

Population pharmacokinetic and cardiotoxic modelling of the antimalarial drug piperazine

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OBJECTIVES & METHODS

Objectives: This study aimed to characterise the pharmacokinetic properties of the antimalarial drug piperazine and its propensity for QTcF prolongation, and its potential drug-drug interaction with the transmission blocking agent primaquine.

Methods: Sixteen healthy volunteers were recruited to this study and randomly administered primaquine alone, dihydroartemisinin-piperazine alone, and dihydroartemisinin-piperazine with primaquine at three occasions. Piperazine concentrations were measured by LC-MS/MS [1,2] at the Department of Clinical Pharmacology, Bangkok, Thailand. Nonlinear mixed-effects modelling was performed to characterise the pharmacokinetic properties of piperazine. The effect of primaquine co-administration was evaluated separately as a categorical covariate on all individual pharmacokinetic parameters and by using a full covariate approach. All remaining covariates were evaluated by a stepwise addition/elimination approach. Double-delta Fredericia-corrected QT measurements ($\Delta\Delta\text{QTcF}$) were modelled as a linear direct-response pharmacodynamic model in NONMEM 7.3.

RESULTS

Pharmacokinetic-Pharmacodynamic Model

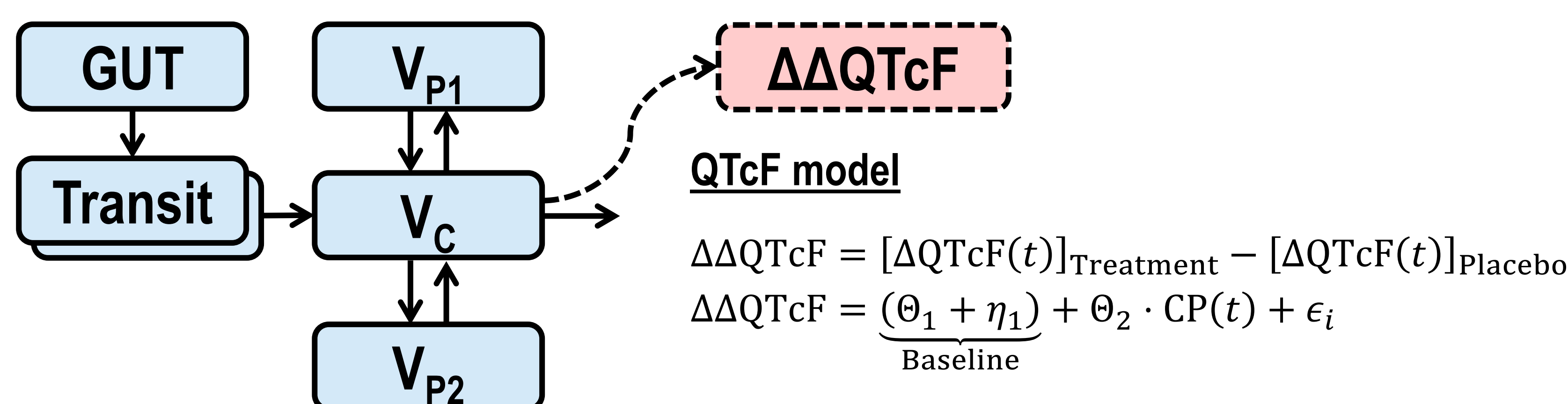


Figure 1. Final structural pharmacokinetic and pharmacodynamic model of piperazine.

