

# UConn

AN ONGOING CE PROGRAM  
of the University of Connecticut  
School of Pharmacy

## EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Differentiate between anticoagulation therapies based on mechanism of action and safety profile
- Discuss the various interactions that are possible for patients on anticoagulation therapy
- Identify the various anticoagulation reversal agents
- Maximize the ability to effectively counsel patients on their anticoagulation therapy

After participating in this activity pharmacy technicians will be able to:

- Discover resources for patient information
- Identify the medications used in anticoagulation therapy
- Recall the medications used to reverse anticoagulation therapy
- Determine when to refer the patient to the pharmacist regarding anticoagulation therapy



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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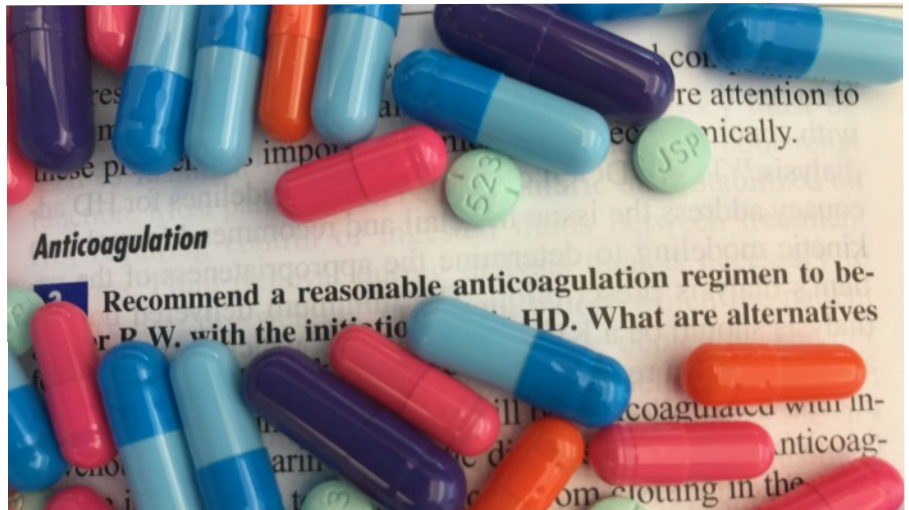
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Use your NABP E-profile ID and the **session code 19YC51-ABF78 for pharmacists or 19YC51-PXB94 for pharmacy technicians** to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

**For questions concerning the online CPE activities, email [joanne.nault@uconn.edu](mailto:joanne.nault@uconn.edu).**

## You Asked for It! CE



## Anticoagulants and Reversal Agents: Algorithm for Patient Safety

**ABSTRACT:** Anticoagulation therapy is a common treatment used by millions of Americans. Anticoagulants carry a high risk of adverse events, from treatment failures that may result in life-altering medical events to serious side effects that include internal bleeding. Pharmacists and technicians can play an important role in the safe use of these medications in the ambulatory setting. Ensuring the proper medication is used at the correct dose and taken appropriately by the patient; recognizing when greater intervention is necessary; and providing comprehensive counseling to patients will increase the patient's chance for safe, effective management. Pharmacy staff in community or ambulatory settings can use an algorithm—a problem solving plan that helps them achieve specific goals—to conduct fast, accurate assessment; standardize procedures; and improve the margin of safety for patients who take anticoagulants.

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## INTRODUCTION

The medication class known as anticoagulants, as the name suggests, disrupts the body's coagulation system leading to a relative state of decreased clot production. More commonly referred to as "blood thinners," these medications are the mainstays of treatment for common medical conditions. Venous thromboembolism (VTE; a clot in any vein but most often in the leg) and pulmonary embolism (PE; a clot in the lung), and protection from stroke due to atrial fibrillation or the presence of mechanical heart valves are common indications. Oral anticoagulants can be classified into two main groups: vitamin K antagonists and direct acting oral anticoagulants (DOAC).<sup>1</sup> Prescribers wrote more than 31 million prescriptions for oral anticoagulant drugs in 2016.<sup>2</sup> For this reason, pharmacists who work with patients who take oral anticoagulants need to have standardized approaches to ensure patient safety. In other words, they need an algorithm (see Sidebar, next page).

