**
FIX	**10:100**	**4:1**	**40%**

Proposed location of the FIX extravascular store

Immunohistochemical detection of factor IX and collagen IV in human popliteal artery



Pink staining indicates localization of FIX and collagen IV

FIX and collagen IV appear to be localized on the endothelial surface in human vessels

Gui T, et al. *Blood* 2002;100:153–58.

Changes in Water Spaces during Childhood

Age (y)	TBW Males %	TBW Females %	ECW %
Birth	80	80	44
2	60	60	30
5	59	59	27
10	57	57	25
20	62	54	23

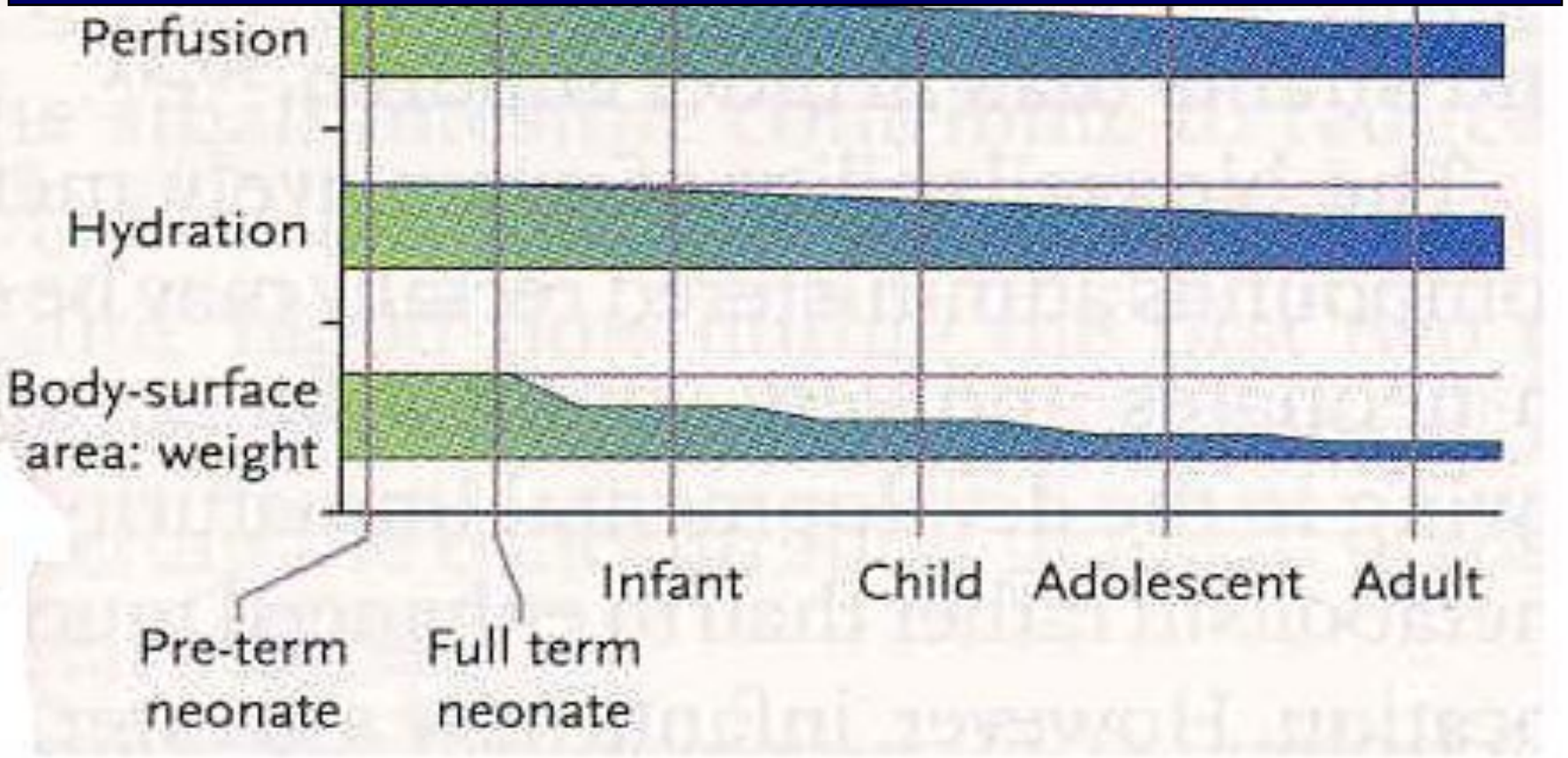
Adult: 175 cm, 70 kg = 1.84 m^2

0.026 m^2/kg

Neonate: 50 cm, 3.5 kg = 0.22 m^2

0.063 m^2/kg

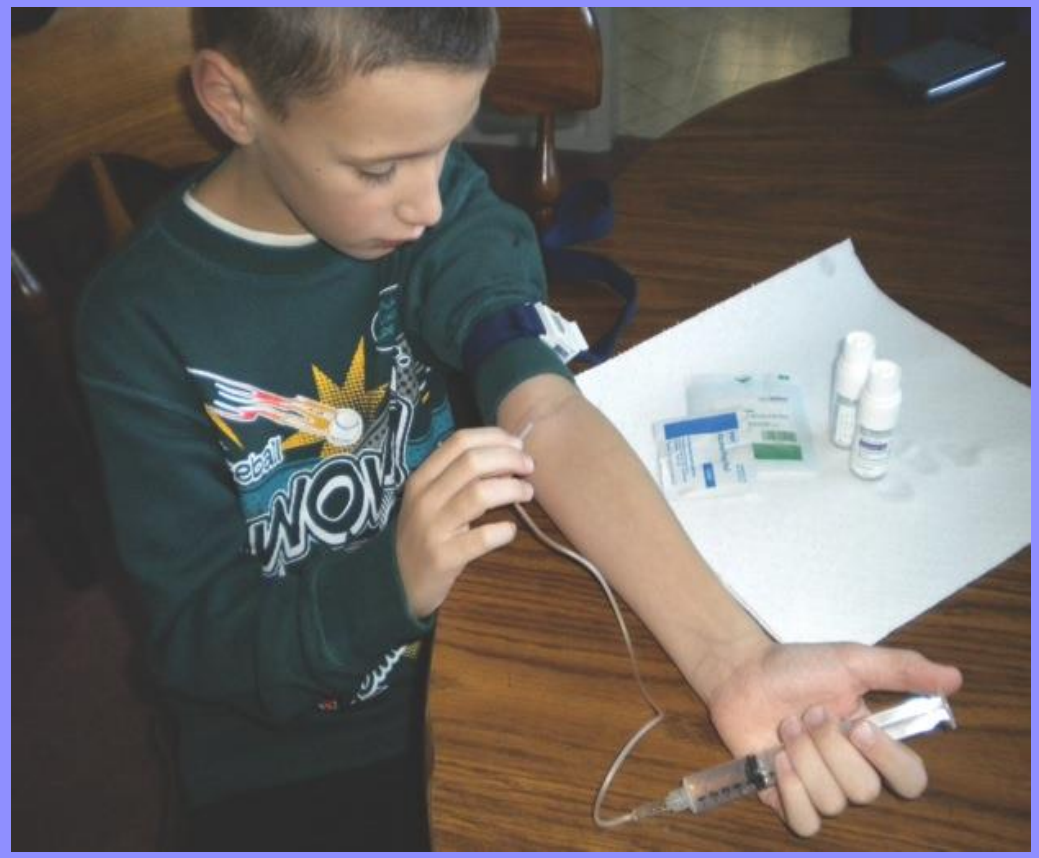
(Neonate has 2.4 X more BSA/kg)



