Anticoagulants: Agents, Pharmacology and Reversal

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How Familiar Are you with the Novel Anticoagulants (Dabigitran, Apixaban, Rivaroxaban, Edoxaban)

1. Very
2. A little
3. Somewhat
4. What?
The way it was......

ASA

Heparin

Coumadin
History of anticoagulant therapy

- Anticoagulant in spoiled sweet clover (K.P. Link)
- First clinical use of 4-hydroxycoumarin (O. Meyer et al)
- Warfarin mechanism elucidated (J. Suttie)
- Warfarin dosing/INR
- Warfarin clinical trials
- Oral thrombin and Xa Inhibitors

- Heparin discovered by medical student (McLean)
- Clinical use of heparin
- Requirement for plasma cofactor discovered (K. Brinkhous)
- Cont infusion of heparin; aPTT monitoring
- LMWH trials
- Fondaparinux trials
- LMWH (J. Hirsch)
- Fondaparinux trials
- Oral thrombin and Xa Inhibitors
FDA Approves Edoxaban for Stroke Prevention in AF and DVT/PE Prevention

Michael O'Riordan | Disclosures
January 09, 2015

Looking for Information About ELIQUIS? Start Here.

ELIQUIS is a prescription medicine used to treat blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE), and reduce the risk of stroke in people with atrial fibrillation (AF) who are at risk for a stroke. ELIQUIS is also used to reduce the risk of blood clots in patients who have had a hip or knee replacement surgery.

FDA Approves XARELTO® (rivaroxaban tablets) to Help Prevent Deep Vein Thrombosis in Patients Undergoing Knee or Hip Replacement Surgery

Doctors prescribe Bayer’s billion-dollar blood thinner Xarelto to prevent blood clots and reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Xarelto is now the only NOAC approved for patients undergoing knee or hip replacement surgery.

U.S. FDA Approves ELIQUIS® (apixaban) to Reduce the Risk of Blood Clots and Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

PRADAXA received approval for NVAF in October 2010 and for DVT/PE in April 2014.

OVER 4 YEARS OF PRESCRIBING EXPERIENCE

Pradaxa® (dabigatran etexilate) – first new oral anticoagulant in nearly 60 years receives final NICE recommendation for stroke prevention in atrial fibrillation in the UK

FDA Approves Xarelto® (rivaroxaban tablets) to Help Prevent Deep Vein Thrombosis in Patients Undergoing Knee or Hip Replacement Surgery
Warfarin

• No safe INR
• Antiplatelet agents + warfarin doubles risk (regardless of dose)

• Between 1988-1999 Warfarin distribution doubled in US
  – Incidence of OAC ICH quintupled

• ICH causes 90% deaths and most of permanent disability from warfarin-associated bleeding

Flaherty, Neurology - Volume 68, Issue 2 (January 2007)
In patients with Atrial Fibrillation

Meta-Analysis: NOACS v. Warfarin

Relative Risk to Warfarin (%)

- Stroke or Systemic Embolism: p<0.0001, -19% (-31, -2)
- Ischemic Stroke: p<0.0001, -8% (-17, +2)
- Hemorrhagic Stroke: p<0.0001, -51%
- ICH: p<0.0001, -52%
- All-Cause Mortality: p=0.0003, -10% (-15, -5)
- Major Hemorrhage: p=0.06, -14% (-17, 0)
- GI Hemorrhage: p=0.04, 25% (+1, +55)

~20% RR REDUCTION OF ISCHEMIC STROKE COMPARED TO WARFARIN (RE-LY TRIAL)

~60% RR REDUCTION OF ISCHEMIC STROKE COMPARED TO ASPIRIN (AVERROES TRIAL)

Adapted from Ruff CT, et al. Lancet 2013 Online; S0140-6736(13)62343-0
### Comparison

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<th>Oral VKA</th>
<th>NOACs</th>
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Coagulation Cascade

Intrinsic Pathway (surface contact)
- XIIa
- XIa
- IXa

Extrinsic Pathway (tissue factor)
- Xa
- VIIa

Thrombin (IIa)

Fibrinogen

PT, aPTT

Thrombin Inhibitors

Xa Inhibitors

Coumadin

Platelet

Fibrin Clot
Thrombin (IIa)

- Fibrinogen $\rightarrow$ Fibrin
- Activates factors $\rightarrow$ more thrombin
- Stimulates Platelets
- X-links fibrin $\rightarrow$ stabilizes clot
Direct Thrombin Inhibitors

- IV
  - Bivalrudin (Angiomax)
  - Argatroban

- PO
  - Dabigatran (Pradaxa)
Indications:
- Atrial Fibrillation
- Treatment DVT/PE
- Secondary prevention DVT/PE

Fixed dose - BID
No monitoring required

Immediate onset; peak 2-3 hours after dose

½ dose in renal insufficiency
THROMBIN TIME

Linear dose-response curve
BUT Reagents not standardized
And at > 600 TT does not measure
Most sensitive for determining if present

aPTT

Curvilinear
Not sensitive within range
Qualitative measure
Can tell you if excess

PT/INR

Minimal effect
Should not be used

Thromb Haemost. 2010 Jun;103(6):1116-27
CrCl $\leq$ 30 ml/min

Active pathological bleeding or conditions with high risk of bleeding

Significant liver failure (>2 ↑ ALT/AST)

History of a serious hypersensitivity reaction to Dabigatran

Concomitant treatment with: dronedarone, ketokonazole, itraconazole, voriconazole, posaconazole, rifampicin; carbamazepine, phenytoin; phenobarbital

1. Non-valvular AF
2. DVT and PE
3. DVT/PE prevention

Fulfill indication for NOAC?

