Use of New Oral Anticoagulants (NOACs) in Stroke

Practical Considerations

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Aims and objectives

• Introduction to NOACs and the evidence

• Basic pharmacology

• Starting NOACs

• Special clinical scenarios

• Monitoring and reversal

• Bleeding and its management

• Follow-up
Vitamin K antagonists

- Historically the standard of care and the only oral option
- Widespread use but many limitations
- Narrow therapeutic range
- Needs regular laboratory monitoring
- Affected by diet, genetics, and drug interactions
- Antidotes easily available: Vitamin K and Prothrombin Concentrate Complex.
Introduction to NOACs

- Predictable effect without need for regular monitoring
- Fewer food and drug interactions
- Easy fix dosage
- Shorter plasma half-life
- Improved efficacy/safety ratio
# Pharmacokinetics of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>5-9 hrs</td>
<td>3 hrs</td>
<td>2 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-9 (pts 20-45 years) 11-13 hrs (older pts)</td>
<td>~12 hrs</td>
<td>12-17 hrs</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80-100%</td>
<td>50%*</td>
<td>3-7%</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>36%</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Potent dual inhibitors of CYP3A4 &amp; P-gp</td>
<td>Potent dual inhibitors of CYP3A4 &amp; P-gp</td>
<td>P-gp inducers ±</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>95%</td>
<td>87%</td>
<td>35%</td>
</tr>
</tbody>
</table>

*from Averroes trial; ± P-gp inducer (rifampin), No clinically significant interactions with P-gp inhibitors except ketoconazole and verapamil; CYP = cytochrome P450.

The evidence

Dabigatran
Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY):

• Published in NEJM in 2009

• Enrolled 18113 patients with non-valvular AF (NVAF) and at least one of the risk factors i.e. Previous stroke/TIA, systemic embolism, LVEF <40%, symptomatic heart failure, NYHA Class ->2, > 75 years, or age -> 65 y and with one or more of DM, CAD, hypertension.

• 951 centres in 44 countries
• Dabigatran was given in a blinded fashion, Warfarin administered unblinded

• **Primary outcome:**
  • Stroke/systemic embolism 1.53%/year in patients receiving 110 mg, 1.11%/year receiving 150 mg
  • (1.69%/year in patients receiving Warfarin).
  • Both doses of Dabigatran non-inferior to Warfarin (150 mg superior to Warfarin)

• Risk of haemorrhagic stroke was 0.38%/year with Warfarin, 0.12% with 110 mg and 0.10%/year with 150 mg of Dabigatran
• Risk of major bleeding:
  3.36%/year with Warfarin
  2.71%/year with 110 mg Dabigatran
  3.31% with 150 mg Dabigatran

• The risk of GI bleeding was significantly higher with 150 mg Dabigatran 9.51 v 7.02 Warfarin cases per 100 person years
Apixaban

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial:

- Published in NEJM in 2011
- Multicentre double blind comparative trial
- N18201, Warfarin: 9081, Apixaban: 9120

- **Primary outcome:**
  - Stroke or systemic embolism 1.27%/year with Apixaban and 1.6% with Warfarin (P<0.001 for non-inferiority and 0.01 for superiority)
• The rate of haemorrhagic stroke was 49% lower in the Apixaban group

• Major bleeding risk was 2.13% with Apixaban and 3.09%/year with Warfarin

• **AVERROES**: In patients with AF thought to be unsuitable candidates for anticoagulation with a VKA, Apixaban significantly reduced the risk of stroke and systemic embolism without increasing the risk of major bleeding or intracranial haemorrhage when compared to Aspirin.
The evidence (cont....)

- **Rivaroxaban:**
  - The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)
  - Published in NEJM in 2011
  - Multicentre (1178 sites in 45 countries), randomised, double-blind trial

- **Primary outcome:**
  - Stroke or systemic embolism 1.7% in Rivaroxaban group v 2.2% with Warfarin
  - Major bleed: Rivaroxaban 3.6%, Warfarin 3.4%
• Rates of major bleeding were similar (Rivaroxaban 3.6% v 3.4% Warfarin).

• ICH rates were 0.5% Rivaroxaban v 0.7% Warfarin per year.

• Risk of major GI bleed was higher with Rivaroxaban (3.2% v 2.2%)
Practical considerations

- 75-year-old male patient admitted with right PACS, CHA2DS2Vasc =5, HAS-Bled=2, PSM mitral area on auscultation.

