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

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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 (AF) management. Dronedarone is a moderate inhibitor of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp). All direct oral anticoagulants (DOACs) are P-gp substrates, and apixaban and rivaroxaban are in addition metabolized by CYP3A4. The current study aims to investigate the impact of dronedarone co-administration on exposure as well as bleeding risk 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 collected 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 and consequent increase in major bleeding risk of apixaban or rivaroxaban in both healthy subjects and AF patients with renal impairment.

Result

The developed PBPK models accurately describe dronedarone pharmacokinetics following single-oral dose in healthy subjects. The model also predicts DDIs between dronedarone and CYP3A4 and P-gp substrates well, with all fold errors less than 1.5. Co-administration of dronedarone would lead to a 1.23-fold increase and a 1.36-fold increase in AUC_{24h} for rivaroxaban and apixaban in healthy subjects, respectively. In addition, patients with moderate and severe renal impairment co-administered with dronedarone and apixaban would have 1.78-fold and 1.89-fold increase of major bleeding risk, respectively. In contrast, while dronedarone would also increase exposure of rivaroxban in patients with moderate and severe renal impairment, increases in major bleeding risk were 1.18-fold and 1.3-fold, respectively..

Conclusions

Dronedarone co-administration would increase major bleeding risks of rivaroxban and apixban. Reduced apixaban dosing regimen of 3.75mg q12h was recommended when dronedarone is co-

administered, for AF patients with both normal and impaired renal functions. Reduced rivaroxban dosing regimen of 10mg q24h was recommended when dronedarone is co-administered for AF patients with both moderate and severe impaired renal functions.

Keywords: dronedarone, apixaban, rivaroxaban, renal impairment, physiologically based pharmacokinetic modeling, drug-drug interaction, major bleeding risk

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. After oral administration, 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 plasma concentration by 4-fold [6].

With oral admnistration, the bioavailabilities of apixaban and rivaroxban are 50% and above 66%, respectively. The plasma protein binding of apixaban and rivaroxaban are 87% and 95%, respectively. Both apixaban and rivaroxaban are P-glycoprotein (P-gp) substrates [7]. In addition, rivaroxaban is substrates of CYP3A4 and CYP2J2, and apixaban is mainly metabolized by CYP 3A4 [7]. While both drugs are renally eliminated, apixban (27% renally excreted) is less dependent on renal pathway than rivaroxban (35% renally excreted) [8]. Therefore, rivaroxaban or apixban are prone to pharmacokinetic interactions, especially when P-gp pathway or CYP3A4 dependent metabolism is altered due to co-administered drugs or disease states.

Concurrent use of dronedarone and oral anti-coagulants are common since both are essential to AF management [2]. Previous pharmacokinetic (PK) study suggests that co-administration of dronedarone would lead to a 1.7-fold increase in trough plasma concentration of dabigatran [9], based on which European Medicines Agency suggests contraindication of two drugs administered concurrently [10]. However, PK studies on the concomitant use of apixaban and rivaroxaban with dronedarone are not available. A recent 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 and disease stateswould mask the association between exposure and outcome. nor would it provide adjusted dosing regimens for clinical scenarios when concomitant administration of DOACs and dronedarone are unavoidable [11].

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 [12]. While PBPK modelling of dronedarone has been previously reported, the model has not been validated with clinical data of drug-drug interactions [13]. The primary objective of this study was to quantitatively evaluate changes in exposure and bleeding risk of rivaroxaban and apixaban 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 Figure 1.

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 between apixaban or rivaroxaban with dronedarone as a perpetrator. Forth, exposure-response relationship was established to predict the change in major bleeding risk when co-administration of apixaban or rivaroxaban. Last, the optimal regimen was proposed to match the exposure of monotherapy of apixaban or rivaroxaban. The information and characteristics of observed clinical data are summarized in Table 1.

2.2 Dronedarone basic PBPK model development and validation

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.

First, a model for oral administration of dronedarone was developed, with the drug physicochemical and disposition properties from drugbank (https://go.drugbank.com/) and Djebli et al [13]. The *in vivo* absorption of dronedarone was described using the Advanced Dissolution Absorption and Transit (ADAM) module in Simcyp, with permeability and dissolution data acquired from Djebli et al [13]. A minimal PBPK distribution model was applied, with the volume of distribution at steady state (V_{ss}) acquired from literature [13]. 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 [13], and the fu_{mic} was optimized with sensitivity analysis.