Il problema dell'accesso venoso: il maggior ostacolo attuale alla profilassi precoce!

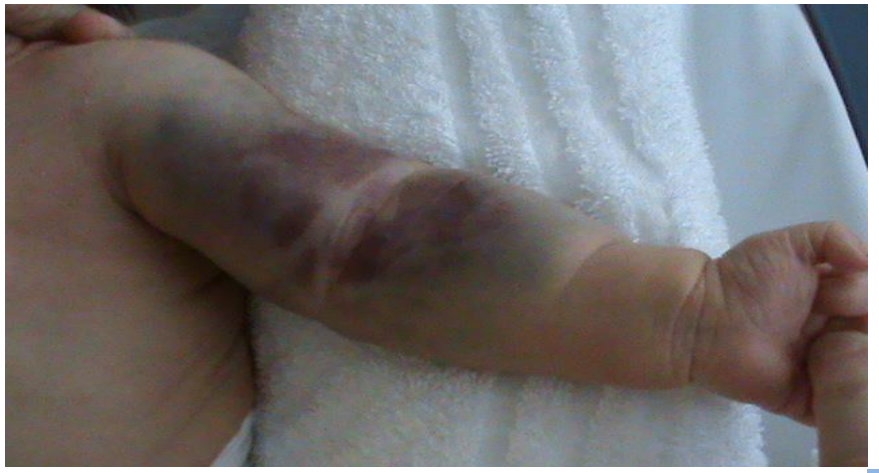
- Nei primi 18-24 mesi: catetere venoso centrale (CVC), esterno (Broviac) o tunnellizzato (Porth a cat).
- Complicanze del CVC:
  - accurata gestione, medicazioni frequenti
  - peggiore Qualità della vita
  - nel 50% infezioni e trombosi
- Dopo i primi 24 mesi: Fistola Artero-Venosa (FAV)
- Vantaggi della FAV:
  - non necessita di mantenimento
  - estrema facilità alla venopuntura
  - non disturbi della crescita dell'arto
  - reversibile nell'età adulta

Self-treatment is the faster way of therapy!
As shorter is the gap between bleeding and treatment, better the outcome is!
And prophy does prevent the bleedings!

