HISTORY OF INTRODUCTION OF DIRECT ORAL ANTICOAGULANTS AND MECHANISM OF ACTION

Naina Manoj (1), Saura Nahar (1), Harshika Lekkala (1), Anterpreet Dua (1), Atul Laddu (1), and Jawed Fareed (2), 1= Global Thrombosis Forum, Suwanee, GA, and 2 = Loyola University, Chicago, IL

BACKROUND

DOACs (apixaban, betrixaban, debigatran, and rivaroxdaban), were introduced at the start of the 21st century as a more convenient alternative to traditional anticoagulants and have quickly become attractive alternatives to the long-standing standard of care in anticoagulation, VK antagonists. Heparin and VK antagonists have been the most commonly used anticoagulants for decades. DOACs demonstrate superiority or noninferiority to prior standards of care, anticoagulation VKA, and LMWHs in reducing the risk of thromboembolic complications with similar or reduced bleeding risk. Although effective, they were characterized by several limitations. To overcome these limitations, new anticoagulants have been developed in recent years, specifically targeting activated clotting factors, either Factor IIa (thrombin) or Factor Xa. DOACs are indicated for the prevention and treatment of several cardiovascular conditions.

HISTORY OF DOACS

Until the second decade of the 21st century, the primary drugs used to treat patients with VTE were heparin and Vitamin K Antagonists, the main of which was warfarin.
Warfarin is a water-soluble drug that treats thrombotic events, VTE, myocardial infarction, and atrial fibrillation because of many issues with warfarin, around 2010, DOACs were introduced as an alternate VTE treatment to warfarin.

The stages of development of anticoagulants are displayed in Figure 1.

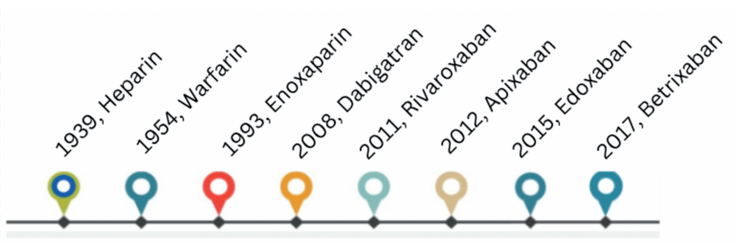

Figure 1: Stages of development of Anticoagulants

MECHANISM OF ACTIONS OF DOACS

DOACs are of two types: Direct Thrombin Inhibitors (e.g., dabigatran) and Factor Xa Inhibitors (apixaban, rivaroxaban, edoxaban, betrixaban). DTIs block thrombin to prevent fibrin formation (Figure 2) and can be reversed with idarucizumab. Factor Xa inhibitors block thrombin generation, preventing clot formation, and are reversible with andexanet alfa. Both offer rapid onset/offset, predictable effects, no routine monitoring, and fewer dietary restrictions than warfarin.

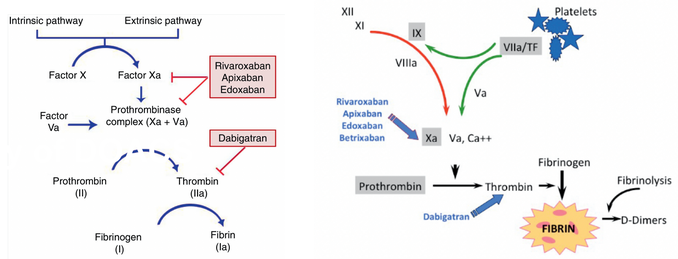

Figure 2: Mechanism of Action for DOACS

SITES OF ACTION OF DOACS

- Direct oral anticoagulants (DOACs) primarily act on the blood coagulation process by inhibiting specific proteins.
- DOACS directly target either Factor Xa or Thrombin (Factor IIa), which are crucial for the formation of blood clots.
- By inhibiting these factors, DOACs reduce the risk of clot formation and are used to prevent and treat conditions such as atrial fibrillation, deep vein thrombosis, and pulmonary embolism.
- Unlike traditional anticoagulants like warfarin, which act on multiple pathways,
- DOACs provide a more targeted and faster action by binding directly to these clotting factors.

INDICATIONS FOR DOACS

- Stroke Prevention in Nonvalvular Atrial Fibrillation (NVAF)
- Treatment of Deep Vein Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Prevention of Recurrent DVT and PE
- Prophylaxis in Surgical Patients

ADVANTAGES OF DOACS VS WARFARIN

- DOACs act quickly.
- Have predictable responses, making dosing easy, better QOL.
- No need for routine monitoring of INR.
- No food restrictions.
- Controllable blood levels.
- Fewer ischemic and bleeding events compared to warfarin.

DISADVANTAGES OF DOACS VS WARFARIN

- Expensive.
- Not all have FDA-approved antidotes in case of complications.
- One missed dose can increase the risk of clots.
- May not be suitable for everyone and can have risks such as bleeding and kidney function impairment.

DISCUSSION

DOACs demonstrate superiority or noninferiority to prior standards of care, anticoagulation VKA, and LMWHs in reducing the risk of thromboembolic complications with similar or reduced bleeding risk.
Traditional anticoagulants such as warfarin require monthly blood tests, and the patients need to attend to what they eat. There is also important to be aware of the risk of uncontrolled bleeding. DOACs are highly effective. They don't require regular blood testing or special diets. They have also been found to lower the risk of bleeding when taken to prevent a stroke. DOACs work and clear the system faster than warfarin.

REVERSAL AGENTS

-Idarucizumab (Praxbind): A monoclonal antibody approved in 2015 as a reversal agent for dabigatran.
-Andexanet alfa (Andexxa): Approved in 2018 for Factor Xa inhibitors (rivaroxaban and apixaban).

CONCLUSIONS

The development of DOACs has revolutionized anticoagulant therapy, offering a safer and more convenient alternative to traditional anticoagulants. By specifically targeting specific steps in the coagulation cascade, DOACs offer predictable anticoagulation with greater advantages that have significantly improved patient outcomes and QOL.