All NOACs are equal, but some are more equal than others....

Dr Puneet Kakar MRCP LLM MSc
Consultant Stroke physician
Epsom general hospital

Declarations

• Have received academic and speaker funding from Pfizer, BMS and BI.
• Research grants obtained from Multiple Sclerosis Society and British Geriatrics Society
• Do not have any financial holdings in pharmaceutical industry [or elsewhere...]
Focus of this talk

• Overview of NOACs and their specific role in non valvular AF
• Biological and pharmacological differences
• The evidence so far..
• Clinical implications

Overview

• Warfarin has been [??? will be] cornerstone of risk reduction in non valvular AF
• Still the best prophylactic treatment for Stroke prevention in valvular AF, thrombophilic conditions, metallic valves, LV thrombus etc
• Enter NOACs in the specific arena of ‘Non Valvular AF and Stroke prevention’
NOACs

- Anti II a – Dabigatran
- Anti X a – Rivaroxaban and Apixaban
- Oral
- Direct
- Lack direct reversibility
- Lack economical monitoring methods
- More expensive than Warfarin
- Onset of action is within 3 hours – similar to LMWH

The evidence so far for SPAF...

<table>
<thead>
<tr>
<th>NOAC</th>
<th>STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran – 150 mg bd</td>
<td>RE-LY [Mean age 71]</td>
</tr>
<tr>
<td>Dabigatran -110 mg bd</td>
<td>RE-LY</td>
</tr>
<tr>
<td>Rivaroxaban – 20 mg od</td>
<td>ROCKET –AF [Median age 73]</td>
</tr>
<tr>
<td>Apixaban - 5mg bd</td>
<td>ARISTOTLE [Median age 70]</td>
</tr>
<tr>
<td>Apixaban – 5 mg bd [reduced dose in Patients with ≥2 of the following: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 μmol/L).]</td>
<td>AVERROES [comparison vs Aspirin/nothing]</td>
</tr>
<tr>
<td>Edoxaban – 30 mg and 60 mg</td>
<td>ENGAGE AF</td>
</tr>
<tr>
<td>[Not licensed in the UK as yet]</td>
<td></td>
</tr>
</tbody>
</table>
## Biological properties

<table>
<thead>
<tr>
<th>Product characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosing regime</td>
<td>Bd</td>
<td>Od</td>
<td>Bd</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Reversibility</td>
<td>No specific antidote</td>
<td>No specific antidote</td>
<td>No specific antidote</td>
</tr>
<tr>
<td>Monitoring requirements</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Adjustment in renal failure</td>
<td>Yes [Avoid if CrCl&lt;30 ml/min]</td>
<td>Yes [Reduce dose to 15 mg od if CrCl&lt;30 ml/min]</td>
<td>Yes [Reduce dose to 2.5 mg bd if CrCl&lt;30 ml/min]</td>
</tr>
<tr>
<td>Others</td>
<td>Advise taking with food</td>
<td>Advise taking with food</td>
<td></td>
</tr>
</tbody>
</table>

## Key points

- **Dabigatran** – Renal function [lower threshold to discontinue]
- **Apixaban** – Food requirements not as stringent
- **Rivaroxaban** – o.d dosing
Individual drug Evidence...

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Stroke or Embolic event rate</th>
<th>Major Bleeding rate</th>
<th>ICH rates</th>
<th>GI bleed rates</th>
<th>MI rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg bd RE-LY</td>
<td>1.11% vs 1.69%</td>
<td>3.11% vs 3.36%</td>
<td>0.30% vs 0.74%</td>
<td>1.51% vs 1.02%</td>
<td>0.74% vs 0.53%</td>
</tr>
<tr>
<td>Dabigatran 110 mg bd RE-LY</td>
<td>1.53% vs 1.69%</td>
<td>2.71% vs 3.36%</td>
<td>0.23% vs 0.74%</td>
<td>1.12% vs 1.02%</td>
<td>0.72% vs 0.53%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg od ROCKET-AF</td>
<td>1.7% vs 2.2%</td>
<td>14.9% vs 14.5%</td>
<td>0.5% vs 0.7%</td>
<td>3.15% vs 2.16%</td>
<td>1.43% vs 1.78%</td>
</tr>
<tr>
<td>Apixaban 5 mg bd ARISTOTLE</td>
<td>1.27% vs 1.6%</td>
<td>2.13% vs 3.09%</td>
<td>0.33 % vs 0.80%</td>
<td>0.76% vs 0.86%</td>
<td>0.53% vs 0.61%</td>
</tr>
</tbody>
</table>
### Dabigatran 150 mg bd [RE-LY]

