

Do we need a perfect basic structural model before exploring the covariate model ? Example with enoxaparin

The PROPHRE.75 study

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Background

- **Low-molecular-weight heparin (LMWH) = anticoagulant mainly excreted by the kidney**
- **Risk of accumulating effect in patients with renal impairment**
 - Risk of major bleeding complications
 - French recommendations = to monitor LMWH treatment in special populations, such as the elderly
- **Which target prophylactic range in the elderly ?**

➔ Population PK study of enoxaparin at prophylactic dosage in patients ≥ 75 years

Study design

➤ Prospective cohort of consecutive patients ≥ 75 years

- Prophylaxis venous thrombotic disease
- Enoxaparin SC 4000 IU once daily

➤ Data collected in routine

- Covariates age, gender, weight, renal function, concomitant disease...
- Exact times of injection and blood samples
- PK marker = Anti-Xa activity (chromogenic assay)

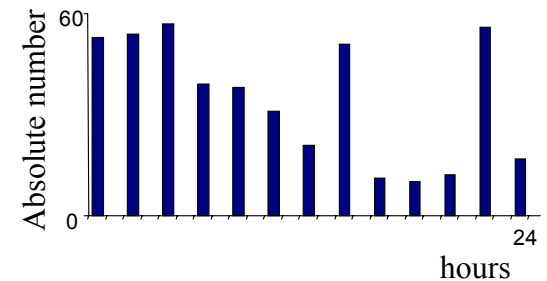
Patient and data description

➤ **189 patients included**

- 62 % medical patients, 15 % surgical, 22 % stroke
- 82 ± 5 years , 62 % of female gender
- 22 % small body weight (< 55 kg)
- 50 % moderate or severe renal impairment (CrCL < 50 ml/min)

➤ **451 blood samples collected**

- 2.4 samples per patient (sparse data)
- Distribution of samplings over the day



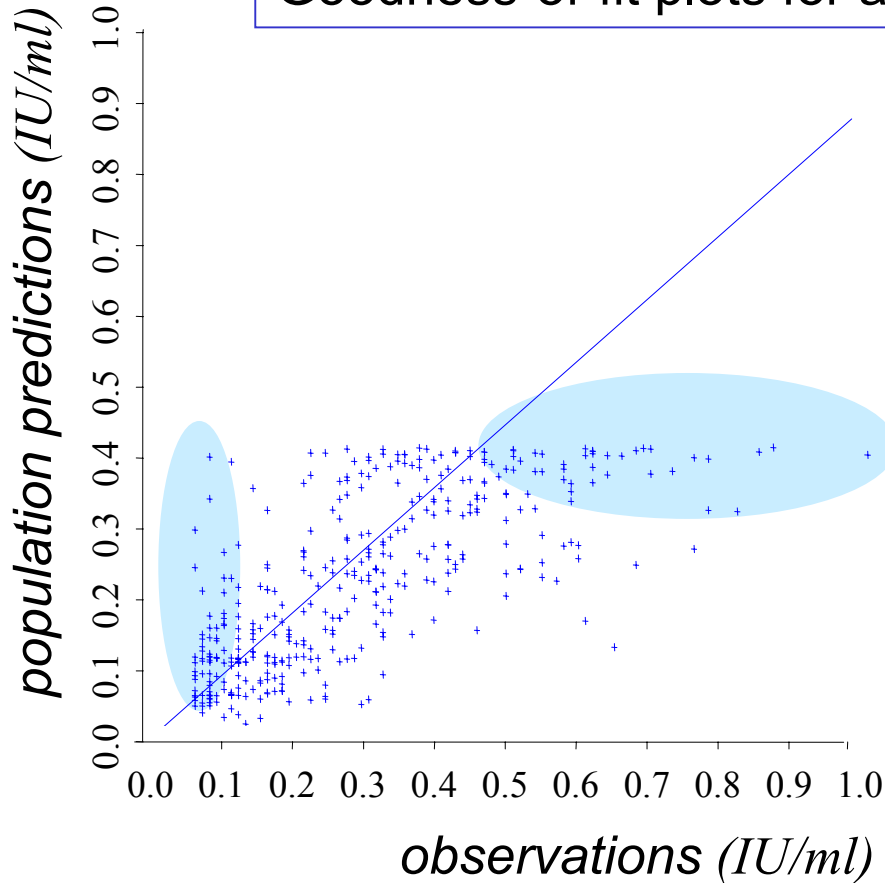
Basic model building

- **Pharmacological properties of the drug**
- **Literature data with subcutaneous LMWH**
 - 2 cpt. model, proportional error model
 - NONMEM: ADVAN4 TRANS4, FOCE Interaction

