

Clinical Overview of Direct Oral Anticoagulants

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1

Disclosures

- Dr. White has no financial relationships with ineligible companies.
- This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

2

Learning Objectives

At the completion of this activity, the participant will be able to:

1. Describe DOAC pharmacology and pharmacokinetics.
2. Identify an appropriate DOAC regimen based on DOAC indications, contraindications, and pharmacokinetics.
3. Identify important counseling points for DOACs.
4. Discuss special considerations for DOACs, including adherence, special populations, and transitioning between anticoagulants.

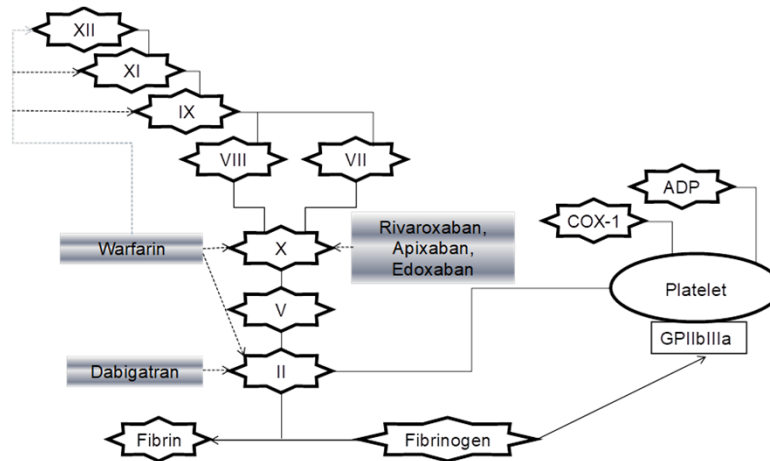
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Background

- Direct oral anticoagulants = DOACs, includes:
 - Direct thrombin inhibitor: dabigatran (Pradaxa)
 - Factor Xa inhibitors: rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa)
- Used to treat and prevent thrombosis
- Demonstrated superiority and noninferiority to prior standards of care (vitamin K antagonist warfarin and low-molecular-weight heparins) in reducing risk of thromboembolic complications
- Has similar or reduced bleeding risk

4

Pharmacology



White CM, Kalus JS. Cardiac Arrhythmias. *Applied Therapeutics*. 2021.

5

Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Peak	~1-2 hours	~2-4 hours	~2 hours	~1-2 hours
Half-life	12-17 hours	5-12 hours	~12 hours	~10-14 hours
Bioavailability	3-7%	80-100%	50%	62%
Renal excretion	80%	33%	27%	50%
3A4 substrate	No	Yes	Yes	No
P-gp substrate	Yes	Yes	Yes	Yes

Choi R, Kapoor K, Mackman N, Jovin IS. Direct Oral Anticoagulants and Coronary Artery Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2022.

6

Common Interacting Drugs: Inhibitors Increase DOAC Exposure

- Strong CYP3A4 inhibitors and combined PgP inhibitor: significant DOAC exposure increase
 - Itraconazole, ketoconazole, ritonavir
- Moderate CYP3A4 inhibitors and combined PgP inhibitor: moderate DOAC exposure increase
 - Clarithromycin, diltiazem
- PgP inhibitors: DOAC exposure increase
 - Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin, ivacaftor, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

7

Common Interacting Drugs: Inducers Decrease DOAC Exposure

- Strong CYP3A4 inducer and combined PgP inducer: significant DOAC exposure decrease
 - Carbamazepine, rifampin, St. John's wort
- Strong CYP3A4 inducers: significant DOAC exposure decrease
 - Phenytoin
- PgP inducers: significant DOAC exposure decrease
 - Rifampin

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

8

Patient Case

- NW is a 75-year-old female with hypertension, hyperlipidemia, and severe persistent asthma. She has been recently diagnosed with non-valvular atrial fibrillation and will be started on a DOAC for stroke prevention. Her current medications are as follows:
 - Diltiazem extended release 120 mg PO once daily
 - Atorvastatin 40 mg once daily
 - Budesonide 160 mcg/formoterol 4.5 mcg 2 inhalations twice daily
 - Prednisone 30 mg PO twice daily as needed for acute exacerbation
- Which medication may increase NW's exposure to her new DOAC?

