Transformative Medicine (T-Med)

Volume 3 | Number 2 Article 5

June 2024

Direct Oral Anticoagulants: A Review for Health Care Providers

Mary Hoang
Reading Hospital - Tower Health

Maley Zents
Reading Hospital - Tower Health

Christina Swiger
Reading Hospital - Tower Health

Emily Wagner
Reading Hospital - Tower Health

Recommended Citation

Hoang M, Zents M, Swiger C, Wagner E. Direct Oral Anticoagulants: A Review for Health Care Providers. *Transformative Medicine (T-Med)*. 2024; 3(2):65-70. doi: https://doi.org/10.54299/tmed/udyw3699.

Direct Oral Anticoagulants: A Review for Health Care Providers

Cover Page Footnote

We thank Dr. Adam Sigal, MD for providing guidance on the article. We thank Dr. Matt Alspach, PharmD and Dr. Regine Ghoubrial-Waibel, PharmD for precepting the project.

Direct Oral Anticoagulants: A Review for Health Care Providers

Mary Hoang[1], Maley Zents[1], Christina Swiger[1], Emily Wagner[1]

Pharmacy Department, Reading Hospital – Tower Health. West Reading, PA

Published June 2024

ABSTRACT

Direct oral anticoagulants (DOACs) are a novel class of anticoagulants. They include rivaroxaban, apixaban, edoxaban, and dabigatran. Benefits of DOACs over many older anticoagulants include oral administration, quicker onset of action, less monitoring requirements, and fewer drug interactions. Since the DOACs were first introduced, their use has increased tremendously. This article aims to help providers become more familiar with DOACs and the specific factors that may impact prescribing practices. Several drugs used for the reversal of DOACs will also be discussed. Lastly, the article will describe certain situations in which warfarin is preferred over DOACs.

INTRODUCTION

Anticoagulants are drugs that antagonize coagulation. They are used for a variety of indications, including stroke prevention in non-valvular atrial fibrillation (NVAF) and treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] Anticoagulants work by targeting coagulation factors within the coagulation cascade.[2] Historically, the first anticoagulants were unfractionated heparin and vitamin K antagonists.[2] Although effective, these agents require careful monitoring to ensure appropriate use. For example, the anti-Xa is used to measure plasma levels of unfractionated heparin, and the international normalized ratio (INR) is used to measure the effect of vitamin K antagonists like warfarin. Vitamin K antagonists also have many drug interactions that can affect their efficacy and safety.

In 2010, direct oral anticoagulants (DOACs) were approved by the Food and Drug Administration (FDA).1 DOACs are classified into two classes, direct factor Xa inhibitors and direct thrombin inhibitors.[1] Direct oral factor Xa inhibitors include rivaroxaban, apixaban, and edoxaban, and direct oral thrombin inhibitors include dabigatran.[1] DOACs work by binding to the catalytic site of factor Xa or thrombin, preventing their ability to activate their substrates in the coagulation cascade.[2] Benefits of DOACs over previous anticoagulants include oral administration, quicker onset of action, less monitoring requirements, and fewer drug interactions.[1] Select labeled indications, dosing, and special considerations for DOACs are listed in the Tables 1 and 2.

DECIDING WHICH DOAC TO PRESCRIBE

Because many of the DOACs have similar indications, efficacy, and safety profiles, it may be difficult to decide which one to prescribe for each patient. Another limitation of prescribing DOACs is that there are currently no head-to-head trials compar-

Correspondence to Mary Hoang at Mary.Hoang@towerhealth.org

Disclosure Statement: The authors have no conflicts of interest to declare.

TABLE 1. Select Labeled Indications and Dosing of DOACs

	Apixaban[3]	Rivaroxaban[4]	Edoxaban[5]	Dabigatran[6]
NVAF	5 mg twice daily 2.5 mg twice daily if two of the following are present: • Weight ≤ 60 kg • Age ≥ 80 years • SCr ≥ 1.5 mg/dL	20 mg once daily CrCl < 50 mL/min: 15 mg once daily	60 mg once daily CrCl > 95 mL/min: avoid CrCl 15-50 mL/min: 30 mg once daily	150 mg twice daily CrCl 15-30 mL/min: 75 mg twice daily CrCl < 15 mL/min: no guidance
DVT and PE	10 mg twice daily for 7 days, then 5 mg twice daily	15 mg twice daily for 21 days, then 20 mg once daily CrCl < 15 mL/min: avoid	60 mg once daily following 5-10 days of initial parenteral anticoagulation CrCl 15-50 mL/min: 30 mg once daily Weight < 60 kg: 30 mg once daily	150 mg twice daily following 5-10 days of initial parenteral anticoagulation CrCl < 30 mL/min: no guidance
Ortho Ppx	2.5 mg twice daily	10 mg once daily CrCl < 15 mL/min: avoid		Hip replacement only 110 mg on day 1, then 220 mg once daily CrCl < 30 mL/min: no guidance
Recurrent DVT and PE Ppx	2.5 mg twice daily	10 mg once daily		150 mg twice daily following 5-10 days of initial parenteral anticoagulation CrCl < 30 mL/min: no guidance
VTE Ppx		10 mg once daily		

