Direct Oral Anticoagulants (DOACs): Challenges and Decisions

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Topic Overview

Anticoagulant drugs inhibit blood coagulation and reduce clot development, which leads to a reduced risk of recurrent thrombosis. Despite a long history of available anticoagulants, such as coumarins and heparin, the unmet medical need for therapeutic alternatives continues. Direct oral anticoagulants (DOACs), which inhibit thrombin or activated factor X, are frequently prescribed in diverse healthcare settings. Optimizing patient outcomes requires consideration of a patient's risk of thrombosis and drug-dependent risk of bleeding. Apixaban, dabigatran, edoxaban, and rivaroxaban have similarities in their mechanisms of action and specific overlapping indications. It is imperative for pharmacy team members to be aware of the individual DOAC efficacy and safety profiles for therapeutic decision-making and patient counseling. Navigating dosing, side effects, and drug interactions contribute to optimizing treatment and patient counseling.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From October 18, 2022, through October 18, 2025, participants must:

1. Read the "learning objectives" and "author and planning team disclosures;"
2. Study the section entitled "educational activity;" and
3. Complete the Post-test and Evaluation form. The Post-test will be graded automatically. Following successful completion of the Post-test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Identify** the indications and dosing for various direct oral anticoagulant (DOAC) agents
2. **Identify** the contraindications and potential side effects within the DOAC class
3. **Apply** this information to answer patient or prescriber questions

Disclosures

The following individuals were involved in the development of this activity: Pamela Sardo, Pharm.D., B.S., and Susan DePasquale, MSN, PMHNP-BC. Pamela Sardo, Pharm.D., B.S., was an employee of Rhythm Pharmaceuticals until March 2022 and has no conflicts of interest or relationships regarding the subject matter discussed. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Thrombotic disorders place a heavy burden on patients and the healthcare system. Reducing morbidity and mortality due to thromboembolic events is critical. Anticoagulants are essential in the management of patients presenting with complex coagulation disorders. Clinicians can improve a patient's health outcomes by knowing the indications and dosing for various direct oral anticoagulant (DOAC) agents, and the contraindications or potential side effects of this class of medications. Pharmacists are in a particularly ideal position to discuss a patient's DOAC treatment options with the healthcare team.

Evolution of Anticoagulants

The history of anticoagulant development is interesting. Remarkably, the 1916 discovery of heparin is made by a medical student.[1] In the 1920s, cows that died from intestinal bleeding after consuming sweet clover and moldy hay, revealed a 'plasma prothrombin defect.'[2] In the 1950s, subsequent research led to the discovery of coumarins and warfarin. In the 1990s, low molecular weight heparin (LMWH) appears as a new option due to a longer biological half-life and more predictable dose-response.[3]

Today, interest remains high in identifying effective therapeutics with anticoagulant properties. As an alternative, since 2010, orally administered direct oral anticoagulants (DOACs) selectively targeting the coagulation cascade have been available.[4] Pharmacy teams are supporting treatment decisions while considering multiple indications, contraindications, dosing, various side effects, and specific drug interactions to achieve favorable patient outcomes.

Direct Oral Anticoagulants

The burden of thrombotic disorders is huge. For example, ischemic heart disease (IHD) and stroke remain leading causes of mortality and disability despite primary prevention and positive outcomes with traditional anticoagulants. The total number of disability-adjusted life years (DALYs) due

to stroke has risen steadily since 1990, reaching 143 million DALYs and 6.55 million deaths in the year 2019.[5]

Reducing morbidity and mortality due to thromboembolic events is critical. Anticoagulation is an essential tool in the management of patients presenting with complex coagulation disorders. Clinicians are focusing on direct oral anticoagulants because they can be orally administered at fixed doses and have less intense laboratory monitoring requirements. Within the coagulation cascade, thrombin is a key enzyme for direct fibrin formation, activating platelets, and is essential for clot formation. Dabigatran (Pradaxa) is a thrombin inhibitor. Factor Xa is a second enzyme in coagulation since it is essential for thrombin activation. Factor Xa inhibitors include apixaban (Eliquis), edoxaban (Savaysa) and rivaroxaban (Xarelto). Direct inhibition of thrombin or factor Xa results in the inhibition of blood coagulation.[6]

Direct Thrombin Inhibition

Dabigatran

Dabigatran etexilate is a prodrug that converts to active dabigatran after absorption from the gastrointestinal tract. It is available in 75 mg, 110 mg, and 150 mg capsules and is available in 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg pellets in a packet for pediatric dosing. Not all dabigatran dosage forms are approved for the same indications and age groups. Do not substitute different dosage forms on a milligram-to-milligram basis, and do not combine more than one dosage form to achieve the total dose.[7] See the Table below for DOAC dosing in specified indications.