2.2.2 Dronedarone basic PBPK model verification

The concentration-time profile of single oral dose of 800 mg dronedarone was simulated with the established PBPK model, with characteristics of study subjects and trial design followed the clinical trials. The simulated PK profiles and PK parameters were compared against the observed data [14]. The fold error of 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 [15].

$$\text{Fold error} = \frac{\text{predicted value}}{\text{observed value}} \ (\text{if prediction} > \text{observation})$$

$$\text{or} \qquad (1)$$

$$\text{Fold error} = \frac{\text{observed value}}{\text{predicted value}} \ (\text{if observation} > \text{prediction})$$

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 [16]. 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 [13,15,17,18]. Second, to calibrate the magnitude of CYP3A4 inhibition of dronedarone, the CYP3A4 inhibition parameters were adjusted so that the model predictions can fit the clinical data investigating the impact of multiple oral doses of dronedarone on the PK profile of simvastatin and verapamil. Likewise, the magnitude of P-gp inhibition of dronedarone were calibrated with clinical data investigating the impact of multiple oral doses of dronedarone on the PK profile of digoxinand dabigatran. In each step of the 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 those in the absence of dronedarone, respectively (Eq.2 and Eq.3).

$$AUC\ ratio = \frac{AUC\ with\ inducer\ or\ inhibitor}{AUC\ without\ inducer\ or\ inhibitor} \quad \text{Eq. 2}$$

$$C_{max}\ ratio = \frac{C_{max}with\ inducer\ or\ inhibitor}{C_{max}without\ inducer\ or\ inhibitor} \quad \text{Eq. 3}$$

The Simcyp provided compound files of simvastatin (SV-simvastatin), dabigatran (SV-dabigatran) were applied as substrates during dronedarone DDI-PBPK model development. The verapamil minimal PBPK model was built and optimized based on Simcyp compound profile (SV-verapamil) and the study by Yamazaki et al [19]. The Simcyp provided digoxin (SV-digoxin) model was also adjusted based on a previous study to improve goodness of fit [20]. Additional model verification and refinement were conducted for simvastatin, digoxin, and verapamil models in order to fit the observed clinical PK data when these substrates were administered alone. Evaluation criteria of fitness of each model were the fold error less than 2 [15]. Details of PBPK compound profiles of simvastatin, digoxin, and verapamil are provided in supplementals.

2.4 Prediction of the Drug-Drug Interaction with dronedarone as a perpetrator

The established dronedarone DDI-PBPK model were used to predict potential DDI risks with anti-coagulants, apixaban, rivaroxaban. Dosing regimen of dronedarone used in the prediction was 400 mg 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 100 Simcyp healthy volunteers in a fasted state (10 trials×10 subjects). It was assumed that AF patients without co-morbidities can be represented by Simcyp healthy volunteers virtual population.

The apixaban and rivaroxaban PBPK models were based on the study by Otsuka et al. and were kindly provided by the authors [21]. In the study by Otsuka et al., the rivaroxaban model was validated with the DDI study between rivaroxaban and ketoconazole, ritonavir, clarithromycin, erythromycin, verapamil, or rifampicin. The apixaban model was validated with the DDI study results with ketoconazole, diltiazem, cyclosporine, and rifampicin.

2.5 Prediction of the Drug-Drug-Disease Interaction with dronedarone as a perpetrator

To evaluate the impact of renal impairment on the DDI of dronedarone and apixaban/rivaroxaban, the DDIs were simulated in virtual population of renal impairment. The Simcyp in-built moderate (glomerular filtration rates (eGFR) of 30–60 ml/min) and severe renal impairment (eGFR <30 ml/min) populations were used for simulations. The pathophysiological changes incorporated within the renal impairment populations were reduced kidney weight, reduced hepatic CYP expression (e.g., 2C9, 2J2, 2D6, and 3A4), reduced serum albumin and hematocrit levels, as well as altered blood flows [22, 23].

2.6 Estimation of major bleeding risk

For rivaroxban, previous exposure-response analysis has identified relationship between the steady-state median AUC_{24h} of rivaroxaban and risk of major bleeding within 60 days as follows

[24]:

$$\text{Risk of major bleeding of rivaroxban (\%)} = 1.79 \times 1.32^{AUC_{24h}(\text{mg}\cdot\text{h/L})} \quad \text{Eq. 4}$$

The exposure-response analysis was generated from a phase 2, randomized, double-blind, multicenter study of rivaroxban, condcucted in patients undergoing elective total hip replacement. The duration of follow-up time was up to 60 days post-operation [25].

