Anticoagulation, including the use of novel oral anticoagulants in DVT/PE & atrial fibrillation

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## Disclosures

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>Leo Pharma (PERIOP 01 Trial)</th>
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<tbody>
<tr>
<td>Employee</td>
<td>No relevant conflict of interest to declare</td>
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<td>Consultant</td>
<td>No relevant conflict of interest to declare</td>
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<td>Major Stockholder</td>
<td>No relevant conflict of interest to declare</td>
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<td>Speakers’ Bureau</td>
<td>No relevant conflict of interest to declare</td>
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<td>Honoraria</td>
<td>Sanofi Aventis, Pfizer, Boehringer Ingelheim, Leo Pharma, Bayer.</td>
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<td>Scientific Advisory Board</td>
<td>Sanofi Aventis, Leo pharma.</td>
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Objectives

1. Discuss the use of novel oral anticoagulants for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation

2. Review of the efficacy and safety data regarding the use of anticoagulation in the management of deep vein thrombosis and pulmonary embolism
82 yo man with new onset atrial fibrillation

**PMHx:** Dementia, HTN, VRE, EtOH abuse

**Allergy:** NKDA

**Meds:** Trazodone 50 mg qhs, seroquel 50 mg BID, galantamine 24 mg daily, cipralex 10 mg PO daily.

Wt: 78 kg; BP 106/62; HR: 62

Hb: 116, eGFR: 55 cc/min
What anticoagulant will you use for stroke prevention?

A. Warfarin (target INR 2.0-3.0)
B. Dabigatran 150 mg BID
C. Dabigatran 110 mg BID
D. Rivaroxaban 20 mg daily
E. Apixaban 5 mg BID
Atrial Fibrillation (AF)
The “CCS Algorithm” FOR OAC Therapy in AF

**PRACTICE POINTS:** Consider and modify (if possible) all factors influencing risk of bleeding on OAC (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low eGFR, age ≥ 75, low body weight)**

- **Age ≥ 65**
  - **NO**
    - **Any of the following?**
      - Prior Stroke / ITA
      - Hypertension
      - Heart Failure
      - Diabetes Mellitus
        (CHADS, risk factors)
  - **YES**
    - **Oral Anticoagulant (OAC)**
  - **NO**
    - **CAD or Arterial vascular disease**
      (coronary, aortic, peripheral)
  - **YES**
    - **Oral Anticoagulant (OAC)**
  - **NO**
    - **No Antithrombotic**
  - **YES**
    - **ASA**

Warfarin is highly effective for the prevention of stroke in patients with AF.

- **Warfarin vs. Placebo**: 64% RRR
- **Warfarin vs. ASA**: 38% RRR
- **Warfarin vs. ASA + Clopidogrel**: 40% RRR

Hart et al Ann Intern Med. 2007;146:857-867
Warfarin

• **Advantages**
  - Active by oral route
  - Once daily dosing
  - Can be monitored
  - Rapidly-acting antidote available
  - Low cost

• **Disadvantages**
  - Delayed onset of action
  - Long-half life
    - i.e. Needs to be held for many days pre-op
  - Many drug-drug and drug-food interactions
  - Needs monitoring
New oral anticoagulants (NOACs)

Figure from: Steffel et al. J Cardiovasc Med 2009;10:616-23
## Properties of new oral anticoagulants (NOACs)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>Ila</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability ($F_{rel}$)</td>
<td>80%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Peak action ($t_{max}$)</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92–95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &gt; 80 ml/min</td>
<td>15.1 hr</td>
<td>13.8 hr</td>
<td>8.3 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 50–79 ml/min</td>
<td>14.6 hr</td>
<td>16.6 hr</td>
<td>8.7 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 30–49 ml/min</td>
<td>17.6 hr</td>
<td>18.7 hr</td>
<td>9.0 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &lt; 30 ml/min</td>
<td>17.3 hr</td>
<td>27.5 hr</td>
<td>9.5 hr</td>
</tr>
</tbody>
</table>

NOACs vs. warfarin - Stroke prevention

Warfarin, rivaroxaban, dabigatran and apixaban are effective in preventing strokes and systemic embolism in patients with atrial fibrillation.

