UNIVERSITE PAUL SABATIER TOULOUSE III

INSTITUT CLAUDIUS REGAUD

Cystatin C as a new covariate to predict drugs renal elimination

F Thomas(1), S Séronie-Vivien(1), F Bouissou(2), M Tafani(2), JP Delord(1), L Gladieff(1), E Chatelut(1)

(1) EA3035, Institut Claudius-Regaud ;(2) Centre Hospitalier Universitaire, Toulouse, France

Cystatin C

- Small Protein (120 amino-acids) expressed in all nucleated cells. Inhibitor of cysteine proteases.
- Marker of Glomerular Filtration Rate (GFR)
  - **Glomerular filtration +++**
  - Not secreted
  - Completely reabsorbed and catabolised
- Independent on age, gender, muscle mass.

→ Conflicting results about cystatin's performance compared to creatinine…

→ Cystatin and digoxin clearance (O'Riordan et al. Br J Clin Pharmacol,2002) → not better

Studies and objectives

Carboplatin

- Mainly eliminate **glomerular filtr**
- Carboplatin clea predicted by sev formulae includ creatinine level
- **Cystatin: new c for individual d**

Thomas et al, Clin Pharmacokinet 2005

Topotecan

- Renal elimination accounts for 50% of t
- Its c crea
- If Cl 20 <
- **Cou pre clea**

Hoppe e

^{51}Cr-EDTA

- Direct measure of GFR by determination of ^{51}Cr-EDTA plasma concentrations after a bolus dose.
- Children (1.4 to 21.4 years)
- GFR estimated by Schwartz formula (serum creatinine, height, coefficient specific of the laboratory)
- **Cystatin: new covariate for GFR estimation?**

Bouvet et al, Ped Nephrol in press 2006

Methods (1)

Carboplatin study
- 45 patients
- Sparse data of ultrafilterable plasma concentration
- database = 188 patients

Topotecan study
- 59 patients
- topotecan data

^{51}Cr-EDTA study
- 100 children
- 4 samples

Carboplatin study, Topotecan study →

1) Run without covariates
- NONMEM analysis
- Two-compartment model
- FOCE
- Proportional error model

^{51}Cr-EDTA study →

1) Run without covariates
- NONMEM analysis
- One-compartment model
- FO
- Proportional error model

→ POSTHOC clearance = Cl_{actual}

Methods (2)

Carboplatin study
- 45 patients

Topotecan study
- 59 patients

^{51}Cr-EDTA study
- 100 children

↓

DATA SPLITTING

Model Building Data Set
→ 2/3 of patients

↓

Find the best covariates models

Validation Data Set
→ 1/3 of patients

↓

Prospective validation of models

Methods (3)

Model building data set → $TVCL = \theta_1$ → OFV and IIV

<u>Covariate analyses</u>

Scr (serum creatinine), CysC (serum cystatin C), Alb, Sun, Age, sex, PS, BW (body weight), IBW, BSA

