Managing Drug Interactions with Direct Oral Anticoagulants

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Jeff Langford, PharmD, BCPS-AQ Cardiology, BCCP, is a board-certified cardiology pharmacist with strong clinical, teaching, and interpersonal skills developed through experience in both inpatient and outpatient pharmacy. Dr. Langford is an Assistant Editor at TRC Healthcare and adjunct assistant professor at University of South Carolina College of Pharmacy. His inpatient practice includes focus in cardiovascular pharmacotherapy, and his outpatient practice includes extensive patient interaction and departmental management experience.

Faculty Disclosure

Contributing faculty, Jeff Langford, PharmD, BCPS-AQ Cardiology, BCCP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, and nurses involved in the care of patients who require anticoagulation therapy.

Accreditations & Approvals

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A complete Works Cited list begins on page 10.

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NetCE designates this continuing education activity for 1 ANCC contact hour.

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NetCE designates this continuing education activity for 1.2 hours for Alabama nurses.

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This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address drug-drug interactions that occur in patients taking direct oral anticoagulants.

Learning Objectives

Upon completion of this course, you should be able to:

1. Summarize common mechanisms of drug interactions with direct oral anticoagulants.
2. Identify commonly used medications that may increase or decrease the effects of direct oral anticoagulants.
3. Implement appropriate management of drug interactions with direct oral anticoagulants.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Direct oral anticoagulants (DOACs) are often used if oral anticoagulation is required, such as to prevent thromboembolism for patients with nonvalvular atrial fibrillation or for treatment and prevention of venous thromboembolism. One advantage of DOACs is their predictable response and limited need for routine laboratory monitoring. However, drug-drug interactions with these agents are common and may increase the risk of bleeding or thrombosis. Important DOAC interactions are often due to medications that increase bleeding propensity or affect cytochrome P450 (CYP450) enzymes or transport proteins. Clinicians require practical considerations for managing common drug interactions involving DOACs [1; 2].

REVIEW OF CYP450 AND TRANSPORTER INTERACTIONS

The characterization of drug interactions by metabolic pathways is complex. Simply because a medication interacts with one substrate of a particular cytochrome P450 pathway does not mean it affects all substrates of that isozyme. Genetics, age, nutrition, stress, liver function, hormones, and other endogenous chemicals also influence drug metabolism. Additional influences on drug interactions include dosing (e.g., dose, timing, sequence, route of administration, duration of therapy), concomitant medications, potential for a concurrent pharmacodynamic interaction (e.g., a DOAC plus aspirin), and specific drug features (e.g., narrow therapeutic index, high extraction ratio, side effect profile, multiple metabolic pathways) [3].

Pharmacokinetics can also be affected by drug transporters (e.g., P-glycoprotein, breast cancer resistance protein [BCRP], multidrug and toxin excluders [MATEs], organic anion transporting polypeptides [OATPs]). All of these proteins help move medications into or out of cells, which can impact drug absorption, distribution, or elimination [4; 5].

We are still learning about the significance of these transporters on pharmacokinetics. Most of the available data are related to P-glycoprotein (P-gp, multidrug resistance protein 1 [MDR1]). P-gp is a drug efflux pump found in the gut, liver, kidney, blood-brain barrier, and cancer cells. It pumps drugs out of cells and into the gut, bile, and/or urine for excretion [6]. Other examples include BCRP, which pumps drugs out of cells in the gut, liver, and kidney, and OATPs (e.g., OATP1B1, OATP1B3), which move drugs into the liver [5].

Generally, CYP450 interactions and drug transporter interactions involve substrates, inhibitors, and inducers. Inhibitors may increase levels of CYP450 or P-gp substrates, and inducers may decrease levels of CYP450 or P-gp substrates. For many interactions, CYP450 enzyme inhibition or induction is also involved, and P-glycoprotein substrates are often also CYP3A4 substrates, so the contribution of P-gp inhibition/induction versus CYP450 inhibition/induction can be difficult to discern [7; 8; 9]. For example, apixaban and rivaroxaban are metabolized by CYP3A4 (***Table 1***), and absorption of all DOACs is affected by P-glycoprotein (***Table 2***) [2; 10].