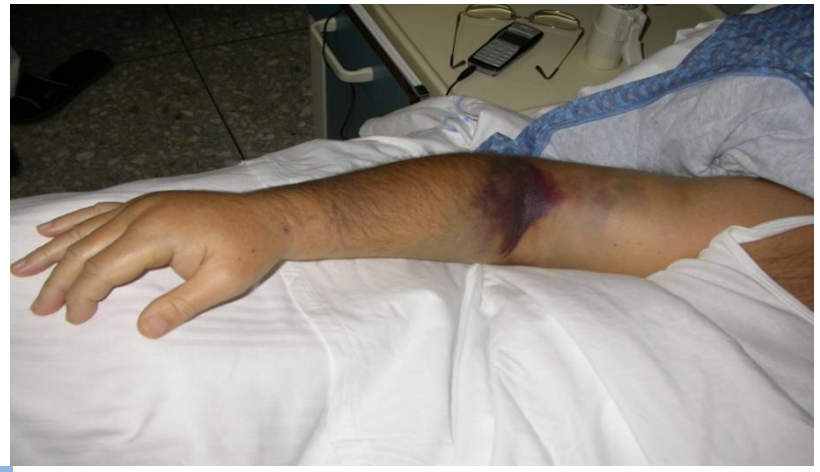


HAEMOPHILIA CENTER ,Karolinska Hospital

By courtesy of Pia Petrini

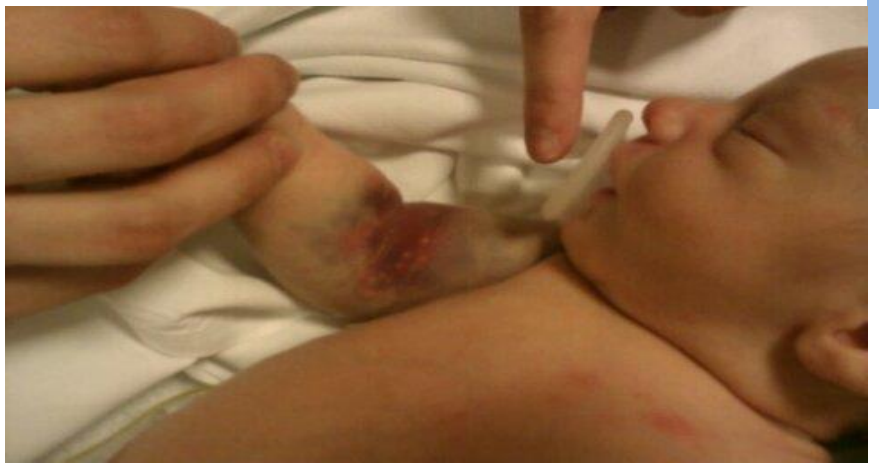


Severe haemophilia B baby, 4 days old

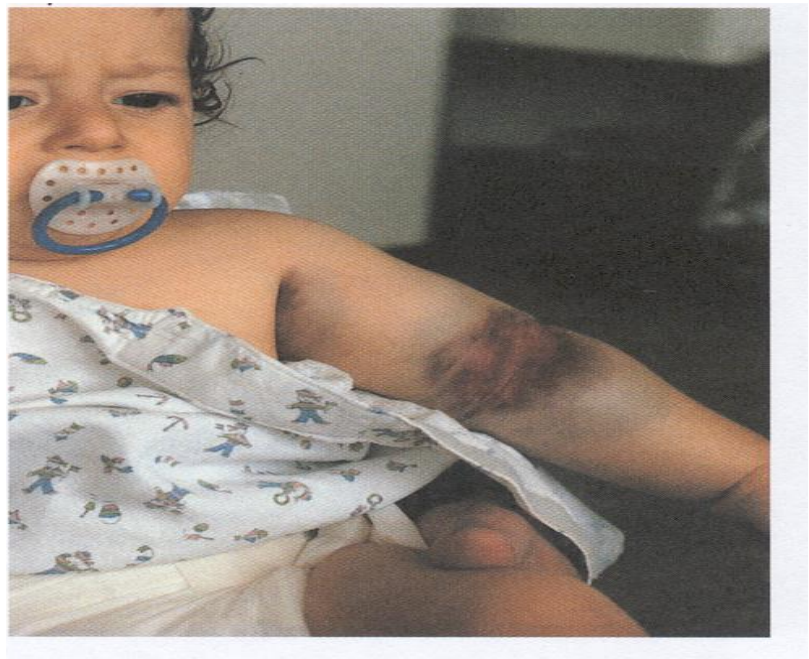


Acquired haemophilia, 65 years old man,

Venous access may be a concern !



Severe haemophilia A baby, 4 days old



Given the very large inter-patient variability, how can we optimise prophylaxis in haemophilia?