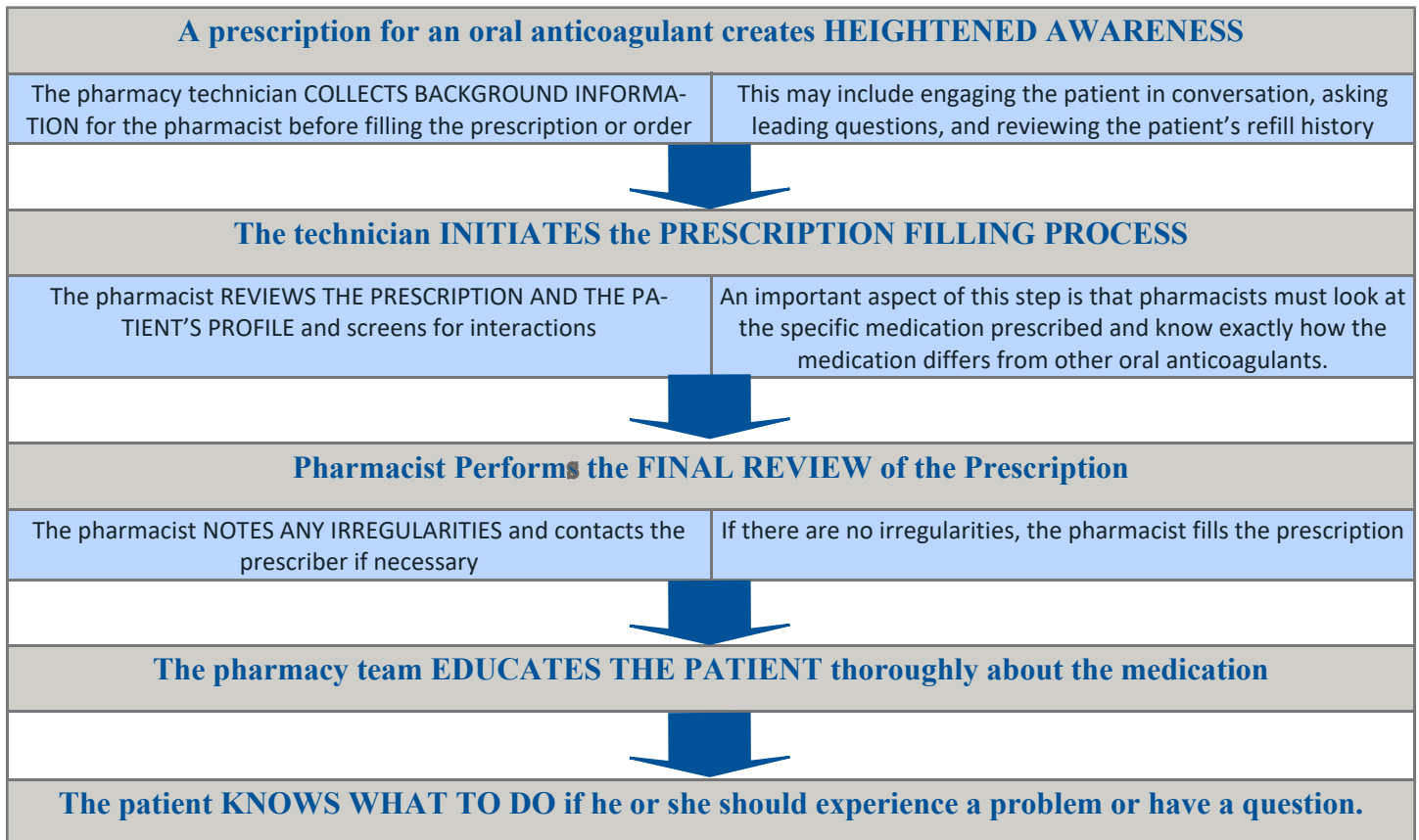
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## SIDEBAR: What is an Algorithm for Patient Safety?

An algorithm is a method of problem solving that relies on one or more steps. In healthcare systems, computer programmers build some algorithms into their computer program's software based on current information and research. These steps prevent error. An example might be a rule in the software that prevents two drugs from being dispensed concurrently if their interaction is life-threatening.

Many pharmacists and technicians think that algorithms must be computerized, but actually, we apply algorithms using our knowledge instinctively in many situations. Simply put, an algorithm is a rule that says, "If THAT happens, do THIS." Its goal is to ensure that the same "input" should always trigger the same "output."

In the case of oral anticoagulation, the trigger would be a new prescription or order for an oral anticoagulant, or a refill of an existing prescription. Or, it might be failure to fill or refill such a prescription or order. When that happens, pharmacy staff needs to be prepared with a standard way of dealing with those issues. An algorithm for patient safety in anticoagulation might look like this:



This boils down to logical thinking, and an appreciation for the benefits and risks of anticoagulation. Each person's or workplace's algorithm may be slightly different, but all algorithms will share the same evidence-based foundation. And, individuals need to revise their algorithms as things change (e.g., a new drug is introduced, research identifies at-risk populations or new indications for old drugs, or dosing strategies change).

As you proceed through this activity, make note of facts that would fit in any of the boxes in this algorithm. Also consider how you might work with your information management team to automate some steps. You may be surprised to find that your software can already do much of this screening, but you need to turn the function on!



Photo credit: Laura Nolan

The benefit of taking anticoagulant medications when indicated is striking. When used properly they reduce the risk of stroke due to atrial fibrillation as much as two thirds and prevent the recurrence of VTE by as much as 86%.<sup>3,4</sup> Their risks must be considered along with their benefits. Disrupting the coagulation system increases risk of bleeding. Major bleeding—which includes internal bleeding, intracranial hemorrhages, and bleeding requiring medical attention—occurs in 2.5% to 3% of patients treated with anticoagulants per year.<sup>5</sup> In total, anticoagulants account for nearly 18% of all emergency department visits for adverse drug effects, more than any other class of drugs.<sup>6</sup>

The sharp contrast of risks and benefits for these medications necessitates that healthcare providers focus on ensuring anticoagulants are used appropriately to maximize the treatment's benefit and reduce risk of an adverse outcome (treatment failure or a significant bleed). Pharmacists and pharmacy technicians can improve the risk/benefit balance through proper counseling; verifying the agent selected and dose is appropriate; drug interaction screening; and ensuring proper follow-up and coordination during transitions of care. Careful review of the various oral anticoagulants will point out how they differ, and essential monitoring.

