Internal and external evaluation of a pharmacometric model for warfarin using prediction corrected visual predictive check (PC-VPC)

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Conclusion

- ✓ The internal evaluation did not indicate any major differences between observed and model predicted INR.
- ✓ The external evaluation showed evidence of model misspecification with signs of under prediction especially at INR > 2.
- ✓ A plausible explanation to the model misspecification is the difference in INR methods between Sweden (Owren) and UK (Quick), and this will be further explored.

Background

- Warfarin therapy is challenging due to its narrow therapeutic range and pronounced variability in individual dose requirements.
- We have developed a K-PD model (see Figure 1) for the relationship between warfarin dose and anticoagulant response (INR), with final model parameters estimated on data from 1426 Swedish patients starting warfarin therapy [1]. The model include age and genetic variations in *CYP2C9* (on CL) and *VKORC1* (on EC_{50}) as covariates.

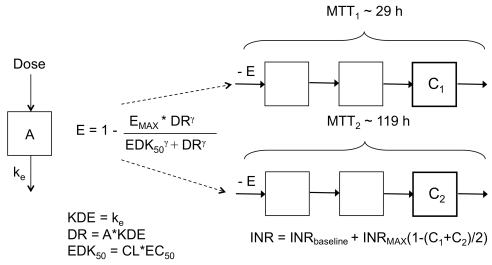

Figure 1. Schematic overview of the published warfarin K-PD-model [1]

- Visual predictive checks (VPCs) are rapidly becoming an important diagnostic tool for model evaluation [2]. We have used prediction corrected VPC (PC-VPC), which is an adaptation of the standard VPC more suited for data collected in studies with adaptive design [3].

Objective

To evaluate the performance of the warfarin model using PC-VPCs in both the internal [1] and an external dataset [4].

Materials and Methods

Table 1 Details about internal (Swedish) and external (UK) dataset

	Internal dataset	External dataset
Data collection	40 coagul. clinics, Dec 01-Aug 05	2 Liverpool-hospitals, Nov 05-Mar 06
Study duration	Median 6 months, up to 3 years	Up to 6 months
Treatment indication (> 10%)		
- atrial fibrillation	51 %	53 %
- pulmonary embolism	25 %	24 %
- deep vein thrombosis	13 %	14 %
Number of patients in dataset	1426	612
Median Age, years (range)	68 (18-92)	71 (19-95)
CYP2C9 genotype, N (%)		
*1/*1 *2/*2	943 (66.1) 20 (1.4)	399 (65.2) 9 (1.5)
*1/*2 *2/*3	263 (18.4) 17 (1.2)	127 (20.8) 9 (1.5)
*1/*3 *3/*3	175 (12.3) 8 (0.6)	65 (10.6) 3 (0.5)
VKORC1 genotype, N (%)		
G/G	521 (36.5)	247 (40.4)
A/G	691 (48.5)	286 (46.7)
A/A	214 (15.0)	79 (12.9)
Warfarin formulation	2.5 mg tablets (Waran®)	1, 3, 5 mg tablets (Marevan®)
INR method	**Owren-type PT**	**Quick-type PT**
Stable INR (mean)	2.46	2.44
Stable weekly dose (mean)	35.18 mg*	29.57 mg

* + 4.2 mg/week after correcting for age, weight and genotype differences, PT = prothrombin time

The final model and parameter estimates obtained from the analyses of the Swedish study [1] were used in the internal and external model evaluation. PC-VPCs were constructed with median (solid red lines), 5th and 95th percentiles (dashed red lines) for the observed data. Model predictions were based on 100 simulated datasets and presented as non-parametric 95% confidence intervals for the median (purple field), 5th and 95th percentiles (green field). The procedure was repeated on the external dataset.

Results

PC-VPCs for the first 20 days of treatment for the internal and external dataset is shown in Figure 2.

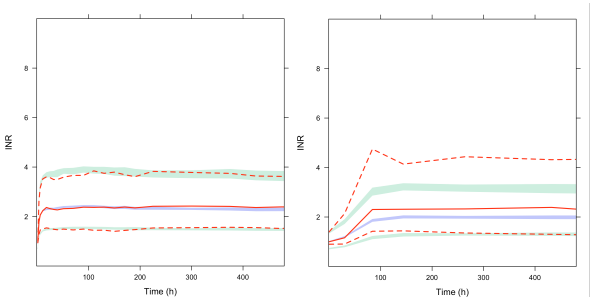

Figure 2. PC-VPCs for the internal (left) and external (right) dataset.

