Population Pharmacokinetic Models for Direct Oral Anticoagulants: A Systematic Review and Clinical Appraisal Using Exposure Simulation

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Available data have shown an association between direct oral anticoagulant (DOAC) plasma concentration and clinical, particularly bleeding, events. Factors that may influence DOAC plasma concentration are therefore the focus of particular attention. Population pharmacokinetic (PopPK) analyses can help in identifying such factors while providing predictive models. The main aim of the present study was to identify all the PopPK models to date for the four most frequently used DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban). The secondary aim was to use these models to simulate different DOAC plasma concentration–time profiles in relevant clinical scenarios. The results of our model-based simulations confirm the clinical relevance of the known major factors influencing DOAC exposure and support the current approved dose adaptation, at least for atrial fibrillation. They also highlight how the accumulation of covariates, not currently considered for dose adaptation due to their seemingly minor influence on DOAC exposure, lead to supratherapeutic blood concentrations and could thus enhance the risk of major bleeding. The present results therefore question DOAC dose adaptation in the presence of these covariates, such as drug–drug interaction or genotypes, alongside the known existing covariates. As the overall effect of accumulation of several covariates could be difficult to apprehend for the clinicians, PopPK modeling could represent an interesting approach for informed precision dosing and to improve personalized prescription of DOACs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Available data have shown an association between direct oral anticoagulant (DOAC) plasma concentration and clinical events, particularly bleeding events. DOAC dose adaptations are available only for a limited number of covariates that may influence the DOAC plasma concentration.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Do existing population pharmacokinetic (PopPK) models help identify other relevant covariates to be considered for DOAC dose adaptation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ PopPK model-based simulations have identified several and diverse covariates, such as drug–drug interactions (DDI), having a significant effect on DOAC exposure, although they are not or almost not considered for dose adaptation. Most of these covariates have minor to moderate effects on DOAC exposure when taken individually but can have a cumulative effect leading to a risk of overexposure.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Poorly considered covariates, such as DDI or genotypes, should receive more attention in DOAC dose adaptation. PopPK modeling could represent an interesting tool for informed precision dosing in the presence of several covariates as the sum of these could be difficult to apprehend in clinical practice.

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Direct oral anticoagulants (DOACs) have become the treatment of choice for the prevention and treatment of venous thromboembolism (VTE) in both neoplastic and non-neoplastic contexts and for the prevention of thromboembolism in patients with atrial fibrillation (AF).[1,2] No required blood monitoring has been recognized as a major benefit when these molecules were compared with vitamin K antagonists. However, when DOACs are used in real-world conditions and populations, outside of the stringent framework of clinical trials, substantial interindividual variations in plasma concentrations can be observed for the same dose, leading to the consideration of dose adjustment in individuals outside of standard risk groups.[3] There is growing evidence of an association between DOAC exposure and clinical, particularly bleeding, events which are more frequently observed in patients with higher DOAC exposure.[4]

Factors that may influence DOAC blood exposure are therefore the focus of a growing body of research. Population pharmacokinetic (PopPK) analyses have the ability to identify such factors as they use both clinical data and routinely measured drug concentration.[5,6] PopPK models aim at accurately describing the drug population mean pharmacokinetic (PK) parameters and their variability as well as the effect size of covariates.[6] They are, therefore, very useful for predicting drug exposure in clinically relevant scenarios, such as drug interactions, renal failure, extreme body weight, or age.[7,8] Such PopPK models are also used in Bayesian therapeutic drug monitoring tools for dosage individualization requiring complex calculations, achieved by dedicated software.[9] This approach has already been successfully used in various fields, such as infectiology or oncology, but a wider expansion in clinical practice should be foreseen.[10–12]

The present study aimed at identifying the available PopPK models for the four most prescribed DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban). These models were then used to simulate DOAC exposure in different relevant clinical scenarios to evaluate the validity of the current recommendations for dose adjustment. This study focuses on DOAC safety issues in relation to overexposure and bleeding risk. The question of efficacy is not addressed.

METHODS

Literature review of the PopPK models

A systematic search was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The following keywords were used for the PubMed search: "population pharmacokinetic model" OR "PopPK" OR "nonlinear mixed effect model" AND "doac" OR "noac" OR "rivaroxaban" OR "edoxaban" OR "apixaban" OR "dabigatran." The following keywords were used for the EMBASE search: "population pharmacokinetic model" OR "PopPK" OR "nonlinear mixed effect model" AND "doac" OR "noac" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban." For the CENTRAL search, the following keywords were used: "population pharmacokinetic model" AND "dabigatran"; "population pharmacokinetic model" AND "rivaroxaban"; "population pharmacokinetic model" AND "apixaban"; "population pharmacokinetic model" AND "edoxaban." The following exclusion criteria were applied: duplicate studies, PopPK model duplicates (a study using an already developed PopPK model), nonparametric models or models that are not based on nonlinear mixed effect, and purely pharmacodynamic population models. The literature search was performed on articles published up to October 2020. The search stopped in October 2020 in order to start the simulations.

The formulation used (p.o. or .i.v), the aim of the study, the number of patients, the origin of the data set, as well as type (healthy, patients with AF or VTE, and patients with VTE thrombophylaxis) and demographic characteristics of the subjects used for the model were collected. Final model characteristics (e.g., number of compartments, absorption and elimination order, and PK parameters estimates) including the significant covariate effects were also retrieved. The method of validation was considered as internal if the study used the same or split data set for model development and validation, and as external if the model was validated on a true external population. Descriptive statistics were conducted in using STATA version 14.2 (StataCorp LLC, College Station, TX, 2016).

Model-based simulations of drug exposure

All models with available and explicit equations for clearance calculation together with clearance interindividual variability (IIV) explicitly and correctly given were selected. A table summarizing the quality assessment of the models used for the simulations can be found in the **Table S1**. In brief, an arbitrary qualitative score (high, medium, and low) was established by consensus for each of the following criteria: phases of clinical trials, population size, number of blood sample/patient, PopPK results description, relevancy of covariates tested by the model, appropriateness of internal validation, and presence of an external validation.

