Drugs (2019) 79:1625–1634
https://doi.org/10.1007/s40265-019-01183-0

REVIEW ARTICLE

Clinical Management of Pharmacokinetic Drug Interactions with Direct Oral Anticoagulants (DOACs)

Megan C. Herink[1] · Yan F. Zhuo[1] · Craig D. Williams[1] · Thomas G. DeLoughery[2]

Published online: 22 August 2019

Abstract

Compared with warfarin, the direct-acting oral anticoagulants (DOAC) have fewer pharmacokinetic drug interactions. However, significant drug interactions do exist with documented changes in DOAC concentrations, which can exceed 100%. Unlike warfarin, DOACs have no validated surrogate test to monitor the intensity of anticoagulation. However, several analyses of major outcomes trials with DOACs have demonstrated that serum concentrations do affect both the thrombotic benefits and the hemorrhagic risks of these agents. This paper reviews the known significant pharmacokinetic interactions with DOACs and includes considerations for their use in the presence of interacting medications.

Key Points

Direct-acting oral anticoagulants (DOACs) are increasingly used in clinical practice.

These agents have fewer drug interactions than warfarin, but significant drug interactions do still occur. Many of these interactions occur through drug transport enzymes rather than drug metabolism enzymes, and some may change DOAC concentrations by > 100%. Little information is available on how to manage these drug interactions, and existing clinical outcomes trials for these agents frequently excluded patients on medications with significant interactions.

It is reasonable to use alternative therapy when drugs that have been found to change DOAC concentrations by > 25% are needed, particularly in patients with multiple risk factors for bleeding. More data are needed to recommended routine DOAC dose-reduction strategies.

✉ Megan C. Herink
herink@ohsu.edu

[1] Department of Pharmacy Practice, OSU/OHSU College of Pharmacy, 2730 SW Moody Ave., CL5CP, Portland, OR 97201, USA

[2] Department of Hematology, OHSU School of Medicine, Portland, OR, USA

1 Introduction

Direct-acting oral anticoagulants (DOACs) have been a welcome addition to clinical practice, but the lack of a surrogate marker for monitoring anticoagulation has raised some concerns [1–3]. This is especially true when these agents are used in patients with characteristics that were not well represented in the clinical outcomes trials. These include extremes of weight, kidney dysfunction and the presence of interacting medications.

Drug interactions have been documented to raise DOAC concentrations by over 150% and to lower them by more than 60% [4, 5]. While there is no accepted threshold for a concentration change that defines clinical significance, the anticoagulant effects of DOACs are concentration dependent, and concentrations may affect clinical outcomes [6–9].

In the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial, dabigatran 110 mg resulted in less major bleeding and a higher risk of stroke than did dabigatran 150 mg [10]. The difference in average trough concentration between those two doses was 28% [11]. The difference in clinical outcomes between doses led the US FDA to decline approval of dabigatran 110 mg. A similar association between concentration and major bleeding was observed with edoxaban [8]. It seems reasonable in practice to be concerned about drug interactions that produce similar or even greater changes in DOAC concentrations.

Additionally, many of the largest clinical trials that have documented the benefits of these agents excluded the use of interacting medications during the trial [12–15]. Therefore,

the published literature may not accurately reflect the balance of risk and benefit when DOACs are used in the presence of drugs with significant pharmacokinetic interactions.

In this paper, we review the documented pharmacokinetic drug–drug interactions with DOACs and quantify the effects of those interactions. Clinical guidance is offered when the documented interaction results in a greater than 25% change in DOAC concentration.

1.1 Pharmacokinetic Interactions with Direct-Acting Oral Anticoagulant (DOAC) Agents

There are key differences in the pharmacokinetic profiles of currently available DOACs that are relevant to their drug interactions [16]. While rivaroxaban and apixaban are heavily dependent on cytochrome P450 (CYP450) enzymes for metabolism, edoxaban is only minimally metabolized, and dabigatran undergoes no CYP450 metabolism. There are also differences in the extent of involvement of CYP3A4 in the metabolism of apixaban (~25%) and rivaroxaban (~18%), which is a main mediator of drug–drug interactions. However, all four agents are substrates of P-glycoprotein (P-gp), which is a drug-transport protein and an important mediator of drug–drug interactions [17]. P-gp is an efflux transporter located on the luminal membrane of the small intestine and blood–brain barrier and in the apical membranes of hepatocytes and proximal renal tubule epithelia. Although dabigatran is not metabolized by the CYP450 enzyme system, its bioavailability is low (< 10%) and depends on the activity of P-gp after absorption in the gut [18]. Inhibition of this pathway will result in increased plasma levels. Drug transport enzymes are also known to play a role in the renal elimination of some drugs, including rivaroxaban, by controlling concentrations in tubular fluid [17].