**PAUSE AND PONDER:** What questions could you ask at the time of a prescription refill to ensure safe use of anticoagulant medications? What is Step 1 in your algorithm?

## Warfarin

Warfarin is a vitamin K antagonist that has been used therapeutically since 1954. Unlike other oral anticoagulants, the dose of warfarin is not determined by patient factors such as age, weight, or renal function. Instead, prescribers determine the dose using repeated blood tests and dose adjustments. Using a coagulation test known as the International Normalized Ratio (INR), prescribers titrate the dose until the patient's INR

results are consistently within the defined therapeutic range (generally 2 to 3 for most patients). The therapeutic range represents the desired range of INR results that, if maintained, effectively balances warfarin's therapeutic effectiveness with risk of adverse events. If the INR is low, the prescriber increases the dose; conversely if the INR is too high, the prescriber lowers or may hold the dose until the INR decreases. Typically, the average dose is 4 mg/day to 6 mg/day. However it is not uncommon for doses to be as low as 0.5 mg/day or as high as 10 mg/day to 15 mg/day or more. Often, patients will take different doses every day; patients may receive a mixed regimen with one dose on some days of the week and another dose the remainder. And even though warfarin is available in tablet strengths from 1 mg to 10 mg, patients often split tablets to make half-doses.<sup>1,7</sup> In these situations it often helps if patients to use a pill box and a medication diary to manage the dosing and aid adherence.

Blood testing can be performed by conventional venipuncture or a simpler finger-prick point-of-care (POC) test. A POC test can be performed at a doctor's office, an anticoagulation management service, or for select, well-educated and supported patients, home self testing is an option. The need to test the patient's INR can be as frequent as daily at the onset of the therapy or in response to out-of-control results. Most patients are tested twice a month, and highly stable patients can potentially be tested as infrequently as every six weeks. Maintaining the INR level within the therapeutic range will not only maximize warfarin's benefit and reduce risk, it will also decrease the frequency of testing.<sup>1,7</sup> That is, as the patient's INR test results repeatedly remain within the range of 2 to 3, the provider will reduce the test frequency.

Complicating warfarin's dosing are dietary and drug interactions and concomitant diseases. Warfarin's mechanism of action involves interfering with the production of vitamin K-dependent coagulation factors. Vitamin K is present in significant amounts in many green leafy vegetables (e.g., lettuce, spinach, kale), soybean and canola oils, and cashews and in smaller amounts in many other foods. Vitamin K intake from food has the potential to alter warfarin's effectiveness and create a need for dose adjustments.

In general the more vitamin K consumed, the higher the warfarin dose required. However, the exact effect on an individual patient is hard to predict. Differences in food preparation, amounts eaten, the presence of extrahepatic vitamin K stores, and genetic variances all play a role. The majority of patients will only experience minor fluctuations in dietary intake with no clinical relevance. There is no need to avoid vitamin K containing foods, many of which are healthy choices. Rather, patients should be instructed to avoid large changes that occur over several days. If dietary changes occur, patients should report them to the healthcare provider who monitors their warfarin therapy. Significant changes in diet are handled much like drug interactions are, with a period of close monitoring for adverse events, increased blood testing, and potential dose adjustments.<sup>1,7,8</sup>

Warfarin is metabolized through the CYP enzyme system, more specifically CYP2C9 and to a lesser extent CYP3A4. It is also highly protein bound and therefore has multiple interaction mechanisms—perhaps more than any other drug. Lexi-comp lists 217 interacting agents from acetaminophen to zileuton.<sup>10</sup> Most interactions are minor in nature and can be managed through closer INR monitoring and small dose adjustments if necessary. More severe interactions will necessitate INR monitoring within a few days and then every few days until the results stabilize or the interacting medication is discontinued. Medications of greatest concern include co-trimoxazole, fluconazole, metronidazole, and flouroquinolones. Amiodarone and levothyroxine also often have a dramatic effect on INR results, but the onset is commonly delayed for a week or more due to their long half-lives. As important as it is to identify a drug interaction when a patient starts a new medication, it's also important to monitor when they discontinue the use of an interacting agent. Stopping an interacting medication will also necessitate more frequent INR monitoring (and related dose adjustments) until the results stabilize within the therapeutic range.<sup>1,7,9,10</sup>

Patients on warfarin who also suffer from congestive heart failure, thyroid disease, renal dysfunction, hepatic disease, hypoalbuminemia, infections, and diarrhea may also experience frequent fluctuations in their INR results. Changes in the severity of these concomitant disease states will alter warfarin's pharmacokinetics and pharmacodynamics, leading to necessary dose changes to maintain a therapeutic INR result.<sup>1</sup>

## DOACs

The U.S. Food and Drug Administration approved dabigatran etexilate (Pradaxa) in 2010. Its approval ushered in a series of new oral anticoagulation options. Nine years later, four other non-warfarin oral anticoagulants are now available: rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Sayvasa), and more recently betrixaban (Bevyxxa). Besides having different mechanisms of action, the major difference between warfarin

is that the DOACs have predictable pharmacokinetics that allow stable dosing with no need for routine blood monitoring. The DOACs can be divided into two main groups based on their mechanisms of action: direct thrombin inhibitors (DTI) and factor Xa inhibitors. The DOACs are suitable substitutions for almost all uses of warfarin with one important exception: they have not been shown to be safe for use in patients with prosthetic heart valves.<sup>1</sup> Therefore, patients who have prosthetic heart valves must take warfarin.