Monte Carlo simulations of 1,000 individuals with selected demographic/clinical characteristics were performed using the R software (version 4.0.6) based on the reported equations and the model-specific IIV to compute drug apparent clearance (CL/F) and exposure (area under the curve (AUC)) using the following equation:

$$\mathrm{AUC} = \frac{D}{\mathrm{CL/F}}$$

where D is the administered standard dose, CL/F the apparent clearance (i.e., true drug clearance divided by its bioavailability) directly estimated by the PopPK models.

A uniform distribution was assumed for age, sex, body weight, and creatinine clearance for their inclusion in the simulations. Stratification of the degree of renal impairment was performed according to creatinine clearance (CrCL) and literature ranges used for dose adjustments: normal renal function (130–50 mL/minute), moderate (49–30 mL/minute), and severe (29–15 mL/minute) renal impairment. End-stage renal disease was not included in the analyses because of the lack of sufficient relevant data. For the other variables, two distribution ranges were considered: 40–79 and 80–100 years for age and 40–59 and 60–120 kg for bodyweight. For each study, exposure was normalized to a typical patient with a CrCL of 100 mL/minute without concomitant treatments, assessed with the Cockroft-Gault (CG) formula.[14] The recommended on-label dosages were used as the reference dosages for clinical scenario simulations.

RESULTS

PopPK models

A total of 74 and 24 studies were identified through PubMed and EMBASE/CENTRAL, respectively, of which 35 were retained for the analysis after applying previously defined exclusion criteria (**Figure 1**).

Over half of the models (51%; **Tables S2–S5**) were originally developed for descriptive purposes, whereas 49% tested a specific hypothesis. The main objectives of the studies were exposure-response analysis (11.0%), dose selection validation (9.0%), drug–drug interaction (DDI; 9%), effect of body weight on exposure (6.0%), pharmacogenomics (5.7%), effect of food on exposure (2.9%), pediatric analyses (2.9%), and exposure analysis before percutaneous coronary intervention (2.9%). The number of subjects included in the models was highly variable (range: 7–10,522

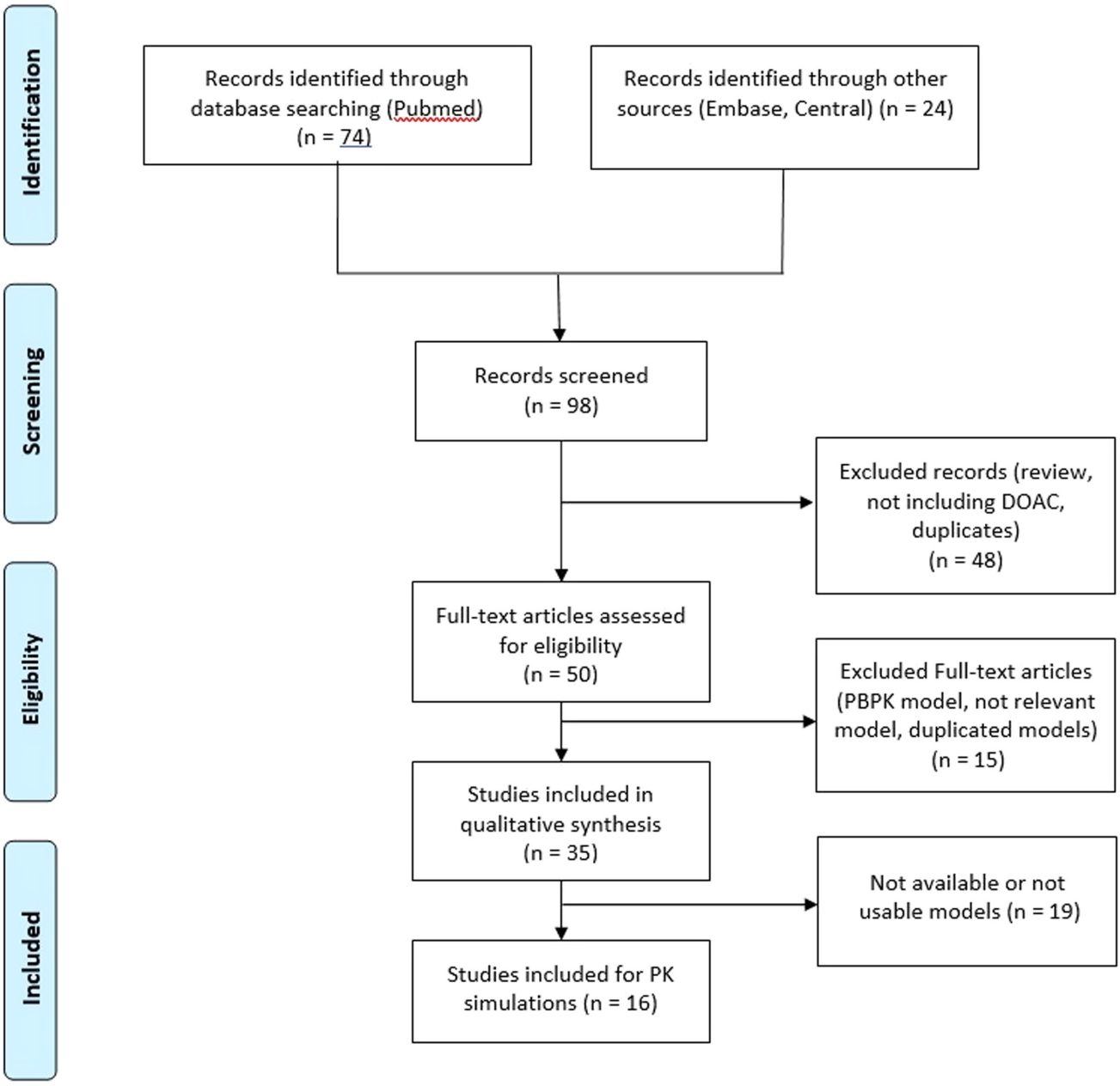

Figure 1 Flow chart of the study. DOAC, direct oral anticoagulant; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic.

patients). Only 8.6% of these models were externally validated, whereas the remaining 91.4% were internally validated. Most of the models included a mix of phase I to III studies (34.3%) followed by outpatients from postmarketing studies (14.3%), phase I studies (14.3%), phase II studies (14.3%), phase III studies (11.4%), inpatients form postmarketing studies (5.7%), and a mix of in- and outpatients from postmarketing studies (5.7%). Studies included subjects with a variety of conditions: mostly AF (34.3%), mixed populations of AF and VTE (20.0%), VTE prophylaxis (14.3%), healthy volunteers or VTE (11.4% each), patients with end-stage renal disease (5.7%), and acute coronary syndrome (2.9%).