2 Search Methods

A comprehensive search for relevant articles was performed that included a MEDLINE search from 1996 through July 2018. The terms dabigatran, edoxaban, apixaban and rivaroxaban were each individually combined with the terms pharmacokinetics and drug interactions. In addition, we searched the references of identified review papers for relevant pharmacokinetic studies and reviewed the pharmacology sections of the FDA review packets for each DOAC agent (accessed at http://www.fda.gov/drugs). Betrixaban was approved after the initial literature search and was excluded from the review.

Identified studies were selected for inclusion if they were prospective, pharmacokinetic trials that reported the magnitude of effect of a drug or drugs on one or multiple pharmacokinetic properties of a DOAC agent. Primary pharmacokinetic properties studied included total drug exposure [measured as area under the concentration-time curve (AUC)], maximum concentration measured after a dose (C_{max}), minimum concentration measured during a dosing cycle (C_{min}) and half-life. When available, data describing changes with chronic dosing were prioritized over effects seen from a single dose. A change of < 25% in any of those kinetic parameters was considered clinically unimportant, whereas a change of ≥ 25% was considered important and was defined as significant. This degree of variation in intensity is consistent with accepted therapeutic international normalized ratio (INR) fluctuations on warfarin [19]. For clinical recommendations, we included a range of 25–100% as a precaution for use and > 100% as a contraindication (Table 1). This is consistent with FDA guidance that suggests no clinically significant drug interaction if drug concentrations are within the equivalence range of 80–125% [20].

3 Summary of Pharmacokinetic Interactions

A total of 15 medications were found to have statistically significant pharmacokinetic interactions with at least one DOAC (Table 1); another 13 were shown not to have a significant interaction (Table 2). Five of the significant interacting medications resulted in more than a doubling of a DOAC concentration. Three drugs (amiodarone, diltiazem and naproxen) were found to significantly interact with one DOAC but not with another. The trials that quantitatively documented the pharmacokinetic interactions are briefly summarized in the following. Clinically relevant aspects of the trials are included to facilitate application of the findings.

3.1 Dabigatran

Four published pharmacokinetic trials were found that showed significant drug–drug interactions with dabigatran. Unpublished data in the FDA package insert were also found. Since dabigatran is not metabolized by CYP450, drug interactions are due to effects on absorption mediated through P-gp.

The first published trial evaluated the effect of cobicistat, which inhibits both P-gp and CYP3A4 [21]. Dabigatran was administered in the absence of cobicistat and again after 5 days of use. The authors also tested whether separation of administration times by 2 h would have any effect on the interaction. Thrombin time testing was performed as a measure of the impact of the interaction on coagulation. Cobicistat was found to raise dabigatran C_{max} by 175% and AUC and C_{min} by 127%. Thrombin time was

Table 1 Significant pharmacokinetic drug–drug interactions with direct-acting oral anticoagulants

