Anticoagulation:
From AF to CVD Risk Reduction

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Chief Clinical Executive Affinity Care
Declaration of interests

• The Westcliffe Partnership has received funding from: Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn, INRStar, Medtronic, Oberoi Consulting, Pfizer, Roche, Sanofi-Aventis, Servier.

• An advisor to: Anticoagulation UK, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust

• A trustee of Thrombosis UK and AF Association
Who is this?
The Yellow Emperor

‘When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades’

Huang Ti Nei Ching Su Wen

As lessons from ancient history are still pertinent in today’s society, the saying of the Yellow Emperor is unfortunately still daily practice:

AF patients have a doubled mortality risk.
Who is this?
William Harvey

• 1628 Published *De Motu Cordis*
  • *Anatomical Account of the Motion of the Heart and Blood*

• Incited considerable controversy within the medical community.

• Some doctors affirmed they would "rather err with Galen than proclaim the truth with Harvey."
Who is this?
Johann Jakob Wepfer

- 1658- Shows intracerebral haemorrhage is the cause of apoplexy
- Defined
  - sanguineous apoplexy
  - serous apoplexy
- In his declining years he suffered from a slow irregular pulse, breathlessness and orthopnoea
- Before his death asked his son in law, Johann Conrad Brunner to ensure he underwent a post mortem
  - Fluid in chest and abdomen
  - Enlargement of the heart
  - Hardening of the aorta and other major arteries
  - Diagrams are probably the first demonstration of atherosclerosis
Atrial Fibrillation-Stroke

- c 4000: Yellow Emperor
- c 1600’s Sir William Harvey
  - observed chaotic motion of atria in open chest animal
- c 1650’s Wepfer
- 1909 Sir Thomas Lewis
  - “irregular or fibrillatory waves and irregular ventricular response”
  - “absent atrial activity with grossly irregular ventricular response”
## Atrial Fibrillation - Clinical Practice

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<th>Age (Yrs)</th>
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Incidence per 100,000 patient years. Prevalence per 1000,000 patients.
Atrial Fibrillation-Stroke

- First half 20\textsuperscript{th} century Harvey and Levine demonstrated AF with mitral stenosis increased the incidence of auricular (atrial) thrombosis
- Series of autopsy by Hey and Levine demonstrated that those with mitral stenosis and AF had increased thrombus compared with those without AF
- Further 1970s, the Framingham study was the first to demonstrate that the risk of stroke extended to those with AF and without mitral stenosis (although lower risk 5- vs 17 fold increase)
- 1980s brought early attempts to delineate the association between paroxysmal AF and stroke
- Connection between stroke and nonrheumatic AF led to trials evaluating the role of anticoagulation for stroke prevention (anticoagulation seen to be of value in rheumatic valvular AF)
- Adjusted-dose warfarin reduced stroke by 62%
  - Absolute risk reductions 2.7% per year for primary prevention and
  - Absolute risk reduction 8.4% per year for secondary prevention.
  - Major extracranial bleeding was increased by warfarin therapy (absolute risk increase, 0.3% per year)
- Aspirin reduced stroke by 22%
  - Absolute risk reductions 1.5% per year for primary prevention
  - Absolute risk reduction 2.5% per year for secondary prevention
Warfarin

• 1920’s Dead cows on the prairies of north America and Canada died from internal bleeding
• Fed of spoilt sweet clover hay, contaminated with mould
• Frank W. Schofield and Lee M. Roderick showed removing the hay or transfusing blood from healthy cows aided recovery
• 1940: Link and colleagues show natural substance called coumarin was oxidized in mouldy hay to produce as dicoumarol
• 1945: Link considered using a coumarin derivative as a rodenticide, took 42 modifications to develop Warfarin that was marketed in 1948
• 1951: US Army inductee attempted suicide warfarin in rodenticide, but fully recovered after being treated with vitamin K in hospital
• 1955: US president Dwight D. Eisenhower prescribed the drug after a myocardial infarction
• 1978: John W. Suttie and colleagues demonstrated that warfarin disrupts vitamin K metabolism by inhibiting the enzyme epoxide reductase.
Atrial Fibrillation-Case Finding
SAFE study