## Dabigatran

Dabigatran is currently the only DTI and the other DOACs are Factor Xa inhibitors. A major safety concern with dabigatran is ensuring patients swallow the capsules whole and do not chew or crush them. Dabigatran is formulated as a lipophilic prodrug in multiple small pellets of dabigatran etexilate within the outer capsule with an absolute bioavailability (the amount of drug that is absorbed into the systemic circulation) of only 6.5%. If the capsule is not swallowed intact, the bioavailability may increase as much as 75% and lead to excessive serum levels and potentially serious bleeding adverse effects. For this reason, community pharmacy teams should be absolutely certain to apply the auxiliary label that says, "Do not chew or crush. SWALLOW WHOLE." Dabigatran is also the only oral anticoagulant that needs to be dispensed in its original container to protect against degradation from moisture.<sup>1,11</sup>

Dabigatran's absorption is also affected by the activity of the P-glycoprotein (P-gp) efflux system. P-gp is a transporter pump that pumps substrates from inside the walls of the intestines back into the gastrointestinal tract lumen, thus reducing absorption. Drugs that interact with P-gp through induction will decrease absorption and lower serum levels and conversely, P-gp inhibition will increase absorption and serum levels of dabigatran. The manufacturer's recommendations concerning drug interactions differ based on the indications for use as explained in the next few paragraphs.<sup>1,10,11</sup>

When dabigatran is prescribed to reduce risk of stroke and systemic embolism in non-valvular atrial fibrillation, strong P-gp inducers should not be used concurrently. Patients with moderate renal impairment (creatinine clearance [CrCl] 30-50 mL/min) who are taking the P-gp inhibitors dronedarone or ketoconazole should reduce the dose of dabigatran to 75 mg twice daily. The use of other P-gp inhibitors such as verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment. Patients with severe renal dysfunction (CrCl 15-30 mL/min) should avoid concomitant use of all P-gp inhibitors.<sup>11</sup>

For the treatment and reduction in the risk of recurrence of deep venous thrombosis (DVT) and PE, the recommendations state that P-gp inhibitors should be avoided in patients with CrCl less than 50 mL/min. The manufacturer further recommends that if dabigatran is used for the prophylaxis of DVT and PE

following hip replacement surgery in patients with CrCl at or above 50 mL/min, and they are also receiving P-gp inhibitors such as dronedarone or systemic ketoconazole, dabigatran and the P-gp inhibitor doses should be separated by several hours. Patients with CrCl less than 50 mL/min should avoid concomitant use of P-gp inhibitors altogether.<sup>11</sup>

## Rivaroxaban

Rivaroxaban also has unique bioavailability concerns that need close attention. At doses of 10 mg or less, bioavailability is 80% to 100% and patients can take doses with or without food. When higher doses of 15 mg to 20 mg are used, bioavailability is only 66% on an empty stomach but improves to greater than 80% when taken with a meal. Therefore, rivaroxaban's prescribing information recommends that patients should take doses of 15 mg or 20 mg with the largest meal of the day to ensure adequate blood levels.<sup>1,12</sup> Here, too, pharmacy teams need to ensure that the correct auxiliary label is on the bottle. They must also monitor to ensure they counsel carefully if a patient's dose is raised to 15 mg or more, or lowered to 10 mg. Simply switching from a "Take with the largest meal of the day" label to a "Take on an empty stomach" label (or vice versa) will confuse patients. Patients need to know why the administration directions have changed.

Drug interaction concerns for rivaroxaban include not just P-gp, but CYP3A4 as well. Many drugs inhibit both P-gp and CYP3A4 and therefore concomitant use of these agents with rivaroxaban may significantly increase its serum level. Likewise, medications that induce both CYP3A4 and P-gp may significantly decrease the serum levels of rivaroxaban and potentially lead to inadequate protection from unwanted clots and treatment failure. The manufacturer recommends avoiding concomitant administration with combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir, although clarithromycin has been determined to be safe). Rivaroxaban should not be used in patients with CrCl 15 mL/min to less than 80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk. A similar recommendation is made to avoid use of medications that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) unless the potential benefit justifies the potential risk.<sup>1,10,12</sup>

## Apixaban

Apixaban is rapidly absorbed with a bioavailability of 50% that is unaffected by food. Apixaban is also a substrate of both CYP3A4 and P-gp and therefore shares similar drug interaction concerns with rivaroxaban. The manufacturer recommends that when patients are receiving apixaban 5 mg or 10 mg twice daily, the dose should be decreased by 50% when also receiving drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir). If the patient is already receiving the



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lowest dose of apixaban at 2.5 mg twice daily, coadministration with combined P-gp and strong CYP3A4 inhibitors should be avoided. Likewise, avoid concomitant use of dual P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs may decrease the serum levels of apixaban enough to lead to treatment failure. Unique to apixaban is the need to evaluate not just drug interactions and renal function to ensure proper dosing, but patient age and weight as well.<sup>1,13</sup>

The kidneys eliminate only 27% of each dose of apixaban, so there are no dose reductions necessary for kidney dysfunction alone. However the dose should be reduced to 2.5 mg twice daily for the prevention of stroke in patients with atrial fibrillation if patients have at least two of the following risk factors:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg (132 lbs), or
- a serum creatinine level greater than or equal to 1.5 mg/dL.