	Mechanism	AUC	C_{max}	C_{min}	Half-life	Recommendation
Dabigatran						
Clarithromycin [22]	P-gp and strong CYP3A4 inhibitor	↑↑	↑↑↑			Precaution
Cobistat [21]	P-gp and strong CYP3A4 inhibitor	↑↑↑↑	↑↑↑↑	↑↑↑↑		Contraindicated
Dronedarone	P-gp and moderate CYP 3A4 inhibitor	↑↑↑↑	↑↑↑↑		↔	Contraindicated
Ketoconazole	P-gp and strong CYP 3A4 inhibitor	↑↑↑↑	↑↑↑↑			Contraindicated
Ticagrelor [25][a]	P-gp inhibitor	↑↑	↑↑↑			Precaution; give ticagrelor loading dose 2 h after dabigatran
Rifampin [5]	P-gp and strong CYP 3A4 inducer	↓↓↓	↓↓↓		↔	Contraindicated
Verapamil [23]	P-gp and moderate CYP 3A4 inhibitor	↑↑↑	↑↑↑			Precaution; separate administration by at least 2 h
Edoxaban						
Amiodarone [35]	P-gp inhibitor	↑↑	↑↑↑		↓↓	Precaution
Cyclosporine [31]	Moderate CYP3A4 inhibitor	↑↑↑	↑↑↑		↔	Precaution
Dronedarone [35]	P-gp and moderate CYP3A4 inhibitor	↑↑↑	↑↑	↑↑↑↑		Contraindicated
Erythromycin [31]	Moderate CYP3A4 inhibitor	↑↑↑	↑↑↑		↔	Precaution
Ketoconazole [31]	P-gp and strong CYP3A4 inhibitor	↑↑↑	↑↑↑		↔	Precaution
Quinidine [33]	P-gp inhibitor	↑↑↑	↑↑↑	↑↑↑	↑↑	Precaution
Rifampin [32]	P-gp and strong CYP3A4 inducer	↓↓	↔		↓↓	Precaution
Verapamil [35]	P-gp and moderate CYP3A4 inhibitor	↑↑↑	↑↑↑	↑↑		Precaution
Apixaban						
Clarithromycin [42]	P-gp and strong CYP3A4 inhibitor	↑↑↑	↑↑		↔	Precaution
Diltiazem [37]	P-gp and CYP3A4 inhibitor	↑↑	↑↑		↔	Precaution
Ketoconazole [37]	P-gp and strong CYP3A4 inhibitor	↑↑↑	↑↑↑		↑	Precaution
Naproxen [39]	P-gp inhibitor	↑↑↑	↑↑↑		↔	Precaution
Rifampin [38]	P-gp and strong CYP3A4 inducer	↓↓↓	↓↓		↔	Contraindicated
Rivaroxaban						
Clarithromycin [4]	P-gp and strong CYP3A4 inhibitor	↑↑↑	↑↑			Precaution
Erythromycin [4, 45]	Moderate CYP3A4 inhibitor	↑↑	↑↑		↔	Precaution
Fluconazole [4]	P-gp and moderate CYP3A4 inhibitor	↑↑	↑↑			Precaution
Ketoconazole [4]	P-gp and strong CYP3A4 inhibitor	↑↑↑↑	↑↑↑			Precaution to use with 200 mg or less, contraindicated with 400 mg or more
Rifampin [46]	P-gp and strong CYP3A4 inducer	↓↓↓				Contraindicated
Ritonavir [4]	P-gp and strong CYP3A4 inhibitor	↑↑↑↑	↑↑↑			Contraindicated

AUC area under the plasma concentration-time curve, C_{max} peak concentration, C_{min} trough concentration, *CYP* cytochrome P450, *P-gp* P-glycoprotein, *Precaution* combination should be used with caution and avoided when possible, ↔ indicates no significant effect,↑ or ↓ indicates change of ≤25%, ↑↑ or ↓↓ indicates change of 26–49%, ↑↑↑ or ↓↓↓ indicates change of 50–99%, ↑↑↑↑ or ↓↓↓↓ indicates change of > 100%

[a]Interaction with coadministered ticagrelor 180 mg

increased by 51% at the peak, with a 31% increase in total exposure. Separating dosing by 2 h had little impact [21].

The second trial evaluated the effect of rifampin, a potent P-gp and CYP3A4 inducer [5]. Dabigatran was administered alone on study day 1, 9, 16 and 23, with rifampicin administered on days 2–8. Rifampin resulted in AUC and C_{max} reductions of 67% and 66%, respectively. After the 7 and 14-day washouts from rifampin, the AUC and C_{max} were both still reduced by 15–20%, indicating a prolonged time for recovery. Consistent with an interaction mediated mostly through P-gp and drug transport, the time to maximum concentration and half-life were both minimally affected [5].

The third trial found that multiple dosing of clarithromycin 500 mg, a P-gp inhibitor, over a 3-day period increased average bioavailability from 6.5% (range 2.8–12.1) to 10.1% (4.1–26.9) [22]. The C_{max} and AUC were increased by 60% and 49%, respectively. Consistent with the interaction being mediated through P-gp inhibition rather than CYP-mediated metabolism, the half-life of dabigatran was unchanged, as was seen in the previous trials [22].

Last, a study evaluating the effects of verapamil, a P-gp and CYP3A4 inhibitor, found effects on both AUC and C_{max}

Table 2 Medications found to have no clinically relevant pharmacokinetic interactions with direct-acting oral anticoagulant agents and included kinetic parameters