• 50 practices, total 14,802 patients over 65 over 12 months
• 25 intervention practices
  • Systematic screening – invited for ECG
  • Opportunistic screening – pulse check at routine appt and ECG if pulse irregular
• 25 control practice
  • No screening
SAFE study

• Number of new cases of AF identified:
  • Intervention practices 1.63%
  • Control practices 1.04%
  • Difference 0.59% (95%CI 0.20%-0.98%)

• Screening
  • Systematic screening 1.62%
  • Opportunistic screening 1.64%
  • Difference 0.02% (95%CI –0.5%-0.5%)

• Screening is effective to identify new cases of AF
• Opportunistic screening equivalent to systematic screening at lower costs (no recall and fewer ECGs needed)
Screening for Atrial Fibrillation in People aged 65 and over

A report for the National Screening Committee

May 2014
Atrial Fibrillation-Stroke risk reduction
BAFTA study

• BAFTA: RCT of warfarin vs aspirin for stroke prevention in AF in a primary care population aged over 75
  • Aim: To compare the incidence of fatal and non-fatal disabling stroke (ischaemic and haemorrhagic), intra-cranial haemorrhage and other significant arterial embolism in patients randomised to warfarin (target INR 2–3) or aspirin (75mg)
  • 973 patients ≥ 75 yrs with AF assigned to warfarin (INR 2–3) vs aspirin (75 mg/day)

• Primary endpoint – fatal or disabling stroke, ICH or systemic embolism
  • Risk per year
    • Warfarin: 1.8%;
    • Aspirin: 3.8%
    • Relative risk warfarin vs aspirin: 0.48; P = 0.003

• Major extracranial hemorrhage
  • Risk per year
    • Warfarin: 1.4%;
    • Aspirin: 1.6%
    • Relative risk warfarin vs aspirin: 0.87
GRASP Tool and NHS-Improvement Heart
GRASP Tool and NHS-Improvement Heart

Audit of Atrial Fibrillation and CHA2DS2-VASc Scores

Select Risk Score: CHA2DS2-VASc

Practice:

Total Practice Population: 11,286

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<thead>
<tr>
<th>No. with Atrial Fibrillation</th>
<th>Total</th>
<th>Percent</th>
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<tr>
<td>221</td>
<td>1,96</td>
<td>9.26</td>
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</table>

Percent of >= 65 yrs with AF: 9.26

NB: Handling of anticoagulant exclusions

Risk factors in patients with AF:
- HF or LVD
- Hypertension
- Age > 75
- Diabetes
- Stroke or TIA
- Vascular disease
- Age 65-74
- Sex Female

Breakdown of anticoagulant & antiplatelet use by CHA2DS2-VASc score:

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<thead>
<tr>
<th>CHA2DS2-VASc Score</th>
<th>0</th>
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<th>1+</th>
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<td>Anticoagulant</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>22</td>
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<tr>
<td>Both</td>
<td>8</td>
<td>7</td>
<td>8</td>
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<tr>
<td>Antiplatelet</td>
<td></td>
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<tr>
<td>None</td>
<td>102</td>
<td>62</td>
<td>22</td>
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Anticoagulant use in high risk patients:

<table>
<thead>
<tr>
<th>Percentage</th>
<th>On anticoagulant</th>
<th>Not on anticoagulant</th>
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</thead>
<tbody>
<tr>
<td>3.8</td>
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</table>

Strokes expected annually in the 84 high risk untreated

Review or score in last year

Advice

References

Podcast

This dashboard was developed by PRIMIS+ for use with CHART

©PRIMIS+ 2011
Marked under use of a cheap and effective intervention that cuts stroke risk by 60%

This is not news.

