Application of physiologically-based pharmacokinetic modeling to predict drug-drug interactions of dronedarone as a perpetrator with oral anti-coagulants

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Research Article

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Abstract

Background

Concurrent use of dronedarone and oral anti-coagulants are common since both classes of medications are essential to atrial fibrillation management. Dronedarone is a moderate inhibitor of CYP3A4 and P-glycoprotein (P-gp). To date, no drug-drug interaction (DDI) studies between dronedarone and apixaban or rivaroxaban were reported. The current study aims to study the impact of dronedarone co-administration on exposure of apixaban or rivaroxaban with physiologically based pharmacokinetic (PBPK) modeling.

Method

Modeling and simulation were conducted with Simcyp Simulator. The input parameters required for dronedarone modeling were obtained from literature. The developed dronedarone PBPK model was extensively validated with reported DDIs between dronedarone and CYP3A4 and P-gp substrates. After model validation, the model was applied to evaluate DDI potential of dronedarone on exposure of apixaban or rivaroxaban in both healthy population and patients with renal impairment.

Result

The developed PBPK models accurately describe dronedarone pharmacokinetics following single-dose oral administration in healthy volunteers. The model also predicts DDIs between dronedarone and CYP3A4 and P-gp substrates well, with all fold errors less than 1.5. The AUC of apixaban was increased by 1.36-fold in healthy population due to dronedarone co-administration. In addition, for patients with moderate renal impairment, the AUC of apixaban and rivaroxaban would increase by 1.38-fold and 1.25-fold, respectively.

Conclusions

The established PBPK model of dronedarone was well validated with previously reported DDI studies. Reduced dosing regimens were recommended for patients administered apixaban and dronedarone together. For patients with renal impairment, both dosages of apixaban and rivaroxaban should be adjusted to avoid overexposure when dronedarone is co-administered.

Introduction

Atrial fibrillation (AF) is the most encountered cardiac arrhythmia world-widely. AF is associated with significant morbidity, as it increases the risk of stroke, heart failure and other heart-related complications [1]. Therapeutic cornerstones with regards to AF management include rhythm control with antiarrhythmic therapy, rate control, and stroke prevention using anti-coagulants [2].

Dronedarone is a non-iodinated benzofuran derivative of amiodarone, specifically developed with the intention of improving safety profile of antiarrhythmics. After oral administration, dronedarone is well

absorbed but undergoes significant first-pass metabolism, which reduces its net bioavailability to 15% [3]. Dronedarone undergoes extensive hepatic metabolism by cytochrome P450 enzymes (CYP) 3A [4, 5]. It is mainly excreted in the feces (84%), while 6% is excreted in the urine [5]. Though designed to be a safer alternative to amiodarone, drug-drug interactions with dronedarone raise lots of concern since dronedarone is a moderate inhibitor of CYP3A4 and P-glycoprotein (P-gp) [5]. To illustrate, the co-administration of dronedarone and simvastatin would lead to an increase of simvastatin levels by 4-fold [6].

Concurrent use of dronedarone and oral anti-coagulants are common since both are essential to AF management [2]. All direct oral anti-coagulants (DOAC) are P-glycoprotein (P-gp) substrates, and apixaban and rivaroxaban are substrates of CYP3A4 [7]. Previous pharmacokinetic (PK) study suggests that co-administration of dronedarone would lead to a 1.7-fold increase in trough plasma concentration of dabigatran [8], based on which European Medicines Agency suggests contraindication of two drugs administered concurrently [9]. However, PK studies on the concomitant use of apixaban and rivaroxaban with dronedarone are not available. A recent real-world retrospective observational study has found increased bleeding events with rivaroxaban or dabigatran co-administered with dronedarone. Due to the nature of observational study, confounding factors such as renal functions, dosage appropriateness of each medication were not investigated, nor would it provide adjusted dosing regimens for clinical scenarios when concomitant administration of DOACs and dronedarone are unavoidable [10].

Physiologically based pharmacokinetic (PBPK) modeling provides a mechanistic approach to quantitatively predict drug-drug interactions (DDIs), which may offer an alternative to dedicated clinical trials [11]. While PBPK modelling of dronedarone has been previously reported, the model has not been validated with clinical data of drug-drug interactions [12]. The primary objective of this study was to quantitatively evaluate changes in rivaroxaban and apixaban exposure in individuals when dronedarone is co-administered, based on validated physiologically based pharmacokinetic (PBPK) modeling and simulation approach.

Methods

2.1 General approach

All PBPK model development, PK and DDI simulations were performed using the population-based PBPK simulator Simcyp® version 20.1 (Certara UK Limited, Sheffield, UK). The observed clinical PK data were obtained from the literature with GetData Graph Digitizer v2.26 (http://getdata-graph-digitizer.com/). The overall workflow of the present analysis is shown in Fig. 1.

