



BRIDGE/HSS 2021: Direct Oral AntiCoagulants (DOAC's)

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Abstract

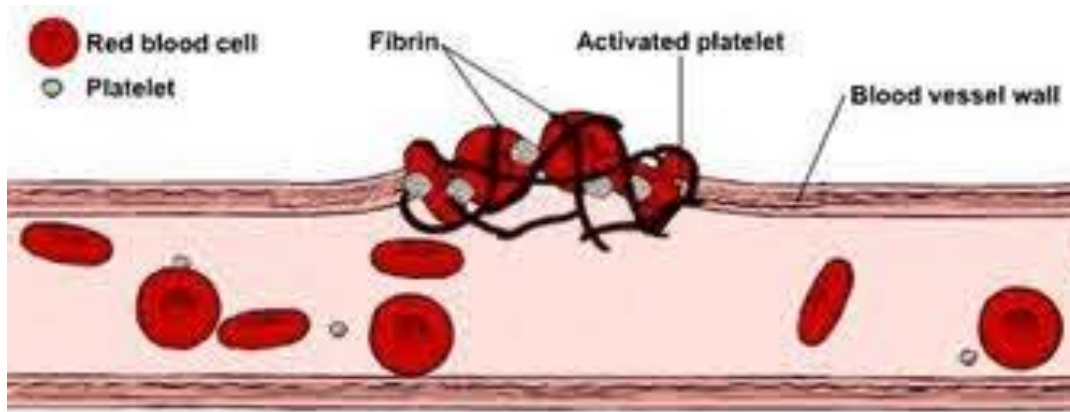
Over the past many years we have seen a steady increase in the options for anticoagulants. Direct Oral AntiCoagulants (DOACs), introduced in 2010, are the latest addition to the list of anticoagulant agents: Direct thrombin inhibitors (DTIs) and direct factor Xa inhibitors. The DOACs possess several advantages over the traditional agents such as warfarin and heparin. The DOACs have one disadvantage: the high cost. Bleeding following the use of DOACs can be managed using reversal agents. Despite the cost and safety issues, DOACs have carved a major role in medicine.

Introduction

1. Over the past many years we have seen a steady increase in the options for anticoagulants.
2. Today we are going to present a brief overview of **D**irect **O**ral **A**nti**C**oagulants. (DOACs) that were introduced in 2010 as alternative agents to warfarin.

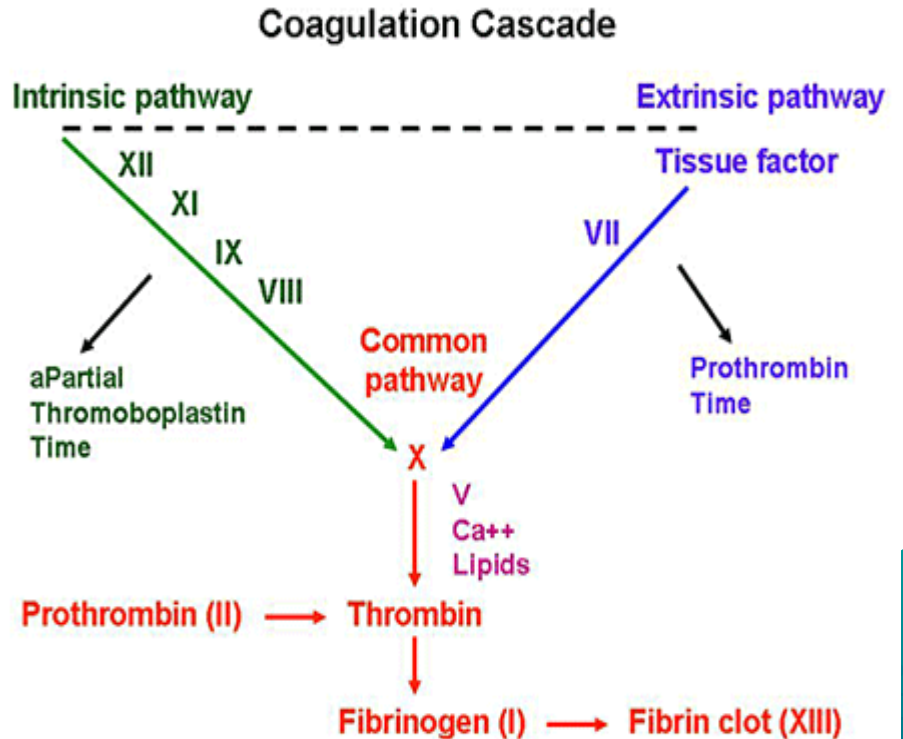
Mechanism of Action of Hemostasis

Hemostasis involves several processes. The coagulation cascade is a very intricate process that occurs within the body when a blood vessel is injured.



