

NEWER ORAL ANTICOAGULANTS

THE BEGINING OF THE NEW ERA

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- Scientists around the world had been trying hard to invent a suitable alternative to warfarin for the last one decade.
- They have invented two groups of drugs:
 1. Direct inhibitor of coagulation factor II (thrombin)
 2. Direct inhibitor of coagulation factor Xa.

- We will discuss only the newer drugs that are scientifically proven to be effective and safe.
- For example the oral direct thrombin inhibitor *ximelagatran* was the first new oral anticoagulant to be compared with warfarin for prevention of thromboembolism in AF. It was found effective but declared unsafe due to its hepatotoxicity.

The drugs to be discussed are:

a) The factor II inhibitor:

- Dabigatran

b) The factor Xa inhibitors:

- Rivaroxaban,

- Apixaban, and

- Edoxaban.

Dabigatran Etxilate

- *Dabigatran etexilate* is a small-molecule direct thrombin inhibitor.
- This is now approved in North America, Europe, and elsewhere for prevention of stroke in AF.
- Maximum activity 1 hour after administration.
- Its bioavailability is 10%,
- It is 80% renally metabolized,
- And its half-life is 12 to 17 hours.
- It has been developed to be administered twice daily.

Rivaroxaban

- Rivaroxaban is a small-molecule oral direct inhibitor of factor Xa
- With high bioavailability,
- Approximately one third renal metabolism,
- A half-life of 9 to 12 hours, and
- Peak plasma concentration 2.5 to 4 hours after dosing.

Apixaban

- *Apixaban* is an oral direct factor Xa inhibitor
- Half-life of 12 hours
- Developed for AF with twice-daily administration.
- Metabolism is 25% renal
- Bioavailability is high.
- Similar to rivaroxaban, cytochrome P450 3A4 is involved with the metabolism so that strong inhibitors substantially increase drug levels

Edoxaban

- *Edoxaban* is an oral, small-molecule direct inhibitor of factor Xa
- Maximum plasma concentration 1 to 2 hours after administration and
- Half-life of 8 to 10 hours.
- Approximately 40% of elimination is renal.

Bird's Eye View of Different Trials

- **RE-LY study:**

- Stroke or systemic embolism, %/year is 1.53 and 1.11 in Dabigatran 110 and 150 mg twice per day respectively. In compare to 1.69 in warfarin.
- Major bleeding, %/year 2.71 and 3.11 in Dabigatran 110 and 150 mg twice per day respectively. In compare to 3.36 in warfarin.

- **ROCKET-AF :**

- Stroke or systemic embolism, %/year is 2.12 in Rivaroxaban 20 mg per day. In compare to 2.42 in warfarin.
- Major bleeding, %/year 3.60 in Rivaroxaban 20 mg per day . In compare to 3.45 in warfarin.

- **ARISTOTLE:**

- Stroke or systemic embolism, %/year is 1.27 in Apixaban 5 mg twice per day. In compare to 1.60 in warfarin.
- Major bleeding, %/year 2.13 in Apixaban 5 mg twice per day . In compare to 3.09 in warfarin.

- ENGAGE AF-TIMI 48:

Trial between Endoxaban and Warfarin.

It included more than 20,000 AF patients.

Result expected this year.

THANK YOU VERY MUCH