# Oral Anticoagulants

Frank Dalichow, MD
Hematology
Tuba City Regional Healthcare

1

## Disclosures

- None

2

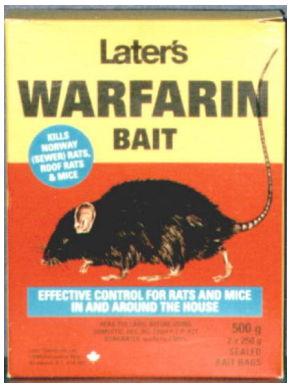
# Outline

- History of the development of anticoagulants
- Indications and contraindications
- Dosing and dose adjustments
- Checking factor Xa levels
- Bleeding and reversal agents
- Periprocedural management



# History

- Heparin discovered in 1916 by Jay McLean, a medical student at Johns Hopkins
- Dicoumerol, the toxic element in hemorrhagic disease of cattle, identified in 1940.
- Warfarin, a synthetic dicoumarol derivative, used as a rodenticide in 1948
- Warfarin is approved for humans 1954
- LMWH developed in 1980's
- Fondaparinux, synthetic pentasaccharide, 2001
- Ximelagatran, first oral direct thrombin inhibitor, 2004



# FDA Approval Timeline

| 2010 | 2011 | 2012 |
|---|---|---|
| Dabigatran | Rivaroxaban | Apixaban |



# Indication: Atrial Fibrillation

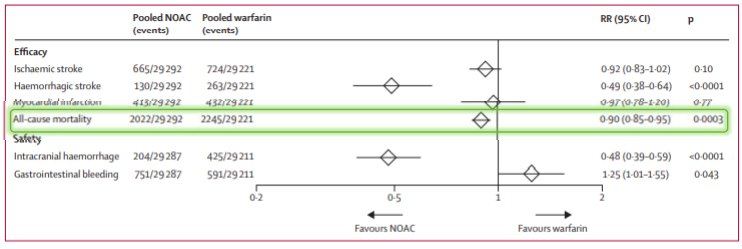



*Figure 2:* **Secondary efficacy and safety outcomes**
Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke $I^2$=32%, p=0·22; haemorrhagic stroke $I^2$=34%, p=0·21; myocardial infarction $I^2$=48%, p=0·13; all-cause mortality $I^2$=0%, p=0·81; intracranial haemorrhage $I^2$=32%, p=0·22; gastrointestinal bleeding $I^2$=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

Ruff C. et al Lancet. 2014 Mar 15;383(9921):955-62.

# Indication: Thrombosis

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report 2016

7

# Future Indications

- ✓Coronary Artery Disease
- ✓Peripheral Vascular Disease
- ✓Heparin Induced Thrombocytopenia
- ✓Malignancy-associated thrombosis

# Not Indicated

- ✓Antiphospholipid Antibody Syndrome (warfarin)
- ✓Mechanical heart valve (warfarin)
- ✓Pregnancy (LMWH)

8

## When should newer anticoagulants not be the first choice?

- Cancer-associated thrombosis
- Severe renal impairment (CrCl < 30 ml/min)
- Moderate to severe hepatic impairment
- Extremely high body weight (> 120 kg)
- Poorly compliant patient
- Prohibitive cost



## Testing

- CBC
- Hepatic function
- Renal function
- Coags

# Dosing

| Anticoagulant | Nonvalvular AF-Stroke | VTE Treatment | VTE Prophylaxis |
|---|---|---|---|
| Dabigatran | 150mg BID | 150mg BID (after parenteral anticoagulation for 5-10 days) | 110mg first day, then 220mg daily |
| Apixaban | 5mg BID | 5mg BID (after 10mg BID loading dose for one week) | 2.5mg BID |
| Rivaroxaban | 20mg daily (with food) | 20mg daily (after 15mg BID loading dose for 3 weeks, with food) | 10mg daily |
| Edoxaban | 60mg daily | 60mg daily (after parenteral anticoagulation for 5-10 days) | |
| Betrixaban | | | 160mg first day, then 80mg daily (with food) |