$$\mathbf{TVCL} = \theta_1 \cdot \left(\frac{cov}{mean(cov)}\right)^{\theta 5}$$

ΔOFV, Δ IIV

INTERMEDIATE MODEL

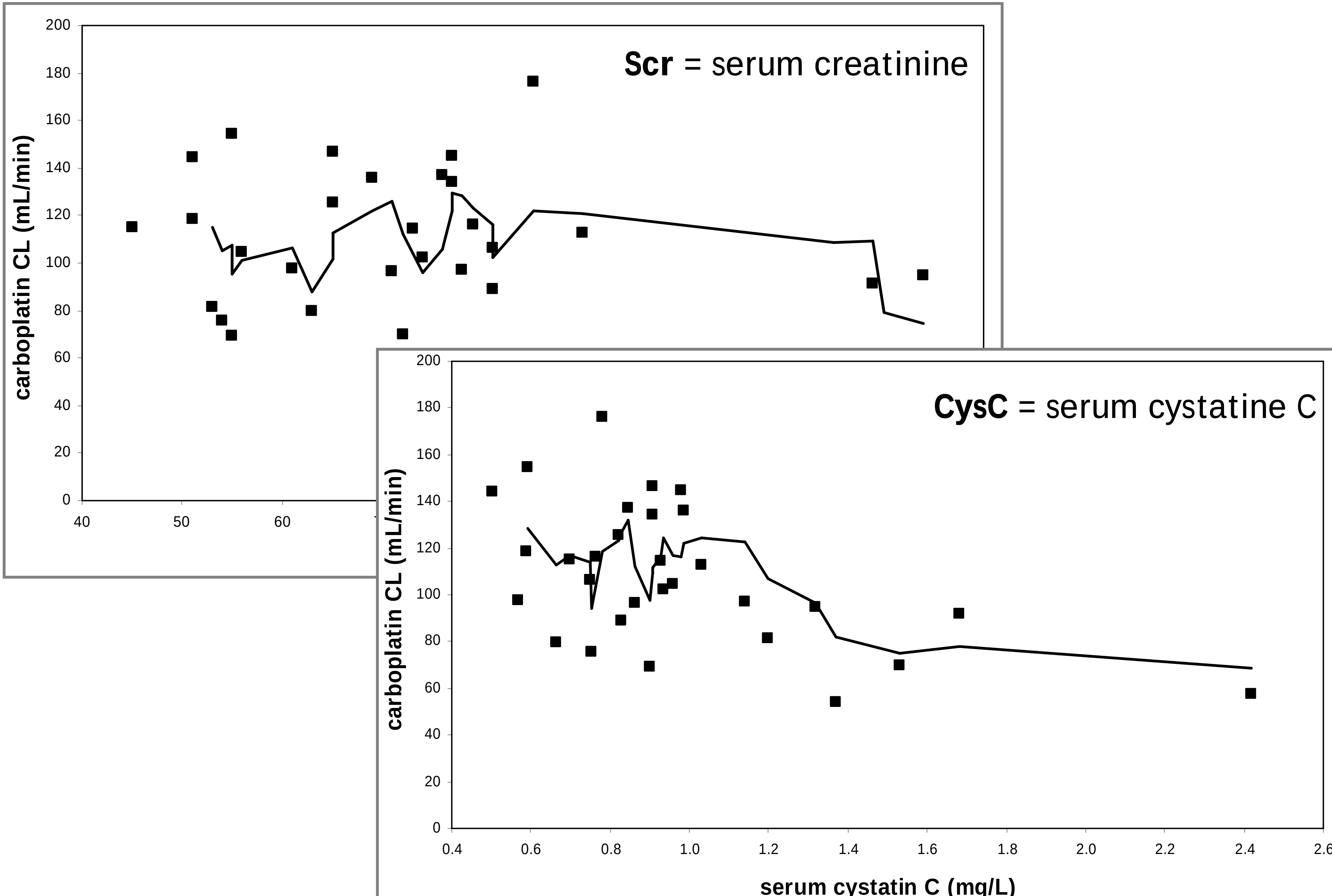
$$\mathbf{TVCL} = \theta_1 \cdot \left(\frac{cov1}{mean(cov1)}\right)^{\theta 2} \cdot \left(\frac{cov2}{mean(cov2)}\right)^{\theta 3} \ldots$$

Stepwise backward elimination

FINAL MODEL → Validation data set

ΔOFV, Δ IIV

Carboplatin (1)



Carboplatin (2)

Final covariate model	IIV
$$CL_{(mL/min)} = 113 \cdot \frac{(BW/65)^{0.463} \cdot 0.85^{sex}}{(SCr/75)^{0.399} \cdot (CysC/1)^{0.306} \cdot (age/56)^{0.407}}$$	14%

Alternative models	ΔOFV	P	IIV
➢ $$CL_{(mL/min)} = 112 \cdot \frac{(BW/65)^{0.331} \cdot 0.86^{sex}}{(\mathbf{CysC}/1)^{0.507} \cdot (age/56)^{0.369}}$$	+6.4	<0.02	16%
➢ $$CL_{(mL/min)} = 110 \cdot \frac{(BW/65)^{0.625} \cdot 0.90^{sex}}{(\mathbf{SCr}/75)^{0.654} \cdot (age/56)^{0.507}}$$	+6.2	<0.02	16%