Schoemaker R 1996	Barrett JS 2001	Bruno R 2003	Green B 2003	Green B 2004	Hulot JS 2004
12 pts	425 pts	448 pts	96 pts	38 pts	60 pts
10 samples	6 samples	2 samples	3 samples	10 samples	3 samples
1 or 2 cpt.	2 cpt.	1 cpt.	2 cpt.	2 cpt.	1 cpt.

Basic model building

Goodness-of-fit plots for a two-compartment model



➤ Unsatisfactory prediction of anti-Xa activity near LOQ

➤ Underestimation of high anti-Xa activities (>0.5 IU/ml)

➔ Reassessment of basic model building

Improvement considered

➤ Literature data with subcutaneous LMWH

Schoemaker R 1996		Barrett JS 2001	Bruno R 2003	Green B 2003	Green B 2004	Hulot JS 2004
First order absorption, linear elimination						
LOQ -	- ENDO	LOQ ENDO	LOQ -	- -	- ENDO	LOQ -
add. error -		mix. error -	prop. error IOV	add. error -	mix. error -	add. error -

LOQ = limit of quantification ; ENDO = endogenous anti-Xa activity

structural model

data set

error models

Improvement considered (1)

structural model

- | | |
|----------------------------------|-----------------------|
| ➤ 3 compartment model | <i>No improvement</i> |
| ➤ Michaelis-Menten elimination | <i>No improvement</i> |
| ➤ Lag time in absorption process | <i>No improvement</i> |
| ➤ Endogenous anti-Xa activity | <i>No improvement</i> |

Improvement considered (2)

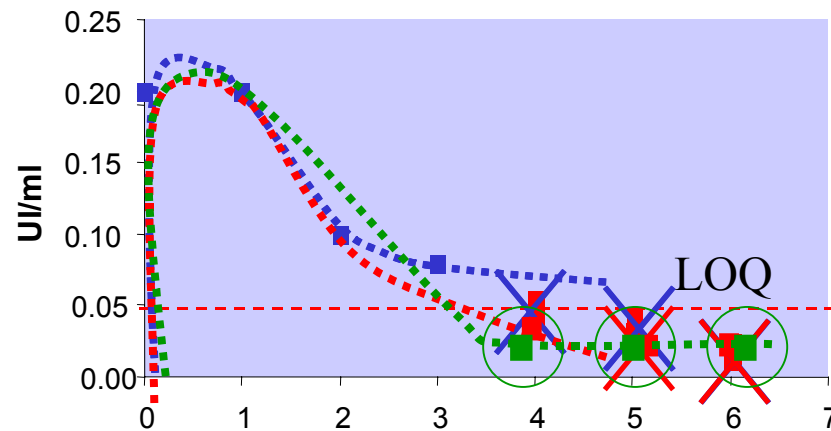
data set

➤ What's about LOQ ?

No improvement

- Several methods tested:

- to omit data $< \text{LOQ}$
- to replace by $\text{LOQ}/2$
- to replace by $\text{LOQ}/2$ and omit



➤ Log-transformation of data

No improvement

Duval V & Karlsson M, Pharmaceutical Res 2002; 19: 1835-40

Girard P, PAGE 2002

Improvement considered (3)

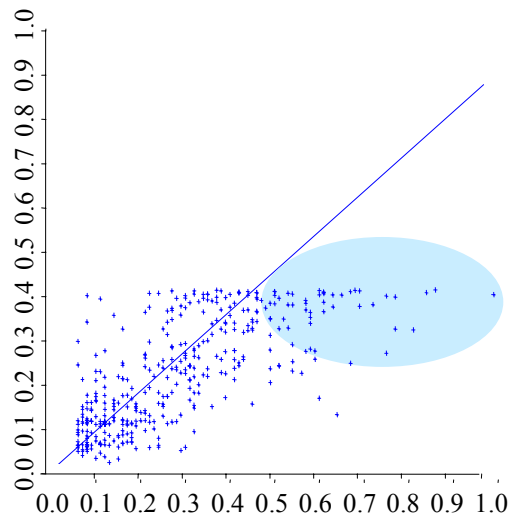
error models

➤ Additive or mixed error models

No improvement

As a last resort...