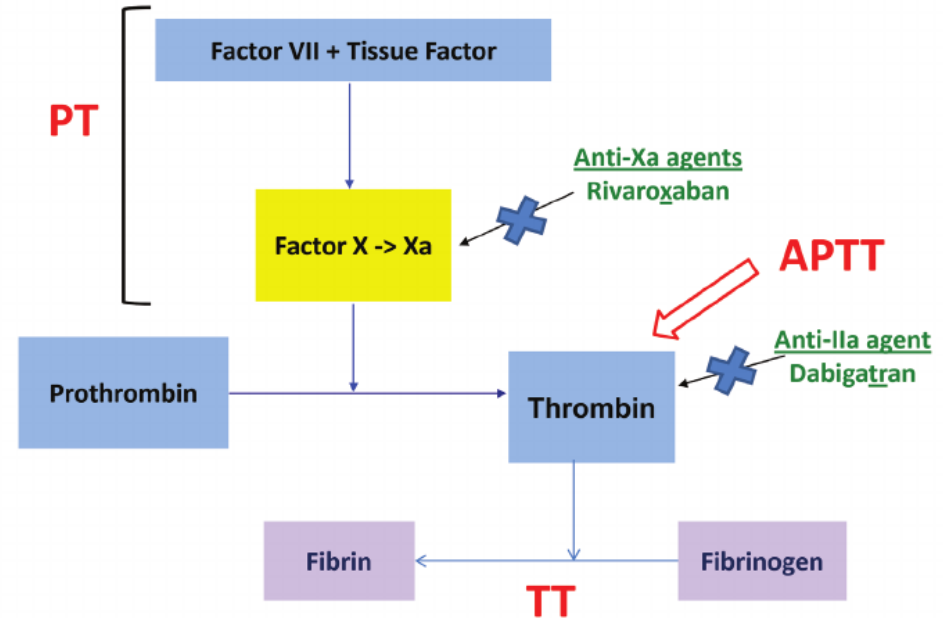
Mechanism of Action of Hemostasis, contd.

- Several protein factors work together in a “cascade” effect at the injured site and form a blood clot.
- Of these, thrombin (Factor IIa) and Factor Xa are of particular interest for DOACs



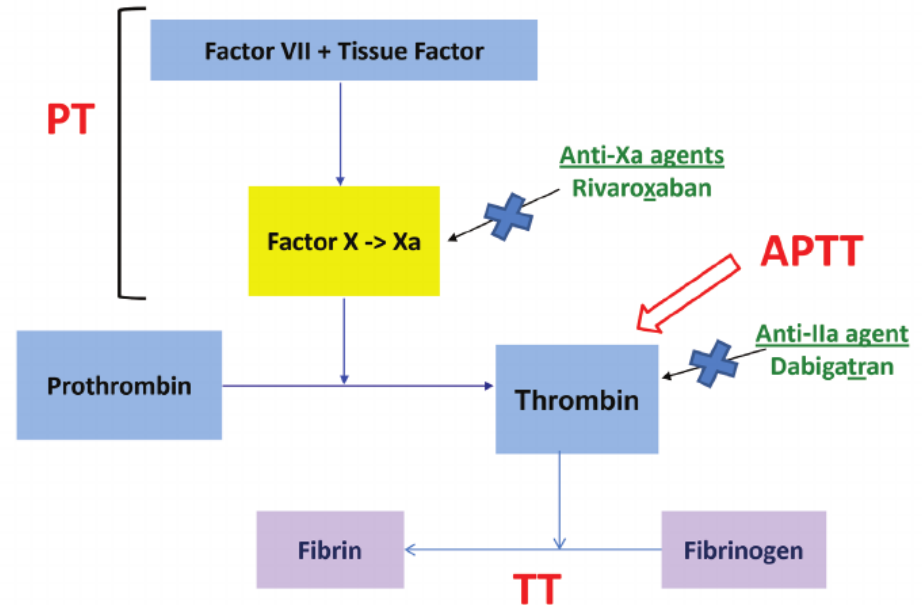
Mechanism of Action of Hemostasis, contd.

- Thrombin is the final enzyme of the clotting cascade that produces fibrin.
- Direct thrombin inhibitor (dabigatran) binds to the active site of thrombin and inhibits its action.