The full prescribing information should be consulted for each of the DOAC agents regarding weight-based dosing recommendations in pediatric patients. It should also be the resource for individuals with renal impairment and for converting to, or from, parenteral anticoagulants or warfarin and for consideration of comprehensive safety and efficacy information.

There is a boxed warning in the dabigatran full prescribing information regarding the risk of thrombosis if premature discontinuation occurs. The boxed warning also describes the risk of spinal/epidural hematoma. Dabigatran is contraindicated in active pathological bleeding, history of hypersensitivity reaction to the drug, and in patients with a mechanical prosthetic heart valve. Dabigatran is not recommended in individuals with Triple-Positive Antiphospholipid Syndrome. The most common adverse reactions (> 15%) are gastrointestinal adverse reactions and bleeding. The prescribing information discusses the similarity of risk of major bleeding between dabigatran and warfarin. There is a trend for higher DOAC-associated incidence of major bleeding in individuals over age 75.[7]

Factor Xa Inhibition

Apixaban

Apixaban is a selective inhibitor of factor Xa. It does not require antithrombin III for activity. It has no direct effect on platelet aggregation but indirectly inhibits platelet aggregation. By inhibiting factor Xa, it decreases thrombin generation and thrombus development. It is available in 2.5 mg and 5 mg tablets.[8]

Apixaban is contraindicated in active pathological bleeding or a history of hypersensitivity reaction to the drug. There is a boxed warning regarding the risk of thrombosis if premature discontinuation occurs. The boxed warning also describes the risk of spinal/epidural hematoma. Apixaban is contraindicated in active pathological bleeding and a history of hypersensitivity reaction to the drug. It is not recommended for use in patients with prosthetic heart valves. Apixaban is not recommended in individuals with Triple-Positive Antiphospholipid Syndrome. The most common adverse events (> 1%) are related to bleeding.[8]

Edoxaban

Edoxaban is a selective inhibitor of factor Xa. It does not require antithrombin III for activity. It inhibits free factor Xa, and prothrombinase activity and inhibits thrombin-induced platelet aggregation. Inhibiting factor Xa decreases thrombin generation and thrombus formation. It is available in 15 mg, 30 mg, and 60 mg tablets.[9]

Edoxaban is contraindicated in active pathological bleeding. The boxed warning describes reduced efficacy in nonvalvular atrial fibrillation (NVAF) patients with creatinine clearance > 95 ml/min. It warns of thrombosis risk if premature discontinuation occurs. The boxed warning also describes the risk of spinal/epidural hematoma. The most common adverse reactions (≥ 5%) are bleeding and anemia in patients presenting with NVAF. The most common adverse reactions (≥ 1%) in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) with edoxaban are bleeding, rash, abnormal liver function tests, and anemia.[9]

Rivaroxaban

Rivaroxaban is a selective oral direct factor Xa inhibitor. It is available in 2.5 mg, 10 mg, 15 mg, and 20 mg tablets and as a 1 mg/ml oral suspension once reconstituted. The full prescribing information should be consulted for weight-based dosing recommendations in pediatric patients.[10]

Rivaroxaban is contraindicated in active pathological bleeding and a history of hypersensitivity reaction to the drug. There is a boxed warning in the full prescribing information regarding the risk of thrombosis if premature discontinuation occurs. The boxed warning also describes the risk of spinal/epidural hematoma. The most common adverse reaction (> 5%) in adult patients was bleeding. The most common adverse reactions (> 10%) in pediatric patients were bleeding, cough, vomiting, and gastroenteritis.[10]

Table: DOAC Dosing in Adults with Specified Indications

Specified Indication	Dabigatran[7]	Apixaban[8]	Edoxaban[9]	Rivaroxaban[10]
Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation	For patients with CrCl >30 mL/min: 150 mg twice daily For patients with CrCl 15-30 mL/min: 75 mg twice daily	5 mg orally twice a day*	60 mg once daily in patients with CrCl < 95 ml/min 30 mg once daily with CrCl 15-50 ml/min	20 mg once daily with evening meal when CrCl >50 ml/min 15 mg once daily with evening meal when CrCl ≤50 ml/min
Prophylaxis of DVT following hip or knee replacement surgery	For patients with CrCl >30 mL/min: 110 mg orally first day, then 220 mg once daily§	2.5 mg orally twice daily		Hip: 10 mg once daily for 35 days with or without food Knee: 10 mg once daily for 12 days with or without food
Treatment of DVT and PE	For patients with CrCl >30 mL/min: 150 mg twice daily after 5-10 days of parenteral anticoagulation	10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily	60 mg once daily following 5-10 days of initial parenteral anticoagulant 30 mg once daily when CrCl 15-50 ml/min, patients <60 kg, or patients taking certain P-gp‡ inhibitor medications	15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining time when CrCl ≥15 ml/min
Reduction in the risk of recurrent DVT and PE following initial therapy	For patients with CrCl >30 mL/min: 150 mg twice daily after previous treatment	2.5 mg taken orally twice daily		10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment when CrCl ≥15 ml/min
Prophylaxis of VTE^ in Acutely Ill Medical Patients at Risk for				10 mg once daily, with or without food, in hospital and after hospital