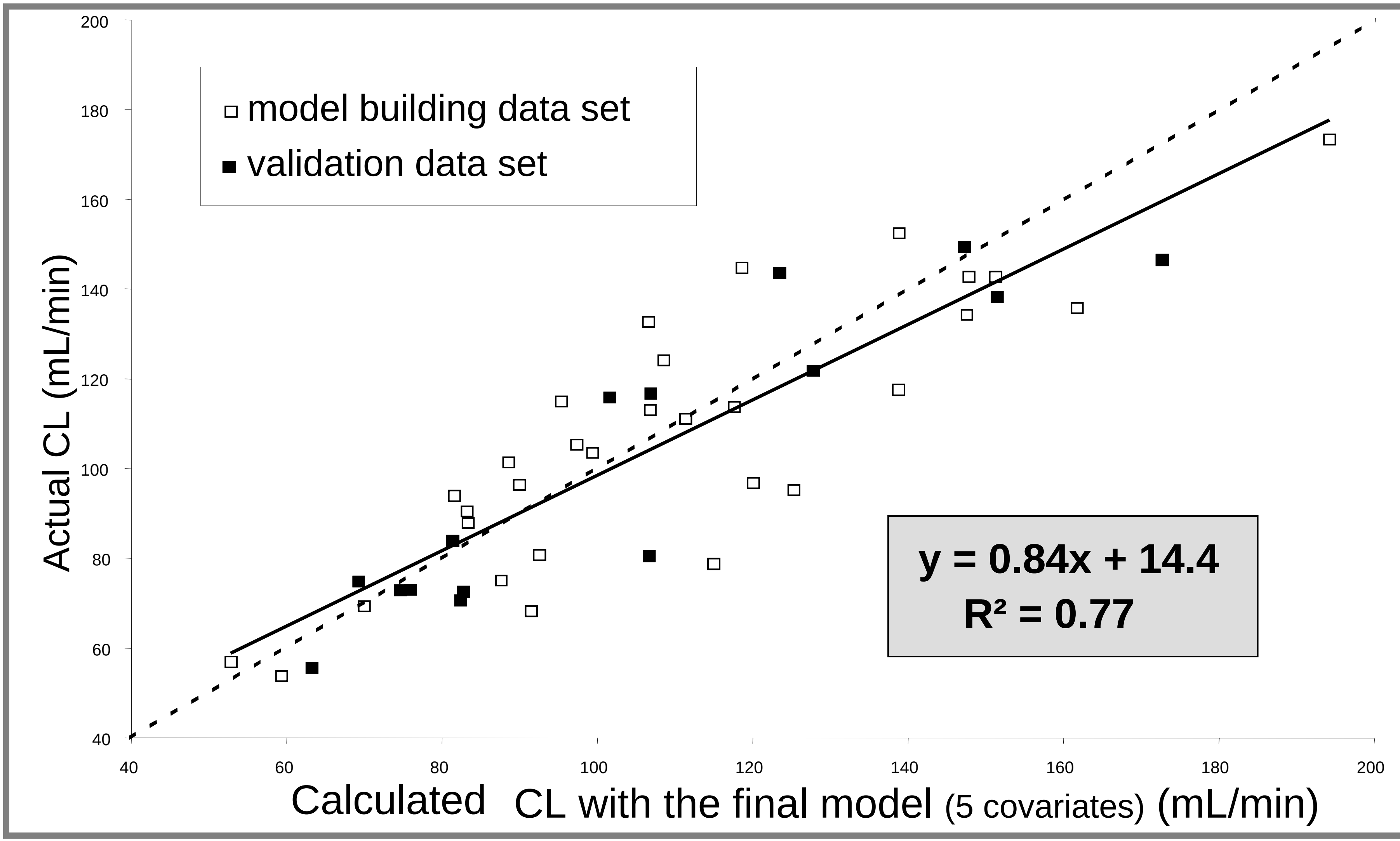
Carboplatin (3)

→ Prospective validation: predicted vs. actual CL

	Scr	CysC	Scr and CysC
R^2	0.70	0.72	0.80
MAPE (%) Mean Absolute Percentage of Error	17%	15%	13%
MPE (%) Mean Percentage of Error	+11%	+6%	+7%

Carboplatin (4)