- ECG shows sustained AF (new finding)

Would you consider Warfarin or NOAC for secondary prevention?
How to define valvular Atrial fibrillation (AF)

- Remains a matter of debate

- Current widely accepted definition includes mitral stenosis or artificial (mechanical) heart valves (and valve repair in North American guidelines only)

- ‘*mechanical and rheumatic mitral valvular AF*’ (acronym: MARM-AF)

eurheartj.oxfordjournals.org/content/35/47/3328
Initiating NOAC

• The decision about whether to start treatment with Warfarin or a NOAC should be made after an informed discussion between the prescriber and the patient/relative about the relative risks and benefits of each agent.

• If a NOAC is considered then establish the principal reason for the decision

• Documentation is vital
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>Not compatible with enteric route</td>
<td>PO/enteral route</td>
<td>PO/enteral route</td>
</tr>
<tr>
<td><strong>Stroke prevention</strong></td>
<td>Slightly superior with 150mg, non-inferior with 110mg</td>
<td>Superior to Warfarin</td>
<td>Superior to Warfarin</td>
</tr>
<tr>
<td><strong>Major bleeding risk</strong></td>
<td>Similar with 150mg, less with 110mg</td>
<td>Reduced</td>
<td>Similar</td>
</tr>
<tr>
<td><strong>Major GI bleeding</strong></td>
<td>Higher with 150mg</td>
<td>similar</td>
<td>higher</td>
</tr>
<tr>
<td>Warfarin</td>
<td>NOAC</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
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</tr>
<tr>
<td>Prescribed for more than 90 years</td>
<td>In practice for just over 7 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low acquisition cost</td>
<td>More expensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range (TTR) 65% or &gt; needed</td>
<td>The benefit over Warfarin declines if TTR for Warfarin -&gt;65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR gives good indication of compliance</td>
<td>Difficult to monitor compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective and well known antidote(s)</td>
<td>The only available specific antidote is Idarucizumab (Praxbind) for Dabigatran only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to peak 3-5 days</td>
<td>Time to peak 1-4 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients may have difficulty around INR monitoring</td>
<td>No routine monitoring required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Many interactions with other drugs and food</td>
<td>Fewer interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No limitations with renal function</td>
<td>CrCl dependant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer half life and less effect of a missed dose</td>
<td>Missed dose can result in greater risk of thromboembolism due to shorter half life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established support by the GPs and Anticoagulation clinics</td>
<td>Main responsibility of the prescriber</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical audit: Anticoagulation in ischaemic stroke with Atrial fibrillation at Royal Hallamshire Hospital Sheffield

Project lead: Muhammad Fozan Khan
Project supervisor: Dr Ali
Data collection contribution: Asad Kazmi
**Standard:**

Consent should be obtained from all patients and/or their relatives before commencing therapeutic anticoagulation:

**Results:**

- Consent obtained from 17/17 (100% of newly diagnosed AF)
- Consent obtained from 6/7 (85.7%) known to have AF but not on anticoagulation on admission
- Consent was obtained from 2 (out of 3) patients for change of anticoagulant.
Standard

CHA2DS2-Vasc and HAS-Bled scores should be documented for all patients with AF and ischaemic stroke:

Results:
New diagnosis of AF: 17
CHA2DS2-Vasc/HAS-Bled scores not documented: 12/17 (70.5%)
Scores documented: 5/17 (29.4%)
When to start NOAC

• Unanimity on postponing anticoagulation after ischemic stroke
• Little consensus on the specifics
• Empiric data and head-to-head data is scant

• This uncertainly is noted in the major society guidelines. The 2012 evidence-based practice guidelines of the American College of Chest Physicians, for example, recommend beginning anticoagulation “within 1 to 2 weeks” after stroke onset.

• **NICE**: People with disabling ischaemic stroke who are in Atrial fibrillation should be treated with Aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.

• Rule of thumb as per expert opinion:

• 72 hours after a small infarct, 1 week after a moderate-sized infarct, and 2 weeks after a large infarct. This is based on expert opinion, without a clear definition of what constitutes a small, moderate or large infarct.

Switching from Warfarin to NOAC

- 70-year-old female patient admitted with multi-territory ischaemic stroke 3 weeks ago. She was on Warfarin for AF prior to the current admission. Warfarin has been restarted one week ago on the ward with latest INR of 2. A review of her INR levels before the admission shows INRs less than 2 on numerous occasions.

After detailed discussion with the patient, she agrees to start Apixaban. When will you start the NOAC?
<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue Warfarin and start Dabigatran when INR &lt;2. Dabigatran can result in falsely high INRs.</td>
<td>Discontinue Warfarin and start Apixaban when INR &lt;2</td>
<td>Stop Warfarin and start Rivaroxaban when INR 3 or below.</td>
</tr>
</tbody>
</table>
Switching one NOAC to another

- NOACs have shorter half-life and converting a NOAC to an alternative NOAC should be theoretically uncomplicated.