Similarly, an exposure-response analysis was also provided in the review of the apixaban New Drug Application [26]. After digitization of the plot with GetData Graph Digitizer v2.26 (http://getdata-graph-digitizer.com/), an exponential regression model was fit to establish the relationship between the mean risk of major bleeding in 3 years and steady state median AUC_{24h} of apixban at steady state.

$$\text{Risk of major bleeding of apixaban (\%)} = 1.69 \times 1.37^{AUC_{24h}(\text{mg}\cdot\text{h/L})} \quad \text{Eq. 5}$$

The relationship between risk of major bleeding events and apixban exposure was generated using apixaban PK data of AFib patients (n = 3071) with at least one apixaban concentration from the Phase 2 (CV185067) and 3 (CV185030) studies [26].

2.7 Simulation for dosage adjustment

Simulations were conducted based on the established PBPK model. In the current study, the optimal dosing of apixaban or rivaroxaban was defined as the dosing regimen with which (1) patients could achieve both AUC_{24h} and C_{max} within 80% to 125% of reference AUC_{24h} and C_{max}; (2) the major bleeing risk of the dosing regimen is comparable to that of the reference regimen. For AF patients without co-morbidities, the reference regimen was defined as the anti-coagulant monotherapy under its FDA approved dosing for stroke prevention. For AF patients with moderate or severe renal impairment, the reference regimen was defined as the anti-coagulant monotherapy under its FDA approved renal-adjusted dosing for stroke prevention in AF patients.

Results

3.1 Development and verification of the basic PBPK model for dronedarone

A summary of model parameters used in the PBPK model and the referred literature are shown

in Table 2.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 Figure 2, the optimized PBPK model resulted in a good agreement between observed and predicted values for single oral dose of 800 mg dronedarone. The established model have satisfactory predictive performance with an C_{max} 0.049 mg/L (fold error=1.14) and AUC_{last} 0.514 mg·h/mL (fold error=1.23), respectively.

3.2 Validation 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.

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 K_i 0f 0.68 μM in previous literature [16], our study has determined a K_i of 0.1 μM based on DDI studies with digoxin and dabigatran.

The dronedarone PBPK-DDI model was then validated with the DDI study results with simvastatin, verapamil, digoxin, and dabigatran as victim drugs. As shown in Table 4, PK profiles of simvastatin, verapamil, digoxin, and dabigatran were well described by established PBPK models, with all fold errors of C_{max} and AUC_{last} less than 2 when the victim drugs were administered alone. Moreover, the model well predicted the pharmacokinetic changes of simvastatin, verapamil, or digoxin in the presence of dronedarone, with the fold ratios of C_{max} and AUC_{last} within 1.5-fold. 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 Figure 3.

3.3 Model-based DDI prediction 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. In AF patients without co-morbidities, co-administration of dronedarone would lead to 1.15-fold and 1.23-fold increase in AUC_{24h} and C_{max} of rivaroxaban, as well as 1.45-fold and 1.36-fold increase in AUC_{24h} and C_{max} of apixaban, respectively.

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

For AF patients with moderate renal impairment, the FDA approved dosing regimens are 15mg q24h rivaroxaban for population with creatinine clereance (CrCl) 15 to 50 mL/minute, and apixaban 5mg q12h for population with serum creatinine ⩾1.5 mg/dL without other risk factors (≥80 years of age or body weight ≤60 kg). Therefore, these two dosing regimens for patients with moderate renal impairment were applied as reference regimens.

As shown in Figure 4, co-administration of dronedarone in patient with renal impairment would increase exposure of apixaban. For patients with moderate renal impairment, apixaban 5mg q12h would lead to an AUC ratio of 1.38 and C_{max} ratio of 1.47. For patients with severe renal impairment, apixaban 5mg q12h would lead to an AUC ratio of 1.43 and C_{max} ratio of 1.47.

In comparison, co-administration of dronedarone would pose bigger impact on exposure of apixaban than that of rivaroxaban. As shown in Figure 5, for patients with moderate renal impairment, rivaroxaban 15mg q24h would lead to an AUC ratio of 1.25 and C_{max} ratio of 1.18. For patients with severe renal impairment, 15mg q24h would lead to an AUC ratio of 1.25 and C_{max} ratio of 1.13, respectively.

3.5 Bleeding risk assessment

According to established exposure-response analysis of apixaban, co-administration of dronedarone would increase major bleeding risk of apixaban. As shown in Figure 6, compared to AF patients without co-morbidities taking 5mg apixaban alone every 12 hours, patients with moderate and severe renal impairment taking 5mg apixaban every 12 hours with dronedarone would have 1.78-fold (90% CI, 1.55–2.21) and 1.89-fold (90% CI, 1.54–2.48) increase of bleeding risk, respectively.