No dose adjustments are recommended based on these criteria for other apixaban indications.<sup>13</sup>

## Edoxaban

Edoxaban's bioavailability is also unaffected by food so it can be administered without concern about meals. Unique to edoxaban is the contraindication to use for the treatment of stroke prevention in atrial fibrillation when the patient's CrCl is greater than 95 mL/min (which is a normal level for most adults). An increased incidence of treatment failure has been demonstrated in this population—a population that would include most non-elderly adults. Like other oral Factor Xa inhibitors, edoxaban is a substrate of P-gp. Concomitant use of strong P-gp inhibitors may increase serum levels as much as 150%, therefore their use should be avoided. The manufacturer also recommends avoiding the use of the strong P-gp inducer rifampin.<sup>14</sup>

**PAUSE AND PONDER:** Daily administration of anticoagulants is important to prevent thrombotic complications, but when is it appropriate for patients to stop taking an anticoagulant on a short, temporary basis?

### Betrixaban

Betrixaban absorption is greatly enhanced when administered with a meal and is recommended to be taken at the same time each day with food. Drug interactions include the P-gp transport system. When coadministered with P-gp inhibitors such as amiodarone, azithromycin, verapamil, ketoconazole, and clarithromycin, the manufacturer recommends cutting the usual 160 mg dose in half to 80 mg on day 1 followed by a daily dose of 40 mg daily. Dose reduction is also necessary in patients with severe renal dysfunction (CrCl 15 mL/min to 30 mL/min) with increased monitoring for adverse events. Betrixaban's indication is limited to prophylaxis in hospitalized inpatients; it can be continued at home once discharged, but the total duration of therapy should be limited to 35 to 42 total days.<sup>15</sup>

### Concerns with All Anticoagulants

As mentioned in the introduction, all anticoagulant drugs elevate risk of bleeding and therefore their use with other drugs that carry the side effect of bleeding must be weighed carefully. This includes the use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and herbal products like St John's Wort and ginkgo. Anticoagulants all share a boxed warning concerning the risk of spinal or epidural hematomas when patients who are receiving anticoagulants undergo spinal anesthesia or puncture. Anticoagulants also have a warning that premature discontinuation may increase risk of thrombotic complications.<sup>1,7,10</sup>

The question of whether to temporarily stop the use of an oral anticoagulant in preparation for a medical procedure requires healthcare professionals to delicately balance the risk of thrombosis if stopped and bleeding if continued. A full examination of this issue is beyond the scope here, but it is important to know that many procedures can be performed safely without stopping anticoagulation; minor percutaneous procedures such as dental extractions, joint and soft tissue injections, arthrocentesis, cataract surgery, and upper endoscopy or colonoscopy with or without biopsy can be performed without stopping anticoagulation. The provider performing the procedure should consult with the patient's primary care provider and/or cardiologist and the patient to reach a decision. If oral anticoagulation is stopped and an injectable agent is used to "bridge" the patient's anticoagulant needs during the peri-procedure, the patient needs to know

- what day to stop taking the oral anticoagulant prior to the procedure,
- the duration of the drug holiday
- the specific day to resume treatment after the procedure.

Clear communication is important for a successful outcome. Pharmacists and pharmacy technicians can aid patients by ensuring patients receive clear directions and understand how to implement the plan.<sup>16</sup>

Healthcare transitions (to or from home, a hospital inpatient stay, or other healthcare facility) are also times when coordination, reinforcement, and proper follow-up should be assured for a positive outcome. Generally, prescribers initiate anticoagulants in a healthcare setting after a new diagnosis of atrial fibrillation or a thrombotic event such as a DVT or PE. Patients may or may not receive adequate information about the new condition and the medications used to treat it. Even if they did receive proper education, there is a chance that they won't remember clearly once they leave the facility. Proper discharge counseling should ensure the patient understands the risks and benefits; when and how to take the medication; what side effects to look for; and when to seek medical help for those side effects. In the case of warfarin, follow-up lab work and management must be in place. Community pharmacists are in a great position to provide and reinforce this information.



**PAUSE AND PONDER:** When reversing the effect of an anticoagulant in a life-threatening bleed, should the cost of therapy be considered?