NOACs are associated with a RRR of 20% compared to warfarin.

NOACs vs. warfarin - Bleeding

- NOACs reduce hemorrhagic stroke, overall mortality and ICH
- …but increase GI bleeding

NOACs: All the same?

Similarities
- Non-inferior to warfarin for efficacy
- Less ICH than with warfarin
- Decrease overall mortality compared to warfarin
- No hepatic toxicity

Differences
- Increase risk of MI in patients taking dabigatran compared to warfarin
- More GI bleeding with rivaroxaban and dabigatran
- Dabigatran (150 mg BID) is associated with lower risk of ischemic strokes compared to warfarin
- Apixaban is associated with both lower risk of stroke and major bleeding compared with warfarin

### Choice of anticoagulation based on patients characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug choice</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Mechanical valve or valvular atrial fibrillation</td>
<td>Warfarin</td>
<td>New agents not studied</td>
</tr>
<tr>
<td>Liver dysfunction with increased INR</td>
<td>Warfarin</td>
<td>New agents require hepatic metabolism</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>Warfarin or nothing*</td>
<td>Missed doses of greater consequence with shorter-acting new agents</td>
</tr>
<tr>
<td>Stable on warfarin</td>
<td>Warfarin</td>
<td>Consider switching at patient request</td>
</tr>
<tr>
<td>CrCl less than 30 mL/min</td>
<td>Warfarin</td>
<td>Such patients were excluded from trials with new agents</td>
</tr>
<tr>
<td>CrCl of 30-50 mL/min</td>
<td>Rivaroxaban or apixaban</td>
<td>Oral factor Xa inhibitors are less affected by impaired renal function than dabigatran</td>
</tr>
<tr>
<td>Dyspepsia or upper gastrointestinal symptoms</td>
<td>Rivaroxaban or apixaban</td>
<td>Dyspepsia in up to 10% given dabigatran</td>
</tr>
<tr>
<td>Recent gastrointestinal bleed</td>
<td>Apixaban</td>
<td>More gastrointestinal bleeding with dabigatran (150 mg twice daily) or rivaroxaban than with warfarin</td>
</tr>
<tr>
<td>Recent ischemic stroke on warfarin</td>
<td>Dabigatran</td>
<td>Dabigatran (150 mg twice daily) associated with lower risk of ischemic stroke than warfarin</td>
</tr>
<tr>
<td>Recent acute coronary syndrome</td>
<td>Rivaroxaban or apixaban</td>
<td>Small myocardial infarction signal with dabigatran</td>
</tr>
<tr>
<td>Poor compliance with twice-daily dosing or request for a once-daily regimen</td>
<td>Rivaroxaban</td>
<td>Only agent given once daily</td>
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DVT and PE

Deep Vein Thrombus of the Right Leg

1. Normal blood flow with a small tear in lumen of vein.

2. Blood clot (thrombus) forms at site of venous damage.


Traditional Treatment of VTE

Initial treatment

5-7 days

LMWH or UFH*

Long-term therapy

>3 months

VKA** (INR† 2.0-3.0)

*UFH = unfractionated heparin
**VKA = vitamin K antagonist
†INR = international normalization ratio
NOACs: All the same?

Take Home Messages

- NOACs (dabigatran, rivaroxaban, apixaban) approved and covered for stroke prevention but are not recommended for:
  - Patients with valvular heart disease, mechanical valves, severe renal impairment, active bleeding

- NOACs (Rivaroxaban, apixaban and dabigatran currently approved) can be used for the initial treatment of VTE
  - Rivaroxaban only NOAC covered in MB for VTE (Part III EDS)
  - Be careful:
    - Patients with severe renal impairment, active bleeding, cancer, etc.
When to consider referral to hematology

- Unprovoked VTE
- Thrombosis at unusual sites
- Recurrent thrombosis despite adequate anticoagulation
Questions?

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