ANTITHROMBOTIC THERAPY
in
NON-VALVULAR ATRIAL FIBRILLATION

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Auckland Heart Group
Waitemata Health

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Disclosures

PFIZER – Lecture series
Prevalence of NVAF is 1–2% 40,000–80,000 people in NZ have AF.

Prevalence of AF is predicted to double by 2050.

Atrial fibrillation is the most common cardiac arrhythmia detected in primary Care - 10% of people >80 years.

Atrial Fibrillation is associated with obesity. Both conditions are reaching epidemic proportions.
Atrial Fibrillation

2 major clinical consequences of AF:

A) Loss of ‘booster pump’ function of atria
   ➔ cardiac output ➔ lethargy, breathlessness, palpitations

B) Formation of thrombus within the atria
   ➔ cardio-embolism

30% of patients with AF are asymptomatic
AF and STROKE

STROKE RISK INCREASES 5 X IN THE PRESENCE OF AF

6000 strokes in NZ per year.

- Hypertension
- Carotid atherosclerosis
- Atrial fibrillation

SILENT AF?
Stroke and AF

Percentage of strokes due to AF Increases with age.

ELDERLY AF PATIENTS NEED SAFE AND EFFECTIVE ANTICOAGULATION

AF produces LARGE EMBOLI

AF strokes tend to be larger

⇒ Resulting in more disability

⇒ Greater mortality – 30 days after stroke ⇒ 24% of patients have died.
‘RED and WHITE Clots’

AF clots are red clots
Consist of red blood cells and fibrin (red clots)
Typical of low-flow venous thrombi
- PREVENTED BY ANTICOAGULANTS

Arterial clots – are white clots
have a high platelet content
- PREVENTED BY ANTIPLATELET THERAPY

ORAL ANTICOAGULANTS ARE THUS FAR SUPERIOR TO ANTIPLATELET DRUGS (Aspirin, Clopidogrel) IN PREVENTING AF RELATED STROKE.
HIGH RISK AF PATIENTS ADMITTED WITH 1st STROKE

- No antithrombotic therapy: 29%
- Subtherapeutic warfarin (INR < 2.0): 29%
- DAPT: 2%
- Single antiplatelet drug: 29%
- Therapeutic warfarin (INR ≥ 2): 10%

90% are not properly anticoagulated

Data from a prospective stroke registry of 597 patients with AF at high risk for stroke (*1 high-risk factor or ≥1 moderate-risk factor according to American College of Chest Physicians guidelines)
WARFARIN IS AN EFFECTIVE ANTICOAGULANT

Annals of Internal Medicine

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Background: Atrial fibrillation is a strong independent risk factor for stroke.

Purpose: To characterize the efficacy and safety of antithrombotic agents for stroke prevention in patients who have atrial fibrillation, adding 13 recent randomized trials to a previous meta-analysis.

Data Sources: Randomized trials identified by using the Cochrane Stroke Group search strategy, 1966 to March 2007, unrestricted by language.

Study Selection: All published randomized trials with a mean follow-up of 3 months or longer that tested antithrombotic agents in patients who have nonvalvular atrial fibrillation.

Data Extraction: Two coauthors independently extracted information regarding interventions; participants; and occurrences of ischemic and hemorrhagic stroke, major extracranial bleeding, and death.

Data Synthesis: Twenty-nine trials included 28 044 participants (mean age, 71 years; mean follow-up, 1.5 years). Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%), respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in major extracranial hemorrhage were small (=0.3% per year) on the basis of meta-analysis.

Limitation: Methodological features and quality varied substantially and often were incompletely reported.

Conclusions: Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy in participants from the trials included in this meta-analysis were less than the absolute reductions in stroke. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation.

For author affiliations, see end of text.
Data on anti-thrombotic therapy and AF

WARFARIN:

Met-analysis 2900 patients (6 TRIALS) ➔ Warfarin was very effective!
- 64% relative risk reduction of stroke
- 26% relative risk reduction in mortality

ASPIRIN

ASPIRIN – 18% relative risk reduction in stroke
Also associated with a substantial risk of haemorrhage- intra-cerebral and GIT

ASPIRIN plus CLOPIDOGREL

ASPIRIN + CLOPIDOGREL – 30% relative risk reduction in stroke
High risk of haemorrhage – 14% higher risk of bleeding versus warfarin
ANTICOAGULATION WITH WARFARIN IS CHALLENGING