“overuse” of anti platelet medicine
Even in really high risk patients
34% anticoagulated
Community dwelling AF stroke survivors
N=3500.
NNT = 10-12
Occam’s Razor

• *The solution that requires the fewest steps should be preferred*
The Bradford AF Quality Improvement Program (QIP)

Acknowledgement:
• Greg Fell (@Felly500) Public Health Consultant Bradford LA
• Maciek Gwozdiewicz South & West Yorkshire and Bassetlaw CSU
• Bradford Districts, Bradford City and ACW CCG
Approach was simple

• Clear quality standard
• Measurable at practice
• Make data available and public to all practices
• Achievable benchmark of care target for each practice – what level are the 2\textsuperscript{nd} quintile performers achieving
• Ten evidence based strategies were consistently applied to the practices that were participating to encourage improvement.
• Bespoke support and advice to practice and more widely - Q&A / Expert events / training / Practice visits / IT tools
• 18 months.
Management of Stroke Risk

**Contraindications to The Initiation of Oral Anticoagulant Therapy in Patients with Atrial Fibrillation in Primary Care**

As a patient’s relative stroke & bleeding risk can change, it is essential that we assess this annually for a re-assessment of their stroke versus bleeding risk & the anticoagulant

**Contraindications listed below apply to BOTH anti-platelet (e.g. aspirin, clopidogrel) & ALL oral anticoagulants (e.g. warfarin, phenindione, dabigatran & rivaroxaban).**

### Absolute Contraindications

- **Known large oesophageal varices.**
- Significant thrombocytopaenia (platelet count < 50 x 10^9/L) - refer to haematologist
- Within 72 hours of major surgery with risk of severe bleeding - defer & reassess risk postoperatively
- Previously documented hypersensitivity to either the drug or excipients
- Acute clinically significant bleed - defer & re-assess stroke versus bleeding risk
- Decompensated liver disease or deranged baseline clotting screen (INR>1.5)
- Pregnancy or within 48 hours post partum
- Severe renal impairment (GFR ≤ 30 mL/min/1.73 m^2 or on dialysis)
- **Severe renal impairment** (GFR ≤ 30 mL/min/1.73 m^2 or on dialysis).
- Hyperthyroidism
- **Relative Contraindications**

#### Previous history intracranial haemorrhage - as some AF patients with high risk (i.e. CHADS2 score ≥3) may benefit from anti-thrombotic therapy, a recent recent intracranial bleed within the last 6 months where the care team feels the decision for oral anti-thrombotic therapy should be deferred.

- **Recent major extracranial bleed** within last 6 months which the care team feels the decision for oral anti-thrombotic therapy should be deferred until treatment for PU completed. In all cases with history PU, consider cardiology opinion.

- **Recent history recurrent ischaemic falls in patient at higher bleeding risk**. A patient at higher bleeding risk is assessed by having 3 or more of the following factors:
  - **age > 85 years**
  - **previous history bleed or predisposition to bleeding (e.g. diverticulitis)**
  - **uncontrolled hypertension**
  - **severe renal impairment (i.e. serum creatinine >200μmol/L, GFR < 30)**
  - **acute hepatic impairment** (e.g. bilirubin >2μmol/L fTPT > 3 x ULN, d.
  - **low platelet count < 80 x 10^9/L or a thrombocytopaenia or anemia of 40% or concomitant drugs associated with an increased bleeding risk e.g. or other immune-suppressing agents**.

#### N.B. A risk of falls is not a contraindication to initiating oral anticoagulation of 5% (CHADS2 score 2-3) would need to fall 285 times for fall risk to outweigh bleeding risk.

- **Dementia or marked cognitive impairment with poor medicines compliance**
- **Chronic alcohol abuse** – especially if associated with binge drinking.

