External validation of six models for model-informed precision dosing of patients treated with voriconazole

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Abstract

Background

Voriconazole dosing is complicated by multiple factors that can lead to relevant changes in voriconazole's pharmacokinetics (PK). Data from several studies suggest that model-informed precision dosing (MIPD) is a tool to predict voriconazole plasma concentrations and to establish the right dose to reach the therapeutic range. (1,2)

Objectives

This study aimed to retrospectively validate existing pharmacokinetic population models of voriconazole to assess their suitability in MIPD.

Method

Retrospective collected TDM data was extracted from the Electronic Health Record (EHR) system HIX v6.3 (Chipsoft, Amsterdam, the Netherlands) of the Catharina Hospital Eindhoven (CZE) database for the past five years (2019-2023). Adult patients treated with voriconazole in this time period were included when trough levels were available. For the retrospective validation suitable models for voriconazole dosing in adults with invasive aspergillosis were identified by a systematic review. The predictive performance of the models was assessed by calculating the mean prediction error (MPE) to establish bias and the relative root mean squared error (RRMSE) to determine precision.

Results

Data was available of 94 patients with 248 trough concentrations. The model made by Liu et al. demonstrated the lowest MPE and RRMSE with an MPE of 34.43% and an RRMSE of 68.18%. After excluding the first and subsequent predictions after the fifth prediction, the model made by Friberg et al. demonstrated the best lowest MPE and RRMSE. It improved to an MPE of 11.35% and a RRMSE of 50.18%. The model made by Friberg et al. demonstrated good bias and precision after exclusion of the first prediction, meaning that TDM still has an important role in dosing voriconazole for the first prediction. The results of this external validation study suggest that the model made by Friberg et al. could be used best in clinical practice to predict future voriconazole trough levels and to advise on dosage after the first observed trough level.

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
CRP	C-reactive Protein
CZE	Catharina Hospital Eindhoven
GGT	Gamma-glutamyl Transferase
MPE	Mean Prediction Error
METC	Medical Ethics Review Committee
MIC	Minimum Inhibitory Concentration
MIPD	Model-informed Precise Dosing
PK	Pharmacokinetics
PKPD	Pharmacokinetic-pharmacodynamic
RRMSE	Relative Root Mean Squared Error
SPSS	Statistical Package for the Social Sciences
TDM	Therapeutic Drug Monitoring

Introduction

Voriconazole dosing is complicated by multiple factors that can lead to relevant changes in voriconazole's pharmacokinetics (PK). The pharmacokinetics of voriconazole involve both linear and nonlinear clearance, meaning that even a small change in dosage can significantly alter the drug's plasma concentrations. (3–6) As a result, this variety can lead to toxicity or subtherapeutic voriconazole levels.

Previous research has shown that the area under the concentration-time curve (AUC) over the minimum inhibitory concentration (MIC) ratio (AUC/MIC) is the pharmacokinetic-pharmacodynamic (PK-PD) parameter that most accurately predicts voriconazole efficacy. (6–11) Data from several studies suggest that the trough concentration in steady state can serve as a surrogate therapeutic marker. The therapeutic range concentration of voriconazole is generally considered to be between 1-6 mg/L. (3,6,7,12,13) Therapeutic drug monitoring (TDM) is applied to maintain therapeutic plasma concentrations to ensure that patients receive an effective dose. (12,13)

Recent studies demonstrate that various covariates affect the metabolism of voriconazole. These variables include CYP2C19, inflammation, liver function, age, race, and the use of various substances known to inhibit or induce CYP2C19, St. John's Wort, phenytoin, rifampicin, prednisone, methylprednisolone, dexamethasone, ritonavir, esomeprazole, omeprazole, pantoprazole, lansoprazole, and carbamazepine. (3,4,6,14–22)

Data from several studies suggest that a tool to predict voriconazole plasma concentrations is model-informed precision dosing (MIPD). (1,2) MIPD is an approach that uses a PK-PD model to establish optimal therapeutic plasma concentrations. This approach allows for the treatment of each patient based on individual characteristics. (11) The advantages of MIPD are that voriconazole plasma concentrations do not have to be in a steady state, that sample collection does not require precise timing, and that a single individual voriconazole concentration can predict an entire time-concentration profile. (12)

While several pharmacokinetic population models are described in literature, hardly any model is clinically used in daily practice to determine the voriconazole dose. For proper use in daily clinical practice, it is important that PK models are externally validated. To the best of our knowledge, there have yet been two external validations to determine which model is the most suitable for clinical practice. (23,24)

This study aimed to retrospectively validate existing pharmacokinetic population models of voriconazole to assess their suitability in MIPD using InsightRX. InsightRX is a software for drug dosage regimen and TDM calculation. The primary endpoint is to determine the performance of voriconazole PK-PD model assessing the Mean Prediction Error (MPE) for bias and the Relative Root Mean Squared Error (RRMSE) for precision. (25) This study also consists of a review to provide an

overview of the best pharmacokinetic models, which were validated. The findings should provide an important contribution to the field of dosing voriconazole for individuals in clinical practice.

Method

Study design

This was a retrospective validation study to determine the performance of various voriconazole population PK models. In order to select the most appropriate models for performance testing, First, a systematic review was performed using the PUBMED database with the following research terms: voriconazole, model, and pharmacokinetic or pharmacokinetics. Three reviewers (Abdul Roda, Brouwer, Bruggeman) independently screened the studies, and the final selection was made by a single reviewer (Brouwer). A variety of variables were noted for comparison of the individual studies.

We included all pharmacokinetic population models for voriconazole which met the following inclusion criteria: 1) Parametric models; 2) A nonlinear, mixed effect population pharmacokinetic modeling (NONMEM) approach was employed; 3) A minimum of 50 included patients. Studies were excluded when: 1) Only IV or oral administration was available; 2) No CYP2C19 was tested; 3) There were missing model parametric; 4) Articles were not available in English; 5) In vitro or animal studies reviews or methodology articles.

Besides model selection through the systematic literature search, the performance of additional models previously available in InsightRX was also assessed, since they have proven to be suitable models for clinical practice as determined by the company InsightRX.

Patients and data

Little is known about sample size in validation of pharmacokinetic models. Studies demonstrate varieties in the necessary sample size ranging from at least 50 to 100 patients. (31,32) This study sets the minimum number of patients for enough power at 50.

Retrospective TDM data was extracted from the Catharina Hospital Eindhoven (CZE) database of the past five years (2019-2023). The criteria to be eligible for inclusion in this study were to be ≥ 18 years old and underwent treatment with voriconazole. The data consisted of gender, age, height, weight, CYP2C19, pharmacogenetic status, Alanine aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline phosphatase (ALP), Gamma-glutamyl Transferase (GGT), C-reactive Protein (CRP), galactomannan and the use of co-medication. In CZE, sampling of trough concentrations was implemented as a standard of care to guide the dosing of voriconazole. The voriconazole-related data consisted of the voriconazole dose, the total daily dose, the frequency of dosing, the dose adjustments, the duration of the voriconazole therapy, and the number of courses of voriconazole therapy. The data was anonymously transferred in InsightRX and SPSS. Patients younger than 18 years old, patients without voriconazole plasma concentrations, and patients without essential covariates (age, length, weight) for the models were excluded.