Median ages ranged from 0.5 to 97 years (**Tables S6–S9**). Between 12 and 52.9% of women were included in the studies. Weight ranged from 6.2 to 223 kg. Half of the studies included White or predominantly White subjects, 31.0% of diverse ethnicities, 15.0% Asian-Japanese (mostly for edoxaban), and 4% Asian subjects (undetermined). Only a few studies ($n = 5$) reported hepatic enzymes. CrCL estimated according to CG equation[14] ranged from 21.8 to 130 mL/minute.

Models included a relatively high number of samples per patients (range: 1–44) and most were best described by a two-compartment model with first-order elimination for edoxaban (100% of the studies), dabigatran (83.0%), and apixaban (75.0%). Rivaroxaban was mostly best described by a one-compartment model (81.0%; **Tables S10–S13**). The dabigatran median CL/F estimate for a typical patient ranged from 12.4 to 111.0 L/h with an IIV ranging from 40.4 to 108.6% (**Table S14**). CL/F for the other molecules was more consistent across studies (**Tables S15–S17**): rivaroxaban median CL/F ranged from 4.4 to 9.2 L/h (IIV from 17.4 to

80.8%), apixaban median CL/F ranged from 3.1 to 4.4 L/h (IIV from 14.1 to 33.1%), and edoxaban median CL/F ranged from 11.4 to 36.0 L/h (IIV from 9.4 to 20.1%). Population estimates for the other PK parameters are summarized in **Tables S14–S17**.

Significant covariates on CL/F are detailed in **Tables S18–S21** and in **Tables S22** and **S33** for other PK parameters. As expected, CrCL or serum creatinine was found to be the main covariate influencing CL/F for the four molecules (50.0% of the studies for dabigatran, 75.0% for rivaroxaban, 50.0% for apixaban, and 63.0% for edoxaban). Age (only in 33.0% of dabigatran studies and 38.0% of rivaroxaban studies) was identified as a significant and independent covariate inversely correlated with CL/F. Body weight was observed to impact CL/F in only one rivaroxaban study[15] but affected non-renal apparent clearance in one study involving edoxaban.[16] Weak/moderate CYP3A4/5 or P-glycoprotein (P-gp) inhibitors were found to decrease CL/F in 12.5% of the rivaroxaban models, strong CYP3A4/5 or P-gp inhibitors in 50.0% of apixaban models, and moderately strong P-gp inhibitors in 22.0% of edoxaban models. However, no dabigatran models neither found nor studied the association with P-gp inhibitors. Only one rivaroxaban model found a significant effect of CYP3A4/5 inducers.[15] In addition, two models studied genotypes as a covariate. A rivaroxaban model[17] reported a correlation between ABCB1 expression and CL/F, whereas an apixaban model[18] described an increase in CL/F associated with the *CYP3A5*1/*1* vs. *CYP3A5*1/*3* or **3/*3* genotype and *ABCG2 421C/C* or *C/A* genotype vs. *ABCG2 421A/A* genotype.

Interestingly, in 33.3% of dabigatran, 12.5% of edoxaban, and 6.3% of rivaroxaban studies, a decreased CL/F was observed in women when compared with men. AF was found to negatively impact CL/F when compared with the VTE population in a study involving rivaroxaban.[15] Two apixaban studies found ethnicity to be of influence[19,20] suggesting a decrease in CL/F in Asian vs. non-Asian individuals. Hematocrit was seldomly reported to correlate positively with CL/F in two rivaroxaban models.[15,21] One study found an association between concentrations of fasted serum gastrin and CL/F for dabigatran.[22] Interestingly, in a single small study, an increase in alanine aminotransferase (ALT) was found to be associated with a decrease in CL/F for rivaroxaban.[23]

Model-based simulations

Quality criteria for rating of PopPK models used for the simulation can be found in **Tables S34–S37**. All quality criteria are medium to high for dabigatran and edoxaban except for the trial phases criteria, as all the models are based on populations from premarketing studies. With the exception of the number of blood samples per patient, rivaroxaban models have medium to high ratings for all the criteria. The two apixaban models scored medium to high for all the quality criteria.

As already mentioned in the Methods, all models used for the simulation qualify for having an explicit and clear equation allowing to calculate the clearance and results with clearly indicated IIV for this covariate. **Figures 2–5** show the simulations performed for the four studied molecules, using 16 of the 35 identified published PopPK models with available and usable equations (unusable equations being those with, for example, no available or observed IIV for clearance, blood urea nitrogen used for renal function instead of CrCL)—2 for Apixaban, 5 for edoxaban, 3 for dabigatran, and 6 for rivaroxaban. The reported available equations for the AUC simulations can be found in **Data S1–S4**. Tables where the mean increases in AUC and confidence intervals are detailed for each model and different covariates can be found in **Tables S38–S41**.

Dabigatran

Severe renal insufficiency consistently increased dabigatran exposure by a factor of 2.34–4.41 times (range from different studies), both with the reduced dosage of 110 mg b.i.d. and with the dosage of 75 mg b.i.d. (2.49 times; **Figure 2**). This was compared with a standard dose of 150 mg b.i.d. in patients with normal renal function. We also observed a 1.80–2.77 times increase in dabigatran exposure with the reduced dosage of 110 mg b.i.d. in moderate renal insufficiency. The large study of Dansirikul (n = 2045) suggested an additional independent influence of P-gp inhibition and age.[24] Interestingly, these two factors seem to have a modest effect on dabigatran elimination when taken independently (2.20–2.89 and 2.07–2.70 times increase, respectively, and depending on the severity of renal insufficiency), but a combination of the two can lead to a greater increase in drug exposure (of 2.53–3.32 times) in patients with moderate/severe renal impairment, even at a reduced dosage. Gastrin concentrations = 69 pmol/L (indicating increased gastric pH) led to a decrease of 10–27% (more pronounced effect for patients with severe renal impairment) in dabigatran exposure in a population using DOACs for thrombophylaxis after surgery.