9

Patient Case: Answer

- NW is a 75-year-old female with hypertension, hyperlipidemia, and severe persistent asthma. She has been recently diagnosed with atrial fibrillation and will be started on a DOAC for stroke prevention. Her current medications are as follows:
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 - Atorvastatin 40 mg once daily
 - Budesonide 160 mcg/formoterol 4.5 mcg 2 inhalations twice daily
 - Prednisone 30 mg PO twice daily as needed for acute exacerbation
- Which medication may increase NW's exposure to her new DOAC?
 - Diltiazem (moderate CYP3A4 inhibitors and combined P-gp inhibitor)

10

Recommendations for Drug Interactions

- Dabigatran
 - PgP inhibitor: reduce dose or avoid depending on renal function
 - PgP inducer: avoid use
 - Antacids: no dose adjustments required
 - Consider spacing regimens by 2 hours
- Rivaroxaban
 - Strong CYP3A4 inhibitor and combined PgP inhibitor: avoid use
 - Moderate CYP3A4 inhibitor and combined PgP inhibitor: no precaution necessary
 - Avoid use in patient with severe renal insufficiency
 - Strong CYP3A4 inducer or PgP inducer: avoid use

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

11

Recommendations for Drug Interactions Cont.

- Apixaban
 - Strong CYP3A4 inhibitor and combined PgP inhibitor: reduce dose or avoid use
 - Moderate CYP3A4 inhibitor and combined PgP inhibitor: no dose adjustments required but use with caution
 - Avoid use in patient with severe renal insufficiency
 - Strong CYP3A4 inducer or PgP inducer: avoid use
- Edoxaban
 - PgP inhibitors:
 - AF: Do not reduce dose
 - VTE treatment: Reduce dose
 - PgP inducers: avoid use with rifampin

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

12

Patient Case Continued

- NW enters your pharmacy to fill her new prescription for apixaban for stroke prevention due to her non-valvular atrial fibrillation. Considering the interaction between her current prescription for diltiazem and this new prescription, how would you proceed?
 - a. Call the prescriber and recommend use of dabigatran instead
 - b. Call the prescriber and recommend a reduced dose of apixaban
 - c. Alert the prescriber about the interaction but do not recommend a medication change
 - d. Counsel the patient to space the apixaban at least 2 hours from the diltiazem

13

Patient Case Continued

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 - d. Counsel the patient to space the apixaban at least 2 hours from the diltiazem

14

Indications: Dabigatran

- FDA approved indications:
 - Stroke and systemic embolism prevention in NVAf (nonvalvular atrial fibrillation)
 - Treatment of deep vein thrombosis and pulmonary embolism
 - Prevention of recurrent deep vein thrombosis and pulmonary embolism
 - Prevention of thromboembolism after total hip replacement
- Off-label indications:
 - Prevention of thromboembolism after total knee replacement
 - Prevention of thromboembolism after PCI with NVAf

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020. Dabigatran [package insert]. Ridgefield, CT. Boehringer Ingelheim. 2023.

15

Indications: Rivaroxaban

- FDA approved indications:
 - Stroke and systemic embolism prevention in NVAf
 - Treatment of deep vein thrombosis and pulmonary embolism
 - Prevention of recurrent deep vein thrombosis and pulmonary embolism
 - Prevention of thromboembolism after total knee replacement and after total hip replacement
 - Prevention of thromboembolism in hospitalized acutely ill medical patients
 - Prevention of major cardiovascular events in patients with chronic CAD/peripheral artery disease
- Off-label indications:
 - Prevention of thromboembolism after PCI with NVAf

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020. Rivaroxaban [package insert]. New Brunswick, NJ. Johnson and Johnson. 2024.

16

Indications: Apixaban

- FDA approved indications:
 - Stroke and systolic embolism prevention in NVA
 - Treatment of deep vein thrombosis and pulmonary embolism
 - Prevention of recurrent deep vein thrombosis and pulmonary embolism
 - Prevention of thromboembolism after total knee replacement and after total hip replacement
- Off-label indications:
 - Treatment of heparin-induced thrombocytopenia
 - Prevention and treatment of cancer-associated deep vein thrombosis
 - Prevention of thromboembolism in hospitalized acutely ill medical patients
 - Prevention of thromboembolism after PCI with NVA

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020. Apixaban [package insert]. Princeton, NJ. Bristol-Myers Squibb. 2021.