- **Stroke or Embolic event rate vs Warfarin** - 1.11% vs 1.69%  
  $[RR 0.66; 95\% CI 0.53 \text{ to } 0.82; P<0.001]$  
- **Major bleed rate vs Warfarin** - 3.11% vs 3.36%  
  $[RR 0.93; 95\% CI, 0.81 \text{ to } 1.07; P=0.31]$  
- **ICH rates vs Warfarin** - 0.30% vs 0.74%  
  $[RR -0.40; 95\% CI 0.27 \text{ to } 0.60; p<0.05]$  
- **GI bleed rates vs Warfarin** – 1.51% vs 1.02%  
  $[RR 1.50; 95\% CI, 1.19 \text{ to } 1.89; p<0.001]$  

- Superior efficacy  
- Similar major bleed risk  
- Superior ICH risk benefit  
- More GI bleeds

### Dabigatran 110 mg bd

- **Stroke or Embolic event rate vs Warfarin** – 1.53% vs 1.69%  
  $RR - 0.91; 95\% CI 0.74 \text{ to } 1.11; P=0.34$  
- **Major bleed rate vs Warfarin** – 2.71% vs 3.36%  
  $RR - 0.80; 95\% CI, 0.69 \text{ to } 0.93; P=0.003$  
- **ICH rates vs Warfarin** – 0.23% v 0.74 %  
  $RR – 0.31, 95 \% CI 0.20 – 0.47; p< 0.001$  
- **GI bleed rates vs Warfarin** – 1.12% vs 1.02%  
  $RR 1.10; 95\% CI 0.86 \text{ to } 1.41; p – 0.43$  

- Non inferior efficacy  
- Superior major bleed risk benefit  
- Superior ICH risk benefit  
- No increase in GI bleed risk
Dabigatran and MI risk

- RELY data suggestive of a possible small increase in risk
  - Rate – 0.72% vs 0.53% [RR – 1.35; 95% CI 0.98 – 1.87; p = 0.07] for the 110 mg bd dose
  - Rate – 0.74% vs 0.53% [RR – 1.38; 95% CI 1.00 – 1.91; p = 0.048] for the 150 mg bd dose
- Further meta-analyses also suggest this small increased risk
- FDA – surveillance continues. No conclusive inferences drawn so far. Caution advised!!

Rivaroxaban in SPAF – ROCKET-AF

- Stroke or Embolic event rate vs Warfarin – 1.7% vs 2.2%
  HR - 0.79; 95% CI, 0.66 - 0.96; P<0.001 for non-inferiority
- Major [plus clinically relevant] bleed rate vs Warfarin – 14.9% vs 14.5%
  HR - 1.03; 95% CI, 0.96 - 1.11; P=0.44
- ICH rates vs Warfain – 0.5% vs. 0.7%;
  HR 0.67; 95% CI, 0.47 - 0.93; P=0.02
- GI bleed rates vs Warfarin - 3.15% vs 2.16% [p<0.001]
- Myocardial infarction rate - 1.43% vs 1.78%
  HR - 0.81 95% CI, 0.63 - 1.06; p = 0.121
- Non inferior efficacy
- Major bleeds risk similar
- ICH bleed risk lower
Apixaban in SPAF – ARISTOTLE

- Stroke or Embolic event rate vs Warfarin – 1.27% vs 1.6%  HR 0.79; 95% CI, 0.66 to 0.95; P<0.001
- Major bleed rate vs Warfarin – 2.13% vs 3.09%  HR 0.69; 95% CI, 0.60 to 0.80; P<0.001
- ICH rates vs Warfain – 0.33 % vs 0.80%  HR 0.42; 95% CI, 0.30 to 0.58; P<0.001
- GI bleed rates vs Warfarin – 0.76% vs 0.86%  HR 0.89; 95% CI 0.70 – 1.15; p = 0.37
- Myocardial infarction rate – 0.53% vs 0.61%  HR – 0.88 95% CI 0.66-1.17; p = 0.37

Superior efficacy
- Superior major bleed risk
- No worse GI bleed risk or MI risk

