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REVIEW ARTICLE

Edoxaban and the Issue of Drug-Drug Interactions: From Pharmacology to Clinical Practice

Alberto Corsini[1,2] · Nicola Ferri[3] · Marco Proietti[4] · Giuseppe Boriani[5]

Abstract

Edoxaban, a direct factor Xa inhibitor, is the latest non-vitamin K antagonist oral anticoagulants (NOACs). Despite being marketed later than other NOACs, its use is now spreading in current clinical practice, being indicated for both thromboprophylaxis in patients with non-valvular atrial fibrillation (NVAF) and for the treatment and prevention of venous thromboembolism (VTE). In patients with multiple conditions, the contemporary administration of several drugs can cause relevant drug-drug interactions (DDIs), which can affect drugs' pharmacokinetics and pharmacodynamics. Usually, all the NOACs are considered to have significantly fewer DDIs than vitamin K antagonists; notwithstanding, this is actually not true, all of them are affected by DDIs with drugs that can influence the activity (induction or inhibition) of P-glycoprotein (P-gp) and cytochrome P450 3A4, both responsible for NOACs disposition and metabolism to a different extent. In this review/expert opinion, we focused on an extensive report of edoxaban DDIs. All the relevant drugs categories have been examined to report on significant DDIs, discussing the impact on edoxaban pharmacokinetic and pharmacodynamic and the evidence for dose adjustment. Our analysis found that, despite a restrained number of interactions, some strong inhibitors/inducers of P-gp and drug-metabolising enzymes can affect edoxaban concentration, just as it happens with other NOACs, implying the need for a dose adjustment. However, our analysis of edoxaban DDIs suggests that given the small propensity for interaction of this agent, its use represents an acceptable clinical decision. Still, DDIs can be significant in certain clinical situations and a careful evaluation is always needed when prescribing NOACs.

Key Points

Despite a restrained number of interactions, some strong inhibitors/inducers of P-gp and drug-metabolising enzymes can affect edoxaban concentration, implying the need for a dose adjustment.

Notwithstanding, our analysis of edoxaban DDIs suggests that given the small propensity for interaction of this agent, its use represents an acceptable clinical decision in most of the cases

DDIs can be significant in certain clinical situations and a careful evaluation is always needed during the prescription process of any NOAC.

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✉ Marco Proietti
marco.proietti@unimi.it

[1] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

[2] Multimedica IRCCS, Milan, Italy

[3] Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy

[4] Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Giuseppe La Masa 19, 20156 Milan, Italy

[5] Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy

1 Introduction

Four non-vitamin K antagonist oral anticoagulants (NOACs) have been approved for clinical use by many regulatory medicines' agencies around the world. The use of these drugs is increasing in routine practice for the treatment of non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE). NVAF is the most common sustained arrhythmia in clinical practice, especially in the elderly [1–3] and, even if the arrhythmia is asymptomatic, it is associated with adverse outcomes, with a significantly increased risk of stroke, death and heart failure [4]. VTE, categorised as deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with high morbidity and a relevant financial burden on patients and health systems. Both acquired and hereditary risks factors contribute to VTE; in particular, VTE is a common complication of cancer and its therapy [5].

Oral anticoagulant therapy significantly reduces the risk of NVAF-related thromboembolic events and mortality, and is recommended in every patient at risk, according to guidelines [6, 7]. The new class of NOACs, also named Direct Oral Anticoagulants (DOACs) are nowadays an effective treatment with a safer profile compared to vitamin K antagonist (VKA) and are currently implemented in "real-world" clinical practice, in patients with so-called NVAF and VTE, settings characterised by patients with complex clinical scenarios, in terms of comorbidities and polypharmacy. Comorbidity and polypharmacy have a high prevalence in elderly patients, a population where the estimated prevalence of NVAF is particularly high (9–10% for patients aged > 80 years and lower than 0.1% in patients aged < 55 years) [8–10]. In addition, NVAF is associated with a 4- to 5-fold increased risk of embolic stroke with an estimated increased stroke risk of 1.45-fold per decade in aging [11, 12]. Since VKA warfarin shows many clinically significant interactions with drugs, foods and herbal medicines [13, 14] resulting in frequent adjustment of its dosage in order to achieve a safe and effective anticoagulant effect, the use of new NOACs may represent a significant clinical advantage. Among NOACs, edoxaban is the last to reach the market indicated for the prevention of stroke and systemic embolism in adult patients with NVAF and for treatment of DVT and PE, and prevention of recurrent DVT and PE [15, 16].

Thus, in view of the need to prescribe oral anticoagulants to patients with various concurrent disease and on treatment with various drugs or agents, we will focus this review on drug interactions, considering edoxaban, a NOAC with a favourable safety profile in terms of studied and predicted drug-drug interactions (DDIs) as well as interactions with herbs and natural products. Considering that many DDIs are not specifically studied, only theoretical pharmacological considerations can be done of specific anticoagulants in order to predict if an interaction is possible (Fig. 1). In view of the increasing number of patients with oncological pathologies who need treatment with anticoagulants, for VTE or NVAF [5, 17], we will include interactions between NOACs and chemotherapies. Moreover, taking into account the underweighted and commonly undisclosed use of nutraceuticals or herbs in practice, which may account for up to half of the patients [18, 19], we will consider the basis for evaluating their potential interaction with edoxaban.

2 Pharmacodynamic and Pharmacokinetic Characteristics of Edoxaban

Edoxaban is an oral, selective, direct and reversible inhibitor of activated clotting factor X (FXa), the serine protease responsible for the generation of thrombin [20]. The drug binds directly to the active site of FXa and blocks the interaction with prothrombin [21], thus eliciting its anticoagulant activity. In vitro, edoxaban inhibits the human FXa in a

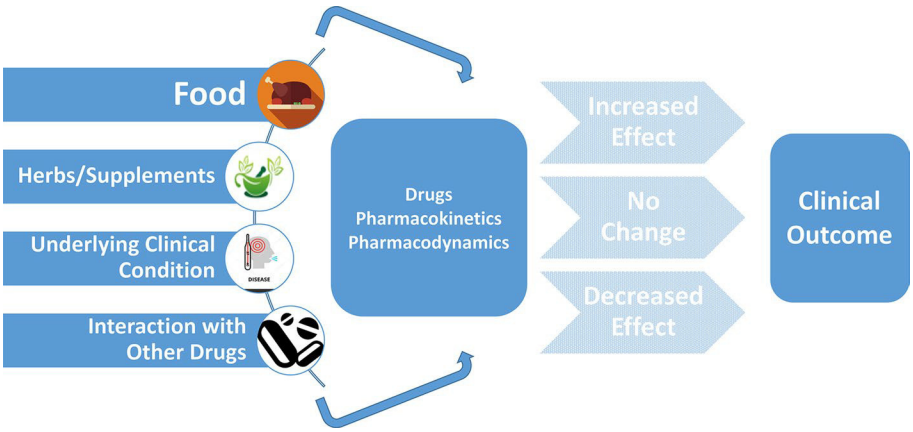

Fig. 1 The complex interplay of factors influencing drugs pharmacokinetic and pharmacodynamic and the possible effects on outcomes

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concentration-dependent and -competitive manner, with an inhibition constant (Ki) value of 0.561 nM [22].

Edoxaban is rapidly absorbed after oral administration with a time to peak plasma concentration of 1–2 h, and a bioavailability of 62% (Table 1) [23, 24]. Its absorption, which is not related to solubility, occurs predominantly in the proximal small intestine and it is limited in the colon (13%) [25].

Surgeries such as Roux-en-Y gastric bypass could reduce the absorption of edoxaban by shifting it to the distal small intestine and ascending colon, segments of the gastrointestinal tract with low edoxaban absorption capability [26]. Differences in the permeability of edoxaban along the length of the gastrointestinal tract rather than poor solubility per se, has been suggested to be the reason for reduced colonic absorption [25]**.** The solubility of edoxaban is pH dependent with maximal values at pH 3–5, while is slightly soluble at neutral pH (pH 6–7), and practically insoluble at a basic pH (8–9) [25]. Another interesting characteristic of edoxaban is that concomitant food intake has a clinically insignificant effect on its absorption [27] so its administration can be independent of meals.

Terminally ill or elderly patients with dysphagia may report reduced patient adherence to medications [28, 29]. Therefore, solid oral formulations crushed and mixed into food or provided as a water suspension via a nasogastric tube are often utilised as alternative methods of drug administration. However, these manipulations may alter the bioavailability of a drug, also potentially exposing patients to unexpected DDIs [30]. Within this clinical setting, a Phase I, open-label, randomised trial was conducted to assess the pharmacokinetic, safety, and tolerability profiles of the edoxaban 60-mg tablet in healthy adults when crushed and administered either via a nasogastric tube or mixed with apple puree and ingested [31]. The results demonstrated that edoxaban tablet crushed and administered either via a nasogastric tube or with apple puree displays similar total exposure, although time to maximum plasma concentration was significantly shorter for the nasogastric tube suspension and apple puree versus the whole tablet [31]. Thus, edoxaban can be considered a valid option for patients who are unable to swallow solid oral dose formulations [31].

Edoxaban, as well as all other NOAC absorption is dependent on the intestinal P-glycoprotein (P-gp) system [32]. P-gp is an efflux transporter primarily expressed in the apical/luminal membrane of epithelia of the small intestine, hepatocytes, renal proximal tubules, and other sites. With broad substrate specificity and high transport capacity, P-gp can limit the systemic exposure of various xenobiotics by decreasing intestinal absorption and increasing renal excretion and biliary excretion [33]. Indeed, Phase I studies after single- and multiple-dose administration showed a low intersubject variability and dose linearity, suggesting a predictable and consistent pharmacokinetic profile (Table 1) [24].

The mean apparent volume of distribution of edoxaban is approximately 300 L and 100 L after oral and IV administration, respectively [23, 24]. This difference indicates biliary excretion of edoxaban and a possible enterohepatic circulation through a glucuronidation processes (data on file) [34]. The relatively high volume of distribution of edoxaban in comparison to other NOACs is not predicted to have any clinically relevant implication on the safety or efficacy of the drug according to the large experience in the Phase III trials, including patients with frailty [35, 36], obesity, older age [37] and mild-to-moderate CKD [38, 39].

Edoxaban shows a relatively low total plasma protein binding (≈55%), whereas the human-unique metabolite M-4 is approximately 80% bound to plasma proteins over a concentration range of 0.2–2 µg/mL [34].