17

Indications: Edoxaban

- FDA approved indications:
 - Stroke and systolic embolism prevention in NVA
 - But NOT in patients with CrCl >95 mL/min
 - Treatment of deep vein thrombosis and pulmonary embolism
- Off-label indications:
 - Prevention and treatment of cancer-associated deep vein thrombosis
 - Prevention of thromboembolism after total knee replacement and after total hip replacement
 - Prevention of thromboembolism after PCI with NVA

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020. Edoxaban [package insert]. Basking Ridge, NJ. Daiichi Sankyo. 2023.

18

Warnings and Contraindications

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Active pathological bleeding	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Severe hypersensitivity	Contraindicated	Contraindicated	Contraindicated	Acceptable
Mechanical prosthetic heart valve	Contraindicated	Not recommended	Not recommended	Not recommended
Bioprosthetic heart valves	Not recommended*	Acceptable	Acceptable	Acceptable
Moderate to Severe Mitral Stenosis	Acceptable	Acceptable	Acceptable	Not recommended
Triple-Positive Antiphospholipid Syndrome	Not recommended	Not recommended	Not recommended	Not recommended

*Warning in package insert, but small-cohort studies support safe and effective use in patients with bioprosthetic valves

Dabigatran [package insert]. Ridgefield, CT. Boehringer Ingelheim. 2023.
 Rivaroxaban [package insert]. New Brunswick, NJ. Johnson and Johnson. 2024.
 Apixaban [package insert]. Princeton, NJ. Bristol-Myers Squibb. 2021.
 Edoxaban [package insert]. Basking Ridge, NJ. Daiichi Sankyo. 2023.

19

Patient Case

- You are talking to MM about her new prescription for dabigatran for stroke prevention in atrial fibrillation. She tells you that she has been plagued by atrial fibrillation since her heart valve replacement surgery.
- What additional information would you want to know about her heart valve surgery to make sure apixaban is not contraindicated for her?

20

Patient Case: Answer

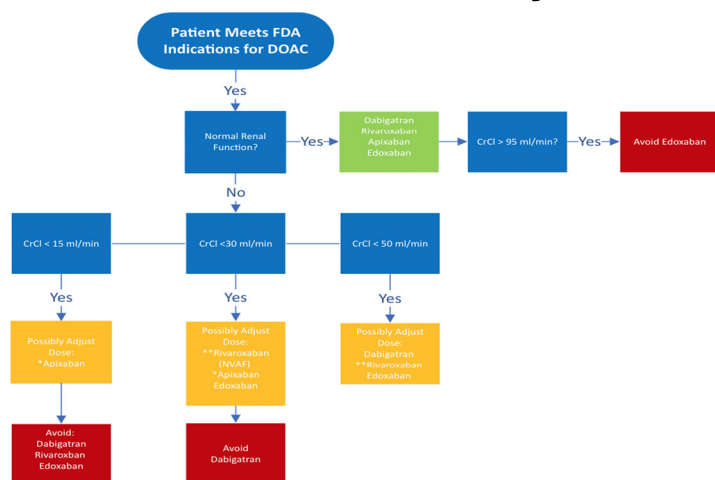
- You are talking to MM about her new prescription for dabigatran for stroke prevention in atrial fibrillation. She tells you that she has been plagued by atrial fibrillation since her heart valve replacement surgery.
- What additional information would you want to know about her heart valve surgery to make sure dabigatran is not contraindicated for her?