→ Whole data set: predicted vs. actual CL

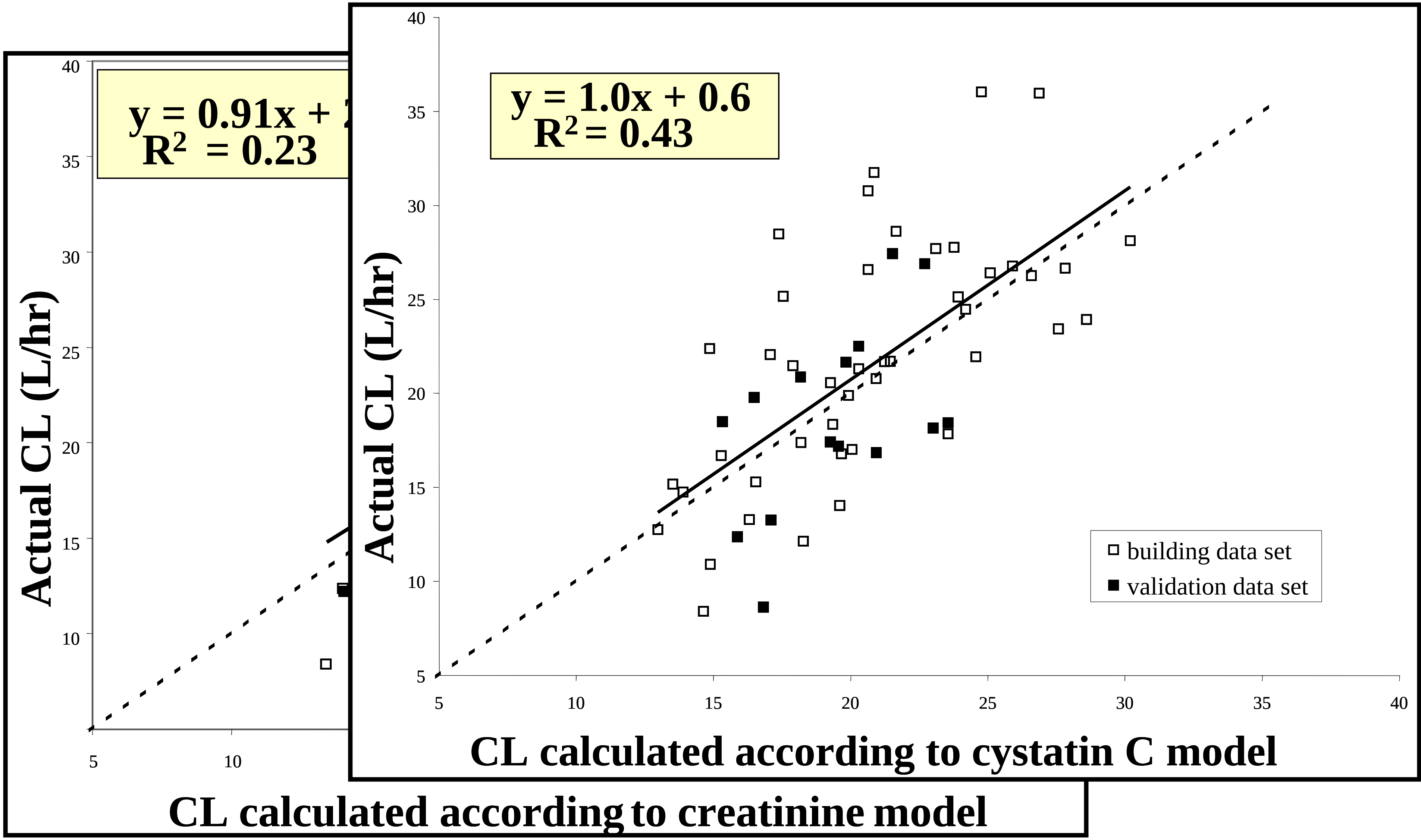


Topotecan (1)

Equation to estimate topotecan clearance (L/h)	IIV	OFV	P
Intermediate model			
$CL = 20.1 \cdot \frac{(IBW/57)^{0.98} \cdot (age/57)^{0.001}}{(CysC/1.06)^{0.52} \cdot (Scr/85.2)^{0.14}}$	23%	480.2	
Final models			
➢ $CL = 20.2 \cdot \frac{(IBW/57)^{0.95}}{(CysC/1.06)^{0.6}}$	23%	480.8	<0.0001
➢ $CL = 20.2 \cdot \frac{(IBW/57)^{1.23}}{(Scr/85.2)^{0.52}}$	26%	490.1	<0.001

Topotecan (2)

→ Whole data set: predicted vs. actual CL



^{51}Cr-EDTA (1)

Equation to estimate ^{51}Cr-EDTA clearance (mL/min)	IIV		
Final model $$CL = 62.8 \cdot \frac{(BW/45)^{0.33} \cdot (age/14)^{0.36}}{(Scr/96)^{0.41} \cdot (CysC/1.2)^{0.49}}$$	19%	ΔOFV	P
Alternative models			
➢ $$CL = 62.6 \cdot \frac{(BW/45)^{0.33} \cdot (age/14)^{0.22}}{(CysC/1.2)^{0.82}}$$	**22%**	**+16**	<0.001
➢ $$CL = 64 \cdot \frac{(BW/45)^{0.23} \cdot (age/14)^{0.52}}{(Scr/96)^{0.76}}$$	24%	+19	<0.001