In contrast, major bleeding risk of rivaroxaban is less influenced by dronedarone, with all fold-changes of major bleeding risk due to co-administration of dronedarone are less than 1.5. As shown in Figure 7, compared to AF patients with normal renal function taking 20mg rivaroxaban alone every 24 hours, patients with moderate and severe renal impairment taking 15 mg rivaroxban every 24 hours with dronedarone would have 1.18-fold (90% CI, 1.09–1.64) and 1.3-fold (90% CI, 0.93–2.37) increase of bleeding risk, respectively.

3.6 Strategies for dosage adjustment

According to abovementioned criteria for dosage adjustment, for AF patients without co-morbidities, a reduced apixban dosing regimen of 3.75mg q12h is recommended when dronedarone is co-administered, since the regimen would result in 1.09-fold of C_{max} and 99% of AUC_{24h}, compared against the reference regimen (Table 5). In contrast, co-administration of rivaroxaban and dronedarone needs no dosage adjustment in AF patients without co-morbidities.

A dose reduction regimen of 3.75 mg apixaban q12h is recommended to reach bioequivalence, with the AUC and C_{max} ratio of 1.02 and 1.07 for patients with moderate renal impairment. The same dose regimen is also adequate for patients with severe renal impairment, with the AUC and C_{max} ratio of 1.03 and 1.07, respectively. As shown in Figure 6, the proposed dosing regimens would result in comparable bleeding risks to the reference value.

As shown in Figure 5, a dose reduction regimen of 10 mg q24h is recommended to reach bioequivalence, with the 91% of AUC and 100% of C_{max} achieved for patients with moderate renal impairment. The regimen of 10 mg q24h is also adequate for patients with severe renal impairment, with 92% of AUC and 90% C_{max} achieved, respectively. As shown in Figure 7, the proposed dosing regimens would result in similar bleeding risks to the reference value.

Discussion

To our best knowledge, this is the first reported assessment of increase in exposure and major bleeding risk of rivaroaxaban or apixaban due to dronedarone co-administration, based on the physiolocally based pharmacokinetic and pharmacodynamic analysis. 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, a reduced dosing regimen of 3.75mg q12h apixaban is recommended when AF patients are co-administered with dronedarone, with or without renal impairment. Also, a reduced dosing regimen of 10mg q24h rivaroxban is recommended for AF patients co-administered with dronedarone with moderate or severe renal impairment.*In vitro* data were refined in the current study to match 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 the 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 [16,17]. 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 DDI studies *in vivo*. The result indicates a lower potency of CYP3A4 inhibition of dronedarone *in vivo* than *in vitro*, and previous *in vitro* study could have over-predict the inhibitory effect of drondarone on CYP3A4 substrates. This can be explained by the fact that CYP3A4 inhibition *in vitro* is often probe substrate-dependent, which sometimes leads to inaccurate in *vitro-in vivo* extrapolation of CYP3A4 interaction [27].

Based on *in vitro* studies, 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 only CYP3A4 metabolism accounted for [16]. A recent study by Willmann et al predicts a “small to moderate” increase in a rivaroxaban AUC in combination with dronedarone based on level of CYP3A4 inhibition of dronedarone [28]. Our study has revealed that co-administration of dronedarone would increase AUC_{24h} by 23% with inhibition of CYP3A4, CYP2J2, and P-gp incorporated in dynamic PBPK model. Although the extent of dronedarone co-administration on rivaroxaban is similar with previous results, the current study has included more elimination pathways with less contribution of CYP3A4 inhibition.

Impact of co-administered dronedarone on major bleeding risks of apixaban and rivaroxaban were also assessed in current study. According to the established exposure-response analysis, compared with AF population without comorbidities, co-administration of dronedarone would increase major bleeding risk of apixaban in patients with moderate and severe renal impairment by

1.78-fold (90% CI, 1.55–2.21) and 1.89-fold (90% CI, 1.54–2.48), respectively. To protect patients from increased major bleeding events, the reduced dosing regimen of 3.75mg q12h apixaban is recommended to achieve both bioequivalence and comparable bleeding risks to reference regimens, when dronedarone is co-administered to AF patients with or without renal impiarment.