In general, the dronedarone PBPK model was developed first, with its simulated concentration-time profiles verified with clinical PK data. Second, dronedarone DDI-PBPK model as a perpetrator was established with *in vitro* profiles from literature, and verified with clinical PK data when CYP3A4 and p-gp substrates were co-administered with dronedarone, respectively. Third, the established model was used to

predict potential DDI risks with dronedarone as a perpetrator. The information and characteristics of observed clinical data are summarized in Table 1.

Table 1
Characteristics of observed PK data used for model development and verification

Substrate	Inhibitor	Dosing regimen	Length of observation	Trial number	Reference
Dronedarone	/	Single dose of dronedarone 800 mg	48hour	NDA 022425 (ALI3180)	[13]
Simvastatin	Dronedarone	Repeated oral administration of simvastatin 40mg q24h alone or in combination with repeated oral administrations of dronedarone 400 mg q12h	14days	NDA 022425 (INT4880)	[13]
Verapamil	Dronedarone	Repeated oral administration of verapamil 240mg q24h alone or in combination with repeated oral administrations of dronedarone 400 mg q12h	14days	NDA 022425 (INT4882)	[13]
Digoxin	/	Repeated oral administration of digoxin 0.25mg q24h alone	10days	/	[26]
	Dronedarone	Repeated oral administration of digoxin 0.25mg q24h alone or in combination with repeated oral administrations of dronedarone 400 mg q12h	10days	NDA 022425 (INT5189)	[13]
Dabigatran	Dronedarone	Single dose of 150 mg dabigatran etexilate alone or in combination with a single dose of 400 mg dronedarone	48hour	NCT01306162	[8]

2.2 Dronedarone basic PBPK model development and verification

2.2.1 Dronedarone basic PBPK model development

The dronedarone PBPK model was developed based on *in vitro*, *in vivo*, and *in silico* data obtained from the public domain. A summary of model parameters used in the PBPK model and the referred literature are shown in Table 2.

Table 2
Summary input data for dronedarone as a substrate in Simcyp Simulator simulation

Parameters	Value	Source
Physiochemical parameters		
Molecular Weight (g/mol)	557	drugbank
Log P	7.8	drugbank
Compound type	Monoprotic base	
pKa	9.3	Djebli et al[12]
Hematocrit (%)	45	Simcyp library
B:P ratio	1	
f_{up}	0.003	Djebli et al[12]
Absorption parameters		
ADAM model		
fa; *Ka* (h^{-1})	0.898; 0.816	Djebli et al[12]
P_{eff} (10^{-4} cm/s)	1.98	
Dissolution	time profile Time (h): 0, 0.083, 0.167, 0.25, 0.33, 0.42, 0.5, 0.75, 1 and 1.5 Dissolution (%): 0, 6.6, 12.8, 28.5, 38.9, 47.7, 55.2, 75.9, 92.2 and 100	
fu_{Gut}	1	
Distribution parameters		
mPBPK		
V_{ss} (l/kg)	10	Djebli et al [12]
Elimination parameters		
Clearance type	Enzyme kinetics	
In vitro metabolic system	Recombinant	
rhCYP3A4		
Vmax (pmol/min per pmol)	13.7	Djebli et al [12]

Parameters	Value	Source
KM (mM)	4.2	
fu_{mic}	0.003	Sensitivity analysis
rhCYP3A5		
Vmax (pmol/min per pmol)	4.87	Djebli et al [12]
KM (mM)	3.1	
fu_{mic}	0.003	Sensitivity analysis
Additional liver clearance		
Cl_{int}(l/min per mg)	40	Djebli et al [12]

First, a model for oral administration of dronedarone was developed, with the physicochemical and ADME properties from drugbank (https://go.drugbank.com/) and Djebli et al [12]. The *in vivo* absorption of dronedarone was determined using the Advanced Dissolution Absorption and Transit (ADAM) models, with permeability and dissolution data acquired from Djebli et al. A minimal PBPK distribution model was applied, with the volume of distribution at steady state (V_{ss}) acquired from literature [12]. Dronedarone was reported to be extensively metabolized via CYP3A4/5 [4]. Thus, the enzyme kinetics module was used to describe the *in vivo* clearance of dronedarone. The maximum velocity (V_{max}) and Michaelis–Menten constant (K_m) were acquired from the previously reported literature [12], and the fu_{mic} was obtained with sensitivity analysis.