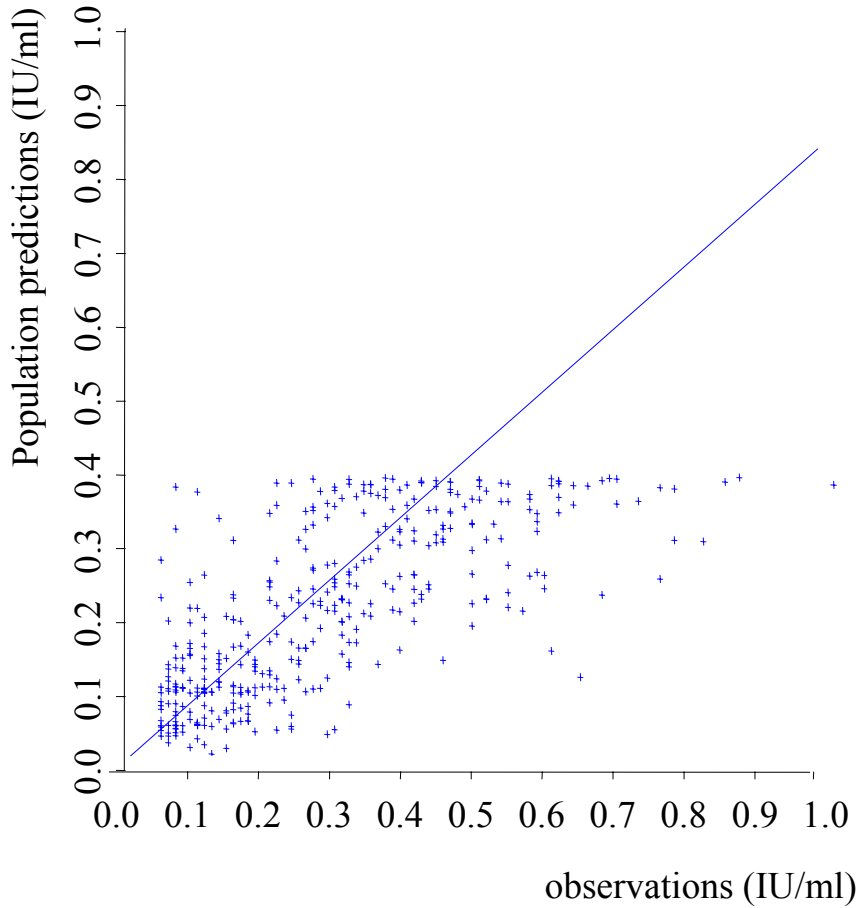
- Need to explore other models?
 - mixture models
 - inter-occasion variability...
- Need to complete the dataset with rich data?