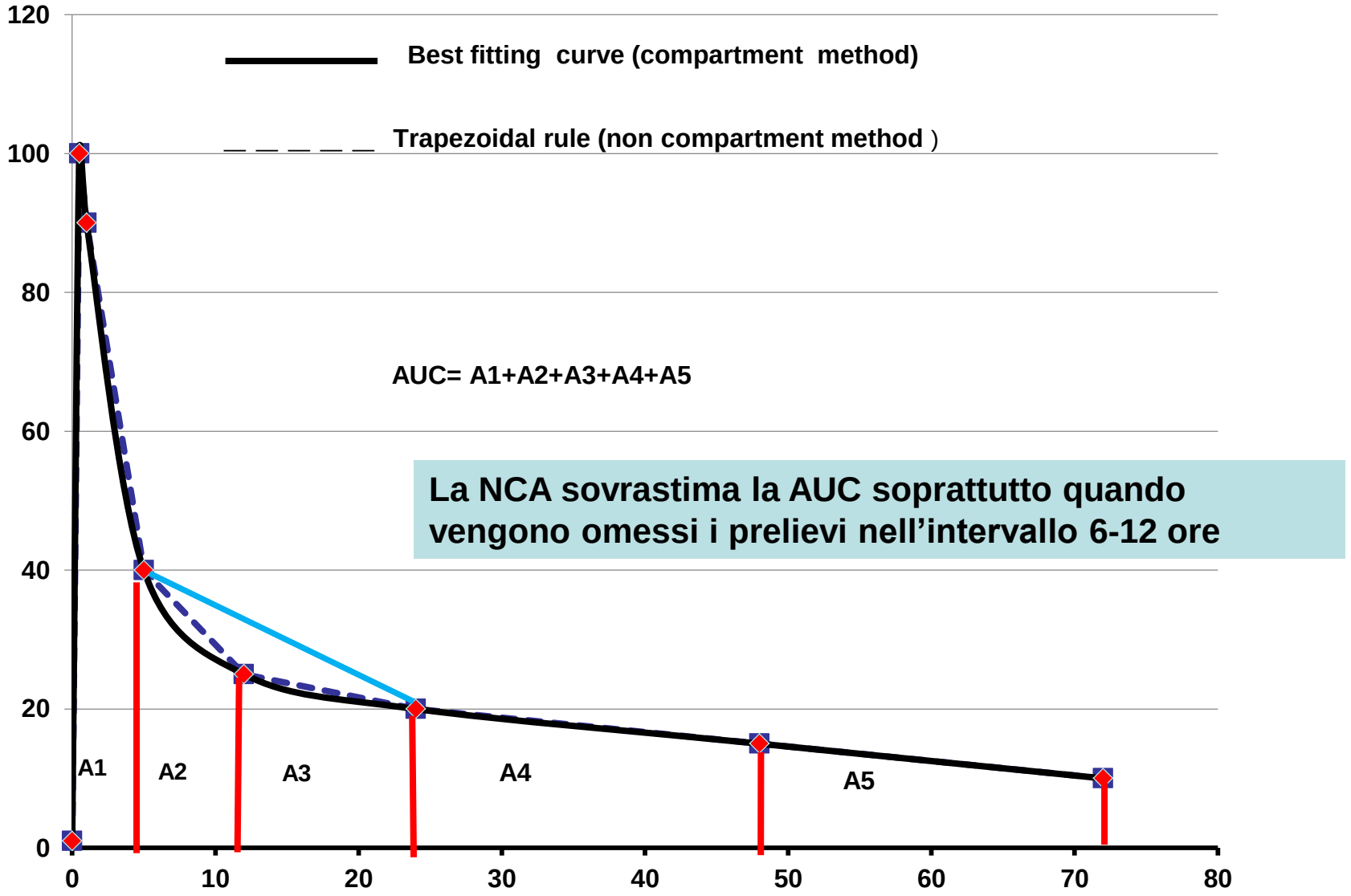
Empirical dosing: Dose optimization based on clinical outcome

Bleeding end point should be avoided!
One single hemarthrosis matters!!!

BY INDIVIDUALIZATION OF THERAPY

PK-based dose tailoring
Might PK parameters allow:

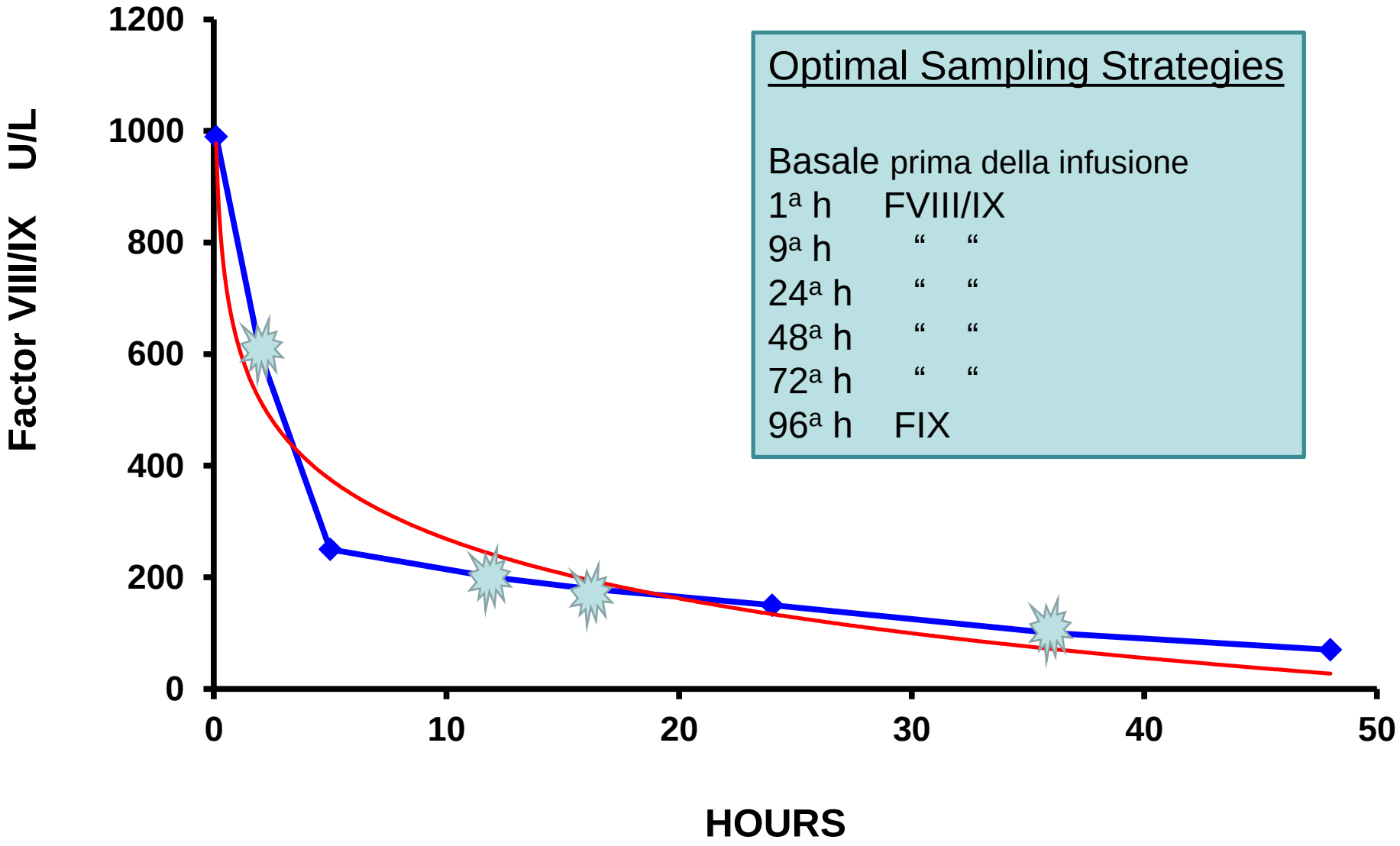
- **better tailoring of prophylactic regimens ?**
- **better utilization of these therapies ?**
- **increase the cost/effectiveness of replacement therapy?**