GARFIELD

GARFIELD: Inadequate INR Control With VKA Treatment

- 9971 patients in preliminary 12-month analysis
- 5724 patients treated with VKA
- 4665 patients with INR recordings
- 2099 patients with adequate INR control

INR control:
Frequency in Range
- Adequate control ≥60% of measurements (INR 2-3)
- Poor control <60% of measurements (INR 2-3)

1/5 adequately treated with OAC

VKA = vitamin K antagonist
Time in Therapeutic Range (TTR)

ARISTOTLE
Median of Patients TTR in Different Countries

REAL WORLD
Warfarin Difficulties

Delayed onset of action – 72 hours to be therapeutic
MAY TAKE A NUMBER OF WEEKS BEFORE THE PATIENTS ARE STABLY ANTICOAGULATED

Multiple environmental and genetic factors – influence dose – drugs and foods.

Narrow therapeutic Index
➔ Difficult to maintain patients in the therapeutic range
➔ Over anticoagulation leads to bleeding
➔ Under anticoagulation leads to thrombo-embolism

Regular monitoring- difficult with travel
NOACs or DOACS

NOACs for Stroke Prevention in AF

Dabigatran
- RE-LY
- Open label
- 2 doses
- Twice daily

Apixaban
- ARISTOTLE
- Double blind
- 2 doses
- Twice daily

Rivaroxaban
- ROCKET AF
- Double blind
- 2 doses
- Once daily

Edoxaban
- ENGAGE AF-TIMI 48
- Double blind
- 2 doses
- Once daily

Happy 5th Birthday: How Has AF Stroke Prevention Changed?
NOAC TRIALS

DABIGATRAN vs WARFARIN
18000 Patients
CHADS$_2$ -2.1
F/U 2 yrs

RIVAROXABAN Vs WARFARIN
14264 Patients
CHADS$_2$ 3.48
F/U 1.9 yrs

APIXABAN Vs WARFARIN
18201 Patients
CHADS$_2$ 2.1
F/U 1.8 yrs

No graphic description provided.
# Meta-analysis of NOAC Trials

## Efficacy

<table>
<thead>
<tr>
<th>Result</th>
<th>Pooled NOAC</th>
<th>Pooled Warfarin</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>665/29292</td>
<td>724/29221</td>
<td>0.92</td>
<td>0.83-1.02</td>
<td>.10</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49</td>
<td>0.38-0.64</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29292</td>
<td>432/29221</td>
<td>0.97</td>
<td>0.78-1.20</td>
<td>.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90</td>
<td>0.85-0.95</td>
<td>.0003</td>
</tr>
</tbody>
</table>

## Safety

<table>
<thead>
<tr>
<th>Result</th>
<th>Pooled NOAC</th>
<th>Pooled Warfarin</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>204/29287</td>
<td>425/29211</td>
<td>0.48</td>
<td>0.39-0.59</td>
<td>&lt; .0001</td>
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<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>591/29211</td>
<td>1.25</td>
<td>1.01-1.55</td>
<td>.043</td>
</tr>
</tbody>
</table>

*Edoxaban is not approved for clinical use in AF*

CASE

87 Year old male patient

ASYMPTOMATIC AF – uncertain duration

Very well for his age – plays 2 rounds of golf per week

Treated hypertension – Chlorthalidone 25mg/d
Rate control Rx – Metoprolol 95mg/d
No diabetes, no prior CVA, no vascular disease, no bleeding.
2 beers after golf

Moderately dilated left atrium on echo
– may potentiate sluggish blood flow
QUESTION

1) Patient is 87 years old (too old) - **no Anti-thrombotic therapy required**

2) Patient should he receive **Antiplatelet Therapy** – safer than anticoagulation
   - Aspirin
   - Clopidogrel

3) Patient should he be **anticoagulated with**
   - Warfarin

4) Patient should be **anticoagulated with**
   - NOAC
### STROKE versus BLEEDING

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Patients (n = 7329)</th>
<th>Adjusted stroke rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk of Hemorrhage</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
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<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>&lt; 12.5</td>
</tr>
</tbody>
</table>

\[ \text{CHA}_2\text{DS}_2\text{-VASc} - 3 \]

\[ \text{HAS-BLED} 1-2 \]
To Anticoagulate *or not to* Anticoagulate

Why is it such a tough decision?
We are always told about the haemorrhagic strokes we cause  
BUT  
we never hear about the cardio-embolic strokes we prevent.