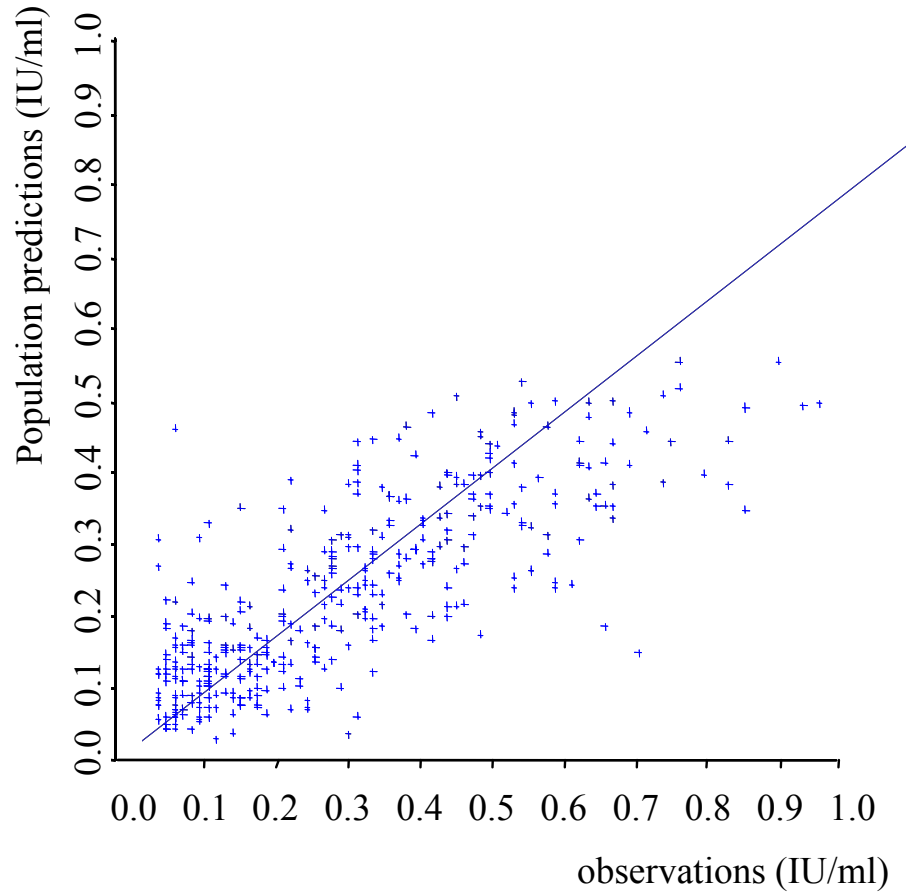
- Older
- Thiner
- Women

➔ Introduction of covariates
in spite of basic model bias

As a last resort...



without covariates



with covariates
body weight and gender

Issues

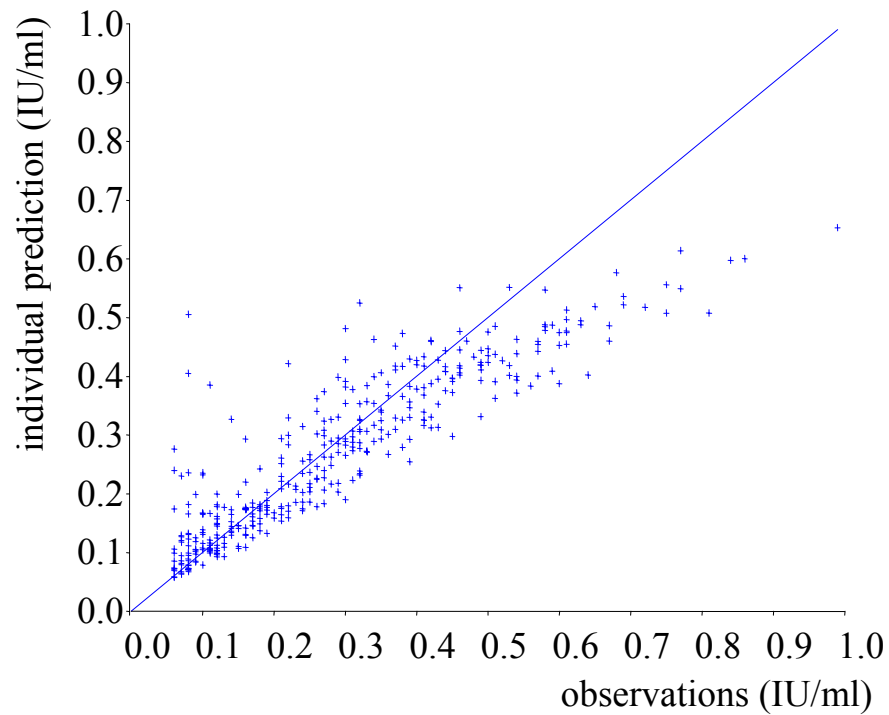
- Is there a typical reason for underestimating high concentration values?
 - With a better baseline model, would the covariate model be more precise?
 - Is it worth exploring a mixture model with sub-populations before introducing covariates?
- ➔ Do we need a perfect basic structural model before exploring the covariate model?

