Direct Oral Anticoagulant (DOAC) Drug-Drug Interaction Guidance

Pharmacodynamic Interactions

Antiplatelet therapies, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) may not affect DOAC plasma concentrations, but may increase risk of bleeding in DOAC patients via pharmacodynamic interaction. Antiplatelet and NSAID therapies in particular have been shown to increase the risk of bleeding when combined with DOAC therapy, so **clinicians can intervene by ensuring these therapies are only combined when the antithrombotic benefit clearly outweighs the known risk of bleeding accompanying concomitant therapy.**

Pharmacokinetic Interactions

P-glycoprotein: All DOACs are substrates of p-glycoprotein (p-gp), which is an efflux transporter located in the gut mucosa and regulates absorption of drugs. Therefore, **all DOACs are subject to interactions with drugs that modify p-gp.**

- *P-gp Inducers may reduce plasma DOAC concentrations (increasing risk of thrombosis).*
- *P-gp Inhibitors may increase plasma DOAC concentrations (increasing risk of bleeding).*

CYP3A4: Rivaroxaban and apixaban are both substrates for hepatic CYP3A4 metabolism (18%, <32%, respectively). The alternate elimination pathways for these DOACs should dampen the effect of CYP3A4-based drug-drug interactions. **However, drugs that modify BOTH p-gp and are STRONG modifiers of CYP3A4 could become clinically significant interactions with rivaroxaban and apixaban.** The potential clinical significance of p-gp and MODERATE modifiers of CYP3A4 is controversial, although expected to be less than that of STRONG CYP3A4 modifiers.

It is important to recognize the most clinically significant drug-drug interactions with DOACs will likely be those that have been reported to occur:

- In vivo (in a real-life scenario vs in a test tube)
- In humans
- In actual patients taking the drug at a recommended dose for the appropriate disease state

Unlike warfarin, DOACs have a relatively wide therapeutic index (the difference between toxicity and therapeutic efficacy). So even if interactions are present, the DOAC patient may be able to tolerate shifts in drug concentration that remain clinically insignificant.

As drug interaction reports and reviews in the literature may vary, it is important to apply a standard set of criteria when determining the relevance of potential DOAC drug interactions in the context of clinical decision-making (Table 1).

TABLE 1 – Criteria for p-gp and CYP3A4 Modifiers

P-gp Modifiers	**INDUCERS** (must meet criteria from both items 1 and 2): 1. Evidence from in vitro studies showing the drug is capable of inducing the transporter **OR** label statements that identify the drug as an inducer of the transporter. **AND** 2. Clinical study data showing at least a 20% decrease in AUC **OR** a 25% increase in clearance of a probe substrate.	**CYP3A4 Modifiers**	**INDUCERS** • **Strong**: ≥ 80% mean decrease in a sensitive substrate AUC **OR** ≥5 fold increase in clearance in clinical study • **Moderate**: ≥ 50% but < 80% mean decrease in a sensitive substrate AUC or ≥ 2-fold but < 5-fold increase in clearance in clinical study •**Weak**: ≥ 20% but < 50% mean decrease in a sensitive substrate AUC or ≥ 1.25-fold but < 2-fold increase in clearance in clinical study
	INHIBITORS (must meet criteria from both items 1 and 2): 1. Evidence from in vitro studies showing the drug is capable of inhibiting the transporter **OR** label statements that identify the drug as an inhibitor of the transporter. **AND** 2. Clinical study data showing at least a 25% increase in AUC **OR** a 20% decrease in clearance of a probe substrate.		**INHIBITORS** • **Strong**: ≥ 5-fold mean increase in a sensitive substrate AUC **OR** 80% decrease in clearance in clinical study • **Moderate**: ≥ 2-fold but < 5-fold mean increase in a sensitive substrate AUC or ≥ 50% but < 80% decrease in clearance in clinical study •**Weak**: ≥ 1.25-fold but < 2-fold mean increase in a sensitive substrate AUC or ≥ 20% but < 50% decrease in clearance in clinical study

AUC=area under the curve; p-gp=p-glycoprotein

Drug Interaction Guidance for Dabigatran and Edoxaban

Neither dabigatran nor edoxaban undergo CYP3A4 metabolism, so the pharmacokinetic drug interactions of note involve modifiers of p-gp.