Thromboembolic Complications Not at High Risk of Bleeding				discharge for a total recommended duration of 31 to 39 days when CrCl ≥15 ml/min
CAD or PAD				2.5 mg twice daily with or without food, in combination with aspirin (75-100 mg) once daily

*****In patients with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.
§and PE
ǂP-gp P-glycoprotein
^VTE venous thromboembolism

Discussion

Indication Similarities

Direct oral anticoagulants can be orally administrated at a fixed dosage and have rapid action, generally between 1 and 3 hours after ingestion. As shown in the Table above, each DOAC is indicated for nonvalvular atrial fibrillation, DVT, and PE in adults. Healthcare providers should refer to the full prescribing information. There are distinctions in other diagnoses (see Table above), in pediatric use, when a patient is converting to or from warfarin or parenteral anticoagulants, and recommendations for discontinuation around surgery.[11]

DOAC Monitoring Challenges and Special Populations

Patients remain at potential risk of increased bleeding throughout treatment due to the inhibitory effect on coagulation pathways. DOAC use does not require routine lab monitoring; however, testing may be helpful in certain conditions or populations. Testing in cases involving drug accumulation, overdosage, thrombotic or bleeding events, acute stroke,

trauma, renal function impairment, and upcoming surgery may be warranted. Use in patients with obesity (≥120 kg) or low body weight (≤50 kg) should also be evaluated. The optimal laboratory assay to monitor DOAC concentrations may not be available in every institution. The ideal approach depends on test availability, the level of information required (drug presence or drug concentration), and the turnaround time for the result.[12]

There is limited data available for the use of DOACs in pregnancy. Breastfeeding is not recommended while undergoing anticoagulation. At the other end of the age spectrum, there is a risk of bleeding, which increases with age. Warnings regarding DOAC use include assessing patients with indwelling epidural catheters, and the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants. Lower DOAC doses may be recommended in patients taking P-glycoprotein inhibitors.[11] Thrombocytopenia has been reported with these P-gp medications, but its clinical significance is still debated.[3]

Another challenge is knowing when to terminate DOAC treatment. Beyond recommendations during specific indications, such as DVT while using rivaroxaban, stopping a DOAC prior to an invasive procedure or operation must be assessed. Cessation of treatment prior to surgery may depend on the half-life of the drug, creatinine clearance, and the risk of bleeding.[13] Healthcare professionals should evaluate individual comorbidities and remain vigilant for unexpected adverse events.

Drug Interactions

The hepatic enzyme CYP3A4 is important in the metabolism of rivaroxaban and apixaban, and all DOACs are substrates of the P-glycoprotein transporter system. Enzyme inducers can cause a reduction in DOAC plasma concentration and could increase the risk of thromboembolic events. Strong P-gp inducers possibly lowering the DOAC concentration include rifampin, St. John’s Wort, carbamazepine, and phenytoin.

Inhibitors can potentiate the DOAC concentration and could result in bleeding. Strong P-gp inhibitors possibly increasing the DOAC concentration include ketoconazole, ritonavir, and cyclosporin.[13]

In rare cases, a reversal agent may be appropriate. There are two reversal agents for DOACs have been. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa) is a modified human factor Xa protein indicated for patients treated with rivaroxaban or apixaban when reversal is needed due to life-threatening or uncontrolled bleeding. It is not approved for the treatment of bleeding with any other factor Xa inhibitors.[14] Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment (Fab) indicated in patients when reversal of dabigatran's anticoagulant effects is needed.[15,16]

Future Research

Large, randomized trials of DOACs in patients with morbid obesity are needed. Despite limited evidence, the use of DOACs for VTE treatment and prevention is seen in this complex population. A recent analysis of Medicare and commercial claims databases found that of the 34,910 patients with morbid obesity (BMI ≥40 kg/m2) on anticoagulation for non-valvular AF, 63.4% of them were anticoagulated with a DOAC.[17]

These are exciting times. DOAC research is ongoing. Clinicaltrials.gov has posted a trial in Italy evaluating DOAC use in unusual sites. The anatomical sites poised for DOAC treatment include splanchnic vein thrombosis, cerebral vein thrombosis, retinal vein thrombosis, ovarian vein thrombosis, and renal vein thrombosis.[18] Another trial will evaluate DOAC use in women who experience heavy menstrual bleeding.[19]