References of enoxaparin s.c. trials

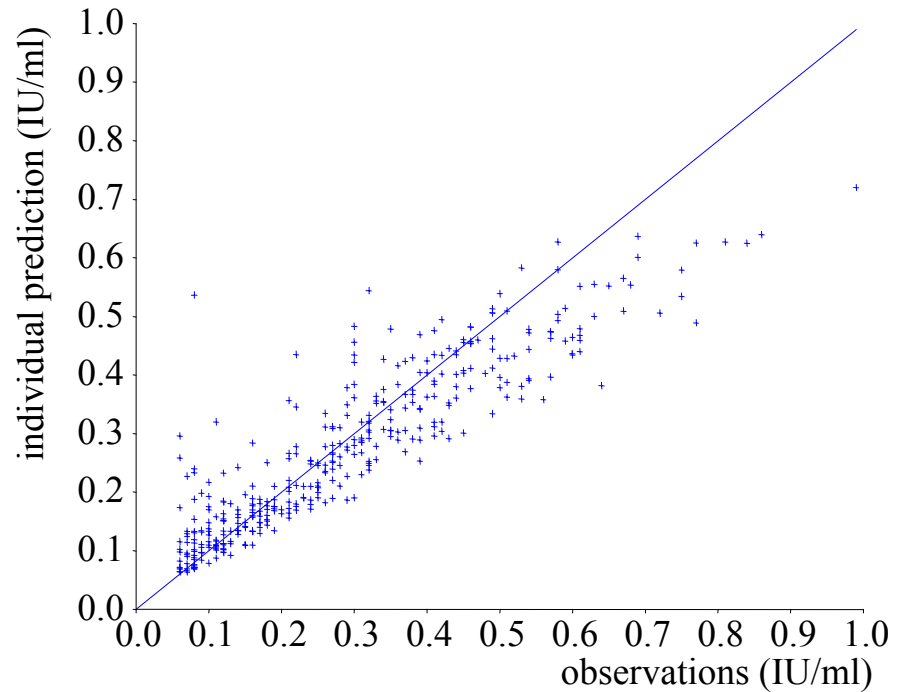
- Schoemaker E & Cohen A, Br J Clin Pharmacol 1996; 42: 283-90.
- Barrett JS et al. Int J Clin Pharmacol Ther 2001; 39: 431-46.
- Bruno R et al. Br J Clin Pharmacol 2003; 56: 407-14.
- Green B & Duffull S, J Clin Pharmacol 2003; 56: 96-103.
- Green B et al. Br J Clin Pharmacol 2004; 59: 281-290
- Hulot JS et al. Ther Drug Monit 2004; 26: 305-10.