Since both drugs have some degree of renal elimination (dabigatran 80%, edoxaban 50%), patients with renal impairment who are co-administered these DOACs and a p-gp inhibitor can be at increased risk for bleeding due to accumulating drug levels. **See Table 2** for examples of p-gp modifiers, and associated guidance on DOAC use.

Created by University of Utah Health, authors: Sara Vazquez, PharmD, BCPS, CACP & Ryan Fleming, PharmD, DPLA, CACP

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TABLE 2 – Drug Interaction Guidance for Dabigatran (Pradaxa®) and Edoxaban (Savaysa®)

P-gp INDUCERS (examples):	Apalutamide Carbamazepine Fosphenytoin	Phenytoin Rifampin St. John's Wort	**Guidance**	Avoid Use
P-gp INHIBITORS (examples):	Amiodarone* Azithromycin (systemic) Carvedilol Clarithromycin* Cyclosporine (systemic) Daclatasvir Dronedarone Elagolix Eliglustat Erythromycin (systemic) Flibanserin Fostamatinib Glecaprevir/pibrentasvir Itraconazole (systemic) Ivacaftor	Ketoconazole (systemic) Lapatinib Ledipasvir Neratinib Osimertinib Propafenone Quinidine* Quinine Ranolazine Ritonavir Rolapitant Simeprevir Velpatasvir Vemurafenib Verapamil*	**Guidance**	**DABIGATRAN:** AF: Consider reducing dabigatran dose from 150 mg BID to 75 mg BID for patients with CrCl 30-50 mL/min and taking dronedarone or ketoconazole Avoid use of dabigatran in patients with CrCl < 30 mL/min and taking p-gp inhibitors VTE: Avoid use of dabigatran in patients with CrCl <50 mL/min and taking p-gp inhibitors **EDOXABAN:** AF: No dose adjustment necessary VTE: Reduce dose from 60 mg once daily to 30 mg once daily for verapamil, quinidine, azithromycin, clarithromycin, dronedarone, erythromycin, itraconazole, ketoconazole. Use of other p-gp inhibitors with edoxaban has not been studied, but a similar dose reduction approach is likely reasonable.

*No dose adjustment necessary for amiodarone, verapamil, quinidine, or clarithromycin (per manufacturer prescribing information)

Drug Interaction Guidance for Rivaroxaban and Apixaban

Both rivaroxaban and apixaban are substrates of p-gp and CYP3A4, so the pharmacokinetic drug interactions of note involve modifiers of p-gp and STRONG modifiers of CYP3A4.

The clinical significance of p-gp and MODERATE modifiers of CYP3A4, and STRONG CYP3A4-only inducers is uncertain. They are included in the table below for clinical consideration.

Since both drugs have some degree of renal elimination (rivaroxaban 33%, apixaban 24%), patients with renal impairment who are co-administered these DOACs and a p-gp/STRONG CYP3A4 inhibitor can be at increased risk for bleeding due to accumulating drug levels. **See Table 3** for examples of p-gp/CYP3A4 modifiers, and associated guidance on DOAC use.

TABLE 3 – Drug Interaction Guidance for Rivaroxaban (Xarelto®) and Apixaban (Eliquis®)

COMBINED p-gp AND STRONG CYP3A4 INDUCERS (examples):	Apalutamide Carbamazepine Fosphenytoin	Phenytoin Rifampin St. John's Wort	**Guidance**	Avoid use
STRONG CYP3A4 INDUCERS (no p-gp induction) (examples):	Enzalutamide Lumacaftor Mitotane	Phenobarbital Primidone	**Guidance**	Limited data assessing the clinical significance of this possible interaction; consider patient's thrombotic risk.
COMBINED p-gp AND STRONG CYP3A4 INHIBITORS (examples):	Clarithromycin* Itraconazole (systemic)	Ketoconazole (systemic) Ritonavir	**Guidance**	**RIVAROXABAN:** Avoid use **APIXABAN:** If taking 5 mg or 10 mg BID, reduce dose by 50%; if already taking 2.5 mg BID, avoid use. *clarithromycin does not significantly increase rivaroxaban or apixaban exposure so concomitant use is acceptable without dose adjustment (per manufacturer prescribing information)
COMBINED p-gp AND MODERATE CYP3A4 INHIBITORS (examples):	Dronedarone Erythromycin (systemic) Verapamil		**Guidance**	**RIVAROXABAN:** Avoid in patients with CrCl 15-80 mL/min unless benefit justifies risk. **APIXABAN:** No specific dose reduction recommended.

References:
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