2.2.2 Dronedarone basic PBPK model verification

The pharmacokinetics of dronedarone was simulated with the established PBPK model, with characteristics of study subjects and trial design followed the clinical trials. The simulated PK parameters and plasma concentration profiles were compared against the observed data [13]. The fold error of the main pharmacokinetic parameters (C_{max} and AUC) was used to assess the predictive accuracy of the model, which referred to the ratio of the simulated to the observed values (Eq. 1). The model's fitness was evaluated with a fold error of less than 2 [14].

$$\text{Fold error} = \frac{\text{predicted value}}{\text{observed value}} \ (\text{if predicted} > \text{observed})$$
$$\text{or} \qquad (1)$$
$$\text{Fold error} = \frac{\text{observed value}}{\text{predicted value}} \ (\text{if observed} > \text{predicted})$$

2.3 Dronedarone DDI-PBPK Model development and verification

Previous studies have found that dronedarone exhibits low to moderate potential to inhibit metabolism of CYP3A, CYP2J2, as well as P-gp substrates [15]. The dronedarone DDI-PBPK model was established in a stepwise method. First, in order to establish dronedarone DDI-PBPK model as a perpetrator, *in vitro* inhibition data including reversible inhibition and mechanistic based inhibition (MBI) of 3A4 and 2J2, as well as inhibition of P-gp mediated efflux, were extracted from previous studies and incorporated into the basic PBPK model [12, 14, 16, 17]. Second, to calibrate the magnitude of CYP3A4 inhibition of dronedarone, the CYP3A4 inhibition parameters were adjusted so that the model generated simulations can fit the clinical data investigating the impact of repeated oral doses of dronedarone on the PK profile of simvastatin (INT4880) and verapamil (INT4882). Likewise, the magnitude of P-gp inhibition of dronedarone were calibrated with clinical data investigating the impact of repeated oral doses of dronedarone on the PK profile of digoxin (INT5189) and dabigatran (NCT01306162). In each step of the DDI-PBPK modeling, evaluation criteria were set with a fold error of AUC ratio and C_{max} ratio less than 1.5. The AUC ratio and C_{max} ratio were referred to as the mean AUC and C_{max} in the presence of dronedarone versus the absence, respectively (Eq. 2 and Eq. 3).

$$AUCratio = \frac{AUCwithinducerorinhibitor}{AUCwithoutinducerorinhibitor} \quad \text{Eq. 2}$$

$$C_{max}ratio = \frac{C_{max}withinducerorinhibitor}{C_{max}withoutinducerorinhibitor} \quad \text{Eq. 3}$$

The Simcyp provided compound files of simvastatin (SV-simvastatin), dabigatran (SV-dabigatran) in were applied as substrates during dronedarone DDI-PBPK model development. The verapamil minimal PBPK model was based on Simcyp compound profile (SV-verapamil) and the study by Yamazaki et al [18]. The Simcyp provided digoxin (SV-digoxin) model was also adjusted based on a previous study to improve goodness of fit [19]. Additional model verification and calibrations were conducted for simvastatin, digoxin, and verapamil models in order to reproduce observed clinical PK data when these substrates were administered alone. Evaluation criteria of fitness of each model were the fold error less than 2 [14]. Details of PBPK modeling of simvastatin, digoxin, and verapamil are provided in supplementals.

2.4 Application of the PBPK model to predict the Drug-Drug Interaction with dronedarone as a perpetrator

The established dronedarone DDI-PBPK model was used to predict potential DDI risks with CYP3A4 and/or P-gp substrates. As an antiarrhythmic drug for atrial fibrillation treatment, dronedarone is often co-administered with anti-coagulants. Thus, effects of co-administered dronedarone on *in vivo* PK of apixaban, rivaroxaban were investigated based on the established model. Dosing regimen of dronedarone used in the prediction was 400mg twice daily [5]. Regimen of each substrate follows its therapeutic doses for AF management: apixaban 5mg every 12 hours, rivaroxaban 20mg every 24 hours, respectively [9]. Each substrate is co-administered with dronedarone for 14 days. Simulations of all DDI outcomes were performed using Simcyp healthy volunteers in a fasted state with 100 subjects (10 trials×10 subjects).

The apixaban and rivaroxaban PBPK models were based on the study by Otsuka et al. and were kindly provided by the authors [20]. In the study by Otsuka et al., the rivaroxaban model was validated with the DDI study results with ketoconazole, ritonavir, clarithromycin, erythromycin, verapamil, and rifampicin. The apixaban model was validated with the DDI study results with ketoconazole, diltiazem, cyclosporine, and rifampicin.

In the current study, the bioequivalence criteria for dosage adjustment were defined as the dosing regimen with which patients could achieve AUC_{24h} or C_{max} within 80.00–125.00% range of reference AUC_{24h} or C_{max}. The reference AUC_{24h} or C_{max} was defined as the AUC_{24h} or C_{max} of the anti-coagulant when it was administered alone under AF therapeutic dose. Additional simulations with alternative dosing regimens were conducted when bioequivalence was not achieved due to dronedarone co-administration.

2.5 Application of the PBPK model to predict the Drug-Drug-Disease Interaction with dronedarone as a perpetrator

To assess the impact of renal impairment on the DDI of dronedarone and apixaban/rivaroxaban, the DDIs were simulated in virtual population of renal impairment (RI). The Simcyp in-built moderate (glomerular filtration rates (eGFR) of 30–60 ml/min) and severe RI (eGFR < 30 ml/min) populations were used for simulations. The pathophysiological changes incorporated within the RI populations were reduced kidney weight, reduced hepatic CYP expression (e.g., 2C9, 2J2, 2D6, and 3A4), reduced serum albumin and hematocrit levels, altered blood flows [21, 22].