Backup slides

IPRED

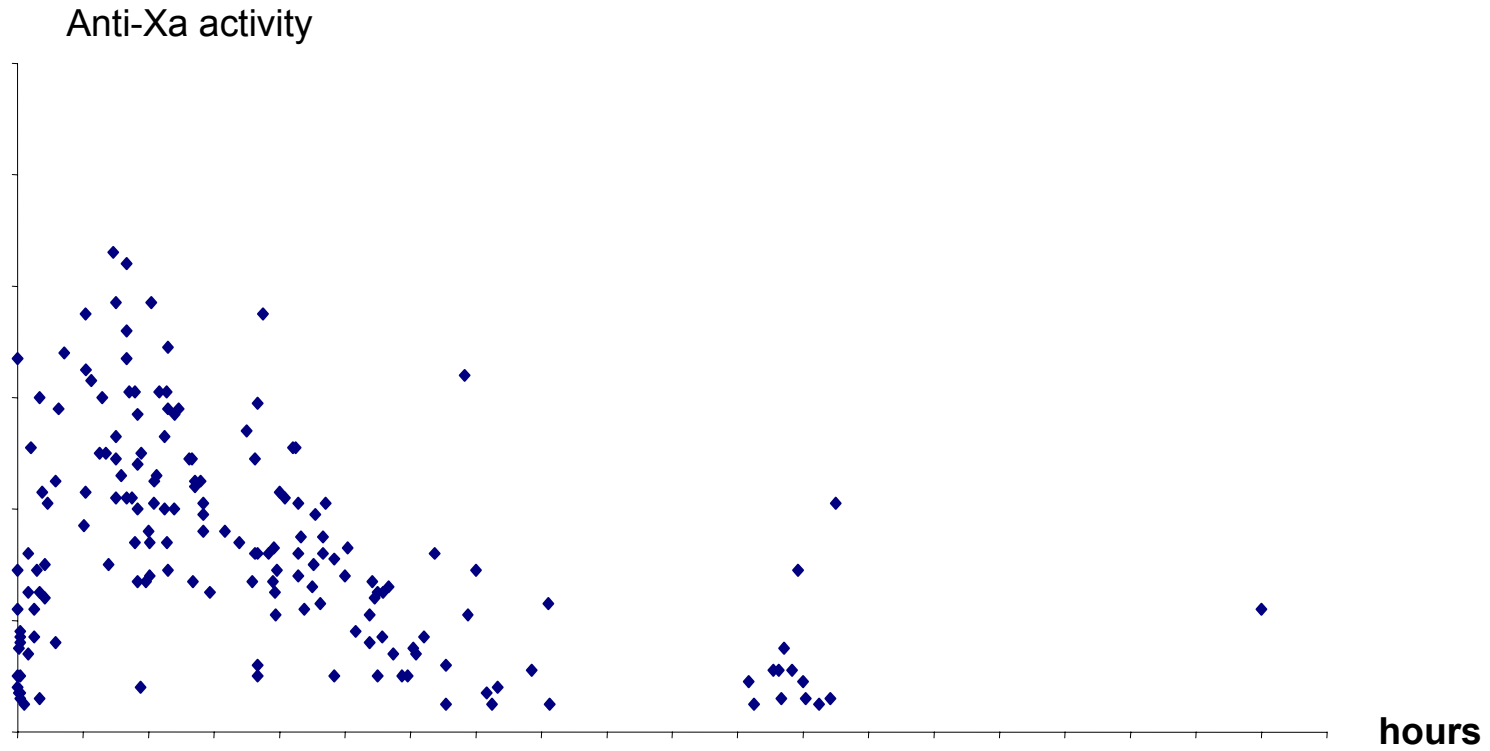


without covariates

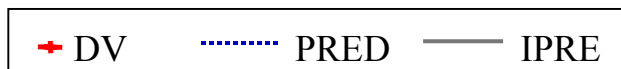
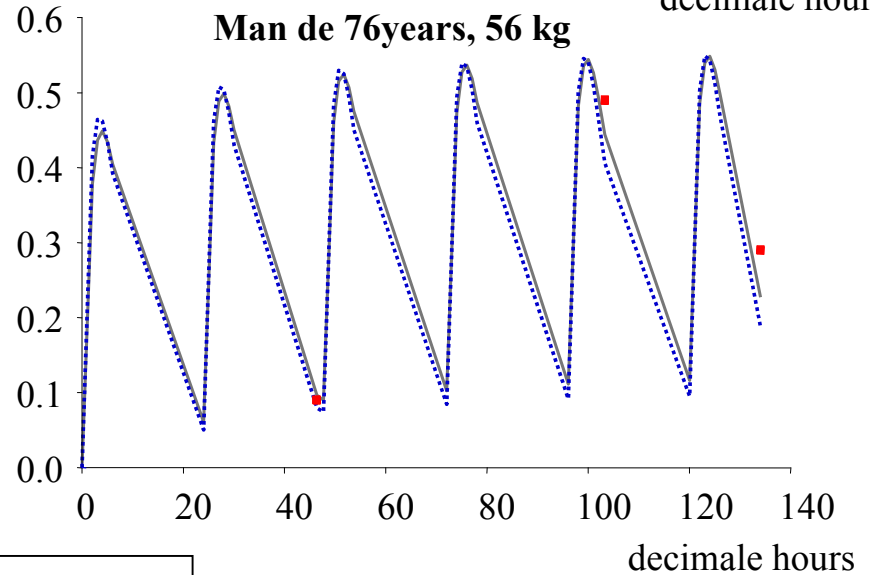
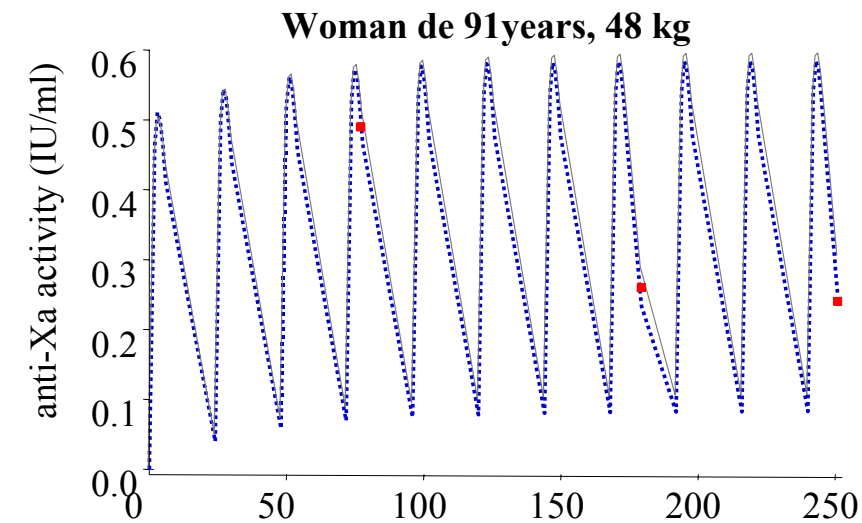
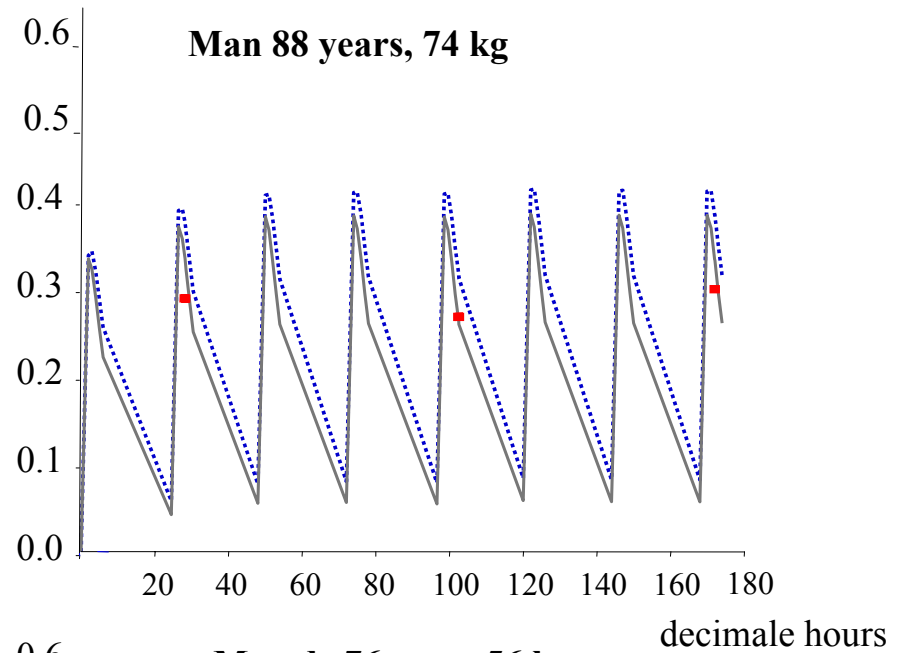