Rivaroxaban

Moderate renal dysfunction leads to an increase in rivaroxaban blood concentrations (1.33–1.63), compared with normal renal function for the standard dosage and including patients with VTE (**Figure 3**).

The reduced rivaroxaban dosage (15 mg q.d.) limits this increase for moderate but not for severe renal insufficiency (1.33–1.64 times). We observed a slight increase (1.26 times) in exposure in the presence of a strong CYP3A4/5 and P-gp inhibitor in the largest study,[15] whereas P-gp inhibition was associated with an almost 1.52 times increase in rivaroxaban exposure according to another smaller study.[23] A small 96 patients study showed a 5- to 10-fold increase in ALT values was associated with a 1.49–1.90 times increase in exposure, respectively.[23] In the same study, the concomitant presence of a P-gp inhibitor and an elevation of ALT values can lead to an increase of 2.45 times in exposure in patients with a moderate renal insufficiency and a reduced 15 mg dosage.

Apixaban

The impact of renal function on apixaban exposure is depicted in **Figure 4**.[25] A dosage of 5 mg b.i.d. only modestly increased the exposure of the drug (1.36-fold) in the presence of a moderate renal function, based on the estimation based on the data from the study by Ueshima *et al.*,[18] this, however, is with a large confidence interval associated to a high IIV. A reduced dosage of 2.5 mg b.i.d. in the presence of a moderate renal insufficiency leads to a 32% decrease in exposure compared with a 5 mg b.i.d. regimen given to patients with normal renal function. CYP3A5*1/*3 or *3/*3 and ABCG2 421A/A genotypes lead to an increase in apixaban exposure of 1.36 times and 1.30 times,

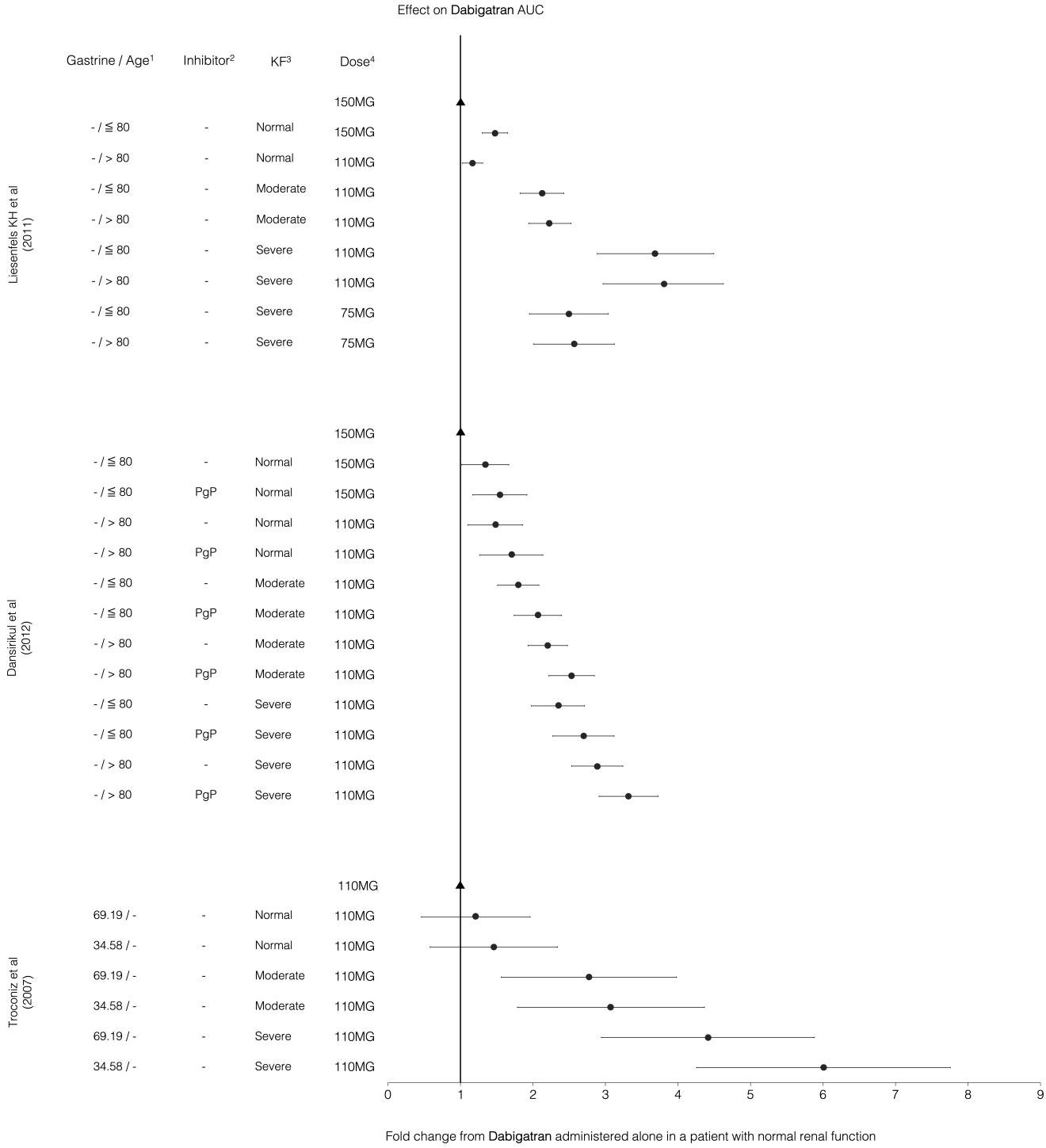

Figure 2 Simulation for dabigatran AUC. Black dots represent the mean simulated AUC normalized to the AUC calculated for a patient with a kidney function of 100 mL/minute and a standard dosage. Covariates used for the simulations: (1) Gastrin plasma concentrations in pmol/L or age in years; elevated gastrin concentrations indicate low gastric acid secretion, resulting in increased gastric pH. (2) P-gp inhibitor. (3) Kidney function according to Cockcroft and Gault in mL/minute. Normal: 50–130 mL/minute. Moderate: 30–49 mL/minute. Severe 15–29 mL/minute. (4) Dose of dabigatran. AUC, area under the curve, KF, kidney function.