Analysis

The MPE and the RRMSE are the two endpoints for external validation of the selected models. The bias and precision of the PK model were tested by calculating the MPE for bias and the RRMSE for precision. An acceptable bias and precision were set at <15%. The MPE and the RRMSE were calculated with the following formulas:

$$MPE\% = \frac{1}{N}\sum_{1}^{N}\left(\frac{C_{pre} - C_{obs}}{C_{obs}}\right) \times 100$$

$$RMSE\% = \sqrt{\frac{1}{N}\sum_{1}^{N}\left(\frac{C_{pre} - C_{obs}}{C_{obs}}\right)^2} \times 100$$

$$RRMSE = \frac{RMSE}{\bar{O} \text{ or } \tilde{O}}$$

Formula 1; Formulas for the MPE%, RMSE% and RRMSE

C_{pre} is the predicted voriconazole concentration, C_{obs} is the observed voriconazole concentration, N is the number of observations, $\bar{O}$ is the mean observed value, and $\tilde{O}$ is the median observed value. In addition, the percentage of PE within 20% (F20), 30% (F30), and 50% (F50) were calculated for further evaluation of the models. The F20 is the percentage of observations of the MPE that is ≤ 20%. For F30 the percentage is ≤ 30% and for ≤ F50 the percentage is 50%.

The a priori predictions were solely based on patient covariates and previous voriconazole trough levels, whereas a posteriori prediction, also known as Bayesian forecasting, was based on both covariate data as well as at least one observed voriconazole concentration for predicting future trough levels of voriconazole.

Data were analyzed with Statistical Package for the Social Sciences (SPSS) version 29.0.0.0. Data was tested for normality with normal distribution expressed as mean and data without a normal distribution expressed as median. All voriconazole plasma concentrations were calculated with a posterior Bayesian fitting using the algorithm from InsightRX.

Each continuous variable was assessed for normality using the homogeneity test. A t-test was assessed for comparison of the measurement data. The $\chi 2$ test was applied to compare categorical data. All tests were two-tailed. A p-value $p < 0.05$ was considered significant.

Ethics

The medical ethics review committee (METC) approved this non-WMO research. The study was conducted in accordance with good clinical practice guidelines and the declaration of Helsinki. All data was anonymous and not traceable to an individual patient. All data was handled and stored according to the Dutch General Data Protection Regulation (AVG) and it complies with the Code of Conduct for Health Research.

Results

Review

The systematic literature search retrieved a total of 73 potential articles. After screening, 14 articles were eligible for full-text evaluation. Six models were retained after the exclusion criteria. See the supplementary materials for the search strategy. Three out of the six identified models (26,28,29) were available in InsightRX and could be validated. The other three studies (33–35) could not be validated, because they were not available in InsightRX at the time of this study, and no other tool was available to otherwise test these performances. Besides the models obtained through literature search, InsightRX had three additional pharmacokinetic models (12,27,30) which were also validated. This means that during the research period, 6 out of 9 models could be tested. Tables 2, 3, and 4 demonstrate the characteristics of the nine models.

The number of patients in the studies ranged from 54 to 778 patients with 233 to >10490 samples. One study utilized a three-compartment model, whereas four utilized a two-compartment model and four models utilized a one-compartment model. Weight and CYP2C19 were mainly incorporated as covariates in the models, being present in six out of the nine models. Six models were developed with NONMEM, one with Edsim ++ and two were non-parametric. CYP2C19 genotype was known in seven out of the nine studies.

Validation

Data on voriconazole were available from an initial cohort of 173 patients, 79 of whom were excluded due to missing data, voriconazole level determinations from other institutions, or top-level determination of voriconazole. Voriconazole data of the remaining 94 patients was available with a median of 2 voriconazole trough concentrations per patient. In total, 248 trough concentrations were available for analysis. Table 1 displays the baseline characteristics of the population. None of the patients used St. Jacobs, phenytoin, rifampicin, lansoprazole, or ritonavir during their voriconazole treatment. Additionally, CYP2C19 enzyme activity was known in 16 patients, obtained through genetic testing.

Figure 1 and Figure 2 demonstrate the predicted vs the observed concentration which were scattered around the line of unity. Some models demonstrate better correlation than other models. Figure 3 presents the MPE for bias, the RRMSE for precision, and the predicted vs. observed trough concentrations of voriconazole. The lowest absolute percentage of the MPE was found in the model made by Liu et al., while the lowest absolute percentage of the RRMSE was found in the model made by Friberg et al. The model of Friberg et al. and Liu et al. demonstrated an MPE within the 30% range, but none within the 15% range. None of the models demonstrated an RRMSE within 15%, meaning none of these models demonstrated good accuracy. The PK model of Liu et al. had the lowest absolute

score of the MPE and RRMSE and the model of McDougall et al. had the highest score. The MPE, RRMSE, F20, F30, and F50 are shown in Table 3. Posterior bias and precision were for all the models below 50%.

The multivariable analysis revealed that no covariates were found with a significant influence on the MPE and RRMSE. Switching from IV voriconazole to oral voriconazole, or the other way around, did not affect the MPE or RRMSE. Patients treated in the clinical setting compared to patients treated at home did not affect the MPE or RRMSE. The data demonstrated that the first voriconazole prediction and the predictions after the fifth prediction had a relatively worsened MPE and RRMSSE. These predictions have been excluded in Figure 5. Table 5 demonstrates the MPE and RRMSE between the first and fifth prediction. It can be observed from Figure 5 compared to Figure 3 that the bias and accuracy improved by excluding the a priori prediction of the first trough level and the levels after the fifth prediction.

Discussion

This study retrospectively validated existing pharmacokinetic population models of voriconazole to assess their suitability in MIPD.

The systematic review does provide a selection of the most complete pharmacokinetic models to our knowledge. These six models did take CYP2C19 genotype, IV and oral administration, and NONMEM models into account. Therefore, these six models have the most potential to achieve the best MPE and RRMSE.

The models made by Liu et al., Friberg et al., and Dolton et al. of the MPE performed the best on the MPE and RRMSE. Notably, the model made by Liu et al. had the lowest MPE and the RRMSE. This finding conflicts with Huang et al. study, which indicates that the RRMSE and MPE are worse for the model made by Liu et al. (23) Huang et al. demonstrated an MPE of 136.20% and an RRMSE of 235.48% for the model made by Liu et al. This conflict could be addressed because Huang et al. used a more homogenous patient group, namely patients with a hematological malignancy. This patient group may have affected the model's performance because in this study patients with different kinds of diseases were treated. The model made by Friberg et al. and the model made by Dolton et al. has not yet been externally validated. The models demonstrated that the model made by Liu et al., Friberg et al., Dolton et al. incorporated the covariates and the patient characteristics most effectively. The posterior analysis demonstrated good MPE and RRMSE for all six models. This means that the models all demonstrated good posterior fit and indicates that the models demonstrate suitability for forecasting dose advisements after the first TDM observation.