CrCl ≥ 30 ml/min

Contraindication?

Significant liver failure (>2 ↑ ALT/AST)

History of a serious hypersensitivity reaction to Dabigatran

Concomitant treatment with: dronedarone, ketokonazole, itraconazole, voriconazole, posaconazole, rifampicin; carbamazepine, phenytoin; phenobarbital

Currently on VKAs?

<60% of INR in therapeutic range
Haemorrhagic stroke
Ischaemic stroke under optimal INR range
Patient preference

At least 1 of:

- Age ≥ 80 years
- Concomitant treatment with Verapamil

2 or more:

- Age 75-80 years
- Weight < 60 kg
- CrCl 30-49 ml/min
- Concomitant treatment with antiplatelet, NSAIID, steroids
- Thrombocytopenia
- History or non-severe active GI bleeding
- HAS BLED ≥ 3

SUITE FOR DABIGATRAN

110 mg/12h

150 mg/12h

Choose other OAC
Coagulation Cascade

Intrinsic Pathway (surface contact)

Extrinsic Pathway (tissue factor)

Xa Inhibitors (AT-III independent) Direct

Platelet

Platelet

Fibrin Clot

Xa

Thrombin (IIa)
Indirect Xa Inhibitors

Intrinsic Pathway (surface contact)

- XIIa
- Xla
- IXa
- Xa
- ATIII

Platelet

Thrombin (IIa)

- Fondaparinux
- LMWH
- UFH

- Platelet

- Thrombin (IIa)
**Direct Xa Inhibitors**

**Rivaroxaban**
- Afib - Fewer ICH
- VTE - tx and prevention
- QD dosing (mostly)
- Shorter T½ 5-13 hrs
- Contraindicated
  - severe renal
  - severe hepatic

**APIXABAN**
- Afib - Fewer ICH
- VTE tx and prevention
- ACS - more bleeding
  - Halted early
- BID dosing
- Longer T½ 8-15 hrs
- Multiple excretion mech
  - 25% renal

**EDOXABAN**
- Afib - Fewer ICH
- VTE tx
- QD dosing
- Longer T½ 9-11 hrs

References:
- Hematology/Oncology Clinics of North America - Volume 24, Issue 4
- N Engl J Med. 2011 Mar 3;364(9):806-17
Direct Xa Inhibitors - Monitoring

• No good monitoring lab tests
  – **Anti-Xa** levels best

• PT does show prolongation
  – Short-lived 1-4 hrs after administration
  – Do not accurately reflect the intensity of anticoag
  – Depends on the reagent (can be linear)
  – Normal PT does NOT rule out significant blood levels

• Cannot use INR
  – Calibrated only for warfarin

*Current Pharmaceutical Design, 2010, 16, 3436-3441*

*Thromb Haemost. 2010 Dec;104(6):1263-71*
Cost per month

Rivaroxaban (20 mg/day) : $290
Dabigatran (150 mg bid): $290
Edoxaban (60 mg QD): $269
Apixaban (5 mg bid): $147
Warfarin (7.5 mg/day): $31
2 groups – n = 90
A. Overt, uncontrollable or life-threatening bleeding (n=51)
B. Required emergent procedures that could not wait 8 hours (n=39)

5 g IV idarucizumab (2.5 gm x 2)

Deaths – 18 patients (9 each group)
Thrombotic events – 5 patients (1 early, 4 late)

Reversed effects of dabigatran in 88-98% of patients
Dabigatran Reversal: Idarucizumab!!

Antibody fragment (Fab) – specific dabigatran antidote

Anticoagulant effect - immediately reversed

Restarting dabigatran 24 hours after Idarucizumab restored anticoagulation
Dabigatran Emergency Reversal

1. If ingestion within 2 hours:
   A. Charcoal 50 gram
2. Draw PTT/TT
3. Idarucizumab 2.5 gm IV x 2

Keep up urine output
1. Charcoal if ingestion within last 2 hours
2. Check PT/Anti-Xa levels
3. K-Centra 25 U/KG
4. Repeat PT 15 min after K-centra
5. Repeat PCC dosing not recommended
Coming Soon... Factor Xa Inhibitor Antidote: Andexanet

Factor Xa decoy - targets and sequesters Xa inhibitors

Phase III trials - Release? Mid 2016?
Emergency Reversal Indirect Xa Inhibitors: Fondaparinux (Aratrixa)

1. K-Centra 25 U/KG
2. Anti-Xa Level

Protamine not effective