CrCl: creatinine clearance
NVAF (non-valvular atrial fibrillation): reduce the risk of stroke and systemic embolism in patients with NVAF
DVT (deep vein thrombosis) and PE (pulmonary embolism): treatment of DVT and PE
Ortho Ppx (prophylaxis): prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery
Recurrent DVT and PE Ppx: reduce the risk of recurrent DVT and PE after at least 6 months of treatment
VTE (venous thromboembolism) Ppx: prophylaxis of VTE in adult patients 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

ing one DOAC over another in safety and efficacy. Following are some considerations that may support the use of one DOAC over another based on select indications and comorbidities.

Stable Atherosclerotic Cardiovascular Disease

Rivaroxban is FDA-approved for secondary prevention for patients with ASCVD (atherosclerotic cardiovascular disease).[1] The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial demonstrated significant reduction in major cardiovascular events, a composite of cardiovascular death, stroke, and myocardial infarction, with low doses of rivaroxaban in combination with aspirin.[1] The dose for ASCVD prevention is 2.5 mg twice daily, in combination with daily low-dose aspirin.[4]

https://scholarcommons.towerhealth.org/t-med/vol3/iss2/5
DOI: https://doi.org/10.54299/tmed/udyw3699

TABLE 2. Special Considerations with DOACs

	Apixaban[3]	Rivaroxaban[4]	Edoxaban[5]	Dabigatran[6]
Administration	Taken without regard to food Tablets may be crushed* May be delivered through a NG tube	Doses of 15 mg or higher should be taken with food Tablets may be crushed* May be delivered through a NG tube or gastric feeding tube	Taken without regard to food Tablets may be crushed* May be delivered through a gastric feeding tube	Taken without regard to food Capsules cannot be opened
Missed Doses	Take the missed dose as soon as possible. The dose should not be doubled to make up for a missed dose.	2.5 mg twice daily: Skip the missed dose and restart at the next scheduled dosing time 15 mg twice daily: Ensure intake of 30 mg per day. Two 15 mg tablets may be taken at once. 20 mg, 15 mg or 10 mg once daily: Take the missed dose immediately. Do not take two doses on the same day to make up for a missed dose.	Take the missed dose as soon as possible. The dose should not be doubled to make up for a missed dose.	Take the missed dose as soon as possible, at least 6 hours before the next dose. The dose should not be doubled to make up for a missed dose.
Adverse Reactions (> 10%)	Hemorrhage	Hemorrhage	Hemorrhage	Hemorrhage, gastrointestinal effects
Drug Interactions	Strong CYP3A4 and P-gp inhibitors and inducers	Strong CYP3A4 and P-gp inhibitors and inducers	Avoid use with rifampin	P-gp inhibitors and inducers
Other		Available as an oral suspension		Must use within 4 months of opening Must be kept in the original container

NG: Nasogastric
*See the package insert for compatible food and beverages

Cancer-Associated Thromboembolism

Historically, the drugs of choice for cancer-associated thromboembolism were low-molecular-weight heparins (LMWHs).[1] Trials comparing edoxaban and rivaroxaban with dalteparin showed that both edoxaban and rivaroxaban reduced recurrent VTE, but with increased risks of major bleeding.[1] The ADAM VTE (Apixaban, Dalteparin, in Active Cancer Associated Venous Thromboembolism) trial comparing apixaban with dalteparin showed that apixaban reduced recurrent VTE with no increased risks of major bleeding.[1] Therefore, apixaban is the

TABLE 3. Hepatic Considerations with DOACs

	Apixaban[3]	Rivaroxaban[4]	Edoxaban[5]	Dabigatran[6]
Child-Pugh A (Mild)	No dose reduction			
Child-Pugh B (Moderate)	No dosing recommendation	Not recommended	Not recommended	No dosing recommendation
Child-Pugh C (Severe)	Not recommended			

Not recommended: Agent should not be prescribed

preferred DOAC for cancer-associated VTE.[1]

Renal Impairment

DOACs are generally safe for patients with moderate renal impairment (CrCl 30-50 mL/min) when doses are renally adjusted appropriately. For severe renal impairment (CrCl < 30 mL/min), certain DOACs should be renally dose-adjusted or avoided altogether based on the indication. Edoxaban should be avoided for CrCl > 95 mL/min.[5] Please refer to Table 1 for specific renal dose adjustments based on CrCl and indication.