Mechanism of Action of Hemostasis, contd.

- Factor Xa acts immediately upstream of thrombin (Factor IIa) in the clotting cascade.
- Direct factor Xa inhibitors bind to the active site of factor Xa and inhibit its action.



Terminology

1. Antithrombotic agent: Antiplatelet agents (aspirin, clopidogrel) and anticoagulants.
2. Anticoagulant: Variety of agents that inhibit one or more steps in the coagulation cascade. Unfractionated heparin, low molecular weight heparin, fondaparinux, direct thrombin inhibitors and direct factor Xa inhibitors.

Terminology, contd.

1. Direct thrombin inhibitors (DTI): Prevent thrombin from cleaving fibrinogen to fibrin
 - a. Parenteral DTI: bivalirudin, argatroban, desirudin
 - b. Oral DTI: dabigatran
2. Direct factor Xa inhibitors: Prevent factor Xa from cleaving prothrombin to thrombin
 - a. No parenteral forms available
 - b. Oral agents: rivaroxaban, apixaban, edoxaban, betrixaban
3. Orally acting direct thrombin inhibitors (DTIs) and direct factor Xa inhibitors are together called **Direct Oral AntiCoagulants (DOACs).**

Heparin, warfarin, and DOACs

Clinician familiarity with dosing:

1. Clinicians are more familiar with dosing of heparin and warfarin than with dosing of DOACs.
2. This will change as more and more clinicians are using DOACs and gain more experience with DOACs.

Heparin, warfarin, and DOACs, contd.

Chronic kidney disease (CKD):

1. DOACs are excreted by the kidney to some degree.
2. Despite this DOACs appear to be safe and effective in mild to moderate CKD.

Heparin, warfarin, and DOACs, contd.

Drug adherence:

1. Some DOACs need twice daily dosing. Warfarin is taken once a day.
2. Half life of DOACs is shorter than that of warfarin.
3. A single missed dose of DOAC has greater potential to result in inadequate anticoagulation than a single missed dose of warfarin.
4. Drug adherence appears to be similar in large populations.

Advantages of using DOACs over Heparin and Warfarin

1. Overall DOACs have a lower bleeding risk than warfarin.
2. Laboratory monitoring - Heparin and warfarin need to be monitored frequently, but DOACs do not require monitoring.



Advantages of using DOACs over Heparin and Warfarin, contd.

3. Preferable pharmacokinetics: warfarin is affected by changes in diet, other medications, gastrointestinal disorders, poor oral intake. These factors don't affect DOACs as much.

4. Some foods and drinks that are restricted when using warfarin are:

- ⊙ Kale
- ⊙ Spinach
- ⊙ Brussel Sprouts
- ⊙ Parsley
- ⊙ Collard greens
- ⊙ Mustard greens
- ⊙ Endive
- ⊙ Red cabbage
- ⊙ Green lettuce
- ⊙ Chard
- ⊙ Green tea
- ⊙ Grapefruit Juice
- ⊙ Cranberry Juice
- ⊙ Alcohol

Settings in which Heparin and Warfarin are Preferred

1. DOACs are more expensive, so patients may prefer heparin and warfarin over DOACs. Warfarin costs around \$8 per month, when DOACs cost around \$406-\$489 for one month's supply.
2. Dosing convenience: Once a day vs. twice a day dosing.

Standard dosing of direct oral anticoagulants

Anticoagulant	Nonvalvular AF - stroke prophylaxis*	VTE treatment
Dabigatran (Pradaxa)	150 mg twice daily	Parenteral anticoagulation 5 to 10 days; then dabigatran 150 mg twice daily
Apixaban (Eliquis)	5 mg twice daily	10 mg twice daily for one week, then 5 mg twice daily
Edoxaban (Savaysa, Lixiana)	60 mg once daily	Parenteral anticoagulation 5 to 10 days; then edoxaban 60 mg once daily
Rivaroxaban (Xarelto)	20 mg once daily with the evening meal	15 mg twice daily with food for the first 3 weeks; then 20 mg once daily with

Settings in which Heparin and Warfarin are Preferred, contd.

1. Prosthetic heart valves: Greater risk of valve thrombosis with DOACs.
2. Pregnancy: Lack of clinical experience with DOACs in pregnancy.
3. Heparin and warfarin are preferred in chronic kidney and liver disease.