The PC-VPC of the internal dataset (left) did not indicate any major difference between observations and model predictions (more plots presented on the backside of the hand-outs). The PC-VPC of the external dataset (right) show evidence of model misspecification with signs of under prediction of the measured INR response, especially at the higher range. Overall the results suggest a difference in the relationship between dose and measured INR-response between Swedish and British warfarin patients. To explore possible reasons for this the following were tested:

(1) estimation of a scale factor for bioavailability (to adjust for possible difference in bioavailability between SE and UK formulation)

(2) re-estimation of model parameters on the external dataset (results presented on the backside of the hand-outs)

(3) estimation of scale factors for INR (to adjust for potential bias in INR response between Swedish and UK INR methods [5], [6].

PC-VPCs for the external dataset with these three models are shown in Figure 3.

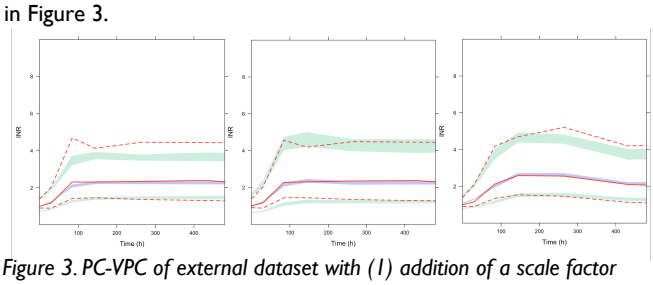

Figure 3. PC-VPC of external dataset with (1) addition of a scale factor (1.26) for bioavailability (left), (2) re-estimated model parameters (middle) and (3) addition of scale factors for INR ≤ 2 (1.09), INR > 2 and < 4 (1.33) and INR ≥ 4 (1.60).

References:

[1] A-K Hamberg *et al.* Clin Pharmacol Ther, 2010; 87

[2] M.O Karlsson, N Holford. PAGE 17 (2008)[www.page-meeting.org/?abstract=1434

[3] M Bergstrand *et al.* ACoP(2009) AbstractF7 [http://www.go-acop.org/sites/all/assets/webform/Poster_ACoP_VPC_091002_two_page.pdf]

[4] A.L Jorgensen *et al. Pharmacogenetics and Genomics* 2009; 19

[5] J. Horsti *et al.* Clinical Chemistry, 2005; 51

[6] J.Horsti *et al.* Scand J Clin Lab Invest, 2003; 63

Additional results - internal evaluation

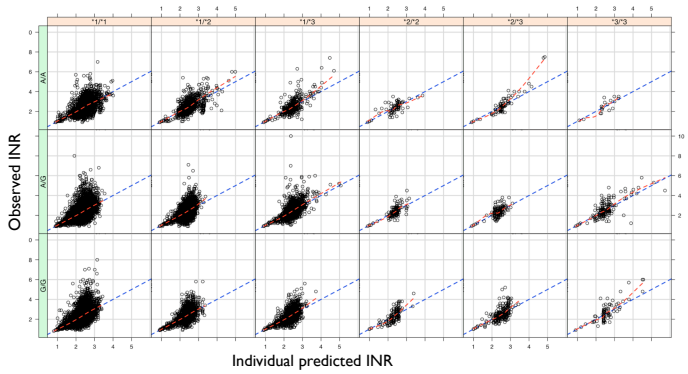

Figure 4. Observed INR vs. Individual predicted INR for the internal dataset presented per genotype combination. CYP2C9 genotype is in the columns and VKORC1 genotype in the rows. The blue dashed line is the line of identity and the red dashed line is a smooth.

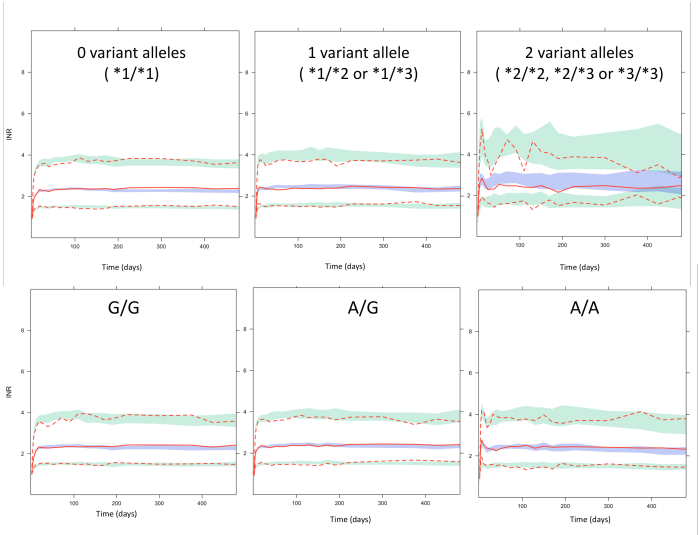

Figure 5. PC-VPCs of internal dataset stratified by number of CYP2C9-variant alleles (upper panel) or VKORC1-genotype (lower panel).