→ What type of new heart valve she has (dabigatran is contraindicated in patients with a mechanical prosthetic heart valve)

21

Safety Considerations: Renal Insufficiency

- Renal insufficiency
 - Apixaban dose adjustment for Afib (remember your ABCs)
 - Age ≥ 80 years
 - Body weight ≤ 60 kg
 - Creatinine (serum) ≥ 1.5 mg/dL
 - Rivaroxaban dose adjustments are based on patient indication



Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

22

Safety Considerations: Hepatic Impairment

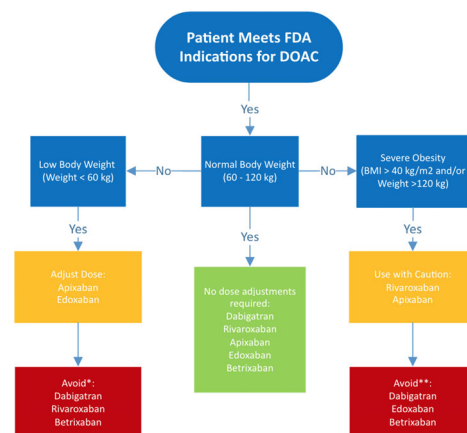
- All DOACs are contraindicated in severe hepatic impairment
- All DOACs can be used in mild hepatic impairment without dose adjustment
- Dabigatran, apixaban, and edoxaban can be used in moderate hepatic impairment

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

23

Safety Considerations: Extreme Body Weights

- Limited data
- Recommendation for patients >120 kg and/or >40 kg/m²: avoid dabigatran and edoxaban, may use rivaroxaban and apixaban with caution
- Dose adjustments required for apixaban and edoxaban for patients ≤ 60 kg



Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

24

Counseling Points

- Inform patient they may bleed and bruise more easily and it might take longer to stop bleeding
- Report signs of unusual bleeding (black/tarry stools, vomit with blood or that looks like coffee grounds, bleeding that won't stop) to a primary care provider
- Dabigatran
 - Take capsule with a full glass of water
 - Do not chew or open capsule before taking
 - Must be kept in original container: do not store in pill box or pill organizer
 - Must use within 4 months of opening container

Dabigatran [package insert]. Ridgefield, CT. Boehringer Ingelheim. 2023.
 Rivaroxaban [package insert]. New Brunswick, NJ. Johnson and Johnson. 2024.
 Apixaban [package insert]. Princeton, NJ. Bristol-Myers Squibb. 2021.
 Edoxaban [package insert]. Basking Ridge, NJ. Daiichi Sankyo. 2023.

25

Counseling Points Continued

- Rivaroxaban
 - 15 mg and 20 mg doses for VTE treatment should be taken with food
 - 10 mg doses for VTE prevention can be taken with or without food
 - Tablets can be crushed and mixed with applesauce followed by food
 - Can be administered via NG tube
- Apixaban
 - Tablets can be crushed and mixed with water, apple juice, or applesauce
 - Can be administered via NG tube
- Edoxaban
 - Tablets can be crushed and mixed with water or applesauce
 - Can be administered via NG tube

Dabigatran [package insert]. Ridgefield, CT. Boehringer Ingelheim. 2023.
 Rivaroxaban [package insert]. New Brunswick, NJ. Johnson and Johnson. 2024.
 Apixaban [package insert]. Princeton, NJ. Bristol-Myers Squibb. 2021.
 Edoxaban [package insert]. Basking Ridge, NJ. Daiichi Sankyo. 2023.

26

Patient Case

- RT is picking up his prescription for rivaroxaban 15 mg twice daily to treat a DVT. He is wondering if there's anything important for him to know about how to take his new medication. How should you counsel him?

27

Patient Case: Answer

- RT is picking up his prescription for rivaroxaban 15 mg twice daily to treat a DVT. He is wondering if there's anything important for him to know about how to take his new medication. How should you counsel him?
 - Take your rivaroxaban twice daily with food; if he has trouble swallowing it, he can crush it and mix it with applesauce and then eat food

28

Adherence

- Adherence is important: patients should not stop taking their DOAC unless instructed by the prescriber
- In a recent retrospective cohort study, a 10% decrease in adherence to DOAC regimen was associated with a significant 14% increased hazard (95% CI: 9.4–18.7) of stroke and systemic embolism
- Area for pharmacist intervention!

Safari A, Helisaz H, Salmasi S, et al. Association Between Oral Anticoagulant Adherence and Serious Clinical Outcomes in Patients With Atrial Fibrillation: A Long-Term Retrospective Cohort Study. J Am Heart Assoc. 2024.