11

# Dose Adjustments

| | | Rivaroxaban | Apixaban |
|---|---|---|---|
| Kidney Function | CrCl >30 | 20mg daily | 5mg twice daily* |
| | CrCl 15-30 | No | 2.5mg twice daily |
| | CrCl <15 | No | No |
| Hepatic Function Childs-Pugh | A | Yes | Yes |
| | B | No | Yes |
| | C | No | No |

* For patients >80 and weight <60, 2.5mg BID dose is used

# Dialysis

- Rivaroxaban: not dialyzable; avoid use; limited & conflicting data
- Apixaban: not dialyzable; use with extreme caution (not FDA approved); retrospective data suggests similar efficacy and no increased bleeding risk with use when compared to warfarin

12

# What about dabigatran?

- Thromboembolism treatment needs pretreatment with heparin for at least 5 days before transitioning to dabigatran
- High rate of gastrointestinal side effects (25-40%)
- Higher rate of gastrointestinal bleeding when compared to warfarin

**Table 1. Incidence rates and adjusted hazard ratios comparing matched new user cohorts treated with Pradaxa 75 mg or 150 mg* or warfarin for non-valvular atrial fibrillation based on 2010-2012 Medicare data. Warfarin is the reference group.**

| | Incidence rate per 1,000 person-years | | Adjusted hazard ratio (95% CI) |
|---|---|---|---|
| | Pradaxa (dabigatran) | Warfarin | |
| Ischemic stroke | 11.3 | 13.9 | 0.80 (0.67-0.96) |
| Intracranial hemorrhage | 3.3 | 9.6 | 0.34 (0.26-0.46) |
| Major GI bleeding | 34.2 | 26.5 | 1.28 (1.14-1.44) |
| Acute MI | 15.7 | 16.9 | 0.92 (0.78-1.08) |
| Mortality | 32.6 | 37.8 | 0.86 (0.77-0.96) |

* Primary findings for Pradaxa are based on analysis of both 75 and 150 mg together without stratification by dose.

FDA Drug Safety Communication 5-13-2014: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin



# Checking levels

- Not routinely done since these agents are administered at a fixed dose without monitoring.
- Anti-factor Xa activity can be measured in unusual circumstances.
- Test is specific to the drug.
- Peak level is checked (2-4 hours after last dose).

## Bleeding

- Low Risk: Epistaxis and hemorrhoidal bleeding, where local contral measures are effective
- Moderate Risk: Stable GI bleed
- High Risk: Intracranial bleed, unstable GI bleed, bleeding into a closed space (lung, pericardium, spine)



## Indications for reversing a DOAC

- Intracranial hemorrhage
- Hemodynamically unstable GI bleed not controlled by endoscopy or interventional radiology
- Bleeding into an enclosed, fixed space (lung, pericardium, spinal cord)
- Emergency surgery

# Reversing the anticoagulant effect of a DOAC

- Consider timing of last ingestion
  - ❑If 1-2 hours prior or intentional overdose, consider charcoal
  - ❑If more than 12 hours, the anticoagulation effects have likely worn off and reversal is likely unnecessary.
- For rivaroxaban and apixaban
  - ❑Use 4 factor prothrombin complex concentrate (PCC) at a dose of 50 IU/kg, up to 2,000 units.
  - ❑Use tranexamic acid, 1 gm over 10 minutes and then 1 gm over the next 8 hrs if 4-factor PCC is ineffective or not available.
- Andexanet Alfa is a decoy antigen; it competitively binds rivaroxaban and apixaban and is given as an ongoing infusion.

17

# Periprocedural management

- Low bleeding risk: dental, eye, endoscopy, superficial
- High bleeding risk: thoracic, abdominal, orthopedic, biopsy of liver or kidney, spinal anesthesia

- How long to wait after last dose of rivaroxaban or apixaban

| Kidney Function | Low Risk | High Risk |
|---|---|---|
| CrCl ≥ 30 | 24 hours | 48 hours |
| CrCl 15-30 | 36 hours | 48 hours |
| CrCl <15 | No data | No data |
| | | |

18

# Emergency surgery

- Stop DOAC
- Try to delay surgery for at least 12 and ideally 24 hours after last dose
- Idarucizumab 5gm IV reverses the anticoagulation without pro-thrombotic side effects
- Andexanet 400 or 800mg bolus, followed by infusion
- 4 factor PCC