respectively, and a cumulative effect can be observed with the combination of the two and/or the presence of renal impairment.[18] For instance, apixaban exposure is doubled (2.56-fold) in patients with a moderate reduction in renal function and the presence of both unfavorable genotypes. Based on data from the study by Leil *et al*., we found that age had a modest effect in patients receiving apixaban for thrombophylaxis.[26] This effect is more pronounced beyond the age of 80 years and the increase in renal insufficiency (up to a 1.81-fold increase in exposure for a 90-year-old patient with a severe renal insufficiency).

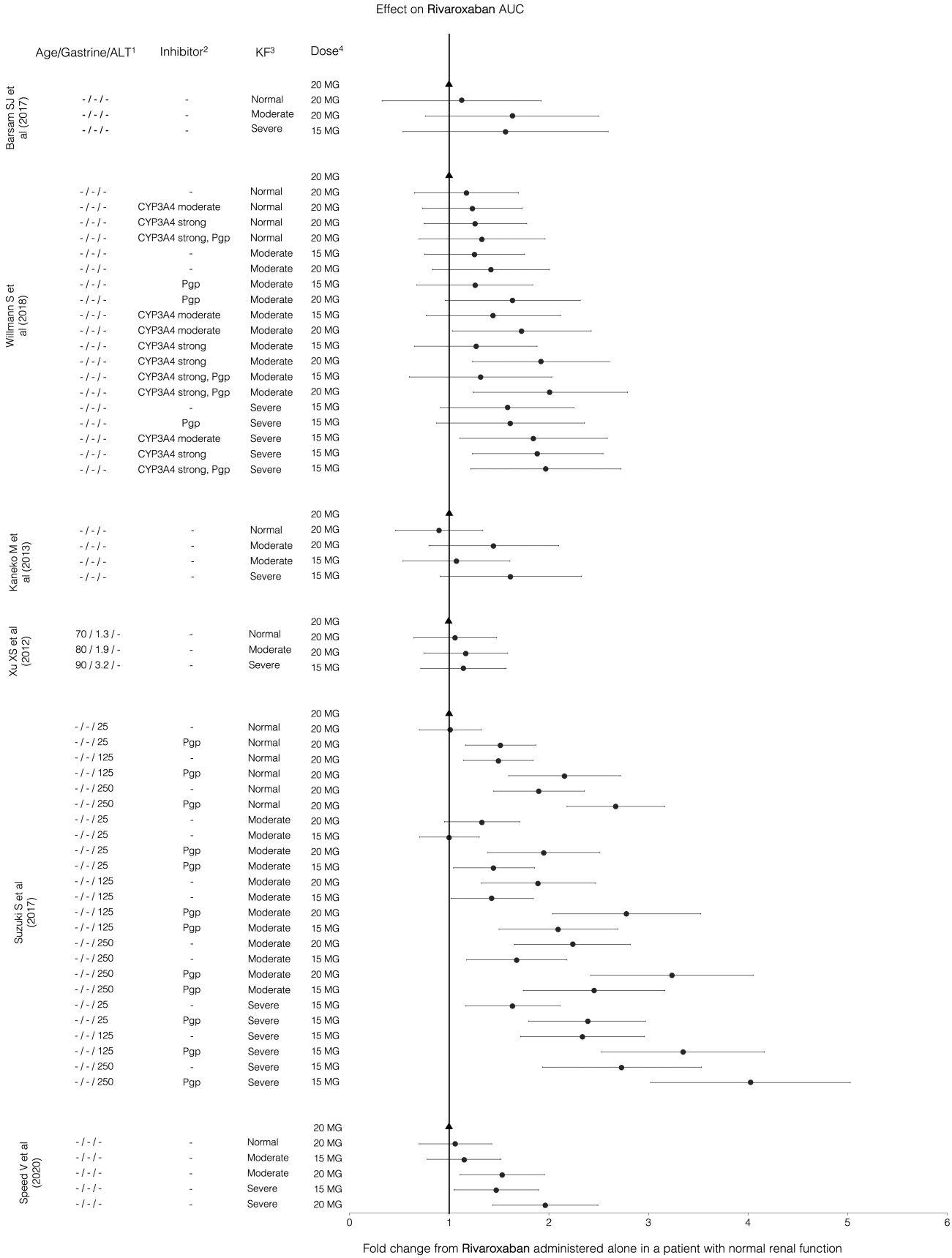

Figure 3 Simulation for rivaroxaban AUC. Black dots represent the mean simulated AUC normalized to the AUC calculated for a patient with a kidney function of 100 mL/minute and a standard dosage. Covariates used for the simulations: (1) Age in years/creatinine in mg/dL/ALT in IU/L. (2) Presence of a P-gp inhibitor or/and moderate/strong CYP3A4/5 inhibitor. (3) Kidney function according to Cockcroft and Gault in mL/minute. Normal: 50–130 mL/minute. Moderate: 30–49 mL/minute. Severe 15–29 mL/minute. (4) Dose of rivaroxaban. ALT, alanine aminotransferase; AUC, area under the curve, KF, kidney function.