Furthermore, it was noted that the MPE and RRMSE improved after the first prediction and all predictions after the fifth prediction were excluded from the analysis. This improvement can be linked, when looking for excluding the first prediction, to the lack of prior information on TDM observations. Thereby the first prediction relies on covariates and dose. On the other hand, the second prediction and the subsequent predictions do have prior TDM observations which can enhance the accuracy of the prediction. This underlines the importance of the current use of TDM. For subsequent predictions, the performance worsened because the data was analyzed with the tool PsN. This tool does not have a weighting tool. A weighing tool that can be clinically used is Bayesian weighing. Bayesian weighing takes prior information with earlier TDM observations into account and determines which of those observations enhances the accuracy. The model by Friberg et al. demonstrated the best MPE and RRMSE after excluding the first observation and all the observations after the fifth observation.

A possible explanation for the relatively high MPE and RRMSE in this research is that the population used in this external validation differs from the populations used to create the models. One model included only patients with invasive aspergillosis, one model included patients treated with

voriconazole, one model included children, and three models used a variety of populations for model creation. (12,26–30) The population in this study consisted of patients treated with voriconazole meaning that could perform worse in models which used a different population.

For clinical practice, our findings imply that TDM still plays an important part in predicting the voriconazole trough levels. The results demonstrated that the model of Friberg et al. demonstrates good precision and bias after the first observation, which means that it can be used in clinical practice in combination with TDM. The normal dosing regimen of two doses of 6 mg/kg followed by 4 mg/kg voriconazole can be maintained to start therapy. After three doses of voriconazole, TDM should be applied, and the model can be used to predict the next voriconazole trough level and to suggest a possible dosage change.

However, there are multiple limitations to our model validation. First of all, the CYP2C19 genotype, which was a covariate for some of the models, was not available for the majority of patients in this study. Moreover, not all of the patients had a measured CRP at the time of treatment, while CRP was used as a covariate in the model made by Van den Born et al. However, after an analysis that only included patients with a known CRP, the model made by Van den Born et al. still did not demonstrate good precision or bias. To avoid this limitation in future research, efforts could be made to collect all the necessary covariate data in prospective research.

In addition, in this research, only trough levels were included instead of top levels because trough levels are more commonly measured. These results are more applicable for clinical practice because in clinical practice trough levels are measured. For further research, the error in the MPE and RRMSE can be reduced by including more samples.

Another notable limitation is the potential bias that may have resulted from analyzing with PsN, which does not have a weighting tool. PsN cannot weigh individual observations which can lead to discrepancies in model performance. Future research could use an alternative analysis tool that can weigh individual observations to resolve these inconsistencies.

Lastly, the models in this study were validated when available InsightRX. In this study, a review was conducted before this research to choose the best possible models, but not all models could be tested. Therefore, future research is currently conducted to use all the pharmacokinetic models that came out of the systematic review.

Conclusion

The validation of various pharmacokinetic models of voriconazole for the use of MIPD in clinical practice demonstrated that the best bias and precision after the first prediction was achieved with the model made by Friberg et al. This demonstrates that TDM still has an important role in dosing voriconazole for the first observation. The models demonstrated that weight, age, CYP2C19, and co-medication are important factors for understanding the pharmacokinetics of voriconazole. By incorporating TDM alongside MIPD, clinicians could improve treatment with voriconazole. In clinical practice, the model made by Friberg et al. can be used to predict future voriconazole trough levels and to recommend dosage after the first TDM observation.

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Table 1; Patient characteristics

Characteristics	*Median [min – max] or N (number of patients)*	*Mean ± SD*	*N (% No. of concentrations)*
No. of subjects	94		
No. of concentrations	248		
Continuous Covariates			
Age (years)	65.5 [24 – 89]	65.0 ± *12.8*	
Height (cm)	174.0 [152 – 191]	172.9 ± 8.7	
Body weight (kg)	75.9 [41.1 – 120]	72.8 ± 15.1	
Body mass index, BMI (kg/m^2)	24.5 [14.4 – 41.4]	24.1 ± 4.6	
Sex, female/male	60/34		
CYP2C19 (UM/RM/EM/IM/PM)	1/3/9/3/0		51 (20.6%)
ALAT (U/l) [1]	36 [9 – 240]	52 ± 50	30 (12.1%)
ASAT (U/l) [1]	38 [16 – 130]	51 ± 35	29 (11.7%)
GGT (U/l) [1]	149 [19 – 897]	254 ± 262	28 (11.3%)
CRP (mg/l) [1]	60 [6 – 390]	101 ± 112	40 (16.1%)
Alkalic phosphatase (U/l) [1]	120 [44 – 482]	171 ± 117	28 (11.3%)
IV or oral (IV/Oral)	90/158		248 (100%)
St. Jacobs [1]	0		0 (0.0%)
Phenytoin [1]	0		0 (0.0%)
Rifampicin [1]	0		0 (0.0%)
Prednisone [1]	64		64 (25.8%)
Methylprednisolone [1]	5		5 (2.0%)
Dexamethasone [1]	34		34 (13.7%)
Ritonavir [1]	0		0 (0.0%)
Esomeprazole [1]	37		37 (14.9%)
Omeprazole [1]	7		7 (2.8%)
Lansoprazole [1]	0		0 (0.0%)
Carbamazepine [1]	2		2 (0.8%)
Clopidogrel [1]	9		9 (3.6%)

[1] At the moment of the taking the monster

Table 2; Population characteristics of the studies

Study	N[male/female]	Age, y [range]	Body weight, kg [range]	CYP2C19 genotype [*n*]	Subject characteristics [*n*]	Routes	Voriconazole concentration	Assay
Dolton et al. (28)	240 [152/88]	NA [18 – 88]	NA [39 – 115]	NM and RM [56] IM and PM [38] UK [146]	Healthy adults [63], Adult patients with fungal infection or at risk for fungal infections [177]	IV/PO	NA	LC–MS/MS and HPLC
Friberg et al. (29)	173 [101/72]	12.9 [2–55]	38.7 [10.8–97]	UM [4], NM [98] IM [66] PM [5]	Immunocompromised Children [112], Adolescents [26], Healthy adults [35]	IV/PO	NA	LC–MS/MS and HPLC
Jiang et al. (34)	69 [NA]	48.2 [20-65]	57.4 [38–87]	PM [8] IM [31] EM [30]	Patients with talaromycosis	IV/PO	Between 0.23 mg/L and 16.95 mg/L	2D-HPLC
Kim et al. (35)	193 [164/29]	34 [18-80]	66.0 [40.8-88.5]	EM [75] IM [70] PM [48]	Healthy adults [93], Adult patients with fungal infection [100]	IV/PO	NA	NA
Liu et al. (26)	305 [181/124]	54 [17–83]	68 [35–121]	NM [153] IM [65] PM [9] UK [78]	Adult patients with invasive aspergillosis	IV/PO	NA	LC–MS/MS
McDougall et al. (27)	778 [517/261]	NA [2-99]	NA [10-125]	UM [28], NM [289], IM [131], PM [27] UK [265], IM and PM [38][1]	Healthy patients, patients with invasive fungal infection, liver transplant, lung transplant, patients with malignancy	IV/PO	NA	Combination[2]: Hope; HPLC (36) Friberg; LC–MS/MS and HPLC(29) Karlsson; NA(37) Dolton; LC–MS/MS and HPLC(28) Pascual; HPLC-UV(38) Wang; HPLC(34) Han: HPLC(39)
Neely et al. (12)	141 [NA]	16 [2–55]	43.8 [10.8-97]	NA	Children [85], adults [56]	IV/PO	NA	Liquid chromatography tandem mass spectrometry
Van den Born et al. (30)	54 [38/16]	52 [19-73]	77 [49-118]	NA	Treatment and prophylaxis of patients with invasive fungal infection	IV/PO	NA	LC-MS/MS
Wang et al. (34)	151 [104/47]	59 [18-99]	59.1 [35-80]	EM [64] IM [65] PM [19] UM [3]	Adult patients with invasive aspergillosis	IV/PO	NA	HPLC