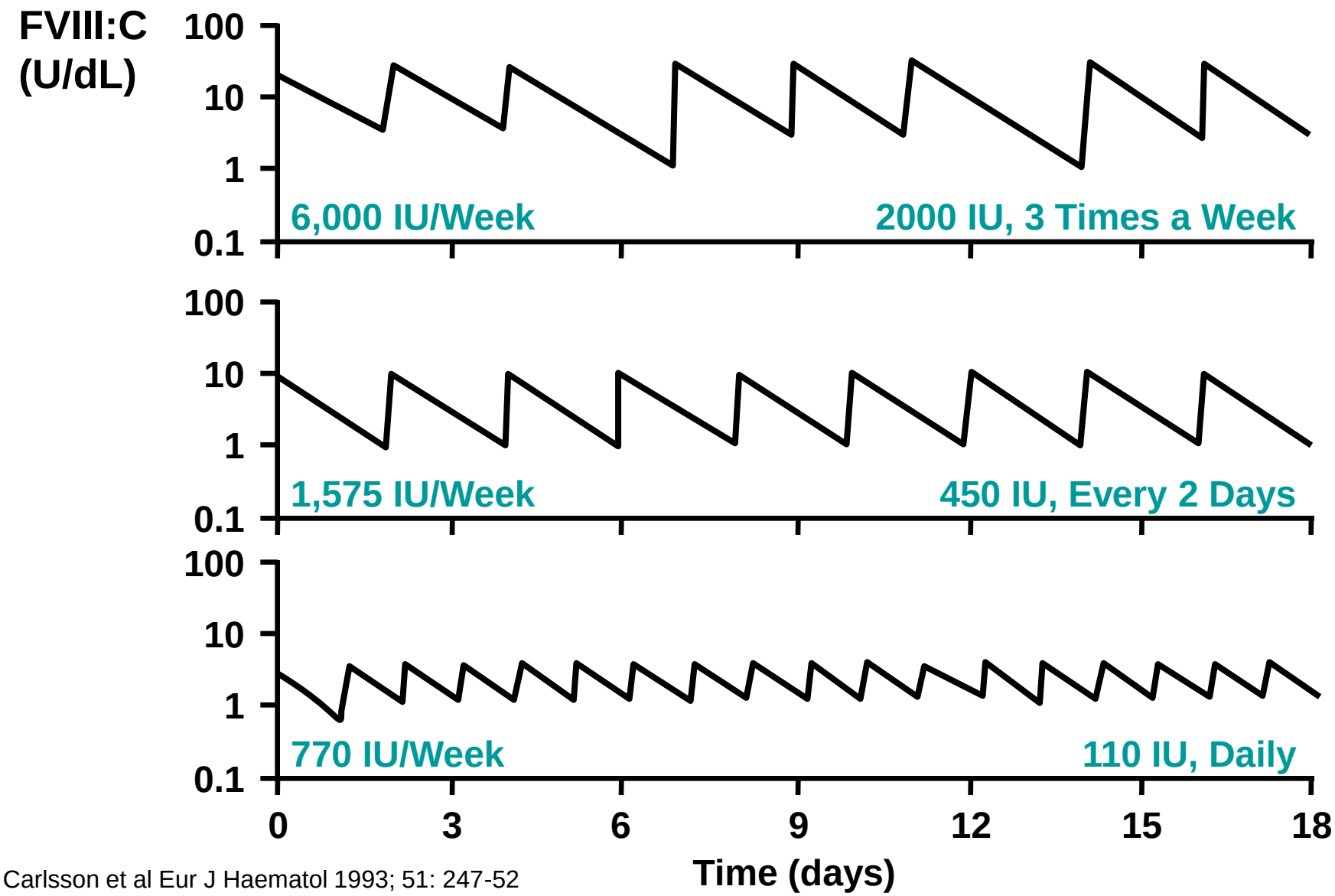
La NCA sovrastima la AUC soprattutto quando vengono omessi i prelievi nell'intervallo 6-12 ore

La necessità di avere numerosi punti concentrazione/tempo è il maggior ostacolo alla esecuzione della PK, soprattutto nei piccolo pazienti e anche per motivi logistici