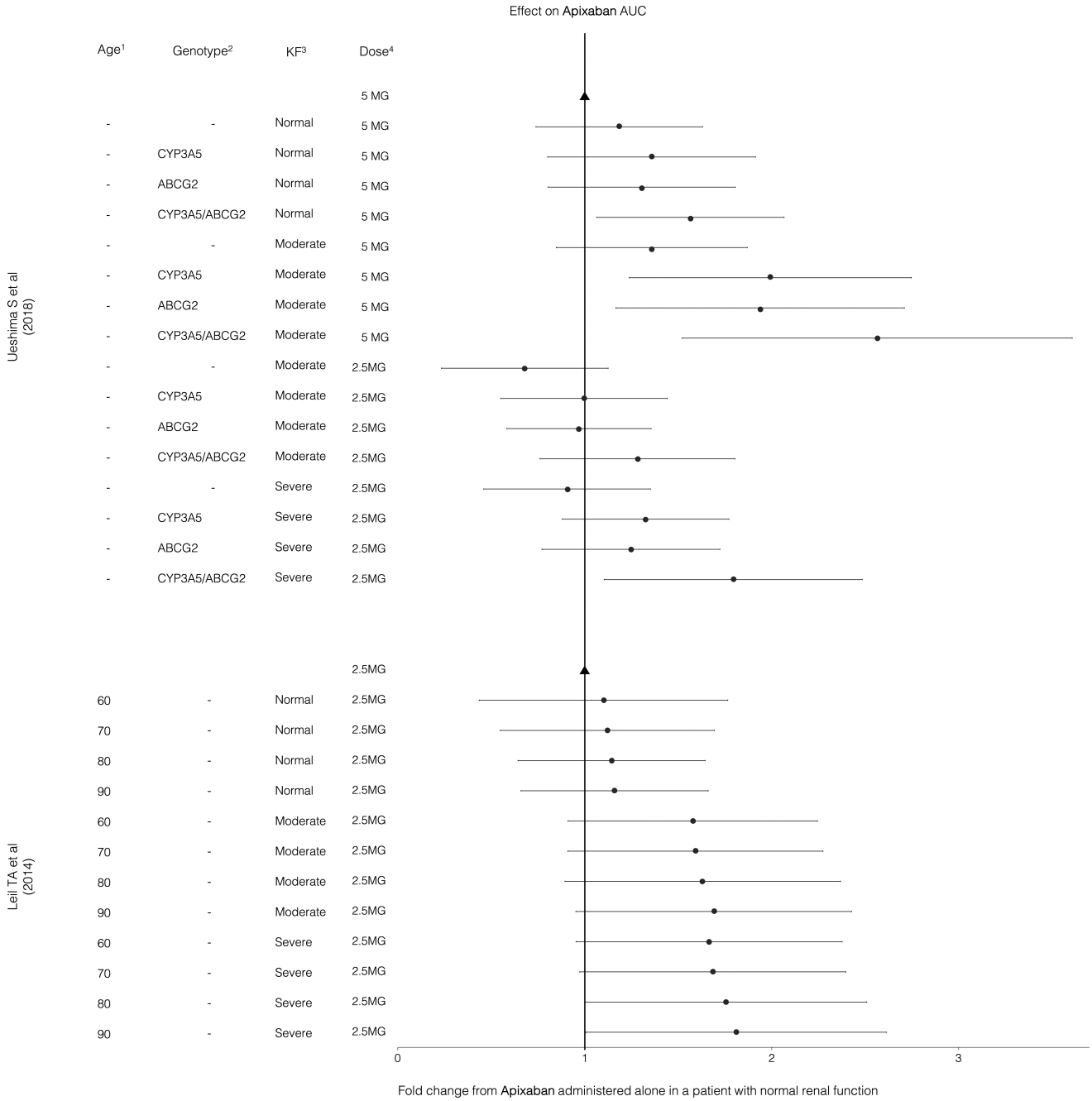

Figure 4 Simulation for apixaban AUC. Black dots represent the mean simulated AUC normalized to the AUC calculated for a patient with a kidney function of 100 mL/minute and a standard dosage. Covariates used for the simulations: (1) Age in years. (2) Presence of CYP3A5*1/*3 or *3/*3 or/and ABCG2 421A/A genotypes. (3) Kidney function according to Cockcroft and Gault in mL/minute. Normal: 50–130 mL/minute. Moderate: 30–49 mL/minute. Severe 15–29 mL/minute. (4) Dose of apixaban. AUC, area under the curve, KF, kidney function.