CYP cytochrome P450, HPLC high-performance liquid chromatography, IM intermediate metabolizer, IV intravenous administration, LC-MS/MS liquid chromatography–tandem mass spectrometry, NA not available, NM normal metabolizer, PM poor metabolizer, PO oral administration, RM rapid metabolizer, UK unknown metabolizer, UM ultra-rapid metabolizer

[1]Dolton MJ. Did not distinguish IM and PM

[2]The model made by McDougall is made of seven models with different assays

Table 3; Model characteristics of the studies

Study	Samples (n)		Modeling			Simulation	
	Per subject[2]	Total	Data	Software	Evaluation method	Dosing regimen	Target
Dolton et al. (28)	14	3352	Rich data from five PK studies and sparse data from a TDM study	NONMEM	pvcVPC	NA	NA
Friberg et al. (29)	19.3	3336	Rich data from five PK studies	NONMEM	pcVPC and bootstrap	Children: 4 and 8 mg/kg IV or 9 mg/kg orally twice daily Adolescents: depends on weight	The reference adult AUC
Jiang et al. (34)	4	233	Sparse data from a study	NONMEM	VPC and bootstrap	intravenous VRC 6 mg/kg q12 h on day 1 (or oral 400 mg q12h on day 1) and followed by a maintenance dose of 4 mg/kg q12h (or oral 200mg q12h) thereafter.	Trough concentration (1.0–5.5 mg/L)
Kim et al. (35)	9.5	1828	Rich sampled pharmacokinetic data	NONMEM	pcVPC	Study 1: a single dose of intravenous voriconazole 200 mg, followed by single and multiple doses of oral voriconazole 200 mg every 12 h Study 2: a single dose of oral voriconazole 400 mg Study 3: a single dose of intravenous voriconazole 200 mg Study 4: a single dose of intravenous voriconazole 200 mg, followed by a single dose of oral voriconazole 200 mg Study 5: loading dose of intravenous voriconazole 6 mg/kg or oral voriconazole 400 mg every 12 h on the first day, followed by TDM-based maintenance doses of intravenous voriconazole 4 mg/kg or oral voriconazole 200 mg every 12 h	2.0-5.5 mg/L
Liu et al. (26)	3.2	965	Sparse data from a PK study	NONMEM	VPC	NA	NA
McDougall et al. (27)	13.5	>10490	NA[1]	Non parametric	VPC and NPC	NA[1]	NA[1]
Neely et al. (12)	36.5	3769	Rich sampled pharmacokinetic data	Non parametric	NA	NA	NA
Van den Born et al. (30)	19.6	1060	Rich sampled pharmacokinetic data	Edsim ++	Bootstrap	two voriconazole loading doses of 6 mg/kg on day 1 followed by a maintenance dose of 4 mg/kg twice daily intravenously, or a loading dose of 400 mg twice daily followed by a maintenance dose of 200 mg twice daily orally	1.5 – 5.5 mg/l
Wang et al. (34)	4	406	Rich sampled pharmacokinetic data	NONMEM	Bootstrap	NA	NA

[1]The model made by McDougall is made by seven studies, see original data in studies (27–29,34,36,38,39)
[2]If not available; total samples divided by number of patients.

Table 4; Pharmacokinetic models of the studies

Study	Structural model	Pharmacokinetic parameters	Model variability	Covariates tested	Retained covariates in the model
Dolton et al. (28)	Two-compartment model with first order absorption, with a lag time, and Michaelis–Menten elimination	K_a = 0.53 h^{-1} Absorption Lag time = 0.162 h F = 0.942 V1 = 27.1 L V2 = 127 L Q = 35.1 L/h K_m = 3.33 mg/L V_{max} = 43.9 mg/h	BSV Ka = 41.6% BSV F = 36.7% BSV V1 = 83.4% BSV V2 = 38.1% BSV Q = 37.4% BSV Km = 64.5% BSV Vmax = 26.8% PREE = 33.8%	WT, age, sex, study population, CYP2C19 genotype, co-administration of proton pump inhibitors (pantoprazole, omeprazole, esomeprazole, and rabeprazole), phenytoin, rifampicin, short-term ritonavir (300 mg twice daily for 2 days), St John's wort, and glucocorticoids	Vmax: CYP2C19 genotype, short-term ritonavir, St John's wort, phenytoin, rifampicin, glucocorticoids (prednisone, prednisolone, methylprednisolone, dexamethasone), study population
Friberg et al. (29)	Two-compartment model with first order oral absorption, with a lag time, and mixed linear and Michaelis–Menten elimination	K_a = 1.19 h^{-1} F = 0.585 Lag time = 0.949 h V1 = 79.0 L * (WT/70) V2 = 103 L * (WT/70) Q = 15.5 L/h * (WT/70) CL = 6.16 L/h * (WT/70) Vmax,1 = 114 mg/h * (WT/70) Vmax,inh = 1.50 mg/h T50 = 2.41 h K_m = 1.15 mg/L	BSV logit (F) = 0.78 BSV V1 = 14% BSV V2 = 77% BSV Q = 42.4% BSV CL = 44% (adults) BSV Vmax,1 = 79% (adult) BSV Vmax,1 = 28% (adolescents) BSV Km = 136% Prop REE = 37–43%	Age, WT, CYP2C19 genotype, injection/suspension/tablet, study population	Age, WT
Jiang et al. (34)	One-compartment model with first-order absorption and elimination	CL = 4.34 L/h CRP on CL = −0.135 V = 97.4 L K_a = 1.1 h^{-1} F = 0.951	BSV CL = 100.5% BSV V = 31.2%	Sex, age, weight, height, HIV, voriconazole medication information (date, dose, administration time, interval time), co-medication (PPIs, glucocorticoids), WBC, HGB, PLT, NEU, ALT, AST, ALB, TP, TBIL, GGT, urea, CRP, CYP2C19 genotype	CRP
Kim et al. (35)	Three-compartment model with an inhibition compartment	V1 = 35.7 L CL = 45.3 L/h V2 = 58.9 L Q = 10.9 L/h V3 = 25.4 L Q2 = 54.6 L/h K_a = 1.23 h^{-1} F = 0.876 Absorption lag-time = 0.237 h RCLF = 0.162 IC_{50} = 0.01 K_{IC} = 0.002	BSV V2 = 40.2 BSV CL = 21.4 BSV V3 = 20.6 BSV Q2 = 28.8 BSV K_a = 87.8 BSV F1 = 0.844 BSV RCLF = 54.4	Age, WT, AST, ALT, SeCr, and EGFR, sex, CYP2C19 phenotype, liver function abnormality grade (the Common Terminology Criteria for Adverse Events), and proton pump inhibitors or glucocorticoids	WT, CYP2C19 IM and PM, liver function