SELECT CYP450-3A4 PATHWAY DRUG INTERACTIONS		
DOAC Substrates[c]	**Select Inhibitors**	**Select Inducers**
Apixaban Rivaroxaban	Amiodarone Amlodipine Atazanavir[a] Cimetidine Ciprofloxacin[a] Clarithromycin[b] Cobicistat[b] Conivaptan[a] Cyclosporine[a] Diltiazem[a] Dronedarone[a] Erythromycin[a] Ethinyl estradiol Fluconazole[a] Fluoxetine Fluvoxamine[a] Fosamprenavir[a] Grapefruit[b] Indinavir[b] Isoniazid Itraconazole[b] Ketoconazole[b] Lansoprazole Lopinavir/ritonavir[b] Mifepristone Nefazodone[b] Nelfinavir[b] Nicardipine Posaconazole[b] Ritonavir[b] Saquinavir/ritonavir[b] Ticagrelor Tipranavir/ritonavir[b] Verapamil[a] Voriconazole[b] Voxelotor	Carbamazepine Modafinil Nafcillin Nevirapine Oxcarbazepine Phenobarbital Phenytoin Rifabutin Rifampin Rifapentine St. John's wort Topiramate
[a]Moderate inhibitors (≥2 to <5-fold increase in exposure, or 50% to 80% decrease in clearance of substrate). For many medications, strength of inhibition in vivo is undetermined. [b]Strong inhibitors (≥5-fold increase in exposure or >80% decrease in clearance of substrate) [c]Dabigafran is not a substrate, inducer, or inhibitor of CYP450 enzymes. Edoxaban is only minimally metabolized by CYP450.		
Source: [1; 2; 3]		*Table 1*

SELECT P-GLYCOPROTEIN DRUG INTERACTIONS		
DOAC Substrates	**Select Inhibitors**	**Select Inducers[a]**
Apixaban Dabigatran Edoxaban Rivaroxaban	Amiodarone (moderate or strong inhibitor) Atorvastatin Azithromycin Canagliflozin (weak inhibitor) Captopril Carvedilol Clarithromycin[c] (strong inhibitor) Cobicistat Conivaptan[b] Cyclosporine[b] (strong inhibitor) Diclofenac Diltiazem[b] Dronedarone[b] (strong inhibitor) Erythromycin[b] (strong inhibitor) Esomeprazole Ibuprofen Indomethacin Itraconazole[c] Ketoconazole[c] (strong inhibitor) Lansoprazole Lopinavir/ritonavir[c] Lovastatin Mirabegron Naproxen Nefazodone[c] Nelfinavir[c] Nifedipine Omeprazole Posaconazole[c] Propafenone Quinidine (strong inhibitor) Quinine Rabeprazole Ranolazine Ritonavir[c] Saquinavir/ritonavir[c] Simvastatin Spironolactone Telmisartan Tetracycline Ticagrelor Trimethoprim Tipranavir/ritonavir[c] Verapamil[b] (strong inhibitor) Vilazodone Voriconazole (strong inhibitor)	Carbamazepine Phenobarbital Phenytoin Rifabutin Rifampin St. John's wort Venlafaxine
[a]All are strong inducers, except venlafaxine. [b]Moderate CYP3A inhibitors [c]Strong CYP3A inhibitors		
Source: [4]		*Table 2*

MANAGING DOAC INTERACTIONS

Drug experts from *Pharmacist's Letter* and *Prescriber Insights* provide the following practical approach to managing DOAC interactions [11]:

- Pinpoint critical DOAC interactions, and act if necessary.
- Generally avoid combining DOACs with strong CYP3A4 and P-glycoprotein inducers (e.g., phenytoin, rifampin, St. John's wort). These may lower DOAC levels and increase thrombosis risk.
- If these interacting medications cannot be avoided, switch to warfarin, because it is easier to monitor than a DOAC.
- Watch for strong CYP3A4 and P-glycoprotein inhibitors (e.g., ritonavir, itraconazole), as these may raise DOAC levels and increase bleeding risk.