### N.B. Poor compliance with any oral anticoagulant agent will reduce benefits but increase the risk of complications.

**Anticoagulants for prevention of stroke and systemic embolism in NVAF**

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<tr>
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<th>Dosage</th>
<th>Use</th>
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<td><strong>Apixaban</strong></td>
<td>5 or 2.5mg bd</td>
<td>For patients with <strong>body weight ≤60kg</strong>, serum creatinine ≤1.33 mmol/L, or on warfarin or dabigatran (150mg bd)</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>110mg bd</td>
<td>For patients with <strong>body weight &gt;60kg</strong> or on warfarin or dabigatran (150mg bd)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>2.5mg bd</td>
<td>For patients with <strong>body weight ≤60kg</strong>, serum creatinine ≤1.33 mmol/L, or on warfarin or dabigatran (150mg bd)</td>
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**Female 60kg**

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**Male 70kg**

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<thead>
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<th>Serum creatinine</th>
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AF QIP achievements

65% of patients with CHADS2 ≥1 on Warfarin

6% absolute improvement
AFQIP Improvement by CHADS2

- CHADS2=0: 27%
- CHADS2=1: 35%
- CHADS2=2: 52%
- CHADS2=3: 55%
- CHADS2=4: 54%
- CHADS2=5: 63%
- CHADS2=6: 67%

NNT = 13

Sep-11 vs Mar-13
Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, Hans-Christoph Dieringer, M.D., Ph.D., Robbe Greg Flaker, M.D., Akhilesh Avezum, M. Rafael Diaz, M.D., Mario Talajic, M. Jia Andzoe Budaj, M. Ph.D., Alexander Paul Patrick Commentford, M.B., Ch.B., Ru San Basili S. Lewis, M.D., Walter Van Mieghem, Jao Hyung Kim, M. Ph.D., Ph.D., Antonio Gonzalez-Hermosillo, Muhammad Munawar, M.D., Ph.D., John Lawrence, M.D., Gary, and Salim Yusuf.

Background

Warfarin reduces the risk of ischemic stroke, but at the risk of hemorrhage and is difficult to use. Apixaban is a new oral direct thrombin inhibitor.

Methods

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke of 1.0% or higher per year in the warfarin arm — 120 mg or 150 mg of dabigatran (P=0.31). The primary outcome was a composite of the first occurrence of stroke or systemic embolism.

Results

Rates of the primary outcome with 1.53% per year in the dabigatran (0.93%; 99% confidence interval [CI], 0.73 to 0.82; P<0.001 for noninferiority) group, as compared with 1.11% per year in the warfarin group (1.11%; 95% CI, 0.95 to 1.28; P=0.21). The rate of death from any cause was 4.8% per year in the aspirin group (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P=0.051).

Conclusions

The use of warfarin reduces the rate of stroke but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral direct factor Xa inhibitor, may provide more effective and safer anticoagulation than warfarin.

Rivaroxaban versus Warfarin: A Randomized Trial of Long-Term Anticoagulation Therapy

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., and the ROCKET AF Steering Committee and Investigators*

Background

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, a novel direct factor Xa inhibitor, may provide more effective and safer anticoagulation than warfarin.

Methods

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk of stroke (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority) on a daily dose of 20 mg) or dose-adjusted warfarin therapy. The mean follow-up period was 2.0 years in both groups.

Results

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.3% per year) and 206 patients in the warfarin group (1.4% per year), a difference of 0.1% per year (P=0.44), with significant reductions in the risk of major bleeding (0.2% vs. 0.5%, relative risk ratio, 0.41; 95% CI, 0.25 to 0.67; P<0.001) and fatal bleeding (0.02% vs. 0.05%, relative risk ratio, 0.44; 95% CI, 0.24 to 0.81; P=0.007).