BIPHASIC DECAY



Pharmacokinetic dosing with prophylactic treatment



Carlsson et al Eur J Haematol 1993; 51: 247-52

Pharmacokinetic dosing

- Studies in hemophilia A and B at our centre have shown the clinical feasibility of optimizing prophylactic treatment of severe hemophilia by the use of PK (E. Bertnorp)

Hemophilia A. Modeling study

- Aim
  - To investigate the use of individual PK as a tool for optimal dosage of FVIII, with special emphasis on the impact of different dosage regimens on the cost of treatment
- 8 patients on prophylaxis because of clinically severe disease (FVIII <1% - 3%)
- PK-curves obtained and multiple-dose activity curves computer-simulated. Plasma samples obtained to verify the model
- Theoretical dosing regimens calculated to maintain a trough level of 1 % exogenous FVIII

Carlsson et al Eur J Haematol 1993; 51: 247-52

Randomized cross over study in hemophilia A

- Aim
  - To investigate the feasibility of optimizing prophylactic dosing of FVIII by the use of individual PK data
- A suitable eod dosage to maintain a trough level of ≈ 1% calculated. Dose rounded off to nearest vial size (PK-dosing)
- Randomized to standard regimen or PK regimen for 2 x 6 months
- 21 patients enrolled, 14 completed

Carlsson et al Haemophilia 1997

Randomized cross over study in hemophilia A Main Results

	Standard dosage	PK dosage
Trough level % mean and (SD)	0.89 (0.73)	2.2 (1.5)
Bleedings during 6 months (total number)	10	9
Mean FVIII consumption and (SD) in kU during 6 months	124 (30)	84 (31)

Saving during 6 months of PK dosing in 14 patients after deduction of work-up cost $ 420,000

Carlsson et al Haemophilia 1997

Hemophilia B

- Aim
  - Investigate the use of single-dose PK data to predict multidose pharmacokinetics and explore their use for PK dosing
- 8 patients with severe B (FIX<1%)
- Theoretical dosing regimens calculated to maintain a trough level of 1 IU/mL
- 2 x 2 week cross-over study on standard dosing vs. dosing q/3 days based on individual PK

Carlsson et al Haemophilia 1998

Theoretical dose requirements to maintain a 1 % trough level of IX:C with various treatment schedules (n=8)

FIX consumption with dosage (kU yr^{-1})				
	Every 3 days	Every 2 days	Daily	By infusion
Mean	91.6	68.3	60.0	24.4
SD	±21.1	±10.8	±6.8	±4.0

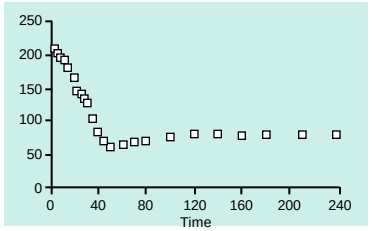
Why tailoring replacement therapy in hemophilia treatment ?

- Large inter-patients variability

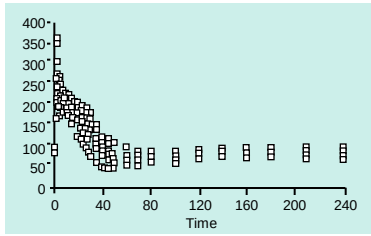
Individualization of Factor VIII dosage. Messori A. et al. J.Clin.Hosp.Pharm. 1984 Jun;9(2):95-103.

- Intra-patient or inter-occasions variability bur lower than inter-patients variability
- Definition and validation of minimal hemostatic FVIII/FIX plasma concentrations
- Definition of the best cost/effectiveness ratio of therapy regimens in prophylaxis and surgery
- Avoid extra-large doses and very high, unnecessary, FVIII/IX levels
- Financial constrains: HC's budget, Regional/National tender !
- New long acting concentrates are coming in !

Single dose PK vs Population PK



From one to multiple subjects

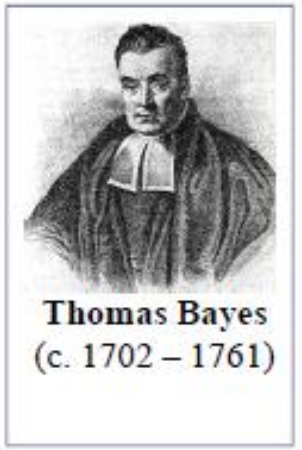


Advantages/Disadvantages

- Simple procedure, current FVIII/IX assays
- Even only 5 points are enough, but higher the number of points, better the fitting is!
- Model independent analysis: very robust but may over-estimate AUC
- One- or Two-compartment methods, which the best?
- Intra-patint-variability < Inter-patient variability

- Very large patient population
- Can identify co-variates
- PK data pooling across trials, even incomplete PK profiles
- A robust basis for dosing regimen simulation
- Population data are product specific ?
- Statistical definition of outliers
- Validation of the model, predictability and reliability
- Adherence of the treaters/patients

Bayesian Analysis


Thomas Bayes
(c. 1702 – 1761)

Bayesian analysis is a procedure in which the most likely PK parameter values in the individual patient are estimated from the limited data available, based on previous knowledge about the PK of the drug in the general population of patients studied

HAEMATOLOGICA

Vol. 70, No. 5, pp. 454-456, 1985.