29

Once vs. Twice Daily Dosing

- Dabigatran and apixaban are twice daily while rivaroxaban and edoxaban are once daily
 - No comparative studies on these products and adherence
 - Studies in general found once daily better than three times daily or four times daily
 - Studies haven't found once daily superior to twice daily
 - Fewer missed doses but more missed days of therapy with once daily
 - Shared decision-making with patients may identify those for which twice daily dosing is an issue

Alam T, Clyne CA, White CM. JCER 2012;1:225-39.

30

Monitoring at Follow-up Visits

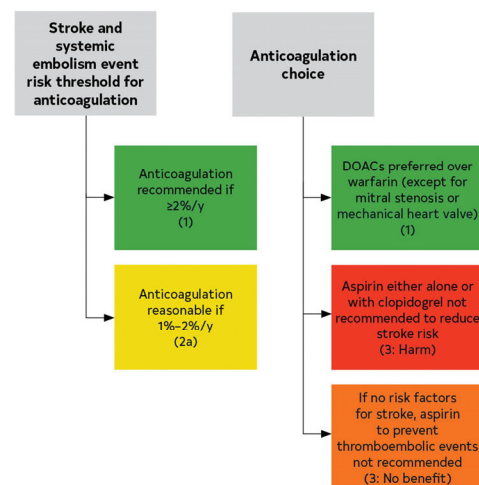
- Quantitative tests (e.g. anti-factor Xa levels, prothrombin time, etc.) have no established clinical role and do not need to be monitored
- Adherence
- Bleeding and thrombotic events
 - Signs and symptoms of bleeding, complete blood count
- Adverse events
- Complete medication review for drug interactions
 - P-gp and CYP3A4 inducers especially
- Reassessment of appropriateness of therapy
 - Renal function, liver function, weight and age (apixaban with Afib),

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association*. 2020.

31

Special Populations: Atrial Fibrillation

- Evaluate the CHA₂DS₂-VASc and HAS-BLED scores to determine risk vs. benefit at least annually
- DOACs are 1st line over warfarin, except in moderate-severe mitral stenosis or mechanical heart valve recipients
- Therapy is indicated if the patient has an estimated annual risk of stroke of thromboembolism of 2% or greater



Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023.

32

Special Populations: VTE

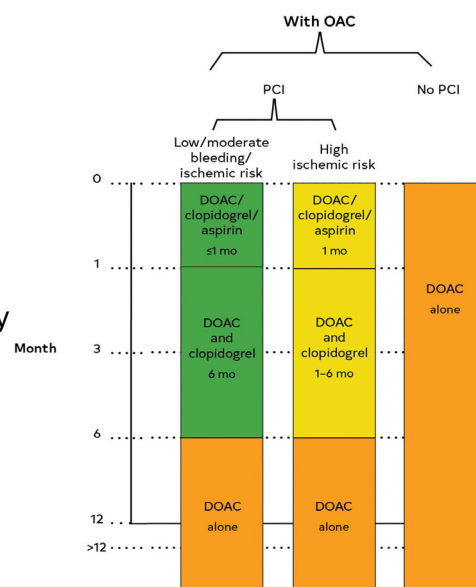
- DOACs are preferred over warfarin unless contraindicated
- Treatment of VTE: 3 months of anticoagulation
- Secondary prevention for unprovoked VTE or VTE provoked by a persistent risk factor (e.g. active cancer, inflammatory bowel disease, autoimmune disorders, chronic infections, chronic immobility)
 - Use anticoagulant indefinitely unless the patient has a high risk for bleeding complications
 - Can use lower doses (10 mg rivaroxaban daily or 2.5 mg apixaban twice daily)

Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020.
Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest.* 2021.

33

Special Populations: Coronary Artery Disease

- After elective PCI, patients who require oral anticoagulation (e.g. patients with atrial fibrillation) would be treated with:
 - DOAC plus dual antiplatelet therapy for 1-4 weeks
 - Then DOAC plus clopidogrel for 6 months
 - Finally, DOAC alone



Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation.* 2023.

34

Special Populations: Pregnancy and Lactation

- Not enough data for DOAC use during pregnancy and lactation to say it's safe
- DOACs cross the placenta and have the potential to cause reproductive toxicity
- DOACs are recommended against during lactation
- LMWH preferred during pregnancy
- UFH, LMWH, warfarin, acenocoumarol, and fondaparinux are safe options during lactation

Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv.* 2018.