## MANAGEMENT OF BLEEDING AND ANTICOAGULATION REVERSAL

While on anticoagulants, patients can often handle minor bleeding such as nose bleeds, gum bleeding, and bleeding from minor injuries with simple first aid and need not visit a healthcare provider or alter therapy. Minor bleeding that is prolonged or occurs frequently would warrant a discussion with a healthcare provider. Many times the anticoagulation effect can be lessened temporarily by decreasing the dose or holding a dose for a day or two until the acute issue has passed. All healthcare providers need to remind patients to withhold doses only on the advice of a healthcare professional.<sup>17,18</sup>

Major bleeding into any organ space should prompt immediate attention and referral to an emergency medical center. Gastrointestinal bleeding, urinary bleeding, or intracranial hemorrhage can become disastrous. Reversing anticoagulation therapy itself is a risky endeavor and is usually only performed in a hospital-based emergency department. Patients take oral anticoagulants to prevent serious thrombotic events because they are at high risk for clotting. Thrombosis itself can be life-threatening as well. The indication to reverse anticoagulation is generally life-threatening bleeding or an urgent need for life-saving surgery. Whenever anticoagulation is reversed by clinical necessity, therapy should be restarted as soon as it is determined safe to do so.<sup>17,18</sup>

### Reversing Warfarin and General Approaches

The ability to rapidly reverse warfarin's effects has long been considered a key advantage when deciding which anticoagulant to use as long-term treatment. However, in the last few years researchers have developed new pharmacological agents with direct ability to halt the actions of many DOACs. This has decreased the concern of treating major bleeding episodes in patients receiving DOACs.

With any anticoagulant, merely stopping the drug will allow the patient's anticoagulation system to return to baseline homeostasis once the drug is eliminated from the body and coagulation factors return to normal. This process can take from one day to several days depending on the drug used and the patient's renal function (for drugs predominately eliminated through the kidneys).

Reversing warfarin's clinical effects is largely dependent on the situation's urgency. A quicker reversal of warfarin's effect can be accomplished by administering vitamin K, available as phytonadione. Vitamin K will reverse warfarin's effects in a dose-dependent manner. It can be administered orally or injected.

Patients with markedly elevated INR levels (greater than 10) but without active bleeding should receive 2.5 mg to 5 mg of vitamin K and experience a significant reduction in INR level within 24 hours. A more rapid effect will occur by using higher doses administered intravenously (IV). For patients with active bleeds, 10 mg IV should be administered to lower the INR to baseline levels within six hours. Fresh frozen plasma (FFP) is a blood product that is rich in coagulation factors. Administering FFP will begin to normalize the INR value almost immediately, although the risks of blood products (transfusion reactions and transfusion-related acute lung injury), high volumes needed, and time to administer are drawbacks to its use.<sup>18</sup>

Four factor prothrombin complex concentrate (PCC), marketed as Kcentra, is indicated for the urgent reversal of coagulation factor deficiency induced by warfarin in adults with acute major bleeding or a need for an urgent surgical procedure. It is a mixture of multiple coagulation factors including factors II, VII, IX, and X and also contains proteins C and S and heparin. The product's approved labeling (see **Table 1**) describes dosing according to patient weight and pre-treatment INR. However, an off-label dosing strategy that uses a 'flat dose' or single low dose for patients regardless of INR has been shown to be effective, simpler, and less expensive. The mechanism of action is simple: PCC rapidly restores vitamin K-dependent coagulation factors to therapeutically effective levels. It is important to note that the dosing and potency of this product is defined by its factor IX content.<sup>19</sup>

**Table 1. Prothrombin Complex Concentrate Dosing<sup>19</sup>**

Pretreatment INR	Dose	Maximum Dose
2 to <4	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
>6	50 units/kg	5000 units

Four factor PCC is contraindicated in patients with disseminated intravascular coagulation. This product also contains heparin and is contraindicated in patients with heparin-induced thrombocytopenia. The most frequent adverse reactions in clinical trials were minor and included headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, PE, and DVT.<sup>19</sup>

Clinical data for the off-label use of PCC as a reversal agent for factor Xa inhibitors indicates it is effective. Limited studies in healthy volunteers demonstrate that PCC can normalize various measurements of anticoagulation. Positive results reported in case series and retrospective studies have lead expert panels to formally recommend off-label use of PCC at a dose of 25units per kg to 50 units per kg, maximum of 5000 units in severe, life-threatening situations.<sup>17,20</sup>

**Table 2. Andexanet Alfa Dosing Strategy**

Drug	Last Dose	Time Since Last Dose	
		< 8 hours or unknown	≥8 hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High Dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High Dose	

Low dose = 400 mg bolus followed within 2 minutes by infusion of 4 mg/min for 2 hours  
High dose = 800 mg bolus followed within 2 minutes by infusion of 8 mg/min for 2 hours

### Idarucizumab

Idarucizumab (Praxbind) was the first DOAC-targeted reversal agent. The FDA approved it in October 2015 for reversal of dabigatran’s anticoagulant effect for emergency surgery/urgent procedures, or life threatening or uncontrolled bleeding. Idarucizumab is a monoclonal antibody fragment with a strong affinity to dabigatran. Once administered intravenously it binds to dabigatran *in vivo* and neutralizes its clinical effect. The onset of this effect is very rapid (five minutes) and lasts for 24 hours. The idarucizumab-dabigatran complex is renally cleared although no dose changes are necessary in patients with any degree of renal dysfunction. The approved dose is 5 gm, administered IV as two separate 2.5 gm vials given sequentially. Unlike PCC, idarucizumab does not contain coagulation factors and is therefore considered non-thrombogenic with a low risk of developing a thrombosis after administration. However, its use will reverse the effectiveness of dabigatran and therefore expose patients to the thrombotic risk of their underlying disease.<sup>28</sup> The labeling recommends restarting dabigatran therapy as soon as 24 hours after administering idarucizumab if no significant risk of bleeding remains.<sup>21</sup>