Edoxaban is primarily eliminated unchanged in urine and through biliary secretion, with a mean elimination half-life in the range of 10–14 h [24, 34]. The total clearance of edoxaban is estimated to be ≈22 L/h, with renal clearance estimated to be about 10 L/h [34]. Due to the relevant renal clearance, the edoxaban exposure has been shown in a pharmacokinetic study of patients with NVAF in the ENGAGE AF-TIMI 48 study, to be higher in patients with creatinine clearance (CrCl) above 90 mL/min [40]. The lower exposure of edoxaban is associated with an apparent lower relative efficacy for edoxaban compared to warfarin in patients

Table 1 Geometric mean (% coefficient of variation) of pharmacokinetic parameters after single or multiple administration of 30 and 60 mg edoxaban. Modified from Ogata et al. [24]

Edoxaban dose	30 mg single ($n=10$)	60 mg single ($n=10$)	60 mg multiple ($n=9$)
$AUC_{0-\infty}$, ng/h/mL	993 (13.7)	1779 (11.6)	1572 (11.2)
C_{max}, ng/mL	152 (21.8)	302 (33.9)	266 (25.3)
t_{max}, h[a]	1.00 (0.50–2.00)	1.27 (0.50–2.50)	2.00 (1.00–3.50)
$T_{1/2}$, h	8.92 (36.2)	8.90 (20.2)	10.4 (30.2)
CLR_{0-48}, mL/min	194 (9.21)	222 (15.9)	237 (28.0)

AUC area under the curve

[a] Median (minimum – maximum)

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with a CrCl > 95 mL/min [39]. On this basis, the Cardio-renal Division of the US Food and Drug Administration recommended that edoxaban not be used in patients with a CrCl > 95 mL/min for stroke prevention in NVAF [41]. The position of FDA was not followed by other regulatory agencies in Europe by the European Medicines Agency (EMA), in three Asian countries (Japan, Korea and Taiwan) [39] as well as in Canada [42], which did not restrict the use of edoxaban in these patients. In addition, further analysis showed a similar behaviour at high glomerular formulation rate (GFR) (> 95 CrCl) for other NOACs [43]. Notwithstanding, the same analysis that documented the lower relative efficacy in patients with a CrCl > 95 mL/min, showed that the overall net clinical benefit of edoxaban remained unchanged irrespective of renal function [39].

In healthy human subjects, six phase 1 metabolites (M-1, M-2, M-4, M-5, M-6 and M-8) and a glucuronide (M-3) were detected in plasma [34]. M-4 is the major metabolite and it is produced from the hepatic carboxylesterase-1 (CES1). Cytochrome P450 isoenzyme (CYP) 3A4 mediates the formation of M-5, while a minor metabolite M-8 derives spontaneously (non-enzymatically) from an intermediary, hydroxymethyl edoxaban, formed via CYP3A4/5 [34, 44].

Three of the metabolites (M-4, M-6 and M-8) have anticoagulant activity, with IC_{50} values for anti-FXa of 1.8 nM (M-4), 6.9 nM (M-6) and 2.7 nM (M-8) [34]. However, due to the low plasma concentration and high protein binding, the most abundant metabolite, M-4, is not expected to contribute significantly to the overall pharmacological activity of edoxaban [45]. Importantly, the relative increase in edoxaban and M-4 systemic exposure is identical, and the AUC ratio (M-4 over edoxaban) is constant over varying kidney function, body weight, and doses [45]; however, a significant increase of M-4/edoxaban ratio is predictable in the presence of drugs that induce edoxaban metabolism (see paragraph Interaction with antifungal, antibiotics and antiepileptic drugs).

Unlike the other factor Xa inhibitors rivaroxaban and apixaban, CYP3A4-type cytochrome P450-dependent elimination is marginally involved in the hepatic clearance of edoxaban [46].

3 Pharmacological Interactions

3.1 Pharmacologist and Clinician Point of View: General Considerations

As previously discussed, edoxaban and all other NOACs are substrates for P-gp, therefore strong inhibition of P-gp can increase absorption and exposure of NOACs, thus increasing the bleeding risk. On the other hand, an induction of P-gp can reduce NOACs absorption, therefore reducing the antithrombotic therapeutic effect of edoxaban. Indeed, an important interaction mechanism for all.

NOACs consists of significant gastrointestinal re-secretion over a P-gp transporter after absorption in the gut and in their renal clearance [47]. Conversely, edoxaban was shown not to be a substrate of uptake transporters like OATP1B1 in the liver or OAT1, OAT3 and OCT2 in the kidney [32], thus excluding possible DDI with other substrates of these drug transporters.

The activity of the inhibition or induction of P-gp transporters, can help predict the entity of the change in edoxaban exposure (Table 1). This approach was adopted by the recently published "The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation" [6]. Thus, P-gp inhibitors may increase systemic absorption and decrease elimination of P-gp substrates, such as edoxaban, resulting in increased exposure. In this regard, it is relevant to consider that the extent of the inter-individual variability of a drug plasma concentration may have a significant impact of the interaction with P-gp inhibitors or inducers [48–50].

Since edoxaban metabolism, by CES1, CYP3A4 and via glucuronidation, is only marginally involved in its clearance, inhibitors or inducers of these enzymes are unlikely involved in clinically relevant interactions with edoxaban [34]. Indeed, unlike other direct anti Xa inhibitors such as rivaroxaban and apixaban, edoxaban is minimally involved in hydrolysis, conjugation and oxidation through CYP3A4 metabolism (< 4%) and theoretically we could expect fewer DDIs with agents that strongly inhibit or induce cytochrome P450 enzymes, in particular the CYP3A4 variant (Table 2).

In the following paragraphs we will summarise the clinical evidence of DDI of edoxaban with different classes of drugs and with phytotherapy or nutraceuticals, but also some tools to predict non-studied DDIs. These predictions are based on the pharmacological profile of edoxaban and the profile of the specific class of drugs that are being considered. The issue of how to identify and distinguish the clinically relevant DDIs from non-relevant interactions will also be discussed.

4 Edoxaban Drug-drug Interactions (DDI)

4.1 DDIs with Rate and Rhythm Control Drugs

Many classes of cardiovascular drugs might interact with NOACs via inhibition of P-gp and/or CYP3A4, thus leading to increased exposure and possibly increased bleeding risk. Interestingly, the Phase III clinical trials ENGAGE AF TIMI 48 [52] and Hokusai VTE [53], were the only pivotal trials that contemplated dose reduction with concomitant

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Table 2 Main inducers and inhibitors of CYP3A and P-gp Modified from Stöllberger et al. [51]

	P-gp inhibitor	Non-P-gp inhibitor	P-gp inducer
Strong CYP3A inhibitor	Itraconazole, ketoconazole, clarithromycin, lopinavir, indinavir, ritonavir, telaprevir	Voriconazole	
Moderate CYP3A inhibitor	Erythromycin, verapamil, diltiazem, amiodarone, dronedarone	None-identified	Doxorubicin
Weak CYP3A inhibitor	Lapatinib, quinidine, cyclosporine, felodipine, azithromycin, ranolazine	Cimetidine	Vinblastine
CYP3A inducers			Carbamazepine, phenytoin, phenobarbital, rifampin, dexamethasone, St John's Wort

CYP cytochrome P 450, *P-gp* P-glycoprotein

P-gp inhibitor drugs, in order to compensate for the increase in edoxaban absorption.

Many cardiovascular drugs are commonly prescribed with edoxaban in patients with NVAF (Table 3). For this reason, specific pharmacokinetic studies and post-hoc analysis of Phase III clinical trial ENGAGE AF-TIMI 48 has been performed. In particular, Mendell et al., reported results from six studies evaluating the potential pharmacokinetic interactions between edoxaban and cardiovascular drugs such as digoxin, atorvastatin, verapamil, quinidine, amiodarone, and dronedarone [54]. The relevance of the inhibition of P-gp on the final exposure of edoxaban was strikingly demonstrated by comparing the effect of drugs displaying differing degrees of P-gp inhibition, with verapamil, quinidine, dronedarone, and amiodarone, which are recognised as strong P-gp inhibitors [6], while digoxin and atorvastatin are recognised P-gp substrates [6, 55]. Indeed, verapamil, quinidine, dronedarone and amiodarone increased the AUC of edoxaban by about 50%, while digoxin or atorvastatin had relatively minor effects on the pharmacokinetic of edoxaban [54]. Interestingly, quinidine increased edoxaban exposure by only 35% after intravenous administration, thus significantly less than after oral administration (+77%) [54], further assessing the effect of P-gp inhibition at gastrointestinal level on the bioavailability of edoxaban [23].

The potential clinically relevant effect of drug interaction between edoxaban and amiodarone was also investigated by a subgroup analysis of the ENGAGE AF-TIMI 48 trial. Amiodarone was associated with significantly increased trough levels of edoxaban 60 mg (high dose, HD). Specifically, the concentrations were 58.5 ± 53.2 ng/mL with amiodarone versus 43.2 ± 41.1 ng/mL without amiodarone [56]. No significant interaction with respect to amiodarone use at baseline was observed for HD edoxaban on efficacy endpoint and safety endpoint, although an increase in clinically relevant non-major bleeding compared with warfarin was observed [56]. The SmPC does not require reduction of edoxaban dosage with amiodarone concomitant use [16, 57].

As for quinidine and verapamil, pharmacological data show a total increase in edoxaban exposure of respectively 77% and 53% [54], but after analysis of Phase III data these interactions alone were not considered clinically relevant

Table 3 Commonly co-prescribed cardiovascular drugs in patients with atrial fibrillation and effects on edoxaban exposure and indications of dosage recommendation

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
Cardiovascular drugs			
Amiodarone	Moderate P-gp competitive inhibition	+40% AUC [24]	No dose adjustment (use with caution) [6, 59]
Digoxin	P-gp competitive inhibition	No significant effect on AUC [24]	No dose adjustment [6, 59]
Diltiazem	P-gp competitive inhibition and weak CYP3A4 inhibition	No significant effect on AUC predicted	No dose adjustment [6]
Dronedarone	P-gp inhibitor and CYP3A4 inhibitor	+85% AUC [24]	Use edoxaban 30 mg [6, 59]
Quinidine	P-gp competitive inhibition	+77% AUC [24]	No dose adjustment (use with caution) [6, 59]
Verapamil	P-gp competitive inhibition and weak CYP3A4 inhibition	+53% AUC [23]	No dose adjustment (use with caution) [6, 59]

AUC area under the curve, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

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so no dose reduction is required in the European SmPC, but caution if other factors that might increase edoxaban exposure are present [6]. No action is then recommended with atorvastatin and digoxin [6] that did not alter edoxaban exposure.