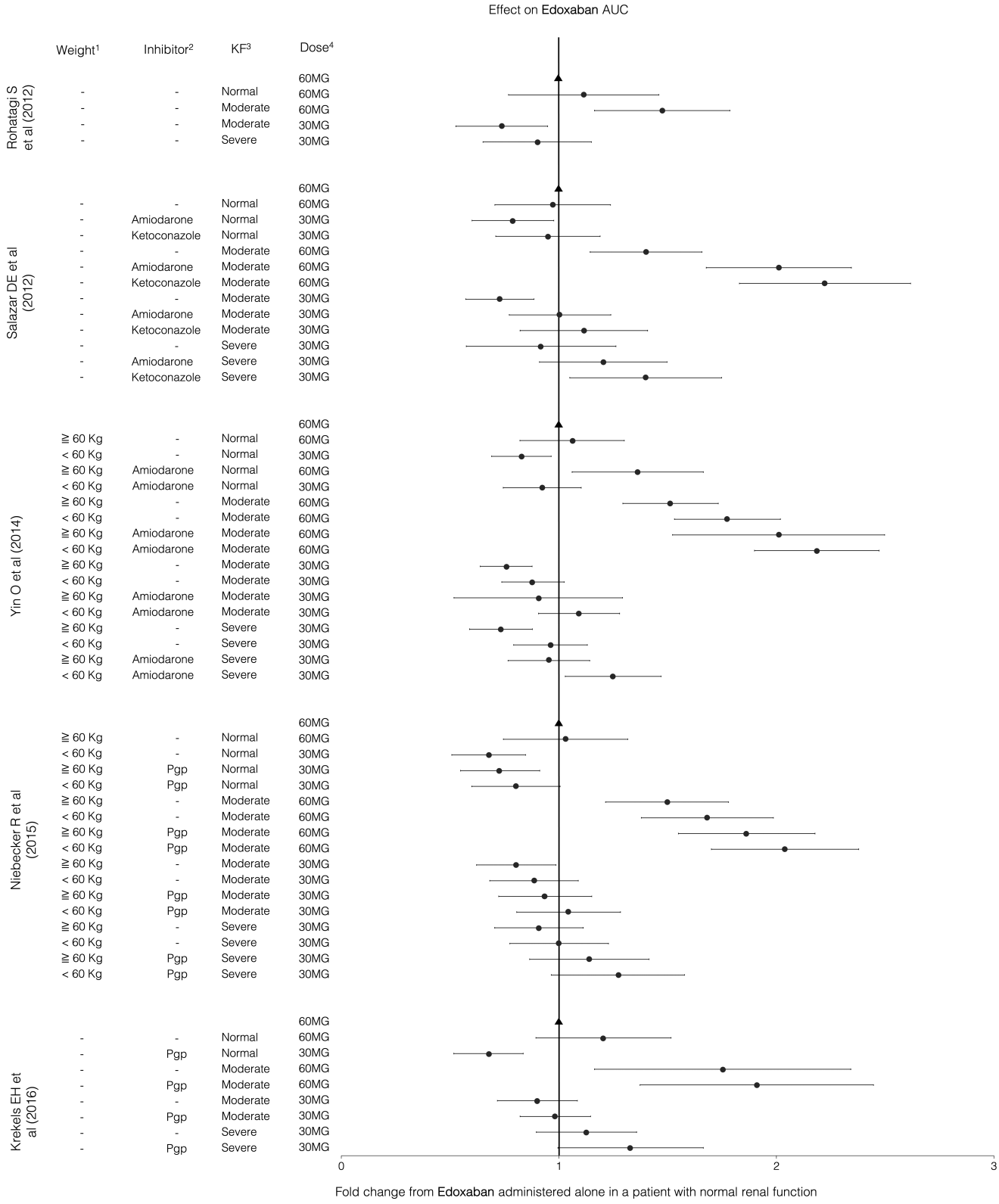

Figure 5 Simulation for edoxaban AUC. Black dots represent the mean simulated AUC normalized to the AUC calculated for a patient with a kidney function of 100 mL/minute and a standard dosage. Covariates used for the simulations: (1) Weight: < 60 or ≥ 60 kg. (2) Presence of ketoconazole, amiodarone, or P-gp inhibitor. (3) Kidney function according to Cockcroft and Gault in mL/minute. Normal: 50–130 mL/minute. Moderate: 30–49 mL/minute. Severe 15–29 mL/minute. (4) Dose of edoxaban. AUC, area under the curve, KF, kidney function.

Edoxaban

Simulations from several studies showed that moderate renal insufficiency or the presence of P-gp inhibitors consistently led to an increase of 1.24–1.75 times in edoxaban exposure when administered with a dosage of 60 mg (**Figure 5**). A 50% dosage reduction leads to a decrease approaching 30% of the AUC in the presence of only one of the above-mentioned factors. Only the concomitant presence of at least two risk factors allowed edoxaban exposure to approach the exposure observed with a typical patient. The reduced dosage is resilient to accumulation of covariates because simultaneous presence of the three risk factors (P-gp inhibitor, moderate renal insufficiency, and weight below 60 kg) leads to a very slight increase in edoxaban AUC with the 30 mg dosage (1.04–1.09 times). Based on the simulation from Salazar *et al*. (2012),[27] the increase is slightly larger in the presence of ketoconazole compared with amiodarone (0.10–0.20 times in absolute difference depending on the degree of renal insufficiency).

DISCUSSION

PopPK studies are becoming a prerequisite for drug registration with regulatory agencies, as they allow the quantification of variability among patients and the identification of relevant covariates influencing drug exposure, guiding dose selection, and adaptation in specific clinical scenarios.[7] This approach is additionally used in postmarketing to confirm these findings and/or to find new factors not accounted for during drug development phases.[9] However, application of this methodology has not yet commonly been applied to DOACs in postmarketing studies, with only one-third of postmarketing studies identified in the present study. The rare models built from real-world data have small study sample sizes, and are thus unlikely to have the significant number of patients with covariates of interest to be studied.

Despite similarities in the metabolism, distribution, and/or bioavailability of the various DOACs[25] (e.g., P-gp for edoxaban and dabigatran, and P-gp/CYP3A4/5 for rivaroxaban and apixaban), wide disparities for dose adaptation have been proposed, based primarily on the indication (VTE vs. AF). Our literature review showed an effect of CL/F on the population studied, with a reduction of this PK parameter in patients with AF vs. patients with VTE but only in studies involving rivaroxaban[15] and edoxaban.[28,29] Differences in demographics and comorbidities between the two populations are, however, not so obvious,[30] raising questions about the difference in dose adaptation for these two populations.

In patients with AF, dose adaptation for DOACs starts from < 50 mL/minute of CrCL with the exception of apixaban, which needs a second covariate (> 80-year-old or < 60 kg) in addition of a creatinine blood concentration of > 133 µmol/L for dose adaptation to be applicable.[31] This is in line with our simulations, which mostly showed an increase of a minimum of 1.5-fold in exposure for all the DOACs except apixaban. Weight was barely observed as an independent factor influencing CL/F and thus DOAC exposure, probably partially explained by the collinearity observed with CrCL. Based on our simulations, the adaptation for weight (< 60 kg for edoxaban), even with normal renal function, could lead to an underexposure, with all the uncertainty related to the large IIV. Unfortunately, our review did not identify a model to simulate apixaban exposure with body weight as an independent factor.

As expected, renal function was found to be the key player in DOAC exposure in almost all the models. With respect to the DOAC elimination physiology, apixaban exposure was found to be the less impacted by renal function and dabigatran the most impacted.[32] The absence of the need for dose adaptation for apixaban in case of a moderate renal insufficiency was confirmed by our simulations.

Age represents the third most important covariate for dabigatran and apixaban adaptation.[31] As for body weight, age is included in the calculation of CrCL, thus reducing the factor's independent effect. Age can, however, influence hepatic clearance.[33] Our simulations showed a limited effect of age on dabigatran and even more so on apixaban exposure. The additive effect in a patient with moderate to severe renal insufficiency or in the presence of a P-gp inhibitor can, however, be expected, justifying the known dose adaptation for dabigatran and apixaban.