Model Diagnostic

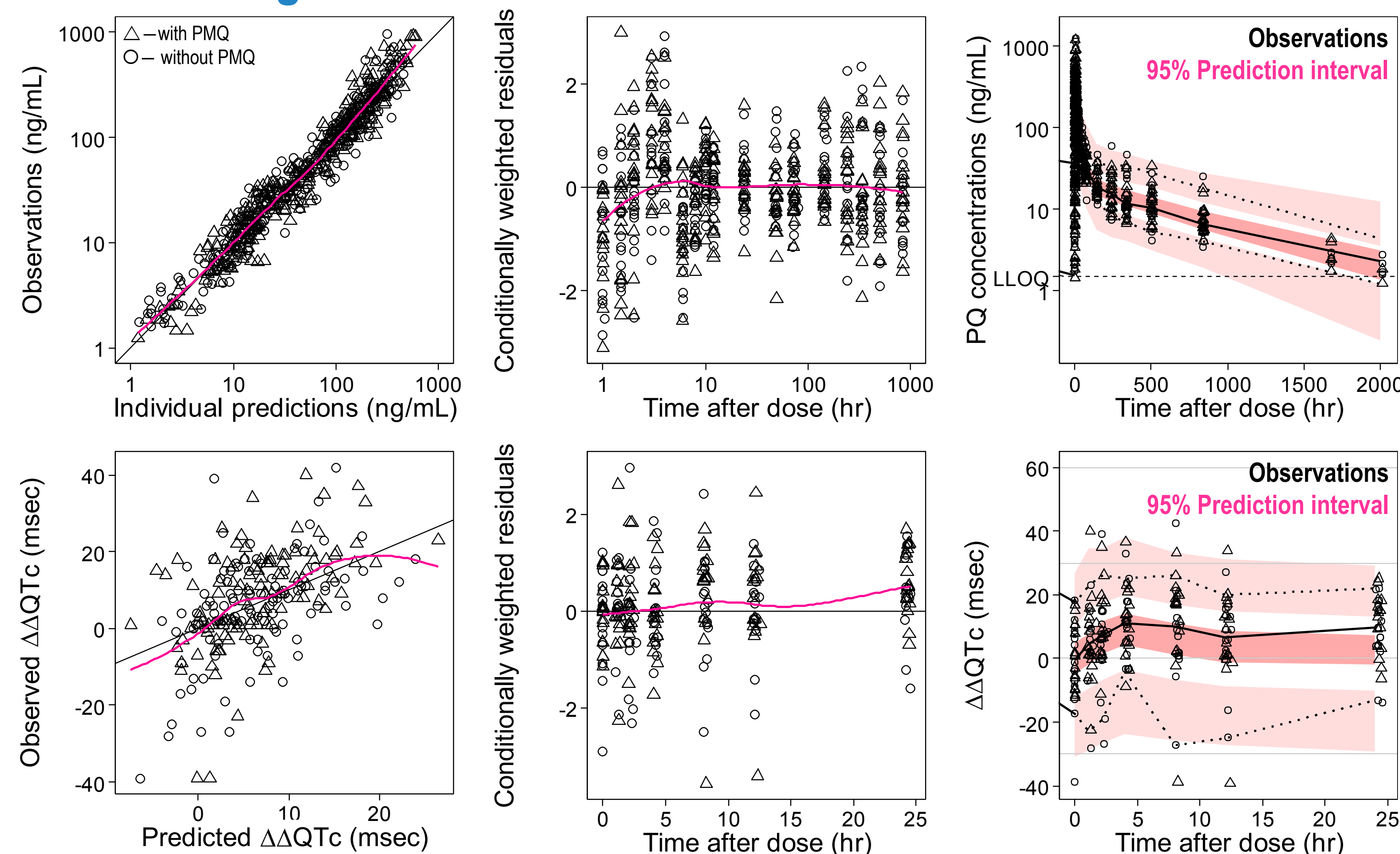


Figure 2. Goodness-of-fit plots and visual predictive checks of the final population pharmacokinetic model (top row) and the linear direct-response model of $\Delta\Delta\text{QTcF}$ intervals (bottom row). The visual predictive plots based on 1000 simulations.