Liu et al. (26)	two- compartment model with first-order absorption and mixed linear and time-dependent nonlinear elimination	Ka = 1.2 h^{-1} F = 0.595 V1 = 77.6 L × (WT/70) V2 = 89.5 L × (WT/70) Q = 15.9 L × (WT/70) CL = 5.3 × (WT/70) Vmax,1 = 0,113 mg/h * (WT/70) Vmax,inh = 1.50 mg/h T50 = 2.42 h K_m = 1.15 Absorption lag-time = 1 h Residual error = 12.8	BSV F = 71.3% BSV V1 = 13.9% BSV V2 = 83.1% BSV Q = 45.9% BSV CL = 63.4% BSV Vmax,1 = 111% BSV Km = 191% BSV Rate = 91% PREE = 53% (IV) PREE = 61% (oral)	Sex, age, WT, CYP2C19 genotype, POT, WBC, HGB, PLT, ALT, AST, ALB, TBIL, DBIL, SeCr, co-administration of anidulafungin, lansoprazole, ilaprazole, and methylprednisolone	POT, WT, CYP2C19 genotype
McDougall et al. (27)	Two-compartment disposition model with mixed linear and nonlinear time-dependent clearance	K_m = 1.92 mg/L Vmax,1 = 110 mg/h CL = 3.60 L/h Exponent of LBW on CL and Vmax = 0.31 V1 = 59 L V2 = 79 L Q = 27 L/h K_a = 1 h^{-1} F = 0.79 T_{50} = 2.41 h Vmax,inh = 0.82 PM_Vmax = 0.59 Enzyme inhibitor = 0.5 Enzyme inducer = 2	BSV KM = 100% BSV Vmax = 70% BSV CL = 45% BSV V1 = 55% BSV V2 = 55% BSV F = 70%	CYP2C19 genotype, ALT, Rifampicin, cholestasis, age, ALP, INR, WT, POT, HT	SEX, WT, HT, AGE, PM, ENZ_INH, ENZ_IND, CYP2C19 genotype
Neely et al. (12)	One-compartment model with first-order absorption and elimination	K_a = 1.53 h^{-1} Vmax = 1.82 mg/h/$kg^{0.75}$ Km = 1.54 mg/L V1 = 1.20 L/kg F = 0.85 KCP = 0.40 h^{-1} KPC = 0.15 h^{-1}	NA	WT, age	WT
Van den Born et al. (30)	One-compartment model with non-linear elimination	F = 0.83 K_a = 0.62 h^{-1} V_d = 145 L K_m = 5.7 mg/l Vmax = 86 mg/h CRPE.k = 0.0046 Additive error = 0.31 mg/L Proportional error = 12%	NA	WT, CRP, ALT, AST, ALP and GGT	CRP

Wang et al. (34)	One-compartment model with first-order absorption and elimination	Cl = 6.95 L/h V_d = 200 L F = 0.895	BSV Cl = 28.7% BSV V = 25.4% BSV F = 18.9%	Age, WT, creatinine clearance rate, platelet count and the levels of serum creatinine acid, aspartate transaminase, ALP, ALT, albumin, TBIL and hemoglobin, concomitant medications (CYP2C19 inhibitors, CYP2C19 inducers, CYP3A4 inhibitors and CYP3A4 inducers, CYP2C19 genotype status	Age, CYP2C19 genotype, and ALP

ALB albumin, ALP alkaline phosphatase, ALT alanine transaminase, AST aspartate transaminase, BSV between-subject variability, CL clearance, CRPE.k exponential factor of CRP on Vmax, CRP C-reactive protein, CYP cytochrome P450, DBIL direct bilirubin, EGFR estimated glomerular filtration rate, F bioavailability, GGT γ-glutamyl transferase, HGB hemoglobin, HIV human immunodeficiency virus, HV healthy volunteers, IC_{50} concentration in the inhibition compartment yielding 50% of maximum clearance inhibition, IM intermediate metabolizer, INR international normalized ratio, IV intravenous administration, k_a absorption rate constant, K_{IC} rate constant in to inhibition compartment, k_m Michaelis–Menten constant, Lag time lag time in drug absorption, LBW low body weight, LoF loss of function, NA not available, NEU neutrophil granulocyte, NM normal metabolizer, PLT platelets, PM poor metabolizer, PM_Vmax Proportion of Vmax for poor metabolizers, POT postoperative time, PPIs proton pump inhibitors, PRRE proportional residual random error, Q intercompartmental clearance, Q2 intercompartmental clearance 2, RCLF fraction of clearance which cannot be inhibited, RM rapid metabolizer, RRE additive residual random error, SeCr serum creatinine, T50 the time required for 50% drug to be released, TBIL total bilirubin, TP total protein, V volume of distribution in whole blood, V1 central volume of distribution, V2 peripheral volume of distribution, V3 peripheral volume of distribution 2, Vmax maximum elimination rate after the start of dosing, Vmax,1 maximum elimination rate at 1 h after the start of dosing, Vmax,inh maximum fraction of Vmax inhibition, WBC white blood cell, WT weight