Edoxaban is the only DOAC with a suggested dose adaptation in the presence of a P-gp inhibitor.[34] Several early phase PopPK studies have quantified the impact of strong and moderate P-gp inhibitors on edoxaban exposure.[27] On the contrary, other DOAC PopPK models included very few patients with P-gp/CYP3A4/5 strong inhibitors, who were excluded from most phase II–III trials, which likely explains the absence of this effect on the other DOACs exposure.[35–37] Interestingly, smaller PopPK models built with observational data from real-life conditions showed a more pronounced effect of P-gp/CYP3A4/5 inhibition.[23] This finding aligns with real-world retrospective evidence showing an increase in bleeding risk associated with P-gp/CYP3A4/5 inhibitors.[38,39] This highlights the need to conduct PopPK analysis using real-world data involving polymedicated and comorbid patients.

From the present study, it is clear that covariates with minor to moderate effects on exposure can have an important cumulative effect. Our findings confirm previous evidence of an additive effect on rivaroxaban exposure in patients taking verapamil with moderate renal insufficiency.[40] In the same line, amiodarone, for which a dose adaptation of edoxaban is not required, leads to a doubling of its exposure in the presence of a moderate renal insufficiency according to our simulations. Because it is unlikely that manufacturers will test and validate every possible combination of influencing covariates, a more realistic approach would be to develop models which include specific risk factors (e.g., renal insufficiency and polymedication) and to validate this approach in dedicated studies. Both PopPKs and physiologically-based pharmacokinetics (PBPKs) could offer such an approach .[41–43] PopPK-pharmacodynamic studies could also be carried out to better define therapeutic intervals, at least for at-risk patients.[44] Although not validated by the American and European guidelines,[45,46] DOAC blood monitoring remains the most feasible current approach, as suggested by the International Council for Standardization in Hematology in high-risk situations, such as extreme age and weight, severe renal failure, DDI, high bleeding risk procedures, and acute bleeding.[47]

In addition, our literature review revealed many significant covariates that are not currently considered in DOAC dose adaptation. One of those areas is demographic data, such as sex. Women were associated with a slight (< 25%) decreased in DOAC clearance. The clinical impact of sex (also considered in the calculation for CrCL according

to CG), is probably minor, as shown in a retrospective study where DOACs were associated with a lower risk of intracranial hemorrhage and all-cause mortality in women.[48] Although the vast majority of covariates seems to have a modest individual impact on exposure, their accumulation has a significant impact on DOAC exposure.

Genotypes were also found to have a significant effect on exposure but, again, the effect is modest and it is still uncertain if it is associated with clinical events.[49] As previously mentioned, it is the cumulative influence of these covariates which probably becomes clinically relevant. Two recent case reports showing bleeding events in patients presenting both unfavorable genotypes and DDI reinforce the impact of complex drug–drug gene interaction.[50,51] The increased accessibility of genotyping and CYP450 phenotyping now allows the integration of these parameters into future PopPK models. More anecdotal parameters that were found to be significant in only a few studies, such as the hematocrit and liver enzymes ALT, deserve more studies to confirm these observations.

The present study has several limitations. First, although the majority of the major trials were included in the present analysis, not all the studies provided the equations for the AUC simulation, and their derivation from published parameters could not be performed. Second, most simulations were based on models predominantly built on early phase trials. These cannot be applied per se to real-world patients, and their interpretation must be considered with caution in polymorbid patients, due to a probable underestimation of the actual effect of some covariates. Conversely, some covariates may have been found to be improperly significant, particularly when derived from small sized samples with multiple tests lacking adequate statistical correction potential leading to false-positive findings. Bottom-up approaches, such as PBPK modeling could represent an interesting and complementary approach for that purpose because it only relies on *in vitro* and *in silico* data in its purest form.[43] Consequently, PBPK could overcome the caveats associated with this lack of power and allow studying the effect of some covariates without needing long and costly human studies. Third, as we simulated AUC, direct comparison with expected populational plasma concentrations were not possible as AUC values are not easily available in literature.[44,47] Last, we focused our analysis on accumulation and thus safety rather than efficacy of DOACs, the latter requiring further research with PopPK analysis.

In conclusion, the present study revealed that PopPK modeling is a valuable approach in identifying covariates influencing DOAC exposure. Our simulation results confirm the major known factors that influence DOAC exposure and justify the known dose adaptations for patients with AF. It also questions the absence of similar adaptations in patients with VTE. In addition, it highlights how the accumulation of certain risk factors, which are rarely considered for dose adaptation, could lead to a dangerous increase in blood exposure and thus increase the risk of major bleeding. The recent recommendations from the European Heart Association (2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation) acknowledge the risk of DOAC accumulation in presence of a moderate P-gp/3A4/5 inhibitors or/and inducers in the presence of comorbidities, such extreme weights, age, or renal insufficiency. The present study also questions the discrepancies between DOACs for dose adaptation in the presence of some covariates, such as DDI. Often, this not due to an absence of underlying evidence, but rather because these were not considered in the PopPK models based on premarketing studies, used to guide dose adaptation. It appears then to be important to undertake postmarketing studies to develop and validate PopPK models in large real-world polymorbid and polymedicated patients, to aid prescribing to these individuals identified as being at risk. These approaches already exist for other molecules and should be encouraged in and applied to DOACs. As we have highlighted, the effect of the presence of several covariates can be difficult to apprehend in clinical practice. Our findings suggest that PopPK modeling could represent a particularly interesting tool for informed precision dosing in such situations. The place of model-informed precision dosing should therefore be considered after proper validation of its effectiveness using dedicated studies.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.T., F.G., M.G., P.F., Y.D., C.C., and J.L.R. wrote the manuscript. J.T. and J.L.R. designed the research. J.T. and F.G. performed the research. J.T., F.G., M.G., P.F., Y.D., C.C., and J.L.R. analyzed the data.

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