Clinical Pearls for Patient and Provider Discussions

The pharmacy team is ideally poised to advise patients and prescribers. Conversations may instruct:

- not to discontinue their anticoagulants without talking to their physician first
- bruising may be visible
- to immediately report any unusual bleeding
- tell all physicians and dentists that anticoagulants have been prescribed
- tell all physicians and dentists, and pharmacy staff if taking over-the-counter products
- inform if pregnant or plan to become pregnant or planning to breastfeed
- do not substitute anticoagulants for one another
- aspirin or antiplatelet medications may not be required once a DOAC is started
- asking questions is important

There is a clinical risk resulting from a lack of awareness of DOACs. In one study, DOAC patients with major bleeding had a fatality rate of 6% to 9%.[20] Pharmacists can share their expertise and support patient safety. For example, if a pharmacist sees a prescription for a DOAC and enoxaparin or LMWH at the same time, call the doctor.

Summary

Education about DOACs remains critical for the assessment of patient safety and clinical outcomes. Clinicians are faced with increasingly complex decisions involving anticoagulation therapy. Pharmacists are in an ideal position to discuss treatment options with the healthcare team, evaluate the condition for which the DOAC is prescribed, monitor for efficacy and safety, and appropriately counsel patients and caregivers.

Course Test

1. **Which of the following conditions is appropriate for a DOAC?**

    a. NVAF
    b. VTE
    c. UTI
    d. a and b are correct

2. **Which of the following would prevent the use of a DOAC?**

    a. The patient is at high risk for a bleeding episode
    b. The patient is scheduled for a hip replacement
    c. The patient has wisdom teeth extraction planned
    d. None of the above

3. **A patient with a CrCl of 20 ml/min, comes to you with a prescription for dabigatran 500 mg daily, after traveling to Asia for 14 hours with a resulting DVT. How should you proceed?**

    a. It is appropriate to fill the prescription and provide patient counseling.
    b. Contact the physician for alternatives due to the patient's CrCl and daily dose.
    c. Counsel her that clopidogrel would be a lower-cost therapeutic alternative.
    d. Advise her to stop aspirin for 2 days before beginning the dabigatran.

4. **What is a correct statement on the use of DOAC reversal agents?**

    a. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa) is a modified human factor Xa protein indicated for patients treated with dabigatran.
    b. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa) is a modified human factor Xa protein indicated for patients treated with rivaroxaban or apixaban.
    c. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa) is a modified human factor Xa protein indicated for patients treated with only high dose edoxaban.
    d. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa) is a modified human factor Xa protein indicated for acetaminophen overdose.

5. **A second-year medical school fellow asks you whether to include recommendations for apixaban to be utilized in patients with CAD or PAD. What do you suggest?**

    a. Yes, apixaban can be dosed 2.5 mg twice daily with or without food, in combination with aspirin once daily for CAD or PAD.
    b. Yes, apixaban can be dosed as 150 mg twice a day in patients with CrCl >30 mL/min who develop CAD or PAD.
    c. No, apixaban is for NVAF, DVT following knee or hip surgery, treatment of DVT or PE, or reducing recurrent DVT and PE.
    d. No, apixaban is approved for prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications.

6. **A patient informs you that their family member has just received a prescription for a DOAC and is asking for more information. What do you tell them?**

    a. A DOAC is prescribed to increase clotting ability in the body when there is too much bleeding.
    b. A DOAC will not cause bruising to be visible and will not cause bleeding risk.
    c. Patients do not have to share if pregnant or planning pregnancy or breastfeeding.
    d. Patients should tell physicians, dentists, and pharmacists if taking OTC products.

7. **Which of the following drugs is a p-glycoprotein inducer?**

    a. Ketoconazole
    b. Ritonavir
    c. Cyclosporine
    d. Carbamazepine

8. **Which of the following doses are correct for the agent described?**

    a. Dabigatran is available in 75 mg, 110 mg, and 150 mg capsules
    b. Edoxaban is available in 2.5 mg, and 5 mg tablets
    c. Apixaban is available in 15 mg, 30 mg, and 60 mg tablets
    d. Rivaroxaban is available in 25 mg, 40 mg, and 50 mg tablets

9. What is a contraindication associated with the use of a DOAC?

a. History of hypersensitivity reaction to the drug
b. Presence of a mechanical heart valve
c. Active pathological bleeding
d. All of the above

10. A patient approaches the pharmacy counter with a prescription for rivaroxaban for the reduction in the risk of recurrent DVT. The patient cannot remember everything the doctor told him and asks whether food is required. The response from the pharmacist should be:

a. It must be taken daily with an evening meal.
b. It can be taken with or without food.
c. It can be taken with dairy products but not red meat.
d. It must be taken with grapefruit juice.

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