Prior versus posterior

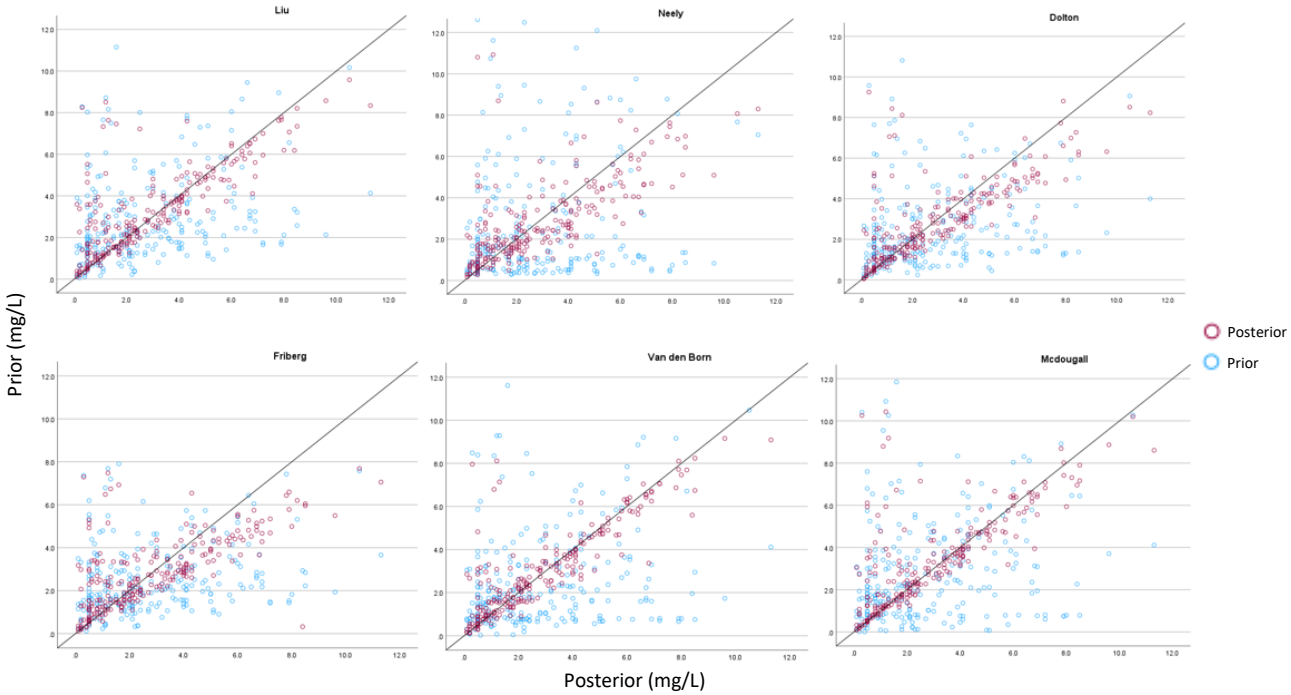


Figure 1; This scatterplot demonstrates the relation between the prior and posterior concentrations of the various models. The dots present the posterior and prior values for the models, with the prior on the y-axis and the posterior on the x-axis.

Prior versus observed

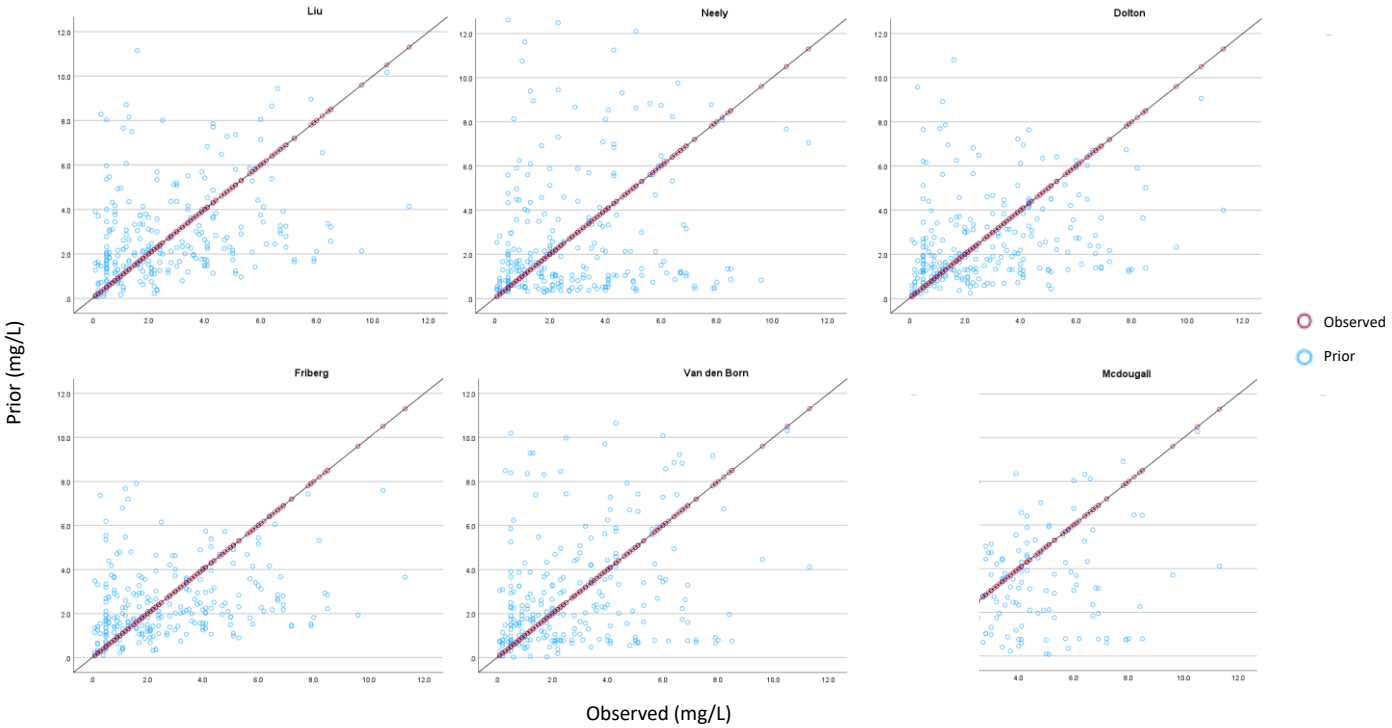
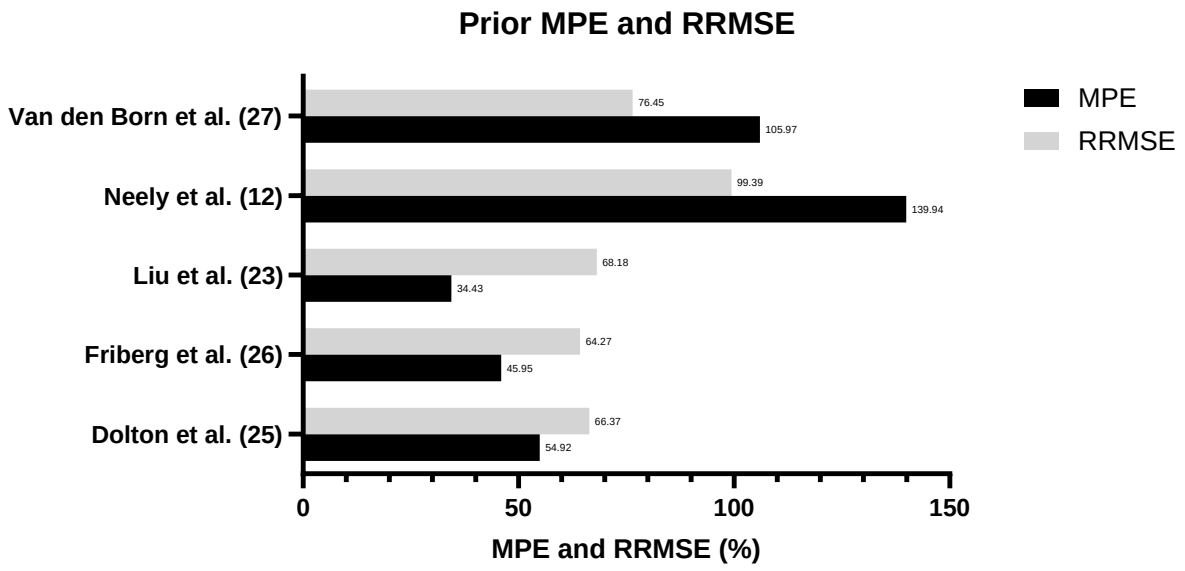
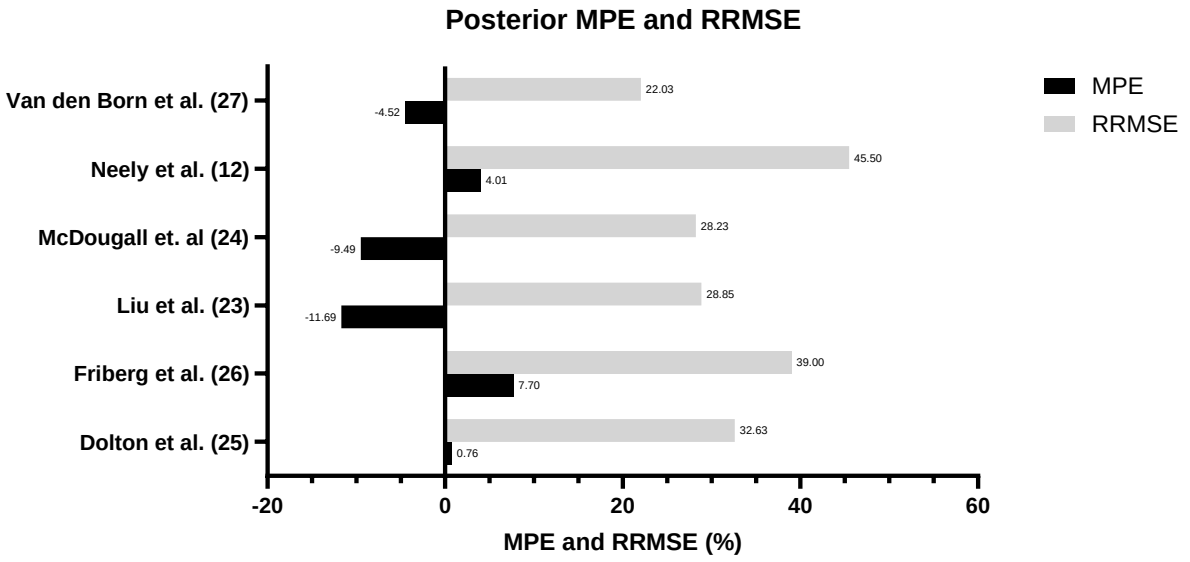


