History of Introduction of DOACs and Mechanism of Action

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Background

Introduced in the early 21st century, DOACs quickly became a preferred alternative to traditional anticoagulants like VKAs (Vitamin K Antagonists) and heparin, which had been limited by several drawbacks. By directly targeting activated clotting factors such as Factor IIa or Xa, DOACs have demonstrated non-inferiority or superiority in reducing thromboembolic events with comparable or lower bleeding risk, and are now widely used for both prevention and treatment of various cardiovascular conditions.

Objectives

1. Review the mechanism, pros, cons, and quality of life impact of DOACs, which directly inhibit clotting factors.
2. Understand prior use of heparin and warfarin, a water-soluble VKA used for VTE, MI, thrombosis, and AF (Atrial Fibrillation).
3. Recognize DOACs apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban as newer alternatives introduced around 2010.

Methods

DOACs were categorized by mechanism:

1. Direct Thrombin Inhibitor:

Dabigatran inhibits thrombin (IIa), blocking fibrin formation; fast-acting, predictable, reversible with idarucizumab.

2. Factor Xa Inhibitors:

Apixaban, rivaroxaban, edoxaban, betrixaban inhibit Factor Xa, reducing thrombin and fibrin; rapid onset, no routine monitoring, reversible with Andexanet Alfa.

Results

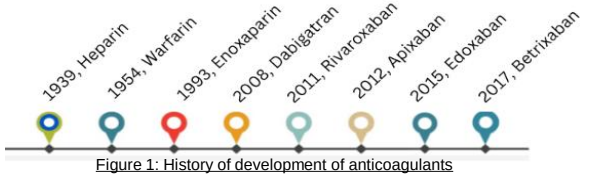

Figure 1: History of development of anticoagulants

Compared to warfarin, DOACs show comparable QOL (Quality of Life), higher treatment satisfaction, lesser hospitalization, and a non-significant trend toward fewer bleeding episodes.

Direct Binding and Specificity

Unlike indirect anticoagulants (e.g., heparin) that enhance antithrombin, DOACs bind directly to Factor Xa or IIa. This bypasses the need for cofactors, allowing rapid onset and reduced pharmacodynamic variability compared to traditional agents (Figure 2).

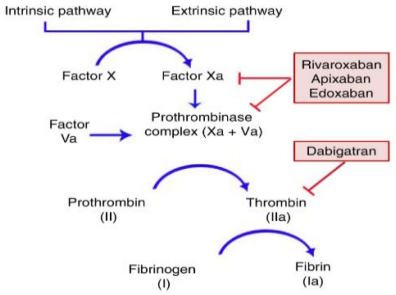

Figure 2: Sites of Action of DOACs

Selectivity and Reversibility

DOACs specifically target Factor Xa or IIa without affecting the rest of the cascade. In emergencies, their effects can be reversed with idarucizumab (for dabigatran) or andexanet alfa (for Factor Xa inhibitors).

Advantages of DOACs

1. DOACs act quickly, providing rapid anticoagulation.
2. Have predictable responses, making dosing simpler.
3. No need for routine monitoring of INR (International Normalized Ratio)
4. Fewer ischemic and bleeding events, compared to warfarin.
5. Fewer food restrictions, controllable blood levels.

Disadvantages of DOACs

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

Conclusion

DOACs have transformed anticoagulant therapy by offering a safer, more convenient alternative to traditional agents. By targeting thrombin or Factor Xa, they provide predictable anticoagulation with clear advantages, improving patient outcomes and quality of life.

References

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