Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

Direct Oral Anticoagulant (DOAC) Drug-Drug Interaction Guidance

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BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Do check various sources when encountering drug(s) with uncertain interaction status	• Don't use DOACs with STRONG CYP3A4 *inducers* or P-gp *inducers* • Don't forget to review dietary supplements and alternative remedies in addition to Food and Drug Administration approved prescription and over the counter products	• Consider DOACs have a wide therapeutic index. Even if interactions are present, a patient may tolerate clinically insignificant shifts in DOAC concentration • Consider the most clinically significant drug interactions with DOACs will likely be those that have been reported: – 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 • Consider renal function status within the context of the drug interaction assessment	• Caution combining agents that have pharmacodynamic interactions with a DOAC; benefit needs to outweigh the risk • Caution with rivaroxaban and apixaban, the clinical significance of p-gp and MODERATE modifiers of CYP3A4, and STRONG CYP3A4-only inducers is uncertain; benefit needs to outweigh risk

Mechanisms of Drug-Drug Interactions[1]

Pharmacodynamic	One drug alters the sensitivity of responsiveness of tissues to another drug by having the same (agonistic) or a blocking (antagonistic) effect
Pharmacokinetic	A drug alters absorption, distribution, protein binding, metabolism, or excretion of another drug.
Pharmaceutical	Physical or chemical incompatibilities that may be an enhancement or a detriment to the effect. This mechanism will not be a focus of this resource

Pharmacodynamic Drug Interactions with DOACs

Example Agents:
Aspirin
NSAIDs
SSRIs
Bruton's TKIs

\+ DOAC = Bleeding Risk

ACTION:
Only combine therapies if benefit outweighs risk of bleeding; monitor for bleeding

NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TKI, tyrosine kinase

Pharmacokinetic Drug Interactions with DOACs

P-glycoprotein (P-gp): efflux transporter located in the gut mucosa that regulates drug absorption

CYP3A4: hepatic metabolizing enzyme

All DOACs affected by P-gp modifiers

Apixaban (~25%)
Rivaroxaban (18%)
affected by CYP3A4 modifiers

Inducer:
↓DOAC Concentration
↑**Thrombosis** Risk

Inhibitor:
↑ DOAC Concentration
↑ **Bleeding** Risk

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.

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.

CYP3A4 Modifiers

INDUCERS

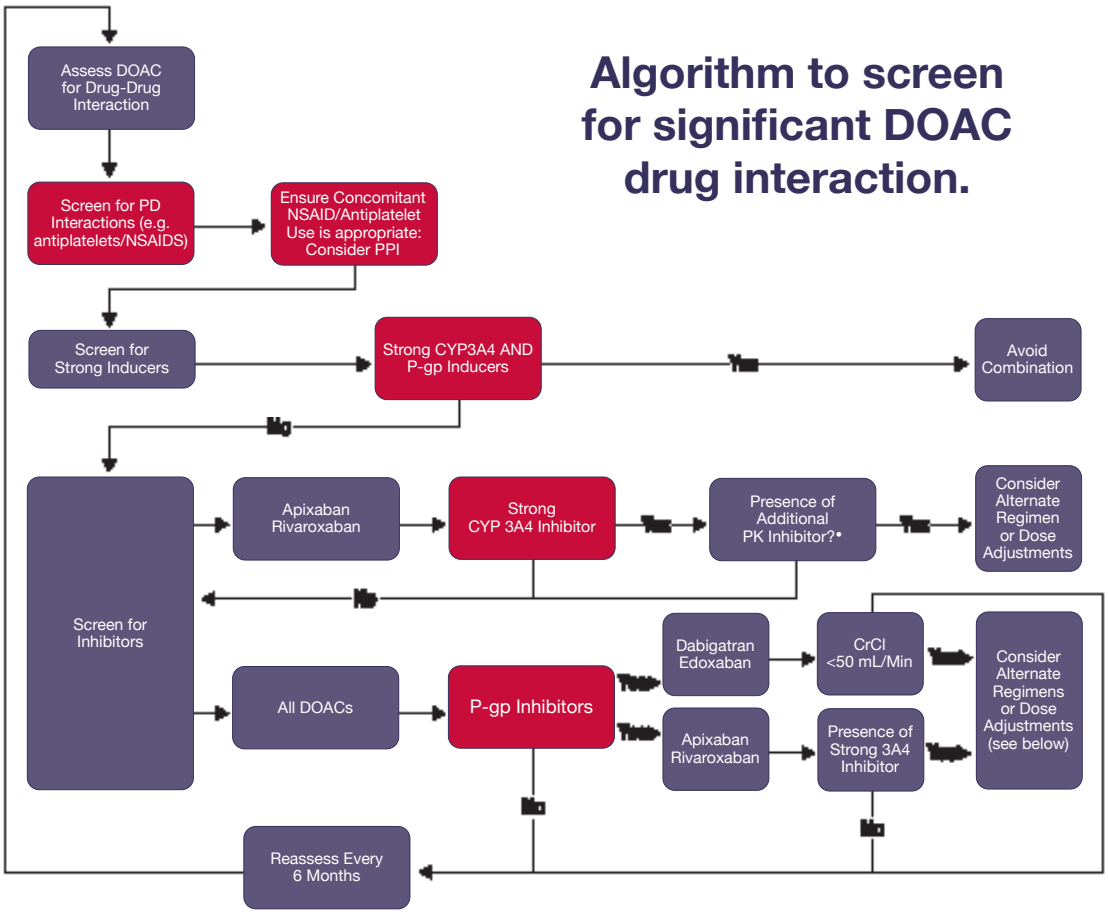
- **Strong**: ≥ 80% mean decrease in a sensitive substrate AUC **OR** ≥5 fold increase in clearance in clinical study
- **Moderate**: ≥ 50% but < 80% mean decrease in a sensitive substrate AUC **OR** ≥ 2-fold but < 5-fold increase in clearance in clinical study
- **Weak**: ≥ 20% but < 50% mean decrease in a sensitive substrate AUC **OR** ≥ 1.25-fold but < 2-fold increase in clearance in clinical study