The bioequivalence criteria for dosage adjustment were the same as the abovementioned one. The reference AUC_{24h} of the anti-coagulant was defined as the AUC_{24h} of dronedarone when it was administered alone under its FDA approved renal-adjust dose for AF management. Additional simulations were conducted when bioequivalence was not achieved due to dronedarone co-administration.

Results

3.1 Development and verification of the basic PBPK model for dronedarone

Based on the previous work by Djebli et al, the fu_{mic} was fixed as 0.003 to fit the observed PK data best. As shown in Fig. 2, the optimized PBPK model resulted in a good agreement between observed and predicted values for dronedarone 800 mg oral PK profiles after single-dose administration. The observed C_{max} and AUC were 0.0429 mg/L and 0.416 mg·h/mL when a single dose of dronedarone 800 mg was administered alone. The established model predicts an C_{max} 0.049 mg/L (fold error = 1.14) and AUC 0.514 mg·h/mL (fold error = 1.23), respectively. The model meets the pre-specified acceptance criterion of fold error less than 1.5.

3.2 Verification of the DDI-PBPK model for dronedarone

As dronedarone showed CYP3A4, CYP2J2 and P-gp inhibition potential in vitro, PBPK models incorporating in vitro CYP3A4, CYP2J2 and P-gp inhibition parameters were developed. The input drug-drug interaction parameters for dronedarone as an inhibitor were summarized in Table 3, where parameters were extracted from literature and refined based on *in vivo* DDI studies. The model simulations were compared with the results from the cocktail DDI studies, as shown in Table 4. The predicted along with observed mean plasma concentration-time curves of simvastatin, verapamil, and digoxin in the presence or absence of dronedarone are described in Fig. 3.

Table 3
Summary input drug-drug interaction parameters for dronedarone as an inhibitor in Simcyp Simulator simulation

Parameters	Value		Reference
	Initial value	Refined	
CYP3A4 (MBI)			Hong et al [16]
K_{app} (μM)	0.87	1.0	
k_{inact} (h^{-1})	2.34	0.2	
fu_{mic}	/	0.003	
CYP2J2 (RI)			Cheong et al [15]
K_i (μM)	0.93	/	
fu_{mic}	0.003	/	
CYP2J2 (MBI)			
K_{app} (μM)	0.031	/	
k_{inact} (h^{-1})	0.021	/	
fu_{mic}	0.003	/	
P-gp inhibition			Cheong et al [15]
K_i (μM)	0.68	0.1	

Note: K_{app}: concentration of mechanism-based inhibitor associated with half-maximal inactivation rate; k_{inact}: inactivation rate of the enzyme; fu_{mic}: fraction of unbound drug in the in vitro incubation; K_i: concentration of inhibitor that supports half-maximal inhibition.

Table 4
Comparison of observed and model-predicted drug–drug interactions between CYP 3A4 or P-gp substrates and dronedarone

Victim	Without dronedarone		With dronedarone		C_{max} ratio	AUC_{last} ratio
	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)		
Simvastatin						
observed	10.70	34.40	38.60	125.80	3.75	3.90
predicted	6.73	29.42	29.19	155.43	4.34	5.28
fold error	1.59	1.17			1.16	1.35
Verapamil						
observed	135.00	895.00	188.00	1310.00	1.42	1.48
predicted	76.76	1048.71	136.37	2041.61	1.78	1.95
fold error	1.76	1.17			1.25	1.32
Digoxin						
observed	1.32	12.50	1.71	18.00	1.75	1.44
predicted	1.31	17.29	2.34	25.66	1.79	1.48
fold error	1.01	1.38			1.02	1.03
Dabigatran						
observed	149.00	1160.00	282.00	2520.00	1.89	2.17
predicted	110.80	1950.00	310.00	4342.45	2.80	2.23
fold error	1.34	1.68			1.48	1.03

After the parameter was refined with *in vivo* DDI studies with simvastatin and verapamil as probe substrates, we determined the CYP3A4 inactivation constant k_{Inact}/K_I as 3.33 $minute^{-1} \cdot mM^{-1}$. While dronedarone demonstrated competitive inhibition of P-gp with a Ki 0f 0.68 mM in previous literature [16], our study has determined a Ki of 0.1 mM based on DDI studies with digoxin and dabigatran.

As shown in Table 4, PK profiles of simvastatin, verapamil, digoxin, and dabigatran were well described by established PBPK models, with all fold error of C_{max} and AUC less than 2 when substrates were administered alone. Moreover, the model well predicted the pharmacokinetic changes of simvastatin,

verapamil, or digoxin in the presence of dronedarone, with the C_{max} and AUC ratios (observed/predicted) were all within the acceptable criteria of 1.5-fold.