To manage these drug interactions, consider the specific DOAC, dose, and indication (***Table 3***). One example that blends consideration of these factors is use of nirmatrelvir/ritonavir for treatment of COVID-19 in patients receiving a DOAC. This combination introduces potential risk for drug interactions, because ritonavir is a strong CYP3A4 and P-glycoprotein inhibitor. For instance, when a patient is receiving nirmatrelvir/ritonavir for COVID-19, apixaban being given for atrial fibrillation should be reduced to 2.5 mg twice per day during treatment and for three days after. However, coadministration of nirmatrelvir/ritonavir and rivaroxaban should be avoided [12].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Family Physicians recommend that apixaban should be avoided or reduced in dose when combined with P-glycoprotein and strong CYP3A4 inhibitors.

(https://www.aafp.org/pubs/afp/issues/2019/1001/p426.html. Last accessed October 12, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

It is also important to be aware that management of some DOAC interactions may vary based on kidney function. For example, verapamil increases DOAC levels. Rivaroxaban with verapamil should typically be avoided in patients with creatinine clearance less than 80 mL/min. In these cases, use of apixaban is acceptable [1].

Caution should be exercised when prescribing DOAC and medications that increase the risk of bleeding (e.g., antiplatelets, non-steroidal anti-inflammatory drugs [NSAIDs]). Ensuring the need for both agents is the first step. For example, aspirin used for cardiovascular primary prevention can usually be discontinued; aspirin for cardiovascular primary prevention is no longer routinely recommended, regardless of DOAC use [13; 14]. Duration of combination therapy is another concern. For instance, clopidogrel can be discontinued one-year post-stent placement for most patients with atrial fibrillation on a long-term DOAC. Limited evidence suggests that DOAC monotherapy is often sufficient at this point [15].

CONCLUSION

Managing drug-drug interactions with DOACs is of high importance to minimize preventable adverse effects. Clinicians should assess the importance of specific DOAC interactions and act to minimize their impact, if necessary. Therapeutic modification or additional monitoring may be necessary with some interactions [1; 2].

COMPARISON OF DOACs		
Drug	**Approved Indications and Dosing (Adults)**	**Select Interactions**
Apixaban (Eliquis)	Thromboembolism (e.g., stroke) prevention in nonvalvular atrial fibrillation: 5 mg BID or 2.5 mg BID for patients with ≥2 of the following: • Age ≥80 years • Weight ≤60 kg • Serum creatinine ≥1.5 mg/dL VTE prevention post-hip or knee replacement: 2.5 mg BID for 35 days (hip) or 12 days (knee) starting 12 to 24 hours post-operative DVT/PE treatment: 10 mg BID for seven days, then 5 mg BID DVT/PE prevention of recurrence: 2.5 mg BID after at least six months of treatment Atrial fibrillation: A reasonable anticoagulant choice for patients with CrCl <15 mL/min or on dialysis	Reduce dose by 50% with strong inhibitors of both CYP3A4 and P-gp (e.g., itraconazole, ketoconazole, ritonavir). Avoid in patients already taking 2.5 mg BID. Resume usual dose three days after the last dose of nirmatrelvir/ritonavir (Paxlovid). Avoid strong inducers of both CYP3A4 and P-gp (e.g., phenobarbital, carbamazepine, phenytoin, St. John's wort, rifampin). Caution with antiplatelets and anticoagulants. Dual antiplatelet therapy about doubles bleeding risk.
Dabigatran (Pradaxa)	Thromboembolism (e.g., stroke) prevention in nonvalvular atrial fibrillation: 150 mg BID DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant) or prevention of recurrence: 150 mg BID. Start 0 to 2 hours before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip. VTE prevention post-hip replacement: 220 mg once daily for 28 to 35 days. If started on day of surgery (1 to 4 hours post-surgery, assuming hemostasis achieved), initial dose is 110 mg. Atrial fibrillation: Use 75 mg BID if CrCl 15 to 30 mL/min. No dosing information for CrCl <15 mL/min or dialysis. DVT/PE treatment/prevention (adults) and VTE prevention post-hip replacement: No dosing information for CrCl ≤30 mL/min or dialysis	P-gp inhibitors may increase dabigatran levels. For atrial fibrillation indication: Avoid P-gp inhibitors (e.g., amiodarone) if CrCl <30 mL/min. Reduce dose to 75 mg BID with ketoconazole or dronedarone if CrCl 30–50 mL/min. For VTE/PE treatment/prevention (including post-hip replacement): Avoid use of P-gp inhibitors if CrCl <50 mL/min. Consider separating by several hours if CrCl ≥50 mL/min (hip replacement indication). P-gp inducers could decrease dabigatran efficacy. Avoid P-gp inducers per labeling. Use caution with antiplatelets. Co-administration with aspirin or clopidogrel about doubles bleeding risk. Drugs that increase gastric pH could reduce efficacy. Take dabigatran at least two hours before antacids.
Edoxaban (Savaysa)	Thromboembolism (e.g., stroke) prevention in nonvalvular atrial fibrillation: 60 mg once daily in patients with CrCl >50 to ≤95 mL/min DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant): 60 mg once daily, or 30 mg once daily if body weight ≤60 kg Atrial fibrillation: 60 mg once daily for CrCl >50 to ≤95 mL/min, or 30 mg once daily for CrCl 15–50 mL/min. Not for use in patients with CrCl >95 mL/min. DVT/PE treatment: 30 mg once daily for CrCl 15–50 mL/min (after 5 to 10 days of parenteral anticoagulant) Not recommended if CrCl <15 mL/min	Use with other anticoagulants is not recommended, except when switching. Caution with antiplatelets. Can use with aspirin ≤100 mg/day, with caution. Avoid rifampin (a P-gp inducer). Reduce dose to 30 mg once daily for DVT/PE indication in patients taking certain P-gp inhibitors (e.g., azithromycin, clarithromycin, erythromycin, itraconazole [oral], ketoconazole [oral], quinidine, verapamil).