Medication	Total exposure (AUC)	Peak concentration (C_{max})	Half-life	Notes
Dabigatran				
Amiodarone [24]	↔	↔		
Atorvastatin [28]	↔	↔		
Bosutinib [26]	↔	↔	↔	
Clopidogrel (75 mg) [29]	↔	↔	↔	C_{max} and AUC of apixaban increased with higher doses of clopidogrel (300 and 600 mg)
Digoxin [27]	↔	↔	↔	
Pantoprazole [30]	↔	↔	↔	Approximate 20% decrease in AUC and C_{max} of apixaban. Author concluded dose adjustment not necessary
Diltiazem [24]	↔			
Edoxaban				
Aspirin [36] (100 mg/day)	↔	↔		Higher dose of aspirin (325 mg/day) resulted in an approximate 30% increase in AUC and C_{max} of apixaban
Atorvastatin [35]	↔	↔		
Digoxin [35]	↔	↔		
Naproxen [36]	↔	↔		
Apixaban				
Atenolol [44]	↔	↔		
Famotidine [43]	↔	↔	↔	
Rivaroxaban				
Aspirin [49]	↔	↔	↔	
Atorvastatin [47]	↔	↔		
Digoxin [47]	↔	↔		
Midazolam [4]	↔	↔		
Naproxen [48]	↔	↔	↔	
Omeprazole [50]	↔	↔	↔	
Ranitidine [61]	↔	↔	↔	

No pharmacokinetic interactions (↔), defined by less than a 25% increase or reduction in AUC and C_{max}, were observed with coadministration of DOAC agents and medications shown in Table 2, except with high-dose aspirin and clopidogrel. The mechanism of high-dose aspirin increasing AUC and C_{max} of edoxaban is currently unknown [32]. Clopidogrel may be a substrate of P-gp [27]. High-dose clopidogrel may increase the bioavailability of dabigatran by competitively inhibiting intestinal P-gp and therefore increasing AUC and C_{max} of dabigatran [27]. Interestingly, medications that are either P-gp substrates, CYP3A4 inhibitors or CYP3A4 substrates, including atorvastatin, digoxin, amiodarone and midazolam, did not have pharmacokinetic interactions with coadministration of the DOAC agent

AUC area under the plasma concentration-time curve, C_{max} peak concentration, *CYP* cytochrome P450, *DOAC* direct-acting oral anticoagulant, *P-gp* P-glycoprotein

that varied according to dosage, formulation and timing of administration [23]. The greatest effect was observed with a single dose of verapamil. After achieving steady state on verapamil 120 mg twice daily, the increases in AUC and C_{max} were 54% and 63% (90% confidence interval (CI) 19–99), respectively. Doubling the verapamil dose to 120 mg four times daily did not result in further increases. The authors demonstrated that administering dabigatran 2 h before verapamil minimized the interaction (< 20% increase in C_{max} and AUC), even in the chronic phase of verapamil dosing [23]. Since dabigatran should be completely absorbed by 2 h, separating the administration should minimize the interaction. However, a pharmacokinetic substudy of the RE-LY trial of 9522 participants only demonstrated a 23% increase in dabigatran AUC when coadministered with verapamil. This analysis also showed a minimal 12% increase in AUC when coadministered with amiodarone [24]. Coadministration with diltiazem, a strong CYP inhibitor and an inhibitor of P-gp, had no effect [24].

A 2015 update to the FDA package insert for dabigatran included a significant interaction with ticagrelor, ketoconazole and dronedarone, known inhibitors of P-gp [25]. While

the data remain unpublished, they state that, when coadministered with a loading dose of ticagrelor 180 mg, the AUC and C_{max} of dabigatran increases by 49% and 65%, respectively [25]. When the dose of ticagrelor is halved (maintenance dose) or the administration is separated by 2 h, the magnitude of the interaction is reduced by about 50%. Additionally, dabigatran exposure more than doubled after administration with both dronedarone and ketoconazole.

Finally, four pharmacokinetic studies of drugs that are substrates of P-gp—clopidogrel, digoxin, atorvastatin and bosutinib—showed no significant interactions with dabigatran and one additional study showed no effects from coadministration with pantoprazole (Table 2) [26–30].

3.2 Edoxaban

Four studies found significant effects of eight different drugs on the pharmacokinetics of edoxaban, and one study documented a lack of interaction with naproxen and aspirin.

In the first trial, three drugs that inhibit P-gp and have varying degrees of CYP3A4 inhibition were studied in a crossover trial [31]. All subjects were given edoxaban alone and then edoxaban co-dosed with ketoconazole (a strong CYP3A4 inhibitor), erythromycin (a moderate CYP3A4 inhibitor) or cyclosporine (a weak CYP3A4 inhibitor). In addition to pharmacokinetic measurements, changes in prothrombin time (PT) were also collected. All three drugs affected edoxaban pharmacokinetics similarly. Compared with edoxaban alone, ketoconazole, erythromycin and cyclosporine increased edoxaban AUC by 87%, 85% and 73%, and peak concentrations were raised by 89%, 68% and 74%, respectively. None of the drugs significantly affected half-life, which suggests that the primary mechanism of the interaction was due to altered bioavailability through P-gp- rather than CYP-mediated metabolism. While the effect on PT was not reported for cyclosporine, both ketoconazole and erythromycin nearly doubled the effect of edoxaban on PT, with changes from baseline of 57% and 45%, respectively, compared with 32% and 25% for edoxaban alone.