35

SNEAK PEAK: Transitioning Between Anticoagulants

- Goal: limit interruption of therapeutic anticoagulation during the transition to minimize the risk of thrombosis
- Warfarin to DOAC: Stop VKA and start DOAC once INR is <2 or lower INR limit of therapeutic range
 - Measure INR before and after DOAC initiation because DOAC may falsely elevated INRs
- DOAC to DOAC: Stop current DOAC regimen and begin the new DOAC agent at the same time the next dose of the original DOAC would have been given
- DOAC to parenteral: Stop DOAC and start parenteral anticoagulant at the same time that the next dose of DOAC would have been given
- Parenteral to DOAC:
 - Intravenous: Start DOAC 0 to 2 h after stopping UFH
 - Subcutaneous: Stop LMWH and start DOAC at the same time that the next dose of LMWH would have been given
- **There's an entire other module on transitioning in the perioperative period!**

Chen A, Stecker E, Warden BA. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *Journal of the American Heart Association.* 2020.

36

SNEAK PEAK Patient Case

- JE is an 82-year-old male who is currently hospitalized on your floor recovering from a pulmonary embolism. He is currently on IV unfractionated heparin, but the doctor would like to switch him to a DOAC in preparation for discharge. The doctor asks you, the pharmacist, how to make that switch. What would you tell the doctor?

37

SNEAK PEEK Patient Case: Answer

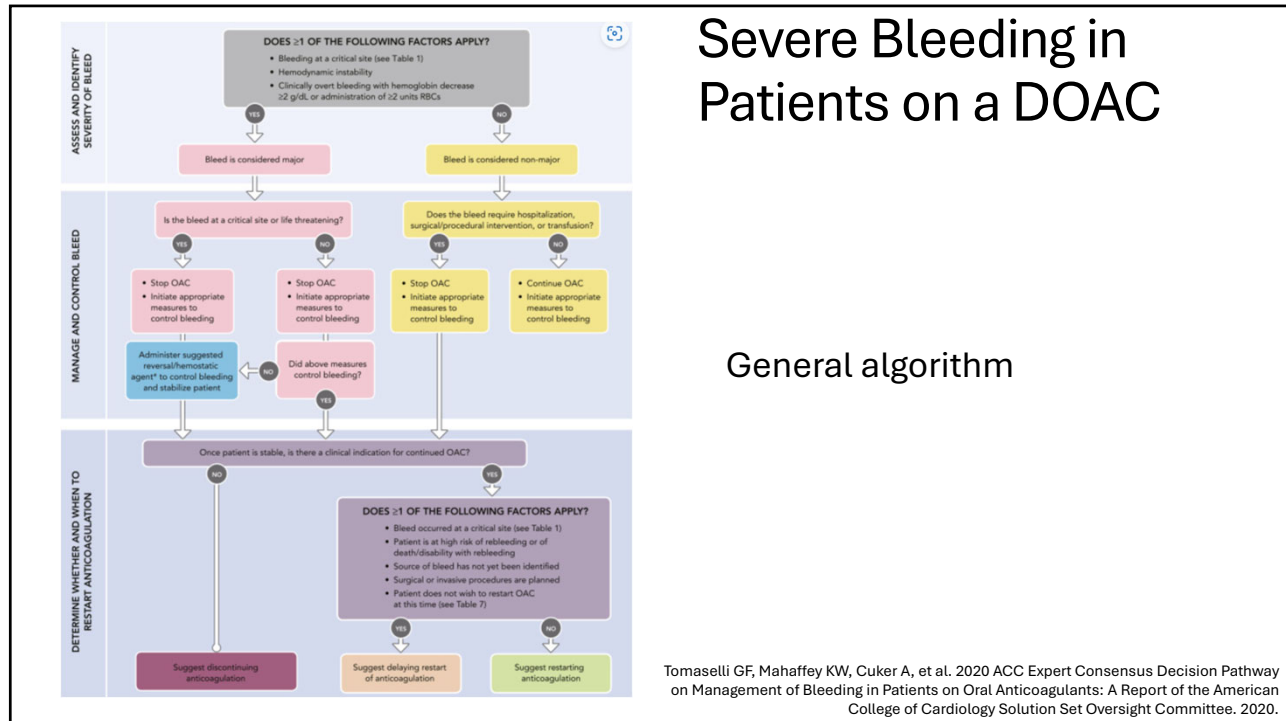
- JE is an 82-year-old male who is currently hospitalized on your floor recovering from a pulmonary embolism. He is currently on IV unfractionated heparin, but the doctor would like to switch him to a DOAC in preparation for discharge. The doctor asks you, the pharmacist, how to make that switch. What would you tell the doctor?