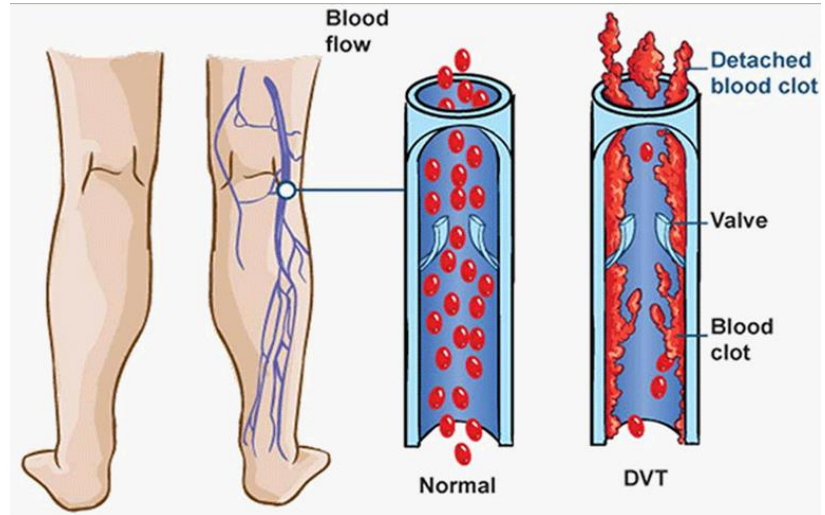


Cost of DOACs

- ① The high cost is one of the factors that prohibits patients from using it. The reason for the high cost is that currently there is no generic version available for any of the DOACs
- ① The FDA has granted permission to create a generic for apixaban (Eliquis). However the drug makers went to the court. The courts ruled in the drug makers favor. So there won't be a generic apixaban available at least until 2024-26.
- ① Hence DOACs continue to be costly medications.

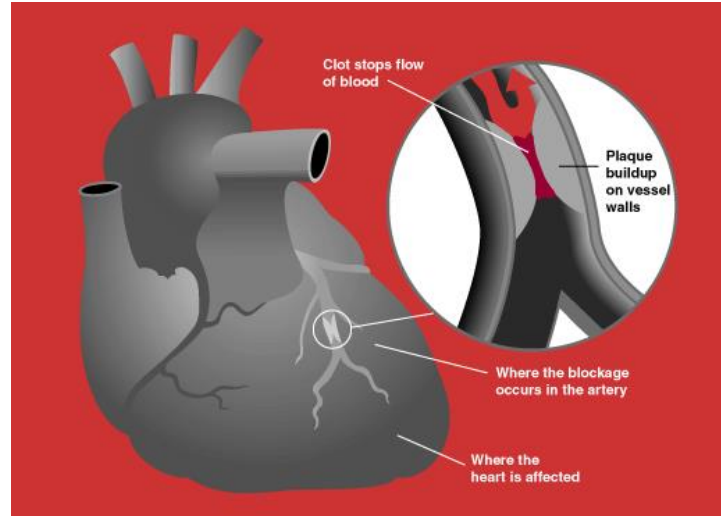
Indications for the use of DOACs

1. Venous thromboembolism (VTE) prophylaxis
2. VTE treatment



Indications for the use of DOACs, contd.

1. Atrial fibrillation: Most common cardiac arrhythmia. Patients are increased risk for stroke and peripheral embolization.
2. Acute coronary syndrome: Blockage in coronary artery leading to heart attack.