- To date there is little evidence of such practice and it would be advisable to seek advice from specialist anticoagulant team.
Special clinical situations

Patients eligible for rTPA for acute ischaemic stroke and on NOAC:

• Only arbitrary recommendation

• European Heart Rhythm Association Guideline suggests to avoid rTPA if NOAC given within last 48 hours.

• In case of uncertainty about the last dosage, a prolonged APTT (for Dabigatran) or prolonged PT (for Fxa inhibitors) suggest that patient is anticoagulated.

• Only in exceptional circumstances where specific tests are available and show normal coagulation, rTPA can be considered, otherwise mechanical thrombectomy should be considered.
A patient taking one of the NOACs who experiences an AIS should not be considered a candidate for thrombolysis unless his/her clinical history and the results of laboratory tests reliably indicate the absence of an anticoagulant effect, or until at least two half-lives have elapsed since the most recent dose in patients with normal renal function (which is approximately 24 h for the NOACs).

Minimum time interval should be at least 24 hours if renal function is normal, but both European and American guidelines recommend 48 hours since last NOAC dose (4 half-lives).

Monitoring

Dabigatran:

• No routine monitoring required

• aPTT provided an approximate estimation

• Diluted thrombin time (dTT) – provides an estimation of Dabigatran plasma concentration that can be compared to the expected Dabigatran plasma concentrations

• Ecarin clotting time (ECT) – provides a direct measure of the activity of direct thrombin inhibitors

• INR test is unreliable for Dabigatran monitoring and should not be used for this purpose
• **Factor Xa inhibitors:**

  • Factor Xa-inhibitors demonstrate a concentration-dependent prolongation of the PT. Nevertheless the effect on the PT depends both on the assay and on the FXa inhibitor.

  • For Rivaroxaban, the PT may provide some quantitative information, even though the sensitivity of the different PT reagents varies greatly.

  • INR (and certainly a point-of-care determined INR) is completely unreliable for the evaluation of FXa inhibitory activity.

• **Anti-FXa ‘chromogenic assays’ have been developed which are more reliable**
The antidote

- FDA approved Praxbind, the first reversal agent for the anticoagulant Dabigatran Oct 2015
- Praxbind (Idarucizumab) now available and approved.
- It is the first and currently the only specific reversal agent available for NOACs
- A ready to use IV dose of 5 grams (two 2.5 grams vials)
- No prothrombotic effect
- Provided immediate, complete and sustained reversal
- Discussions should place with the Haematology.

Idarucizumab for Dabigatran Reversal — NEJM
## Surgery and NOACs

<table>
<thead>
<tr>
<th></th>
<th>Low bleeding risk</th>
<th>High bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Stop 24 hours before procedure</td>
<td>Stop 2-4 days before the procedure</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>24 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
</tbody>
</table>
Management of bleeding

• Principals of ABCD approach

• Stop the NOAC

• Discuss urgently with Haematology

• Document the time of last NOAC dose and consider activated charcoal if within 2 hours

• IV fluids as adequate diuresis will help renal clearance
• Send blood samples for FBC, Renal profile, LFTs, Clotting tests (PT, aPTT, TT, Factor Xa level, any available specific assay)

• Consider platelets infusion if thrombocytopenic or on antiplatelets
<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>A normal TT indicates no significant anticoagulant activity. Specific reversal agent Idarucizumab available.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>PT, aPTT most accessible but can be normal, a normal FXa level would indicate minimal anticoagulant activity. In addition to general measures, consider PCC.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Measurement of Fxa more accurate. In addition to general measures, consider PCC.</td>
</tr>
</tbody>
</table>
Dosage

Dabigatran:

• Patients <80 y: 150 mg B.D, can be reduced to 110mg B.D if risk of haemorrhage increases.

• Patients ≥80y or ≥ or taking Verapamil:

• 110 mg B.D

• Contraindicated if CrCL <30 mL/min
• **Rivaroxaban:**

• 20 mg daily (if CrCl 50 ml/min or above)

• 15 mg daily if CrCl 15-49ml/min

• Contraindicated if CrCl < 15ml/min
Apixaban:

5 mg B.D.

2.5 mg B.D if CrCl between 15-29 ml/min

2.5 mg B.D if 2 of 3 of the following:

1: Age 80 y or above
2: Body weight less than 60Kg
3: Serum creatinine 133 micromole/L or above
Follow-up
KEEP CALM AND CHOOSE NOACs
References

- Europace (2013) 15, 625–651
- eurheartj.oxfordjournals.org/content/35/47/3328
- Idarucizumab for Dabigatran Reversal — NEJM
Thanks

• Any questions...