Impact of covariate model building methods on the evaluation of clinical relevance of covariate effects in population pharmacokinetic analysis

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CONTEXT

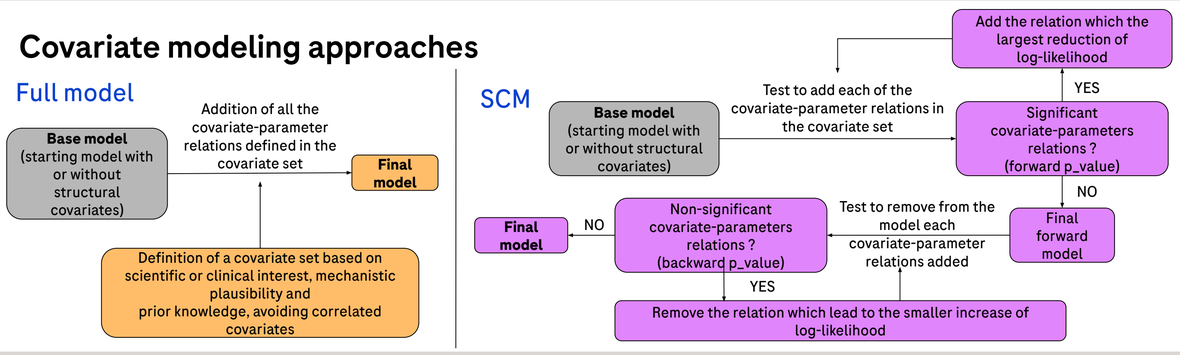
- Covariate analysis is a key step of drug development as it notably allows to adjust the dose in subpopulations of interest and performed predictions under new experimental conditions;
- Covariates of interest are represented on a forest plot where the 90% CI of change in parameter value is expressed as a ratio for given values or categories of the covariates and relatively to a reference value;
- Forest plots are important tools used by clinicians to make decisions about drug dosing. Consequently, precise and accurate estimation of covariate effect ratios and their associated uncertainty is critical;
- In pharmacometrics, there are several covariate modeling methods including the commonly used stepwise covariate model (SCM) [1] and the full model [2];
- Until now, studies comparing different methods have focused mainly on the correctness of the selected covariate model and covariate effect estimates accuracy, however, none was conducted on assessing the associated uncertainty and its impact on the evaluation of clinical relevance of covariate effects.

OBJECTIVE

To evaluate and compare the adequacy of decisions on covariates clinical relevance using full model and SCM

METHODS

Covariate modeling approaches



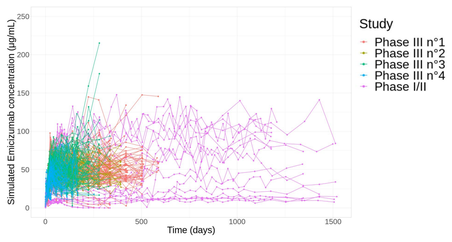
Simulation study

Data simulation

- Inspired from a real case study conducted on N = 387 hemophilia A patients, a X-linked recessive deficiency of factor VIII (FVIII) activity resulting in lifelong bleeding, treated with emicizumab, a monoclonal antibody developed for routine prophylaxis of bleeding, from 5 clinical studies
- S = 200 datasets simulated with two models (derived from the model developed by Retout et al. [3])
  - **Base model** → one compartment model with first order absorption and linear elimination + body weight (BW) effect on V/F and CL/F
    - $CL/F_i = \mu_{CL/F} \times (\frac{BW_i}{70})^{\beta_{CL/F,BW}} \times e^{\eta_{CL/F,i}}$
    - $V/F_i = \mu_{V/F} \times (\frac{BW_i}{70})^{\beta_{V/F,BW}} \times e^{\eta_{V/F,i}}$
    - $KA_i = \mu_{KA} \times e^{\eta_{KA,i}}$

    → with μ the fixed effects and $\eta_i \sim N(0,\Omega)$ the between subject random-effects of individual i, Ω being the variance-covariance matrix
  - **Covariate model** → base model + age and black (BLK) race effect on V/F and age and albumin (ALB) effect on CL/F
    - $CL/F_i = \mu_{CL/F} \times (\frac{BW_i}{70})^{\beta_{CL/F,BW}} \times (\frac{AGE_i}{30})^{\beta_{CL/F,AGE}} \times (\frac{ALB_i}{45})^{\beta_{CL/F,ALB}} \times e^{\eta_{CL/F,i}}$
    - $V/F_i = \mu_{V/F} \times (\frac{BW_i}{70})^{\beta_{V/F,BW}} \times (\frac{AGE_i}{30})^{\beta_{V/F,AGE}} \times (1 + \boldsymbol{\beta}_{V/F,BLK} \times \boldsymbol{BLK}_i) \times e^{\eta_{V/F,i}}$
    - $KA_i = \mu_{KA} \times e^{\eta_{KA,i}}$