Conclusions

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin in reducing the risk of stroke or systemic embolism, without increasing the risk of major bleeding.
### Atrial Fibrillation-Stroke risk: CHA$_2$DS$_2$VASc

<table>
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<th>CHA$_2$DS$_2$VASc risk criteria</th>
<th>Score</th>
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<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 yrs</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA (previous history)</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (IHD, PAD)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Sex Category</td>
<td>1</td>
</tr>
</tbody>
</table>
# AF Bleeding Risk: HASBLED

<table>
<thead>
<tr>
<th>HAS-BLED risk criteria</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (i.e. Uncontrolled BP)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (e.g. age &gt;65 years, frail condition)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points
## DOAC Technology Appraisals

<table>
<thead>
<tr>
<th></th>
<th>Primary prevention of VTE in adults undergoing elective hip and knee replacement</th>
<th>Prevention of stroke of systemic embolisation in patients with non-valvular AF</th>
<th>Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults</th>
<th>ACS with elevated cardiac biomarkers, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong>&lt;sup&gt;8-10&lt;/sup&gt;</td>
<td>✓ Technology Appraisals (TA245) Jan 2012</td>
<td>✓ Technology Appraisals (TA275) Feb 2013</td>
<td>✓ Technology Appraisals (TA341) Jun 2015</td>
<td>✗</td>
</tr>
<tr>
<td><strong>Edoxaban</strong>&lt;sup&gt;11,12&lt;/sup&gt;</td>
<td>✗</td>
<td>✓ Technology Appraisals (TA355) Sept 2015</td>
<td>✓ Technology Appraisals (TA354) Sept 2015</td>
<td>✗</td>
</tr>
</tbody>
</table>

5. NICE. TA327 Available at: [https://www.nice.org.uk/guidance/ta327](https://www.nice.org.uk/guidance/ta327). Accessed: May 2017;
Use of Novel Oral Anticoagulants (NOACs) across Clinical Commissioning Groups (CCGs) in England

NOAC uptake is symptomatic of local variations in AF management and the need to provide all patients high quality anticoagulation.
"Hold it, I wonder if I might try the warfarin again?"
**Guide to the Management of AF: Detection and stroke consideration**

**Bleeding Risk**
- Bleeding risk can be calculated using the HASBLED score
- HASBLED score should not be used to preclude anticoagulation
- Modifiable risk factors should be adjusted:
  - Reduce blood pressure
  - Reduce alcohol intake
  - Review medication

**Contraindications to oral anticoagulation**

**Absolute Contraindications**
- Known large oesophageal varices.
- Significant thrombocytopenia (platelet count < 50 x 10^9/L)
- Within 72 hours of major surgery with risk of severe bleeding - defer & re-assess risk postoperatively.
- Previously documented hypersensitivity to either the drug or excipients.
- Acute clinically significant bleed - defer & re-assess stroke versus bleeding risk within 3 months.
- Decompensated liver disease or deranged baseline clotting screen (INR>1.5)
- Pregnancy or within 48 hours post partum

**Relative Contraindications**
- Previous history intracranial haemorrhage: seek the opinion of a stroke specialist.
- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer within last 3 months – decision for oral anti-thrombotic therapy should be deferred until treatment for PU completed & given PPI cover whilst on anti-thrombotic agent.
- Recent history recurrent iatrogenic falls in patient at higher bleeding risk.
  - **N.B. A risk of falls is not a contraindication to initiating oral anticoagulation.**
- Dementia or marked cognitive impairment with poor medicines compliance & no access to carer support.
- Chronic alcohol abuse – especially if associated with binge drinking.

---

**Emergency admission to hospital**
- If advised to admit to hospital

**Discuss with on call cardiology**

**Patient presents with an irregular pulse**
- Consider checking the pulse on all >65yrs or with known CVD

**Haemodynamic compromise, marked dyspnoea, hypoxia or chest pain?**
- Yes
  - Emergency admission to hospital

**Clear onset within the last 72 hours**
- Yes
  - Discuss with on call cardiology

**Take history and examination**
- FBC, U&Es, LFTs, Hba1c, Lipids, TFT, ECG and possible *echo

**Is the patient <65yrs with no CVD?**
- No
  - Undertake CHA2DS2-VASc score
  - Is the patient low risk?
  - Yes
    - No thromboprophylaxis required
  - No
    - Discuss anticoagulation, this should include reference to bleeding risk.