In this regard, it is important to point out that the characterisation of edoxaban population pharmacokinetics and the identification of potential intrinsic and extrinsic factors affecting variability in edoxaban exposure, demonstrated that edoxaban exposure in patients with moderate renal impairment receiving strong P-gp inhibitors could potentially increase the steady state AUC (AUC_{ss}) and C_{min} ($C_{min,ss}$) exposure up to ~2.5- and threefold of the expected exposure in patients with normal renal function [58]. Thus, in the presence of a moderate renal impairment (creatinine clearance 30–50 mL/min), either quinidine or verapamil may significantly increase edoxaban exposure (Fig. 2).

In view of the pharmacokinetic and clinical data, the SmPC [16, 57] and European Heart Rhythm Association (EHRA) practical guide, it is suggested dose reduction in case of a co-treatment of edoxaban with dronedarone, no dose reduction, but caution with amiodarone (+40% of edoxaban AUC), quinidine (+77% of edoxaban AUC) and verapamil (+53% of edoxaban AUC) and no action with a digoxin [6] (Table 3).

4.2 DDIs with Antiplatelet and Antithrombotic Drugs

Given the common occurrence of coronary artery disease with NVAF, the possible interactions of edoxaban with antiplatelet drugs could be clinically relevant (Table 4).

Dual-antiplatelet therapy with aspirin and $P2Y_{12}$ antagonist is currently recommended after percutaneous coronary

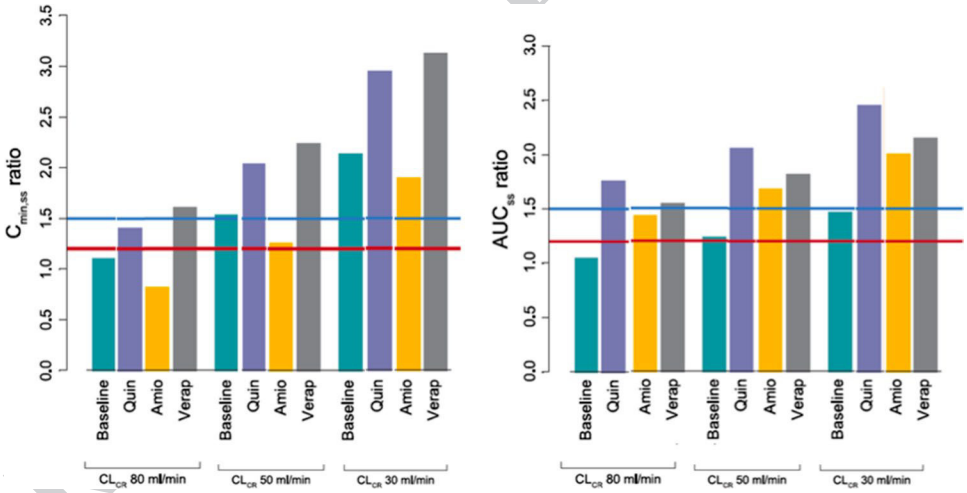

Fig. 2 Edoxaban pharmacokinetic modifications according rate/rhythm control drugs and renal function. Red line shows 20% increase in exposure, blue line shows 50% increase in exposure. *Amio* amiodarone, *AUC* area under the curve, CL_{CR} creatinine clearance, *Quin* quinidine, *Verap* verapamil. Modified from Salazar et al. [58]

Table 4 Predicted effects of antiplatelet and antithrombotic drugs on edoxaban exposure and indications of dosage recommendation

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
Cardiovascular drugs			
Aspirin	No relevant interactions known/assumed	Increased AUC for high doses of aspirin; pharmacodynamically increased bleeding time [62]	No dose adjustment; Chronic use not recommended [59]
Clopidogrel	No relevant pharmacokinetic interactions known/assumed	No significant effect on AUC predicted; pharmacodynamically increased bleeding time	No dose adjustment[a]
Ticagrelor	P-gp competitive inhibition [66, 67]	Predicted increased of AUC; pharmacodynamically increased bleeding time	No dose adjustment [6] (use with caution for harmacodynamics effect[a])
Prasugrel	P-gp substrate [68]	Predicted pharmacodynamically increased bleeding time	No dose adjustment (use with caution for harmacodynamics effect)[a]

AUC area under the curve, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

[a]Expert opinion

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intervention (PCI) with stent placement, and further oral anticoagulation is required for patients with NVAF. Therapy with a NOAC, aspirin, and clopidogrel ($P2Y_{12}$ inhibitor) is considered the standard of care for patients with NVAF following coronary stent placement. However, this triple therapy is associated with a 3- to 4-fold increased risk of bleeding complications [60, 61]. This was the rational of studying a possible pharmacokinetic and pharmacodynamic interaction between edoxaban and aspirin [62].

Low-dose aspirin (100 mg) did not alter the edoxaban pharmacokinetic parameter, whereas the combination with aspirin 325 mg increased edoxaban systemic exposure by approximately 30% (AUC) and 34% for C_{max} [62]. The reason for increased exposure with high-dose aspirin is not clear and unknown, but high-dose aspirin did not alter the effect of edoxaban on the coagulation biomarkers, and the inhibition of platelet aggregation (arachidonic acid induced) by aspirin was not affected by edoxaban [62]. Nevertheless, the administration of edoxaban with aspirin 100 mg (low dose), or aspirin 325 mg (high dose) resulted in an approximately additive effect of the agents administered alone with a final twofold increase in bleeding time [62], thus suggesting a potential pharmacodynamics interaction between the two drugs [62].

The subgroup analysis of the ENGAGE AF-TIMI 48, observed that single antiplatelet therapy in addition to an anticoagulant had a similar risk of stroke/SEE and higher rates of bleeding than those not receiving the antiplatelet drug. Edoxaban exhibited similar relative efficacy and reduced bleeding compared to warfarin, with or without concomitant use of antiplatelet therapies, including clopidogrel and ticagrelor [63]. Nevertheless, a potential pharmacodynamic interaction with increasing risk of major bleeding is predictable in patients treated with NOACs under mono- or dual-antiplatelet therapy. Indeed, some of these drugs are substrates (clopidogrel, enoxaparin), or inhibitors (ticagrelor, naproxen) of P-gp [64–67], suggesting a possible pharmacokinetic interaction with NOACs.

4.3 DDIs with Statins and Lipid-modifying Agents

Considering the high rate of CVD in the elderly, especially CHD in concomitance with NVAF, the co-administration of a lipid-modifying agent and NOACs is quite common. Several statins interact with P-gp and CYP450, being both their substrates and inhibitors [69, 70] (Table 5). For example, atorvastatin, lovastatin and simvastatin inhibit or compete with P-gp-mediated drug transport and are metabolised by CYP3A4. These characteristics might lead to an increased absorption of NOACs [51]. Lovastatin is a CYP2C9- and P-gp inhibitor. In a population-based, nested case–control study involving 45,991 Ontario residents who started dabigatran, the use of lovastatin was associated with a higher

Table 5 Predicted effects of lipid-modifying agents on edoxaban exposure and indications of dosage recommendation

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
Lipid-lowering agents			
Atorvastatin	P-gp substrate and moderate inhibitors; CYP3A4 substrate and moderate inhibitors	No significant effect on AUC predicted	No dose adjustment(12. 6)
Lovastatin, simvastatin	P-gp substrate and moderate inhibitors; CYP3A4 substrate	Minor effect on AUC predicted	No dose adjustment[a]
Pravastatin	No relevant interactions known/assumed	No significant effect on AUC predicted	No dose adjustment[a]
Rosuvastatin	CYP2C9 substrate	No significant effect on AUC predicted	No dose adjustment[a]
Fluvastatin	CYP2C9 substrate and inhibitor	No significant effect on AUC predicted	No dose adjustment[a]
Gemfibrozil	CYP2C8 inhibitor	No significant effect on AUC predicted	No dose adjustment[a]
Fenofibrate	CYP3A4 inhibitor, moderate P-gp inhibition	Minor effect on AUC predicted	No dose adjustment (use with caution)[a]
Ezetimibe	Minor CYP3A4 inhibition, P-gp substrate	No significant effect on AUC predicted	No dose adjustment[a]
Evolocumab	No relevant interactions known/assumed	No significant effect on AUC predicted	No dose adjustment[a]

AUC area under the curve, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

[a]Expert opinion

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risk of major haemorrhage [71]. Similar effects can also be predicted for edoxaban.

The pharmacokinetics of edoxaban is not affected by atorvastatin (weak inhibitor of P-gp) [55, 72]. Indeed, atorvastatin induces a non-significant increase of 1.7% in edoxaban AUC and a decrease by 14.2% in C_{max} [54]. Other statins such as pravastatin and rosuvastatin have limited involvement in the CYP3A4 metabolism, while fluvastatin is metabolised by CYP2C9.

Other commonly used lipid-lowering agents that might interact with NOAC metabolism are fibrates. Medicaid claims data showed that fibrates that are metabolised by CYP3A4 appear to increase the risk of gastrointestinal bleeding in warfarin users [73]. Fenofibrate is an inhibitor of CYP3A4 [74] while gemfibrozil is not a CYP3A4 inhibitor, but it is a competitive inhibitor of CYP2C8 [75]. The only fibric acid that showed moderate P-gp inhibition in vitro is fenofibrate [76, 77]. By virtue of the minor involvement of CYP3A4 metabolism, the only fibrate that might alter edoxaban exposure is fenofibrate, because of the possible inhibition on the P-gp transporter, although this interaction may not be clinically relevant.

Another cholesterol-lowering agent that can be used alone or in combination with statins is ezetimibe. Ezetimibe does not induce or inhibit CYP3A4 or P-gp, interactions with NOACs seem to be improbable.

Finally, considering PCSK9 inhibitor evolocumab and alirocumab, no CYP and P-gp involvement is expected as its metabolism and elimination follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids [78]; thus, no interactions are predicted with edoxaban or other NOACs. To date, no pharmacokinetic studies of interaction between edoxaban and fibrates, ezetimibe and PCSK9 inhibitors exist.

4.4 DDIs with Antibiotics and Antifungal Drugs

It is well established that antibiotic and fungistatic medications have strong interference with VKAs. Among these drugs, erythromycin, clarithromycin, rifampin, ketoconazole, fluconazole, posaconazole may also alter NOAC concentrations by interfering with the P-gp pathway and with the CYP3A4 metabolism, and certain concomitant antibiotic treatments should require accurate evaluation and an eventual dose adjustment (Table 6).