Primaquine co-administration

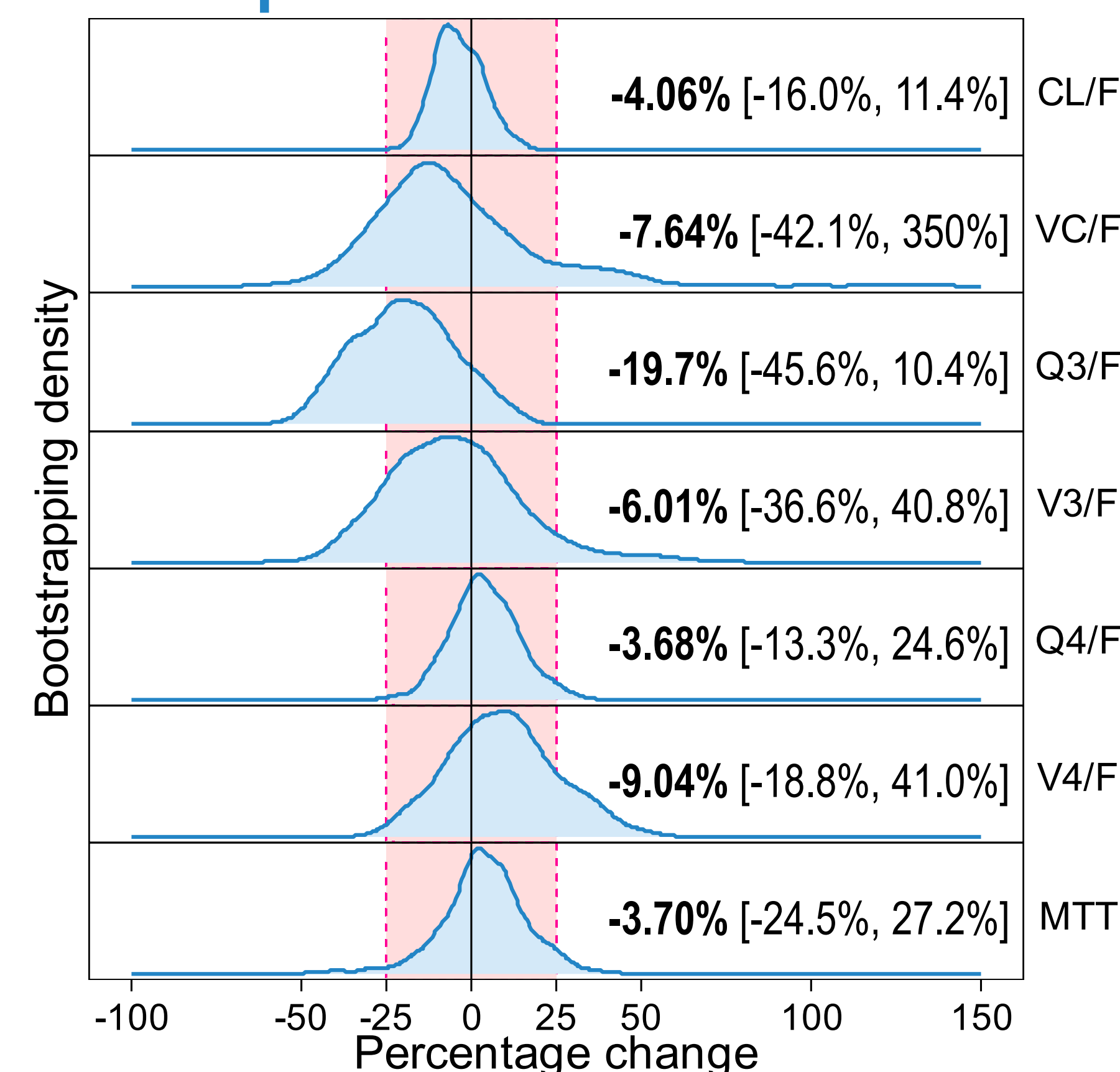


Figure 3. Primaquine co-administration does not affect piperazine pharmacokinetics, determined by a full covariate approach (1,000 bootstraps). Numbers represent median [95% confidence interval]. Shaded area represents $\pm 25\%$ change, which was considered to be a non-clinically relevant change.