WE ARE TEMPTED TO USE ASPIRIN RATHER THAN AN ANTICOAGULANT  
IN PATIENTS WITH AF –especially in the elderly
BAFTA Study Design, Efficacy, and Safety Outcomes

Patients (≥75 years) with AF or atrial flutter demonstrated by ECG

Randomized 1:1

Warfarin (INR 2.0-3.0)  Aspirin (75 mg once daily)

Mean duration of follow-up = 2.7 years

Primary efficacy outcome: fatal or disabling stroke (ischemic or hemorrhagic), ICH or clinically significant arterial embolism; secondary outcome: major extracranial hemorrhage

Study design

AVEROES\(^1\d\)
Superiority, phase III, randomised, double blind trial of aspirin vs ELIQUIS in warfarin unsuitable NVAF patients (n=5,599)
(mean duration 1.1 years)

**ELIQUIS**
5mg BD\(^a\)
(n=2,808)

**Aspirin**
81–324mg/day\(^b\)
(n=2,791)

**Primary efficacy endpoint**
Stroke (ischaemic or haemorrhagic) or SE

**Primary safety endpoint**
Major bleeding (ISTH criteria)

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Adapted from Connolly SJ et al. 2011.\(^1\)
Updated Guidelines for AF

**ESC** (2012)

- **Yes**
  - < 65 years and lone AF (including women)
  - No
- Assess risk of stroke (CHA$_2$DS$_2$-VASc score)
  - 0
  - 1
  - > 2
  - Oral anticoagulant therapy
  - Assess bleeding risk (HAS-BLED score)
  - Consider patient values and preferences
  - NOAC
  - VKA*

**NOAC** should be considered over VKA

**AHA/ACC/HRS** (2014)

- Assess risk of stroke in patient with nonvalvular AF (CHA$_2$DS$_2$-VASc score)
  - 0
  - 1
  - > 2
  - No antithrombotic therapy
  - Oral anticoagulant or aspirin may be considered
- Oral anticoagulant
- Warfarin
- NOAC (dabigatran, apixaban, rivaroxaban)

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## RE-LY: Dabigatran and Elderly Patients

<table>
<thead>
<tr>
<th></th>
<th>Annual rate (%)</th>
<th>D110 vs warfarin</th>
<th>D150 vs warfarin</th>
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<tr>
<td></td>
<td>D110</td>
<td>D150</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>0.14</td>
<td>0.26</td>
<td>0.61</td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>0.37</td>
<td>0.41</td>
<td>1.00</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yrs</td>
<td>1.76</td>
<td>1.91</td>
<td>2.44</td>
</tr>
<tr>
<td>≥75 yrs</td>
<td>4.10</td>
<td>4.68</td>
<td>3.44</td>
</tr>
</tbody>
</table>
### The Elderly

**Apixaban vs Warfarin in Pts ≥80 and <80 Yrs**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>Interaction P-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>260(1.93)</td>
<td>366(2.78)</td>
<td>0.70(0.60, 0.82)</td>
<td>0.7404</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>67(3.55 )</td>
<td>96(5.41 )</td>
<td>0.66(0.48, 0.90)</td>
<td></td>
</tr>
<tr>
<td><strong>All Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>1964(17.0)</td>
<td>2558(24.4)</td>
<td>0.71(0.67, 0.76)</td>
<td>0.8332</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>392(26.4)</td>
<td>502(37.4)</td>
<td>0.73(0.64, 0.83)</td>
<td></td>
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<tr>
<td><strong>Intracranial Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>43(0.32)</td>
<td>98(0.73)</td>
<td>0.43(0.30, 0.62)</td>
<td>0.6656</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>9(0.47)</td>
<td>24(1.32)</td>
<td>0.36(0.17, 0.77)</td>
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<tr>
<td><strong>Stroke/Systemic Embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>179(1.23)</td>
<td>225(1.55)</td>
<td>0.79(0.65, 0.96)</td>
<td>0.9080</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>33(1.53)</td>
<td>40(1.90)</td>
<td>0.81(0.51, 1.29)</td>
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<tr>
<td><strong>All-cause Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age &lt; 80</td>
<td>452(3.03)</td>
<td>507(3.42)</td>
<td>0.88(0.78, 1.00)</td>
<td>0.7259</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>151(6.86)</td>
<td>162(7.44)</td>
<td>0.93(0.74, 1.16)</td>
<td></td>
</tr>
</tbody>
</table>

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*From Thought Leadership to Clinical Practice*

Duke Clinical Research Institute

Halvorsen S. et al., Eur Heart J 2014;35:1864–1872
1) Patient is 87 years old (too old) - **no Anti-thrombotic therapy required**