Additional results - external evaluation

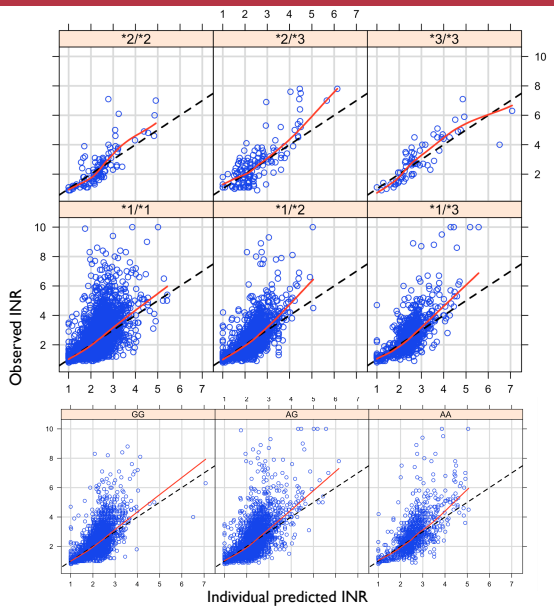

Figure 6. Observed INR vs. Individual predicted INR for the external dataset presented per CYP2C9 (top panels) or VKORC1 genotype (lower panel). The black dashed line is the line of identity and the red solid line is a smooth.

Table 2 Final model parameters from internal (Swedish) dataset and following re-estimation with external (UK) dataset with model structure unchanged.

	Internal dataset	External dataset
EC_{50} GG (mg/l)	4.10	3.06
EC_{50} GA (mg/l)	3.01	2.24
EC_{50} AA (mg/l)	1.92	1.43
MTT_1 (h)	28.6	33.8
MTT_2 (h)	118.3	85.7
Slope factor	1.15	1.19
IIV_{EC50}	0.341	0.420
IIV_{ke}	0.589	0.784
Residual variability (%)	20	29

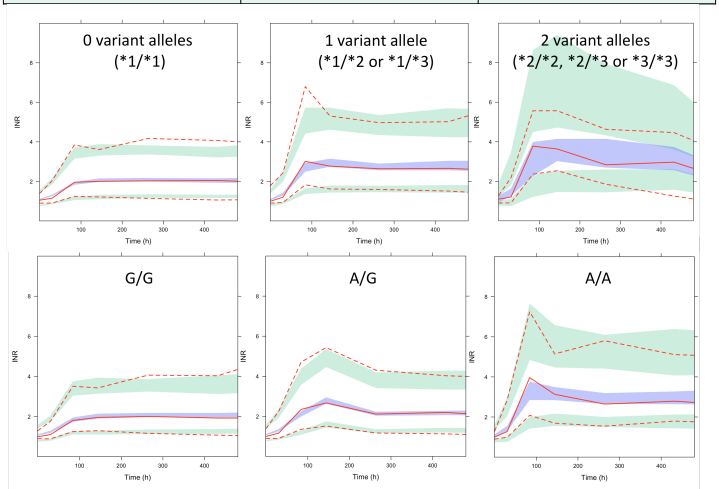

Figure 7. PC-VPCs of external dataset with INR scale factors included in the model and stratified by number of CYP2C9-variant alleles (upper panel) or VKORC1-genotype (lower panel).

Acknowledgement

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Theory - Prediction Corrected VPCs [7]

- The Visual Predictive Check (VPC) is based on a graphical comparison between the observed data and prediction intervals of simulated data.
- The VPC will diagnose both the fixed and random effects in a mixed effects model.
- When dose adaptation has been performed to achieve a target response, a traditional VPC can be completely uninformative.
- A PC-VPC differs from a standard VPC in that both the observations and the model predictions are normalized for the typical model predictions in each bin of independent variables (Equation 1 and 2).

Equation 1

$$\ln(pcY_{ij}) = \ln(Y_{ij}) + (\ln(\tilde{PRED}_{bin}) - \ln(PRED_{ij}))$$

Equation 2

$$\ln(pc\hat{Y}_{ij}) = \ln(\hat{Y}_{ij}) + (\ln(\tilde{PRED}_{bin}) - \ln(PRED_{ij}))$$

Y_{ij} = Observation for the i^{th} individual and j^{th} time point

$\hat{Y}_{ij}$ = Model prediction for the i^{th} individual and j^{th} time point

pcY_{ij} = Prediction corrected observation

$pc\hat{Y}_{ij}$ = Prediction corrected model prediction

$PRED_{ij}$ = Typical population prediction for the i^{th} individual and j^{th} time point

$\tilde{PRED}_{bin}$ = Median of typical population predictions for the specific bin of independent variables

References:
[7] M Bergstrand, *Simulation based model diagnostics – Recent advances*, Research seminar 3/12/2010, Department of Pharmaceutical Biosciences, Uppsala University