3.3 Model-based prediction the DDI with dronedarone as a perpetrator

The developed PBPK model was used to simulate other clinical DDI scenarios for co-administration of dronedarone with CYP3A and P-gp substrates. Simulated exposure changes of anti-coagulant drugs with dronedarone co-administration for 14 days are presented in Table 5.

Table 5
Simulated exposure changes of anti-coagulant with dronedarone co-administration

Oral Anti-coagulant	Dosing regimen	Length of therapy	C_{max} (mg/L)	AUC_{24h} (mg·h/mL)	C_{max} ratio	AUC_{24h} ratio
Rivaroxaban	20mg q24h	14days	0.14	1.53	/	/
Rivaroxaban + DDE	20mg q24h	14days	0.17	1.88	1.15	1.23
Apixaban	5mg q12h	14days	0.11	2.14	/	/
Apixaban + DDE	5mg q12h	14days	0.16	2.9	1.45	1.36
Apixaban + DDE	2.5mg q12h	14days	0.08	1.42	0.73	0.66
Note: DDE, dronedarone. Dosage of co-administered dronedarone was 400mg q12h.						

Co-administration of dronedarone would lead to a 1.23-fold increase and a 1.36-fold increase in AUC for rivaroxaban and apixaban, respectively. Compared to the reference regimen, taking dronedarone concomitantly with apixaban 2.5mg q12h would lead to a 0.73-fold increase in C_{max}, 0.6-fold increase in C_{min}, and 0.66-fold increase in AUC.

3.4 Drug-Drug-Disease interaction with dronedarone as a perpetrator

For patients with renal impairment, the FDA approved dosing regimens of rivaroxaban 15mg q24h and apixaban 2.5mg q12h for population with moderate renal impairment were applied as reference regimens, respectively. Figure 4 and Fig. 5 have compared the AUC and C_{max} ratio when dronedarone was co-administered for patients with moderate or severe renal impairment.

As shown in Fig. 4, co-administration of dronedarone in patient with renal impairment would increase exposure of apixaban and undermine pre-specified bioequivalence. For patients with moderate renal impairment, apixaban 2.5mg q12h would lead to an AUC ratio of 1.38 and C_{max} ratio of 1.47, whereas a dose reduction regimen of 2.5mg q24h would lead to a C_{max} ratio of 1.14. Similarly, for patients with severe renal impairment, a dose reduction regimen of 2.5mg q24h would result in an AUC ratio of 0.72 and C_{max} ratio of 1.

As shown in Fig. 5, dosage adjustment of rivaroxaban is recommended for patients with renal impairment when dronedarone is administered together. For patients with moderate renal impairment. A dose reduction regimen of 10 mg q24h would lead to an AUC ratio of 0.91 and C_{max} ratio of 1. For patients with severe renal impairment, a dose reduction regimen of 10 mg q24h would lead to an AUC ratio of 0.92 and C_{max} ratio of 0.9.

Discussion

To our knowledge, this is the first validated PBPK modelling of dronedarone as a perpetrator. The PBPK model of dronedarone was validated with five datasets of clinical trials, with four datasets investigating DDI between dronedarone and CYP34A4 or P-gp substrates. Based on the established model, adjusted dosing regimens were recommended when dronedarone was co-administered with apixaban in healthy volunteers, as well as in patients with moderate and severe renal impairment.

In vitro data were refined in the current study to qualify the extent of CYP3A4 inhibition and P-gp inhibition, respectively. While Hong et al have reported the CYP3A4 inactivation kinetic constant (k_{Inact}/K_I) of dronedarone as 44.83 $minute^{-1}\cdot mM^{-1}$ by inactivation of testosterone–6b-hydroxylation, Cheong et al found the inactivation rate (k_{Inact}/K_I) of dronedarone was 185 $minute^{-1}\cdot mM^{-1}$ when rivaroxaban was used as the probe substrate [15, 16]. The current study has determined the CYP3A4 inactivation constant (k_{Inact}/K_I) of dronedarone as 3.33 $minute^{-1}\cdot mM^{-1}$, which was validated with two *in vivo* DDI studies. Moreover, reversible CYP3A4 inhibition of dronedarone was determined *in vitro*; however, the current study removed reversible CYP3A4 inhibition based on the fitness of observed data. The result indicates a lower potency of CYP3A4 inhibition of dronedarone *in vivo* than *in vitro*.

Compared with the P-gp inhibition constant (Ki) 0.68 mM, our study determined the Ki value as 0.1 mM based on DDI studies with digoxin and dabigatran as victim drugs [15]. Instead of extensive metabolism, both digoxin and dabigatran undergo excretion with transport by the drug efflux pump P-gp. Though both digoxin and dabigatran are intestinal P-gp probe drugs, a recent study proved that digoxin and dabigatran exhibit different transporter profiles, therefore the AUC/C_{max} ratio would be different [23, 24]. It was also proposed that dabigatran was a more specific substrate for P-gp and not transported by other major efflux transporters expressed in the intestine [24]. In the current study, both DDIs between dronedarone and dabigatran or digoxin were well validated with the refined parameters.