CONCLUSIONS

- The PK/PD properties of piperazine were characterized accurately.
 - Pharmacokinetic model:* Two-transit absorption model followed by three disposition compartments.
 - Pharmacodynamic model:* Linear direct-response model of piperazine concentrations and the $\Delta\Delta\text{QTcF}$ interval.
- Primaquine did not affect the pharmacokinetic properties of piperazine.
- Increasing piperazine concentrations resulted in an increasing QTcF prolongation.
 - The final model suggested that 95% of individuals will have a QTcF prolongation below 60 msec at piperazine peak concentrations below 850 ng/mL.
 - Piperazine peak concentrations after the standard 3-day treatment of dihydroartemisinin-piperazine are substantially below 850 ng/mL.
- The PK/PD model was used to suggest a therapeutic window for piperazine.
 - The developed model framework could be applied to evaluate cardio-safety of other antimalarial drugs (e.g. chloroquine, halofantrine etc.).

Final PK-PD Model Parameter Estimates

Parameters	Population estimate	95% CI	%RSE
Primary parameter estimates			
MTT (hr)	4.50	3.60-5.02	8.07%
CL/F (liters/hr)	27.0	23.3-29.0	4.96%
V_c/F (liters)	230	147-483	33.1%
Q_{p1}/F (liters/hr)	240	196-292	10.4%
V_{p1}/F (liters)	2,410	1,910-2,910	10.6%
Q_{p2}/F (liters/hr)	69.0	59.4-80.6	8.05%
V_{p2}/F (liters)	14,100	11,900-16,300	8.05%
σ_{PQ}	0.134	0.112-0.160	9.41%
Inter-individual variability (%CV)			
CL/F	0.0354 (18.8%)	0.00240-0.0725	51.0%
MTT	0.0208 (14.4%)	0.000510-0.0587	57.4%
F	0.0528 (23.0%)	0.00724-0.0958	52.6%
Inter-occasion variability (%CV)			
V_c/F	1.04 (102%)	0.280-1.85	38.7%
F	0.0353 (18.8%)	0.0156-0.0550	29.8%
Pharmacodynamic parameters			
BASE (msec)	0 Fixed	-	-
SLOP (msec/(ng/mL))	0.0314	0.0206-0.0426	17.4%
IIV on BASE (msec)	5.64	2.54-8.63	54.1%
$\sigma_{\Delta\Delta\text{QTcF}}$ (msec)	11.7	8.98-14.7	25.5%