2) Patient should he receive **Antiplatelet Therapy** – safer than anticoagulation
   - Aspirin
   - Clopidogrel

3) Patient should be **anticoagulated with**
   - Warfarin

4) Patient should be **anticoagulated with** NOAC
54 year old male patient

Recurrent **paroxysmal atrial fibrillation**

**Hypertension** – adequately controlled – Lisinopril 10mg/d, Amlodipine 10mg/d.

Obese – BMI-32

PM/SH-nil else

MEDICATION - Lisinopril 10mg/d
Amlodipine 5mg/d

**CHA\(_2\)DS\(_2\)-VASc** -1
**HAS-BLED** - 0
Question

CHA2DS2 VASC 1 - Would you treat this patient with:-

1) Aspirin

2) NOAC

3) Warfarin

4) No anti-thrombotic therapy required – low risk
Updated Guidelines for AF

ESC (2012)

- Yes
  - < 65 years and lone AF (including women)
  - No
    - Assess risk of stroke (CHA₂DS₂-VASc score)
      - 0
        - No antithrombotic therapy
      - 1
        - Oral anticoagulant therapy
        - Assess bleeding risk (HAS-BLED score)
        - Consider patient values and preferences
      - > 2
        - Oral anticoagulant therapy

AHA/ACC/HRS (2014)

- Yes
  - Assess risk of stroke in patient with nonvalvular AF (CHA₂DS₂-VASc score)
    - 0
      - No antithrombotic therapy
    - 1
      - No antithrombotic therapy
        - or Oral anticoagulant or aspirin may be considered
    - > 2
      - Oral anticoagulant
      - Warfarin
      - NOAC (dabigatran, apixaban, rivaroxaban)

* NOAC should be considered over VKA

Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA$_2$DS$_2$-VASc Score of 1

Leif Friberg, MD, PhD,* Mika Skeppholm, MD, PhD,* Andreas Terént, MD, PhD

Should Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA$_2$DS$_2$-VASc Score (Beyond Sex) Receive Oral Anticoagulation?

Tze-Fan Chao, MD,† Chia-Jen Liu, MD,‡ Kang-Ling Wang, MD,§ Yenn-Jiang Lin, MD,¶ Shih-Lin Chang, MD,¶ Li-Wei Lo, MD,¶ Yu-Feng Hu, MD,¶ Ta-Chuan Tuan, MD,¶ Tzeng-Ji Chen, MD,¶ Gregory Y.H. Lip, MD,¶ Shih-Ann Chen, MD,*

Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA$_2$DS$_2$-VASc Score

Gregory Y.H. Lip, MD,*‡ Flemming Skjøth, MSc, PhD,*† Lars Hvilsted Rasmussen, MD, PhD,* Torben Bjerregaard Larsen, MD, PhD*†
CHA₂DS₂-VASC = 0-1
AVERROES (n=5,600, CHADS≥1) – Apixaban vs. Aspirin

Stroke or SSE

- Apixaban
- Aspirin

Cumulative Hazard

Months
HR 0.45
95% CI 0.32-0.62
p<0.001

Major Bleeding

- Apixaban
- Aspirin

Cumulative Hazard

Months
HR 1.13
95% CI 0.74-1.75
p=0.57

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Connolly et al. NEJM 2011; 364:806-17
Question

CHA2DS2 VASC 1 - Would you treat this patient with:-

1) Aspirin

2) NOAC

3) Warfarin

4) No anti-thrombotic therapy required – low risk
Indications for Anticoagulation in Non-Valvular AF are Increasing

<65 years
CHA$_2$DS$_2$VASC - 1

65 to 80 years
CHA$_2$DS$_2$VASC >2

>80 year old

Need TIME to discuss and individualize patient treatment
COMBINATION THERAPY

NOAC PLUS ANTIPLATELET THERAPY
NOAC in combination with anti-platelet Therapy

CHA2DS2-VASc -3
DABIGATRAN 110mg bd

NSTEMI

PCI to LAD
AF and requirement for PCI commonly co-exist

~30% of patients with AF and an indication for continuous OAC have co-existing CAD and may require PCI

Need dual antiplatelet therapy – to prevent stent thrombosis

AND

Need anticoagulation to prevent STROKE from AF
Combination Therapy

NOAC is stopped

Aspirin and P2Y12 inhibitor is given

Once the patient is stable (48hrs)
– warfarin commenced as an in-patient

Patient is discharged on triple therapy
(Warfarin, clopidogrel, aspirin) x 4weeks

After 4 weeks – aspirin is dropped
Dual therapy x 11 months
(Warfarin and Clopidogrel)

After 12 months - anticoagulation

QUESTION:
NOAC INSTEAD OF WARFARIN

NEED MORE DATA
OAC in Coronary artery disease

Warfarin is excellent in CAD. Can be used as monotherapy to prevent re-infarction. Aspirin can be stopped.