Previous study by Cheong et al has developed a static model to investigate the DDI between rivaroxaban and dronedarone, which yields an AUC fold change of 1.31 with hepatic and gut metabolism by CYP3A4 accounted for [15]. A recent study by Willmann et al predicts a “small to moderate” increase in a rivaroxaban AUC in combination with dronedarone since level of p-gp inhibition was not investigated [25]. Our study has revealed that co-administration of dronedarone would increase AUC by 23% with inhibition of CYP3A4, CYP2J2, and P-gp considered. Taken together, the impact of dronedarone co-administration on rivaroxaban is consistent with previous studies.

There are several limitations of the study. First, while the *in vitro* parameter of dronedarone CYP2J2 inhibition was acquired using rivaroxaban as the probe drug, the extent of inhibition was not qualified due to a lack of observed data. Second, clinical outcomes of the proposed dosing strategies, such as the occurrence of stroke or bleeding risks, remain to be validated with prospective clinical trials.

Conclusion

This is the first PBPK modeling-based study of drug-drug interaction between dronedarone and novel oral anti-coagulants. The established PBPK model of dronedarone was well validated with previously reported DDI studies. According to the established model, dosage adjustment was recommended for co-administration of dronedarone and apixaban in otherwise healthy patients. Additionally, reduced dosage regimens of rivaroxaban and apixaban were suggested for patients with moderate or severe renal impairment when dronedarone was co-administered.

Declarations

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Hai-ni Wen: Methodology, Validation, Software, Visualization, Writing – Original Draft, Writing - Review & Editing. **Qing-feng He**: Methodology, Software, Formal analysis, Writing -Original Draft, Writing - Review & Editing. **Zheng Jiao:** Conceptualization, Supervision, Writing -Review & Editing. **Xiaoqiang Xiang:** Methodology, Supervision, Writing - Original Draft, Writing -Review & Editing. **Jianguang Yu:** Conceptualization, Supervision, Writing - Original Draft, Writing -Review & Editing.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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Figures