A second trial examined the effects of rifampin, a potent CYP3A4 and P-gp inducer, on edoxaban. The AUC was reduced by 34%, with a 50% reduction in half-life [32]. The total exposure (AUC) of the active metabolite of edoxaban was also increased, consistent with more rapid conversion via CYP3A4 [32].

A third study examined the effects of quinidine, a P-gp inhibitor, on intravenous edoxaban [33]. The intravenous formulation was used to eliminate the P-gp interaction on intestinal absorption. Quinidine increased edoxaban AUC by 35%, with a 48% increase in half-life [33]. While edoxaban exhibited a small amount of clearance through CYP3A4, the inhibitory effects of quinidine were only at CYP2D6 [34]. Therefore, the observed effects of quinidine on the half-life and trough concentration of intravenous edoxaban are likely mediated through inhibition of renal P-gp and reduced kidney clearance.

Last, the effects on oral edoxaban of six different cardiovascular medications known to be P-gp inhibitors or substrates were studied [35]. The drugs included quinidine, digoxin, amiodarone, verapamil, atorvastatin and dronedarone. Quinidine increased edoxaban AUC and C_{max} by 77% and 85%, respectively. Verapamil, amiodarone and dronedarone increased the AUC of edoxaban by 53%, 40% and 85%, respectively, and C_{max} by 53%, 66% and 46% [35]. Effects on trough concentrations occurring 24 h after the dose were also demonstrated, with increases of 29% and 158% with verapamil and dronedarone, respectively, whereas amiodarone decreased the trough level by 26% [35].

Coadministration with digoxin or atorvastatin, which are both P-gp substrates, did not result in a clinically significant effect on the C_{max} or AUC of edoxaban [35]. Another study documented a lack of effect on the pharmacokinetics of edoxaban when coadministered with naproxen or low-dose aspirin of 100 mg [36].

3.3 Apixaban

Apixaban is a combined substrate of CYP3A4, P-gp, and breast cancer resistance protein (BCRP) and thus has potential for drug–drug interactions. However, non-metabolic clearance of apixaban also occurs, and only four published pharmacokinetic studies have revealed significant drug interactions with apixaban. The first study examined ketoconazole and diltiazem, both of which inhibit both CYP3A4 and P-gp [37]. Ketoconazole increased the AUC and C_{max} by 99% and 62%, respectively, and prolonged the half-life by 22%. Diltiazem increased the AUC and C_{max} by 40% and 31%, respectively, but had no effect on half-life.

The second study examined the effects of rifampin on apixaban. Rifampin is a strong inducer of both CYP3A4 and P-gp and, as expected, reduced apixaban exposure, with reductions in AUC and C_{max} of 54% and 42%, respectively [38]. The half-life of oral apixaban was unaffected.

Third, a study evaluated the effects of naproxen on apixaban and found effects similar in magnitude to those on diltiazem [39]. In this study, naproxen 500 mg administered simultaneously with apixaban raised the AUC and C_{max} by 54% and 61%, respectively, with no significant effect on half-life. Consistent with the increase in apixaban exposure, peak anti-Xa activity was also elevated, by approximately 60% [39]. Naproxen is metabolized by CYP2C9 and CYP1A2 but is not an inducer or inhibitor of CYP3A4, so this interaction was unexpected. In vitro data suggest that naproxen may increase apixaban bioavailability through inhibition of intestinal P-gp [40, 41]. However, the mechanism is not entirely clear.

Last, a study of repeated doses of clarithromycin 500 mg twice daily found that apixaban AUC and C_{max} were raised by 60% and 30%, respectively [42]. Consistent with the effect being mediated primarily through the drug transporter P-gp, clarithromycin did not change the half-life of apixaban or the time to C_{max}.

Due to concerns about potential effects of gastric pH on apixaban bioavailability, a study was performed using the histamine 2 receptor blocker famotidine. No effect was found on apixaban AUC or C_{max} (Table 2) [43]. Changes in gastric pH are unlikely to affect apixaban pharmacokinetics. Similarly, a pharmacokinetic study confirmed that apixaban has no clinically significant interaction with atenolol or effects on digoxin pharmacokinetics, both of which are P-gp substrates [44].

3.4 Rivaroxaban

Three published trials were found for rivaroxaban, two of which showed significant pharmacokinetic drug interactions.