Simulations of maximum PQ concentration vs. $\Delta\Delta\text{QTcF}$

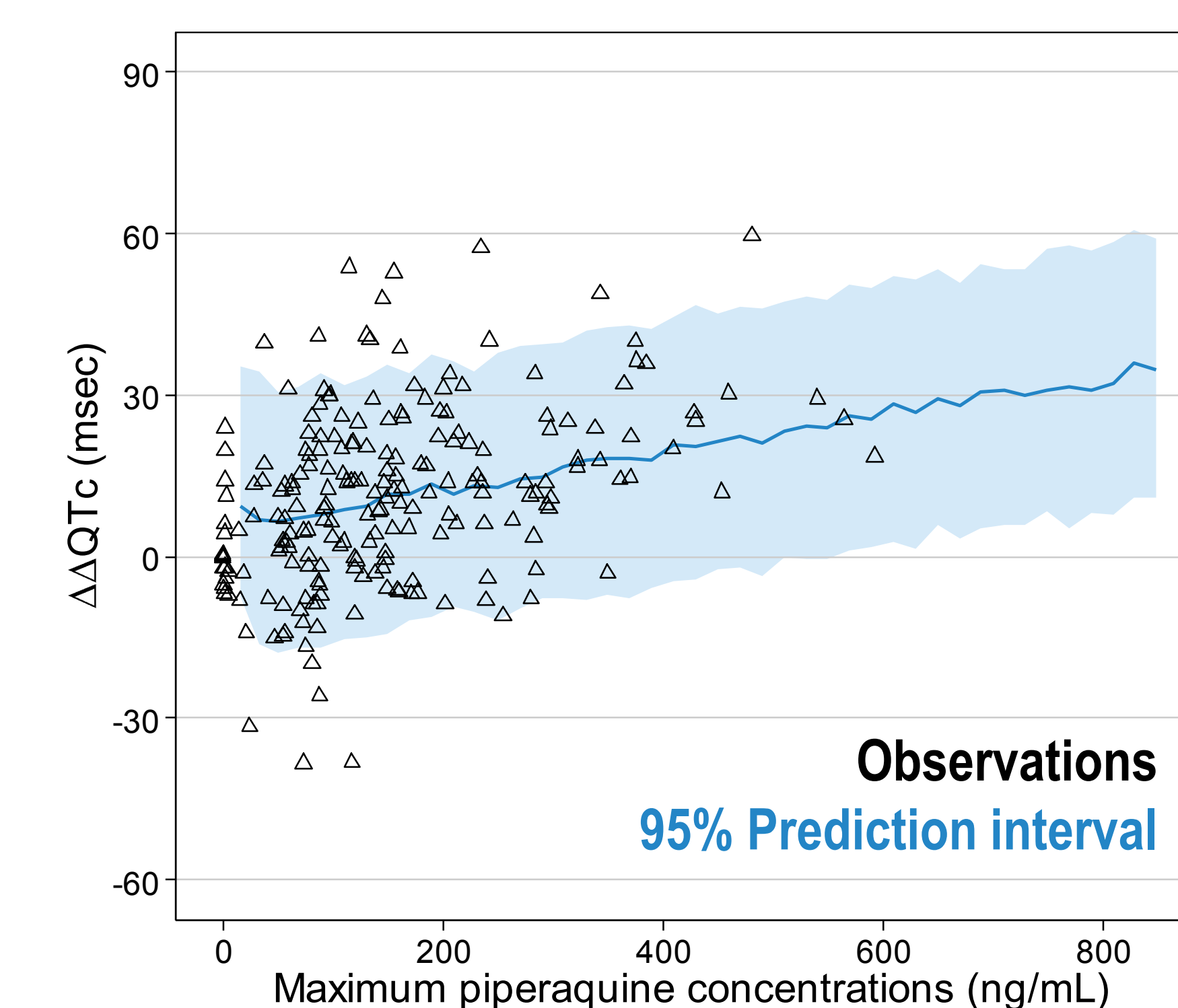


Figure 4. Simulations of maximum piperazine concentrations vs. $\Delta\Delta\text{QTcF}$. Open triangles represent the observed $\Delta\Delta\text{QTcF}$ interval with respect to the observed piperazine concentration. The solid black line represents the median prediction, and the shaded area represents the 95% confidence interval (1,000 simulations).

DISCUSSIONS

Pharmacokinetic model:

- The observed data was best described by a two-compartment transit-absorption model followed by a three-compartment distribution model. The final pharmacokinetic model was robust and accurate according to internal and external model evaluations.
- Primaquine co-administration does not affect the pharmacokinetic properties of piperazine.

Pharmacodynamic model:

- This study evaluated potential cardio-toxic effects of the antimalarial drug piperazine, using a population pharmacokinetic-pharmacodynamic modelling approach. A linear direct-response model described accurately the increasing $\Delta\Delta\text{QTcF}$ interval with increasing piperazine concentration.
- The final pharmacokinetic-pharmacodynamic model was used to simulate expected QTcF prolongation after different dosing regimens.
- The final model can be useful for translational medicine, especially for predicting safety and potential cardio-toxicity, after piperazine and other antimalarial drug therapy.

References: [1] Lindegardh N, et al., Development and validation of a liquid chromatographic-tandem mass spectrometric method for determination of piperazine in plasma stable isotope labeled internal standard does not always compensate for matrix effects. J Chromatogr B Analyt Technol Biomed Life Sci. 2008; 862(1-2): p. 227-36.
[2] Lourens C, et al., Benefits of a pharmacology-antimalarial reference standard and proficiency testing program provided by the Worldwide Antimalarial Resistance Network (WWARN). Antimicrob Agents Chemother. 2014; 58(7): p. 3889-94.

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