History of introduction of Direct Oral Anticoagulants and Mechanism of Action

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Background

Direct Oral Anticoagulants (DOACs) were introduced at the beginning of the 21st century and have gradually replaced traditional agents such as warfarin. They represent a better manageable alternative to vitamin K antagonists for preventing stroke in patients with nonvalvular atrial fibrillation and for preventing and treating venous thromboembolism.

Objectives

Until the second decade of the 21st century, heparin and Vitamin K Antagonists were the primary drugs used to treat patients with VTE. Because of many issues with warfarin, around 2010, DOACs were introduced as an alternate therapy for VTE.

Methods

There are two types of DOACs, based upon their action on the segments in the coagulation cascade:

Factor XA inhibitors (apixaban, edoxaban, and rivaroxaban)

Direct thrombin inhibitors (DTI): dabigatran.

We conducted a systemic literature review of the mechanism of action, advantages, disadvantages, and their effect on the QOL.

Results

Figure 1: History of development of anticoagulants

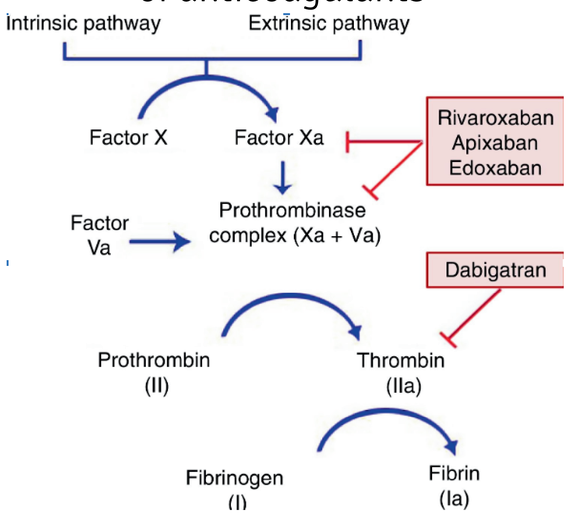

Figure 2: Sites of action of DOACs

Direct Binding /Specificity

Unlike indirect anticoagulants (e.g., heparin), which enhance natural inhibitors like antithrombin, DOACs bind directly to their target coagulation factors Xa or IIa.This direct inhibition bypasses the need for co-factors, resulting in rapid onset of anticoagulant activity, and fewer pharmacodynamic variabilities compared to traditional anticoagulants.

Selectivity/Reversibility

DOACs are designed to specifically target their respective factors without broadly affecting other components of the coagulation cascade.

Their actions can be reversed in emergencies using targeted antidotes (e.g., idarucizumab for dabigatran, andexanet alfa for Factor Xa inhibitors).

Advantages of DOACS

DOACs act quickly, providing rapid anticoagulation, and have predictable responses, making dosing simpler. There is no need for routine monitoring of INR, have fewer ischemic and bleeding events compared to warfarin, and fewer food restrictions, controllable blood levels.

Disadvantages of DOACS

DOACs are expensive, and have only a few FDA-approved antidotes in case of complications. One missed dose can increase the risk of clot. They may not be suitable for everyone and can have risks such as bleeding and kidney function impairment.

Reversal Agents

Idarucizumab (Praxbind): A monoclonal antibody, a reversal agent for dabigatran.

Andexanet alfa (Andexxa): For Factor Xa inhibitors (rivaroxaban and apixaban).

Conclusion

DOACs have revolutionized anticoagulant therapy with a safer, more convenient alternative to traditional anticoagulants and predictable anticoagulation with greater advantages that have significantly improved patient outcomes and quality of life.