The first trial examined the effects of erythromycin and found increases in AUC and C_{max} of 39% and 40%, respectively [45]. These findings were replicated and expanded upon in the second trial, which examined multiple drugs that share elimination pathways with rivaroxaban [4].

In this trial, the strong CYP450 inhibitors ketoconazole and ritonavir increased the AUC and C_{max} by 158% and 72% and 153% and 55%, respectively. A dose-dependent effect was observed, with ketoconazole 400 mg having twice the effect of 200 mg. When coadministered with the modest CYP450 inhibitors erythromycin, clarithromycin and fluconazole, the rivaroxaban AUC was increased by 34%, 54% and 42%, respectively, and C_{max} was increased by 38%, 40% and 28%, respectively [4]. In an interesting finding, the pure CYP3A4 inhibitor midazolam had no significant interaction with rivaroxaban. Significant interactions therefore are likely mediated through drug transporter enzymes rather than through altered hepatic metabolism. Erythromycin and clarithromycin inhibit P-gp, whereas fluconazole inhibits the BCRP transporter. Unpublished data from the prescribing information suggest that coadministration with rifampin led to a 50% decrease in mean AUC [46].

Additional studies found no significant effects from digoxin, atorvastatin, aspirin, naproxen, omeprazole or ranitidine (Table 2) [47–50].

4 Discussion

The four DOAC agents examined all have significant pharmacokinetic drug interactions that clinicians should be aware of. This is important because patients taking medications with strong interactions were frequently excluded from the clinical trials of DOACs, including several trials used by the FDA for approval of these agents [12–14, 51]. Therefore, the risk versus benefit of using a DOAC in the presence of interacting drugs is not necessarily reflected in the outcomes of these trials.

The anticoagulant effects of DOACs are concentration dependent, and rises in drug concentrations may come from higher doses or from drug interactions [21, 39, 45]. One analysis suggested that the concomitant use of interacting drugs is an independent risk factor for drug concentrations exceeding the normal range (odds ratio 3.3; 95% CI 1.20–9.05) [52]. While the correlation between serum concentration and surrogate anticoagulant effect is well-established for DOACs, the relationship between these surrogate measures and clinical outcomes is more complex [8, 11, 24]. However, accumulating data do demonstrate an elevated bleeding risk associated with both positive drug interactions (those that raise serum concentrations) and an elevated anti-Xa level on a DOAC [53, 54]. These findings of a greater risk of bleeding in the setting of greater exposure to a DOAC is consistent with several available analyses of the large outcomes trials.

In the original RE-LY trial with dabigatran, a dose of 150 mg twice daily resulted in a higher rate of bleeding and less thromboembolic events compared with the 110 mg twice daily dose [10]. In a prespecified subanalysis designed to better understand the relationship between drug exposure and clinical outcomes, plasma concentrations were collected in a significant subset of patients [11].

Higher concentrations of dabigatran were associated with a higher risk for bleeding (Fig. 1). The median trough concentration in those who experienced a major bleed was 55% higher than in those without a major bleed (116 vs. 75.3 ng/ml) [11]. However, several patient characteristics that might also be associated with a higher risk for bleeding were also associated with higher serum concentrations. These included

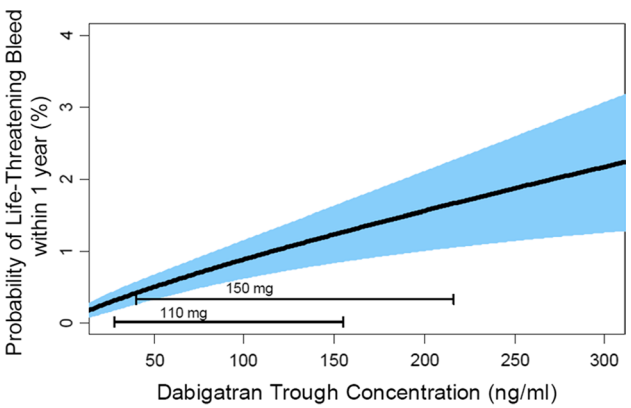

Fig. 1 Probability of a major bleed within 1 year vs. dabigatran predose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th–90th percentiles of observed dabigatran predose concentrations in the RE-LY trial [60]