NOACS in CAD – safe 20% of pts in RE-LY had CAD – CAD pts did well.

NOACS as monotherapy to prevent re-infarction – NEED MORE DATA
RE-DUAL PCI™ addresses the need for innovative new treatment regimens and is the largest ongoing OAC study in this setting.
NOAC level monitoring
Reversal agents
Drug Interactions
Switching and Interruption
Theoretical Framework for monitoring Dabigratran plasma levels

Dabigratran

- Gut
- P-gp
- esterase-mediated hydrolysis
- no CYP450
- Dabigratran
- t_{1/2} = 12-17h
- Bio-availability 3–7%
- ~80%
Theoretical framework for monitoring Dabigratran plasma levels

A level of <10 ng/mL should be safe for most types of surgery.

Monitoring Drug Levels

Monitoring drug levels is complex – what is the ideal drug level? Drug levels may vary with age? Drug levels vary in different clinical situations e.g. patients on Amiodarone. No data to back up that there is better clinical outcome with monitoring levels.

Should the level be a little on the high side – no data to say the patients will do better with a change in dose.
No monitoring required but.......... DOSE SELECTION is necessary!

**DABIGATRAN:**
- <80 years with normal renal function – 150mg bd
- Cr Cl 30-50ml/min: 110mg bd
- >80 years – 110mg bd

**RIVAROXABAN**
- All age groups: 20mg/d
- Cr Cl 30-49mls/min 15mg/d

**APIXABAN:**
- Standard dose is 5mg bd
- If >2 of the following dose reduce 2.5mg bd -
  (Age > 80 years, Creatinine >133umol/l, Weight <60kg)
Reversal Agents for NOACs

- A reversal agent is not necessary to use NOACs safely and effectively.
- BUT a reversal agent would improve the uptake of the drugs.
- The biggest problem is not bleeding "but millions of people out there not being treated ... One of the barriers is lack of a reversal agent."
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (direct thrombin inhibitor)</th>
<th>Rivaroxaban/Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td>IDARUCIZUMAB</td>
<td>ANDEXANET-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANDEXANET-R</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Binds Dabigatran with great affinity</td>
<td><strong>Factor Xa look alike that binds Apixaban or Rivaroxaban</strong></td>
</tr>
<tr>
<td></td>
<td>IVI administration- rapid onset of action</td>
<td></td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Trials underway</td>
<td>Approval lodged with FDA and EMA</td>
</tr>
</tbody>
</table>
Healthy volunteer study: immediate, complete, and sustained reversal of dabigatran anticoagulation

End of idarucizumab injection (5 min infusion)

Dabigatran plus:
- Placebo (n=9)
- 1 g idarucizumab (day 4) (n=9)
- 2 g idarucizumab (day 4) (n=9)
- 4 g idarucizumab (day 4) (n=8)
- Normal upper reference limit (n=86)
- Mean baseline (n=86)

Dabigatran + placebo

Dabigatran
Antidote

Time after end of infusion (hours)
Transitioning between OAC

TRANSITION

NOAC to VKA – continue NOAC until INR>2

VKA to NOAC – start NOAC when INR<2

NOAC to NOAC – just stop and start
# Drug Interactions

## Dabigatran

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Impact on Dabigatran</th>
<th>Impact on Edoxaban</th>
<th>Impact on Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>P-gp/CYP3A4</td>
<td>+18%</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp/wk CYP3A4</td>
<td>+12–180%</td>
<td>+53% (slow release)</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp/wk CYP3A4</td>
<td>no effect</td>
<td>+40%</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp</td>
<td>+50%</td>
<td>+80%</td>
<td>+50%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp</td>
<td>+12–60%</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-gp/CYP3A4</td>
<td>+70–100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole; itraconazole; voriconazole; posaconazole; clarithromycin; erythromycin</td>
<td>P-gp and BCRP/CYP3A4</td>
<td>+140–150%</td>
<td>+100%</td>
<td>up to +160%</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>P-gp and BCRP/CYP3A4</td>
<td>no data</td>
<td>strong increase</td>
<td>no data</td>
</tr>
<tr>
<td>Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital</td>
<td>P-gp and BCRP/CYP3A4/CYP2J2</td>
<td>-66%</td>
<td>-54%</td>
<td>-35%</td>
</tr>
</tbody>
</table>