In contrast, though co-administration of dronedarone would increase exposure of rivaroxban, the corresponding increases in major bleeding risk were 1.18-fold (90% CI, 1.09–1.64) and 1.3-fold (90% CI, 0.93–2.37) in patients with moderate and severe renal impairment, respectively. For one side, as shown in Figure 4 and Figure 5, the inhibitory effects of dronedarone on rivaroxban is much smaller than that on apixaban. For second, it should be noted that the established exposure-response analyses of rivaroxaban were based on population with deep venous thrombosis, with major bleeding events post total hip replacement surgeries for 60 days measured [25]. Whether the same quantitative relationship can be extrapolated to AF population remains to be validated with clinical trials. Taken together, DDI between dronedarone and rivaroxban could be less clinical significant, however, dosage adjsutement of 10mg q24h for patients with moderate or severe renal impairment is still recommened to protect patients from potential risks.

Both amiodarone and dronedarone are CYP3A4 and P-gp inhibitors, and neither were evaluated for interaction with rivaroxaban *in vivo* before [10]. Cheong et al has predicted that co-administered amiodarone loading dose (200mg q8h for 3days) would increase the AUC of rivaroxaban by 1.61-fold among patients with moderate renal impairment, based on PBPK modelling [29]. In contrast, dronedarone has demonstrated a smaller impact on rivaroxaban with 1.25-fold increase in AUC with the same population. Consistently, amiodarone and its active metabolite have demonstrated higher inhibitory potencies on hepatic and gut CYP3A4 and P-gp efflux in vitro [16]. Taken together, dronedarone has exhibited a smaller DDI potential than amiodarone when rivaroxaban is the victim drug.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, despite the impact on drug elimination, renal impairement is an independent risk factor of bleeding events due to pathological changes in coagulation systems [30, 31], which would lead to an under-prediction of major bleeding risks among population with moderate and severe renal impairment in

the current study.Therefore, 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 rivaroxaban or apixaban. The established PBPK model of dronedarone was well validated with previously reported DDI studies. According to the established model, a reduced dosing regimen of 3.75mg q12h was recommended for apixban when patients with normal or impaired renal function were co-administered with dronedarone. A reduced dosing regimen of 10mg q24h was recommened for rivaroxban when patients with moderate or severe renal impairment were co-administered with dronedarone.

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CRediT author statement

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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Tables

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)	[14]
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)	[14]
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)	[14]
Digoxin	/	Repeated oral administration of digoxin 0.25mg q24h alone	10days	/	[32]
	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)	[14]
Dabigatran	Dronedarone	Single dose of 150 mg dabigatran etexilate alone or in combination with a single dose of 400 mg dronedarone	48hour	NCT01306162	[9]

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[13]
Hematocrit (%)	45	Simcyp library
B:P ratio	1	
f_{up}	0.003	Djebli et al[13]
Absorption parameters		
ADAM model		
fa; *Ka* (h^{-1})	0.898; 0.816	Djebli et al[13]
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 [13]
Elimination parameters		
Clearance type	Enzyme kinetics	
In vitro metabolic system	Recombinant	
rhCYP3A4		
Vmax (pmol/min per pmol)	13.7	Djebli et al [13]
KM (mM)	4.2	
fu_{mic}	0.003	Sensitivity analysis
rhCYP3A5		
Vmax (pmol/min per pmol)	4.87	Djebli et al [13]
KM (mM)	3.1	
fu_{mic}	0.003	Sensitivity analysis
Additional liver clearance		
Cl_{int}(l/min per mg)	40	Djebli et al [13]

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 [17]
K_{app} (μM)	0.87	1.0	
k_{inact} (h^{-1})	2.34	0.2	
fu_{mic}	/	0.003	
CYP2J2 (RI)			Cheong et al [16]
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 [16]
K_i (μM)	0.68	0.1	

Note: fu_{mic}: fraction of unbound drug in the in vitro incubation; K_{app}: concentration of mechanism-based inhibitor associated with half-maximal inactivation rate; k_{inact}: inactivation rate of the enzyme; K_i: concentration of inhibitor that supports half-maximal inhibition; MBI: mechanism-based 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						
observation	10.7	34.4	38.6	126	3.75	3.90
prediction	6.73	29.4	29.2	155	4.34	5.28
fold error	1.59	1.17			1.16	1.35
Verapamil						
observation	135	895	188	1310	1.42	1.48
prediction	76.8	1049	136	2042	1.78	1.95
fold error	1.76	1.17			1.25	1.32
Digoxin						
observation	1.32	12.5	1.71	18.0	1.75	1.44
prediction	1.31	17.3	2.34	25.7	1.79	1.48
fold error	1.01	1.38			1.02	1.03
Dabigatran						
observation	149	1160	282	2520	1.89	2.17
prediction	111	1950	310	4342	2.80	2.23
fold error	1.34	1.68			1.48	1.03