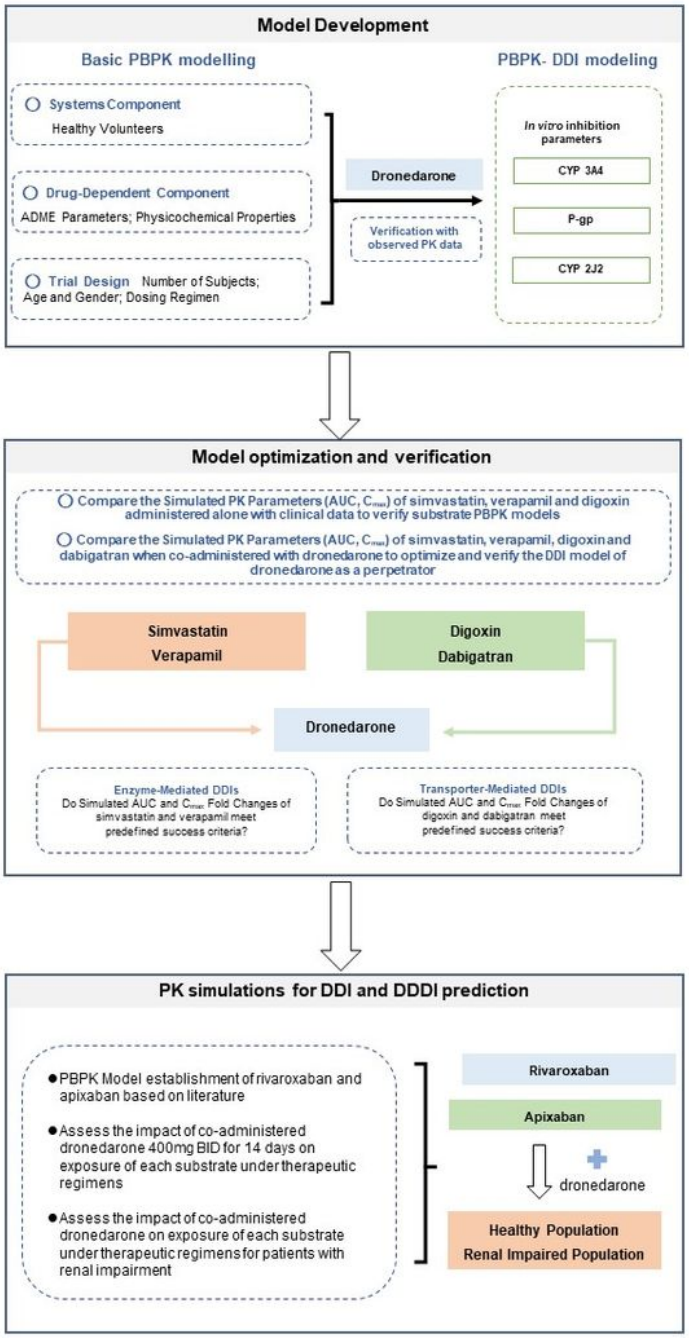

Figure 1

General approach and workflow of the presented study

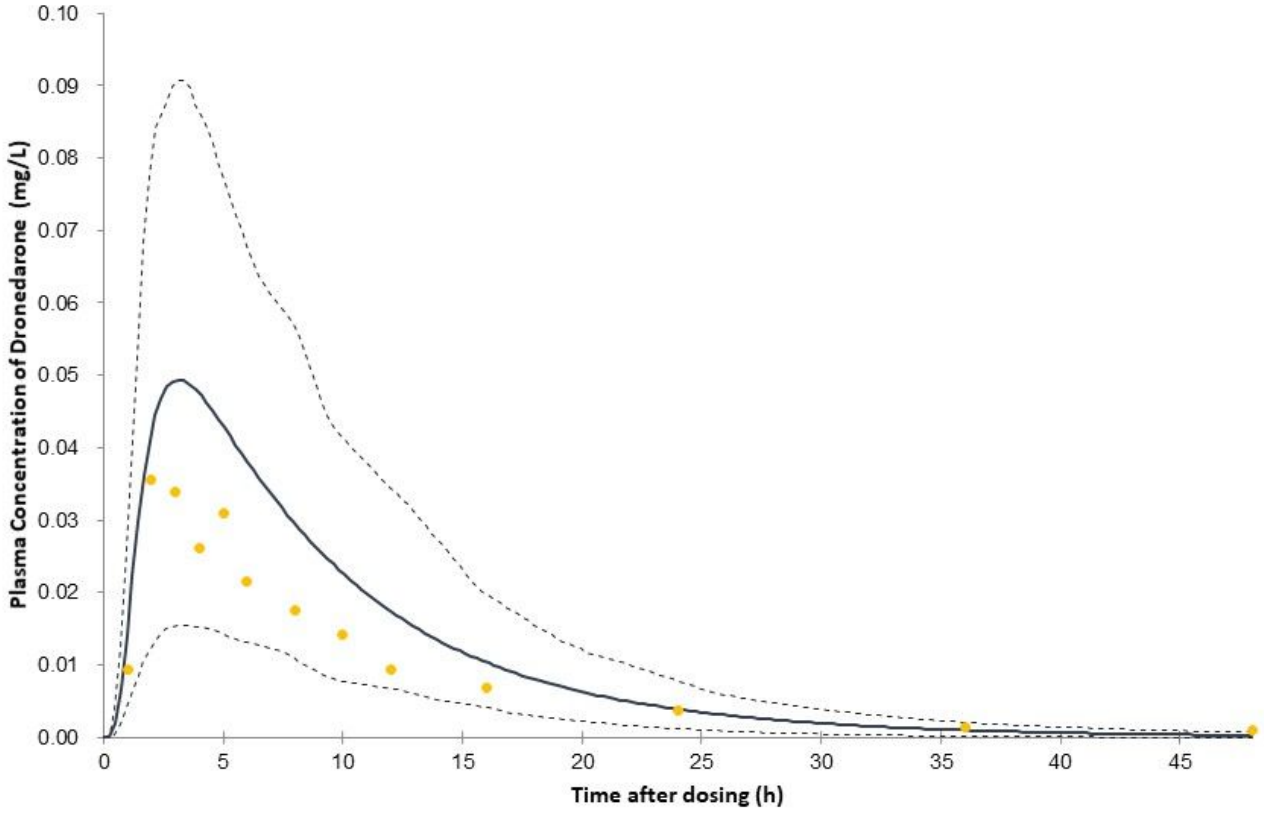

Figure 2

Predicted and observed mean plasma concentration–time curves of dronedarone following a single oral dose of 800mg in healthy volunteers. The solid line and dotted lines represent the simulated median dronedarone time-concentration, 5^{th} percentile, and 95^{th} percentile of the time-concentration profiles, respectively. The yellow dots represent observed data.