Adverse effects appear to be minor with only headache occurring in more than 5% of healthy volunteers studied. There are no labeled contraindications. The idarucizumab formulation contains sorbitol. For this reason, its labeling includes a warning about use in patients with hereditary fructose intolerance. Parenteral administration of sorbitol may lead to serious adverse reactions including hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, and acute liver failure.<sup>2,20</sup>

### Andexanet alfa

Andexanet alfa (Andexxa) is a modified factor Xa molecule. The FDA designated andexanet alfa as a breakthrough therapy and approved it through an accelerated pathway based on limited clinical data. It is administered as a bolus followed by a continuous infusion for up to two hours. It binds to oral factor Xa inhibitors to negate their effect. Currently it is labeled for patients treated with rivaroxaban or apixaban when reversal of

anticoagulation is needed due to life-threatening or uncontrolled bleeding. It is important to note that it is not approved for reversing the effect of any other anticoagulants with factor Xa activity such as edoxaban and betrixaban.<sup>22</sup>

Dosing of andexanet alfa consists of a high dose and low dose strategy and is based on which specific factor Xa agent was being used, the dose, and the time since the last dose was taken if known (see **Table 2**). The most common side effects include infusion-related reactions, urinary tract infections, and pneumonia. Thromboembolic events and cardiac events, including sudden death, have occurred during treatment with andexanet alfa. As with other reversal agents, prescribers should have patients resume anticoagulant therapy as soon as medically appropriate following reversal.<sup>22</sup>

Andexanet alfa’s place in therapy is currently controversial. Although it is the only agent currently FDA-approved for reversing apixaban and rivaroxaban, its high cost and limited clinical data has lead clinicians to hesitate to use it. Published clinical outcomes data supporting its use was demonstrated in a single study: the Annexa-4 trial published in February 2019. Results demonstrated that 82% of treated patients had excellent or good hemostatic efficacy at 12 hours. Many critical patients were excluded from the trial including patients with planned surgery within 12 hours, intracranial hemorrhage with a Glasgow Coma Score of less than 7, and patients with a suspected survival of less than one month.<sup>23</sup>

The average wholesale prices for the low dose and high dose regimens are \$33,000 and \$59,400, respectively,<sup>24</sup> compared to roughly \$7,000 for a comparable dose of PCC.<sup>25</sup> It’s easy to see why without clear evidence of therapeutic difference, clinicians may resist using andexanet alfa and prefer PCC. Currently a trial is underway to compare PCC and andexanet alfa directly, but results are not expected for a few years.<sup>23</sup>



## Implications for Pharmacy Teams

Anticoagulation therapy is essential for millions of Americans. Ensuring the right medications are prescribed at the right dose, identifying significant drug interactions or health changes, screening for compliance problems, performing comprehensive counseling, and providing important information about reversal agents are critical. **Table 3** summarizes many of these points. Knowing when and how to intervene with patients who take oral anticoagulants ensures pharmacists have an algorithm for patient safety.

<b>Warfarin (Coumadin, Jantoven)</b>	Adjunct to reduce risk of systemic embolism (e.g., recurrent myocardial infarction, stroke) after MI	Initial dosing must be individualized. Consider the patient and the clinical situation. Start 2 to 5 mg once daily or for healthy individuals, 10 mg once daily for 2 days, then reduce dose; Adjust dose according to INR results; usual maintenance dose ranges from 2 to 10 mg daily
	Prophylaxis and treatment of thromboembolic disorders (e.g., venous, pulmonary) and embolic complications arising from AF or cardiac valve replacement	
<b>Dabigatran etexilate (Pradaxa)</b>	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	For patients with CrCl >30 mL/min: 150 mg orally BID For patients with CrCl 15-30 mL/min: 75 mg orally BID
	For the treatment of DVT/PE in patients who have been treated with a parenteral anticoagulant for 5-10 days	For patients with CrCl >30 mL/min 150 mg orally BID after 5-10 days of parenteral anticoagulation
	To reduce the risk of recurrence of DVT and PE in patients who have been previously treated	For patients with CrCl >30 mL/min: 150 mg orally, twice daily after previous treatment
	For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery	For patients with CrCl >30 mL/min: 110 mg orally first day, then 220 mg once daily
<b>Rivaroxaban (Xarelto)</b>	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	For patients with CrCl >50 mL/min: 20 mg orally, once daily with the evening meal For patients with CrCl ≤50 mL/min: 15 mg orally, once daily with the evening meal
	For the treatment of DVT, PE, and for the reduction in the risk of recurrence of DVT and of PE	15 mg orally twice daily with food for the first 21 days for the initial treatment of acute DVT or PE. After the initial treatment period, 20 mg orally once daily with food for the remaining treatment and the long-term reduction in the risk of recurrence of DVT and of PE.
	For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery	10 mg orally once daily with or without food
	In combination with aspirin, to reduce the risk of major CV events (death, myocardial infarction, and stroke) in patients with chronic coronary or peripheral artery disease	2.5 mg orally BID, with or without food
<b>Apixaban (Eliquis)</b>	To reduce the risk of stroke and systemic embolism in patients with nonvalvular AF	5 mg orally twice daily. 2.5 mg orally twice daily in patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine greater than or equal to 1.5 mg/dL.
	For the prophylaxis of DVT, which may lead to PE after hip/knee replacement surgery	2.5 mg orally BID
	For the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy	10 mg taken orally BID for the first 7 days of therapy. After 7 days, 5 mg BID. For the reduction in DVT/PE recurrence risk: 2.5 mg BID after at least 6 months of treatment for DVT or PE
<b>Edoxaban (Sayvasa)</b>	To reduce risk of stroke and systemic embolism in patients with non-valvular AF	60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use in patients with CrCL > 95 mL/min Reduce dose to 30 mg once daily in patients with CrCl 15 to 50 mL/min
	For the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant	60 mg once daily. The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight ≤ 60 kg or who use certain P-gp inhibitors.
<b>Betrixaban (Bevyxxa)</b>	VTE prophylaxis in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.	Initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. Reduce dose for patients with severe renal impairment or taking P-gp inhibitors
For the calculation of CrCl in patients receiving DOACs, the Cockcroft-Gault equation using actual body weight is recommended.		
<b>ABBREVIATIONS: AF = atrial fibrillation; BID = twice daily; CrCl = creatinine clearance; CV = cardiovascular; DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism; VTE = venous thromboembolism</b>		