Table 5. Simulated exposure changes of anti-coagulant with dronedarone co-administration in AF patients without co-morbiditiesfor 14 days

Oral Anti-coagulant	Dosing regimen	C_{max} (mg/L)	AUC_{24h} (mg·h/mL)	C_{max} ratio	AUC_{24h} ratio
Rivaroxaban	20mg q24h	0.14	1.53	/	/
Rivaroxaban + DDE	20mg q24h	0.17	1.88	1.15	1.23
Apixaban	5mg q12h	0.11	2.14	/	/
Apixaban + DDE	5mg q12h	0.16	2.9	1.45	1.36
Apixaban + DDE	3.75mg q12h	0.12	2.14	1.09	0.99
Apixaban + DDE	2.5mg q12h	0.08	1.42	0.73	0.66

Note: DDE, dronedarone. Dosage of co-administered dronedarone was 400mg q12h.

Figure legends

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, 5^{th} percentile, and 95^{th} 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

Figure 6. Estimated median bleeding risk of apixaban based on simulated AUC_{24h} for AF patients with or without concomitant dronedarone. The dashed horizontal lines are the bleeding risk of reference regimen for each population. The box-and-whisker plots show the distribution of model-predicted risk of major bleeding in different population. AUC indicates area under the plasma concentration-time curve of apixaban for 24 hours under steady state; DDE stands for dronedarone.

Figure 7. Estimated median bleeding risk of rivaroxaban based on simulated AUC_{24h} for AF patients with or without concomitant dronedarone. The dashed horizontal lines are the bleeding risk of reference regimen for each population. The box-and-whisker plots show the distribution of model-predicted risk of major bleeding in different population. AUC indicates area under the plasma concentration-time curve of rivaroxaban for 24 hours under steady state; DDE stands for dronedarone.