**Patient prefers to have warfarin**
- Refer to warfarin clinic for maintenance of INR 2-3

**After 3 months has there been**
- INR >5
- 2 consecutive INRs <1.8
- Frequent INR testing required

**After 3 months is the iTTR >65**
- Consider DOAC

**Commence rivaroxaban (adjust dose due to the creatinine clearance).**
- If there is very poor dietary intake then use edoxaban (adjusted dose for creatinine clearance)
- Refer to the anticoagulation service for on going surveillance of the DOAC

**Continue oral anticoagulation indefinitely with annual reassessment of FBC, U&E, LFTs, TTR (Warfarin) and consideration of bleeding risk**

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*Echocardiogram consideration*

The default option should be to undertake an echocardiogram however if due to the clinical setting the echo will not change management then it should not be undertaken.
Study objective: To assess the safety of two rivaroxaban treatment strategies compared with the current standard of care in patients with paroxysmal, persistent or permanent NVAF undergoing PCI with stent placement
The WOEST study showed oral anticoagulation in combination with clopidogrel was associated with significantly lower bleeding than triple therapy with no increase in thrombotic events. This strategy has not yet been tested in a large study.

Where US guidelines recommend triple therapy with a VKA, recent European guidelines suggest that a NOAC may be used in triple and dual therapy after PCI.

Triple therapy with a VKA plus DAPT followed by dual therapy with VKA plus ASA is the standard of care for patients with AF and ACS, as recommended by US guidelines.

References:
Rivaroxaban is the First NOAC to Provide Data From a Dedicated RCT in AF-PCI

**Design:** An open-label, randomized, controlled phase IIIb safety study

**Population:**
patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

**N=2,124**

**Decision for DAPT duration:**
1, 6 or 12 months

**Rivaroxaban 15 mg OD***
plus single antiplatelet‡

**Rivaroxaban 2.5 mg BID**
plus DAPT§

**VKA (INR 2.0–3.0)**
plus DAPT§

**Rivaroxaban 15 mg OD***
plus low-dose ASA

**VKA plus low-dose ASA**

**DAPT duration**
(1, 6 or 12 months)

**End of treatment**
(12 months)

*CrCl 30-50 ml/min: 10 mg OD; ‡clopidogrel (75 mg daily) [alternative use of prasugrel or ticagrelor allowed, but capped at 15%]; §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) [alternative use of prasugrel or ticagrelor allowed, but capped at 15%]

Both Rivaroxaban Strategies Were Associated With A Significantly Improved Safety Profile

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001
Conclusions

- Administration of either rivaroxaban 15 mg OD plus a single antiplatelet for 1 year, or rivaroxaban 2.5 mg BID plus 1, 6 or 12 months of DAPT reduced the risk of clinically significant bleeding compared with a standard VKA plus DAPT strategy.

- Although the study was not powered to detect differences in efficacy endpoints, both rivaroxaban strategies demonstrated similar efficacy compared with a standard VKA plus DAPT strategy.

- Both rivaroxaban strategies showed a reduced risk of recurrent hospitalization compared with the VKA strategy.

Mortality rate after hospital discharge for ACS remains high

### Death from hospital discharge to 6 months

<table>
<thead>
<tr>
<th>Days</th>
<th>STEMI (%)</th>
<th>NSTEMI (%)</th>
<th>Unstable angina (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>60</td>
<td>1.2</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>90</td>
<td>2.0</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>120</td>
<td>3.0</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>150</td>
<td>4.0</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>180</td>
<td>5.0</td>
<td>2.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Diagram showing the percentage of mortality over different time periods from hospital discharge to 6 months for STEMI, NSTEMI, and unstable angina.
• Xarelto 2.5mg, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.
Event rate of CV death, MI or stroke at 12 months post event remains ~10%
ATLAS ACS 2 TIMI 51: a randomized, double-blind, event-driven phase III trial in patients hospitalized with ACS

 Patients with prior stroke were excluded from the study.