Figure 2; This scatterplot demonstrates the relation between the prior concentrations of the various models and the observed concentrations. The dots present the observed and prior values, with the prior on the y-axis and the observed on the x-axis.



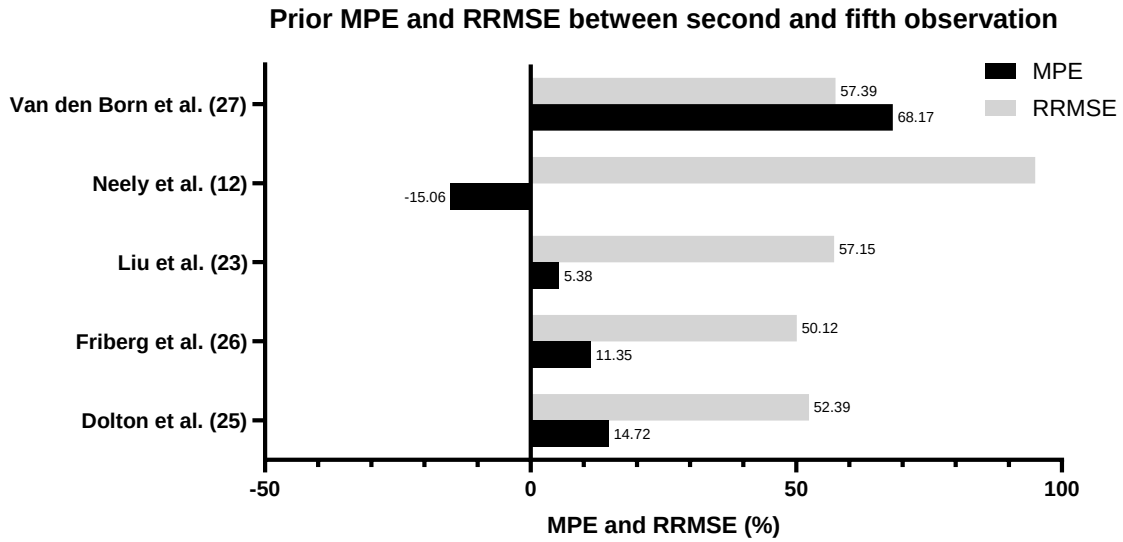
Prior (n = 248)	*MPE [%]*	*RRMSE [%]*	*F20 [%]*	*F30 [%]*	*F50 [%]*
Dolton et al. (25)	54.92	66.37	19.76	27.02	40.32
Friberg et al. (26)	45.95	64.27	16.53	22.58	37.90
Liu et al. (23)	34.43	68.18	15.73	22.58	40.32
McDougall et. al (24)	467.52	72.53	16.53	24.60	40.73
Neely et al. (12)	139.94	99.39	12.10	18.55	32.26
Van den Born et al. (27)	105.97	76.45	13.31	22.18	40.73

Figure 3; Predictive performance of the models. The model made by McDougall et al. has been excluded for visual benefits.