Table 3 continues on next page.

COMPARISON OF DOACs *(Continued)*		
Drug	**Approved Indications and Dosing (Adults)**	**Select Interactions**
Rivaroxaban (Xarelto)	VTE prevention post-hip or knee replacement: 10 mg once daily for 35 days [hip] or 12 days [knee] starting 6 to 10 hours post-surgery, assuming hemostasis achieved. Avoid if CrCl <15 mL/min. Thromboembolism (e.g., stroke) prevention in nonvalvular atrial fibrillation: 20 mg once daily with evening meal to improve absorption. Dose is 15 mg with evening meal for CrCl ≤50 mL/min. Consider rivaroxaban 10 mg or 15 mg once daily in patients undergoing hemodialysis based on pharmacokinetic and limited clinical outcome data. DVT/PE treatment or prevention of recurrence: 15 mg BID (with food to improve absorption) for three weeks, then 20 mg once daily with food for at least six months, then 10 mg once daily. Avoid if CrCl <15 mL/min. VTE prevention in acutely ill medical patients at risk for VTE but without high risk of bleeding: 10 mg once daily for 31 to 39 days. Avoid if CrCl <15 mL/min. Cardiovascular risk reduction in patients with CAD or PAD: 2.5 mg BID, with aspirin 75–100 mg once daily. (Patients with eGFR <15 mL/min were excluded from clinical trial, and <1% of included patients had eGFR <30 mL/min.)	Avoid use with drugs that are both P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, ritonavir, cobicistat). In patients with CrCl 15 to <80 mL/min, the decision to use a combined P-gp/moderate CYP3A4 inhibitor (e.g., erythromycin) is a risk/benefit determination. Avoid with amiodarone or verapamil if CrCl is <80 mL/min. Drugs that are P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) may decrease efficacy and should be avoided. Avoid use with other anticoagulants. Caution with antiplatelets, including clopidogrel.
BID = twice per day, CAD = coronary artery disease, CrCl = creatinine clearance, DVT = deep vein thrombosis, eGFR = estimated glomerular filtration rate, PAD = peripheral arterial disease, PE = pulmonary embolism, VTE = venous thromboembolism.		
Source: [16]		*Table 3*

RESOURCES

Indiana University School of Medicine
Drug Interactions Flockhart Table
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

National Institutes of Health
Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications
https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions

University of Liverpool COVID-19 Drug Interaction Checker
https://www.covid19-druginteractions.org

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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