*184 patients were excluded from the efficacy analyses prior to unblinding because of trial misconduct at three sites.

ATLAS ACS 2 TIMI 51: Study endpoints

- **Primary efficacy endpoint**: composite of cardiovascular death, MI or stroke (ischaemic, haemorrhagic or uncertain)

- **Secondary efficacy endpoint**: composite of all-cause death, MI or stroke

- **Main safety endpoint**: incidence of major bleeding not associated with CABG surgery (assessed according to the TIMI bleeding definition)

- **Other safety endpoints**:
  - Other bleeding events classified according to the TIMI, GUSTO and rivaroxaban programme scales
  - Adverse events
  - Clinical laboratory tests
  - Liver safety assessments

Xarelto 2.5mg bd reduces Cardiovascular death, MI or stroke among patients with elevated biomarkers and no prior stroke or TIA

Summary

- Among patients with a recent ACS with cardiac biomarker elevation and no prior stroke or TIA, rivaroxaban 2.5 mg twice daily as compared with placebo:
  - Reduces CV death, MI, or stroke
  - Reduces CV death and all-cause death
  - Increases non-CABG TIMI major bleeding, without an increase in fatal bleeding
Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

BACKGROUND
Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result

CONCLUSIONS
Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909.)

stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.
A Dual Pathway Strategy Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

**Objective:** To determine the efficacy and safety profile of rivaroxaban plus aspirin, rivaroxaban alone or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD

The independent DSMB recommended early study termination due to clear and consistent benefit in the rivaroxaban treatment arms

**Population:**
- Chronic CAD (91%)
- PAD (27%)

**Treatment Arms:**
- Rivaroxaban 5.0 mg bd
- Aspirin 100 mg od
- Rivaroxaban 2.5 mg bd + Aspirin 100 mg od

**Study Design:**
- Factorial Design ± pantoprazole*
- 30-day run-in, ASA 100mg

**Follow-up:**
- Average follow up: 23 months at early termination of study
- Final follow-up visit
- Final washout period visit

**Notes:**
- * pantoprazole arms ongoing

A Dual Pathway Strategy Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

• Primary study objectives
  • To determine whether rivaroxaban 2.5 mg bd + ASA 100 mg od or rivaroxaban 5 mg bd alone reduces the risk of a composite of MI, stroke and CV death compared with ASA 100 mg od in patients with CAD or PAD

• Secondary study objectives
  • To determine, in patients with CAD or PAD, whether rivaroxaban 2.5 mg bd + ASA 100 mg od or rivaroxaban 5 mg bd alone versus ASA 100 mg od:
    • Reduces risk of composite of major thrombotic events: (1) coronary heart disease, MI, ischaemic stroke, acute limb ischaemia; (2) CV death, MI, ischaemic stroke, acute limb ischaemia
    • Reduces the risk of mortality

Inclusion and Exclusion Criteria Ensure That Patients Are Chronic CAD and PAD Patients

### Key inclusion criteria*

- PAD
- CAD with $\geq 1$ of:
  - Age $\geq 65$ years
  - Age $< 65$ years plus atherosclerosis in $\geq 2$ vascular beds or $\geq 2$ additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR $< 60$ ml/min)
    - Heart failure
    - Non-lacunar ischaemic stroke $\geq 1$ month ago

### Key exclusion criteria†

- Stroke $\leq 1$ month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction $< 30\%$ or NYHA class III or IV symptoms
- Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
- eGFR $< 15$ ml/min

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*Including but not limited to; †Any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

Dual Pathway Inhibition with Rivaroxaban Vascular Dose
2.5mg bd + Aspirin Reduced Stroke, CV Death and MI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cumulative Incidence (%)</th>
<th>MACE%</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 100mg OD</td>
<td>5.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rivaroxaban 5mg bd</td>
<td>4.9</td>
<td>0.90  (0.79-1.03)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 2.5mg bd + Aspirin 100mg OD</td>
<td>4.1</td>
<td>0.76  (0.66-0.86)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Rates as at mean follow up of 23 month