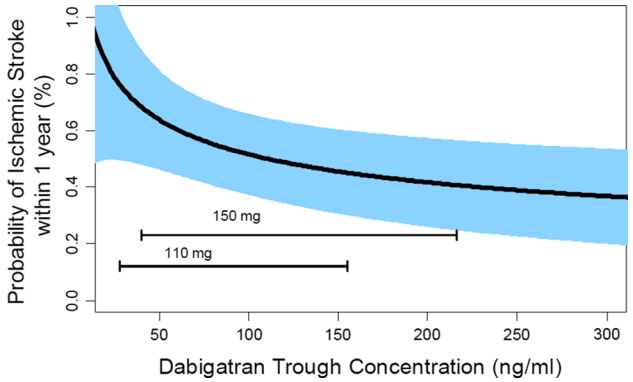

Fig. 2 Probability of ischemic stroke within 1 year vs. dabigatran predose concentration. The blue shaded region represents the standard error. The bars on the bottom on the plot region represent the 10th–90th percentiles of observed dabigatran predose concentrations in the RE-LY trial [60]

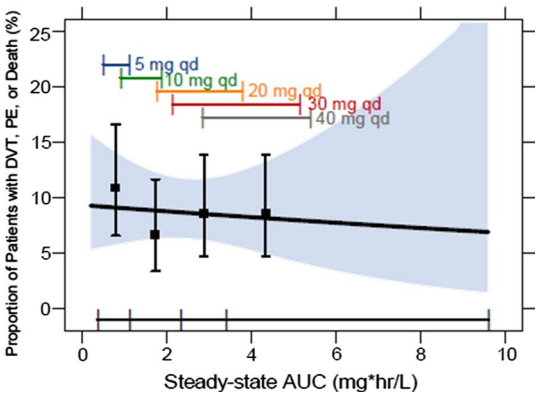

Fig. 3 Proportion of patients with DVT, PE or death vs. rivaroxaban drug exposure as measured by AUC_{0-24} quartiles and associated 95% CI in dose ranging trial of 11,527 patients. The horizontal black bar shows steady-state AUC_{0-24} quartiles; colored bars illustrate 10th–90th percentile of AUC [55]. *AUC* area under the plasma concentration–time curve, *CI* confidence interval, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *qd* once daily

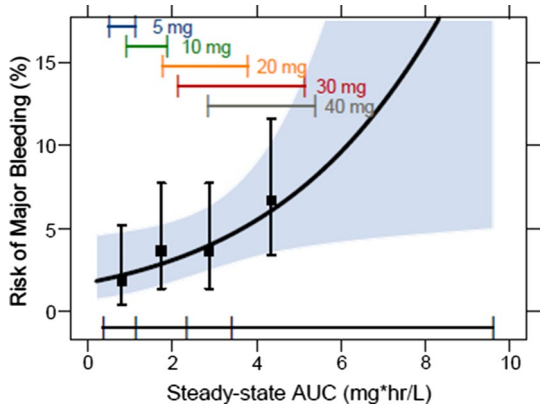

Fig. 4 Proportion of patients with major bleeding vs. rivaroxaban drug exposure as measured by AUC_{0-24} quartiles and associated 95% CI in dosing ranging trial of 11,527 patients. The horizontal black bar shows steady-state AUC_{0-24} quartiles; colored bars illustrate 10th–90th percentile of AUC [55]. *AUC* area under the plasma concentration-time curve, *CI* confidence interval

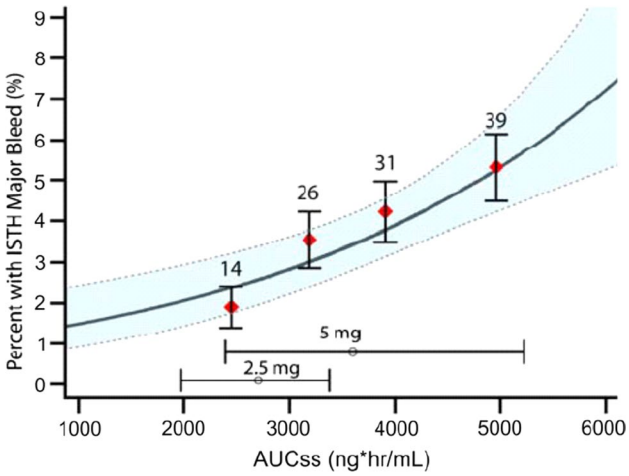

Fig. 5 Major bleeding events increased with increasing apixaban exposure measured by AUC at steady state. The horizontal black bars illustrate 10th–90th percentile of AUC at respective apixaban doses [56]. *AUC* area under the plasma concentration-time curve, *ISTH* International Society on Thrombosis and Haemostasis, Inc.

renal impairment, advanced age and female sex [11]. Unlike the risk for bleeding, higher serum concentrations were not associated with a reduced risk for stroke or systemic embolism (Fig. 2). The median trough concentration was 80.6 versus 78.3 ng/ml in patients who did versus did not experience a thromboembolic event [11].