Among the different classes of antibiotics, macrolides, such as clarithromycin and erythromycin, are the best-known P-gp inhibitors which reduce CYP3A4 activity. Macrolide antibiotics have been associated with increased exposure of NOACs, even though there are no data available about azithromycin [6, 79, 80]. The entity of the DDI between edoxaban and erythromycin has been investigated in a pharmacokinetic study on healthy subjects [81]. Erythromycin decreased the total apparent clearance of edoxaban by about 47%, which translated to a significant increase in both peak (+68%) and total exposure (+85%) of edoxaban. Similarly,

Table 6 Predicted effects of antibiotics and antifungal drugs on edoxaban exposure and indications of dosage adjustment

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Reasonable indication and suggested dosage adjustment
Antibiotics			
Erythromycin	P-gp substrate; CYP3A4 inhibition	AUC: +85% [81]	Adjust dose to edoxaban 30 mg [6, 59]
Clarithromycin	P-gp substrate; CYP3A4 inhibition	Predicted increase of AUC	Adjust dose to edoxaban 30 mg [59]
Rifampin	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	AUC: −35%, compensatory increase of active metabolites	No dose adjustment (use with caution) [6, 59]
Metronidazole	CYP3A4 inhibitor	No significant effect on AUC predicted	No dose adjustment[a]
Levofloxacin	CYP1A2 inhibitor	No significant effect on AUC predicted	No dose adjustment[a]
Ciprofloxacin	CYP1A2 inhibitor	No significant effect on AUC predicted	No dose adjustment
Meropenem	CYP3A4 and CYP2C19 inhibition	No significant effect on AUC predicted	No dose adjustment[a]
Antifungals			
Ketoconazole	Potent P-gp and BCRP competitive inhibition; CYP3A4 inhibition	AUC: +87% [81]	Adjust dose to edoxaban 30 mg [6, 59]
Itraconazole, voriconazole	Potent P-gp and BCRP competitive inhibition; CYP3A4 inhibition	Predicted increase of AUC	Adjust dose to edoxaban 30 mg [6, 59]

AUC area under the curve, *BCRP* breast cancer resistance protein, CYP cytochrome P 450, *P-gp* P-glycoprotein

[a]Expert opinion

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the peak and total exposure of M-4 were approximately 75% and 78% higher, respectively, when administered with erythromycin, with no change in the formation of M-4 metabolite [81]. Given the decreases in both apparent clearance and volume of distribution, these data suggest that bioavailability increased owing to inhibition of P-gp in the gut by erythromycin [81]. This pharmacological interaction is considered clinically relevant and the EHRA indicated dose adjustment [6], in line with the SmPC [15, 57]. In addition, the exposure to other NOACs increases if macrolides are taken in concomitance, but no specific dose reduction was studied in this contest. The EHRA 2018 practical guide suggests considering dose adjustment if another factor for increased exposure is present, while for other NOACs, dose adjustment is recommended only with other concomitant factors for risk reduction [6], given the pharmacological data on the impact of clarithromycin on their metabolism [79]. It is our expert opinion that with macrolides, edoxaban 30 mg could be a facilitating approach.

Rifampin is one of the most relevant inducer of CYP3A4/5 and P-gp [82, 83]. Concomitant use of rifampin may lead to a decrease in edoxaban and NOAC exposure due to induction of P-gp and CYP3A4/CYP2J2. The effect of rifampin on edoxaban exposure has been evaluated in a specific pharmacokinetic study of multiple doses of the antibiotics on a single-dose of edoxaban and its active metabolites M-4 and M-6 [84]. Rifampin determined an approximate 34% decrease in total exposure to edoxaban (AUC), when compared with administration of edoxaban alone, and unlike other NOACs, a concomitant compensatory 5- and 4-fold increase of C_{max} values of metabolites M-4 and M-6, respectively [84]. These results demonstrate a significant drug interaction of edoxaban and its metabolites with rifampin. However, the concomitant increase in both M-4 and M-6 metabolites led to a final neutral effect, suggesting that the co-administration of the two drugs is possible [16]. Edoxaban is the only NOAC that can be used with rifampin. Nevertheless, since not tested prospectively, the EHRA indicated that this combination should be used with caution, and avoided when possible [6]. Apart from edoxaban, other NOACs are contraindicated with rifampin in Europe [6]. Nonetheless, US SmPC suggest to avoid concomitant use, even though on scarce evidence [57].

Metronidazole is known for having a major interaction with VKAs and dose reductions are often necessary to maintain INR in range. There is no direct evidence with NOACs, but metronidazole has been reported to increase plasma concentration and toxicities in a number of CYP3A4 substrates [85]. It has been suggested that metronidazole, among other drugs, is a CYP3A4 inhibitor and concomitant administration of certain CYP3A4 substrates should be avoided [86]. In contrast, a pharmacokinetic study provided evidence that metronidazole does not act as an inhibitor of P-gp-mediated disposition in humans [87]. On the basis of current evidence, we do not recommend dose adjustment for metronidazole concomitant use.

The antifungals itraconazole, ketoconazole, and voriconazole, are strong inhibitors of P-gp, breast cancer resistant protein (BCRP) and CYP3A4, suggesting a potential pharmacological interaction with NOAC, including edoxaban. This hypothesis has been tested in an open-label, randomised, two-period, two-treatment crossover study in healthy subjects under co-treatment with ketoconazole and edoxaban [81]. As predicted, ketoconazole increased total exposure of edoxaban by approximately 90%. Exposure to the metabolite M-4 was higher when edoxaban was co-administered with ketoconazole, with approximately 46% higher total exposures, potentially due to increased bioavailability without a significant alteration of its formation mediated by CES-1. On the contrary, both peak and total exposure to the metabolite M-6, derived from the CYP3A4 activity, was decreased by 51% and 43%, respectively [81]. The inhibitory effect of ketoconazole on CYP3A4 is also demonstrated by the fact that the metabolite-to-parent drug ratio was decreased from 4.44 to 1.45 [81]. From this analysis, it is suggested to reduce the dose of edoxaban by 50% in case of a co-administration with antifungals (itraconazole, ketoconazole, and voriconazole) [6]. Similar indication has been decided for posaconazole, whereas fluconazole is not expected to interact with edoxaban [6]. While other NOACs are contraindicated in this eventuality, edoxaban can be used in concomitance reducing the dosage to 30 mg due to increased exposure [6, 81].

4.5 DDIs with Antineoplastic and Immune-modulating Agents

Cancer patients are at higher risk for thromboembolic events due to the presence of comorbidities, surgical interventions and chemotherapy [88]. Data on the use of NOACs in cancer patients is very limited and little clinical information is available when considering the effect that specific antineoplastic drugs might have on NOAC exposure. However, the results of the Hokusai VTE Cancer trial clearly demonstrated that treatment with a fixed once-daily dose of oral edoxaban for up to 12 months was noninferior to treatment with subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding in patients predominantly with advanced cancer and acute symptomatic or incidental venous thromboembolism [89].

Among the 1046 patients enrolled in the study, only 16 (3.0%) were, at randomisation, under treatment with P-gp inhibitors in the edoxaban group and 21 in the dalteparin group [89]. In more detail, the trial excluded patients anticipated to continue therapies with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or saquinavir, while the use of

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ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin was permitted with appropriate dose reduction of edoxaban [89].

Patients in the edoxaban group, were exposed to many different classes of anticancer drugs, such as antimetabolites, platinum-based chemotherapy, taxanes, topoisomerase inhibitors, alkylating agents, anthracyclines, vinca alkaloids, kinase inhibitors and antitumor antibiotics [89] (Table S1). These agents might have significant influence on CYP3A4 and/or P-gp metabolism, thus altering NOAC exposure.

Since antineoplastic agents usually undergo hepatic metabolism and transformation, to a variable extent, the pharmacokinetic profile of edoxaban appears particularly favourable in this setting in view of its limited CYP3A4 metabolism, even if the interaction with P-gp has to be carefully considered (Table S2). For example, the Bruton's tyrosine kinase ibrutinib significantly increases risk of NVAF, with an estimated cumulative incidence of 5.9% at 6 months and increasing to 10.3% by 2 years of treatment [90]. The management of NVAF induced by ibrutinib is complicated by the fact that this drug is also a P-gp inhibitor, thereby increasing exposure to substrates such as NOACs [91]. It has been suggested that NOACs such as edoxaban and dabigatran that have limited influence on CYP3A4 metabolism might have a lower risk of DDI with ibrutinib [92], but caution has been suggested with its use (Table S2).

Given the clinical evidence provided by the Hokusai VTE Cancer and the expert opinion [6] regarding the pharmacological interactions of NOACs and antineoplastic agents, edoxaban use might be a good choice in case of treatment with the following agents:

- Antimitotic agents: paclitaxel, docetaxel, vincristine.
- Topoisomerase inhibitors: etoposide.
- Anthracycline: idarubicin.
- Alkylating agents: ifosfamide, cyclophosphamide, lomustine.
- Tyrosine kinase inhibitors: vemurafenib, dasatinib.
- Hormonal agents: bicalutamide, anastrozole.
- Immune-modulating agents: cyclosporine, prednisone, temsirolimus, sirolimus.

4.6 DDIs with Antiepileptic Drugs

Seizures are seen in up to 10% patients after stroke and and account for 30% to 40% of all cases of epilepsy in the elderly [93]. Most of these patients require long-term antiepileptic drug treatment. Furthermore, the same drugs are also prescribed for neuropathic pain, migraine, headaches, or psychiatric disorders. Thus, it is conceivable to conclude that a considerable number of patients under treatment with NOACs would be on concomitant therapy with antiepileptic drugs (Table 7). Little clinical evidence exists regarding interactions between antiepileptic drugs and NOACs. There is evidence that a number of these drugs induce CYP3A4 and P-gp leading to reduced NOAC exposure [94].

Human, animals, and in vitro evidence has demonstrated that carbamazepine [95], levetiracetam [96], phenobarbital [97], phenytoin [98] are potent inducers of P-gp, and therefore may lead to reduced edoxaban and NOAC plasma concentrations and clinical efficacy. In the summary of product characteristics, it is suggested that edoxaban should be used with caution when co-administered with such P-gp inducers, although direct evidence for a clinically relevant pharmacological interaction with these drugs is still missing.

According to the EHRA practical guide, the use of carbamazepine, phenobarbital, and phenytoin is only possible with edoxaban and apixaban [6]. In this case the concomitant use should be made with caution if it cannot be avoided, because there still is a decreased absorption that might lead to minor efficacy of these NOACs [6], even though no data about edoxaban are available.

A more stringent indication was deserved for valproic acid and levetiracetam, whose con-administration with edoxaban and all other NOACs is contraindicated [6], probably due to their more potent effect on P-gp [99, 100]. On the contrary, other antiepileptic drugs, that do not affect P-gp function, such as ethosuximide, gabapentin, lamotrigine [101], pregabalin [101], and zonisamide, are not predicted to interact with edoxaban [6]. Finally, the use of oxcarbazepine and topiramate is possible without relevant DDIs only with edoxaban and dabigatran due to absence of CYP3A4 metabolism. Unfortunately, the clinical relevance of these drug interactions is largely unknown since mainly data from in vitro and animal studies are available [94]. Although all NOACs are consider to interact with P-gp inducers [6], the influence of these drugs on edoxaban can be considered less problematic due to the compensatory increase of the active metabolite M-4. Indeed, in the EHRA guidelines, in contrast to dabigatran and rivaroxaban, the use of carbamazepine, phenobarbital and phenytoin is not contraindicated with edoxaban and apixaban [6]. It can be hypothesised that antiepileptic drugs that do not have an effect on CYP3A4 and P-gp, such as ethosuximide, gabapentin, lamotrigine, pregabalin and zonisamide, can be used with all NOACs without relevant pharmacological interaction [6, 94].