COMPARATIVE VIEW

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<tr>
<th>NOAC</th>
<th>Total Stroke rates</th>
<th>Ischaemic Stroke rates</th>
<th>Haemorrhagic Stroke rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran 150 mg bd RE-LY</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1.01% vs 1.57%</td>
<td>0.92% vs 1.20%</td>
<td>0.10% vs 0.38%</td>
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<td></td>
<td>[RR – 0.64, 95% CI – 0.51 – 0.81; p &lt; 0.001]</td>
<td>[RR 0.76; 95% CI – 0.60 – 0.98; p = 0.03]</td>
<td>[RR 0.26; 95% CI – 0.14 – 0.49; p&lt;0.001]</td>
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<tr>
<td><strong>Dabigatran 110 mg bd RE-LY</strong></td>
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<td>[RR -0.92; 95% CI – 0.74 -1.13; p= 0.41]</td>
<td>[RR 1.11, 95% CI – 0.89-1.40; p = 0.35]</td>
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<td>[RR – 0.85, 95% CI – 0.70 -1.03; p = 0.09]</td>
<td>[HR – 0.94; 95% CI - 0.75 -1.17 p = 0.581]</td>
<td>[HR - 0.59 ; 95% CI - 0.37 -0.93; p = 0.024 ]</td>
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### AVERROES

**A quick note!**

- Compared Apixaban 5 mg bd [with suitable dose reduction where apt] vs Aspirin [75 - 300mg] [i.e. where Warfarin was deemed unsuitable]
- Early termination
- Superior Ischaemic Stroke efficacy
- Non inferior Haemorrhagic Stroke risk!!!
Interpretation [personal view..]

• Dabigatran 150 mg bd – offers powerful total stroke reduction rate driven both by ischaemic stroke reduction and favourable haemorrhagic stroke reduction rates [Caution – GI bleed rates and MI rates]
• Dabigatran 110 mg bd and Rivaroxaban 20 mg bd – offer non inferior total and ischaemic stroke reduction and favourable haemorrhagic stroke reduction] [Caution- Rivaroxaban GI risk greater than Dabigatran 110 mg bd]
• Apixaban 5 mg bd – offers powerful total stroke reduction rate driven through haemorrhagic stroke reduction [No extra caution reqd with GI bleed and MI risk]

Translation into clinical practice –

• Cerebral Microbleeds
• High ischaemic stroke risk
• Over 80 s
• High HASBLED
• CKD
• GI bleed risks
• High Coronary risk
Eg 1

• 68 yr old man – retired professor
• known AF – admission INR 1.6
• Acute severe stroke – NIHSS 24
• Right sided symptoms
• ECG – AF
• Carotids – NAD
• Normal CrCl
Decision making rationale for future event reduction

- Warfarin
- Dabigatran
- Apixaban
- Rivaroxaban
- Aspirin
- Clopidogrel
- Aspirin plus Clopidogrel

Parameters..

- CHA2DS2-VASc - 3
- HASBLED - 2
- Renal function - normal
- Compliance, lifestyle and choice
- Biological characteristics of NOACs
- Priority –
  - High Ischaemic stroke risk
  - Low bleeding risk
  - No specific coronary or GI risk factors
Eg 2

- 84 yr old man
- Lives in RH – Mild dementia
- Acute admission – R weakness – 6hrs
- NIHSS – 8
- MRS – 3 [moderately independent]
- ECG – AF [not previously known]
Anticoagulation decision

- Warfarin
- NOACs – Which
- Antiplatelets
- Nothing

Parameters

- CHA2DS2-VASc - 5
- HASBLED - 4
- Renal function – CrCl 35ml/min
- Compliance, lifestyle and choice
- Biological characteristics
  - Priority
  - High Ischaemic stroke risk
  - High bleeding risk
  - Abn renal functions
A quick note on CMBs and anticoagulation

• Not currently in guidelines or risk assessment scores
• Huge area of concern
• Long term risks unclear although evidence points to increased bleeding risk
  – Charidimou, A; Werring, DJ; Kakar, P; Fox, Z; (2013) Cerebral microbleeds and recurrent stroke risk: Systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts. *Stroke*, 44 (4) 995 – 1001
• Decision making is difficult!

Which drug and when?

• Remains a clinical choice
• No right or wrong
• The NICE guidelines make Warfarin prescription onerous
• Choice of drug depends on
  – Patient demographics – Age, Renal function, bleeding risk
  – Biological profile – CHA2DS2-VASC/HASBLED
  – Clinical and past medical history
Thank you

Questions?