## Technician Talk Sidebar

Technicians can have a significant impact on the safe use of anticoagulants through simple interventions.

- Take a thorough medication history; it will allow identification of interacting drugs.
- Consult each patient's refill history and identify patients who may need extensive counseling or show signs of poor adherence.
- Ask patients if they would like to enroll in automatic refills to guard against gaps in adherence, but be sure to stop the refills if the patient reports no longer needing the medication.
  - ❑ Take a minute to open the bag and review each medication when patients pick up automated refills.
- Bring patients with financial difficulties to the pharmacist's attention to ensure they do not go without a vital treatment for their conditions.
- Ask this simple question: Have you had any health changes or medical interventions since your last refill? It will identify patients in need of further evaluation for potential dosage changes.
- Ensure that the FDA required drug-specific Medication Guides are provided to patients along with their anticoagulant medications.
- Refer patients to online resources for further information
  - ❑ The American Heart Association's "A Patient's Guide To Taking Warfarin"  
[https://www.hopkinsmedicine.org/hematology/anticoagulation/patient\\_information/resources.html](https://www.hopkinsmedicine.org/hematology/anticoagulation/patient_information/resources.html)
  - ❑ The Michigan Anticoagulation Quality Improvement Initiative's "Patient Toolkit"  
<https://anticoagulationtoolkit.org/patients>

## All Done? Does Your Anticoagulant Algorithm Include All of the Following?

### Ensure correct prescribing:

- ❑ Medication correct for the patient's condition?
- ❑ Dose correct for age, renal function, and concomitant drugs?

### Provide education:

- ❑ The risks of OTC use, specifically aspirin and NSAIDs and potential drug interactions with herbal supplements
- ❑ Symptoms of adverse events:
  - ❑ Stroke (FAST- facial drooping, Arm weakness, Speech difficulties, Time to call 911)<sup>26</sup>
  - ❑ VTE (swelling, redness, and or pain in lower leg)
  - ❑ PE (shortness of breath, painful breathing, cough)
- ❑ Manage minor bleeding events and know when to notify a healthcare provider or seek urgent attention
- ❑ Monitor for serious bleeding events:
  - ❑ black stools
  - ❑ blood in urine or sputum
  - ❑ sudden extreme headache
  - ❑ stroke symptoms

### Warfarin

- ❑ If necessary, do patients have the dexterity to split tablets?
- ❑ If using more than one tablet strength, do they understand the different tablet strengths/colors?
- ❑ Do they have follow-up blood test monitoring in place?

### DOACs

- ❑ Apixaban or rivaroxaban for VTE treatment: Is it the correct strength for their current time point in therapy and do they know when to change to the maintenance dose?
- ❑ Dabigatran: Do not open, chew or crush capsules, and keep in original container
- ❑ Betrixaban should only be taken for a total of 35 to 42 days
- ❑ Rivaroxaban: 15 mg and 20 mg doses should be taken with a meal

### Review refill history

- ❑ Are there adherence issues that need to be addressed?
- ❑ Is there an opportunity to provide automatic refills?
- ❑ Since the last refill, have there been any medication or significant health change that should prompt a review of the prescribed dose?
- ❑ Is there an opportunity to reinforce medication education or clarify any questions or concerns?

### If recently discharged from hospital

- ❑ Have they resumed therapy?
- ❑ Any dose changes, new medications added, or previous medications stopped that could affect therapy?

## CONCLUSION

Pharmacy teams see more patients than ever who are taking oral anticoagulation therapy. Warfarin, despite its limitations, is still an important drug. Newer oral anticoagulants are safer in many ways, but they still need to be monitored.

When patients taking anticoagulants present at the pharmacy, each staff member needs to be sure that to turn on the “anticoagulant algorithm” light bulb, and start a rational, enlightened process. The process must include patient education, a quick review of adherence, ensuring appropriate use, and monitoring for safety. What else have you added to your Anticoagulant Algorithm?

**Figure 2. Advancing Pharmacists and Pharmacy Technicians Role in Anticoagulation Safety**



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