Dataset n°1 simulated with the covariate model



- Number of patients, PK sampling schema (mixing patients with either rich or sparse schema) and covariate distributions similar to the real data

Estimation

- PK data analysis performed with NONMEM version 7.4
- First order conditional estimation with interaction (FOCEi) algorithm for parameters estimation
- SE were derived from the covariance matrix computed as $R^{-1}SR^{-1}$, with R and S the Hessian and the Cross-Product Gradient matrix, respectively

Covariate investigation

- Full model and SCM applied to each of the simulated datasets
  - SCM → BW effect not included in the set of covariates to investigate (structural covariate)
  - SCM with BW selection → BW effect included in the set of covariates to investigate

Continuous covariates (med [min - max])	CL/F	V/F	KA	Categorical covariates, category (N [%])	CL/F	V/F	KA
Body Weight (BW, kg) , 69.1 [9.50–156]	**Base: β=0.939 Cov: β=0.801**	**Base: β=1.066 Cov: β=0.867**		**Status** Non-inhibitor, 195 [50%] FVII inhibitor (INH), 192 [50%]	β=0	β=0	β=0
Age (AGE, years), 30.0 [1.22 - 77.00]	**β=0.127**	**β=0.139**	β=0				
Albumine (ALB, g/L), 45.0 [33.0–56.6]	**β=-0.918**	β=0		**Race** White, 242 [63%] Black (BLK), 31 [8%] Asian (ASN), 89 [23%] Other (OTH), 25 [6%]	β=0 β=0 β=0	**β=-0.212** β=0 β=0	
Aspartate aminotransferase (AST, U/L), 23.0 [11.0–91.0]	β=0						
Bilirubin (BILI, µmol/L), 10.5 [0.33–46.0]	β=0						

→ with β the simulated covariate effect value

- Perl-speaks-NONMEM version 5.3.0 used to launch full model and SCM
- Simulated model fitted to the data to get a reference model
- Full model launched with 5 retries and best fit kept
- SCM and SCM with BW selection launched with p_forward = 0.05 and p_backward = 0.01

Covariate effect ratios calculation

Continuous covariates

Ratio between the covariate effect value computed at the 10th or 90th quantile of the observed covariate distribution (Q10 or Q90) and the covariate effect value computed at the median (MED)

$$r_{Q10,\beta_{par,cov}} = (\frac{Q10}{MED})^{\beta_{par,cov}}$$

$$CI90_{r_{Q10,\beta_{par,cov}}} = e^{\left(\beta_{par,cov} \pm 1.64 \times SE(\beta_{par,cov})\right) \times log(\frac{Q10}{MED})}$$

Categorical covariates

Ratio between the covariate effect value of one category and the covariate effect value of the reference category

$$r_{\beta_{par,cov}} = 1 + \beta_{par,cov}$$

$$CI90_{r_{\beta_{par,cov}}} = 1 + \beta_{par,cov} \pm 1.64 \times SE(\beta_{par,cov})$$

When a covariate is not selected with SCM
→ covariate effect estimate and its SE set to 0
→ ratio estimate set to 1 with an CI of width 0

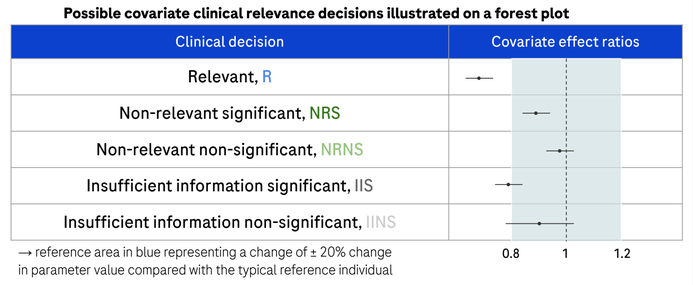
Evaluation

- Upset plots of the different model combinations obtained using SCM
- Relative estimation errors (REE) of ratio estimates in %

$$REE = \frac{(\hat{r}_{\beta_{par,cov}} - r_{\beta_{par,cov}})}{r_{\beta_{par,cov}}} \times 100$$