Figures

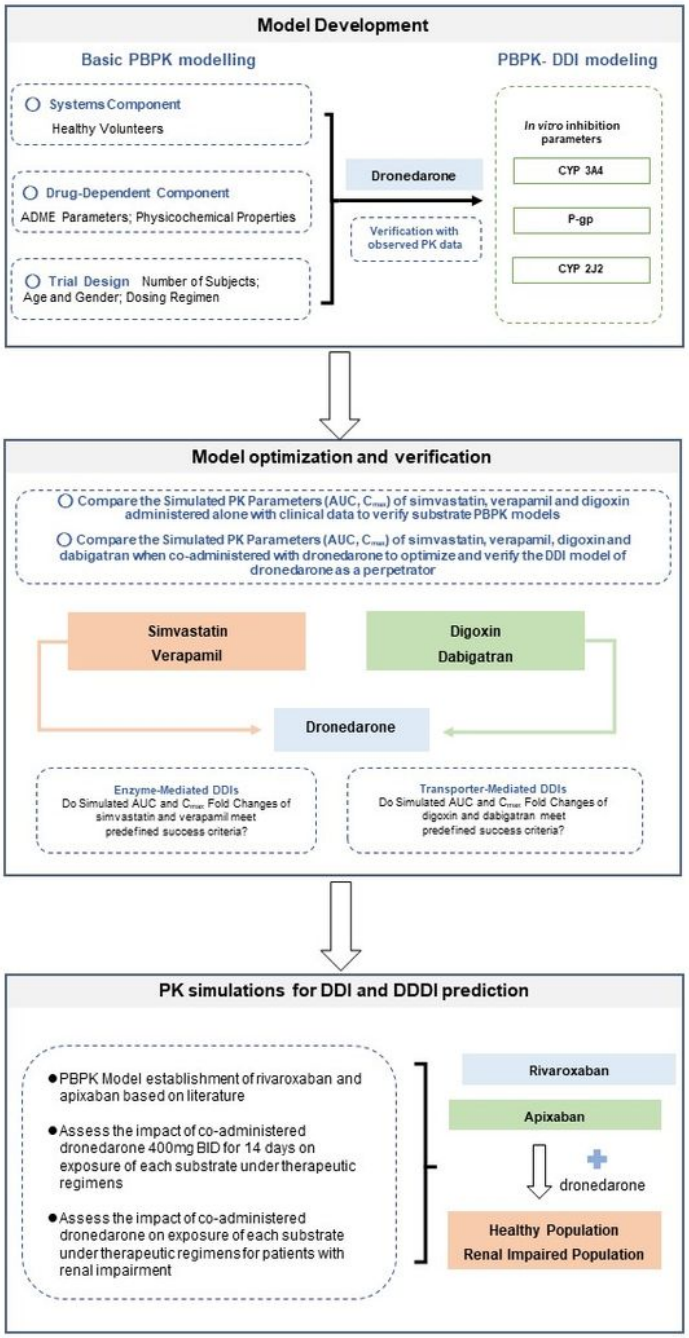

Figure 1

General approach and workflow of the presented study

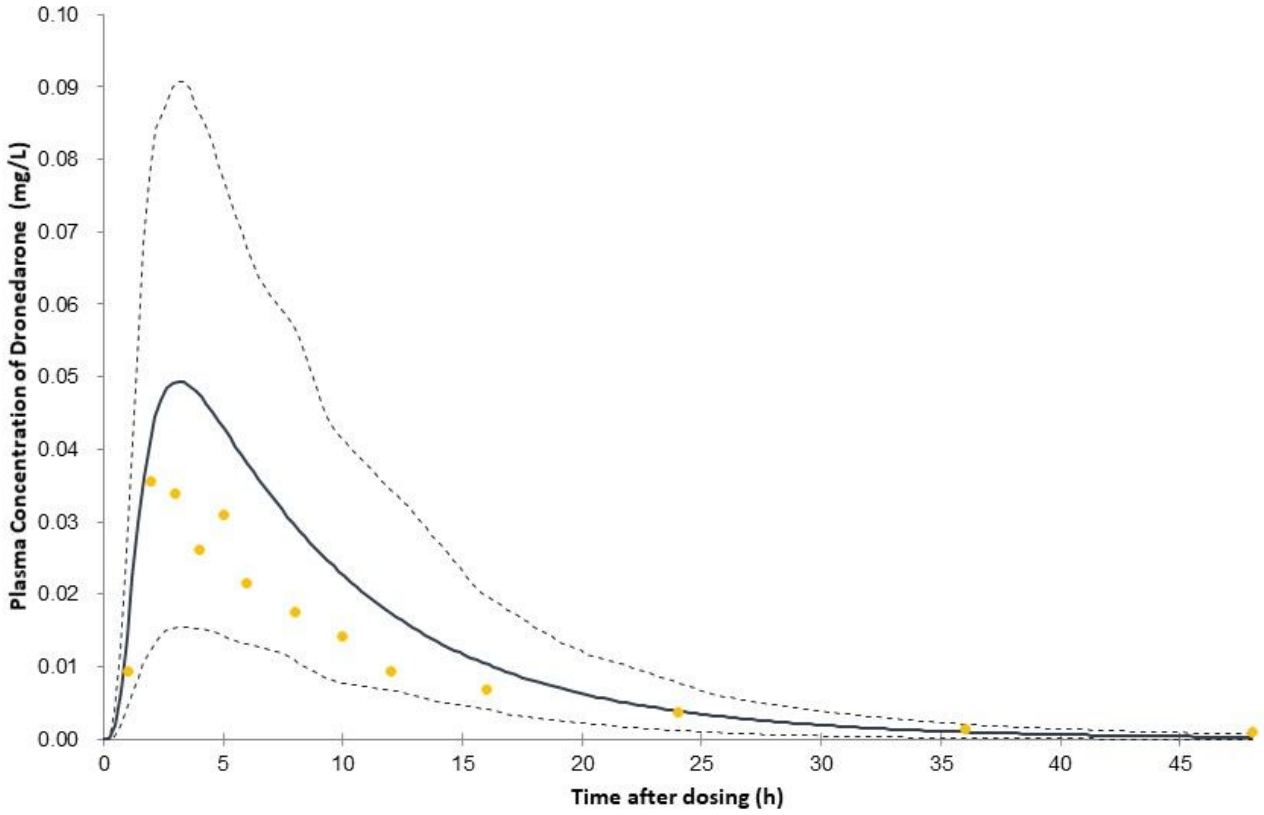

Figure 2

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.

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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.