Risk of Bleeding with Anticoagulants

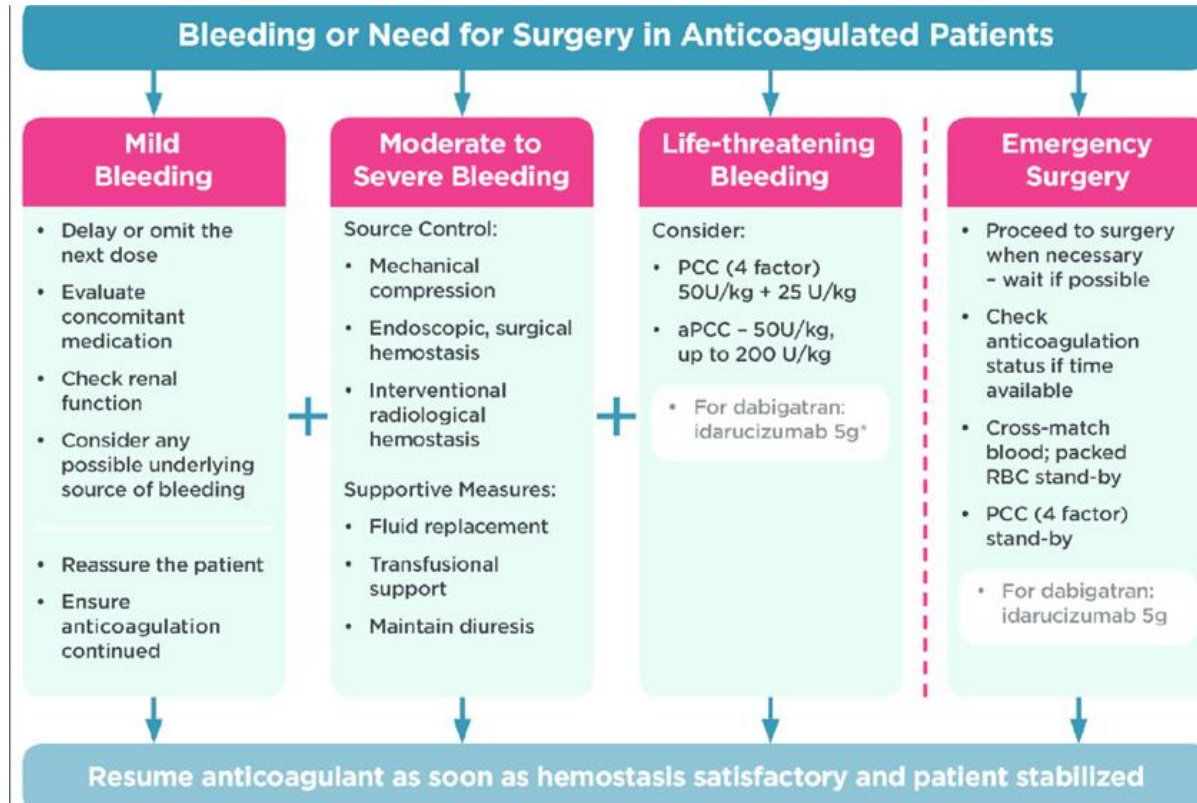
- ① Using any type of anticoagulant can significantly increase the chance of bleeding and life-threatening complications.
- ① It can be difficult to manage the bleeding from the use of DOAC because some of the reversal agents are difficult to find.



Management of Bleeding following DOACs

1. Treatment options for managing bleeding associated with DOACs include:
 - a. Reversal agents: Idarucizumab for dabigatran, Andexanet alpha for oral factor Xa inhibitors.
 - b. Activated and non-activated prothrombin complex concentrate.
 - c. Antifibrinolytic agents (tranexamic acid, epsilon-aminocaproic acid).

Management of Bleeding following DOACs, contd.



Conclusion

- ① The DOACs act by intervening in the coagulation cascade.
- ① Protein factors work together to form a blood clot and DOACs inhibit these protein factors to prevent blood clots.
- ① Advantages of DOACs over warfarin: lack of food interactions, lower risk of bleeding, no need for lab monitoring.
- ① DOACs are more expensive, however, if we take into consideration of the disadvantages of warfarin, they offer some major benefits.
- ① Bleeding following the use of DOACs can be managed by the use of reversal agents
- ① Despite the issues, DOACs have definitely carved a role in medicine.

Future Directions

We would like to study and compare the different DOAC's and identify if there is a DOAC suitable for use for a particular disease condition

Acknowledgments

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References

1. https://www.researchgate.net/figure/An-algorithm-for-management-of-patients-treated-with-a-DOAC-who-present-with-mild-fig1_305888438
2. <https://www.uptodate.com/contents/management-of-bleeding-in-patients-receiving-direct-oral-anticoagulants>
3. https://www.uptodate.com/contents/direct-oral-anticoagulants-doacs-and-parenteral-direct-acting-anticoagulants-dosing-and-adverse-effects?search=doac&source=search_result&selectedTitle=3~140&usage_type=default&display_rank=2

References, contd.

4. https://journals.lww.com/critpathcardio/fulltext/2019/09000/Management_of_Severe_Bleeding_in_Patients_Treated.7.aspx
5. <https://www.stoptheclot.org/about-clots/blood-clot-treatment/direct-oral-anticoagulants/>
6. <https://www.healthline.com/health/dvt/warfarin-diet#foods-to-limit>
7. <https://www.aafp.org/afp/2013/0415/p556.html>
8. <https://www.goodrx.com/anticoagulants>