4.7 DDI with Antidepressants and Antipsychotic Drugs

It is estimated that 7.2% of the general European population in the EU had used antidepressant in 2010 [102]. Given the high prevalence of the use of this type of drug, it is quite common to have concomitant anticoagulant use in patients with atrial fibrillation or VTE, thus exposing the patients to the risk of pharmacological interactions (Table 8).

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Table 7 Predicted effects of antiepileptic drugs on edoxaban exposure and indications of dosage recommendation. Modified from Steffel et al. [6]

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competitive inhibition	Decrease in AUC [59]	No dose adjustment (use with caution for potential decrease of plasmatic concentration) [59]
Ethosuximide	CYP3A4 competitive inhibition; no relevant interaction known/assumed	No significant effect on AUC predicted	No dose adjustment$_{(6)}$
Gabapentin	No relevant interactions known/assumed	No significant effect on AUC predicted	No dose adjustment [6]
Lamotrigine	P-gp competitive inhibition; no relevant interaction known/assumed	No significant effect on AUC predicted	No dose adjustment [6]
Levetiracetam	P-gp induction; P-gp competitive inhibition	Significant decrease in AUC predicted	Should not be used [6]
Oxcarbazepine	CYP3A4 induction; P-gp competitive inhibition	No significant effect on AUC predicted	No dose adjustment [6]
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competitive inhibition	Decrease in AUC [59]	No dose adjustment (use with caution for potential decrease of plasmatic concentration) [12]
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competitive inhibition	Decrease in AUC [59]	No dose adjustment (use with caution for potential decrease of plasmatic concentration) [59]
Pregabalin	No relevant interactions known/assumed	No significant effect on AUC predicted	No dose adjustment [6]
Topiramate	CYP3A4 induction; CYP3A4 competitive inhibition	No significant effect on AUC predicted	No dose adjustment [6]
Valproic acid	CYP3A4/P-gp induction	Significant decrease in AUC predicted	Should not be used [6]
Zonisamide	CYP3A4 competitive inhibition; no relevant interactions known/assumed	No significant effect on AUC predicted	No dose adjustment [6]

AUC area under the curve, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

Many psychotropic drugs interact with anticoagulants both on a pharmacokinetic and a pharmacodynamic level. For instance, it has been shown that selective serotonin reuptake inhibitors (SSRIs) can cause an antiplatelet effect [103]. Indeed SSRIs have been clinically associated with an increased risk in bleeding with concurrent coumarins [104], also with dabigatran, in the RE-LY study and with rivaroxaban in the clinical trial programme, where the association with SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) was related to an increased risk of bleeding in all treatment groups [105, 106]. Due to its effect on platelets, SSRIs and SNRIs could have an increased risk of bleeding with all concomitant anticoagulants.

Considering the potential pharmacokinetic interactions, in vitro data showed that sertraline and paroxetine have a relevant P-gp inhibition, bearing a large potential to influence the absorption of co-administered drugs at the level of P-gp, while citalopram, venlafaxine had only a very weak inhibition [107]. Fluoxetine showed no significant effect on P-gp function in vitro or in vivo [108].

On this basis, we could hypothesise that edoxaban and the other NOACs might interact especially with paroxetine and sertraline.

Examining the influence on the metabolism of cytochromes, the only SSRI that appears to moderately inhibit CYP3A4 is fluvoxamine, while sertraline, citalopram, paroxetine, venlafaxine, duloxetine have no any effect on CYP3A4 and fluoxetine has only a mild effect [109]. Fluvoxamine, therefore, might influence the metabolism of NOACs that are metabolised by CYP3A4.

Other psychoactive drugs that might bear potential for interaction with NOACs are antipsychotics, such as clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole and amisulpride. These drugs are substrates of P450 cytochrome, but are unlikely to interfere with the elimination of other drugs through this path [110]. However, most antipsychotics act as inhibitors of P-gp, and can therefore influence plasma and brain concentrations of other drugs. Risperidone and olanzapine are the most likely agents that may relevantly inhibit P-gp activity [111, 112]. Therefore, we could predict that these antipsychotics have

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Table 8 Predicted effects of antidepressants and antipsychotic drugs on edoxaban exposure and indications of dosage recommendation

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
SSRI			
Sertraline, paroxetine	P-gp inhibition, CYP2D6 inhibition	Possible increase of AUC predicted	No dose adjustment (use with caution)[a]
Citalopram	Weak P-gp inhibition, CYP2D6 inhibition	No significant effect on AUC predicted	No dose adjustment[a]
Fluoxetine	Mild CYP3A4 inhibition, CYP2D6 inhibition, CYP2C19 inhibition, CYP2C9/10 inhibition	No significant effect on AUC predicted	No dose adjustment[a]
Fluvoxamine	Moderate CYP3A4 inhibition, CYP2C19 inhibition, CYP2C9/10 inhibition, CYP1A2 inhibition	No significant effect on AUC predicted	No dose adjustment[a]
SNRI			
Duloxetine	No relevant interactions known/assumed, CYP2D6 inhibition	No significant effect on AUC predicted	No dose adjustment[a]
Venlafaxine	Weak P-gp inhibition,	No significant effect on AUC predicted	No dose adjustment[a]
Antipsychotics			
Risperidone, olanzapine	P-gp inhibition	Possible increase of AUC predicted	No dose adjustment (use with caution)[a]
Clozapine, quetiapine, sertindole, ziprasidone, aripiprazole, amisulpride	Possible P-gp inhibition	No significant effect on AUC predicted	No dose adjustment[a]

AUC area under the curve, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

[a]Expert opinion

the highest potential to interfere with edoxaban and other NOAC concentrations.

4.8 DDIs with Antiparkinsonian and Anti-Alzheimer's Disease Drugs

Age is the most important risk factor for the most highly prevalent diseases in Western countries and neurodegeneration is a particularly relevant concern in the elderly patient. Along with the ageing of the population, neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are becoming more common [113, 114]. PD affects 1–2 per 1000 of the population at any time and it affects 1% of the population above 60 years [115]. Dementia is especially prevalent in North America and Western Europe (6.4 and 5.4% of the population at age 60) with the risk that rises exponentially with age [116].

Given the high prevalence of NVAF, many of these patients are treated in concomitance with antiparkinsonian or AD medication and NOACs but the direct pharmacological evidence for DDIs is poor. For some of these patients, other clinical concerns could emerge such as the risk of falling that might increase the haemorrhage risk or compliance issues that might reduce the efficacy of NOACs (Table S3).

Considering pharmacokinetics, levodopa is reported to be a P-gp substrate [117, 118], but neither levodopa nor carbidopa are reported to influence P-gp or CYP3A4 so a relevant pharmacokinetic interaction between edoxaban and levodopa/carbidopa seem to be improbable.

Dopamine agonists like pergolide, bromocriptine or pramipexole are substrates of the P-gp transporter system but only bromocriptine is reported to be a P-gp inhibitor [118]. Bromocriptine is also a strong CYP3A4 inhibitor in vitro, while pergolide and pramipexole are CYP2D2 inhibitors [119].

Taking into account MAO-B inhibitors, there is no evidence of interaction between P-gp and selegiline, rasagiline and safinamide [120, 121]. Safinamide seem to have no activity on the CYP systems [122]; moreover, rasagiline and selegiline are metabolised by the CYP1A2 and CYP2D6 [121] respectively, but do not have any inhibitory or induction influence on the cytochrome CYP. Taking into account these considerations an interaction with edoxaban or other NOACs seem to be unlikely.

With respect to catechol *O*-methyltransferase (COMT) inhibitors, the DDIs with edoxaban seem to be equally improbable. Entacapone, nebicapone and opicapone were not identified in vitro as P-gp substrates [123, 124].

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Tolcapone and entacapone might inhibit CYP2C9; thus, influencing warfarin INR [125, 126], but this would have little or no influence on edoxaban, as its metabolism is minimally involved through the cytochrome system.

Another drug used to treat side effects of PD is the antiviral agent amantadine. This medication was shown to be a non-substrate for P-gp [127] so a DDI with edoxaban seems unlikely.

Considering the most commonly prescribed medications in patients affected by AD, donepezil is reported to have a low P-gp affinity and a weak CYP3A4 inhibition [128] so any DDIs in vivo seem to be improbable with edoxaban. The same might apply with galantamine—a CYP3A4 and CYP2D6 substrate [129], but has no effect on warfarin cynetics and INR and no P-gp inhibition is reported [130]. Rivastigmine, on the other hand, is not involved in the CYP-450 metabolism [131], but was shown to have an inductive effect on P-gp in the mouse model [132]. Further studies are necessary to determine if the same could apply to human P-gp, and in that case a reduction of NOACs and edoxaban absorption could verify.

4.9 DDIs with Anti-human Immunodeficiency (HIV) and Anti-hepatitis C Virus (HCV) Drugs

Several combinations of agents belonging to at least two drug families are recommended for treating HIV [133] (Table 9). Integrase inhibitors (e.g. dolutegravir or raltegravir) and non-nucleoside analogue polymerase inhibitors (e.g. rilpivirine) are currently the preferred third agents used along with a two nucleos(t)ide analogue backbone, either abacavir/lamivudine or tenofovir/emtricitabine [134]. The use of HIV protease inhibitors has progressively been deferred, due to increased potential for DDIs and metabolic complications. Darunavir boosted with ritonavir or cobicistat is the only protease inhibitor still recommended as first-line HIV therapy [135]. With the exception of tipranavir, all HIV protease inhibitors are inhibitors of CYP3A4 [136], with ritonavir being the most potent and saquinavir the least. Ritonavir is also a strong P-gp inhibitor interfering with many drugs, and it may be expected to increase edoxaban exposure. Therefore, its co-administration with edoxaban, as well as other NOACs is not recommended [6]. Similarly, the pharmaco-enhancer cobicistat, in addition to being a potent inhibitor of cytochrome CYP3A4, also inhibits P-gp and BCRP transporters [137], and is predicted to increase the bioavailability of edoxaban and other NOACs [138].