- Covariate clinical relevance decisions

Possible covariate clinical relevance decisions illustrated on a forest plot

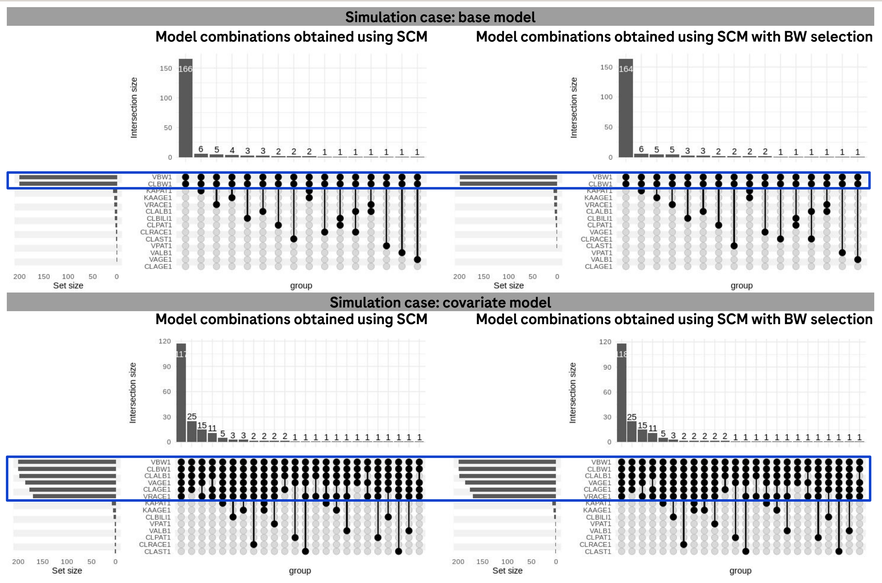


→ reference area in blue representing a change of ± 20% change in parameter value compared with the typical reference individual

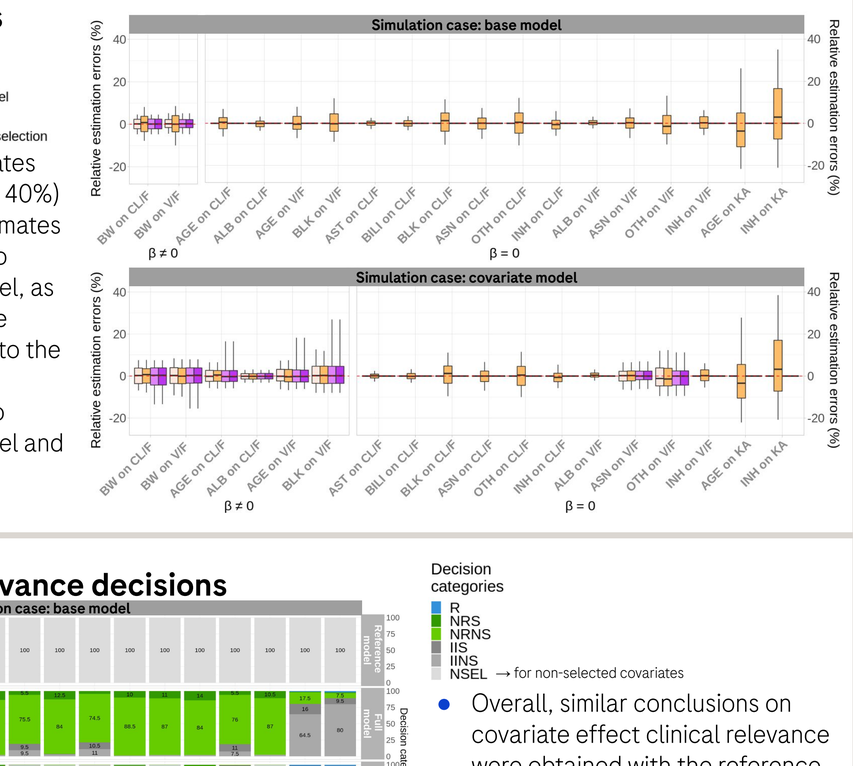
RESULTS

SCM upset plots

- The true model was selected in more than 80% and 50% of the cases for the base and the covariate model, respectively
- BW effect was always selected on CL/F and V/F for both the base and the covariate model
- Covariate effects simulated at 0 are not selected in more than 95% of cases