Hepatic Impairment

Recommendations for DOAC use in hepatic impairment are based on the Child-Pugh classification system, which assesses severity of hepatic dysfunction based on bilirubin, albumin, INR, ascites, and encephalopathy.[1] Table 3 lists recommendations for hepatic dosing of DOACs based on Child-Pugh score.

Pediatric Patients

The only DOAC in which efficacy and safety in pediatric patients have been established is rivaroxaban.[4] Rivaroxaban is indicated for VTE treatment and reduction of recurrent VTE risk in pediatric patients from birth to less than 18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure.[4]

Geriatric Patients

In clinical trials, there were no clinically significant differences in safety or efficacy between older and younger patients with the use of apixaban or edoxaban.[3,5] In clinical trials, the efficacy of rivaroxaban was similar in older and younger patients.[4] However, the rates of thrombotic and bleeding events were higher in patients 65 years and older.[4] Similarly, with dabigatran use in clinical trials, the risk of stroke and bleeding increased with age.[6]

REVERSAL STRATEGIES

The reversal of DOACs depends on which DOAC is involved, the severity of the bleed, and risk of thromboembolism. The severity of the bleed and degree of urgency is an important factor to consider before deciding to reverse a patient's anticoagulation.[7] Reversal is not indicated in patients who have minor bleeding events and who are hemodynamically stable. Patients who present with minor bleeding events should be directed to hold their anticoagulant, monitor clinical status, and check labs.[7]

The reversal of DOAC therapy is indicated in patients in need of urgent reversal due to life-threatening bleeding associated with DOACs or perioperative coagulation. Reversal agents include andexanet alfa (Andexxa®), idarucizumab (Praxbind®), and four factor prothrombin concentrate complex (4F-PCC) (Kcentra®, Balfaxar®) (*Table 4*). Other pharmacologic interventions that have been used to reverse anticoagulant therapy include fresh frozen plasma (FFP). FFP is the fluid portion of blood which contains all coagulation factors except for platelets.[8]

Due to the high costs, quality of research, and availability of andexanet alfa and idarucizumab, PCC is often used. Studies have been completed comparing andexanet alfa and idarucizumab to PCC showing non-inferiority.[9,10] Recently, a study comparing andexanet alfa and PCC showed superiority with increased rates of thrombotic events. Notably, this trial had significant bias in the study design.[11]

WARFARIN AS THE PREFERRED AGENT

Since their introduction in 2010, DOACs have come to replace warfarin as the preferred therapy for common indications for chronic anticoagulation, such as VTE and PE treatment and prophylaxis, stroke prevention in patients with atrial fibrillation, and in patients with a history of a transient ischemic attack (TIA) or cardiovascular attack (CVA). Despite their

https://scholarcommons.towerhealth.org/t-med/vol3/iss2/5
DOI: https://doi.org/10.54299/tmed/udyw3699

TABLE 4. Reversal Agents for DOACs

Reversal Agent	DOAC Reversal	Mechanism of Action
Andexanet alfa (Andexxa®)[12]	FDA Label: Apixaban Rivaroxaban Off Label: Edoxaban	Humanized monoclonal antibody fragment that binds specifically to dabigatran
Idarucizumab (Praxbind®)[13]	Dabigatran	Binds and sequesters factor Xa inhibitors and increases tissue factor-initiated thrombin generation
4F-PCC (Kcentra®, Balfaxar®)[14]	Off label: Apixaban Rivaroxaban Edoxaban Dabigatran	Provides a rapid increase in plasma levels of vitamin K-dependent coagulation factors (factors II, VII, IX, and X) and proteins C and S

efficacy, reduced monitoring, consistent dosing, fewer drug interactions, and a lower rate of adverse events, there are certain instances in which warfarin may be the anticoagulant of choice.[15] The scenarios where warfarin may be preferred over DOACs include:

1. Cost: Warfarin is often cheaper than DOACs, which may be significant for some patients, especially those without insurance coverage or with limited financial resources.
2. Severe renal impairment: DOACs are mainly eliminated through the kidneys and may not be suitable for patients with significant renal impairment. Warfarin is primarily metabolized by the liver and does not require dose adjustment based on renal function.
3. Antiphospholipid syndrome: Research on DOACs in antiphospholipid syndrome is limited, with a trend towards a lack of efficacy observed in different studies.[16]
4. Mitral stenosis: Mitral stenosis (MS) remains under-investigated in randomized controlled trials of DOACs. Patients with mild MS were included in phase 3 trials investigating the use of dabigatran, apixaban, and edoxaban in atrial fibrillation; however, moderate/severe MS was a major exclusion factor for all phase 3 clinical trials.[17]
5. Prosthetic valve: For patients undergoing mechanical valve replacements, indefinite anticoagulation is indicated. Current data is limited and not supportive of DOAC use in place of warfarin. Results of studies have led to an FDA warning and are the basis for the American College of Cardiology (ACC) / American Heart Association (AHA) recommendation to avoid DOACs in patients with mechanical valves.[18]

CONCLUSION

Due to their ease of administration, few monitoring requirements, and minimal drug interactions, DOACs have become a key anticoagulant class for a plethora of indications, including stroke prevention in NVAF, DVT and PE treatment and prevention, and even ASCVD prevention. In many cases, DOACs have been prescribed to replace agents like heparin and warfarin, which have been used for decades.