The anti-Xa agents rivaroxaban and apixaban have a similar association between higher drug concentrations and a greater bleeding risk without any further reduction in thrombotic risk (Figs. 3, 4, 5). While these data have yet to be published, they have been made available by the FDA [55, 56].

Interestingly, the finding that higher concentrations of a DOAC are associated with an increased risk of bleeding but not a reduced risk of a thrombotic event is similar to the findings for these same outcomes with a higher INR on warfarin [57]. Thus, similar to lowering the dose of warfarin in the setting of an elevated INR due to a drug interaction, reducing the dose of a DOAC in a similar setting of elevated drug concentrations would seem prudent. However, without prospective trials to guide a dosing strategy, the lack of readily available anti-Xa assays and given the small number of dosage strengths available for titration of a DOAC, a strategy of avoiding these agents in the setting of significant interactions seems more practical at this time.

A strategy of lowering the dosage in the setting of use with interacting medications has been evaluated in one study. In the ENGAGE AF-TIMI 48 trial, edoxaban dosing was reduced in

some patients who were chronically taking a known inhibitor of P-gp, whereas it was not reduced in other patients receiving these same medications [8]. A 50% reduction in dose led to a 29–35% reduction in edoxaban exposure, resulting in a lower rate of major bleeding without a significant increase in thromboembolic events. While this is in agreement with the previously discussed subanalyses of DOAC exposure and clinical outcomes, the number of clinical events in the drug interaction subgroup was small overall and no conclusions could be drawn regarding intracranial hemorrhage, which is the most important adverse clinical outcome [8].

4.1 Clinical Guidance

Based on the pharmacokinetic studies reviewed and the documented association of increased bleeding risks with greater exposure to DOAC agents, it is reasonable to avoid DOACs in combination with several drugs that have been shown to more than double the serum concentration of the DOAC (listed as contraindicated in Table 1). Drugs that result in a more modest but still significant change of 25–100% should be used with caution and avoided when possible (listed as precaution in Table 1). Switching concurrent medications to alternatives that have not been shown to interact with the particular DOAC or using warfarin with INR monitoring is suggested. While more data are needed before targeted serum monitoring and dose reductions can be widely recommended, reduced dosing and/or plasma level monitoring in the presence of drug interactions that raise DOAC concentrations by 25–100% should be considered only in cases in which alternate therapy cannot be used. This is especially important in patients with a history of major bleeding or with multiple risk factors for bleeding, which include advanced age, weight ≤ 60 kg, decreased renal function, use of another antithrombotic agent and chronic use of drugs known to increase risk of bleeding (corticosteroids and nonsteroidal anti-inflammatory agents).

While data did not demonstrate consistent and precise pharmacokinetic effects from naproxen and aspirin with each DOAC, coadministration with these and other drugs that further increase the risk of bleeding should be used and monitored carefully. Additionally, since pharmacokinetic data cannot be all inclusive, and not all possible combinations of drug interactions have been tested, DOACs should be used with great caution with drugs that are known to be strong inhibitors or inducers of CYP3A4 and P-gp. Strong inhibitors include ketoconazole as well as ritonavir, and strong inducers include phenytoin and carbamazepine [58, 59].

4.2 Limitations

This paper has many limitations. First, we included only pharmacokinetic studies, which consist of small numbers of relatively healthy patients who have fewer chronic disease states and are likely taking fewer medications. Second, we did not include studies evaluating pharmacodynamic interactions, so some clinically important drug–drug interactions may not have been discussed. Lastly, there is limited evidence to better define clinically important changes in DOAC concentrations that will strongly correlate with changes in clinical outcomes.

5 Conclusion

Drug interactions are increasingly implicated as a source of bleeding risk with the use of DOACs. We identified 14 drugs resulting in 26 pharmacokinetic interactions in which the concentration of a DOAC was increased by at least 25% (Table 1). Five of these drugs resulted in six interactions that increase DOAC exposure by more than 100%; four of those were with dabigatran (Table 1). Additionally, rifampin reduced concentrations of multiple DOACs by $> 50\%$ and should also be considered contraindicated with these agents (Table 1).

Of the nine remaining drugs, which cause 20 pharmacokinetic interactions that raise DOAC concentrations by $> 25\%$, a vitamin K antagonist with INR monitoring should be considered. This is especially true when the interaction results in concentration increase of $> 50\%$ or when the patient is at a higher than average risk of bleeding. A dose reduction strategy may be an appropriate option as more studies become available to validate and support this approach. Additionally, more data are needed to evaluate the significance of changes in DOAC concentrations on clinical outcomes.

Compliance with Ethical Standards

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflict of interest MH, YZ, CW and TD have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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