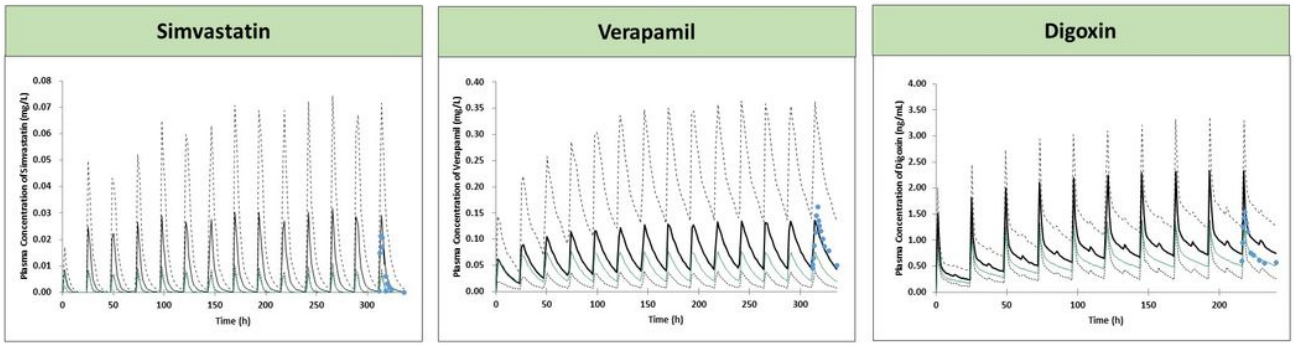

Figure 3

Predicted and observed mean plasma time-concentration curves of each substrate with or without co-administration of 400 mg dronedarone q12h. The green and black lines represent substrates' time-concentration curves in absence and in presence of dronedarone, respectively. The solid line and dotted lines represent the simulated median dronedarone time-concentration, 5th percentile, and 95th percentile of the time-concentration profiles. The blue dots represent observed data in presence of dronedarone.

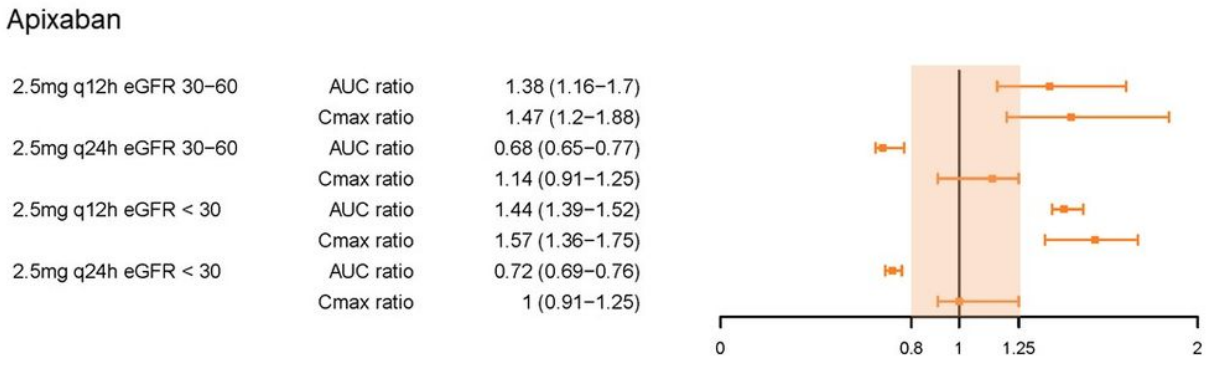

Figure 4

Predicted AUC_{24h} and C_{max} ratio of apixaban under different dosing regimens for patients co-administered with dronedarone with renal impairment. The AUC_{24h} and C_{max} ratio were computed against the reference AUC_{24h} and C_{max} when apixaban 5mg q12h were administered for patients with moderate renal impairment.

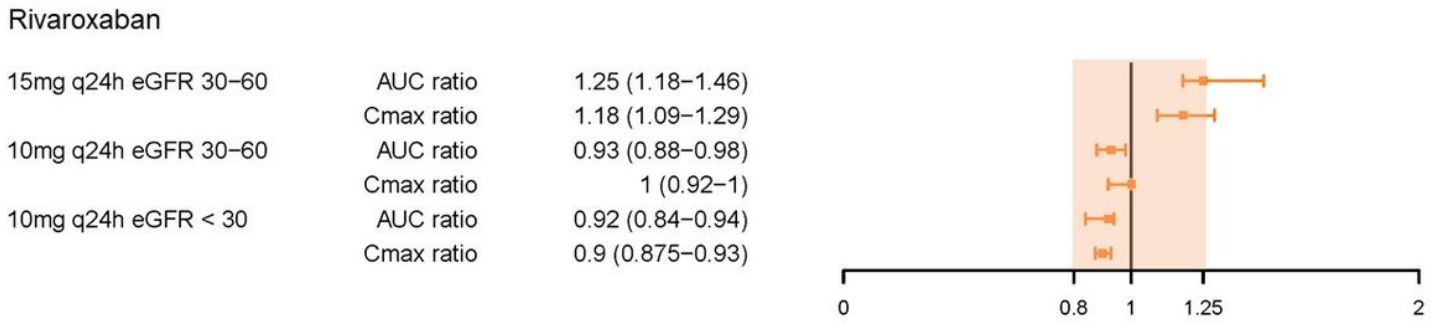

Figure 5

Predicted AUC_{24h} and C_{max} ratio of rivaroxaban under different dosing regimens for patients co-administered with dronedarone with renal impairment. The AUC_{24h} and C_{max} ratio were computed against the reference AUC_{24h} and C_{max} when rivaroxaban 15mg q24h were administered for patients with moderate renal impairment