Among the HCV protease inhibitors, simeprevir is a substrate and inhibitor of CYP3A4 and P-gp enzymes and through this action may increase the exposure of substrates for P-gp, such as edoxaban (Table 10). Paritaprevir is an HCV protease inhibitor that is boosted with ritonavir and thus this combination is predicted to increase the exposure of edoxaban. Grazoprevir is not a P-gp inhibitor based on

Table 9 Predicted effects of anti-HIV therapies on edoxaban exposure and indications of dosage recommendation Modified from West et al. [133]

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
DTG + ABC/TDF + 3TC	No inhibition	No significant effect predicted	No dose adjustment
DTG + TDF/TAF + FTC	No inhibition	No significant effect predicted	No dose adjustment
RAL + TDF/TAF + FTC	No inhibition	No significant effect predicted	No dose adjustment
EVGc + TAF/TDF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure	Not recommended
DRVc + ABC + 3TC	Cobicistat is a potent CYP3A4 and P-gp inhibitor and darunavir is a CYP3A4 inhibition	Possible increased exposure	Not recommended
DRVc + TDF/TAF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor and darunavir is a CYP3A4 inhibition	Possible increased exposure	Not recommended
ATVc + TDF/TAF + FTC	Cobicistat is a potent CYP3A4 and P-gp inhibitor	Possible increased exposure	Not recommended
DRVr + TDF/TAF + FTC	Ritonavir is a potent CYP3A4 and P-gp inhibitor	Likely increased exposure	Not recommended
DRVr + ABC + 3TC	Ritonavir is a potent CYP3A4 and P-gp inhibitor	Likely increased exposure	Not recommended
EFV + TDF/TAF + FTC	Inhibition of CYP3A4 and P-gp	Likely increased exposure	Not recommended
RPV + TDF/TAF + FTC	Inhibition of CYP3A4 and P-gp	Likely increased exposure	Not recommended
AZT + 3TC + EFV	Inhibition of CYP3A4 and P-gp	Likely increased exposure	Not recommended
TDF + 3TC/FTC + EFV	Inhibition of CYP3A4 and P-gp	Likely increased exposure	Not recommended
TDF + 3TC/FTC + NVP	Inhibition of CYP3A4 and P-gp	Likely increased exposure	Not recommended

3TC lamivudine, *ABC* abacavir, *ATVc* atazanavir + cobicistat, *CYP* cytochrome P450, *DRVc* darunavir + cobicistat, *DRVr* darunair + ritonavir, *DTG* dolutegravir, *EFV* efavirenz, *EVG* elvitegravir, *FTC* emtricitabine, *P-gp* P-glycoprotein, *RAL* raltegravir, *RPV* rilpivirin, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

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Table 10 Predicted effects of anti HCV drugs on edoxaban exposure and indications of dosage recommendation

Concomitant drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
HCV protease inhibitors			
Simeprevir	Substrate and inhibitor of CYP3A4 and P-gp	Possible increase in AUC predicted	No dose adjustment (use with caution)[a]
Grazoprevir	No relevant interactions described	No significant effect on AUC predicted	No dose adjustment[a]
NS5B polymerase inhibitors			
Sofosbuvir	P-gp substrate	No significant effect on AUC predicted	No dose adjustment[a]
Ledipasvir	P-gp/BCRP substrate and inhibitor	Possible increase in AUC predicted	No dose adjustment[a]
NS5A replication complex inhibitor			
Daclatasvir	CYP3A4 and P-gp substrate, P-gp and OATP1B1 moderate inhibition	Possible increase in AUC predicted	No dose adjustment[a]

AUC area under the curve, *BCRP* breast cancer resistance protein, *CYP* cytochrome P 450, *P-gp* P-glycoprotein

[a]Expert opinion

in vitro data, and thus it is not expected to interact with edoxaban.

Non-structural protein 5AB (NS5B) polymerase inhibitor, sofosbuvir, depicts an excellent pharmacokinetic profile, without significant interactions with other drugs because its metabolism does not involve the CYP450 pathway although it is a P-gp substrate [139].

Daclatasvir was the first-in-class developed HCV non-structural protein 5A (NS5A) replication complex inhibitor. Daclatasvir is a substrate for CYP3A4 and P-gp, and moderately inhibits P-gp and OATP1B1 [140]. Its interaction with edoxaban has not been evaluated; however, daclatasvir increases rosuvastatin exposure [140, 141], thus a similar effect with the OATP and/or BCRP substrates are predicted, including edoxaban [142]. A similar effect has been observed with ledipasvir, a substrate and inhibitor of P-gp/BCRP [143].

4.10 DDIs with Antacid Drugs

Consult the Supplementary Materials.

4.11 DDIs with NSAIDs Drugs

Consult the Supplementary Materials.

4.12 DDIs with Monoclonal Antibodies and Interleukin 6 (IL6)

Consult the Supplementary Materials.

4.13 DDIs with Omega-3 Polyunsaturated Fatty Acids

Consult the Supplementary Materials.

4.14 DDIs with Dietary Supplements, Nutraceuticals and Herbs

Consult the Supplementary Materials.

5 Conclusions

DDIs have received a great deal of recent attention from the regulatory, scientific, and health care communities worldwide. A large number of drugs are introduced every year, and new interactions between medications are increasingly reported. The co-administration of multiple therapies (polypharmacy) in patients with concomitant comorbidities may determine a significant and clinically relevant modification of a drug's absorption, distribution, metabolism and excretion phases.

The different pharmacokinetic properties of each NOAC may significantly influence the potential DDIs, although some similitudes exist. For instance, all NOACs are substrate of the P-gp and their bioavailability may be influenced by the presence of inducers or inhibitors of this drug transporter. For this reason, the inter-individual variability of drug plasma concentrations, lower for apixaban and edoxaban and higher for rivaroxaban and dabigatran, is a determining factor for triggering a clinically significant DDI.

The DDIs of NOACs can also be affected by inducers or inhibitors of CYP3A4. Edoxaban involvement in cytochrome catalysed elimination is negligible, thus less prone to interaction with inducers or inhibitors of CYP3A4 compared to other anti-Xa inhibitors. Furthermore, through hydrolysis, edoxaban metabolism produces the active metabolite M-4. For this reason, the reduction of edoxaban exposure by strong inducers of

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drug-metabolising enzymes, i.e. rifampin, may be partially compensated by the formation of M-4, an effect that is not observed with other NOACs.

In response to anticipated DDIs, possible strategies are recommended, including dosage reduction or different times of administration. In particular, in order to avoid the DDIs, it is possible to administer edoxaban two hours before the interacting drug or six hours after the use of P-gp inhibitors. It is then important not to underestimate the potential interactions of NOACs with dietary supplements, nutraceuticals and herbs, often utilised in elderly patients.

The introduction of NOACs in the clinical practice has certainly facilitated the use of anticoagulant therapies in patients under polypharmacy, with a significantly lower incidence of clinically relevant DDIs as compared to warfarin. However, additional studies and/or sub-analysis will be necessary to ascertain the DDIs, which currently are mainly derived from hypothetical conclusions.

The differences found between EU and US labelling, as well as with expert documents, could make it difficult to make specific decisions in some circumstances. It is important to underline the need for more data. The integration between all available data, together with the assistance of expert opinions, can help when making decisions, but this will need to be managed cautiously.

The present review/expert opinion has focused on edoxaban and on its DDIs with other commonly prescribed drugs and, although not every possible interaction has been studied from a clinical or pharmacological point of view, there are many situations in clinical practice where a decision must be made even if the evidence is sometimes weak. In accordance with EHRA suggestion, we point out how specific attention is needed with some drugs classes that present already known or possible significant DDIs. An evaluation of all the concomitant drugs is pivotal, addressing the more relevant ones, and eventually changing prescriptions of concomitant drugs. In this regard, the analysis of edoxaban DDIs suggests that the small propensity for interaction of this agent make its use a fairly acceptable clinical decision if the DDIs have been properly considered and correctly evaluated.

Compliance with Ethical Standards

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Drugs

Edoxaban and the Issue of Drug-Drug Interactions: from Pharmacology to Clinical practice

Alberto Corsini, Nicola Ferri, Marco Proietti*, Giuseppe Boriani

* Corresponding Author:
Dr Marco Proietti, MD FESC
Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Via Giuseppe La Masa 19, 20156, Milan, Italy
Tel: +39-02-39014458
e-mail: marco.proietti@unimi.it
ORCID ID: 0000-0003-1452-2478

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Table S1. Anticancer drug therapies continuing after randomization to edoxaban or dalteparin. From Raskob G.E et al. [1]

Anticancer drugs	**Edoxaban (N=522)**	**Dalteparin (N=524)**
Antimetabolites – no. (%)	124 (23.8)	118 (22.5)
Platinum-based chemotherapy – no. (%)	105 (20.1)	107 (20.4)
Monoclonal antibodies – no. (%)	42 (8.0)	54 (10.3)
Bevacizumab – no. (%)	13 (2.5)	17 (3.2)
Taxanes – no. (%)	40 (7.7)	47 (9.0)
Hormonal therapy – no. (%)	41 (7.9)	37 (7.1)
Topoisomerase inhibitors – no. (%)	30 (5.7)	48 (9.2)
Alkylating agents – no. (%)	30 (5.7)	38 (7.3)
Anthracyclines – no. (%)	22 (4.2)	25 (4.8)
Vinca alkaloids – no. (%)	16 (3.1)	18 (3.4)
Kinase inhibitors – no. (%)	18 (3.4)	18 (3.4)
Immunomodulating agents – no. (%)	16 (3.1)	9 (1.7)
Proteasome inhibitors – no. (%)	7 (1.3)	8 (1.5)
Antitumor antibiotics – no. (%)	5 (1.0)	5 (1.0)
Miscellaneous – no. (%)	14 (2.7)	14 (2.7)

Table S2. Predicted Effects of antineoplastic drugs on edoxaban exposure and indications of dosage recommendation; Modified from Steffel et al. [2]