INHIBITORS

- **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

General Evaluation Process for DOAC Drug-Drug Interaction Management

Algorithm to screen for significant DOAC drug interaction.



How to Check CYP/P-gp Status

Check a current and reliable drug reference

- View the interactions section
- It will list whether the drug is a substrate or modifier of P-gp or CYP3A4

Evaluate the most recent medical literature

- The most relevant and valuable reports are going to come from actual patients taking the drug for the disease state in question.

Use the FDA criteria to interpret your findings

- See P-gp and CYP modifier tables above.

Adapted from Circ Arrhythm Electrophysiol. 2022;15:e007956. DOAC, direct acting oral anticoagulant; CrCl, creatinine clearance; NSAID, non-steroidal anti-inflammatory drug; PD, pharmacodynamic; PK, pharmacokinetic; PPI, proton pump inhibitor. *Refers to additive P-gp inhibition from the same interacting agent, or another agent that the patient is taking with either CYP3A4 or P-gp inhibition.

The below lists provide represented P-gp and CYP 3A4 modifiers in the literature. Based on new evidence, the list can change and one should consider an independent assessment.

Drug-Drug Interaction Guidance for Dabigatran (Pradaxa®) and Edoxaban (Savaysa®)[1-10]

P-gp INDUCERS (examples):	Guidance
Apalutamide, Carbamazepine, Lorlatinib, Phenytoin, Rifampin, St. John's Wort	**AVOID USE**
P-gp INHIBITORS (examples):	**Guidance**
Abrocitinib, Amiodarone*, Azithromycin (systemic), Capmatinib, Carvedilol, Clarithromycin*, Cobicistat, Cyclosporine (systemic), Daclatasvir, Dronedarone, Elagolix, Eliglustat, Erythromycin (systemic), Flibanserin, Fostamatinib, Glecaprevir/pibrentasvir, Isavuconazonium sulfate, Itraconazole (systemic), Ivacaftor, Ketoconazole (systemic), Lapatinib, Ledipasvir, Neratinib, Osimertinib, Posaconazole, Propafenone, Quinidine*, Quinine, Ranolazine, Ritonavir, Rolapitant, Simeprevir, Tucatinib, Valproate Velpatasvir, Vemurafenib, Verapamil*, Voclosporin	**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 **No dose adjustment necessary for amiodarone, verapamil, quinidine, or clarithromycin (per manufacturer prescribing information)* **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.

Drug-Drug Interaction Guidance for Rivaroxaban (Xarelto®) and Apixaban (Eliquis®)[1-10]

COMBINED P-gp AND STRONG CYP3A4 INDUCERS (examples):	Guidance
Apalutamide, Carbamazepine, Fosphenytoin, Phenytoin, Rifampin, St. John's Wort	**AVOID USE**
STRONG CYP3A4 INDUCERS (no P-gp induction) (examples):	**Guidance**
Enzalutamide, Lumacaftor, Mitotane, Phenobarbital, Primidone	Limited data assessing the clinical significance of this possible interaction; consider patient's thrombotic risk.
COMBINED P-gp AND STRONG CYP3A4 INHIBITORS (examples):	**Guidance**
Clarithromycin*, Cobicistat, Itraconazole (systemic), Ketoconazol (systemic), Posaconazole, Ritonavir, Tucatinib	**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):	**Guidance**
Dronedarone, Erythromycin (systemic), Isavuconazonium sulfate, Verapamil	**RIVAROXABAN:** Avoid in patients with CrCl 15-80 mL/min unless benefit justifies risk. **APIXABAN:** No specific dose reduction recommended.

References: 1. Circulation 2022; 145:3811-838. 2. Circ Arrhythm Electrophysiol. 2022;15:e007956 3. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2022; August 4, 2022. 4. JAMA Intern Med 2014;174:947-53.5. Blood 2018;132:2230-39 6. Eliquis [package insert]. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer Inc: 2022. 7. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc: 2022. 8. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc: 2022. 9. Savaysa [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.: 2022. 10. Food and Drug Administration. Drug Interactions | Relevant Regulatory Guidance and Policy Documents | FDA; August 4, 2022.

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