Rivaroxaban led to Significant Reduction in the Primary Efficacy Outcome in Patients with Chronic CAD or PAD

Dual pathway inhibition with rivaroxaban vascular dose 2.5mg bd and aspirin 100mg OD, versus aspirin alone:

• Significantly reduced the combined risk of stroke, CV death and MI by 24%
• Demonstrated 42% reduction in stroke and 22% reduction in CV death
• Resulted in an increase in major bleeding rates (of 70%) compared to aspirin alone, with no significant increase in intracranial, critical organ or fatal bleeding
• Showed an improvement in net clinical benefit of 20% and 18% nominal reduction in all-cause mortality

Claudication-Survival

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Causes</td>
<td>3.1 (1.9-4.9)</td>
</tr>
<tr>
<td>CVD</td>
<td>5.9 (3.0-6.6)</td>
</tr>
<tr>
<td>CHD</td>
<td>6.6 (2.9-14.9)</td>
</tr>
</tbody>
</table>

Claudication-10 year natural history survival

## COMPASS:-Affinity Care Implications

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agent</td>
<td>90.3</td>
</tr>
<tr>
<td>At time of event Aspirin with</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>50.60</td>
</tr>
<tr>
<td>Clopidoger*</td>
<td>32.10</td>
</tr>
<tr>
<td>Prasagrel</td>
<td>1.23</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>12.35</td>
</tr>
<tr>
<td>Anticoagulation**</td>
<td>3.72</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>89.59</td>
</tr>
<tr>
<td>Statin</td>
<td>89.96</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
</tr>
<tr>
<td>Fibrate</td>
<td></td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>89.96</td>
</tr>
<tr>
<td><strong>Combination of therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent and Beta-blocker (BB)</td>
<td>76.69</td>
</tr>
<tr>
<td>Antiplatelet agent, BB and Statin</td>
<td>72.64</td>
</tr>
<tr>
<td>Antiplatelet agent, BB, Statin, ACEI/ARB</td>
<td>70.61</td>
</tr>
<tr>
<td>Antiplatelet agent and Statin</td>
<td>77.03</td>
</tr>
<tr>
<td>Antiplatelet agent, statin and ACE-I/ARB</td>
<td>74.32</td>
</tr>
<tr>
<td><strong>Other indices</strong></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>19.70</td>
</tr>
<tr>
<td>Systolic blood pressure&lt; 131mmHg</td>
<td>61.15</td>
</tr>
<tr>
<td>Systolic blood pressure&lt; 141mmHg (QOF target)</td>
<td>76.35</td>
</tr>
</tbody>
</table>

Across just the PAD/CAD population this is 1.7% of the population
Known Occlusive Cardiovascular Disease

- **Occlusive Vascular Disease Vascular Protection**
  - **Type 2 Diabetes**
    - Using: SGLT2 inhibitors, Metformin, Other agents
  - **Blood pressure control**
    - Using: ACE-I/ARB, DHP, Thiazides
  - **Anti-Platelet/Anticoagulant**
    - Acute CAD/PAD
    - Acute CVA/TIA
      - Clopidogrel 75mg
      - Rivaroxaban 2.5mg bd
      - Aspirin 75mg
      - After 12 months switch to
      - Rivaroxaban 2.5mg bd and Aspirin 75mg
  - **Smoking**
    - Supporting smoking withdrawal
  - **Lifestyle**
    - Continue healthy lifestyle

- **Atrovastatin 80mg**
- **Hba1c <58mmol**
- **Systolic Blood Pressure Target 130mmHg**
- **CAD/PAD**
  - Encourage smoking cessation at every contact

**Atrial fibrillation identified**
**Oral Anticoagulation Alone**
Thank you for your attention

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