→ Start the DOAC within 2 hours of stopping the unfractionated heparin

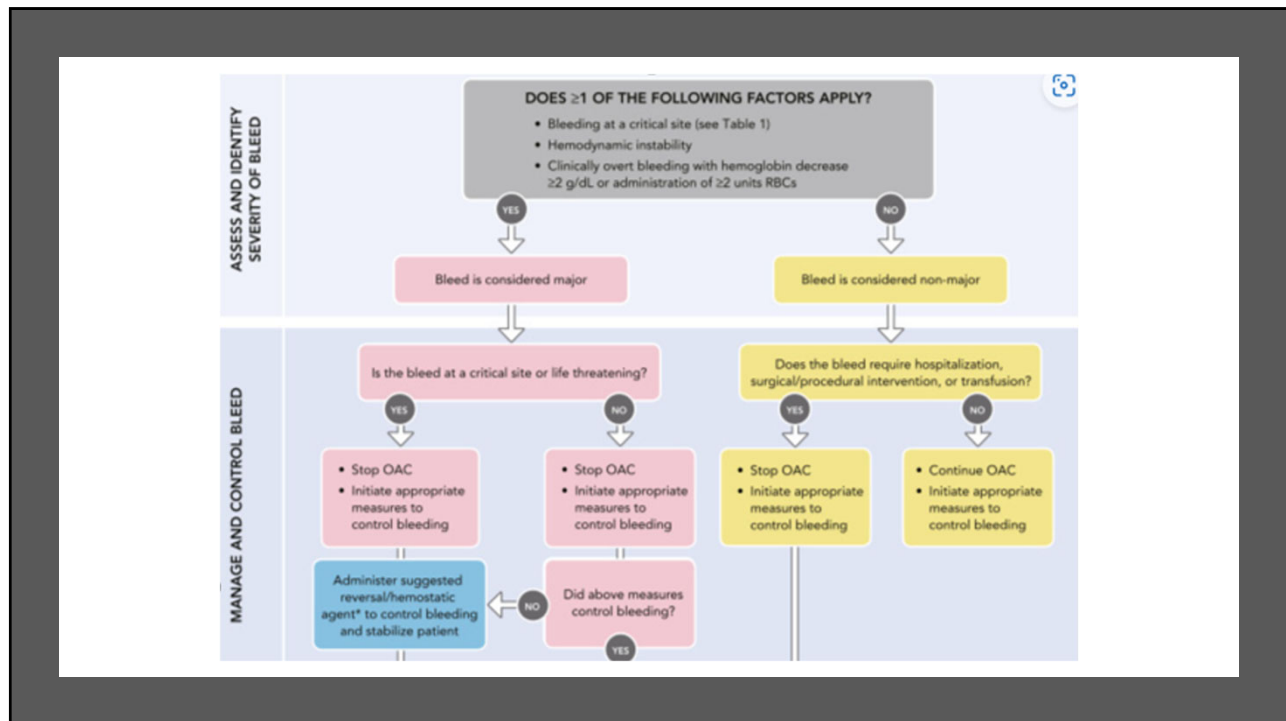
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Severe Bleeding in Patients on a DOAC