Concomitant Drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Reasonable indication and dosage recommendation for edoxaban
Antimitotic agents			
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competitive inhibition	significant decrease in AUC predicted	Not recommended due to reduced plasma levels
Docetaxel, Vincristine	Moderate CYP3A4 induction; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Vinorelbine	Moderate CYP3A4 induction; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Antimetabolites			
Metotrexate	P-gp competitive inhibition; no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Topoisomerase inhibitors			
Topotecan	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Irinotecan	CYP3A4/P-gp competitive inhibition; no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Etoposide	Mild CYP3A4 induction; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Anthracyclines / Anthracenediones			
Doxorubicin	Strong P-gp induction; Mild CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	significant decrease in AUC predicted	Not recommended due to reduced plasma levels
Idarubicin	Mild CYP3A4 inhibition; P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Daunorubicin	P-gp competitive inhibition; no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Mitoxantrone	no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Alkylating agents			
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Lomustine	Mild CYP3A4 inhibition	no significant effect on AUC predicted	no dose adjustment
Busulfan	CYP3A4 competitive inhibition; no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Bendamustine	P-gp competitive inhibition; no relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Platinum-based agents			
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Intercalating agents			
Bleomycin, Dactinomycin	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Mitomycin C	No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Tyrosine kinase inhibitors			
Imatinib, Crizotinib	Strong P-gp inhibition; Moderate CYP3A4 inhibition; CYP3A4/P-gp competitive	significant increase in AUC predicted	Not recommended due to increased plasma levels

	inhibition		
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition; mild CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	possible increase in AUC predicted	use with caution - Consider dose adjustment if another moderate to strong P-gp inhibitor is used
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Vandetanib, Sunitinib	Strong P-gp induction; CYP3A4 competitive inhibition	significant decrease in AUC predicted	Not recommended due to reduced plasma levels
Erlotinib, Gefatinib	CYP3A4 competitive inhibition, No relevant interaction anticipated	no significant effect on AUC predicted	no dose adjustment
Ibrutinib	P-gp inhibitor; CYP3A4 competitive inhibition	possible increase in AUC predicted	no dose adjustment (use with caution)
Monoclonal antibodies			
Brentuximab	CYP3A4 competitive inhibition; No relevant interactions anticipated	no significant effect on AUC predicted	no dose adjustment
Rituximab, Alemtuzumab, Cetuximab, Trastuzumab, Bevacizumab	No relevant interactions assumed	no significant effect on AUC predicted	no dose adjustment
Hormonal agents			
Abiraterone	Moderate CYP3A4 inhibition; Strong P-gp inhibition; CYP3A4/P-gp competitive inhibition	significant increase in AUC predicted	Not recommended due to increased plasma levels
Enzalutamide	Strong CYP3A4 induction; Strong P-gp inhibition; CYP3A4/P-gp competitive inhibition	significant increase in AUC predicted	Not recommended due to increased plasma levels
Bicalutamide	Moderate CYP3A4 inhibition	no significant effect on AUC predicted	no dose adjustment
Tamoxifen	Strong P-gp inhibition; Mild CYP3A4 inhibition; CYP3A4 competitive inhibition	possible increase in AUC predicted	use with caution - Consider dose adjustment if another moderate to strong P-gp inhibitor is used
Anastrozole	Mild CYP3A4 inhibition	no significant effect on AUC predicted	no dose adjustment
Flutamide	CYP3A4 competitive inhibition; No relevant interactions anticipated	no significant effect on AUC predicted	no dose adjustment
Letrozole, Fulvestrant	CYP3A4 competitive inhibition; No relevant interactions anticipated	no significant effect on AUC predicted	no dose adjustment
Raloxifene, Leuprolide, Mitotane	No relevant interactions anticipated	no significant effect on AUC predicted	no dose adjustment
Immune-modulating-agents			
Cyclosporine	Strong to moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	+73% AUC [3]	use edoxaban 30 mg [4]
Dexamethasone	Strong CYP3A4/P-gp induction; CYP3A4/P-gp competitive inhibition	significant decrease in AUC predicted	Not recommended due to reduced plasma levels
Tacrolimus	Strong to moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	significant increase in AUC predicted	use edoxaban 30 mg
Prendisone	Moderate CYP3A4 induction; CYP3A4 competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competitive inhibition	no significant effect on AUC predicted	no dose adjustment
Everolimus	CYP3A4 competitive inhibition; No relevant interactions anticipated	no significant effect on AUC predicted	no dose adjustment
AUC Area under the curve, *CYP* Cytochrome P 450, *P-gp* P-glycoprotein.			

Table S3. Predicted effects of antiparkinsonian and anti-Alzheimer's disease drugs on edoxaban exposure and indications of dosage recommendation.

Concomitant Drug	Effect on P-gp and CYP	Effect on edoxaban concentration	Indication and dosage recommendation for edoxaban
L-dopa			
L-dopa/ carbidopa	substrate for P-gp inhibitors	no significant effect on AUC predicted	no dose adjustment*
Dopamine agonists			
Pergolide	substrate for P-gp Cyp2D2 inhibition [5]	no significant effect on AUC predicted	no dose adjustment*
Bromocriptine	P-gp inhibitor 51; CYP3A4 inhibition [5, 6]	possible increase of AUC predicted	no dose adjustment (use with caution)*
Pramipexole	substrate for P-gp and CYP2D2 inhibition [5, 6]	no significant effect on AUC predicted	no dose adjustment*
MAO B inhibitors			
Selegiline	CYP2D6 substrate	no significant effect on AUC predicted	no dose adjustment*
Rasagiline	CYP1A2 substrate	no significant effect on AUC predicted	no dose adjustment*
Safinamide	No relevant interactions known/assumed	no significant effect on AUC predicted	no dose adjustment*
COMT inhibitors			
Tolcapone	CYP2C9 inhibitor	no significant effect on AUC predicted	no dose adjustment*
Entacapone	CYP2C9 inhibitor	no significant effect on AUC predicted	no dose adjustment*
Others			
Amantadine	No relevant interactions known/assumed	no significant effect on AUC predicted	no dose adjustment*
Acetylcholinesterase inhibitors			
Donepezil	weak CYP3A4 inhibition	no significant effect on AUC predicted	no dose adjustment*
Galantamine	CYP3A4, CYP2D6 substrate	no significant effect on AUC predicted	no dose adjustment*
Rivastigmine	P-gp induction	Possible decrease in AUC predicted	no dose adjustment (use with caution)*

* Expert opinion
AUC Area under the curve, *CYP* Cytochrome P 450, *P-gp* P-glycoprotein.

DDIs with antacid drugs

The prevalence of gastro-esophageal reflux disease (GERD) is significant worldwide and evidence indicate, especially in the western countries, an increase in its incidence [7]. This suggests that an increasingly higher portion of the population is using antacid medication.

Theoretically, antacid medications are not devoid of risk of DDIs with NOACs. Especially considering gastric acidity might play a role in NOAC absorption (Table S4). From a pharmacological point of view, a small reduction of dabigatran bioavailability has been observed with concomitant PPIs or H2-blockers, while no effect has been observed with other NOACs [2]. Also, PPIs can have an influence on cytochrome P450 metabolism, especially CYP2C19 [8] and some PPIs like omeprazole, lansoprazole and pantoprazole can also have an inhibitory influence on P-gp [9]. In a pharmacological study, esomeprazole was shown to have no significant effect on the peak and total exposure of edoxaban during concurrent dosing [10].

The histamine II receptor blocker cimetidine was shown to inhibit certain cytochrome P450 enzymes, including CYP1A2, CYP2C9, CYP2D6 and CYP3A3/A4, and CYP2C18 [11], while ranitidine has a minor effect on the CYP isoenzymes [12].

Aluminum-Magnesium Hydroxide Tablets have no influence on P-gp or CYP isoenzymes but they might alter the absorption of drugs that are concomitantly administered if taken within 1 hour [13].

Table S4. Predicted effects of antacid drugs on edoxaban exposure and indications of dosage recommendation.

Concomitant Drug	**Effect on P-gp and CYP**	**Effect on edoxaban concentration**	**Indication and dosage recommendation for edoxaban**
PPIs			
Esomeprazole	CYP2C9 and CYP2C19 inhibition,	no significant effect on AUC observed	Minor effects (no dose adjustment)
Omeprazole	CYP2C19 inhibition; CYP3A4 substrate; moderate P-gp inhibition	no significant effect on AUC predicted	no dose adjustment*
Pantoprazole,	P-gp inhibition	no significant effect on AUC predicted	no dose adjustment*
Lansoprazole	CYP2C19 inhibition, P-gp inhibition	no significant effect on AUC predicted	no dose adjustment*
H2 antagonists			
Cimetidine	Inhibition of CYP1A2, CYP2C9, CYP2D6, CYP3A3/A4, CYP2C18	no significant effect on AUC predicted	no dose adjustment*
Ranitidine	No interactions predicted	no significant effect on AUC predicted	no dose adjustment*
Aluminium-magnesium hydroxide	No interactions predicted	no significant effect on AUC predicted	no dose adjustment*
* Expert opinion *AUC* Area under the curve, *CYP* Cytochrome P 450, *P-gp* P-glycoprotein.			

DDIs with NSAIDs drugs

Patients with AF tend to be elderly and to have other inflammatory disorders, which may require the use of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs increase bleeding risk with NOACs due to a pharmacodynamics interaction and the chronic use is not permitted by the respective SmPCs (Table S5).

Mendell et *al*, conducted a pharmacokinetic study to assess the potential pharmacokinetic/pharmacodynamic interactions between edoxaban and the NSAID naproxen [14]. Naproxen undergoes to an extensive metabolism through the CYP1A2 and CYP2C9 [15], therefore, the likelihood of pharmacokinetic interaction with edoxaban is minimal, although, a pharmacodynamic interaction is likely. Indeed, no significant effect of naproxen was observed in systemic exposure to edoxaban (AUC and C_{max}) whereas it was shown an additive effect on bleeding time [14]. Interestingly, naproxene has shown to increase apixaban exposure by more than 50%, an effect potentially related to the inhibition of the intestinal efflux transporter P-gp [16]. Naproxene use and has not been studied with other NOACs [2]. For the acute concomitant use of naproxene, edoxaban could constitute a reasonable choice for a concomitant anticoagulant.

Table S5. Predicted effects of NSAIDs drugs on edoxaban exposure and indications of dosage recommendation.

Concomitant Drug	**Effect on P-gp and CYP**	**Effect on edoxaban concentration**	**Indication and dosage recommendation for edoxaban**
NSAIDs			
Naproxen	P-gp competitive inhibition; CYP1A2 and CYP2C9 inhibition	no significant effect on AUC; Pharmacodynamically increased bleeding time effect [14]	no dose adjustment; Chronic use not recommended [4]
Aspirin	No relevant interactions known/assumed	Increased AUC for high doses of aspirin; Pharmacodynamically increased bleeding time [14]	no dose adjustment; Chronic use not recommended [4]
* Expert opinion *AUC* Area under the curve, *CYP* Cytochrome P 450, *P-gp* P-glycoprotein.			