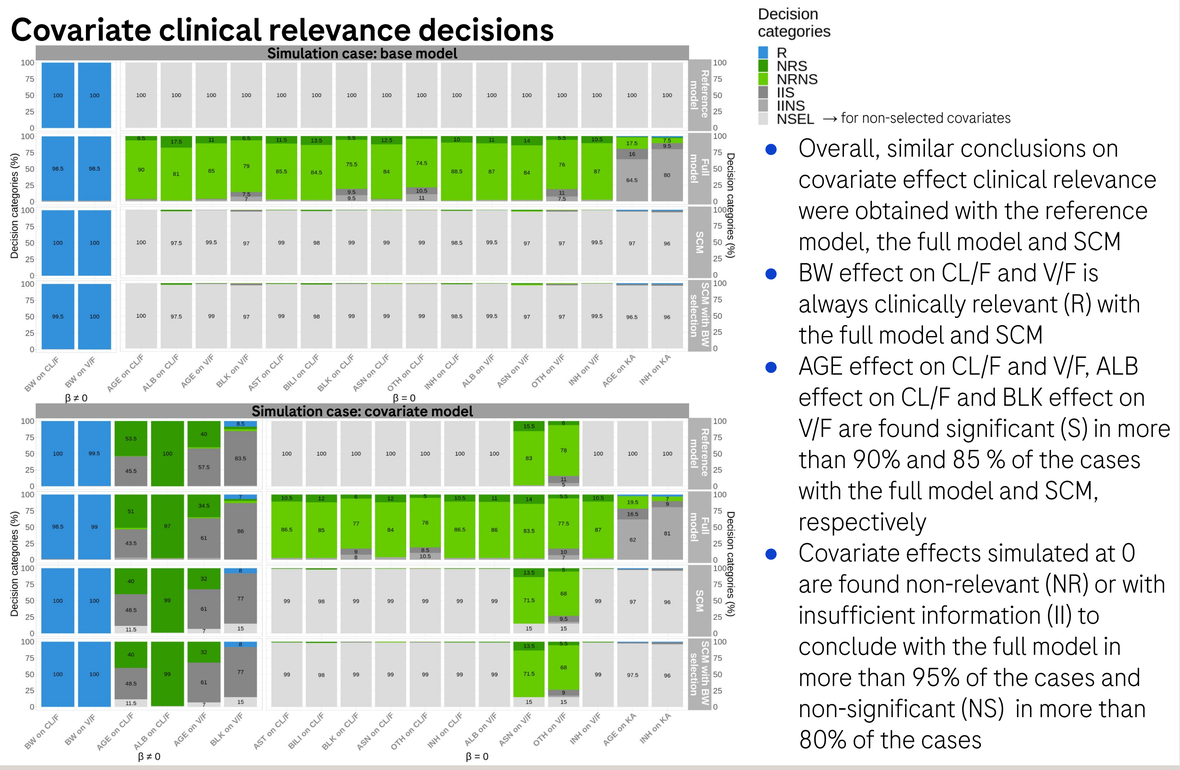


REE of ratio estimates



- Low REE of the ratio estimates (around 5%, not exceeding 40%)
- Overall, unbiased ratio estimates
- Wider variability of the ratio estimates with the full model, as all the covariate effects are estimated, unlike SCM due to the selection process
- Same variability of the ratio estimates with the full model and SCM when the covariate is selected

Covariate clinical relevance decisions



- Overall, similar conclusions on covariate effect clinical relevance were obtained with the reference model, the full model and SCM
- BW effect on CL/F and V/F is always clinically relevant (R) with the full model and SCM
- AGE effect on CL/F and V/F, ALB effect on CL/F and BLK effect on V/F are found significant (S) in more than 90% and 85 % of the cases with the full model and SCM, respectively
- Covariate effects simulated at 0 are found non-relevant (NR) or with insufficient information (II) to conclude with the full model in more than 95% of the cases and non-significant (NS) in more than 80% of the cases

CONCLUSION

Covariates effect ratios were unbiased with both full model and SCM. SCM seems to perform better in terms of estimation precision thanks to the selection process when no effects are simulated.The evaluation of clinical relevance of covariate effects was satisfactory for the two approaches. Because of the selection process, significant covariates may sometimes not be selected with SCM. Some additional methods such as SCM plus and FREM will also be investigated. These methods deserve to be evaluated in a context of more complex simulated covariate model or sparse data.

References
[1] Ahamadi et al. *Pharmacokinet. Pharmacodyn.* 2019; [2] Xu et al. *Br. J. Clin. Pharmacol.* 2018; [3] Retout et al. *Clin. Pharmacokinet.* 2020;