^{51}Cr-EDTA (2)

→ Prospective validation: predicted vs. actual CL

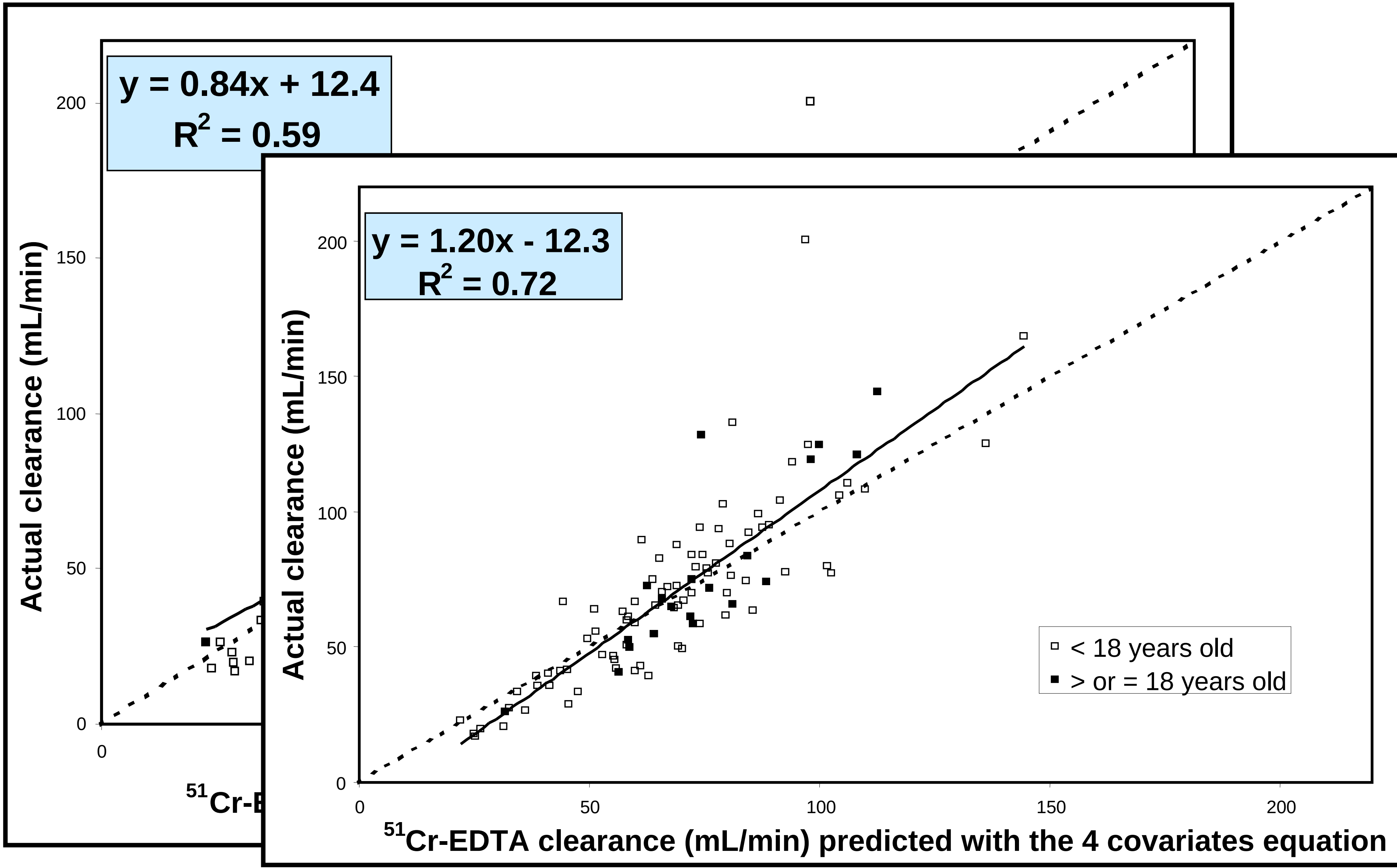
$$CL = 62.8 \cdot \frac{(BW/45)^{0.33} \cdot (age/14)^{0.36}}{(Scr/96)^{0.41} \cdot (CysC/1.2)^{0.49}}$$