## Rivaroxaban

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Impact on Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>P-gp/CYP3A4</td>
<td>+18%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp</td>
<td>no effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp/wk CYP3A4</td>
<td>+12–180%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp/wk CYP3A4</td>
<td>no effect</td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp</td>
<td>+50%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp</td>
<td>+12–60%</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-gp/CYP3A4</td>
<td>+70–100%</td>
</tr>
<tr>
<td>Ketoconazole; itraconazole; voriconazole; posaconazole; clarithromycin; erythromycin</td>
<td>P-gp and BCRP/CYP3A4</td>
<td>+140–150%</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>P-gp and BCRP/CYP3A4</td>
<td>no data</td>
</tr>
<tr>
<td>Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital</td>
<td>P-gp and BCRP/CYP3A4/CYP2J2</td>
<td>-66%</td>
</tr>
</tbody>
</table>

## Apixaban

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Impact on Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>P-gp/CYP3A4</td>
<td>+18%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp</td>
<td>no effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp/wk CYP3A4</td>
<td>+12–180%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp/wk CYP3A4</td>
<td>no effect</td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp</td>
<td>+50%</td>
</tr>
<tr>
<td>Amiodarone</td>
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<td>Dronedarone</td>
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<td>Ketoconazole; itraconazole; voriconazole; posaconazole; clarithromycin; erythromycin</td>
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<tr>
<td>Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital</td>
<td>P-gp and BCRP/CYP3A4/CYP2J2</td>
<td>-66%</td>
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</tbody>
</table>

## Metabolism

- **Gut**: Absorption and metabolism in the digestive tract.
- **P-gp**: A protein involved in the transport of substances across cell membranes.
- **CYP3A4**: An enzyme involved in drug metabolism.
- **Bio-availability**: The percentage of a drug that reaches the systemic circulation after administration.

## Examples

- **Dabigatran**: Esterase-mediated hydrolysis in the gut leading to absorption.
- **Rivaroxaban**: Absorption in the gut with a bio-availability of 66% (without food) and 80% (with food).
- **Apixaban**: Absorption in the gut with a bio-availability of 50%.
CRYPTOGENIC STROKE

- Cardioembolic 25.8%
- Cause unknown 22.8%
- Large Artery 21.1%
- Small-vessel 20.7%
- Dissection 15.1%
- Coagulopathy 7.0%
- Vasculitis 0.3%
- Hematologic 0.2%

SILENT AF?
CASE:

69 year old Female patient
Transient left arm weakness
Loss of fine motor skills

Past history:
HYPERTENSION

With adequate monitoring could this patient have PAF?
Long-term Monitoring

CRYSTAL AF Study

Stroke/TIA

Cryptogenic Stroke/TIA

Continuous Monitoring

Control

Follow-up until study closure (minimum 12 months)

Time to first documented AF
% patients with documented AF

CRYSTAL AF
AF Detection at 6 Months

- Cardioembolic 25.8%
- Small-vessel 20.7%
- Large Artery 21.1%
- Cause unknown 22.8%
- Multiple 7.0%
- Dissection 1.5%
- Coagulopathy 0.7%
- Vasculitis 0.3%
- Hematologic 0.2%

AF-8.9%
CONCLUSION

NOAC PROVIDE RAPID AND RELIABLE ANTICOAGULATION, MINIMAL DRUG:DRUG INTERACTIONS AND DRUG LEVEL MONITORING IS NOT REQUIRED.

ESC GUIDELINES-In patients with non-valvular AF and an estimated stroke risk exceeding 1% per year CHA$_2$DS$_2$VASC $\geq$ 1 males, CHA$_2$DS$_2$VASC $\geq$ 2 females – consider anticoagulation with DOAC. **Aspirin is no longer recommended.**

Aspirin is 1/3 as effective as OAC in preventing AF related stroke and with similar bleeding risk (BAFTA and AVERROES)

Elderly patients – ¼ of strokes are AF mediated – emphasizing the importance of accurate anticoagulation in this age group.

Risk of intracranial haemorrhage is lower with NOAC vs VKA (OR .46) – this benefit was even larger in the elderly (OR 0.36)

Reduce dose in elderly patients – monitor renal function function 3 x per year

Can be safely stopped and restarted for elective surgery – will be reversal agents available to facilitate emergent surgery
THANK YOU

Colin Edwards