Despite having minimal monitoring requirements, DOACs do have special considerations, such as renal dose adjustments. Prescribers of these agents should be aware of CrCl cutoffs for the various indications, as well as specific administration instructions and missed dose recommendations. Because the individual DOACs may be similar in many aspects, it is also important to determine which DOAC is best to prescribe based on indications and patient comorbidities.

Because DOACs are anticoagulants, they inevitably carry bleeding risks. Therefore, situations may arise in which agents must be used to reverse anticoagulation and manage adverse effects. Reversal agents include andexanet alfa, idarucizumab, and 4F-PCC. Before initiating a reversal agent, it is crucial to assess each patient's clinical status and pertinent labs to determine if DOAC reversal is truly indicated.

Although DOACs have replaced warfarin in many cases, there are instances in which warfarin is still preferred over DOACs, such as in antiphospholipid syndrome and mitral stenosis. Outside of these few specific scenarios, DOACs continue to be a mainstay of treatment for an expanding list of indications.

REFERENCES

1. Chen A, Stecker E, Warden B. Direct oral anticoagulant use: a practical guide to common clinical challenges. J. Am. Heart Assoc. 2020;9(13):e017559. doi: 10.1161/JAHA.120.017559
2. Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L. Anticoagulants: a short history, their mechanism of action, pharmacology, and indications. Cells. 2022;11(20):3214. https://doi.org/10.1161/JAHA.120.017559
3. Apixaban. Package insert. Bristol-Myers Squibb Company; 2016.
4. Rivaroxaban. Package insert. Janssen Pharmaceuticals, Inc; 2021.
5. Edoxaban. Package insert. Daiichi Sankyo, Inc; 2019.
6. Dabigatran. Package insert. Boehringer Ingelheim Pharmaceuticals, Inc; 2015.
7. Managing and reversing direct oral anticoagulants: A discussion guide. The American Society of Health-System Pharmacists (ASHP). Accessed May 19, 2024. https://ashpadvantagemedia.com/doacresources/files/doacresources-discussion-guide.pdf
8. Khawar H, Kelley W, Stevens JB, et al. Fresh frozen plasma (FFP) [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513347/
9. Troyer C, Nguyen W, Xie A, Wimer D. Retrospective review of andexanet alfa versus 4-factor prothrombin complex concentrate for reversal of DOAC-associated intracranial hemorrhage. J Thromb Thrombolysis. 2023;55(1):149-155. doi:10.1007/s11239-022-02715-4
10. Honickel M, Braunschweig T, Rossaint R, Stoppe C, Ten Cate H, Grottke O. Reversing dabigatran anticoagulation with prothrombin complex concentrate versus idarucizumab as part of multimodal hemostatic intervention in an animal model of polytrauma. Anesthesiology. 2017;127(5):852-861. https://doi.org/10.1007/s11239-022-02715-4
11. Connolly SJ, Sharma M, Cohen AT, et al. Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024;390(19):1745-1755. https://doi.org/10.1056/NEJMoa2313040
12. Andexanet alfa (inactivated coagulation factor Xa [recombinant]): drug information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on May 18, 2024.)
13. Idarucizumab: drug information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on May 18, 2024.)
14. Prothrombin complex concentrate, 4-factor, unactivated, from human plasma: drug information. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on May 18, 2024.)
15. Wadsworth D, Sullivan E, Jacky T, Sprague T, Feinman H, Kim J. A review of indications and comorbidities in which warfarin may be the preferred oral anticoagulant. J Clin Pharm Ther. 2021;46(3):560-570. https://doi.org/10.1111/jcpt.13343
16. Martinelli I, Abbattista M, Bucciarelli P, et al. Recurrent thrombosis in patients with antiphospholipid antibodies treated with vitamin K antagonists or rivaroxaban. Haematologica. 2018;103(7):e315-e317. https://doi.org/10.3324/haematol.2017.185132
17. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2017;135(25):e1159-e1195. https://doi.org/10.1161/CIR.0000000000000503
18. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206-1214. https://doi.org/10.1056/NEJMoa1300615