Posterior [n = 248]	*MPE [%]*	*RRMSE [%]*	*F20 [%]*	*F30 [%]*	*F50 [%]*
Dolton et al. (25)	0.76	32.63	41.94	56.45	79.84
Friberg et al. (26)	7.70	39.00	31.85	46.77	74.19
Liu et al. (23)	-11.69	28.85	57.26	68.55	81.05
McDougall et. al (24)	-9.49	28.23	66.13	75.00	84.68
Neely et al. (12)	4.01	45.50	27.42	43.95	67.74
Van den Born et al. (27)	-4.52	22.03	57.66	66.53	83.06

Figure 4; Predictive performance of the models



Prior [n = 127]	*MPE (%)*	*RRMSE (%)*	*F20 (%)*	*F30 (%)*	*F50 (%)*
Dolton et al. (25)	14.72	52.39	22.83	32.28	52.76
Friberg et al. (26)	11.35	50.12	22.83	31.50	48.82
Liu et al. (23)	5.38	57.15	22.05	32.28	52.76
McDougall et. al (24)	604.47	56.03	20.47	29.92	50.39
Neely et al. (12)	-15.06	94.98	17.32	27.56	44.09
Van den Born et al. (27)	68.17	57.39	18.11	27.56	52.76

Figure 5; Predictive performance of the models

Table 5; Predictive performance of the models per individual observation

	Observation 1 [n = 92]		*Observation 2 [n = 54]*		*Observation 3 [n = 36]*		*Observation 4 [n = 25]*		*Observation 5 [n = 12]*	
Prior	MPE [%]	RRMSE [%]	MPE [%]	RRMSE [%]	MPE [%]	RRMSE [%]	MPE [%]	RRMSE [%]	MPE [%]	RRMSE [%]
Dolton et al. (25)	138.26	81.41	29.73	57.48	-9.70	48.61	7.85	54.69	34.74	36.01
Friberg et al. (26)	119.31	79.86	20.70	48.28	-5.67	45.59	3.64	65.90	36.33	39.09
Liu et al. (23)	95.70	75.83	12.31	52.72	-16.73	59.78	14.33	67.23	21.91	48.13
McDougall et. al (24)	376.18	87.95	36.98	52.53	0.94	58.67	37.33	63.49	6150.37	48.37
Neely et al. (12)	410.87	101.41	-6.61	94.73	-30.58	113.08	-20.39	91.49	4.61	49.06
Van den Born et al. (27)	180.56	96.67	92.84	60.02	21.65	57.28	4.88	48.12	228.56	65.22

Supplementary

Table S1; Flow diagram of study selection

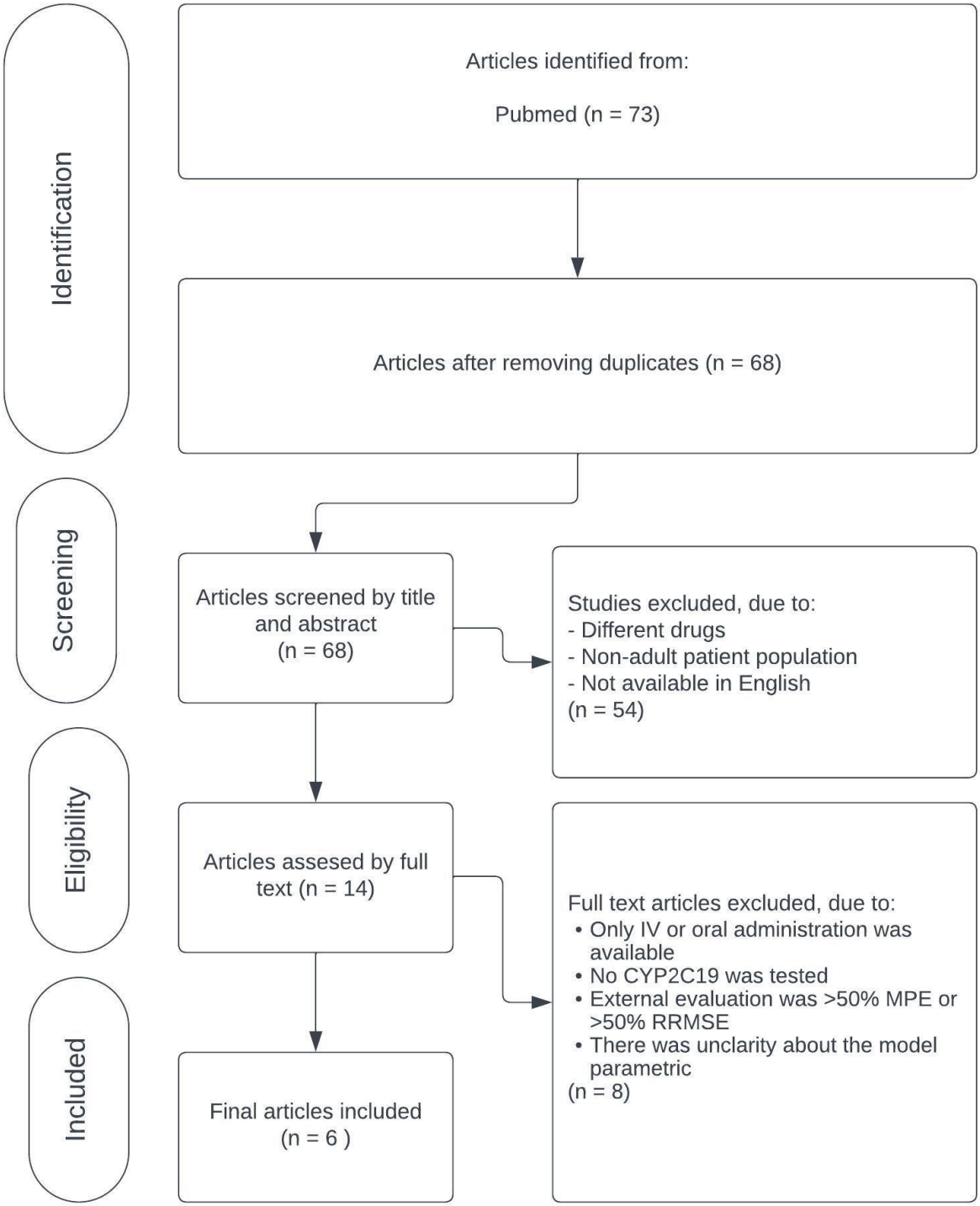


Table S2; Search strategy and results in PubMed

Search	Query	Results
1	Search: **(Voriconazole [Title/Abstract])) AND (("Pharmacokinetics"[Mesh]) OR (Pharmacokinetic* [Title/Abstract])**	199,143
2	Search: **("pharmacokinetic model"[Title/Abstract]) AND (("Voriconazole"[Mesh]) OR (Voriconazole[Title/Abstract]))**	45
3	Search: **(model*[Title/Abstract]) AND (("Voriconazole"[Mesh]) OR (Voriconazole[Title/Abstract]))**	721
4	Search: **((Voriconazole[Mesh]) OR (Voriconazole[Title/Abstract])) AND ((Pharmacokinetics[Mesh]) OR (pharmacokinetic*[Title/Abstract]) OR (model*[Title/Abstract]))**	1343
5	Search: **(Voriconazole[Mesh]) OR (Voriconazole[Title/Abstract]) AND ((Pharmacokinetics [Mesh]) OR (Pharmacokinetic [Title/Abstract]) OR (drug kinetic*[Title/Abstract]))**	622
6	Search: **((Voriconazole[Mesh]) OR (Voriconazole[Title/Abstract])) AND ((Pharmacokinetics[Mesh]) OR (Pharmacokinetic*[Title/Abstract]) OR (drug kinetic*[Title/Abstract])) AND ((model*[Title/Abstract]) OR ("modeling"[Title/Abstract]))**	231
7	Search: **(Voriconazole[Title/Abstract]) AND (Pharmacokinetic* [Title/Abstract])) AND (models [Title/Abstract])**	73