DDIs with monoclonal antibodies and interleukin 6 (IL6)

The clearance of therapeutic monoclonal antibodies (mAbs) typically does not involve CYP450-mediated metabolism or interaction with P-gp, therefore their pharmacokinetic interactions with small molecule drugs are limited. However, mAbs directed against circulating cytokines, such as interleukin (IL)-6, IL-1β, or TNF-α, for the treatment of immunologic disorders like rheumatoid arthritis, celiac disease, and Crohn's disease may have a significant impact on drug metabolism. Specific studies have, indeed, demonstrated that IL-6 reduces the CYP3A4, 2B6 and 2C8 mRNA expression [17, 18]. Even more relevant for NOAC disposition, is the observation that IL-6-treated mice displayed a 70% reduction in protein expression of all P-gp isoforms [19]. On these basis, it is possible that tocilizumab, a monoclonal antibody anti IL-6, may induce P-gp and reducing NOAC intestinal absorption. A case report of possible DDI between tocilizumab and dabigatran has been described. The authors claim that the coadministration of tocilizumab with dabigatran had induced a progressively decreased anticoagulant effect of dabigatran, favoring mesenteric arterial thrombosis [20]. A possible interaction can also be predicted for edoxaban.

Similar effect can be hypothesized with the monoclonal antibody dupilumab that inhibits IL-4 and IL-13 signaling. An open-label drug–drug interaction study was performed to assess whether a possible interaction of dupilumab with the pharmacokinetics of drugs metabolized by cytochrome P450 (CYP450) enzymes, including warfarin. The results clearly show no significant DDI of drugs metabolized by CYP3A, CYP2C19, CYP2C9, CYP1A2, and CYP2D6 after IL-4/IL-13 signaling inhibition by dupilumab [21].

DDIs with omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (n3-PUFA) are an important component of human metabolism and cellular function [22]. After some initial evidence of a beneficial role in reducing significantly the risk of all-cause death, n3-PUFA have been largely investigated as possible beneficial dietary supplement to reduce the risk of major adverse cardiovascular events [22]. Notwithstanding, current evidence available pointed out that only a small advantage is due to the consumption of n3-PUFA, which seems to possibly increase over time [22].

Metabolism of n-3 PUFA does not involve P-gp or any CYP450 [23], so no direct effect on edoxaban pharmacokinetic and concentration, nor any other NOAC, is predicted. Conversely, it is known that n-3 PUFA have a significant role in modulating platelet activation [23], hence this action associated with the concomitant assumption of antiplatelet agents or other anticoagulant drugs has been hypothesized to increase the risk of bleeding, even though no evidence seems to support this hypothesis [24]. Currently, no evidence is available to recommend any dose adjustment for edoxaban nor any other NOACs.

DDIs with dietary supplements, nutraceuticals and herbs

Approximately half of the older population taking prescription medication also regularly use dietary supplements [25] and the often-unregulated nature of supplements means that potential interactions with NOACs should be considered.

Herbs and supplements for the prevention and treatment of cardiovascular disease have been associated with adverse effects and interactions [26-34]. For example, garlic inhibits platelet aggregation and can cause significant anticoagulation, and the Chinese herb danshen (*Salvia miltiorrhiza*) may potentiate warfarin [35].

Dong quai is a Chinese herbal medicine used for the treatment of menstrual cramping, irregular menses, and menopausal symptoms. Dong quai has a number antithrombotic constituents, particularly coumarins, and a case report of DDI with warfarin has been reported [36].

Practitioners should be aware of the possibility of such an interaction that cannot be excluded with NOACs. Green tea contains significant quantities of vitamin K and therefore may antagonize the anticoagulant effect of warfarin [37]. Considering the vitamin K-independent mechanism of action of NOAC, it is not expected a significant DDI with green tea.

Horse chestnut (*Aesculus hippocastanum*) is used as an herbal medicine for chronic venous insufficiency. The main constituents of horse chestnut are triterpene saponins (escin), flavonoids (e.g., quercetin, kaempferol, EC, proanthocyanidin A2, anthocyanins), and coumarins (e.g., esculin, esculetin) [38]. Clinical trials are suggested to investigate whether or not the coumarins, present in horse chestnut, may play a therapeutic role in reducing hypercoagulation [39]. The combination of vitamin E and alpha-lipoic acid increases bleeding tendencies and therefore may have an impact on long-term anticoagulant therapies [40]. Beyond the effect on coagulation system and platelet function, many foods and herbal drugs may modulate P-gp activity, as well as CYP3A4 metabolism and thus NOACs exposure (Table 4) [41]. *Camellia sinensis, Hypericum perforatum*, *Ginkgo biloba* increase P-gp activity while Curcumin from *Curcuma longa*, piperine and silymarin inhibit this protein. Grapefruit juice is a strong CYP3A4 and P-gp inhibitor and may lead to increased exposure of drugs metabolized in this manner or P-gp substrates, such as NOACs [42]. In addition, a study by Honda and colleagues showed that grapefruit and orange juice extracts and their constituents also inhibited P-gp transcellular transport [43]. At present, however, none of the NOACs is cautioned with grapefruit juice.

Additionally, St. John's Wort is one of the most commonly used herbal remedies for minor and major depression. Use of St. John's Wort often goes unreported to medical practitioners, despite safety concerns about its tendency for clinically relevant drug interactions [44].

The effect of St. John's wort affects both the expression level of P-gp and CYP3A4 and therefore a series of interactions that lead to the decrease of P-gp and CYP3A4 substrates have been reported [45].

It is noteworthy that a single-dose administration of St. John's wort decreases intestinal P-glycoprotein expression, while the opposite effect is observed if the same substance is administered long-term [46]. Due to the frequent use of this substance, the non standardized dosages and the expected increased plasma concentrations with all NOACs, their use should be avoided in concomitance [41, 47].

Taken together, the scenario of potential interaction of herbal medicine with NOACs is mainly unexplored, excluding the well established P-gp inducer St. John's Wort, which is contraindicated with any NOACs [2].

Table 16 lists a series of substances that are present in many commonly used medicinal plants and their potential effect on P-gp and Cythochromes. These substances, theoretically, might have the potential to alter NOAC plasmatic concentration thus, their use should be limited or carefully evaluated in case of concomitant administration. Considering that CYP3A4 is involved to a minor extent in the metabolism of edoxaban, the substances that alter this path might have less influence on edoxaban compared to other anti-Xa inhibitors.

Table 16. Effect of herbs and derived substances on P-glycoprotein activity and function. Modified from Bogacz A et al and Di Minno A, et al [41, 46]

Substance	**Herb source of substance**	**Induction of P-gp**	**Inhibition of P-gp**	**Effect on CYP450**
Apigenin	Matricaria chamomilla		X [26]	Inhibition of CYP3A4
Berberine	Berberis		X [27]	Inhibition of CYP2D6, 2C9, and CYP3A4
Capsaicin	Capsicum (chili peppers)		X [28]	Induction of CYP3A4
Carum Ajowan	*Carum copticum*			Inhibition of CYP3A4
Citrus aurantium	Orange			Inhibition of CYP3A4
Coraria lactone	*Alisma orientalis (Alismataceae)*	X		
Curcumin	*Curcuma longa* (*Zingiberaceae*)		X	Inhibition of CYP3A4
Dehydroepiandrosterone	Soybean (Glycine max)			Inhibition of CYP3A4
Echinacea	purpurea and/or angustifolia			Inhibition of CYP3A4
Ephedrine	*Angelica sinensis* (*Apiaceae*)		X	
Eucalyptus	Eucalyptus globulus			Inhibition of CYP1A2, 2C9, 2C19, 3A4
Fo-ti-root	*Fallopian multiflora*			Inhibition of CYP1A2, 2C9, 2C19, 3A4
Garlic extract	garlic	X		Inhibition of CYP2C9, 2C19, 3A4
Ginkgo biloba extract	*Ginkgo biloba* (*Ginkgogaceae*)		X [29]	
Glabridin	*Glycyrrhiza glabra* (*Glycyrrhizaceae*)		X	Inhibition of CYP3A4
Glycyrrhetinic acid	Licorice	X		Inhibition of CYP3A4
Grape juice	Vitis vinifera			Induction of CYP1A2, 3A4
Grapefruit juice	Grapefruit		X [30]	Inhibition of CYP3A4
Guggulsterone	Guggul (Commiphora mukul)		X [10]	CYP3A4 induction
Honokiol	*Pseudolarix kaempferi* (*Pinaceae*)		X	
Hydrastis canadensis extract	goldenseal			Inhibition of CYP3A4
Hyperforin, hypericin	St. John's wort (*Hipericaceae*)	X (at long term) [31]	X (acute)	Induction of CYP1A2, 2C9, 3A4
Kava	Piper methysticum	X		Inhibition of CYP1A2, 2C9, 2C19, 3A4
Licorice root	Glycyrrhiza glabra	X [31, 32]		CYP3A4 induction
Lime extract	Lime			Inhibition of CYP3A4
Paeoniflorin	*Paeonia alba (Paeoniaceae)*	X		

Phellamurin	*Phellodendron wilsonii* (*Rutaceae*)		X	
Piperine	*Piper nigrum; Piper longum* (*Piperaceae*)		X [33]	Inhibition of CYP3A4
Pyranocoumarins	*Peucadanum praeruptorum* (*Apiaceae*)		X	
Polyphenols	*Green tea leaf* (*Theaceae*)	X		short-term inhibition, and longterm induction of CYP3A4
Protopanaxatriol ginsenosides	*Panax ginseng* (*Araliaceae*)	X		Potent CYP3A4 competitive inhibition; moderate CYP2C9 inhibition
Prunus avium extract	wild cherry			CYP3A4 inhibition
Quercetin	Dietary flavonoids	X [31]		Inhibiton of CYP1A2, induction of CYP2A6
Resveratrol	*Vaccinium corymbosum, Rubus idaeus, Morus nigra*			Inhibition of CYP1A2, 3A4
Rutin	*Carpobrouts edulis*		X [26]	Potent CYP3A4 inhibition
Scutellaria	*Lamiaceae*	X [31]		CYP3A4 inhibition
Silymarin	*Silybum marianum* (*Asteraceae*)		X	CYP3A4 inhibition
Soy milk and miso	soybeans	X [32]		CYP3A4 induction [32]
Sucralose		X [34]		CYP3A4 induction [32]
Tanacetum parthenium	*feverfew*			Inhibition of CYP1A2, 2C9, 2C19, 3A4
Tenacissimoside A	*Marsdenia tenacissima* (*Asclepiadaceae*)		X	
Tetrandrine	*Stephania tetrandra* (*Menispermaceae*)		X	Moderate CYP3A4 inhibition
Trifolium pretense	*Red clover*			Inhibition of CYP1A2, 2C9, 2C19, 3A4
Uncaria	Una de gato			CYP3A4 inhibition
Valerenic acid	Valeriana officinalis			CYP3A4 inhibition
Vauqueline	*Angelica sinensis (Apiaceae)*		X	

AUC Area under the curve, *BCRP* breast cancer resistance protein, *CYP* Cytochrome P 450, *P-gp* P-glycoprotein.

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