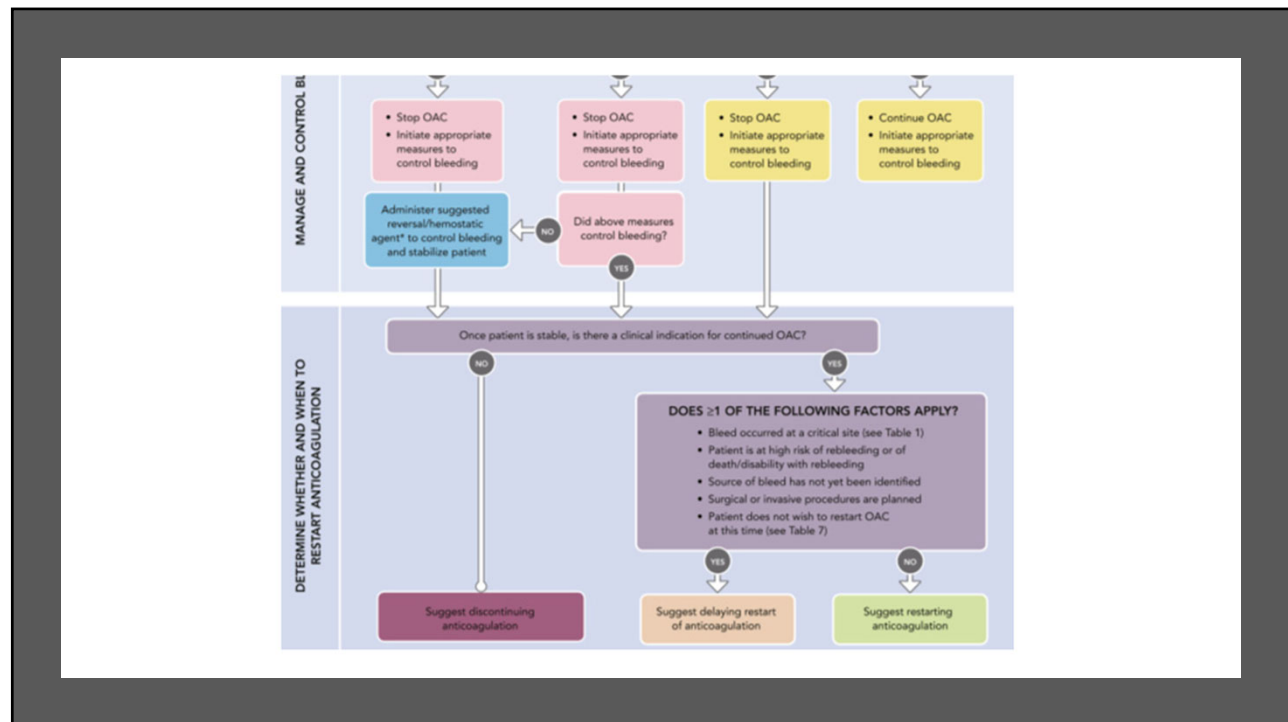
General algorithm



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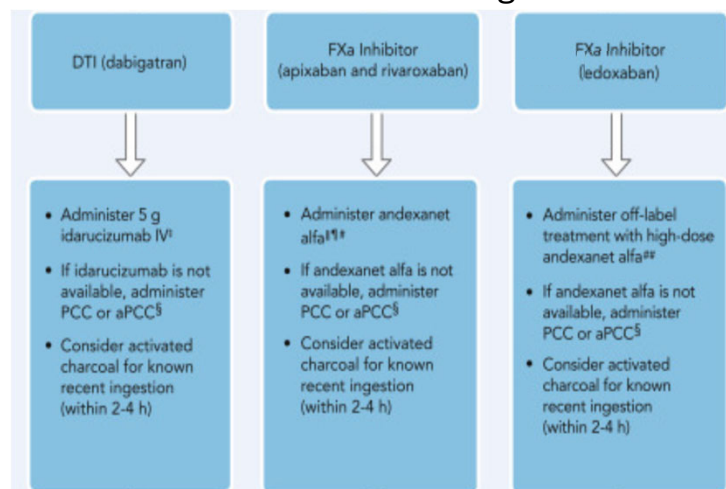
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41

Severe Bleeding in Patients on a DOAC

Reversal Strategies



Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. 2020.

42

Conclusion

- DOACs include dabigatran, rivaroxaban, apixaban, and edoxaban
- DOAC selection depends on individual agent indications, contraindications, and PK
- Important areas for pharmacist intervention include proper counseling, supporting adherence, knowing treatment differences for special populations, and making recommendations for patients transitioning between anticoagulants