$$GFR = k \cdot \frac{height}{Scr}$$

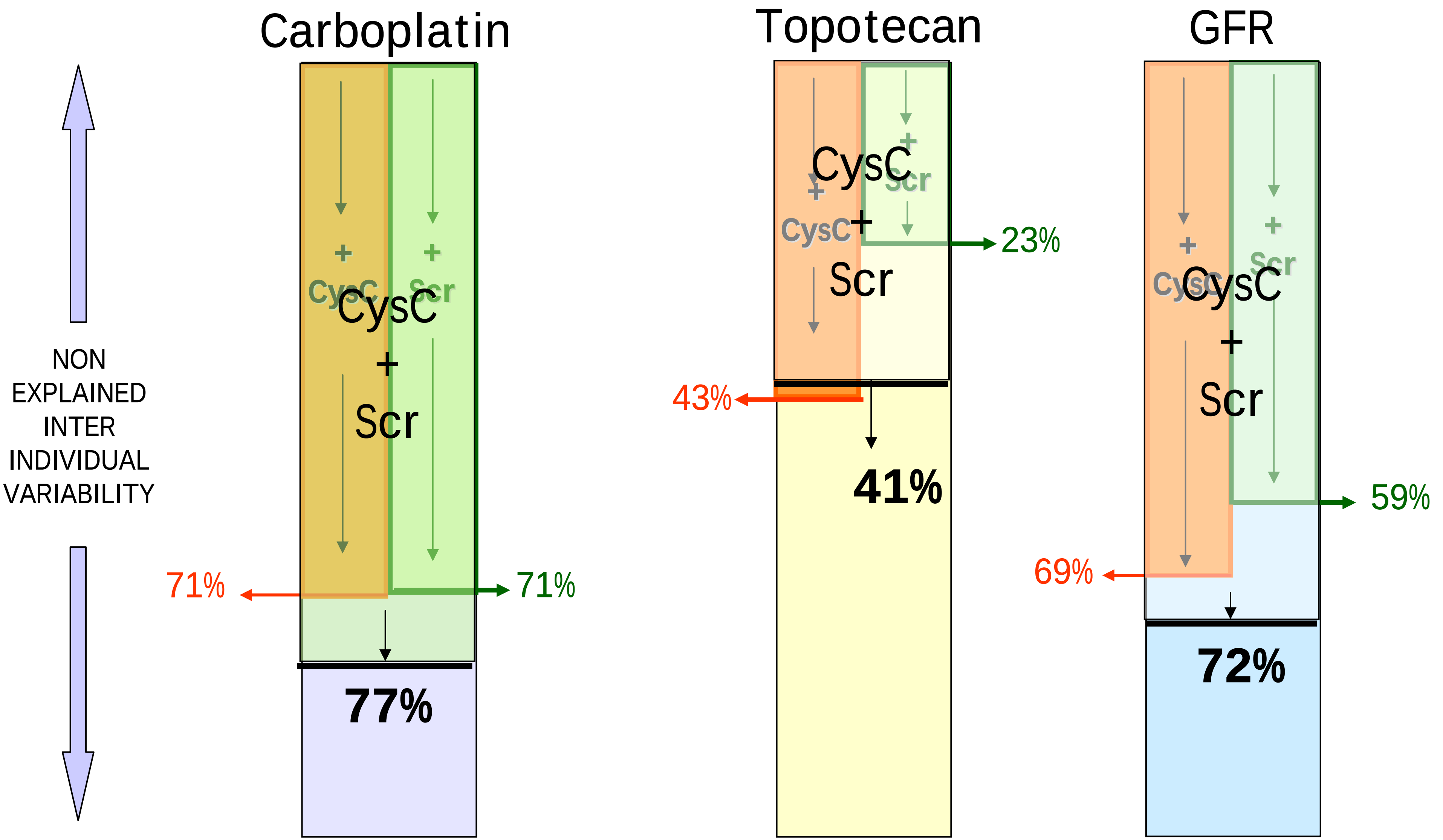
	Final model	Schwartz
R^2	0.59	0.37
MAPE (%)	17.4	17.3
MPE (%)	+0.9	-8.2
Min % error	-45	-62
Max % error	+44	+431

^{51}Cr-EDTA (3)

→ Whole data set: predicted vs. actual CL



Inter individual variability
(whole data set, R^2)



Conclusions

- Cystatine C is a better covariate than creatinine to predict drug renal clearance.
- Limits:
  - Should be studied with others covariates (BW, age…)
  - 2.51 euros/analysis versus 0.03 euros for creatinine.
- Advantages:
  - Nephelometric immunoassay (Dade-Behring) less variable than creatinine (Jaffé vs. Enzymatic)
  - Superiority over creatinine larger at a multicenter level
  - Likely to be more adapted for equation-based dose adjustment