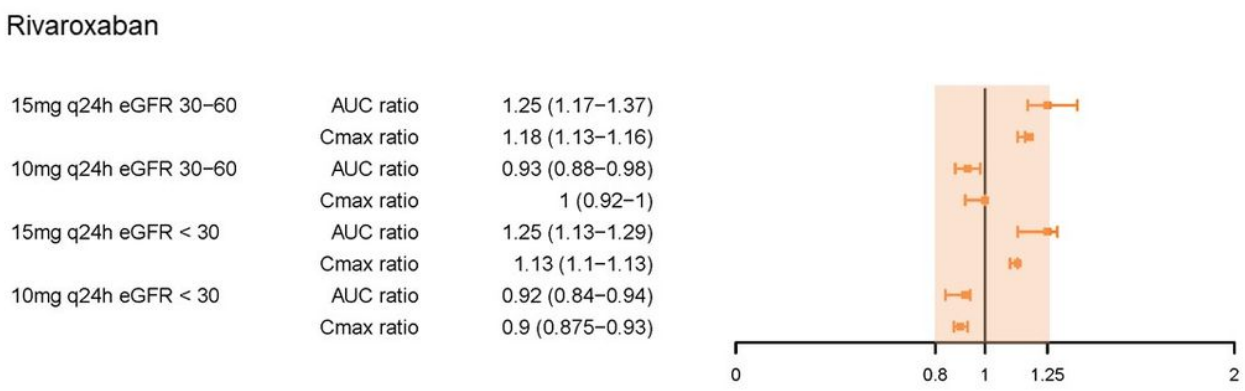
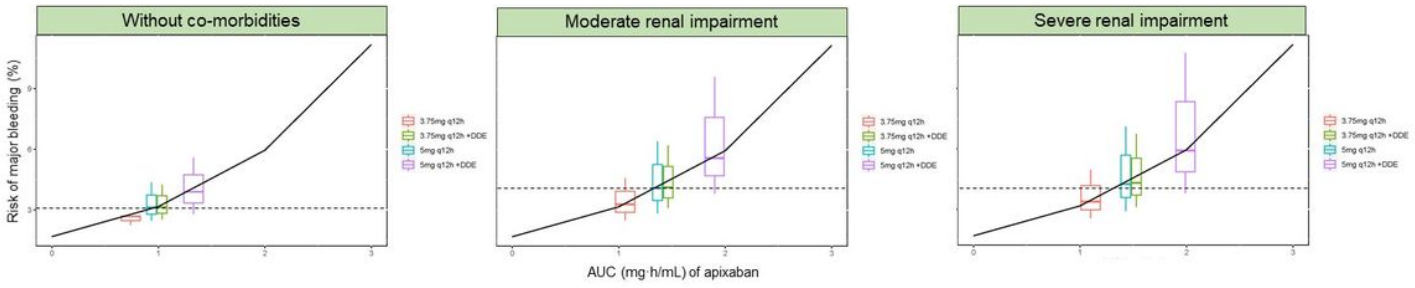


Figure 5

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



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Estimated median bleeding risk of apixaban based on simulated AUC_{24h} for AF patients with or without concomitant dronedarone. The dashed horizontal lines are the bleeding risk of reference regimen for each population. The box-and-whisker plots show the distribution of model-predicted risk of major bleeding in different population. AUC indicates area under the plasma concentration-time curve of apixaban for 24 hours under steady state; DDE stands for dronedarone.

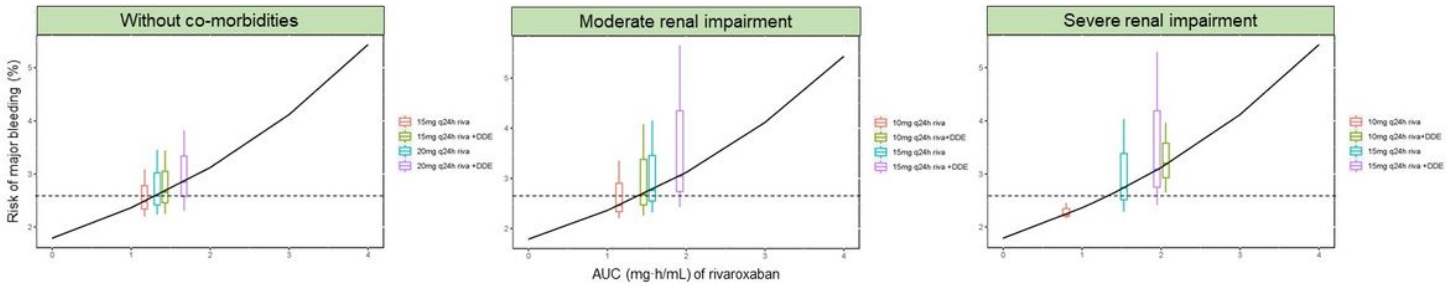

Figure 7

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