COMPARISON OF TWO PHARMACOKINETIC TECHNIQUES FOR INDIVIDUALIZING FACTOR VIII DOSAGE IN HAEMOPHILIA PATIENTS (*)

MASSIMO MORFINI - THADDEUS H. GRASELA - GIOVANNI LONGO
MARZIA MATUCCI - ANDREA MESSORI - SILVIA VANNINI
PIERLUIGI ROSSI-FERRINI

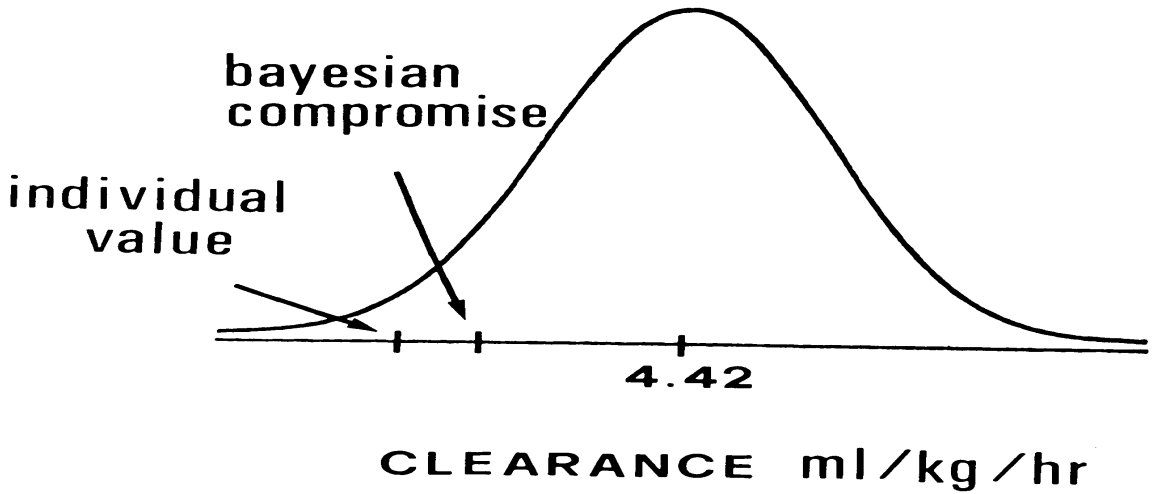
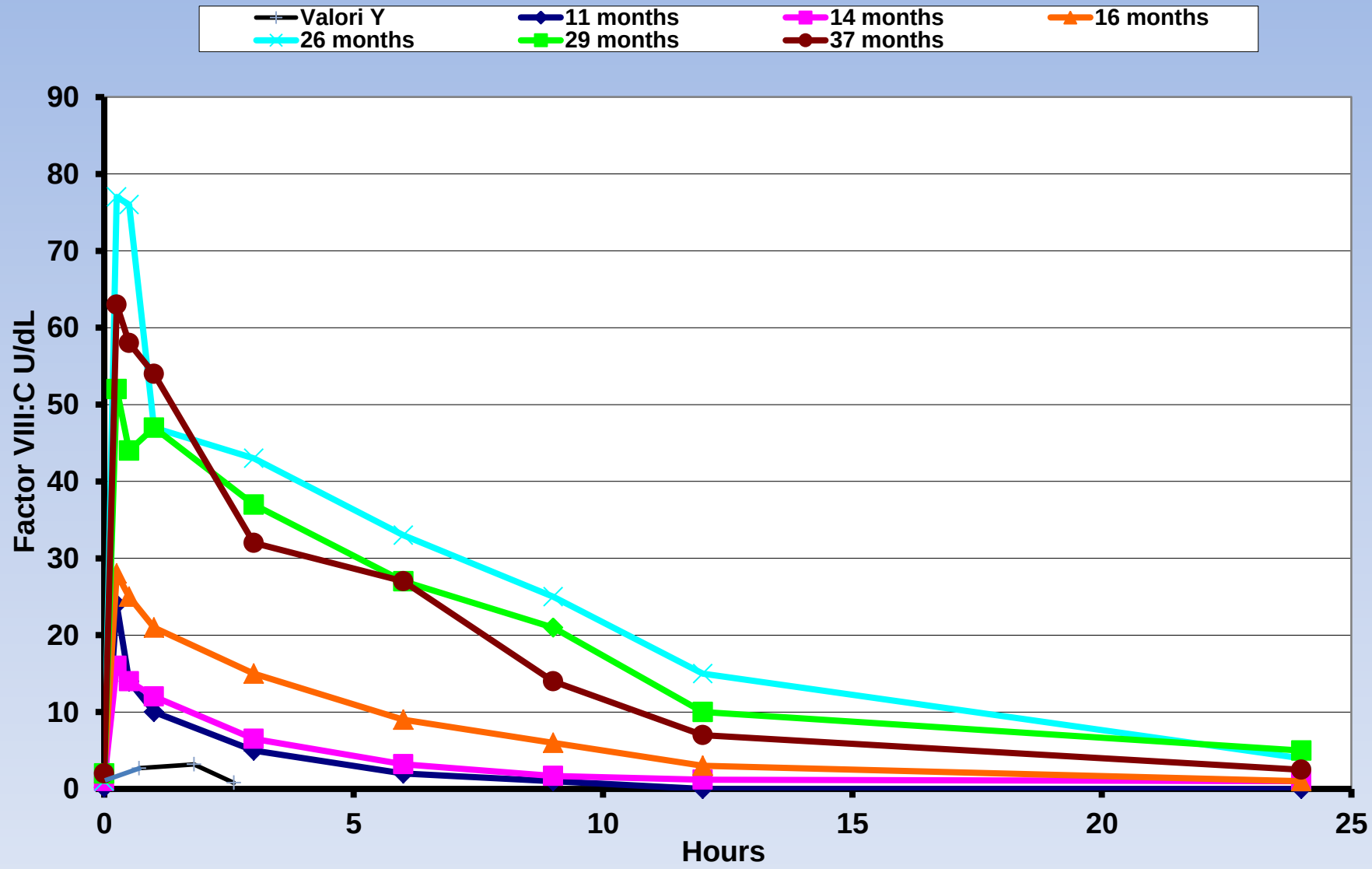
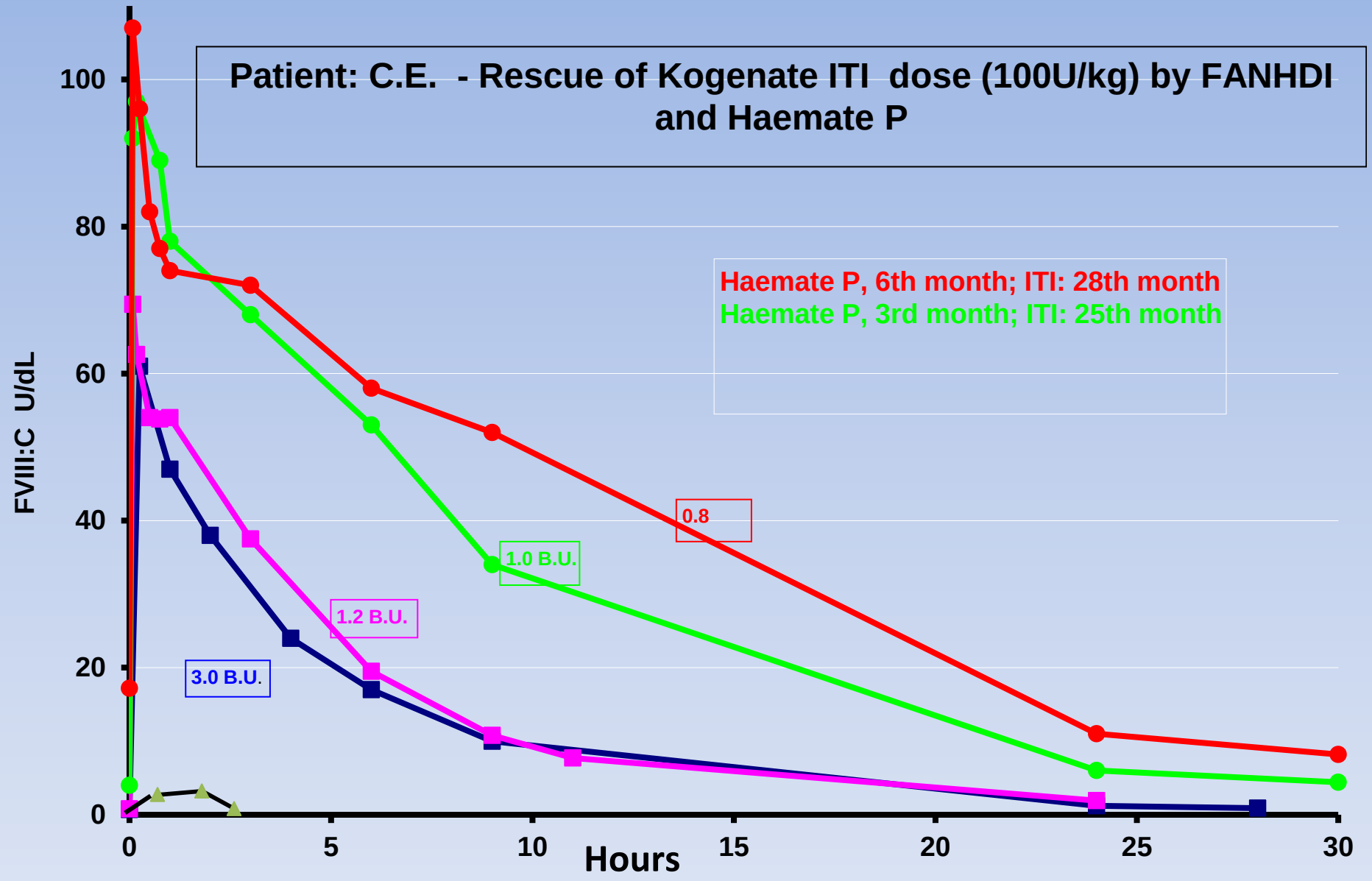


Fig. 1.
Normal distribution of the values of Factor VIII clearance in haemophiliacs (mean=4.42 ml/kg/hr, SD= 1.81 ml/kg/hr; data from Ruffo et al. [7]). The Figure shows the individual value of clearance for Patient 2 (1.27 ml/kg/hr) as well as the value resulting from the bayesian compromise (1.77 ml/kg/hr).

G.K.-PK during ITI with ReFacto



Follow up della ITI mediante PK



Follow up della ITI mediante PK

“Even very limited PK information is better than none….PK can then be utilized to complement clinical empiricism in the prophylactic treatment of hemophilia”

Sven Björkman

Björkman S Haemophilia 2010;16:597-605