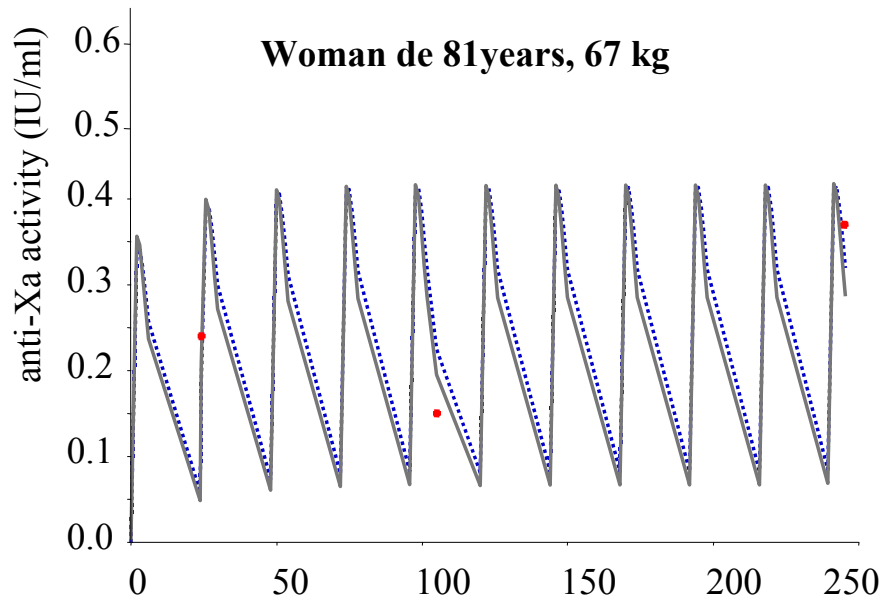


with covariates

Data study



some profiles



Comparison observations > 0.5IU/ml & < 0.5IU/ml

Covarites		DV 0.5UI/ml	DV>0.5UI/ml
clairance (ml/min)		51±18	40±12
weight (kg)		65±14	54 ±17
sex	female	103 (61%)	32 (78%)
	male	65 (39%)	9 (22%)